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Pattern of practice for palliative radiotherapy in oesophageal carcinoma - a retrospective analysis at Charlotte Maxeke Johannesburg academic hospital (2007-2012)

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PATTERN OF PRACTICE FOR PALLIATIVE RADIOTHERAPY IN OESOPHAGEAL CARCINOMA – A RETROSPECTIVE ANALYSIS AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL (2007-2012)

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

Johannesburg, 2016

DECLARATION

I, Sudeshen Manickum Naidoo declare that this research report is my own unaided work, except where otherwise acknowledged. It is being submitted for the degree of Master of Medicine in the branch of Radiation Oncology in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

_____

S.M. Naidoo

Signed on this ____ th day of June 2016

DEDICATION

"With gratitude to GOD and my beloved family"

ABSTRACT

Purpose: To assess the improvement in swallowing status, overall survival and treatment related complications in patients with Carcinoma of the Oesophagus treated with palliative radiotherapy.

Methods: A retrospective analysis of patients with advanced squamous cell carcinoma of the oesophagus who were treated for palliation from May 2007 to June 2012 at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) was done. Ninety- nine patients received palliative radiation therapy during this period, 63% were male and 37% female with a mean age of 60, 6 years. The predominant site of lesion was middle 3rd (56%) and 86, 9% of patients had lesions more than 5cm in length. Patients received palliative External beam irradiation (EBRT) with or without High dose rate brachytherapy (HDRBT) as per the CMJAH, Department of Radiation Oncology protocol.

Results: There was an overall significant improvement in swallowing status (p<0,001). Eighty –four patients (85%) had an improvement in swallowing score after treatment. The effect of treatment was not significant in the relationship between the change in swallowing status and treatment group. Overall mean time to progression was 3, 7 months. The median overall survival was 7, 7 months. The type of treatment did not affect survival significantly, unadjusted (p=0, 31) or adjusted for prognostic parameters (age, sex, length of lesion, site of lesion, and pre-treatment swallowing status) (p=0.29). There were treatment related complications in 32% of cases, consisting of ulcerations (24%), tracheo-oesophageal fistula (5%) and strictures (3%).

Conclusion: In patients with advanced squamous cell oesophageal carcinoma, palliative radiotherapy is an effective modality in improving a patient's dysphagia and thus quality of life.

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NOMENCLATURE

AIDS	Acquired immune deficiency syndrome
AP-PA	Antero-posterior, postero-anterior fields
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
EBRT	External Beam Radiotherapy
ECOG	Eastern Cooperative Oncology Group
Gy	Gray (unit of radiation)
HDRBT	High dose rate brachytherapy
HIV	Human immunodeficiency virus
ILBT	Intraluminal brachytherapy
MV	Megavoltage
SEMS	Self expanding metal stent
SMIC	Skin marking isocenter
TOF	Tracheo-oesophageal fistula

1. INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction

Oesophageal carcinoma is a highly lethal malignancy, and is the sixth most common malignancy worldwide in males, and eleventh in females.[1]

In South Africa there is a high incidence of oesophageal cancer and it ranks fourth in males and sixth in females.[2]

Men are more commonly seen with oesophageal cancer than women and squamous cell carcinomas are the most common histological type.[3]

The major risk factors accounting for more than 80% of cases are alcohol and tobacco use. Other factors include diets with minimal fruits and vegetables which are associated with an increase in squamous cell carcinoma.[4, 5]

The most common presenting symptom of oesophageal cancer is dysphagia, which may progress rapidly to a stage where patients are unable to swallow even liquids and saliva. Dysphagia makes them prone to nutritional compromise and aspiration pneumonia.[6]

Oesophageal cancer has a poor prognosis because the majority of patients present in a poor general condition and with advanced disease, where curative options are limited.[7] In addition, the oesophagus has a rich lymphatic and vascular supply, hence local invasion

and early metastasis are common in newly diagnosed patients.[8] A median survival time of 2, 5 to 9, 9 months has been reported in patients with advanced oesophageal cancer.[9]

The main aim of treatment remains palliation of dysphagia, to improve a patient's quality of life.[10] Various treatment modalities for palliation have been used in an attempt to relieve dysphagia and improve quality of life. These include surgery (bypass, resection), dilatation, chemotherapy, intubation, external beam radiotherapy (EBRT) and intraluminal brachytherapy.[11] A combination of the aforementioned modalities has been reported to only marginally improve the results in advanced cases.

The administration of intraluminal brachytherapy allows a rapid tumour reduction of the luminal aspects, thereby restoring swallowing quickly. An added advantage of brachytherapy is the rapid falloff of dose, which decreases the risk of injury to the surrounding normal tissues.[12,13] Previous studies have identified high dose rate intraluminal brachytherapy as an efficient and safe monotherapy, where palliation is the primary concern.[7,9,10]

The use of EBRT is an effective and non – invasive modality, however a reported disadvantage was that relief of dysphagia occurred over a period of 4-6 weeks.[14]

At the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Department of Radiation Oncology a combination of palliative EBRT dose schedules with or with HDRBT are used to improve the swallowing status and quality of life in patients with advanced / non-operable oesophageal carcinoma.

1.2 Literature Review

The review has been grouped into prospective and retrospective studies.

1.2.1 Prospective Studies

Amdel C et al. (2013) reported on a prospective study that included 41 patients at the Norwegian Radium Hospital with advanced oesophageal cancer. Their aim was to assess whether a combination of self – expanding metal stent (SEMS) and brachytherapy provided more rapid and prolonged effect on dysphagia without increased pain compared to brachytherapy alone. Patients were randomised to SEMS followed by brachytherapy, 24Gy in 3 fractions of 8Gy each or brachytherapy alone. Patients that received SEMS followed by brachytherapy had a significantly improved dysphagia at 3 weeks post treatment compared to patients who received brachytherapy alone (p=0,02). At 7 weeks post treatment patients in both arms had less dysphagia. The authors concluded that for the relief of dysphagia, SEMS followed by brachytherapy is a preferable and safe method in patients for immediate alleviation. They also concluded that brachytherapy with or without preceding SEMS provides relief within a few weeks after treatment.[15]

Homs MYV. et al. (2004) reported on a prospective multicentre randomised trial that compared the outcomes of brachytherapy and stent placement in patients with oesophageal cancer. Between December 1999 and June 2002, 209 patients from 9 hospitals in the Netherlands with advanced oesophageal or oesophagogastric junction carcinoma were randomised to stent placement (n=101) or single dose 12Gy HDRBT (n=101) and were followed up after treatment. It was found that dysphagia improved more rapidly after stent placement than after brachytherapy, however long-term relief of dysphagia was better after brachytherapy. More complications were seen with stent placement than brachytherapy

(36% vs 21%; p=0, 02). The authors recommended that HDRBT be used as primary modality for treatment of palliation of dysphagia from oesophageal carcinoma.[16]

Taal BG et al. (1996) reported on a prospective trial of 74 patients from the Netherlands Cancer Institute with advanced inoperable oesophageal cancer. Patients were treated between February 1991 and September 1994 with a combination of a single dose HDRBT 10Gy followed by 40Gy in 20 fractions EBRT which started 2 weeks after HDRBT. The aim of this study was to assess how quickly relief of dysphagia occurs in these patients. This study showed that brachytherapy improved dysphagia in 39% of the patients in a few days and achieved improvement in 70% of the patients at the end of treatment. Acute side effects occurred in 42% and late effects with ulceration in 7% of the patients after a median time of 4 months. The authors recommended that HDRBT prior to the administration of EBRT was a safe and effective modality to induce a rapid relief of dysphagia especially when combined with EBRT.[17]

1.2.2 Studies done in South Africa or included South Africa

Rosenblatt et.al. (2010) prospectively randomised 219 patients from six countries (Sudan =73; South Africa = 66; India = 29; Croatia = 20; China = 16; Brazil = 15) with squamous cell carcinoma of the oesophagus in order to determine whether the addition of EBRT to high dose – rate brachytherapy (HDRBT) is superior to HDRBT alone for the palliation of oesophageal cancer. Patients in that study were treated from March 2003 to June 2006. Each HDRBT consisted of 8Gy prescribed at 1cm from the active dwell positions, using equal dwell times, with the treatment length including the tumour plus a 2cm margin at both ends. The EBRT consisted of 30Gy in 10 fractions. The dysphagia relief experience was 82, 7% for combined therapy. The median overall survival was 188 days with an 18%

survival rate at 1 year. The authors had concluded that the addition of EBRT to standard HDRBT improved symptoms and the combination is well tolerated and relatively safe.[11]

Sur RK. et. al. (2002) prospectively compared two high dose rate brachytherapy fractionation regimens in the treatment of patients with surgically inoperable squamous cell oesophageal carcinomas between September 1996 and August 1999 at CMJAH. That study included 232 patients who were treated with either HDRBT of 16Gy given in 2 alternate fractions of 8Gy each (Group A) or HDRBT of 18Gy given in 3 fractions on alternate days of 6Gy each (Group B). Dysphagia scoring was done according to the Mellow and Pinkas scoring system with 0 = able to swallow normal diet; 1= able to swallow some solid foods; 2 = able to swallow any semi-solid foods; 3 = able to swallow liquids only; 4 = unable to swallow anything / total dysphagia.
The dysphagia – free survival for the whole group was 7, 1 months (Group A, 7.8 months; Group B, 6, 3 months; p>0, 05). Overall survival was 7, 9 months. The incidence of strictures (Group A, n=12; Group B, n=13; p>0, 05) and fistulas (Group A, n=11; Group B, n=12; p>0, 05) was similar in both groups.[18] The authors concluded that fractionated HDRBT alone was an effective method for palliating patients with advanced oesophageal cancers. Both types of fractionation modalities yielded similar dysphagia- free survival, overall survival, toxicities and were equally effective as a palliation modality for advanced oesophageal cancer.

Sur RK et al. (1998), reported on a prospective randomised trial of 172 patients with advanced oesophageal cancer at CMJAH. The aim of this study was to assess the optimised dose of fractionated HDRBT in the palliation of advanced oesophageal cancer. Patients were randomised to 3 Groups, Group A (12Gy in 2 fractions); Group B (16Gy in 2

fractions) and Group C (18Gy in 3 fractions). Overall survival was 19, 4% at the end of 12 months for the whole group. The dysphagia – free survival was 28, 9% at 12 months for the whole group. The authors concluded that fractionated HDRBT was the best modality for palliation of advanced oesophageal cancer. The optimal dose ranged between 16Gy in 2 fractions and 18Gy in 3 fractions given 1 week apart.[10]

1.2.3 Retrospective Studies

Murray JL et al. (2012) reported on a retrospective study that included 148 patients with inoperable oesophageal cancer. Patients were treated between 2005 and 2010 with palliative EBRT. The dose ranged between 20Gy to 30Gy were 89% of the patients (n=132) received a dose of 20Gy in 5 fractions. An improvement in dysphagia was seen in 75% of the patients and the median overall survival was 6, 1 months. The authors concluded that EBRT remained an effective, non-invasive well tolerated modality to palliate dysphagia in selected patients.[19]

Homs M. et al. (2003) reported on a retrospective study which included 149 patients from Netherlands treated with HDRBT only for inoperable oesophageal cancer, between January 1990 to December 1999 in order to assess the outcome of HDRBT alone in patients with malignant dysphagia. Patients were treated with a median dose of 15Gy in one or two sessions. Six weeks after HDRBT there was a statistical improvement of dysphagia score in 51% of the patients. Late complications of fistula formation or bleeding occurred in 7% of the patients (n=11). Median survival was 160 days with a 1 year survival rate of 15%. At follow up (median of 3 months), 37% of the patients experienced recurrent dysphagia.

The authors concluded that HDRBT is a moderately effective treatment for the palliation of malignant dysphagia. Early major complications were low, however persistent and recurrent dysphagia occurred frequently.[20]

Sharma V. et al. (2002), reported on a retrospective study which included 58 patients from Tata Memorial Hospital with advanced/recurrent oesophageal cancer. Treatment consisted of HDRBT with or without EBRT from November 1994 to May 2000 to assess the improvement in swallowing status, complication rate and overall survival. All patients received two fractions of HDRBT of 6Gy per fraction one week apart, and 35% of the patients received a combination of EBRT and HDRBT. The EBRT dose was either 20Gy in 5 fractions or 30Gy in 10 fractions. There was an overall improvement in swallowing status in 22 patients (48%) and 24 (41%) maintained pre – treatment swallowing status. The median dysphagia – free survival was 10 months and the overall complication rate was 30%. Median overall survival was reported for the entire group as 7 months. The authors concluded that HDRBT afforded patients with advanced/recurrent oesophageal good palliation with acceptable complications.[9]

Hujala K et al. (2002) reported on a retrospective study that included 40 patients from Turku University Central Hospital (Finland) with inoperable oesophageal cancer, to assess if a combination of EBRT and HDRBT would increase local control. Patients were treated between 1989 and 1999, with EBRT 40Gy in 20 fractions and a week later HDRBT 10Gy in 4 fractions. Dysphagia could be relieved in 40% of the patients immediately and in most cases the progression of the disease could be delayed as evidenced by post – treatment serial endoscopy. The 1 and 2 year survival rates were 30 and 17, 5% respectively. The

authors concluded that HDRBT is a safe and efficient treatment modality to palliate patients advanced oesophageal cancer.[21]

Brewster AE et al. (1995) reported on a retrospective study that included 197 patients from Christie Hospital in the United Kingdom who presented with advanced oesophageal carcinoma. Patients were treated between June 1988 and June 1992 with a single HDRBT fraction, the dose ranged from 7, 5Gy to 20Gy. This study showed an improvement in dysphagia in 54% of the patients.[22]

The above prospective and retrospective studies from various countries have made no reference to patient characteristics in terms of risk factors for oesophageal cancer.

Although the number of South Africans infected with HIV has increased by 2.17 million since 2002, when 4.02 million South Africans were living with the virus, none of the local studies above have taken HIV into consideration.

At Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), approximately 100 -150 new cases of oesophageal cancer are seen in the Department of Radiation Oncology every year, and more than 85% of those patients are in an advanced stage with dysphagia as the main complaint.[23]

Different treatment schedules have been suggested in the literature, and the choice of treatment is guided by the patient's age, performance status and site of lesion.

The information obtained in this report would be of value to the Oncologists at CMJAH, in guiding them when choosing a treatment regimen, to palliate dysphagia in advanced/ non - resectable oesophageal carcinoma.

1.3 Aims of the study

1.3.1 The primary aim of this study was:

To assess the improvement in swallowing in patients of advanced carcinoma oesophagus who received different palliative radiation treatments, controlling for prognostic parameters (age, sex, length of lesion, site of lesion, and pre-treatment swallowing status).

1.3.2 The secondary aims of the study were to asses:

a) The variation in time to progression between treatment groups, controlling for the prognostic factors listed above

b) The variation in overall survival between treatment groups, controlling for the prognostic factors listed above

c) The variation in treatment related complications between treatment groups

2. METHOD

This was a retrospective single institution study. Patients with advanced oesophageal cancer were treated with palliative radiation at the Charlotte Maxeke Johannesburg Academic Hospital, between May 2007 and June 2012 so that a follow up of 12 months is available in the records.

The patient inclusion criteria included:

1. Carcinoma of the oesophagus unsuited for radical radiation and curative surgery.
2. Histologically proven squamous cell carcinoma of the oesophagus.
3. Any length of lesion in the oesophagus.
4. With or without metastatic disease.

Exclusion criteria included:

1. Adenocarcinoma histology
2. Previous radiation treatment

The treatment protocol used in the Department of Radiation Oncology at CMJAH for palliative radiotherapy during the period between May 2007 and June 2012 was either external beam radiotherapy or a combination of external beam radiation and fractionated high dose brachytherapy.

2.1 **Technique of EBRT and treatment dose**

Patients were X-ray simulated in the supine position, with their arms at the side. Barium was given as contrast at the time of simulation to delineate the length of tumour as a filling defect. Antero-posterior, postero – anterior fields (AP-PA) were used to administer either 20Gy in 5 fractions in 1 week or 30Gy in 10 fractions over 2 weeks to the mid-line, and with upper and lower fields to be 3cm proximal and distal from the tumour limits and laterally to cover the pleural reflection. The energy used was either Cobalt 60 or 6 MV. The treatment schedule used depended on the treatment length and the performance status of the patient. If the treatment length was less than 12 cm and / or if the patient was in a poor performance status then the shorter treatment schedule was used (20Gy in 5 fractions in 1 week). If the treatment length was more than 12 cm and / or if the patient was in a good performance status then the longer treatment schedule was used (30Gy in 10 fractions in 2 weeks).

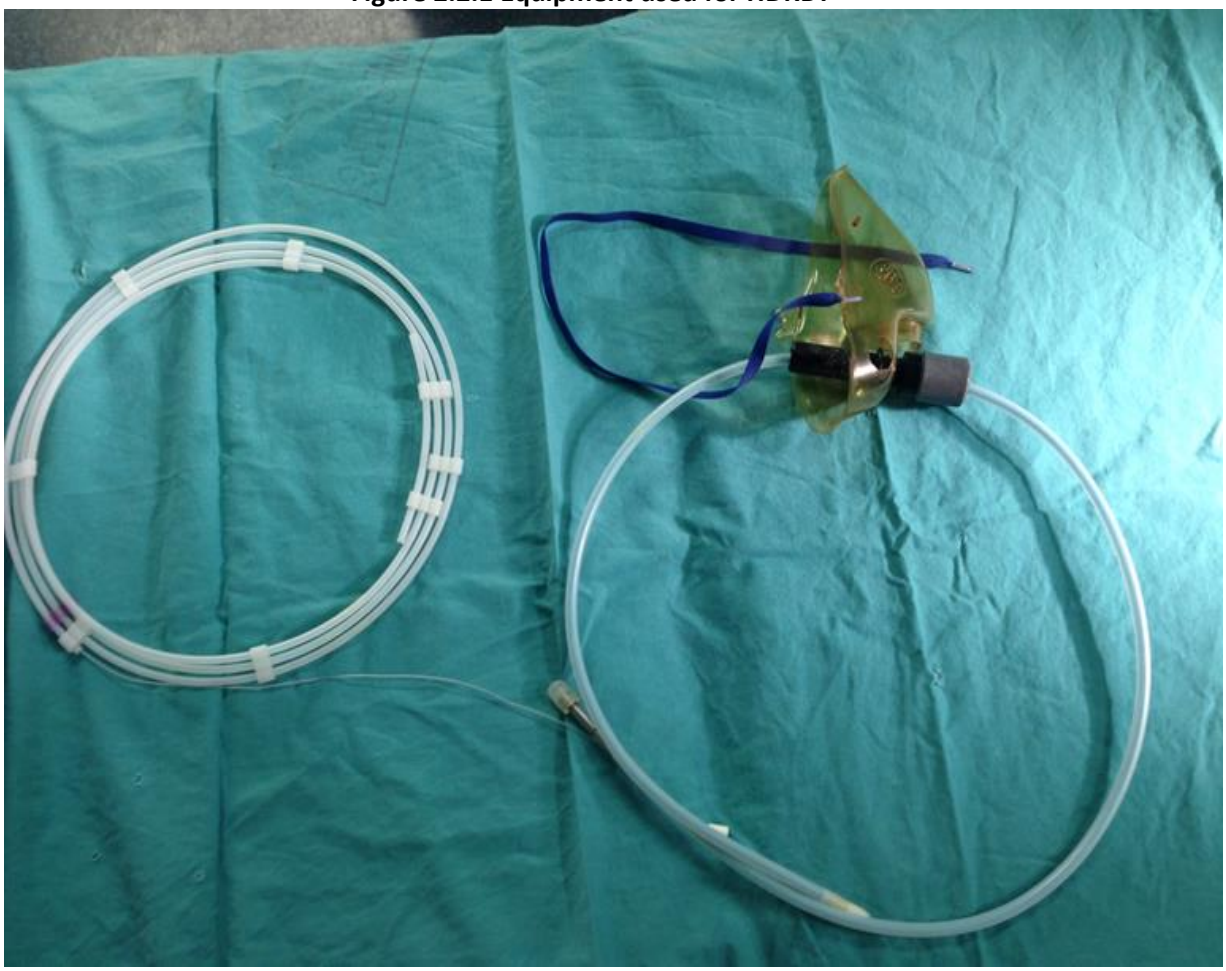
2.2 Technique of HDRBT and treatment dose

The patient swallowed barium at simulation and the field was placed to include the area of interest. The skin marking isocenter (SMIC) was then tattooed, and the films taken at the simulator were used in the brachytherapy procedure. The simulator procedure also serves to screen for a tracheo-oesophageal fistula (TOF), which is a contraindication to brachytherapy, and is most common in mid-third lesions. A stent can be used if there is a fistula. The patients' were starved overnight and Pethidine 50mg and maxolon 20mg were given intramuscularly one hour prior to the procedure. The patient lies supine and the

SMIC tattoo was marked with a wire. Xylocaine was sprayed into the patient's throat to anaesthetise the pharynx. As no barium was used in the procedure, there is no risk of aspiration. The doctor stands at the patient's right side, and his index finger is placed just above the patient's epiglottis, before passing the jellied oesophagus catheter to this level, anterior to his finger. The catheter is thus prevented from touching the pharyngeal wall to prevent gagging. The patient is then asked to swallow and the epiglottis moves over the trachea, and the tube passes down the oesophagus. A 4mm and a 6mm catheter is available. The patient tends to bite on the tube, thus damaging it hence the equipment comes with a bite block which slips over the tube, and is held in place by a simple mask, to prevent the biting of the tube. The commonly used tube diameter at our centre is 6mm. A dummy source catheter is inserted into the tube and the tube fixed in the area of interest (tumour) under fluoroscopic guidance. With the oesophagus tubes, no transfer tube is required, as the distal end of the tube fits into the unit. The source offset and the treatment length must be clearly communicated to the treating radiographer. The treatment time is set according to the length of the treatment area and the dose to be given.

Patients receive two sessions of HDRBT, 7 days apart. The total dose is 16Gy given in 2 fractions. A dose of 8Gy is prescribed at 1cm from the central axis, and a margin of 2cm is given proximally and distally to the visible tumour (as already known from the simulator film). The prescription can either be optimised or non-optimised depending on the site of the lesion.

Figure 2.2.1 Equipment used for HDRBT



2.3 Data collection

Case notes from patient files were reviewed to obtain information pertaining to pre-treatment and post – treatment dysphagia, duration of any response, toxicities and survival. The protocol within the Department of Radiation Oncology at CMJAH during the period (May2007- June 2012) was to review patients 6 weeks post treatment and then every 3 months thereafter. The data was recorded on the specially designed proforma for this study. (Appendix 1)

Dysphagia was scored according to the system described by Mellow and Pinkas (1985) with 0 = able to swallow normal diet; 1= able to swallow some solid foods; 2= able to swallow any semi-solid foods; 3= able to swallow liquids only; 4= unable to swallow anything / total dysphagia.[24]

2.4 Data analysis

Statistical analysis was carried out using SAS software version 9.3 for Windows.[25]
The overall change in swallowing status was assessed by the paired sample t-test. The relationship between the change in swallowing status and treatment group, and each of the prognostic parameters (age, sex, length of lesion, site of lesion, and pre-treatment swallowing status) was determined by a General Linear Model. Post-hoc tests were conducted using the Tukey-Kramer tests, due to unequal treatment group sizes.
Overall survival was determined from the day of first treatment to the last day of follow up or death using Kaplan – Meier analysis. The relationship between the survival and

treatment group and each of the prognostic parameters was determined by a Cox proportional hazards model.

The X^2 test was used to assess the relationships between categorical variables. Fisher's exact test was used for 2x2 tables or where the requirements for X^2 test could not be met. The strength of the associations was measured by Cramer's V and the phi coefficient respectively.

3. RESULTS

3.1 **Clinical Characteristics**

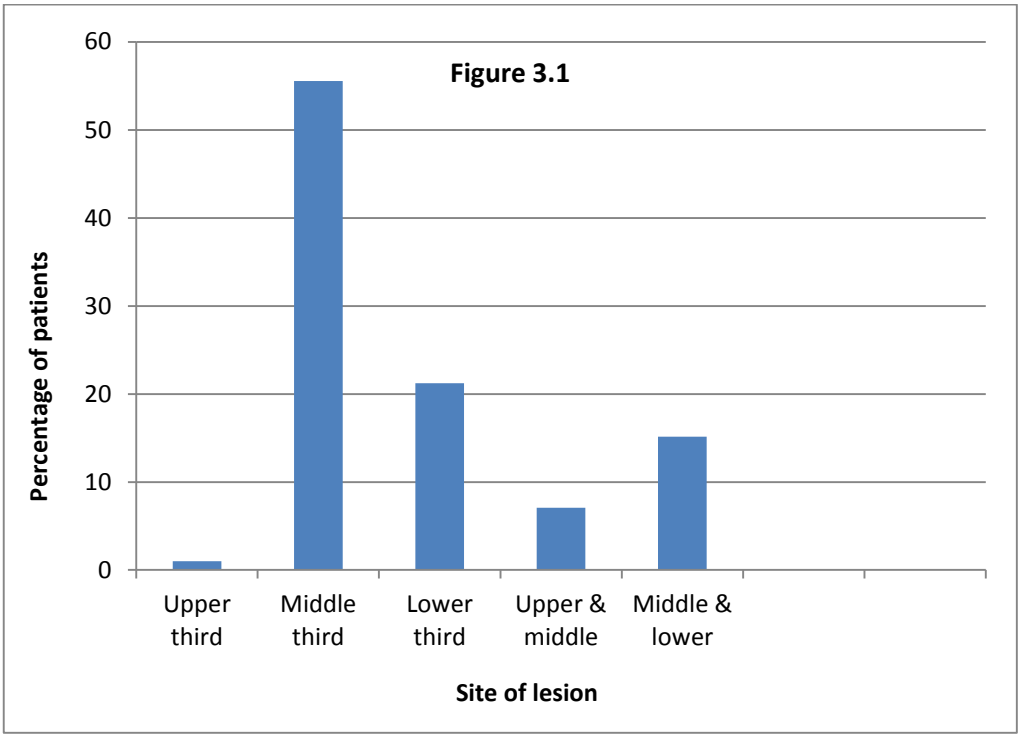
Data from the records of 99 patients that fitted the inclusion criteria were collected for this study. The mean age of patients was 60.6 years (range: 40-83 years), 63% were male and 37% female. The overall performance status of the sample was divided between ECOG 1 (18%), ECOG 2(34%) and ECOG 3(48%). The pre – treatment dysphagia scores were either 2 (44%) or 3 (56%) as shown in table 3.1.

TABLE 3.1 Patient Characteristics

		Frequency (n=99)	Percentage of total sample
Age	40-49y	14	14.1
	50-59y	31	31.3
	60-69y	37	37.4
	70y+	17	17.2
Sex	Male	62	62.6
	Female	37	37.4
Site of lesion	Upper third	1	1.0
	Middle third	55	55.6
	Lower third	21	21.2
	Upper & middle	7	7.1
	Middle & lower	15	15.2
Length of lesion	<5 cm	8	8.1
	5-10 cm	86	86.9
	>10 cm	5	5.1
Dysphagia score PRE	0	0	0.0
	1	0	0.0
	2	44	44.4
	3	55	55.6
	4	0	0.0
ECOG	1	17	18
	2	33	34
	3	47	48

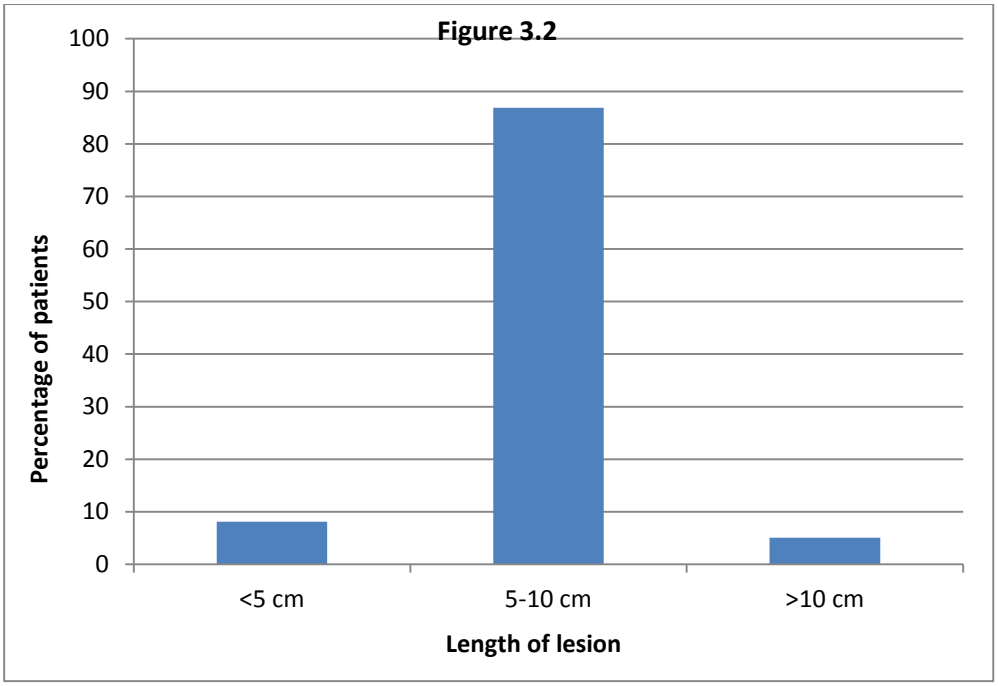
3.1.1 **Site distribution of lesions**

Figure 3.1 illustrates that the predominant site of lesions were in the middle third (56%).



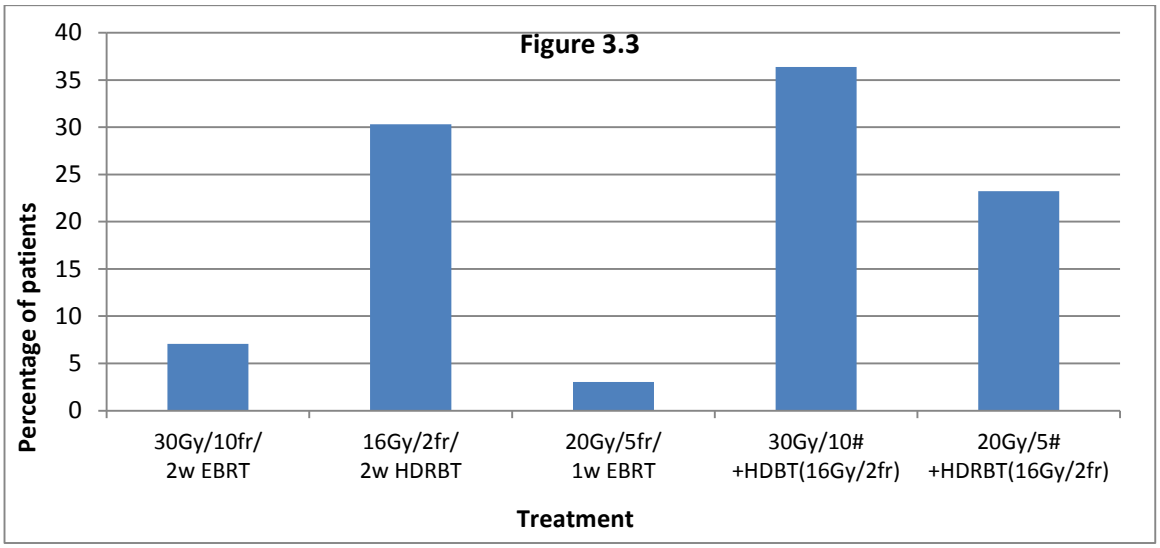
3.1.2 **Length of lesion**

The predominant lesion length was in the range of 5-10cm (87%) (Figure 3.2).



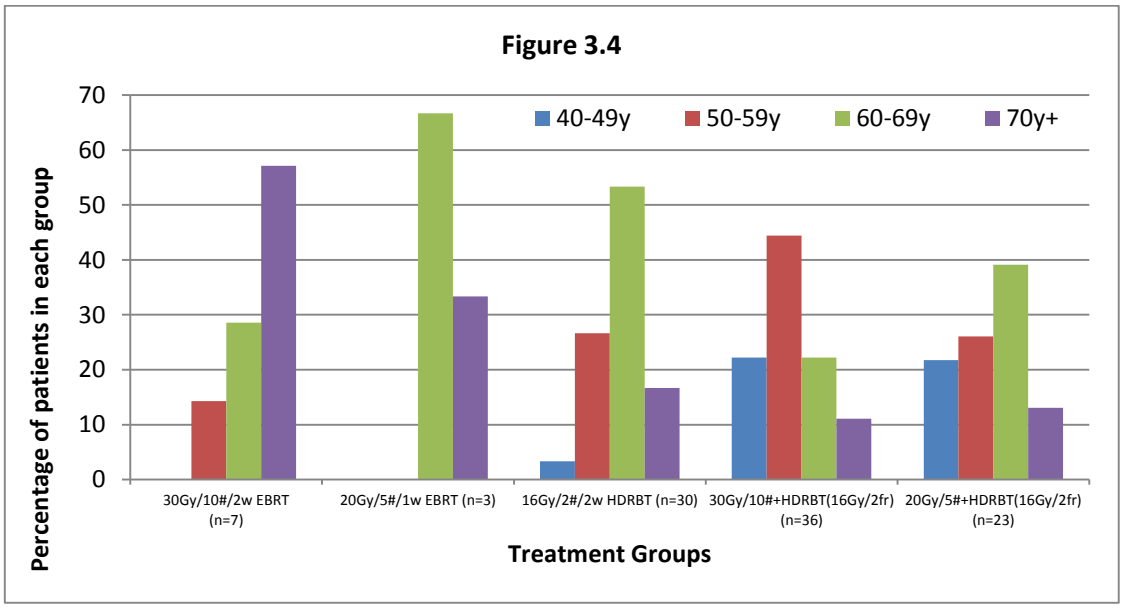
3.1.3 **Distribution of treatment schedules**

The frequency distribution (Figure 3.3), of the different treatments show that the distribution of patients between the treatment groups is variable. The number of patients that received 30Gy in 10 fractions EBRT (n=7) and 20Gy in 5 fractions EBRT (n=3) were very small in comparison to the other treatment arms which were: 16Gy in 2 fractions HDRBT alone, 30 Gy in 10 fractions EBRT with HDRBT, or 20Gy in 5 fractions EBRT with HDRBT). This makes inference about these groups very difficult.



3.1.4 **Correlation between age and treatment group**

As illustrated in Figure 3.4, there was a significant association between age and treatment group (X^2 test; p=0, 0023; Cramer's V=0, 28). The use of 30Gy in 10 fractions EBRT plus HDRBT 16Gy in 2 fractions was lower for older patients, while 16Gy in 2 fractions HDRBT tended to be used more for older patients. The use of a shorter palliative radiotherapy regimen is decided by the treating Radiation Oncologist at the time of patient assessment based on performance and clinical status of the patient.



3.2 Swallowing Status

There was an overall significant improvement in swallowing status (paired sample t-test; p<0.001). Eighty five percent (n=84) of the patients had an improvement in swallowing score of 1 or more points after treatment.

Univariate analysis showed that the effect of treatment was not significant (p=0, 06), in the relationship between swallowing status and treatment group (Table3.2).

However, in the multivariate model, the effect of treatment group controlling for all the covariates was significant (p=0,041).

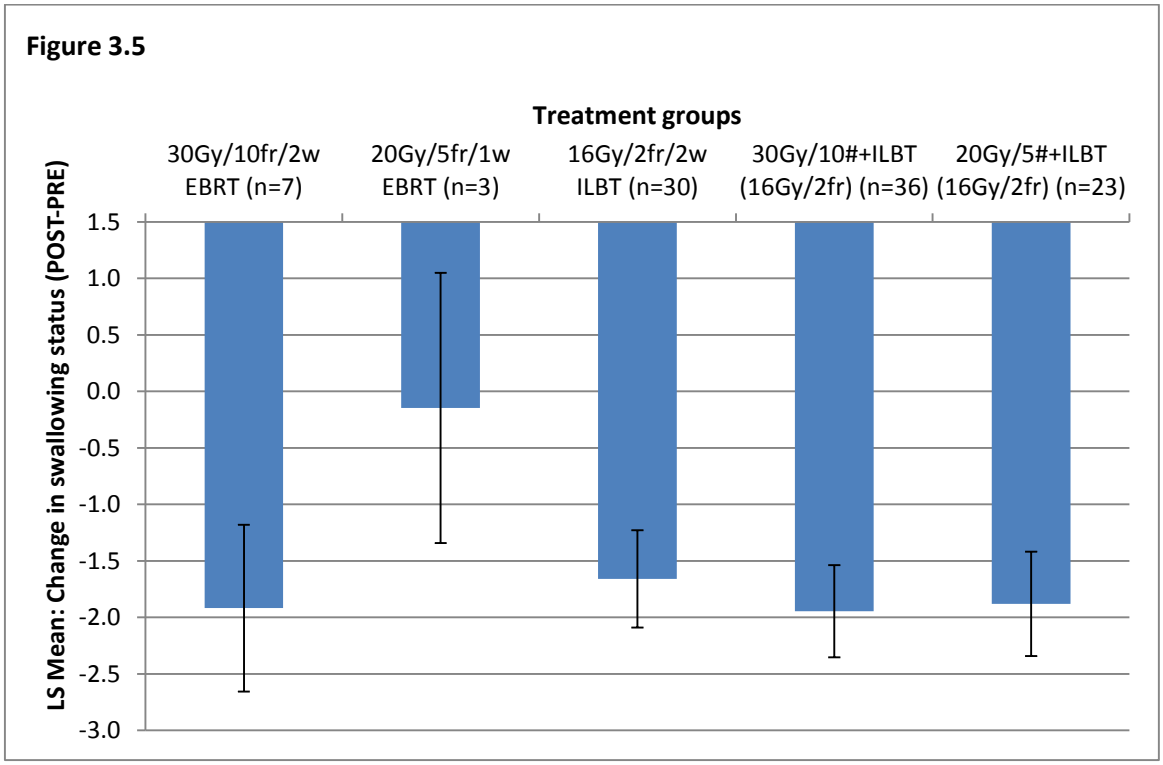
TABLE 3.2 Relationship between Swallowing and Treatment Regimen

Variable	Univariate	Multivariate
	p-value	p-value
Treatment group	0.060	0.041
Age	0.092	0.30
Sex	0.033	0.021
Site	0.013	0.002
Length	0.16	0.11
Dysphagia score (PRE)	0.058	0.41

Post – hoc tests using the Tukey-Kramer adjustment for unequal group sizes showed that the change in swallowing status was less effective for the use of 20Gy in 5 fractions EBRT

as compared with the use of 20Gy in 5 fractions EBRT plus HDRBT 16Gy in 2 fractions, 30Gy in 10 fractions EBRT plus HDRBT 16Gy in 2 fractions, and 30Gy in 10 fractions EBRT. Given the small patient numbers in the 20Gy in 5 fractions EBRT treatment group (n=3) and 30Gy in 10 fractions EBRT group (n=7), this conclusion cannot be generalised. There were no other significant, between-group differences in change in swallowing status. The results are depicted in Figure 3.5

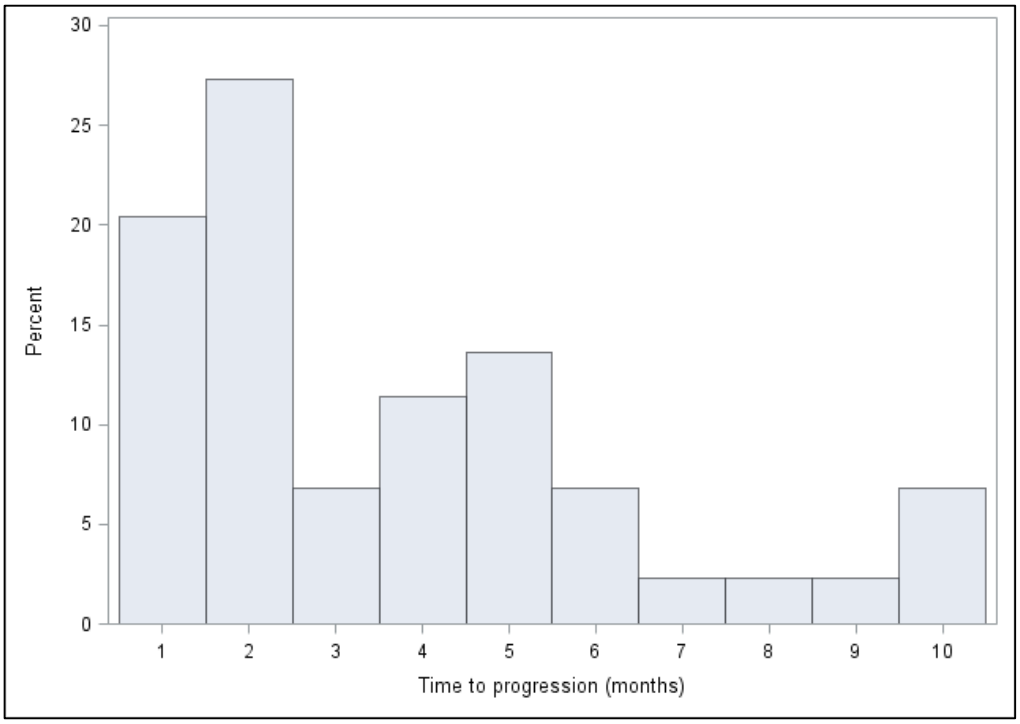
Figure 3.5



3.3 **Dysphagia Relapse**

The overall mean time to dysphagia was 3, 7 months for 46% of the patients. (Figure 3.6).

Figure 3.6



3.4 **Survival**

The median survival time was 7, 7 months and an estimated 33, 9% surviving to 12 months (Figure 3.7) (Table 3.3).

Figure 3.7 Survival Curve

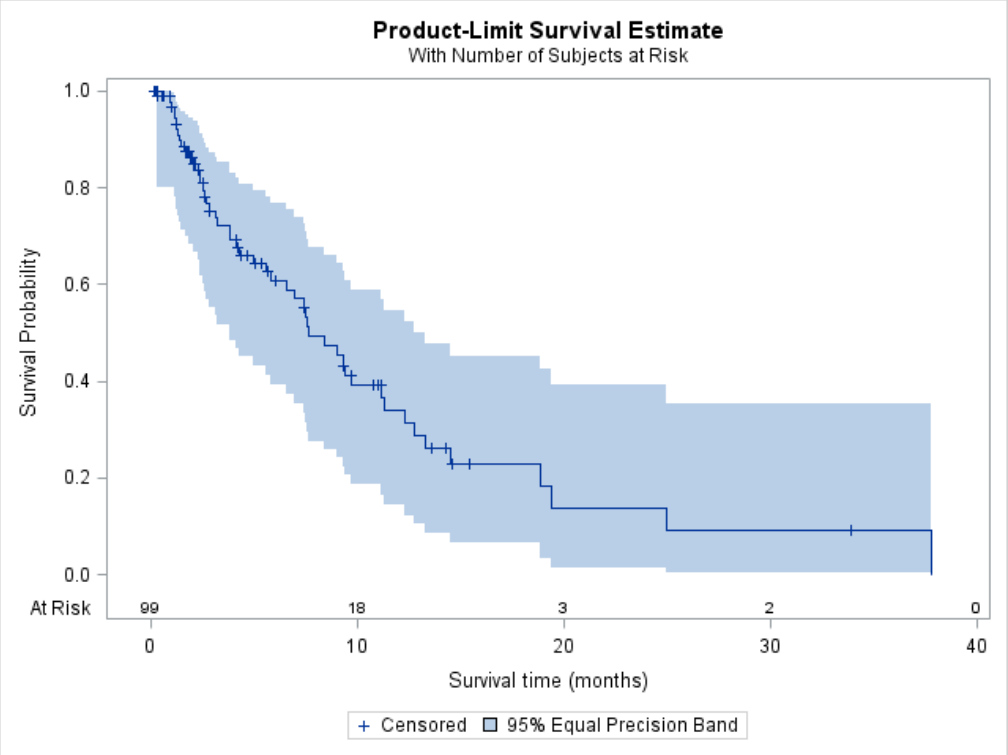


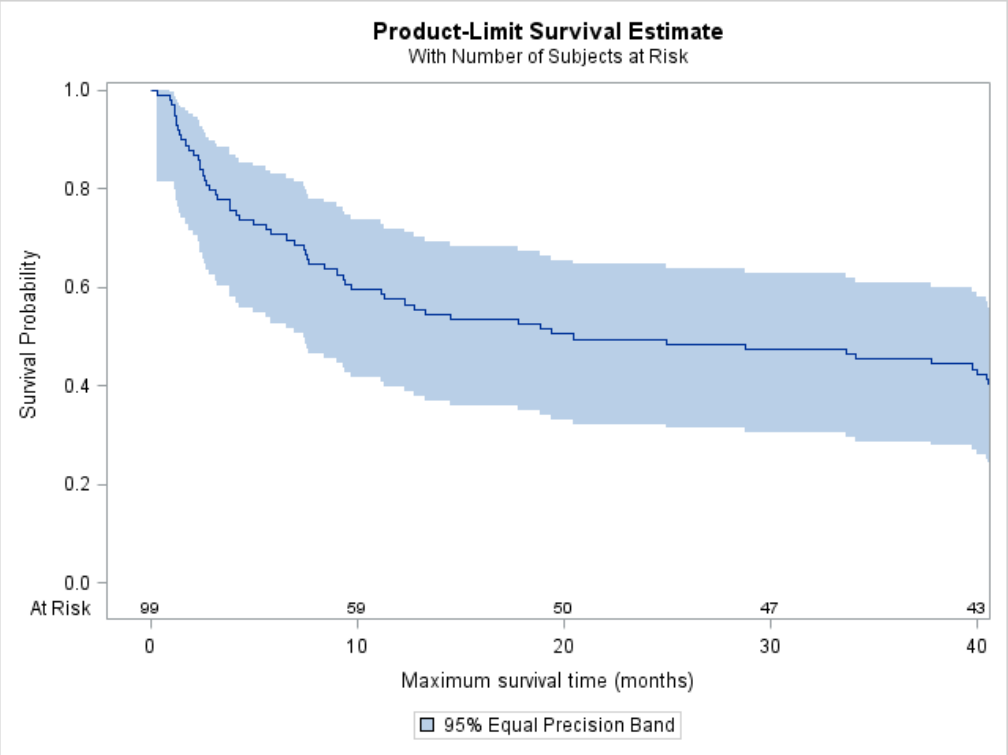
Table 3.3 Survival Times

		Overall (n=99)	
		estimate	95% CI
Actual data	Median survival time (months)	7.7	(5.8-11.2)
	Percentage surviving to 12 months	33.9	(20.9-46.9)
Max. survival time	Median survival time (months)	20.4	(9.7-40.6)
	Percentage surviving to 12 months	57.6	(47.8-67.4)
Min. survival time	Median survival time (months)	3.2	(2.5-4.4)
	Percentage surviving to 12 months	13.1	(6.4-19.8)

To determine the effect of bias due to loss to follow-up, maximum and minimum survival rates were determined:

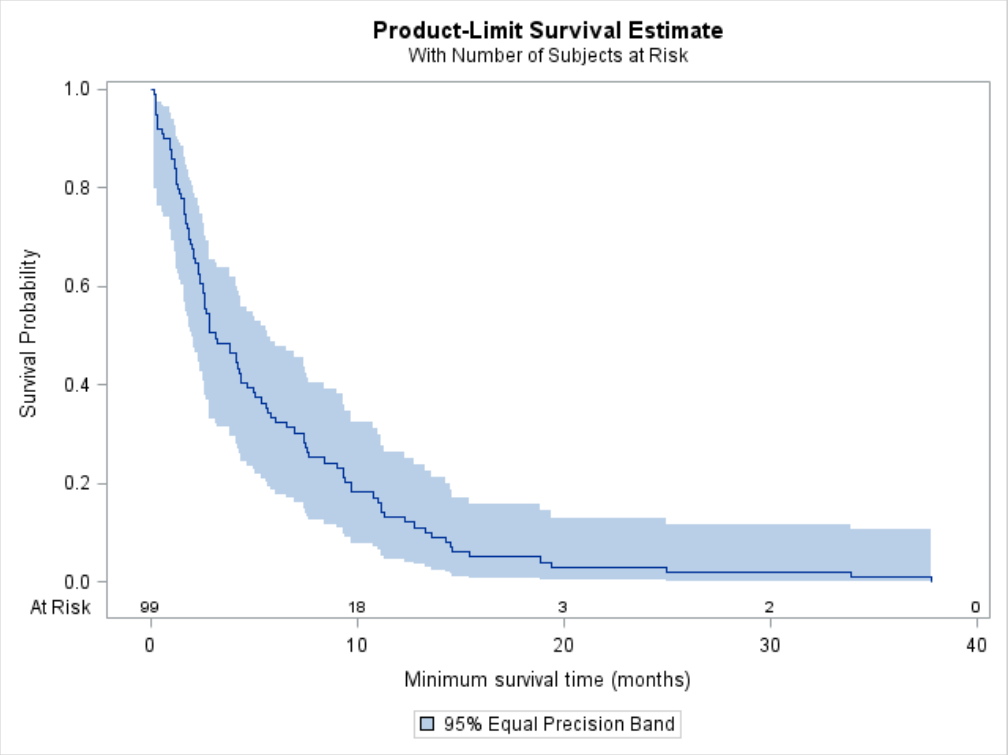
To determine the maximal survival rate, it was assumed that patients who were lost to follow-up are alive at the end of the study which ended on 4/12/2013. The median survival time was estimated as 20, 4 months and 57, 6% surviving to 12 months (Table 3.3) (Figure 3.8).

Figure 3.8 Maximum Survival



The minimum survival rate was determined by assuming that all patients lost to follow up died at the last follow up date. The median survival time was 3, 2 months and 13, 1% surviving to 12 months (Table 3.3) (Figure 3.9).

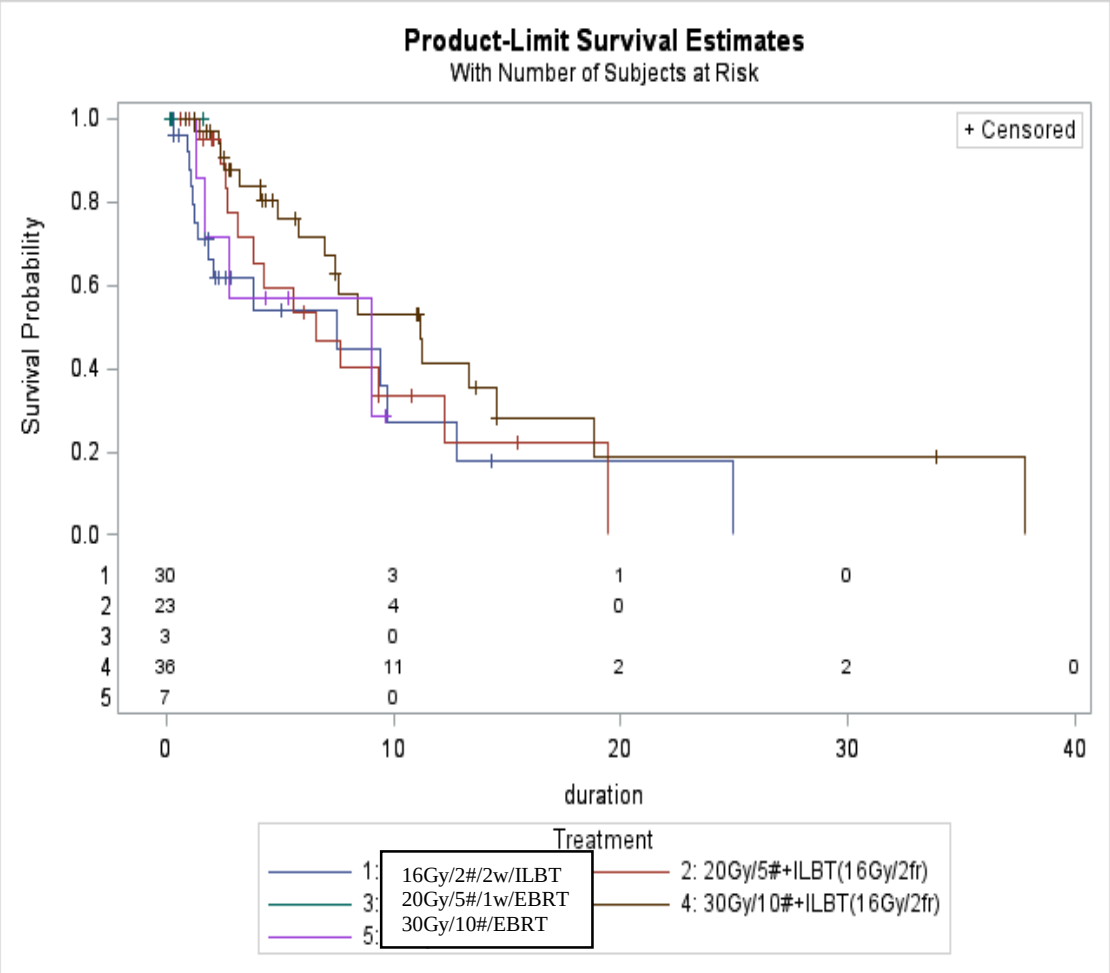
Figure 3.9 Minimum Survival



The figures seen in the maximal and minimal survival times are extremes. If follow up of patients was aggressive, the figures between the actual data, maximum and minimal could actually be somewhere in the middle.

The relationship between the survival group and treatment group and each of the covariates in turn was determined by Cox proportional hazards model. The below graph (Figure 3.10) illustrates that the longest median survival time was obtained by the 30Gy in 10 fractions EBRT and HDRBT group of patients.

Figure 3.10 Relationship between Survival Group and Treatment Group



As illustrated in Table 3.4 below, we see that the effect of treatment on univariate analysis was not significant for survival (p=0, 31). The results of the multivariate model, which considers the simultaneous influence of the prognostic factors, show that there were no significant differences in the survival curve between treatment groups (p=0, 29)

TABLE 3.4 Relationship between Survival and Treatment Groups

Variable	Univariate	Multivariate
	p-value	p-value
Treatment group	0.31	0.29
Age	0.44	0.30
Sex	0.36	0.22
Site	0.51	0.44
Length	0.58	0.55
Dysphagia score (PRE)	0.46	0.52

3.5 **Complications**

Treatment complications were recorded in 32% of the cases. The complications were divided between ulcerations (24%), tracheal oesophageal fistula (5%), and stricture (3%) (Figure 3.11).

Figure 3.11 Complications arising from treatment

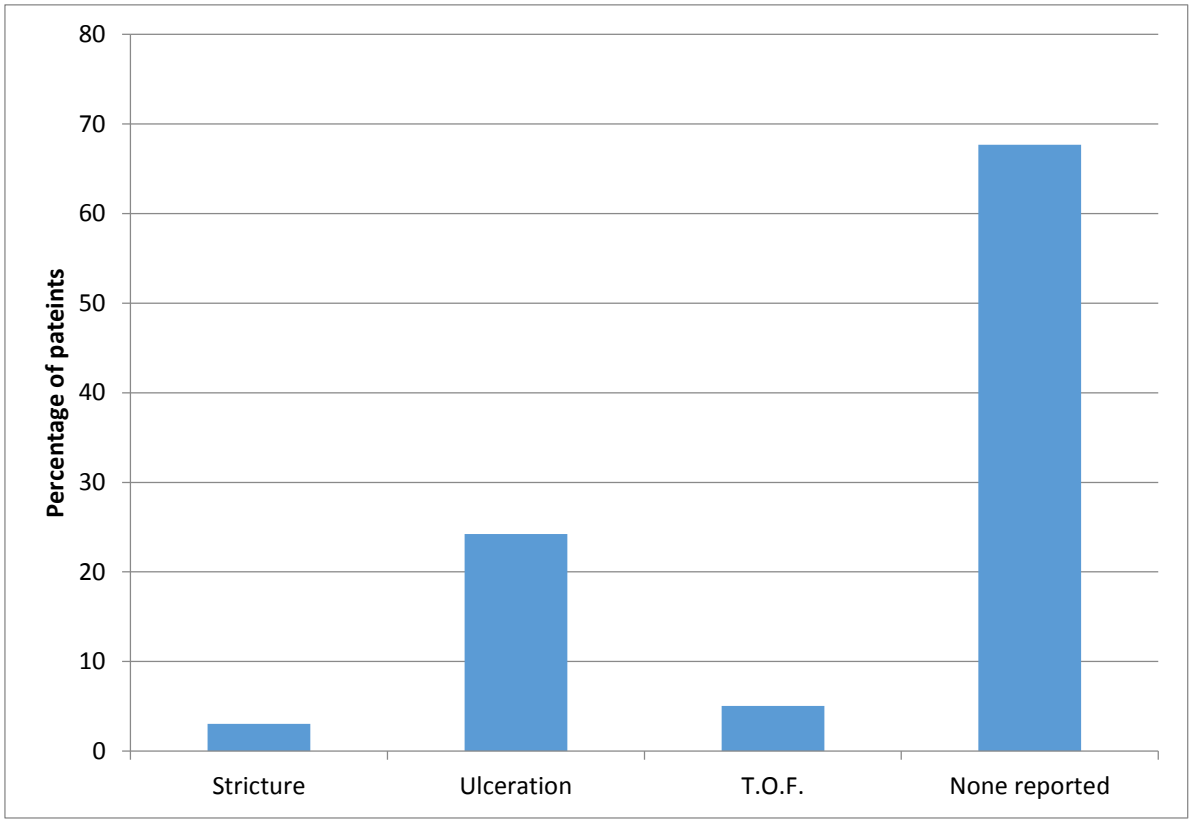
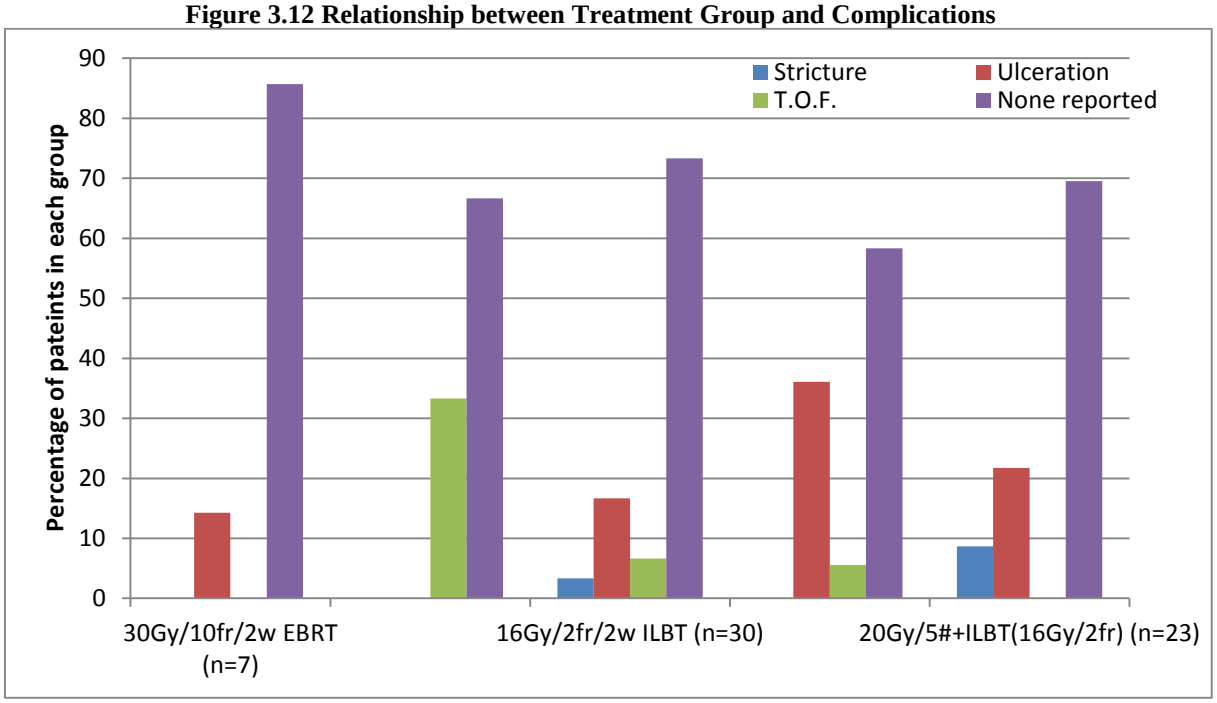


Figure 3.12 Relationship between Treatment Group and Complications



There was no significant association between treatment group and treatment related complications (Fisher's exact test; p=0, 12), (Figure 3.12)

4. DISCUSSION

At CMJAH, Department of Radiation Oncology, approximately 100-150 new cases of oesophageal cancer are seen every year, with more than 85% of those patients having advanced oesophageal cancer.[23] Dysphagia is a distressing symptom in advanced oesophageal cancer, and is the main complaint in 80% of the patients.[6] Palliation of dysphagia is the major goal in the treatment of advanced oesophageal cancer, however there is no consensus on the best approach to achieve this goal. The protocol being followed at CMJAH is to offer patients palliative EBRT with or without HDRBT depending on the patients clinical condition. Poor follow up of the patients that received palliative radiotherapy at CMJAH make it difficult to assess treatment response, therefore the aim of this study was to assess improvement in swallowing status of patients that received palliative radiotherapy for advanced oesophageal carcinoma. The information obtained in this study can help guide the clinician in choosing the optimal palliative radiotherapy regimen to relieve symptoms and reduce suffering caused by cancer.

From the data collected in the 99 patients it can be noted from Table 3.1, the patients were of advanced age as the mean age was 60,6 years and majority of the patients were between an intermediate (ECOG 2: 34%) and poor (ECOG3: 48%) performance status. The predominant lesion length in Figure 3.2 was in the range of 5-10cm (87%). The above data confirms and correlates with the literature that majority of patients are diagnosed with locally advanced oesophageal cancer and are clinically unwell due to poor nutrition from their dysphagia at the time of assessment.[23] The different treatment regimens namely 30Gy in 10 fractions EBRT only, 20Gy in 5 fractions EBRT only, 30Gy in 10 fractions EBRT plus 16Gy in 2 fractions HDRBT, 20Gy in 5 fractions EBRT plus 16Gy in 2 fractions or

HDRBT alone 16Gy in 2 fractions were allocated to the above patients at the time of initial assessment based on the expert opinion of the individual treating radiation oncologist. As shown in Figure 3.3 and Figure 3.4 the shorter radiation treatment schedules: 30Gy in 10 fractions EBRT only, 20Gy in 5 fractions EBRT only and 16Gy in 2 fractions HDRBT only, were allocated to older patients as they would not tolerate a longer course of treatment due to their clinical status, as well would be a burden with their short life expectancy and quick relief of their dysphagia would be the aim.

Studies in the literature have shown that EBRT with or without HDRBT is an effective palliative treatment modality in advanced oesophageal carcinoma.[9,10,11,18] Dysphagia in those studies were scored according to Mellow and Pinkas, were 0=able to swallow normal diet, 2=able to swallow any semi-solid foods, 3=able to swallow liquids only and 4= unable to swallow anything.[24] An improvement in swallowing status was measured by assessing the post-treatment dysphagia score to the pre-treatment dysphagia score, a positive change in one or more points of dysphagia was an improvement.

In this study the same dysphagia scoring system was also used. From the data collected in the 99 patients it was noted in Table 3.1 that the pre-treatment dysphagia scores were either 2 (44%) or 3 (56%), which correlates with the literature that majority of patients with advanced oesophageal cancer have dysphagia as their main complaint. This study had shown that 85% (n=84) of the patients had an improvement in swallowing score of 1 or more points after treatment with palliative radiation and overall had an improvement in swallowing status ($p<0.001$). The results obtained in this study were comparable to that reported in the literature (Table 4.1).

Table 4.1 Swallowing Response Rates

AUTHORS	PATIENT NUMBERS	TREATMENT	IMPROVEMENT IN SWALLOWING STATUS
Rosenblatt et al. (2010)	110	EBRT + HDRBT	82,7% (p=0.019)
	109	HDRBT	66,7% No p value stated
Sur RK et al. (2002)	232	HDRBT	80% No p value stated
Taal BG et al. (1996)	74	EBRT + HDRBT	70% No p value stated
Murray JL et al. (2012)	148	EBRT	75% No p value stated
Present Study	99	EBRT +/- HDRBT	85% (p=<0.0001)

However due to the limitations of a retrospective study, and the small patient numbers in the 30Gy in 10 fractions EBRT and 20Gy in 5 fractions EBRT treatment groups, a specific treatment regimen could not be identified that statistically improved the swallowing status (Table 3.2 and Figure 3.5). Further studies with larger patient numbers per treatment arm are recommended.

Patient survival reported in the literature range from 5 – 9, 9 months (Table 4.2).

Table 4.2 Patient Survival

AUTHORS	MEDIAN SURVIVAL	ONE YEAR O.S.
Murray JL et al. (2012)	6,1 months	Not Reported
Rosenblatt et al. (2010)	7 months	18%
Homs et al (2003)	5,3 months	15%
Sur RK et al. (2002)	6,2 months	Not Reported
Hujala et al. (2002)	Not Reported	30%
Present Study	7,7 months	33,9%

In this study the median overall survival was 7, 7 months and an estimated 33, 9% surviving to 12 months. Although the result obtained are comparable to that seen in the literature, caution should be noted in the interpretation of the median survival time and the estimated surviving patients at 12 months in this study. The maximum and minimal survival rates as previously stated (Table 3.3) are very different to those of the actual data. This implies bias to patients who are lost to follow up and to those whom the date of death is unrecorded, which plays a large role in this data set.

The dysphagia free survival reported in the literature ranges from 7 – 12 months for EBRT with or without HDRBT.[9,11,18] In this study the overall mean time to dysphagia relapse was short at 3, 7 months for 44% of the patients that were recorded. The possible reasons for the short time in this study could be that only 44% of the patient population was recorded, or using the shorter radiation treatment schedules could have decreased the duration of palliation.

As reported in the literature, palliative EBRT with or without HDRBT is a safe modality in the management of advanced non-operable oesophageal carcinoma.[7,9,10,11,17] In this study detailed reporting of toxicity was not possible as sufficient detail was provided in only 32% of the cases (Figure 3.12).

Limitations were encountered in this study, many of which are common to any retrospective analysis such as small sample size per treatment group, poor patient follow up and poor record keeping in patient files.

In the proforma (Appendix 1) attached there were many variables that we hoped to have collected such as prognostic factors for survival (Weight loss, laboratory assessment and histological grade) and risk factors for disease such as social habits (smoking, alcohol) and HIV status. Unfortunately due to poor record keeping the above information could not be attained and analysed.

However, within those limitations, the results of the current study revealed that palliative radiotherapy in patients with incurable oesophageal cancer provided an improvement in dysphagia in 84% of the treated patients.

5. CONCLUSION

In this retrospective pattern of care analysis of patients with advanced oesophageal cancer, it was found that palliative radiotherapy is an effective modality in improving a patient's dysphagia, despite the limitations encountered.

Clinicians should choose a treatment regimen for a patient that is tailored to their age, performance status and extent of disease.

It is recommended that further studies with larger sample sizes per treatment group are needed to address the role of a specific treatment regimen on improving swallowing status, the dysphagia free survival, overall survival, and assessing the treatment related complications associated with palliative radiation. As HIV/AIDS in South Africa is a prominent health concern, it should feature when larger local studies are being performed to ascertain if it is a prognostic factor in the palliation of locally advanced oesophageal cancer.

6. APPENDICES

APPENDIX 1

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

DEPARTMENT OF RADIATION ONCOLOGY

CARCINOMA OESOPHAGUS PROFORMA

1. Code No.: ____
2. Age: ☐
3. **Suitability:**

   00. Suitable ☐
   01. Not suitable
4. Registration date: DD / MM / YYYY
5. Age (years) ☐
6. **Gender** ☐
   00- Male
   01- Female

CLINICAL PRESENTATION

7. **Difficulty swallowing** ☐
   00- Not applicable
   01- Not known (5)
   02- Able to eat normal diet(0)
   03- Able to swallow some solids(1)
   04- Can swallow semi solids(2)
   05- Can swallow liquids(3)
   06- Total obstruction(4)

8. **Weight. Loss** ☐
   00- Not known
   01- Present
   02- Absent

If present ☐ Kg

9. **Other presentations**
   00- Not applicable
   01- Not known
   02- Chest pain
   03- Hoarseness
   04- Back pain
   05- T.O.F.
   06- S/C node involvement
   07- Abdominal node involvement
   08- Liver involvement
   09- Combination
   10- Other (Specify) ☐

Period ☐ months

10. **Habits** ☐
    00- None
    01- Smoking
    02- Drinking
    03- Both

11. **Performance status** ☐
    00- Not applicable
    01- Not known
    02- Fully active (ECOG0)
    03- Able to carry out work of a light nature (ECOG1)
    04- Capable of all self-care. Up and about >50% of waking hours (ECOG2)
    05- Capable of limited self-care, confined to bed or chair >50% of waking hours (ECOG3)
    06- Completely disabled. Totally confined to bed (ECOG4)

Laboratory ASSESSMENT

12. HB ☐ (gms/100ml)

13. WBC ☐ (cu/mm)

14. Albumin ☐ (gms/ml)

15. Alk. Phos ☐ (U/L)

16. **HIV**
    00- Not done
    01- Positive
    02- Negative.

CD4 count ☐ ARVs: Y/N

17. A. **Barium swallow (Lesion length – cm)**

00- Not applicable
01- Not known
02- <5 cm
03- 5-10 cm
04- > 10 cm

B. Vertebral height:

C. Endoscopy, distance from incisor

18. **Site of lesion**

00- Not applicable
01- Not known
02- Upper 3rd
03- Middle 3rd
04- Lower 3rd
05- Upper + mid
06- Mid+ lower
07- Whole length
08- Lower

19. **Initial treatment**

00- Not applicable
01- Not known
02- No treatment
03- Radiotherapy
04- Other (Specify)

20. **Histological grade**

00- Not applicable
01- Not known
02- Well differentiated
03- Moderately differentiated
04- Poorly differentiated
05- Undifferentiated
06- No Grade

21. **Planned Radiotherapy**

00. Date of start DD / MM / YYYY

01. Date of completion: DD / MM / YYYY

22. **Dosage schedule**

00- Not applicable
01- Not known
02- 30Gy/10fr/2 weeks EBRT
03- 16Gy/2fr/2weeks ILBT
04- 20Gy/5fr/1week EBRT
05- 30Gy/10# + ILBT (16Gy/2fr)
06- 20Gy/5# + ILBT (16Gy/2fr)

23. **Complications**

00- Not applicable
01- Not known
02- No complications
03- Stricture
04- Ulceration
05- T.O.F.

24. **Immediate response**

00- Not applicable
01- Not known
02- Complete response
03- Partial response(30%+)
04- Poor response
05- Progressive disease

25. **Site of recurrence**

00- Nil
01- Local
02- Loco regional
03- Distant

26. **Response to treatment**

00. Not applicable
01. Not known
02. Complete response
03. Partial response (30 %+)
04. Poor response

27. **Follow up swallowing (Swallowing score)**

00. Able to eat normal diet (0)
01. Able to swallow some solids (1)
02. Can swallow semi solids (2)
03. Can swallow liquids (3)
04. Total obstruction (4)
05. Not known (5)

28. **Time of relapse:**

Months ☐

29. **Disease free survival**
00. Not applicable
01. Not known
02. Alive without disease
03. Died of other causes
04. Suffered relapse

☐

30. **Overall Survival Status**
00. Not applicable
01. Not known
02. Alive
03. Died of disease

☐

31. Last follow up date DD / MM / YYYY

32. Overall Survival (period) ☐

APPENDIX 2

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M131047

NAME: (Principal Investigator)	Dr Sudeshen M Naidoo
DEPARTMENT:	Department of Radiation Oncology CM Johannesburg Academic Hospital
PROJECT TITLE:	Patterns of Practice for Palliative Radiotherapy in Oesophageal Carcinoma-A Retrospectivre Analysis at CM Johannesburg Academic Hospital (2007-2012)
DATE CONSIDERED:	25/10/2013
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof V Sharma
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 22/11/2013

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University

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 resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature M131047 26/11/2013 Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 3

Faculty of Health Sciences
Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172040

Reference: Ms Mpumi Mnqapu
E-mail: mpumi.mnqapu@wits.ac.za

17 October 2013
Person No: 587838
PAG

Dr SM Naidoo
Unit 15 canterbury Close
North Avenue
Riviera
Johannesburg
2136
South Africa

Dear Dr Naidoo

Master of Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *Pattern of practice for palliative radiotherapy in oesophageal carcinoma: A retrospective analysis at Charlotte Maxeke Johannesburg Academic Hospital (2007-2012)* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

APPENDIX 4

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PATTERN OF PRACTICE FOR PALLIATIVE RADIOTHERAPY IN OESOPHAGEAL CARCINOMA – A RETROSPECTIVE ANALYSIS AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL (2007-2012)

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7. REFERENCES

1. GLOBOCAN 2008 database (version1,2); (http://globocan.iarc.fr)
2. NCR-SA 2005 statistics (http://www.nioh.ac.za);5-6
3. Jemal A et al. Cancer statistics,2010, CA Cancer J Clin 2010; 60(5):277-300
4. Schottenfeld D. Epidemiology of cancer of the oesophagus. Semin Oncol 1984;11:92-100
5. van Rensburg SJ. Epidemiologic and dietary evidence for a specific nutritional predisposition to esophageal cancer. J Nat. Cancer Inst 1981;67:243-251
6. Javle M, Ailawadhi S, Yang GY et al. Palliation of Malignant Dysphagia in Esophageal Cancer: a literature - review. J Support Oncol 2006;4:365-73
7. Sharma V, Dinshaw KA, Agarwal JP, et al. Intraluminal brachytherapy for palliation of advanced/recurrent carcinoma oesophagus. J Brachytherapy Int 1999; 15:85-92
8. Gunderson L, Tepper E, editors. Clinical Radiation Oncology, 3rd edition, Philadelphia: P.A. Saunders Company, 2012, pp839.
9. Sharma V, Mahantshetty, Dinshaw k et al. Palliation of advanced/recurrent esophageal carcinoma with high dose- rate brachytherapy. Int J Radiat Oncol Biol Phys 2002;52:310-315
10. Sur RK, Donde B, Levin CV, et al. Fractionated high dose intraluminal brachytherapy in palliation of advanced esophageal cancer. Int J Radiat Oncol Phys 1998; 40(2):447-453
11. Rosenblatt E, Jones G, Sur RK et al. Adding external beam to intra-luminal brachytherapy improves palliation in obstructive squamous cell oesophageal

cancer: A prospective multi-centre randomized trial of the International Atomic Energy Agency. Radiother Oncol. 2010;97(3):488-94

12. Berry B et al. Pathological findings in total esophagectomy specimens after intracavitory and external beam radiotherapy. Cancer 1989;64:1833-1837
13. Peterson AT et al. Brachytherapy of oesophageal cancer: Some considerations on dose to adjacent normal tissue structures. Endocuriether Hypertherm Oncol 1996;12:225-229
14. Siersema PD. Dees J et al. Palliation of malignant dysphagia from oesophageal cancer. Rotterdam oesophageal Tumour Study Group. Scandinavian J Gastro 1998;225:75-84
15. Amdal CD, Jacobsen A, Standstad B et al. Palliative brachytherapy with or without primary stent placement in patients with oesophageal cancer, a randomised phase III trial. J Radiother Oncol 2013;107:428-433
16. Homs MYV et al. Single – dose brachytherapy vs metal stent placement for the palliation of dysphagia from oesophageal cancer: a multicentre randomised trial. Lancet 2004;364:1497-504
17. Taal BG, Aleman BM, Koning CC et al. High dose rate brachytherapy before external beam irradiation in inoperable oesophageal cancer. Br J Cancer 1996;74:1452-7
18. Sur RK, Levin CV, Donde B, et al. A prospective randomized trial of HDR brachytherapy as a sole modality in palliation of advanced esophageal cancer. An IAEA study. Int J Radiat Oncol Biol Phys 2002;53:127-33
19. Murray LJ, Kumar VS, Dixon LM et al. Palliative radiotherapy in patients with oesophageal carcinoma: A retrospective review. Prac Radiat Oncol 2012;2:257-264

20. Homs M, Eijkenboom W, Coen V et al. High dose rate brachytherapy for the palliation of malignant dysphagia. J Radiother Oncol. 2003;66:327-32
21. Hujala K, Sipila J, Minn H et al. Combined external and intraluminal radiotherapy in the treatment of advanced oesophageal cancer. J Radiother Oncol 2002;64:41-45
22. Brewster AE, Davidson SE, Makin WP et al. Intraluminal brachytherapy using the high dose rate microSelectron in the palliation of carcinoma of the oesophagus. Clin Oncol 1995;7:102-5
23. Sharma V. Charlotte Maxeke Johannesburg Academic Hospital stats. (Unpublished)
24. Mellow MH, Pinkas H. Endoscopic laser therapy for malignancies affecting the oesophagus and GOJ: analysis of technical and functional efficacy. Arch Intern Med 1985;145:1443-6
25. SAS Institute Inc, SAS Software, version 9,3 for Windows, Cary, NC, USA: SAS Institute Inc. (2002-2010)