RISK FACTORS AFFECTING SURVIVAL FOLLOWING ONCOLOGIC ESOPHAGECTOMY AT KENYATTA NATIONAL HOSPITAL

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A Dissertation Submitted in Partial Fulfilment for The Award of Master of Medicine in Thoracic and Cardiovascular Surgery at The University of Nairobi

STUDENT'S DECLARATION

I, **Dr. George Kimani Kinyanjui**, do hereby declare that this dissertation is my original work and has not been presented for a degree or any other award in any other university

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DEPARTMENTAL APPROVAL

This dissertation was presented on 8th September, 2022, and approved by the Kenyatta National Hospital – University of Nairobi, Ethics and Research committee and hereby submitted for examination with my approval as the Chairman, Department of Surgery.

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LIST OF ABBREVIATIONS

AC-	Adenocarcinoma
AJCC-	American Joint Committee on Cancer
AHA-	American Heart Association
CTC-	Cancer Treatment Centre
CA-	Cervical Esophagogastric Anastomosis
EC-	Esophageal Cancer/Cancer of the Oesophagus
EGJ-	Esophagogastric Junction
HR-	Hazard Ratio
ILE-	Ivor Lewis Esophagectomy
KNH-	Kenyatta National Hospital
MKE-	McKeown Esophagectomy
OE-	Open Esophagectomy
POMR-	Perioperative Mortality Rate
SCC-	Squamous Cell Carcinoma
THE-	Transhiatal Esophagectomy
TA-	Thoracic Esophagogastric Anastomosis
UoN-	University of Nairobi

DEFINITION OF TERMS

Oncologic Esophagectomy: A surgical procedure in which part or the entire oesophagus is removed and replaced with a neo-oesophagus in patients with oesophageal cancer.

Independent Variable: A variable whose variation does not depend on that of another, and whose changes are assumed to have a direct effect on the dependent variable

Dependent Variable: Represents outcome being tested/ measured resulting from altering inputs (independent variables) e.g., death

Day-of-Surgery Death Ratio: Number of deaths on the day of surgery, irrespective of cause, divided by the number of surgical procedures in a given year or period, reported as a percentage.

Perioperative in-hospital death ratio: Number of deaths in the hospital following surgery, irrespective of cause, and limited to 30 days, divided by the number of surgical procedures done in a given year or period, reported as a percentage.

Number of surgical procedures done in an operating room per year: The absolute number of all surgical procedures, defined as the incision, excision, or manipulation of tissue that requires regional or general anaesthesia or profound sedation to control pain, undertaken in an operating room.

Event: The event is the response variable i.e., death after oncologic esophagectomy.

Time to Event/Serial Time: A variable that measures the duration from the intervention to the event that is defined by the status variable i.e., the time taken by the subject from the time of oncologic esophagectomy to the event of death, or when the subject is censored from the study. Time was measured in months.

Time of Enrolment: The time of the intervention i.e., the month when the oncologic esophagectomy was performed.

Survival:	2-year overall survival defined as the time from the surgery to the date of death, with patients still censored on the date of last follow-up (2-years).
Risk Factors:	Patient characteristics (age and sex), tumour characteristics (pathologic "T" stage, histological type, and location of tumour) and Therapeutic Approach (neoadjuvant therapy, adjuvant therapy and surgical approach).

ABSTRACT

Background: Globally, oesophageal cancer (EC) is the 6th most common cause of death and ranks 8th in the most commonly diagnosed cancers. Esophagectomy is the gold standard treatment for patients with only locally advanced resectable EC with neoadjuvant chemotherapy and radiotherapy as important adjuncts. Oncologic esophagectomy has been documented to carry one of the highest perioperative mortality rates of up to 57.8% with 2-year survival rates of 26% - 80%. Although Kenyatta National Hospital is classified as a medium to high volume centre in performing oncological esophagectomy, no data exists about the operation's overall survival.

Objectives: To determine the two-year survival following oncologic oesophagostomy performed in Kenyatta National Hospital, and to establish the risk factors affecting poorer survival as well as to establish the Perioperative Mortality Rate.

Methodology: This was a retrospective cohort study. The study cohort were all subjects that underwent oncologic esophagectomy during the ten-year period between 1st January 2011 and 31st December 2020. The main outcome variable was the observed 2-year overall survival of these patients. Exposure variables were the patient characteristics (age and sex), tumour characteristics (pathologic "T" stage, histological type, and location of tumour) and therapeutic approach (exposure to neoadjuvant or adjuvant therapy, surgical approach). Overall, two-year Survival was reported using Kaplan-Meir estimates. The log-rank test was used to evaluate significant differences in overall survival by different variables. The Perioperative Mortality Rate was calculated

Results: 90 subjects were selected for this study. The overall two-year survival rate was 53% (95%CI: 43%-66%). Women [overall 2-year survival 35% (95%CI:22%-56%)] had poorer two-year survival when compared to men [overall 2-year survival 70% (95%CI:57%-85%)]. Subjects who had their operation at Stage III-IVA [40% (95%CI:25%-63%)] had poorer survival when compared to those that presented at "TNM" Stage I-II [61% (95%CI:49%-76%)]. There was no significant difference in the two year survival probability in with age 60 and older [overall 2 year survival 56% (95%CI: 40%-78%)], squamous Cell Carcinoma [overall 2 year survival 53% (95%CI:42-66)], poorly differentiated tumours [overall 2 year survival 51% (95%CI:35%-75%)] tumour located in the lower third of the oesophagus [overall 2 year survival 57% (95%CI:45%-72%)], exposure to neoadjuvant [overall 2 year survival 54% (95%CI:41%-71%)] or adjuvant therapy [overall 2 year survival 51% (95%CI:35%-85%)], and

McKeown's approach [overall two year Survival of 51% (95%CI:36%-68%)]. Perioperative Mortality Rate was calculated to be 43.3%

Conclusion: The two-year survival following oncological esophagectomy in Kenyatta National Hospital is comparable to other centres globally and above the two-year actuarial survival rate. Female sex and late presentation may be a risk factor affecting two-year survival following oncological esophagectomy. Age, histological subtype, tumour grade and location, exposure to neoadjuvant or adjuvant therapy, and surgical approach may not affect the two-year survival following oncological esophagectomy.

1.0 CHAPTER ONE: INTRODUCTION

1.1 Background Information

In Kenya, cancer of the oesophagus (EC) ranks second as most frequently diagnosed cancer in men and 3rd in women (1,2). Internationally, EC comes in eighth in the most frequently diagnosed cancers. EC ranks as the sixth highest cause of mortality following malignancy with a five year survival rate of 15% - 25% in North America (1,2).

Squamous Cell Carcinoma (SCC) and Adenocarcinoma (AC) contribute to the bulk of these tumours with other histological subtypes of sarcomas, small-cell melanomas, carcinoid and lymphomas contributing to less than 2% of EC (1,2).

The 8th edition of American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) staging of epithelial cancers of the oesophagus and esophagogastric junction (EGJ) stages EC by the system tumour, node, metastasis (TNM)(3).

Esophagectomy is a surgical procedure in which part or the entire oesophagus is removed and replaced with a Neoesophagus in patients with EC (4).

Patients with locally advanced resectable EC typically receive esophagectomy as treatment, with neoadjuvant chemotherapy and radiotherapy as important adjuncts (4). Common perioperative complications following Oncologic esophagectomy include cardiac and pulmonary complications, anastomotic leaks and stricture, conduit stenosis , ischaemia and denervation, injury to recurrent laryngeal nerve, chylothorax, surgical site infections and death (5–11).

Oncologic esophagectomy has been documented to carry one of the highest perioperative mortality rates of up to 27.8%, (with a global average of 8.9%) and a two-year survival rate of 26% - 80.8% (5,6,12–20).

The major risk factors affecting perioperative mortality and survival in oncologic esophagectomy include patient characteristics (age, preoperative functional state, and exposue to neoadjuvant therapy), tumour characteristics (tumour stage, histological type, and tumour location) and operative characteristics (surgical approach, and perioperative complications) (6–8,13–15,21–23).

This study was targeted to ascertain the perioperative mortality rate and survival following oncologic esophagectomy performed in Kenyatta National Hospital over a ten-year period by proxy of in-hospital death ratio and two-year survival. We also wanted to work out whether some risk factors have poorer survival in our local population; these are patient characteristics (age >60yrs and sex), tumour characteristics (pathological “T” stage, histological type, and

location) and therapeutic characteristics (exposure to neoadjuvant or adjuvant therapy, surgical approach).

2.0 CHAPTER TWO: LITERATURE REVIEW

2.1 Cancer of the Oesophagus

2.1.1 Burden of Disease

Globally, EC ranks as the sixth highest cause of mortality following malignancy. It ranks 8th in the most commonly diagnosed cancers (1). The disease displays uneven geographical distribution, with some "hot spot" areas having very high incidences of EC (2,24). These include the countries in Eastern, Southern and Northern Africa as well as the expansive region coined the "Asian esophageal cancer belt" extending from Northeast China to the Middle East (2,24).

According to the Kenya Cancer registry, EC is the third most prevalent cancer in women and the second most prevalent cancer in men. (25). Local studies have found EC to be the third most typical cancer in women and the second most typical cancer in men with a 1.5:1 female to male ratio (26–28). This is in contrast to earlier work showing a male predominance of 8:1 with a peak incidence of the 4th decade (29).

EC carries a heavy toll in terms of mortality, with a documented five-year survival rate of 15% - 25% in America (30).

Squamous Cell Carcinoma (SCC) and Adenocarcinoma (AC) are frequent histological subtypes of EC (SCC)(1,2). Other subtypes, such as the sarcoma and small-cell variety contribute to less than 1% - 2% of cancers of the oesophagus (1,2). Rarely, other variants such as melanomas, carcinoid and lymphomas, may arise in the oesophagus (1,2).

2.1.2 Pathophysiology of EC

SCC has comprised the majority of EC in the western world for most of the 20th century with a high incidence in developing countries (31). The prevalence of SCC as a whole rise with age, peaking in the seventh decade of life. In the middle and lower one-third of the oesophagus, its incidence is equal.(32). The major risk factors of SCC are smoking use and alcohol consumption. When both are consumed simultaneously, the relative risk of developing SCC is 149.2 in black men (32). It is speculated that high alcohol consumption decreases the metabolic rate of cells, decreasing their detoxification processes and increasing their oxidation (33). This causes cellular injury at the molecular level by damaging DNA. Tobacco has been found to have numerous carcinogens including phenols, polycyclic aromatic hydrocarbons, aromatic

amines, aldehydes, and nitrosamines (33).SCC has also been connected to other cancer causing agents, including nitrosamines, which are present in preserved foods like salted vegetables and smoked salmon. This pathology is attributed to dysplastic changes of the squamous epithelium leading to cellular metaplasia. (34)

In the past 40 years, adenocarcinoma incidence has increased, according to research. attributing this to the rising number of cases of Barrett's oesophagus (31). A major risk factor for developing Adenocarcinoma is long standing and untreated Gastroesophageal Reflux Disease (GERD), a condition where chronic inflammation of the mucosa may undergo metaplasia complicating into Barrett's oesophagus (35).

2.1.3 Staging of EC

The tumour, node, metastasis (TNM) system was employed in the 8th edition of American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) staging of epithelial cancers of the esophageal and esophagogastric junction (EGJ) (3). Included here were EGJ tumours whose epicentre extends within 2 cm into the stomach. Clinical (cTNM), post-neoadjuvant (ypTNM), pathologic (pTNM), all underwent separate staging. "T" focuses on the mural penetration of the oesophagus by the tumour. N characterises the nodal involvement while M outlines the presence or absence of metastasis to other tissues and organs. T stage is assessed via endoscopy and histology, N stage is assessed through endoscopic ultrasound and CT scan, M stage is assessed through PET Scan and CT scan. Laparoscopy and/or thoracoscopy are more invasive strategies which are at times employed to improve diagnostic accuracy of the non-invasive methods (3).

Due to the lack of endoscopic ultrasonography and PET that are employed in more resourceful centres, the decision about the resectability of esophageal malignancies in KNH is primarily based on the surgeons' interpretation of CT scans for diagnosis and planning of appropriate therapeutic approach.

CT is used to characterise the tumour (including its extents in the oesophagus, degree of luminal narrowing), assess the nodal status, and classify loco-regional spread to surrounding structures. CT is also used to screen for distant metastasis.

A tumour is deemed unresectable if distant metastasis is detected (brain, liver, adrenals, bone) or if the tumour invades the neighbouring structures (aorta, vertebral bodies or airway). Also, loss of dissecting/fat planes between the oesophagus and the pericardium, pleura, azygous vein, diaphragm or peritoneum preclude any attempt at tumour resection in our institution.

Relative contraindications to esophagectomy include advanced cardiopulmonary diseases and poor physical status as defined by the ASA assessment.

2.1.4 Surgical Management of Resectable EC

Patients with only locally advanced resectable EC typically receive esophagectomy as treatment, with neoadjuvant chemotherapy and radiotherapy as important adjuncts (4). There has been an increased use of Endoscopic approaches to definitive therapy for superficial EC with its role limited to Cis and T1No disease (argon plasma coagulation [APC], laser therapy, photodynamic therapy [PDT], and endoscopic resection [ER]) (36).

2.2 Oncologic Esophagectomy

2.2.1 Introduction

Oncologic esophagectomy is a surgical procedure in which part or the entire oesophagus is removed and replaced with a neoesophagus in patients with EC. It continues to be the industry standard for treating locally advanced resectable EC (4,11,37,38). However, its role as the solo first line therapy was challenged by advocates for esophagectomy following neoadjuvant chemotherapy, solely or in combination with radiotherapy, in the Neoadjuvant chemo-radiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS) trial (4,11,37,38).

The choice of conduit for the neo-oesophagus can be the stomach, jejunum or colon, each with its own unique advantages (4,11).The stomach is the preferred conduit locally, since it can be mobilised rather easily to reach the neck and requires just one anastomosis.(39,40).

Common perioperative complications following Oncologic esophagectomy include cardiac and pulmonary complications, anastomotic leaks and stricture, conduit stenosis, ischaemia and denervation, injury to recurrent laryngeal nerve, chylothorax, surgical site infections and death (5–11).

Contraindications to oncological esophagectomy include extra regional lymph node spread (e.g., para-aortic or mesenteric lymphadenopathy), poor functional performance scores, and presence of metastasis to the lung, peritoneum, adrenal glands, liver, brain or bones (11).

2.2.2 Types of Esophagectomy

Common Surgical approaches to esophagectomy include; Minimally Invasive Esophagectomy (MIE), Hybrid Minimally Invasive Esophagectomy and Traditional Open Esophagectomy (OE).

OE can further be divided into esophagectomy with a thoracotomy or esophagectomy without a thoracotomy. Common techniques of OE are Ivor - Lewis two stage gastro-esophagectomy (laparotomy and right thoracotomy), modified McKeown three stage / tri-incisional esophagectomy (Right sided posterolateral thoracotomy, midline laparotomy and a cervical incision), Transhiatal esophagectomy (laparotomy and cervical incision), and left sided thoracoabdominal esophagectomy (left thoraco-laparotomy) (11).

Because it allows for resection of middle and lower third tumours as well as extensive lymph node resection, direct visualisation of the intrathoracic dissection, and avoidance of an intrathoracic anastomosis, the modified McKeown three stage/ tri-incision esophagectomy is preferred in our setting. (40) The technique begins with the mediastinal phase where a standard right posterolateral thoracotomy is made with entry into the 5th - 7th intercostal space, depending on the tumour location. The tumour is identified and the oesophagus mobilised from its proximal attachment to the stomach. A chest drain is introduced and the thoracotomy is closed. In the abdominal phase of this esophagectomy, the patient is repositioned supine for a midline laparotomy. It involves mobilisation and tubulirisation of the gastric conduit with kocherization of the duodenum, followed by pyloroplasty and insertion of a jejunostomy feeding tube. The cervical phase involves a neck incision anterior to the sternocleidomastoid, through which the cervical oesophagus is mobilised followed by the fashioning of a cervical esophagogastric anastomosis (11).

Thoracic and esophagogastric junction (EGJ) esophageal tumours can be removed with transhiatal esophagectomy, which avoids a thoracotomy. It is performed through an upper midline laparotomy incision and a left neck incision, without a thoracotomy. The abdominal phase involves an upper midline laparotomy for the transhiatal dissection of the thoracic oesophagus and also to mobilise the stomach. In cervical phase, a neck incision anterior to the sternocleidomastoid is made through which the cervical oesophagus is dissected and freed from the trachea and then mobilised down to the level of the carina. The mobilised cervical and thoracic oesophagus is exteriorised through the neck incision and divided. From the laparotomy, the stomach and thoracic oesophagus are delivered followed by tubulirisation of the gastric conduit. Next, the neoesophagus is manually manipulated caudally via the laparotomy incision through the hiatus and the posterior mediastinum to reach the neck. A cervical esophagogastric end to end anastomosis is then fashioned (11,17,41).

Targeting tumours of the lower and middle one-third of the oesophagus, Ivor Lewis esophagectomy is performed via right thoracotomy and an upper midline laparotomy. It begins with an abdominal phase where a midline laparotomy is performed for mobilisation of the

gastric conduit, followed by pyloroplasty and insertion of a feeding option, commonly a jejunostomy feeding tube. The laparotomy is closed, the patient positioned in the left lateral decubitus position for a right sided thoracotomy. The oesophagus and node are dissected en-block from the cervical part to the stomach. The oesophagus is resected proximally. Next, the stomach is pulled through the diaphragmatic hiatus into the mediastinum where it is detached from the distal oesophagus (with systemic lymph node dissection) and tubularized. A thoracic esophagogastric anastomosis is fashioned, chest drains introduced and the thoracotomy closed (11).

When compared to McKeown three stage esophagectomy, the Ivor Lewis technique is linked with fewer occurrences of perioperative morbidity manifestations such as a fewer pulmonary complications, more ventilator free days, less surgical site infections and fewer incidences of anastomotic leaks (11,42,43).

A MIE performed by a right sided Video assisted thoracoscopy, upper abdominal laparotomy and completed with a cervical incision. Although it requires specialised equipment and technical training, when compared to OE, MIE has been shown to have fewer perioperative complications with similar survival but is limited to M0 and N0. (5,6,22,43,44).

2.2.3 Mortality and Survival Following Esophagectomy

Depending on the surgical approach, oncologic esophagectomy has an established five year survival rate of 15% to 62%, three year survival rate of 26.7 - 62%, a two year survival rate of 26% - 80.8% as summarised in Table A (6–8,13–15,21–23).

Brumeister BH et. al. examined the risk factors affecting overall survival following oncologic esophagectomy. In their 2005 paper, they documented that patients with poorly differentiated tumours, patients with lower third esophageal tumours, patients with tumours with non-squamous histology and patients aged 60 years and older showed both decreased overall survival and decreased disease free progression when compared to patients with well differentiated tumours, patients with tumours in the upper and mid oesophagus, patients with tumours with squamous histology and patients aged less than 60 years respectively.(Table B) (45)

Patients who have esophagectomy when they have an early diagnosis of the condition live longer than those who receive esophagectomy when they have a late diagnosis.(23).

Patients have higher survival rates when Transhiatal esophagectomy is performed for tumours in the distal oesophagus compared to those performed for tumours in the mid oesophagus (23).

Some studies show a 18% reduction in all cause three- year survival after minimally invasive esophagectomy as compared to open esophagectomy (hazard ratio 0.82,95%CI 0.76–0.88). The five-year survival is also lower by 18% in the MIE group as compared to the OE group (hazard ratio 0.83, 95% CI 0.76–0.89). Disease specific three-year mortality shows a 16% decrease in the MIE group compared to the OE group in meta-analysis (7).

On the other hand, other studies of MIE techniques did not show a decrease in five-year survival when compared to OE (HR 0.92; 95% CI 0.72 -.1176; P = 0.505) with similar survival of 46.6 months for the MIE group and 48.7 months for the OE group (5,6,22,44).

There is evidence that oncologic esophagectomy has one of the highest perioperative mortality rates, reaching up to 28.9% locally and internationally (5,6,12–20,40).

Thirty-day mortality does not differ much when comparing esophagectomy with thoracic esophagogastric anastomosis (14.3%) with those of cervical esophagogastric anastomosis (9.3%) (10). Both cohorts have similar median survival time, 20 months for thoracic anastomosis, and 23 months for cervical anastomosis (10,11,13,18,46,47).

Postoperative complications have a significant impact on mortality after esophagectomy. Of these, ARDS (odds ratio 7.48) re-intubation (odds ratio 6.55), renal failure (odds ratio 5.9), central neurological event, Myocardial infarction, ventricular arrhythmia, and reoperation for bleeding has the strongest association with operative mortality following esophagectomy (odds ratio between 4.0 - 7.5). (9,48) A local study observed a Cervical Esophagogastric anastomotic leak (CEGAL) incidence of 21% of which 12% required surgical intervention but there was no association between CEGAL and operative mortality (39,40).

When esophagectomy is performed in high volume centres (more than 20/year), both morbidity and mortality significantly drop when compared to medium (more than 11 - 20/year) and low volume centres (more than 5 -10/year). Median mortality rates of 4.9% in high volume centres vs median mortality rates of 13.8% in low volume centres have been observed (49,50). Other studies have found no significant association between a hospital's inpatient mortality with its surgical procedure volume (8).

Table 1:Perioperative Mortality rate, and Survival Rate following Oncologic Esophagectomy

Reference	Sample Size	Study Type	Perioperative Mortality Rate (POMR)	2- year survival rate	3 - year survival rate	5 - year survival rate
CROSS TRIAL (2015) (37)	368	RCT				Neoadjuvant + Surgery 47%Surgery Alone 34%
Lee et al. 2004 (51)	101	RCT		Neoadjuvant + Surgery 57% Surgery Alone 55%		
Urba et al. 2001 (52)	100	RCT			Neoadjuvant + Surgery 30% Surgery Alone 16%	
Tepper et al. 2008 (53)	575	RCT				Neoadjuvant + Surgery 39% Surgery Alone 16%
Walsh et al. 1996 (54)	113	RCT		Neoadjuvant + Surgery 37% Surgery Alone 26%	Neoadjuvant + Surgery 32% Surgery Alone 6%	
Nygaard et al. 1992 (55)	186	RCT				Neoadjuvant + Surgery 45.5% Surgery Alone 25%
Yang et al. 2021 (56)	451	RCT			Neoadjuvant + Surgery 65.8% Surgery Alone 57.8%	Neoadjuvant + Surgery 59.9% Surgery Alone 49.1%
Le Prise et al. 1994 (57)	86	RCT			Neoadjuvant + Surgery 46.6% Surgery Alone 46.7%	
Bosset et al. 1997 (58)	297	RCT		Neoadjuvant + Surgery 49% Surgery Alone 32%		
Finks et al. 2011 (20)	8719	Retrospective	8.9%			
Sabra et al. (2020) (42)	6136	Retrospective	CA - 2.26% TA - 2.75%			
(Schieman et al. (2012) (12)	1522	Retrospective	2.3% - 3.3%			
Mitzman et al.(2017) (22)	977	Retrospective	2.9%		57.6%	
Rao et al. 2002 (17)	411	Prospective	CA - 6%	54%		38%
Chasseray et al. (1989) (18)	123	Prospective	TA - 14.3% CA - 9.3%	47%		
Braghetto et al. (2006) (5)	119	Retrospective	CA - 10.1% TA - 11.6%		CA - 30% TA - 33.9%	
Smithers et al. (2007) (59)	114	Prospective	2.6%			
Walther et al.(2003) (14)	112	Prospective	TA - 1.8% CA - 1.8%			TA - 29% CA - 30%
Okuyama et al. (2007) (15)	32	Prospective	TA - 7% CA - 17%			85.7%

Reference	Sample Size	Study Type	Perioperative Mortality Rate (POMR)	2- year survival rate	3 - year survival rate	5 - year survival rate
Swanson et al. (2001) (60)	342	Retrospective	3.6%		44%	
Lada et al. (2018) (21)	471	Prospective				30% - 47%
Visbal et al. (2001) (61)	220	Retrospective	1.4%			25.2%
Ogendo (2005) (40)	201	Retrospective	28.9%			

TA – Thoracic esophagogastric Anastomosis CA - Cervical esophagogastric Anastomosis

Table 2:Univariate analysis of survival following esophagectomy

	n	Progression-free survival		Overall survival	
		Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Chemoradiotherapy and surgery *vs* surgery alone	128/128	0·82 (0·61–1·10)	0·18	0·89 (0·67–1·19)	0·44
Men *vs* women	206/50	1·28 (0·86–1·90)	0·22	1·36 (0·93–1·99)	0·11
Performance status 1 *vs* 0	84/172	1·24 (0·91–1·70)	0·18	1·26 (0·93–1·70)	0·14
Lower oesophageal tumour *vs* middle or upper	203/53	2·11 (1·37–3·24)	0·001	1·50 (1·03–2·18)	0·04
Squamous *vs* non-squamous	95/161	0·49 (0·35–0·69)	<0·0001	0·69 (0·51–0·94)	0·02
Tumour length >5 cm *vs* ⩽5 cm	90/162*	1·35 (0·99–1·84)	0·06	1·32 (0·98–1·78)	0·07
Tumour differentiation moderate or well *vs* poor	111/107†	0·73 (0·53–1·00)	0·05	0·64 (0·47–0·88)	0·01
Age >60 years *vs* age ⩽60 years	148/108	1·43 (1·06–1·99)	0·02	1·53 (1·14–2·06)	0·01

*Tumour length not recorded for four patients. †Tumour grade not assessable for 38 patients.

Note: Reprinted from Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial , by Burmeister BH, Smithers BM, Gebski V, Fitzgerald L, Simes RJ, Devitt P, et al., Lancet Oncol. 2005 Sep;6(9):659-68. (45)

2.2.4 Neoadjuvant Therapy and Esophagectomy

Patients who receive neoadjuvant chemotherapy or neoadjuvant chemo radiation prior to transhiatal esophagectomy have been shown to have improved survival while some studies show no association at all (23,37,45).

The rationale for neoadjuvant chemo-radiotherapy lies in the coupling of the radio-sensitising effects of chemotherapy with radiotherapy's power to reduce tumour bulk resulting in maximal local control (62,63).

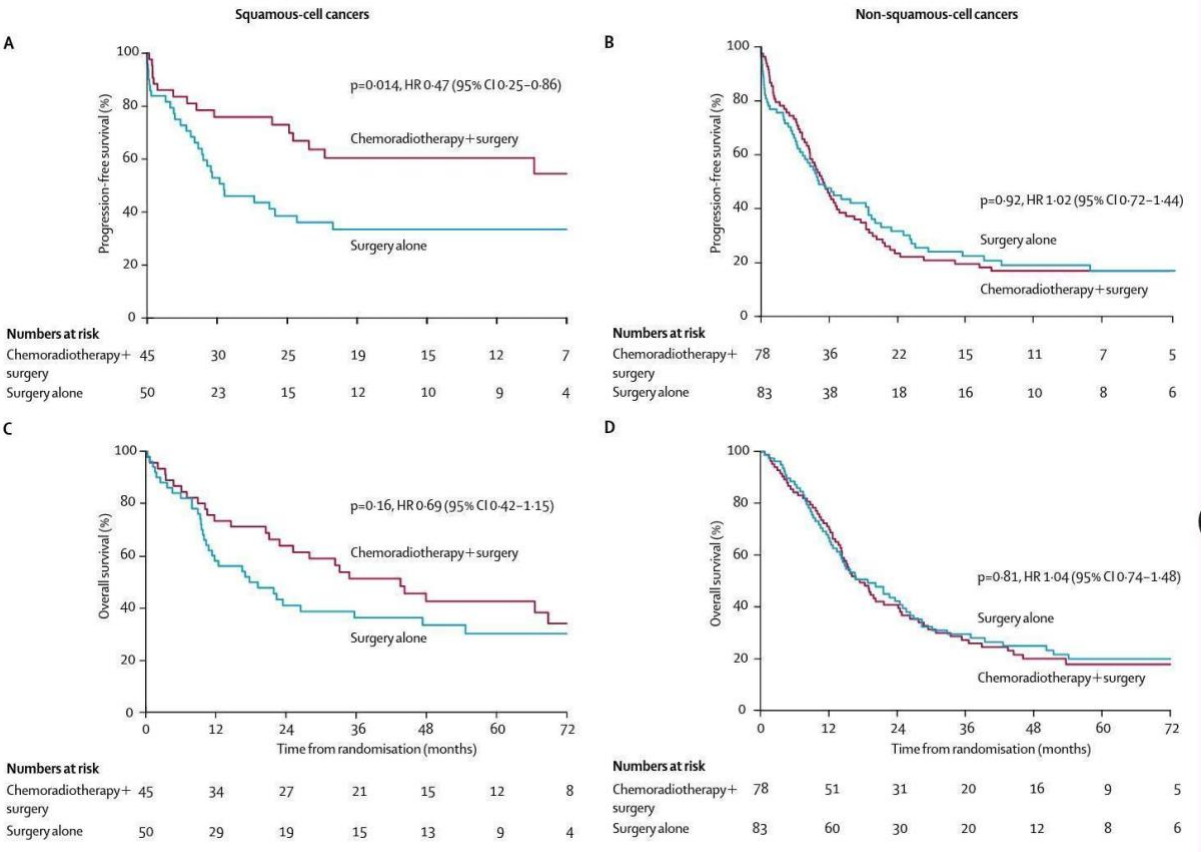
Some papers report that patients with AC who receive neoadjuvant chemotherapy have a significantly higher chance of surviving than those who only have surgery.(23,37,62) This benefit is not well demonstrated in patients with SCC as shown in Figure 1 (62). The Survival

benefit of neoadjuvant chemotherapy differs according to the histological subtypes, favouring patients with AC (HR 0.78, [0.64 – 0.95]; p=0.014) over those with SCC (HR 0.88 [0.75 – 1.03]; p=0.12), undergoing neoadjuvant chemotherapy versus to those offered surgery only (62).

When compared to patients who have only surgery, patients who receive neoadjuvant chemotherapy have an absolute difference in two-year survival of 13%. (23,37,62).

Reports document a survival benefit for patients with AC (HR 0.75, [0.59 – 0.95]; p=0.002) as well those with SCC (HR 0.84, [0.71 – 0.99]; p=0.04), undergoing combined neoadjuvant chemoradiotherapy as compared to those who had surgery alone while other studies show no association at all (Table B)(45,62).

According to the Enhanced Recovery after Surgery (ERAS) guidelines, esophagectomy should be done three to six weeks after neoadjuvant chemotherapy is finished and six to ten weeks after the final day of radiotherapy in neoadjuvant chemo-radiation. (6).



Note: Reprinted from Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial , by Burmeister BH, Smithers BM, Gebski V, Fitzgerald L, Simes RJ, Devitt P, et al., Lancet Oncol. 2005 Sep;6(9):659-68. (45)

Figure 1:Survival after esophagectomy by Histological Subtype

2.2.5 Survival Analysis

The Kaplan–Meier estimator is a nonparametric statistic commonly employed in medical research during survival analysis of a therapeutic intervention. Here the effectiveness of the therapy is gauged by enumerating subjects saved after administration of that therapy over a period of time (64).

The "event" is defined as the response variable (e.g., death). The "time to event" is a variable that measures the duration from the intervention to the event that has been defined by the status variable (e.g., the time taken by the subject from the time of oncologic esophagectomy to the event of death, or when the subject is censored from the study). The "patient survival" is defined by the "time from the therapeutic intervention to the time of the event of interest" (e.g. time from oncologic esophagectomy to death) (64,65).

A Kaplan-Meier estimator plot is a series of horizontal steps that, when drawn with a sufficiently large sample size, resembles the populations' true survival function.

An advantage of the Kaplan-Meier estimator is its accountability for censoring, which is the "total survival time for which a subject cannot be accurately determined". This can happen when the study is over before the event happens, the person withdraws from the study, gets lost to follow-up, or the data is inaccessible.

The log rank test compares the survival experience between groups where it checks for significant statistical differences in survival curves i.e., "tests the null hypothesis of no difference in survival between two or more independent groups". (66)

2.3 Statement of The Problem

Reports showed an improvement of the In- hospital mortality following oncologic esophagectomy from 28.9% (1998 - 2004) to 5.8% (2014 - 2021) (39,40). Despite numerous surgeries conducted in KNH and across the country, little data exist on the survival following oncologic esophagectomy. The purpose of this study was to ascertain the two-year survival rate following an oncologic esophagectomy at Kenyatta National Hospital, and whether certain risk factors provoke poorer survival. The information from the study will help in comparing our data with other international institutions.

2.4 Study Justification

Death is a frequent outcome in oncologic esophagectomy worldwide. Quantifying survival following oncologic esophagectomy would follow the recommendations of the World Journal of Surgery and the Society of Enhanced Recovery after Surgery by serving as an indicator of

access to and safety of surgery and anaesthesia as well as gauging its effectiveness as a therapeutic intervention in the local setting.

2.5 Study Question

What are the risk factors affecting two-year survival following oncologic esophagectomy performed in Kenyatta National Hospital?

2.6 Study Hypothesis

Null: The two-year survival following oncologic esophagectomy is not greater than 33%.
Alternate: The two-year survival following oncologic esophagectomy is greater than 33%.

2.7 Objectives

2.7.1 Broad Objective

To determine the two-year survival following oncologic oesophagostomy performed in Kenyatta National Hospital, and to establish the risk factors affecting poorer survival

2.7.2 Specific Objectives

a) To determine the two - year survival following oncologic esophagectomy in Kenyatta National Hospital.
b) To determine the risk factors associated with poorer survival following oncologic esophagectomy in Kenyatta National Hospital.
c) To determine the Perioperative Mortality rate following oncologic esophagectomy in Kenyatta National Hospital.

2.8 Conceptual Framework

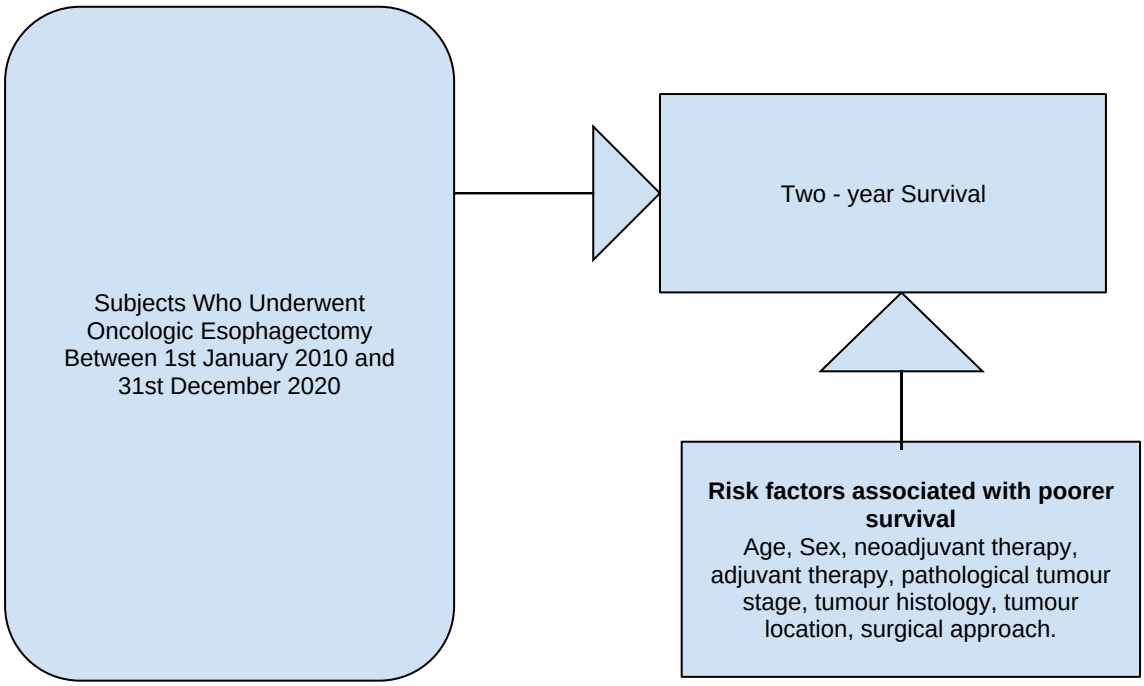


Figure 2:Conceptual Framework

3.0 CHAPTER THREE: METHODOLOGY

3.1 Study Design

This was a retrospective cohort study. The study population was all subjects that underwent oncologic esophagectomy during the study period (census). After meeting the inclusion and exclusion criterion, the subjects were further segregated into different study groups: subjects whose age was less than 60 years against those 60 years and older, male vs. female, subjects with EC in the upper ⅓ and middle ⅓ against lower ⅓ of the oesophagus, subjects who underwent esophagectomy following neoadjuvant or adjuvant therapy against those who did not, subjects who underwent esophagectomy with a histological diagnosis of AC against those with a diagnosis of SCC, and subjects who underwent esophagectomy at "T"stage 1, 2,3 and 4, and subjects whose surgical approach involved a thoracotomy vs those that did not involve a thoracotomy. The POMR was calculated for the entire group.

Each subject was characterised by three variables: the time to event (without respect to when they entered the study, they are organised from the shortest to the longest.), their status at the end of their "time to event" (event occurrence or censored), and their study cohort. This data was captured in Table D.

3.2 Study Site

The study was carried out at Nairobi's KNH, a major referral hospital which provides a range of specialised treatments. It caters to people from all over the country and parts of East Africa. Medical records were obtained from the records department and the Cancer Treatment Centre (CTC) from which data was extracted.

3.3 Study Duration

The medical records of patients who underwent oncologic esophagectomy between January 1, 2011, and December 31, 2020, was analysed for the study. This duration allows the researcher to determine the observed two - year overall survival of these patients.

3.4 Study Population

The target population was all patients who underwent oncologic esophagectomy following a confirmed histological diagnosis of oesophageal cancer, and within the ten-year period.

3.4.1 Inclusion Criteria

All patients who underwent oncologic esophagectomy at Kenyatta National Hospital; following a confirmed histological diagnosis of oesophageal cancer.

3.4.2 Exclusion Criteria

a) Patients found to have unresectable disease intraoperatively.
b) Patients who underwent other surgeries that are classified as high risk by ACC/AHA.
c) Patients with confirmed histological diagnosis of cancers other than esophageal cancer.

3.5 Sample Size

From the target population, a sample of 340 patients was obtained. This is calculated by the Cochran formula below:

$$n = \frac{(z\ score)^2 \times p(1-p)}{(d)^2}$$

Where:

n = sample size for the population

Z score = standard normal deviation, corresponding to 1.96 at 95% confidence level

p = Two-year actuarial survival rates estimated at 33% according to a report by Gebski et al. (2007) (62).

d = margin of error

Therefore:

$$340 = \frac{(1.96)^2 \times 0.33(1-0.33)}{(0.05)^2}$$

The sample size for the study was determined using a sample size formula by Schoenfeld (Latouche, Porcher, & Chevret, 2004; Schoenfeld, 1983) defined as :

$$n = \frac{(z_1 - \frac{\alpha}{2} + z_1 - \beta)^2}{[log(\theta)]^2 p(1-p)\psi(1-\rho^2)}$$

Where:

n = sample size,

p=11.6%, the proportion of perioperative mortality due to TA(Braghetto et al., 2006),

θ= 1.5 (approximated), ıthe hazard ratio of surgery alone to adjuvant treatment + surgery

Ψ = 7% (Okuyama et al., 2007) proportion of subjected expected to die of the disease after surgery

ρ = 0.6 (approximate) association between therapy and perioperative mortality.

$z_1 - \frac{\alpha}{2}$ =1.96 is the standard normal deviation, corresponding to 95% confidence level

$z_1 - \beta$ = power of the study.

The minimum sample required was estimated to be 90 subjects.

3.6 Sampling Procedure

Every patient who had an oncologic esophagectomy between January 1, 2011, and December 31, 2020 was recruited as a cohort in this study through a non-random consecutive sampling approach, where each patient who is eligible was enrolled in the study (census). Operation records of all patients were reviewed to get the surgical approach of the esophagectomy done.

3.7 Data Collection

Data was only obtained from patients who fit the inclusion criteria, facilitated by a structured data collection sheet (Table D). The choice of the data to be collected was based on literature of previous studies in the same field of interest. Data sources for this study were the files and theatre logbooks for patients who underwent oncologic esophagectomy at Kenyatta National Hospital during the period 2010-2020.

Clinical information was analysed and entered into a data collection tool and recorded in a password-protected Microsoft Excel spreadsheet. Retrieval of files were done using ICD 10 coding system after which, patients' files were filtered to obtain those which meet the inclusion criteria. Anonymity was ensured by assigning serial numbers to each patient. COVID -19 Precautions were observed throughout the data collection process.

3.8 Quality Assurance

Data was gathered by research assistants, who were medical students at or above the fifth year. They will undergo one-day training on the study protocol and how to extract data from the files.

3.9 Variables

3.9.1 Independent Variables

a) Patient characteristics (age and sex)
b) Tumour characteristics (pathologic "T" stage, histological type, and location of tumour)
c) Therapeutic approach (exposure to neoadjuvant or adjuvant therapy, and surgical approach).

3.9.2 Dependant Variable

The dependent variable was the "overall two-year survival" defined as "the time from the surgery to the date of death, with patients still censored on the date of last follow-up" (2-years).

3.10 Data Management

Hard copies of the data collected were reviewed for accuracy and completeness before entry into Microsoft Excel. The cleaned data was stored in a password protected format with access granted only to the principal investigators. All data management and analysis was conducted in Kenya, the country of the study site.

3.11 Data Analysis

All analyses were conducted in RStudio (R version 4.1.3 (2022-03-10)) using survival package. Descriptive statistics were summarised for the study sample. Categorical variables were described as frequency with percentages, whereas continuous were described using median and interquartile range (IQR). OS was reported using Kaplan-Meir estimates. The log-rank test was used to evaluate significant differences in overall survival by different variables; patient characteristics (age and sex), tumour characteristics (pathologic "T" stage, "TNM" stage, histological type, and location of tumour) and therapeutic approach (exposure to neoadjuvant or adjuvant therapy and surgical approach).

The socio-demographic and clinical factors were included in a Cox proportion hazard regression model to examine any association with the overall survival. Factors significantly associated with the overall survival or are known to be clinically significant in explaining the overall survival were incorporated into a multivariable Cox proportional hazard regression model. Hazard ratio (HR), 95% confidence intervals (CI), and p-values were reported. A p-value < 0.05 was set as the level of statistical significance.

3.12 Ethical Considerations

Consent of waiver permission was requested from the Ethics and Research Committee and the KNH research department to access patients' files. Retrieval of files was done using ICD 10 coding system after which, patients' files were filtered to obtain those which meet the inclusion criteria. Anonymity was ensured by assigning serial numbers to each patient and all the data was kept under lock and key.

4.0 CHAPTER FOUR: RESULTS

4.1 Patient Characteristics

Characteristics of the 90 patients enrolled in the study are shown in Table F. The median age in years was 56.5 (IQR: 49.0-64.8), with 55 (61.1%) below the age of 60 years, while 35 (38.9%) were aged 60 years and above. Fifty (55.6%) of the patients were male, whereas 40 (44.4%) were female.

Table 3:Patient Characteristics

Characteristics	**N = 90[1]**
Age in years, Median (IQR)	**56.5 (49.0 – 64.8)**
Age-group in years, n (%)	
Below 60	**55 (61.1)**
60+	**35 (38.9)**
Gender, n (%)	
Female	**40 (44.4)**
Male	**50 (55.6)**

[1]Median (IQR) or Frequency (%)

4.2 Tumour Characteristics

The tumour characteristics based on postoperative histological analysis showed that 76 (84.4%) of the subjects were squamous cell carcinoma histological subtype, while 8 (8.9%) were Adenocarcinomas sub-type. No tumour was identified in five (5.6%) of the subjects.(Table G) 30 (33.3%) of the tumours were well differentiated (G1), 19 (21.1%) were moderately differentiated (G2), and 41 (45.6%) were poorly differentiated (G3).(Table G)

In terms of the pathological "T" stage, 3 (3.3%) patients were pT1, 34 (37.8%) were pT2, 43 (47.8%) were pT3, and 4(4.4%) were pT4A. (Table G)

TNM stage II and III were predominant among the patients at 50 (55.6%) and 25 (27.8%) respectively. (Table G)

Over half of the tumours (66.6%) were located in the lower third of the oesophagus while 30 (33.3%) of the tumours were located in the middle third. (Table G)

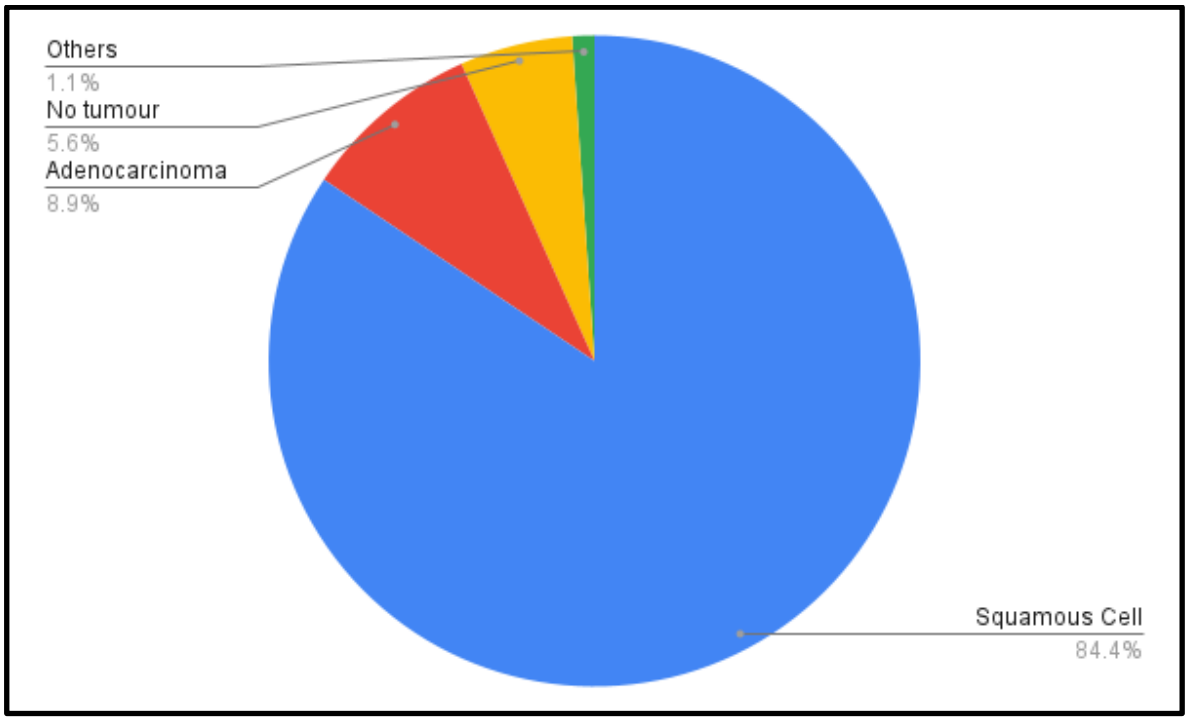


Figure 3:Tumour Characteristics by Histological Subtypes

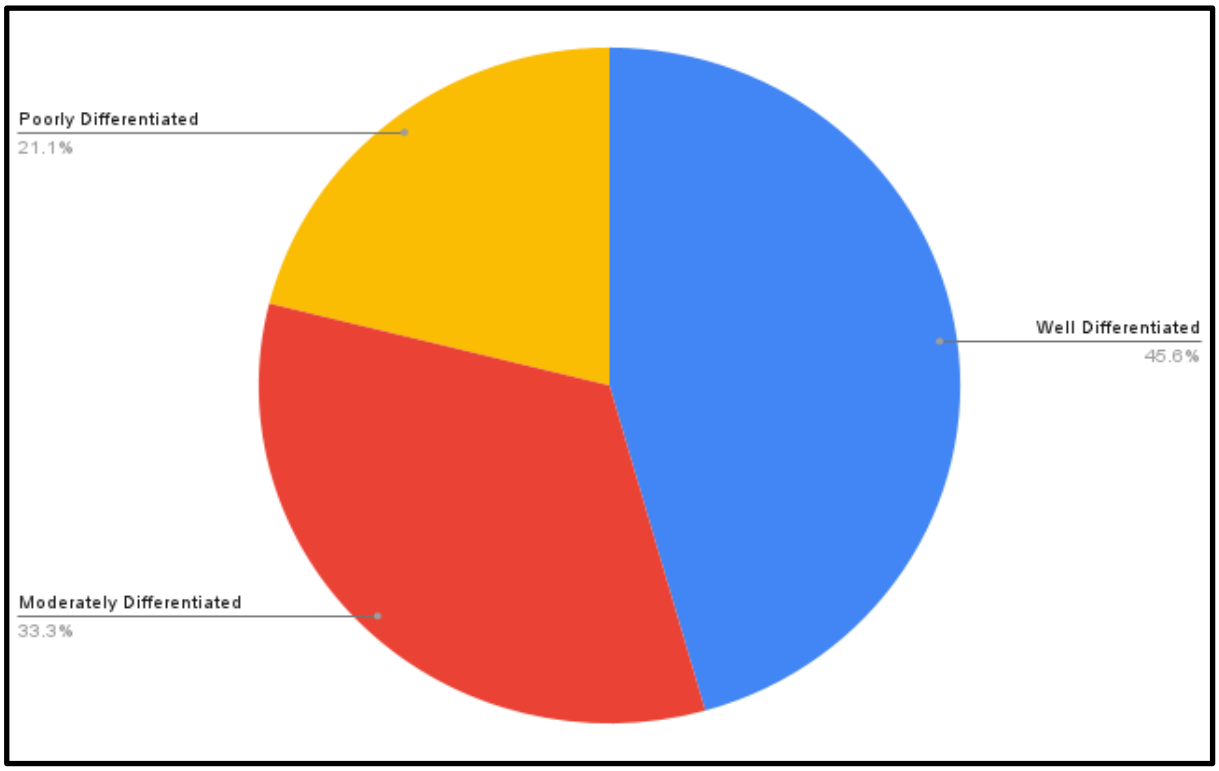


Figure 4:Tumour Characteristics by Grade

Table 4:Tumour Characteristics

Characteristics	N = 90[1]
Histology sub-type, n (%)	
Squamous Cell Carcinoma	**76 (84.4)**
Adenocarcinoma	**8 (8.9)**
No tumour	**5 (5.6)**
Others	**1 (1.1)**
Tumour grade, n (%)	
G1-Well Differentiated	**41 (45.6)**
G2-Moderately Differentiated	**30 (33.3)**
G3-Poorly Differentiated	**19 (21.1)**
T stage, n (%)	
pT1	**3 (3.3)**
pT2	**34 (37.8)**
pT3	**43 (47.8)**
pT4A	**4 (4.4)**
TNM stage, n (%)	
I	**3 (3.3)**
II	**50 (55.6)**
III	**25 (27.8)**
IV	**2 (2.2)**
IVA	**5 (5.6)**
No Tumour	**5 (5.6)**
Tumour location, n (%)	
Lower Third	**60 (66.7)**
Middle Third	**30 (33.3)**

[1]Median (IQR) or Frequency (%)

4.3 Operative Approach

Percentage of patients who received neoadjuvant and adjuvant therapy was 17.8%(n=16) and 25.6%(n=23) respectively. McKenown's esophagectomy was performed on 54 (60.0%) of the patients, followed by Transhiatal esophagectomy at 24 (26.7%) and Ivor Lewis' esophagectomy at 12 (13.3%). The perioperative mortality rate was 39 (43.3%) of the total enrolled patients (Table H).

Table 5:Therapeutic Approach

Characteristic	N = 90[1]
Chemo/Radiotherapy, n (%)	
Neoadjuvant therapy	**16 (17.8)**
Adjuvant therapy	**23 (25.6)**
Surgical Approach, n (%)	
Ivor Lewis esophagectomy	**12 (13.3)**
McKeown's esophagectomy	**54 (60.0)**
Transhiatal esophagectomy	**24 (26.7)**
Perioperative mortality, n (%)	
Perioperative mortality	**39 (43.3)**
Discharged alive	**51 (56.7)**

[1]Median (IQR) or Frequency (%)

4.4 Overall Two - Year Survival

The overall survival rate for the subject was 46% (95%CI: 39%-63%), and two-year overall survival rate was 53% (95%CI: 43%-66%) (Figure 5).

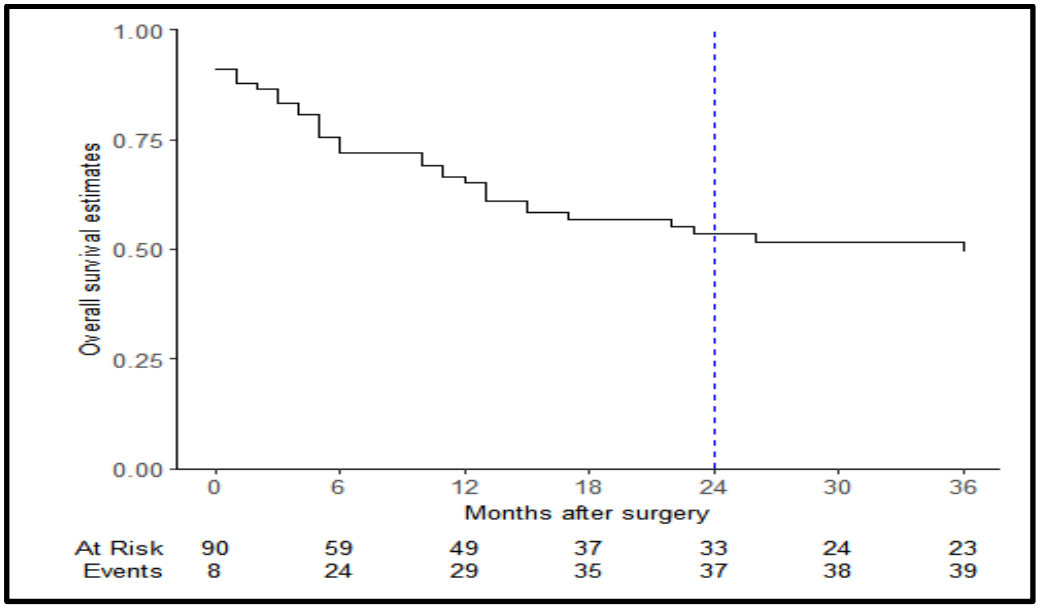


Figure 5:Overall survival estimates of the subjects

The survival rates at time two years for subjects aged below 60 years was 53% (95%CI: 40%-69%), while that of those aged 60 and above was 56% (95%CI: 40%-78%). (Figure 6)

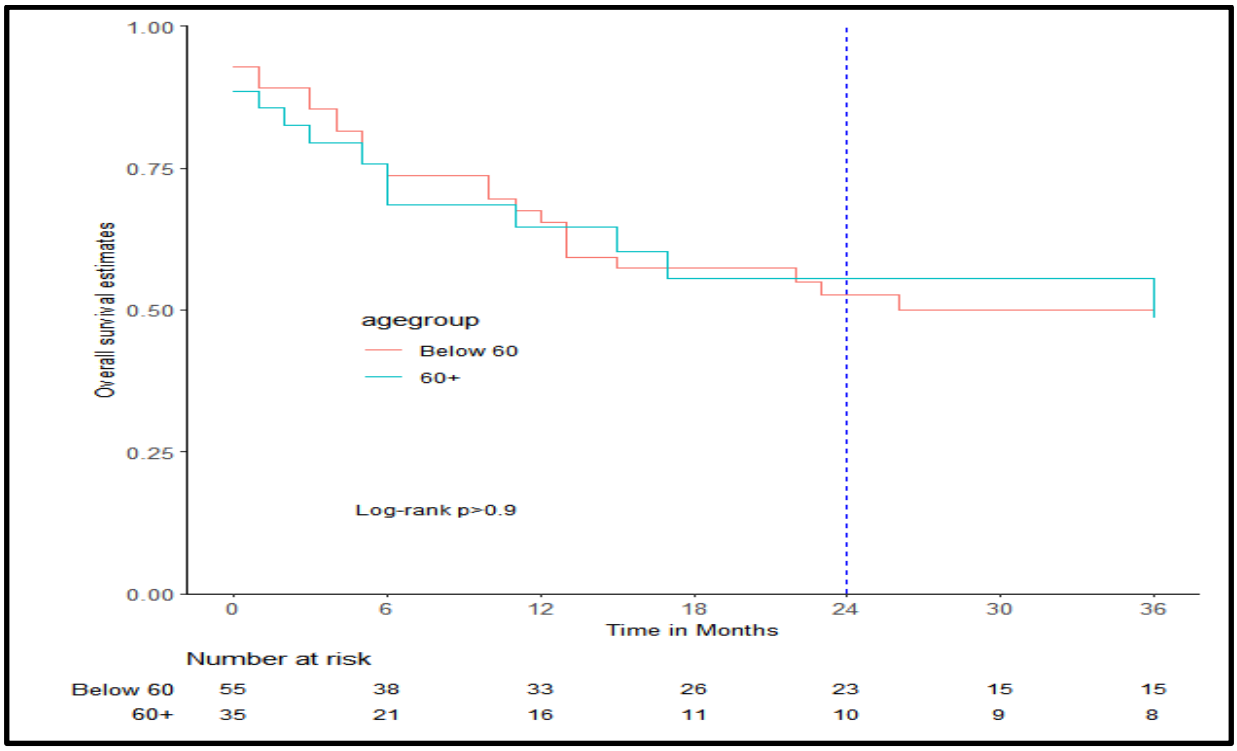


Figure 6:Overall survival estimates by age

Males had a higher two-year survival rate at 70% (57%-85%) than females 35% (95%CI:22%-56%). (Figure 7).

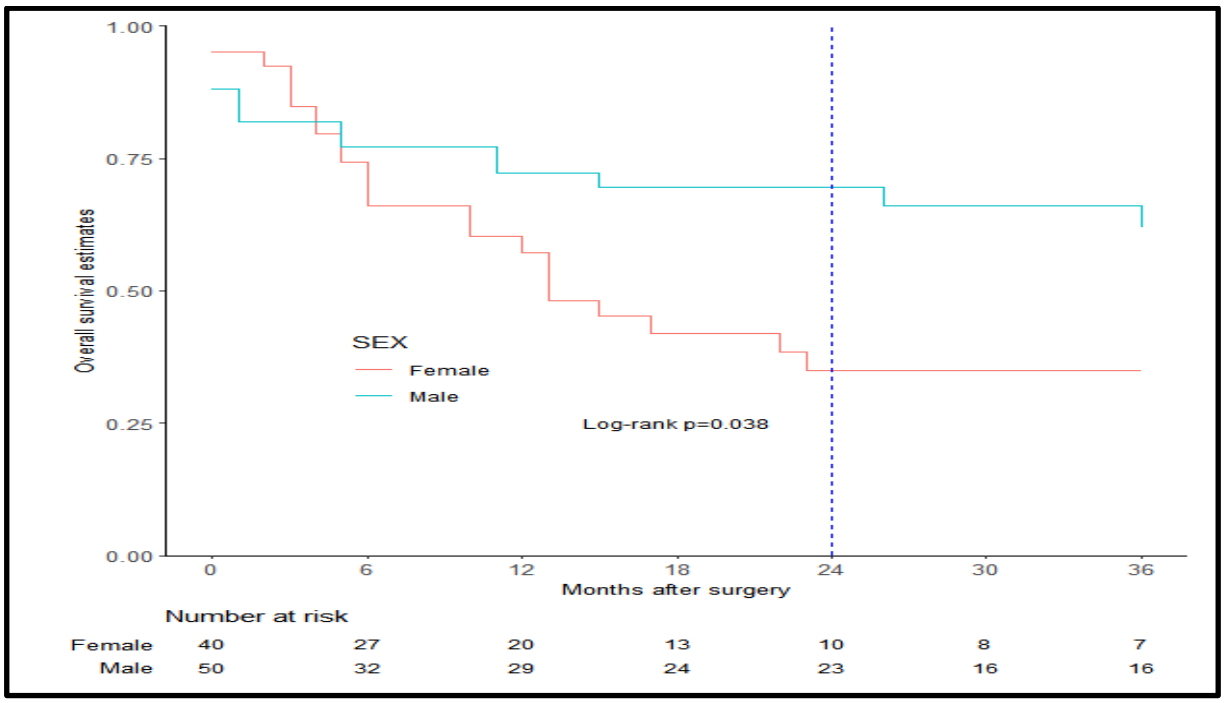


Figure 7:Overall survival estimates by sex

Subjects with tumours of squamous histological subtypes had two-year survival rates of 53%(95%CI:42-66) while those of those of non-squamous variety had two-year survival rates of 59%(95%CI:34-100). (Figure 8)

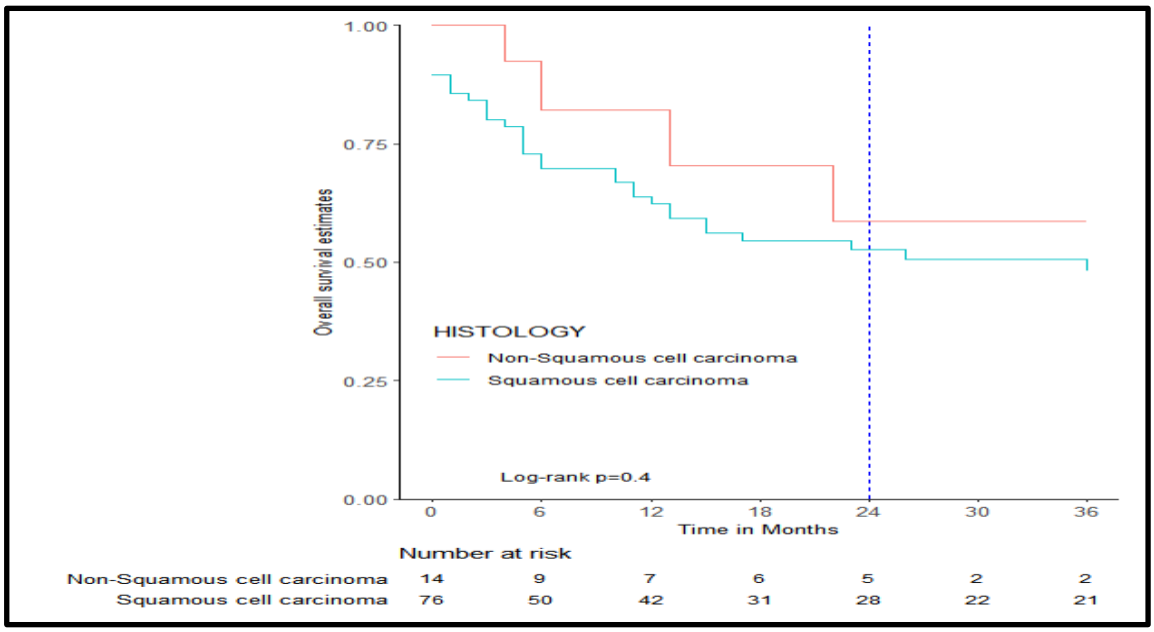


Figure 8:Overall survival estimates by Histological Subtype.

With regards to grading, subjects presenting with tumours that were poorly, moderately, and well differentiated had survival rates of 51% (95%CI:35%-75%), 52% (95%CI:31%-87%), and 56% (95%CI:42%-74%) respectively. (Figure 9)

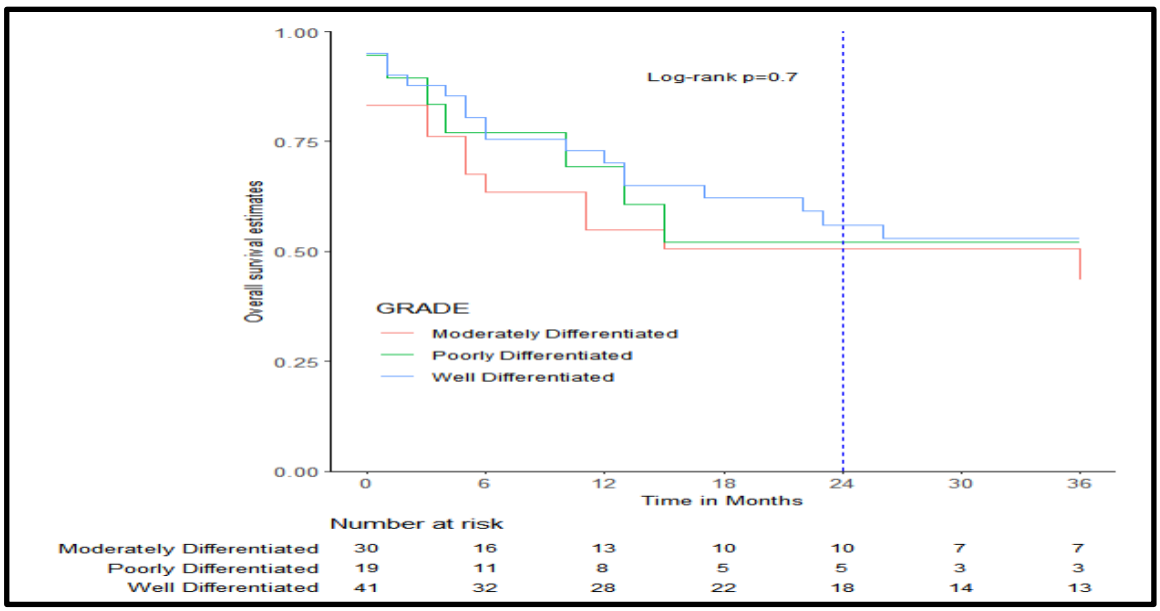


Figure 9:Overall survival estimates by Tumour Grade

Subjects who presented at “TNM” Stage I-II had an overall two-year Survival of 61% (95%CI:49%-76%) while those presenting at “TNM” Stage III-IVA had an overall two-year Survival of 40% (95%CI:25%-63%). (Figure 10)

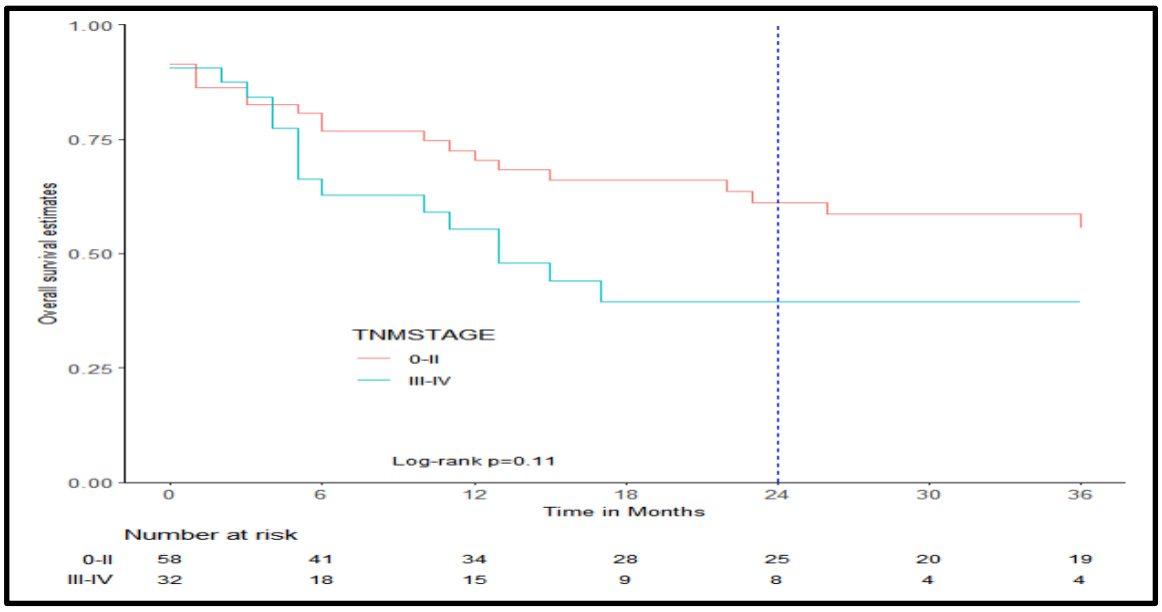


Figure 10:Overall survival estimates by “TNM” Stage

Subjects who presented with tumours at the middle third of the oesophagus had an overall two-year Survival of 47% (95%CI:31%-71%) while those with tumours at the distal third had an overall two-year Survival of 57% (95%CI:45%-72%). (Figure 11)

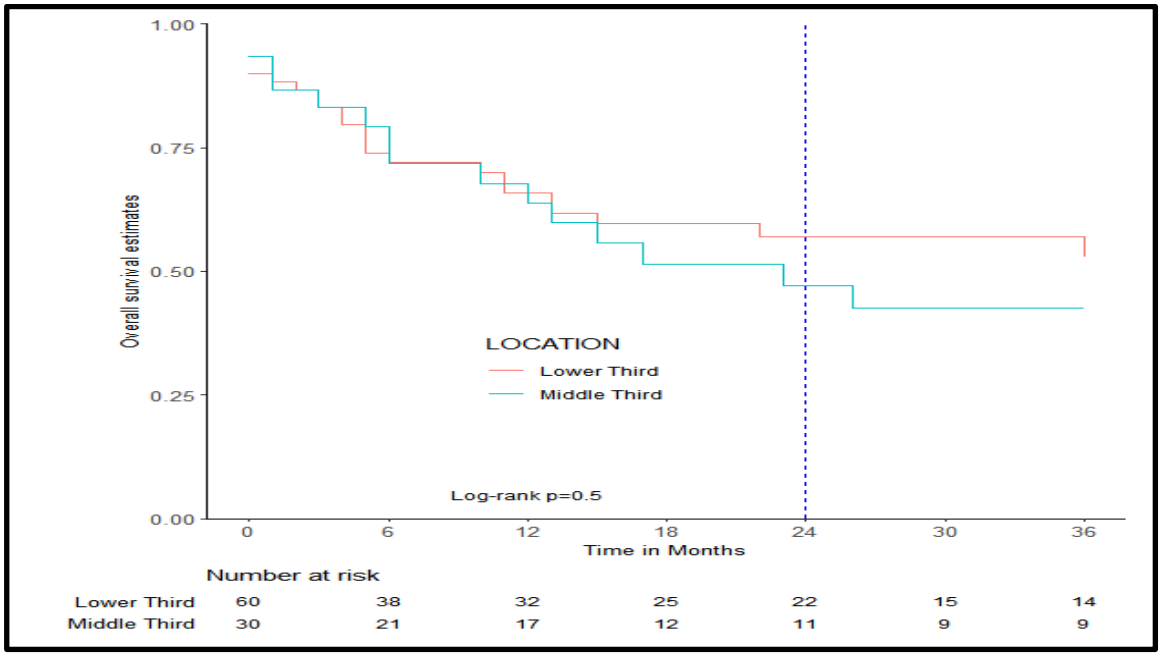


Figure 11:Overall survival estimates by Tumour Location

Subjects who were offered neoadjuvant chemotherapy before surgery had an overall two-year Survival of 54% (95%CI:41%-71%) while those that underwent surgery alone had an overall two-year Survival of 58% (95%CI:40%-83%). Those that had adjuvant therapy had an overall two-year Survival of 51% (95%CI:35%-85%). (Figure 12)

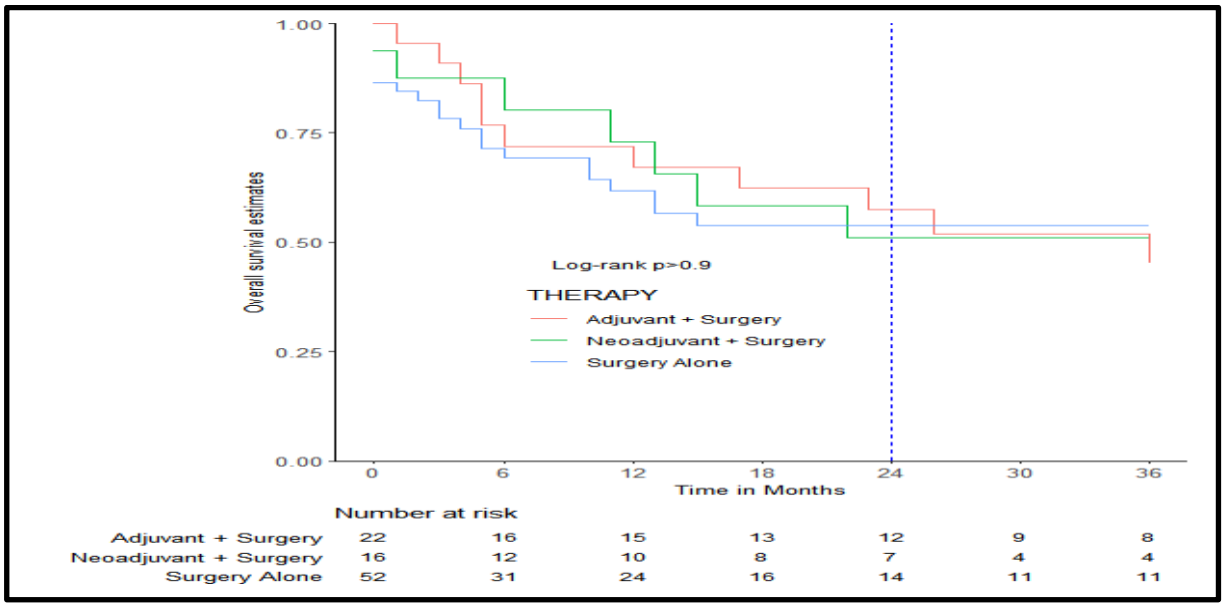


Figure 12:Overall survival estimates by Therapeutic Approach

Subjects who underwent McKeown's esophagectomy had an overall two-year Survival of 51% (95%CI:36%-68%) while those that had a transhiatal approach had an overall two-year Survival of 53% (95%CI:35%-80%). Those that underwent Ivor Lewis' approach had an overall two-year Survival of 64% (95%CI:41%-100%). (Figure 13)

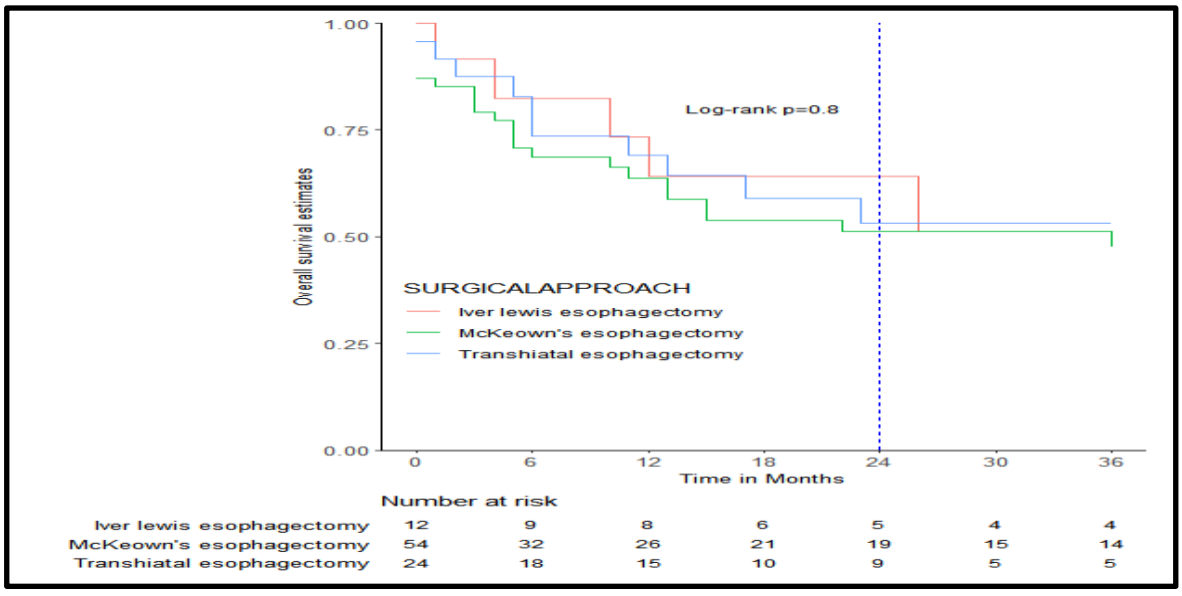


Figure 13:Overall survival estimates by Surgical Approach4.5 Univariate Analysis of Survival Following Esophagectomy

After adjusting for all other covariates in the cox proportion hazard model, only sex was significantly associated with time to in-hospital mortality. Being a male was associated with reduced risk of mortality by 55% compared to the female (AHR: 0.45; 95%CI:0.23-0.90). There was poorer survival in subjects with squamous cell carcinoma, moderated differentiated tumour grade, "T" stage III-IV, neoadjuvant + surgery and operation with thoracotomy, even though no significant association was found (Table 6).

Table 6:Hazard ratios, with 95% confidence intervals for the Risk Factors Affecting Survival Following Oncological Esophagectomy at Kenyatta National Hospital

	Univariable		Multivariable	
Variable	**HR (95%CI)**	**P-value**	**AHR (95%CI)**	**P-value**
Age-group				
Below 60				
60+	1.03 (0.53-1.98)	0.932	0.80 (0.38-1.66)	**0.545**
Sex				
Female				
Male	0.52 (0.27-0.98)	0.044	0.45 (0.23-0.90)	**0.023**
Histology subtype				
Non-squamous cell carcinoma				
squamous cell carcinoma	1.61 (0.57-4.54)	0.367	1.83 (0.56-5.94)	**0.317**
Tumour Grade				
G3-Poorly differentiated				
G2-Moderately differentiated	1.25 (0.50-3.09)	0.636	1.20 (0.43-3.40)	**0.725**
G1-Well differentiated	0.90 (0.37-2.16)	0.813	0.80 (0.32-2.01)	**0.638**
TNM Stage				
0-II				
III-IV	1.67 (0.88-3.16)	0.115	1.81 (0.90-3.64)	**0.094**
Therapeutic Approach				
Surgery alone				
Adjuvant+Surgery	0.94 (0.45-1.95)	0.859	0.99 (0.43-2.28)	**0.982**
Neoadjuvant+Surgery	0.88 (0.37-2.07)	0.766	1.39 (0.50-3.87)	**0.528**
Surgical Approach				
Operation without thoracotomy				
Operation with thoracotomy	1.18 (0.57-2.41)	0.659	1.19 (0.53-2.70)	**0.672**

AHR; adjusted hazard ratio; HR: Hazard ratio; CI: confidence interval

We analysed the population dynamics between women and men to try and find differences in the other risk factors. (Table 7). We did not find any glaring differences between the two cohorts

Table 7:Risk factors of Women Vs Men

	Gender		**p-value**[2]
	Female, N = 40[1]	**Male**, N = 50[1]	
Age in years, Median (IQR)	57.0 (46.0 – 64.0)	56.5 (51.0 – 65.8)	**0.53**
Age-group in years, n (%)			**0.81**
Below 60	25 (62.5)	30 (60.0)	
60+	15 (37.5)	20 (40.0)	
Histology sub-type, n (%)			**0.65**
Non-Squamous cell carcinoma	7 (17.5)	7 (14.0)	
Squamous cell carcinoma	33 (82.5)	43 (86.0)	
Tumour grade, n (%)			**0.49**
G2-Moderately Differentiated	12 (30.0)	18 (36.0)	
G3-Poorly Differentiated	7 (17.5)	12 (24.0)	
G1-Well Differentiated	21 (52.5)	20 (40.0)	
TNM stage, n (%)			**0.73**
0-II	25 (62.5)	33 (66.0)	
III-IV	15 (37.5)	17 (34.0)	
Tumour location, n (%)			**0.10**
Lower Third	23 (57.5)	37 (74.0)	
Middle Third	17 (42.5)	13 (26.0)	
Therapy, n (%)			**0.48**
Adjuvant + Surgery	11 (27.5)	11 (22.0)	
Neoadjuvant + Surgery	5 (12.5)	11 (22.0)	
Surgery Alone	24 (60.0)	28 (56.0)	
Thoracotomy, n (%)			**0.42**
Operation with thoracotomy	31 (77.5)	35 (70.0)	
Operation without thoracotomy	9 (22.5)	15 (30.0)	

[1]*Median* (IQR) or Frequency (%); [2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

5.0 CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Discussion

The objective of this study was to assess the risk factors affecting oncological esophagectomy at Kenyatta National Hospital in a ten-year period.

5.1.1 Population Characteristics

We found that the majority of the subjects undergoing esophagectomy were men (55.6%) under the age of 60 years (61.1%), at "TNM" stage II (55.6%). In comparison, western data cites male predominance presenting with a median age of 62.5yrs at TNM stage I. (24) The most common histological subtype was Squamous cell (84.4%) with majority of the tumours being poorly differentiated (45.6%) of a pathological "T" stage pT3 (47.8%) located at the lower third of the oesophagus (66.6%). The preferred surgical approach was McKeown's esophagectomy (60%). In comparison, western data cites predominance of Adenocarcinoma (61% - 63%), with majority of the tumours being poorly differentiated (37% - 47%) of a pathological "TNM" stage I/II (85%) located at the lower third of the oesophagus (77% - 81%). (45)

5.1.2 Perioperative Mortality Rate (POMR)

The perioperative Mortality Rate was calculated to 43.3% with an In-hospital patient mortality of 9.8%. This is similar to earlier reports of In - patient mortality of 5.8% (2014 - 2021), showing improvement from 28.9% (1998 - 2004) to (39,40). These findings suggest that oncologic esophagectomy bears a significant mortality risk in the immediate postoperative period.

5.1.3 Risk Factors Affecting Survival

The overall two-year survival for 90 patients who underwent oncologic esophagectomy was 53% (95%CI: 43%-66%). This is within the international range quoted in the literature review as 26% - 80.8%, and above the average two year actuarial survival rate of 33%.(6–8,13–15,21–23)

Although statistically insignificant, we found that poorer survival is associated with subjects who underwent oncological esophagectomy at age 60 and above [56% (95%CI: 40%-78%)] and tumours that were poorly differentiated [51% (95%CI:35%-75%)], when compared to those below 60 years [53% (95%CI: 40%-69%)] and tumours that were moderately [52%

(95%CI:31%-87%)]/well differentiated [56% (95%CI:42%-74%)] respectively . This is consistent with the findings of previous studies.(45)

There was poorer survival in subjects with squamous cell carcinoma [53%(95%CI:42-66)], and tumour located in the middle third [47% (95%CI:31%-71%)], when compared to subjects with non - squamous cell tumours [59%(95%CI:34-100)], and tumours located in the lower third of the oesophagus [57% (95%CI:45%-72%)], even though no significant association was found. This differed with previous study found that subjects with lower third esophageal tumours, and tumours with non-squamous histology had both decreased overall survival and decreased disease-free progression when compared to subjects with tumours in the upper and mid oesophagus, and subjects with tumours with squamous histology respectively. (45)

Subjects at "TNM" Stage III-IVA [40% (95%CI:25%-63%)] had poorer survival when compared to those that presented at "TNM" Stage I-II [61% (95%CI:49%-76%)]. This followed previous findings showing that subjects who had esophagectomy when they had an early diagnosis of the condition lived longer than those who were offered esophagectomy with a late diagnosis.(23).

There was no statistical difference in two-year survival for subjects who underwent McKeown's esophagectomy [overall two-year Survival of 51% (95%CI:36%-68%)] transhiatal approach [overall two-year Survival of 53% (95%CI:35%-80%)] or those that underwent Ivor Lewis' approach [overall two-year Survival of 64% (95%CI:41%-100%)]. Several studies cited in the literature review had similar findings.(10,11,13,18,46,47). This is despite the fact that generally, operations involving a thoracotomy are associated with higher morbidity than those without a thoracotomy. Interestingly, this did not translate to poorer survival as demonstrated in this study.

Curiously, we found that women [35% (95%CI:22%-56%)] had significantly poorer two-year survival when compared to men [70% (57%-85%)]. Males started with a lower survival probability up to the sixth month after surgery but went on to have a higher survival probability compared to females (p=0.038). There were no statistical differences of other risk factors between the two cohorts. Unfortunately, variability in preoperative functional state and postoperative complications was not considered in this study and may have confounded the findings.

5.1.4 Chemoradiotherapy and Esophagectomy

Interestingly, there was no statistical difference in survival for patients who had surgery alone [58% (95%CI:40%-83%)] when compared to those whose operation were accompanied by neoadjuvant [54% (95%CI:41%-71%)] and adjuvant therapy [51% (95%CI:35%-85%)]. This is in contrast to a meta-analysis that found an absolute difference in two-year survival of 13%

when comparing subjects who have only surgery, with those who received neoadjuvant chemotherapy (23,37,62). Some of these studies agreed with the findings that adjuvant chemo/radiotherapy did not offer any statistically significant reduction in two-year survival. (62)

5 patients out of the 15 that received neoadjuvant chemoradiotherapy achieved pathological complete response (30%), as no tumour was detected on histological analysis after surgery. Of these two died (14 and 22 months) and three were alive at the time of the study (censored at 13 months, 44 months and 46 months). All had a preoperative diagnosis of SCC on biopsy, showing the benefit of neoadjuvant therapy for this cohort. Most of the studies in the literature review were done in populations with Adenocarcinoma as the predominant histological subtype. SCC that is endemic in our population may have skewed the results in an unexpected direction showing no difference in two-year survival following exposure to neoadjuvant therapy, in contrast to the quoted studies.

5.2 Study Limitations

As with all retrospective studies, the quality of the data depends on the accuracy of the records. No records were found before 2015. Due to limitations in achieving sample size, the findings of this study are of a confidence level of 70% with a margin of error of 5%. Availability of the data required to gauge the ramification of survival is limited to all-cause mortality and not disease specific mortality that would offer a more accurate picture of the mortality benefit of this surgical procedure.

Confounding effects of patient factors may have contributed to surgical outcomes such as preoperative functional state and postoperative complications. Two-year survival offers a good picture of mortality outcomes of surgical procedures. However, including a five- year survival or ten- year survival analysis would give a more complete picture.

5.3 Conclusion

Overall, the two-year survival following oncological esophagectomy in Kenyatta National Hospital is comparable to high volume centres across the world. Except for sex and stage, which is a non-modifiable variable, none of the other risk factors showed a statistically significant contribution to poorer survival. This implies that the outcome of the operation may depend, to a large extent, on the surgeon's decision to operate based on their preoperative evaluation (as described in section 2.1.3).

The described protocol utilising multislice CT scans of the chest and abdomen to determine resectability of esophageal tumours does not result in poorer overall two-year survival when

compared to other centres globally. The study found these staging techniques offered outcomes that are just as good to those of more resourceful centres that offer advanced radiological preoperative investigations such as PET And Endoscopic ultrasound. Therefore, the authors of this study felt that the conventions to determine oesophageal tumour resectability employed in KNH are appropriate for resource limited environments.

5.4 Recommendations

The decision to operate based mainly on CT scans of the chest and abdomen employed in KNH does not offer poorer survival compared to resourceful institutions that utilise more advanced preoperative radiological workup. The authors feel that these techniques are appropriate for settings with limited resources.

Two-year survival offers a good picture of mortality outcomes of surgical procedures. However, we recommend future studies with a five- year survival or ten- year survival analysis with a greater sample size to give a more complete picture.

This study was limited to all-cause mortality and not disease specific mortality. Future studies with the latter would offer a more accurate picture of the mortality benefit of this surgical procedure.

We found that patients who presented in later stages of the disease had poorer survival. We feel that increasing public health measures in patient education, and resource mobilisation into early diagnosis and intervention for oesophageal cancer, may improve survival outcomes for cancer of the oesophagus patients.

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APPENDICES

Appendix I: Data Collection Tool

Form Number	
Age of Subject (years)	
Sex	☐ Male ☐ Female
Histological Diagnosis	☐ AC ☐ SCC ☐ Other (specify)
Tumour Location	☐ Upper ⅓ ☐ Mid ⅓ ☐ Lower ⅓
pathologic "T" stage	☐ Stage 1/2/3 ☐ Stage 4
Neoadjuvant therapy	☐ Yes ☐ Chemotherapy ☐ Radiotherapy ☐ Chemo radiotherapy ☐ No
Adjuvant therapy	☐ Yes ☐ Chemotherapy ☐ Radiotherapy ☐ Chemo radiotherapy ☐ No
Esophagectomy Approach	☐ Mckeown/ Tri - incisional ☐ Transhiatal ☐ Other (specify)
Day of Surgery	*dd/mm/yyyy*
In - Hospital Mortality	☐ Yes ☐ No Date of Death (*dd/mm/yyyy)*
Out-of Hospital Mortality	☐ Yes ☐ No Date of Death (*dd/mm/yyyy)*
Last date of Follow-up	*dd/mm/yyyy*

Appendix II: KNH/UoN-ERC Letter of Approval

UNIVERSITY OF NAIROBI
FACULTY OF HEALTH SCIENCES
P O BOX [illegible] Code 00202
Telegrams: varsity
Tel: 254-020/ 272630 Ext 44355

KNH-UON ERC
Email: [illegible]
Website: http://www.[illegible]
Facebook: https://www.facebook.com/[illegible]
Twitter: @254[illegible]

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
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Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/99

2nd March, 2023

Dr. George Kimani Kinyanjui
Reg.No.H58/10516/2018
Dept. of Surgery
Faculty of Health Sciences
University of Nairobi

Dear Dr Kinyanjui,

RESEARCH PROPOSAL: RISK FACTORS AFFECTING SURVIVAL FOLLOWING ONCOLOGICAL ESOPHAGECTOMY AT KENYATTA NATIONAL HOSPITAL (P802/10/2022)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P802/10/2022**. The approval period is 3rd March 2023 – 2nd March 2024.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
i. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
ii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH-UoN ERC within 72 hours
v. Clearance for export of biological specimens must be obtained from relevant institutions
v. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC

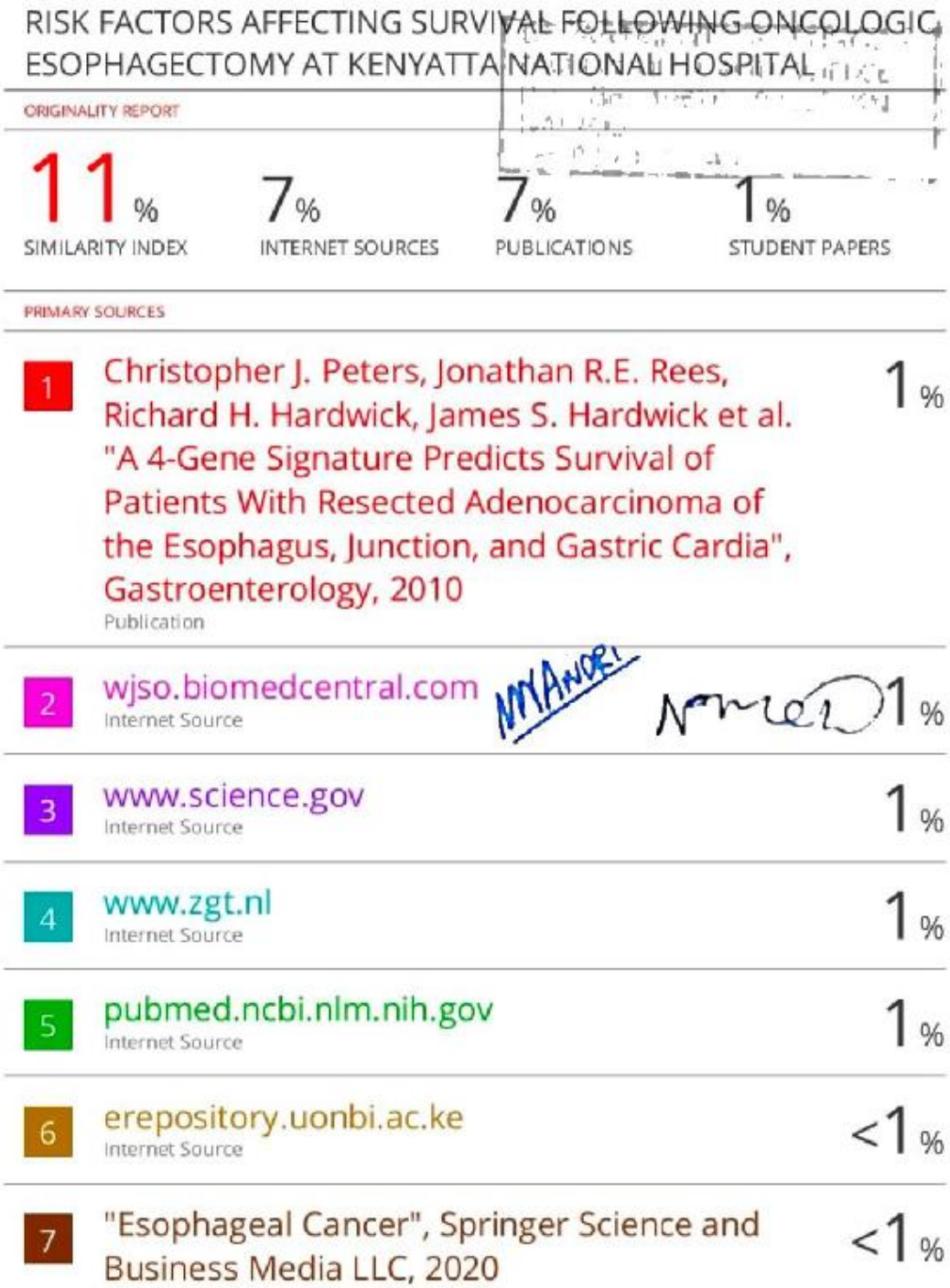
Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://research-portal.nacosti.go.ke and also obtain other clearances needed.

Yours sincerely,

DR. BEATRICE K.M. AMUGUNE
SECRETARY, KNH-UoN ERC

c.c. The Dean, Faculty of Health Sciences, UoN
The Senior Director, CS, KNH
The Assistant Director, Health Information Dept., KNH
The Chairperson, KNH- UoN ERC
The Chair, Dept. of Surgery, UoN
Supervisors: Dr. Aword Mark Nelson Dept. of Surgery, UoN
Dr. Nikita Mehta, Dept. of Surgery, UoN

Appendix III: Certificate of Plagiarism



RISK FACTORS AFFECTING SURVIVAL FOLLOWING ONCOLOGIC ESOPHAGECTOMY AT KENYATTA NATIONAL HOSPITAL

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