A RETROSPECTIVE STUDY IN THE UTILIZATION OF 18F-FDG PET/CT IN STAGING OESOPHAGUS CANCER AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL (2012-2021)

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A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in the fulfilment for the degree of Master of Medicine
in the division of Radiation Oncology

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DECLARATION

I, Muhammed Bapeekee, declare that this research protocol is my own work. It has been submitted for the Degree of Master of Medicine, in Radiation Oncology, at the University of Witwatersrand, Johannesburg. It has not been submitted before, for any postgraduate degree or examination, at this or any other University.

Muhammed A.S. Bapeekee

Signed _____31___ day of _____December_____ 2024.

DEDICATION

My Lord: The Most Gracious, the Most Merciful.

My wife: Fazila: My best friend, my strength, my rock. Thank you for your love and support during this journey.

My parents: Ahmed Sadeck and Khatija: I am what I am because of you, thank- you for guiding me throughout my life.

My siblings and their families: You all have given me so much strength and support during this journey.

Dr Presha Bipath: My dear friend and mentor for the constant support and encouragement throughout this journey.

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ABSTRACT

Introduction

Cancer of the oesophagus has dramatically increased worldwide, and patients present with advanced disease in the South African context. Adequate staging investigations are imperative to guide treatment intent. Staging of oesophageal cancer requires a multimodality of investigations. Pre-treatment 18F-FDG PET/CT provides more accurate staging, assesses prognostic stratification, improves radiotherapy treatment planning, and can change management in more than one third of patients.

Objective

This study aimed to assess if there is a discordance between the initial TNM and group stage and post 18F-FDG PET/CT TNM and group stage in patients referred for radiation therapy at CMJAH. The secondary aim is to determine if additional information (such potential secondary cancers) is picked up on 18F-FDG PET/CT.

Method

A retrospective, cross-sectional analysis of all patients with cancer of the oesophagus, from 1st January 2012 to 31st December 2021, referred for radiation therapy at Charlotte Maxeke Johannesburg Academic Hospital. Patient clinical information was reviewed to extract data regarding demographics, histology, site, pre and post 18F-FDG PET/CT group stage and if any additional information was seen on the 18F-FDG PET/CT report.

Results

Four hundred and fifteen patients were identified of which 33 met the inclusion criteria. The median age was 60.5 (IQR 52.8-68.5) with males accounting for

63.6% (n=21/33) of the population. The thoracic oesophagus was the most prevalent location of primary lesion (78.8%), with histological subtype squamous cell carcinoma (93.9%). There was a discordance between the initial TNM and group stage and post 18F-FDG PET/CT TNM and group stage in the patients investigated. On 18F-FDG PET/CT, 12% (n=4/33) of study participants showed uptake in different sites suggesting potential secondary primaries.

Conclusion

18F-FDG PET/CT imaging may provide additional staging information not observed in initial conventional staging studies. This additional information can change treatment strategies and treatment intent. Further studies are required to confirm the incremental staging value that 18F-FDG PET/CT could have in staging cancer of the oesophagus in the LMICs setting.

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ABBREVIATIONS:

- AC: Adenocarcinoma
- AJCC: American Joint Committee on Cancer
- CMJAH: Charlotte Maxeke Johannesburg Academic Hospital
- CT: Computed tomography
- DFS: Disease free survival
- EUS: Endoscopic ultrasound
- FDG PET/CT: Fluoro-2-deoxyglucose Positron Emission Tomography / Computed Tomography
- FNA: Fine-needle aspiration
- MTV: Metabolic Tumour Volume
- LMICs: Low- and middle-income countries
- OG junction: Oesophago-gastric junction
- OS: Overall survival
- SCC: Squamous Cell Carcinoma
- SUV: Standardized Uptake Value
- UICC: Union for International Cancer Control

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CHAPTER ONE: BACKGROUND AND LITERATURE REVIEW

1.1 Epidemiology of cancer of the oesophagus globally

The global prevalence of oesophageal cancer varies, with Northern China, South Africa and Turkey having the highest rates (1). Its prevalence has dramatically increased over the last decade, resulting in a significant global disease burden. Globally, it is the seventh most prevalent cancer diagnosed and sixth leading cause of cancer related death (2).

Oesophageal squamous cell carcinoma (SCC) is the most prevalent histological subtype and predominates in low- and middle-income countries (LMICs) in oesophageal cancer belts that includes areas in Africa and Asia (1). In high-income countries (HIC), oesophageal adenocarcinoma (AC) is common in areas in America and Europe (2).

1.2 Epidemiology of cancer of the oesophagus in South Africa

In the South African context, oesophageal cancer is a disease with majority of the patients presenting at an advanced stage (3). Significant delays exist between onset of symptoms and time to definitive treatment; these delays are caused by insufficient patient awareness of symptoms, barriers to health care and delays in the final diagnosis and staging at health facilities (3).

As most patients present with advanced disease, definitive treatment is aimed at palliation, with some authors mentioning less than 5% of patients are eligible for curative treatment (4).

1.3 Histological subtypes

Squamous cell carcinoma and adenocarcinoma of the oesophagus are the two most common histological subtypes seen in clinical practice. Other rare histologies include small cell carcinoma and sarcoma.

1.3.1 Squamous cell carcinoma

SCC of the oesophagus is the commonest histological subtype in LMICs, with advanced age, tobacco smoking, alcohol consumption, male gender, low socio-economic status, achalasia, tylosis and dietary factors such as foods containing N-nitroso compounds, drinking hot drinks, and chewing areca nuts the common risk factors in its development (3,5). Oesophageal SCC tends to localize at or higher than the tracheal bifurcation and is associated with a poorer prognosis (6). Patients diagnosed with oesophageal SCC are more likely to have synchronous secondary primary tumours especially of the head and neck region due to the shared risk factors between the two primary lesions (2). The risk for SCC decreases substantially after smoking cessation reflecting reduced rates in North America and Europe due to reduced tobacco and alcohol use. (6). Genetic abnormalities in SCC of the oesophagus development include p53 mutations and amplifications of cyclin D1 and epidermal growth factor receptor (EGFR) (6). These mutations lead to cell hyperplasia, low - and high- grade dysplasia and ultimately malignancy.

1.3.2 Adenocarcinoma

Adenocarcinoma of the oesophagus is less common in the LMIC setting, with lifestyle factors having a role in its development. Its prevalence has increased in the West, reflecting growing rates of obesity, with factors such has high body mass index associated with gastro-oesophageal reflux disease in the development of Barrett's oesophagus (6). Over the last two decades, adenocarcinoma of the oesophagus has progressively increased, affecting mostly white males with pathogenesis linked to gastro-oesophageal reflux disease and Barrett's oesophagus. Barrett's oesophagus is a precancerous condition in which the normal squamous epithelium of the oesophagus is replaced by metaplastic columnar epithelium. Patients diagnosed with Barrett's oesophagus have a 30 to 60 times greater risk of developing adenocarcinoma of the oesophagus (6). In contrast to oesophageal SCC, AC of the oesophagus usually affects the mid to lower oesophagus and has a better prognosis (6). The risk for adenocarcinoma of the oesophagus remains unchanged even post cessation of smoking (6). Genetic abnormalities in the

development of AC of the oesophagus include overexpression of p53, EGFR and human epidermal growth factor receptor 2 (HER-2) (6).

1.4 Classification and staging

Oesophageal cancer includes tumours located throughout the oesophagus and oesophago-gastric junction (OG junction). The current staging recommendations are the 8th edition of the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) TNM staging categories (6).

The Cancer categories include primary tumour (T), regional lymph nodes (N) and metastases (M). Table 1 list the 8th edition of the AJCC TNM staging categories.

Table 1: 8th edition of the AJCC and UICC TNM staging categories.

T: PRIMARY TUMOUR	TX	Primary tumour cannot be assessed adequately
	To	No evidence of primary tumour noted
	Tis	High grade dysplasia
	T1	Tumour invades to the lamina propria or muscularis mucosae (T1a), tumour invades to the submucosa (T1b)
	T2	Tumour invades to the muscularis propria
	T3	Tumour invades to the adventitia
	T4	Tumour invades to adjacent structures: pleura, pericardium, azygos vein, diaphragm, or peritoneum (T4a), other structures such as aorta, vertebra body or airway (T4b)
N: REGIONAL LYMPH NODES	Nx	Regional lymph nodes cannot be assessed adequately
	N0	No regional lymph node metastasis noted
	N1	Metastasis in one or two regional lymph nodes only
	N2	Metastasis in three to six regional lymph nodes only
	N3	Metastasis in seven or more regional lymph nodes only
M: DISTANT METASTASIS	M0	No distant metastasis noted
	M1	Distant metastasis noted

Source: Adopted from (6).

Tables 2 and 3 show the AJCC clinical prognostic stage groups for SCC and AC of the oesophagus.

Table 2: 8th edition of the AJCC and UICC clinical prognostic stage groups for SCC of the oesophagus

Stage	*T*	*N*	*M*
Stage 0	Tis	N0	M0
Stage 1	T1	N0-1	M0
Stage 2	T2	N0-1	M0
	T3	N0	M0
Stage 3	T3	N1	M0
	T1-3	N2	M0
Stage 4A	T4	N0-2	M0
	Any T	N3	M0
Stage 4B	Any T	Any N	M1

Source: Adopted from (6).

Table 3: 8th edition of the AJCC and UICC clinical prognostic stage groups for AC of the oesophagus.

	T	N	M
STAGE 0	Tis	N0	M0
STAGE 1	T1	N0	M0
STAGE 2A	T1	N1	M0
STAGE 2B	T2	N0	M0
STAGE 3	T2	N1	M0
	T3	N0-1	M0
	T4a	N0-1	M0
STAGE 4A	T1-4a	N2	M0
	T4b	N0-2	M0
	Any T	N3	M0
STAGE 4B	Any T	Any N	M1

Source: Adopted from (6).

1.5 Evaluation of patients

Following endoscopy and biopsy, oesophageal cancer is staged using a complementary mix of multiple modalities of investigations, including endoscopic ultrasound (EUS), computed tomography (CT), and 18F-Fluoro-2-deoxyglucose positron emission tomography / computed tomography 18F-FDG PET/CT) (2).

1.5.1 Endoscopic Ultrasound

EUS combines direct visualization endoscopy with high-frequency ultrasound to define the separate layers of the oesophagus. It is regarded as the most accurate diagnostic method in evaluating locoregional tumour status in oesophageal cancer (7). EUS assesses the extent of mucosal involvement by tumour, evaluating T stage and peritumoral nodal metastases. EUS allows interpretation of nodal status based on size, shape, borders, and internal characteristics of the imaged nodes (2). EUS can also assist in providing cytological proof of malignancy of peritumoral nodes and coeliac nodes by fine-needle aspiration (FNA) (2).

1.5.2 CT

CT provides limited value for evaluation of depth of invasion of the primary tumour due to poor soft tissue resolution (8). Loss of fat planes between tumour and adjacent organs may indicate invasion. CT is useful in deciding operability by surgeons.

CT has a low sensitivity for detecting nodal metastases (2). Lymph nodes greater than 1cm are considered enlarged and likely to be metastatic. As CT does not provide functional imaging, enlarged nodes may be false positive and be reactive in nature (7).

CT of the chest and abdomen remains the most used non-invasive diagnostic modality to evaluate metastatic disease in patients undergoing workup of oesophageal cancer (9).

1.5.3 18F-FDG PET/CT

18F-FDG PET detects metabolically active tissue based on the kinetics of glucose utilization. Fluorine-18 (18F) is one of the isotopes used for PET with positron emitting properties, a favourable half-life and short positron range (7). Thus, 18F has higher resolution in metabolically active tissues, and allows for delayed imaging protocols, if required and can be transported over long distances due to the longer half-life of 109 minutes. 18F-FDG is preferentially

taken up by cells with a high rate of glucose utilization, including malignant, inflammatory, and infective cells. PET/CT is a hybrid modality that combines both multislice CT and PET images in one imaging timeframe, allowing for the assessment of structural and functional parameters in evaluating the pathology (7,10). Thus, the functional information gathered from PET is fused with the anatomical information gathered from CT. 18F-FDG PET/CT has been shown to provide incremental nodal and distant metastases staging information in the workup of patients diagnosed with oesophageal cancer (11).

1.5.3.1 18F-FDG PET/CT for primary T staging

18F-FDG PET/CT has a limited use in T staging as PET provides no information on the depth of tumour invasion (2). Both SCC and AC of the oesophagus will show avidity on 18F-FDG PET (2). 18F-FDG PET/CT will be of value where disease of the primary site is inadequate following EUS and CT (12). Synchronous neoplasms of the oesophagus may also be detected by 18F-FDG PET/CT (12). These synchronous lesions may impact radiation treatment volumes (14).

1.5.3.2 18F-FDG PET/CT for regional nodes

The oesophagus has a rich lymphatic supply with drainage to lymph nodes of the neck, abdomen, and retroperitoneum. Nodal staging is one of the most important prognostic factors in patients diagnosed with oesophageal cancer - patients with node positive disease have a worse prognosis than patients with node negative disease (15). There is variation amongst studies with regards to the accuracy of 18F-FDG PET/CT for detecting regional nodal disease. However, 18F-FDG PET/CT has a higher specificity than CT for detecting nodal involvement (15). 18F-FDG PET is unable to detect peritumoral (nodes in the direct vicinity of the tumour) lymphadenopathy as avid tumoural uptake by the primary lesion obscures the uptake in nearby nodes. Most studies reasonably conclude that avid nodes on 18F-FDG PET/CT are likely to contain active disease if lying in the usual drainage pattern. 18F-FDG PET/CT compared with other modalities is more accurate in detecting nodes in the coeliac axis (12). As such the anatomical information gathered from CT

combined with functional imaging gathered by 18F-FDG PET, assist greatly in accurately determining nodal status in oesophagus cancer patients.

1.5.3.3 18F-FDG PET/CT for distant metastases

The incremental value in 18F-FDG PET/CT lies in its ability to adequately determine the M stage in a patient diagnosed with oesophagus cancer. 18F-FDG PET/CT assists in identifying indeterminate sites of disease on CT and identifies unsuspected metastatic disease which can be present in up to 30% of patients at initial diagnosis (15). Literature consistently shows that 18F-FDG PET/CT is more accurate than other imaging modalities for detecting disease beyond regional nodes (12,14,15). 18F-FDG PET/CT therefore assist in identifying sites of biopsy to rule out unsuspected metastatic disease and conversely provides information to confidently prove metastatic disease, reducing the need for invasive procedure/s thus upstaging or downstaging patients to receive suitable treatment intent. The most common sites of distant metastases detected on 18F-FDG PET, but missed by CT were in the lung, bone, liver, and non-regional nodes (2,7).

1.5.3.4 18F-FDG PET/CT for radiotherapy planning

Accurate delineation of target volume for radiation is imperative for cure of disease. CT is not always able to precisely assist with delineation of tumour for radiotherapy planning due to poor soft tissue resolution (14). This low soft tissue resolution may make delineation of gross disease difficult to contour for radiotherapy planning. A study of patients with oesophageal cancer undergoing radiotherapy demonstrated that 18F-FDG PET co-registration to planning CT, modified gross tumour volume (GTV) in 56% of patients (15). With the addition of PET to CT-based radiation therapy planning, target volume of both primary and nodal disease has drastically improved, whilst minimising dose to normal tissues such as lung and heart (11,14). This will improve loco-regional disease control and reduce radiation-induced complications. However, there is no uniform method or guidelines for delineation which is performed by visual inspection using SUV threshold (14). Additional validation studies are required to demonstrate these modifications prior to 18F-FDG PET/CT be recommended for target delineation (14,15).

1.5.3.5 18F-FDG PET/CT for detection of occult secondary primaries

Occult secondary primaries can be detected by 18F-FDG PET/CT in patients undergoing staging for oesophageal cancer (14). 18F-FDG avid lesions are considered an occult secondary primary if they occur at a site atypical for metastases from the primary lesion (16). Other features include a marked discordance in the FDG avidity of the primary site and potential secondary site, and there is no prior detection of the lesion on previous conventional imaging (16). Additional investigations may be needed including histopathological confirmation of a potential occult secondary primary. Confirmation of occult secondary primary may impact on initial treatment plan (14).

1.5.4 Other investigations

Assessment of tumour invasion locally can be determined by triple endoscopy which includes laryngoscopy, bronchoscopy, and endoscopy especially for tumours above the carina (6). Absence of serosa in the oesophageal wall allows spread of tumour to adjacent structures including airway, blood vessels and heart. Invasion can lead to fistula formation which can alter definitive management (2).

Recommendations for lower oesophageal tumours and oesophago-gastric tumours include laparoscopy which can yield distant metastases in the peritoneal cavity in up to 15-20% of patients (6,7).

1.6 Pitfalls of 18F-FDG PET/CT

Inflammation and infection are also 18F-FDG avid due to the increased glucose utilization (2). Other pathologies like reflux oesophagitis and candidiasis must be clinically distinguished from malignancy, as they can result in a false positive finding. 18F-FDG uptake can occur in nodes infiltrated by sarcoid, lymphoma and in HIV positive patients with generalized lymphadenopathy caused by infectious agents (7). Small sub-centimetre metastatic deposits in organs may be challenging to detect due to camera

resolution and will need additional investigation. The overall cost and waiting times of PET/CT may be challenging, especially in resource limited settings.

False positive findings of PET/CT are lower in the hands of experienced Nuclear Medicine physicians, as experience of increased metabolism due to other aetiologies are somewhat easier to identify. Overall, PET/CT studies should be combined with other imaging and relevant clinical history to ensure accuracy and confident correlation (12).

1.7 Can 18F-FDG PET/CT replace conventional CT?

The integration of 18F-FDG PET/CT as a complementary modality to conventional CT in the staging pathway of patients with oesophageal cancer can lead to improved diagnostic accuracy, especially in the detection of unsuspected nodal and distant metastases (10,11,12,14,15).

The College of Nuclear Physicians (CNP) of the College of Medicine of South Africa (CMSA) has developed a list of recommendations of the appropriate use of 18F-FDG PET/CT in the oncology setting (17). This list gives recommendations of the utilization of 18F-FDG PET/CT where PET/CT could result in the highest patient impact with the intention of optimizing cost effectiveness and need of clinical benefit.

For oesophageal cancer, 18F-FDG PET/CT is “recommended in select cases” for staging, restaging/response to treatment and suspected recurrence. For radiotherapy planning and surveillance, 18F-FDG PET/CT “may be considered” (17).

In the South African context, the use of PET/CT is constrained by cost, infrastructure, and expertise. Routine use of utilization of 18F-FDG PET/CT in staging oesophageal cancers may not be achievable in the LMICs setting.

More large clinical trials are needed to expand if 18F-FDG PET/CT can replace conventional CT in the staging of oesophageal cancer. To date, literature suggest that 18F-FDG PET/CT is complementary to conventional CT in staging oesophageal cancer (10,11,12,14,15).

1.8 Treatment

All patients diagnosed with oesophageal cancer should be discussed in a multidisciplinary team meeting to ensure the best treatment options are rendered. Surgery via oesophagectomy is generally recognised as the best prospect for cure, but is a major procedure associated with morbidity and mortality (10). If staging confirms irresectable metastatic disease or if patient has a poor performance status not amenable to definitive treatment modalities for both SCC and AC of the oesophagus, treatment strategies are aimed at symptom amelioration and improvement of quality of life. These include reversal of oesophageal obstruction, radiotherapy modalities, systemic therapy, and palliative care (6).

1.8.1 Squamous cell carcinoma

For patients diagnosed with early-stage resectable SCC oesophageal tumours, curative treatment options include surgery (via endoscopic resection or oesophagectomy) or definitive chemoradiation in patients with cervical oesophageal lesions or significant comorbid disease (11). In locally advanced disease, neoadjuvant chemoradiation is often used in combination with surgery to improve outcomes (11). Patients with medical co-morbidities or advanced locoregional disease may be offered definitive chemoradiation (6).

1.8.2 Adenocarcinoma

For patients diagnosed with early-stage resectable AC oesophageal tumours, curative treatment options include surgery (via endoscopic resection or oesophagectomy) or definitive chemoradiation in patients with significant comorbid disease (11). In locally advanced disease, neoadjuvant therapy can be considered including chemoradiation or systemic therapy in combination with surgery to improve outcomes (6). Patients with medical co-morbidities or advanced locoregional disease may be offered definitive chemoradiation (6).

1.9 Summary

In summary, oesophageal cancer requires a multimodality of investigations to adequately stage a patient to provide optimal treatment. 18F-FDG PET/CT has been proven to be a worthwhile investigation in the evaluation of patients with oesophageal cancer. The addition of 18F-FDG PET/CT is associated with reduced treatment-associated morbidity and significant improved treatment outcomes (18). Pre-treatment 18F-FDG PET/CT provides more accurate staging, assesses prognostic stratification, improves radiotherapy treatment planning, and can change management in more than one third of patients (11). 18F-FDG PET/CT can be incorporated in the initial workup of patients diagnosed with oesophageal cancer to provide optimal treatment intent.

1.10 Justification for the study

Oesophageal cancer is a disease with an overall poor prognosis, both globally and more specifically in the South African context (3). Adequate staging to evaluate disease extent prior to definitive management is imperative to prevent both over and under treatment. In the South African public hospital setting, with resource constraints, it is important to identify patients who may not benefit from radical treatment and institute palliative management at an early stage to improve the quality of life. This study will therefore aim to evaluate the additional staging information provided by 18F-FDG PET/CT in the initial workup of patients diagnosed with oesophageal cancer.

1.11 Aim

To evaluate the role of staging with 18F-FDG PET/CT in the management of patients, diagnosed with oesophagus cancer, scheduled for radiation therapy at the Department of Radiation Oncology, Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)

1.12 Objectives

i. Primary: To determine if there is a discordance between the initial TNM and group stage and post 18F-FDG PET/CT TNM and group stage in patients diagnosed with oesophagus cancer referred for radiation therapy at CMJAH.

ii. Secondary: To determine if additional information such as potential secondary primaries are identified on 18F-FDG PET/CT.

CHAPTER TWO: METHODOLOGY

2.1 Study setting:

The study was conducted at the Department of Radiation Oncology, CMJAH.

2.2 Study period:

The study population included all patients referred to the Department of Radiation Oncology, CMJAH with diagnosed oesophageal cancer between 1 January 2012 to 31 December 2021

2.3 Study design:

This is a retrospective study from January 2012 to December 2021. A case analysis was performed of patients referred to the Radiation Oncology department at CMJAH with biopsy proven oesophageal cancer, who have had a 18F-FDG PET/CT as part of initial staging workup. Radiation Oncology files were reviewed to extract data regarding demographics, histology, site of disease, pre and post 18F-FDG PET/CT TNM and group stage and if any additional information picked up on the 18F-FDG PET/CT report. Staging information from 18F-FDG PET/CT was assessed as per the report generated by the Nuclear Medicine Physician. This report included information about the primary disease, lymph node metastases, distant metastases and potential secondary primaries. Data was captured onto an anonymous data sheet (Appendix 1).

2.4 Study population:

All patients who have been referred to the Radiation Oncology department at CMJAH, during the study period, who have had a 18F-FDG PET/CT as part of initial staging evaluation.

2.5 Inclusion criteria:

i. All patients with histologically confirmed oesophageal (any site) and oesophago-gastric junction tumours during the study period who

have had any initial staging investigation/s and then had an 18F-FDG PET/CT scan were included.

ii. The time period between the initial staging investigations and the 18F-FDG PET/CT scan must be less than 90 days.

iii. Patients must be over the age of 18 years.

2.6 Exclusion criteria:

i. Patients without a biopsy confirmed histology of oesophageal cancer.

ii. Patients without any initial staging investigations.

iii. Histology of carcinoma in situ

2.7 Measurement tool:

The measurement tool for data collection was data sheets (Appendix 1).

2.8 Source data:

Radiation Oncology files were obtained from the secure filing vault (with permissions from the CEO of the hospital, postgraduate committee of the University of Witwatersrand approval, and Ethics clearance: Clearance Certificate M220920) at CMJAH. (Appendix 2 and 3)

2.9 Study definitions:

i. Initial investigations: any investigation done prior to 18F-FDG PET/CT to determine tumour, nodal or metastatic stage of the diagnosed oesophageal cancer. These included CT Staging, endoscopic ultrasound, chest Xray, ultrasound reports and bone scans.

ii. Group stage: determined using the 8th edition of the AJCC and UICC clinical prognostic stage groups for SCC and AC of the oesophagus.

iii. Synchronous tumour: presence of a synchronous tumour should be confirmed on histology.

2.10 Data Processing and Data Analysis:

Each patient was allocated a unique study number and anonymity was maintained. Data was collected onto the data sheet and analysed with the assistance of a qualified statistician.

Statistical Analysis

Continuous variables such as patient ages were summarised as mean (standard deviation (SD)) and median (interquartile range (IQR)) and compared using Student's t-test. Categorical variables such as gender, was expressed as proportions and compared using the two tailed Chi-square test. Descriptive statistics was used to summarize the frequency of concordant and discordant cases and imaging findings. All percentages were calculated on a per-patient basis, not on the number of discordant findings. These analyses were performed using the Statistical Package for Social Sciences (SPSS) version 27 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp) and Stata Statistical Software (STATA) (Release 16. College Station, TX: StataCorp LP. StataCorp. 2019.

2.11 Permissions:

i. The study proposal was submitted to the Postgraduate Committee of the University of the Witwatersrand
ii. Consent was obtained from the CEO of the hospital (Appendix 2) and HOD of Radiation Oncology.

2.12 Ethics:

i. The study proposal was submitted to the Human Research Ethics Committee (HREC) of the University of the Witwatersrand to get approval for the study (Certificate number: M220920). (Appendix 3)
ii. No patient identifiers were used, and all patients were allocated a unique study number.
iii. All patient records were obtained personally from the patients Radiation Oncology files.

CHAPTER THREE: RESULTS

During the study period, 415 files of patients diagnosed with oesophageal cancer were reviewed. Of the 415 patients only thirty- three (33) patients met the inclusion criteria for the study. The most common reason for patients not being able to meet the inclusion criteria was that an initial staging 18F-FDG PET/CT was not done.

Table 4: Total number of patients

	Year	Number of patients with oesophageal cancer referred	Number of patients meeting inclusion criteria
	2012	47	0
	2013	38	0
	2014	50	0
	2015	40	1
	2016	27	0
	2017	31	2
	2018	60	2
	2019	33	3
	2020	68	20
	2021	21	5
Total		415	33 (7.9%)

3.1 Age

Figure 1 shows the age distribution of participants in our study. The standard deviation of patients reviewed is 61.4 ± 10.8 (95% CI 57.6-65.1). The median age is 60.5 (Interquartile range 52.8 – 68.5).

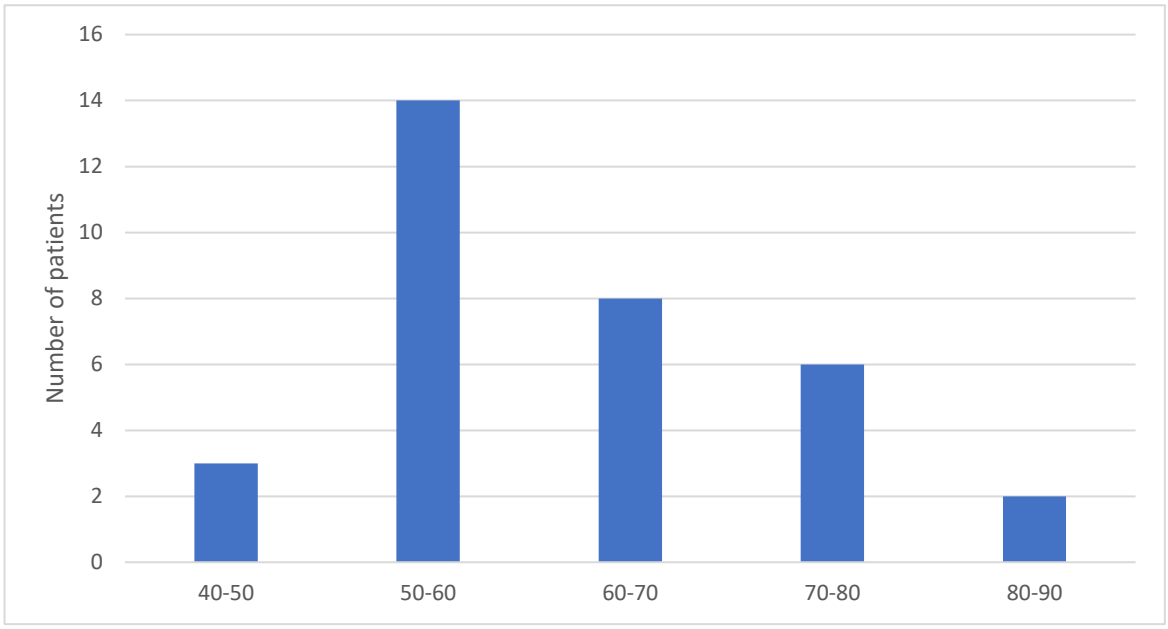


Figure 1: Age distribution of patients in the study.

3.2 Gender

Figure 3 depicts the percentages of each gender. Twelve (36%) of the 33 participants were females, while 21 (64%) were males.

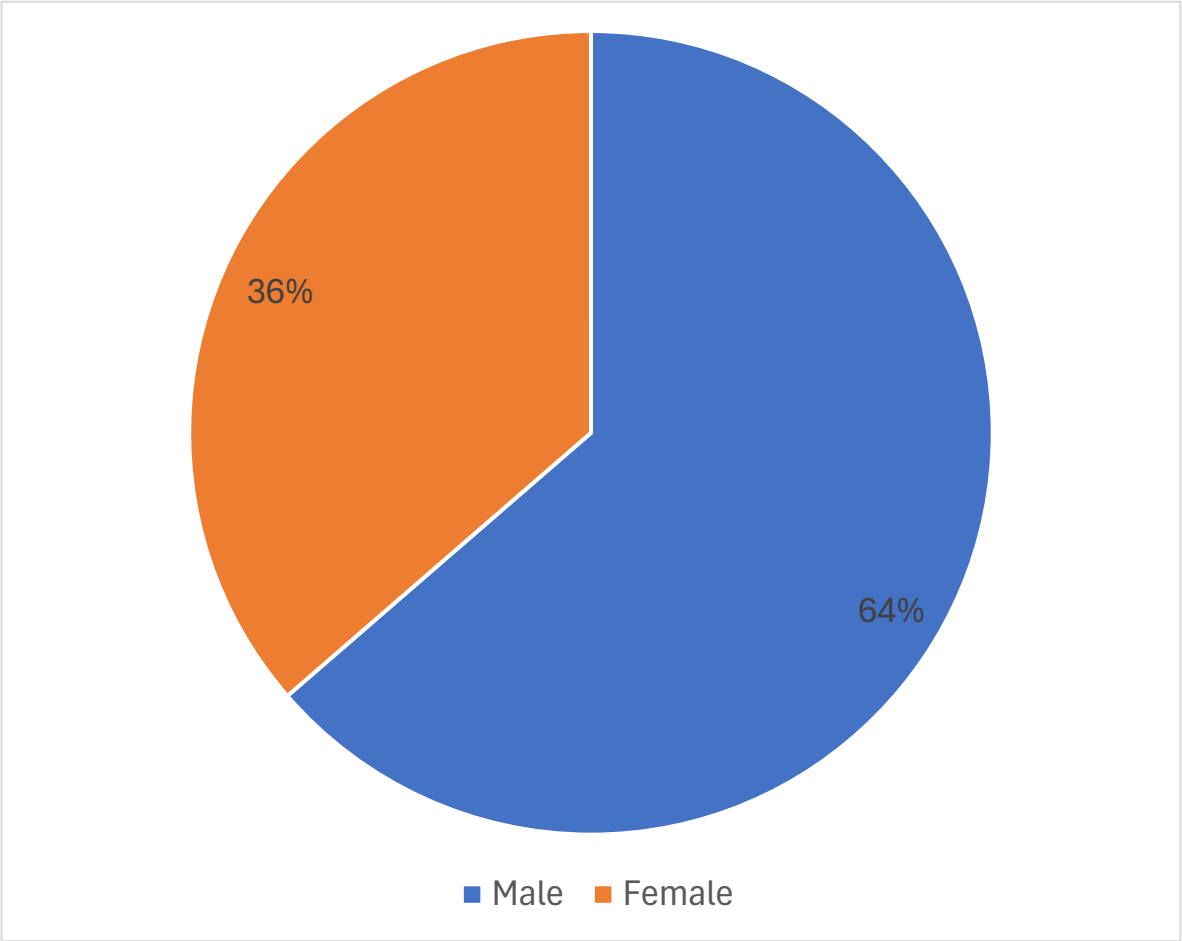


Figure 2: Percentages of gender difference in study.

3.3 Histology

The different histological subtypes are depicted in Figure 3. The histology of 31 (93.9%) patients was squamous cell carcinoma, while that of 2 (6.1%) patients was adenocarcinoma.

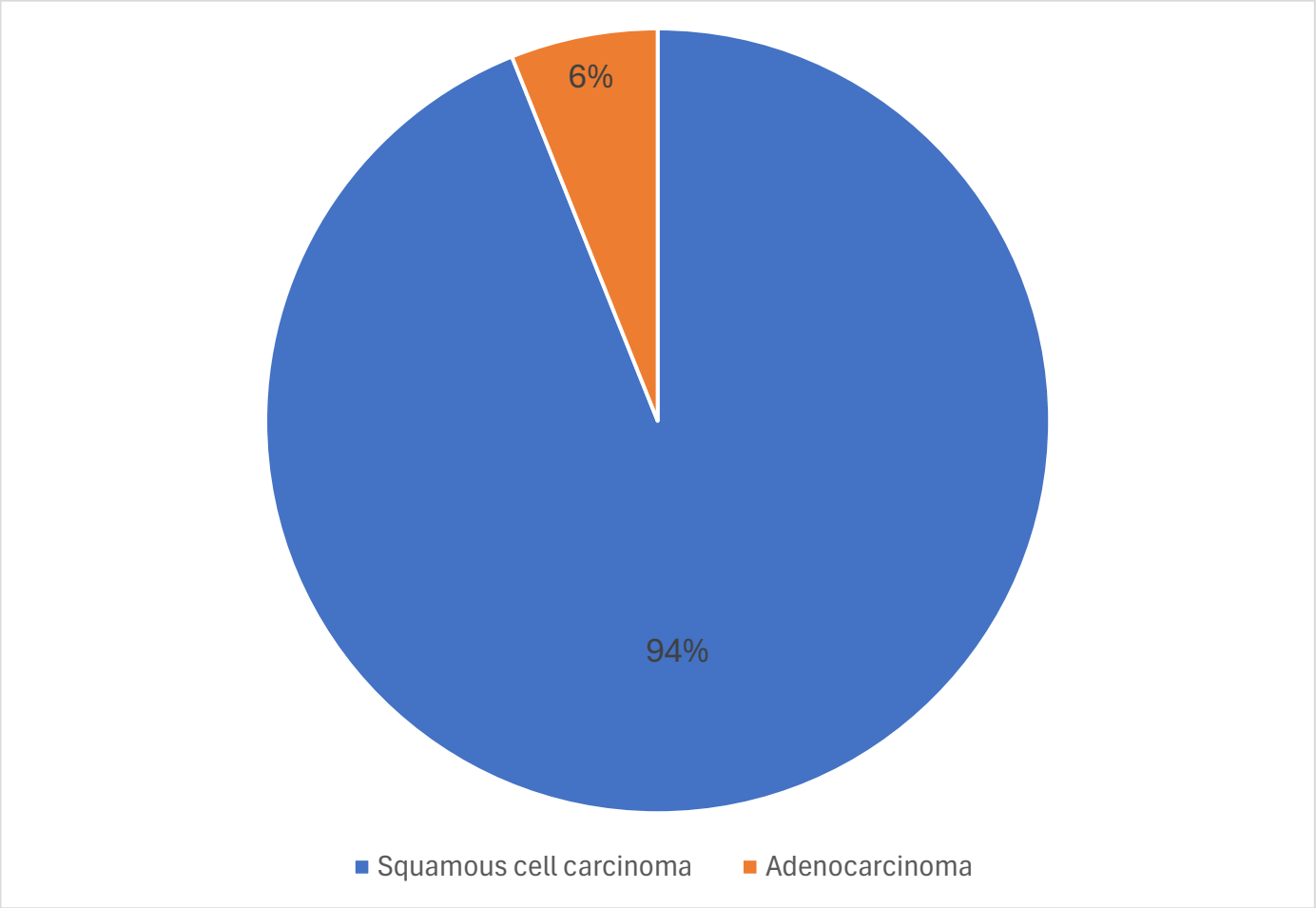


Figure 3: Percentages of histology difference in study.

3.4 Sites of primary

Figure 4 shows the different sites with percentages and table 5 shows the sites of disease with histological subtype.

Four (12%) patients have a primary site of cervical oesophagus, 26 (79%) of thoracic oesophagus and 3 (9%) of OG junction.

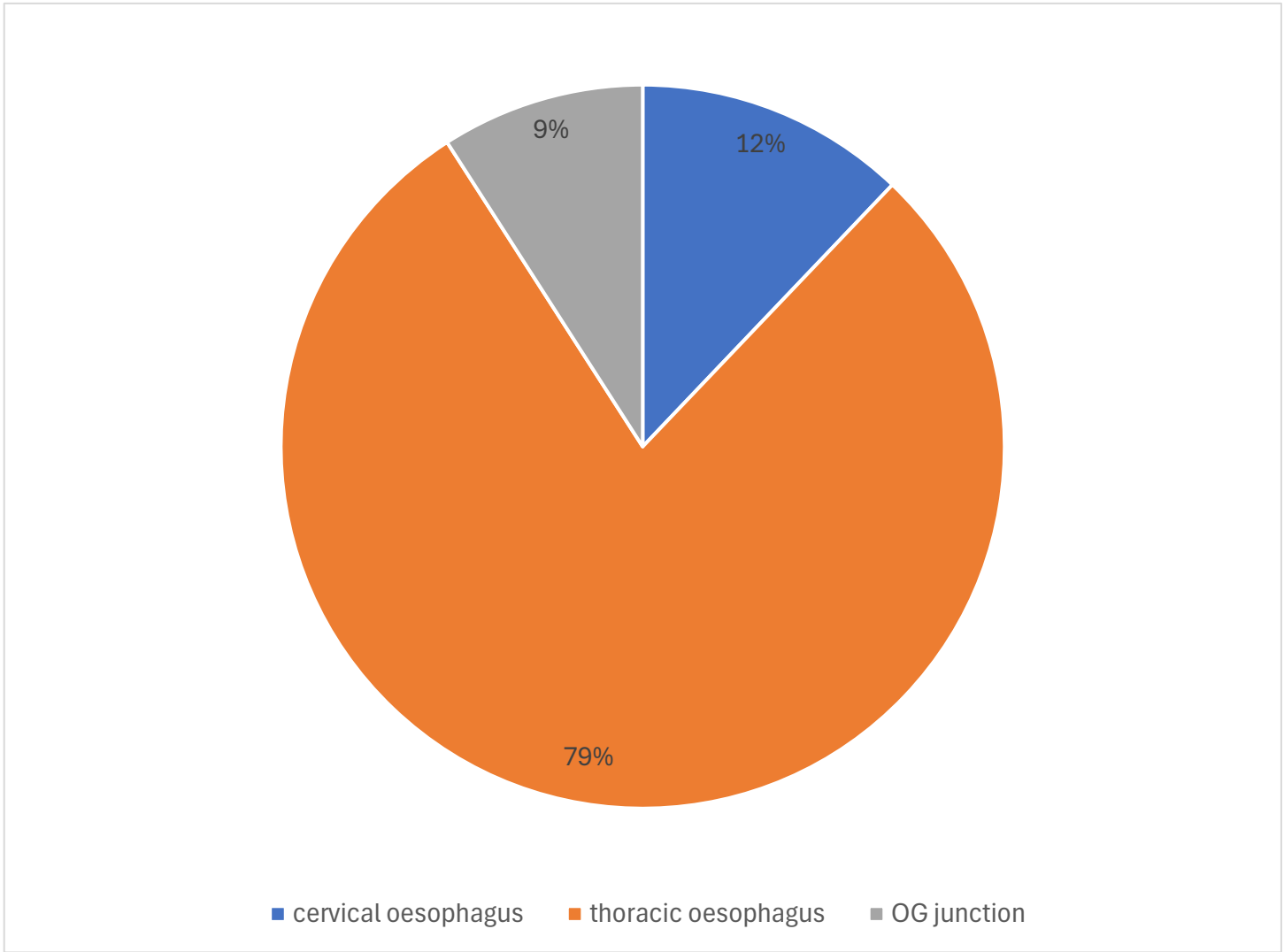


Figure 4: Different sites of oesophagus primaries with percentages.

Table 5: Sites of disease and histology

Site of primary of oesophageal lesion	Number of patients with involved site	Number of patients with SCC of site	Number of patients with AC of site
Cervical	4	3	1
Thoracic	26	26	0
Abdominal	0	0	0
OG junction	3	2	1
Total	33	31 (93.9%)	2 (6.1%)

3.5 Initial investigations performed.

Table 6 indicates the types of initial investigations performed to determine the initial TNM and group stages and number with percentages.

Table 6: Initial investigations performed.

Type of investigation	Number of patient's investigation performed in.	Percentage of patient's investigation performed in
CT chest and abdomen ± pelvis	33	100
Endoscopic ultrasound	0	0
Chest Xray	17	51
Ultrasound	12	36
Bone Scan	3	9

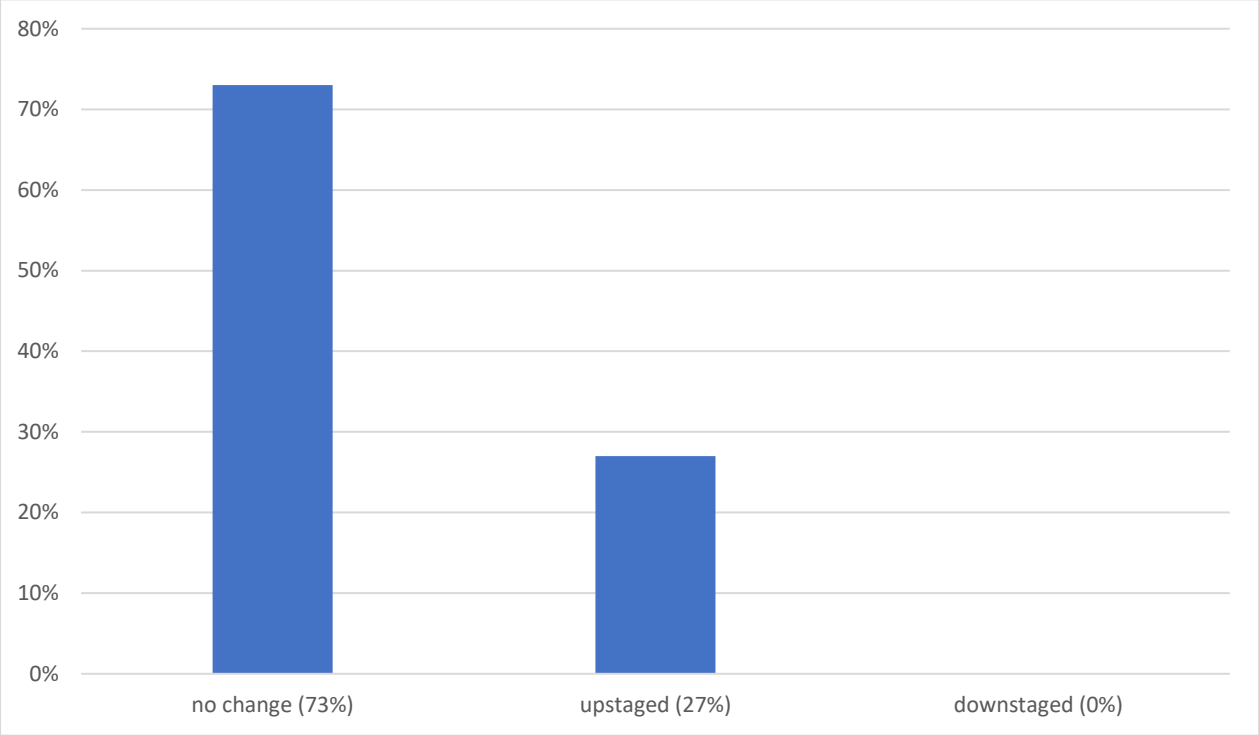
3.6 Initial TNM and group stages vs post 18F-FDG PET/CT TNM and group stages

3.6.1 T stage:

Table 7 indicates the initial T stages determined using CT staging vs the post 18F-FDG-PET/CT T stages with the magnitude and percentage of change. Figure 5 is a graphical representation of changes in T stage post 18F-FDG PET/CT.

Table 7: Initial T stages vs post 18F-FDG PET/CT T stages

Initial T Stage (prior to 18F-FDG-PET/ CT) (i)	**Post 18F-FDG-PET/CT T Stage (p)**	**Magnitude of Stage Change (i-p) (∆)**	**Frequency**	**Outcome (%)**	**Overall Outcome for each initial stage (%)**	**Overall Outcome for T-Staging (%)**
T1	T1	0	1	No Change (100)	No Change (100)	
	Total		1			
T2	T2	0	1	No Change (50)	No Change (50)	No Change 24 (73)
	T3	+1	1	Upstage (50)	Upstage (50)	
	Total		2			
T3	T3	0	21	No Change (91)	No Change (91)	Upstage 9 (27)
	T4	+1	1	Upstage (4)	Upstage (8)	
	T4b	+1	1	Upstage (4)		
	Total		23			
T4a	T4a	0	1	No change (14)	No change (14)	
	T4b	+b	6	Upstage (86)	Upstage (86)	
	Total		7			
Overall Total			33			



All upstaged T stage participants had a SCC histology.

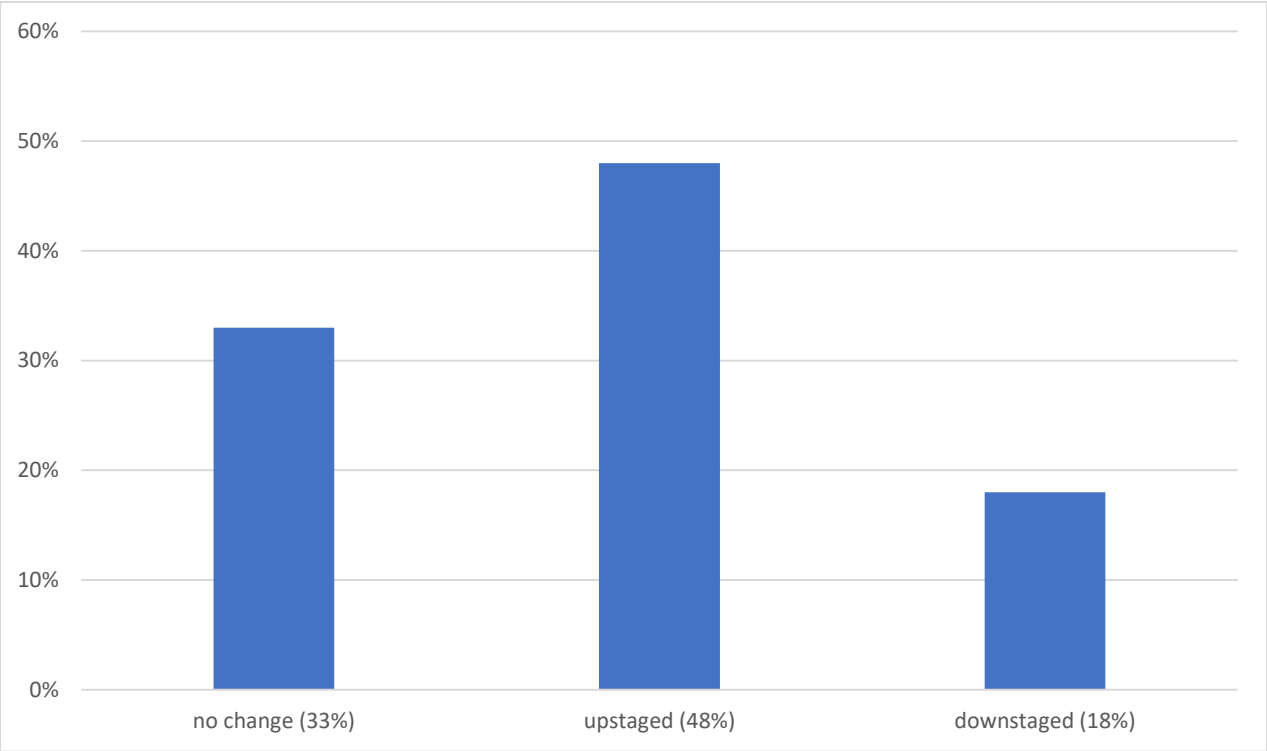
Figure 5: changes in T stage post 18F-FDG PET/CT.

3.6.2 N stage:

Table 8 indicates the initial N stages determined using CT staging vs the post 18F-FDG-PET/CT N stages with the magnitude and percentage of change. Figure 6 is a graphical representation of changes in N stage post 18F-FDG PET/CT.

Table 8: Initial N stages vs post 18F-FDG PET/CT N stages

Initial N Stage (prior to 18F-FDG-PET/CT) (i)	**Post 18F-FDG-PET/CT N Stage (p)**	**Magnitude of Stage Change (i-p) (Δ)**	**Frequency**	**Outcome (%)**	**Overall Outcome for each initial stage (%)**	**Overall Outcome for N-Staging(%)**
N0	N0	0	3	No Change (42)	No Change (42)	No Change 11 (33)
	N1	+1	3	Upstage (8)	Upstage (58)	
	N2	+2	5	Upstage (33)		
	N3	+3	1	Upstage (17)		
	Total		12			
N1	N1	0	1	No Change (17)	No Change (17)	Upstage 16 (48)
	N2	+1	3	Upstage (50)	Upstage (83)	
	N3	+2	2	Upstage (33)		
	Total		6			
N2	N0	-2	1	Downstage (14)	Downstage (14)	Downstage 6 (18)
	N2	0	4	No Change (57)	No Change (57)	
	N3	+1	2	Upstage (29)	Upstage (29)	
	Total		7			
N3	N1	-2	2	Downstage (24)	Downstage (62)	
	N2	-1	3	Downstage (38)		
	N3	0	3	No Change (38)	No Change (38)	
	Total		8			
Overall Total			33			



All upstaged and downstaged N staged participants had a SCC histology.

Figure 6: Changes in N stage post 18F-FDG PET/CT.

3.6.3 M stage:

Table 9 indicates the initial M stage determined using CT staging, bone scan and ultrasound reports vs the post 18F-FDG-PET/CT M stage with the magnitude and percentage of change. Figure 7 is a graphical representation of changes in M stage post 18F-FDG PET/CT.

Table 9: Initial M stages vs post 18F-FDG PET/CT M stages

Initial M Stage (prior to 18F-FDG-PET/CT) (i)	**Post 18F-FDG-PET/CT M Stage (p)**	**Magnitude of Stage Change (i-p) (∆)**	**Frequency**	**Outcome (%)**	**Overall Outcome for each initial stage (%)**	**Overall Outcome for M-Staging (%)**
M0	M0	0	20	No Change (66)	No Change (66)	No Change 23 (70)
	M1	+1	8	Upstage (34)	Upstage (34)	
	Total		28			Upstage 8 (24)
M1	M0	-1	2	Downstage (40)	Downstage (40)	Downstage 2 (6)
	M1	0	3	No Change (60)	No Change (60)	
	Total		5			
Overall Total			33			

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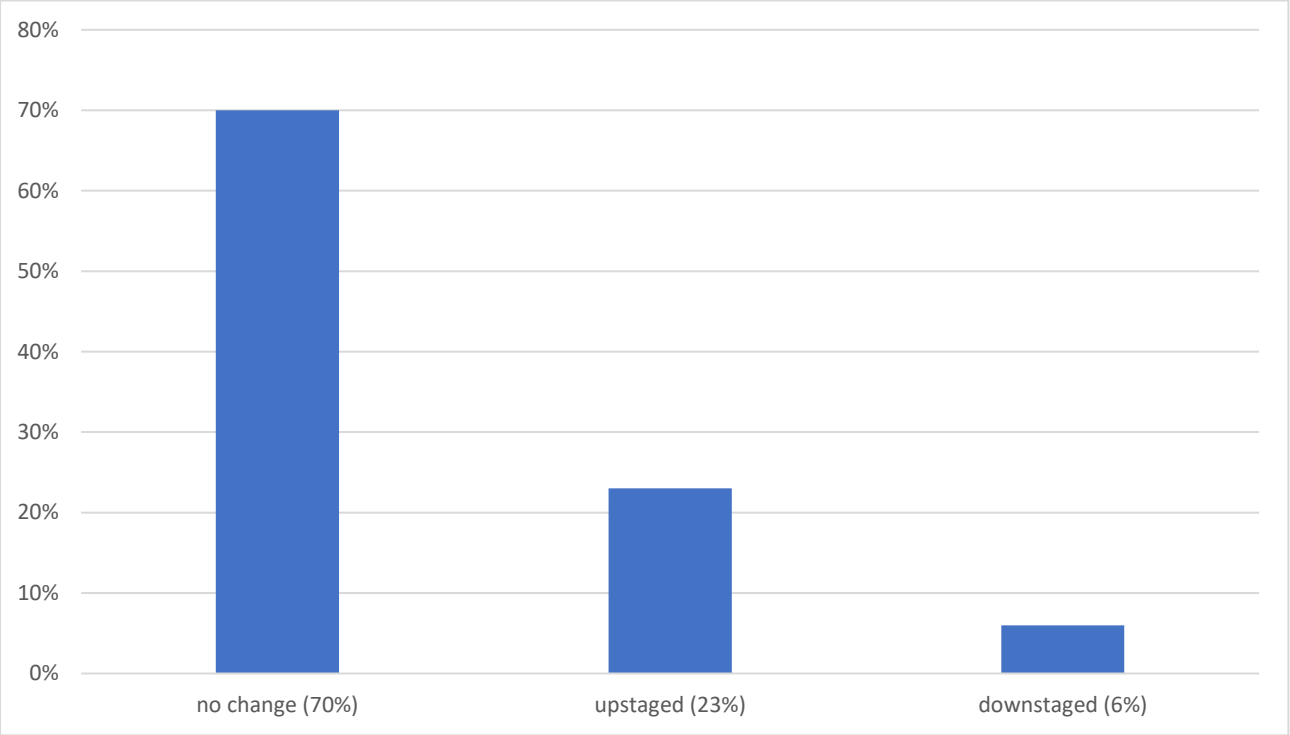

Figure 7: Changes in M stage post 18F-FDG PET/CT

Sites of distant metastases:

Table 10 shows the sites of distant metastases in patients upstaged. Eight (24%) of the study patients showed uptake in different sites on 18F-FDG PET/CT suggesting a site of distant metastases not detected on initial staging investigation/s. The sites comprised of lung (4), liver (3) and bone (1). Unfortunately, data was not available if these lesions were biopsied or not to confirm a metastatic lesion. Two (6%) of study participants were downstaged to M0 disease. The sites of downstaging were lung (1) and ascites (1)

Table 10: Sites of distant metastases in patients upstaged.

Site	**Number of patient's**	**Percentage of patient's**
Lung	4	12
Liver	3	9
Bone	1	3
Total	8	24

Histological subtype of patients with change in M stage:

Figure 8 shows the histological subtypes for patients with no change and changes in the M stage. Of the 8 (23%) study participants with an upstage of M stage, 7 (21%) had a SCC histology and 1 (2%) an AC histology. Of the patients with a downstage in M stage, all 2 (6%) participants had a SCC histology.

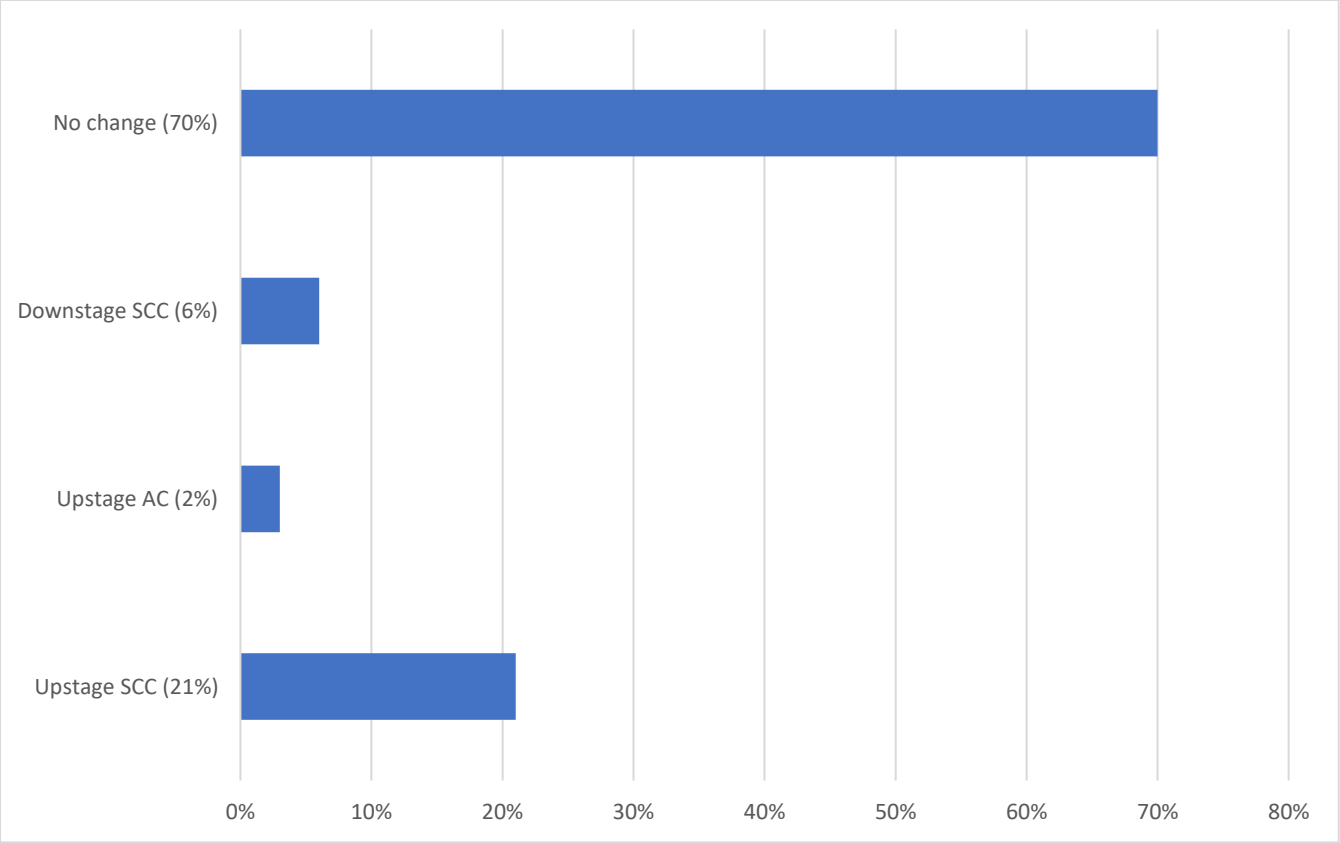

Figure 8: Different histological subtype changes in M stage post 18F-FDG PET/CT.

3.6.4 Group stage:

Table 11 indicates the initial group stage determined using CT staging, bone scan and ultrasound reports vs the post 18F- FDG-PET/CT group stage with the magnitude and percentage of change. Figure 9 is a graphical representation of changes in group stage post 18F-FDG PET/CT and figure 10 is a graphical representation of the different histological subtype changes in group stage post 18F-FDG PET/CT.

Table 11: Initial group stages vs post 18F-FDG PET/CT group stages

Initial Group Stage (prior to 18F-FDG-PET/CT) (i)	Post 18F-FDG-PET/CT Group Stage (p)	Magnitude of Stage Change (i-p) (Δ)	Frequency	Outcome (%)	Overall Outcome for each initial stage (%)	Overall Outcome for Group-Staging (%)
1	1	0	1	No Change (100)	No Change (100%)	
	Total		1			
2	2	0	2	No Change (20)	No Change (50)	No Change 17 (52)
	3	+1	3	No Change (30)		
	4a	+2	2	Upstage 20)	Upstage (50)	
	4b	+2	3	Upstage (30)		
	Total		10			
3	3	0	6	No Change (75)	No Change (75)	Upstage 10 (30)
	4b	+1	2	Upstage (25)	Upstage (25)	
	Total		8			
4a	3	-1	2	Downstage (29)	Downstage (29)	Downstage 6 (18)
	4a	0	2	No Change (29)	No Change (29)	
	4b	+b	3	Upstage (42)	Upstage (42)	
	Total		7			
4b	3	-1	1	Downstage (14)	Downstage (57)	
	4a	-	3	Downstage (43)		
	4b	0	3	No Change (43)	No Change (43)	
	Total		7			
Overall Total			33			

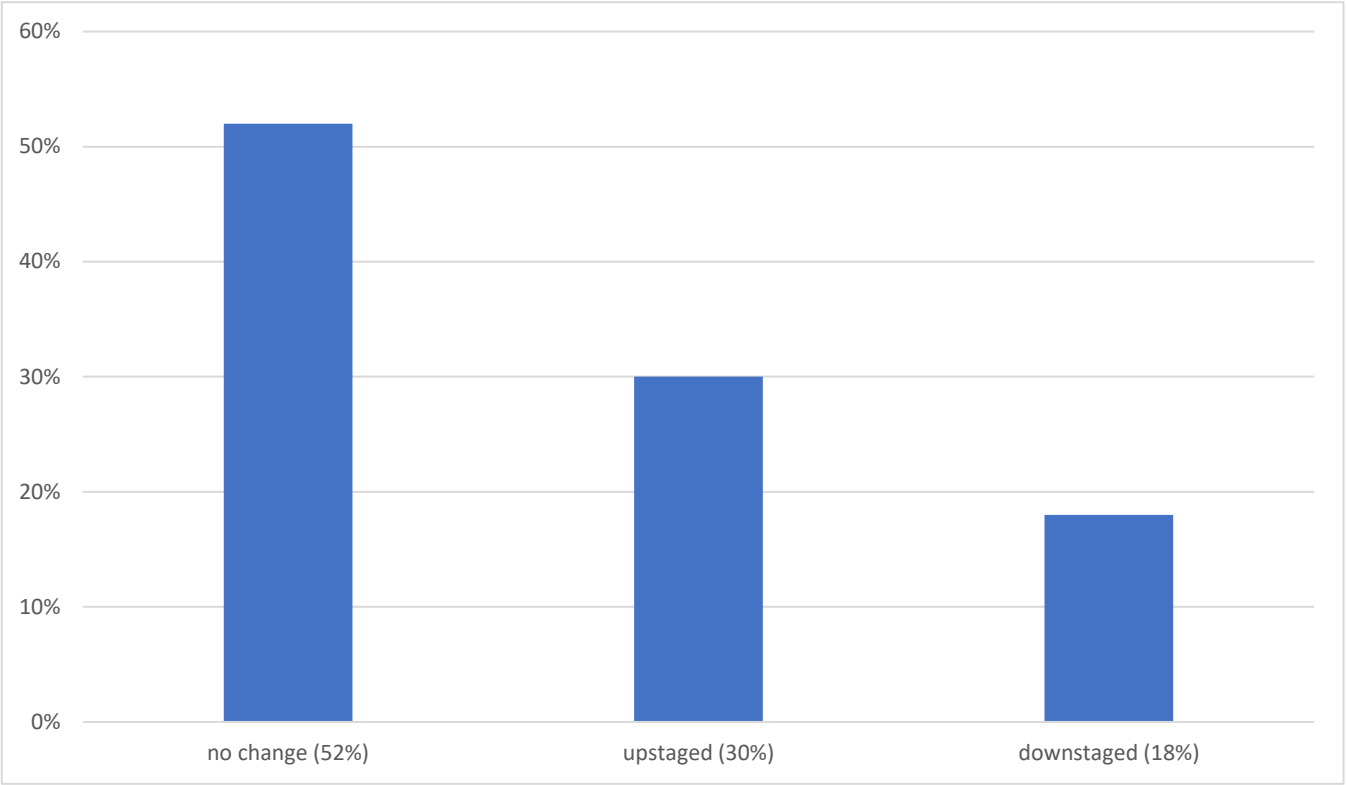

Figure 9: Changes in group stage post 18F-FDG PET/CT.

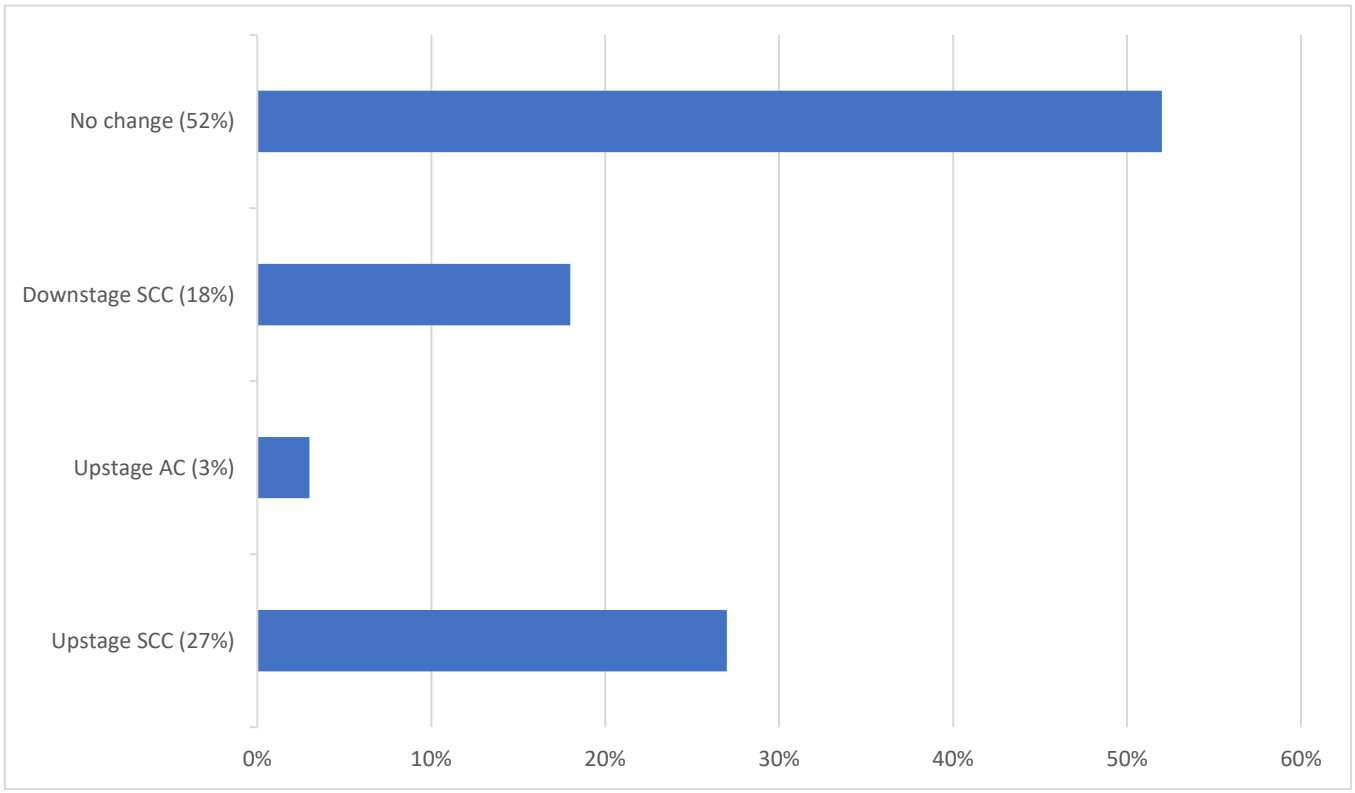

Figure 10: Different histological subtype changes in group stage post 18F-FDG PET/CT.

3.7 Other 18F-FDG PET/CT information

3.7.1 Potential synchronous oesophageal lesions:

There was no uptake on FDG PET/CT in any of the patients, indicating a synchronous oesophageal primary.

3.7.2 Potential secondary primaries:

Table 12 shows the potential sites of secondary primaries picked up by 18F-FDG PET/CT. Four (12%) of the study patients showed uptake in different sites on FDG PET/CT suggesting potential secondary primaries. The sites comprised of lung (2), adrenal (1) and ovary (1). All these study participants had a SCC histology. Unfortunately, data was not available if these lesions were biopsied or not to confirm secondary primaries.

Table 12: Sites of potential secondary primaries

Site	**Number of patient's**	**Percentage of patient's**
Lung	2	6
Adrenal	1	3
Ovary	1	3
Total	4	12

CHAPTER FOUR: DISCUSSION

The primary aim of the study was to establish if there is a discordance between the initial TNM and group stage and post 18F-FDG PET/CT TNM and group stage in patients referred for radiation therapy at CMJAH. The secondary aim was to determine if 18F-FDG PET/CT can detect additional information such potential secondary cancers. To the best of the authors' knowledge this is the first study of this nature conducted in South Africa.

During the study period, 415 files of patients diagnosed with oesophageal cancer were reviewed. Of the 415 patients only thirty- three (33) patients met the inclusion criteria for the study. The most common reason for patients not being able to meet the inclusion criteria was that an initial staging 18F-FDG PET/CT was not done. It was also noted that 18F-FDG PET/CT was performed more frequently in the second 5 years of the study.

Possible reasons as to why FDG PET/CT not done/done sparsely in the first 5 years of the study include:

1) Only one PET/CT available at CMJAH thus causing long waiting times to scan and delaying management.
2) Non availability of PET/CT due to machine breakdowns.
3) Physician unawareness of 18F-FDG PET/CT in staging oesophageal cancer thus leading to underutilization.

Possible reasons as to why 18F-FDG PET/CT was done more often in the second 5 years of the study include:

1) Availability of PET/CT without often machine breakdowns.
2) Shorter waiting times to PET/CT as priority given to oncology patients.
3) Physician awareness of utilization of 18F-FDG PET/CT in staging oesophageal cancer.

4.1 Age

In this study, the standard deviation of patients reviewed is 61.4 ± 10.8 (95% CI 57.6-65.1). The median age is 60.5 (Interquartile range 52.8 – 68.5). Advanced age is considered a risk factor for oesophageal cancer particularly SCC of the oesophagus (1,4). The age distribution in this study is similar to studies performed in the South African context, confirming that the prevalence of oesophageal cancer increases with age to peak in the seventh decade (1,3,4).

4.2 Gender

In this study, twelve (36%) of the 33 participants were females, while 21 (64%) were males. This is in keeping with studies showing that oesophageal cancer has a male preponderance (1, 3, 4, 8, 15). In sub-Saharan Africa, the reported male to female ratio is 2:1 (4). The ratio was 1.7:1 in our study and this could be due to the small study population recruited with possible under representation of males.

4.3 Histology

In this study, the histology of 31 (93.9%) patients was squamous cell carcinoma, while that of 2 (6.1%) patients was adenocarcinoma. SCC is the commonest histological subtype in LMICs (3,5). Studies performed in the South African context have also confirmed SCC to be the commonest histological subtype seen in patients diagnosed with oesophageal cancer (1,3,4).

4.4 Sites of primary

In this study, four (12%) patients have a primary site of cervical oesophagus, 26 (79%) of thoracic oesophagus and 3 (9%) of OG junction. As per literature oesophageal SCC tends to localize at or higher than the tracheal bifurcation and oesophageal AC affecting the mid to lower oesophagus (6). As most of our patients have disease of the thoracic oesophagus, this is in keeping with

the commonest histological subtype of SCC, which usually localizes to the proximal oesophagus. 93.9% (31 participants) of our patients had SCC of the oesophagus and 6.1% (2 participants) had AC. Our data showed that 1 (3%) patient had an adenocarcinoma of the cervical oesophagus and 2 (6%) patients a SCC of the OG junction. The reason for this tendency is unknown.

This study found a few discordant findings between initial staging investigations and 18F-FDG PET/CT findings in the cohort of patients investigated.

4.5 Initial T stages vs Post 18F-FDG PET/CT T stages

In this study only 27% of patients had an upstaged T stage, with the majority (73%) having “no change” of the T stage. 18F-FDG PET/CT has a limited use in upstaging the T stage after CT Staging, and its role of 18F-FDG PET/CT is of value when disease of the primary is insufficient following EUS and CT (12). CT itself has limited value for depth of invasion due to poor soft tissue resolution (8). The investigation of choice for assessing T stage is EUS (7). Unfortunately, none of our patients had an EUS done as part of prestaging evaluation as equipment was not available to perform the investigation. In this study, the most common reason for upstaging of T staging was from T4a to T4b with possible airway invasion on FDG PET/CT.

Literature indicates that co-registration of 18F-FDG PET/CT to planning CT may assist with target volume/s (11,14,15). Co-registration of 18F-FDG PET/CT was used to assist in delineation of volumes in patients for definitive radiotherapy in our study. Fusion may assist to delineate gross disease and minimise dose to organs at risk. As organs at risk (airway, heart, and lung) are in close proximity to the oesophagus, it is imperative to adequately delineate tumour volume.

4.6 Initial N stages vs Post 18F-FDG PET/CT N stages

Nodal staging is an important prognostic factor (15) in oesophageal cancer and is required for proper radiation planning. The findings from this study demonstrated that 18F-FDG PET/CT can potentially play an important role in nodal staging: 48.4% of patients were upstaged, 18.1% were downstaged and

33.3% had “no change” in nodal staging. Adequate nodal staging is required to determine intent of treatment (12,15). Upstaging of nodal status is important for radiation planning because gross nodal disease must be taken to a definitive dose to ensure curability. Similarly, non-pathological nodes can be subjected to a lower dosage to reduce toxicity to organs at risk surrounding radiated volumes, thus decreasing long term sequelae of radiation-based treatment. As EUS was not available at our centre, none of these avid nodes picked up on 18F-FDG PET/CT were biopsied to confirm malignancy.

There is variation amongst studies with regards to the accuracy of 18F-FDG PET/CT for detecting regional nodal disease (2,7,10,11). 18F-FDG PET/CT has a higher specificity than CT for detecting nodal involvement but a lower sensitivity than CT and EUS (7,15). Some literature suggests that there is no advantage of 18F-FDG PET/CT over EUS in assessing locoregional nodes (14). Most studies reasonably conclude that avid nodes on 18F-FDG PET/CT are likely to contain active disease if lying in the usual drainage pattern of the primary lesion (7,10). Parameters such as SUV, MTV and total lesion glycolysis can be used to evaluate metastatic nodal lesions (2). False positives can occur in patients with inflammation and infection particularly in a LMICs setting (2). A complementary mix of investigations of EUS, CT and 18F-FDG PET/CT is required to provide adequate nodal staging.

4.7 Initial M stages vs Post 18F-FDG PET/CT M stages

The most incremental value of 18F-FDG PET/CT is its ability to detect sites of distant metastases (12,14,15). This study found with the addition of 18F-FDG PET/CT, the M stage of 29% of patients changed: 23% were upstaged, 6% downstaged and the majority (70%) had “no change”. 18F-FDG PET/CT detected distant metastasis in the lung (12%), liver (9%), and bone (3%) which had not been identified during initial investigations. Of the 23% upstaged, 21% had a SCC histology and 2% an AC histological subtype.

Literature consistently shows that 18F-FDG PET/CT is more accurate than other imaging modalities for detecting distant metastases in patients

diagnosed with cancer of the oesophagus (12,14,15). 18F-FDG PET/CT can identify unsuspected metastatic disease in 5-30% of patients at initial diagnosis (15). In this study 23% of participants were upstaged to group stage 4B disease with the addition of 18F-FDG PET/CT. Patients with distant metastases have an overall poor prognosis (6) and are unlikely to benefit from definitive treatment. In this study, the patients upstaged to group stage 4B had treatment intent changed from definitive to palliative. In keeping with literature, the most common sites of distant metastases were lung, liver, and bone (14,15). Data was not available to confirm if these lesions were biopsied to confirm metastatic disease. However, these lesions were termed “highly suggestive” of a metastatic deposit as per report done by the Nuclear Medicine physician. Features of a metastatic lesion include a site typical for metastases from the primary lesion with similar FDG avidity of the primary lesion (16). Oesophageal SCC has a poorer prognosis with a higher affinity for metastatic spread than oesophageal AC (6). In this study a higher number of patients were upstaged with a SCC histology than AC histology, but due to the small sample size and under representation of AC histology in this study, it is difficult to draw any viable conclusions.

4.8 Initial Group stages vs Post 18F-FDG PET/CT Group stages

Overall, 18F-FDG PET/CT upstaged 30% of patients’ group stages, 18% downstaged and 53% had a “no change”. Patients nodal and distant metastases were the most important factors changing group stages. With the addition of 18F-FDG PET/CT, 48% of patients’ group stages were changed. These factors did change treatment intent (radical vs palliative treatment) and strategies (radiation planning volumes).

4.9 Other 18F-FDG PET/CT information

None of the patients reviewed showed synchronous oesophageal primaries on 18F-FDG PET/CT that had not been detected by initial staging investigations. Four (12%) of study patients had uptake in different sites on 18F-FDG PET/CT, suggesting potential secondary primaries. The sites included lung (2), adrenal (1) and ovary (1). 18F-FDG avid lesions are considered an occult

secondary primary if they occur at a site atypical for metastases from the primary lesion (16). Other features include that if there is a marked discordance in the FDG avidity of the primary site and there is no prior detection of the lesion on previous conventional imaging (16). These patients were referred to base specialities for further investigations (biopsy, surgery and further radiological investigations). Unfortunately, data was not available regarding the results of these investigations to confirm a secondary primary or a metastatic lesion as these patients did not return to the department for any radiation treatment. Differentials for this uptake include infection, inflammation, metastatic lesion, or a secondary primary.

Patients diagnosed with oesophageal SCC are more likely to have synchronous secondary primary tumours especially of the head and neck region due to the shared risk factors between the two primary lesions (2,12). In our study and in the LMICs setting, majority of the patients have a SCC histology subtype (3,4) and may benefit from a 18F-FDG PET/CT to exclude secondary primary lesions which may alter management.

4.10 Limitations of study

Since 18F-FDG PET/CT was not routinely performed for all patients, a small study population was recruited. 18F-FDG PET/CT is not routinely available in many hospitals, and long waiting periods for the investigation often cause treatment to be delayed. Other factors include non-availability of scan due to machine breakdowns and a period when the nuclear medicine department was closed due to an unfortunate circumstance, i.e. a fire during April 2021, resulting in closure of the Nuclear Medicine department for several months.

EUS was not performed as an initial investigation to assess T stage since it was not available at referral centres. Studies have shown the best investigation to assess T stage is EUS (2,7). T stages may not have been accurately determined on CT scan due to poor soft tissue delineation.

However, the most incremental findings of 18F-FDG PET/CT in this study, are the upstaging of nodal and distant metastases.

CHAPTER FIVE: CONCLUSION

There is substantial evidence that 18F-FDG PET/CT provides additional staging information not seen on initial conventional staging investigations (2,6,7,10,11,12,14,15,16,17). All patients for curative management (especially radiation-based therapy) for oesophageal cancer should have complementary staging modalities that include 18F-FDG PET/CT performed as an initial investigation (2,6,10,14).

Is there is a discordance between the initial TNM and group stage and post FDG PET/CT TNM and group stage in patients diagnosed with oesophagus cancer referred for radiation therapy at CMJAH during this study period?
The data from this study suggest that the additional use of 18F-FDG PET/CT changed a patient's TNM and group stages. The incremental value of the addition of FDG PET/CT was in the change of N and M stage and group stage. This impacted on treatment strategies and treatment intent.

Is additional information regarding potential secondary primaries identified on 18F-FDG PET/CT?
The data from this study show that 12% of study participants had uptake in different sites on 18F-FDG PET/CT, suggesting potential secondary primaries. Information was not available if these sites were biopsied to confirm a secondary primary.

As oesophageal cancer is a disease with an overall poor prognosis especially in the LMIC setting (3), it is important to adequately stage a patient to prevent over and/or undertreatment, especially in a resource constrained environment. Patients who are not for curative treatment can be identified early to institute palliative care and improve quality of life.

Although, the integration of functional imaging has greatly enhanced our understanding of oncological processes and provided insight into changing the landscape of management protocols, growth of PET/CT is constrained by cost,

infrastructure, and expertise, especially in the LMICs setting (17). As such, literature suggest the routine use of the utilization of 18F-FDG PET/CT in staging oesophageal cancers may not be achievable in the LMICs setting (17).

Further studies on a larger scale are required to confirm the incremental staging value that 18F-FDG PET/CT could have in staging cancer of the oesophagus in the LMICs setting.

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APPENDICES

Appendix 1: Data sheet

DATA SHEET

1) Demographics

1.1) Study number ☐ 1.3) Age: ☐

1.2) Gender: Male ☐
Female ☐

2) Histology

2.1) Squamous cell carcinoma ☐ 2.3) Adenosquamous ☐
2.2) Adenocarcinoma ☐ 2.4) Other ☐

3) Site of primary

3.1) Cervical oesophagus ☐ 3.3) Abdominal oesophagus ☐
3.2) Thoracic oesophagus ☐ 3.4) Oesophago-gastric junction ☐

4) Initial group stage

4.1) T stage: ☐
4.2) N stage: ☐
4.3) M stage: ☐
4.4) Group stage: ☐

5) Post FDG-PET/CT group stage

5.1) T stage: ☐
5.2) N stage: ☐
5.3) M stage: ☐
5.4) Group stage ☐

6) Outcome

6.1)Upstaged ☐ 6.3) No change ☐
6.2)Downstage ☐ 6.4)Indeterminate ☐

7) Other FDG-PET/CT information

7.1) Synchronous oesophageal lesions: Yes ☐ No ☐

7.2) Potential secondary primaries: Yes ☐ No ☐ Site/s**:** _____

Appendix 2: Permission from CEO CMJAH

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL (CMJAH)
OFFICE OF THE SENIOR CLINICAL MANAGER

Enquiries: Ms N. Mzila
Email: Nolwazi.Mzila@gauteng.gov.za
Tel: 011 488 3365
Ref: 1/7/2
Date: 04 November 2022

GP_202207_106

Dr Muhammed Ahmed Sadeck Bapeekee

RE: FINAL APPROVAL OF STUDY

TITLE: A RETROSPECTIVE STUDY IN THE UTILIZATION OF 18F-FDG PET/CT IN STAGING OESOPHAGUS CANCER AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL (2012-2021)

Permission is granted for you to conduct the above-mentioned study as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not in any way incur or inherit costs as a result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall always be observed.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or Sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported/~~Not Supported~~

Signed by:Jayshlina Punwasi
Signed at:2022-11-07 07:20:06 +02:00
Reason:Witnessing Jayshlina Punwasi

Dr J. Punwasi
Senior Clinical Manager

Approved/~~Not Approved~~

Signed by:Gladys Magugudi Bogoshi
Signed at:2022-11-07 07:37:04 +02:00
Reason:Witnessing Gladys Magugudi Bo

Ms. G Bogoshi
Chief Executive Officer: CMJAH

Appendix 3: Ethics clearance

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Dr MAS Bapeekee

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220920

NAME: (Principal Investigator)	Dr MAS Bapeekee
DEPARTMENT:	School of Clinical Medicine Department of Radiation Sciences Division of Radiation Oncology Medical School University
PROJECT TITLE:	*A retrospective study in the utilization of 18F-FDG PET/CT in staging oesophageal cancer at Charlotte Maxeke Johannesburg Academic Hospital (2012-2021)*
DATE CONSIDERED:	2022/09/30
DECISION:	Approved unconditionally
CONDITIONS:	Previous condition (CEO approval) satisfied on 2022/11/21
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Drs K Phurboo and F Mohamed
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/10/12

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **September** and therefore reports and re-certification will be due in the month of **September** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator _____ Date _____

Appendix 4: Turn it in

mmed Bapeekee turnitin.docx

ORIGINALITY REPORT

13%	4%	11%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Wai Lup Wong. "Role of PET/PET CT in the staging and restaging of thoracic oesophageal cancer and gastro-oesophageal cancer: a literature review", Abdominal Imaging, 03/2008 Publication	2%
2	Chowdhury, F.U.. "The role of ^1^8F-FDG PET/CT in the evaluation of oesophageal carcinoma", Clinical Radiology, 200812 Publication	1%
3	worldwidescience.org Internet Source	1%
4	"EANM'14", European Journal of Nuclear Medicine and Molecular Imaging, 2014 Publication	1%
5	"EANM'16", European Journal of Nuclear Medicine and Molecular Imaging, 2016 Publication	1%
6	"EANM'15", European Journal of Nuclear Medicine and Molecular Imaging, 2015 Publication	1%