The Pathophysiological effects of adjuvant pre-operative chemotherapy and/or radiotherapy on patients with advanced rectal cancer

‘Neoadjuvant treatment is a two edged sword in patients with advanced colorectal cancer’

Samir Rahmani

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Main investigator and author: Mr. Samir Rahmani BSc, MB.ChB, MRCS, MSc

The John Goligher Colorectal Department, Room D156, D floor Clarendon Wing

The General Infirmary at Leeds, Great George Street, Leeds. LS1 3EX

0113 3923557, 07919408043

rahmanisamir@hotmail.com,

samir.rahmani@wales.nhs.uk

Supervisor one: Mr. Dermot Burke

The John Goligher Colorectal Department, Room D156, D floor Clarendon Wing

The General Infirmary at Leeds, Great George Street, Leeds. LS1 3EX

0113 3923557, Dermot.burke@leedsth.nhs.uk

Supervisor two: Dr. Simon Howell

Academic Unit of Anaesthesia, B floor Brotherton Wing, The General Infirmary at

Leeds, Great George Street, Leeds. LS1 3EX

0113-392-6360, Simon.howell@leedsth.nhs.uk

Supervisor three: Dr. Shelagh Turvill

Academic Unit of Anaesthesia, B floor Brotherton Wing, The General Infirmary at

Leeds, Great George Street, Leeds. LS1 3EX

0113-392-6360, Shelagh.Turvill@leedsth.nhs.uk

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1- ABBREVIATIONS

Phrase		Abbreviation
Gastrointestinal tract		GIT
Chemotherapy		CT
Radiotherapy		RT
Head and Neck		HN
Quality of life		QoL
Health Related Quality of Life		HRQL
Resting energy expenditure		REE
Adjuvant pre-operative therapy		APT
Oxygen consumption per unit time		VO_2
Carbon dioxide output		VCO_2
Stroke volume		SV
Cardiac output		CO
Anaerobic threshold		AT
Peak VO_2		$PkVO_2$
Cardiopulmonary exercise test		CPEX
Neutral killer		NK
Bone mineral content		BMC
Dual energy x-ray absorptiometry		DXA
Air displacement plethysmography		ADP
Bioelectrical impedance analysis		BIA
Body mass index		BMI
Fat-free mass		FFM
Colorectal cancer		CRC
C-reactive protein		CRP
Lean Body Mass		LBM
Resting heart rate		RHR
Systolic blood pressure		SBP
Diastolic blood pressure		DBP
High density lipoprotein		HDL-C
Plasma triglyceride (TG)		TG

Table (1) shows the abbreviation used in this thesis

2-ABSTRACT

Introduction

The modern treatment of colorectal cancer consists of surgery, with or without adjuvant pre-operative radiotherapy, chemotherapy or chemoradiotherapy (APT) for selected cases. In the United Kingdom, therapy may be given prior to surgery in an attempt to facilitate surgical excision and improve survival. However, there is some evidence that APT in other cancers may adversely affect the patient's health and increase the risk of operative morbidity.

The association between functional capacity, represented by the maximum oxygen consumption per unit time (VO_2max) as measured by cardiopulmonary exercise testing (CPEX), and the perioperative outcome is well established. A reduction in cardiopulmonary reserve may increase the perioperative mortality and morbidity; however, sufficient data to demonstrate this are not available yet.

This study examined the affect of APT on the cardiopulmonary status, body composition, cytokines assay, nutritional status and quality of life in patients with colorectal cancer.

Methods

This is a pilot observational study performed on two groups of patients, no intervention was used at this stage. Group one received combined ChemoRadiotherapy and Group two received only pelvic radiotherapy. Cardiopulmonary function was measured with exercise bicycle to achieve Anaerobic Threshold (AT) and Maximum Oxygen consumption (VO_2max) using CPEX testing. Anthropometric parameters such as mid-arm circumference (MAC), Triceps skin fold (TSF), grip strength measurements (GS), Body weight, height and body mass index as well as extracellular water (ECW), intracellular water (ICW), total body water (TBW) and fat free mass (FFM) were measured using a Bio-electrical impedance analyser. 9 cytokines were measured using a Luminex assay in addition to CRP and albumin assessment. Nutritional status and quality of life were evaluated using two validated questionnaires (EORTC QLQ-C30 and PG-SGA). These assessments were made before and within two weeks after the administration of APT. Wilcoxon rank sum test represented in median and interquartile range was used to compare results before and after the exposure to APT.

Results

Between January 2010 and January 2011, a total of 36 patients with rectal cancer were recruited, 24 patients in group 1 had combined chemoradiotherapy (mean age 59.4, 18 males and 6 females) and 12 patient in group 2 had radiotherapy only (mean age 71.8, 10 males and 2 females). Group 1 had a significant decline in VO_2max with p=0.005, an increase in the ventilatory equivalent ratio for CO_2 (VE/VCO_2) with p= 0.001, a reduction in TSF, MAC, GS and TBW with p- values of 0.007, 0.006, 0.010 and 0.000 respectively after APT exposure. Group 2 had no significant changes in their CPEX data, however, they showed a marked decline in TSF, MAC, GS, TBW and FFM with p- values of 0.013, 0.013, 0.002 and 0.034 respectively after APT exposure. Both groups showed a highly significant overall reduction in the health related quality of life data with no significant changes in their plasma cytokines, CRP and albumin post APT.

Conclusions

These data suggest that APT has a significant effect upon the cardiopulmonary capacity with reduced VO_2max as well as an increased VE/VCO_2. There were also signs of fluid depletion and reduced muscle bulk represented by a significant reduction in TBW, FFM, MAC and TSF. Therefore, these important physiological changes could be deleterious and affect the peri and post-operative recovery and increase the morbidity of surgery in colorectal cancer patients. In view of this, a period of optimisation following APT and prior to surgery may serve to minimise the risk of such complications.

3.0 INTRODUCTION

3.1 Colorectal Cancer (CRC)

3.1.1 Background

Colorectal Cancer (CRC) is the second commonest cancer causing death from malignant disease in the United Kingdom (UK). Approximately 35,000 new cases and over 16,000 deaths each year related to CRC with an overall 5 year survival of approximately 55% [1].

Nearly 20% of colorectal tumours are rectal with an additional 10% in the rectosigmoid junction. Approximately 25% of CRC develop in the sigmoid colon and 20% arise in the caecum [2, 3]. Around 3% of patients with CRC present with more than one tumour (synchronous tumours) and a previous colonic neoplasm increases the risk of a second tumour (metachronous tumour). 98% of CRC are adenocarcinomas, however, rectal cancers can also present as lymphoma (1.3%), carcinoid (0.4%) and sarcoma (0.3%) [2, 3].

Colorectal cancer is about equal for both males and females with a peak age of 65 years old. Furthermore, the incidence, pathogenesis, aetiology, epidemiology and screening methods are the same for both colonic cancer and rectal cancer.

Over the last 30 years, there has been a considerable advance in the management of CRC, although very little overall reduction in patients' mortality and morbidity.

The time of diagnosis remains the gold standard prognostic factor for many cases [4, 5]. Early detection through various screening programmes plays an important role in improving the outcome of patients with colorectal cancer in developed countries. For example, in the United States, the mortality rate of colorectal cancer patients was reduced by 50% when appropriate screening methods were applied [6]. The UK CRC screening programme will be discussed in more details in the screening section of this chapter.

In order to direct research programmes towards improving patients management and outcome, it is important to fully understand the CRC biological and genetic behaviour.

3.1.2 Pathogenesis

The large bowel mucosa usually regenerates every 6 days. Crypt cells migrate from its base to the surface, where differentiation and maturation start to occur. Cancers are believed to arise within pre-existing adenomas [7, 8]. These develop, through a series of molecular and genetic mutations, which occur over 10-20 years, from normality, through dysplasia to invasion [9].

The majority of cases of CRC (75%) are sporadic and develop in people with no specific risk factors [10].

A further 25% of cases are known to have a positive family history, definite environmental factors and/or a history of previous colonic polyps.

Factors that have been recognised to increase the incidence of CRC include dietary red meat, animal fat and low-fibre [13], increased consumption of tobacco [11], increased alcohol intake (more than 30g daily) [12], lack of exercise and obesity [13, 14]. Meta-analysis of case-controlled studies showed that high-fibre diet has a protective mechanism against colorectal cancer as it forms a bulky and soft stool that dilutes carcinogens as well as decreases the colonic transit time and allowing less time for harmful substances to be in contact with the colonic mucosa [8].

High dietary calcium has been identified to reduce the risk of colorectal neoplasia. This is achieved by the binding of calcium to the bile and fatty acids to form calcium salts which may have anti-proliferative effects to reduce the crypt cell production at the mucosal level. Other dietary vitamins and minerals, such as selenium, carotenoids, and vitamins A, C, and E, may have protective effects by scavenging free-oxygen radicals in the colon [15].

Patients having undergone a cholecystectomy may theoretically have a higher risk of developing CRC as there is a continuous exposure of the intestinal mucosa to the free flow of bile acids by-products which have a carcinogenic effect [16]. A meta-analysis by Giovannucci *et al* revealed that the resultant bile acid metabolism increases the risk of cancer of the proximal colon [17]. However, the increased incidence is not sufficient to warrant screening of this cohort of patients [2].

Additionally, about 10% of the CRC cases have a genetic pathogenesis which can happen via three recognised genetic pathways [18]. These are:

a) The adenomatous polyposis coli gene (APC) adenoma-carcinoma pathway (responsible for 1% of all CRC cases).

This process of mutation usually starts with an event at the adenomatous polyposis coli (APC) gene. This is located on the long (q) arm of chromosome 5 between positions 21 and 22 and considered to be a tumour suppressor gene that prevents the uncontrolled cellular growth that might result in cancerous transformation. APC mutation normally activates oncogene c-Myc and Cyclin D1 via its encoded protein. These oncogenes drive the mutation process to a malignant phenotype [19]. APC was initially discovered in patients with familial adenomatous polyposis (FAP), which is rare autosomal dominant inherited syndrome characterised by the development of more than 100 colonic adenomas. It accounts for 1% of cases of colorectal cancer. However, APC mutations are very frequently involved in sporadic colorectal cancers [20, 21]. FAP can be associated with, desmoid tumours, bone osteoma, and rarely brain neoplasia. Independently, these polyps do not possess a higher risk of neoplastic change compared with polyps found in other normal individuals [22]. Nevertheless, the presence of a large number of these polyps in FAP patients gives them a 100% risk of developing CRC if the colon is not surgically removed before the age of 40 years [23].

b) The hereditary nonpolyposis colorectal cancer (HNPCC) pathway (responsible for 4-7% of all CRC cases).

HNPCC is an autosomal dominant inherited syndrome that is characterised by the lack of DNA mismatch repair. This is caused by mutations of *MSH2, MLH1,* and *PMS2* genes. This will lead to high frequency microsatellite instability (H-MSI), which is found in approximately 4-7% of CRC cases [24, 25]. These patients have the same risk of developing colonic polyps as other people; however, these HNPCC polyps are more likely to have neoplastic transformation [26, 27]. Additionally, they have a higher incidence of endometrial, gastric, thyroid and brain cancers [28].

The revised Amsterdam criteria [29] are used to determine patients who are at high risk of HNPCC. All criteria (below) must apply for a diagnosis to be made [30]:

1. Three or more relatives who are diagnosed with an HNPCC-associated cancer (colorectal, endometrium, small bowel, ureter, or renal pelvis).
2. One affected individual is a first-degree relative of the other two.
3. One or more cases of cancer are diagnosed before the age of 50 years.
4. At least two generations are affected.
5. FAP should be excluded.
6. Tumours have undergone a pathological review.

c) The ulcerative colitis dysplasia pathways (responsible for 1% of all cases).

Patients with Inflammatory Bowel Disease (IBD) have a relatively higher risk of developing CRC through a different pathway (non adenoma-carcinoma sequence). The incidence of colorectal cancer in patients with ulcerative colitis (UC) increases 1% per year after having the disease for more than 10 years [31, 32]. Patients should have an annual colonoscopy screening to rule out dysplastic changes as the latter has a 30% risk of CRC [33, 34].

KRAS oncogene may also be involved in CRC pathogenesis. Loss of heterozygosity (LOH) in chromosome 18 region q21 will lead to the inactivation of SMAD4 (DPC4), and deleted in colon cancer (DCC) tumour suppression genes [35, 36]. This will ultimately increase the chance of developing CRC. In addition, deletion of chromosome arm 17p and mutations affecting *p*53 tumour suppressor gene allow resistance to apoptosis and play role in colonic carcinogenesis [37, 38].

Apart from the previously described genetic mutations, epigenetic events such as abnormal DNA methylation can also play an important role in the colorectal carcinogenesis via silencing of tumour suppressor genes or activation of oncogenes, which will eventually lead to neoplastic transformation [39-41].

3.1.3 Incidence

The incidence and mortality rates of CRC have been declining in the last 20 years due to the implementation of modern screening procedures that allow the detection and removal of colorectal polyps before any malignant transformation. In 1985, the incidence rate in the UK was 66.3/100,000 population which has declined to 45.5/100,000 in 2006 [3].

The incidence rate of CRC varies significantly across the world with an approximate 944,717 new cases identified in 2000. The majority of those CRC patients were found in US, Australia, New Zealand, Israel, Japan, Canada and Eastern Europe. However, lower incidence rates were identified in Algeria and India [2]. Hence, incidence is higher in westernised countries compared to the developing nations. It has also been found that five-year survival rates are lower among blacks (55%) compared to whites (66%) [3].

Males carry higher risk of developing CRC with worse prognosis than women. Roughly, the male-female ratio is about 1.37-1 with a mortality rate of 25.4/100,000 in males and 18/100,000 in females in 1999 [3].

Around 90% of CRC occur after the age of 50 years [2]. However, it can still occur in younger adults and children. Usually, the incidence of CRC increases after age of 35 years with a rapid rise after age of 50 years, peaking at the seventh decade of life [42].

3.1.4 Screening

The aim of colorectal cancer screening is to decrease mortality through diagnosis and treatment of precancerous lesions (adenomatous colorectal polyps) before malignant transformation [43] as well as detection of early curable cancerous lesions.

Four randomised controlled trials (RCTs) of mass screening using the faecal occult blood (FOB) test have been carried out: one in the UK [44], one in Denmark [45], one in the USA [46] and one in Sweden [47]. These trials demonstrated a reduction in bowel cancer specific mortality in the screened groups, using biennial screening, annual screening or a combination of the two with follow up periods ranging from 11 to 18 years.

A meta-analysis of these four trials [48] reported a 16% reduction in bowel cancer specific mortality with screening [odds ratio (OR) 0.84; confidence interval (CI) 0.78–0.89], and a 15% reduction in those trials using only biennial screening (OR 0.85; CI 0.78–0.93).

In 2009, published figures from the National Cancer Intelligence Network showed that screened patients who were picked up with Dukes' stage A colorectal cancer had more than 90% chance of surviving the disease compared to only about 15% survival before the introduction of the FOB screening [49].

The proportions of cancers detected by screening for each Dukes' stage during the first phase of the screening pilot in England is as fellow: 16.8% of un-staged polyp cancers, 25.2% of Dukes' stage A, 26.0% Dukes' stage B, 25.2% Dukes' stage C and 1.5% of Dukes' stage D [50].

Following these demonstrations of mortality reduction, the Department of Health commissioned a pilot screening programme to assess the feasibility of using biennial FOB test screening as a population screening tool for bowel cancer in the UK. Three pilot screening rounds for men and women aged 50–69 years were successfully implemented in Coventry and Warwickshire in England and in Tayside, Grampian and Fife in Scotland. The first round of screening demonstrated that screening for bowel cancer using the FOB test is feasible within the context of the NHS [51].

Therefore, the National Health Service (NHS) has officially started the Bowel Cancer Screening Programme. The specifics of the programme vary according to the location of the population:

- In England, people aged 60 to 75 will be offered screening every two years.
- In Scotland, people aged 50 to 74 will be offered screening every two years.
- In Wales, people aged 60 to 71 will be offered screening every two years.
- In Northern Ireland, people aged 60 to 69 will be offered screening every two years [52].

FOB testing can detect around 26% of CRC cases. It is easy, cheap, non-invasive, widely acceptable by the population and can pick up large number of patients with less advanced, symptoms free, disease [53-56].

The sensitivity of FOB test (proportion of individuals who have bowel cancer that test positive) has been reported to be 55.0–92.2% in RCTs [48, 57]. It has a false-positive result mostly caused by red meat or vegetables with high peroxidase content. FOB is the main screening method used by the NHS Bowel Cancer Screening Programme followed by a lower gastrointestinal endoscopy, if FOB was positive, to investigate these patients further [52]. FOB is a newly screening method introduced to the NHS, hence, its long term results are not known yet. However, a recent study showed that around 2,500 patients could potentially be saved every year in the UK by 2025 FOB screening test [58, 59].

Higher risk patients will be offered an early regular CRC screening method regardless to their age, as per the guidelines for colorectal cancer screening and surveillance in moderate and high risk groups. These groups are [60, 61]:

A. Individuals with inherited conditions such as familial adenomatous polyposis (FAP), hereditary non-polyposis colorectal cancer (HNPCC), Peutz-Jeghers syndrome and juvenile polyposis syndrome. This group also include screening of their close relatives.
B. Patients with previously treated CRC.
C. Acromegaly patients.
D. Patients with ulcerative colitis or Crohn's disease.
E. Patients with previous benign colonic polypectomy.
F. First-degree relatives of patients who had colorectal cancer, especially if they were below 45 years of age.

CRC screening can also be done through other methods such as:

1. Colonoscopy or flexible sigmoidoscopy: Colonoscopy is usually performed for right colonic lesions while flexible sigmoidoscopy is done for left colonic tumours. The later method can not be used in assessing rectal cancers as these lesions are too low and could be easily missed [62]. Both are expensive and invasive procedures which carry some risks of perforation and bleeding. It is not widely acceptable by patients, although, it allows direct visualisation of the colonic mucosa, estimation of the size of the lesion and degree of obstruction plus the capability of obtaining a diagnostic biopsy assess ulceration and determine the degree of fixation [55, 63]. Sometimes, this method is used to place a colonic stent as a palliative procedure for obstructing bowel cancer.

2. Rigid proctosigmoidoscopy: Again, this method allows direct visualisation of the colonic mucosa, estimation of the size of the lesion and degree of obstruction plus the capability of obtaining a diagnostic biopsy, ulceration assessment and determines the degree of fixation. It is easy to perform, inexpensive and more acceptable compared to the previous method as it can be done in the outpatient clinics with no sedation. Moreover, proctoscopy gives an accurate measurement of the distance/level of the lesion from the anal verge as this is important to decide the type of the subsequent surgical resection needed for such patients [62, 64]. However, only the rectum and the lower part of the sigmoid colon could be visualised with this method.
3. Stool DNA screening: Sloughed mucosal cells in the patient stool is tested by using polymerase chain reaction (PCR). It is useful to assess genetic changes in CRC cases plus it is cost effective and has high sensitivity for invasive cancer [65, 66].
4. Faecal immunochemical test: This is a monoclonal antibody assay to spot human haemoglobin in the patient stool. The presence of the globin molecule is suggestive of colorectal bleeding as this molecule usually broken down in the upper GI tract. Hence, this could be used as a screening tool as it is easy and non invasive, however, this procedure is slightly expensive and not available in many health centres [67, 68].
5. Double-contrast barium enema: This is a traditional diagnostic method for detecting colonic lesions with low sensitivity compared to the newer techniques used for CRC screening, thus, not widely used recently [69, 70]. However, recent studies from the UK proven around 90% sensitivity of barium enema in detecting CRC cases. This method is easy, cheap, non invasive and acceptable by most patients [71, 72].

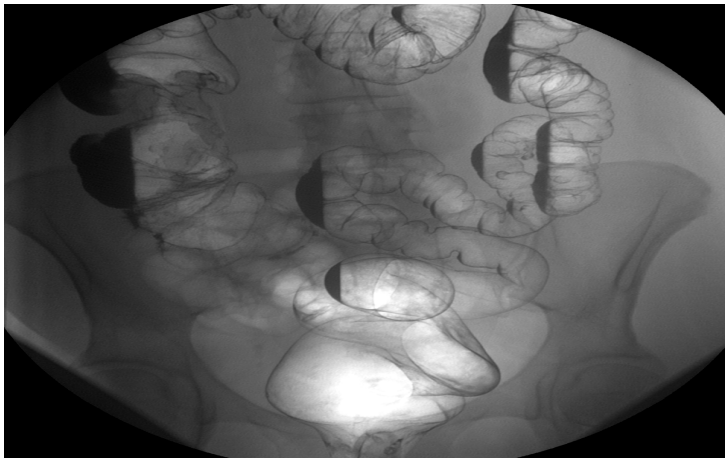


Figure (1) shows the double-contrast barium enema

6. CT colonography (Virtual colonoscopy): This method was introduced in 1994 with a diagnostic performance likely exceeding barium enema and optical colonoscopy [73, 74]. By employing state-of-the-art multislice technology, CT colonography allows a complete examination of the colon and surrounding organs in less than 30 seconds. Then, these images are reconstituted into a 3-dimensional replica of the entire colon and rectum. This provides a good visualization of the entire colon, including the antegrade and retrograde views of the flexures and haustrations [75]. However, this is a diagnostic test only, thus, patients with positive finding will require a subsequent colonoscopy to obtain a tissue diagnosis. It is also expensive, not widely available and need expert radiologist to interpret the results.

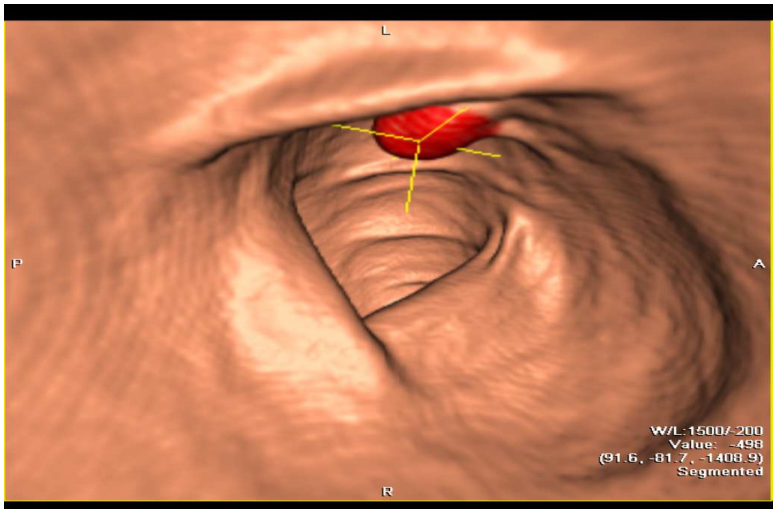


Figure (2) shows CT colonography (Virtual colonoscopy)

Each of the above screening tests has some advantages and limitations. Eventually, tests availability and patient preference guide the selection of the screening method. People with positive FOB test are normally offered a colonoscopy. If bowel cancer is detected at colonoscopy (or via other further investigations), the care of the patient will be handed over from the screening centre to the relevant multidisciplinary team (MDT). Following consultation by the MDT and discussion with the patient, an individual programme of treatment and care will be agreed. Around 8 in 10 people who have bowel cancer detected will have surgery to remove the cancer. After surgery, over 50% of people will live for more than five years. Pre- or postoperative chemotherapy or radiotherapy may be offered to patients. CRC screening is very important as shown in the previous figures to diagnose the condition early and give the best chance of a cure.

3.1.5 Presentation

Detailed patient and family history should be obtained in any suspected case with a thorough assessment of risk factors for the development of CRC. Despite the modern screening programmes, patients with CRC can present with rectal bleeding which occurs in 60% of rectal neoplasm [76, 77]. This is usually not profuse and can sometimes be associated with mucous discharge. Change in bowel habit (43% of cases) is another symptom. It can be either constipation or diarrhoea, which is due to the presence of large rectal villous component [78]. Additional symptoms are iron-deficiency anaemia, abdominal pain (20% of the cases), intestinal obstruction, intestinal perforation, incomplete evacuation and tenesmus. At later stages when the CRC is started to invade the spinal nerves and bladder/prostate, patients will suffer from back pain as well as urinary urgency, frequency and dysuria. Furthermore, patients can have generalised non-specific constitutional symptoms such as malaise, appetite and weight loss, fatigue, pelvic pain plus possible symptoms and signs e.g. hepatic and pulmonary. Lesions in the right colon are more likely to cause microscopic per rectal bleeding and diarrhoea, while tumours in the left hemicolon could present with bowel obstruction, perforation or rectal bleeding. Clinical findings are usually non specific and vary between localised abdominal mass and/or tenderness, ascitis, lymphadenopathy and hepatomegally. Digital per rectal examination (DPR) can pick up low rectal tumours and also can show any per rectal bleeding. DPR can assess tumour size, mobility and ulceration as well as local lymphadenopathy and anal sphincteric function. If the rectal tumour is more than 8cm from the anal verge, rigid sigmoidoscopy is performed to take a biopsy. However physical findings could be absent in such patients [79].

The National Institute for Health and Clinical Excellence (NICE) recommends urgent referral for the following patients [80]:

• Aged ≥ 40 years who report rectal bleeding with a change of bowel habit towards looser stools and/or increased stool frequency persisting for six weeks or more.

• Aged ≥ 60 years who report rectal bleeding persisting for six weeks or more without a change in bowel habit and without anal symptoms.

• Aged ≥ 60 years who report a change in bowel habit to looser stools and/or more frequent stools persisting for six weeks or more without rectal bleeding.

• Of any age with a right lower abdominal mass consistent with involvement of the large bowel.

• Of any age with a palpable rectal mass (intraluminal and not pelvic; a pelvic mass outside the bowel would warrant an urgent referral to a urologist or gynaecologist).

• Who are men of any age with unexplained iron deficiency anaemia and a haemoglobin level of ≤ 11 g/100 ml.

• Who are non-menstruating women with unexplained iron deficiency anaemia and a haemoglobin level of ≤ 10 g/100 ml.

3.1.6 Investigation

Haematological investigations are usually performed on patients with CRC to assess their end organ function as well as evaluation of the body tumour load. These include full blood count which can sometimes show a hypochromic, microcytic anaemia, suggesting iron deficiency due to a microscope or macroscopic blood loss. Hence, all middle-aged male patients and postmenopausal females with iron deficiency anaemia should have their gastrointestinal tract investigated [81, 82].

Further investigations include liver and renal function tests plus serum electrolytes and carcinoembryonic antigen (CEA) level. CEA has a sensitivity of 76% and specificity of 90% [83].

The later should be obtained pre and postoperatively from CRC patients as elevated CEA might indicate a disseminated disease with advanced stage and/or recurrence [84].

A raised serum CEA level more than 100 ng/mL generally indicates metastatic disease and warrants further work up [85]. Hence, it is a bad prognostic indicator to have an elevated serum CEA in patients with CRC, although, it has not yet been included in the colorectal cancer conventional TNM staging guidelines by the American Joint Committee on Cancer AJCC [86]. CEA is mainly used in the follow up post CRC resection.

Preoperative imaging of the chest and abdomen should be obtained for staging purposes. This is usually done by chest radiograph, chest and abdominal computerized tomography (CT scan) [87], ultrasound of the abdomen and liver plus abdominal and pelvic magnetic resonance imaging (MRI) for rectal cancers [88-90].

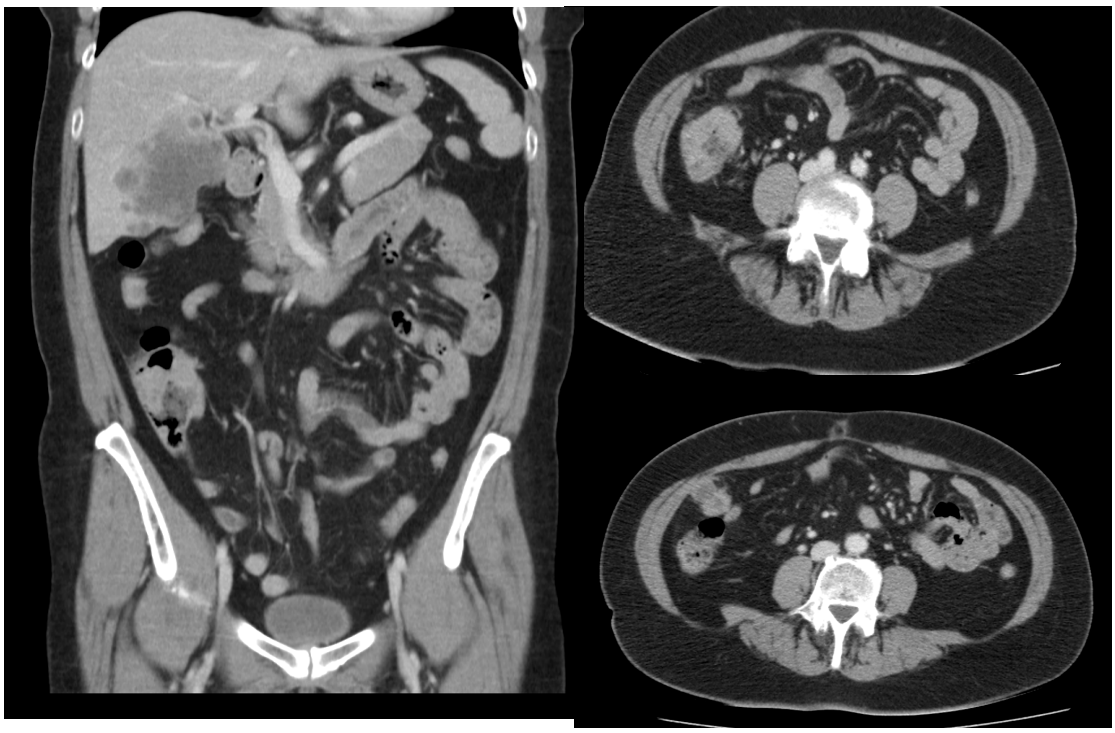


Figure (3) shows CT scan of the abdomen showing Caecal Cancer

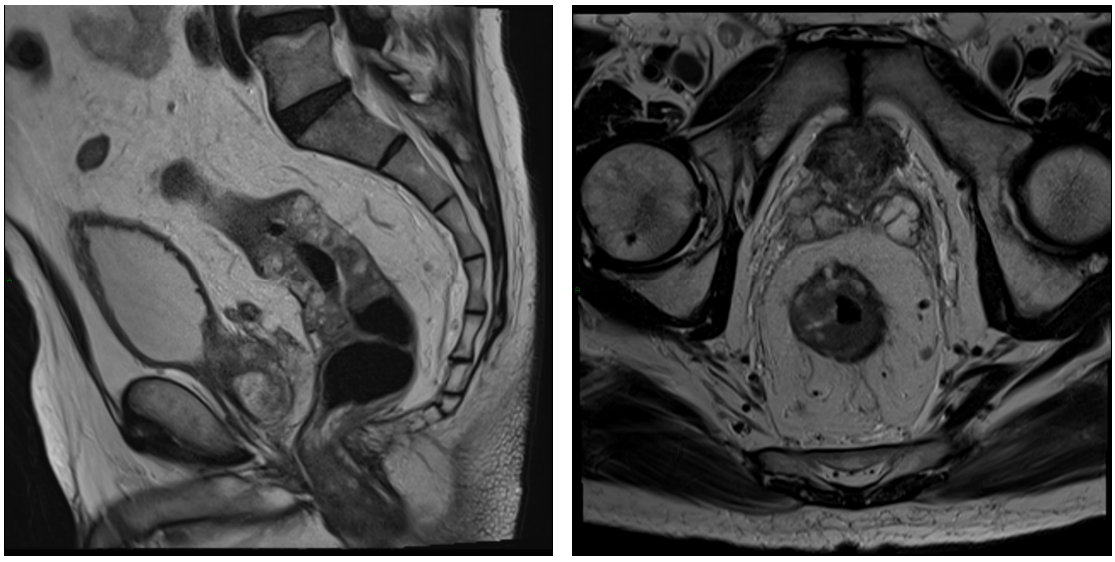


Figure (4) shows rectal cancer in a Pelvic MRI scan

If the CT scan results are not very clear or there is a doubt in the pre-operative disease staging, then Positron emission tomography (PET) is used to properly evaluate the thoracic and abdominal disease [91]. The newest addition, a fusion PET-CT scan, allows for detection of metastatic deposits and has added tissue-based resolution of CT scan. A combination of positron emission tomography and computed tomography (PET/CT) can increase the detection rate of colorectal metastases [92, 93].

Colonoscopy and CT pneumocolon are used to identify the primary site of disease in patients with of colorectal cancer [94], also colonoscopy and sigmoidoscopy are useful in obtaining an endoscopic guided biopsy to confirm the diagnosis [95, 96]. The sensitivity and specificity of CT pneumocolon is 95.2%, 40.9% in detection of local invasion, and 75.0%, 90.9% in detection of lymph node metastasis [97].

Hence, detecting transmural extension, perienteric spread of tumours and distant lymph node involvement is still an area of conflict to most radiologist and oncologists [98].

3.1.7 Histopathology

A recent study is the United States showed that about 96% of CRCs were adenocarcinomas, approximately 2% were other specified carcinomas (including carcinoid tumors), about 0.4% were epidermoid carcinomas, and about 0.08% were sarcomas [99]. Adenocarcinoma may be well-differentiated or poorly differentiated.

3.1.8 Staging, classification and prognosis

Colorectal cancer is staged pre and postoperatively. Preoperative staging is made by radiological imaging, such as CT and MRI scan, to find out the presence of cancer and/or metastasis; depth of the tumour as well as obtaining the final staging of the colorectal cancer [100]. On the basis of these imaging, a decision will be made at the MDT to proceed to surgery or Adjuvant Pre-operative Therapy (APT) first.

Colorectal cancer in the UK was originally divided into 3 pathological stages, as determined by Cuthbert Dukes, a pathologist at St. Mark Hospital in London, in 1932.

These are Dukes A (confined to the bowel muscle), Dukes B (invasion through the outer layer of the bowel wall), Dukes C (spread to lymph nodes). Dukes D was added later, denoting spread to distant organs (liver and lung most commonly). Stage B was subdivided into B1 (no penetration into muscularis propria) and B2 (penetration through muscularis propria). Stage C was also subdivided into C1 (tumour limited to the rectal wall with nodal involvement) and C2 (tumour penetrating through the rectal wall with nodal involvement).

The TNM staging system for all solid tumours was devised by Pierre Denoix between 1943 and 1952, using the size and extension of the primary tumour, its lymphatic involvement and the presence of metastases to classify the progression of cancer [101]. This has superseded Dukes' classification.

TNM is developed and maintained by the International Union Against Cancer (UICC) to achieve consensus on one globally recognised standard for classifying the extent of spread of cancer. The TNM staging system, developed by the American Joint Committee on Cancer (AJCC) and the International Union against Cancer (UICC) in 2002, is used to stage the primary tumour after excision by pathological assessment.

Tumour categories (T)

Tx: No description of tumour's extent or incomplete information.

Tis: In situ carcinoma; the tumour involves only the muscularis mucosa.

T1: Cancer has grown through muscularis mucosa and extends into the submucosa.

T2: Cancer has grown through submucosa and extends into the muscularis propria.

T3: The cancer has grown through the muscularis propria and into the outermost layers of the colon but not through them; it has not reached any nearby organs or tissues.

T4a: The cancer has grown through the serosa (visceral peritoneum)

T4b: The cancer has grown through the wall of the colon and is attached to or invades nearby tissues or organs.

Node categories (N)

Nx: No description of lymph node involvement or incomplete information.

N0: No cancer in nearby lymph nodes.

N1a: Cancer cells found in 1 nearby lymph node.

N1b: Cancer cells found in 2 to 3 nearby lymph nodes.

N1c: Small deposits of cancer cells found in areas of fat near lymph nodes, but not in the lymph nodes themselves.

N2a: Cancer cells found in 4 to 6 nearby lymph nodes

N2b: Cancer cells found in 7 or more nearby lymph nodes

Metastasis categories (M)

M0: No distant spread seen

M1a: The cancer has spread to 1 distant organ or set of distant lymph nodes

M1b: The cancer has spread to more than 1 distant organ or set of distant lymph nodes, or has spread to distant parts of the peritoneum [102].

Staging of colorectal cancer is based on the TNM classification as below:

Stage 0: Tis, N0, M0: The cancer is in the earliest stage. It has not grown beyond the inner layer (mucosa) of the colon or rectum. This stage is also known as carcinoma in situ or intramucosal carcinoma.

Stage I: T1-T2, N0, M0: The cancer has grown through the muscularis mucosa into the submucosa (T1) or it may also have grown into the muscularis propria (T2). It has not spread to nearby lymph nodes or distant sites.

Stage IIA: T3, N0, M0: The cancer has grown into the outermost layers of the colon or rectum but has not gone through them (T3). It has not reached nearby organs. It has not yet spread to the nearby lymph nodes or distant sites.

Stage IIB: T4a, N0, M0: The cancer has grown through the wall of the colon or rectum but has not grown into other nearby tissues or organs (T4a). It has not yet spread to the nearby lymph nodes or distant sites.

Stage IIC: T4b, N0, M0: The cancer has grown through the wall of the colon or rectum and is attached to or has grown into other nearby tissues or organs (T4b). It has not yet spread to the nearby lymph nodes or distant sites.

Stage IIIA: One of the following applies.

T1-T2, N1, M0: The cancer has grown through the mucosa into the submucosa (T1) and it may also have grown into the muscularis propria (T2). It has spread to 1 to 3 nearby lymph nodes (N1a/N1b) or into areas of fat near the lymph nodes but not the nodes themselves (N1c). It has not spread to distant sites.

T1, N2a, M0: The cancer has grown through the mucosa into the submucosa (T1). It has spread to 4 to 6 nearby lymph nodes (N2a). It has not spread to distant sites.

Stage IIIB: One of the following applies.

T3-T4a, N1, M0: The cancer has grown into the outermost layers of the colon or rectum (T3) or through the visceral peritoneum (T4a) but has not reached nearby organs. It has spread to 1 to 3 nearby lymph nodes (N1a/N1b) or into areas of fat near the lymph nodes but not the nodes themselves (N1c). It has not spread to distant sites.

T2-T3, N2a, M0: The cancer has grown into the muscularis propria (T2) or into the outermost layers of the colon or rectum (T3). It has spread to 4 to 6 nearby lymph nodes (N2a). It has not spread to distant sites.

T1-T2, N2b, M0: The cancer has grown through the mucosa into the submucosa (T1) or it may also have grown into the muscularis propria (T2). It has spread to 7 or more nearby lymph nodes (N2b). It has not spread to distant sites.

Stage IIIC: One of the following applies.

T4a, N2a, M0: The cancer has grown through the wall of the colon or rectum (including the visceral peritoneum) but has not reached nearby organs (T4a). It has spread to 4 to 6 nearby lymph nodes (N2a). It has not spread to distant sites.

T3-T4a, N2b, M0: The cancer has grown into the outermost layers of the colon or rectum (T3) or through the visceral peritoneum (T4a) but has not reached nearby organs. It has spread to 7 or more nearby lymph nodes (N2b). It has not spread to distant sites.

T4b, N1-N2, M0: The cancer has grown through the wall of the colon or rectum and is attached to or has grown into other nearby tissues or organs (T4b). It has spread to at least one nearby lymph node or into areas of fat near the lymph nodes (N1 or N2). It has not spread to distant sites.

Stage IVA: Any T, Any N, M1a: The cancer may or may not have grown through the wall of the colon or rectum, and it may or may not have spread to nearby lymph nodes. It has spread to 1 distant organ (such as the liver or lung) or set of lymph nodes (M1a).

Stage IVB: Any T, Any N, M1b: The cancer may or may not have grown through the wall of the colon or rectum, and it may or may not have spread to nearby lymph nodes.

It has spread to more than 1 distant organ (such as the liver or lung) or set of lymph nodes, or it has spread to distant parts of the peritoneum (the lining of the abdominal cavity) (M1b).

In England and Wales, about 90% of patients diagnosed at stage I and 78% diagnosed with stage II will survive the disease beyond 5 years. However, only 48% of patients with stage III and 7% with stage IV will survive the disease beyond five years [103].

Colorectal cancer survival rates were compared across Europe by Gatta *et al* which showed significant inter-country differences [104]. Late presentation and/or delay in treatment initiation has contributed to the poorer survival in the UK compared with the rest of Western Europe [105]. Therefore, cancer governance groups, multidisciplinary meetings, urgent 2-weeks referrals and 30-days diagnosis to treatment policies were adopted in the UK to improve patients care and survival.

The prognosis of patients with CRC is a function of clinical and histopathological stage [102]. Emergency presentation with large bowel obstruction or bowel perforation has been shown to be associated with worse prognosis [106].

Molecular prognostic indicators such as mutations of deleted in colon cancer gene (DCC), p53, EGFR amplification, loss of heterozygosity for 18q and KRAS mutations have all been investigated but have not been shown to be of clinical value [107]. However, a retrospective metanalysis showed that deficient mismatch repair (dMMR) is associated with better clinical outcome for patients with resectable colorectal cancer [108, 109]. Moreover, fluorouracil-based adjuvant chemotherapy benefited patients with stage II or stage III colonic cancer with microsatellite-stable tumours or tumours exhibiting low-frequency microsatellite instability, but not those with tumours exhibiting high-frequency microsatellite instability [110].

Local recurrence in rectal cancer is more common than colon cancer [111, 112]. This is due to the anatomy and the lymphatic drainage of rectum. Local recurrence is multifactorial and widely dependent on the surgeon experience, location of the primary tumour, grade and stage of the primary tumour as well as the specimen resection margins [113, 114].

Therefore, pelvic exenteration and/or abdominal perineal resection of rectum might be the surgical treatment of choice for local recurrence. Otherwise, palliative radiotherapy is a potential treatment for locally unresectable disease [115-118].

3.1.9 Follow up of CRC

Follow up patients with CRC is important to detect any postoperative complications such as wound infection/dehiscence, stoma problems, or urinary and sexual difficulties after rectal surgery. It is also essential to detect early signs of recurrent disease and metachronous tumours with initiation of specific management plans. Moreover, follow up is important to provide a psychological support to patients and finally it is a way of performing audit to improve the clinical service.

Previous reported trials show that around 85% of CRC recurrence occurs within the first 3 years of the surgical resection of the primary tumour [119-121]. Hence, CRC patients should undergo a rigid and systematic follow up protocol for at least 5 years following the primary tumour resection.

Any CRC follow up programme usually include outpatient visits as well as clinical, haematological, radiological and colonoscopic evaluation.

There are many possible protocols in clinical practice combining the type and the frequency of these tools [122]. Therefore, follow up programmes are widely dependent on the availability of tools and local resources.

In the United States, the American Society of Clinical Oncology guidelines on colorectal cancer surveillance panel recommends an annual computed tomography (CT) of the chest and abdomen for 3 years after primary therapy and patients who could be candidates for curative-intent surgery. In addition, pelvic CT scan for rectal cancer surveillance, especially for patients with several poor prognostic factors, including those who have not been treated with radiation. Moreover, colonoscopy at 3 years after operative treatment, and, if results are normal, every 5 years thereafter; flexible proctosigmoidoscopy every 6 months for 5 years for rectal cancer patients who have not been treated with pelvic radiation. They also recommended taking a full history and physical examination every 3 to 6 months for the first 3 years, every 6 months during years 4 and 5, and subsequently at the discretion of the physician.

Carcinoembryonic antigen (CEA) is recommended to be done every 3 months postoperatively for at least 3 years after diagnosis, if the patient is a candidate for surgery or systemic therapy. Chest x-rays, full blood counts, and liver function tests are not recommended and molecular or cellular markers should not influence the surveillance strategy based on available evidence [6, 123].

In the UK, there are no rigid rules and guidelines for CRC follow up protocols. It is widely dependent on the hospital resources, local experience and regional guidelines. This could be any of the above combination with any frequency aiming mainly to balance risks and benefits with cost-effective considerations. Although, most of these protocols include an intense follow up programme during the first 3 years after primary resection due to the high probability of tumour recurrence.

3.1.10 Surgical Treatment

The definition of the rectum is different according to Surgeons and Anatomists. Surgical definition of the rectum starts at the level of the sacral promontory, while anatomists define the rectum as starting at the level of the 3rd sacral vertebra. Hence, the length of rectum varies from 12 cm to 15 cm. The rectum is different from the rest of the colon, in that the outer layer is made of longitudinal muscle.

The rectum contains 3 folds, namely valves of Houston. The superior (10 cm to 12 cm) and inferior (4 cm to 7 cm) folds are located on the left side and middle fold (8 cm to 10 cm) is located at the right side [124].

The Dutch Colorectal Cancer Group study defined rectal cancer as tumour located within 12 cm of the anal verge by rigid proctoscopy. They also found that the risk of recurrence of rectal cancer depends on the location of the cancer [125].

Planning for surgical management of rectal cancer is a complicated matter, as special attention should be directed towards long-term benefits, lifestyle as well as genitourinary and anal function preservation. Of course, the main aim of any surgery for rectal cancer is to achieve a complete tumour resection in order to reduce the chance of pelvic local recurrence, which carries a subsequent poor prognosis. Then careful consideration should be directed towards patient functional capacity, anal and rectal reservoir function as well as quality of life [126, 127].

Surgical resection of primary rectal neoplasia is often difficult because the edges of the tumour may lie adjacent to or invade vital structures such as; iliac vessels, sacrum and prostate urinary bladder, uterus, adenxa and vagina.

Radical surgical therapy for rectal cancer comprises of 2 main techniques; anterior resection (AR) and abdominal perineal resection (APR). Selection method is dependent upon surgeon experience as well as disease and patient-related factors. Preservation of the anal sphincter is more difficult in obese males, patients with preoperative incontinence, direct involvement of anal sphincter muscles with carcinoma and bulky tumours within 5 cm from the anal verge [128].

Transanal Excision

Patients with early stages of rectal cancer might undergo this procedure when the tumour has the following characteristic; a low rectal lesions (within 8-10 cm) or occupying less than one third of the rectal circumference, mobile exophitic or polypoid lesions which are less than 3 cm in size [129], T1 well or moderately differentiated tumours and finally clinical and radiographical negative nodal status [130]. In this method, full-thickness rectal wall containing the lesion is excised leaving a 1 cm margin of normal tissue with or without primary closure of the defect.

This method has possible downsides such as perineural invasions, lymph node metastasis, positive resection margins, lymphovascular invasion and recurrent lesion [131]. Failure of transanal excision of rectal cancer might need a subsequent radical surgery such as AR or APR with or without with en bloc resection the pelvic side wall with autonomic nerves, coccyx, prostate, seminal vesicle, bladder, vagina, ureter, ovary and uterus [132, 133]. A recent study in 2011 showed that local excision in early-stage rectal cancer may result in high local recurrence rate; hence, it is only recommended in highly selective groups of patients with a tumour size of 2.5 cm or less [134]. Transanal local excision has advantages such as sphincter preservation, rapid recovery low perioperative morbidity [135]. The 5-year survival rate after transanal excision ranges from 65-100% with a risk of local recurrence of up to 40% [136]. Therefore, rigid selection criteria should be applied for this method and patients should be informed about the possible risks.

Endocavitary Radiation

With the same selection methods applied for transanal excision, stage I rectal cancer can also be treated with Endocavitary Radiation. This is different from external beam radiotherapy as a larger dose of radiation is delivered to a smaller area over a shorter period of time via a special proctoscope in theatre, with sedation, as a day case [137]. Weekly radiotherapy is performed for a total of 6 weeks with high-dose (20Gy to 30 Gy) and low-voltage radiation (50kV). This can cause a quick shrinkage of the rectal cancer with an overall survival rate of 83% and a local recurrence rate as high as 30% [138].

Transanal Endoscopic Microsurgery (TEM)

This is another method of local excision for rectal cancer performed by the use of a special rigid proctoscope with CO_2 insufflation. TEM has not come into wide use yet because of it requires a significant learning curve and there is a lack of availability [139]. A recent study showed that TEM had a lower rate of positive margins and longer disease-free survival when compared with transanal excision. TEM was superior to standard resection concerning morbidity, whilst less effective in obtaining negative surgical margins, and was associated with higher local and overall recurrence. No survival advantage was observed in favour of either procedure. Unfavourable tumour preoperative histology did not seem to influence the selection between TEM and SR [140, 141].

Anterior resection of rectum (AR)

The main sphincter-preservation surgery performed for rectal neoplasia is anterior resection of the rectum (AR). This should be performed for fit patients with no extensive pelvic disease and good pre-operative sphincter function. In this type of surgery, primary colorectal or coloanal anastomosis is performed with or without a temporary defunctioning loop ileostomy to protect the anastomosis. Possible complications of AR include urinary dysfunction, secondary detrusor muscle weakness (3-15%) as well as sexual dysfunction such as retrograde ejaculation and impotence (5-70% of men patients) [142, 143]. The local recurrence rate after TME (total mesorectal excision) is around 4%, which is lower than after transanal excision (20%) [144, 145].

The rate of anastamotic leak in AR ranges from 3-11% for upper and middle third colorectal anastomosis while it is higher for the lower third, up to 20% [144, 145]. Therefore, many surgeons elect to protect lower anastomosis with a temporary defunctioning loop ileostomy, especially if patients had neo-adjuvant treatment [146].

During AR, full mobilization of the rectum, sigmoid colon, and usually the splenic flexure is performed. Mobilization of the rectum is done by sharp dissection in the avascular plane that separates the entire mesorectum from the surrounding structures; this is called total mesorectal excision (TME). Dissection involves the anterior peritoneal reflection and Denonvilliers fascia anteriorly and preserves the inferior hypogastric plexus posteriorly and laterally with direct visualisation. Mesorectal spread can occur by direct invasion, lymphatic spread, or perineural invasion of tumour [62, 143, 147]. Maurer *et al* has showed an impressive reduction of the local recurrence rate after the introduction of TME in rectal cancer with a marked survival improvement in patients without systemic disease [148].

Resection and colo-anal anastomosis (CAA)

Ultra low rectal cancer, which is located close to the anal sphincter, can be treated via this method with an immediate protective temporary loop ileostomy [149]. TME is carried out in the pelvis down to the levator ani muscles followed by a straight tube CAA via the double-stapled technique. This procedure does not require permanent colostomy and is considered as a good alternative to abdomino-perineal excision [150].

However, it is associated with morbidity such as increased frequency and urgency of bowel plus incontinence of stool and flatus [147, 151]. To avoid these adverse events, a colonic J-pouch may be created, which acts as a reservoir, and immediately stapled to the anal canal to form a new colo-anal anastomosis. This creation of a neorectum makes the functional result of a coloanal anastomosis more predicable [152, 153].

Abdominal perineal resection (APER)

This is used for low rectal tumours where successful achievement of a negative resection margin will result in loss of anal sphincter function.

APER is mainly offered to patients with low rectal cancer as well as those with significant co-morbidities or based on patients' preference as well as involvement of sphincter or dysfunction and pelvic fixation of the tumour [154, 155].

APER has certain disadvantages such as the need for permanent colostomy, slightly higher short-term and long-term morbidity and mortality [156] plus higher rate of sexual and urinary dysfunction [126].

The mainstay of treatment of colonic cancer is surgical excision. This comprises excision of both the primary tumour and the regional lymph nodes. The aim of surgery is to remove the whole tumour and achieve a clear margin of tissue around the tumour.

Right hemicolectomy

This is usually indicated for caecal and right hemicolonic neoplasia. During this method, the caecum as well as the ascending colon are mobilised up to the middle third of the transverse colon. The ileocolic, right colic and right branch of the middle colic pedicles are ligated, divided and excised. Some patients might have omental deposits of neoplasia, this should have en bloc with the primary tumour [157, 158].

Neoplastic lesions located at the proximal or middle third of the transverse colon are treated with extended right hemicolectomy where the ileocolic, right colic, and middle colic pedicles are divided and the specimen is removed together with its mesentery [157, 158].

Left hemicolectomy

Lesions at the splenic flexure and the left hemicolon usually require this type of resection. The inferior mesenteric vein, the left branch of the middle colic vessels and the left colic vessels along with their mesenteries are ligated/divided and included with the specimen [157, 158].

Sigmoid colectomy

is performed for sigmoid colonic cancer where the inferior mesenteric artery is divided at its origin with pelvic dissection towards the rectum until reaching adequate resection margins. Careful mobilisation should be performed to avoid injury of the left ureter and the left ovarian or testicular vessels [157-159].

Subtotal colectomy with ileorectal anastomosis

Patients with HNPC, FAP or metachronous lesions in a separate colonic segment are required to have this surgery [157-159].

These days, colorectal resections of cancerous lesions are often performed with a minimally invasive, laparoscopic approach. The same oncological principles with appropriate resection margins rules are applied here. Prospective randomized trials have shown no significant differences in the peri and postoperative complications, peri-operative mortality rates, re-admission or re-operation rates or the rate of surgical wound recurrence. At a median follow-up of 7 years, no significant difference was found in the 5-year disease-free survival rate (69% versus 68% in the laparoscopy-assisted colectomy and open colectomy groups, respectively) or overall survival (76% versus 75%). Overall laparoscopic colectomy provides comparable oncologic outcomes (cause-specific survival, disease recurrence, number of lymph nodes harvested) to those achieved with an open approach [160-166].

Over the last 10 years, improvements have been made for those patients with advanced colonic cancer and distant metastasis who present with intestinal obstruction. with the intraluminal colonic stent may be used as a palliative method. However, a recent multi-centre randomised controlled trial has showed that colonic stent has no decisive clinical advantages to emergency surgery. It could be used as an alternative treatment in as yet undefined subsets of patients, although with caution because of concerns about tumour spread caused by perforation [167],[48]

Major surgery remains a high risk undertaking for many patients. The UK MRC-CLASICC study, a multicentre project comparing open and laparoscopic surgery for colorectal cancer reported significant 30% complications in both arms of the study. The perioperative mortality rate was 5% whilst 12% of patients suffered from surgical complications such as wound dehiscence or infection, anastomotic leak or bleeding. More patients had non-surgical complications such myocardial infarction, chest infection or thromboembolic event [168]. Risk factors such as advanced age and limited functional capacity are linked to the development of such complications, however, the biological mechanisms behind this are not fully understood yet.

3.1.11 Adjuvant pre-operative therapy (APT)

Although radical surgical resection of colorectal cancer is the mainstay of treatment, surgery alone has a high local recurrence rate of up to 30-50% in patients with advanced stages of rectal cancer [169, 170]. Rectal adenocarcinomas are sensitive to ionizing radiation. Radiation therapy can be delivered preoperatively, intraoperatively, or postoperatively with or without chemotherapy.

Over the last 15 years, noticeable advances have been made in systemic therapy for colorectal cancer, which has considerably improved outcome. Before this, the only approved cytotoxic agent for colorectal cancer was 5-fluorouracil (5FU). This blocks the methylation of deoxyuridylic acid to thymidylic acid, thereby interfering with DNA synthesis. Over the last 15 years, new regimes have been introduced into the oncology practice such as oxaliplatin and irinotecan [171], oral fluoropyrimidines (capecitabine and tegafur) as well as biologic agents such as bevacizumab, cetuximab, and panitumumab. Most of these are used post operatively as adjuvant treatment. These new agents have improved the cure rate for stage 2 and 3 as well as improved the survival rate for stage 4 CRC.

Treatment with fluorouracil and leucovorin, treatment with irinotecan, fluorouracil, and leucovorin resulted in significantly longer progression-free survival (median, 7.0 vs. 4.3 months; P=0.004), a higher rate of confirmed response (39 percent vs. 21 percent, P<0.001), and longer overall survival (median, 14.8 vs. 12.6 months; P=0.04).

Results for irinotecan alone were similar to those for fluorouracil and leucovorin. Severe diarrhoea was more common during treatment with irinotecan, fluorouracil, and leucovorin than during treatment with fluorouracil and leucovorin, but the incidence of grade 4 (life-threatening) diarrhea was similar in the two groups (<8 percent). Grade 3 or 4 mucositis, grade 4 neutropenia, and neutropenic fever were less frequent during treatment with irinotecan, fluorouracil, and leucovorin. Adding irinotecan to the regimen of fluorouracil and leucovorin did not compromise the quality of life [172].

It is established that combination regimens provide improved efficacy and prolonged progression-free survival in patients with colorectal cancer [173].

Over the past two decades it has become clear that large rectal tumours can be downstaged with preoperative radiotherapy or chemoradiotherapy.

Similarly, evidence is being gathered that suggests large colonic tumours can be downstaged by chemotherapy with or without an immuno-modulator. Both preoperative treatments (collectively known as adjuvant preoperative therapy - APT) increase the chances of complete removal of the tumour with surgery.

APT is widely used in the UK where patients are generally managed from the outset by multidisciplinary teams including surgeons, oncologists, pathologists and radiologists. It is widely used in the treatment of breast cancer [174] and gastro-oesophageal cancer as demonstrated by the UK MRC oesophageal cancer (OEO2) and MAGIC trials [175, 176].

Adjuvant Preoperative Therapy (APT) offers advantages in comparison with adjuvant post-operative treatment. It is important to reduce the size of the tumour and viability, make it operable, improve the survival rate, preserve anal sphincters, reduce the chance of local recurrence and eradicate micrometastasis [177-183]. Treatment of micrometastasis is important prior to an operation as surgery promotes growth factor activity in early postoperative period which may lead to tumour progression [184].

Both short course radiotherapy and combined chemoradiotherapy have a place in the preoperative treatment of rectal cancer [185]. In rectal cancer, the response rate after treatment with preoperative chemotherapy and radiotherapy is approximately double that after radiotherapy alone (20% vs. 10%) [178].

Pre-operative Radiotherapy (Rectal cancer)

Preoperative high-dose short-course radiotherapy for five days has been shown to reduce the risk of local recurrence and to improve survival, after curative surgery to rectal cancer [186, 187]. Pre-operative radiotherapy is thought to work better on well-oxygenated tissues that is present before the surgical resection. Postoperatively, tissues are relatively hypoxic and may be more resistant to radiotherapy. Furthermore, preoperative radiotherapy carries less risk of radiation enteritis as the small bowel loops are matted together in the pelvis after the major surgical resection of rectum [147, 188]. It does not reduce the risk of distant metastasis and has no effect on sphincter function in rectal cancer surgery [189]; however, radiotherapy decreases the risk of tumour recurrence and the overall mortality in patients with stage II or III rectal disease [190, 191]. In rectal cancer, pre-operative radiotherapy might delay the surgical resection due to its complication [192, 193]. It can also change the accuracy of the pathological staging due to the radiation damage of the cellular protein [194, 195].

Pre-operative ChemoRadiotherapy (Rectal cancer)

In locally advanced and initially unresectable rectal cancers (T3 or greater, node positive), combined chemoradiotherapy may downstage the tumour and allow potentially curative surgery [196]. Pre-operative 5-fluorouracil (5-FU) administration increases the bowel sensitivity to radiotherapy, hence, reducing its side effects such as diarrhoea. This combined therapy improves local control, distant spread and survival [197]. Until recently, APT has not been widely used in the treatment of colonic cancer because of the poor response to chemotherapy and limited accuracy of radiological staging. Radiotherapy is not used for colonic tumours as the resulting damage to the adjacent small bowel would be too severe.

Pre-operative Chemotherapy and Immuno-modulators (Colonic cancer)

Recently, however, The National Cancer Research Institute (NCRI) has designed a trial to evaluate the efficacy of neoadjuvant treatment by using preoperative chemotherapy with or without an anti-Epidermal Growth Factor Receptor (EGFR) monoclonal antibody to improve outcome in high-risk operable (T3 or greater, node positive) colonic cancer. This is called the FOxTROT trial (Fluoropyrimidine, Oxaliplatin and Targeted Receptor pre-Operative Therapy) [198].

The systemic effect of chemotherapy alone, radiotherapy alone or combined chemoradiotherapy may place the patient at a stage to be less able to cope with the physiological demands of anaesthesia and surgery.

It is generally well known that chemotherapy can cause nausea, vomiting, diarrhoea, weight and appetite loss, generalised weaknes and hair loss. The effects of the chemical agents are multiple, such as fatigue [199], impaired exercise tolerance [199], malnutrition [200, 201], an induction of an inflammatory response [202] and a reduced quality of life [203]. These are due to the hypoxia induced at cellular level affecting normal and tumour cells.

Radiotherapy can also cause radiation enteritis. This progressive disease causes intestinal fibrosis and obliterative endarteritis, results in significant morbidity and mortality [204]. Clinical or subclinical radiotherapy-induced diarrhoea, enteritis, and colitis occur in around 60% of patients with colorectal cancer [205, 206]. The severity of enteritis is mainly dependent on the primary tumour, radiation dose, and type and combination of radiation injuries. Radiation can also cause a stimulation of an inflammatory response [202] and a reduced quality of life via the direct effect on the gastrointestinal tract [203].

There is enough evidence that combination chemoradiotherapy increases the rate of complications compared to one therapy alone [207]. This synergetic effect might lead to potential problems related to adjuvant preoperative therapy such as perianal sepsis, delayed surgical wound healing and a higher rate of anastomotic dehiscence [177-179, 208, 209]. Therefore, it is not known yet what might be the possible adverse effects of the APT on the real body physiology, functional capacity, inflammatory status and quality of life.

Below are the available preoperative regimes in the United Kingdom:

A- Short course Radiotherapy (Rectal tumours)

Short-course preoperative radiotherapy usually involves 5 Gray (Gy) administered daily over 5 days without chemotherapy, followed by surgery [210]. External radiotherapy regime is delivered according to the guidelines provided in Report 50 of the International Commission on Radiation Units and Measurements. This includes radiation applied to the primary tumour as well as the regional, mesorectal, presacral, and internal iliac lymph nodes.

The radiotherapy dose is 25Gy in 5 fractions. This will involve all sites of gross tumour including diseased lymph nodes and extramural vascular invasion including the intervening normal rectal wall. Then a 1cm margin is applied in all directions (superior, inferior, laterally anteriorly and posteriorly). The superior limit is usually the S2/3 interspace for mid and lower third rectal cancers and is determined on the sagittal or scout view on the planning system. This will extend above the S2/3 interspace in some patients. The inferior limit is at the superior limit of puborectalis.

The lateral border in the true pelvis is the medial aspect of obturator internus (in the absence of pelvic lymph node involvement and the lateral aspect – bony side wall – in the presence of pelvic lymph node involvement). The posterior border is the anterior aspect of the bony sacrum. Normal critical tissues such as small bowel, femoral heads, and bladder can be contoured at the discretion of the clinician and doses to these organs kept to a minimum [185, 211, 212].

The immediate associated side effects with this type of therapy are perianal skin erythema, lethargy, increased bowel frequency as well as urinary urgency, frequency and dysuria. Other late effects involves bowel (urgency, frequency, faecal incontinence); sexual (dypareunia, vaginal stenosis in females; erectile and ejaculatory failure males); sterility (men and women); delay in healing of perineal wound and secondary malignancy [213, 214].

B- Long course intravenous Chemoradiotherapy (Rectal tumours)

This is a 5-weeks course (25 days with weekends off) of combined treatment. It usually entails 25 fractions of 45Gy pelvic radiotherapy together with Leucovorin 20mg/m^2 flat dose followed by 5-Fluorouracil 350mg/m^2 administered on days 1-5 and 29-33.. Patients need to have Weekly full blood count, renal function tests and liver profile to monitor any possible regime adverse events [179, 215, 216].

C- Long course oral Chemoradiotherapy (Rectal tumours)

This is a 5-weeks course (25 days with weekends off) of combined treatment. It usually entails 25 fractions of 45Gy pelvic radiotherapy and Oral Capecitabine (5-Fluorouracil based chemotherapy) 900mg/m^2 twice/day, taken on the days of radiotherapy only.. Patients need to have Weekly full blood count, renal function tests and liver profile to monitor any possible regime adverse events [179, 215-217].

D- Chemotherapy only (colonic tumours)

It is now established that adjuvant combination chemotherapy produces a moderate but persistent improvement in survival for patients with stage III (node-positive) CRC. There is now also good evidence, from the QUASAR1 study [109] and metanalysis, that chemotherapy in stage II (node-negative) disease reduces the risk of recurrence and death from CRC.

Nevertheless, for many patients the current treatment strategy of surgical excision followed by adjuvant chemotherapy fails either to clear locoregional spread or to eradicate distant micrometastases [218]. Around 10% of recurrence of colonic cancer is confined to the resection site. However, the proportion of metastases that subsequently occur due to incomplete local clearance is much higher with a more aggressive phenotype [219].

APT has been studied in many solid tumour types and has been shown to be of great benefit in oesophageal, gastric and rectal cancers. There is no enough strong evidence that pre-operative anti-cancer therapy is effective in colonic cancers. This is due to two reasons:

- Drug therapy used to give a low response rates, leaving a significant risk of tumour growth during the neoadjuvant treatment phase.
- Radiological staging was inaccurate, and the value of chemotherapy in node-negative disease was unproven.

However, recent advances in radiology and in chemotherapy allowed the possibility to investigate neoadjuvant chemotherapy for patients with locally advanced colon cancer.

FOxTROT (Fluoropyrimidine, Oxaliplatin and Targeted Receptor pre-Operative Therapy) is a large national multi-centre randomised trial run by the University of Birmingham to assess the efficacy of using preoperative chemotherapy with or without an anti-Epidermal Growth Factor Receptor (EGFR) monoclonal antibody to improve outcome in high-risk operable (T3 or greater, node positive) colonic cancer. FOxTROT is aiming to establish whether giving chemotherapy regimen pre-operatively improves disease-free survival and/or whether the addition of an EGFR targeted monoclonal antibody (panitumumab) increases tumour shrinkage for patients with normal KRAS tumours.

Arm A of the trial entails giving six weeks of pre-operative oxaliplatin/fluoropyrimidine (OxFP) chemotherapy followed by surgery then 18 (or 6) weeks of post-operative OxFP chemotherapy while arm B of the randomisation includes the same chemotherapy regimen with concomitant panitumumab for the first 6 weeks [198].

Patients in Arms A and B receive neoadjuvant treatment for six weeks starting as soon as possible after randomisation.

This comprises three 2-week cycles of OxMdG or, optionally for patients not randomised for panitumumab, two 3-week cycles of OxCap. Patients in Arm B (who will have been established to have KRAS-wild type tumours) also receive panitumumab, by IV infusion over 60 minutes on day 1 of each cycle of neoadjuvant OxMdG chemotherapy: i.e. panitumumab (2-weekly) for 3 cycles at 6 mg/kg.

In our study, we have only recruited patients with rectal cancer as its adjuvant pre-operative therapy is different from the FOxTROT trial used for colonic cancers, hence, the pathophysiologial changes will be different too. Patients with rectal cancers were divided into two groups according to their APT regiment:

Group 1: Patients who received combined preoperative ChemoRadiotherapy.

Group 2: Patients who received preoperative pelvic radiotherapy only.

3.1.12 Area of concern

The timing of surgical resection after APT administration is widely dependent on the size, location, extent and grade of the rectal carcinoma. It might also be surgeon dependent.

From previous published literatures, there are some evidences that APT has a significant effect on the postoperative mortality and morbidity as it can be associated with an increased risk of intestinal obstruction, intestinal failure and faecal incontinence. A comparative analysis of the available studies is difficult because of the different inclusion criteria and chemoradiotherapy modalities used and because of variations in the standardization of surgical procedures [220-227].

There is concern that APT is a two-edged sword. It is debilitating for an individual, and so affects the individual's fitness for subsequent major surgery.

Although enabling better treatment of the cancer, it might increase the risks of the subsequent operation. APT may reduce the functional capacity of the patient. It can change the preoperative body physiology, which is a risk factor for both postoperative complications and early disease recurrence [228].

If APT has a demonstrably detrimental effect, health professionals should devise methods to then improve patients physiological fitness before major excisional surgery is performed to reduce the morbidity of the surgery.

The current practice in the UK is to wait for a maximum of 6-8 weeks after finishing the APT course before undergoing any surgical resection. This is considered as the optimal period for pathological response [229, 230]. A recent study showed that delay in surgical resection after APT administration has a significantly better physiological outcome for patients with rectal cancer [231].

Therefore, the aim of this research programme is to employ specific tests to assess the effect of APT on functional capacity and subsequently fitness for surgery on patients awaiting colorectal cancer resection. Also, we aim to explore the mechanism by which APT might affect body composition, physical and nutritional status, inflammatory cascade and health related quality of life (HRQL).

3.2 Surgical physiology and Cardiopulmonary exercise testing (CPEX)

3.2.1 Metabolic response to surgery

Major surgery makes considerable physiological demands on patients. Previous data from both cardiac and non-cardiac surgery indicate that patients who suffer postoperative complications have evidence of increased oxygen extraction and increased arterio-venous oxygen difference in the postoperative period [232, 233]. The reasons behind this are increased oxygen demand after surgery with insufficient oxygen delivery in the postoperative period.

The metabolic response to surgery may increase oxygen demand in that period and other factors such as shivering may increase this further. It has previously been suggested that patients with inadequate oxygen delivery are unable to meet the demands of surgery [234].

3.2.2 Preoperative assessment

Different tests have been used in practice to investigate patients undergoing major non-cardiac surgery to assess their perioperative risk. These include: treadmill testing, nuclear cardiology studies and dobutamine stress echocardiography. The main limitation of these methods is that they give information only on response of the cardiovascular system to stress. Cardiopulmonary exercise (CPEX) testing provides a global assessment of the integrated response to increasing aerobic work involving the cardiovascular, respiratory, neuro-pyschological and skeletal muscle systems, all of which are activated during the neurohumoral stress response to surgery [235].

There is a strong association between limited exercise capacity and postoperative complications. Limited functional capacity is identified as an important component of preoperative risk stratification in the American college of Cardiology guidelines on preoperative risk assessment in non-cardiac surgery [236]. Hence, cardiopulmonary exercise (CPEX) testing is of value to asses the functional capacity of an individual.

It is well established that there is an association between the patient's response to cardiovascular stress such as exercise or inotropic drugs and the risk of complications following non-cardiac surgery [237]. Patients with limited cardiac reserve or those who demonstrate inducible myocardial ischemia are more likely to suffer major perioperative complications [236].

3.2.3 CPEX testing

CPEX testing has been used in physiological research and in the assessment of patients with cardiopulmonary disease [238]. In recent years, it has been widely used for measuring functional reserve prior to surgery. A number of studies have demonstrated an association between functional capacity expressed in terms of oxygen uptake at anaerobic threshold (AT) or peak exercise (VO_2 peak) and the incidence of postoperative complications [239, 240].

Patients with reduced functional capacity have changes in oxygen delivery and handling at cellular level which might contribute to a delayed and impaired recovery after surgery [241]. This might be due to increased vasoconstriction, mitochondrial dysfunction and/or autonomic imbalance [242].

During cellular metabolism, skeletal muscle fatigue reflects the failure to maintain peak cytosolic (Ca^{2+}) during contraction.

In healthy muscle, fatigue-dependent changes in sarcoplasmic reticulum (SR) function appear to be the main cause of a loss in force production. However, a decrease in store operated Ca^{2+} entry has been linked to age related exercise intolerance [243]. In addition, the ability to sustain skeletal muscle force production is related to the rapid attainment of high rates of oxidative phosphorylation [244].

The CPEX test is an incremental exercise test using a bicycle or a treadmill during which the patient's gas exchange and ECG changes are monitored. It allows the objective measurement of a patient's functional capacity by measuring the ability of an individual to perform aerobic work. The test produces a number of measures of cardiopulmonary performance, of which the two most commonly used in the perioperative setting are anaerobic threshold (AT) and peak oxygen uptake (VO_2 peak).

3.2.4 Evidence to support CPEX

In a study in 1993, the CPEX test identified patients at greatest risk of postoperative death [245]. Important additional information to that provided by the standard exercise test included: a precise determination of aerobic capacity, the causes of dyspnea with exertion, respiratory gas exchange and prognosis in patients with heart failure.

Under steady-state conditions, oxygen consumption per unit time (VO_2) and carbon dioxide output (VCO_2) measured at the mouth are equivalent to oxygen utilization and carbon dioxide production occurring in the cell; thus, external respiration equals internal respiration [246].

In healthy people, predictable physiologic changes occur during exercise. These changes include a reduction in systemic vascular resistance, increases in oxygen extraction, and augmentation of stroke volume (SV) and heart rate, resulting in an increase in cardiac output (CO). When the metabolic demands of exercise begin to exceed oxygen delivery to working muscles, anaerobic metabolism ensues [247, 248].

However, even with low-intensity exercise, anaerobic energy production may make a small contribution that markedly increases at exercise intensities greater than the anaerobic threshold (AT). This is evidenced by rising blood lactate levels and lactate-pyruvate ratios. Lactic acid is then buffered by bicarbonate, producing excess non-metabolic carbon dioxide via the carbonic anhydrase reaction.

The peak VO_2 ($PkVO_2$) is the highest VO_2 achieved during the cardiopulmonary exercise test and generally occurs at or near peak exercise. Moreover, if the VO_2 curve demonstrates a plateau, such that VO_2 no longer increases despite progressive increments in workload, then the $PkVO_2$ can be labelled the VO_2max.

The VO_2max is the best and most reproducible index of cardiopulmonary fitness or disability. The $PkVO_2$, VO_2max, and AT are reported as a weight-adjusted value in millilitres of VO_2 per kilogram of body weight per minute to facilitate inter-subject comparisons [249, 250].

Cardiopulmonary exercise testing is a relevant modality in the clinician's diagnostic armamentarium for evaluation and treatment of many commonly encountered clinical problems. Measurement of exercise gas exchange provides objective and reproducible indices of functional capacity, generates information in determining the origin of dyspnoea on exertion, and provides prognostic capabilities in the assessment of patients with heart failure [177-179, 251]. CPEX testing mimics the postoperative situation, as it requires an increased cardiac output to satisfy the increased oxygen demand. Patients identified as having poor oxygen delivery on the bicycle ergometer are expected to have a poor ability to increase cardiac output following surgery [177-179, 252]. Compromised results of CPEX testing might be associated with an increased risk of cardiopulmonary mortality and morbidity in the postoperative period [253, 254].

A recent consensus statement of assessment of functional capacity identified both VO_2peak and AT as acceptable measures of functional capacity [255]. Older and colleagues reported that patients with an AT of <11ml/kg/min and myocardial ischemia had a significantly increased risk of peri-operative death [252]. Swart and Carlisle reported a significantly higher incidence of postoperative cardiac events in patients with an AT <11ml/kg/min who were randomly allocated to receive ward care instead of HDU care (absolute difference 15%, 95% CI 5%-30%, p=0.005) (Swart, 2007). They also found that hospital length of stay was lowest in those with an AT > 10.9 ml/kg/min.

It is even more reliable at detecting those not at risk, in that there were no deaths related to cardiopulmonary complications in any patient identified through CPEX testing as fit for major surgery with ward management [252].

3.3 Body composition and Nutrition

3.3.1 Body composition and Malnutrition in relation to APT

Body composition is a general term which refers to hydration, nutrition/wasting, bone mineral content and total body fat [256]. There are some data to suggest that APT can affect the body fluid and fat distribution. This will subsequently alter the body physiology at cellular level during and after surgery by changing the fluid distribution and the lean body mass [257].

The incidence of malnutrition in patients with cancer ranges from 40 to 80% [258] and most frequently occurs in patients with cancer of the gastrointestinal tract [259].

Malnutrition has a detrimental effect on patients with gastrointestinal tract cancers as it increases the risk of infections related to treatment whilst reducing the response to treatment, HRQL and life expectancy [260-262].

Chemotherapy can affect the intracellular protein synthesis, which in turn deteriorates the overall nutritional status [263]. It also has indirect general effects such as nausea, vomiting, anorexia, and mucositis.

Patients submitted to radiotherapy, particularly of the gastrointestinal tract, are also at higher risk of malnutrition [264], as it can cause mucositis, nausea, vomiting, diarrhoea and anorexia [200, 201]. Although these effects are transient, the effect on nutritional status can affect patients' well-being and clinical outcome. There is some evidence that APT may be associated with a degree of subclinical Inflammation which in turns lead to an increased risk of protein energy malnutrition [265].

While symptomatic manifestations of radiation injury and their nutritional consequences have long been recognized, the potential for therapy has rarely been explored. It is recommended that all patients identified as being malnourished or at risk of malnutrition receive early and ongoing nutrition intervention by a dietician to help maintain energy and protein intakes during radiotherapy treatment [266].

Traditionally, body weight and BMI have been used as outcome measures in dietetic practice, but these measures do not reflect the body composition changes that may occur during chronic disease such as cancer. It is the loss of fat-free mass (FFM) that is responsible for the reduced functional status, increased mortality and other negative outcomes associated with malnutrition. Body fat is easier to gain than FFM, so studies that show improved body weight may not translate into reductions in morbidity or improvements in functional status [267].

3.3.2 Overview on body compartment

In order to adequately understand the figures from body composition studies and interpret the results towards patients management, it is crucial to be familiarised with the basic theory of body composition analysis and the different compartments that may be measured [256, 268].

The basic two-compartment model divides the body into a homogenous fat mass (FM) and a heterogeneous fat-free mass (FFM). FFM which is also called lean body mass (LBM) includes bone mineral and “lean” tissue. The major component of lean tissue is water. Typically, TBW accounts for 73% of FFM. However, this percentage may vary among normal individuals [269]. ECW can be further split into extravascular fluid (reflecting tissue hydration and oedema) and intravascular volume (impacting on blood pressure and cardiac function).

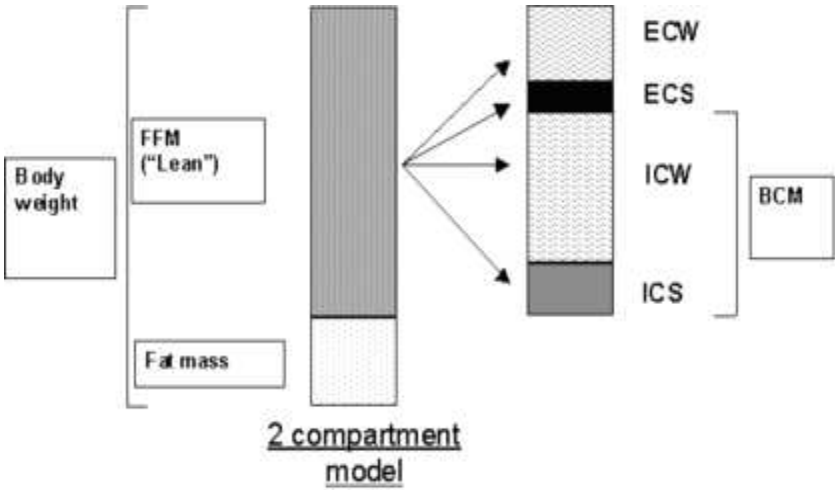


Figure (5) Diagram illustrating two-compartment model of body composition and division of fat-free mass (FFM) into its constituents. Fat-free mass is divided into extracellular water (ECW), extracellular solids (ECS), including bone mineral, intracellular water (ICW), and intracellular solids (ICS). ICW + ICS comprises body cell mass (BCM) [270]

Changes in FFM correspond to changes in nutrition and/or hydration. In some patients however, such as renal failure patients, FFM is stable due to concurrent wasting with fluid retention, while changes in BCM specifically reflect body nutrition and wasting status. Extracellular water is the compartment that predominantly changes with hydration [271].

3.3.3 Available methods of measuring body compartments in clinical practice

Direct estimation of the body fat mass (FM) has never been easy and it is still a major challenge for many clinicians. A number of body composition techniques are available to assess body composition and FM directly such as hydrodensitometry, air-displacement plethysmography, computed tomography (CT) scan, dilution method, magnetic resonance imaging (MRI), densitometry, in vivo neutron activation, measurement of total body potassium and dual-energy x-ray absorptiometry (DXA).

Although, they have been crucial in the development of the field of body composition analysis and act as standards for evaluation of newer techniques, these are complicated techniques [272]. They are not applicable to be used in the routine clinical practice due to relatively high cost, radiation exposure, and portability/availability [256].

Hydrodensitometry or underwater weighing (UWW) is the earliest and most common method of directly assessing FM. This technique was initially formulated at an academic level based on Archimedes' principle with a special focus on body fitness, exercise and sports performance. Different equipments are available to do underwater weighing ranging from easy to sophisticated machines. The patient will be initially weighed outside a water tank, then inside after complete body immersion. The volume of water displaced and/or the subject’s weight underwater, combined with the subject’s outside weight are used to calculate the density of the whole body. Bones and muscles density is more and fat is less dense than water [273].

Therefore, a person with more bone and muscle will weigh more in water than a person with less bone and muscle, meaning they have a higher body density and lower percentage of body fat [273]. This is based on the 2-compartment body composition model and assuming that the water or potassium content of the FFM is constant for all ages, 0.732 l/kg for body water [274] and 68.1 meq/kg for body potassium [275].

There is still a considerable uncertainty regarding the individual's percentage of fat due to normal variations in body hydration, protein, and mineral content.

Thus, it has been estimated that the total cumulative error for body fatness (% fat) is around 3–4% of body weight for the individual [276, 277]. However, this method is not ideal for everyone as muscular individuals tend to have denser bones and muscles than thin people, which means an underestimation of their body fat percentage [278]. While the body fat of elderly patients suffering from osteoporosis may be overestimated [279]. There are also a number of individual variations related to gender, ethnicity, growth, sexual maturation, aging, physical activity and different diseases [280]. Also, a direct measurement of the residual lung air volume is required, and a completely still water tank with no wind or movement is necessary [281, 282]. For the residual lung volume correction, the most commonly used method is oxygen dilution with a closed-circuit spirometer system [283].

Hence, many people find it difficult, invasive and uncomfortable as it involvs total submersion and complete air expulsion from the lungs [284].

Another method of directly estimating body composition is the air-displacement plethysmography (ADP), where the individual is immersed not in water but in a closed air-filled chamber [285]. This method uses two chambers, one for the patient and the other serves as a reference volume. After getting the individual inside the ADP, the door is closed and sealed, with a slight increase in the pressure as well as oscillating the diaphragm separating the two chambers to alter the volumes. The relationship of pressure versus volume at a given temperature is used to solve for the volume of the subject chamber. ADP can give multiple readings over a short period of time, which can reflect a true change in body composition of the individual. This technique is better and more acceptable for patients than the UWW, as it doesn't include an immersion in water. However, all of the other technical limitations are the same as for UWW. Data from previous literatures showed nearly similar results could be obtained in healthy individuals from both UWW and ADP methods [286, 287].

Dilution method is another technique of measuring body composition where the compartment volume is estimated by the ratio of the dose of a tracer, administered orally or intravenously, to its concentration in that body compartment within a short time after the dose administration. Two fluid samples are collected from the individual (urine and/or saliva and/or blood) during this method.

The first sample is obtained just before the tracer administration, to measure the background levels, and the second sample is collected after waiting a sufficient amount of time for penetration of the tracer within the compartment of interest (ICW, ECW and TBW) [288].

Sometimes a significant amount of the tracer is excreted before reaching a satisfactory saturation; hence, a cumulative urine sample and/or multiple blood samples must be collected to adjust the dose estimation [289]. This method of assessing body composition is based on four assumptions; the tracer is distributed only in the exchangeable pool, it is equally distributed within this pool, it is not metabolized during the equilibration time and finally the tracer equilibration is achieved relatively rapidly. If any of these requirements is violated, then the ratio of administered dose to fluid concentration must be adjusted [290-292].

Total Body Electrical Conductivity (TOBEC) is another method based on lean tissue being a better conductor of electricity than fat.

The patient lies in a cylinder, which generates a very weak electromagnetic field. The strength of the field depends on the electrolytes found in the person's body water. In about 10 seconds, TOBEC makes 10 conductivity measurements that estimate the FFM. Although very accurate, its use is limited due to the high cost of the equipment, the lack of portability and the need for trained personnel to perform the test [293].

Magnetic Resonance Imaging (MRI) scan is another method to measure exact body composition volumes in which a magnetic field stimulate water and fat molecules in the body to produce a measurable indicator. The individual lies within a strong magnetic device with a field magnitude greater than the earth’s field. Some nuclei will attempt to align with or against the magnetic field [294] while a computer scans the body. This method is repeated at each position along the length of the individual until the whole body is mapped and cross-sectional MRI images at each slice can be generated. High-quality images will eventually show the amount of fat and its distribution. MRI takes about 30 minutes and is very safe as it uses no ionizing radiation, but use is limited due to the high cost of equipment and analysis. It is not portable, needs a special isolated area and trained personnel to perform the test [293]. Also, the patient needs to hold their breath during scanning of the abdomen, to reduce artifacts introduced by movement.

Computed Tomography (CT) scan produces cross-sectional images of the body to measure compartment volume. A collimated x-ray tube provides a fan-shaped beam that is passed through the body, while an array of detectors is positioned on the opposite side of the subject to detect the transmitted radiation. As the beam rotates around a person, data are collected, stored and applied to complex algorithms to build images that determine body composition [256].

This anatomical image is like MRI views, except it contains additional information for the tissue's true density at each pixel. Variable algorithms are available in clinical practice to reconstruct these images to obtain useful clinical data. CT scan is particularly useful in giving a ratio of intra-abdominal fat to extra-abdominal fat. It is non-invasive, accurate and highly sensitive; but potentially limited by the exposure to high dose of radiation needed per pixel of image, high equipment cost and the need for trained personnel to perform the test [293].

Dual energy X-ray absorptiometry (DEXA) is another way of measuring body compartment volumes. It is a relatively new technology, very accurate and precise.

DEXA is based on a three-compartment model that divides the body into total body mineral, FM and FFM. This technique is based on the assumption that bone mineral content is directly proportional to the amount of photon energy absorbed by the bone being studied. When an X-ray or photon source is placed on one side of the body, the intensity of the beam on the opposite side is related to the thickness, density and chemical composition of the intervening tissues [295, 296]. The attenuation through bone, lean tissue and fat is different, reflecting their differences in densities and chemical composition [295]. With increasing photon energy, the differences in the attenuation properties for these tissues decrease.

DEXA uses a whole body scanner that has two low-dose x-rays at different sources that read bone and soft tissue mass simultaneously. The sources are mounted beneath a table with a detector overhead. The scanner passes across a person's reclining body with data collected at 0.5 cm intervals. A scan takes between 10-20 minutes. DEXA is becoming the new "gold standard" because it is very reliable, provides a higher degree of precision in only one reading and has the ability to show exactly where fat is distributed throughout the body. Its disadvantages are that it is not accurate in measuring extremely obese patients, the cost of equipment is quite high and the individual will be exposed to radiation [293]. Also, it is not portable, needs a special isolated area and trained personnel to perform the test.

Another method available in clinical practice to accurately measure, not estimate, changes, in body composition is Bioelectrical Impedance Analysis (BIA). This is one of the most practical, easy and non-invasive methods, which uses a Bioelectrical Body Composition Analyzer to measure intracellular, extracellular and total body water using Weight Manager Software.

The basic concept of this method depends on a dilution analysis of the body weight, assuming that TBW represents 73% of FFM [257].

The ability of tissues, and therefore the whole body, to conduct an electric current has been recognized for a long time. This forms the basis for the technique of BIA. The aqueous tissues of the body, due to their dissolved electrolytes, are the major conductors of an electrical current, whereas body fat and bone have relatively poor conductance properties [297, 298]. It is also possible to indirectly obtain FM data from the BIA machine by deducting FFM from the total body weight (TBW). Furthermore, BIA machine can supply other data such as the body resistance to the two fluid compartments.

A 50 kHz alternating electrical current is passed between skin electrodes placed at the hands and feet and subsequent the measured impedance is inversely proportional to body water content [299]. This technique is probably the most frequently used nowadays, due mainly to the relatively inexpensive cost of the basic instrument, its ease of operation, and its portability.

In our programme, longitudinal measurements are compared on the same patient before and after APT administration, thus, reducing the chance of errors as each patient is controlling him or herself. In recent years, BIA has emerged as a simple, reproducible method used for the evaluation of FFM and body composition [300].

BIA is a validated bed-side technique for the estimate of total body (TBW) and extracellular (ECW) water with reproducible measurements of water spaces and can be used to monitor hydration changes [301, 302].

For these reasons, BIA technique was the chosen method to measure changes in body composition for our study. Changes in body composition in women with breast cancer have previously been demonstrated with this technique in which there was an increase in body fat and a decrease in percentage of lean soft tissue and skeletal mass after chemotherapy [270].

3.3.4 Anthropometric measurements to assess malnutrition

Nutritional status can also be assessed indirectly through changes in body weight, height and body mass index (BMI) [303]. In addition, measuring the subcutaneous skin folds (biceps, triceps, subscapular, suprailiac, and medial calf) using a Holtain caliper, is another method of nutritional screening [304] which uses a special equation is used to derive a body fat percentage. This is based upon the assumption that the subcutaneous fat is a proportional reflection of the total body fat and that the sites selected for measurement represent the average fat thickness all over the body. Furthermore, handgrip calculation is another indicator of muscle strength and fitness, which could be also used in practice [305, 306]. The above anthropometric measurements are easy to do, inexpensive and portable.

However, the obtained results could be very subjective as precision is totally dependent on the clinician skills and the site measured. [293].

3.3.5 Nutritional support during APT

Adequate nutritional support during radiotherapy can decrease the impact of side effects, minimise weight loss, improve Quality of Life (HRQL) and help patients to recover from the radiotherapy more quickly [307].

However, a more pro-active approach may be even better. Ravasco et al. found that concurrent individualized dietary counselling is the most effective means of improving patients' nutritional intake, status, and HRQL, thereby lessening radiotherapy induced morbidity in patients with colorectal cancer [203, 308, 309]. Early intervention and sensible partnership with patients are the keys to success [310].

Therefore, early and intensive nutritional intervention provides beneficial outcomes which in turn yield many benefits such as minimising weight loss, preventing the deterioration in nutritional status, maintaining a reasonable global HRQL and physical function in colorectal cancer patients receiving APT.

3.4 Cytokines and markers of inflammation

3.4.1 Inflammatory markers in relation to CRC and APT

There is high variability in recurrence and survival rates within each TNM stage of CRC, and prognosis is most strongly correlated with the histopathological staging of the tumour [311]. It is increasingly recognised however, that variations in outcome in cancer patients are not solely determined by tumour characteristics but also by host-response factors, such as the release of C- Reactive Protein (CRP) and pro-inflammatory cytokines [311-313]. Cytokine and CRP levels have thus been scrutinised to determine whether they can be utilised as individualised non-invasive prognostic indicators or treatment targets, which could help clinicians optimise cancer care.

In 2001, McDonnell showed that patients with oesophageal cancer who underwent neoadjuvant treatment did not have significant changes in their plasma cytokines [314].

However and in 2003, Wichmann *et al* showed that preoperative chemoradiotherapy for advanced rectal cancer results in a significant preoperative and postoperative immune dysfunction as indicated by depression of lymphocyte subpopulations, monocytes, granulocytes, and proinflammatory cytokine release [315].

These findings are of importance because increased perioperative morbidity and mortality rates have been observed after preoperative chemoradiotherapy [316].

3.4.2 Overview on Cytokines

The systemic inflammatory response is propagated, and the severity modulated, by a number of humeral mediators such as lipid metabolites, reactive nitrogen and oxygen metabolites, nucleotides and cytokines. These mediators interact with each other as a molecular network to regulate the inflammatory response.

Cytokines are a group of soluble, low molecular weight glycoproteins, which act to regulate both the amplitude and duration of the systemic inflammatory response. Cytokines are highly active at very low concentrations and may act on cells in a paracrine and autocrine manner. Activated CD4 cells are programmed to secrete cytokines with one of two distinct antagonistic profiles. Type 1 helper cells (Th1) secrete cytokines with inflammatory properties (TNF-α, IL-1ß, IL-6, IL-8 and IL-12).

Type 2 helper T cells (Th2) produce anti-inflammatory cytokines (soluble TNF-α receptors (sTNF-α R), IL-1Ra, IL-4, IL-10, TGF-β). Tumours can act as an inflammatory insult and so levels of cytokines have been shown to alter in patients with malignancy. There are considerable data to suggest that cytokine profiles (e.g. IL-6) are raised, and associated with a diminished quality of life, in patients with advanced malignancy [317].

Pro-inflammatory cytokines are necessary for initiation of an effective inflammatory process. The early hyper-inflammatory response is followed by a counter regulatory mechanism. This mechanism is characterised by the release of anti-inflammatory cytokines.

An inflammatory cytokine network may influence survival, growth, mutation, proliferation, differentiation, and movement of both tumour and stromal cells. From our literatures search, we have found that IL-6, IL-1 and TNF-α are the most studied cytokines in the context of colorectal cancer and neoadjuvant therapy.

IL-6

Il-6 plays a central role in mediating a cellular and physiological inflammatory response. In this capacity, Il-6 has been found to delay neutrophil apoptosis, thereby inhibiting resolution of inflammation, which has been linked to postoperative mortality in colorectal cancer. Il-6 also affects immunoregulation, angiogenesis, and osteoclast activation. It has been implicated as a promoter of cancer growth by enhancing the colony formation of human colon carcinoma cells, increasing carcinoma cell invasiveness, and promoting secondary tumour formation [318-321]. Clinically, serum IL-6 levels increase in colorectal cancer patients relative to healthy controls, and are correlated with tumour size, stage, and survival in advanced malignancy [322-326]. However, in one study pre-operative Il-6 was not found to be an independent prognostic factor [323], and in another, was not significantly correlated with disease free and overall survival [327]. The loss of expression of the soluble IL6 receptor (sIL-6R) in colorectal cancer is significantly correlated with disease progression, and is thought to be due to consumption of the receptor as a result of Il-6 binding [328].

In vitro and in vivo studies have shown IL-6 can be induced by ionizing radiation [329, 330]. Exposure to radiation initiates a programmed molecular and cellular response to promote tissue repair, which includes the up-regulation of pro-inflammatory cytokines and the induction of nuclear factor κB activity [331].

Whilst studies have speculated that Il-6 may be associated with post radiotherapy fatigue, there is yet to be any definitive evidence [329, 331, 332]. However, raised Il-6 before neoadjuvant radiotherapy has been found to be predictive of weight loss and food intake reductions. In the same study, weight loss and food intake reduction before or after radiotherapy was significantly associated with a raised Il-6 (and TNF α) and non-response to radiotherapy [333].

In neoadjuvant chemoradiotherapy in advanced rectal cancer, IL6 levels were not significantly different from control patients after chemoradiotherapy. However, they were significantly higher in patients without preoperative therapy on Days 1 and 2 after surgery [315]. In an oesophageal cancer study, elevated serum IL-6 levels after neoadjuvant 5FU based chemoradiotherapy, but not before, were correlated with a poor response to chemoradiotherapy and poor survival. In this study, raised Il-6 levels were also positively correlated with residual tumour volume and CRP [334].

Another study investigating a cetuximab enhanced Folfox-4 neoadjuvant chemoradiotherapy regimen for the treatment of oesophageal cancer, showed a significant increase in IL-6 after chemoradiotherapy. However, no major difference between cytokine variation levels among responding and non-responding patients was found [335].

IL-1

It has been reported that raised IL-1 has been associated with a poor prognosis in colorectal cancer patients and is an important mediator of VEGF expression and Il-6 production [322, 336]. However, Il-1's association with survival has not been demonstrated universally [323]. Il-1 receptor antagonist (Il-1ra) blocks IL-1 signal transduction, the Il-1/Il-6 inflammatory cascade, and is a competitive inhibitor of VEGF expression. IL-1ra is produced in the postoperative period in response to IL-6 production. However, in nutritionally depleted patients undergoing surgical stress this negative feedback loop was found not to exist. The attenuation of a pro-inflammatory cytokine network antagonist has potentially negative implications for clinical outcomes in malnourished patients, as peri-operative pro-inflammatory states can adversely affect the prognosis of cancer patients. The use of synthetic IL-1ra (anakinra) to ameliorate these circumstances requires further study, and the effect of neoadjuvant therapy is described below [336-339].

The effect of ionizing radiation on IL-1 has been studied in various tumour types, producing a range of differing results [329]. There is only a small amount of literature concerning the changes to IL-1 during neoadjuvant therapy in colorectal cancer. The role of post neoadjuvant IL-1 as a potential indicator of peri-operative and long term outcomes does not seem to have been investigated.

TNF

Tumour necrosis factor (TNF)-α is a cytokine produced by activated macrophages and tumour cells. It was first identified as a host induced substance that is selectively toxic to tumour cells at high doses [340]. However, at physiological levels it is tumour promoting through its direct effects on cancer cells, its induction of the chemokine system, its activation of NF-κB and Il-6, and its stimulation of epithelial-mesenchymal transition [341, 342].

It induces cellular proliferation, inhibits apoptosis, and is associated with the symptoms of weight loss, and fever. Elevated levels of TNF are found in the majority of colorectal cancer patients, regardless of the stage of disease [343-345]. High TNF-α expression has also been found to be significantly associated with recurrence of colorectal tumours and was found to be an independent prognostic factor in the same study[346]. TNF-α is often found to decrease after surgery, though post-operative patterns seem to vary [323, 344, 347].

TNF-α can also induced by ionizing radiation [329, 330], though significant increases have not been found in all studies [329, 332, 348]. In a rectal cancer study considering neoadjuvant chemoradiotherapy, post chemotherapy TNF-α levels were lower, but not significantly, than controls pre-operatively, but were found to be significantly lower than control patients at 1,2, and 5 days after surgery [315].

In contrast, in the oesophageal cancer study discussed previously [335], TNF-α was found to be significantly lower after a cetuximab enhanced Folfox neoadjuvant chemoradiation regimen. However, as with both Il-6, and Il-1B, there was no significant difference in the increase between responding and non-responding patients. It is thus not yet clear as to how neoadjuvant therapy affects TNF-α production, and how this impacts on survival. Nevertheless, both anti TNF-α drugs (e.g. infliximab & ertanercept) [341] and pro TNF-α drugs (e.g. TNFerade) [349] are being investigated in a range of cancers with varying success [341].

VEGF

Vascular Endothelial Growth Factor (VEGF) is an important cytokine involved in both vasculogenesis and angiogenesis, and can be induced by IL-6 [350]. It has been found that VEGF levels are higher in metastatic tumours, and that a positive VEGF status is associated with a significant reduction in five year survival [327, 343, 351-353]. Preoperative elevated VEGF levels have also been found to be associated with reduced survival, tumour size, and CEA concentrations [327, 354]. One study found no association between neoadjuvant long course radiotherapy, VEGF expression, and response to treatment [355, 356]. However, another study that evaluated VEGF in tumour biopsies before experimental short course neoadjuvant radiotherapy found that VEGF negative tumours were more than four times more likely to undergo complete tumour regression than their VEGF positive counterparts [355].

Moreover, it has also been demonstrated that VEGF positivity is an indicator of poor disease-free survival following preoperative chemoradiotherapy [357].

Further research into the development of more effective neoadjuvant regimens for VEGF positive patients, together with the continued investigation of anti-VEGF drugs or techniques, might yet yield benefits for this subgroup of patients [353, 355, 358-361].

IL-8

Il-8 is a chemokine involved in the growth, signalling and the up-regulation of inflammatory responses as well as the emergence of a vascular supply [362, 363]. In one colorectal study, pre-operative Il-8 was not correlated with survival, but was found to be significantly higher in CRC patients than in those without cancer [323].

It has also been shown that overexpression of Il-8 is associated with liver metastases and poor outcomes in colorectal cancer patients, and resistance to oxaliplatin [362, 364-366]. In a cetuximab enhanced folfox neoadjuvant chemoradiotherapy regimen for oesophageal cancer, Il-8 was seen to decline after both radiotherapy and chemotherapy, but not significantly so.

There are few other studies that consider the use of Il-8 as a prognostic factor in the context of neoadjuvant therapy [335].

IL-23

Il-23 is a pro-inflammatory cytokine that is structurally similar to Il-12, and induces the production of pro-inflammatory cytokine IL-17, which promotes angiogenesis and regulates VEGF. IL-23 has been associated with both pro-tumour [367-369] and anti-tumour activity [368]. One recent study looked at IL-23 before and after adjuvant chemotherapy and found no significant change in serum levels, and no association with disease stage or the presence of metastases [368]. The importance of Il-23 as a prognostic indicator in colorectal cancer patients, with or without neoadjuvant therapy is yet to be determined.

IL-10

IL-10 is an anti-inflammatory cytokine with immunoregulatory functions. This cytokine is produced primarily by monocytes and to a lesser extent by lymphocytes. It down-regulates the expression of pro-inflammatory cytokines. TGFβ is an anti-proliferative factor and so exerts an anti-inflammatory effect.

IL-10 can have both a tumour promoting and a tumour inhibiting factor [342, 369, 370]. Whilst its anti-inflammatory function may be anti-tumoural, it might promote tumour growth by inhibiting apoptosis and stimulating cell proliferation. A high systemic level of Il-10 has been found in advanced colorectal malignancies, and pre and post-operative Il-10 levels have been used to predict tumour recurrence after surgery [369, 371]. There has been very little research into the effects of neoadjuvant therapy on IL-10. In the cetuximab enhanced folfox neoadjuvant study in oesophageal cancer previously discussed, IL-10 significantly increased after radiotherapy and chemotherapy; however, there was no significant difference in cytokine changes between responders and non-responders [335].

CRP

C- Reactive Protein (CRP) is a readily available inflammatory marker that has been studied as a prognostic biomarker in a number of solid tumours. During acute inflammation, the production of CRP in the liver is directly stimulated by IL-6. Once stimulated, CRP rapidly reflects circulating Il-6 levels, and in the context of malignancy, has been found to correlate with the tumour tissue concentration of IL-6 [347, 372].

CRP has a half-life of approximately 19 days, up-regulates the expression of adhesion molecules and stimulates the release of further IL-1, IL-6, IL-18, and TNF-α from mononuclear phagocytes [340, 347]. A raised CRP has been linked with the prognosis of prostate [373, 374], breast [375, 376], colon [377], ovary [343], bone [343], stomach [378], lung [379, 380], pancreatic [381, 382], and skin tumours [343]. The mechanism by which CRP is linked to prognostic outcomes is unknown. However, a raised CRP may be a surrogate marker for a pro-angiogenic environment, a marker of poor T-cell lymphocytic infiltration, and a marker of the compromised cytochrome P450 3A system. These potential associations are all speculated to be the determinants of the CRP-outcomes relationship.

Raised circulating concentrations of CRP were found to be correlated with tumour bulk, and predicted overall and cancer-specific survival, in patients undergoing potentially curative surgery for colorectal cancer whether measured before or after operation. The prognostic value of preoperative CRP was also found to be independent of Duke's stage [312, 383-385]. Later studies have shown that in TNM stage I or II patients, CRP could predict early disease recurrence, even when a CEA test could not [372]. However, in one recent colorectal cancer study, pre-operative CRP levels showed no correlation with regard to disease free survival and overall survival (median follow up duration 18.53 months) [327]. The prognostic value of CRP can be combined with hypoalbuminaemia to create the Glasgow Prognostic Score (GPS) [379, 386]. The GPS has been reported to be superior to CEA and CA 19-9 in predicting survival [339]. The modified GPS (mGPS) also reflects cachexia, loss of weight, lean tissue and performance status [387]. Indeed, mGPS has been found to be independently associated with a risk of post-operative infective complications in those undergoing curative resection. Most importantly however, the mGPS has been reported to have prognostic value independent of high risk pathological tumour features in node negative disease [385, 386, 388, 389]

Radiotherapy can cause a raised CRP, which has been found to be associated with an increased frequency and severity of fatigue symptoms [390, 391]. It is possible that preoperative administration of radiation therapy may induce significant immunologic dysfunction that could influence postoperative recovery as well as metastatic growth of disseminated cancer cells [315]. Unfortunately, potential relationships between radiotherapy, CRP, and morbidity and mortality have not been investigated extensively in the colorectal cancer context.

The majority of studies that consider the relationship between preoperative CRP and colorectal cancer survival tend to have either excluded participants who have undergone neoadjuvant radiotherapy or do not address the issue [312, 337, 339, 344, 372, 383-385, 388, 392-394].

One study found that Glasgow prognostic score (GPS) measured prior to preoperative chemoradiotherapy in non T4 tumours predicted a poor prognosis [395], and another found that preoperative CRP levels were an independent prognostic marker for survival after neo-adjuvant treatment [396]. A very recent study demonstrated that elevated serum CRP levels after preoperative chemoradiotherapy, but not before, was correlated with poor response to chemoradiotherapy [334].

3.4.2 Cytokines, Body physiology and Carcinogenesis

The mechanisms behind the associations between body physiology and the inflammatory markers in colorectal cancer patients are complex. The relationship between CRP and cytokines (predominantly Il-1, Il-6, and TNFα) together with short and long term outcomes has been studied in a number of solid tumours with varying results. Cytokines are small cell signalling proteins which stimulate the release of CRP from hepatocytes, modulate immunological control and may influence survival, growth, proliferation, and differentiation of tumour cells. Cytokines found in tumours are more likely to contribute to tumour growth, immunosuppression and progression than they are able to mount an effective host antitumour response [321, 383, 397].

Inflammation is intimately involved in carcinogenesis and cancer progression in colorectal cancer. An appreciation of this process is necessary to enable us to understand why host response factors might play a role in predicting prognosis. Inflammation, infection and genetic events activate a multiplicity of transcription factors (e.g. nuclear factor-κB (NF-κB)) that coordinate the production of inflammatory mediators such as cytokines and chemokines [341]. These factors activate various leucocytes and further transcription factors in inflammatory, stromal, and tumour cells, resulting in further release of inflammatory mediators. IL-1β, IL-6, IL-23 and TNF-α are the key cytokines involved in cancer related inflammation, and together with chemokines coordinate autocrine and paracrine interactions between malignant cells and infiltrating leukocytes. These interactions affect the growth of the primary tumour, and increase the migration, invasion and survival of malignant cells.

Thus, one might expect all of these cytokines to become more prevalent when the tumour burden is high or the patient is not responding to treatment. Whilst for the most part this seems true, the reality is more complex [341].

Following an inflammatory insult e.g. advanced malignancy; the balance between the biological effects of the pro-inflammatory and anti-inflammatory cytokines is thought to affect the clinical outcome of the disease. An excessive, inappropriate production of pro-cytokines can have a deleterious effect, resulting in: defective tissue microcirculation and hypoxia. In contrast, anti-inflammatory cytokines (IL-4, Il-10 and IL-13) appear to be important in the control and down-regulation of the inflammatory response.

Few studies have examined the effect of APT on levels of cytokines. A small study has shown a rise in inflammatory markers after treatment with chemotherapy, but data are sparse [202].

It has also been shown that in elderly healthy people, higher levels of pro-inflammatory cytokines (IL-6 and TNF-α) were associated with lower muscle mass and lower muscle strength in both men and women. This is relevant as colorectal cancer occurs much more frequently in the elderly [398]. The effect of the various cytokines is thought to be at least partly hereditary, and may affect the surgical outcome [399]. There are also considerable data to suggest that cytokine profiles (e.g. IL-6) are raised, and associated with a diminished quality of life, in patients with advanced malignancy [317].

The colorectal cancer literature in the adjuvant chemotherapy setting broadly supports the notion that inflammation can predict outcomes. An elevated preoperative CRP was found to be predictive of a poor outcome in patients receiving adjuvant 5-FU chemotherapy [400], and the mGPS was found to be a predictor of mortality in the 5FU based ‘Folfiri’ and ‘Folfox’ regimens for advanced or unresectable disease [401].

3.4.3 Exercise and Cytokines

Exercise training and an increase in physical activity has a significant effect on CRP. It has been found that a 6 months course of supervised exercise programme has reduced CRP in adult men and women at risk for developing ischemic heart disease [402].

Nutrition therapy with anti-inflammatory agents and exercise activities will support lean tissue anabolism and prevent the adverse physiological and physical outcomes as well as promoting successful health, functionality, and quality of life outcomes of patients who are being treated with anti-cancer therapy [403].

Short-term rehabilitation programme with moderate exercise leads to a shift to a more pro-inflammatory state (decreased antagonist/cytokine ratio). This might be clinically beneficial (decreased rates of infection, relapses and/or second tumours) but needs long-term studies [404].

At present it is not possible to accurately predict why similarly staged colorectal patients undergoing APT can have remarkably different treatment outcomes. The use of CRP and cytokines as predictive biomarkers in this context is not well researched [210, 327]. In this project, we will discuss what is currently known about the relationship between CRP, cytokines, APT, and outcome of surgery within a clinical context.

3.5 Health related quality of life (HRQL) and Physical activity

3.5.1 HRQL

In recent years, the study of exercise programmes used as an integral part of holistic therapy for patients with cancer has become an increasingly popular area of study. Many such studies specifically look at the resulting effect on health related quality of life (HRQL). These studies are particularly popular in respect to patients with breast cancer, however, there is little information specifically relating to colorectal cancer. Furthermore, no studies look specifically at the effects of exercise on quality of life during a preoperative phase where preoperative adjuvant therapy may be given.

Colorectal cancer results in a number of disease and treatment related factors that can adversely affect HRQL of patients. The symptom profile of disease includes: change in bowel habit, per-rectal bleeding, weight loss, malaise, abdominal pain and tenesmus. These symptoms can easily lead to poor nutritional intake and a change in normal activity levels resulting in malnutrition and reduced physical fitness. This, in turn, will affect HRQL as patients become less able to carry out activities of daily living (ADLs) and leisure time activities [405, 406]; furthermore the side effects of treatment may contribute to a deterioration in HRQL [407].

It is possible that a negative cycle of deterioration is initiated; fitness and inability to perform ADLs leads to further reductions in HRQL, resulting in less activity and further reductions in fitness [405-408].

Health related quality of life is a concept that has developed over recent years. It encompasses a number of domains of HRQL such as physical, nutritional and psychological, as well as profiles of symptoms and treatment side effects.

There are many standardised and validated measuring tools that have been used for studies investigating HRQL. The tools most commonly used in the existing literature are shown in table 2.

Although, the study of exercise as a mediator of HRQL has become increasingly popular it has been skewed to some specific cancer types.

Much of the evidence available currently comes from cohorts of patients with breast cancer. It might be considered that application of these data to colorectal cancer should be done cautiously [409], as the pathology of the diseases, the treatments used, and the demographics of the patients differ significantly between these two types of cancer.

However, several studies have addressed the questions using patient cohorts of mixed malignancy type. One such study showed no diagnosis related pattern of response to the exercise intervention [410] and thus, it seams that those studies of exercise during cancer treatment in any malignancy type can provide evidence to support this investigation.

Tool	Measures
European Organisation for Research and Cancer Treatment Quality Of Life Questionnaire **EORTC QLQ-C30**	9 multi-item scales: 1. functional scales (5): • physical, • role, • cognitive, • emotional, • social 2. symptom scales (3) • fatigue, • pain, • nausea and vomiting 3. global health and quality-of-life scale.
Functional Assessment of Cancer Therapy-Colorectal **FACT-C**	5 multi item scales (36 items in total) • Physical (7 items) • Functional (7 items) • Social/family (7 items) • Emotional well being (6 items) • Colorectal Cancer Subscale (9 items)
Symptom Check List **SCL-90r**	12 multi item scales (90 items in total) • Somatization • Obsessive-Compulsive • Interpersonal Sensitivity • Depression • Anxiety • Hostility • Phobic Anxiety • Paranoid Ideation • Psychoticism • Global Severity Index • The Positive Symptom Distress Index, • Positive Symptom Total
medical outcomes short form 36 **SF-36**	8 multi item scales • physical functioning • role limitations (physical) • bodily pain • general health • vitality (energy/fatigue) • social functioning • role limitations (emotional) • mental health
Satisfaction with Life Scale **SWL**	5 single item scale
Profile of Mood Status **POMS**	6 multi item scales • Tension-Anxiety • Anger-Hostility • Fatigue-Inertia • Depression-Dejection • Vigor-Activity • Confusion-Bewilderment

Table (2) shows different Health Related Quality of Life (HRQL) assessment tools

3.5.2 Physical activity

Little evidence is available in the literature about the impact of physical activity on patient with colorectal cancer and the post-operative course of the disease. However, there are enough data to support the positive role of exercise training in general patient well being and cardiopulmonary function [411].

Recent work has critically examined the effects of exercise in contributing to improvements in health. A number of studies in patients with breast cancer have shown a beneficial effect of exercise on cardiovascular function, in patients who have finished their treatment. These indicate that such an approach is safe and promote the concept of an individualised approach [59].

Most of the studies that examine the relationship between physical activity and quality of life in cancer have been performed in women with breast cancer. The Health, Eating, Activity, and Lifestyle (HEAL) Study developed a tool to investigate changes in physical activity levels after a diagnosis of breast cancer relative to pre-diagnosis levels and to assess the influence of disease stage, adjuvant treatment, age, and body mass index (BMI) on these changes [412].

This was shown to be a reliable indicator. Such studies may have a bearing to our approach to colorectal cancer patients. In patients who have been treated for colorectal cancer, performing moderate intensity exercise (Home-based exercise) 3-5 times per week for 20-30 min each time can increase cardiovascular fitness and is associated with improvements in quality of life, as measured by the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) scale [413].

Studies in animals that have received chemotherapy suggest that exercise can preserve myosin heavy chain isoforms in cardiac muscle [62], and can enhance endothelium-dependent vaso-relaxation, following vasoconstriction induced by 5-FU [63] These protect against the effects of chemotherapy.

In the clinical situation, most studies assess exercise following treatment. However, there are a small amount of data of its effects prior to, and during, treatment. In an Italian study, 8 patients who had been classed as unfit for surgery for lung cancer were allocated to a 4 week supervised exercise programme.

Both FEV_1 and FVC were significantly increased and all 8 patients subsequently had successful surgery. There was no mortality. The authors suggested that physical exercise could have induced a recruitment of dormant lung parenchyma [64]. Seventy patients who were receiving chemotherapy were allocated to a 9 hour weekly training programme over 6 weeks with measurement of VO_2max. Exercise was well tolerated and there was an improvement in aerobic fitness [65].

Exercise appears to be a safe, efficacious strategy to maintain or to improve physical and mental well-being; however, it is critical that exercise be individualized to specific needs of the cancer survivor, who already has a compromised system, to prevent exacerbation of physiological and psychological toxicities that occur as a result of cancer treatments [414].

3.5.3 APT effect on HRQL and their relation to exercise

The effects of APT on health related quality of life (HRQL) are multiple, but the major effects are thought to include: fatigue [199], impaired exercise tolerance [199], malnutrition [200, 201] and a reduced quality of life [203].

Anti-cancer treatment with chemotherapy (CT) and/or radiotherapy (RT) has an impact on the overall HRQL as it is a subjective multidimensional construct reflecting functional status, psychosocial well-being, and health and disease treatment-related perceptions [203, 309].

Exercise training has beneficial effects on cardiopulmonary function and HRQL in postmenopausal breast cancer survivors who had completed surgery, radiotherapy, and/or chemotherapy with or without current hormone therapy use [415].

Different assessment tools are available in the clinical practice to measure HRQL. Some of those are generic tools, such as SF36, which is a multi-purpose health survey to yield a profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures.

In addition, disease-specific assessments tools are also available in the clinical setting to measure HRQL, physical and nutritional changes such as the European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30) and the Patient Generated Subjective Global Assessment (PG-SGA).

PG-SGA is a validated questionnaire used to define a specific nutritional intervention needed to optimise the overall nutritional status in patients with gastrointestinal cancer such as patient and family education, nutritional supplements, enteral and parenteral triage.

While EORTC QLQ-C30 is more a disease-specific tools used to assess HRQL in patients with colorectal cancer such as physical, emotional and cognitive and social functioning as well as social, symptom and financial scales.

4.0 AIMS, OBJECTIVES and RATIONALE

4.1 Primary Aim:

To assess the cardiopulmonary reserve (represented by VO_2max) before and after the administration of adjuvant pre-operative chemotherapy and/or radiotherapy (APT) using the CPEX testing.

4.2 Secondary Aims:

A- To assess changes in body composition before and after APT exposure. Those changes will be assessed using Hand-Grip measurements, anthropometric tools and bioelectrical impedance analysis (BIA).

B- To assess changes in plasma cytokines before and after APT using a venous blood sample to measure pro-inflammatory markers (TNFα, IP-10, RANTES, IL-6, IL-18) and anti-inflammatory markers (IL-1β, IL-1ra, IL-10, MIF) as well as plasma CRP and albumin.

C- To assess changes in the HRQL, physical activity and nutritional status before and after APT using 2 validated instruments (EORTC QLQ-C30 and PG-SGA questionnaires).

D- To establish any correlations between the study outcomes using Spearman correlation test after APT exposure:

1- Primary correlations:

- Inputs: CPEX variables
- Outputs: Demographics, Body composition, Cytokines and HRQL variables

2- Secondary correlations:

- Inputs: HRQL variables
- Outputs: Body composition variables.

E- To assess the trend of changes between the two groups of patients post APT exposure using mixed Anova test.

4.3 Null hypotheses:

Adjuvant pre-operative therapy (APT) has no effect on the cardiopulmonary function, nutritional and physical status, HRQL, inflammatory markers and body composition in patients with colorectal cancer.

4.4 Alternate hypotheses:

Adjuvant pre-operative therapy (APT) has a significant effect on the cardiopulmonary function, nutritional and physical status, HRQL, inflammatory markers and body composition in patients with colorectal cancer.

4.5 Objectives and Rationale:

This study examined the effect of pre-operative adjuvant therapy (APT) on patients with adenocarcinoma of the rectum. Patients were identified from the MDT meeting and those with an advanced tumour on the operative staging, needing APT, were recruited.

CPEX testing was used to measure changes in functional capacity (represented mainly by VO_2max and AT) before and after APT administration. CPEX testing is considered to be one of the practical and reliable methods to interpret the physiology behind oxygen delivery and consumption at tissue level following surgery. The test is capable of identifying high risk patients with an increased risk of cardiopulmonary mortality and morbidity in the postoperative period [177-179, 252], [253, 254].

5.0 METHODS

5.1 Recruitment

Patients were identified from the MDT meeting that comprised oncologists, radiologist, colorectal surgeon, pathologists and nurse practitioners. Those patients with an advanced rectal tumour on pre-operative staging, who were deemed to require adjuvant pre-operative therapy (APT), were recruited.

Patients were selected from the MDT meeting and approached during their first visit to the Oncologist at the outpatient clinic. A brief 10 minutes face to face interview was conducted between the main study investigator and the selected patient after they finished their oncology appointment. The project aims and methods were explained to the participant who was provided with a written covering letter explaining the aims and methods of the study, a patient information sheet, a consent form, a GP letter and two questionnaires in a prepaid self-addressed envelope.

The approached patient was given at least 24 hours to decide about participation in the project. The principal investigator then contacted each participant by phone to enquire about their final decision. After the participant accepted entrance into the study, they were advised to sign the provided written consent and return it together with the first set of fulfilled questionnaires in the enclosed prepaid envelope. A helpline number was provided in the covering letter to allow patients to ask any questions about the study or if they had difficulty completing the questionnaire.

Thereafter, each patient was allocated to one of the two groups, as per the MDT decision:

Group 1: Patients who will receive combined ChemoRadiotherapy.

Group 2: Patients who will receive only pelvic radiotherapy.

Each patient was provided with a single appointment (arranged with the participant by telephone) to attend the project-specific outpatient clinic. This clinic was located at the cardiology physiology department of Leeds General Infirmary.

During this initial visit, the following assessments were made:

- Cardiopulmonary fitness (measured with CPEX test)
- Body composition analysis (measured with BIA)
- Anthropometric measurements - body weight, height, body mass index, triceps skin folds, mid arm circumference and hand grip measurements.
- A single venous blood sample of 5ml to check for inflammatory markers, CRP and albumin.
- Patients were asked to bring their first set of filled questionnaires.

After completion of the adjuvant pre-operative therapy, patients were subsequently contacted by the principal investigator and invited them for a second visit to repeat the same assessments above with filling of the second set of questionnaires.

The study-specific two clinic visits (pre and post APT) were carried out before and within two weeks after the administration of the anticancer treatment. This is to give the best reflection of the APT effects on the physiology of colorectal cancer patients. Patients were provided with travel expenses as well as drinks and snacks during their visits and stay for the tests.

5.2 CPEX

Cardiopulmonary fitness was measured with the CPEX testing at the exercise testing laboratory of Leeds general Infirmary. Changes in VO_2max and anaerobic threshold (AT) were measured before the administration of APT and 14 days within the finish of treatment. Pre-operative cardiopulmonary exercise testing was performed using a standard protocol [416].

5.2.1 Pre-test baseline Data Collection

The following baseline data were collected on all patients who were recruited:

- Age, gender, body weight and height.
- Blood pressure and any history of hypertension
- History of ischemic heart disease including details of any angina, myocardial infarction, cardiac surgery or coronary angioplasty
- Any history of heart failure
- Any history of cerebrovascular disease

- Any history of diabetes mellitus
- Hyperlipidaemia
- Plasma creatinine and any history of any renal impairment
- Details of current medication

5.2.2 Exclusion Criteria for CPEX Testing

- Acute Myocardial infarct (within 7-10 days of transmural infarct or within 5 days if minor and uncomplicated)
- Uncontrolled arrhythmias causing symptoms or haemodynamic compromise;
- Left main stem stenotic lesions in excess of 50%
- Malignant hypertension
- Pulmonary oedema
- De-saturation at rest to less than 85% while breathing room air
- Acute inflammatory conditions (pericarditis, myocarditis)
- Unstable angina (patient should be pain free for 4 days before CPEX)
- Dissecting aneurysm
- Acute or recent pyrexial illness
- Thyrotoxicosis
- Syncope
- Thrombosis of lower extremities

5.2.3 The CPEX Test

The tests were performed by cardiorespiratory technicians and supervised and interpreted by medical staff with training and experience of CPEX testing. The CPEX test equipment consists of an electronically braked cycle ergometer, 12 lead ECG and a gas analyser/metabolic cart. The patient wears a nose clip and breathes through a mouth piece connected to a pneumotachograph and metabolic cart allowing breath by breath analysis of oxygen uptake and carbon dioxide excretion. The patient is connected a 12-lead ECG during the test which, together with a special software, allow ST-segment analysis in real time and full disclosure of all leads if required. CPEX testing uses two main exercise modalities: the treadmill and the stationary cycle ergometer. The work rate can be exactly measured using the bicycle ergometer while it is only estimated by treadmill; therefore, the former method is preferred by many clinicians nowadays.

On the other hand, most patients are familiar with walking as it is a less threatening form of exercise for testing purposes than cycling. As walking treadmill provides a constantly moving platform, subjects may have difficulty in continually maintaining the required forward momentum [235]. Determination of an individual's maximum exercise capacity is influenced by the mode of exercise used [416]. Walking/running treadmill utilises more muscle groups which in turn leads to higher oxygen consumption than the cycle ergometer by around 5-20% [417]. The Coefficient of variation for the CPEX test is less than 5.9% [418, 419]. The test consists of four main phases: rest, unloaded cycling, ramp and recovery. The 12 lead ECG is monitored continuously for the duration of the test.

5.2.4 Rest

The test starts with a 2-5 minutes rest period to allow patient familiarisation with the mouthpiece, gas exchange equipment and bicycle as well as allowing for resting heart rate, blood pressure (BP), ECG and gas exchange values to be established. The proper conduct of this stage of the test is important if valid results are to be obtained when exercise begins. Patients can be anxious prior to the start of the test and hyperventilation often then occurs once the patient is connected to the mouthpiece and other testing equipment. It is important for accurate conduct of the test to establish a regular settled resting breathing pattern before initiation of exercise for the measurement of the baseline respiratory exchange ratio (RER). The RER is the ratio of carbon dioxide output to oxygen uptake. The resting RER should ideally be between 0.7-0.95 [420] indicating that the patient is not hyperventilating.

5.2.5 Unloaded Cycling

When the patient has become used to the equipment during the rest period, unloaded cycling will then start, with a period of 2-3 minutes of steady pedalling at 60 revolutions per minute with no resistance applied to the cycle ergometer. This allows for the oxygen cost of just turning the legs to be evaluated, provides minimum resistance for the particularly detrained or functionally limited and ensures that oxygen kinetics do not disrupt the measurement of anaerobic threshold.

5.2.5 Ramp

The ramp will follow from the unloaded cycling in a continuous fashion where the workload against which the patient must pedal is gradually increased.

Formulae are available to calculate the ideal rate of increase but this is often set on the basis of clinical judgement at a rate of increase of between 10 and 20 Watts per minute. The aim is to increase the workload at a rate that allows a full test to be completed in less than 10 minutes. The patient is asked to exercise until it is deemed that the anaerobic threshold has been passed or the individual can no longer maintain the prescribed rate of peddling or walking/running on the treadmill [235].

5.2.6 Recovery

Exercise finishes with a cool down stage in which the patient pedals the bicycle for a brief period against zero resistance, or the treadmill is slowed to a walking pace. This is to prevent collapse due to hypotension and syncope if exertion is stopped suddenly. Blood pressure measurement is performed throughout the whole test, usually 3-4 times. The ECG is monitored until the heart rate is within 10 beats per minute of the pre test rate.

When on the exercise bike, the patient is instructed to cycle at 50-60 RPM as indicated by a meter on the bicycle handlebars. The electronic braking on the bicycle will be programmed to allow five minutes of cycling with no resistance (unloaded cycling) and then five minutes of cycling with steadily increasing resistance such that the patient achieves anaerobic metabolism, and lactate starts to accumulate in the muscles. Hence, anaerobic threshold (AT) can be determined (ramp) at that point but the patient will continue the programmed exercise up to their VO_2peak. The work rate increments are determined using the following equations:

I. VO_2 unloaded (ml/min) = 150 + (6 x weight (kg)
II. Peak VO_2 (ml/min) Men = height (cm) – age (years) x 20
III. Peak VO_2 (ml/min) Women = height (cm) – age (years) x 14
IV. Work Rate increment (W/min) = (Peak VO_2 –VO_2 Unloaded) / 100

5.2.7 Test Termination

Possible reasons for terminating the test include:

1. VO2peak attained- patient unable to maintain cadence of greater than 40 rpm on cycle one minute and doesn’t respond to encouragement.

2. Signs or symptoms of myocardial ischemia or dysfunction:
    a) Chest pain
    b) New S-T segment changes exceeding –2.0 mm (depression) or +3.0 mm (elevation)
    c) New dysrythmia
3. The patient stops pedalling due to chest pain, dizziness, feeling unwell or light headedness before the other criteria have been obtained.

The CPEX test is a relatively safe procedure, with a quoted risk of death of between 2-5 per 100,000 clinical exercise tests [416]. It is important as with all clinical tests, to gain informed consent prior to the procedure with appropriate discussion of risks.

5.2.8 Peak Workload and Exercise Time

Exercise time and peak workload as well as percentage of predicted peak workload are reported.

5.2.9 VO_2max and VO_2 peak

At VO_2max, a subject has achieved the maximum possible oxygen consumption (ml/kg/min). A plateau in oxygen consumption between the final two work rate increments indicates that maximal oxygen uptake has been achieved and sustained for a brief period. As the work rate increases during exercise, one or more of the determinants of oxygen uptake reaches its maximum limit for that subject. In healthy subjects, oxygen uptake is limited by cardiovascular reserve (heart rate and stroke volume) rather than by respiratory reserve. Maximal oxygen uptake is dependent upon the mode of exercise, age, gender and body weight. Formulae for predicted VO_2max (ml/kg/min) are:

$VO_2 = W \times [50.75 – 0.372(A)]$ (male subjects)

$VO_2 = (W + 43) \times [22.78 – 0.17 (A)]$ (female subjects)

Where W is weight in kilograms and A is age in years. Values of 85% of predicted or more are considered to be within the normal range [235].

VO_2max can be identified only in trained athletes. In most patients a clear plateau in oxygen uptake is not seen before exercise is limited by fatigue or terminated.

Generally, maximal tests in the clinical setting report the result of peak oxygen uptake [235].

VO_2peak is the oxygen consumption (ml/kg/min) at the maximum level of exercise that a subject can attain regardless of whether a plateau in oxygen consumption is seen. VO_2peak has the weakness that it is dependant on volition, i.e. on the subject's willingness to exert themselves to their limit. However, it allows peak oxygen consumption to be reported in subjects in whom a true VO_2max cannot be defined and is an important indicator of exercise capacity in subjects in the clinical setting.

VO_2peak is widely recognised as a risk stratifying measure in patients with cardiovascular disease [255]. It is a widely used measure in the evaluation of chronic heart failure [421].

To make this clear, patients might reach their VO_2peak depending of their physical fitness, but this might not be their VO_2max based on their body calculations.

5.2.10 Anaerobic Threshold (AT)

The anaerobic threshold (AT), also known as the metabolic threshold, identifies the point during the CPEX test where an increase in blood lactate levels during exercise is noted.

The rise in circulating lactate during exercise was attributed by Wasserman and McIlroy to the existence of a critical threshold at which the metabolic needs for oxygen in the muscle exceed the capacity of the cardiovascular system to supply them [422]. In recent years this interpretation has been questioned and alternative explanations for the increase in lactate posited [423].

The first method of measuring anaerobic threshold is the modified V-Slope method which is based on a graph in which carbon dioxide excretion on the y-axis is plotted against oxygen uptake on the x-axis (Figure 6). This produces a straight line (S1) with a gradient of approximately unity as oxygen uptake and carbon dioxide excretion increase with exercise [424].

As exercise intensity increases and the blood lactate concentration begins to rise there is a increase in the steepness of the slope (S2) as an excess of carbon dioxide is produced by the action of the bicarbonate buffer system.

This inflection point identifies the anaerobic threshold. This line has a gradient of one when metabolism is aerobic and it increases as metabolism becomes anaerobic. The inflexion point of the line is taken to indicate the transition to anaerobic metabolism.

The changes seen in respiratory gas analysis are used to identify the point at which the lactic acid concentration in the blood begins to increase. During the initial aerobic part of the CPEX test, carbon dioxide production from working muscles increases linearly with oxygen consumption. Blood lactate levels do not change substantially during this period, since muscle lactic acid production does not exceed the body's capacity for removal [423].

The second method of measuring anaerobic threshold is identified during CPEX testing when there is an increase in carbon dioxide excretion relative to oxygen uptake. The increase in carbon dioxide production is due to the buffering of lactate by the bicarbonate buffer system, causing a rise in CO_2 carbon dioxide production.

AT can be identified as the VO_2 at which there is a systematic increase in the ventilatory equivalent for oxygen (VE/VO_2) (see below) without an increase in the ventilatory equivalent for carbon dioxide (VE/VCO_2) (see below). As with VO_2 peak, anaerobic threshold is reported in ml/kg/min of oxygen uptake.

Whilst the V-slope method is widely used, there is no clear advantage of one of the above methods over another [425].

The guideline of the American Thoracic Society and the American College of Chest Physicians is to use both the V-slope method and ventilatory equivalents method (dual criteria) [416].

5.2.11 Respiratory Function and Ventilatory Equivalents

Static lung function tests are performed at the outset of the test. These include forced expiratory volume at the first second (FEV1), forced vital capacity (FVC) and maximum voluntary ventilation (MVV).

The ventilatory equivalent for oxygen is the ratio of total expired volume to the volume of oxygen taken up at a given point in the test, VE/VO_2. The ventilatory equivalent for carbon dioxide is the ratio of expired volume to the volume of carbon dioxide excreted at a given time point, VE/VCO_2.

These numbers give an indication of the amount of ventilation that is required to take up oxygen and to eliminate carbon dioxide. That is to say they are measures of respiratory efficiency, with higher values indicating that more ventilation (a greater minute volume) is required for a given amount of oxygen uptake or carbon dioxide excretion. The normal pattern of change in VE/VO_2 is a decrease in early exercise to a nadir at or close to the anaerobic threshold and then an increase as maximum exercise capacity is approached.

The increase in ventilation that causes this increase in VE/VO_2 is caused by the increased carbon dioxide production due to the buffering of lactate. The ventilatory equivalent for carbon dioxide also decreases with the start of exercise. The upturn in the equivalent for carbon dioxide occurs after that for oxygen and reflects increasing hyperventilation with a reduction in $PaCO_2$ to compensate for metabolic acidosis [235].

5.2.12 ECG

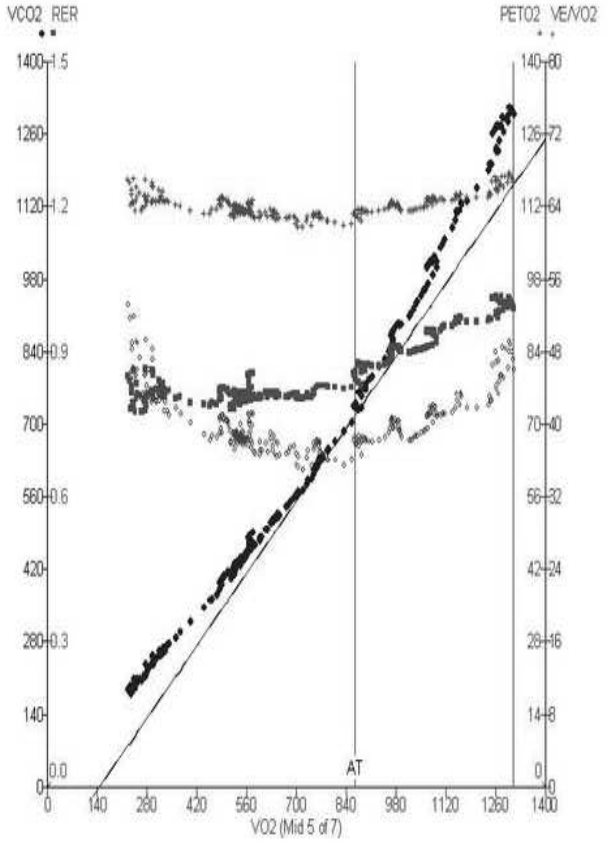
Baseline heart rate, peak heart rate and peak heart rate as a percentage of predicted are recorded. Evidence of myocardial ischemia and arrhythmia are reported.

5.2.13 Oxygen Pulse

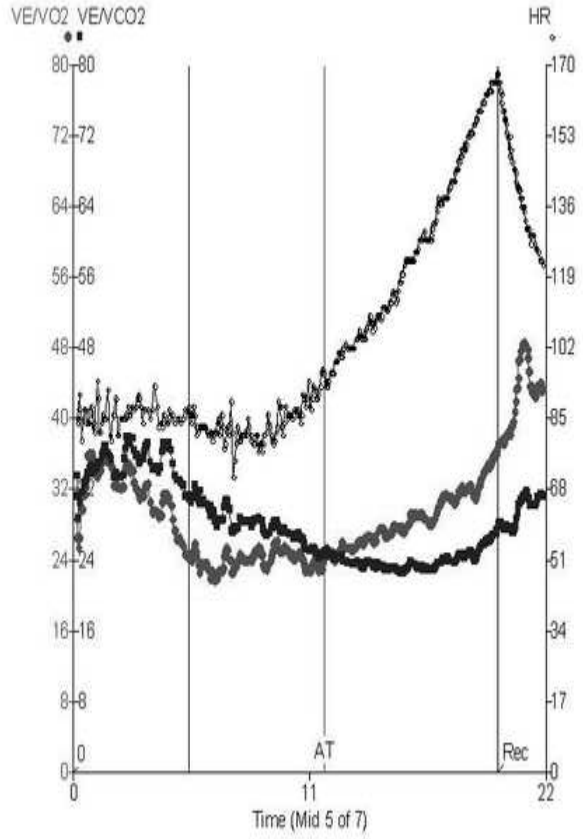
The ratio of heart rate to oxygen uptake (VO_2/HR) is termed the oxygen pulse and is a measure of oxygen extraction per heart beat. In healthy subjects oxygen uptake increases steadily with increasing work at lower exercise intensities. At higher intensities the rate of increase slows.

Failure of the oxygen pulse to increase can be an indicator of poor left ventricular function and is often viewed as an indicator of myocardial ischaemia. Values reported are: baseline, peak value and peak value as a percentage of predicted [235].

A number of CPEX variables were analysed in this chapter. However, our primary outcome measure were AT and VO_2max. AT has been measured in those patients as per the validated V-slope method [426-428].



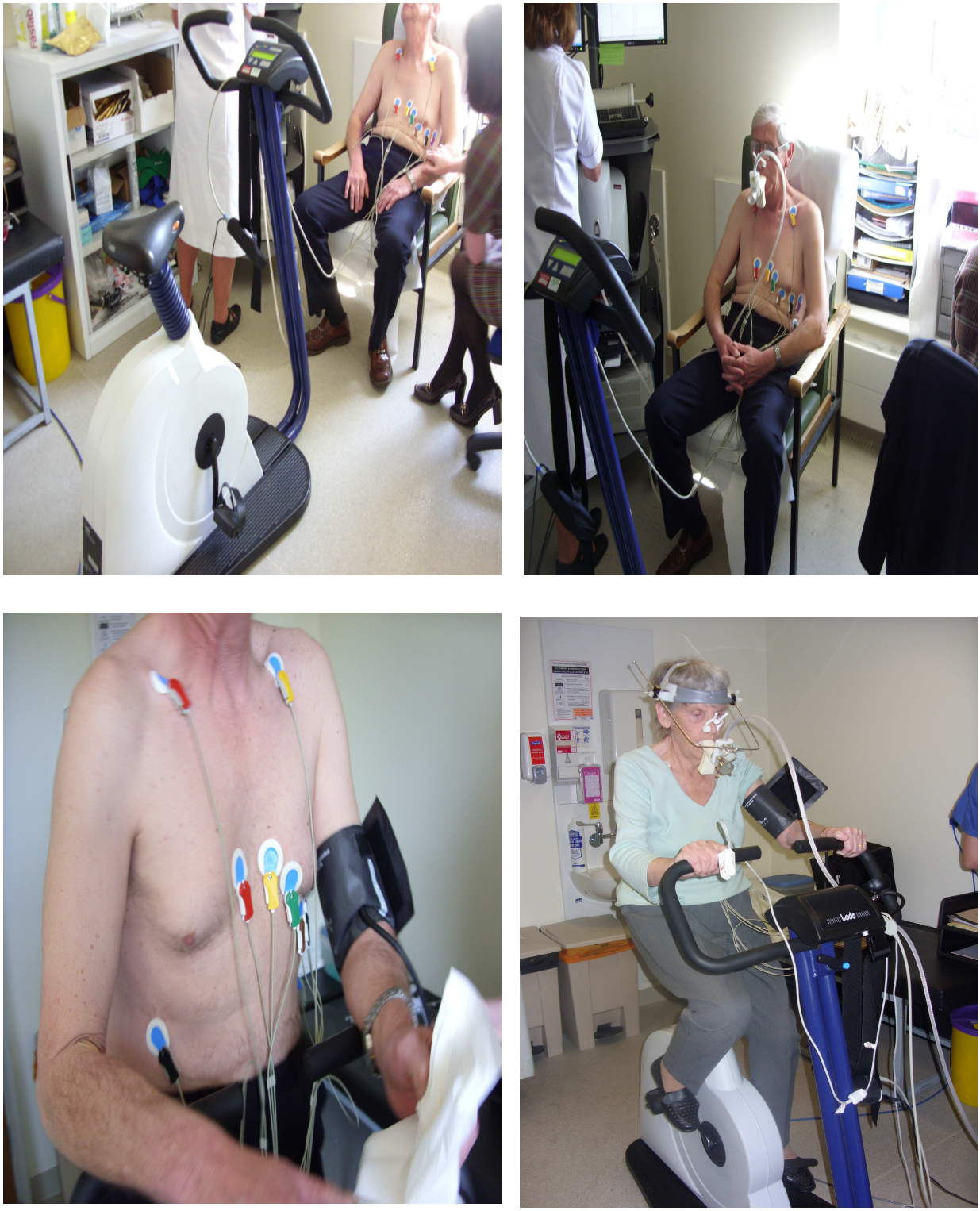
(Modified V-slope method)



(VEVO$_2$ and VEVCO$_2$ method)

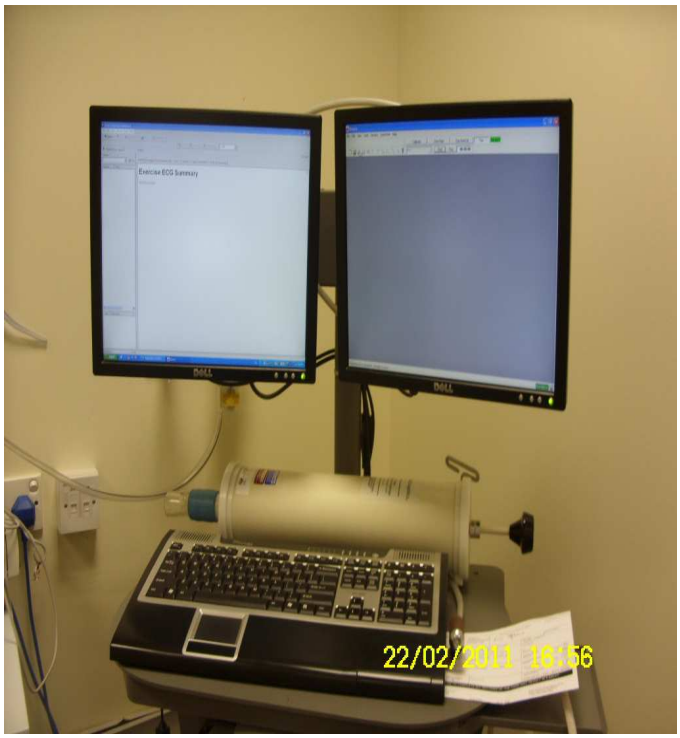
Figure (6) shows the two methods of measuring AT

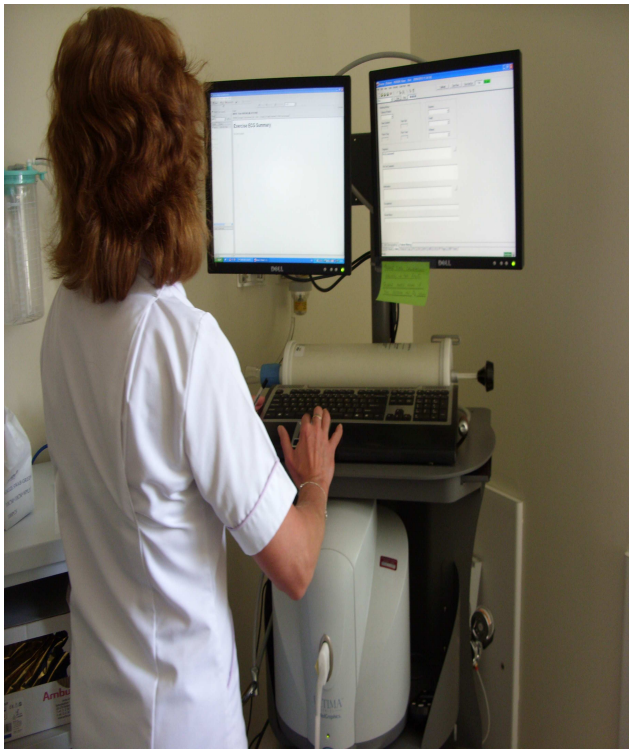
(Cardiopulmonary Exercise test, CPEX)

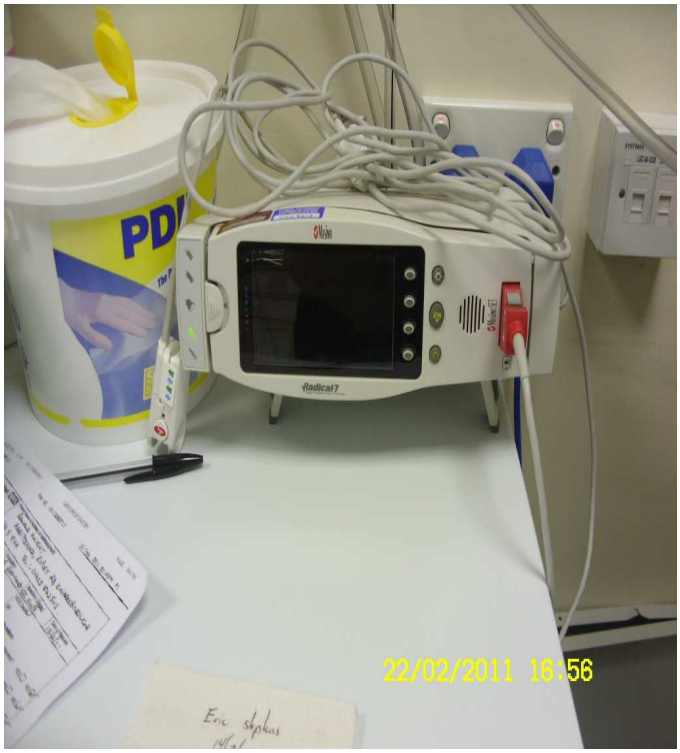


Figures (7) show the Cardiopulmonary Exercise test

(Cardiopulmonary Exercise test, CPEX)







Figures (8) show the Cardiopulmonary Exercise test

5.3 Body composition

Body composition status and changes have been assessed in this project via five methods. These changes are measured before the administration of APT and 14 days within the finish of treatment.

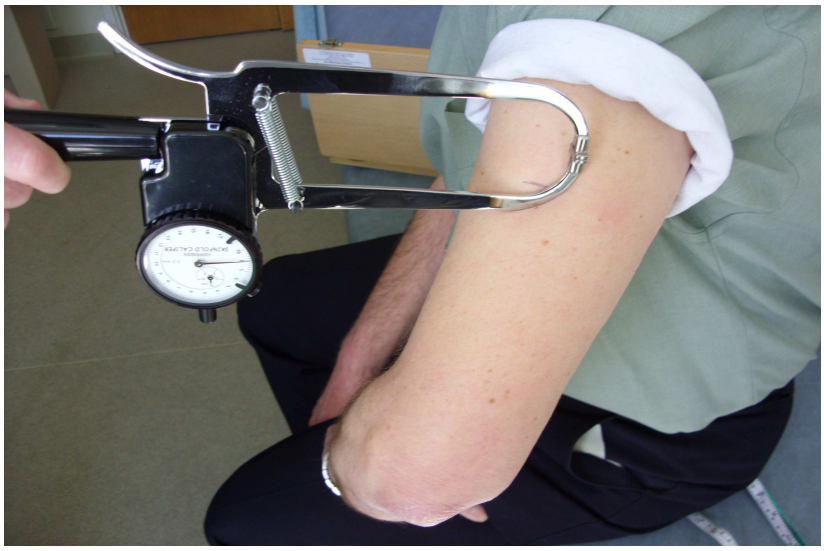
5.3.1 Anthropometric measurements: body weight (kg), height (m) and body mass index (BMI/kg.m^{-2}) using a clinical electrical scale, clinical tape measure and a standard BMI chart. These measurements were obtained prior to conducting the CPEX testing and bioimpedance analysis.

5.3.2 Mid-arm circumference (MAC): To obtain this dimension, the patient is asked to flex the elbow joint to 90 degree in a standing position. Thereafter, the distance between the olecranon process and the tip of the acromion process is measured on the non-dominant side and a mid-point is identified on the extensor surface of the arm (over the triceps muscle) to represent the level of the MAC. Using a tape measure, this arm level circumference is measured with a metric scale to the nearest 0.1 cm.

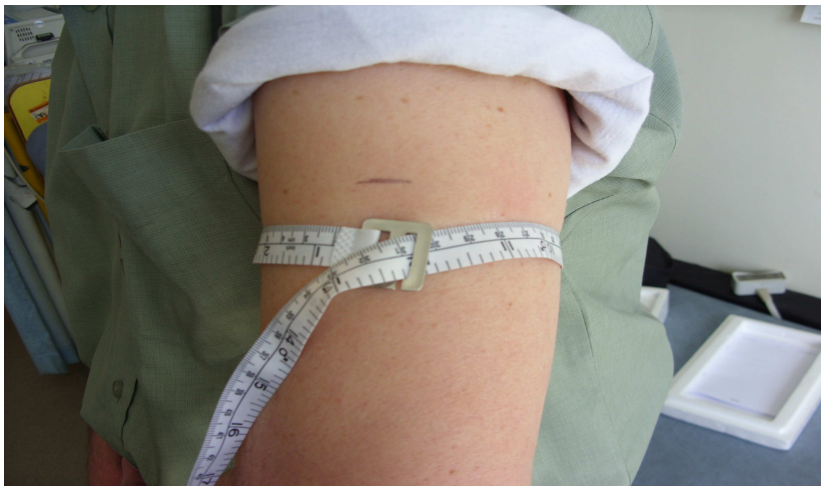
5.3.3 Triceps skin folds (TSF) using a (Holtain Ltd, Dyfed, UK) calliper pressure 10 g/mm2, precise to 0.2 mm. This is performed by grasping the skin and underlying tissue over the mid-arm point of the triceps muscle (the same method of MAC), shaking it to exclude any muscle and pinching it between the jaws of the calliper. Triple readings were obtained within 5 minutes to improve the accuracy and reproducibility of the measurements with an average final reading recorded.

5.3.4 Hand grip measurement (HG) using Takei Hand Grip Dynamometer/Digital A5402. This is used for measuring the flexion of the wrist and provides an accurate reading of grip strength. The Takei Dynamometer is also useful for estimating a general value for upper body strength. The dynamometer is a standard piece of equipment in most physiology testing labs and provides an easy and safe means of measuring muscular strength. It can be adjusted to fit a wide range of hand sizes and normative grip values are available from ages 10 to 70 years. Again, three different readings are obtained within 5 minutes and the mean is used as the final measurement.

(Anthropometric measurements)



Triceps skin-fold (TSF)



Mid-arm circumference (MAC)

Hand-grip measurements (GS)

Figures (9) show the Anthropometric measurements

5.3.5 Bioelectrical impedance Analysis (BIA) using a HYDRA ECF/ICF (Xitron, model 4200). This instrument uses a microprocessor, single conversion and digital signal processing technology to produce a flexible, accurate and reliable measurement of BIA. Although the HYDRA ECF/ICF can be used without the need for a computer, we have opted to use a controlling computer with the BIS4200 System Utilities Software for easy storage of electronic data and analysis. Hence, HYDRA acquisition.exe enables the device to be controlled by a host compatible PC. The BIA coefficients of variation (represented as percentage) on repeated measurements range between 1-5% [429, 430].

HYDRA mode should be set to single frequency measurement with selection of the ankle-wrist method. Also, FFM prediction should be turned on at the same time during the initial setting to get an immediate reading. Subsequently, data must be entered for each single individual including body weight, height and sex.

BIA is used to measure intracellular, extracellular and total body water. It is also possible to obtain other data from the BIA machine such as the fat mass (FM), fat free mass (FFM) or lean body mass, as well as the body resistance to the two fluid compartments [431]. BIA measurements usually take about 1 minute to complete and this conventional method has been successfully validated in the literature on a variety of subject populations [432-437]

The individual is placed in a supine position with legs and arms slightly abducted at 15 degree, on a flat non-metallic bed (the same bed used for measuring bone densitometry body scan) for about 10-15 minutes to get a static measurement of their body composition [438]. HYDRA machine, computer and cables are kept away from the patient to avoid any possible reading interference, as the patient remains motionless throughout the measurement.

The body surface between all contacts is cleaned with alcohol swab and connecting electrodes are attached to a non-hairy skin part of the body. The sticky connecting electrodes should have at least a $5cm^2$ of contact area to get an accurate measurement. The BIA measurements are performed using four electrodes attached via small “alligators” clips, enabling a connection to the body electrode. The Red-voltage detectors are placed proximally and the Black-current injectors are placed distally.

Two clips are attached at the wrist, the black clip is connected to the extensor surface of metacarpal-phalangeal joints and the red clip is attached to the extensor aspect of mid-line between the radial and ulnar heads on the right side. The other two wires are attached at the ankle, with the black clip attached to the dorsal aspect of the metatarsal-phalangeal joints and the red clip attached mid-way between the medial and lateral malleoli on the same side. Red and black electrodes should be at least 5cm away from each other to give the best results.

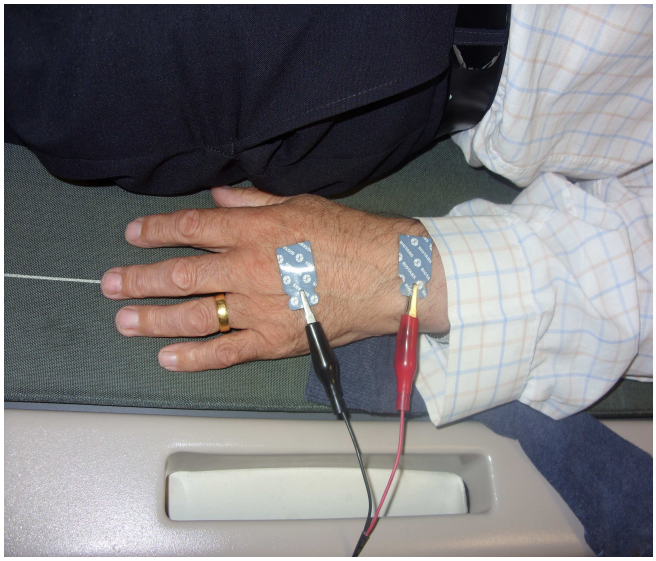
For the multi-frequency measurement (ranges from 5KHz to 1MHz, typically at 50 kHz), a weak alternating current is passed through the outer pair of electrodes, while the voltage drop across the body is measured using the inner pair of electrodes from which the body's impedance is calculated. To convert this information to a volume estimate, two basic assumptions are used. First, the body can be modelled as an isotropic cylindrical conductor with its length proportional to the subject's height (Ht). Second, the reactance (X) term contributing to the body's impedance (Z) is small, such that the resistance component (R) can be considered equivalent to body impedance [256].

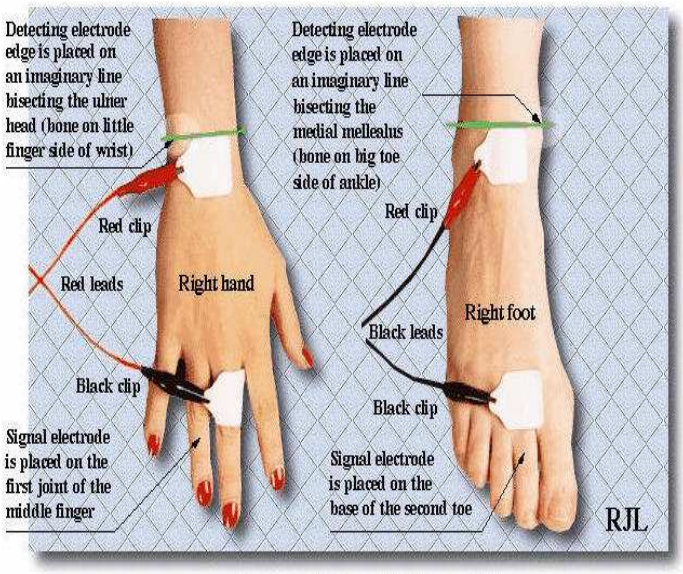
When these two assumptions are combined, it can be shown that the conducting volume is proportional to the term Ht2/R, called the impedance index. It should be noted, however, that the human body is not a cylindrical conductor, nor are its tissues electrically isotropic, and the reactance component of the body's impedance is non-zero [439]. At 50 kHz, the body's impedance has both resistive and reactive components. The reactive component is assumed to be related to the portion of the current that passes through cells, which act like capacitors that shift the voltage and current out of phase.

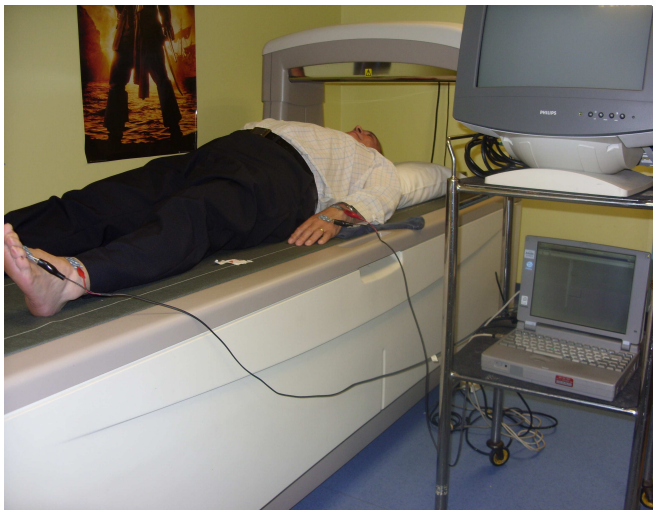
3 consecutive and repeated measurement were taken from each patient within a period of 30 minutes to eliminate any possible errors or variations as suggested by Kushner in 1996 [440]. ICW, ECW and TBW were measured in litres while the FFM was obtained in kilograms. Adhesive conducting electrodes were placed in the exact position pre and post APT administration to avoid any variation made by electrode misplacement [441].

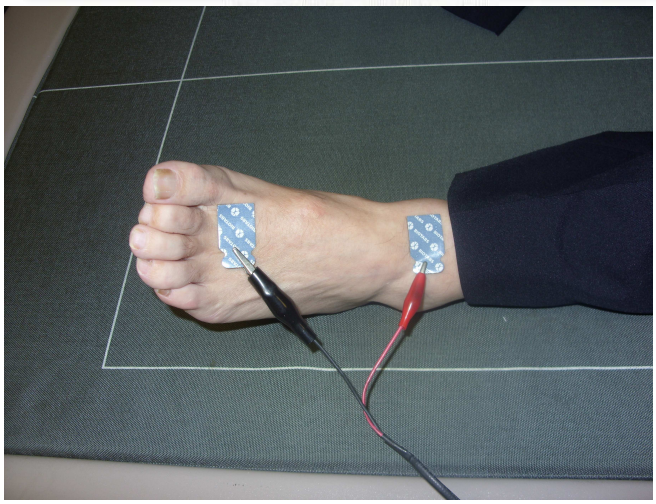
All measured data were saved electronically and on a hard copy after taking the mean of the ECW, ICW, TBW and FFM.

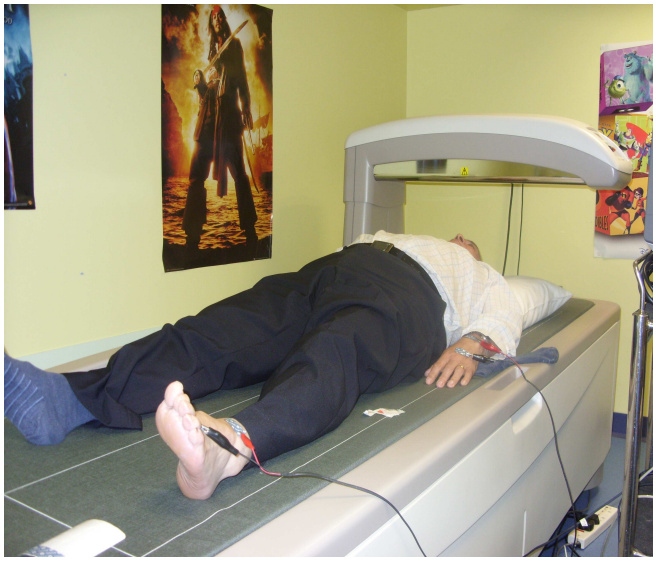
(Bio-electrical Impedance Analysis, BIA)











Figures (10) show the Bio-electrical Impedance Analysis

5.4 Cytokines, albumin and CRP

Changes in the patients inflammatory markers were measured via a plasma sample obtained before the administration of APT and 14 days within the finish of treatment.

5.4.1 Processing the sample

A total of 5mls of venous blood was taken from the patient. This blood sample was placed in a lithium-heparin tube and carried immediately to the laboratory after proper shaking. In the hospital laboratory, disposable pipettes were used to distribute the blood sample into 3 eppendorf tubes, each is 1.5ml size. Subsequently, these tubes were placed in an MSE MicroCentaur for about 8-9 minutes with a 12,000rpm speed to obtain the plasma samples. At the end of this centrifuge process, eppendorf tubes were removed from the rotor and placed on an eppendorf plastic holder for isolation of the plasma samples. Using another clean disposable plastic pipette, the top clear yellow plasma sample was aspirated from the 1st eppendorf and placed into a fresh and newly labelled eppendorf (1st plasma sample).

The same process was repeated for the other two centrifuged samples to get a total of 3 clear plasma samples in new eppendorf tubes. These were labelled with patient initials, patient's date of birth and the date of the procedure, with number 1 for a sample pre-APT administration and number 2 for a post-APT sample. During the aspiration of the top clear yellow layer of plasma from the eppendorf using the pipette, extra caution was directed towards avoidance of contamination of the plasma sample with the buffy coat layer (white cells) or the dark red sediment layer (red cells). If this happened, then this disturbed eppendorf was centrifuged again using the same process mentioned before.

5.4.2 Storage of the sample

Finally, the 3 eppendorf tubes containing the plasma samples were stored in a -80 degree freezer within the same lab. The location of the samples was recorded electronically on a spreadsheet, as well as on a hard copy samples map. Hence, each patient had 3 plasma samples pre-APT and 3 samples post-APT.

We had a total of 32 patients who had completed their pre and post APT blood samples.

This means that 96 pre-APT samples and another 96 post-APT plasma samples were obtained and stored in a confidential -80 degree freezer (3 eppendorf tunes for each patient per single test). The plan was to use the 1st plasma sample for cytokines analysis, 2nd sample for CRP and albumin assay and the 3rd final plasma sample to be stored in the University of Leeds laboratory for future use and reference.

About 18 months after finishing of the trial, 4 eppendorf tubes per patient (2 pre and 2 post APT) were taken from the storage freezer making up a total of 128 plasma samples used for the assay of cytokines, CRP and albumin.

Each cytokine was assayed by multiplex immunoassay on a Luminex 96 cytometer in duplicate. A range of pro-inflammatory markers (TNFα, IP-10, RANTES, IL-6, IL-18) and anti-inflammatory markers (IL-1β, IL-1ra, IL-10, MIF) as well as plasma CRP and albumin were measured in pg/m (picogram/microlitre).

5.4.3 Cytokines Assay Principle

The usual methods of cytokine estimation are either by bioassay or ELISA. These methods are limited to analysis of a single cytokine at a time and are therefore time consuming and require a large sample volume. The Luminex fluid-phase sandwich immunoassay, based on flow cytometry, has been used to quantify multiple cytokines at the same time from a single plasma sample. The Luminex principle utilises up to a hundred colours of coated polystyrene beads each having a distinct spectral address. Antibodies couple with the coloured bead and react with specific cytokines. A secondary biotinylated antibody, specific for another epitope of the cytokine, is added to the mixture to create an antibody sandwich. This secondary antibody is targeted in the final step of the process, which is the addition of Streptavidin-phycoerythrin. The microbeads are aligned in a single file by the cytometer where they are exposed to a twin LASER system in the flow cell. This uses emission spectra to quantitate the amount of antigen bound to each antigen specific bead. The values are compared on a standard curve thereby allowing a conversion of mean fluorescence to concentrations in picograms per microlitre.

Figures (11) show the LUMINEX machine for the Cytokines analysis

Preparation of the sample

1. Preparation of plasma sample

Plasma samples previously stored at -80℃ were thaw ed at room temperature and diluted with equal quantities of plasma diluent. Plasma diluent is required to compensate for the large amounts of non-cytokine protein in the sample. Each eppendorf was de-iced using a Spinmix for about 40 seconds, this method is called Vortex. Microfuse tubes were then centrifuged again for about 4-5 minutes to remove any white coat that is normally precipitated at the base and contains unwanted cell debris, as this might clog the well and alter the cytokines analysis.

2. Preparation of cytokine standard (master stock)

The stock vial of the cytokine standard was reconstituted with 500µl of standard diluents, vortexed for 1-3 seconds and incubated on ice for 30minutes.

3. Preparation of serial dilution of cytokine standard

7 x 1.5ml eppendorf tubes were labelled and 150µl of standard diluent added to each. In the 8th tube, 187.2µl of standard diluent was pipetted. 12.8µl of the master stock was added to tube 8 and the tube was vortexed. This was used for serial dilution with 50µl of the solution being added to tube 7. Following vortexing of tube 7, 50µl of the mixture was added to tube 6, which was then vortexed. 50µl from tube 6 was pipetted to tube 5 and 50µl was subsequently transferred from each successive tube to the next with the last tube being tube 2 which had a serial 4-fold dilution. Tube 1 contained only standard diluent and acted as a reference zero standard.

4. Preparation of anti-cytokine conjugated beads

240µl of stock beads from a 25 x bead stock was prepared by diluting with 5,760µl of Bio-PlexTM assay Buffer, making up a total volume of 6,000ul. Following vortexing for 30 seconds, 50ul of bead mixture containing 2ul of beads was pipetted into each well.

5. Preparation of antibody detection solution

The 10 x stock detection antibody vial was centrifuged for 30 seconds. It was diluted to a 1 x concentration by adding 2,700ul of detection antibody diluent to 300ul of 10 x stock detection antibody. This remained stable for 4 hours at room temperature stored in the dark.

6. Preparation of Streptavidin-phycoerythrin

The Streptavidin–PE 100 x stock vial was centrifuged for 30 seconds and 60µl of the stock was then diluted to a 1 x solution by adding 5,940µl of Bio-PlexTM assay buffer to make a final volume of 6,000µl.

Procedure

1. The 96 well plate was wetted with Bio-PlexTM assay buffer (100µl per well). Samples were analysed within 30 minutes from being out of the ice.

2. The buffer was removed by vacuum filtration by placing the filter plate on a calibrated filter plate vacuum manifold.

3. The filter plate was blotted with a lint-free paper towel.

4. The multiplex bead solution was vortexed for 15-20 seconds and 50µl of solution pipette into each well.

5. The solution was removed using vacuum filtration.

6. The plate was washed twice using Bio-PlexTM wash buffer (100µl per well), which was removed with vacuum filtration.

7. 50µl of standard serial dilution and samples were pipetted into separate wells.

8. The plate was covered with sealing tape and with aluminium foil to prevent exposure to light and photobleaching of the beads. The plate was placed on a shaker; the shaker speed was slowly increased to 1,100rpm for 30seconds then reduced to 300rpm and incubated at room temperature for 30 minutes.

9. The solutions were removed using vacuum filtration.

10. The plate was washed twice using Bio-PlexTM wash buffer as in step 6 and stored in the dark.

11. The antibody detection solution, prepared 10 minutes prior to usage, was vortexed and 25µl pipetted into each well.

12. The plate was covered as in step 8.

13. The solution was removed using vacuum filtration.

14. The plate was washed thrice using Bio-PlexTM wash buffer as in step 6 and stored in the dark.

15. 50µl of vortexed streptavidin-PE solution was added to each well.

16. The plate was covered with sealing tape and aluminium foil, placed on a shaker and shaken at 1,100rpm for 30 seconds and then reduced to 300rpm for 10 minutes at room temperature.

17. The solution was removed using vacuum filtration.

18. The plate was washed thrice using Bio-PlexTM wash buffer as in step 6 and stored in the dark. The plate was blotted with a lint-free towel.

19. 125µl of Bio-PlexTM assay buffer was pipetted into each well.

20. The plate was sealed, placed on a shaker and shaken at 1,100rpm for 30 seconds at room temperature.

21. The sealing tape was removed and the plate immediately read on the Bio-PlexTM system consisting of Luminex-100 cytometer and Bio-Plex Manager software (version 4.1). The coefficient of variation for the Luminex-100 cytometry is not more than 10% [442-444].

5.4.4 Latex Immunoassay for the determination of the C-reactive protein (CRP) concentration in the serum and plasma

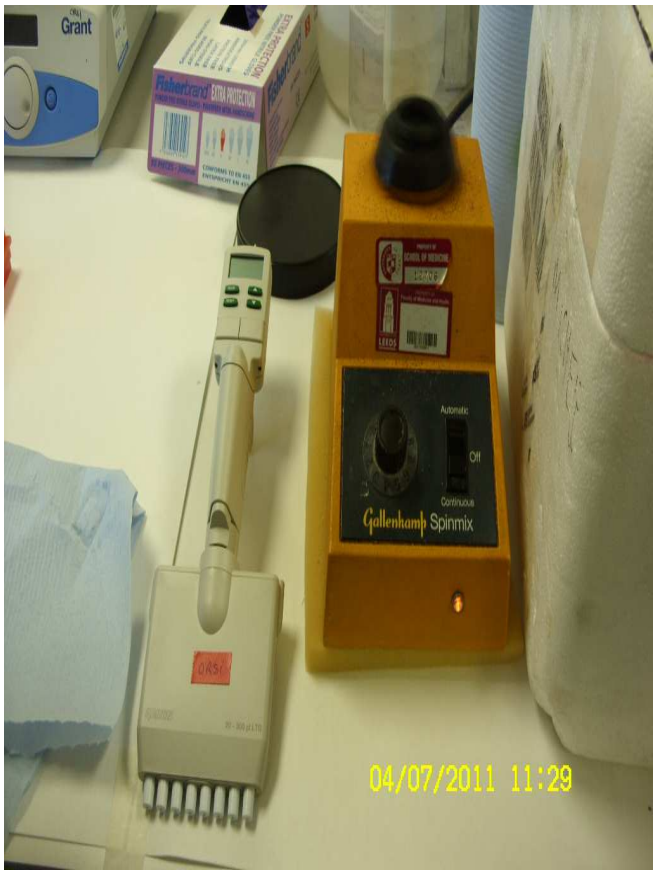
CRP is an acute phase protein whose concentration is to increase as a result of any inflammatory process. This is used as a marker or general diagnostic indicator to detect infections and non-specific inflammation, in addition to serving as a monitor of patient response to pharmacological therapy and/or surgery [445]. CRP is usually measured via *CRP Ultra*, which is a latex immunoassay developed to accurately and reproducibly quantifies CRP levels in serum. When an antigen-antibody reaction occurs between CRP in a sample and anti-CRP antibody, which has been absorbed to latex particles, agglutination results. This agglutination is detected as an absorbance change, with the change in agglutination being proportional to the quantity of CRP in the sample. The Reagents components of the kit, stored in 2-8C in unopened vials, are stable up to the expiry date indicated on the package. These ready-made reagents are:

Reagent 1: Glycine buffer pH 7.0, sodium azide < 0.1%.

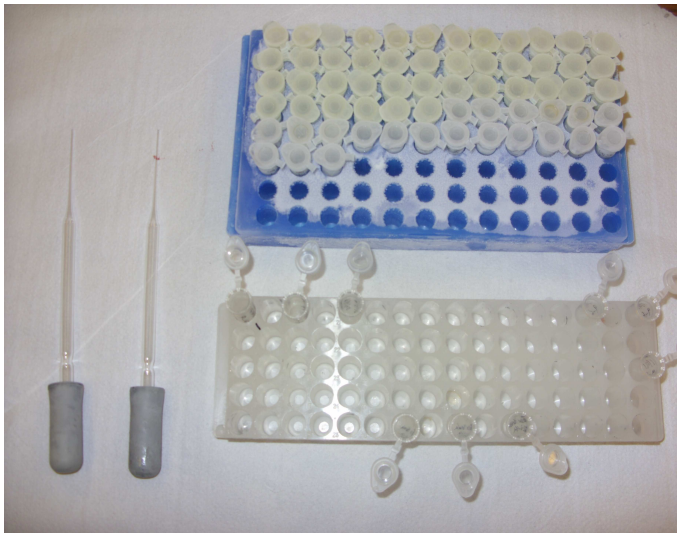
Reagent 2: Anti-CRP polyclonal antibodies absorbed on latex particles in a 0.2% suspension, sodium azide < 0.1%.

Calibration has to be made using either the standard or the ultrasensitive method as per the instruction contained in the kit [446]. Serum, plasma samples (heparin, EDTA) are collected in accordance with the NCCLS procedure [447]. All reagents must reach the working temperature before being used. A proportional variation of the indicated reaction volumes does not change the results.

CRP levels are calculated by plotting a calibration curve on a graph paper by tracing absorbance (y axis) according to corresponding mg/dL concentration (x axis) for each calibration. Then, absorbance values obtained from Samples and Controls are indicated on the calibration curve, which will eventually extrapolated to get the mg/dL value. The conversion factor is CRP (mg/dL) X 10 = CRP (mg/L) with a reference adult value of < 0.5 mg/dL [448].



Figures (12) show the CRP analysis machine and the Lab at the LIMM building
(Leeds Institute of molecular Medicine)



Figures (13) show the centrifuge machines at the LIMM building

(Leeds Institute of molecular Medicine)

5.5 Health Related Quality of Life (HRQL)

HRQL were assessed using 2 validated questionnaires, the European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30) and the Patient Generated Subjective Global Assessment (PG-SGA). After obtaining all of the necessary approvals for using these questionnaires in our research, each patient was given a copy of both assessment tools during the first visit and another copy in the second visit. Before taking the individual to the CPEX or the BIA lab, each patient was given around 15 minutes to complete both questionnaires in a relaxed environment within a private room. This process is done before the APT administration and repeated within 14 days after the finish of the anticancer therapy.

Both assessments tools were used to measure the following variables:

a) Changes in the overall quality of life and psychosocial well-being
b) Physical, emotional, cognitive and social functioning as well financial scales.
c) Symptoms related to weight change (anorexia, nausea, constipation, mucositis, vomiting, diarrhoea, xerostomia, pain), alterations in food intake compared with the usual intake, and functional capacity.
d) Changes in the daily physical activities and function. This included type, duration, and frequency of activities performed such as fast walking, moderate/slow walking, jogging, aerobics, tennis, household cleaning, and yard work.

5.5.1 Patient Generated Subjective Global Assessment (PG-SGA)

Over the last three decades, the oncology nutritional screenings have evolved dramatically to use information in improving the outcome.

The evolution began in the 1980s when Detsky and Baker first showed that the results of clinical assessment of nutritional status correlated with results of assessments using laboratory tests and anthropometric measures. The major factor clinicians use to determine overall nutritional status is loss of subcutaneous tissue, muscle, and weight [449, 450].

Several methods of detecting nutritional deficit have been used in the past including anthropometrics measurements, laboratory tests and various nutritional indices [451].

Patient Generated Subjective Global Assessment (PG-SGA) was developed by Faith Ottery, the University of Toronto in 1987 [452]. This is a reliable assessment tool which is easy to use, cost-effective, reproducible in several clinical settings and able to predict those patients who need nutritional intervention [452].

The PG-SGA is may be used to achieve a restoration of nutrient intake to optimal levels to meet requirements in order to reduce the risk of complication associated with malnutrition

The first four sections of the PG-SGA are completed by the patient, with the remaining portions of the PG-SGA completed by the clinician (physician, nurse, or dietician). Each patient is classified as well-nourished (SGA A), moderately or suspected of being malnourished (SGA B) or severely malnourished (SGA C).

The total PG-SGA score was calculated and all data were represented on an excel spreadsheets for easy analysis and assessment (full details of PG-SGA scoring system can be seen in the appendix section.

Global Assessment of Nutritional Status

Stage A—Well nourished

- No weight loss or recent nonfluid weight gain.
- No deficit in nutrient intake or has had recent improvement.
- Symptoms have had no nutritional impact or there has been a significant recent improvement allowing adequate intake.
- No deficit in functioning or functioning has shown significant recent improvement.
- No deficit on physical examination or the chronic deficits have shown recent clinical improvement.

Stage B—Moderately well nourished or suspected malnutrition

- 5% weight loss within 1 month or 10% in 6 months and continued weight loss with no stabilization or gain.
- Definite decrease in intake.
- Presence of nutrition impact symptoms.
- Moderate functional deficit or recent deterioration.
- Evidence of mild to moderate loss of subcutaneous fat and/or muscle mass and/or muscle tone on palpation.

Stage C—Severely malnourished

- Greater than 5% weight loss in 1 month or greater than 10% loss in 6 months with no stabilization or gain.
- A severe deficit in intake and the presence of nutrition impact symptoms.
- A severe functional deficit or recent significant deterioration.
- Obvious signs of malnutrition such as a severe loss of subcutaneous tissue and possible edema.

Figure (14) shows the PG-SGA final stages after scoring

5.5.2 European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30)

The European Organisation for Research and Treatment of Cancer (EORTC) was founded in 1962, as an international non-profit organisation. The aims of the EORTC are to conduct, develop, co-ordinate and stimulate cancer research in Europe by multidisciplinary groups of oncologists and basic scientists. Research is accomplished mainly through the execution of large, prospective, randomised, multi-centre, cancer clinical trials.

The EORTC Central Office Data Centre, created in 1974, is concerned with all aspects of phase II and phase III cancer clinical trials, from their design to the publication of the final results. Since its inception, over 80,000 patients have been entered in trials handled by the EORTC Data Centre [453].

In 1980, the EORTC created the Quality of Life Group, which in 1986 initiated a research programme to develop an integrated, modular approach for evaluating the HRQL of patients participating in cancer clinical trials. This led to the development of the EORTC QLQ-C30, a quality of life instrument for cancer patients. To date, more than 2200 studies using the QLQ-C30 have been registered.

This European questionnaire (QLQ- C30) was released in 1993 as a validated tool to assess the health-related quality of life (HRQL) for patients with cancer. The QLQ-C30 is a "core questionnaire" which incorporates a range of physical, emotional and social health issues relevant to a broad spectrum of patients with cancer; the core questionnaire should be used, unmodified, in all QLQ assessments [454, 455].

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / HRQL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level

Thus a high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status / HRQL represents a high HRQL, but a high score for a symptom scale / item represents a high level of symptomatology / problems.

The principle for scoring these scales is the same in all cases:

1. Estimating the average of the items that contribute to the scale; this is the raw score.

2. Using a linear transformation to standardise the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms [453, 456].

Data were saved and represented on an excel spread-sheet for easy analysis and assessment of answers (full details of QLQ- C30 scoring system can be seen in appendix 2 and 3).

5.6 Patients characteristics:

Several patients characteristics were collected on this cohort of patients. These were: age, type of APT with dose and duration as well as time interval between APT and surgery.

5.7 Inclusion criteria

A. Adenocarcinoma of rectum.
B. Patients who received adjuvant preoperative therapy (APT).
C. Patients who are fit to go on the CPEX test.
D. Patients who agreed to enroll in this pilot study.

5.8 Exclusion criteria

A. Patients who are unable or decline to give consent.
B. Patients with known malabsorption syndrome.
C. Patients with renal failure.
D. Patients who are not fit enough to go on the CPEX machine.
E. Patients with colonic cancers.

5.9 Power calculation and Statistics

The primary outcome of the study was to identify the impact of APT on VO_2max measured by CPEX testing. The number of patients required for this was estimated based on previous findings, that suggested that a difference in VO_2max of approximately 1.5mls/kg/min might be considered as clinically significant. .Assuming the difference of at least 1.5mls/kg/min [457] between the two groups (pre APT and post APT) in this study, it was calculated that 32 patients would have 80 per cent power to detect a significant difference between the two groups at a 0.05 alpha level.

Test Normality was assessed with a Kolmogorov-Smirnova and Shapiro-Wilk tests. The result was in favour of using parametric test to analyse the study outcome measures. However, its has been recommended by expert statisticians in Leeds and Cardiff to use non-parametric tests to analyse the study data to avoid any statistical errors and to be on the safe side due to the small sample size for the whole group and the subgroups. Therefore, non-parametric tests were used to compare paired related samples (Wilcoxon Rank Sum Test). Results and data are represented in Median and Interquartile range pre and post therapy exposure. HRQL data was analysed with repeated measures analysis. A p-value < 0.05 was considered statistically significant. PASW Statistics 18 software was used, release 18.0.0 (UK, July 30, 2009), using WinWrap basic.

5.10 Consent

The right of the patient to refuse consent without giving reasons was respected. Furthermore, patients were able to withdraw from the study at any time without giving reasons and without prejudicing any further treatment. A copy of the consent was given to the patient and one filed in the study master file. The written consent was taken by a clinician, who has signed and dated the staff authorization / delegation log. The process of obtaining written consent was clearly documented in the patient's medical notes.

5.11 Ethical considerations

The trial was performed in accordance with the recommendations guiding ethical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 48th General Assembly, Somerset West Republic of South Africa, October 1996. Informed written consent was obtained from the patients prior to registration into the study.

The study was submitted to and approved by a main Research Ethics Committee (REC) with reference number of 09/H1306/79 prior to entering patients into the study. In addition, The Leeds Teaching Hospitals have sponsored the project via the Research and Development department (R&D) with reference number of GS09/9007.

5.12 Trial schedule

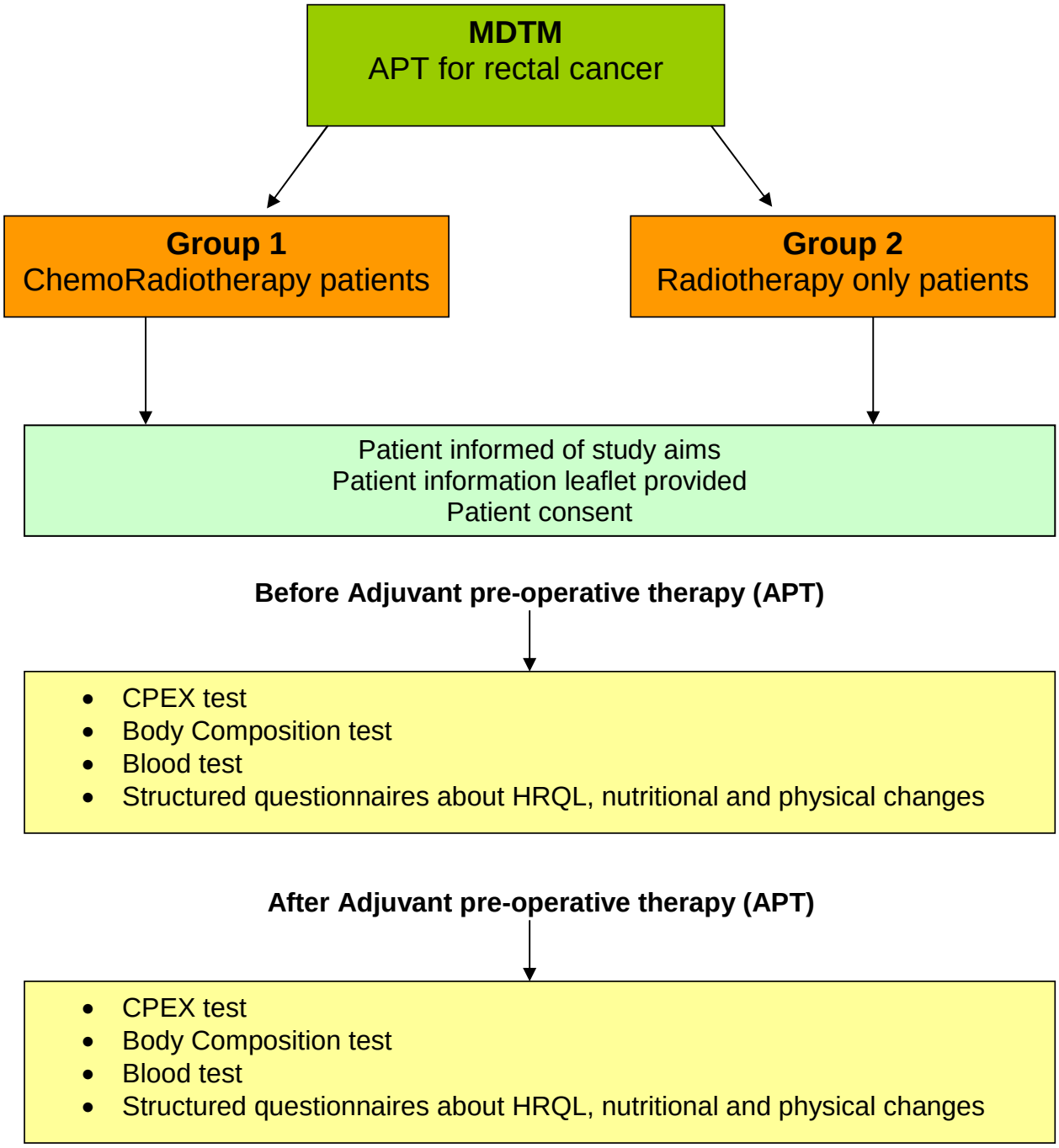


Diagram (1) shows the study design and schedule

5.13 Storage of venous blood sample

Samples were stored in coded format within a locked location for use in future research projects. Storage by research team will be pending for ethical approval to use in another project. The researcher's institution (Leeds General Infirmary) holds a storage licence from the Human Tissue Authority.

5.14 Statement of Indemnity

Clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements. As sponsor, the Trust does not provide indemnification against claims arising from non-negligent harm.

5.15 Publication Policy

Results from the study will be submitted for publication to appropriate peer review journals specific to the area of research. It is intended that the publications will be produced soon after completion of the period of research in September 2014. The sponsor will be informed of acceptance of any and all publications.

5.16 Methods of dissemination

Data will be presented to a local audience. These will include members of the colorectal cancer MDT, together with anesthetists and appropriate nursing staff. It is hoped that sufficient data will be collected for presentation at national / international surgical, oncological and anaesthetic meetings, prior to publication in peer reviewed journals.

6.0 RESULTS

From January 2010 until January 2011, 38 patients were approached for this pragmatic pilot study. One patient had clearly declined an anticipation due to the disease-related overwhelming stress and another patient was excluded due to the presence of a unilateral below knee amputation.

Hence, 36 patients were successfully enrolled in this study and all of them have completed their pre and post-therapy tests. However, 4 patients were excluded from the cytokines assay due to the presence of post APT haemolysed plasma samples despite a repeated centrifuge trials. Hence, we had only 32 pre APT and 32 post APT samples (2 patients from group one and 2 patients from group 2). See diagram 2.

Patients were divided into two groups based on the type of the APT regiment received, combined chemoradiotherapy (24 patients) and radiotherapy only (12 patients) groups.

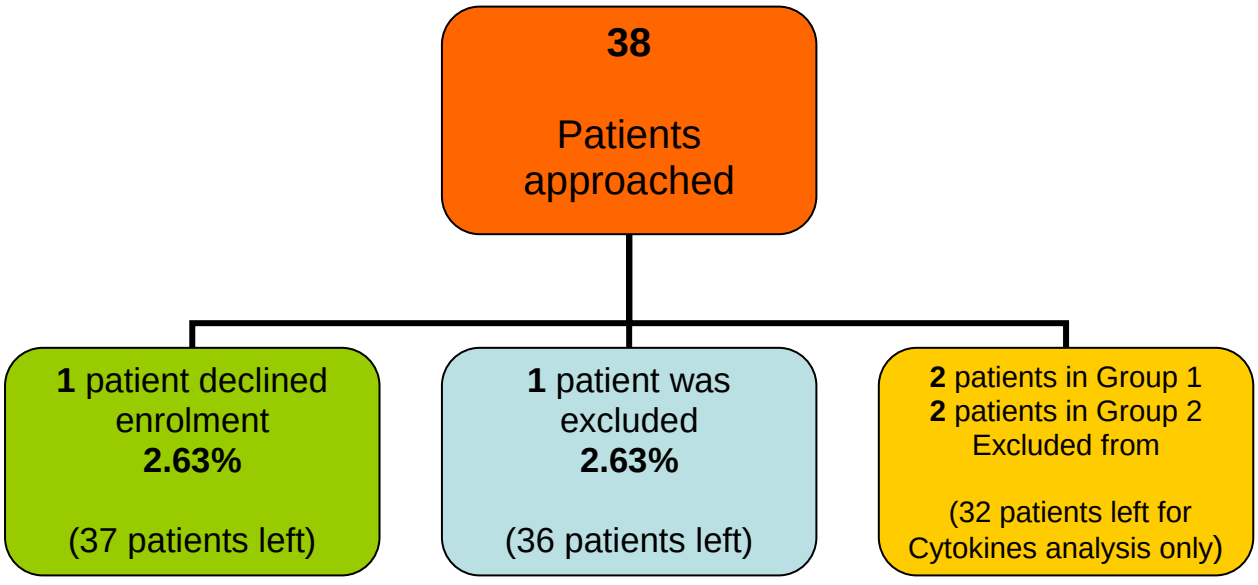


Diagram (2) showing patients demographics and recruitment process

6.1 ChemoRadiotherapy group:

6.1.1 Demographics

This group had 24 patients who had combined chemoradiotherapy. Out of these 24 patients, 11 of them had intravenous chemotherapy and pelvic radiotherapy and the rest of the 13 patients had oral chemotherapy and pelvic radiotherapy.

Chemoradiotherapy group mean age was 59.4 years, SD 13.7 (23.00-80.00) and the length of adjuvant pre-operative treatment (APT), in days, had a mean of 46 days, SD 18.6 (25.00-92.00). The length of time, in days, between finish of the APT and the day of surgery had a mean of 36.6 days, SD 13 (14.00-56.00). This group had 18 males and 6 females.

Variables	**ChemoRadio (n=24)**			
	Mean	**SD**	**Min**	**Max**
Age (Pre-APT)	59.4	13.7	23.00	80.00
Length of APT (days)	46.0	18.5	25.00	92.00
APT to Surgery window (days)	36.5	12.9	14.00	56.00
Gender	Male= 18			Female= 6

Table (3) shows descriptive figures for age, length of APT, window to surgery and gender for the chemoradiotherapy group

6.1.2 CPEX

Different variable were measured during CPEX testing before and after APT treatment to best reflect the functional capacity in patients with rectal cancer. Out of many CPEX variables obtained from the test, only few parameters were compared before and after APT administration due to their relevance in clinical practice and our study hypothesis.

These are: Work load (Watts) at the maximum oxygen consumption, oxygen consumption (ml/kg/min) at anarobic threshold and at peak (or maximum), the ventilatory equivalent ratio for carbon dioxide at anaerobic threshold in addition to the maximum pulse oxygen consumption.

Below is an example of the CPEX test result showing different variables measured during the examination period of a patient.

Diagnosis: Pre Op assessment 20 WATT Ramp

Comments:

Pre Test Comments:

Post Test Comments: Some ST depression in lead V2 approaching VO2 peak-resolved on stopping exercise.

Spirometry

	FEV1	FVC	FEV1/FVC	MVV
Predicted	3.09	3.96	75	129
Pre	3.77	5.41	70	132
% Predicted	122	137	93	103

Exercise

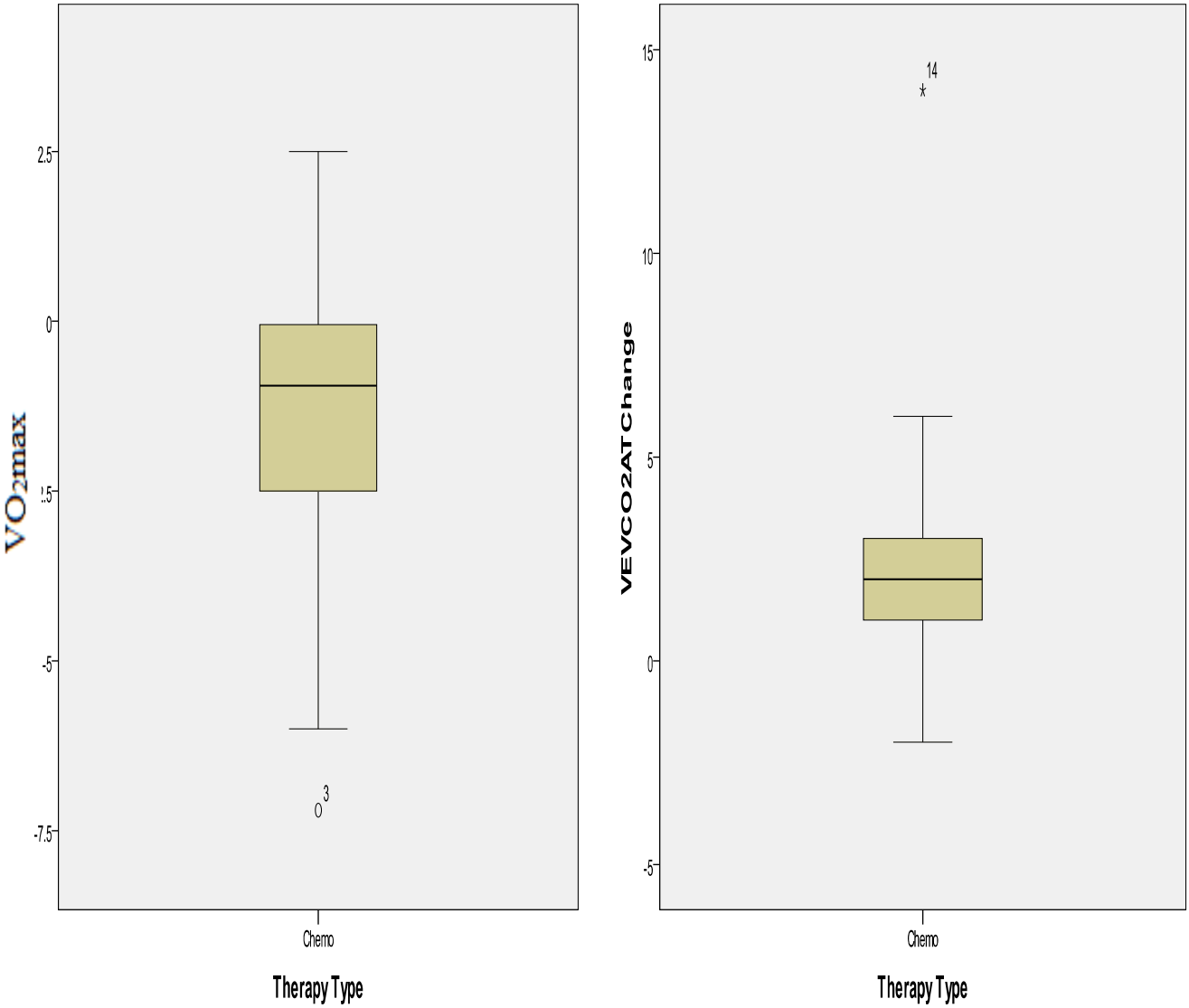
	Pred	Rest	AT	AT / Pred (%)	V02 Max	VO2 Max/Pred (%)
Time (min)		1:56	9:08		11:03	
Ex Time (min)			7:08		9:03	
---- WORK ----						
Work (Watts)	188	0	84	45	122	65
---- VENTILATION ----						
VO2 (L/min)	2.52	0.35	1.04	41	1.46	58
VO2 (mL/kg/min)	31.5	4.4	13.0	41	18.2	58
VCO2 (L/min)	3.04	0.25	0.94	31	1.58	52
PETCO2 (mmHg)		31	35		34	
PETO2 (mmHg)		104	107		113	
VE BTPS (L/min)	132.0	10.8	31.8	24	53.0	40
RR (br/min)		14	18		21	
BR (L/Min)		121.5	100.4		79.3	
RER		0.71	0.91		1.08	
---- CARDIAC ----						
HR (BPM)	156	84	109	70	130	83
VO2/HR (mL/beat)	16	4	10	59	11	70
SaO2 (%)		99	99		99	
---- V/Q ----						
VE/VCO2	30	44	34	111	34	110
VE/VO2	37	31	31	83	36	99
----------						
sysBP (mmHg)			130		130	
diaBP (mmHg)			78		78	

Table (4) shows a full summary output from CPEX test from which only few variables were selected for their hypothesis and clinical relevance. These are Work (Watts) at VO_2max, VO_2 (ml/kg/min) at AT and VO_2max, VO_2/HR (ml/beat) at VO_2 as well as VE/VCO_2 at AT

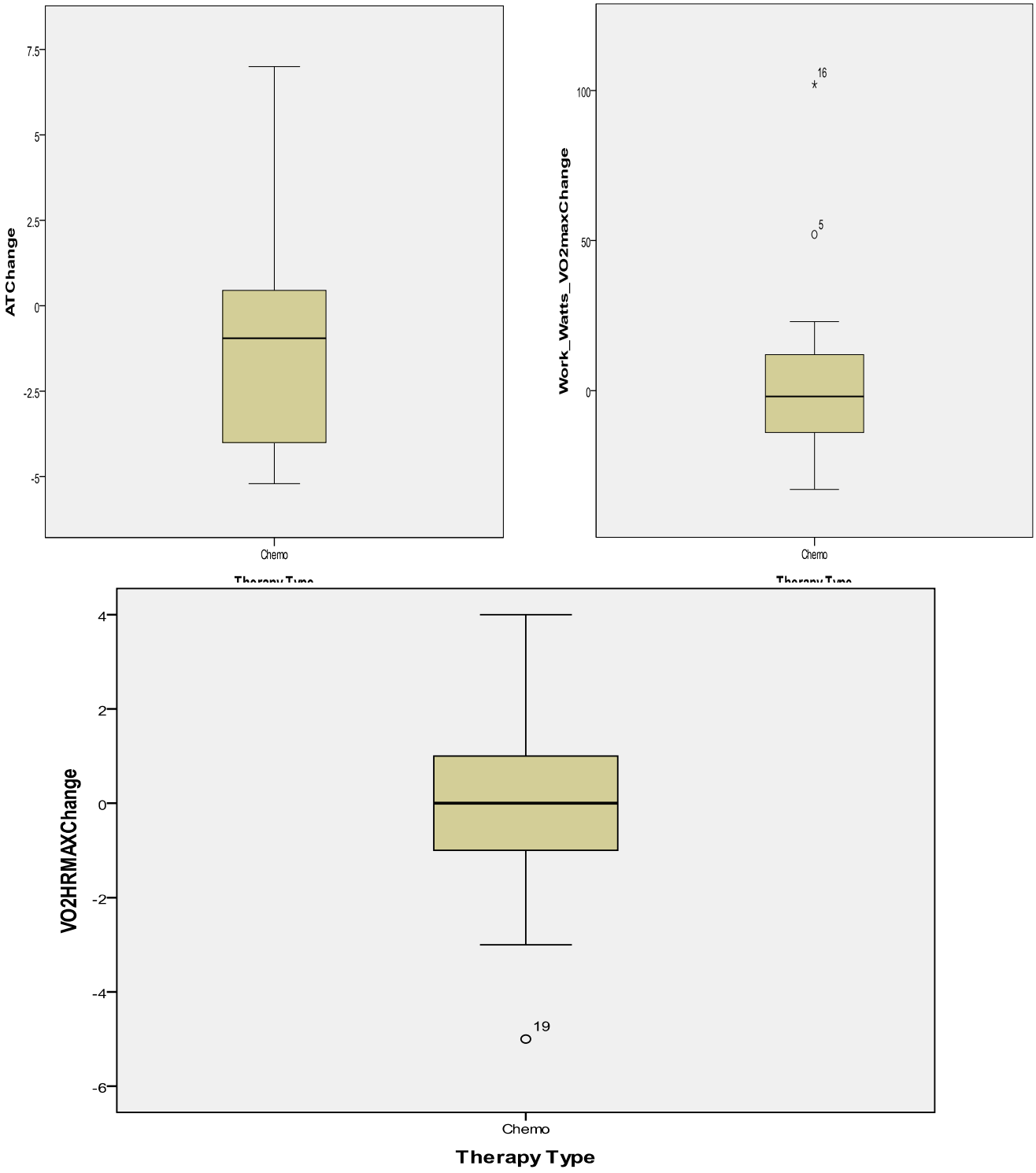
There was a significant decline in the VO_2max after APT exposure with a p-value of 0.005. In addition, there was a significant increase in the $VEVCO_2$AT with a p-value of 0.001, which clinically represent more pulmonary dead space, and/or reduction in the cardiac reserve (cardiac failure). VO_2AT dropped in most of the patients but this difference in median values did not reach significance.

Variable	**Pre APT** Median, (iqr), range	**Post APT** Median, (iqr), range	**z-value**	**p-value**
Work VO_2max	68.5, (46.0), 91.0	61.0, (41.0), 120.0	-1.308	0.191
VO_2AT	13.45, (3.65), 11.2	12.3, (3.5), 19.6	-1.843	0.065
VO_2max	19.35, (6.83), 28.30	17.05, (5.6), 31.90	-2.802	**0.005**
$VEVCO_2$AT	29.5, (6.0), 32.0	32.50, (8.75), 37.0	-3.428	**0.001**
VO_2HRmax	29.5, (6.0), 32.0	10.5, (6.75), 11.0	-0.706	0.480

Table (5) above shows the result of the CPEX test for the ChemoRadiotherapy group before and after the administration of APT represented in medians, IQR and Ranges together with their p- values. Results in bold are significant



Figures (15) above show the changes in VO_2max and $VEVCO_2$AT (before and after APT adminstration) in the chemoradiotherapy group. Both of these results are significant.



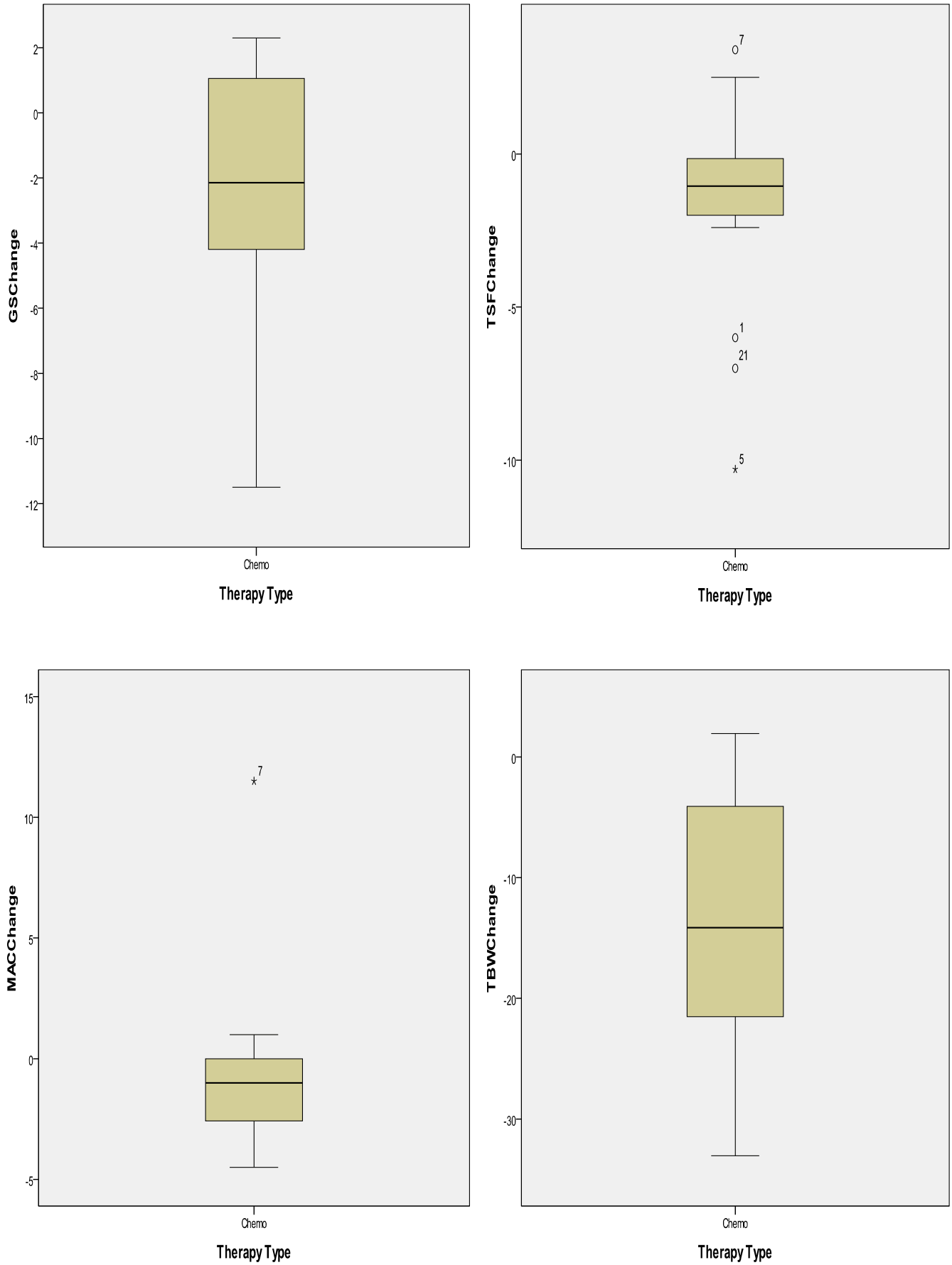
Figures (16) above show the changes in Work (Watts) at VO_2 Max, VO_2 (ml/kg/min) at AT, VO_2/HR (ml/beat) at VO_2 (before and after APT adminstration) in the chemoradiotherapy group. These results are not significant

6.1.3 Body composition

There was no significant change in the body weight and body mass index post APT exposure. However, a significant decline in the median value of the triceps skin fold, mid-arm circumference and grip strength was noticed after the therapy (p-value of 0.007, 0.006 and 0.01 respectively). Moreover, there was a significant ($p<0.001$) reduction in total body water post APT.

Variable	**Pre APT** Median, (iqr), range	**Post APT** Median, (iqr), range	**z-value**	**p-value**
Weight Kg	68.58, (19.83), 70.60	66.5, (22.55), 74.10	-1.100	0.271
BMI kg/m^2	25.97, (7.11), 20.42	25.44, (6.93), 21.64	-0.386	0.700
TSF	**13.0, (8.33), 27.90**	**10.5, (5.87), 32.30**	**-2.709**	**0.007**
MAC	**28.5, (6.13), 19.50**	**27.60, (6.12), 16.0**	**-2.755**	**0.006**
GS	**31.15, (18.48), 29.70**	**30.1, (18.08), 28.4**	**-2.586**	**0.010**
ECW	15.78, (5.4), 16.12	15.86, (6.46), 14.38	-0.814	0.415
ICW	19.08 (8.63), 23.60	17.24, (9.17), 27.83	-0.857	0.391
TBW	**34.76, (14.98), 42.05**	**18.04, (10.34), 38.8**	**-4.143**	**0.000**
FFM	44.81, (18.89), 50.70	42.43, (19.86), 52.39	-0.171	0.864

Table (6) above shows the result of the body composition tests for the ChemoRadiotherapy group before and after the administration of APT represented in medians, IQR and Ranges together with their p- values. Results in bold are significant



Figures (17) above show the changes in GS, TSF, MAC and TBW (before and after APT adminstration) in the chemoradiotherapy group. These results are significant

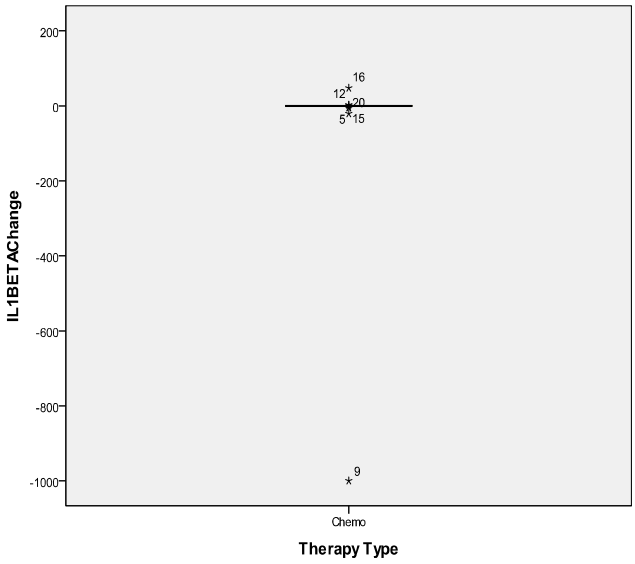
6.1.4 Cytokines

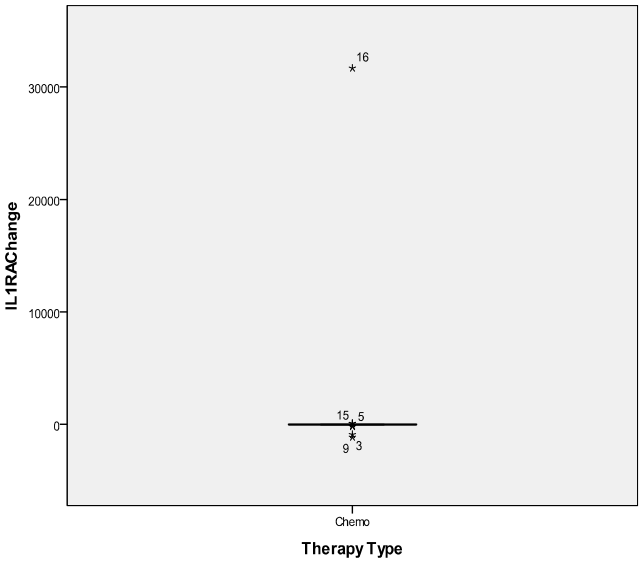
The patients inflammatory status usually reflect a balance between plasma levels of pro-inflammatory markers (TNFα, IP-10, RANTES, IL-6, IL-18) and anti-inflammatory markers (IL-1β, IL-1ra, IL-10, MIF) as well as plasma CRP and albumin.

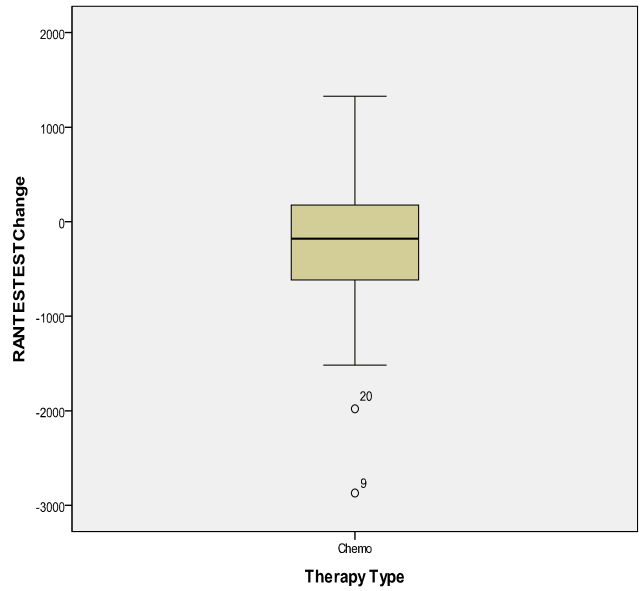
Cytokines behaviours and their effects were explained in the introduction chapter and will be discussed further in the discussion section. There was no distinct changes in median cytokine levels following the APT treatment. Some of them had increased, others decreased and some of them showed no changes post therapy.

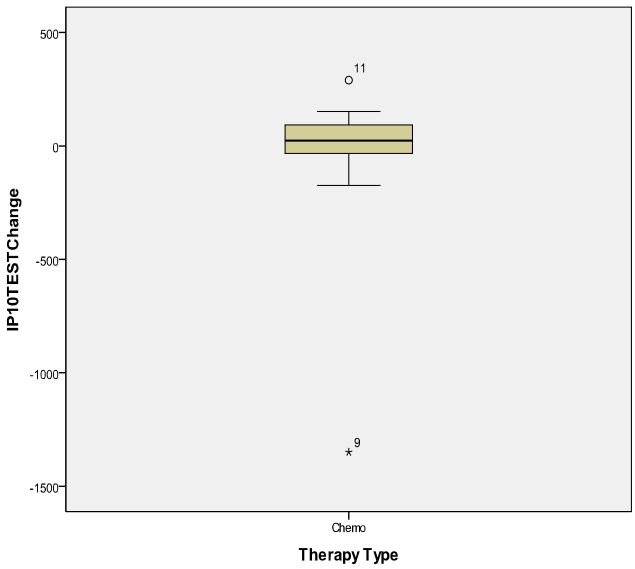
Variable	**Pre APT** Median, (iqr), range	**Post APT** Median, (iqr), range	**z-value**	**p-value**
IL1β	0.65, (0.45), 30.86	0.5750, (0.61), 78.33	-1.079	0.281
IL1RA	17.87, (66.6), 12582.06	11.01, (77.81), 44252.5	-1.651	0.099
IL6	7.99, (37.6), 380.4	10.7, (25.0775), 952.93	-1.120	0.263
IL10	2.5, (39.07), 1404.82	2.16, (37.02), 799.19	-0.633	0.527
IP10	304.0, (209.0), 636.7	366.2, (256.11), 682.53	-1.802	0.072
RANTES	1595.1, (768.8), 2188.4	1506.2, (555.4), 1734.7	-1.315	0.189
IL18	143.8, (109.8), 393.9	178, (111.6), 376.2	-0.016	0.987
MIF	91.8, (96.2), 8219.3	87.1, (78.4), 179.87	-1.932	0.053
TNF-α	7.27, (9.21), 1951.56	3.94, (14.96), 3653.05	-1.700	0.089
CRP	0.52, (0.6), 5.99	0.26, (0.6), 9.29	-1.721	0.085
ALBUMIN	3.96, (0.67), 1.41	3.8, (0.5), 1.2	-1.364	0.172

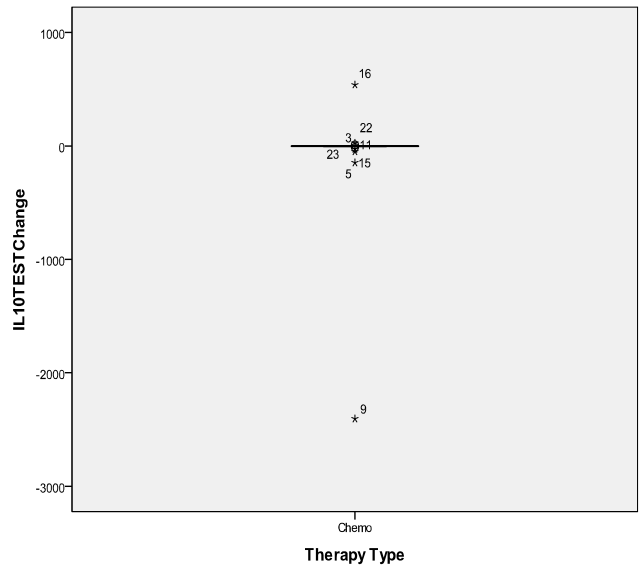
Table (7) above shows the result of the cytokines tests for the ChemoRadiotherapy group before and after the adminstration of APT represented in medians, IQR and Ranges together with their p- values. No significant results were found



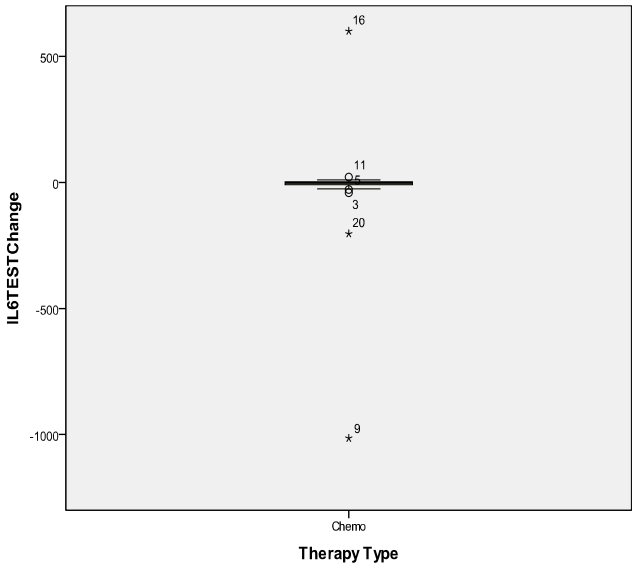


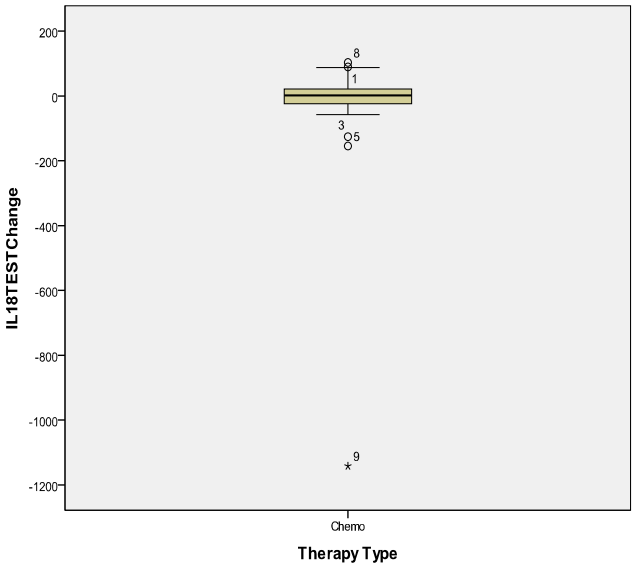


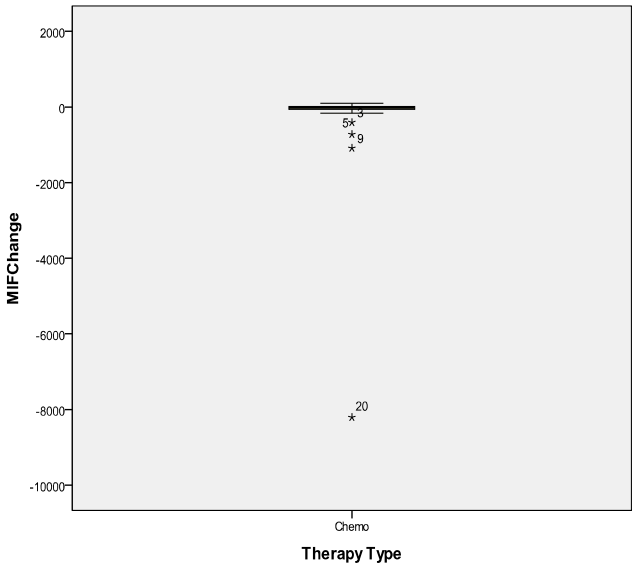


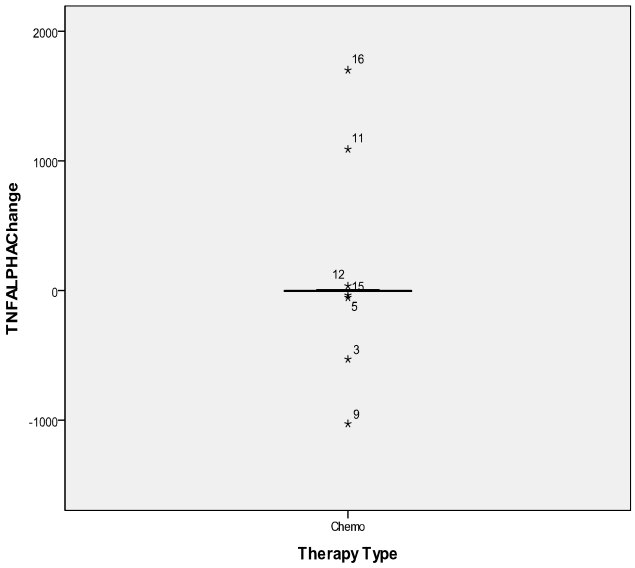


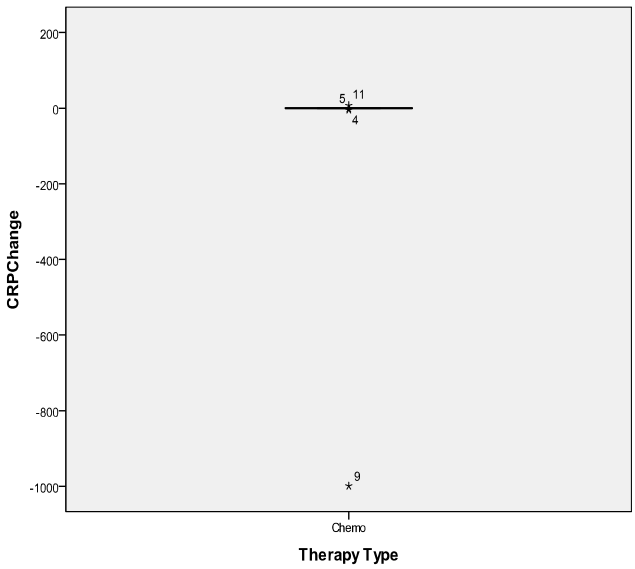
Figures (18) above show the changes in different cytokine levels (before and after APT adminstration) in the chemoradiotherapy group

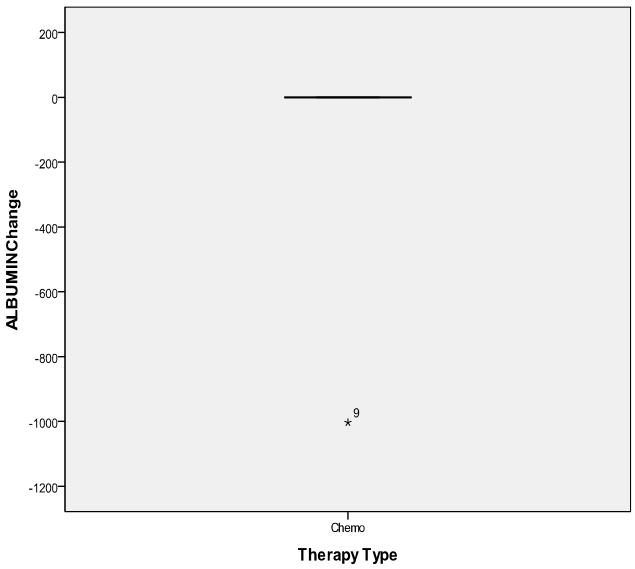












Figures (19) above show the changes in different cytokines, albumin and CRP levels (before and after APT adminstration) in the chemoradiotherapy group

6.1.5 HRQL

There was a significant worsening of all of the health related quality of life (HRQL) endpoints measured with EROTC QLQ C-30 questionnaire. Scoring system used was explained in the Method chapter and is included in the appendices section of this thesis.

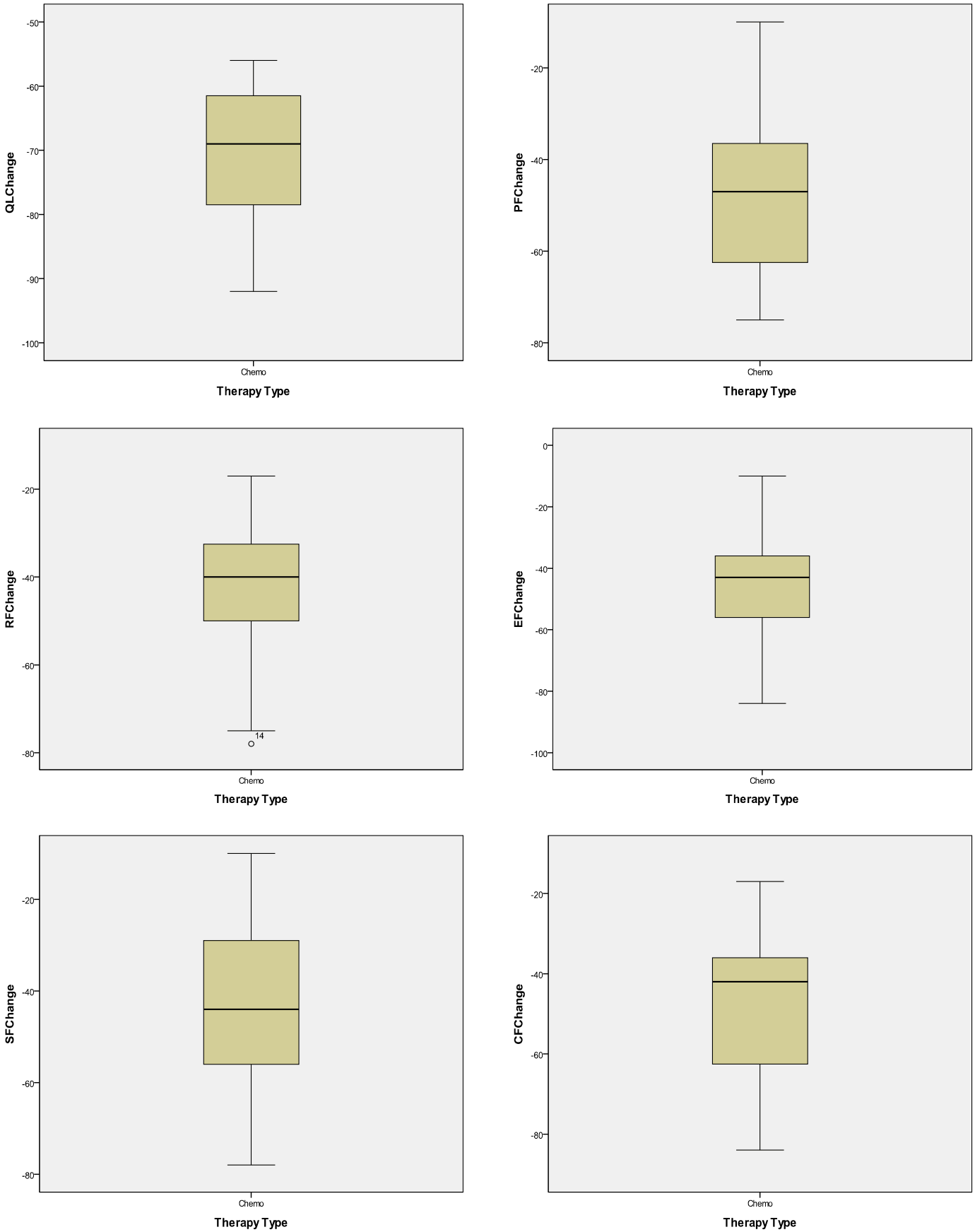
Variable	**Pre APT** Median, (iqr), range	**Post APT** Median, (iqr), range	**z-value**	**p-value**
QL	94.0, (0.0), 13.0	25.0, (23.0), 30.0	-4.299	**0.000**
PF	97.0, (6.0), 13.0	50.0, (28.2), 61.0	-4.290	**0.000**
RF	94.0, (0.0), 13.0	54.0, (14.0), 61.0	-4.298	**0.000**
EF	94.0, (11.5), 13.0	50.0, (28.2), 61.0	-4.292	**0.000**
CF	94.0, (4.5), 13.0	54.0, (28.2), 61.0	-4.299	**0.000**
SF	94.0, (11.2), 13.0	50.0, (14.0), 61.0	-4.292	**0.000**
FA	94.0, (11.2), 13.0	50.0, (33.0), 61.0	-4.292	**0.000**
NV	11.0, (11.0), 33.0	50.0, (14.0), 61.0	-4.207	**0.000**
PA	5.50, (15.5), 33.0	50.0, (14.0), 61.0	-4.206	**0.000**
DYSPNEA	0.0, (33.0), 33.0	50.0, (28.2), 42.0	-4.213	**0.000**
INSOMNIA	0.0, (11.0), 33.0	50.0, (14.0), 61.0	-4.210	**0.000**
AP	0.0, (17.0), 33.0	50.0, (20.2), 61.0	-4.267	**0.000**
CO	5.5, (17.00, 33.0	54.0, (28.2), 61.0	-3.952	**0.000**
DI	0.0, (11.0), 33.0	50.0, (14.0), 61.0	-4.167	**0.000**
FI	5.5, (17.0), 33.0	50.0, (14.0), 61.0	-4.291	**0.000**

Table (8) shows the significant result of the different HRQL variables measured with EROTC QLQ C-30 questionnaire in the chemoradiotherapy group. Global health status (QL), physical function (PF), role function (RF), emotional function (EF), cognitive function (CF), social function (SF), fatigue (FA), pain (PA), appetite loss (AP), constipation (CO), diarrhoea (DI), financial difficulties (FI)

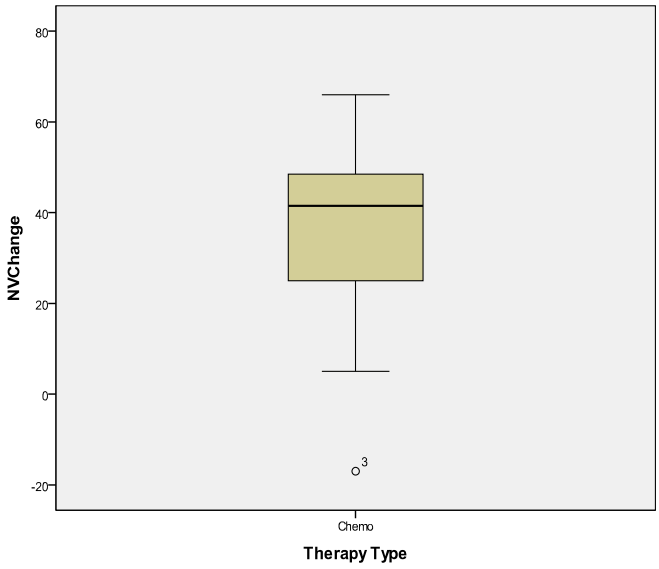
There was also a significant worsening in the final health related quality of life score measured with PG-SGA questionnaire. Scoring system used was explained in the Method chapter and is included in the appendices section of this thesis.

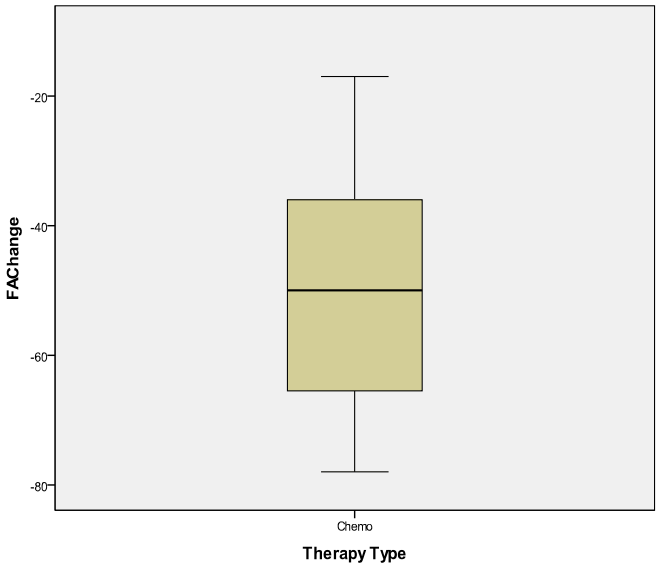
Variable	**Pre APT** Median, (iqr), range	**Post APT** Median, (iqr), range	**z-value**	**p-value**
PGSGA	1.0, (1.0), 1.0	4.5, (3.0), 5.0	-4.308	**0.000**

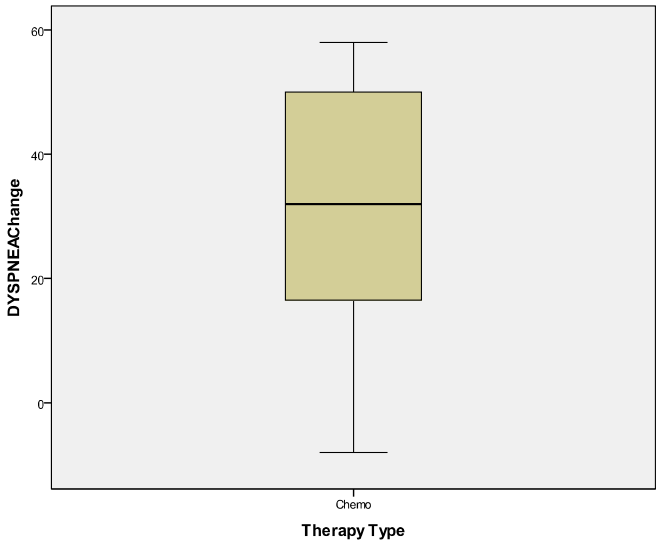
Table (9) shows the significant result of the different HRQL variables measured with PG-SGA questionnaire in the chemoradiotherapy group. This is the final result after using the scoring formula

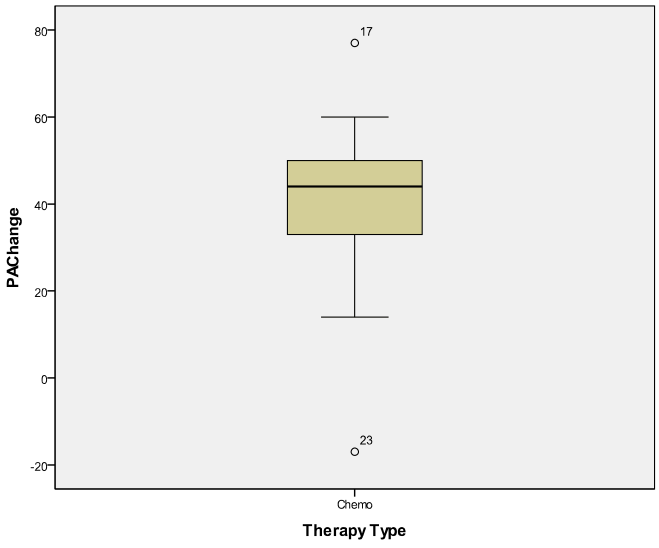


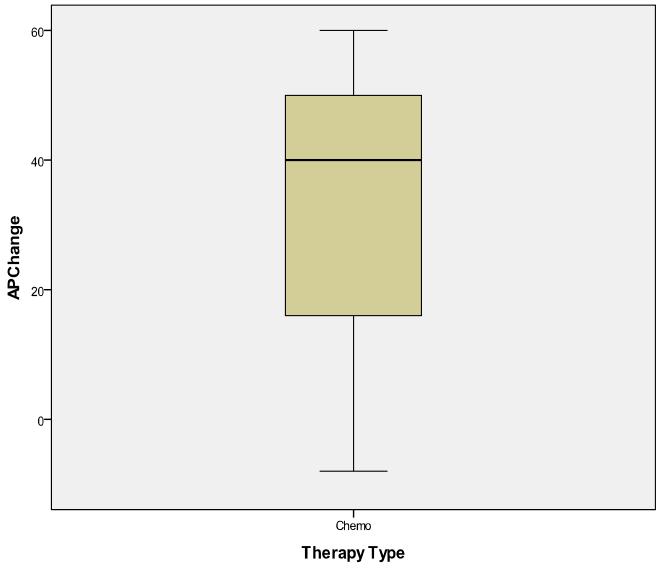
Figures (20) above show the changes in (HRQL) endpoints measured with EROTC QLQ C-30 questionnaire (before and after APT adminstration) in the chemoradiotherapy group. These results are significant

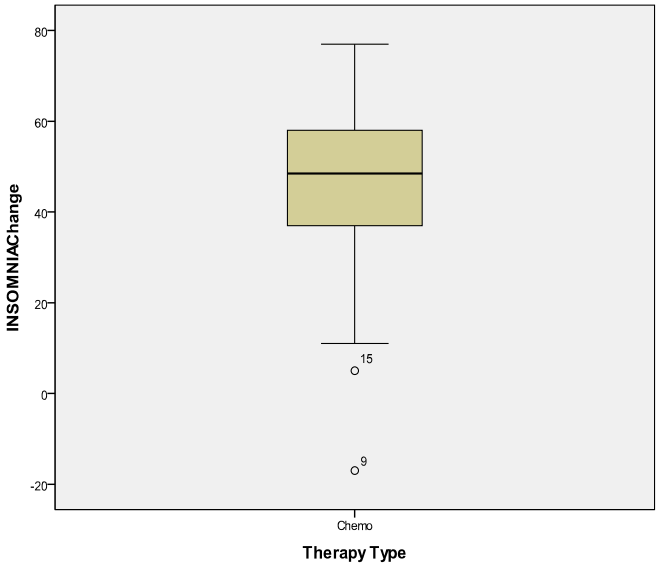












Figures (21) above show the changes in (HRQL) endpoints measured with EROTC QLQ C-30 questionnaire (before and after APT adminstration) in the chemoradiotherapy group. These results are significant

6.1.6 Correlation

Spearman correlation tests were performed between research variables to detect any possible relations among the study end outcomes. Any correlations that appear significant are candidates for subsequent multiple linear regression analysis. Positive correlation means both dependent and independent variables increase together while negative correlation means one increases and the other decreases.

Primary correlations (Hypothesis One):

In this hypothesis, we have assumed that the chosen CPEX variables have an impact on Demographics, Body composition, Cytokines and HRQL variables in the chemoradiotherapy group.

- Independent variables: Changes in CPEX variables
- Dependent variables: Changes in demographics, Body composition, Cytokines and HRQL variables.

Work at VO_2max had a positive correlation with both the individual weight and grip strength. While other CPEX variables had a negative correlation with IL1β, FFM, role and emotional functions.

Independent variables	Dependent variables	Correlation coefficients	Significance p value	Correlation trend
Work (Watts) VO_2max	Weight Kg	0.409	**0.047**	Positive
Work (Watts) VO_2max	GS	0.414	**0.044**	Positive
VO_2max	IL1β	-0.435	**0.034**	Negative
$VEVCO_2AT$	RF	-0.583	**0.003**	Negative
$VEVCO_2AT$	EF	-0.439	**0.032**	Negative
VO_2HRmax	FFM	-0.416	**0.043**	Negative

Table (10) shows only significant correlations (positive and negative) with regard to hypothesis one in the chemoradiotherapy group

Any correlations between this hypothesis variables not included in the above table are not significant. They can be found in the appendix section of this thesis.

Secondary correlations (Hypothesis Two):

In this hypothesis, we have assumed that HRQL variables measured with QLQ-C30 and PG-SGA have an impact on Body composition variables.

- Independent variables: Changes in HRQL variables
- Dependent variables: Changes in Body composition variables.

Please see table below for more details about this hypothesis correlations.

Independent variables	Dependent variables	Correlation coefficients	Significance p value	Correlation trend
QL	TSF	-0.569	**0.004**	Negative
CF	Weight Kg	-0.552	**0.005**	Negative
CF	BMI kg/m^2	-0.659	**0.000**	Negative
CF	TBW	.552	**0.005**	Positive
SF	TSF	0.407	**0.048**	Positive
FA	ECW	0.413	**0.045**	Positive
NV	MAC	0.518	**0.010**	Positive
DYSPNEA	GS	0.407	**0.049**	Positive
DYSPNEA	FFM	0.427	**0.037**	Positive
CO	Weight Kg	0.415	**0.043**	Positive
PGSGA	ECW	0.437	**0.033**	Positive

Table (11) shows only significant correlations (positive and negative) with regard to hypothesis two in the chemoradiotherapy group

Any correlations between this hypothesis variables not included in the above table are not significant. They can be found in the appendix section of this thesis.

6.2 Radiotherapy group:

6.2.1 Demographics

This group included 12 patients who had only pelvic radiotherapy. Their mean age was 71.8, SD 8.9 (55.00-88.00) and the length of adjuvant pre-operative treatment (APT), in days, had a mean of 5.7 days, SD 1.1 (4.00-7.00). The length of time, in days, between finish of the APT and the day of surgery had a mean of 22.1 days, SD 17.6 (8.00-58.00). This group had 10 males and 2 females.

Variables	**Radio (n=12)**			
	Mean	**SD**	**Min**	**Max**
Age (Pre-APT)	71.8	8.9	55.00	88.00
Length of APT (days)	5.7	1.1	4.00	7.00
APT to Surgery window (days)	22.1	17.5	8.00	58.00
Gender	Male= 10			Female= 2

Table (12) shows descriptive figures for age, length of APT, window to surgery and gender for the radiotherapy group

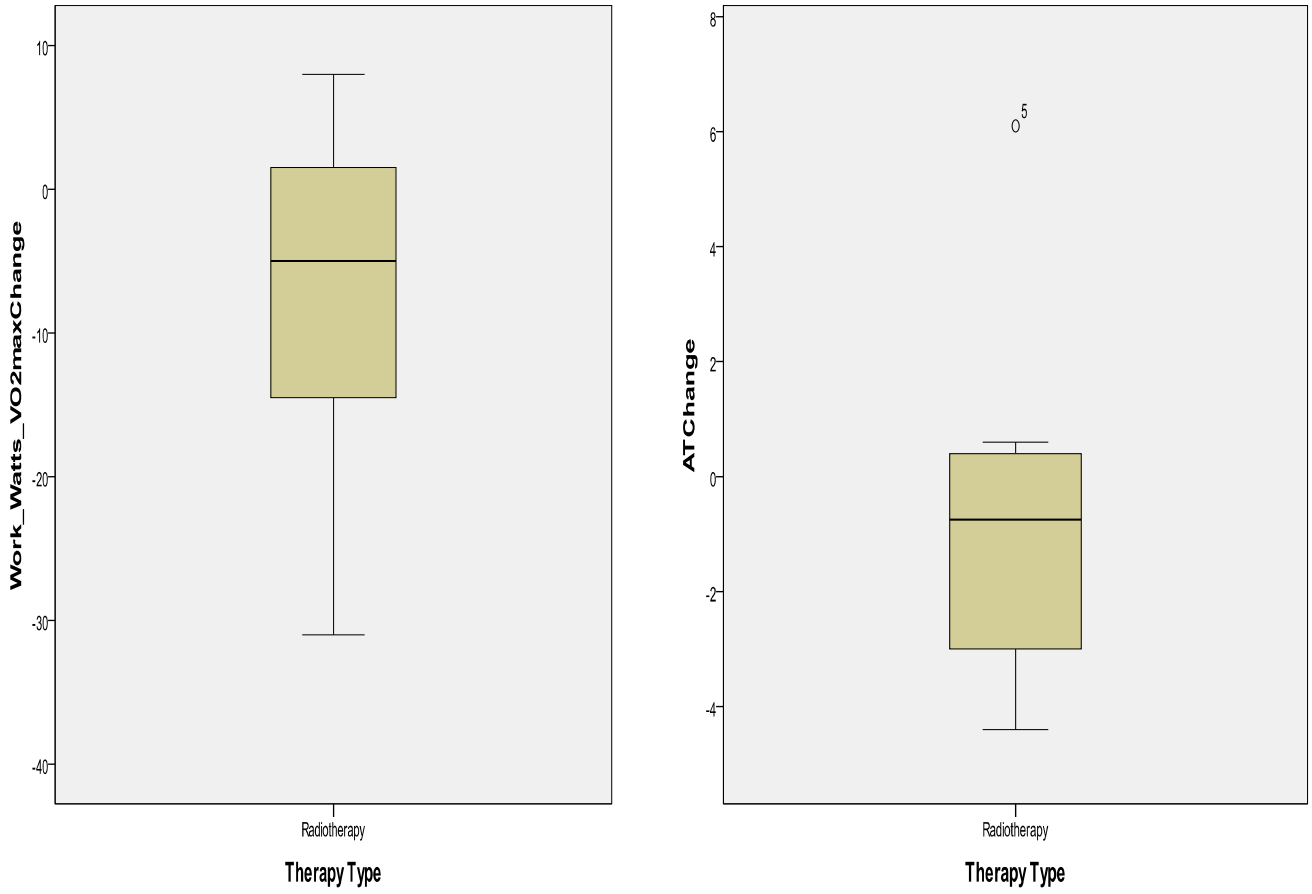
6.2.2 CPEX

Different variable were measured during CPEX testing before and after APT treatment to best reflect the functional capacity in patients with rectal cancer. Out of many CPEX variables obtained from the test, only few parameters were compared before and after APT administration due to their relevance in clinical practice and our study hypothesis. These are: Work load (Watts) at the maximum oxygen consumption, oxygen consumption (ml/kg/min) at anarobic threshold and at peak (or maximum), the ventilatory equivalent ratio for carbon dioxide at anaerobic threshold in addition to the maximum pulse oxygen consumption.

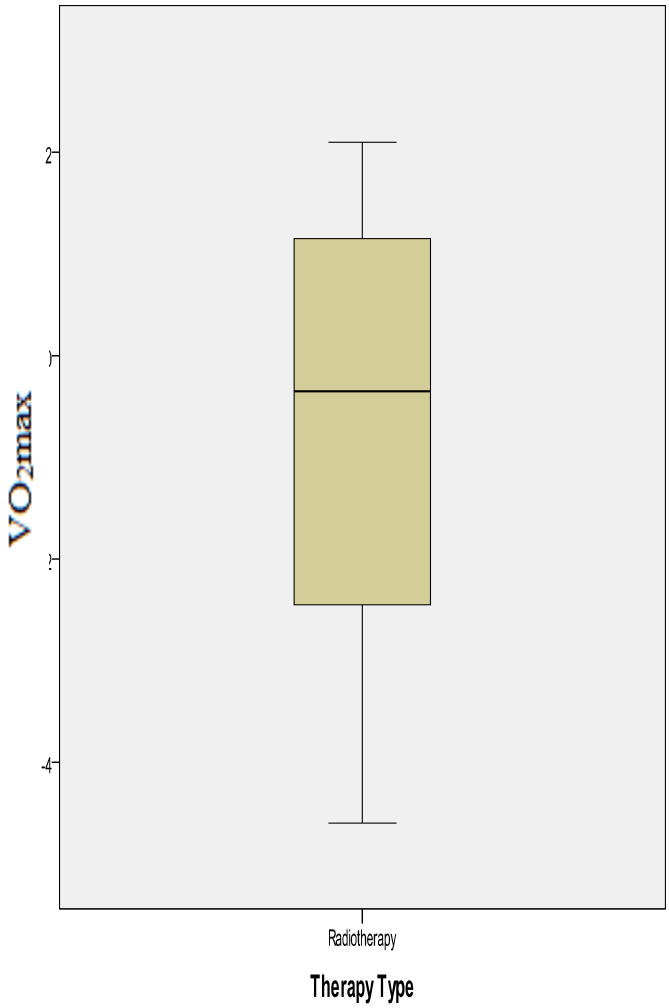
In this group, no significant changes were found in the CPEX variables post APT.

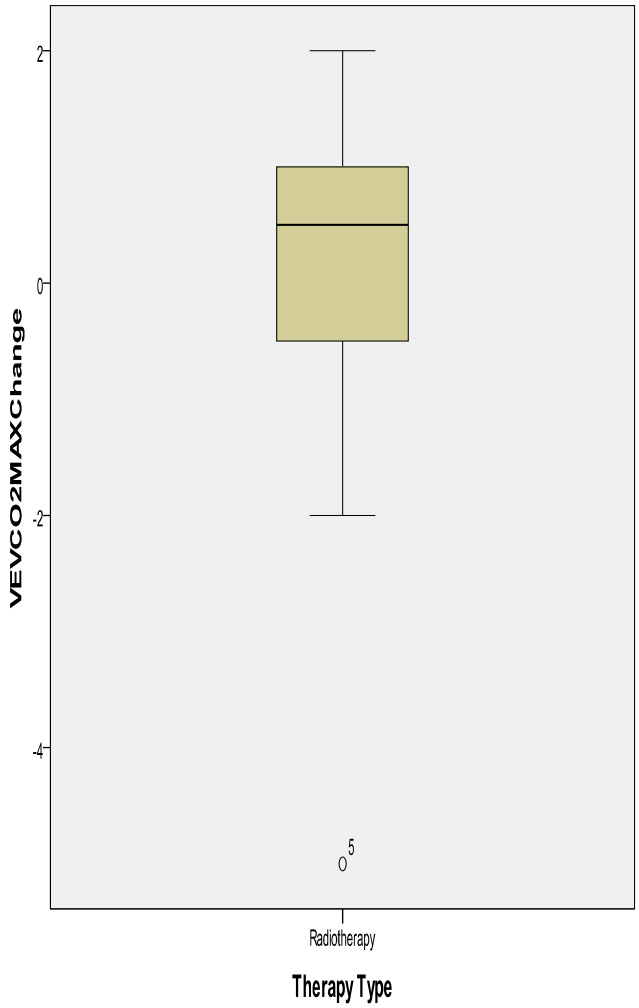
Variable	Pre APT Median, (iqr), range	Post APT Median, (iqr), range	z- value	p-value
Work VO_2max	89.5, (70.25), 118	81, (61.25), 121	-1.926	0.054
AT	11.55, (4.575), 12.5	10.95, (2.8), 16.9	-1.177	0.239
VO_2max	18.35, (9.15), 15.6	16.25, (7.975), 17.3	-0.845	0.398
$VEVCO_2$AT	33, (12), 29	34.5, (12), 37	-1.340	0.180
VO_2HRmax	10, (3), 7	9.5, (3.5), 7	-1.027	0.305

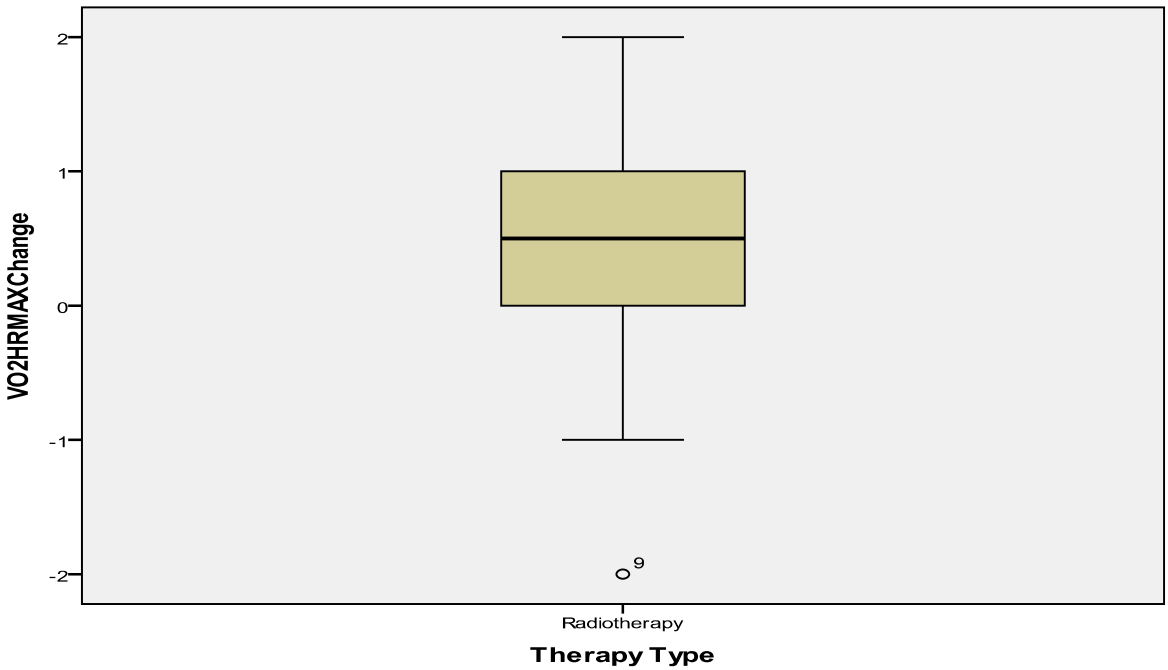
Table (13) above shows the result of the CPEX test for the Radiotherapy group before and after the adminstration of APT represented in medians, IQR and Ranges together with their p-values



Figures (22) above show the changes in the CPEX variables (before and after APT adminstration) in the radiotherapy group







Figures (23) above show the changes in the CPEX variables (before and after APT adminstration) in the radiotherapy group

6.2.3 Body composition

There was a significant decline in the triceps skin fold and mid arm circumference post APT exposure with p- values of 0.013 and 0.013 respectively. In addition, total body water and fat free mass were also reduced significantly post APT with p-values of 0.002 and 0.034 respectively.

Variable	**Pre APT** Median, (iqr), range	**Post APT** Median, (iqr), range	**z-value**	**p-value**
Weight Kg	70.6, (28.3), 45.1	71.5, (28.8), 46.46	-0.078	0.937
BMI kg/m^2	25.8, (6.03), 12.4	25.5, (5.79), 12.76	-1.255	0.209
TSF	12.35, (13.75), 17.8	9.2, (10.8), 16	-2.477	**0.013**
MAC	29.5, (4.9), 9.5	28.5, (5), 7.5	-2.494	**0.013**
GS	34.5, (8.7), 23.7	33.7, (6.8), 26.8	-1.413	0.158
ECW	16.7, (4.7), 11.51	16.94, (4.66), 11.18	-0.392	0.695
ICW	18.02, (7.38), 12.71	17.7, (5.5), 10.11	-0.981	0.327
TBW	36.16, (11.67), 24.22	20.6, (16.4), 23.98	-3.059	**0.002**
FFM	48.14, (14.06), 31.56	44.19, (14.6), 24.63	-2.118	**0.034**

Table (14) above shows the result of the body composition tests for the Radiotherapy group before and after the administration of APT represented in medians, IQR and Ranges together with their p- values. Results in bold are significant

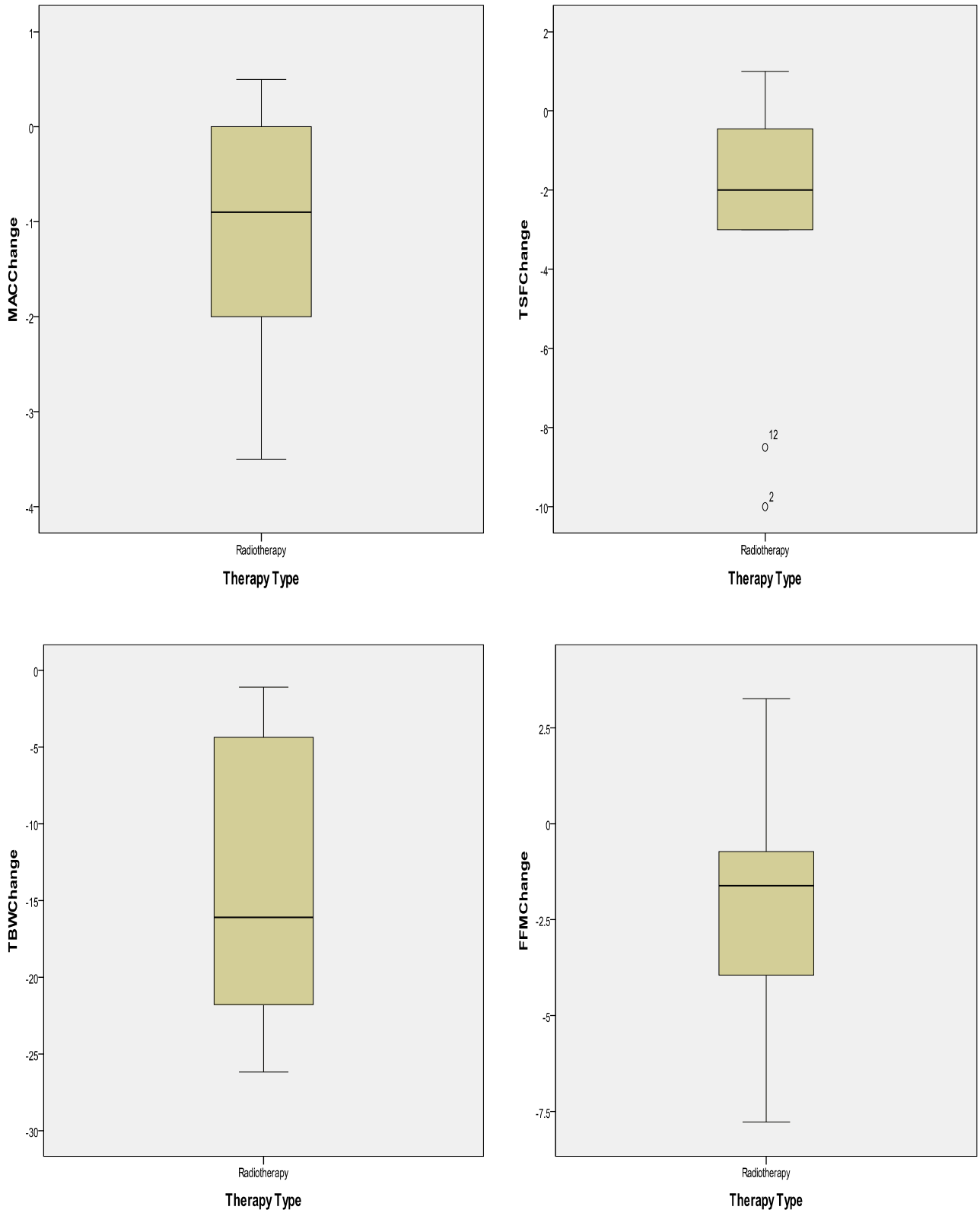


Figure (24) above shows the changes in MAC, TSF, FFM and TBW (before and after APT adminstration) in the radiotherapy group. These results are significant

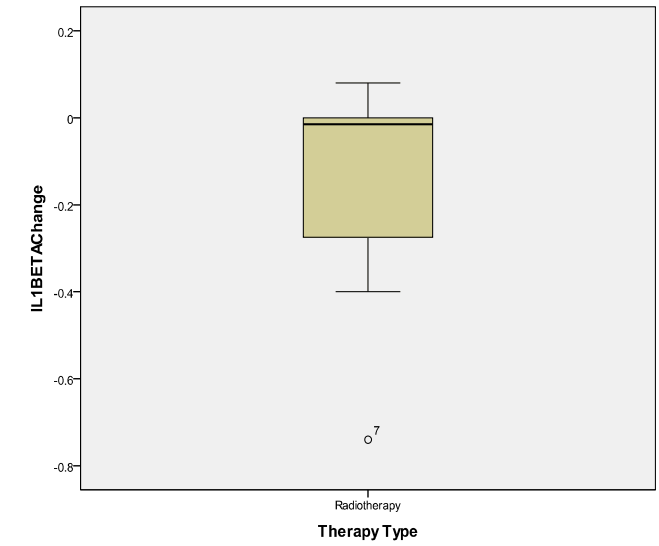
6.2.4 Cytokines

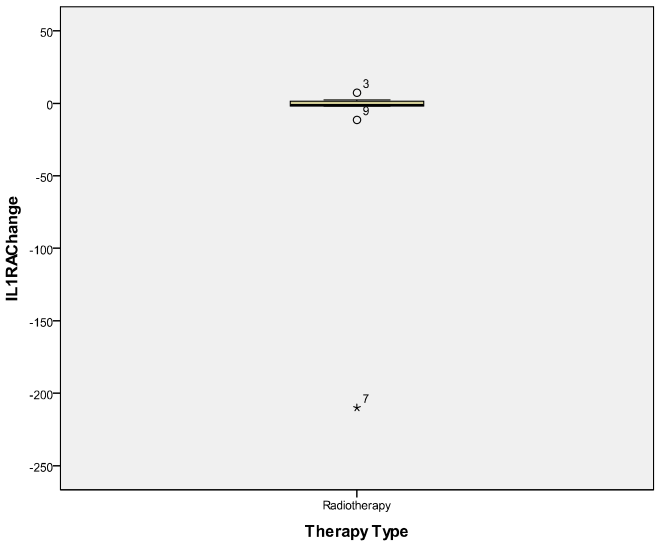
The patients inflammatory status usually reflect a balance between plasma levels of pro-inflammatory markers (TNFα, IP-10, RANTES, IL-6, IL-18) and anti-inflammatory markers (IL-1β, IL-1ra, IL-10, MIF) as well as plasma CRP and albumin.

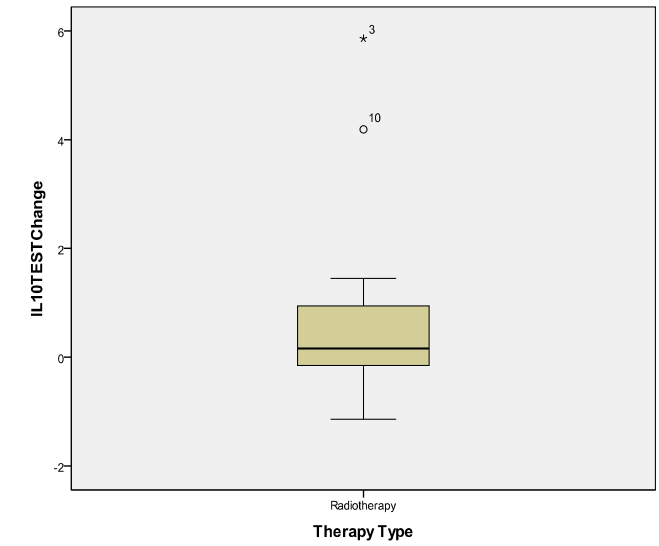
Cytokines behaviours and their effects were explained in the introduction chapter and will be discussed further in the discussion section. There was no distinct change in median cytokine levels following the APT treatment. Some of them had increased, others decreased and some of them showed no changes post therapy.

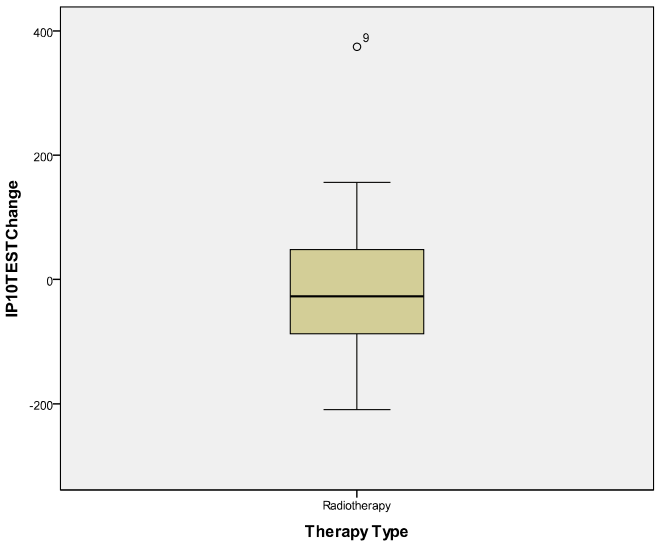
Variable	**Pre APT** Median, (iqr), range	**Post APT** Median, (iqr), range	**z-value**	**p-value**
IL1β	0.53, (0.79), 1.39	0.53, (0.33), 1.07	-1.820	0.069
IL1RA	9.8, (16.76), 212.39	8.6, (7.3), 22.31	-0.534	0.594
IL6	5.85, (4.73), 9.47	6.75, (14.97), 102.16	-1.956	0.050
IL10	1.55, (1.26), 2.98	1.82, (1.63), 6.49	-1.156	0.248
IP10	318.46, (125.94), 878.44	223.1, (333.2), 996.8	-0.622	0.534
RANTES	1353.03, (884.4), 1561.6	1447.2, (988.3), 1590.4	-0.711	0.477
IL18	150.18, (92.46), 190.05	139.17, (105.04), 202.8	-0.089	0.929
MIF	123.8, (182.2), 1357.2	66.05, (184.39), 455.23	0.000	1.000
TNF-α	3.94, (3.29), 11.5	3.00, (1.88), 8.14	-1.481	0.139
CRP	0.14, (0.72), 1.22	0.29, (0.39), 2.82	-1.468	0.142
ALBUMIN	4, (0.42), 1.12	3.89, (0.53), 1.2	0.000	1.000

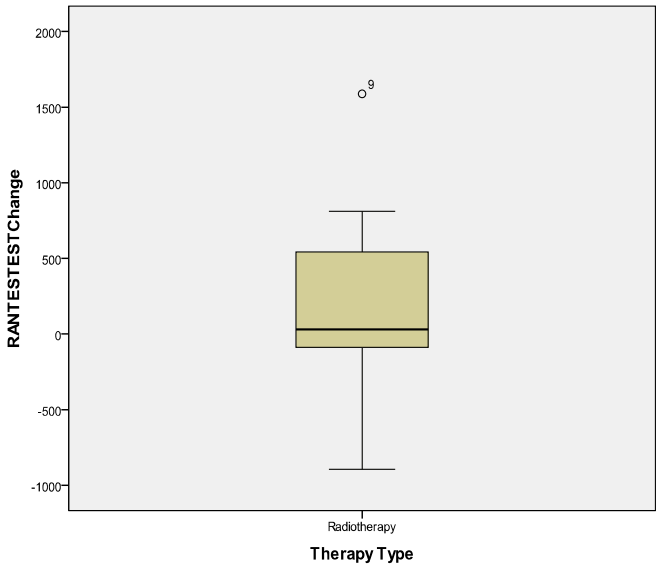
Table (15) above shows the result of the cytokines tests for the Radiotherapy group before and after the adminstration of APT represented in medians, IQR and Ranges together with their p- values. No significant results were found

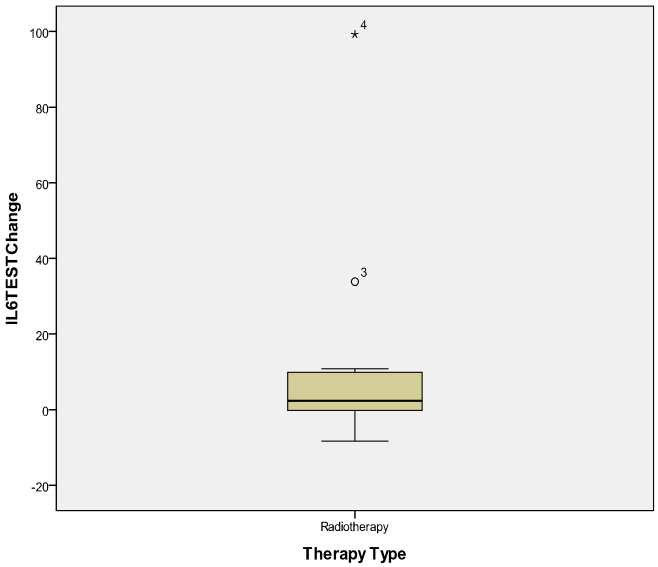




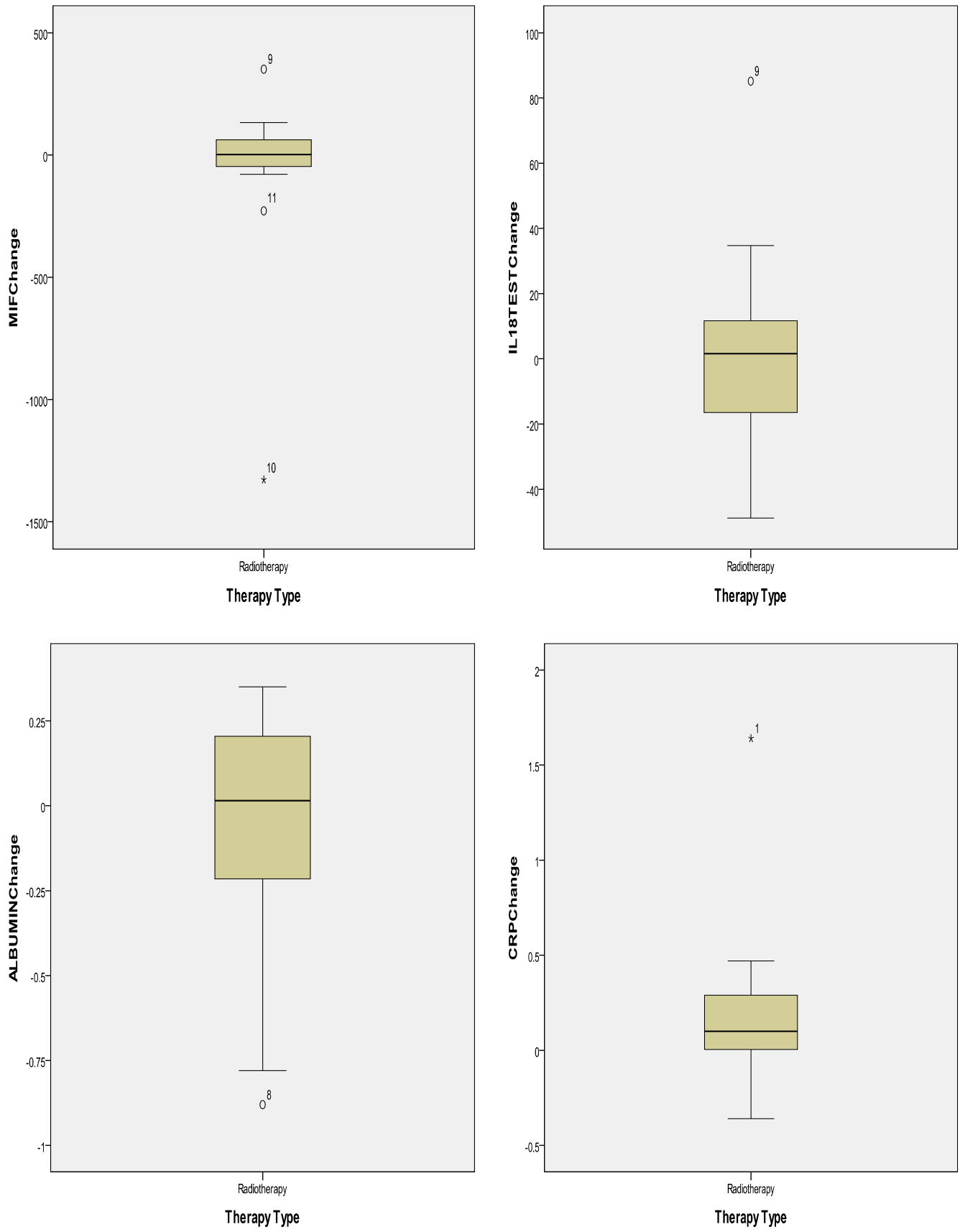








Figures (25) above show the changes of the cytokines tests for the Radiotherapy group before and after the administration of APT represented in medians, IQR and Ranges together with their p- values. No significant results were found



Figures (26) above show the changes in different cytokines, albumin and CRP levels (before and after APT adminstration) in the radiotherapy group

6.2.5 HRQL

There was a significant worsening of all of the health related quality of life (HRQL) endpoints measured with EROTC QLQ C-30 questionnaire. Scoring system used was explained in the Method chapter and is included in the appendices section of this thesis.

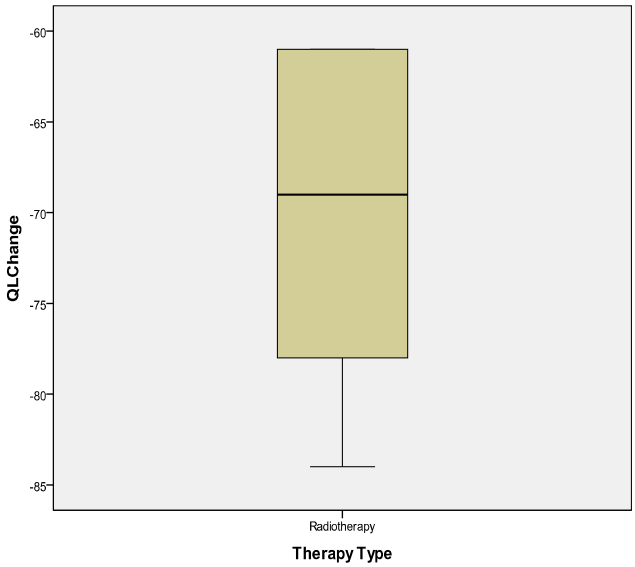
Variable	**Pre APT** Median, (iqr), range	**Post APT** Median, (iqr), range	**z-value**	**p-value**
QL	94, (0), 6	25, (17), 17	-3.081	**0.002**
PF	94, (7), 13	34.5, (31), 61	-3.065	**0.002**
RF	94, (0), 13	50, (28.25), 61	-3.063	**0.002**
EF	94, (6), 13	58, (8), 52	-3.066	**0.002**
CF	94, (0), 13	50, (12.5), 61	-3.065	**0.002**
SF	94, (5.25), 13	58, (8), 52	-3.069	**0.002**
FA	94, (11.25), 13	54, (14), 61	-3.062	**0.002**
NV	0, (11), 11	50, (39.75), 61	-3.066	**0.002**
PA	0, (15.5), 33	34.5, (40), 61	-2.828	**0.005**
DYSPNEA	11, (15.5), 33	50, (31.75), 61	-2.827	**0.005**
INSOMNIA	5.5, (11), 11	50, (33), 42	-3.068	**0.002**
AP	0, (11), 11	47, (42), 61	-3.065	**0.002**
CO	0, (11), 33	47, (28.25), 61	-2.910	**0.004**
DI	5.5, (11), 17	34.5, (34), 61	-2.983	**0.003**
FI	5.5, (11), 33	37.5, (40), 42	-3.068	**0.002**

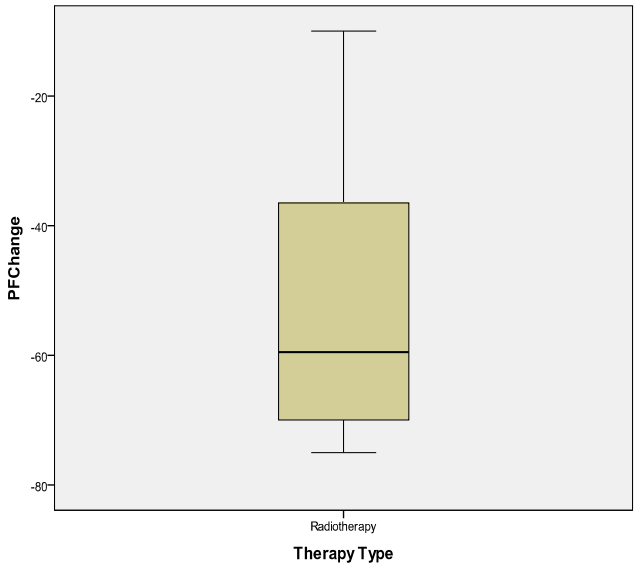
Table (16) shows the significant result of the different HRQL variables measured with EROTC QLQ C-30 questionnaire in the radiotherapy group. Global health status (QL), physical function (PF), role function (RF), emotional function (EF), cognitive function (CF), social function (SF), fatigue (FA), pain (PA), appetite loss (AP), constipation (CO), diarrhoea (DI), financial difficulties (FI)

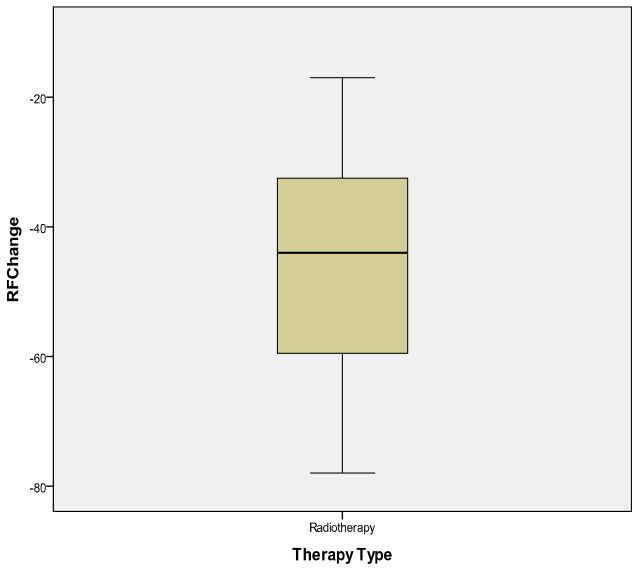
There was also a significant worsening in the final health related quality of life score measured with PG-SGA questionnaire. Scoring system used was explained in the Method chapter and is included in the appendices section of this thesis.

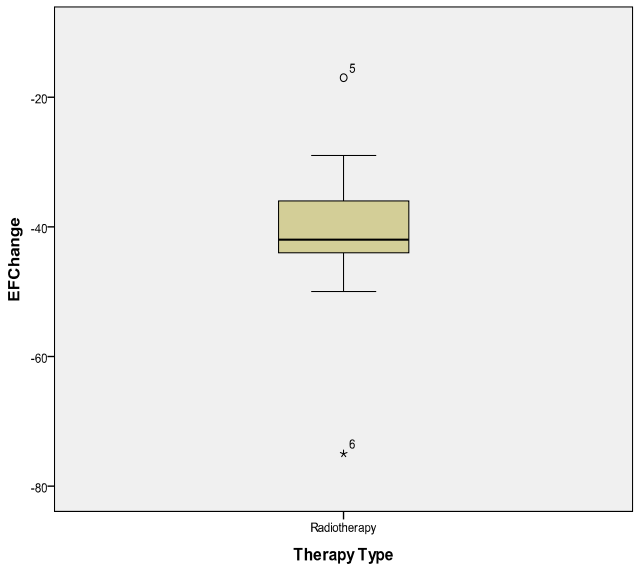
Variable	**Pre APT** Median, (iqr), range	**Post APT** Median, (iqr), range	**z-value**	**p-value**
PGSGA	1, (1), 1	4, (2), 4	-3.077	**0.002**

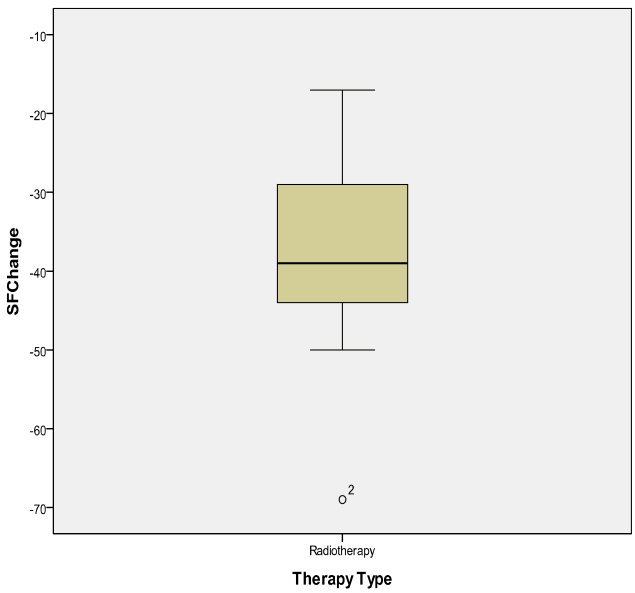
Table (17) shows the significant result of the different HRQL variables measured with PG-SGA questionnaire in the radiotherapy group. This is the final result after using the scoring formula

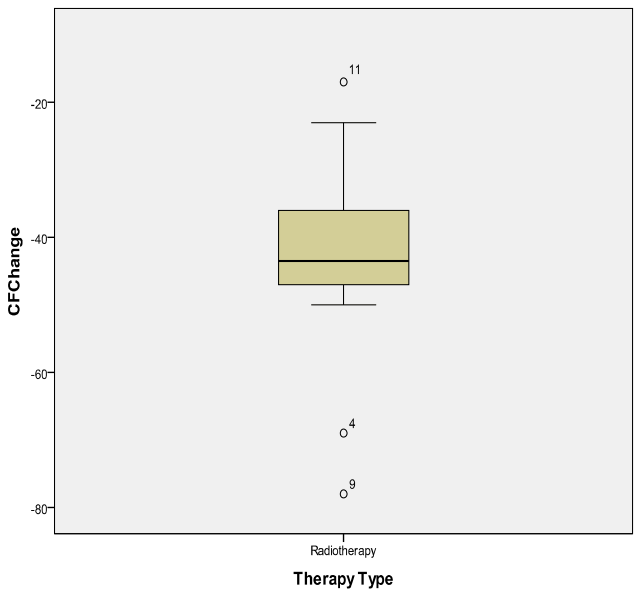




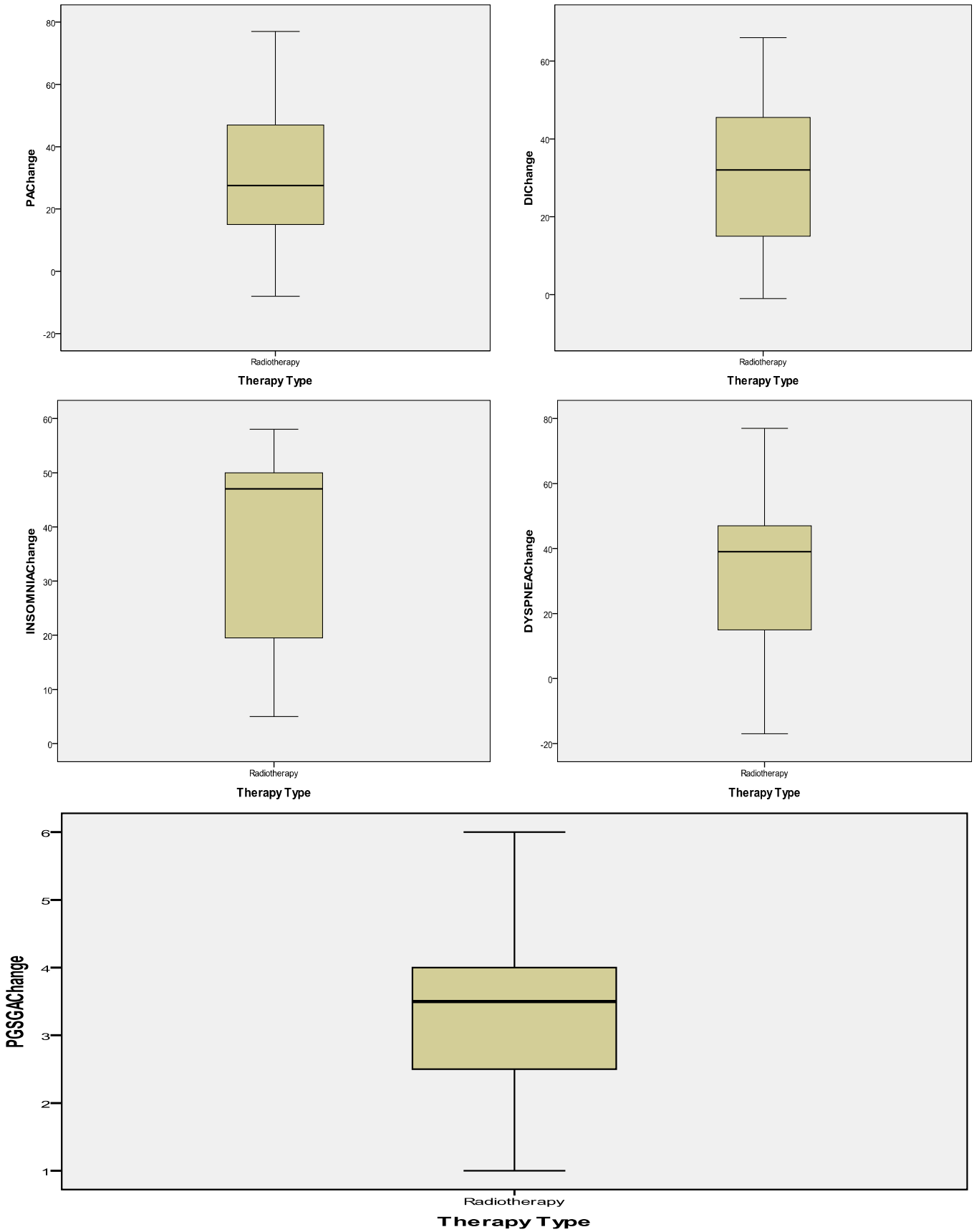








Figures (27) above show the changes in (HRQL) endpoints measured with EROTC QLQ C-30 questionnaire (before and after APT adminstration) in the chemoradiotherapy group. These results are significant



Figures (28) above show the changes in (HRQL) endpoints measured with PG-SGA and EROTC QLQ C-30 questionnaire (before and after APT adminstration) in the chemoradiotherapy group. These results are significant

6.2.6 Correlation

Spearman correlation tests were performed between research variables to detect any possible relations among the study outcomes. Any correlations that appear significant are candidates for subsequent multiple linear regression analysis. Positive correlation means both dependent and independent variables increase together while negative correlation means one increases and the other decreases.

Primary correlations (Hypothesis One):

In this hypothesis, we have assumed that the chosen CPEX variables have an impact on Demographics, Body composition, Cytokines and HRQL variables in the radiotherapy group.

- Independent variables: Changes in CPEX variables.
- Dependent variables: Changes in demographics, Body composition, Cytokines and HRQL variables.

Please see table below for hypothesis one.

Independent variables	Dependent variables	Correlation coefficients	Significance p value	Correlation trend
Work (Watts) VO_2max	INSOMNIA	-0.653	0.021	Negative
AT	Weight Kg	-0.615	0.033	Negative
AT	GS	0.726	0.007	Positive
VO_2max	FA	0.589	0.044	Positive
$VEVCO_2AT$	TBW	0.612	0.035	Positive
$VEVCO_2AT$	PF	0.681	0.015	Positive
VO_2HRmax	CRP	-0.628	0.029	Negative

Table (18) shows only significant correlations (positive and negative) with regard to hypothesis one in the radiotherapy group

Any correlations between this hypothesis variables not included in the above table are not significant. They can be found in the appendix section of this thesis.

Secondary correlations (Hypothesis Two):

In this hypothesis, we have assumed that HRQL variables measured with QLQ-C30 and PG-SGA have an impact on Body composition variables in the radiotherapy group.

- Independent variables: Changes in HRQL variables.
- Dependent variables: Changes in Body composition variables.

Please see table below for hypothesis two.

Independent variables	Dependent variables	Correlation coefficients	Significance p value	Correlation trend
QL	BMI kg/m^2	-0.621	0.031	Negative
QL	FFM	-0.603	0.038	Negative
PF	FFM	0.642	0.024	Positive
RF	ECW	0.662	0.019	Positive
NV	TBW	0.654	0.021	Positive
PA	Weight Kg	0.577	0.049	Positive
AP	FFM	-0.593	0.042	Negative
DI	ECW	0.770	0.003	Positive
DI	ICW	-0.674	0.016	Negative
FI	FFM	0.598	0.040	Positive

Table (19) shows only significant correlations (positive and negative) with regard to hypothesis two in the radiotherapy group

Any correlations between this hypothesis variables not included in the above table are not significant. They can be found in the appendix section of this thesis.

6.3 Measure of changes for the full cohort of patients

Mixed ANOVA test was performed to find out if the changes of both chemoradiotherapy and radiotherapy groups were constant or not. This is a robust test and can deal with non-normally distributed data, in order to detect whether type of therapy acts as an effect on the different variables measured.

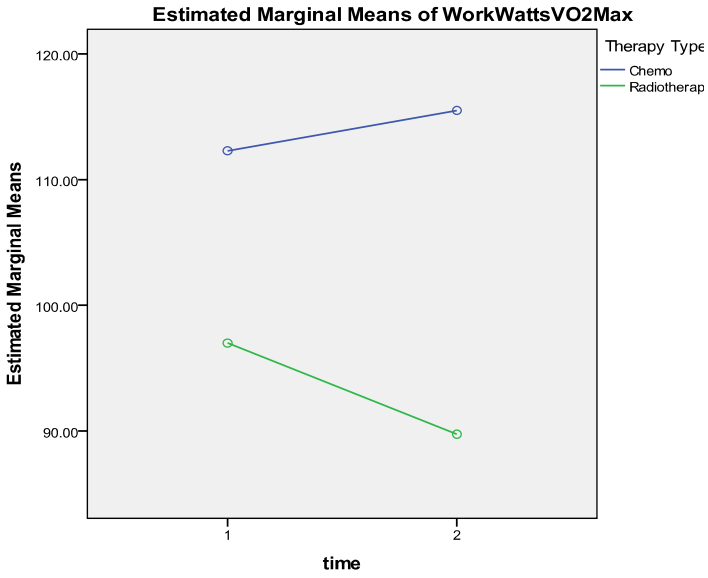
A repeated measures ANOVA was performed using Therapy Type as a between subjects effect. The results in the table show the outcome for the interaction effect between time and Therapy Type.

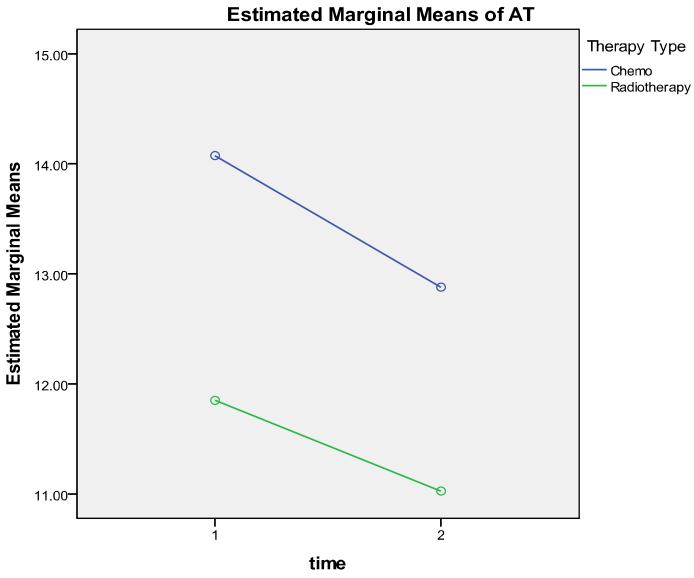
It does show that there are no significant changes in the 36 patients after exposure to either of the APT regimes.

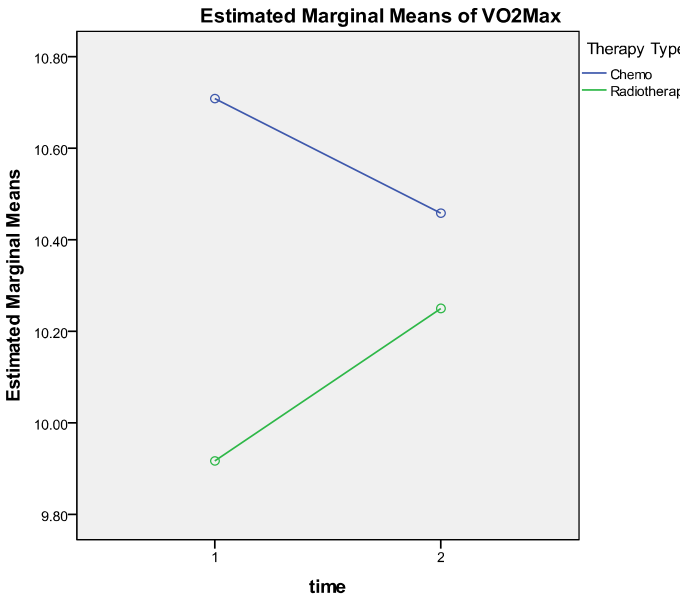
This means that both types of therapies (chemoradiotherapy and radiotherapy alone) have nearly similar effect and trend on study outcomes, ie: either cause an increase or decrease of the variables measured. See table and figures below for more information.

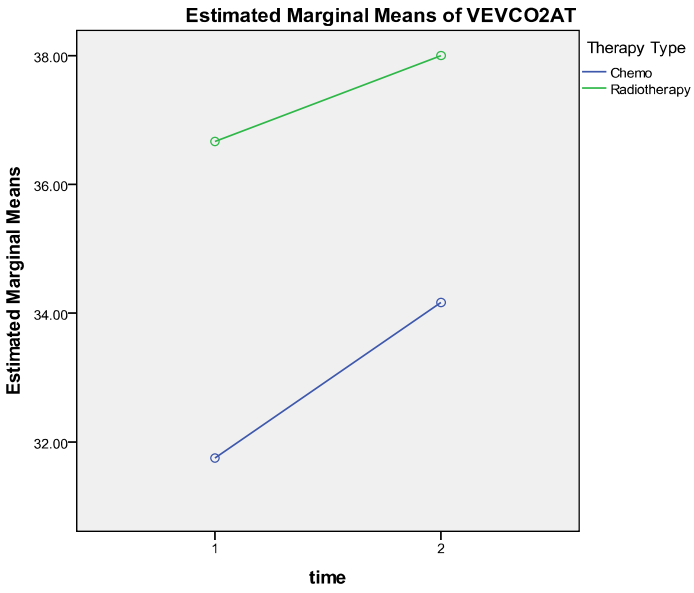
Table (20) below shows the outcome for the interaction effect between time and Therapy Type (Chemoradiotherapy and Radiotherapy). No significant results were found

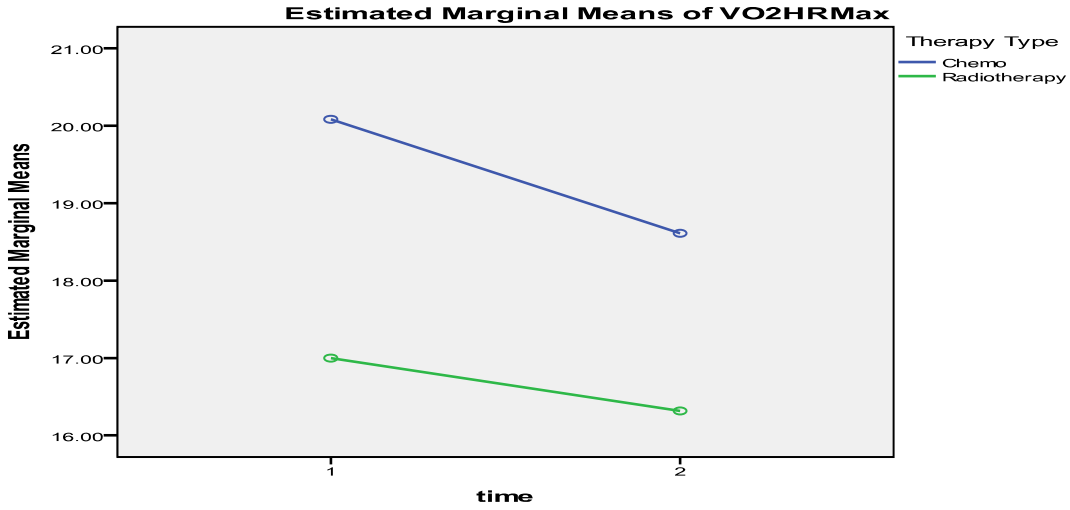
					Interaction: Time*Therapy Type	
Variable	**ChemoradioRx Start**	**ChemoradioRx End**	**RadioRx Start**	**RadioRx End**	**F**	**p**
WorkWatts	112.292	115.500	97.000	89.750	1.495	0.230
VO_2Max						
AT	14.075	12.879	11.850	11.025	0.121	0.730
VO_2Max	10.708	10.458	9.917	10.250	1.038	0.315
$VEVCO_2$AT	31.750	34.167	36.667	38.000	0.900	0.349
VO_2HRMax	20.083	18.608	17.000	16.317	0.962	0.334
Weight	72.564	71.817	75.121	75.095	0.537	0.469
BMI	25.474	25.483	26.173	26.059	0.148	0.703
TSF	13.475	12.008	14.508	11.958	1.016	0.321
MAC	28.171	27.339	29.500	28.433	0.066	0.799
GS	34.035	31.736	33.125	32.342	10.337	0.256
ECW	16.145	16.194	17.342	17.355	0.007	0.934
ICW	18.444	18.109	19.073	18.638	0.019	0.890
TBW	34.153	20.365	37.233	23.174	0.006	0.937
FFM	45.036	44.824	48.883	46.912	2.220	0.145
IL1BETA	3.623	4.519	.835	.675	0.045	0.833
IL1RA	779.937	2163.985	30.623	10.945	0.440	0.512
IL6	59.141	73.354	6.734	20.485	0.433	0.515
IL10	57.544	72.354	1.779	2.724	0.181	0.674
IP10	328.072	364.441	387.424	383.414	0.499	0.485
RANTES	1614.711	1390.320	1256.635	1449.759	0.013	0.911
IL18	180.803	178.698	127.711	130.505	0.001	0.972
MIF	524.296	88.631	235.761	141.257	0.970	0.332
CRP	.863	.764	.409	.634	0.045	0.833
ALBUMIN	3.884	3.756	3.901	3.822	1.671	0.206
QL	94.167	21.792	95.000	25.333	0.636	0.431
PF	95.542	47.125	91.583	39.083	0.364	0.550
RF	94.375	51.875	93.833	47.583	0.364	0.550
EF	93.167	47.417	95.333	54.167	0.469	0.498
CF	94.333	46.583	93.833	50.417	0.474	0.496
SF	94.250	50.000	93.250	55.250	1.098	0.302
FA	94.000	44.958	94.750	50.500	0.499	0.485
NV	8.958	46.667	3.667	43.667	0.102	0.751
PA	8.333	47.833	7.417	37.583	1.573	0.218
DYSPNEA	11.250	44.208	9.250	41.833	0.002	0.961
INSOMNIA	6.917	50.375	5.500	43.750	0.548	0.464
AP	9.458	44.333	4.583	44.167	0.416	0.523
CO	9.250	47.333	6.417	46.583	0.054	0.818
DI	7.125	48.583	6.000	36.417	2.059	0.160
FI	10.167	47.625	7.333	35.750	2.065	0.160
PGSGA	.708	4.417	.583	3.917	0.437	0.513



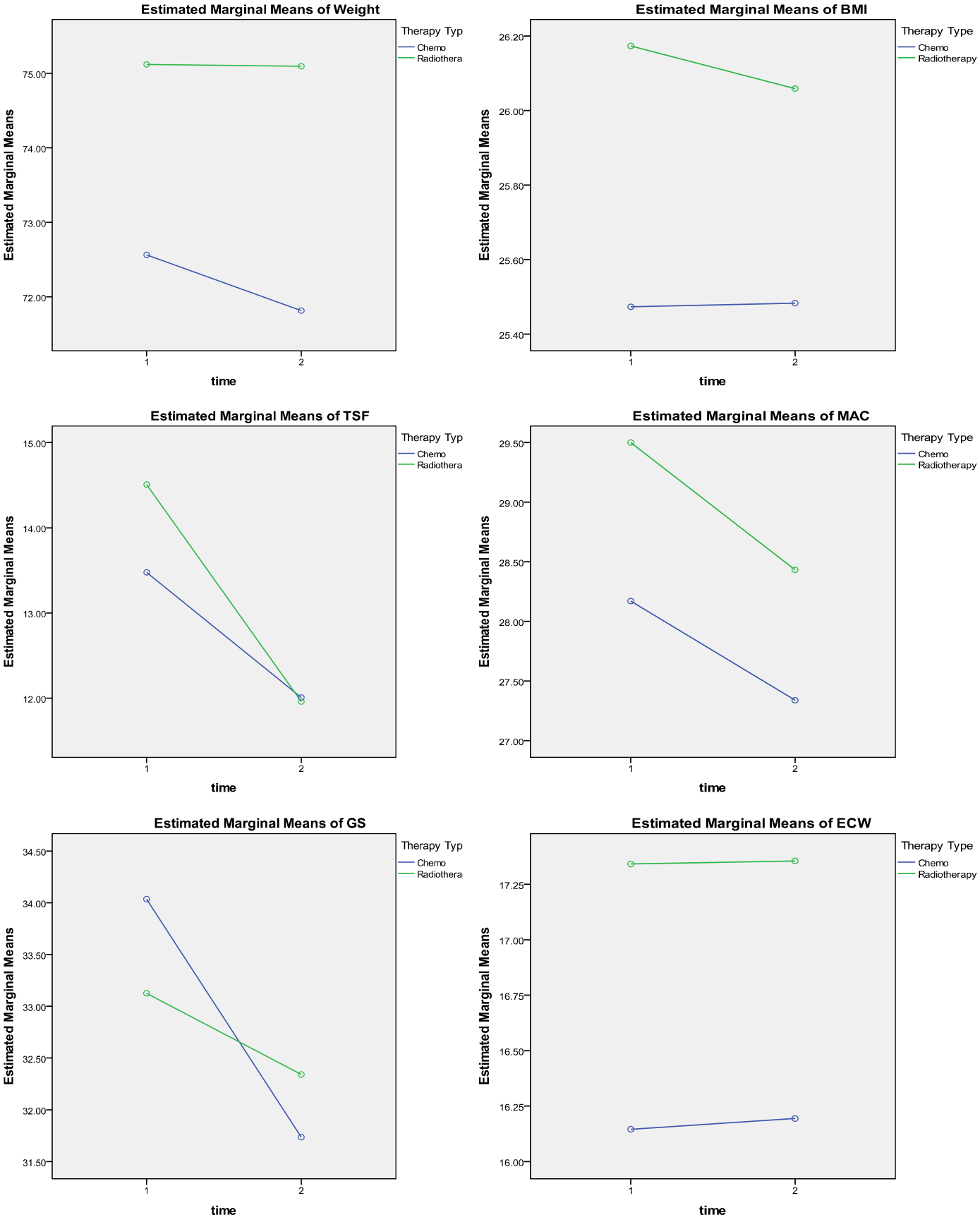




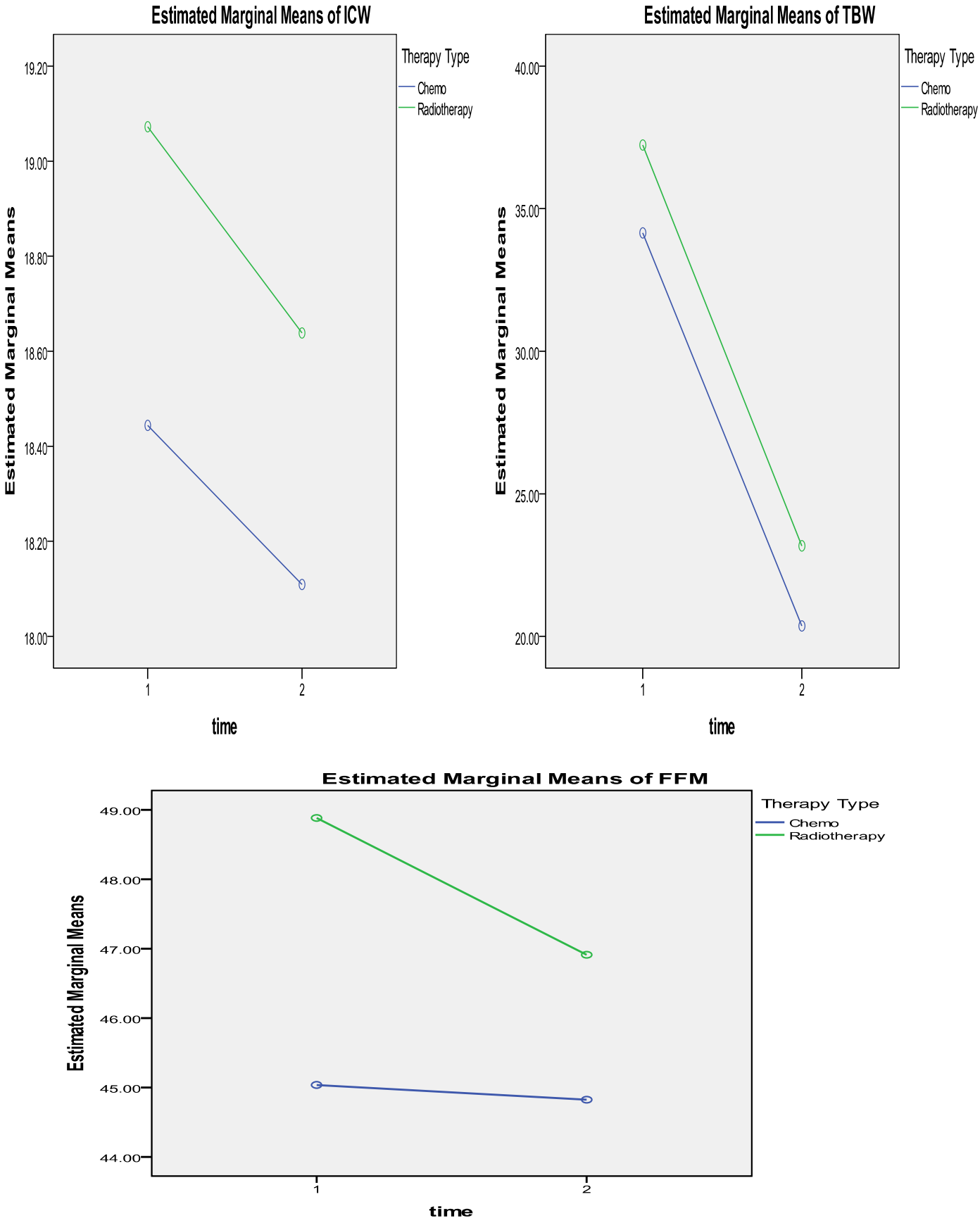




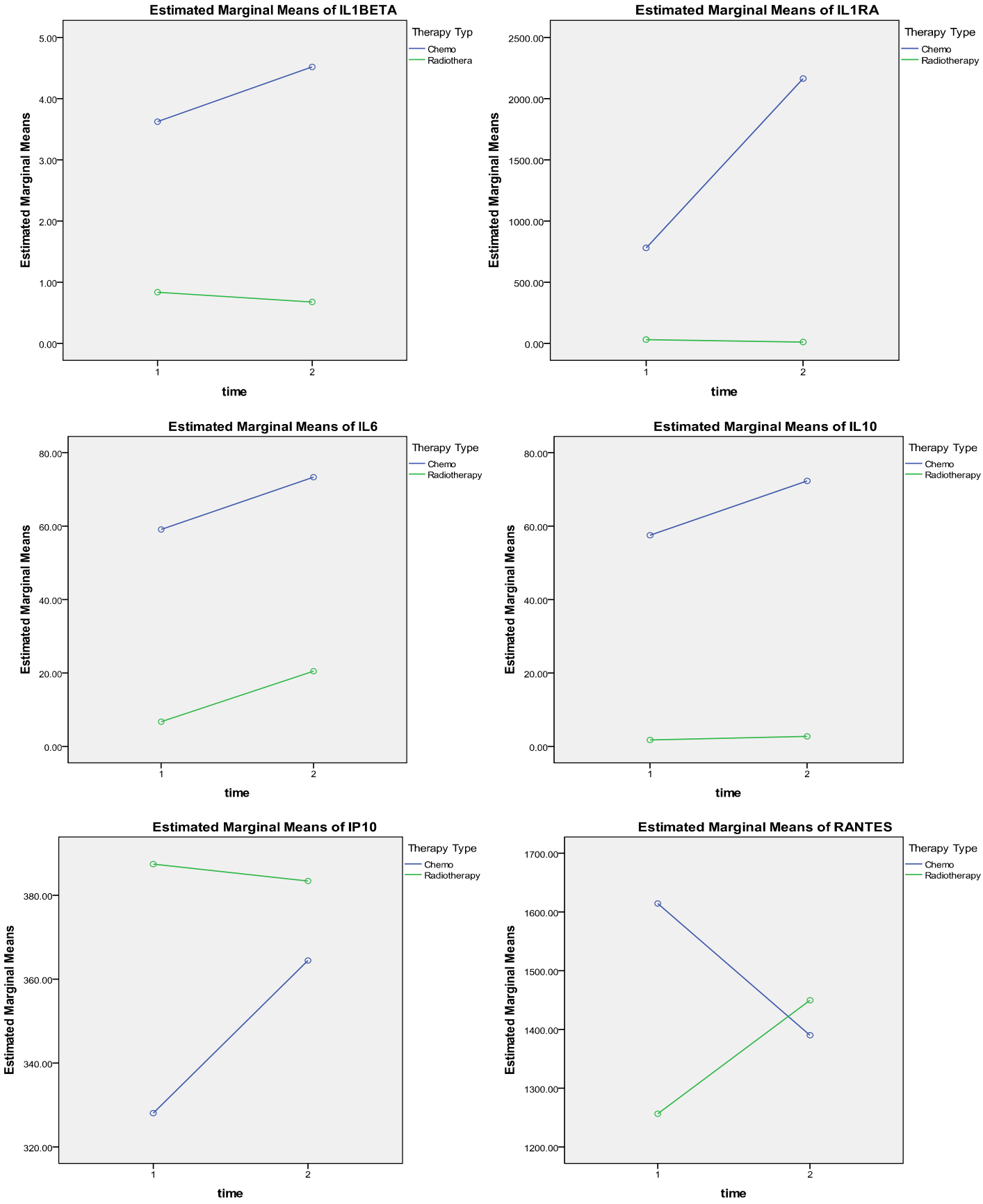
Figures (29) above show the changes in the estimated marginal means in both chemoradiotherapy and radiotherapy groups for the CPEX variables: Work (Watts) at VO_2Max, AT, VO_2Max, $VEVCO_2$AT, and VO_2HRMax



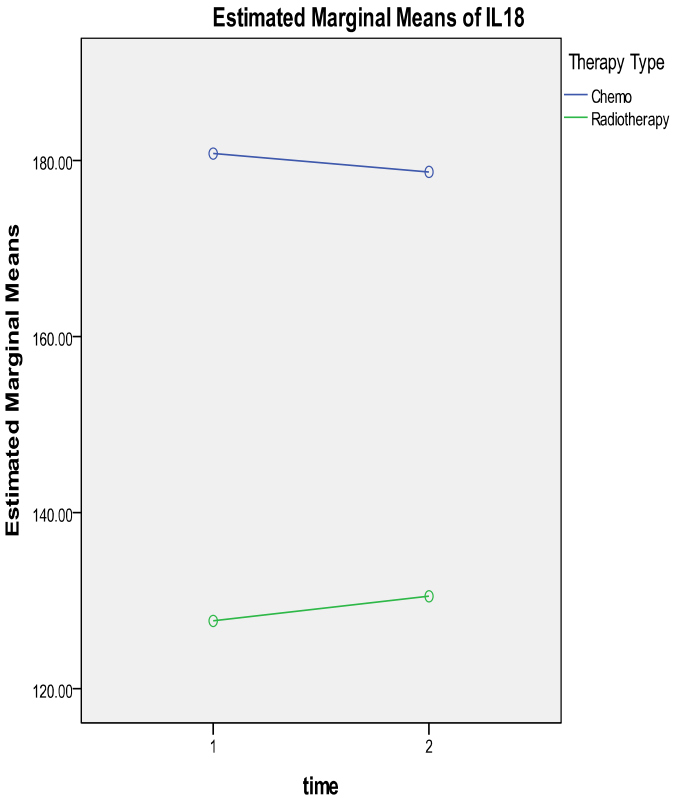
Figures (30) above show the changes in the estimated marginal means in both chemoradiotherapy and radiotherapy groups for the body composition variables: weight, BMI, TSF, MAC, GS and ECW

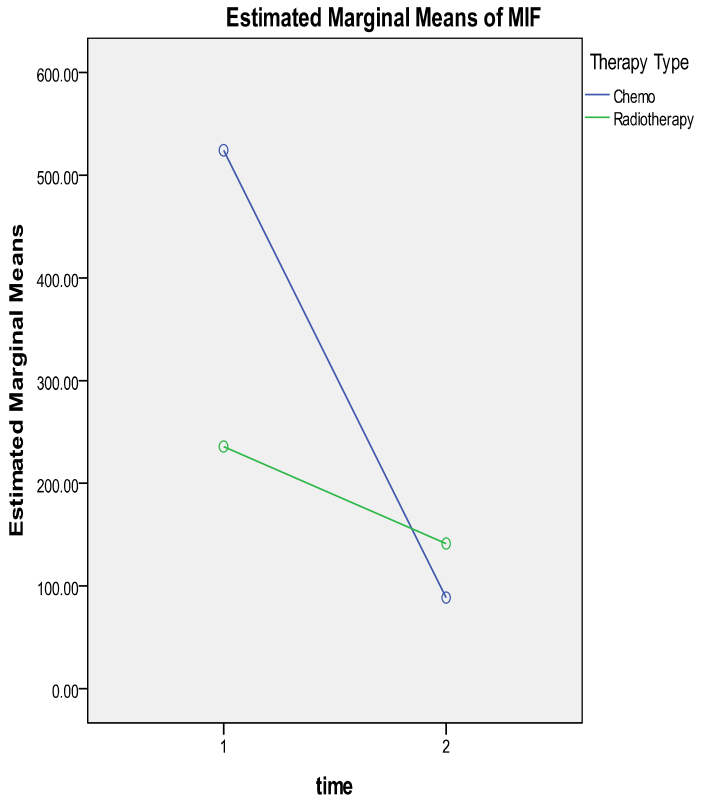


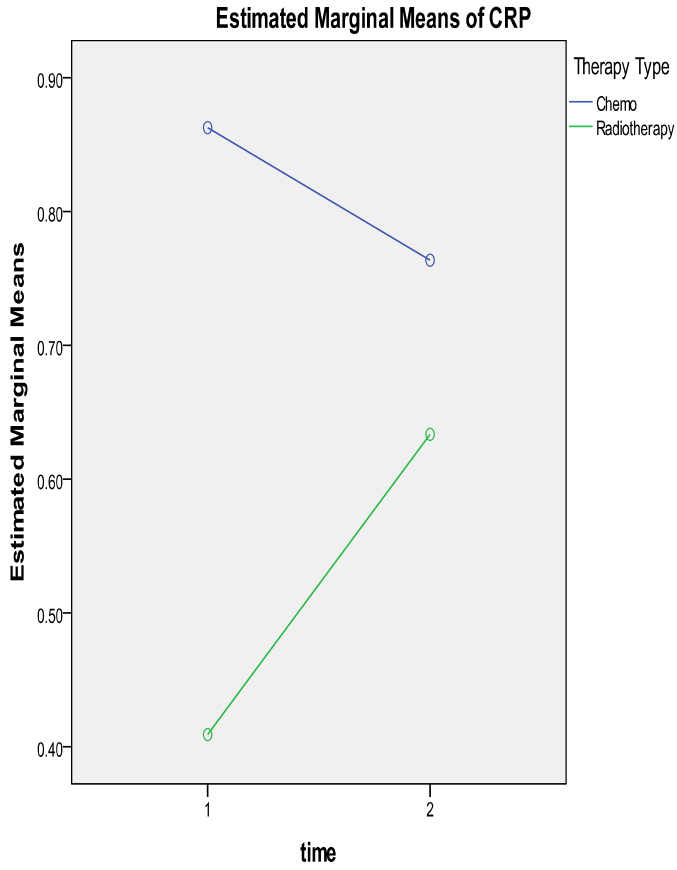
Figures (31) above show the changes in the estimated marginal means in both chemoradiotherapy and radiotherapy groups for the body composition variables: ICW, TBW and FFM

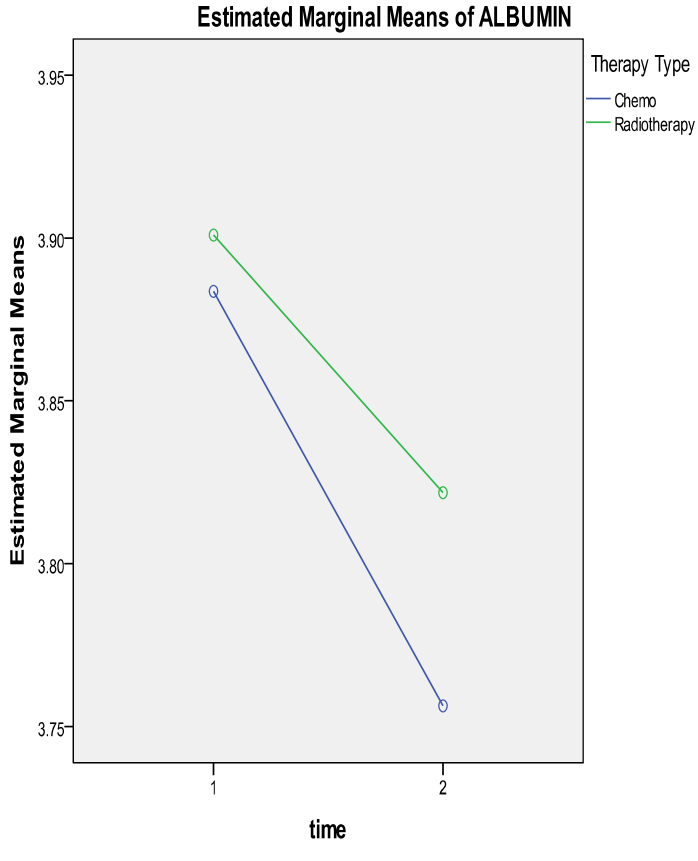


Figures (32) above show the changes in the estimated marginal means in both chemoradiotherapy and radiotherapy groups for the cytokines variables: IL1beta, IL1RA, IL6, IL10, IP10 and RANTES

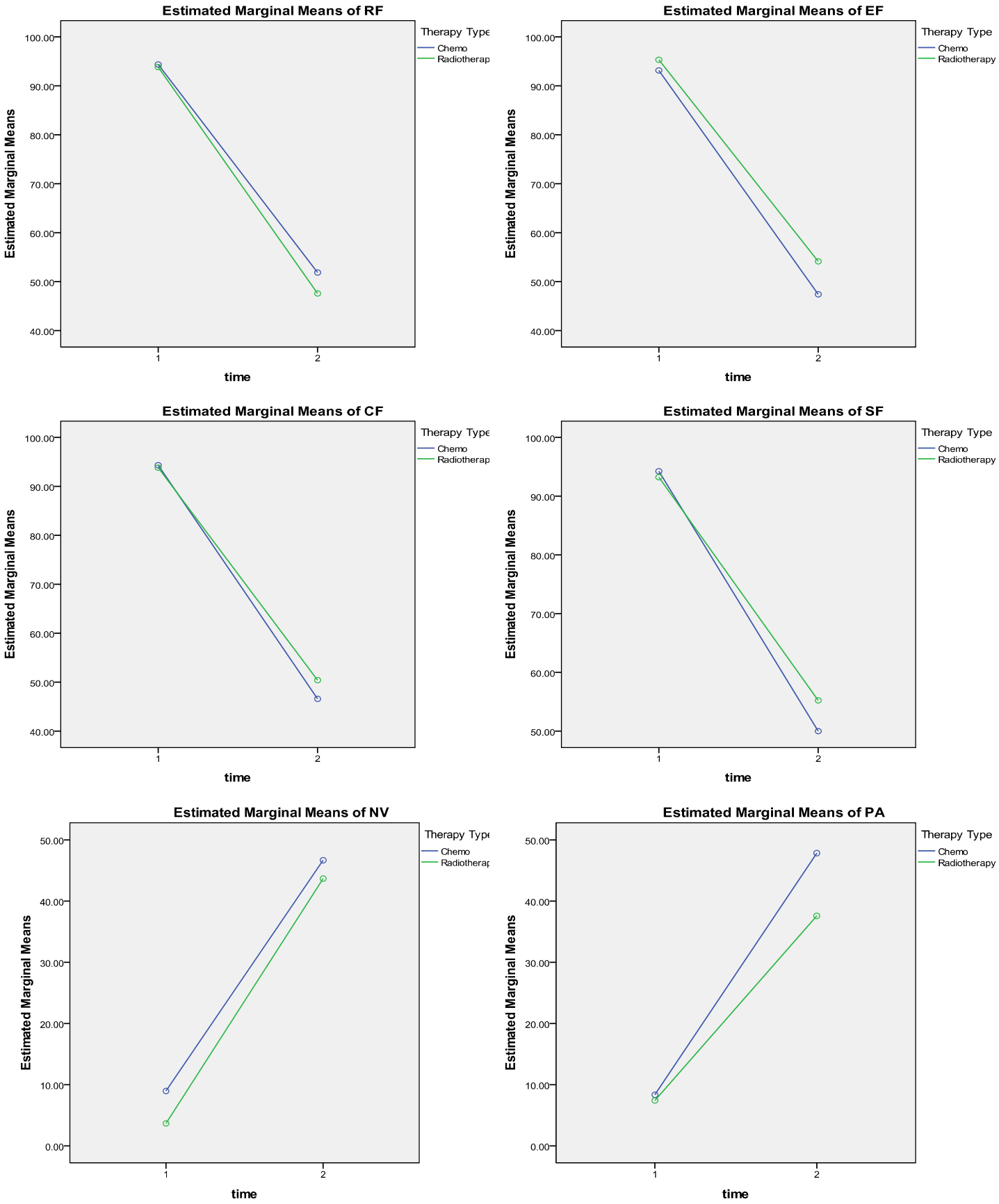




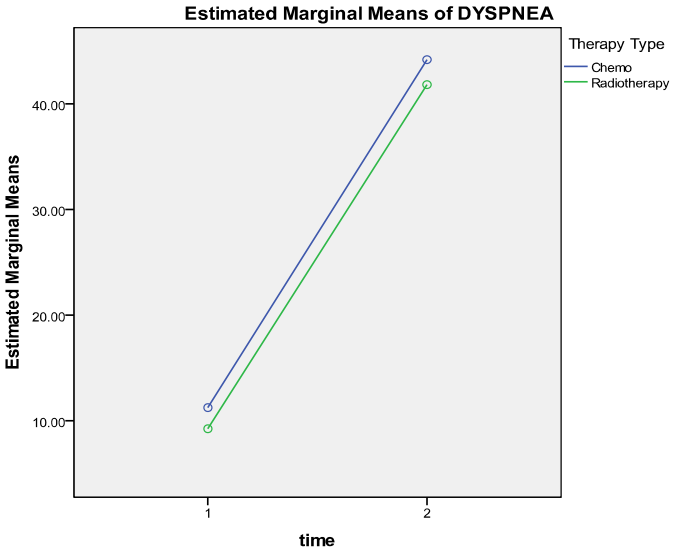


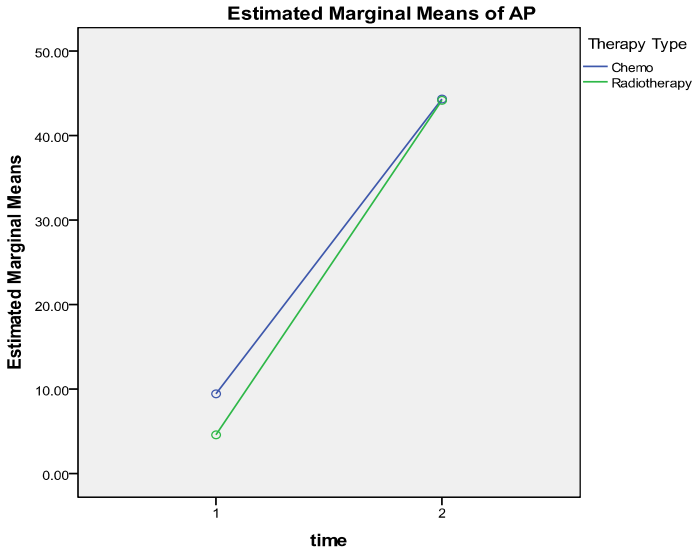


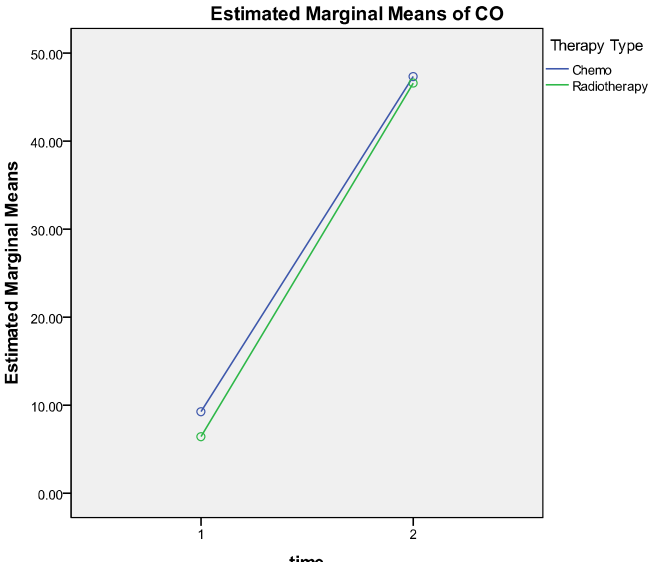
Figures (33) above show the changes in the estimated marginal means in both chemoradiotherapy and radiotherapy groups for the cytokines variables: IL18, MIF, CRP and Albumin

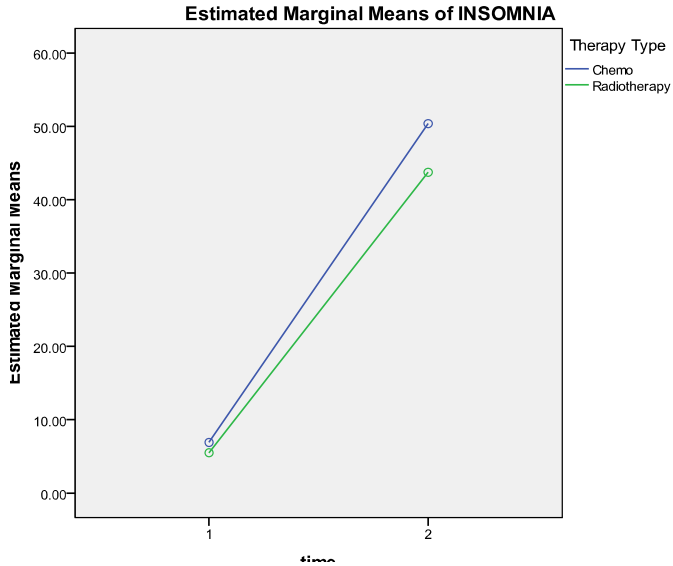


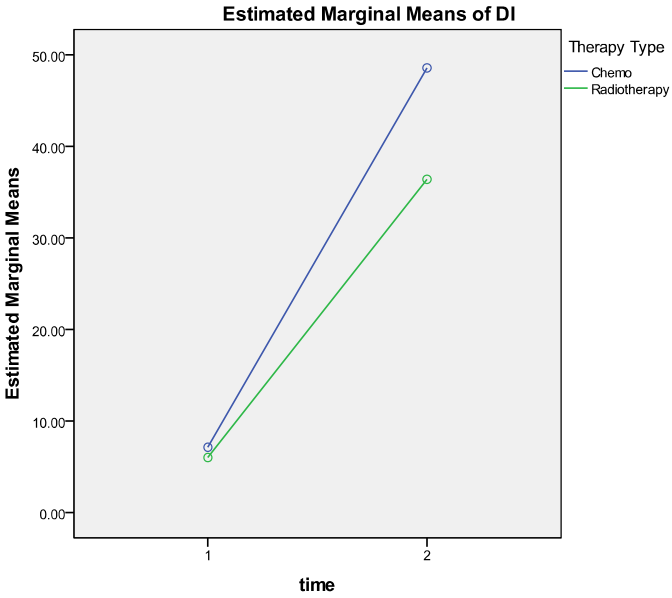
Figures (34) above show the changes in the estimated marginal means in both chemoradiotherapy and radiotherapy groups for the HRQL variables as measured with EROTC QLQ C-30 and PG SGA questionnaires

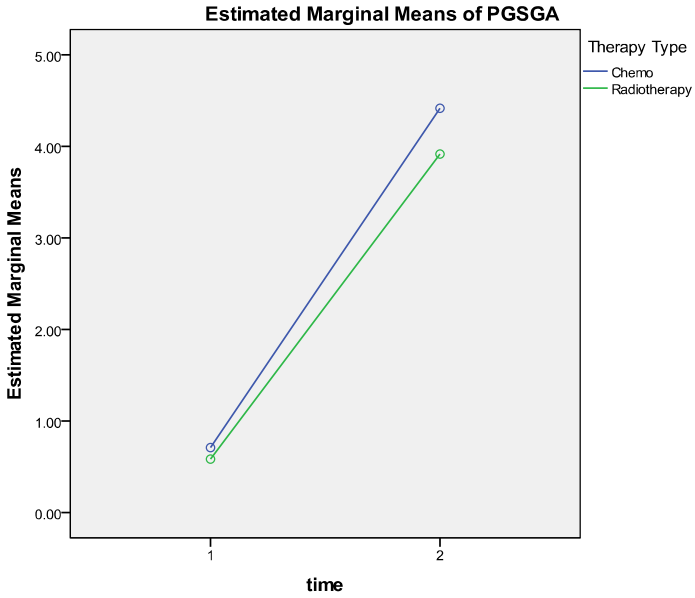












Figures (35) above show the changes in the estimated marginal means in both chemoradiotherapy and radiotherapy groups for the HRQL variables as measured with EROTC QLQ C-30 and PG SGA questionnaires

7.0 DISCUSSION

7.1 Overview

Colorectal Cancer (CRC) is the second commonest cancer causing death from malignant disease in the United Kingdom. Approximately 35,000 new cases and over 16,000 deaths each year related to CRC with an overall 5 year survival of approximately 55% [1].

The behaviour of colorectal neoplasia varies and depends on many pre and postoperative factors that can play an important role in its pathway. This study did not concentrate on tumour behaviour; however, we looked mainly at the possible physiological changes, in patients with rectal cancer, which might occur during the course of the disease incurred by the preoperative neoadjuvant treatment.

Modern CRC management combines surgical resection with or without an adjuvant preoperative therapy (APT) represented by long course chemoradiotherapy (rectum), short course radiotherapy (rectum) or chemotherapy with immuno-modulators (colonic) such as the FOXTROT trial.

APT could potentially reduce the peri-operative natural shedding of the tumour cells. This shedding might contribute to dissemination of tumour cells at the time of operation [62]. 50% of patients with recurrent CRC disease have peritoneal metastases which have a poor response to systemic therapy once established [458].

In 2009, Berardi *et al* showed in a detailed literature review that in the last two decades, new development in the multimodality treatments have improved the prognosis of locally advanced rectal cancer with local recurrences decreasing from 40% to < 10% and overall survival increasing from 50% to 75%. Hence, continuous research is needed to improve these regiments efficacy with minimal patients-related adverse events in clinical practice [459].

APT has a potential impact on the patient's ability to cope with the physiological stress from surgery. This could be due to the cardiotoxic effect of chemotherapy agents, which might reduce myocardial function leading to a reduced cardiac output and so oxygen delivery. This is well documented in the literatures and an indication to discontinue the treatment [460]. However, effects of APT on the functional capacity have not been explored properly yet.

Moreover, subclinical heart failure may produce a degree of pulmonary congestion, which will eventually influence the oxygen uptake during stress [461].

In addition, the neurotoxic effects of APT may insult the autonomic nervous system and interfere with the cardiovascular adaptation to increased oxygen demand and blood flow at tissue level [462]. Finally, changes at the cellular and mitochondrial level might interfere with the cellular respiration and cause tissue hypoxia [463].

Mak *et al* has found that despite widespread and rapid adoption of preoperative radiotherapy for locally advanced rectal cancer, it is still underused in certain sociodemographic groups [464].

Patients with poor physiological reserve preoperatively are more likely to have postoperative complications. These patients are at more risk of having poor short-term outcome after major colorectal resection such as anastomotic leak, infection and other cardiopulmonary events [465, 466].

Patients who are subjected to one-week course of preoperative radiotherapy have significantly shorter period of insult from APT compared to those who are undertaking 5-6 weeks course of combined chemoradiotherapy. However, radiotherapy may still induce an inflammatory response caused by cellular death and ultimately affect fitness for surgery especially in view of shorter interval between the end of APT and surgery in this group of patients [315].

There is a subjective impression among surgeons and anaesthetists that aggressive APT can significantly reduce the physiological reserve of patients awaiting cancer resection and this may account for the uncertain benefits of such treatment in some settings.

In our study, only patients with rectal cancer were recruited as those with colonic cancer were already randomised to the FOXTROT trial. We had two main groups, chemoradiotherapy (24 patients) and radiotherapy only groups (12 patients).

We have found that patients who had chemoradiotherapy were around the age of 59 years while radiotherapy regime was given to older patients with a mean of 72 years. This might explain the selection process by the oncologist at the MDT meetings to recruit younger and fitter patient for long course chemoradiotherapy. All of the radiotherapy patients had T3 rectal tumour.

The mean duration of chemoradiotherapy regime was 46 days and patients in this group waited for a mean of 36.5 days to have their surgical resection while the mean length of radiotherapy treatment was 5.7 days and patients waited for an average of 22 days to have their operation. There were more men than women in both groups.

Cardiopulmonary reserve, as measured with CPEX testing, was significantly compromised in the chemoradiotherapy group of patients, as there was a significant decline in the VO_2max and a significant increase in the pulmonary dead space represented by $VEVCO_2AT$ after APT exposure with p-value of 0.005 and 0.001 respectively. However, CPEX variables had minimal changes in the radiotherapy group post APT. This may be due to the small number of patients recruited in this group or might be related to the regime itself of having less toxic and systemic effects on the cardiopulmonary function.

With regard to the body composition data, both groups showed significant changes in different variables, which indicate the major effect of APT on different body compartments.

In the chemoradiotherapy group, there was a significant decline in the TSF, MAC and GS giving p-values of 0.007, 0.006 and 0.010 respectively. There was also a significant decrease in the TBW with p-value of 0.000 post APT.

In the radiotherapy group of patients, there was also a significant decline in the TSF, MAC and TBW with p-values of 0.013, 0.013 and 0.002 respectively. In addition, there was a significant reduction in the FFM in this group with p-value of 0.034 post APT exposure. No significant changes were noticed in the BMI values of both groups.

Different pro and anti-inflammatory cytokines together with CRP and albumin were compared before and after APT exposure. We could not find any particular trend in the cytokines behaviours. Some of them increased, others decreased and few did not show any changes post therapy exposure. However, in the radiotherapy group, IL6 was nearly significant with a p-value of 0.050. Larger cohort of patients might have an effect on the result of the cytokines behaviours. In addition, the timing of taking the serum samples from patients after finishing the anti-cancer surgery might have an impact on the cytokines levels and trends.

Multiple questions and assessments were applied to measure the health related quality of life and physical wellbeing in both groups of patients pre and post APT using EROTC QLQ C-30 and PG-SGA questionnaires. There had been an impressive significant worsening of all of the endpoints measured with these two validated questionnaires giving a p-value of less than 0.000 post APT exposure.

The body physiological changes are interacting with each other. We have therefore tried to link between the study outcomes to get a possible correlation among these physiological parameters. Hence and in addition to the primary aims of this study to assess functional capacity post APT, Spearman correlation tests were performed to look for any possible interaction among the research variables. Positive correlation means both dependent and independent parameters increase or decrease together while negative correlation means one increases and the other decreases and vice versa.

In chemoradiotherapy group, the work load (watts) at VO_2max of patients are directly proportional to their body weight and grip strength (positive correlation). Moreover, VO_2max, $VEVCO_2$AT and VO_2HRmax are adversely proportional to IL1β, RF, EF variables and FFM (negative correlation). On the other hand, HRQL variables are positively correlated with most of the body composition endpoints (except TSF) while it is negatively associated with TSF and BMI.

In the radiotherapy group, Work (Watts) at VO_2max, AT and VO_2HRmax are negatively correlated with insomnia, body weight and CRP respectively. While AT, VO_2max and $VEVCO_2$AT are positively correlated with GS, fatigue and (TBW + physical function) respectively.

On the other hand, HRQL variables had different correlations with body composition endpoint based on the specific physical function assessed with the two questionnaires.

Additionally, mixed ANOVA test was performed to find out if the changes of both chemoradiotherapy and radiotherapy groups were constant or not. This test did not show any significant results which means that both groups of patients had the same trend of changes in their CPEX, body composition, cytokines and HRQL variables after any type of APT exposure.

Whilst APT has shown an overall benefit in a number of settings, there is also evidence that it may harm patients in different ways. This project allowed us to identify patients at risk of functional deterioration following APT in order to develop certain interventions to obviate the adverse effects of APT. These intervention may include exercise training, nutritional interventions with or without supplements, modifying the interval between APT and surgery, modulation of the inflammatory cascade and, in some cases, modifying the APT regime for a particular patient with careful selection [467].

Our aims in this project were mainly observational to find out the possible physiological deterioration in colorectal cancer patients after APT administration. We did not explore any methods of intervention to optimise this cohort of patients pre-operatively. This might be the next step of the study to select the best way to optimise these patients before the tumour resection in order to reduce the surgical morbidity.

It is currently evident from previous literatures that the pre-operative physiological status of patients with colorectal cancer predicts long and short term outcomes after surgical resection [228, 468]. Hence, multimodal preoperative optimisation with supervised exercise programmes [469], smoking cessation [470], nutritional support, anti-inflammatory treatment (ex: aspirin) [471] and intensive cardiopulmonary support with medication is presently the hot topic drawing the emphasis on improving the postoperative mortality and morbidity in this cohort of patients. Future research work is needed to figure out the interaction of these treatments and their impact on human body physiology.

Further work is needed to explore the effect of APT on a large cohort of patients with advanced colorectal cancer in homogenous population depending on age, type of cancer as well as type and duration of APT as our study was performed on a mixed population. Full biological and physiological mechanism needs to be understood behind the effect of APT on patients with neoplastic tumours.

7.2 The glory of Cardiopulmonary exercise testing (CPEX)

In 1993, Older and colleagues demonstrated an association between cardiovascular mortality and anaerobic threshold as determined by CPEX testing in 187 elderly patients undergoing major intra-abdominal surgery [245]. Patients who had an anaerobic threshold of less than 11 ml/kg/min were identified as being at a higher risk of post-operative death. In a subsequent study, the same group examined risk stratification of patients presenting for major non-cardiac surgery and postoperative outcome. Patients with an anaerobic threshold of greater than 11 ml/kg/min with no inducible ischemia and a ventilatory equivalent for oxygen of less than 35 were considered to be at low risk of complications and were managed on the ward after surgery.

Patients with an adequate anaerobic threshold (AT) but with an elevated ventilatory equivalent for oxygen or evidence of myocardial ischemia received high dependency care in the postoperative period. Those with an AT of less than 11 ml/kg/min were cared for in intensive care after their surgery [252]. The authors pointed out the value of CPEX testing for identifying patients at low risk of complications who are candidates for ward management after surgery.

A review by Smith and colleagues examined the value of CPEX in predicting perioperative complications in non-cardiopulmonary surgery [472]. They reviewed all studies comparing the predictive value of maximum oxygen consumption (VO_2max/peak) or anaerobic threshold, and analysed nine studies in further detail.

They concluded the majority of studies demonstrated that CPEX variables, especially VO_2peak, are associated with periperative morbidity and mortality in non-cardiopulmonary surgery. Six out of the seven studies which reported sufficiently detailed findings on peak oxygen consumption [457, 473-477] and four out of six reporting anaerobic threshold [245, 457, 473, 477] found these variables to be associated with perioperative complications.

In most of the United Kingdom clinical centres, VO_2peak of less than 15 ml/kg/min and/or an AT of less 11 ml/kg/min is considered as clinically significant and carries high risk of mortality and morbidity. Hence, careful patient counselling, MDT selections, considering other non-surgical modality of treatments with pre, peri and postoperative intensive management is vital to meet this poor cardiopulmonary reserve.

An association between poor performance during CPEX testing and mid-term outcome has also been reported for aortic surgery. Carlisle and colleagues found reduced 30 day survival and mid term (2 year) survival in patients who performed less well on preoperative CPEX testing [457]. On multivariable analysis, greater values of the ventilatory equivalent for CO_2 (VE/VCO_2) at anaerobic threshold were found to be associated with both 30 day mortality and worse mid-term survival.

More recently Swart and Carlisle have conducted a randomised control trial of risk stratification based on CPEX criteria in patients undergoing major non-cardiac surgery [457]. Patients with an AT of less than 11 ml/kg/min were randomly allocated to receive either high dependency care or normal ward postoperative care. Patients with an AT greater than >10.9 ml/kg/min were sent back to the ward for their postoperative care. The number of cardiac events (acute LVF and acute coronary syndromes) and length of hospital stay were measured in each group of patients. No reported cardiac events and lowest hospital stay occurred in the patients with an AT of greater than 10.9 ml/kg/min.

In their review, Smith and colleagues speculated that adverse outcomes following different types of surgery might be associated with altered CPEX variables. In addition, the strength of the association between exercise capacity and perioperative risk may be different for different types of surgery as the pre-existing morbidity might affect the predictive value of CPEX results. They also concluded that CPEX testing needs to be validated for each surgical procedure [472].

Our project data showed a significant reduction in the cardiac reserve, represented by VO_2max, of those patients exposed to chemoradiotherapy. In fact, we have measured the VO_2peak for these patients as none of them has reached his/her maximum oxygen consumption (only reached their peak oxygen consumption). This drop in VO_2peak or VO_2max is a marked limiting factor affecting the cardiopulmonary function and might contribute to peri and postoperative morbidity. CPEX testing can be used to quantify the cardiopulmonary aspect of physiological reserve. This is mainly seen in colorectal cancer patients exposed to combined chemoradiotherapy.

The previously mentioned “Dual” method of measuring AT may not be reliable in an anxious subject who has been hyperventilating prior to the start of exercise. Hyperventilation before the start of exercise leads to depletion of body stores of carbon dioxide and may lead to inaccurate estimation of anaerobic threshold with a “pseudo-threshold” being seen before the onset of metabolic acidosis [478].

Such hyperventilation which often occurs in stressed patients subjected to any form of testing procedure.

To obviate this problem, the respiratory rate, respiratory exchange ratio and end-tidal carbon dioxide should be allowed to settle to normal values before the start of exercise. If this cannot be achieved the anaerobic threshold as determined by non-invasive testing has to be regarded as unreliable. The AT represents the exercise intensity that can be sustained indefinitely and is dependent on exercise modality [235]. Values from cycle ergometry are 5-10% less than those obtained from treadmill testing. Exercise intensities above AT are associated with a limited exercise tolerance. AT expressed as a percentage of VO_2max increases with age and it generally occurs at 50-60% of VO_2max but there is a wide range and values between 40% and 85% of VO_2max are considered to be within normal range. Values of anaerobic threshold below 40% of predicted VO_2max are indicative of significant exercise limitation [416].

Furthermore, our study showed a significant increase in the $VEVCO_2$ post chemoradiotherapy. This is an objective measurement of the pulmonary dead space (means more un-recruited alveoli) and strongly associated with poor ventilatory function, pulmonary arterial hypertension and cardiac failure [479]. This parameter had significantly increased at both of the critical point, anaerobic threshold and maximum oxygen consumption. However, this value did not change post radiotherapy regime.

CPEX testing is not suitable for determination of functional capacity in all groups of patients. Those severely limited by musculoskeletal or neuromuscular diseases will find any sort of exercise difficult.

In patients with lower limb weakness it can be possible to gain an estimate of functional capacity using a hand cycle ergometer. However, VO_2peak values obtained from arm ergometry are only about 70% of those obtained from leg exercise and an increase in lactate is often seen early in exercise [480, 481].

Although, both the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) guidelines on cardiac assessment for non-cardiac surgery highlight the importance of estimating exercise capacity in assessing perioperative risk [482]. The value of CPEX testing lies in the insights about cardiopulmonary function offered by the data obtained.

The test may be used to direct patients to the appropriate level of post-operative care. It may also be used to direct the pre-operative preparation of the patient. The presence of inducible myocardial ischemia may indicate the need for appropriate cardiac medications and further cardiological investigation. Poor cardiac function may be manifest by a low oxygen pulse. Elevated ventilatory equivalents throughout a test may represent respiratory insufficiency and suggest a need for preoperative medication changes and for vigorous physiotherapy in the post operative period [235].

As it is well established that there is an association between a limited exercise capacity and the risk of post-operative complications, various risk scores such as the revised cardiac risk index are also available for the pre-operative risk stratification of patients [483]. The logical next stage in the development of pre-operative risk stratification is the development of tools, which integrate the results of pre-operative stress testing, pre-operative risk scoring and biomarkers such as brain natriuretic peptide to give a comprehensive tool for pre-operative risk stratification [484].

This will require the prospective study and follow up of large numbers of patients but has the potential to offer better tools for preoperative risk prediction that either risk scoring or exercise testing alone. In the meantime, preoperative CPEX can reasonably be supported on the basis of an established relationship between exercise capacity and outcome and plausible scientific arguments to support its validity.

In a cancer rehabilitation programme, De Backer *et al* have found that high-intensity strength training was well tolerated by CRC patients with a significant improvement in muscle strength and significant increase in the VO_2max by 10% in men and 13% in women.

It has been concluded that a supervised, high-intensity strength training programme was an effective means to improve muscle strength, cardiopulmonary function, and HRQL and should be incorporated in cancer rehabilitation programmes [485].

Chemotherapy agents, such as 5-Fluorouracil (5FU), are known to cause coronary endothelium toxicity and spasm, myocardium hypoxia and toxicity as well as toxic myocarditis [486, 487]. These systemic agents circulate in the body and cause microvascular damage as well as tissue hypoxia at cellular level leading to an end-organ mal-function or dysfunction.

This explains the proven disturbance in body physiology after the neoadjuvant therapy in our study. Only one patient out of 36 had a witnessed and documented myocardial toxicity post APT exposure. He was a 64 years old who was previously fit and well with no significant past medical history of note. This patient had the first CPEX testing which was normal (AT=13 and VO_2max=18.2 ml/kg/min), then had a 5-week course of 1150mg Capecitabine (oral 5FU chemotherapy agent) and pelvic radiotherapy. Only 1 week after finishing the APT regime, this patient had his second CPEX test at the Cardiology laboratory, as per the study protocol, when he started to have ventricular tachycardia (VT) and fibrillation (VF) only 1 minute after exercising on the CPEX bicycle with a significant drop of AT to 11 and VO_2max to 15 ml/kg/min.

According to the study protocol, a consultant anaesthetist, the senior author (surgical trainee) as well as two trained cardiac physiology personnel must be present all time during the CPEX testing. This patient had a successful cardiopulmonary resuscitation and was reverted to normal sinus rhythm. He was admitted to CCU and had all of the necessary investigation done including blood test, Troponin T, Transthoracic Echo and coronary angiography. They were all normal and did not show any sings of an existing disease. Two experienced cardiologists have labelled this event clearly as 5FU-myocardial toxicity. Subsequently this patient was optimised with Statin, Aspirin, Clopidogrel and Bisoprolol plus all of the Surgical, Oncological and Anaesthetic teams were informed and an HDU bed booked. Thereafter, his surgery was delayed by 8 weeks after finishing his neoadjuvant treatment and he had his surgical resection with no unexpected peri and postoperative complications and discharged home one week later. If this patient did not have his second CPEX test done, he would have been at a high risk of developing these events peri or postoperatively which will increase the surgical mortality and morbidity. This is a clear example about the effect of APT on the cardiopulmonary reserve and the whole idea about this study.

In another study, it has been suggested that although the prognosis of recovery from this myocardial toxicity is good, the mortality rate still ranges between 2.2 and 13% in case of symptomatic cardiotoxicity [488].

Hence, the dose of the chemotherapy agents must be adjusted precisely and the oncologists should carefully select patients prior to the administration of any chemical agents.

In addition, we should frankly point to the invaluable role and importance of the pre-operative CPEX testing as a way of diagnosing and identifying high-risk individuals to avoid any unexpected complications and improve postoperative outcomes.

7.3 Body compartments value in managing colorectal cancer patients

Abnormal fluid balance can affect the cardiovascular function and subsequently alter the end-organ perfusion. Changes in the body composition compartments could be tested by various methods. Body composition techniques subdivide the body into compartments based on differing physical properties. The different compartments reflect hydration, nutrition/wasting, body fat, and bone mineral content. In our study, we have used Bioelectrical impedance analysis (BIA) and anthropometric measurements. BIA is a safe, cheap and acceptable technique by most patients. Multiple serial measurements are important to identify changes in hydration or nutrition earlier than would occur with the ward routine monitoring and charts, allowing appropriate intervention and management to improve patient clinical service and outcomes. BIA information can confirm the clinical impression of some patients as well as detecting changes in others with subclinical manifestation.

This technique has some limitation when used between different individuals, but in our research, the same method was used before and after the administration of APT, hence, reliable results were obtained with comparison of the pre and post APT values.

A wrist-ankle measurement using HYDRA ECF/ICF machine assumes the body is one perfect cylinder when in fact the body is comprised of five imperfect cylinders (two arms, two legs and trunk) with arms and legs contributing to 90% of the measurement [437] as the trunk has a large cross-sectional area [299].

Fluid volume tends to be evenly distributed in healthy subjects, thus the wrist-ankle measurement is useful and accurate [489]. As such, the relationship between a wrist-ankle measurement and total body water is a function of the body water being evenly distributed. However, assuming even distribution of the body fluid is not true in certain medical conditions and between different populations, hence; segmental measurement of body composition might be of good value here [438].

BIA can give wide ranges of normality in the body composition of normal individuals, with wide variation in body fat and skeletal muscle among healthy individuals. However, this technique limitation is not of a great value in this research programme as individuals were controlling themselves plus we measured the mean of three readings pre and post APT exposure. This possible error was even more reduced by excluding patients with renal disease and nutritional deficits of any kind.

Changes in body composition readings could be greatly influenced by the vascular perfusion of the limb. Hence, impaired cardiac function which might result from the APT administration can alter body fluid compartment volumes when measured with the wrist-ankle method [440]. This is actually true as this study demonstrated a significant fluid depletion and generalised body dehydration with a significant drop in the total body water in both groups of patients, which clearly indicates a clinically significant level of dehydration pre-operatively (post APT exposure). This could be explained by the impaired cardiopulmonary function and poor tissue perfusion happening after the anti-cancer therapy. Furthermore, FFM was reduced in the radiotherapy group, which is reflecting a reduced level of nutrition and wasting post neoadjuvant treatment.

Although the HYDRA ECF/ICF technology has been repeatedly used to measure an accurate FFM, the prediction of FMM with impedance is subjected to a significant error as it is directly linked to the ECF volume [432, 490]. An increase in the ECF would result in a large predicted FFM and higher percentage of fat estimation.

ECW can be further split into intravascular volume (has an effect on blood pressure, development of left ventricular hypertrophy, and cardiac dysfunction) and extravascular fluid (affecting tissue hydration and oedema) [270]. Therefore, even subtle changes within these sub-compartments for a given ECW can affect the cardiac reserve and varying the oncotic pressure. Therefore, this might have an effect on the CPEX data and the functional capacity post APT exposure.

Moreover, the overall patients triceps skin fold (TSF) and mid-arm circumference (MAC) showed a significant decline after the neoadjuvant therapy. TSF and MAC are active components in the postoperative rehabilitation programme as both forms the basis of the lean body mass. By this, we mean having more muscle and less fat bulk is important for early mobility, prevent of thrombo-embolic phenomena, prevent chest infection and early hospital discharge.

Recent work and research have suggested that when the HYDRA ECF/ICF technology of measuring TBW is combined with densitometry, the prediction of FFM and fat estimation is greatly improved [491-493].

Gupta *et al* have evaluated the nutritional status of CRC patients using BIA, serum albumin, prealbumin and transferrin, subjective global assessment (SGA) and QLQ-C30. It has been showed that the prevalence of malnutrition, as determined by SGA, was 41%. Well-nourished patients had statistically significantly better quality if life (QoL) scores on the global, physical, and role functions compared to malnourished patients. Interestingly, the median role function score in well-nourished patients was 41.6 points higher than the corresponding score in malnourished patients, indicating a "much better" functioning from a patient's perspective. Similarly, QoL scores on multiple symptom scales were statistically significantly better among well-nourished patients. Hence, malnutrition is a significant cause of morbidity and mortality in advanced colorectal cancer and is associated with poor QoL [494].

We have also found that the individual muscle power, represented by the grip strength (GS), had reduced post chemoradiotherapy. This again is an important and determining factor to tackle any postoperative complications and enhance quick recovery.

Interestingly, BIA can also be used to verify 5-Fluro-Uracil (5FU) clearance and volume of distribution in CRC patients undergoing combined APT. The pharmacokinetic of this chemotherapy is better predicted by BIA; which will lead to an improved dosing with the 5FU [495].

Surprisingly, creatine oral supplementation can improve the deranged BIA parameters resulted from the adjuvant pre-operative therapy but has failed to improve muscle mass or function and QoL in patients with colorectal cancer [496].

Body weight and body mass index (BMI) did not show significant changes after APT. We might need a bigger sample to show changes and make a conclusion. Despite this, individuals body weight had a strong and significant correlations to the cardiopulmonary reserve and HRQL. Hence, neoadjuvant treatment can also indirectly affect the body physiology of CRC patients via its direct effects on the BMI as changes in body weight is strongly linked to the cardiopulmonary function and the patients psychological status.

Interestingly, many studies in the literatures have indicated a reasonable association between obesity and risk of colorectal adenomas and cancer. A recent pooling study by Jacobs *et al* from 8213 patients was performed in 2009 to highlight the association between body mass index (BMI) and metachronous neoplasia varied by the lesions characteristic, family history, sex and colorectal manifestations. Exploratory analyses indicated that BMI was significantly related to most histological characteristics of metachronous adenomas among men but not among women. They have also concluded that body size, mainly in men, may affect colorectal carcinogenesis at comparatively early stages [497].

Our project has confirmed noticeable changes in the body composition after the APT administration and these changes in the body fluid and fat distribution can affect the CRC course and behaviour after the anti-cancer therapy which could be linked to peri and postoperative complications [498].

BIA does not measure fat directly, but in a patients where body weight is changing without corresponding changes in ECW or ICW, it is most likely that there is a change in their body fat that can be calculated [270].

BIA data suggested changes that may not have been clinically apparent. To give a clear image about the individual body composition, we recommend serial BIA measurements over a period of time pre and post APT exposure rather than one-day readings. This is much revealing as there is a normal physiological fluctuation of body weight and composition over time, especially when there is an active colorectal cancer within the body. BIA is a technique that is acceptable to patients and can be readily performed in clinical situations. Therefore, changes in body composition, as tested by BIA and anthropometric tests, are multifactorial and could be caused by direct or indirect insults.

Neoadjuvant treatment itself can have a direct impact affecting the body composition changes represented by fluid depletion, end-organ tissue hypoxia and a significant increase in the catabolic rate [499].

In addition, APT can also have a direct non-specific adverse reactions such as such as nausea, vomiting, weight and appetite loss (the cancer anorexia-cachexia syndrome). These systemic symptoms can indirectly affect the body physiology via different mechanisms involving the cardiopulmonary system, inflammatory cascade and the HRQL status.

On the other hand, the composition of the body compartments could be changed by the indirect effect of the APT such as poor tissue perfusion (impaired cardiopulmonary function), induction of immune response (SIRS, CARS) as well as the psychological impact of the therapy (poor physical and nutritional well-being).

Detecting statistically significant changes for patients can often require serial measurements over a long period especially if the changes are occurring at relative slow rates. Hence, the statistical ability to identify a significant change in body composition is dependent on not only the measurement precision, but also the biological variability of the body composition parameter in the research population and the sample size of the study group.

The limitation and complexity of the BIA dictate careful interpretation of results and data, which should be taken in conjunction with other components of clinical assessment rather than as an alternative technique. Further systematic studies, to evaluate the ability of BIA to alter and improve clinical management compared with conventional standard clinical assessment, are important to refine the BIA ability to define normality within an individual.

7.4 Nutrition in CRC patients; role and methods

It is well known, for years, that malnutrition in patients with neoplastic diseases is associated with a poor prognosis and that weight loss is an important predictor of mortality [500-502].

Cancer patients usually suffer from cachexia because of anorexia and metabolic alterations, such as inflammation, increased muscle proteolysis, as well as changes in the metabolism of lipids, carbohydrates and proteins.

To date, no nutritional, pharmacological or metabolic intervention has proved effective in preventing these metabolic changes [503].

As for energy metabolism, an imbalance between pro-inflammatory and anti-inflammatory cytokines, which is typical of cancer patients, may lead to an increase in resting energy expenditure (REE) and contribute to the development of cachexia. More recently, it has been recognized that the metabolic response to a tumour may differ, leading to a hypometabolic state in some patients.

Malnutrition has been shown to affect post-operative outcome from previous studies, so it would be beneficial to identify those who are malnourished or who are at risk of becoming so preoperatively. In a recent study in 2010 by Burden *et al*, 87 patients were enrolled and over half of these patients had lost weight prior to surgery and one in five were malnourished. Body composition measurements with bioelectrical impedance analysis and anthropometric measurements have demonstrated malnourished patients with significantly less fat free mass compared to patients who were not clinically malnourished. Hence, nutritional screening would be beneficial preoperatively to identify weight-losing patients at an early stage in the care pathway when they initially enter the secondary care system [504]. In addition, Garth *et al* have found that malnutrition and its associated complications are considerable issues for surgical patients with colorectal cancer. Poor nutritional status coupled with delayed and inadequate post-operative nutrition practices are associated with worse clinical outcomes [505].

In our study, we have used the PATIENT-GENERATED SUBJECTIVE GLOBAL ASSESSMENT (PG-SGA) to assess nutritional changes post APT exposure. This tool is reproducible in several clinical settings (inpatient, outpatient, home care and hospice), cost-effective, easy to use, able to predict those patients who need nutritional intervention and who will benefit from nutritional intervention, and have little inter-observer variability. We have found that patients started with stage A (normal and well nourished) and ended up with stage B (moderately mal-nourished) after the chemoradiotherapy regime. This reduction in the SGA rating was obtained via assessing the PGSGA questionnaire parameters as well as the anthropometric measurements (Weight, BMI, TSF, MAC, GS) [506].

Few evidences are available in the literatures supporting the importance of postoperative nutritional support in CRC patients. Chen *et al* have showed that "non-risk" patients who did not receive postoperative nutrition support had a higher rate of postoperative complications than patients who received postoperative nutrition support with a longer postoperative hospital stay. Hence, appropriate and moderate nutritional intervention can improve the postoperative outcome of colorectal cancer patients [507].

A recent in vitro study showed that a lipid emulsion containing fish oil (FO) slows the growth of colorectal cancer cells and enhances their sensitivity to 5-fluorouracil (FU).

A lipid emulsion containing FO has a growth inhibitory effect on a human colon adenocarcinoma cell line, an effect not due to the induction of apoptosis, and potentiated the S phase-halting effect of FU. Thus, an FO lipid emulsion may be of benefit in colorectal cancer [508]. This is a useful evidence to show the importance of preoperative nutritional support in improving the outcome of CRC patients.

Post APT patients awaiting CRC surgical resection might benefit from supportive counselling via meetings with a dietician or specialised nurse about the importance of nutrition and ways to optimise the body nutritional requirements to minimise surgical related complications. Many studies are available in the literatures to support the significance of preoperative individualized nutritional care, based on each patients energy needs, to prevent surgical sites infections, cardiopulmonary events, anastamotic leak and long hospital stay. All these factors will eventually reduce the peri and postoperative mortality and morbidity [509-511].

Recent evidences showed that individualised intervention could improve the overall food intake and the quality of life as well as reducing postoperative complications in cancer patients undergoing chemoradiotherapy. This personalised intervention needs a close collaboration and monitoring with the patient to assess their dietary compliance [203, 308, 512].

Early nutritional support, with proper protocols, is very important in patients with severe malnutrition. Therefore, specific screening tools were developed and validated for malnourished patients such as Patient Generated Subjective Global Assessment, Subjective Global Assessment, Nutrition Risk Index and Malnutrition Universal Screening Tools for cancer patients [513, 514].

If this dietary counselling fails and patients food intake remains below their calories requirements, then the next step will be the provision of oral nutritional supplements (ONS) which is less invasive than other forms of artificial feeding [512].

ONS's are end-products that are ready to use as a supplement to the main intake or as a sole source of food. Successful supplementation depends on the palatability and the volume of these products, which are determining factors for compliance in patients who often experience changes in their sense of taste and smell [515-517].

Oral nutritional supplements are used for patients with variable level of nutritional needs in the clinical practice.

These supplements are only effective in patients with a high risk of malnutrition or in those who are already malnourished, whereas the benefits appear to be uncertain or only slightly visible clinically when used for patients with a low risk of malnutrition or with mild malnutrition [518]. There are no specific guidelines for the use of ONS, however, patients at risk of malnutrition with anorexia and/or partial dysphagia not resolvable within 2 weeks with a calorie intake of less than 50% of requirements should have ONS. Also, it should be given to malnourished patients with a BMI < 18 kg/m^2, anorexia and/or partial dysphagia, who have already lost 5% of their normal weight in the last 6 months, with a calorie intake of less than 50% of total requirements [499].

The total energy requirements for cancer patients is normally calculated using the Harris-Benedict formula multiplied by the stress factor (1.2–1.4) according to the clinical condition of the patient [519, 520]. This should include 20% protein (1.2–2 g/kg/day), 20% fats and 50–60% carbohydrates [512].

In a recent study by Stratton *et al*, ONS has been found to increase body weight and improve body composition (increased lean body mass or fat free mass). It can also improve body function such as muscle strength, walking distance, well being, physical and mental health; hence reducing the peri and postoperative mortality and morbidity [518].

The next step up the feeding ladder is Enteral Nutrition (EN), which requires a shift from the concept oral consumption of food to the infusion of calories and nutrients via nasogastric, nasojejunal tubes, percutaneous endoscopic gastrostomy (PEG) and surgical jejunostomy. Few issues need to be considered before commencing this type of feeding as EN is more invasive and can affect patient's cultural, social and emotional environment [521].

Despite the above, EN is considered as the chosen method when artificial feeding is required and the gastrointestinal tract is intact. It is physiological way of feeding, less prone to complications, less expensive and easier to monitor compared to parenteral nutrition. Moreover, the passage of nutrients through the intestinal tract maintains intact and restores the absorption surface [513, 522].

EN is indicated and prescribed when ONS is failing to meet 50% of the nutritional requirements of the body, severe anorexia as well as more than 5% loss of body weight [499].

EN formula is divided into two main categories: elementary and semi-elementary formulas. In addition, there are formulas enriched with immunonutrients (e.g. glutamine, omega-3, branched amino acids or nucleotides) and special formulas for specific diseases [523].

The use of enteral nutrition in cancer patients has demonstrated an improvement in their appetite, energy intake and nutritional status especially when used preoperatively [524]. It has also showed a noticeable reduction in the gastrointestinal toxicity from the anticancer therapy, due to a better response to treatment [523, 525, 526]. Furthermore, EN was associated with a significant improvement in the quality of life, was cost-effective and had a good compliance for the use at the home [527-530].

If previous nutritional supports fail to meet the individual calories requirements then Total Parenteral Nutrition (TPN) is the next step forward to prevent malnutrition and its associated morbidities. TPN is expensive, invasive and needs a close monitoring with multidisciplinary team involvement and associated with wide range of possible complications. TPN in cancer patients is used when there is high risk of undernutrition, malabsorption, severe mucositis, enteritis and in patients with short bowel syndrome. Studies involving patients treated for short periods of time (normal less than 1 week) have produced poor results or have shown the same efficacy as enteral nutrition [531-534].

A lot of interest has been developed over the last decade about the importance of Omega3 polyunsaturated fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), on the immune system and the inflammatory response as both can potentially reduce the pro-inflammatory and immunosuppressive effects.

EPA and DHA can increase the T-helper/T-suppressor cell ratio and stimulating lymphocyte proliferation leading to a higher natural killer cell activity with benefits at a biochemical, clinical and functional level [533-539]. Interestingly, recent studies showed that preoperative administration of parenteral Omega3 fatty acids have reduced the APT-associated immunosuppression as well as a decrease in the length of hospital stay [535, 536].

Future studies focusing on the importance of early nutritional interventions in cancer patients with caloric optimisations are needed and would be an important topic for subsequent phases of this study.

We strongly think that preoperative nutritional optimisation can improve the APT efficacy and potentiate patients functional capacity by modulating the cardiopulmonary reserve and the cytokines balance, hence, reducing the peri and postoperative morbidity associated with malnutrition.

Patients with colorectal cancer usually have an increase demand for a special protein called Glutamine, which is an amino acid used as a source of energy and nitrogen by the rapidly dividing tumour cells. Hence, CRC patients can be affected by its deficiency, which may lead to changes in their immune status, the integrity of the intestinal mucous membrane and protein-energy metabolism, contributing to cancer cachexia [540, 541]. In addition, branched amino acids (BCAAs) are used as regulators of protein synthesis and degradation, and as a source of energy for the muscles and other tissues. Moreover, they are precursors of glutamine and alanine, which might improve functional capacity and reduce the length of hospital stay. Thus, glutamine and BCAAs supplementation is important for CRC patients especially after APT administration [542-545].

Chemotherapy can cause microvascular ischemia leading to significant damage to the mucous membrane lining the gastrointestinal tract. This could be subclinical or can be associated with nausea, vomiting, diarrhoea, stomatitis and mucositis. Radiotherapy can also cause a direct damage to the small and large bowels named as radiation enteritis. The extent of damage depends on the location and size of the radiation port, size and frequency of fractionation and whether the treatment is part of a multimodality treatment regimen.

In conclusion, nutritional treatment and support should always be linked to the ‘time factor’, because even a good calorie-protein intake is inadequate for cancer patients undergoing chemoradiotherapy, if not timely and early administered.

7.5 Health related quality of life (HRQL) and physical activity in CRC patients

We establish the need for further investigation in specific areas of this field, such as considering the role of exercise in patients with colorectal cancer undergoing preoperative adjuvant therapy.

Many types of exercise programme were tried in the clinical practice, such as: aerobic exercise, resistive exercise, high intensity and low intensity programmes, group or individual programmes, institution based or home based programmes, and programmes with additional components such as dietary advice and relaxation techniques. No consensus has been reached to an 'ideal programme' and there have been no studies comparing different programmes and no published study in favour of one programme on another.

Studies employing home based or self directed exercise programmes have encountered problems with members of the control group initiating their own exercise programme during the trial period despite being advised not to [413]. A formal structure with group based sessions at a health or fitness facility seems to diminish this problem [410].

'Physical' or 'physical role' is a sub-category of most health related quality of life (HRQL) tools. Physical role has been shown by several studies to show improvements after patients have participated in exercise programmes [405, 408, 546-549].

Unfortunately, several studies show positive but non-significant results; with fewer well designed studies showing significant results. Courneya et al [413] performed a 2-group study with a home based exercise programme but unfortunately many of their control group (51%) also began exercising at home during the study period. This meant that their initial analysis showed no difference in physical scores between their intervention group and control group. However, they then performed an ancillary analysis separating the patients into 2 groups according to whether they had improved their fitness or not.

This showed more positive results with a statistically significant difference in HRQL and physical role scores between the 2 groups [413]. Not everyone has been able to show a positive relationship between exercise and physical role improvement.

Stephenson et al [407], did not find a positive association between physical activity levels and HRQL in their cross sectional survey, however, they had a largely metastatic/palliative cohort (60%) and their data came from patient reported activity logs. This cohort is very likely to have affected their results and their study design makes the evidence provided weak [407].

Overall, the literature supports that improvement or avoidance of deterioration is seen in the physical role domain of HRQL following exercise. It is reasonable to assume an improvement in physical role would confer a HRQL advantage; as for patients; this reflects less limitation in their ability to independently perform daily acitivities and spend time performing social and hobby functions.

Fatigue, as a symptom, is a component of many HRQL scores. Several studies investigate the role of exercise in improving fatigue amog patients with cancer undergoing adjuvant therapy; and some relate this to overall HRQL scores [408, 410, 550, 551]. The trend of the literature is towards supporting the use of physical activity for cancer related fatigue. The later can be the result of many factors such as treatment or malignancy related anaemia, de-conditioning due to adopting a sedentary lifestyle, insomnia and anxiety [551]. One-way exercise is thought to help by preserving or improving fitness, meaning less energy is required to perform normal daily tasks; and therefore patients can achieve more before their fatigue becomes insurmountable. These results in lower fatigue scores are often translated in the higher HRQL scores [405, 410]. An alternative theory is that fatigue associated with doing exercise is felt in a positive manner, and is justifiable and satisfying for patients who experience it, whilst fatigue experienced when following a sedentary life style results in negative feelings of fatigue [550].

In our study, we have used version 3.0 of the EORTC QLQ-C30 questionnaire to assess different parameters of the global health status, functional and symptoms scales. Significant deterioration was found in the physical role, emotional, cognitive and social functioning in both groups of patients after the neoadjuvant therapy. In addition, significant worsening symptoms (Fatigue, Nausea, vomiting, Pain, Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhoea, Financial difficulties) was noted after the anticancer treatment in both groups of patients post APT.

Although theories as to the reason for improved fatigue scores are variable, there is a strong agreement that exercise leads to positive results [405, 408, 410, 550, 551].

Young-McCaughan et al suggest that exercise has the strongest evidence base for treating fatigue over all other therapies [405]. Whilst this may be true, post intervention patients still return poorer scores compared to the general population [410].

In fact, Dimeo et al were unable to show a significant reduction in fatigue in their intervention group however, their control group showed a significant increase in fatigue so with this in mind their intervention still had a positive result for their patients [408]. However, a Cochrane review of women with breast cancer performing exercise whilst undergoing adjuvant therapy also only showed a statistically non-significant reduction in fatigue scores across the studies they included but this was not compared to a control group [552].

Symptom profiles are also measured as a sub-category of many HRQL tools and there is evidence to suggest an improvement in symptom profiles for some patients. The meta-analysis performed by Conn et al [553] showed a significant improvement in symptom scales for single group studies but not for studies with 2-group comparison. They did not provide a breakdown of the symptom scale, therefore, it is possible that few symptoms were responsible for this positive result or whether improvements were seen across the board [553]. Adamson et al [410] highlighted insomnia, pain and diarrhoea as the responsible components for returning an improved score in their study. On the other hand, there are studies where no improvement in the symptom scale is seen in the exercise group but when compared to a control group there is a prevention of worsening of some symptoms [408, 553].

As well as considering physical and symptom changes, HRQL is also concerned with emotional and mental functioning. It is relatively common to see emotional responses improve hand in hand with physical scores. This could be because an increase in physical capacity allows for more independence and ability to perform enjoyable activities as well as essential daily tasks [408, 413, 554]. Anxiety showed to be improved after exercise in several chronic conditions and is not exclusive to cancer [408]. The mechanism by which this is achieved is not known but it is statistically significant in several studies [408, 554].

In breast cancer studies, anxiety is often assessed in combination with depression and excellent results were seen in this area [555-560]. Corneya et al showed improvements in depression scores specific to patients with colorectal cancer [408, 413].

Many patients experience problems with insomnia during treatment for cancer; this may be a primary symptom, a treatment side effect or due to anxiety. Some positive response to insomnia has been seen after an exercise intervention. The best example of this is in the study performed by Adamsen et al [410].

They showed an improvement in insomnia; but their study included relaxation and massage as well as exercise. As such, it is difficult to know if this improvement is attributable to the exercise or other elements of their intervention.

Exercise has repeatedly been shown in the literature to result in positive physical and emotional improvements for patients with cancer. However, the relationship between these elements may not be straightforward. It is possible that positive results in these studies come from the sub group of patients in the intervention cohorts who actually increase exercise levels from their pre-morbid levels [405, 561, 562]. Some evidence seams to suggest that it is not the absolute amount of exercise that a patient is doing that is important, but the change in exercise levels from pre diagnosis to post diagnosis [562].

In other words, those who did little exercise prior to diagnosis that subsequently started exercising showed better results than those who already had active lives. It is possible that this is due to the fact that HRQL is related to the degree of change caused by the cancer experience. The patient with sedentary pre-morbid lifestyle may improve their HRQL score whilst the active patient may have seen a significant decline in their ability to perform their normally daily activities despite participating in an exercise programme and thus return a poorer score [408, 550].

This was well shown by Courneya et al [413] who were disappointed to find that many of their control group began exercising during the study period using advice from patients in the intervention group. They performed an ancillary analysis by separating their patients into those who had improved their fitness during the study period and those who had not. They were able to show that improved fitness correlated with improved HRQL [413].

On the other hand, Courneya et al [561] also showed a positive effect on HRQL after low intensity exercise intervention despite no measurable improvement in fitness [561]. This could be interpreted as a psychosocial mechanism where patients find that they are distracted from negative thoughts and feel like they have taken some personal responsibility for their recovery. It is also possible that they enjoy the interaction with peers and health professionals that formal group exercise programmes offers as suggested by Adamsen et al [410]. The literature cannot provide evidence of this theory as none of the current studies provide alternative non-physical programmes for the control arm of their studies.

Thus, it cannot be assessed if there is an effect from group interaction and attention from health professionals leading to improved HRQL [410].

An isolated finding by Stephenson *et al* [407] is that performing physical exercise is negatively correlated with family wellbeing and social wellbeing. The hypothesis that this is due to the time taken to perform physical activities; and that this is considered to take away from valuable time with family or socialising. This is not reported elsewhere and indeed, there is little mention in other papers about the negative effects of performing exercise. Whether this is a publication bias or a simple reflection on the norm findings is difficult to assume.

Despite there being little evidence regarding the negative effects of physical exercise on HRQL some studies do highlight concerns or criteria for excluding patients from completing exercise programmes. The literature is consistent in its support of exercise as a feasible and safe intervention for patients with cancer; however, some studies have highlighted specific exclusions. For example exclusion of patients with brain metastasis, bone metastasis, and platelets <50,000 [546]; others excluded patients with psychiatric disorders, and all those with muscular, cardiovascular or pulmonary disease were excluded as well. Immunocompromised patients secondary to treatment, for example, may limit location of exercise. Public gyms and exercise facilities should be avoided until blood counts are within normal limits. Patients with anaemia may experience dizziness, shortness of breath and angina type pains, which may lead to a significant medical event. Medical appendages such as intravenous lines and catheters should not be exposed to excess risk of infection such as saunas and swimming pools; furthermore care is required to ensure they are not dislodged in the process of performing exercise [547].

Therefore, although exercise seams to be beneficial for patients, these specific concerns should be born in mind before promoting such programmes in order to prevent harm in other ways. The design of studies has improved more recently but the literature suffers from a lack of randomised trials or even two group comparison studies with the majority being single group studies.

It is understandably difficult to perform a randomised trial in this era and the ability to perform double blinded trials is lacking, however, single blinding of the assessors should be attempted. Many studies also have recruitment problems and find that only motivated people who want to perform exercise join the study.

In general, people do not join an exercise study because they want to be in the control group [413]. This has been in part the source of difficulties experienced by some early studies where control group patients pursued their own exercise regimes. It would also be valuable to perform a study that includes a non-exercise based programme for the control group and see if there is any effect from group dynamics or attention from health professionals. There are no multicentre trials performed on subjects other than those with breast cancer. There are some further studies in this area currently being carried out, the results of which will hopefully improve our understanding of exercise as a moderator of HRQL and improved outcomes for patients [563, 564].

A valuable area of study for those concerned with colorectal cancer is that of the role of exercise programmes in patients who receive preoperative adjuvant therapy. This is an ideal target for investigation which could show promising results in terms of preoperative optimisation of patients. Considering the side effects and sequelae of chemotherapy and radiotherapy, it is likely that patients experience a reduction in fitness during their treatment.

A period of recuperation and healing is provided for patients receiving long course combined treatment, and medical optimisation is sought with multiple patients visiting cardiologists or respiratory physicians in the preoperative period. However, it is rare that support is given to them in terms of physical exercise and nutrition excluding some basic advice in clinic. Investigation into this area could provide promising data in support of exercise, both in terms of preoperative optimisation and improved HRQL, which in turn leads to motivated patients who will be more likely to aim for a prompt recovery post operatively. In short, there is a growing body of evidence which points towards a positive effect of exercise for patients with cancer undergoing adjuvant therapies.

A proportion of the literature suggest little benefit is afforded to those performing exercise along side their cancer treatment but there very little to support that it actually has a negative effect.

The current literature suffers from a lack of randomised and multicentre trials and often the small studies currently published are unable to provide statistically significant results. Overall, the literature supports that patients either experienced an improvement in their HRQL after participating in an exercise programme, or in some cases avoided deterioration.

Programmes in a formal class setting at a hospital or similar facility appear more successful in improving HRQL that other forms of programme offered. The effect of exercise is more successful in some categories than others; physical and emotional wellbeing return better result than social and mental wellbeing in most studies. There is still work that needs to be done to confirm that findings from early studies are correct. A particular area of interest which could have dramatic results in coming years is that of pre-habilitation of surgical patients after preoperative adjuvant therapy.

Preoperative exercise training proved to be feasible in other setting and may be practical in colorectal cancer patients depending on the APT regimes [565]. Exercise training has significant effect on the cardiopulmonary function and HRQL in postmenopausal breast cancer survivors who had completed surgery, radiotherapy and/or chemotherapy with or without hormonal treatment [399].

Another study by Morikawa *et al* showed that activation of the WNT signalling pathway and cadherin-associated protein beta 1 (CTNNB1 or beta-catenin) was associated with better colorectal cancer-specific survival and overall survival in obese patients only. Post-diagnosis physical activity was associated with better colorectal cancer-specific survival only among patients with negative status for nuclear CTNNB1. These molecular, pathological and epidemiology findings suggest that the effects of alterations in the WNT-CTNNB1 pathway on outcome are modified by BMI and physical activity [566].

Both CRC and chemoradiotherapy are associated with fatigue. Our data indicate a loss of fat free mass over the course of APT which implies a loss of muscle bulk. This may not be sufficient of itself to explain the fatigue and the loss of the functional capacity associated with the anticancer therapy. It is possible that fatigue experienced by patients may reflect changes within the muscles themselves. Chemoradiotherapy can cause tissue hypoxia at muscular level, can induce an inflammatory process mediated by different cytokines as well as affect the patient cardiopulmonary reserve.

These adverse events will have a direct impact on the body functional capacity and deteriorate all of the above endpoints of the EORTC QLQ-C30 questionnaire. Therefore, further studies to look for the muscle changes at cellular level are required to explain this limited functional capacity of poet therapy patients.

Little evidence is available on patient-reported outcomes after APT for colorectal cancer patients. In a recent multicenter prospective observational trial, HRQL was assessed using (EORTC) QLQ-C30 questionnaire before and 2-3 weeks after completion of APT as well as at 6 and 12 months after surgery. Primary analysis of selected scales included: global quality of life, physical functioning, social functioning, fatigue, body image, future prospective, and gender-related sexual problems. This showed that 78% of patients reported stool fractionation and 72% sensation of incomplete defecation. Only 14% of patients had optimal continence. Physical/social functioning, fatigue, and body image showed a decrease just after APT and returned to baseline levels at 1 year after treatment. Global quality of life was stable over time. Male sexual problems were greatly impaired throughout the study period ($P < 0.001$) with major clinically meaningful changes between baseline and 1 year after treatment [567].

Haydon *et al* have confirmed the beneficial effects of physical activity in reducing colorectal cancer mortality and improving the outcome through interactions with the insulin-like growth factor and insulin-like growth factor binding protein 3 axis [568]. Although this trial was performed on postoperative CRC patients, it clearly shows the importance of supervised exercise programmes to improve patients functional status and QoL. This could be easily used at the post APT stage in order to optimise CRC patients preoperatively.

No trend difference was noted between both chemoradiotherapy and radiotherapy only groups as there was a significant deterioration of functional and symptoms scales post APT exposure in all of the patients. This means that even radiotherapy alone can cause alteration of the body functional capacity, which could be explained by triggering the systemic inflammatory response, nutritional deficit as well as alteration to the body compartment compositions.

7.6 Colorectal cancer markers of inflammation

Colorectal cancer is an immunologic challenge and can modify the systemic immune response in different ways that may causally affect both the preoperative and postoperative clinical outcomes.

Cancer-related malnutrition is associated with the presence of a systemic inflammatory response, as reflected by enhanced levels of pro-inflammatory cytokines. Systemic inflammatory response leads to hypermetabolism-associated malnutrition, which is a common feature of metabolic derangement in patients with neoplasia [569, 570].

The patients inflammatory status usually reflect a balance between plasma levels of pro-inflammatory markers (TNFα, IP-10, RANTES, IL-6, IL-18) and anti-inflammatory markers (IL-1β, IL-1ra, IL-10, MIF) [571].

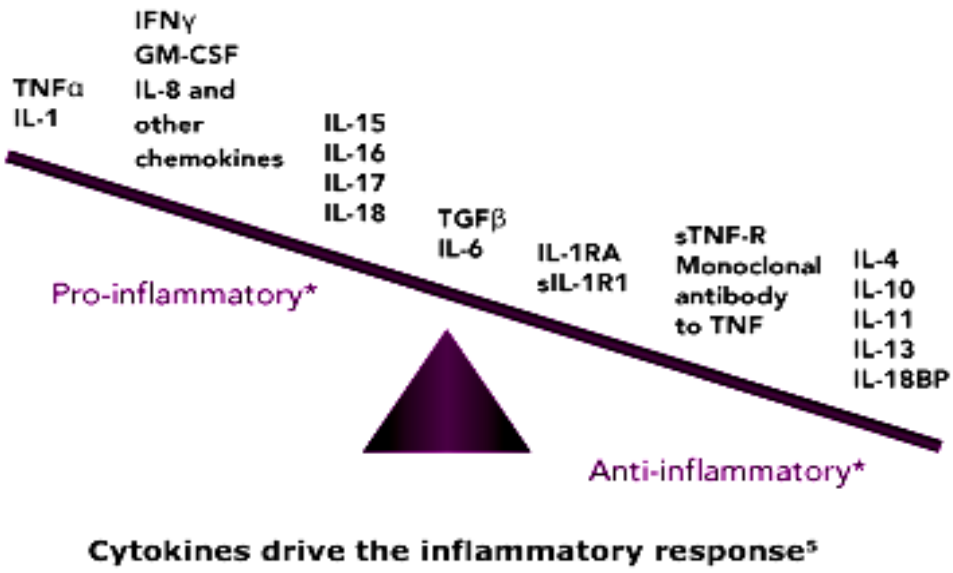


Figure (36) shows the balance of different pro and anti-inflammatory markers and how they drive the inflammatory response [571]

Any imbalance between pro- and anti-inflammatory cytokines or any uncontrolled production of cytokines can result in an inflammatory response [571].

An old concept indicate that septic patients usually begin with systemic inflammatory response syndrome (SIRS), then they transfer to mixed anti-inflammatory response syndrome (MARS) and end up with compensatory anti-inflammatory response syndrome (CARS) [572, 573].

Previous studies showed the presence of proinflammatory status is septic patients could be significant and can predict clinical outcomes [574]. Other studies have demonstrated the presence of anti-inflammatory cytokines at the onset of sepsis [575].

Cytokine		Value
Proinflammatory cytokines		
IL-6	Sensitivity (%)	82
	Specificity (%)	86
Anti-inflammatory cytokines		
IL-1ra	Sensitivity (%)	71
	Specificity (%)	84
IL-10	Sensitivity (%)	84
	Specificity (%)	82
IL-6R	Sensitivity (%)	64
	Specificity (%)	76

Table (21) shows the sensitivity and specificity of pro and anti inflammatory cytokines [572]

Tumour-related changes in the inflammatory response in humans have been largely ignored, and their relationships with the clinical outcome have not been well discussed, especially in colorectal cancer.

Serum cytokines are accepted mediators of host immune response. It is still a debate that these inflammatory markers influence postoperative morbidity and long-term survival in patients with CRC as their exact role is still unknown.

It has been found that there is a significant correlation between plasma IL-6 and IL-10 concentrations and survival as well as between IL-12 and toxicity [576].

Angiogenesis starts at the edge of a malignant epithelial tumour concurrently with tumour cell invasion and stromatogenesis, i.e. the formation of specific connective tissue stroma amenable to easy penetration by endothelial and tumour cells. Angiogenesis is a multistep process in which many growth factors and cytokines have an essential role. Vascular endothelial growth factor (VEGF) is a potent angiogenic agent that acts as a specific mitogen for vascular endothelial cells through specific cell surface receptors. IL-6 pathway is another mechanism linking angiogenesis to malignancy. CRP is a representative marker for inflammation and is associated with disease progression in many cancer types [577-579].

Preoperative serum VEGF and CRP level increased in colorectal cancer patients after APT administration and has been proposed as a poor prognostic factor for overall survival in patients with colorectal cancer [580].

Hatada *et al* have found that a marked activation of the pro-inflammatory cytokine network associated with a decreased antagonistic reaction and an increased consumption of IL-6 became prominent in malnourished CRC patients when they underwent intense surgical stress. These immunological disturbances may be relevant to protein energy malnutrition and subsequent clinical outcome [338].

In 1998, Nozoe has found that a preoperative serum elevation of CRP was an indicator of the malignant potential of the tumours as well as a predictor of the prognosis of patients with colorectal cancer [383].

Subsequently and in a study performed by Chung *et al* to investigate the prognostic significance of preoperative serum CRP, it has been shown that preoperative elevation of this inflammatory marker does not have the independent prognostic significance reported by earlier studies. Whether the elevated CRP can predict the development of cachexia or whether this association characterizes a pattern in tumour behaviour remains to be determined [393].

Kaminska *et al* have investigated serum cytokines (TNFalpha, IL-1ra, IL-6, IL-8, IL-10 as well as CRP) in patients with colorectal cancer, prior to the adjuvant preoperative therapy (APT) and postoperatively. Most of these serum cytokines were raised postoperatively regardless of the tumour stage. On day 10 and 42 after surgery, the levels of cytokines followed various patterns [344].

In our study, looking at both groups of patients undergoing either pre-operative chemoradiotherapy or radiotherapy, various and non-significant pattern of changes were seen in plasma cytokines. However, 21 patients had a reduced plasma level of IL1β and 22 patients had reduced plasma level of IL1ra post therapy exposure in the full cohort of 36 patients. Therefore, there was a general trend of reduction in IL1β and IL1ra [348]. This slightly agreed with one oesophageal cancer study that showed levels of IL-1ra and IL1β significantly decreased after a cetuximab enhanced Folfox chemoradiotherapy neoadjuvant regimen. In this study it was found that there was no significant difference in these changes between responders and non-responders.

However, a further oesophageal cancer study using a different neoadjuvant chemoradiotherapy regimen also found tissue IL-1β to significantly decrease after treatment in complete responders, and remain unchanged in non-responders [581].

We have also found that IL-10 had a very non-specific pattern of change with nearly half of the patients had increased and the other half had reduced plasma levels of IL10. Considerable further investigation of IL-10 is thus required before it can be used as a biomarker in clinical practice.

Whilst a number of cytokines also have the potential to be used as prognostic markers, a considerable amount of further research needs to be conducted before they are useful in clinical practice. Large colorectal cancer studies that measure a multiplicity of cytokine levels before and after each treatment modality (neoadjuvant therapy, surgery, and any adjuvant treatment), and compare levels to traditional staging and morbidity and mortality, are needed in the first instance. Further studies examining elements of the acute inflammatory response as therapeutic targets may also be useful in determining further prognostic elements.

Previous human studies have investigated the influences of nutritional interventions on the body serum cytokines. However, it is unclear whether preoperative nutritional routes influence responses of systemic cytokines in patients after surgery.

Lin *et al* have investigated whether preoperative total parental nutrition (TPN) influences systemic interleukin-6 (IL-6) and interleukin-8 (IL-8) responses in patients following surgery for colorectal cancer. Plasma IL-6 and IL-8 levels were marginally higher before the operation and were significantly higher on the first post-operative day in the TPN group than in the oral group. It has been concluded that routes of nutritional supply have an impact on the production of systemic cytokines after insult and plasma CRP levels did not differ between the two groups. The postoperative systemic IL-6 and IL-8 responses in patients who received standard TPN preoperatively were greater than in patients who received an oral diet. Preoperative nutrition via the enteral route may provide better regulation of cytokine responses after surgery than parenteral nutrition [582].

While our data showed no significant changes of IL8 and CRP with no specific trend in the behaviour of these cytokines post APT exposure.

IL-6 and IL-8 were observed at 24-72 hours postoperatively in patients with colorectal cancer and this indicated a high risk of early postoperative septic complications and anastomotic leak [583]. In addition, low preoperative IL-1Ra is associated with postoperative infection frequently seen in the malnourished patients due to the defective immunoinflammatory adaptation system [584].

Moreover, Ll'yasova has investigated the relationship between circulating levels of the inflammatory markers and the presence of cancer with its outcome. It has been found that the presence of raised IL-6 and CRP are associated with colorectal neoplasia and very much correlated to the tumour behaviour [585]. This is actually a useful piece of information as IL-6 and CRP can be used in the clinical practice to determine the CRC activity post APT that could be modulated by different interventions such as exercise, nutrition, anti-inflammatory and optimisation.

We couldn't get a clear image from the cytokines behaviours in our study as there was no statistical significant difference noted for the plasma levels of IL10, IP10, RANTES, IL18 and MIF after finishing the neoadjuvant treatment. However, all of the above cytokines showed similar trends in both chemoradiotherapy and radiotherapy only groups. Although we have shown some subjective and objective evidences of nutritional deficits, serum albumin levels did not show significant changes after the neoadjuvant treatment as some patients had increased levels and others had dropped their serum albumin post APT exposure.

Cancer-associated immunodeficiency is seriously worsened by surgical trauma. It has been found that short-term preoperative interleukin-2 (IL-2) immunotherapy abolishes postoperative immunodeficiency and can induce immunological control of the growth of minimal residual disease. This amplification of the immune response in the post-operative period is capable of controlling minimal residual disease after radical surgery, of reducing the progression rate, and of improving the prognosis and overall survival [586].

Previous research has showed a correlation between various psychosocial factors, particularly cancer-related concerns and depression, and pre/postoperative level of serum cytokines in patients with newly diagnosed colorectal cancer. However, the clinical significance of these findings needs to be addressed in longitudinal follow-up studies of recurrence and survival [587].

Although cytokines analysis did not provide this study with a clear message about their trends post APT, further studies with larger number of CRC patients might give a better power calculation to show significant changes, which will be useful to understand their roles in SIRS, MARS and CARS. The chosen cytokines in this research are the most relevant pro and anti-inflammatory markers related to colorectal cancer studies in the literatures.

We have previously explained the role of chemotherapy agents on myocardial toxicity and the way 5FU can impair the patients cardiopulmonary reserve by causing mycocardial toxicity.

This is an understandable way of pathophysiology, as the circulating chemical agents have a direct impact on tissue oxygenation and can cause microvascular ischemia. However, health professionals in clinical practice might enquire about why localised pelvic radiotherapy can alter the body physiology and reserve.

This is an interesting argument as we think that targeted radiotherapy can induce a systemic inflammatory response with the production of systemic circulatory pro and anti-inflammatory cytokines (induction of SIRS or CARS) leading to these alteration in body physiology. This was clearly noted in our study as the radiotherapy group showed some derangements of the body cytokines, although not statistically significant, but might be clinically relevant in the disease process and progression as certainly cytokines levels were altered in some way post APT exposure.

In addition, pelvic radiotherapy had a significant impact on psychological well-being, as shown on the HRQL questionnaires, as well as the body compartment distributions, as shown by the body composition parameters. These adverse events will eventually impair the body physiological reserve. Some experiments are still being held to explore the effect of anti-inflammatory medications, such as statins and aspirin to modulate the inflammatory cascade in patients with systemic inflammatory response syndrome.

Previous studies have showed a strong relation between post-operative infective complications and long-term survival in patients with colorectal caner. Poor prognosis is usually associated with anastamotic leak as the later can trigger an inflammatory cascade, including the release of pro inflammatory cytokines and vascular growth factors, which promotes tumour growth, dissemination and even future local recurrence [588, 589].

However, there is enough evidence in the literatures that strong inflammatory cell infiltrate within and around the tumour has a protective effect on disease progression in colorectal cancer [590, 591]. Further work is needed to clarify these relations and its impact of postoperative outcome.

7.8 Brief summary of the study with a suggested hypothesis

Post APT deterioration of the body physiological reserve in patients with CRC is multifactorial as there is a clear interaction between various aspect of body physiology such as cardiopulmonary fitness, body composition, cytokines level and HRQL. Direct and indirect impact of neoadjuvant treatment can alter the patients functional capacity and affect outcomes. This was shown clearly in the above thesis as most of our study variables were inter-linked together causing an overall deterioration in the body physiological reserve of CRC patients pre-operatively.

We strongly think post APT patients awaiting surgical resection have a significant dterioration in their physiological reserve represented by:

1. Reduced VO_2max & AT (Impaired cardiovascular function)
2. Increased VE/VCO_2 (Impaired pulmonary function)
3. Reduced ECW, ICW & TBW (Fluid depletion)
4. Reduced MAC, TSF & FFM (Reduced lean body mass)
5. Impaired HRQL, (poor physiological and psychological well-being)
6. Deranged Cytokines, CRP and Albumin (Triggered SIRS, MARS and CARS)

We also think these patients are not given enough time to fully recover from the APT insult and they are not eminently ready for a major surgical resection. We therefore recommend the following points to be addressed and explored in more details at future studies to optimise CRC patients pre-operatively in order to reduce the possible postoperative mortality and morbidity in colorectal cancer patients.

1. Prolong the window between finishing the APT regime and surgical resection until full recovery is made.
2. Change of APT regime as per individual needs with rigid selection criteria.
3. Supervised exercise training programme to improve physical wellbeing.
4. Supervised dietary programme with or without targeted supplements.
5. Psychological support and appropriate counselling.
6. Anti-inflammatory agents that modulate pathway of SIRS or CARS.

7.9 Limitation of the study and future recommendations

Despite of the hard work done to explore the possible changes at the physiological reserve among colorectal cancer patients, there are still some areas to be improved and needs to be explored in depth with future research and studies.

1. This was only a pilot study on 36 patients with rectal cancer to explore the possible presence of physiological changes after adjuvant pre-operative therapy. Larger sample of patients is needed for future studies with a control group of patients who do not receive any kind of APT in order to eliminate any possible cause of physiological deterioration caused by the course of the neoplastic disease itself.
2. We have used a mixed population to identify the possible trend of changes in patients with rectal cancer undergoing neoadjuvant treatment and awaiting surgical resection. Further studies on homogenous populations are needed as the two types of the APT regiments have different physiological impact on patients with colorectal cancer and might produce different results.
3. As most of the study end-points were inter-linked, we recommend a detailed exploration of the study variables to find any relevant correlations among the study results and their clinical effects on CRC patients.
4. Planning for a multi-centre study to recruit a large number of patients from different background over a short period of time.
5. Our study end-points were measured before the administration and 2 weeks within the finish of APT regiment. We recommend future studies to measure our variables at the following points of time: anytime pre APT, 72 hours post APT, 72 hours pre-operative as well as careful recording of all of the post-operative complications up to 30 days. This will give a clear explanation of the body behaviour during different disease stages.
6. Co-ordinatation with the FOXTROT trial group in order to recruit patients with colonic cancer into a different group and compare outcomes with the rectal cancer group of patients.

8.0 APPENDICES

Appendix 1 (Patient-Generated Subjective Global Assessment, PGSGA)

STANDARDIZED NUTRITIONAL ASSESSMENT

History

1. Weight

In summary of my current and recent weight:

I currently weigh about ---------- pounds
I am about ---------- feet ---------- tall
A year ago I weighed about ---------- pounds
Six months ago I weighed about ---------- pounds
During the past two weeks my weight has:

☐ decreased ☐ not changed ☐ increased

2. Food Intake

As compared to my normal, I would rate my food intake during the past month as either:

☐ Unchanged

☐ More than usual

☐ Less than usual

I am now taking:

☐ Little solid food

☐ Only liquids

☐ Only nutritional supplements

☐ Very little of anything

3. Symptoms

I have had the following problems that kept me from eating enough (check all that apply):

☐ No problem eating

☐ No appetite, just did not feel like eating

☐ Nausea

☐ Vomiting

☐ Constipation

☐ Diarrhoea

☐ Mouth sores

☐ Dry mouth

☐ Pain; where? ----------

☐ Things taste funny or have no taste

☐ Smells bother me

☐ Other ----------

4. Functional Capacity

Over the past month, I would rate my activity as generally:

☐ Normal with no limitations

☐ Not my normal self, but able to be up and about with fairly normal activities

☐ Not feeling up to most things, but in bed less than half the day

☐ Able to do little activity and spend most of the day in bed or chair

☐ Pretty much bedridden, rarely out of bed

THE REMAINDER OF THIS FORM WILL BE COMPLETED BY YOUR DOCTOR, NURSE, OR THERAPIST. THANK YOU.

5. Disease and Its Relation to Nutritional Requirements

Primary diagnosis (specify) ----------
Stage, if known ----------
Metabolic demand (stress):

☐ no stress ☐ low stress ☐ moderate stress ☐ high stress

Physical

For each trait specify: 0 = normal, 1 =mild, 2 = moderate, 3 = severe

loss of subcutaneous fat (triceps, chest) ----------
muscle wasting (quadriceps and deltoids) ----------
ankle oedema ----------
sacral oedema ----------
ascites ----------

SGA rating

Select one

☐ Well nourished

☐ Moderately (or suspected of being) malnourished

☐ Severely malnourished

Appendix 1 continue (Scoring sheet for PG-SGA questionnaire)

Worksheets for PG-SGA Scoring

Boxes 1-4 of the PG-SGA are designed to be completed by the patient. The PG-SGA numerical score is determined using 1) the parenthetical points noted in boxes 1-4 and 2) the worksheets below for items not marked with parenthetical points. Scores for boxes 1 and 3 are additive within each box and scores for boxes 2 and 4 are based on the highest scored item checked off by the patient.

Worksheet 1 - Scoring Weight (Wt) Loss

To determine score, use 1 month weight data if available. Use 6 month data only if there is no 1 month weight data. Use points below to score weight change and add one extra point if patient has lost weight during the past 2 weeks. Enter total point score in Box 1 of the PG-SGA.

Wt loss in 1 month	Points	Wt loss in 6 months
10% or greater	4	20% or greater
5-9.9%	3	10 -19.9%
3-4.9%	2	6 - 9.9%
2-2.9%	1	2 - 5.9%
0-1.9%	0	0 - 1.9%

Score for Worksheet 1 ☐
Record in Box 1

Worksheet 2 - Scoring Criteria for Condition

Score is derived by adding 1 point for each of the conditions listed below that pertain to the patient.

Category	Points
Cancer	1
AIDS	1
Pulmonary or cardiac cachexia	1
Presence of decubitus, open wound, or fistula	1
Presence of trauma	1
Age greater than 65 years	1

Score for Worksheet 2 = ☐
Record in Box B

Worksheet 3 - Scoring Metabolic Stress

Score for metabolic stress is determined by a number of variables known to increase protein & calorie needs. The score is additive so that a patient who has a fever of > 102 degrees (3 points) and is on 10 mg of prednisone chronically (2 points) would have an additive score for this section of 5 points.

Stress	none (0)	low (1)	moderate (2)	high (3)
Fever	no fever	>99 and <101	≥101 and <102	≥102
Fever duration	no fever	<72 hrs	72 hrs	> 72 hrs
Steroids	no steroids	low dose (<10mg prednisone equivalents/day)	moderate dose (≥10 and <30mg prednisone equivalents/day)	high dose steroids (≥30mg prednisone equivalents/day)

Score for Worksheet 3 = ☐
Record in Box C

Worksheet 4 - Physical Examination

Physical exam includes a subjective evaluation of 3 aspects of body composition: fat, muscle, & fluid status. Since this is subjective, each aspect of the exam is rated for degree of deficit. Muscle deficit impacts point score more than fat deficit. Definition of categories: 0 = no deficit, 1+ = mild deficit, 2+ = moderate deficit, 3+ = severe deficit. Rating of deficit in these categories are *not* additive but are used to clinically assess the degree of deficit (or presence of excess fluid).

Fat Stores:				
orbital fat pads	0	1+	2+	3+
triceps skin fold	0	1+	2+	3+
fat overlying lower ribs	0	1+	2+	3+
Global fat deficit rating	0	1+	2+	3+
Muscle Status:				
temples (temporalis muscle)	0	1+	2+	3+
clavicles (pectoralis & deltoids)	0	1+	2+	3+
shoulders (deltoids)	0	1+	2+	3+
interosseous muscles	0	1+	2+	3+
scapula (latissimus dorsi, trapezius, deltoids)	0	1+	2+	3+
thigh (quadriceps)	0	1+	2+	3+
calf (gastrocnemius)	0	1+	2+	3+
Global muscle status rating	0	1+	2+	3+

Fluid Status:				
ankle edema	0	1+	2+	3+
sacral edema	0	1+	2+	3+
ascites	0	1+	2+	3+
Global fluid status rating	0	1+	2+	3+

Point score for the physical exam is determined by the overall subjective rating of total body deficit.

No deficit	score = 0 points
Mild deficit	score = 1 point
Moderate deficit	score = 2 points
Severe deficit	score = 3 points

Score for Worksheet 4 = ☐
Record in Box D

Worksheet 5 - PG-SGA Global Assessment Categories

	Stage A	Stage B	Stage C
Category	Well-nourished	Moderately malnourished or suspected malnutrition	Severely malnourished
Weight	No wt loss OR Recent non-fluid wt gain	~5% wt loss within 1 month (or 10% in 6 months) OR No wt stabilization or wt gain (i.e., continued wt loss)	> 5% wt loss in 1 month (or >10% in 6 months) OR No wt stabilization or wt gain (i.e., continued wt loss)
Nutrient Intake	No deficit OR Significant recent improvement	Definite decrease in intake	Severe deficit in intake
Nutrition Impact Symptoms	None OR Significant recent improvement allowing adequate intake	Presence of nutrition impact symptoms (Box 3 of PG-SGA)	Presence of nutrition impact symptoms (Box 3 of PG-SGA)
Functioning	No deficit OR Significant recent improvement	Moderate functional deficit OR Recent deterioration	Severe functional deficit OR recent significant deterioration
Physical Exam	No deficit OR Chronic deficit but with recent clinical improvement	Evidence of mild to moderate loss of SQ fat &/or muscle mass &/or muscle tone on palpation	Obvious signs of malnutrition (e.g., severe loss of SQ tissues, possible edema)

Global PG-SGA rating (A, B, or C) = ☐

Nutritional Triage Recommendations: Additive score is used to define specific nutritional interventions including patient & family education, symptom management including pharmacologic intervention, and appropriate nutrient intervention (food, nutritional supplements, enteral, or parenteral triage). First line nutrition intervention includes optimal symptom management.

- **0-1** No intervention required at this time. Re-assessment on routine and regular basis during treatment.
- **2-3** Patient & family education by dietitian, nurse, or other clinician with pharmacologic intervention as indicated by symptom survey (Box 3) and laboratory values as appropriate.
- **4-8** Requires intervention by dietitian, in conjunction with nurse or physician as indicated by symptoms survey (Box 3).
- **≥9** Indicates a critical need for improved symptom management and/or nutrient intervention options.

Appendix 1 continue (Outcome/stages of PG SGA questionnaire)

Global Assessment of Nutritional Status

Stage A—Well nourished

- No weight loss or recent nonfluid weight gain.
- No deficit in nutrient intake or has had recent improvement.
- Symptoms have had no nutritional impact or there has been a significant recent improvement allowing adequate intake.
- No deficit in functioning or functioning has shown significant recent improvement.
- No deficit on physical examination or the chronic deficits have shown recent clinical improvement.

Stage B—Moderately well nourished or suspected malnutrition

- 5% weight loss within 1 month or 10% in 6 months and continued weight loss with no stabilization or gain.
- Definite decrease in intake.
- Presence of nutrition impact symptoms.
- Moderate functional deficit or recent deterioration.
- Evidence of mild to moderate loss of subcutaneous fat and/or muscle mass and/or muscle tone on palpation.

Stage C—Severely malnourished

- Greater than 5% weight loss in 1 month or greater than 10% loss in 6 months with no stabilization or gain.
- A severe deficit in intake and the presence of nutrition impact symptoms.
- A severe functional deficit or recent significant deterioration.
- Obvious signs of malnutrition such as a severe loss of subcutaneous tissue and possible edema.

Appendix 2 (EORTC QLQ-C30 questionnaire, version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

Not at all (1)
A little bit (2)
Quite a bit (3)
Very much (4)

1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? 1 2 3 4
2. Do you have any trouble taking a long walk? 1 2 3 4
3. Do you have any trouble taking a short walk outside of the house? 1 2 3 4
4. Do you need to stay in bed or a chair during the day? 1 2 3 4
5. Do you need help with eating, dressing, washing yourself or using the toilet? 1 2 3 4

During the past week:

6. Were you limited in doing either your work or other daily activities? 1 2 3 4
7. Were you limited in pursuing your hobbies or other leisure time activities? 1 2 3 4
8. Were you short of breath? 1 2 3 4
9. Have you had pain? 1 2 3 4
10. Did you need to rest? 1 2 3 4
11. Have you had trouble sleeping? 1 2 3 4
12. Have you felt weak? 1 2 3 4
13. Have you lacked appetite? 1 2 3 4
14. Have you felt nauseated? 1 2 3 4
15. Have you vomited? 1 2 3 4
16. Have you been constipated? 1 2 3 4

During the past week:

17. Have you had diarrhea? 1 2 3 4
18. Were you tired? 1 2 3 4
19. Did pain interfere with your daily activities? 1 2 3 4
20. Have you had difficulty in concentration, like reading a newspaper or watching television? 1 2 3 4
21. Did you feel tense? 1 2 3 4
22. Did you worry? 1 2 3 4
23. Did you feel irritable? 1 2 3 4
24. Did you feel depressed? 1 2 3 4
25. Have you had difficulty remembering things? 1 2 3 4
26. Has your physical condition or medical treatment interfered with your family life? 1 2 3 4
27. Has your physical condition or medical treatment interfered with your social activities? 1 2 3 4
28. Has your physical condition or medical treatment caused you financial difficulties? 1 2 3 4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7
Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7
Very poor Excellent

Appendix 2 continue (Scales and items for the QLQ C30 questionnaire)

	Scale	Number of items	Item range*	Version 3.0 Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

Appendix 2 continue (scoring of QLQ C30 questionnaire)

Technical Summary

In practical terms, if items I_1, I_2, ... I_n are included in a scale, the procedure is as follows:

Raw score
Calculate the raw score
RawScore = $RS = (I_1 + I_2 + ... + I_n)/n$

Linear transformation
Apply the linear transformation to 0-100 to obtain the score *S*,

Functional scales: $S = \left\{1 - \frac{(RS - 1)}{range}\right\} \times 100$

Symptom scales / items: $S = \{(RS - 1)/range\} \times 100$

Global health status / QoL: $S = \{(RS - 1)/range\} \times 100$

Range is the difference between the maximum possible value of *RS* and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of *RS* equals the range of the item values. Most items are scored 1 to 4, giving *range* = 3.

The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with *range* = 6, and the initial yes/no items on the earlier versions of the QLQ-C30 which have *range* = 1.

Version 2.0

Centre Number: GS09/9007

Study Number: 09/H1306/79

INFORMATION SHEET FOR PARTICIPANTS

Study Title:

Physiological effect of adjuvant pre-operative chemotherapy and/or radiotherapy on patients undergoing colorectal cancer resections

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

- ***Part 1*** *tells you purpose of this study and what will happen to you if you take part.*
- ***Part 2*** *gives you more detailed information about the conduct of the study.*

Part 1

What is the purpose of the study?

Cancers of the bowel (colon and rectum) are usually treated by surgical removal, but when the cancers are large, it can be difficult to removal all the cancer. The size of a cancer is shown on a scan, which a patient has once the cancer is diagnosed. This scan is then seen and discussed by all specialists at a weekly team meeting. When the cancer is seen to be large, the specialists will often recommend a course of either chemotherapy, or radiotherapy, and occasionally both therapies, to be given before surgery. The aim being is to shrink the cancer, to make it easier to operate on.

These treatments have been shown previously to improve the results of surgery for rectal cancer and currently being studied, in a national trial, for colonic cancer. However, there is concern that these treatments can actually weaken you and so affects the individual's fitness for a major surgery afterwards. Although enabling better treatment of the cancer, it might increase the risks of the operation. The aim of this study is to look for the possible effects of chemotherapy and radiotherapy on an individual's general health.

This is a pilot study on 40 patients. If our study shows that these important physiological functions are badly affected by chemotherapy or radiotherapy, then the next step will be to focus on how to improve such patients before they undergo a major operation, so that the risk of complications is reduced.

Pre-operative chemo and radiotherapy offer several advantages such as better control of the tumour locally, an increase in the overall survival time and a possible increase in the proportion of patients having surgery without affecting the function of the anus to control defecation.

Preoperative chemotherapy for colonic cancer may improve the likelihood of complete surgical removal of the tumour, and so improve survival.

Nowadays, some surgeons consider that pre-operative chemo and radiotherapy increases the incidence of early postoperative complications, especially causing a higher incidence of anastomotic leakage (join leak).

Potential problems related to preoperative radiotherapy (RT) are wound infection (sepsis), delayed healing and a higher rate of anastomotic leak or dehiscence

Chemotherapy (CT) affects nutritional status directly by lowering the body protein production and has indirect general effects such as nausea, vomiting, loss of weight and appetite, diarrhoea.

Radiotherapy can also cause diarrhoea, taste changes, nausea, vomiting, loss of appetite and may further compromise nutrition and functional ability.

Anti-cancer treatment with CT and/or RT may compromise both nutritional status and functional ability which in turn, impacts Quality of life (QoL).

The resulting nutritional problems occur through direct effects on cancerous and healthy tissues, which may induce loss of weight and appetite, nausea or vomiting, and diarrhoea, leading to physical discomfort and a variety of poor absorption diseases.

Heart and Lung exercise test (Cardiopulmonary exercise test / CPEX test)

CPEX test adds very important additional information to that provided by the standard exercise test such as a precise determination of the actual heart ad lung reserve. CPEX testing closely mimics the postoperative situation, as it requires an increased heart function to satisfy the increased oxygen demand. People identified as having poor oxygen delivery on the CPEX bicycle would be expected to have a poor ability to increase heart function following surgery.

The results of CPEX have a very high predictive value for patients at risk of major complications in the postoperative period. Therefore, it is a reliable

method of detecting patients who are fit to have this major tumour resection surgery.

The CPEX test is non-invasive, it requires minimal preparation, and it may be performed on an outpatient basis. During the test you will be closely monitored by a Consultant anaesthetist and a heart technician.

During your CPEX test, you will be required to perform mild exercise on an upright bicycle whilst breathing through a mouthpiece. Each breath will be measured to assess how the body is performing. The capacity and strength of the lungs is measured before and during exercise. Your heart tracing (ECG) will also be recorded prior to, during and post exercise.

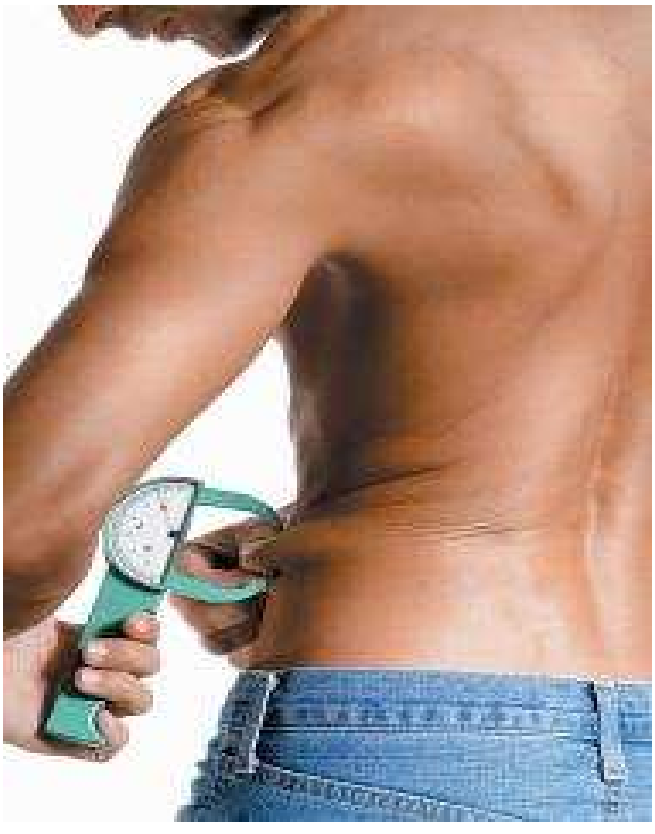
The CPX test will lasts for a total of 60 minutes; however you will only be required to exercise for approximately 10 minutes. The amount of exercise is modest - it does not require you to exert yourself to maximum effort. During the test you will be continuously monitored by the medical team. Results are generally available at the end of the consultation. In the extremely unlikely event that you become unwell, full resuscitation facilities will be available.

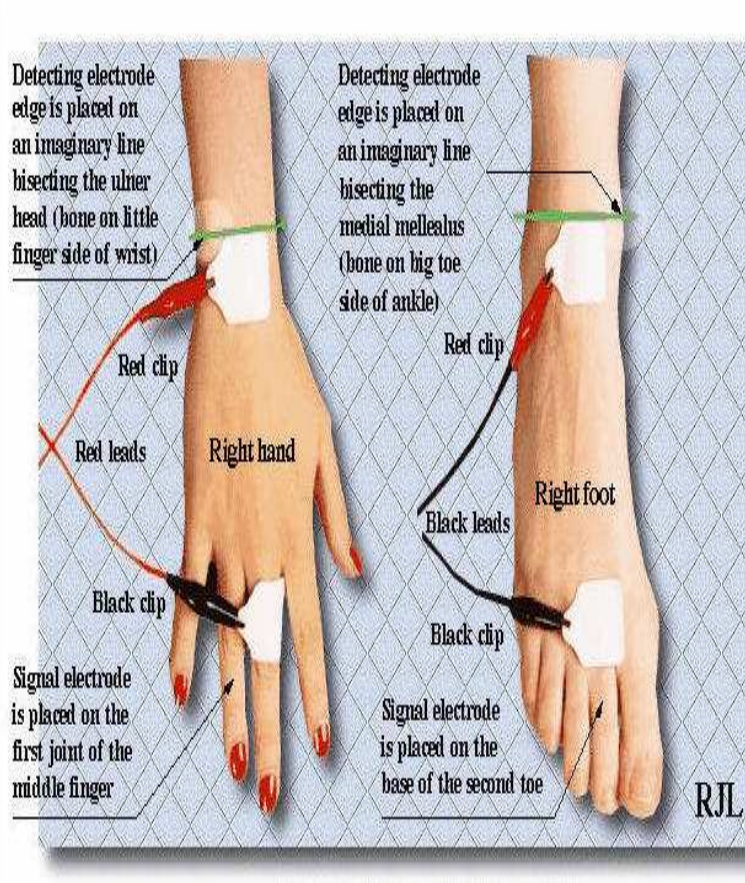
Body composition and fluid distribution test

Changes in body composition reflect hydration, nutrition, and body fat, are all important elements reflecting well-being and efficacy of therapy.

Body composition can be measured indirectly through changes in body weight, body mass index (BMI), and subcutaneous sum of skin folds (biceps, triceps, subscapular, suprailiac, and medial calf).

To optimise fluid balance, a number of techniques have been investigated to measure body composition in clinical practice. Of these, bioelectrical impedance analysis (BIA) has attracted most interest and seems to be of greatest promise. This will be used in this study to measure the fluid and fat distribution in your body. It is very similar to have a heart tracing test (ECG). The BIA measurements are performed using four electrodes: usually two are attached at the wrist and two at the ankle which will take about 10 minutes to do the readings. It is not painful at all and has no recorded adverse effects.





Inflammatory and septic markers

A number of blood markers could be affected after the administration of adjuvant chemotherapy or radiotherapy. We are interested in those related to inflammation. We will obtain a venous blood sample of 15ml to measure the level of inflammation in your body.

Why have you been chosen?

You have a cancer of the bowel. The multidisciplinary team meeting has decided to offer you a pre-operative treatment (chemotherapy or radiotherapy or both) to improve the post-operative outcomes and make the tumour operable. The aim of this study is to find out your overall body changes before and after having this treatment set by the oncologists.

We hope you will be able to help us answer the above question. In order to help us we would ask you to go on the bicycle exercise machine to test you heart and lung as well as measuring your body fluid and contents by a tracing machine placed on your wrists.

In addition, we will need to take a blood sample from your vein plus completing only one questionnaire relating to your current quality of life, physical and nutritional status.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a written consent form before or during your clinic visit.

If you decide to take part you are still free to withdraw at any time without giving a reason. A decision to withdraw at any time or a decision not to take part will not affect the standard of care you receive. If you do decide to withdraw from the study at any point we will destroy all your identifiable samples, but we will need to use the data collected up to your withdrawal.

What would happen to me if I didn't take part?

Your treatment will not be affected in any way and your results will not be included into the study.

What would happen to me if I took part?

You will meet the principal investigator (SR) and have the study explained to you. A brief 10 minutes face to face interview will be conducted between the main study investigator and yourself after finishing your oncology appointment. The project aims and methods will be briefly explained and you will be provided with a written covering letter explaining the aims and methods of the study, a patient information sheet, a consent form and a single questionnaire in a prepaid self-addressed envelope. You will be given at least 24 hours to decide about the study recruitment and participation in the above project. We shall then proceed to contact you by phone to enquire about your final decision.

If you enter into the study, we will advise you to sign the provided written consent and return it together with the fulfilled questionnaires in your assigned clinic appointment. A helpline number will be provided in the covering letter to allow you to ask any questions you feel relevant before agreeing to consent to the study, or if you have difficulty completing the questionnaire.

You will have 2 assessments. The first assessment will be 2 weeks before, and the second assessment 2 weeks after, the therapy. Assessments to be made include: heart and lung fitness on an exercise bike, body composition (fluid, fat and muscle distribution) and nutritional status, blood tests to examine for inflammation within the body, and quality of life by 2 questionnaires.

You will be provided with a single appointment (arranged with the participant by telephone) to attend the project-specific outpatient clinic. During this visit, cardiopulmonary fitness (measured with CPEX test) and body composition analysis (measured with BIA) will be carried out as well as taking a venous

blood sample. This clinic is located at the cardiology physiology department of Leeds General Infirmary and the CPEX test will be carried out under the supervision of a consultant anaesthetist and a cardiopulmonary technician. In addition, measurements will be also done in the same visit to measure body weight, height, body mass index, skin folds and hand grip measurements.

A single venous blood sample of 5ml will be obtained to check for inflammatory markers.

You can bring the fulfilled questionnaires to you first clinic visit. These are 2 validated instruments (EORTC QLQ-C30 and PG-SGA questionnaires) used to figure out patient's QoL, physical and nutritional status which should take approximately 15 minutes to complete the 34 questions.

The same procedure will happen again after finishing the assigned pre-operative chemo and radiotherapy (adjuvant pre-operative chemoradiotherapy/APT). Patient will be contacted via post or telephone and invited for the second study visit to repeat the same procedures above in order to compare the findings pre and post pre-operative chemo and radiotherapy.

The study-specific two clinic visits (pre and post adjuvant therapy) will be carried out two weeks before and two weeks after the administration of the anticancer treatment.

This is to give the best reflection of the adjuvant chemoradiotherapy on the body physiology of colorectal cancer patients.

If a patient deemed to need further adjuvant treatment from the MDT meeting, then the second visit should occur prior to this intervention.

Patients will be provided with travel expenses as well as drinks and snacks during their visit and stay for the tests.

A research team member will be present at the outpatient clinic and be able to go through any potential issues you may have. A helpline number to the

Research Office will provide a point of contact for any questions between 0800hrs - 1700hrs Monday to Friday.

The study requires that you complete the questionnaire as fully as possible and return it to a member of the research team either in clinic or via the Research Office addressed envelope provided.

There is only one short questionnaire to fill in which covers many aspects of your Nutritional and Physical status as well as your current quality of life (QoL).

This project will be conducted within the John Goligher Colorectal Unit, Department of Colorectal Surgery at the General Infirmary at Leeds. Ethical approval has been sought from the Leeds East Regional Ethics Committee.

As a patient within the study you will be recruited into one of the three groups:

Group 1 (Chemoradiotherapy patients)

Group 2 (Radiotherapy patients only)

There will be no difference in your diagnosis or treatment by taking part in this study. You will receive standard care, as any other patient would do.

A flow chart to help you understand the study and a time line of events is provided below:

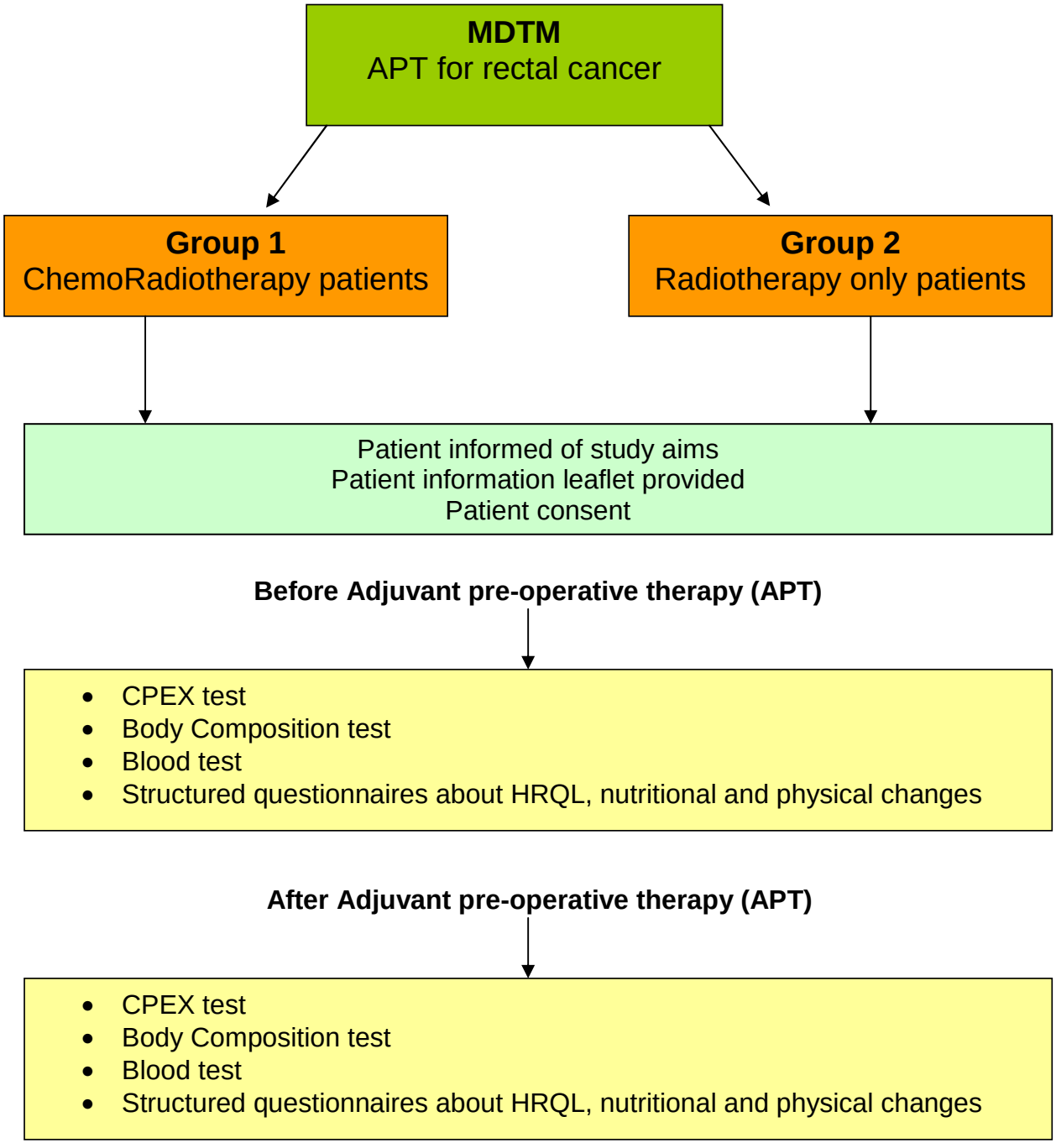


Diagram showing the study design and schedule

What if you have a low score in the questionnaire or you want to discuss issues raised by the questionnaire?

In some cases we anticipate that patients may demonstrate poor scores in the questionnaire survey. In such cases, or in individuals wishing to discuss issues raised by the questionnaire, we shall arrange a further outpatient appointment. Further investigation and referral may be advised to liaison services (Leeds General Infirmary).

Part 2

What are the possible disadvantages and risks of taking part?

With regard to this research, the only potential risk is when you go onto the heart and lung (cardiopulmonary) exercise machine as you might, occasionally, develop chest pain during the procedure. If this happens, the procedure will be immediately stopped and you will be managed as per the hospital protocol to treat a patient with chest pain. You will be in the cardiology department anyway and all of the other needed investigations and interventions are ready there to use if required. The procedure will be done by a cardiology technician with the presence of a consultant anaesthetist to deal with such adverse events if happened. CPEX testing is now routinely performed in Leeds Hospitals for patients about to undergo major abdominal surgery, who are considered high risk e.g. patients with an abdominal aortic aneurysm. The incidence of adverse events as reported in the literature is 2 to 5 per 100.000 patients going onto the CPEX machine.

What are the possible benefits of taking part?

There are no benefits conferred to you by taking part in this study other than the potential to find out the possible downsides of chemo and radiotherapy in the treatment of bowel cancer.

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about our findings. In the event that these findings affect you, your research doctor will inform you about it.

What happens when the research study stops?

Your care will not be affected in any way.

What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you.

Would my taking part in this study be kept confidential?

All information collected about you during the course of the research would be kept strictly confidential. Any information about you, which leaves the hospital or surgery, would have your name and address removed so that you cannot be recognized from it.

Only responsible health professionals from the Department of Surgery at Leeds General Infirmary or regulatory authorities from the NHS trust, involved in the trial, will be allowed to view your medical notes in the context of this study.

All data that is collected throughout the trial will be treated with the strictest confidence.

What will happen to the results of the research study?

Results of the study will be collected and stored on a secure database for the duration of the study (24 months). The results will then be analysed as soon as possible and we aim to publish our findings in peer reviewed medical journals towards the end of 2010. You will be able to obtain a copy of the final publication from most medical libraries. Most libraries will hold copies of the journal and in some instances these journals maybe available on the internet. Results from this study will be used by the researcher as data for further educational research qualification with the University of Leeds.

Who has reviewed the study?

The Leeds East Research and Ethics Committee.

Who is funding this research?

This research will be funded by the Yorkshire Cancer research (YCR) as the award grant has been approved in November 2009. The project will be organised and implemented via John Goligher Colorectal Research Unit/Account at the Leeds General Infirmary.

Who can I contact if I would like to discuss the study or questionnaires in greater detail?

The following number has been provided to help assist patients considering participation or participating in the study:

Mr. Samir Rahmani, Colorectal Research Fellow, Contact No. 0113 392 3557, Monday – Friday 0800 – 1700hrs.

Thank you for reading and participating in this study. Please note that a copy of this information sheet and a copy of the completed consent form will be given to you for your safekeeping.

The Leeds Teaching Hospitals NHS
NHS Trust

CONSENT FORM

VERSION 2.0

Project Title

Physiological effect of adjuvant pre-operative chemotherapy and/or radiotherapy on patients undergoing colorectal cancer resections

Name of Researcher	Samir Rahmani
Centre Number	GS09/9007
Study Number	09/H1306/79
Patient Identification Number	……

Statement of Agreement to Participate in the Trial

1. I confirm that I have read and understand the information sheet dated.....(version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. *Please place your initials in the box of you agree.* ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. *Please place your initials in the box of you agree.* ☐
3. I agree to allow the team running the above study offering the necessary help and intervention when I am on the cardiopulmonary exercise testing machine if needed. *Please place your initials in the box of you agree.* ☐
4. I agree to take part in the above study by completing the questionnaire. *Please place your initials in the box of you agree.* ☐
5. I agree to allow the team informing my doctor (GP) about participation in this study, a subsequent letter will be sent to the surgery. *Please place your initials in the box of you agree.* ☐

……	……	…./…./……..
Name of Patient (BLOCK CAPITALS)	Signature	Date
……	……	…./…./……..
Name of Researcher (BLOCK CAPITALS)	Signature	Date

Centre Number: GS09/9007

Study Number: 09/H1306/79

Version: 1

Patient name:
Patient date of birth:
Patient hospital number:
Patient address:

Letter to the Patient General Practitioner (GP)

Study Title:

Physiological effect of adjuvant pre-operative chemotherapy and/or radiotherapy on patients undergoing colorectal cancer resections

Dear Doctor,

There is the potential that pre-operative treatment with chemotherapy or radiotherapy before surgery for bowel cancer can debilitate the patient and so affect the individual's fitness for major surgery. Although enabling better treatment of the cancer, such treatment might increase the risks of the operation. The aim of this study is to look for the possible effects of chemotherapy and radiotherapy on an individual's general health.

The above named patient, who is registered in your general practice, has been invited to take part in this research study as he/she has a bowel cancer that needs treatment.

The patient has been approached by the principle investigator of the research and was provided with a covering letter, a patient information leaflet and a consent form.

We will appreciate your help and support to the patient, if needed, to clarify any issue.

However, our full contact details have been provided and full communication will be maintained with the patient throughout the study.

Thank you very much for your time.

Yours truly,

Mr. Samir Rahmani, Colorectal Research Fellow

Contact No. 0113 392 3557

Monday – Friday 0800 – 1700hrs

Centre Number: GS09/9007

Study Number: 09/H1306/79

Version: 2

Patient invitation letter

Study Title:

Physiological effect of adjuvant pre-operative chemotherapy and/or radiotherapy on patients undergoing colorectal cancer resections

Dear participants,

There is the potential that pre-operative treatment with chemotherapy or radiotherapy before surgery for bowel cancer can be weakening and so affect the a person's fitness for major surgery. Although enabling better treatment of the cancer, such treatment might increase the risks of the operation. The aim of this study is to look for the possible effects of chemotherapy and radiotherapy on an individual's general health.

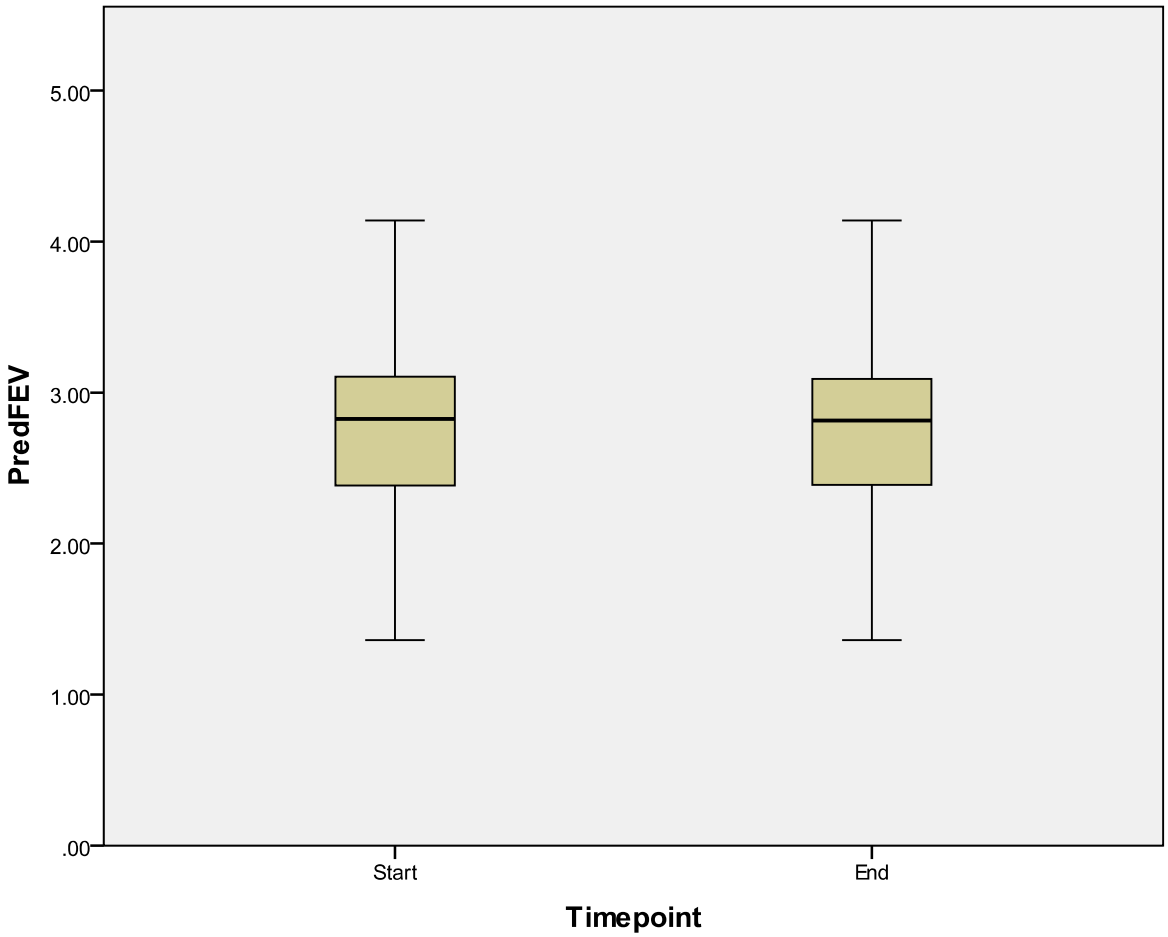
You are being invited to take part in this research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the patient information leaflet carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

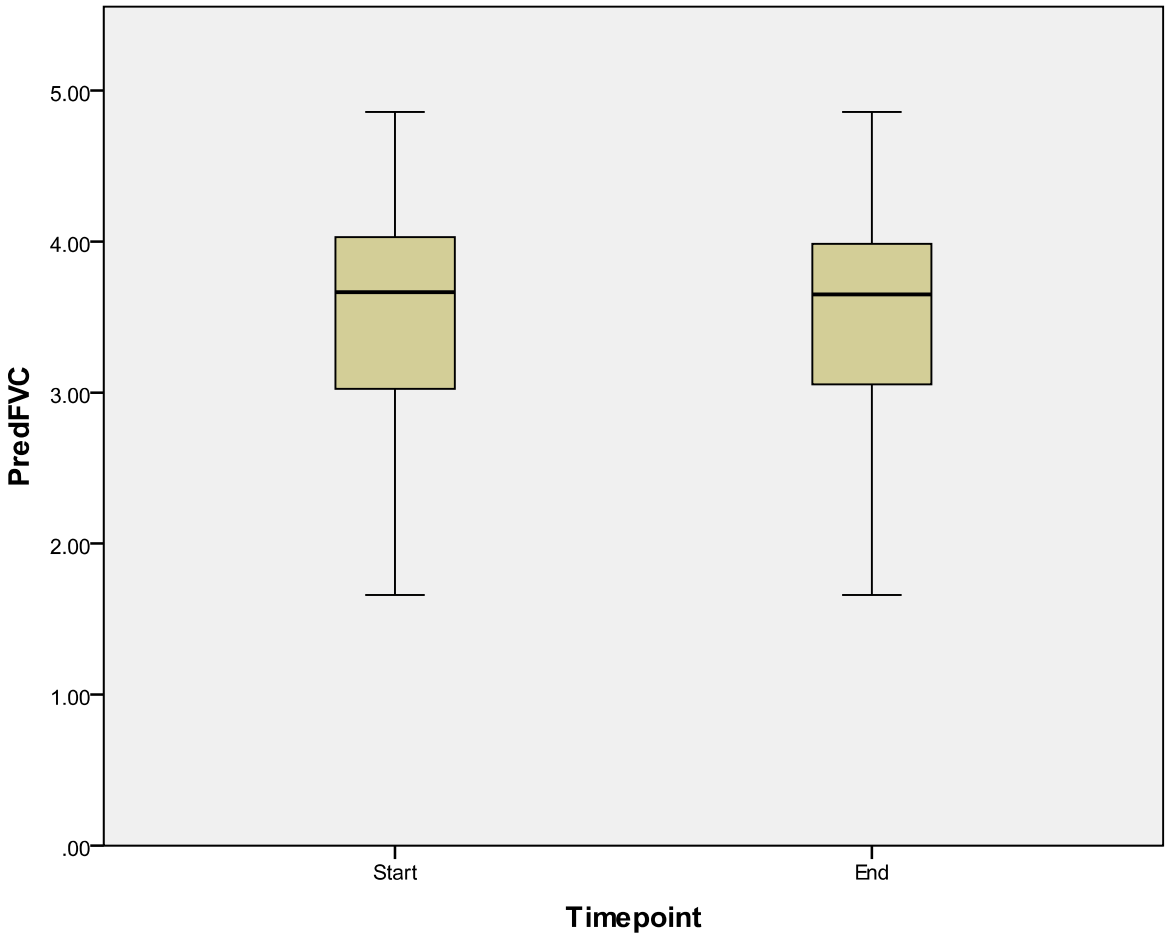
Thank you very much for your time.

Yours truly,
Mr. Samir Rahmani
Colorectal Research Fellow
Contact No. 0113 392 3557
Monday – Friday 0800 – 1700hrs

Result Chapter

These following boxplots showing the changes in score between the start and finish for all study variables (pre and post APT for the full cohort of patients). These charts show the medians, maximum and minimum.


5.00
4.00
3.00
2.00
1.00
.00
PredFEV
Start
End
Timepoint


5.00
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3.00
2.00
1.00
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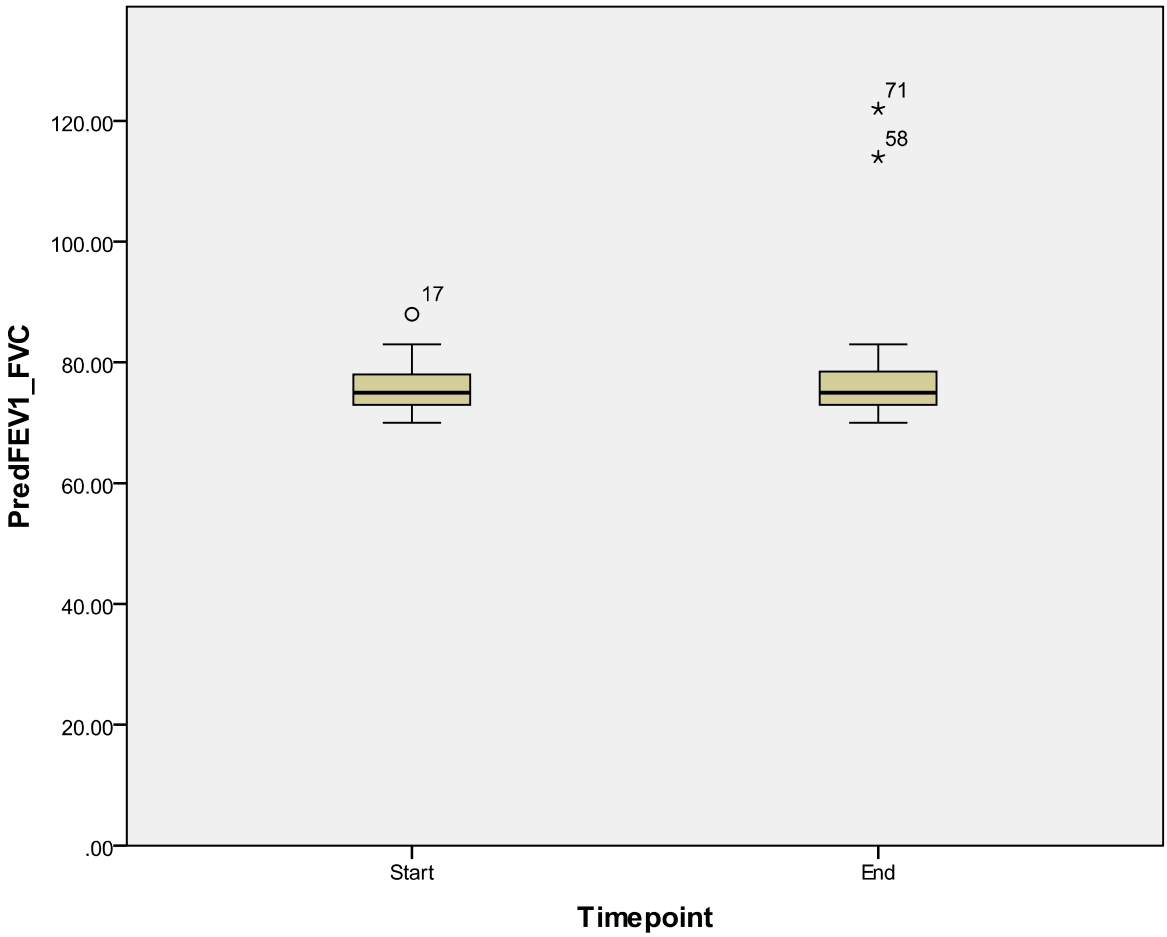
PredFVC
Start
End
Timepoint


PredFEV1_FVC
120.00
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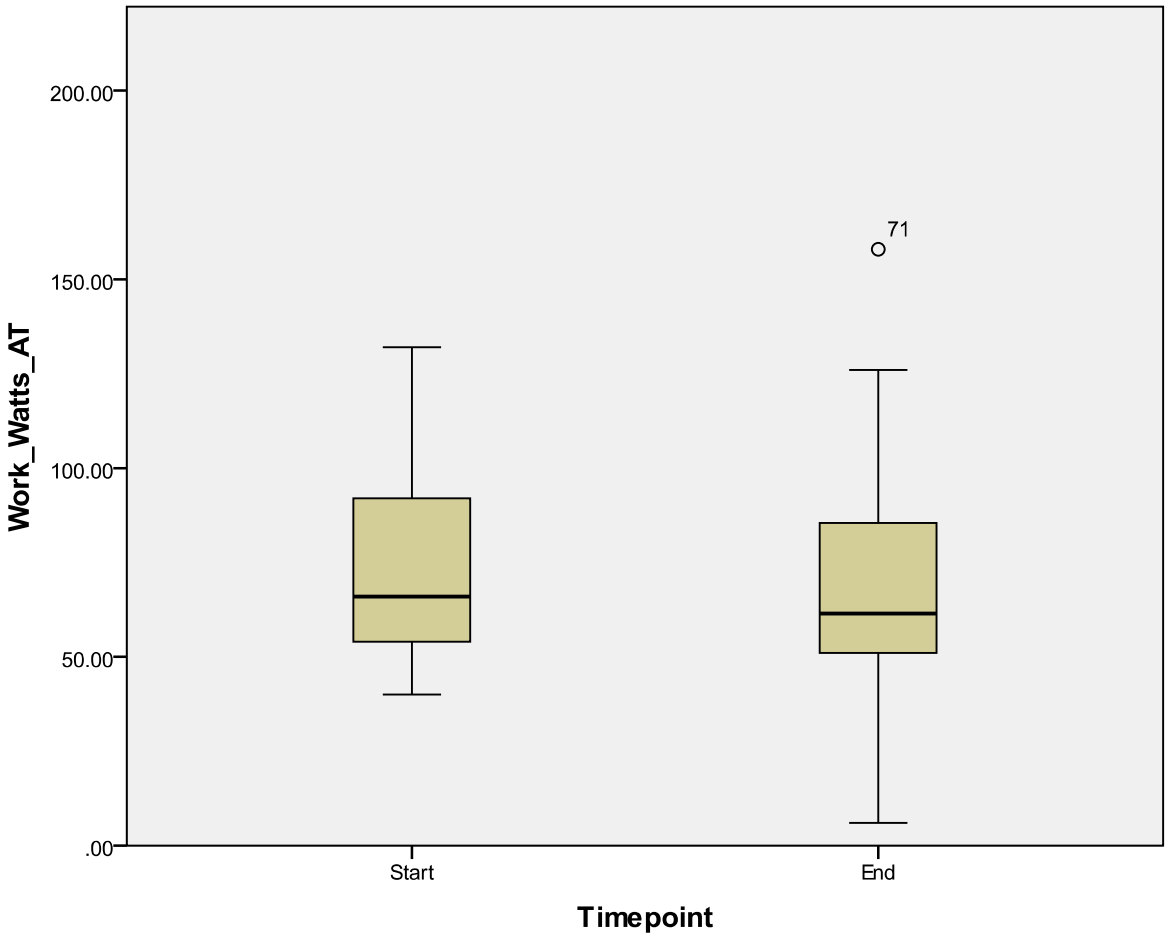
71
58
17
Start
End
Timepoint


200.00
150.00
100.00
50.00
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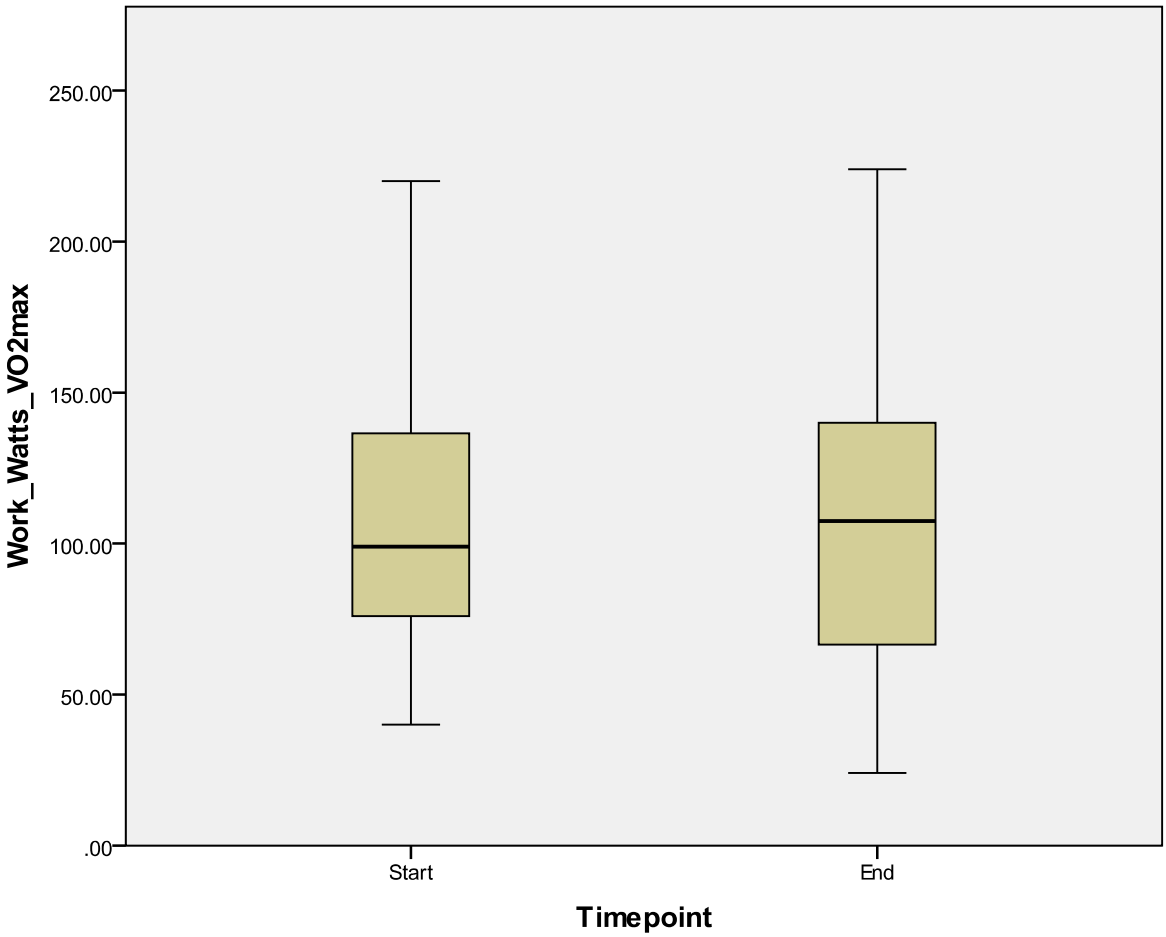
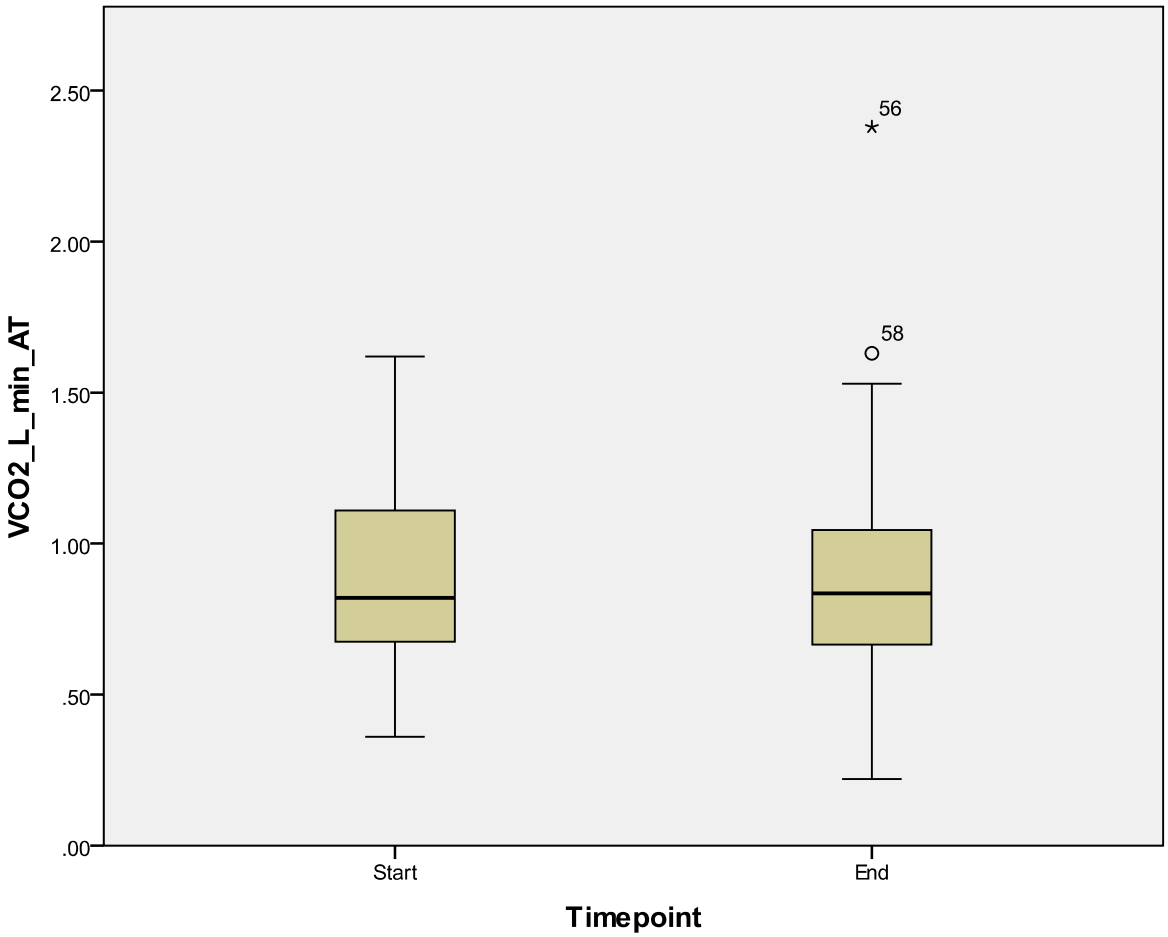
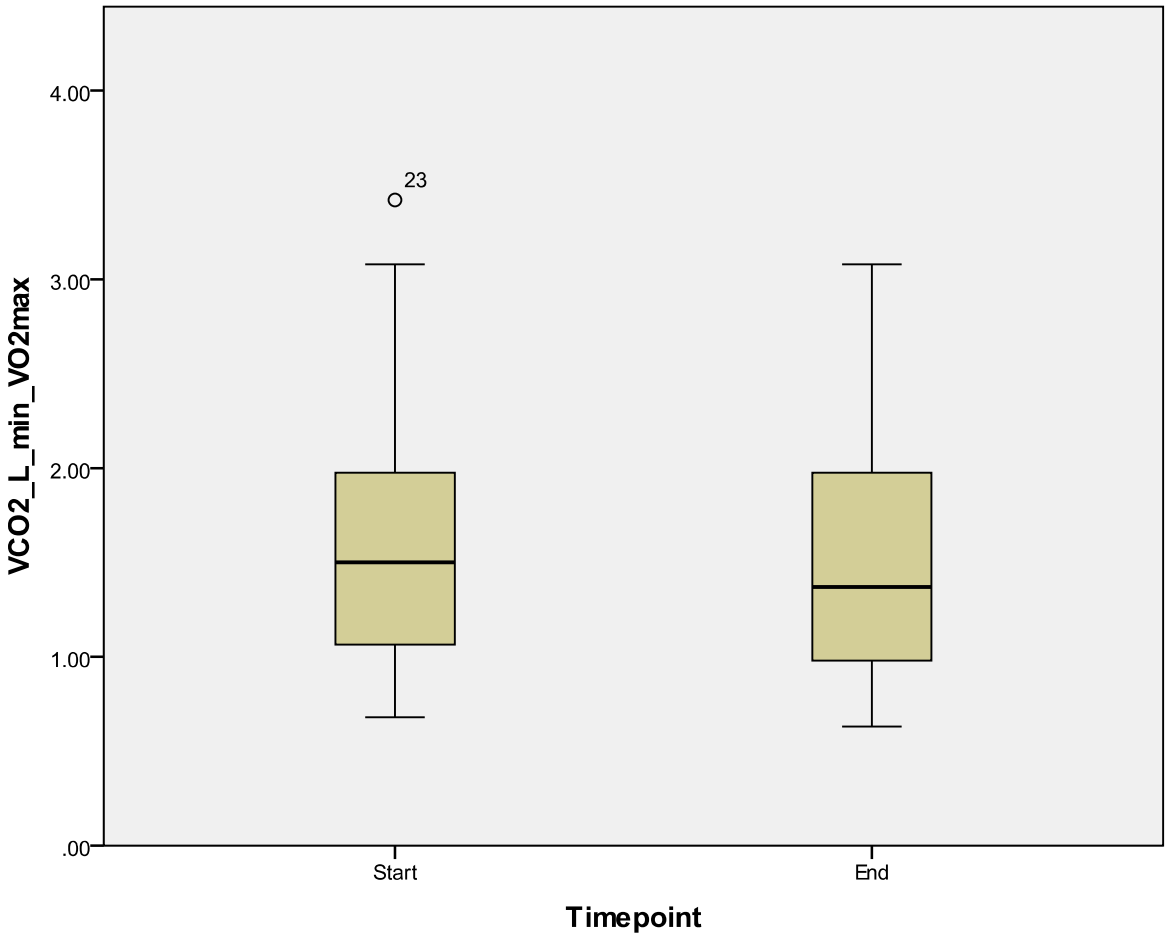
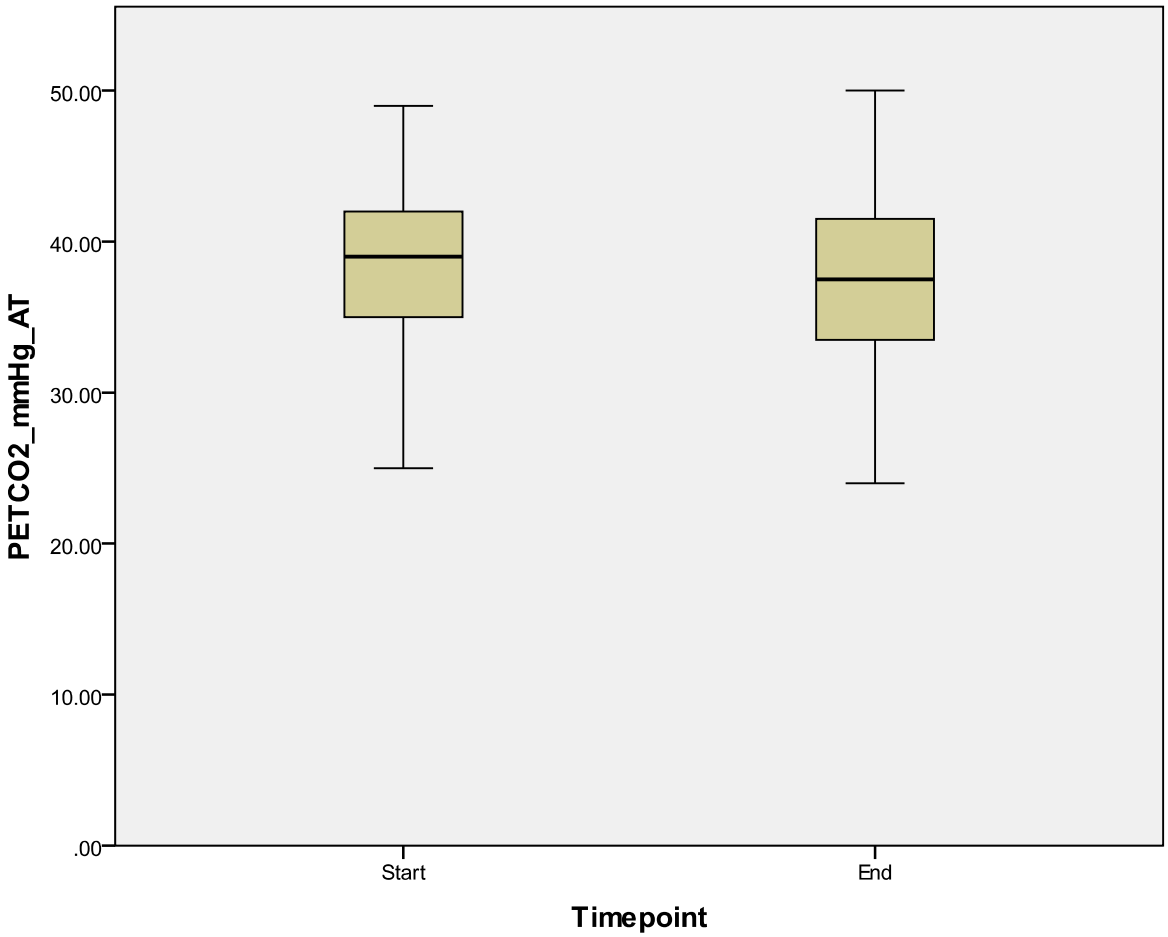
Work_Watts_AT
71
Start
End
Timepoint


250.00
200.00
150.00
100.00
50.00
.00
Work_Watts_VO2max
Start
End
Timepoint


VCO2_L_min_AT
2.50
2.00
1.50
1.00
.50
.00
56
58
Start
End
Timepoint


4.00
3.00
2.00
1.00
.00
VCO2_L_min_VO2max
23
Start
End
Timepoint


50.00
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10.00
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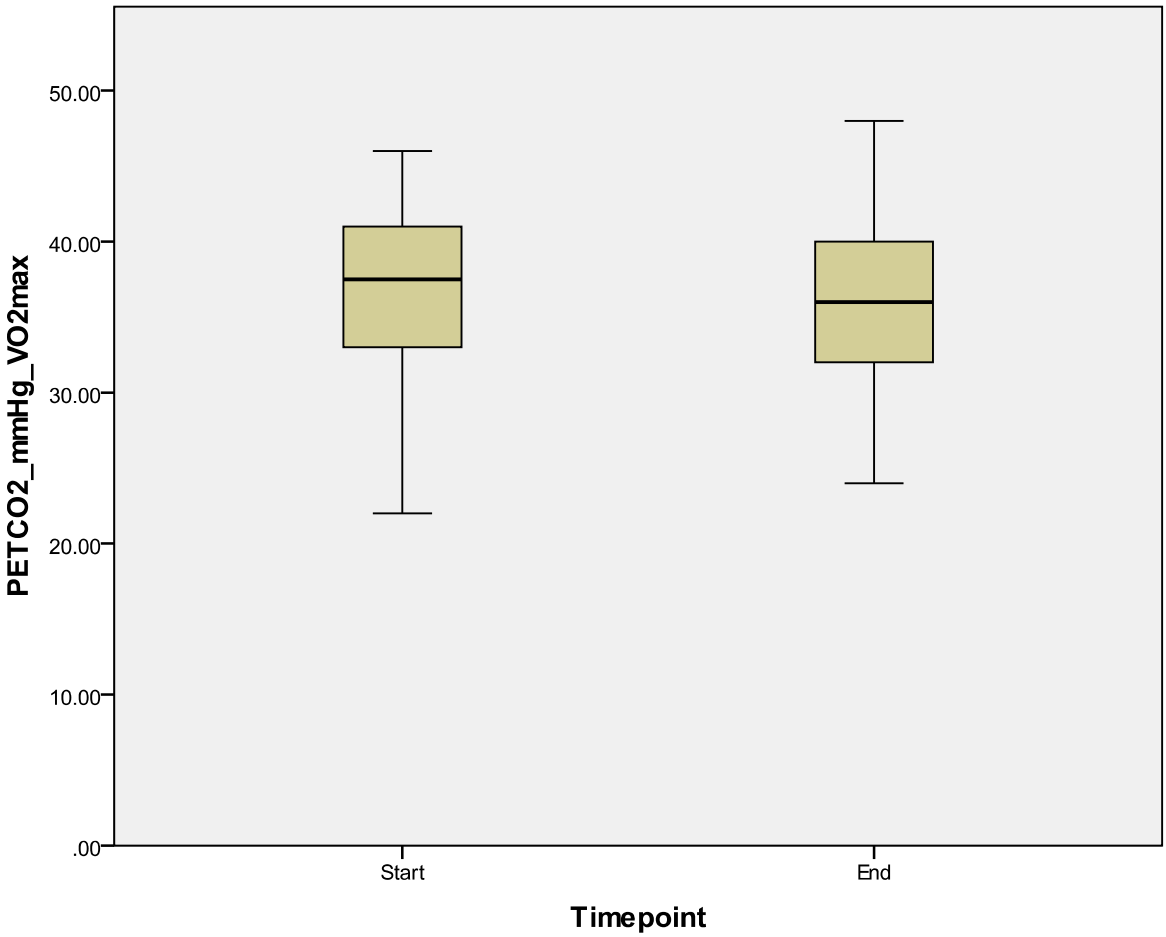
PETCO2_mmHg_AT
Start
End
Timepoint


50.00
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10.00
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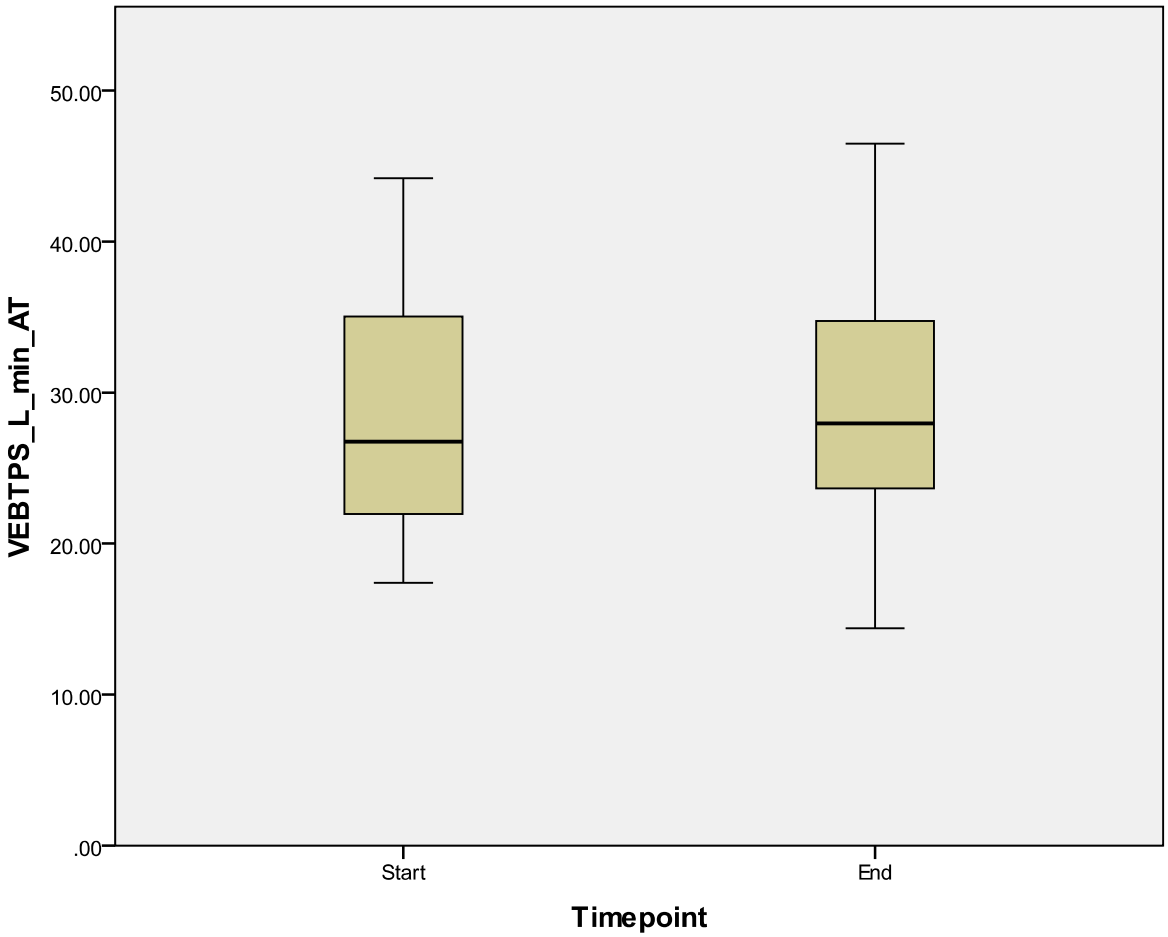
PETCO2_mmHg_VO2max
Start
End
Timepoint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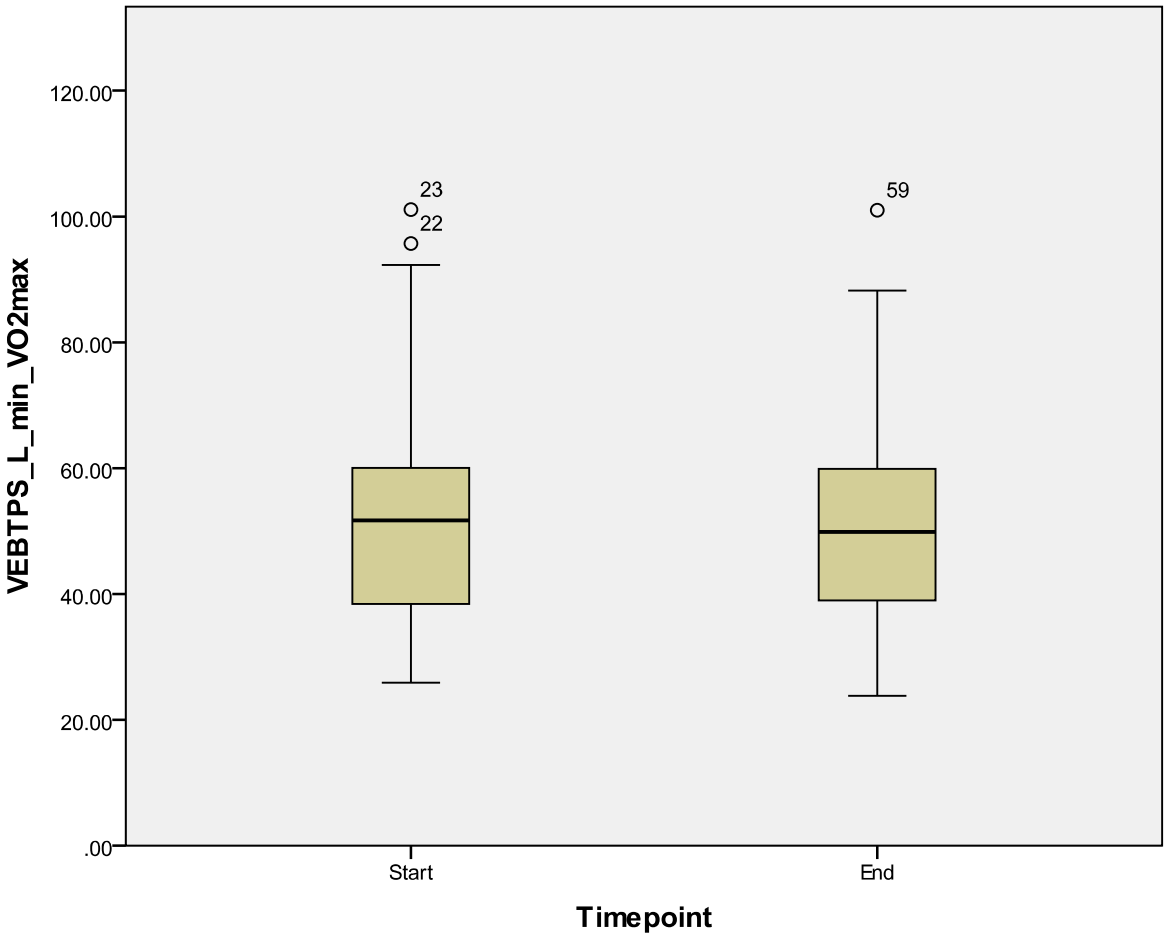
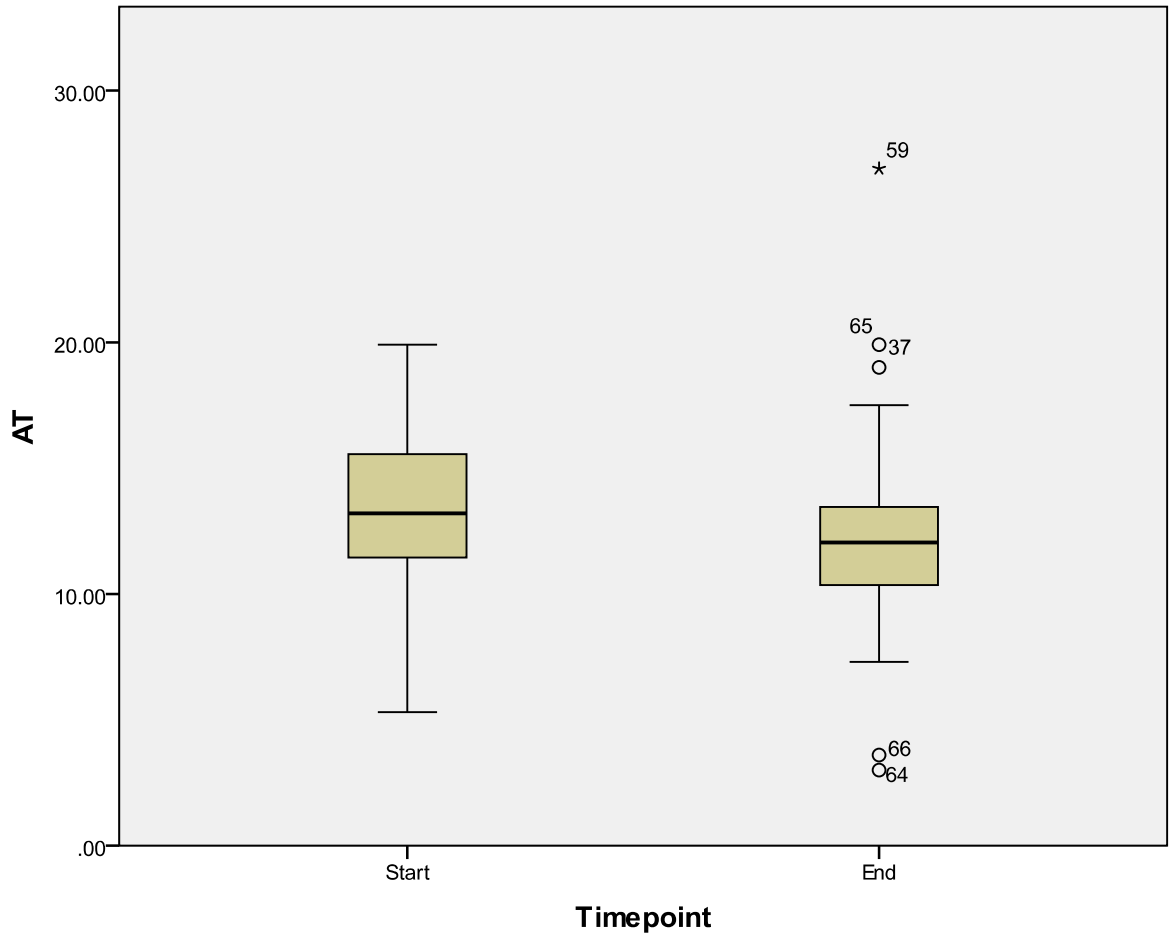
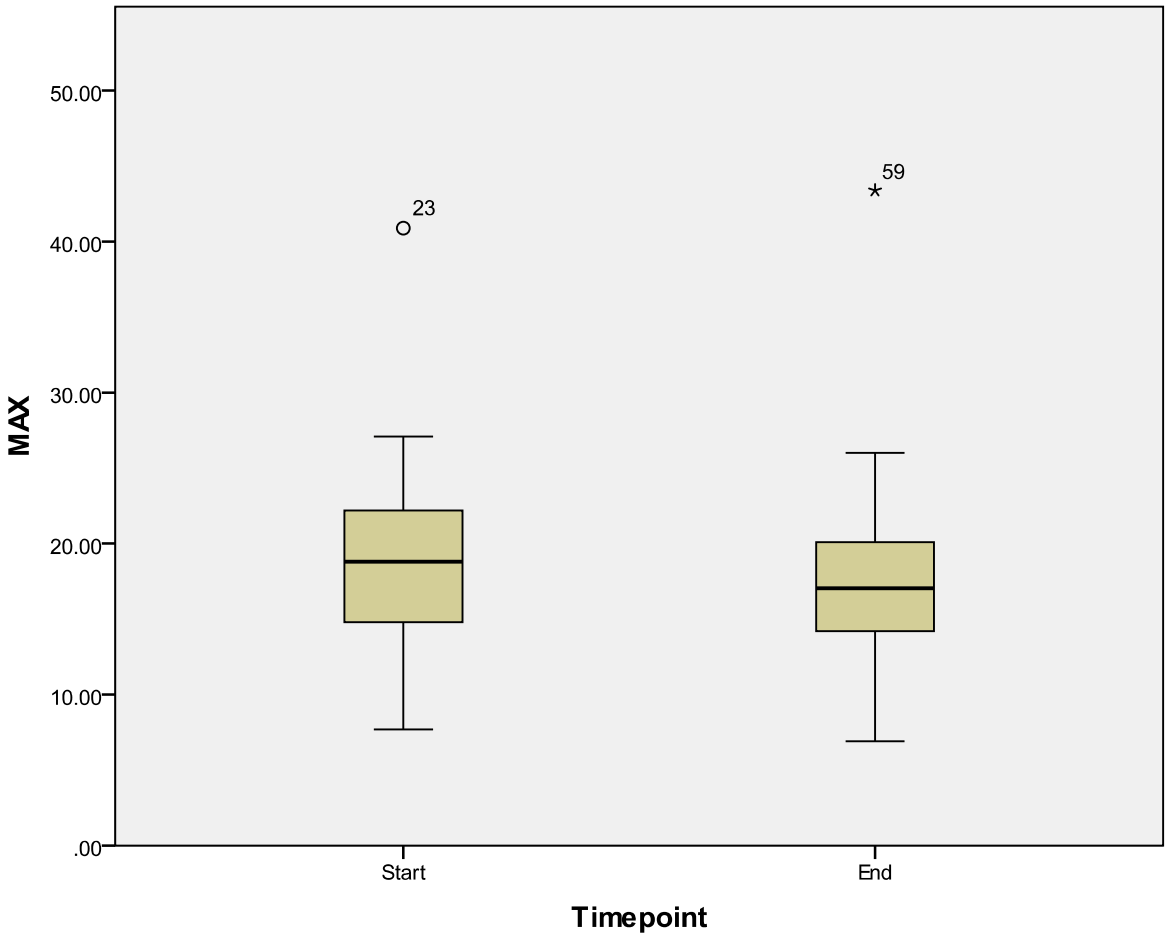
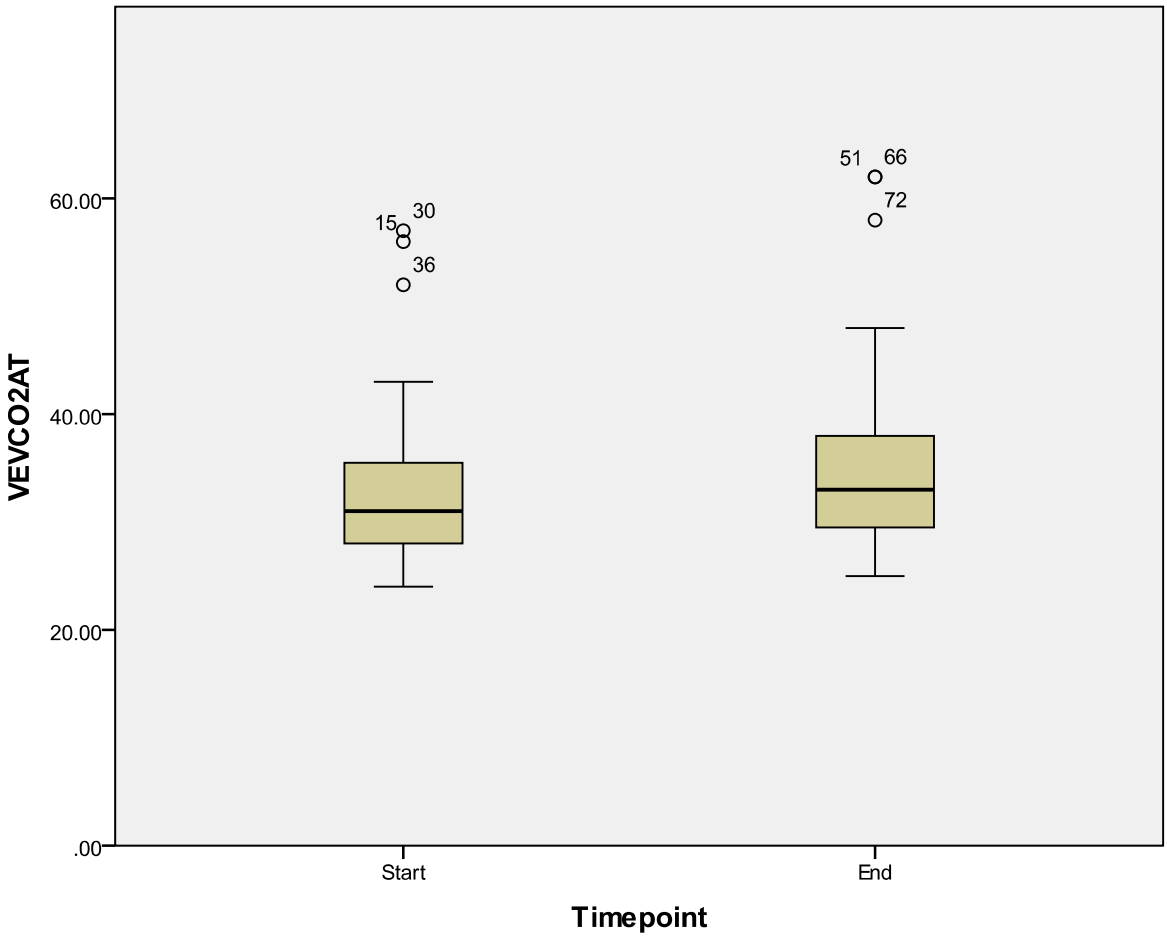
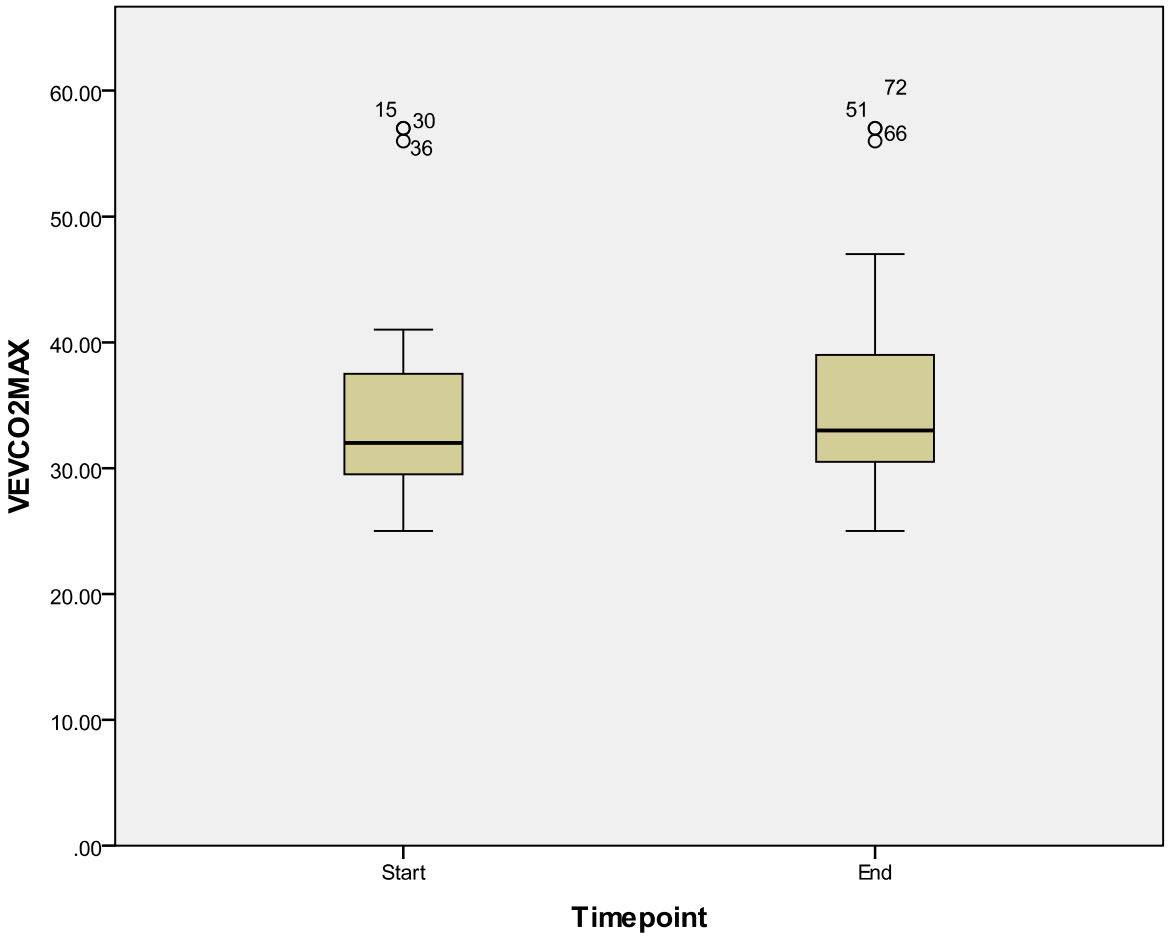
VEBTPS_L_min_AT
Start
End
Timepoint

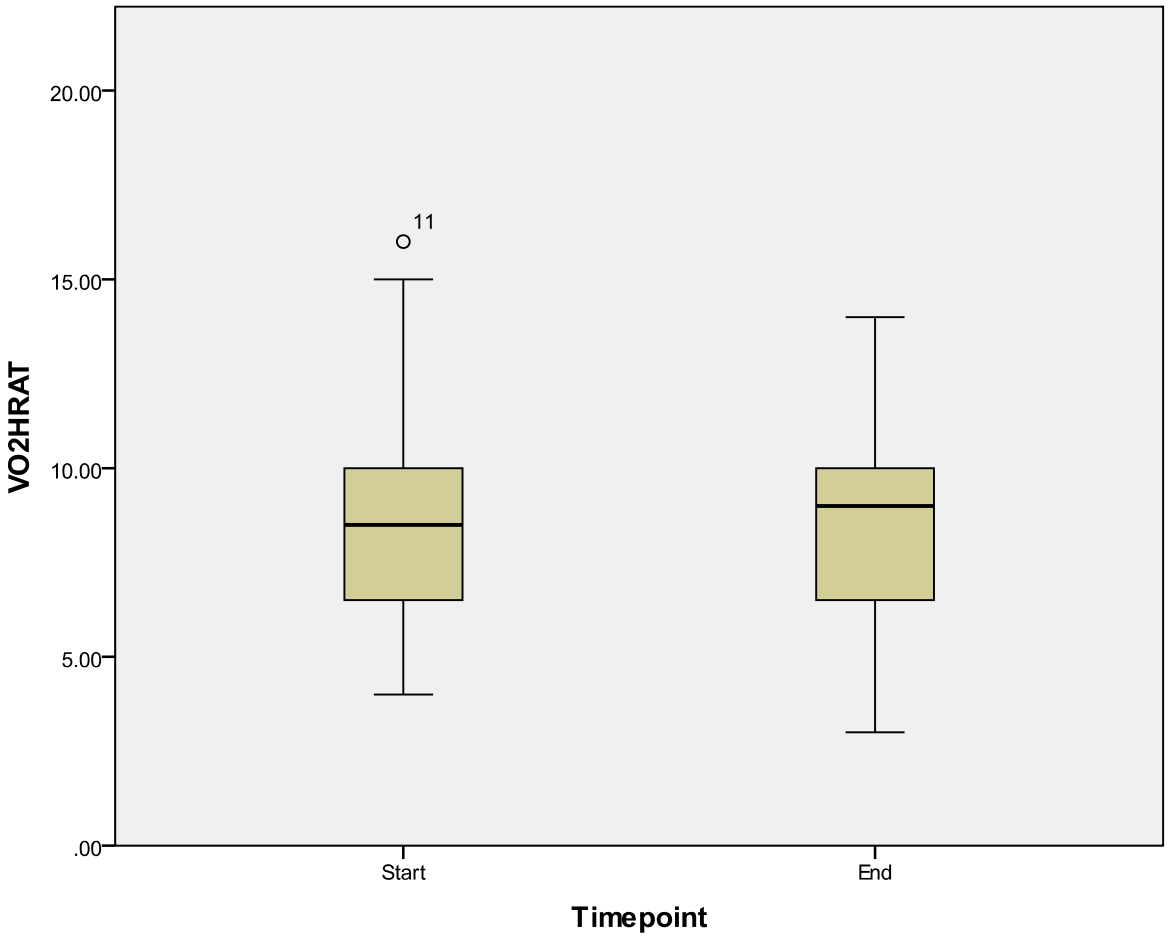

VEBTPS_L_min_VO2max
120.00
100.00
80.00
60.00
40.00
20.00
.00
23
22
59
Start
End
Timepoint

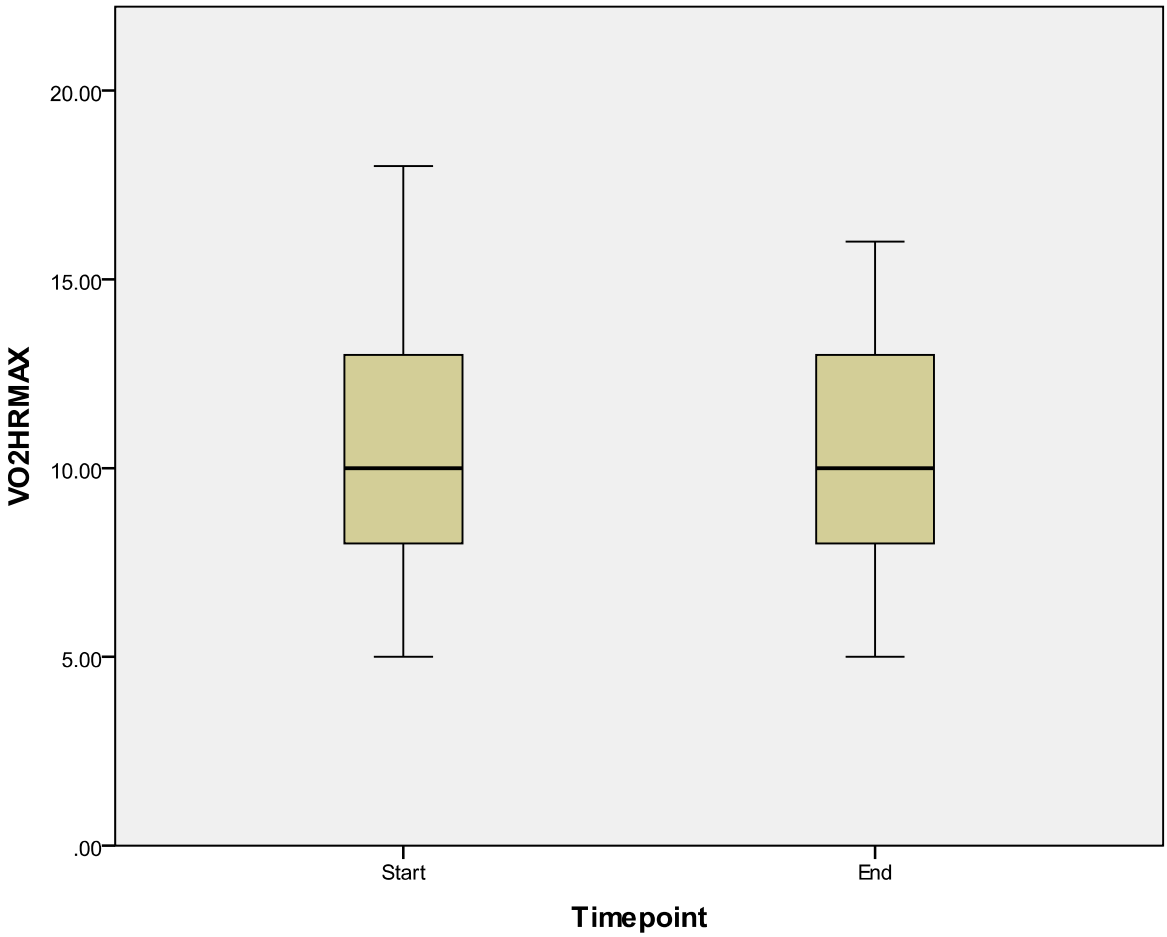

30.00
20.00
10.00
.00
AT
59
65
37
66
64
Start
End
Timepoint

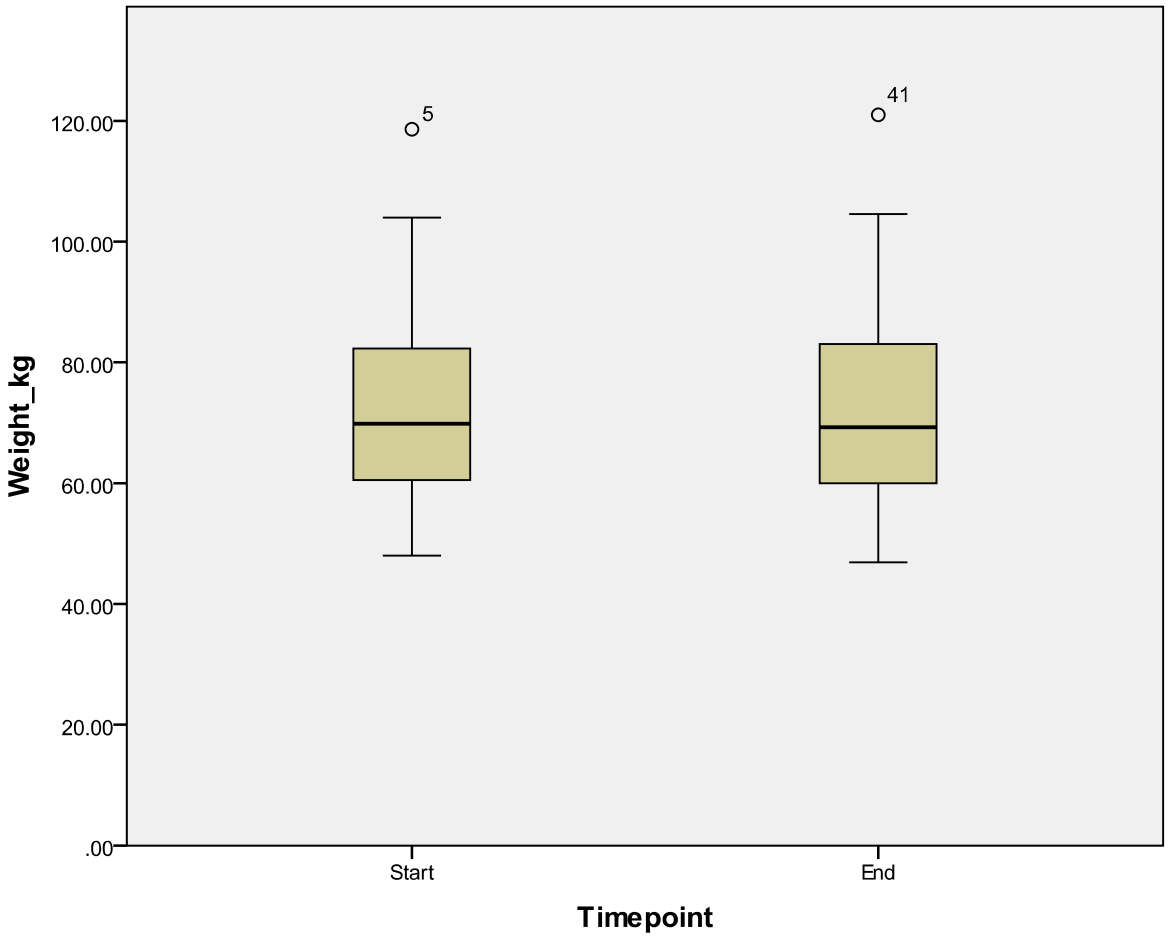

50.00
40.00
30.00
20.00
10.00
.00
MAX
23
59
Start
End
Timepoint

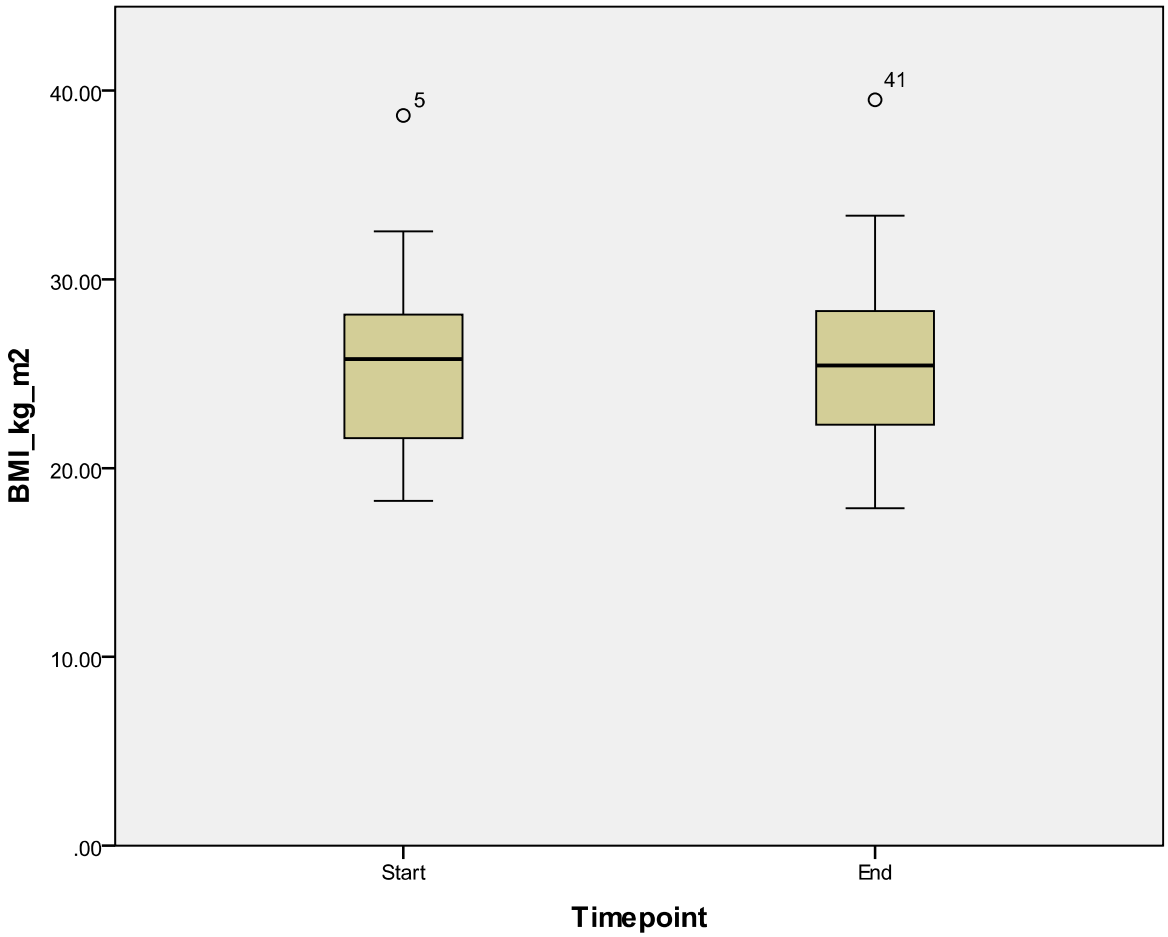

VEVCO2AT
60.00
40.00
20.00
.00
15
30
36
51
66
72
Start
End
Timepoint

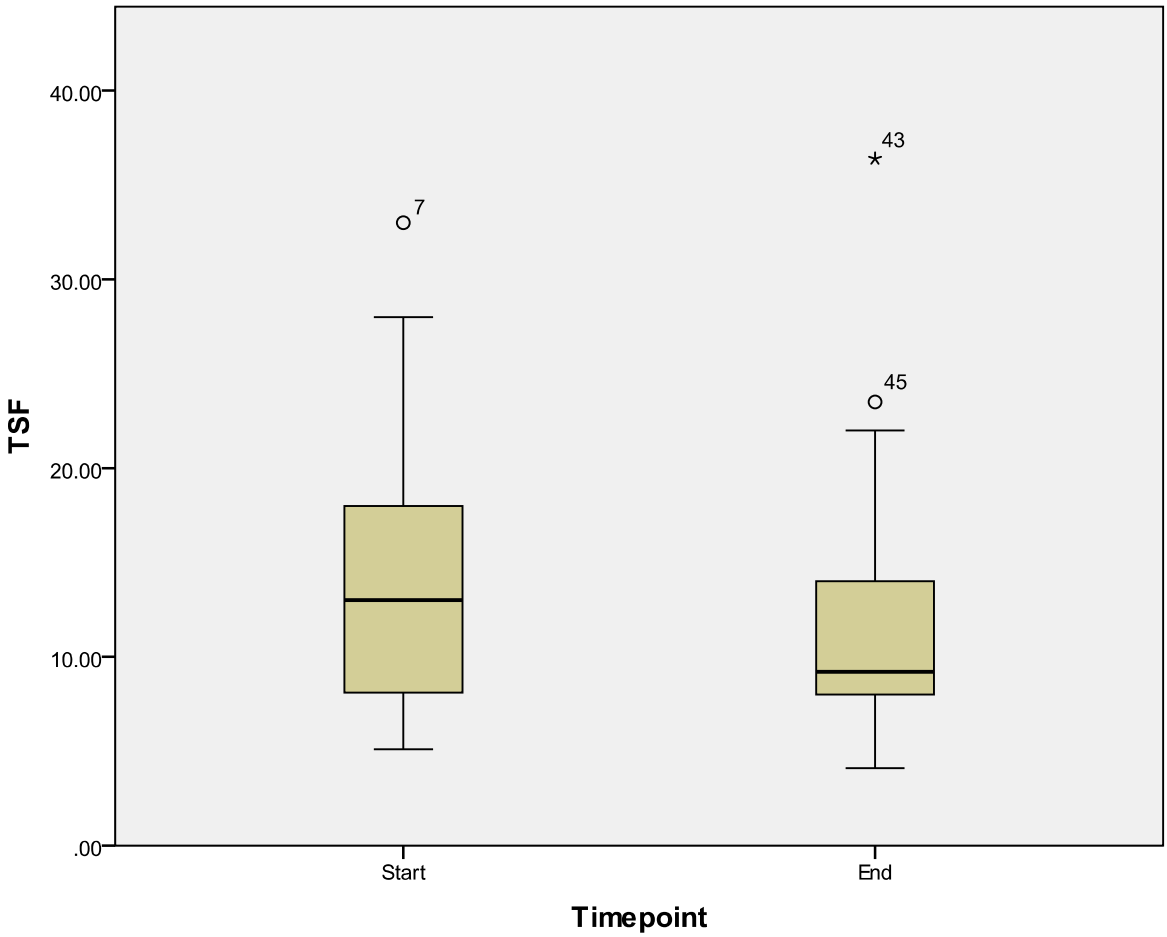

60.00
50.00
40.00
30.00
20.00
10.00
.00
VEVCO2MAX
15
30
36
72
51
66
Start
End
Timepoint


20.00
15.00
10.00
5.00
.00
VO2HRAT
11
Start
End
Timepoint


20.00
15.00
10.00
5.00
.00
VO2HRMAX
Start
End
Timepoint


Weight_kg
120.00
100.00
80.00
60.00
40.00
20.00
.00
5
41
Start
End
Timepoint


40.00
30.00
20.00
10.00
.00
BMI_kg_m2
5
41
Start
End
Timepoint


40.00
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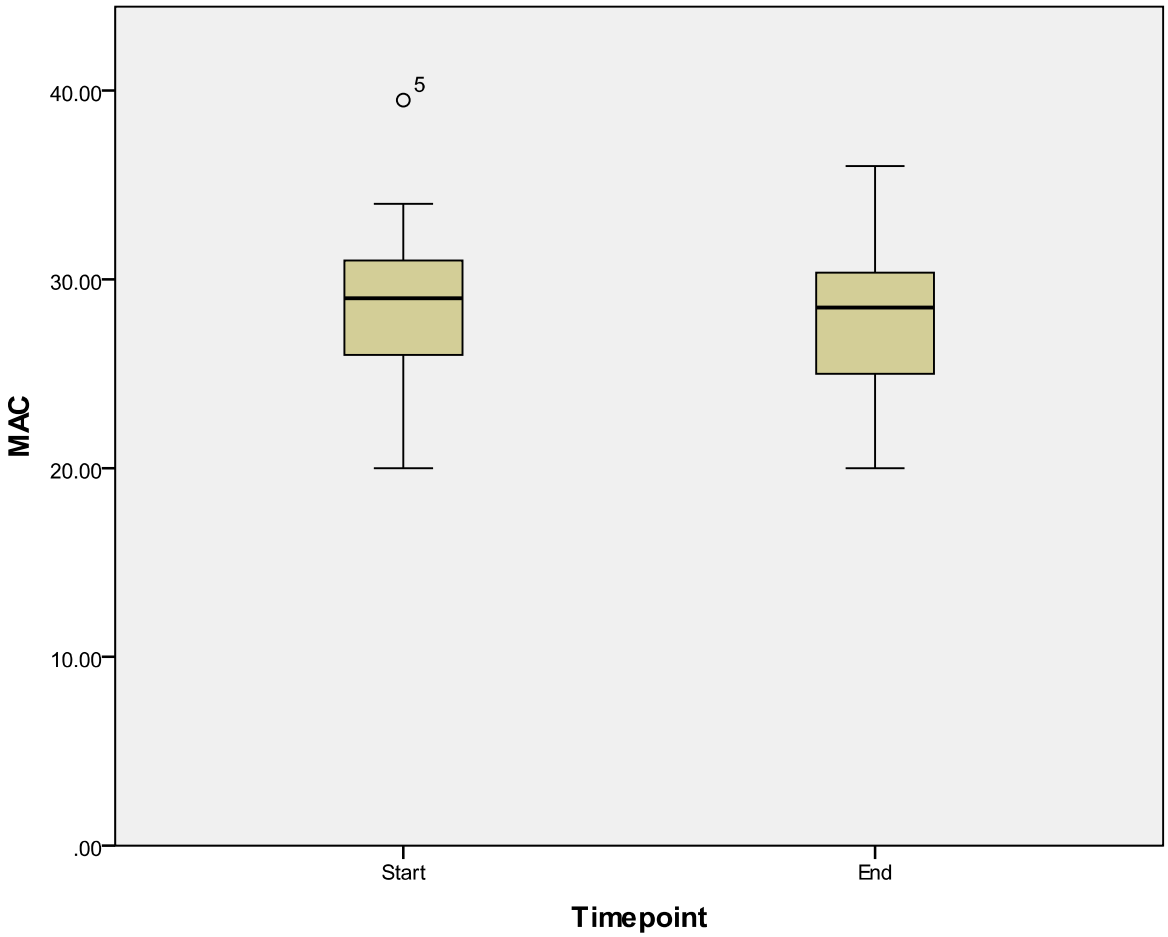
20.00
10.00
.00
TSF
7
43
45
Start
End
Timepoint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30.00
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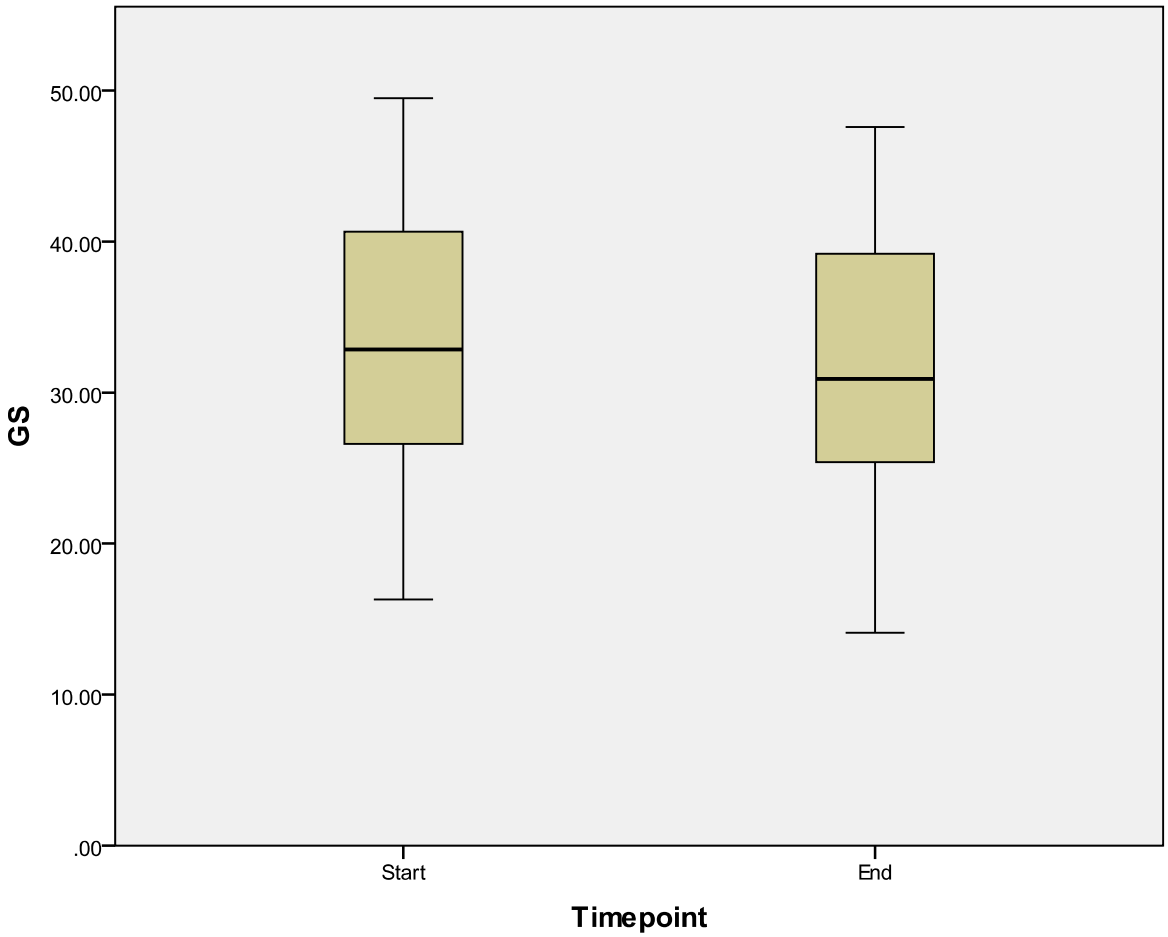
10.00
.00
MAC
5
Start
End
Timepoint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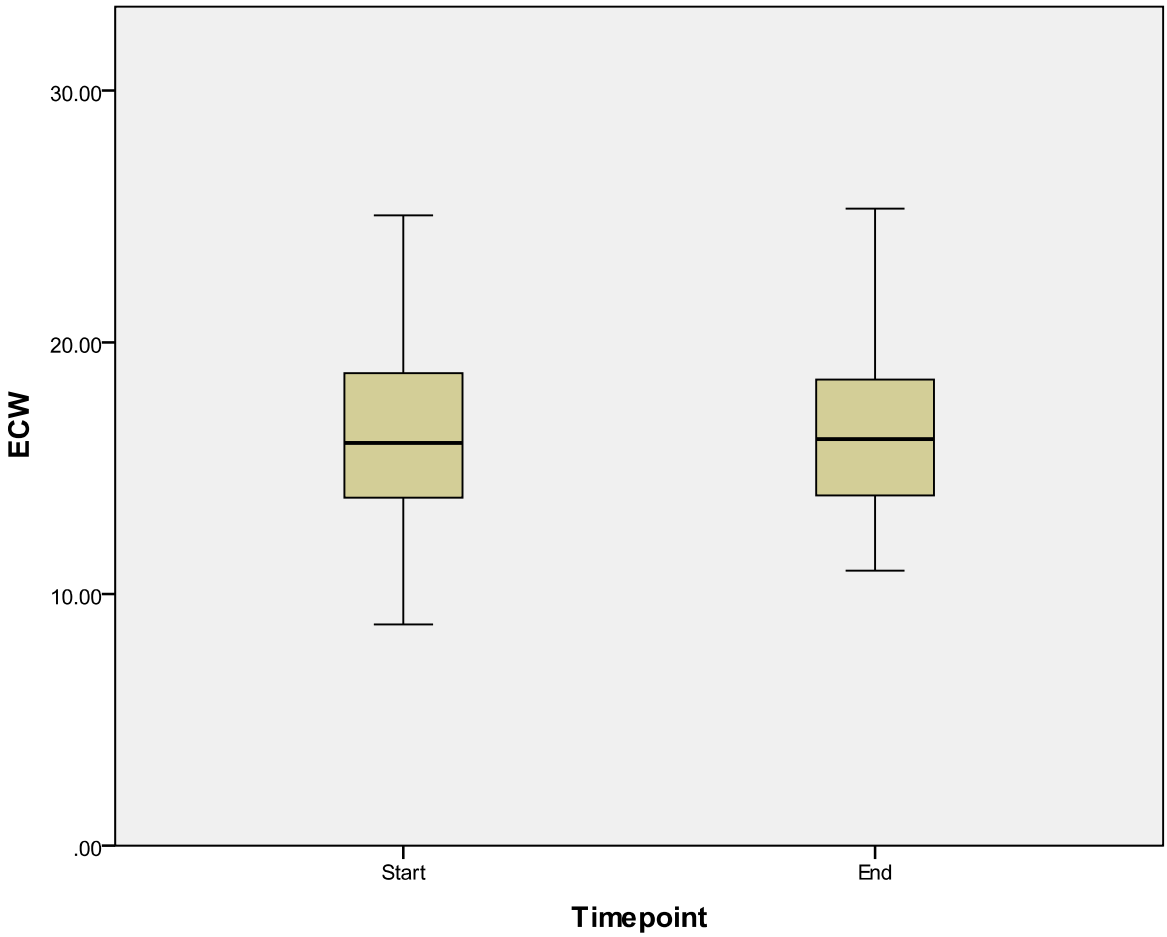
10.00
.00
GS
Start
End
Timepoint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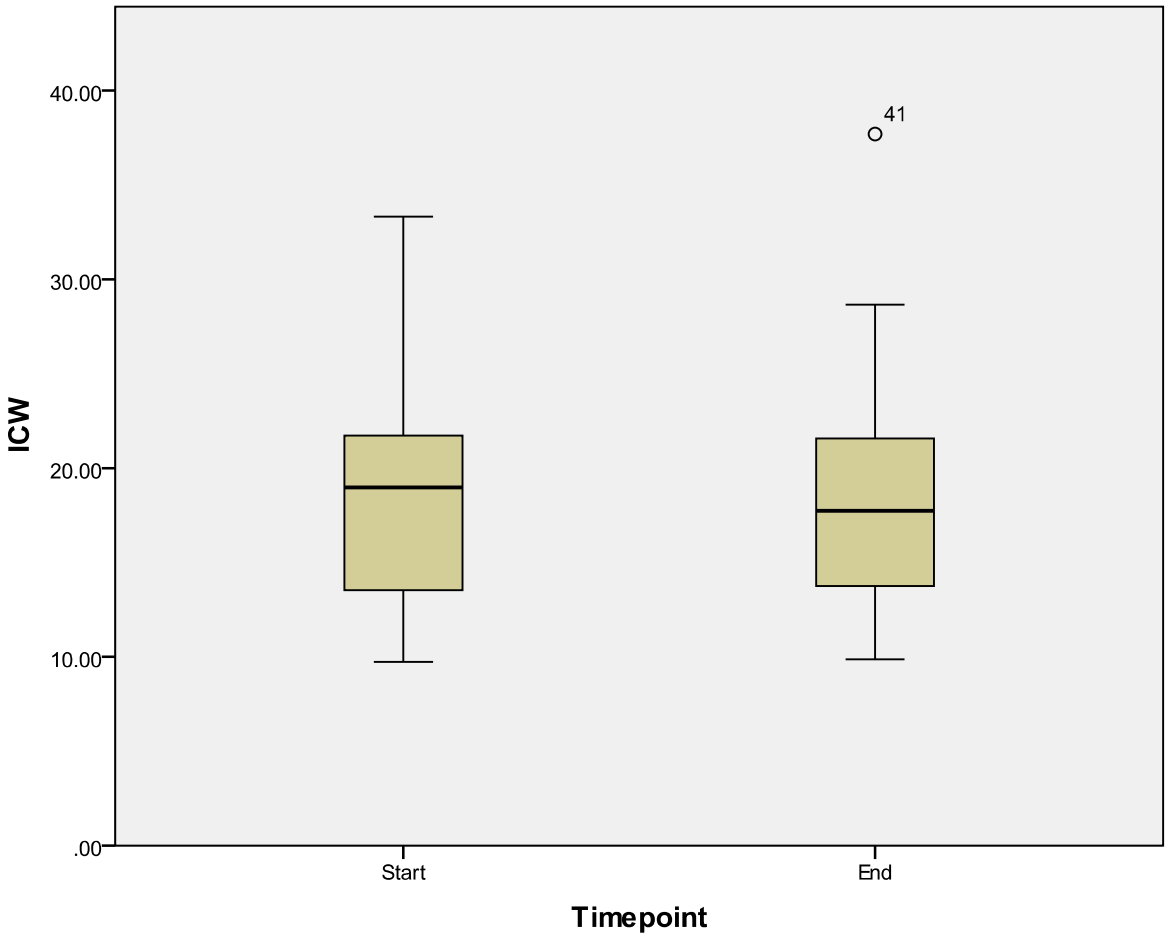
.00
ECW
Start
End
Timepoint


40.00
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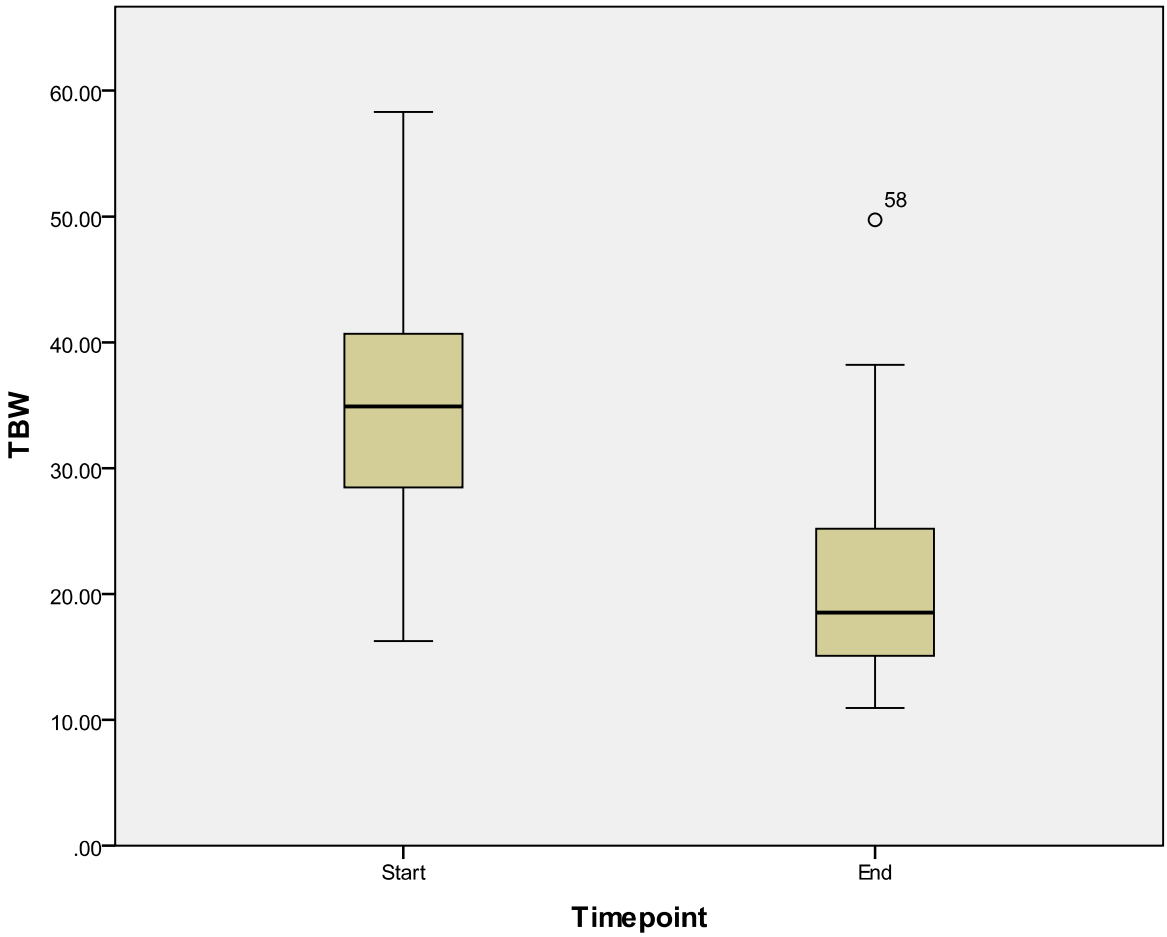
10.00
.00
ICW
41
Start
End
Timepoint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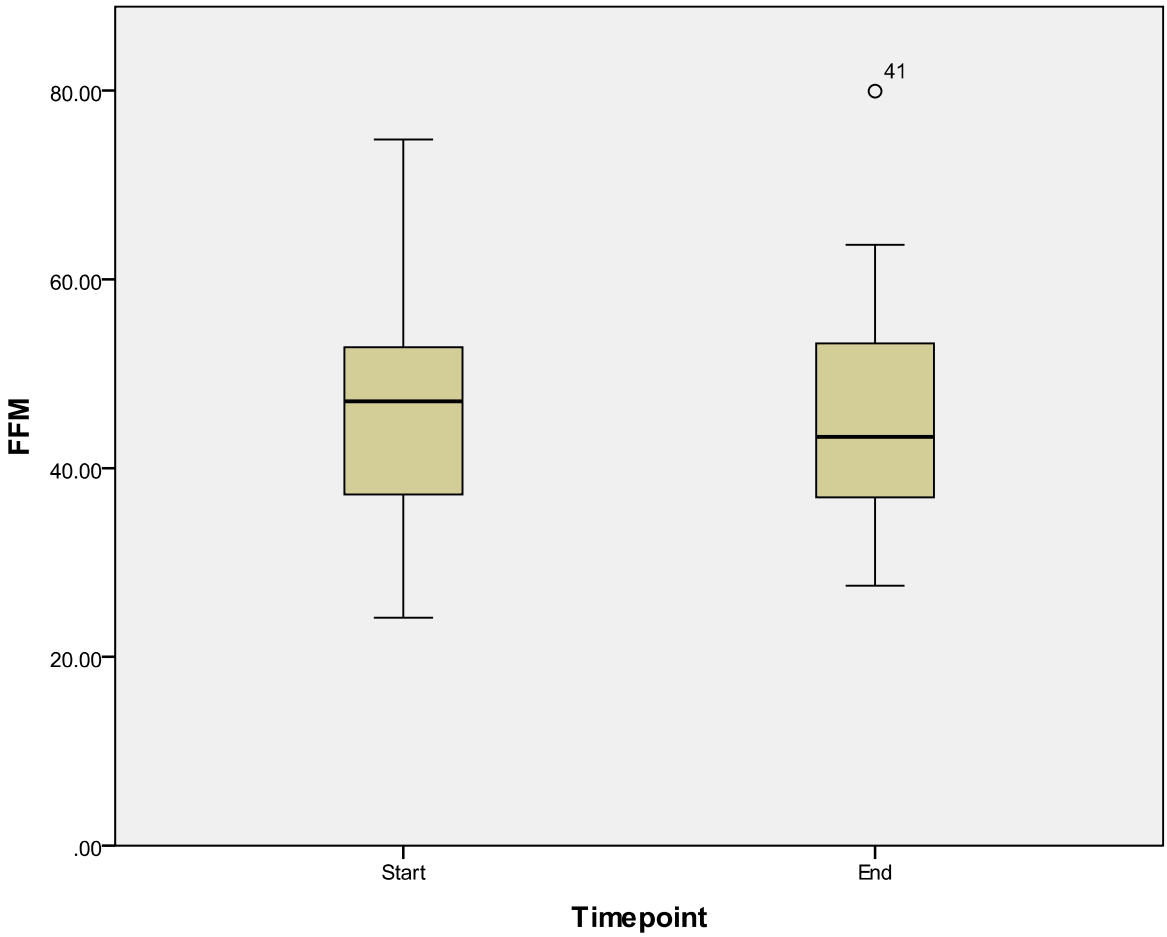
20.00
10.00
.00
TBW
58
Start
End
Timepoint


41
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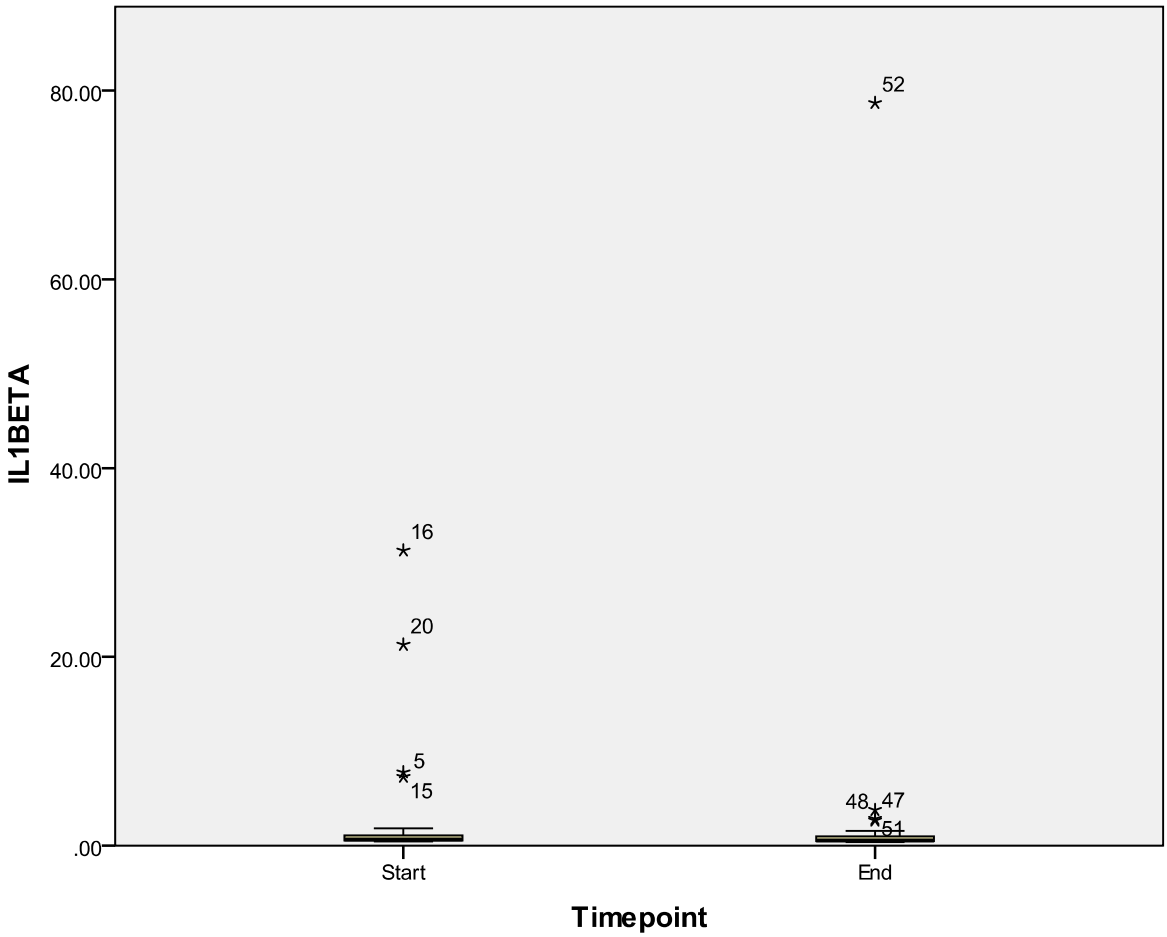
40.00
20.00
.00
FFM
Start
End
Timepoint


80.00
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20.00
.00
IL1BETA
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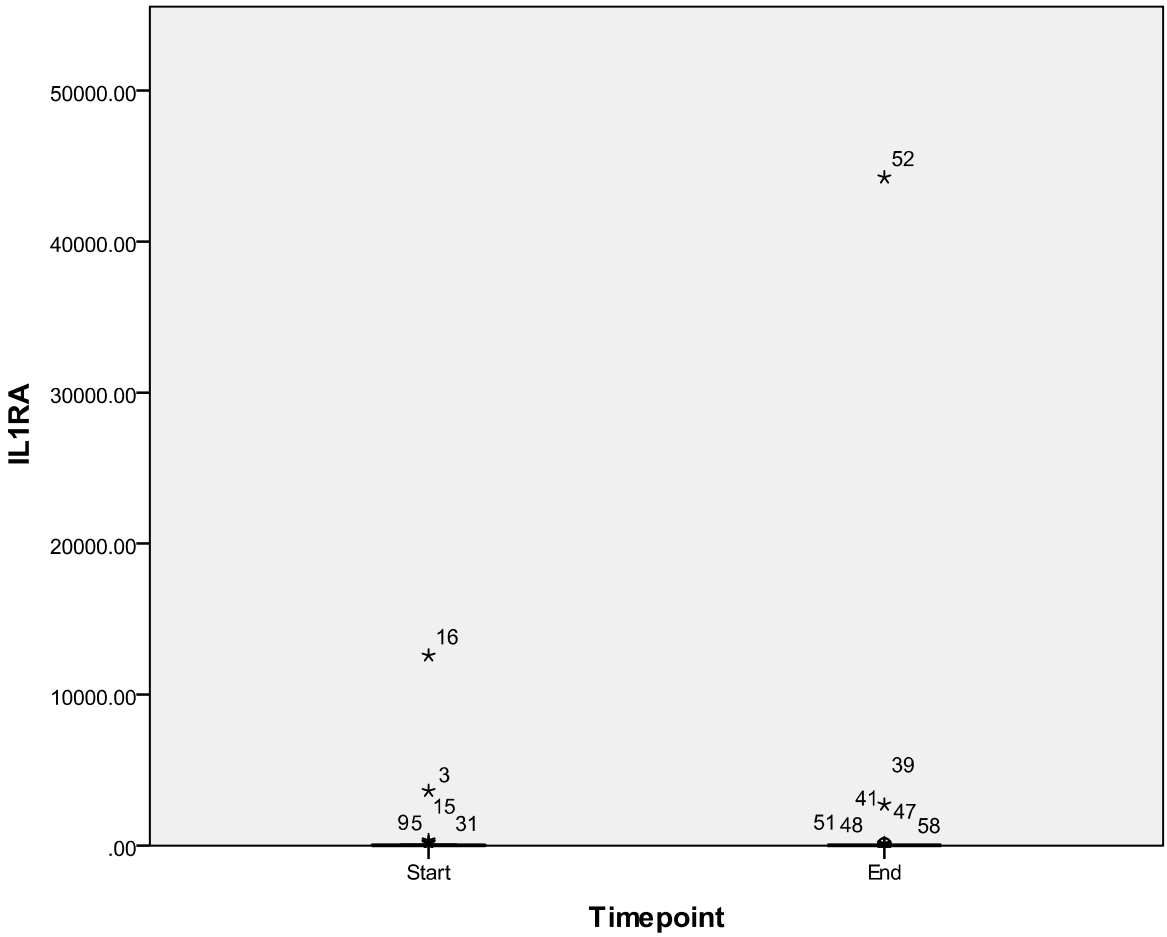
16
20
5
15
48
47
51
Start
End
Timepoint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40000.00
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20000.00
10000.00
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IL1RA
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3
15
95
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41
47
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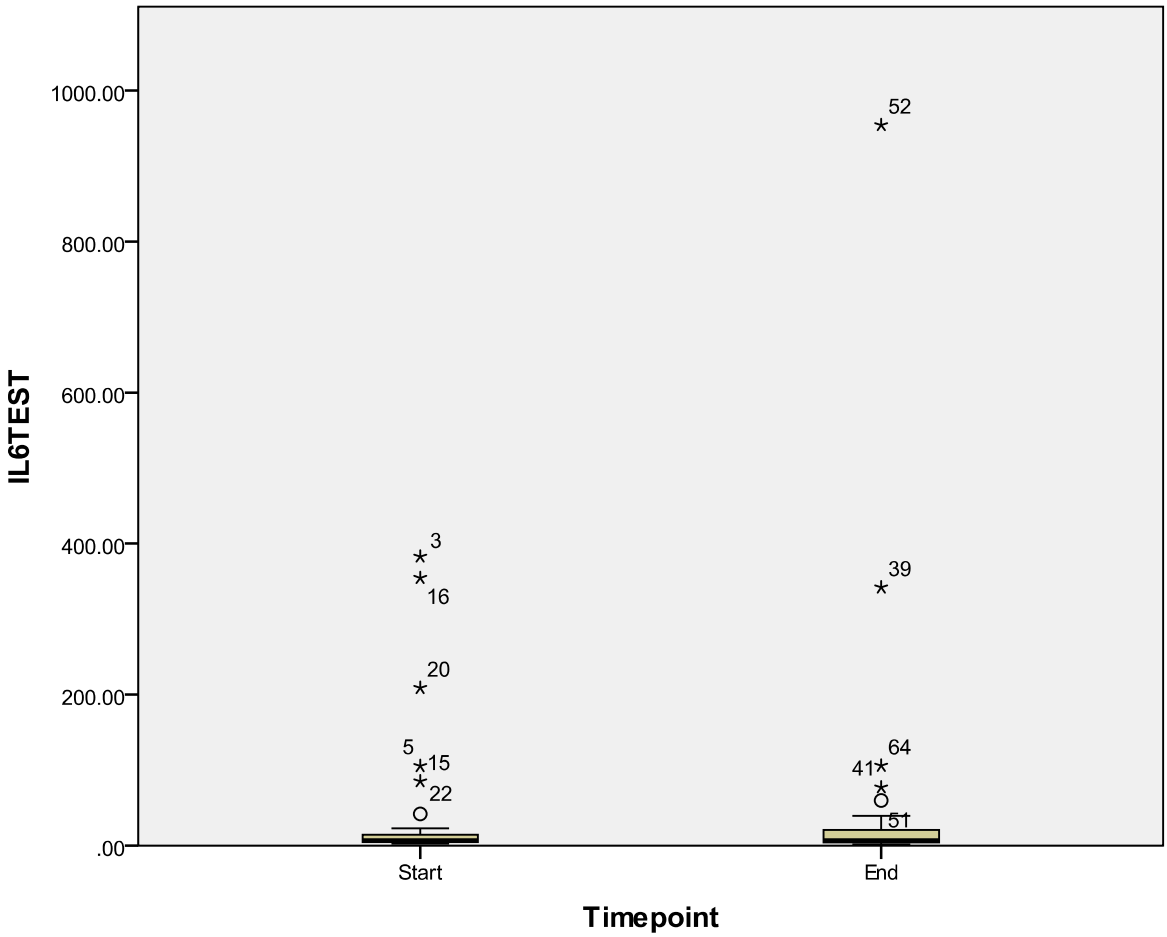
48
58
Start
End
Timepoint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800.00
600.00
400.00
200.00
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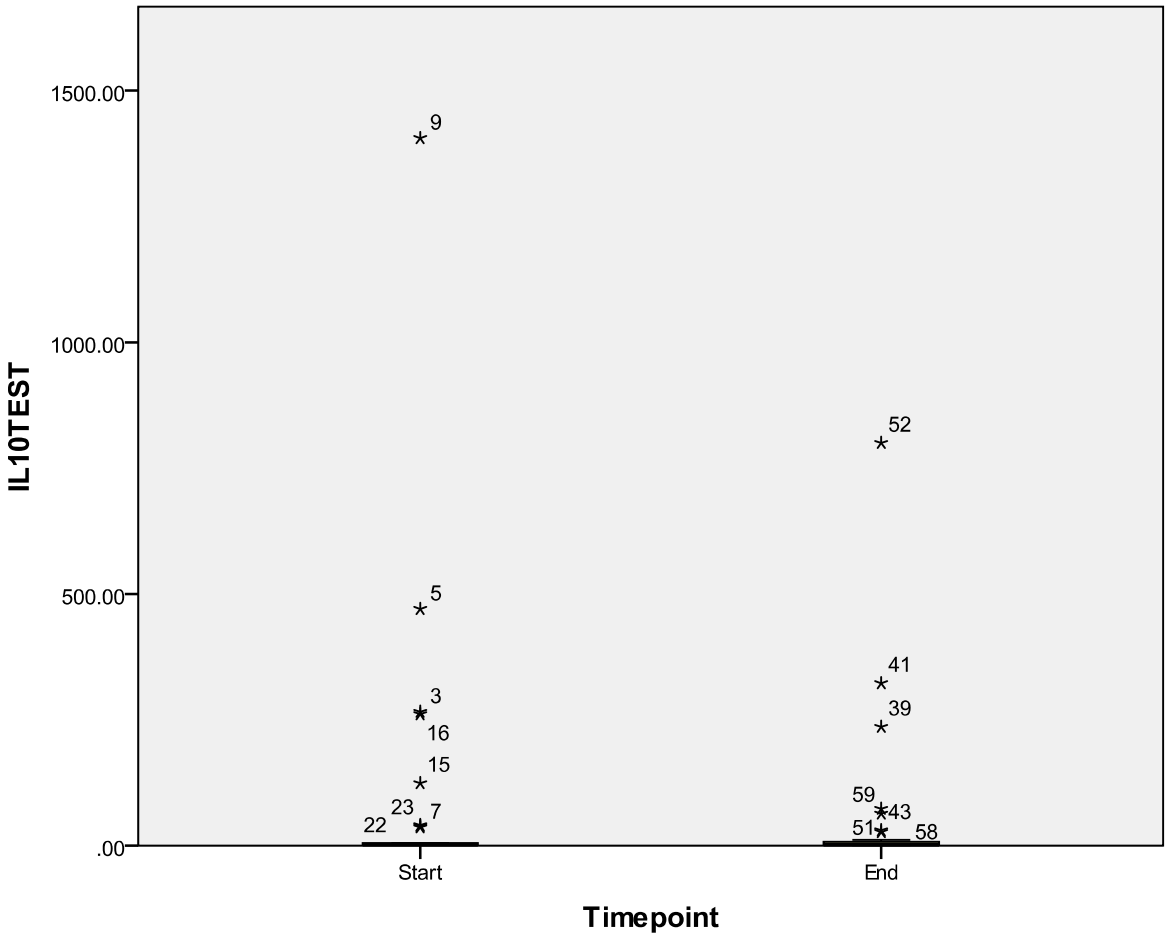
IL6TEST
52
3
39
16
20
5
64
15
41
22
51
Start
End
Timepoint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500.00
.00
IL10TEST
9
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3
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16
15
59
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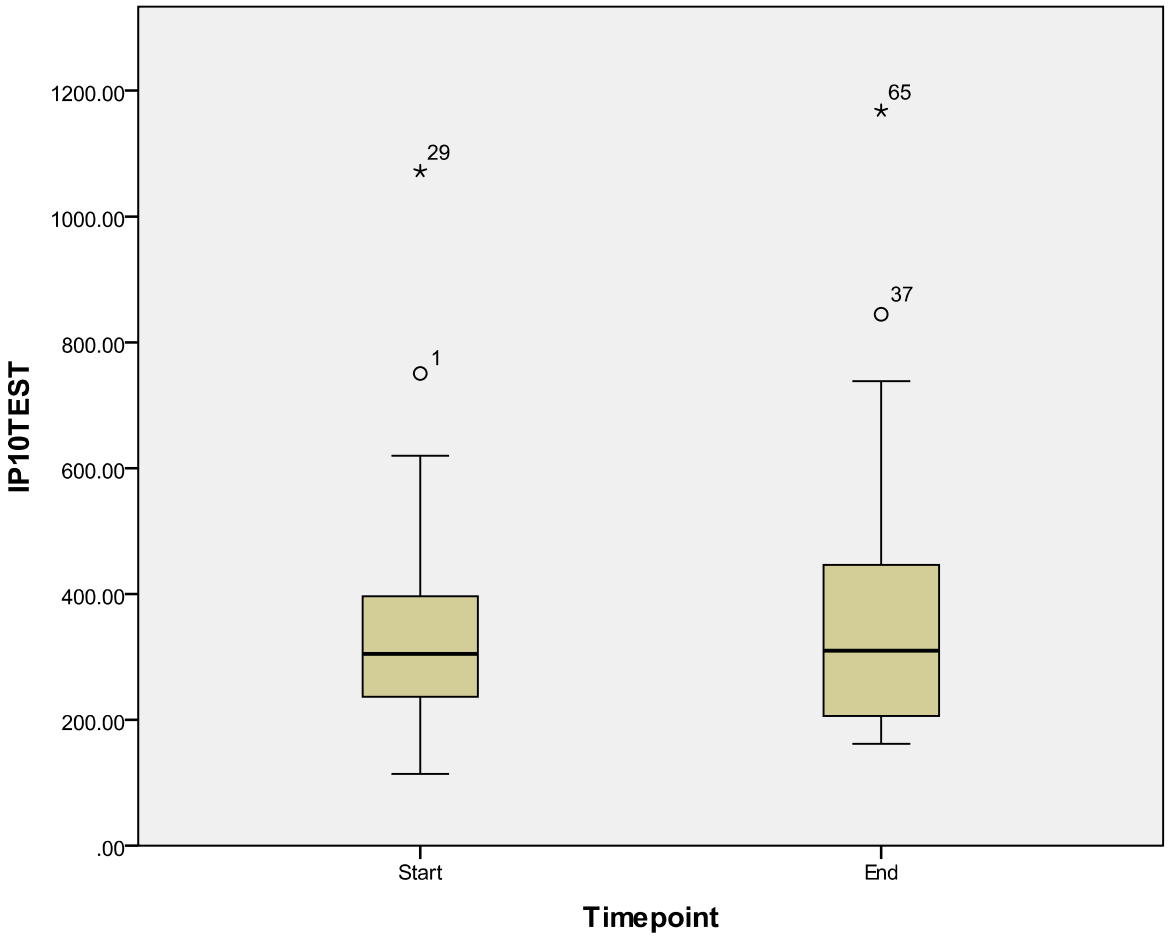
7
43
22
51
58
Start
End
Timepoint


IP10TEST
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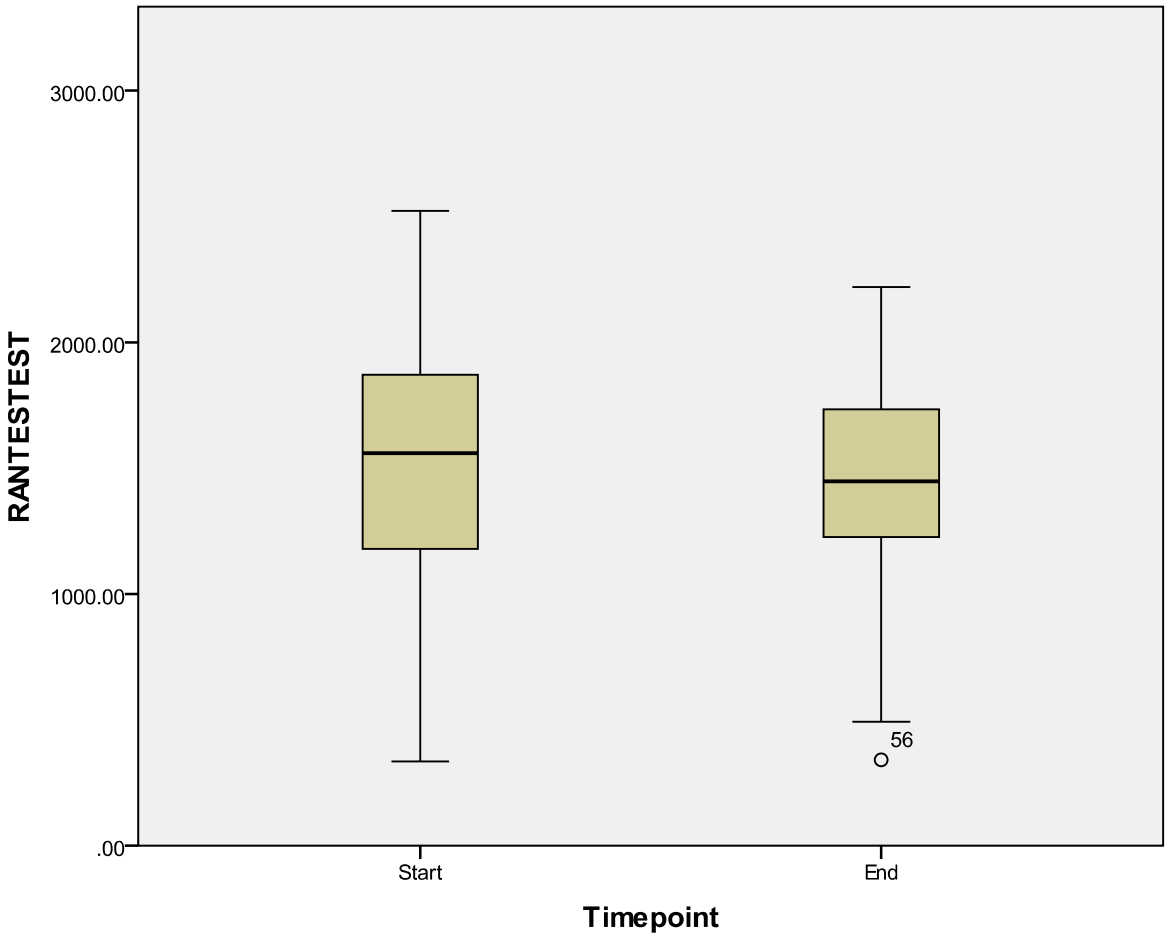
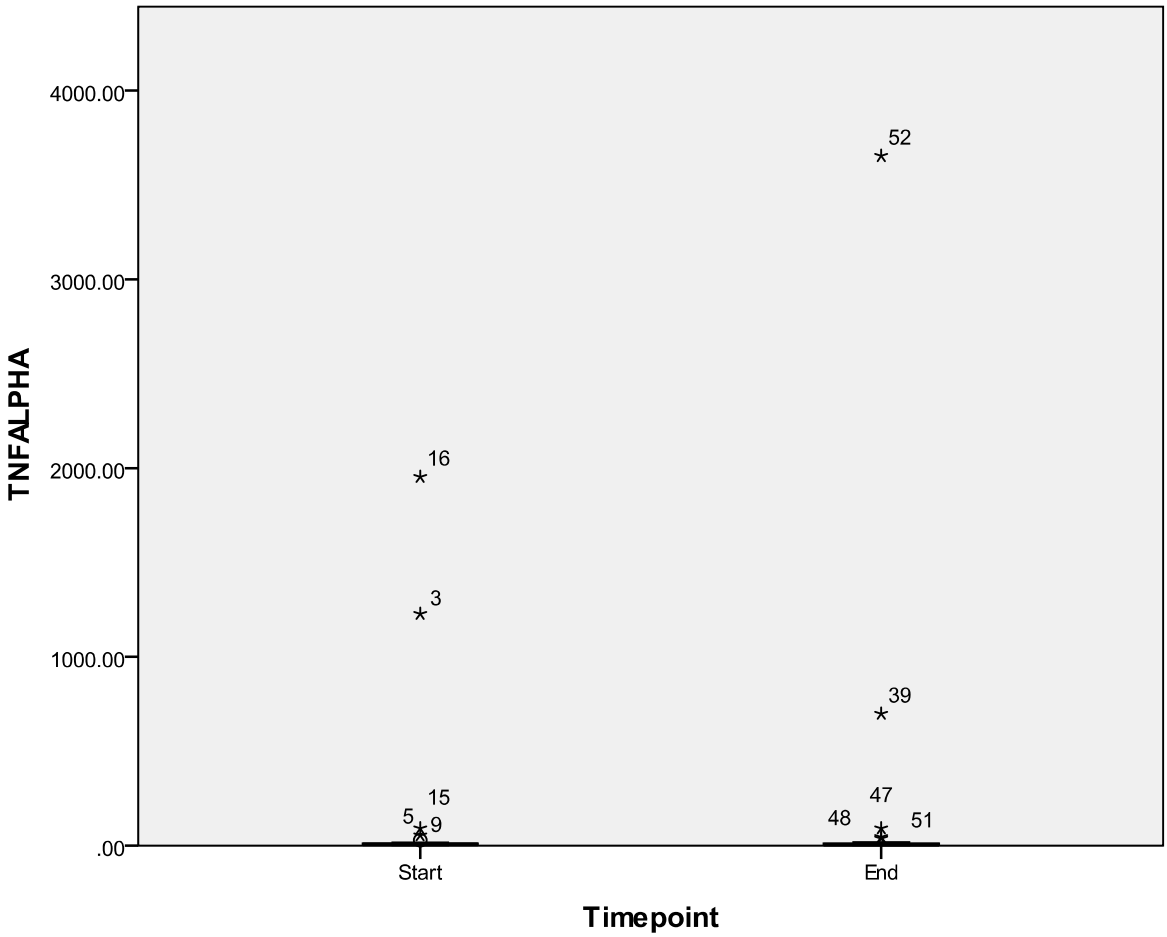
600.00
400.00
200.00
.00
29
65
37
1
Start
End
Timepoint


3000.00
2000.00
1000.00
.00
RANTESTEST
56
Start
End
Timepoint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3000.00
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1000.00
.00
TNFALPHA
52
16
3
39
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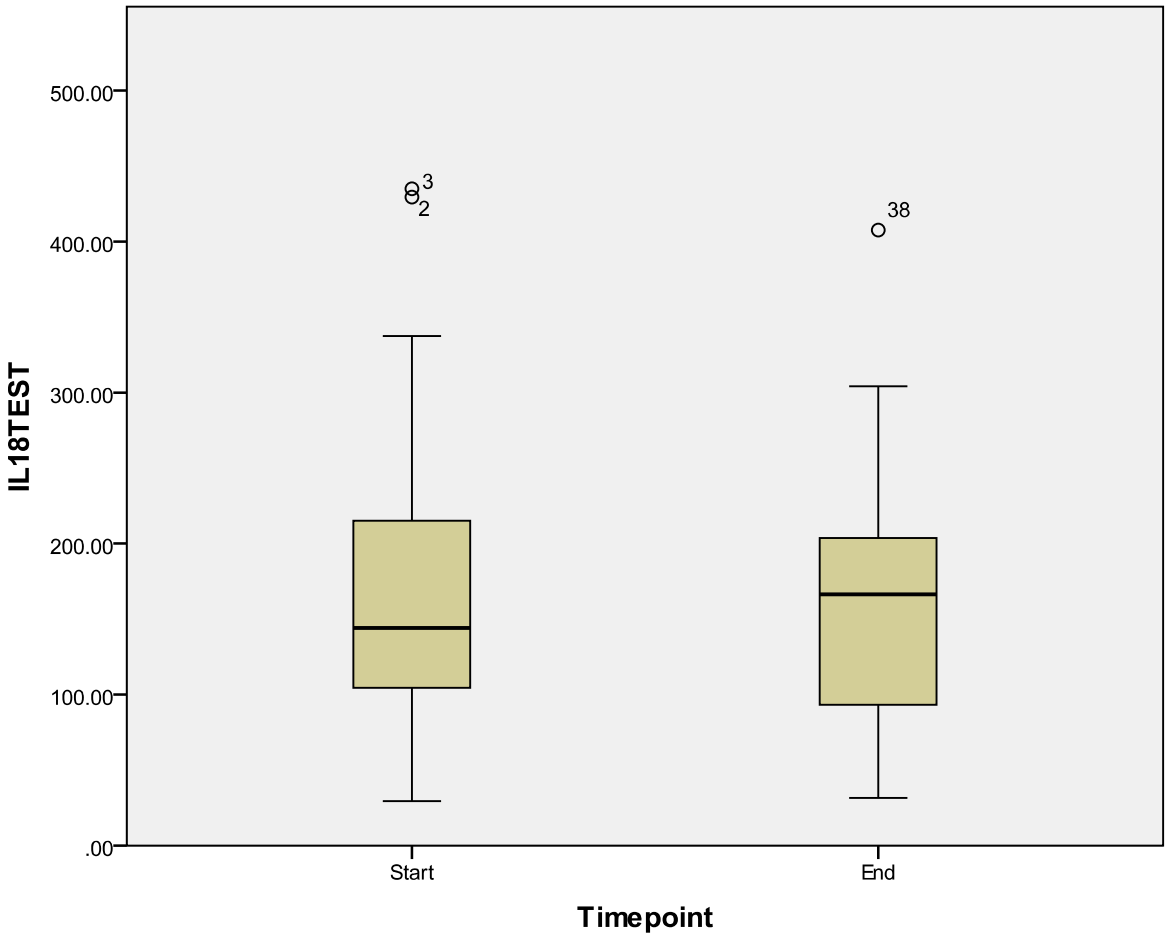
47
5
9
48
51
Start
End
Timepoint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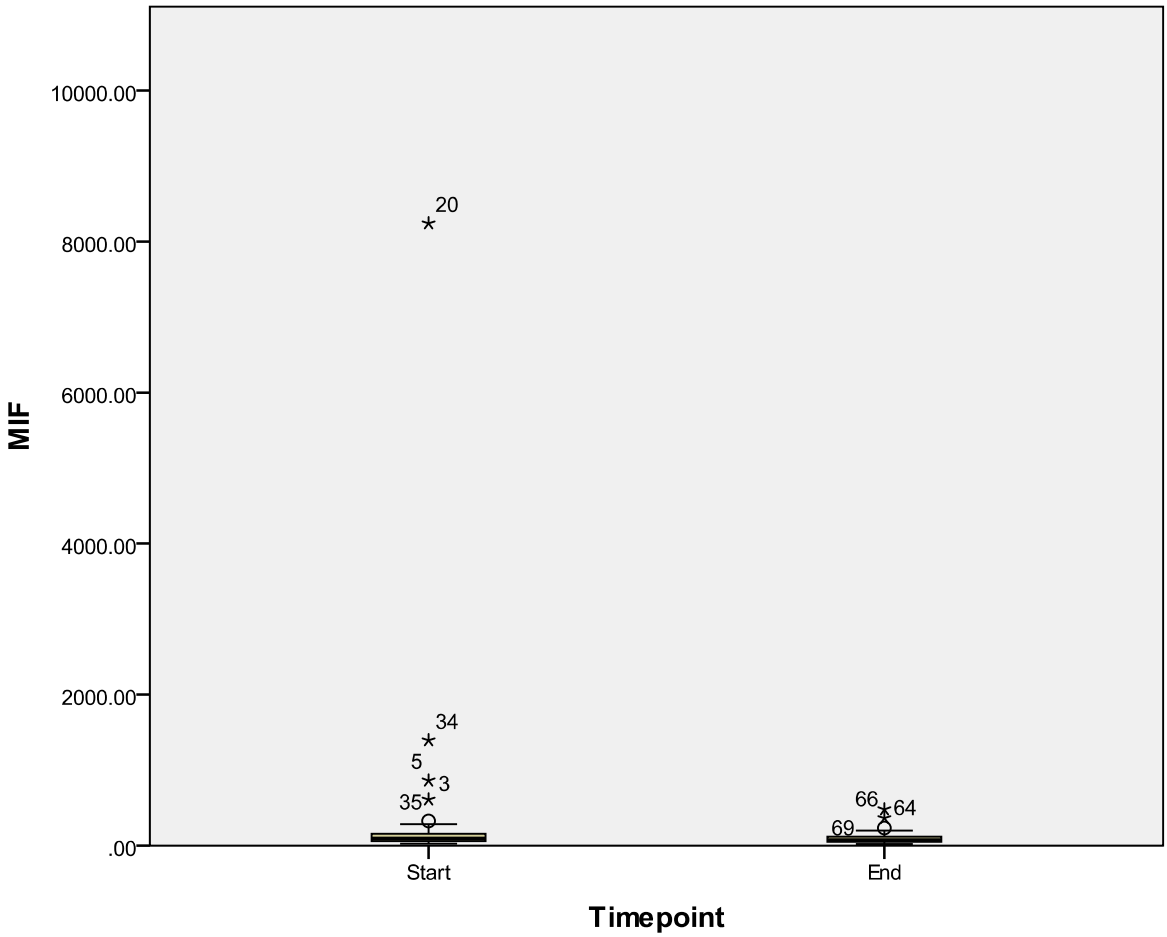
300.00
200.00
100.00
.00
IL18TEST
3
2
38
Start
End
Timepoint


10000.00
8000.00
6000.00
4000.00
2000.00
.00
MIF
20
34
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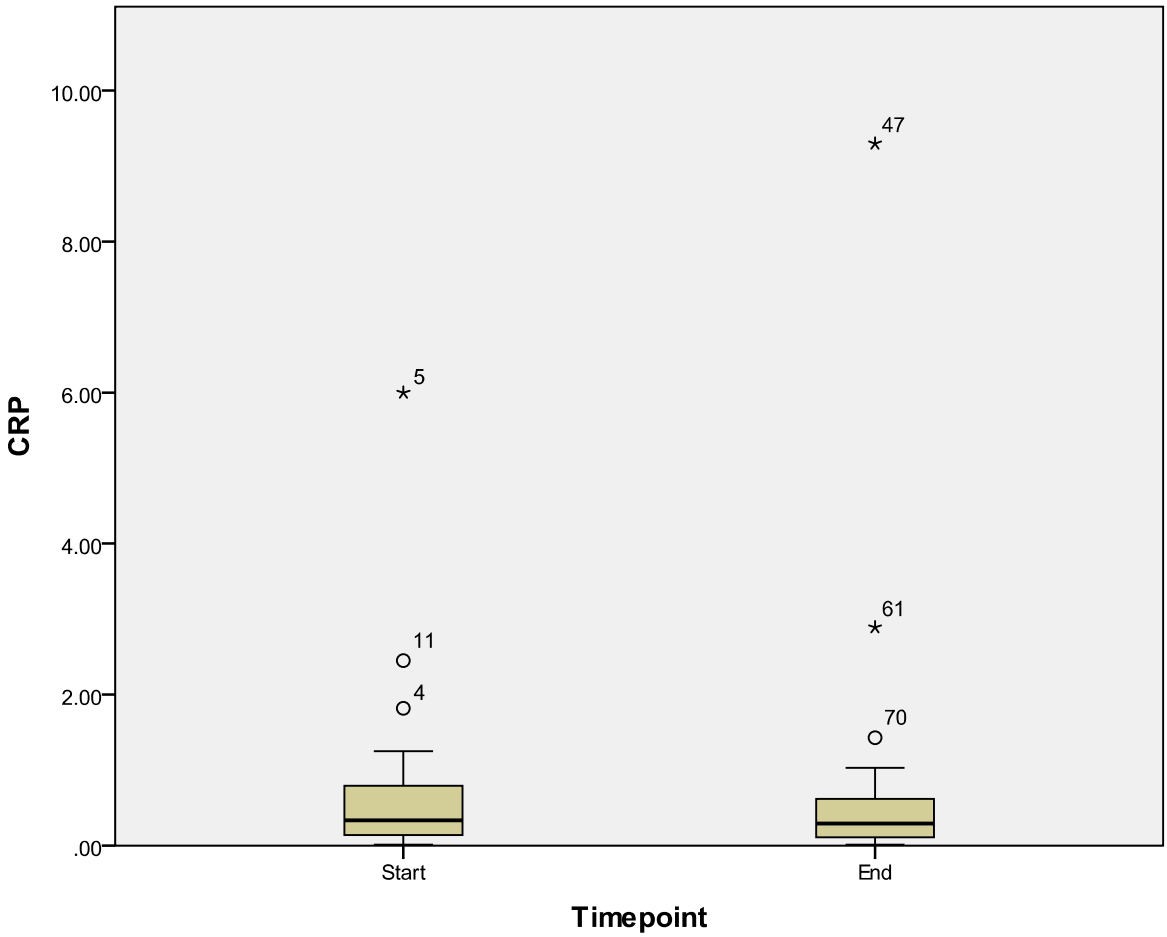
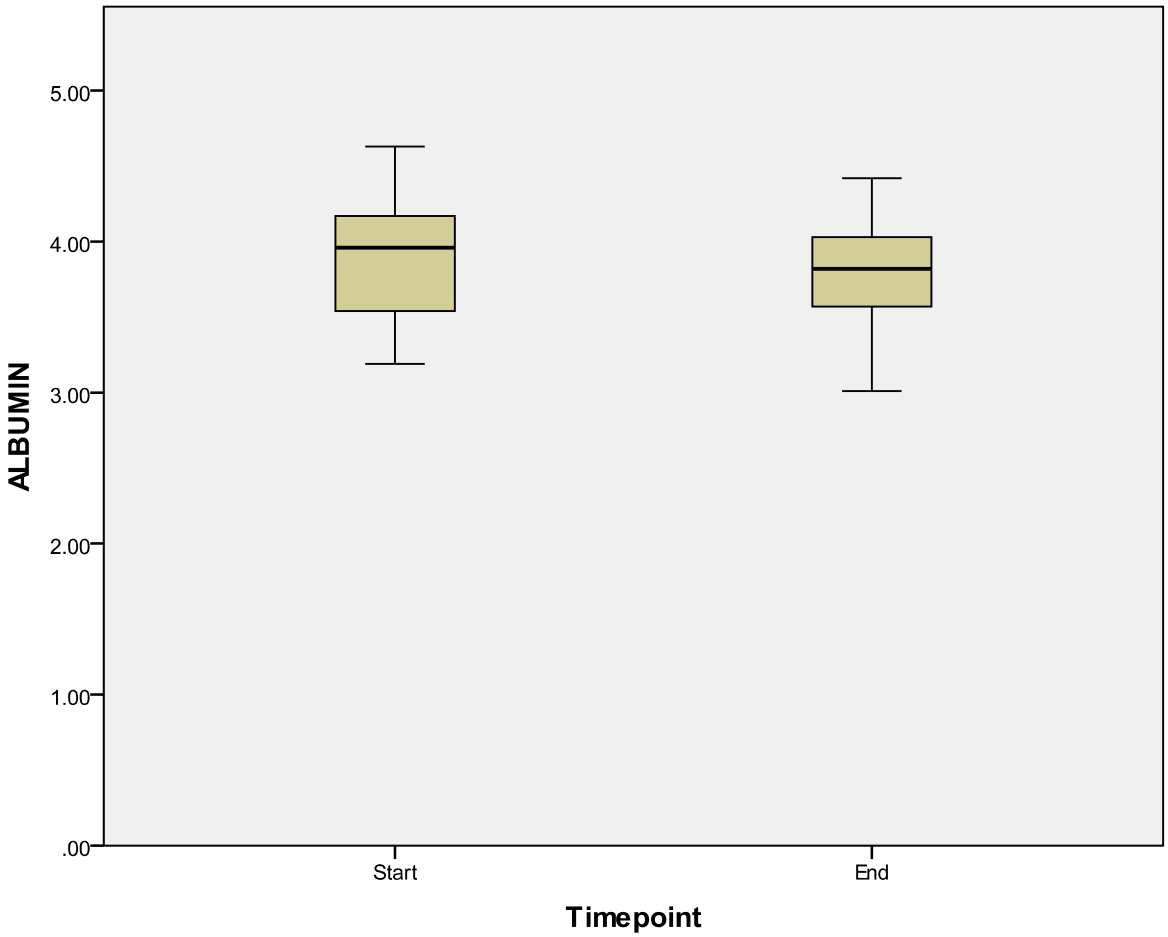
3
35
66
64
69
Start
End
Timepoint


10.00
8.00
6.00
4.00
2.00
.00
CRP
47
5
61
11
4
70
Start
End
Timepoint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3.00
2.00
1.00
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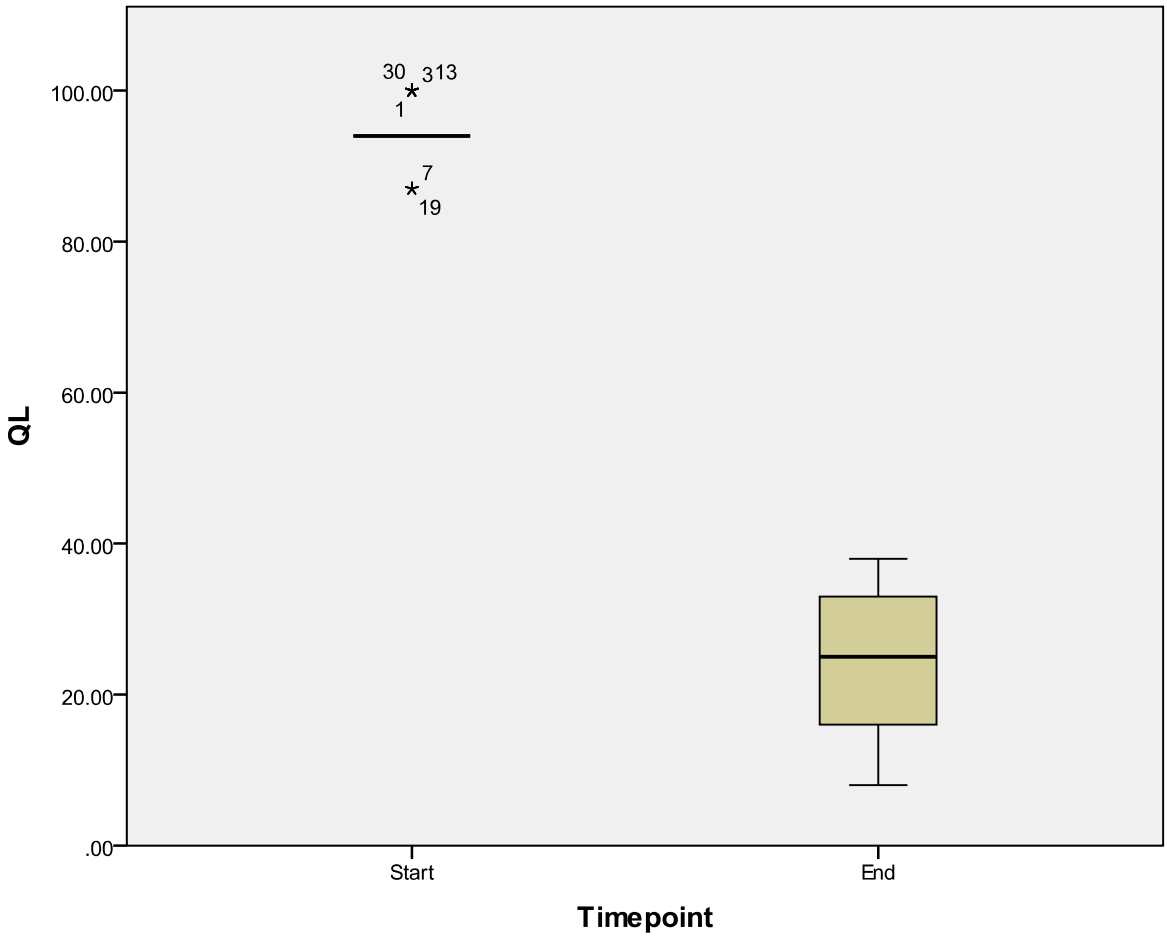
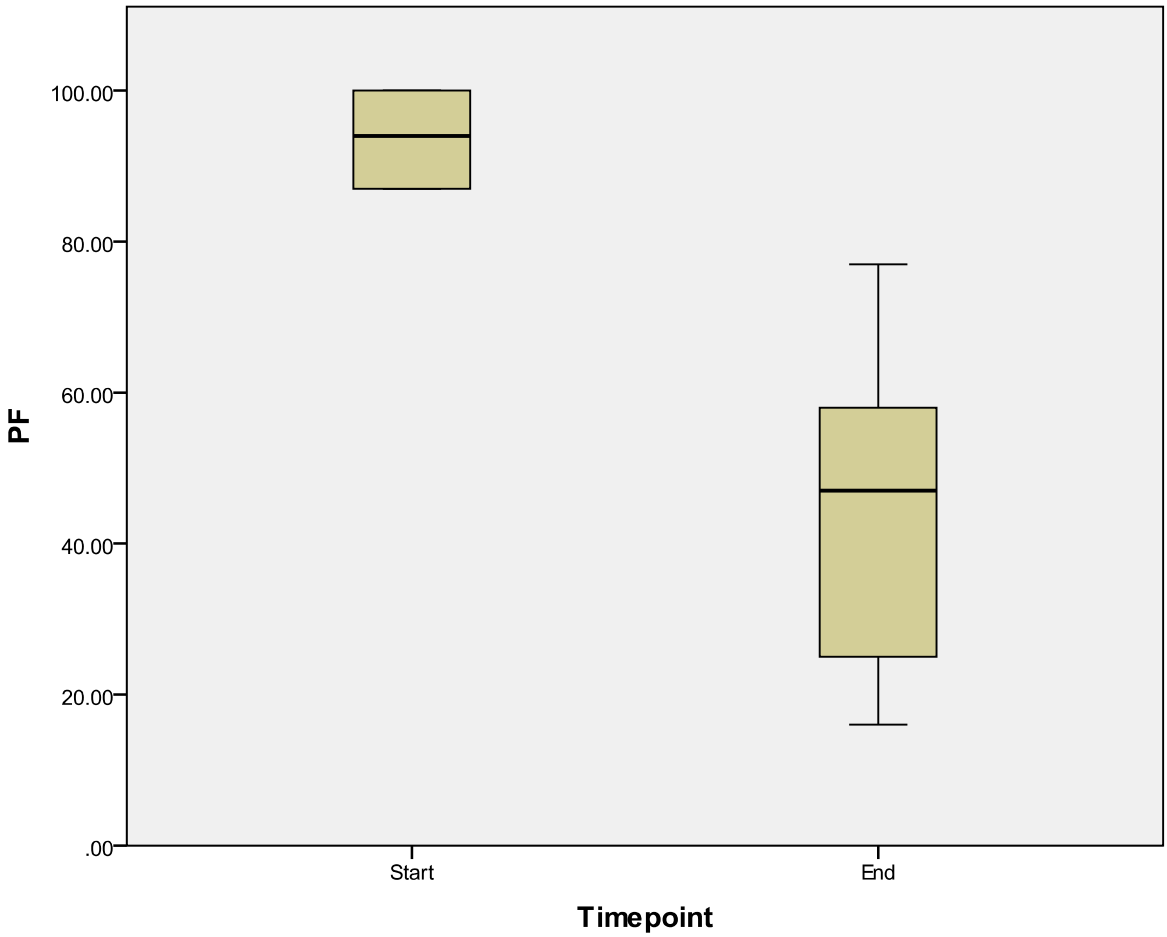
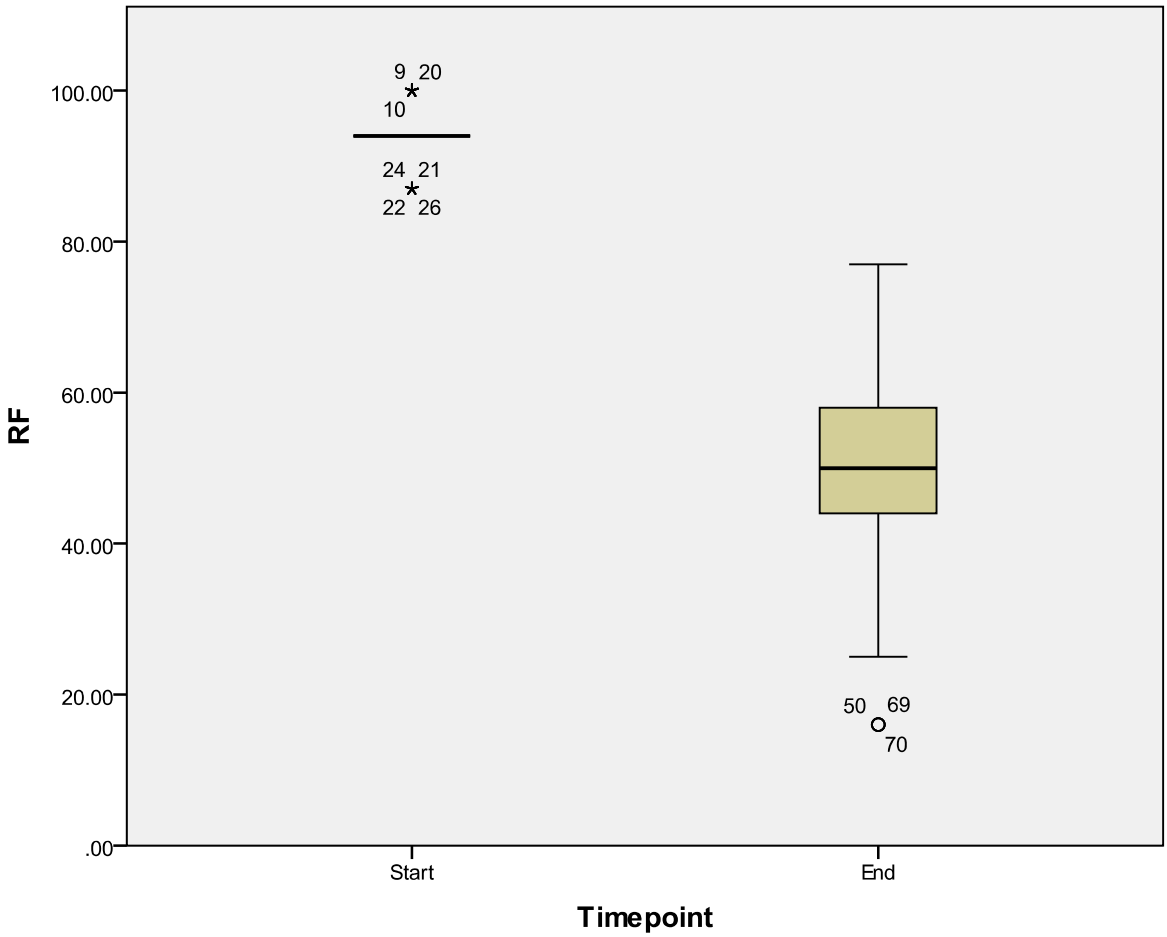
ALBUMIN
Start
End
Timepoint


30
3
13
1
7
19
100.00
80.00
60.00
40.00
20.00
.00
QL
Start
End
Timepoint


100.00
80.00
60.00
40.00
20.00
.00
PF
Start
End
Timepoint


9 20
10
24 21
22 26
50 69
70
100.00
80.00
60.00
40.00
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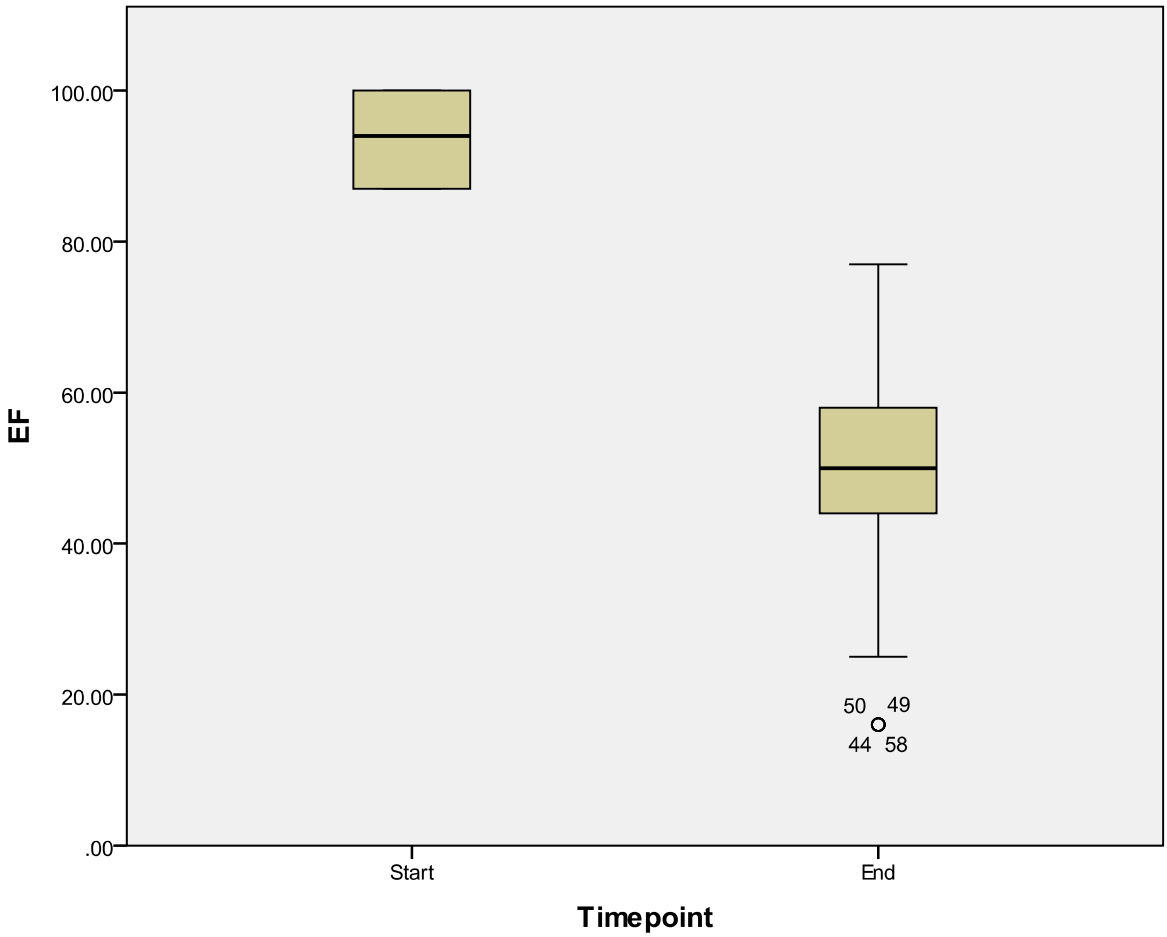
RF
Start
End
Timepoint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EF
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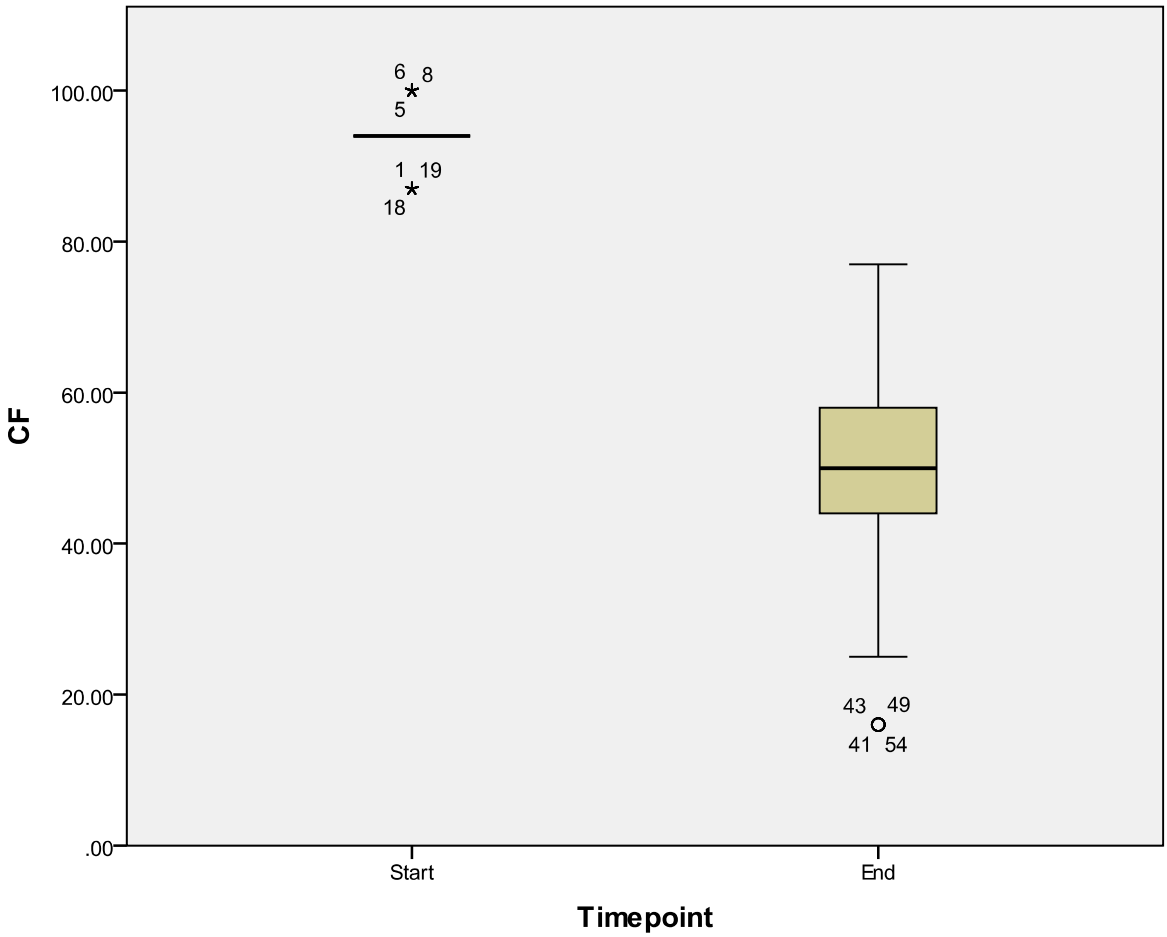
End
Timepoint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CF
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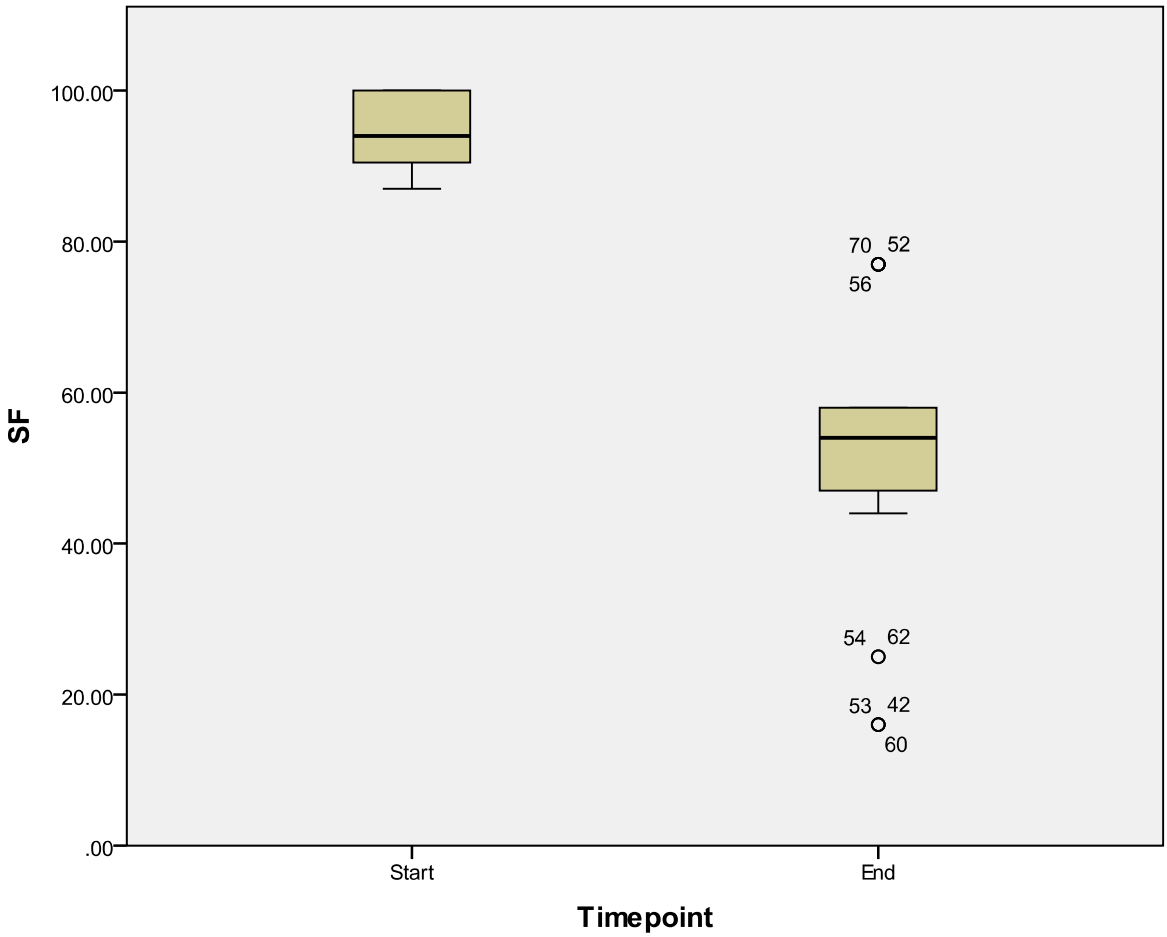
Start
End
Timepoint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SF
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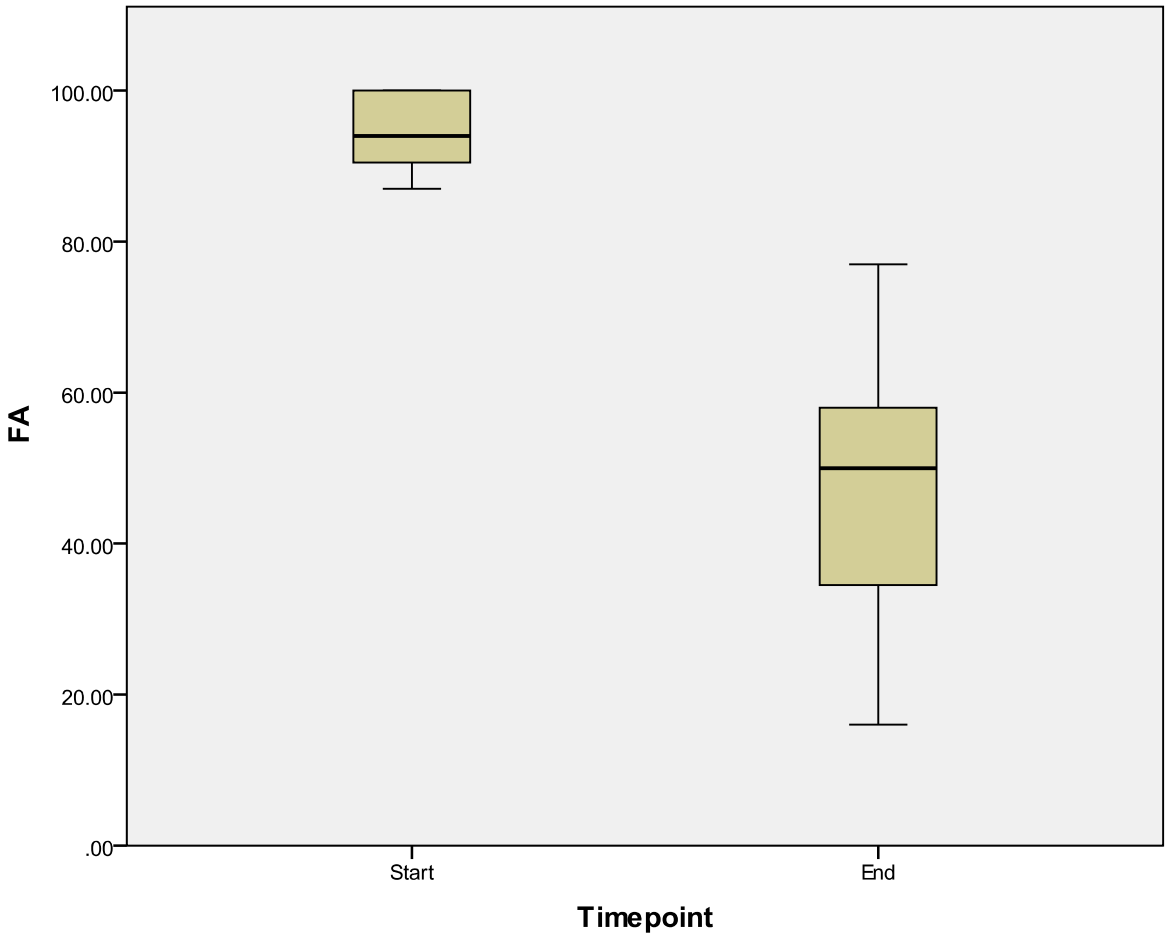
62
53
42
60
Start
End
Timepoint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FA
Start
End
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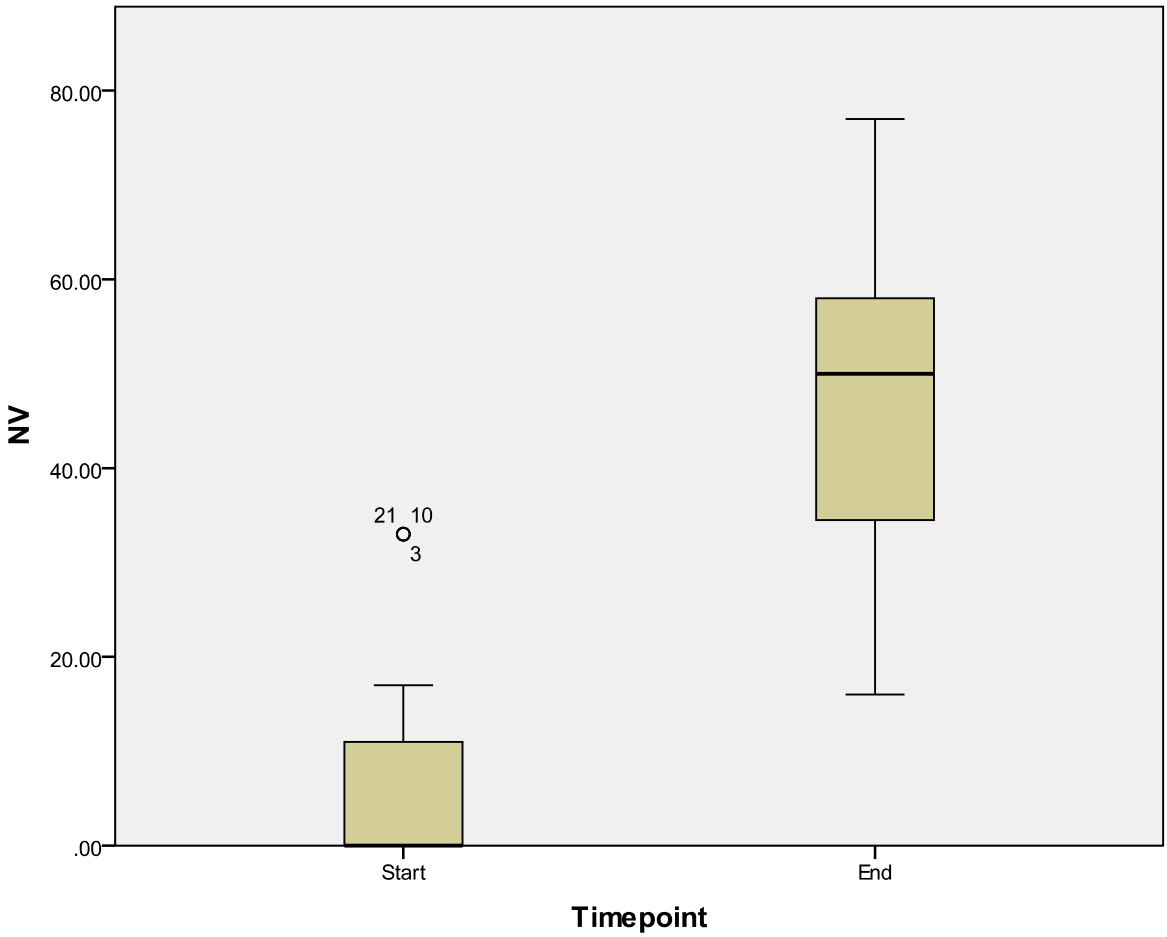
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20.00
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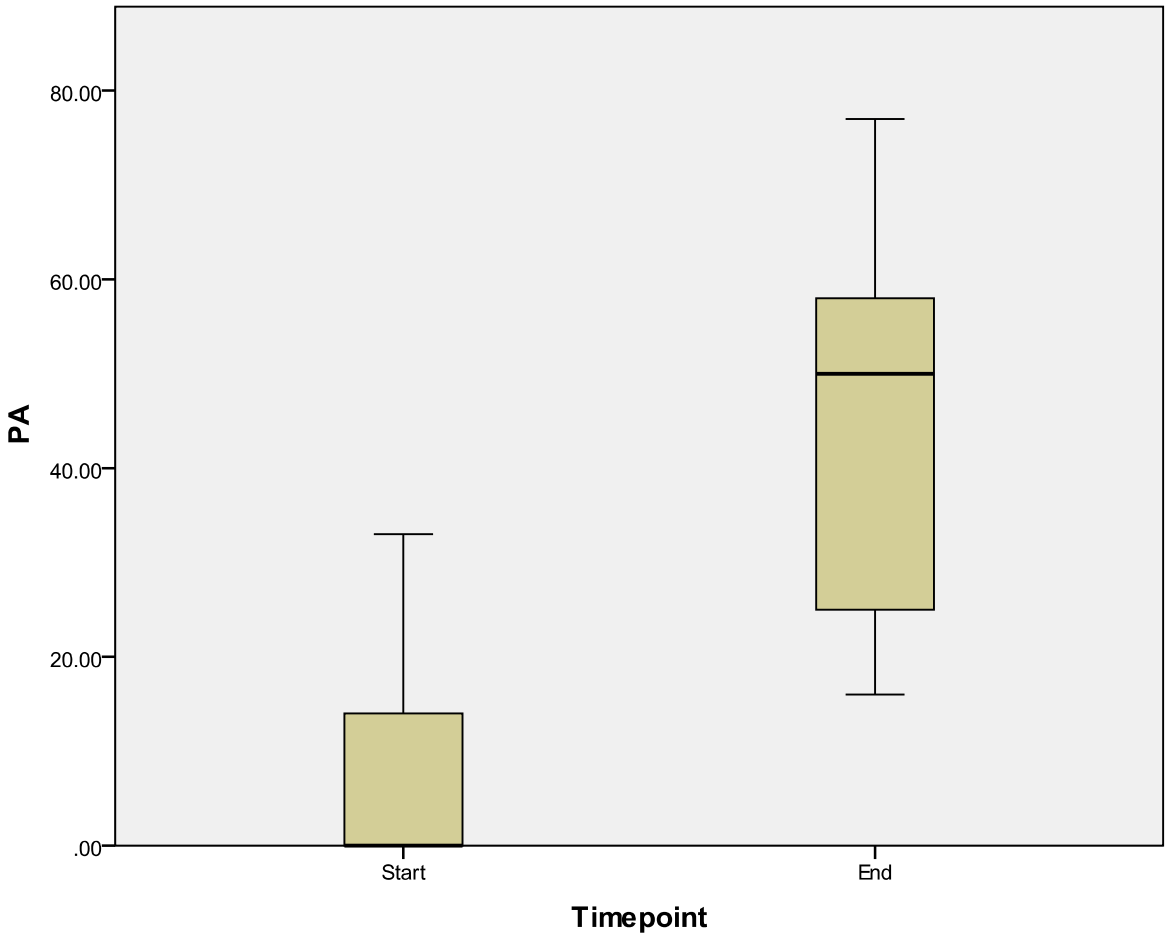
NV
21 10
3
Start
End
Timepoint


80.00
60.00
40.00
20.00
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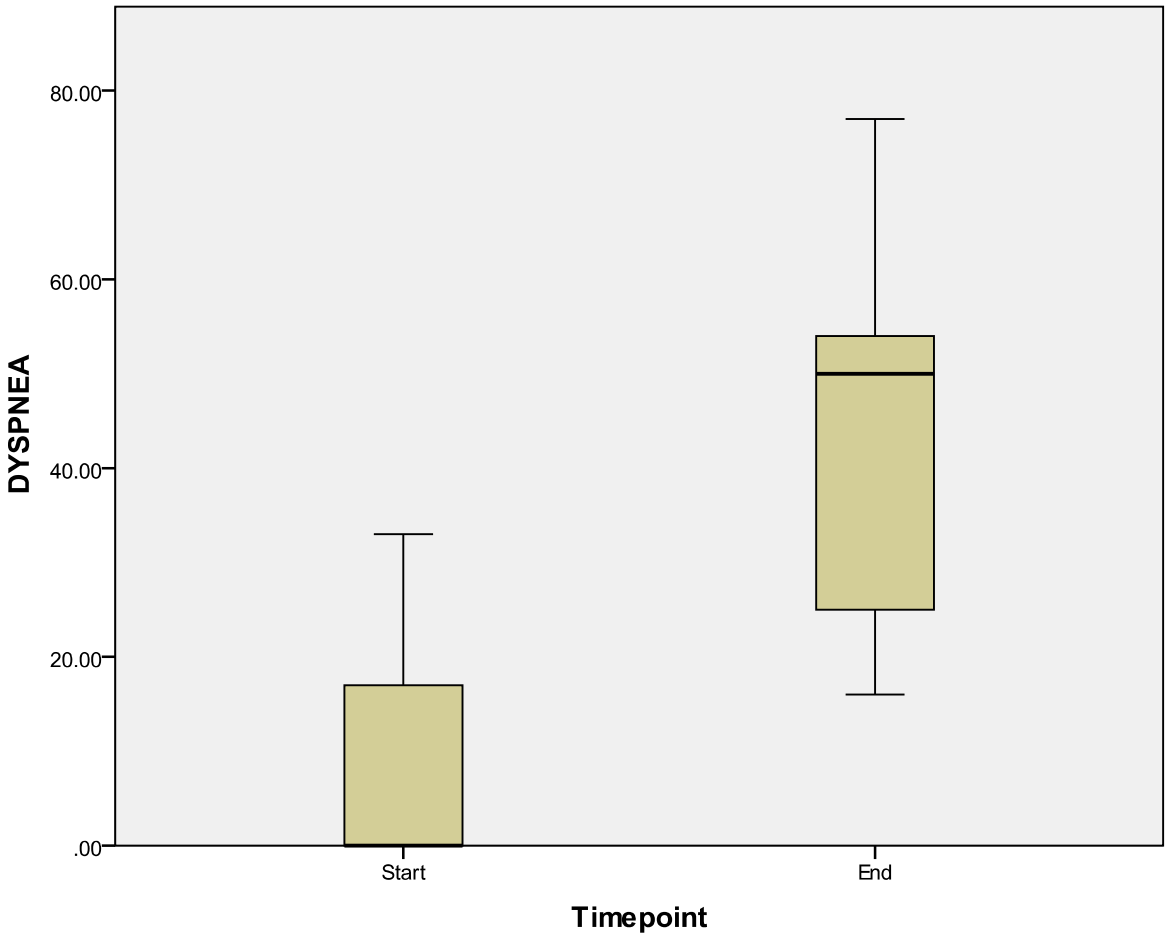
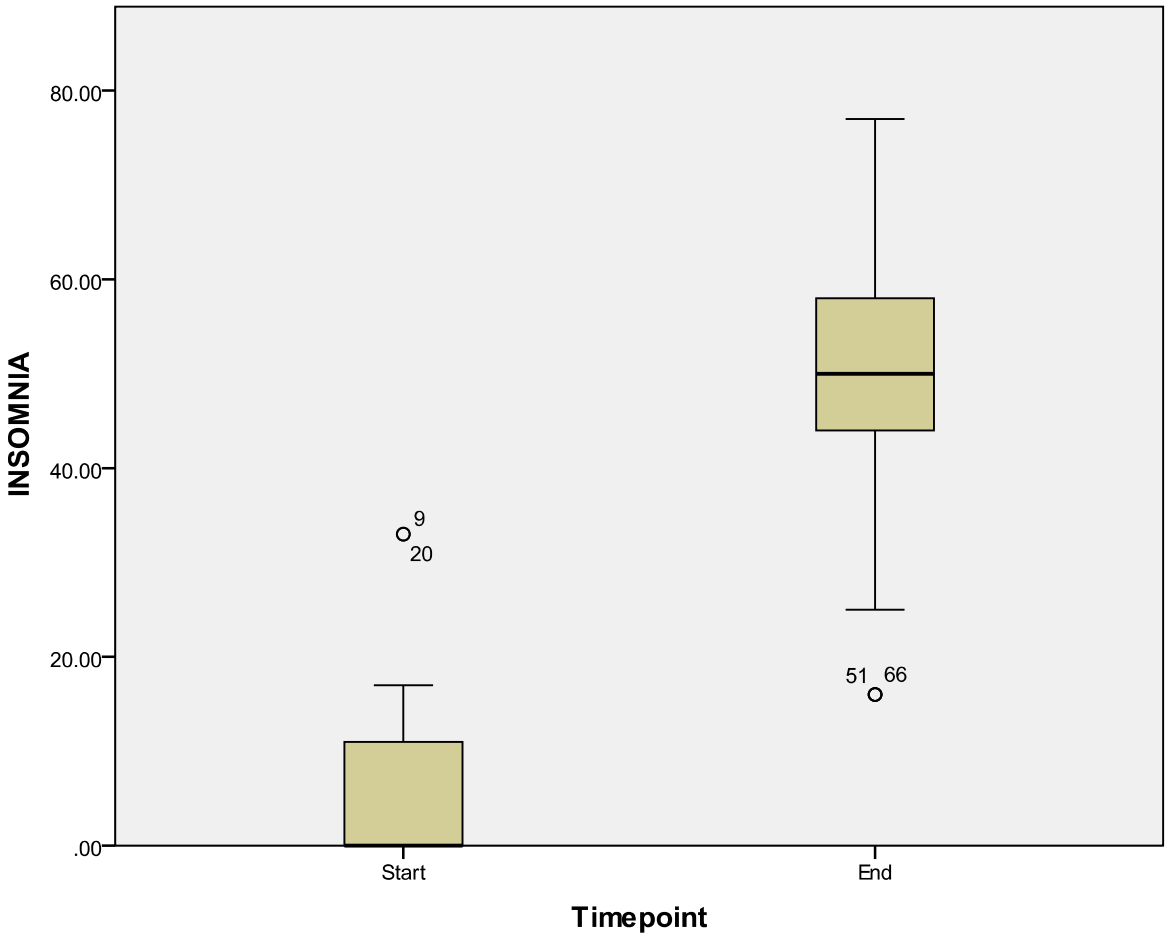
PA
Start
End
Timepoint


80.00
60.00
40.00
20.00
.00
DYSPNEA
Start
End
Timepoint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40.00
20.00
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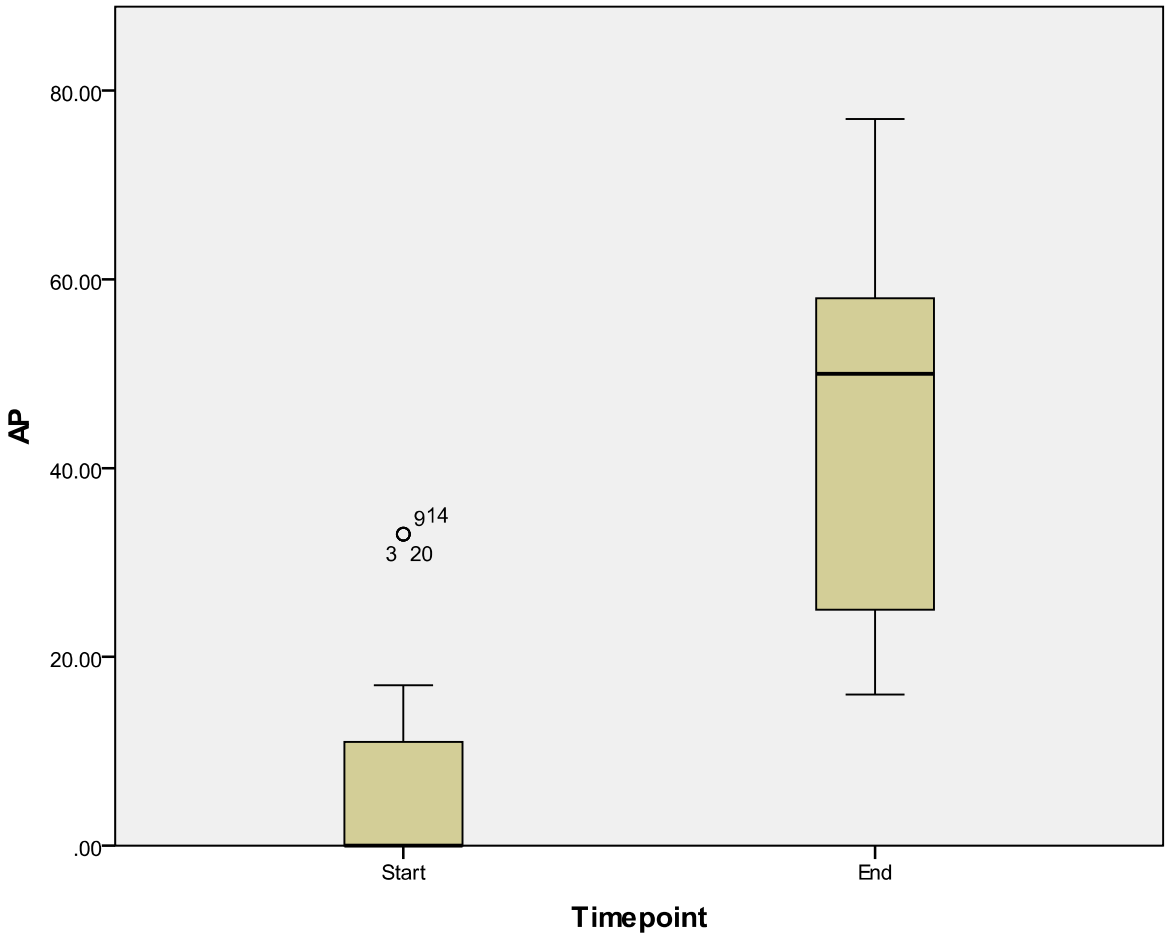
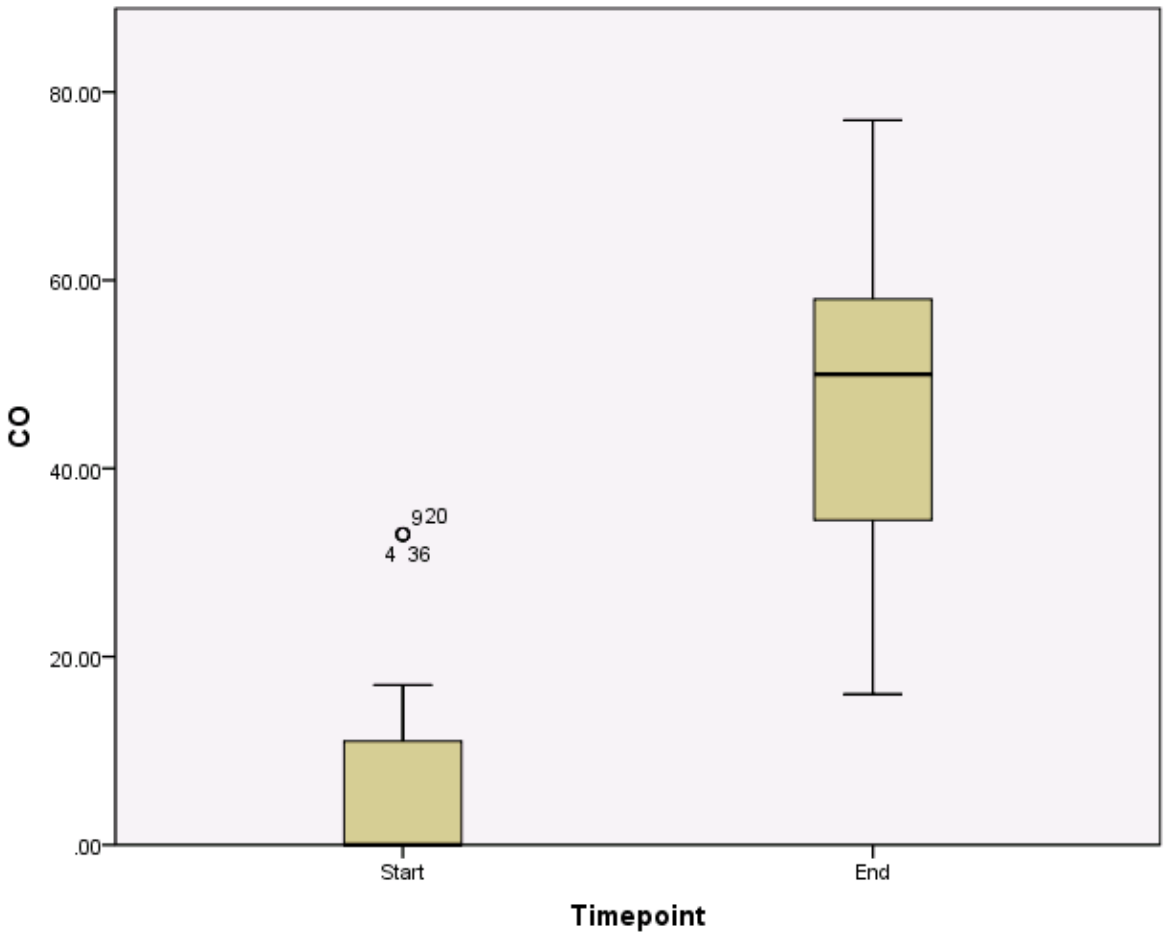
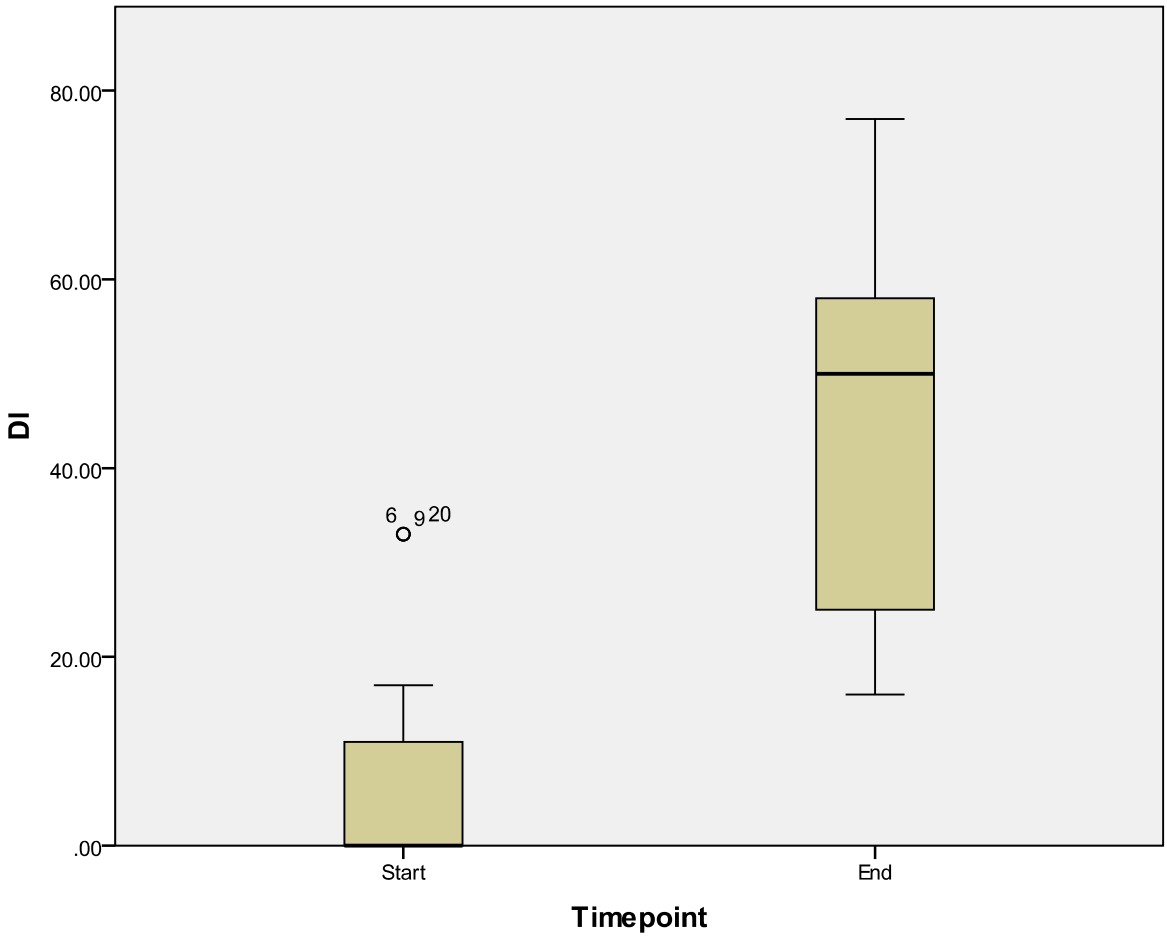
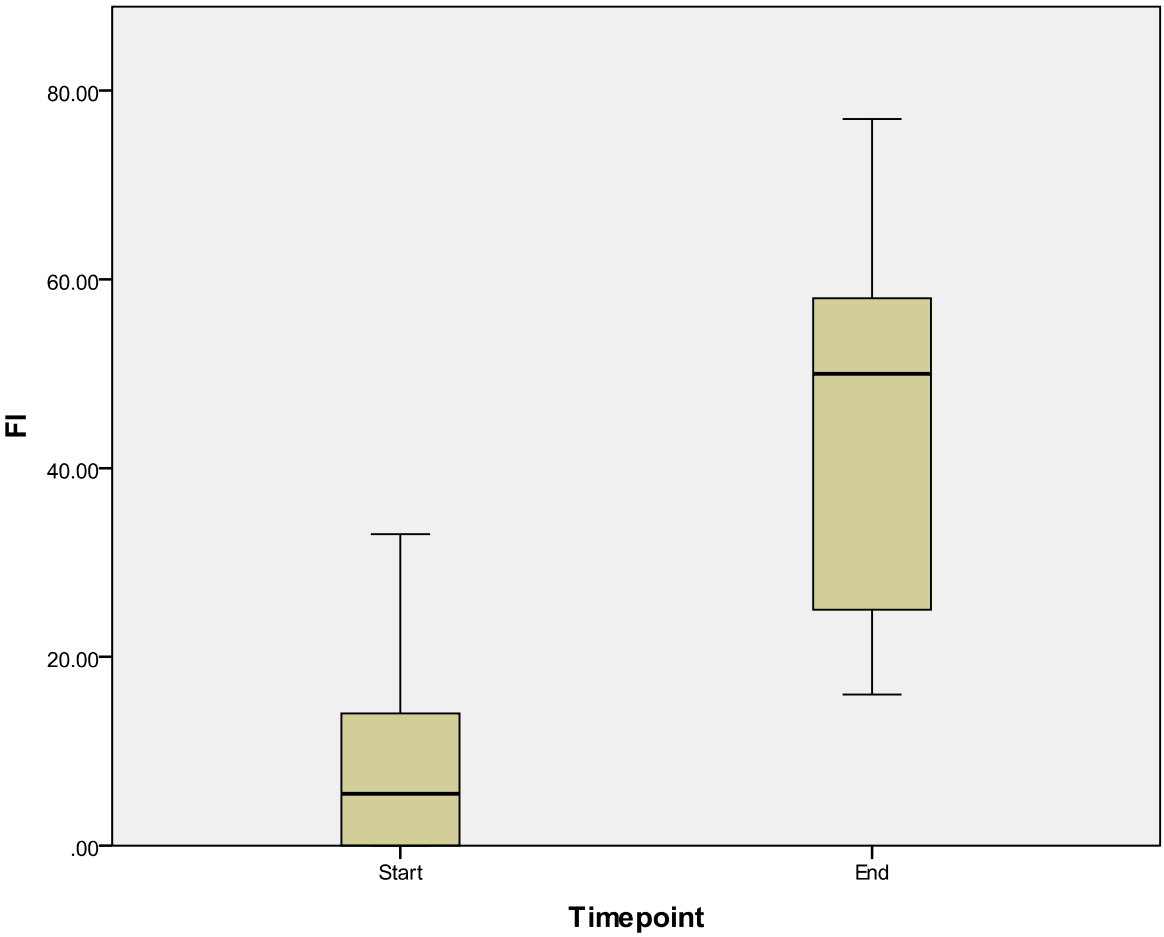
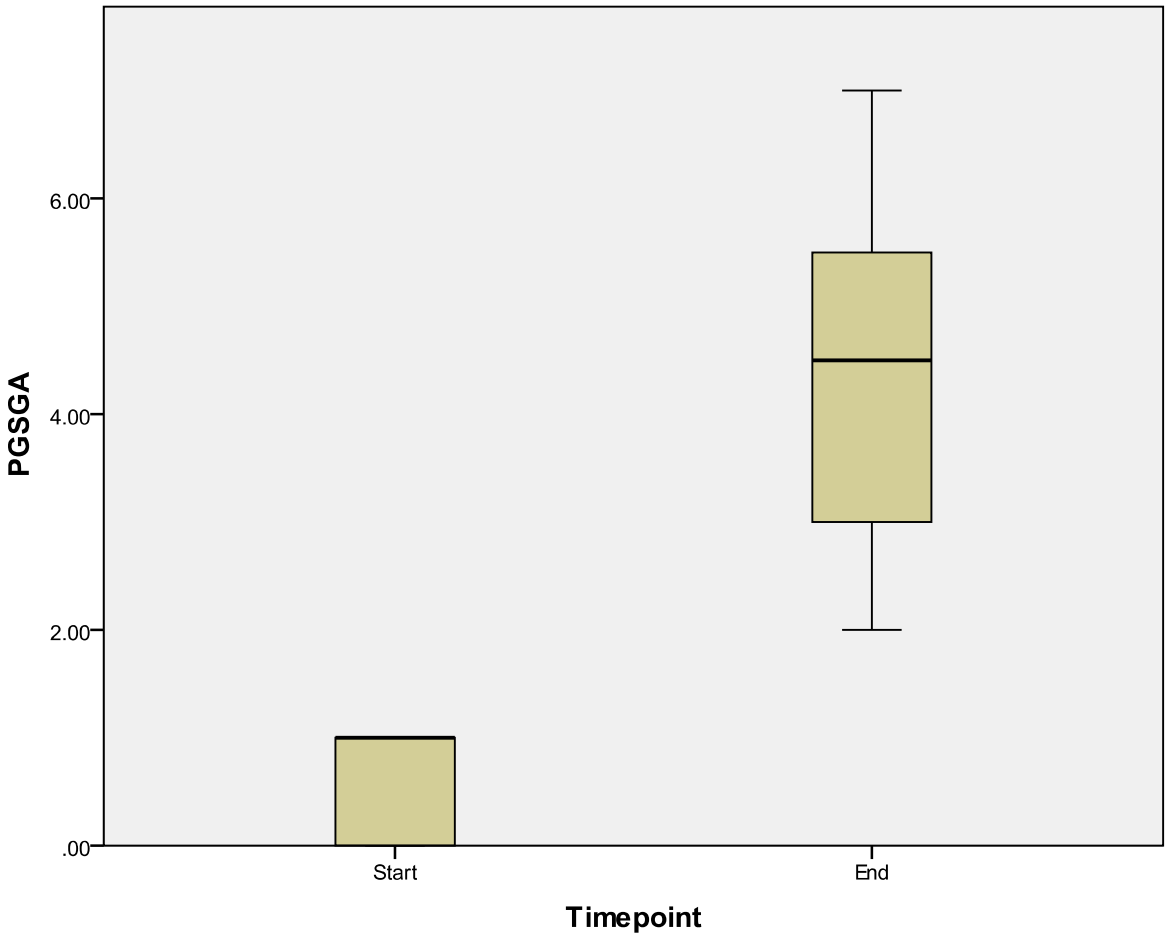
INSOMNIA
9
20
51
66
Start
End
Timepoint


80.00
60.00
40.00
20.00
.00
AP
9 14
3 20
Start
End
Timepoint


80.00
60.00
40.00
20.00
.00
CO
9 20
4 36
Start
End
Timepoint


80.00
60.00
40.00
20.00
.00
DI
6
9
20
Start
End
Timepoint


80.00
60.00
40.00
20.00
.00
FI
Start
End
Timepoint


PGSGA
6.00
4.00
2.00
.00
Start
End
Timepoint

Result Chapter (Chemoradiotherapy group): Primary correlations (Hypothesis One)

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
Work (Watts) VO_2max	Age at start	-.294	.162	Not Significant
Work (Watts) VO_2max	Length of treatment	.100	.641	Not Significant
Work (Watts) VO_2max	Weight Kg	.409	.047	Positive
Work (Watts) VO_2max	BMI kg/m^2	.380	.067	Not Significant
Work (Watts) VO_2max	TSF	.157	.463	Not Significant
Work (Watts) VO_2max	MAC	-.072	.739	Not Significant
Work (Watts) VO_2max	GS	.414	.044	Positive
Work (Watts) VO_2max	ECW	.070	.746	Not Significant
Work (Watts) VO_2max	ICW	.285	.177	Not Significant
Work (Watts) VO_2max	TBW	-.187	.382	Not Significant
Work (Watts) VO_2max	FFM	.242	.254	Not Significant
Work (Watts) VO_2max	IL1β	-.131	.542	Not Significant
Work (Watts) VO_2max	IL1RA	-.057	.791	Not Significant
Work (Watts) VO_2max	IL6	-.115	.593	Not Significant
Work (Watts) VO_2max	IL10	.094	.661	Not Significant
Work (Watts) VO_2max	IP10	.178	.404	Not Significant
Work (Watts) VO_2max	RANTES	-.041	.848	Not Significant
Work (Watts) VO_2max	IL18	-.222	.297	Not Significant
Work (Watts) VO_2max	MIF	-.128	.550	Not Significant
Work (Watts) VO_2max	CRP	.015	.945	Not Significant
Work (Watts) VO_2max	ALBUMIN	.131	.543	Not Significant
Work (Watts) VO_2max	QL	-.346	.098	Not Significant
Work (Watts) VO_2max	PF	.398	.054	Not Significant
Work (Watts) VO_2max	RF	.087	.685	Not Significant
Work (Watts) VO_2max	EF	.147	.492	Not Significant
Work (Watts) VO_2max	CF	-.195	.361	Not Significant
Work (Watts) VO_2max	SF	.067	.756	Not Significant
Work (Watts) VO_2max	FA	-.109	.611	Not Significant
Work (Watts) VO_2max	NV	-.025	.907	Not Significant
Work (Watts) VO_2max	PA	-.133	.535	Not Significant
Work (Watts) VO_2max	DYSPNEA	.005	.981	Not Significant
Work (Watts) VO_2max	INSOMNIA	.022	.919	Not Significant
Work (Watts) VO_2max	AP	.198	.354	Not Significant
Work (Watts) VO_2max	CO	.158	.462	Not Significant
Work (Watts) VO_2max	DI	.093	.666	Not Significant
Work (Watts) VO_2max	FI	.164	.444	Not Significant
Work (Watts) VO_2max	PGSGA	-.181	.399	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
AT	Age at start	-.141	.512	Not Significant
AT	Length of treatment	-.209	.327	Not Significant
AT	Weight Kg	-.175	.414	Not Significant
AT	BMI kg/m^2	-.017	.938	Not Significant
AT	TSF	-.143	.505	Not Significant
AT	MAC	-.082	.705	Not Significant
AT	GS	.144	.503	Not Significant
AT	ECW	.109	.613	Not Significant
AT	ICW	.269	.204	Not Significant
AT	TBW	.272	.198	Not Significant
AT	FFM	.297	.159	Not Significant
AT	IL1β	.078	.715	Not Significant
AT	IL1RA	.095	.658	Not Significant
AT	IL6	.141	.513	Not Significant
AT	IL10	.059	.786	Not Significant
AT	IP10	-.194	.364	Not Significant
AT	RANTES	-.013	.953	Not Significant
AT	IL18	.073	.736	Not Significant
AT	MIF	-.068	.753	Not Significant
AT	CRP	.023	.916	Not Significant
AT	ALBUMIN	-.202	.343	Not Significant
AT	QL	.044	.840	Not Significant
AT	PF	-.353	.091	Not Significant
AT	RF	.118	.582	Not Significant
AT	EF	-.091	.673	Not Significant
AT	CF	.126	.559	Not Significant
AT	SF	-.240	.259	Not Significant
AT	FA	.182	.394	Not Significant
AT	NV	.073	.734	Not Significant
AT	PA	.004	.984	Not Significant
AT	DYSPNEA	.015	.945	Not Significant
AT	INSOMNIA	.096	.657	Not Significant
AT	AP	-.017	.936	Not Significant
AT	CO	-.135	.530	Not Significant
AT	DI	-.067	.754	Not Significant
AT	FI	.085	.692	Not Significant
AT	PGSGA	-.177	.409	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
VO_2max	Age at start	-.303	.150	Not Significant
VO_2max	Length of treatment	.190	.374	Not Significant
VO_2max	Weight Kg	-.044	.840	Not Significant
VO_2max	BMI kg/m^2	.195	.361	Not Significant
VO_2max	TSF	.253	.234	Not Significant
VO_2max	MAC	.258	.224	Not Significant
VO_2max	GS	-.214	.316	Not Significant
VO_2max	ECW	.099	.645	Not Significant
VO_2max	ICW	.168	.433	Not Significant

VO_2max	TBW	-.004	.984	Not Significant
VO_2max	FFM	.086	.690	Not Significant
VO_2max	IL1β	-.435	.034	Negative
VO_2max	IL1RA	-.189	.378	Not Significant
VO_2max	IL6	-.213	.317	Not Significant
VO_2max	IL10	-.067	.757	Not Significant
VO_2max	IP10	-.073	.734	Not Significant
VO_2max	RANTES	.252	.234	Not Significant
VO_2max	IL18	-.017	.937	Not Significant
VO_2max	MIF	.019	.931	Not Significant
VO_2max	CRP	.009	.968	Not Significant
VO_2max	ALBUMIN	-.045	.836	Not Significant
VO_2max	QL	-.063	.770	Not Significant
VO_2max	PF	.208	.329	Not Significant
VO_2max	RF	.082	.704	Not Significant
VO_2max	EF	-.127	.555	Not Significant
VO_2max	CF	-.238	.262	Not Significant
VO_2max	SF	-.192	.370	Not Significant
VO_2max	FA	.215	.313	Not Significant
VO_2max	NV	.189	.378	Not Significant
VO_2max	PA	-.018	.932	Not Significant
VO_2max	DYSPNEA	-.259	.222	Not Significant
VO_2max	INSOMNIA	-.167	.435	Not Significant
VO_2max	AP	-.119	.581	Not Significant
VO_2max	CO	-.386	.063	Not Significant
VO_2max	DI	-.214	.315	Not Significant
VO_2max	FI	-.089	.680	Not Significant
VO_2max	PGSGA	-.281	.184	Not Significant

Independent Variables	**Dependent Variables**	**Correlation coefficients**	**Significance p value**	**Correlation trend**
$VEVCO_2AT$	Age at start	.182	.396	Not Significant
$VEVCO_2AT$	Length of treatment	.098	.648	Not Significant
$VEVCO_2AT$	Weight Kg	-.200	.350	Not Significant
$VEVCO_2AT$	BMI kg/m^2	-.136	.525	Not Significant
$VEVCO_2AT$	TSF	.254	.231	Not Significant
$VEVCO_2AT$	MAC	.361	.083	Not Significant
$VEVCO_2AT$	GS	-.030	.888	Not Significant
$VEVCO_2AT$	ECW	-.211	.321	Not Significant
$VEVCO_2AT$	ICW	-.153	.474	Not Significant
$VEVCO_2AT$	TBW	-.008	.969	Not Significant
$VEVCO_2AT$	FFM	-.279	.187	Not Significant
$VEVCO_2AT$	IL1β	.073	.734	Not Significant
$VEVCO_2AT$	IL1RA	.147	.494	Not Significant
$VEVCO_2AT$	IL6	.055	.799	Not Significant
$VEVCO_2AT$	IL10	.173	.419	Not Significant
$VEVCO_2AT$	IP10	.127	.553	Not Significant
$VEVCO_2AT$	RANTES	-.291	.168	Not Significant
$VEVCO_2AT$	IL18	.086	.690	Not Significant

$VEVCO_2AT$	MIF	-.102	.636	Not Significant
$VEVCO_2AT$	CRP	.230	.280	Not Significant
$VEVCO_2AT$	ALBUMIN	.159	.459	Not Significant
$VEVCO_2AT$	QL	-.163	.447	Not Significant
$VEVCO_2AT$	PF	-.029	.893	Not Significant
$VEVCO_2AT$	RF	-.583	.003	Negative
$VEVCO_2AT$	EF	-.439	.032	Negative
$VEVCO_2AT$	CF	.093	.666	Not Significant
$VEVCO_2AT$	SF	.319	.129	Not Significant
$VEVCO_2AT$	FA	.025	.908	Not Significant
$VEVCO_2AT$	NV	.158	.461	Not Significant
$VEVCO_2AT$	PA	-.109	.611	Not Significant
$VEVCO_2AT$	DYSPNEA	-.202	.345	Not Significant
$VEVCO_2AT$	INSOMNIA	.259	.221	Not Significant
$VEVCO_2AT$	AP	-.212	.321	Not Significant
$VEVCO_2AT$	CO	-.274	.196	Not Significant
$VEVCO_2AT$	DI	-.135	.528	Not Significant
$VEVCO_2AT$	FI	-.440	.031	Negative
$VEVCO_2AT$	PGSGA	.118	.583	Not Significant

Independent Variables	**Dependent Variables**	**Correlation coefficients**	**Significance p value**	**Correlation trend**
VO_2HRmax	Age at start	-.208	.329	Not Significant
VO_2HRmax	Length of treatment	-.025	.909	Not Significant
VO_2HRmax	Weight Kg	.009	.967	Not Significant
VO_2HRmax	BMI kg/m^2	.044	.840	Not Significant
VO_2HRmax	TSF	-.107	.618	Not Significant
VO_2HRmax	MAC	.243	.253	Not Significant
VO_2HRmax	GS	-.193	.365	Not Significant
VO_2HRmax	ECW	-.119	.579	Not Significant
VO_2HRmax	ICW	-.364	.081	Not Significant
VO_2HRmax	TBW	.260	.220	Not Significant
VO_2HRmax	FFM	-.416	.043	Negative
VO_2HRmax	IL1β	.185	.386	Not Significant
VO_2HRmax	IL1RA	.035	.871	Not Significant
VO_2HRmax	IL6	.039	.858	Not Significant
VO_2HRmax	IL10	.067	.755	Not Significant
VO_2HRmax	IP10	-.055	.798	Not Significant
VO_2HRmax	RANTES	-.134	.532	Not Significant
VO_2HRmax	IL18	.200	.349	Not Significant
VO_2HRmax	MIF	-.177	.408	Not Significant
VO_2HRmax	CRP	-.104	.630	Not Significant
VO_2HRmax	ALBUMIN	-.026	.905	Not Significant
VO_2HRmax	QL	.004	.987	Not Significant
VO_2HRmax	PF	.133	.535	Not Significant
VO_2HRmax	RF	-.294	.163	Not Significant
VO_2HRmax	EF	-.063	.770	Not Significant
VO_2HRmax	CF	-.068	.751	Not Significant
VO_2HRmax	SF	.010	.962	Not Significant
VO_2HRmax	FA	-.140	.515	Not Significant

VO_2HRmax	NV	.187	.382	Not Significant
VO_2HRmax	PA	-.142	.507	Not Significant
VO_2HRmax	DYSPNEA	-.480	.018	Negative
VO_2HRmax	INSOMNIA	.018	.935	Not Significant
VO_2HRmax	AP	-.057	.791	Not Significant
VO_2HRmax	CO	-.316	.133	Not Significant
VO_2HRmax	DI	-.152	.479	Not Significant
VO_2HRmax	FI	.028	.898	Not Significant
VO_2HRmax	PGSGA	-.113	.600	Not Significant

Secondary correlations (Hypothesis Two)

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
QL	Weight Kg	-.017	.937	Not Significant
QL	BMI kg/m^2	-.031	.885	Not Significant
QL	TSF	-.569	.004	Negative
QL	MAC	-.251	.237	Not Significant
QL	GS	-.109	.612	Not Significant
QL	ECW	.212	.319	Not Significant
QL	ICW	.296	.160	Not Significant
QL	TBW1	-.102	.635	Not Significant
QL	FFM	.309	.141	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
PF	Weight Kg	.288	.172	Not Significant
PF	BMI kg/m^2	.264	.213	Not Significant
PF	TSF	-.085	.692	Not Significant
PF	MAC	.201	.347	Not Significant
PF	GS	-.015	.943	Not Significant
PF	ECW	-.077	.721	Not Significant
PF	ICW	-.055	.797	Not Significant
PF	TBW1	-.200	.350	Not Significant
PF	FFM	-.185	.386	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
RF	Weight Kg	.132	.538	Not Significant
RF	BMI kg/m^2	.179	.401	Not Significant
RF	TSF	-.116	.590	Not Significant
RF	MAC	-.030	.890	Not Significant
RF	GS	-.074	.730	Not Significant
RF	ECW	.044	.838	Not Significant
RF	ICW	.068	.753	Not Significant
RF	TBW1	-.042	.845	Not Significant
RF	FFM	.078	.718	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
EF	Weight Kg	.191	.372	Not Significant
EF	BMI kg/m^2	-.067	.757	Not Significant
EF	TSF	-.269	.204	Not Significant
EF	MAC	-.231	.278	Not Significant
EF	GS	-.037	.865	Not Significant
EF	ECW	.074	.730	Not Significant
EF	ICW	-.117	.585	Not Significant
EF	TBW1	.014	.948	Not Significant
EF	FFM	.003	.990	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
CF	Weight Kg	-.552	.005	Negative
CF	BMI kg/m^2	-.659	.000	Negative
CF	TSF	-.005	.981	Not Significant
CF	MAC	-.182	.394	Not Significant
CF	GS	-.068	.754	Not Significant
CF	ECW	-.159	.458	Not Significant
CF	ICW	-.137	.523	Not Significant
CF	TBW1	.552	.005	Positive
CF	FFM	-.056	.794	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
SF	Weight Kg	.021	.923	Not Significant
SF	BMI kg/m^2	-.172	.421	Not Significant
SF	TSF	.407	.048	Positive
SF	MAC	.096	.654	Not Significant
SF	GS	.131	.543	Not Significant
SF	ECW	.030	.889	Not Significant
SF	ICW	-.170	.427	Not Significant
SF	TBW1	-.055	.799	Not Significant
SF	FFM	-.159	.459	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
FA	Weight Kg	-.056	.795	Not Significant
FA	BMI kg/m^2	-.168	.432	Not Significant
FA	TSF	.021	.921	Not Significant
FA	MAC	-.023	.914	Not Significant
FA	GS	.045	.834	Not Significant
FA	ECW	.413	.045	Positive
FA	ICW	.245	.248	Not Significant
FA	TBW1	.038	.859	Not Significant
FA	FFM	.266	.209	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
NV	Weight Kg	.274	.195	Not Significant
NV	BMI kg/m^2	.380	.067	Not Significant
NV	TSF	-.029	.892	Not Significant
NV	MAC	.518	.010	Positive
NV	GS	-.115	.594	Not Significant
NV	ECW	.087	.685	Not Significant
NV	ICW	.326	.121	Not Significant
NV	TBW1	-.053	.806	Not Significant
NV	FFM	.251	.236	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
PA	Weight Kg	-.258	.224	Not Significant
PA	BMI kg/m^2	-.089	.680	Not Significant
PA	TSF	-.225	.291	Not Significant
PA	MAC	-.191	.372	Not Significant
PA	GS	.151	.481	Not Significant
PA	ECW	.020	.926	Not Significant
PA	ICW	.121	.573	Not Significant
PA	TBW1	.304	.148	Not Significant
PA	FFM	.078	.716	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
DYSPNEA	Weight Kg	.048	.822	Not Significant
DYSPNEA	BMI kg/m^2	-.078	.718	Not Significant
DYSPNEA	TSF	-.225	.290	Not Significant
DYSPNEA	MAC	-.342	.102	Not Significant
DYSPNEA	GS	.407	.049	Positive
DYSPNEA	ECW	.323	.124	Not Significant
DYSPNEA	ICW	.287	.174	Not Significant
DYSPNEA	TBW1	.200	.349	Not Significant
DYSPNEA	FFM	.427	.037	Positive

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
INSOMNIA	Weight Kg	.024	.912	Not Significant
INSOMNIA	BMI kg/m^2	-.023	.916	Not Significant
INSOMNIA	TSF	-.206	.335	Not Significant
INSOMNIA	MAC	.024	.912	Not Significant
INSOMNIA	GS	.205	.336	Not Significant
INSOMNIA	ECW	-.256	.227	Not Significant
INSOMNIA	ICW	.212	.320	Not Significant
INSOMNIA	TBW1	-.200	.349	Not Significant
INSOMNIA	FFM	.047	.829	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
AP	Weight Kg	.070	.744	Not Significant
AP	BMI kg/m^2	.085	.694	Not Significant
AP	TSF	-.367	.078	Not Significant
AP	MAC	-.116	.591	Not Significant
AP	GS	.203	.342	Not Significant
AP	ECW	.015	.945	Not Significant
AP	ICW	-.028	.896	Not Significant
AP	TBW1	.064	.767	Not Significant
AP	FFM	.013	.953	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
CO	Weight Kg	.415	.043	Positive
CO	BMI kg/m^2	.215	.314	Not Significant
CO	TSF	-.275	.194	Not Significant
CO	MAC	-.158	.460	Not Significant
CO	GS	.280	.186	Not Significant
CO	ECW	.141	.510	Not Significant
CO	ICW	.355	.089	Not Significant
CO	TBW1	-.260	.220	Not Significant
CO	FFM	.386	.063	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
DI	Weight Kg	.244	.251	Not Significant
DI	BMI kg/m^2	.014	.947	Not Significant
DI	TSF	-.078	.716	Not Significant
DI	MAC	.036	.867	Not Significant
DI	GS	.282	.182	Not Significant
DI	ECW	.183	.392	Not Significant
DI	ICW	.215	.312	Not Significant
DI	TBW1	.255	.230	Not Significant
DI	FFM	.150	.485	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
FI	Weight Kg	.073	.733	Not Significant
FI	BMI kg/m^2	-.041	.848	Not Significant
FI	TSF	-.372	.073	Not Significant
FI	MAC	-.209	.326	Not Significant
FI	GS	.070	.745	Not Significant
FI	ECW	-.152	.478	Not Significant
FI	ICW	.274	.195	Not Significant
FI	TBW1	.153	.476	Not Significant
FI	FFM	.217	.308	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
PGSGA	Weight Kg	.388	.061	Not Significant
PGSGA	BMI kg/m^2	.266	.208	Not Significant
PGSGA	TSF	-.048	.823	Not Significant
PGSGA	MAC	.208	.331	Not Significant
PGSGA	GS	.151	.482	Not Significant
PGSGA	ECW	.437	.033	Positive
PGSGA	ICW	.236	.267	Not Significant
PGSGA	TBW1	-.175	.415	Not Significant
PGSGA	FFM	.315	.134	Not Significant

Result Chapter (Radiotherapy group): Primary correlations (Hypothesis One)

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
Work (Watts) VO_2max	Age at start	.475	.119	Not Significant
Work (Watts) VO_2max	Length of treatment	.071	.826	Not Significant
Work (Watts) VO_2max	Weight Kg	-.217	.498	Not Significant
Work (Watts) VO_2max	BMI kg/m^2	.074	.820	Not Significant
Work (Watts) VO_2max	TSF	.316	.317	Not Significant
Work (Watts) VO_2max	MAC	.142	.661	Not Significant
Work (Watts) VO_2max	GS	.181	.573	Not Significant
Work (Watts) VO_2max	ECW	-.109	.736	Not Significant
Work (Watts) VO_2max	ICW	.333	.291	Not Significant
Work (Watts) VO_2max	TBW	.305	.336	Not Significant
Work (Watts) VO_2max	FFM	-.004	.991	Not Significant
Work (Watts) VO_2max	IL1β	-.071	.826	Not Significant
Work (Watts) VO_2max	IL1RA	-.091	.778	Not Significant
Work (Watts) VO_2max	IL6	.203	.527	Not Significant
Work (Watts) VO_2max	IL10	-.060	.854	Not Significant
Work (Watts) VO_2max	IP10	-.462	.130	Not Significant
Work (Watts) VO_2max	RANTES	-.161	.617	Not Significant
Work (Watts) VO_2max	IL18	.336	.285	Not Significant
Work (Watts) VO_2max	MIF	.081	.803	Not Significant
Work (Watts) VO_2max	CRP	.270	.397	Not Significant
Work (Watts) VO_2max	ALBUMIN	.033	.918	Not Significant
Work (Watts) VO_2max	QL	-.237	.458	Not Significant
Work (Watts) VO_2max	PF	-.293	.355	Not Significant
Work (Watts) VO_2max	RF	-.211	.510	Not Significant
Work (Watts) VO_2max	EF	-.366	.241	Not Significant
Work (Watts) VO_2max	CF	-.131	.685	Not Significant
Work (Watts) VO_2max	SF	.014	.965	Not Significant
Work (Watts) VO_2max	FA	.533	.075	Not Significant
Work (Watts) VO_2max	NV	-.034	.917	Not Significant
Work (Watts) VO_2max	PA	.106	.743	Not Significant
Work (Watts) VO_2max	DYSPNEA	.530	.076	Not Significant
Work (Watts) VO_2max	INSOMNIA	-.653	.021	Negative
Work (Watts) VO_2max	AP	-.293	.355	Not Significant
Work (Watts) VO_2max	CO	-.048	.883	Not Significant
Work (Watts) VO_2max	DI	-.390	.210	Not Significant
Work (Watts) VO_2max	FI	-.078	.810	Not Significant
Work (Watts) VO_2max	PGSGA	.475	.119	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
AT	Age at start	-.288	.364	Not Significant
AT	Length of treatment	-.240	.452	Not Significant
AT	Weight Kg	-.615	.033	Negative
AT	BMI kg/m^2	-.420	.175	Not Significant
AT	TSF	-.377	.226	Not Significant
AT	MAC	.523	.081	Not Significant
AT	GS	.726	.007	Positive

AT	ECW	-.116	.721	Not Significant
AT	ICW	.524	.080	Not Significant
AT	TBW	-.322	.308	Not Significant
AT	FFM	.021	.948	Not Significant
AT	IL1β	.164	.611	Not Significant
AT	IL1RA	.172	.594	Not Significant
AT	IL6	-.119	.713	Not Significant
AT	IL10	.287	.366	Not Significant
AT	IP10	-.035	.914	Not Significant
AT	RANTES	.196	.542	Not Significant
AT	IL18	-.336	.286	Not Significant
AT	MIF	.028	.931	Not Significant
AT	CRP	-.210	.513	Not Significant
AT	ALBUMIN	.567	.054	Not Significant
AT	QL	.076	.815	Not Significant
AT	PF	-.159	.622	Not Significant
AT	RF	-.123	.703	Not Significant
AT	EF	.442	.151	Not Significant
AT	CF	.138	.670	Not Significant
AT	SF	-.255	.423	Not Significant
AT	FA	.119	.712	Not Significant
AT	NV	-.353	.260	Not Significant
AT	PA	-.359	.252	Not Significant
AT	DYSPNEA	-.186	.562	Not Significant
AT	INSOMNIA	-.039	.904	Not Significant
AT	AP	-.483	.111	Not Significant
AT	CO	.018	.956	Not Significant
AT	DI	-.256	.422	Not Significant
AT	FI	.312	.324	Not Significant
AT	PGSGA	-.288	.364	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
VO_2max	Age at start	.128	.691	Not Significant
VO_2max	Length of treatment	-.101	.756	Not Significant
VO_2max	Weight Kg	-.354	.259	Not Significant
VO_2max	BMI kg/m^2	-.025	.940	Not Significant
VO_2max	TSF	.269	.399	Not Significant
VO_2max	MAC	.071	.827	Not Significant
VO_2max	GS	.429	.164	Not Significant
VO_2max	ECW	-.260	.415	Not Significant
VO_2max	ICW	.567	.054	Not Significant
VO_2max	TBW	.182	.571	Not Significant
VO_2max	FFM	-.214	.505	Not Significant
VO_2max	IL1β	.039	.904	Not Significant
VO_2max	IL1RA	.063	.845	Not Significant
VO_2max	IL6	.011	.974	Not Significant
VO_2max	IL10	-.032	.923	Not Significant
VO_2max	IP10	-.102	.753	Not Significant

VO_2max	RANTES	.105	.745	Not Significant
VO_2max	IL18	.161	.617	Not Significant
VO_2max	MIF	.063	.846	Not Significant
VO_2max	CRP	-.011	.974	Not Significant
VO_2max	ALBUMIN	.253	.428	Not Significant
VO_2max	QL	-.049	.880	Not Significant
VO_2max	PF	-.442	.151	Not Significant
VO_2max	RF	-.283	.372	Not Significant
VO_2max	EF	.097	.763	Not Significant
VO_2max	CF	-.062	.849	Not Significant
VO_2max	SF	-.050	.878	Not Significant
VO_2max	FA	.589	.044	Positive
VO_2max	NV	-.218	.497	Not Significant
VO_2max	PA	.095	.768	Not Significant
VO_2max	DYSPNEA	.287	.366	Not Significant
VO_2max	INSOMNIA	-.408	.188	Not Significant
VO_2max	AP	-.196	.541	Not Significant
VO_2max	CO	-.225	.482	Not Significant
VO_2max	DI	-.506	.093	Not Significant
VO_2max	FI	-.392	.208	Not Significant
VO_2max	PGSGA	.128	.691	Not Significant

Independent Variables	**Dependent Variables**	**Correlation coefficients**	**Significance p value**	**Correlation trend**
$VEVCO_2AT$	Age at start	.002	.996	Not Significant
$VEVCO_2AT$	Length of treatment	.006	.985	Not Significant
$VEVCO_2AT$	Weight Kg	.218	.496	Not Significant
$VEVCO_2AT$	BMI kg/m^2	-.183	.570	Not Significant
$VEVCO_2AT$	TSF	-.211	.510	Not Significant
$VEVCO_2AT$	MAC	-.082	.801	Not Significant
$VEVCO_2AT$	GS	-.413	.182	Not Significant
$VEVCO_2AT$	ECW	.335	.288	Not Significant
$VEVCO_2AT$	ICW	.070	.828	Not Significant
$VEVCO_2AT$	TBW	.612	.035	Positive
$VEVCO_2AT$	FFM	.373	.233	Not Significant
$VEVCO_2AT$	IL1β	.038	.908	Not Significant
$VEVCO_2AT$	IL1RA	-.283	.372	Not Significant
$VEVCO_2AT$	IL6	-.197	.540	Not Significant
$VEVCO_2AT$	IL10	-.211	.511	Not Significant
$VEVCO_2AT$	IP10	-.155	.631	Not Significant
$VEVCO_2AT$	RANTES	.218	.496	Not Significant
$VEVCO_2AT$	IL18	.457	.135	Not Significant
$VEVCO_2AT$	MIF	.158	.623	Not Significant
$VEVCO_2AT$	CRP	-.067	.837	Not Significant
$VEVCO_2AT$	ALBUMIN	-.354	.259	Not Significant
$VEVCO_2AT$	QL	-.271	.395	Not Significant
$VEVCO_2AT$	PF	.681	.015	Positive
$VEVCO_2AT$	RF	.293	.355	Not Significant
$VEVCO_2AT$	EF	-.261	.412	Not Significant

$VEVCO_2AT$	CF	.085	.793	Not Significant
$VEVCO_2AT$	SF	.075	.817	Not Significant
$VEVCO_2AT$	FA	-.208	.516	Not Significant
$VEVCO_2AT$	NV	.577	.049	Positive
$VEVCO_2AT$	PA	.025	.939	Not Significant
$VEVCO_2AT$	DYSPNEA	.387	.214	Not Significant
$VEVCO_2AT$	INSOMNIA	-.194	.546	Not Significant
$VEVCO_2AT$	AP	-.211	.510	Not Significant
$VEVCO_2AT$	CO	-.199	.535	Not Significant
$VEVCO_2AT$	DI	.058	.857	Not Significant
$VEVCO_2AT$	FI	.283	.373	Not Significant
$VEVCO_2AT$	PGSGA	.002	.996	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
VO_2HRmax	Age at start	-.286	.368	Not Significant
VO_2HRmax	Length of treatment	-.106	.742	Not Significant
VO_2HRmax	Weight Kg	.015	.964	Not Significant
VO_2HRmax	BMI kg/m^2	.144	.655	Not Significant
VO_2HRmax	TSF	.007	.982	Not Significant
VO_2HRmax	MAC	-.058	.858	Not Significant
VO_2HRmax	GS	.378	.225	Not Significant
VO_2HRmax	ECW	.100	.757	Not Significant
VO_2HRmax	ICW	.310	.326	Not Significant
VO_2HRmax	TBW	.044	.891	Not Significant
VO_2HRmax	FFM	.473	.120	Not Significant
VO_2HRmax	IL1β	.308	.329	Not Significant
VO_2HRmax	IL1RA	.346	.270	Not Significant
VO_2HRmax	IL6	-.044	.891	Not Significant
VO_2HRmax	IL10	.336	.285	Not Significant
VO_2HRmax	IP10	-.443	.149	Not Significant
VO_2HRmax	RANTES	-.174	.589	Not Significant
VO_2HRmax	IL18	-.340	.280	Not Significant
VO_2HRmax	MIF	-.203	.526	Not Significant
VO_2HRmax	CRP	-.628	.029	Negative
VO_2HRmax	ALBUMIN	.098	.762	Not Significant
VO_2HRmax	QL	-.464	.129	Not Significant
VO_2HRmax	PF	-.069	.831	Not Significant
VO_2HRmax	RF	.440	.152	Not Significant
VO_2HRmax	EF	-.205	.522	Not Significant
VO_2HRmax	CF	.406	.190	Not Significant
VO_2HRmax	SF	-.367	.240	Not Significant
VO_2HRmax	FA	.202	.529	Not Significant
VO_2HRmax	NV	-.134	.677	Not Significant
VO_2HRmax	PA	.532	.075	Not Significant
VO_2HRmax	DYSPNEA	.141	.662	Not Significant
VO_2HRmax	INSOMNIA	-.296	.351	Not Significant
VO_2HRmax	AP	-.522	.082	Not Significant
VO_2HRmax	CO	-.404	.193	Not Significant
VO_2HRmax	DI	-.339	.281	Not Significant
VO_2HRmax	FI	.079	.808	Not Significant
VO_2HRmax	PGSGA	-.286	.368	Not Significant

Secondary correlations (Hypothesis Two)

Independent Variables	Dependent	Correlation coefficients	Significance p value	Correlation trend
QL	Weight Kg	-.195	.544	Not Significant
QL	BMI kg/m^2	-.621	.031	Negative
QL	TSF	-.142	.660	Not Significant
QL	MAC	-.449	.143	Not Significant
QL	GS	.094	.771	Not Significant
QL	ECW	-.013	.969	Not Significant
QL	ICW	-.430	.163	Not Significant
QL	TBW1	.184	.567	Not Significant
QL	FFM	-.603	.038	Negative

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
PF	Weight Kg	.219	.495	Not Significant
PF	BMI kg/m^2	-.102	.752	Not Significant
PF	TSF	-.311	.325	Not Significant
PF	MAC	-.030	.926	Not Significant
PF	GS	-.388	.213	Not Significant
PF	ECW	.445	.147	Not Significant
PF	ICW	.145	.654	Not Significant
PF	TBW1	.275	.387	Not Significant
PF	FFM	.642	.024	Positive

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
RF	Weight Kg	.534	.074	Not Significant
RF	BMI kg/m^2	.232	.468	Not Significant
RF	TSF	-.309	.329	Not Significant
RF	MAC	-.092	.775	Not Significant
RF	GS	-.236	.460	Not Significant
RF	ECW	.662	.019	Positive
RF	ICW	-.232	.468	Not Significant
RF	TBW1	-.278	.382	Not Significant
RF	FFM	.724	.008	Positive
Independent Variables	**Dependent Variables**	**Correlation coefficients**	**Significance p value**	**Correlation trend**
EF	Weight Kg	-.106	.743	Not Significant
EF	BMI kg/m^2	-.346	.270	Not Significant
EF	TSF	-.332	.292	Not Significant
EF	MAC	-.130	.686	Not Significant
EF	GS	.028	.930	Not Significant
EF	ECW	.281	.376	Not Significant
EF	ICW	.032	.922	Not Significant
EF	TBW1	-.290	.361	Not Significant
EF	FFM	-.092	.776	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
CF	Weight Kg	-.381	.222	Not Significant
CF	BMI kg/m^2	-.459	.134	Not Significant
CF	TSF	-.288	.364	Not Significant
CF	MAC	-.412	.184	Not Significant
CF	GS	-.053	.870	Not Significant
CF	ECW	.004	.991	Not Significant
CF	ICW	.095	.768	Not Significant
CF	TBW1	.423	.170	Not Significant
CF	FFM	.328	.298	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
SF	Weight Kg	.355	.258	Not Significant
SF	BMI kg/m^2	-.092	.776	Not Significant
SF	TSF	.411	.184	Not Significant
SF	MAC	-.158	.624	Not Significant
SF	GS	-.078	.809	Not Significant
SF	ECW	-.036	.913	Not Significant
SF	ICW	-.213	.507	Not Significant
SF	TBW1	.376	.228	Not Significant
SF	FFM	-.404	.192	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
FA	Weight Kg	.077	.812	Not Significant
FA	BMI kg/m^2	.242	.448	Not Significant
FA	TSF	.556	.061	Not Significant
FA	MAC	.268	.400	Not Significant
FA	GS	.287	.366	Not Significant
FA	ECW	-.293	.355	Not Significant
FA	ICW	.211	.511	Not Significant
FA	TBW1	-.004	.991	Not Significant
FA	FFM	-.354	.258	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
NV	Weight Kg	.279	.380	Not Significant
NV	BMI kg/m^2	-.134	.677	Not Significant
NV	TSF	-.182	.572	Not Significant
NV	MAC	-.264	.406	Not Significant
NV	GS	-.316	.318	Not Significant
NV	ECW	.076	.814	Not Significant
NV	ICW	.201	.530	Not Significant
NV	TBW1	.654	.021	Positive
NV	FFM	.187	.560	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
PA	Weight Kg	.577	.049	Positive
PA	BMI kg/m^2	.331	.293	Not Significant
PA	TSF	.476	.118	Not Significant
PA	MAC	-.359	.251	Not Significant
PA	GS	.028	.931	Not Significant
PA	ECW	.127	.694	Not Significant
PA	ICW	-.183	.569	Not Significant
PA	TBW1	.268	.400	Not Significant
PA	FFM	.155	.631	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
DYSPNEA	Weight Kg	.344	.273	Not Significant
DYSPNEA	BMI kg/m^2	-.042	.896	Not Significant
DYSPNEA	TSF	.090	.780	Not Significant
DYSPNEA	MAC	-.281	.377	Not Significant
DYSPNEA	GS	.069	.832	Not Significant
DYSPNEA	ECW	.386	.216	Not Significant
DYSPNEA	ICW	.074	.820	Not Significant
DYSPNEA	TBW1	.460	.132	Not Significant
DYSPNEA	FFM	.228	.475	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
INSOMNIA	Weight Kg	.216	.500	Not Significant
INSOMNIA	BMI kg/m^2	-.106	.743	Not Significant
INSOMNIA	TSF	-.305	.334	Not Significant
INSOMNIA	MAC	-.136	.674	Not Significant
INSOMNIA	GS	-.060	.852	Not Significant
INSOMNIA	ECW	-.259	.417	Not Significant
INSOMNIA	ICW	.032	.922	Not Significant
INSOMNIA	TBW1	.085	.793	Not Significant
INSOMNIA	FFM	-.304	.336	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
AP	Weight Kg	.222	.488	Not Significant
AP	BMI kg/m^2	.187	.561	Not Significant
AP	TSF	.548	.065	Not Significant
AP	MAC	-.308	.329	Not Significant
AP	GS	-.405	.191	Not Significant
AP	ECW	-.442	.151	Not Significant
AP	ICW	-.166	.607	Not Significant
AP	TBW1	.265	.406	Not Significant
AP	FFM	-.593	.042	Negative

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
CO	Weight Kg	-.350	.264	Not Significant
CO	BMI kg/m^2	.209	.515	Not Significant
CO	TSF	.263	.410	Not Significant
CO	MAC	.462	.131	Not Significant
CO	GS	-.322	.308	Not Significant
CO	ECW	-.502	.096	Not Significant
CO	ICW	.138	.669	Not Significant
CO	TBW1	-.237	.458	Not Significant
CO	FFM	-.170	.598	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
DI	Weight Kg	.351	.263	Not Significant
DI	BMI kg/m^2	-.095	.770	Not Significant
DI	TSF	.050	.878	Not Significant
DI	MAC	-.500	.098	Not Significant
DI	GS	-.512	.089	Not Significant
DI	ECW	.770	.003	Positive
DI	ICW	-.674	.016	Negative
DI	TBW1	-.151	.640	Not Significant
DI	FFM	.368	.239	Not Significant

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
FI	Weight Kg	.173	.590	Not Significant
FI	BMI kg/m^2	-.050	.878	Not Significant
FI	TSF	-.423	.170	Not Significant
FI	MAC	.549	.064	Not Significant
FI	GS	.242	.449	Not Significant
FI	ECW	.436	.156	Not Significant
FI	ICW	.060	.853	Not Significant
FI	TBW1	-.255	.424	Not Significant
FI	FFM	.598	.040	Positive

Independent Variables	Dependent Variables	Correlation coefficients	Significance p value	Correlation trend
PGSGA	Weight Kg	.291	.359	Not Significant
PGSGA	BMI kg/m^2	.356	.257	Not Significant
PGSGA	TSF	-.063	.845	Not Significant
PGSGA	MAC	.198	.538	Not Significant
PGSGA	GS	.187	.560	Not Significant
PGSGA	ECW	.295	.352	Not Significant
PGSGA	ICW	.492	.104	Not Significant
PGSGA	TBW1	.050	.877	Not Significant
PGSGA	FFM	.546	.066	Not Significant

The Leeds Teaching Hospitals NHS
NHS Trust

Ref: Amy Dickinson

20/10/2010

Research & Development
Leeds Teaching Hospitals NHS Trust
34 Hyde Terrace
Leeds
LS2 9LN

Tel: 0113 392 2878
Fax: 0113 392 6397

r&d@leedsth.nhs.uk
www.leedsth.nhs.uk

Mr Dermot Burke
Room D166, D Floor Clarendon Wing
Leeds General Infirmary
Great George Street, Leeds
LS1 3EX

Dear Mr Dermot Burke

Re: LTHT R&D Approval of: The physiological effect of adjuvant pre-operative chemotherapy and radiotherapy (APT) on patients with advanced colorectal cancer.
LTHT R&D Number: GS09/9007
REC: 09/H1306/79

I confirm that this study has R&D approval and the study may proceed at The Leeds Teaching Hospitals NHS Trust (LTHT). This organisational level approval is given based on the information provided in the documents listed below.

In undertaking this research you must comply with the requirements of the *Research Governance Framework for Health and Social Care* which is mandatory for all NHS employees. This document may be accessed on the R&D website http://www.leedsth.nhs.uk/sites/research_and_development/

R&D approval is given on the understanding that you comply with the requirements of the *Framework* as listed in the attached sheet "Conditions of Approval".

If you have any queries about this approval please do not hesitate to contact the R&D Department on telephone 0113 392 2878.

Indemnity Arrangements

The Leeds Teaching Hospitals NHS Trust participates in the NHS risk pooling scheme administered by the NHS Litigation Authority 'Clinical Negligence Scheme for NHS Trusts' for: (i) medical professional and/or medical malpractice liability; and (ii) general liability. NHS Indemnity for negligent harm is extended to researchers with an employment contract (substantive or honorary) with the Trust. The Trust

NHS

National Research Ethics Service

Leeds (East) Research Ethics Committee
Room 5.2, Clinical Sciences Building
St James's University Hospital
Beckett Street
Leeds
LS9 7TF

Telephone: 0113 2065652
Facsimile: 0113 2066772

08 October 2009

Mr Samir Rahmani
Clinical Research Fellow
Leeds General Infirmary
Colorectal Research Room 156
D- Floor, Clarendon Wing
Leeds General Infirmary
LS1 3EX

Dear Mr Rahmani

Study Title:	**The physiological effect of adjuvant pre-operative chemotherapy and radiotherapy (APT) on patients with advanced colorectal cancer.**
REC reference number:	**09/H1306/79**
Protocol number:	**1**

Thank you for your email of 22 September 2009, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a sub-committee of the REC. A list of the sub-committee members is attached.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

NHS

National Research Ethics Service

Leeds (East) Research Ethics Committee
Room 5.2, Clinical Sciences Building
St James's University Hospital
Beckett Street
Leeds
LS9 7TF

Telephone: 0113 2065652
Facsimile: 0113 2066772

08 October 2009

Mr Samir Rahmani
Clinical Research Fellow
Leeds General Infirmary
Colorectal Research Room 156
D- Floor, Clarendon Wing
Leeds General Infirmary
LS1 3EX

Dear Mr Rahmani

Study Title:	**The physiological effect of adjuvant pre-operative chemotherapy and radiotherapy (APT) on patients with advanced colorectal cancer.**
REC reference number:	**09/H1306/79**
Protocol number:	**1**

Thank you for your email of 22 September 2009, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a sub-committee of the REC. A list of the sub-committee members is attached.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk. *Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.*

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Referees or other scientific critique report		19 August 2009
Covering Letter		
REC application		21 July 2009
Investigator CV		
Letter from Sponsor		22 July 2009
CV for Dermot Burke		
Protocol	1	15 April 2009
Referees or other scientific critique report		20 July 2009
Summary/Synopsis		
Questionnaire: EORTC QLQ-C30		
Questionnaire: Patient-Generated SGA of Nutritional Status		
Letter of support from Dermot Burke		08 July 2009
Letter of support from Darren Cole		17 September 2009
Protocol and Timetable Summary		
Participant Information Sheet	2	18 September 2009
Participant Consent Form	2	18 September 2009
Letter of invitation to participant	2	18 September 2009
GP/Consultant Information Sheets	1	18 September 2009
Response to Request for Further Information		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views

known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

09/H1306/79	**Please quote this number on all correspondence**

Yours sincerely

Dr Carol Chu
Chair
Email: Amy.Beckitt@leedsth.nhs.uk

Enclosures: List of names and professions of members who took part in the review

"After ethical review – guidance for researchers"

Copy to: R&D office for Leeds Teaching Hospitals NHS Trust

Mr Dermot Burke, Consultant Colorectal Surgeon

Leeds (East) Research Ethics Committee

List of names and professions of REC members who considered the further information in correspondence on 08 October 2009

Name	*Profession*	*Capacity*
Mrs Alison Barraclough	Vice Chair: NHS Training and Development Advisor	Lay
Mr Roly Squire	Consultant Paediatric Surgeon	Expert

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