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DYSPHAGIA PROGRESSION-FREE SURVIVAL IN PATIENTS WITH LOCALLY ADVANCED AND METASTATIC OESOPHAGEAL CANCER RECEIVING PALLIATIVE RADIATION THERAPY

by

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DECLARATION

I, Dr. Nazreen Bhim, declare that the work on this study is originally my work except where acknowledgements are indicated. This is an unsponsored study and was carried out for educational purposes only as a MMed for a postgraduate degree. I therefore declare no conflict of interest whatsoever.

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PART A: ABSTRACT AND STUDY PROTOCOL

DYSPHAGIA PROGRESSION-FREE SURVIVAL IN OESOPHAGEAL CANCER PATIENTS TREATED WITH PALLIATIVE RADIATION THERAPY

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ABSTRACT

Purpose: In patients with advanced oesophageal carcinoma palliation of dysphagia is important to maintaining a reasonable quality of life. The primary aim of this study was to determine the dysphagia progression-free survival (DPFS) in patients with advanced oesophageal carcinoma treated with palliative radiotherapy (RT).

Methods: The medical records of all patients with oesophageal carcinoma presenting to Groote Schuur Hospital, Cape Town between January 2015-December 2016 were reviewed and patients who were not candidates for curative treatment and received palliative RT were selected. For these patients, the dysphagia score (DS) was recorded prior to RT, 6 weeks after RT and at each follow-up visit. The DPFS was calculated as the time from completion of RT to worsening in DS by ≥1 point or until death. Other outcomes measured were objective change in DS and survival post RT.

Results: The study population comprised 84 patients. Squamous cell cancer was the primary histological subtype (93%). The median duration of DPFS after RT was 73 days, with approximately two-thirds of patients remaining able to swallow at least liquids and soft diet until death. The difference in median duration of DPFS was not statistically significant in stented versus non-stented patients (54 days vs 83 days; p =0.224). The mean change in DS was 0.45 ± 0.89 points following RT and the post RT survival was significantly shorter in patients with stent insertion (81 days vs 123 days; p=0.042).

Conclusion: Palliative RT can be used successfully to prolong DPFS in patients with locally advanced and metastatic squamous cell cancer of the oesophagus.

Key Words: Oesophageal cancer, locally advanced, dysphagia score, palliative radiotherapy.

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Research Protocol

Introduction

Worldwide, nearly 456,000 new cases of oesophageal cancer were estimated to have been diagnosed in 2012, with incidence rates varying across the world (1,2). It was described as the 6th leading cause of cancer related death in men and 9th leading cause of cancer related death in women in 2012 (2). Oesophageal cancer was the 8th most common cancer diagnosed in South Africa in 2013 (3). Approximately 70% of cases in England, Scotland and Northern Ireland in 2014 were diagnosed at a late stage (1). Although definitive data is lacking for South Africa, the majority of new cases follow a similar trend with a high percentage of patients presenting with locally advanced or metastatic disease. The average survival in these patients range from 4-6 months and palliation of their symptoms, specifically dysphagia is crucial to maintaining an acceptable quality of life.

Purpose of the Study

The primary aim:

- To determine the mean dysphagia progression-free survival after radiation therapy in patients with locally advanced or metastatic oesophageal cancer.

Primary research hypothesis:

- The mean dysphagia progression-free survival after radiation therapy in patients with locally advanced or metastatic oesophageal cancer is within the range of 3-6 months.

The secondary aims:

- To determine if patients with oesophageal stenting had a longer dysphagia progression-free survival compared to those without oesophageal stenting.
- To determine if there is an overall quantitative objective improvement in dysphagia grade of patients with locally advanced and metastatic oesophageal cancer receiving palliative radiation therapy.
- To determine the overall survival in patients who received palliative radiation therapy.

Secondary research hypotheses:

- Patients who had both oesophageal stenting and palliative radiation therapy had a longer dysphagia progression-free survival when compared to those who received only palliative radiation therapy without oesophageal stenting.

- Radiation therapy increases the mean dysphagia progression-free survival (in months) in patients with locally advanced or metastatic oesophageal cancer.
- Palliative radiation therapy increases the overall survival in patients with metastatic and locally advanced oesophageal cancer.

Background

Palliation of dysphagia in patients with locally advanced and metastatic oesophageal cancer is still an area of contention as there currently are no consensus guidelines for the optimal management. Various studies have been done comparing the benefit of radiotherapy (both external beam radiation therapy and brachytherapy) to endo-luminal stenting while evaluating variables such as time to treatment, time to improvement of dysphagia score and efficacy of treatment for long term control of symptoms. Retrospective studies demonstrated that endoscopic stenting provided earlier and more rapid relief of symptoms, however, was associated with recurrent dysphagia in the long term compared to radiotherapy. These studies suggested the optimal management for palliation of dysphagia in these patients to be a combination of endo-luminal stenting and radiation therapy (4,5). Although previous data suggests long term relief of dysphagia in patients with locally advanced and metastatic oesophageal cancer, limited data is available to suggest the duration of this response. One retrospective study conducted in Germany analysing 139 patients with advanced/incurable oesophageal cancer treated with palliative radiation therapy between 1994 to 2004 reported subjective symptom relief in 72 % of patients with median response duration of 5 months (6). Our study is aimed primarily at examining the median overall duration of response to radiation therapy in this subgroup of patients in our clinical setting. We also aim to identify any contributing factors (such as dose and fractionation, endo-luminal stenting) that may affect the overall response to palliative radiation therapy.

Methodology

This is a retrospective, observational study. The medical records of all patients presenting to a public hospital in South Africa over the period January 2015-December 2016 will be reviewed. The patients presenting with dysphagia secondary to locally advanced or metastatic oesophageal cancer who were treated with palliative radiation therapy will be selected for further data collection and analysis.

Formal sample size calculations will not be performed. The number of subjects was chosen based on feasibility of data collection and is considered sufficient to meet the study

objectives. All patients who meet the inclusion criteria and determined to have a dysphagia grade of 1-4 at the time of presentation or during follow-up using the Knyrim et al (2013) dysphagia score grading system would have been offered oesophageal stenting +/- palliative radiation therapy. They would be reassessed 6 weeks post radiation therapy and then seen routinely every three months or earlier if worsening in dysphagia. The medical records of these patients will be reviewed for objective worsening of dysphagia grade at these visits. The dysphagia progression-free survival will be taken as the time from the completion of radiation therapy to worsening in dysphagia grade by at least one point. Patients who have died without returning to follow-up with complaint of increasing dysphagia are assumed to have dysphagia progression-free survival from time of radiation therapy until death. This information will be used to determine the primary and secondary endpoints of the study.

Characteristics of study population

The study population includes all new patients presenting to the gastro-oesophageal oncology clinic at Groote Schuur Hospital, Cape Town, South Africa (estimated to be approximately 150 patients) with metastatic or locally advanced oesophageal cancer. Of these, the patients to be selected for further analysis must fulfil the following criteria (estimated to be 80-100 patients):

Inclusion criteria:

- At least 18 years of age.
- Presentation between January 2015 to December 2016 with dysphagia either at initial visit or during follow-up.
- Stage I to III oesophageal cancer who are not potentially resectable (not physiologically fit, <5cm from crico-pharyngeus, gastro-oesophageal junction involvement, tumours involving the heart, great vessels, trachea or adjacent organs including the liver, pancreas, lung and spleen or multi-station, bulky lymphadenopathy) or metastatic oesophageal cancer.
- Received palliative radiation therapy for symptom control.
- Performance Status (ECOG): 0-4
- Dysphagia score of 1-4 (at presentation or during follow-up)
- With or without oesophageal stent insertion

Exclusion criteria:

- Less than 18 years of age.

- Stage I to III oesophageal cancer who are potentially resectable (physiologically fit, >5cm from crico-pharyngeus, tumours not involving the heart, great vessels, trachea or adjacent organs including the liver, pancreas, lung and spleen or no multi-station, bulky lymphadenopathy) and hence are amenable to radical treatment.
- Patients qualifying for definitive chemo-radiation therapy treatment (physiologically fit and non-metastatic).
- Dysphagia score 0 (at presentation or during follow-up)
- Patients who received palliative chemotherapy

Recruitment and Enrollment

The patients to be recruited will be determined by reviewing the logs of patients who presented to the clinic and will be performed by the primary investigator. Since the study is a retrospective observational study and the necessary information will be collected by reviewing the medical records in the target population there will be no potential for therapeutic misconception.

Research Procedures and Data Collection Methods

A data collection form will be designed using the REDCap software which would include the basic patient demographics and information regarding diagnosis and treatment details. The selected patients' hospital medical records will be used to fill out the required information for the study. There will be no direct interaction with the patient.

Data Analysis

The data collected will be stored in the REDCap database and the interface will be used to process the data and analyse the variables relevant to the study. The data collected using REDCap software is only accessible to the primary investigator and the student investigator. No identifying information would be collected during data synthesis.

All collected data would be displayed in tables and charts. SPSS software would be used to perform statistical analyses. Dysphagia progression-free survival was defined as the time to worsening of dysphagia by at least one grade.

The raw data collected will be presented in the form of tables and charts. The data will be processed using Kaplan-Meier analysis to determine the dysphagia progression-free survival.

Description of Risks and Benefits

Potential risks and discomforts

This is an observational retrospective study, therefore, the associated research risk is low because the research does not affect the patient's management or outcome in any way and the necessary data can be collected from patients' medical records of routine scheduled clinic visits and national death records. Efforts will be made to ensure patient confidentiality as described above.

Potential benefits

There are no potential benefits to participants in the research as there will be no direct contact with these patients and the study does not affect their management in any way. There is a potential for benefit to the community and health services as there is currently limited data for the outcomes being analysed in our local and regional setting. Therefore, the data can potentially be used to improve patient care and outcomes in the future.

Informed Consent Process

Consent will not be obtained because the study is retrospective and does not directly involve the patients

Privacy and Confidentiality

The data will be collected using RedCap software and will only be accessible to the primary investigator and the student investigator. The data collection form will include the patients' hospital registration number to allow for easier data collection however this information will not be displayed when the data is processed and tabulated and hence will only be visible to the investigators. All data will be kept confidential to protect the patient's privacy.

Reimbursement for Participation

There will be no reimbursement for participation as the study does not involve direct interaction with the patient as all necessary information is collected from the patients' medical records.

What Happens at the End of a Study?

The data will be used to determine the primary and secondary outcomes. This information will then be used to determine further patient management in subgroup of patients examined in the study population. The conclusions of the study will be submitted for publication in a suitable journal and presented to peers in academic meetings and conferences.

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PART B: LITERATURE REVIEW

ABSTRACT

This literature review seeks to examine the relevant existing information regarding the management of dysphagia in patients with locally advanced and metastatic oesophageal cancer. It will examine the methods used in treatment and the outcomes measured in order to assess and determine the quality of response. Appropriate management of dysphagia in patients with oesophageal cancer is crucial to maintaining a reasonable quality of life.

For this literature review, local, regional and global cancer statistics were reviewed for patterns associated with incidence and epidemiology. An online search was conducted using PubMed, EMBASE and MEDLINE for articles related to the management of dysphagia in patients with locally advanced and metastatic oesophageal cancer published in medical journals or in evidence-based databases such as Cochrane database and National Library of Health (UK).

Several studies have been conducted regarding the palliation of dysphagia in patients with oesophageal cancer. Interventions such as endoluminal stenting, external beam radiation therapy, brachytherapy, laser ablation, surgical bypass have been described and compared. However, there is still no consensus regarding the most effective approach to the management of these patients.

This highlights the need for further research in objectively assessing outcomes following the treatment of patients with locally advanced and metastatic oesophageal cancer.

INTRODUCTION

According to international statistics, in 2012, the estimated number of new oesophageal cancer cases was approximately 456,000, with incidence rates varying across the world[1, 2]. The highest incidence rates are in Asia, and in East and South Africa while the lowest rates are found in Western Africa and in parts of Europe and South America in women. In 2013 oesophageal cancer was the 9th most common cancer diagnosed worldwide[3], ranked as the 8th most common cancer diagnosed in developing countries including South Africa[4] and the 20th most common cancer diagnosed in developed countries.

In 2012, approximately 400,200 people died from oesophageal cancer, with developing countries accounting for more than 80% of these deaths. In 2013, oesophageal cancer was

ranked 6th in cancer related mortality worldwide, ranking 5th in developing countries and 11th in developed countries[3].
The prevalence of oesophageal cancer is approximately three to four times higher among men than women. In 2013, it was the 6th leading cause of cancer related death in men and 9th leading cause of cancer related death in women in 2012 worldwide[2].

The incidence of oesophageal cancer also varies with age; with minimal occurrences in people less than 40 years old and increasing thereafter to be the highest in the elderly aged 70-80 years[5]. The two main histological subtypes of oesophageal cancer are squamous cell carcinoma and adenocarcinoma. These two subtypes have distinct aetiologies and the disease course and response to treatment are usually variable[6]. Squamous cell carcinoma (SCC) of the oesophagus is associated mainly with dietary factors, cigarette smoking and alcohol and has a higher incidence in poverty-stricken populations. However, oesophageal adenocarcinoma is a disease of prosperity, with the highest incidence occurring in high income Western countries and the most significant risk factors being gastro-oesophageal reflux and obesity[2, 7, 8]. South-Eastern and Central Asia comprises 79% of the total SCC cases globally, while the highest burden of adenocarcinoma (AC) is found in Northern and Western Europe, Northern America and Oceania[7].

Due to the expansile characteristics of the oesophagus, symptoms related to obstructing or stricturing lesions tend to manifest only in advanced stages of disease. International data reports that in Europe and North America, many patients with oesophageal cancer present with locally advanced or metastatic disease and are not candidates for curative treatment; approximately 70% of cases in Scotland and Northern Ireland in 2014 were diagnosed at a late stage[1] and in the United Kingdom 70-80% of patients were diagnosed with either lymph nodes or distant metastases, and 37-42% had distant metastases at diagnosis[9]. Although definitive data is lacking for South Africa, most new cases follow a similar trend with a high percentage of patients presenting with locally advanced or metastatic disease. One retrospective study conducted by Dandara et al (2016) examining all patients presenting with oesophageal cancer over a 30-year period reported that 76% of patients presented with advanced disease and poor clinical condition requiring palliative care[10]. In patients presenting with locally advanced and metastatic oesophageal cancer, the outcome is very poor resulting in an average survival of 4-6 months[10, 11].

The most common symptoms in patients with oesophageal cancer are dysphagia, weight loss, odynophagia, chest pain, gastro-oesophageal reflux and regurgitation[12]. Dysphagia is defined as the inability to pass liquids or food voluntarily from the mouth to the stomach and is documented as the most common presenting symptom in patients with oesophageal cancer in several studies, occurring in 70-80% of patients at presentation[13, 14]. One large study conducted by the American college of Surgeons (2000) reported dysphagia in 74% of the 5044 patients enrolled[15]. Dysphagia has a significant impact on quality of life and is often associated with weight loss and poor nutritional status. These factors are contributory to the poor clinical condition that precludes many patients from receiving curative treatment[16-18].

Palliation of dysphagia in patients with locally advanced and metastatic oesophageal cancer is an area of contention as currently there are no consensus guidelines for the optimal management. It also presents a significant problem in developing countries because of the high volume of patients diagnosed at advanced stage disease coupled with the added problem of access to resources[19]. Hence, it is particularly important in these regions to establish a cost effective and efficacious method of palliation of dysphagia in this population of patients.

The purpose of this literature review is to examine the existing data regarding palliation of dysphagia patients with locally advanced and metastatic oesophageal cancer and the outcomes following treatment. Focus will be on the use of radiation therapy in this clinical scenario and the outcomes following treatment with respect to the magnitude and duration of response. The outcomes of other interventions used for palliation of dysphagia will also be analyzed and compared to radiation therapy, with an aim of determining the efficacy radiation therapy for palliation of malignant dysphagia which can be adapted to our clinical environment as a developing country.

METHODS

For this literature review, local, regional and global cancer statistics were reviewed for patterns associated with incidence and epidemiology. An online search was conducted using PubMed, EMBASE and MEDLINE (1980 to 2015) for relevant articles and abstracts published in medical journals or in evidence-based databases such as Cochrane database and National Library of Health (UK). A combination of subject headings and text words relating to the management of dysphagia in patients with locally advanced and metastatic oesophageal

cancer was used. This search was repeated in March 2020 prior to submission of the manuscript.

The inclusion criteria were articles relating to any intervention used for palliation of dysphagia in patients with incurable oesophageal cancer. Articles related to intervention in curable patients or patients without dysphagia were excluded. Thirty-seven journal articles were included in this literature review.

DISCUSSION:

There are several options for the palliation of malignant dysphagia, which include stent placement, dilatation, external beam radiotherapy, brachytherapy, chemotherapy, laser treatment, photodynamic therapy or ablation; however, the optimal intervention strategy has not been established[20, 21]. Various studies have been conducted comparing these interventions using various outcomes related to symptom control to determine the efficacy of treatment. One large meta-analysis conducted by Dai et al in 2014 consisted of 53 studies and included 3684 patients aimed to determine the optimal intervention for the palliation of dysphagia in patients with incurable oesophageal cancer. The outcomes assessed were improvement in dysphagia grade, overall survival, time interval to improvement of dysphagia, incidence and time interval to recurrence of dysphagia and need for further interventions, adverse effects and mortality of each intervention and quality of life. The results of the meta-analysis showed “no obvious superiority of any one intervention in palliating dysphagia but established self-expanding metal stent insertion as a safe, effective and rapid treatment in dysphagia palliation compared to other modalities”. It was also reported “due to the high incidence of delayed complications and recurrent dysphagia, rigid plastic tube insertion, chemotherapy alone, and combination chemoradiotherapy and bypass surgery were not recommended for palliation of dysphagia”. The investigators suggest a role for multimodality treatment to improve outcomes[20].

Other studies examining the role of various modalities in palliation of malignant dysphagia support the conclusion of Dai et al and the most pertinent ones will be discussed individually in the text. The results of several large series regarding palliative bypass surgery report a median survival of less than 6 months while the mortality exceeds 20%. Hence, less invasive methods of palliation of dysphagia are preferable to bypass surgical procedures[22].

Brachytherapy has been studied in the palliative setting both as monotherapy and as part of multimodality treatment approach. A prospective study conducted in Netherlands by Homs et

al (2004) between 1999-2002 randomly assigned 209 patients with dysphagia secondary to inoperable carcinoma of the oesophagus or oesophagogastric junction to stent placement or single dose brachytherapy (12Gy). The primary outcome was relief of dysphagia during follow-up and secondary outcomes were complications, treatment for persistent or recurrent dysphagia, health-related quality of life, and costs. The results showed more rapid improvement in dysphagia score after stent placement than after brachytherapy; however, the improvement between both modalities was equivalent at the peak of response. At 30 days after intervention, the dysphagia score had improved by at least one grade in 73% of patients who received brachytherapy and 76% who had stent placement. Subsequently, the dysphagia grade declined more rapidly in the patients who had stent insertions than those who had brachytherapy thus demonstrating a more durable response following brachytherapy. Additionally, patients receiving brachytherapy had better health related quality of life scores on several functional scales and lower complication rates compared to patients with stent insertion (21% versus 33%). There was no significant difference between persistent or recurrent dysphagia, overall survival or costs between both groups. Thus, the investigators recommended single-dose brachytherapy preferentially to stent placement as the initial treatment for patients with dysphagia due to locally advanced cancer of the oesophagus or oesophagogastric junction. They suggested stent placement only for patients with a short life-expectancy and severe dysphagia requiring rapid symptom control and also in cases of persistent or tumour regrowth after brachytherapy[23]. These conclusions have been supported in several other studies evaluating the role of brachytherapy in palliation of dysphagia[24-28]. Further to this, a prospective randomized trial of 232 patients conducted in South Africa by Sur et al (2002) examined two fractionated high-dose-rate (HDR) brachytherapy regimens (18 Gy in 3 fractions on alternate days versus 16 Gy in 2 fractions on alternate days to determine which gives the best results in terms of palliation and survival in advanced esophageal cancer. The dysphagia-free survival (7.8 months vs 6.3 months) and overall survival (9.1months versus 6.9 months) favoured patients receiving 18 Gy in 3 fractions. Thus, the authors reported superiority of fractionated HDR brachytherapy as a single modality therapy in palliation of dysphagia in advanced oesophageal cancer when compared to the results documented in any previous study[29]. Due to the lack of necessary expertise and technology, the use of brachytherapy is not always widely applicable especially in developing countries, hence the use of external beam therapy may be an alternative intervention where resources are available.

One retrospective study of 45 patients conducted by Rueth et al (2012) in Minnesota, USA examined the role of oesophageal stent insertion with or without radiation therapy in the management of malignant dysphagia. In this study, 68.9% of patients reported subjective improvement of dysphagia immediately after stent insertion. The median overall survival was 38 days following oesophageal stent insertion only, however patients who received radiation therapy following stent placement had a longer median survival (98 days). There was no difference in the 30-day mortality or complication rate in patients with the addition of radiation therapy to stent insertion. From this study, it was concluded that endoscopic stent insertion is a quick and effective method to relieve dysphagia in patients with a short life expectancy. However, radiation therapy and stent insertion as part of multimodality treatment, provides a superior means of palliation of malignant dysphagia in the long term and hence is beneficial in patients with a life expectancy >3 months[30].

Another prospective study from India by Javed et al (2010) showed similar results; 84 patients with inoperable oesophageal cancer were randomized to receive oesophageal stenting alone or a combination of oesophageal stenting and external beam radiotherapy (EBRT). Dysphagia scores improved significantly in both groups following stent insertion. However, the duration of response (7 vs. 3 months, p=0.002) was more sustained and overall median survival was significantly higher (180 vs. 120 days, p=0.009) in patients receiving stenting plus EBRT versus stenting alone with similar complication rates between both groups. Interestingly, there was significant improvement in all quality of life parameters after stent insertion, however, there was significant decline immediately after radiotherapy. Nonetheless, these results support previous data that EBRT following stent insertion can effectively prolong the duration of dysphagia control and improve overall survival in patients with inoperable oesophageal cancer[31]. There is limited data regarding the quality of life following interventions for dysphagia and this study highlighted an important finding not previously reported; that despite the improved symptom control, there was a deterioration in health-related quality of life.

Existing data reports that although endo-luminal stenting provided earlier and more rapid relief of symptoms, it was associated with recurrent dysphagia in the long term while radiation therapy provided more durable response and was associated with a lower complication rate. These studies suggested the optimal management for palliation of dysphagia in these patients is a combination of endo-luminal stenting and radiation therapy or

brachytherapy[32, 33]. The addition of chemotherapy to radiation therapy shows a modest but not significant benefit over radiation therapy only[34] and considering the increased toxicity associated with concurrent chemo-radiation therapy may not be considered a viable option in the palliative setting.

Although the available data suggests effective relief of dysphagia in patients with locally advanced and metastatic oesophageal cancer treated with palliative radiation therapy(11), limited data is available to suggest the duration of this response and optimal fractionation regimen. A retrospective study of the use of radiation therapy in palliation of dysphagia conducted in the Netherlands by Caspers et al (1988) compared EBRT regimens (>50Gy versus <50Gy). There was an improvement in dysphagia score in 70.5% of patients with a median dysphagia-free interval of 3.7 months in patients with severe dysphagia and 16.0 months in patients with mild to moderate dysphagia, while overall survival was 6.4 months and 8.7 months respectively. The results showed better outcomes in patients receiving more than 50 Gy and in patients with less dysphagia at baseline[35].

One retrospective study conducted in Germany by Welsch et al (2016) analysed 139 patients with advanced/incurable oesophageal cancer treated with palliative radiation therapy between 1994 and 2014. The radiation was delivered as external beam radiation therapy (30-40 Gy in 2.5-3Gy per fraction) with or without endoluminal high dose rate brachytherapy. The parameters used to assess response were 6-month dysphagia-free survival, improvement in swallowing function, complication rate, and overall survival. The results showed subjective symptom relief in 72% of patients with median response duration of 5 months, 6-month dysphagia-free survival was 73+/- 4% and the median overall survival was 10 months. These results favoured patients receiving external beam radiation therapy (EBRT) with or without brachytherapy and demonstrated its superiority to brachytherapy as monotherapy[36]. The study by Sur et al (2002) that was earlier described in the text had suggested that fractionated HDR brachytherapy yielded superior results in terms of dysphagia-free survival than any other intervention up to that time[29]. It is important to note that the HDR brachytherapy fractionation regimens used in treatment and that the endpoints to establish response were different between these two studies and hence a conclusion cannot be drawn regarding the superiority of either intervention.

Dysphagia, in addition to the impact on nutritional status and performance status, contributes significantly to the poor quality of life in patients with oesophageal cancer[37]. Hence, in

addition to assessing the response in terms of dysphagia improvement and survival outcomes, it is also important to assess the impact on quality of life in these patients following intervention[17]. Several studies have examined the impact of various interventions on health-related quality of life yielding positive results with palliative radiation therapy, endoluminal brachytherapy and stenting all leading to significant improvements in quality of life[16, 18, 23, 38, 39]. However, the magnitude of this impact has not been directly compared hence it is difficult to determine which is superior in this regard.

CONCLUSION

There is abundant data available regarding the palliation of malignant dysphagia. Several interventions have been studied, however there is still no consensus regarding the optimal management. Surgical bypass is associated with high morbidity and mortality and hence less invasive methods of palliation are more acceptable. Concurrent chemo-radiation therapy marginally increases the benefit over radiation therapy only and is associated with increased toxicity and hence is also not recommended in palliation. Oesophageal stent insertion has been associated with rapid relief of symptoms but is associated with a higher rate of complications than other interventions and frequent need for repeat intervention. The duration of response as monotherapy is limited. External beam radiation therapy and brachytherapy have both proven to be effective in relief of dysphagia as monotherapy and in combination or as an adjuvant to stent insertion. The outcomes following multimodality approach are superior to any single intervention and should be tailored to the patient on an individual basis, also taking life expectancy and baseline dysphagia grade into consideration. The optimal dose and fractionation of external beam radiation therapy and brachytherapy required for effective palliation has not been established. Though the response following radiation therapy has been documented in terms of proportion of patients experiencing symptom relief and overall survival, the duration of response to radiation therapy until worsening of dysphagia is unknown. Although there are several studies reporting improvements in quality of life following stent insertion, radiation therapy and brachytherapy, these modalities have not been compared directly in this regard.

Hence further research needs to be done comparing health related quality of life scores, duration of palliation of dysphagia and absolute improvement in dysphagia grade following various interventions as outcomes in assessment of efficacy of palliation of dysphagia. A prospective study comparing HDR brachytherapy to EBRT and brachytherapy, which have

both been suggested to be the most efficacious methods of palliation in independent studies, may also be useful.

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PART C: PUBLICATION-READY MANUSCRIPT

DYSPHAGIA PROGRESSION-FREE SURVIVAL IN OESOPHAGEAL CANCER PATIENTS TREATED WITH PALLIATIVE RADIATION THERAPY

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ABSTRACT

Purpose: In patients with advanced oesophageal carcinoma palliation of dysphagia is important to maintaining a reasonable quality of life. The primary aim of this study was to determine the dysphagia progression-free survival (DPFS) in patients with advanced oesophageal carcinoma treated with palliative radiotherapy (RT).

Methods: The medical records of all patients with oesophageal carcinoma presenting to Groote Schuur Hospital, Cape Town between January 2015-December 2016 were reviewed and patients who were not candidates for curative treatment and received palliative RT were selected. For these patients, the dysphagia score (DS) was recorded prior to RT, 6 weeks after RT and at each follow-up visit. The DPFS was calculated as the time from completion of RT to worsening in DS by ≥1 point or until death. Other outcomes measured were objective change in DS and survival post RT.

Results: The study population comprised 84 patients. Squamous cell cancer was the primary histological subtype (93%). The median duration of DPFS after RT was 73 days, with approximately two-thirds of patients remaining able to swallow at least liquids and soft diet until death. The difference in median duration of DPFS was not statistically significant in stented versus non-stented patients (54 days vs 83 days; p =0.224). The mean change in DS was 0.45 ± 0.89 points following RT and the post RT survival was significantly shorter in patients with stent insertion (81 days vs 123 days; p=0.042).

Conclusion: Palliative RT can be used successfully to prolong DPFS in patients with locally advanced and metastatic squamous cell cancer of the oesophagus.

Key Words: Oesophageal cancer, locally advanced, dysphagia score, palliative radiotherapy.

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INTRODUCTION

Worldwide, an estimated 456,000 new cases of oesophageal cancer were diagnosed in 2012, with varying incidence rates globally[1, 2]. The prevalence of oesophageal cancer is approximately three to four times higher among men than women and oesophageal cancer was the 6th and 9th leading cause of cancer related death in men and women respectively in 2012[2]. In 2013, oesophageal cancer was the 8th most common cancer diagnosed in South Africa[3]. Approximately 70% of cases in England, Scotland and Northern Ireland in 2014 were diagnosed at a late stage [1]. Although definitive data is lacking for South Africa, most new cases follow a similar trend with a high percentage of patients presenting with locally advanced or metastatic disease. One retrospective study conducted in South Africa by Dandara et al (2016) examining all patients presenting with oesophageal cancer over a 30-year period reported that 76% of patients presented with advanced disease and poor clinical condition requiring palliative care [4]. In these patients receiving palliative care, the average survival was approximately 4-6 months[4, 5].

Dysphagia is documented as the most common presenting symptom prompting patients with oesophageal cancer to seek medical care and has a substantial impact on quality of life which becomes more significant in advanced disease[6, 7]. One large study conducted by the American college of Surgeons (2000) reported dysphagia in 74% of the 5044 patients enrolled[8]. Palliation of this symptom is crucial to maintaining an acceptable quality of life in these patients[9-11].

There are currently no consensus guidelines for the optimal management of dysphagia in patients with locally advanced and metastatic oesophageal cancer. Options for palliation include stent placement, dilatation, external beam radiotherapy, brachytherapy, chemotherapy, laser treatment, photodynamic therapy or ablation[12, 13]. Various studies have been done comparing the benefit of radiotherapy, both external beam radiotherapy (EBRT) and brachytherapy to endoscopic stenting while evaluating various endpoints to determine efficacy of treatment. Retrospective studies demonstrated that endo-luminal stenting provided earlier and more rapid relief of symptoms, however was associated with recurrent dysphagia in the long term[11] , while RT provides more durable response[14]. These studies suggested the optimal management for palliation of dysphagia in these patients is a combination of endo-luminal stenting and RT or brachytherapy[13-16]. Palliative chemoradiation shows a modest but not significant benefit over RT alone[17] and considering the increased toxicity associated with concurrent chemoradiation, it is not considered a viable option in palliation. Although

previous data suggests effective relief of dysphagia in patients with locally advanced and metastatic oesophageal cancer treated with palliative RT[5], limited data is available to suggest the duration of this response. One retrospective study of the use of RT in palliation of dysphagia conducted in the Netherlands by Caspers et al (1988) reports improvement in dysphagia score in 70.5% of patients with a median dysphagia-free interval of 3.7months [18]. Another retrospective study conducted in Germany by Welsch et al (2016) analyzing 139 patients with advanced/incurable oesophageal cancer treated between 1994 to 2004 , with either EBRT, brachytherapy or EBRT and brachytherapy combined reported subjective symptom relief in 72% of patients with median response duration of 5 months[19]. Our study was aimed primarily at examining the overall duration of response to RT in our clinical setting and to identify contributing factors that may affect the overall response to palliative RT.

METHODS

Study aims and objectives:

The aim of this study was to assess the benefit of palliative radiotherapy in the management of patients with locally advanced and metastatic oesophageal cancer at a single institution.

The primary objective was to determine the median dysphagia progression-free survival (DPFS) after radiation therapy (RT) in patients with locally advanced or metastatic oesophageal cancer. The secondary objectives were to compare the duration of DPFS in patients with and without oesophageal stenting, to determine the overall quantitative objective improvement in dysphagia score (DS) after receiving palliative RT in patients with advanced oesophageal cancer and to determine the median overall survival (OS) and post RT survival of patients following palliative RT.

Study population:

The records of all new patients who presented with oesophageal cancer to the gastro-oesophageal oncology clinic at Groote Schuur Hospital, Cape Town between the period January 2015 and December 2016 were reviewed. Only patients with stage I to III oesophageal cancer who were not candidates for potentially curative treatment (i.e. not physiologically fit, tumours involving adjacent organs or multi-station and bulky lymphadenopathy) or with Stage IV disease were selected. Further inclusion criteria were patients determined to have a DS 1-4 at initial visit or during follow-up using the Knyrim et

al (1993)[20] dysphagia grading system (see Appendix 1) and were treated with palliative radiation. Patients who were less than 18 years of age, had received chemotherapy for carcinoma of the oesophagus, had percutaneous endoscopic gastrostomy insertion, or patients with trachea-oesophageal fistulae were excluded from the study.

Scientific Design:

This was a retrospective, observational study. The patients meeting the inclusion criteria were selected for further data collection and analysis.

Treatment

All patients were reviewed in the gastro-oesophageal multidisciplinary team meeting for a treatment decision. Patients were selected for palliative treatment based on characteristics at presentation such as poor Eastern Cooperative Oncology Group performance status (PS (ECOG)), significant weight loss ≥10% baseline body weight, low BMI, multiple medical co-morbidities and poor general clinical condition. Due to limited resources, only patients who were being considered for curative treatment were staged with computed tomography (CT) scan of the chest, abdomen and pelvis. All patients who presented with DS grade 3 or 4 were referred to the Upper Gastroenterology surgical service for assessment for stent insertion. They were reviewed post stent insertion; an updated DS was assigned based on current clinical status and they were assessed for palliative RT. Palliative RT was offered to patients who had significant symptoms such as dysphagia and odynophagia and were in reasonable clinical condition. The aim was to maintain swallowing and for pain control, whereas patients whose general condition was too poor that palliative RT was thought not to add benefit were treated supportively.

The choice of fractionation schedule was at the radiation oncologist's discretion and three fractionation regimes were used at our centre; namely: 4.6 Gy x 4# (EQD2= 28.0Gy), 4.0Gy x 5# (EQD2= 28.0Gy) or 3.0Gy x 10# (EQD2=36.0Gy), assuming an α/β ratio of 3 for late effects. In general, the higher dose of RT was offered to patients who were PS (ECOG) 1-2. All patients were planned using a 2D simulation technique. The patients were positioned supine with head rest, knee and ankle stocks for immobilization and an anterior image was taken. In patients with a stent in situ, the field was placed to encompass the stent and an additional 2cm margin superiorly, inferiorly and laterally. In patients without a stent in situ, 10ml of barium was given orally and a fluoroscopic image was taken to determine the site of the tumour, the field was then placed to encompass the lesion with an additional 5cm margin

superiorly and inferiorly and 2cm laterally. The patients were treated with photons, either Co-60 or 6MV x-rays, once per day (Monday to Friday) with a treatment break on weekends.

Patients were reassessed six weeks after completing RT and then routinely every three months or earlier if worsening dysphagia. The medical records of these patients were reviewed for objective worsening of DS at these visits. The DPFS was taken as the date from the completion of RT to worsening in DS by ≥1 point. Patients who died without returning to follow-up with complaint of increasing dysphagia were assumed to have dysphagia progression-free survival from time of radiation therapy until death. This information was used to calculate the median DPFS in the patient population and to compare the median DPFS in patients with and without stent insertions. The objective improvement in DS was calculated by determining the change in DS after RT for each patient. These values were used to determine the mean objective improvement in DS. The OS and post RT survival were measured from the date of diagnosis and date of completion of RT, respectively, to the date of death.

Statistical Analysis

Formal sample size calculations were not performed. The number of subjects was chosen based on feasibility of data collection and was considered sufficient to meet the study objectives.
The data collected was stored in the REDCap (Research Electronic Data Capture) database and the interface was used to process the data and analyze the variables relevant to the study. The data collected using REDCap software was only accessible to the primary investigator and the student investigator.
Stata MP version 14 software was used for data processing and analysis. Continuous variables were presented as mean/ standard deviation (SD) or median/interquartile range (IQR) depending on data distribution. Continuous data were analyzed using Independent t-test or Mann Whitney U test.
Kaplan-Meier survival analysis was performed to determine the DFPS, OS and post-RT survival, and log-rank test was performed to test for significant differences in the probability of survival by stent insertion. Time 0 was defined as the day the patient completed RT. To determine the variables associated with DPFS, change in DS and post-RT survival, multiple linear regression analysis was performed. The variables analyzed were gender, age, PS(ECOG), DS at presentation, time of RT and post RT, histological subtype, site of primary tumour, RT fractionation schedule, stent insertion and weight loss >10% of baseline. Variables

with p<0.20 in the univariate analysis (i.e., simple linear regression) were entered into the adjusted model. Model-building was then performed using a backward elimination technique and p values ≤0.05 were considered statistically significant. These results were displayed as charts and tables.

Results

A total of 84 patients presenting to the gastro-oesophageal carcinoma clinic between the period January 2015 and December 2016 met the inclusion criteria for the study. The patient and disease specific factors were grouped by variables such as gender, age group, PS (ECOG), histological subtype and location of primary tumour as tabulated in Table 1.

Table 1: Demographics and disease related parameters in the study population.

Gender	**Male**	**Female**
No. of patients	46 (54.8%)	38 (45.2%)

Age group (years)	**18-24**	**25-30**	**31-40**	**41-50**	**51-60**	**61-70**	**71-80**	**>80**
No. of patients	0	0	3	16	30	19	13	3
% of patients	0%	0%	3.6%	19.0%	35.7%	22.8%	15.5%	3.6%

Performance Status (ECOG)	**0**	**1**	**2**	**3**	**4**
No. of patients	0 (0%)	27 (32.1%)	33 (39.3%)	21 (25%)	3 (3.6%)

Histological subtype	**Squamous cell carcinoma**	**Adenocarcinoma**
No. of patients	78 (92.9%)	6 (7.1%)

Location of primary tumour	**Upper 1/3**	**Middle 1/3**	**Lower 1/3**	**Gastro-oesophageal junction**
No. of patients	13 (15.5%)	46 (54.8%)	16 (22.6%)	6 (7.1%)

Duration of symptoms	<1mth	>1-3mths	>3-6mths	6-12mths	1-2y	>2y
	1 (1.2%)	22 (26.2%)	34 (40.5%)	20 (23.8%)	6 (7.1%)	1 (1.2%)

Loss of weight	**Yes**	**No**
No. of patients	73 (86.9%)	11 (13.1%)

	<10%	>10%	
	13 (17.8%)	60 (83.2%)	

There was a slight predominance of male patients 46 (54.8%) versus female patients 38 (45.2%). The mean age was 59 years and modal age group was the 51-60. More than 50% of all patients were between 50 and 70 years. No patients in our study population were younger than 31 years of age. Most patients were observed to have a PS (ECOG) 2 or 3. Regarding duration of symptoms, most patients had symptoms for >3-6 months prior to presentation and the mean duration of symptoms was 6.1 months before seeking medical attention. The most common presenting symptoms were dysphagia and weight loss. More than 85% of patients had reported weight loss as shown in Table 1; of these >75% reported losing more than 10% of their baseline body weight.

The most common histological subtype was squamous cell cancer (78 patients; 92.9%) versus adenocarcinoma (6 patients; 7.1%). The most common subsite among all patients was the middle third of the oesophagus (46 patients; 54.8%) followed by the lower third of the oesophagus (16 patients; 22.6%) The least common subsite was the gastro-oesophageal junction (6 patients; 7.1%).

More than 90% of patients had a DS ≥2 at presentation. Approximately half of the patients had insertion of oesophageal stent (43 patients; 51.2%). Most patients presenting with DS ≤2 did not have oesophageal stent insertion. Of the patients with grade 4 dysphagia who were referred for stent insertion, one failed to have the procedure due to poor PS (ECOG). (Table 2). After stent insertion 100% of patients had an improvement in DS by ≥1 point.

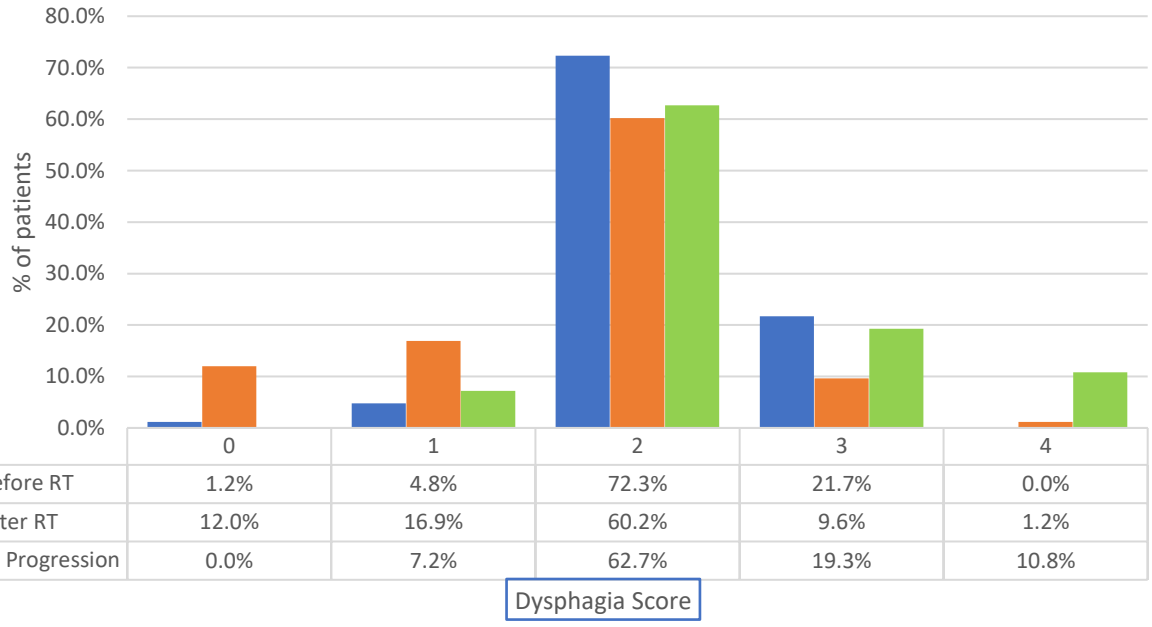
Table 2: Dysphagia score at presentation and in patients having stent insertion.

		Stent insertion	
	Total	**Yes**	**No**
Dysphagia Score			
0	2 (2.4%)	0	2
1	5 (6.0%)	0	5
2	40 (47.6%)	14	26
3	22 (26.2%)	15	7
4	15 (17.9%)	14	1
Total	84	43 (51.2%)	41 (48.8%)

For the delivery of palliative RT of the three fractionation regimens used, 18 (21%) of patients received 20.0Gy in 5#, 60 (71%) received 18.4Gy in 4# and 6 (7%) received 30.0Gy/10#.

The DS, as assessed prior to starting RT, after RT and at time of progression of dysphagia were distributed, as shown in the figure 1. One patient was lost to follow-up and hence the data for the remaining 83 patients were analyzed. Prior to RT, the majority of patients (94%) had DS of grade 2 or grade 3. Our study did not include any patients with grade 4 dysphagia at time of RT as all patients seen post stent insertion with DS of grade 4 either did not meet the inclusion criteria or died prior to receiving RT. At the post RT review, 58 patients (68.9%) had DS of grade 2 or grade 3. One patient (1.2%) had a deterioration in DS to grade 4 following RT.

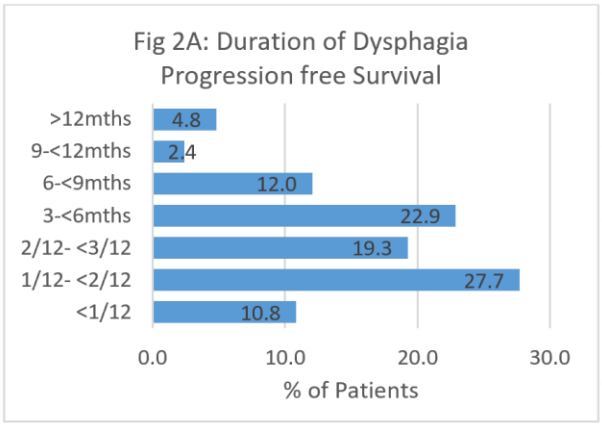
Figure 1: Bar chart showing Dysphagia score at various time intervals

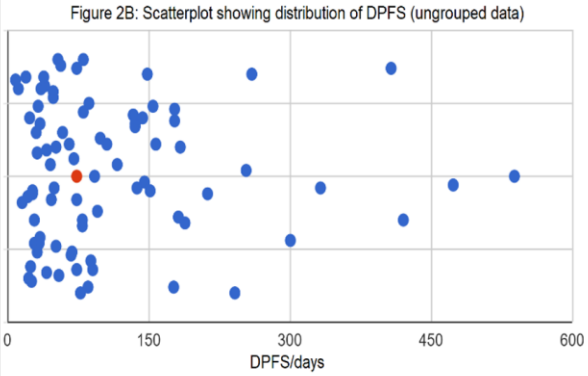


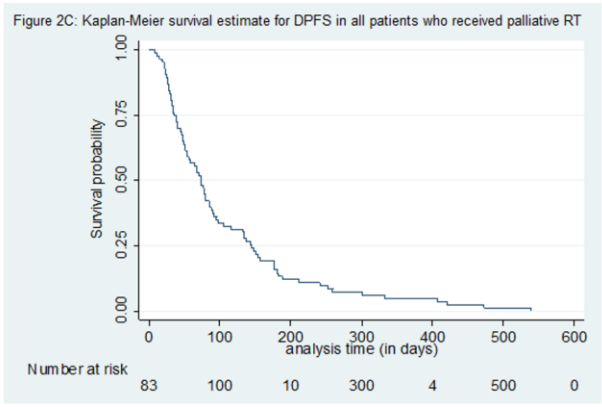
	0	1	2	3	4
Before RT	1.2%	4.8%	72.3%	21.7%	0.0%
After RT	12.0%	16.9%	60.2%	9.6%	1.2%
At Progression	0.0%	7.2%	62.7%	19.3%	10.8%

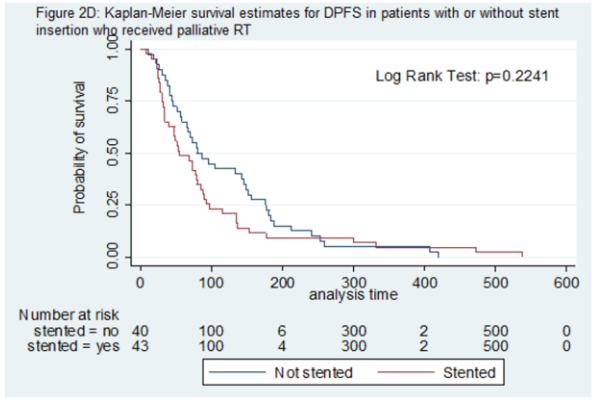
The duration of DPFS is represented in the column chart (Figure 2A) and scatter plot (Figure 2B). The median DPFS calculated using the ungrouped data was 73 days [IQR: 35-145] (Figure 2C). Simple and multiple linear regression analysis was performed to assess the association between DPFS and several variables. The median DPFS appeared to have a numerically significant difference between those with and without stent insertion with patients with a stent having a shorter duration of DPFS (median 54 days; [IQR: 31-98]) compared to those without a stent (median 83 days; [IQR: 45.5-176.5]) (Figure 2D). However, this result in conjunction

with the log-rank test (p=0.224) confirmed that there was no statistical significance between DPFS in patients who were stented and those who were not.









A simple regression analysis showed the median duration of DPFS differed significantly by DS at presentation (p = 0.045), DS after RT (p <0.0001) and PS (ECOG) (p= 0.036) (Table 3). Using multiple linear regression, only the DS after RT (p <0.0001) was found to be significantly associated with DPFS. From this analysis, for every increase in DS by 1 point, the DPFS decreased by 61 days.

Table 3: Simple linear regression analysis for variables associated with DPFS

	Simple linear regression analysis		
	Beta coeff.	**95% CI**	**p value**
Stent insertion *(Ref: No)*	-24.26	-70.65 - 22.13	0.301
Age category *(Ref: <60)*	-6.12	-52.77 - 40.54	0.795
DS at presentation	-24.94	-49.25 - -0.63	**0.045***
DS at time of RT	-40.33	-82.56 - 1.89	0.061
DS after RT	-60.88	-85.05 - -36.71	**<0.0001***

PS *(Ref: PS 1/2)*	-53.66	-103.74 - -3.57	**0.036***
Gender *(Ref: Female)*	-13.43	-60.17 - 33.31	0.569
Histology *(Ref: SCC)*	42.43	-47.20 - 132.05	0.349
Site of tumour *(Ref: Upper 1/3)*			
Middle 1/3	-13.25	-81.53 - 55.03	0.700
Lower 1/3	28.36	-49.31 - 106.02	0.470
GEJ	54.08	-51.23 - 159.40	0.310
RT fractionation sched *(Ref: 20.0Gy/ 5#)*			
18.4Gy in 4#	-32.94	-89.89 - 24.02	0.253
30Gy in 10#	-58.44	-158.15 - 41.26	0.247
Weight loss *(Ref: No)*			
Yes, ≤10%	4.38	-85.58 - 94.3	0.923
Yes, >10%	8.88	-64.17 - 81.93	0.809

The objective changes in DS when reassessed at six weeks after palliative RT were as follows: 4 (4.8%) of patients had worsening of DS, 48 (57.8%) of patients had no change in DS from baseline, however, 31 patients (37.3%) had an improvement in DS following RT; 21 patients (25.3%) reported an improvement in DS by 1 point, 8 patients (9.6%) reported an improvement by 2 points and 2 patients (2.4%) reported an improvement by 3 points. The mean objective change in DS was 0.45 ± 0.89 points in all patients at six weeks post RT treatment and 0.28 ± 0.80 points in stented and 0.63 ± 0.95 points in non-stented patients. Independent t test showed that the difference in mean objective change in DS between the stented and non-stented groups was not statistically significant (p=0.0757).

Simple regression analysis showed DS at time of RT was the only variable significantly associated with mean objective change in DS (p = 0.001) (Table 4). Using multiple linear regression, only the DS at the time of RT (p = 0.001) was found to be significantly associated with DS. From this analysis, for every increase in DS at time of RT by 1 point, the mean objective change post RT decreased by 0.56 points.

Table 4: Simple linear regression analysis for variables associated with mean objective change in DS

	Simple linear regression analysis		
	Beta coeff.	**95% CI**	**p value**
Stent insertion *(Ref: No)*	-0.35	-0.73 - 0.04	0.076
DS at presentation	-0.03	-0.24 - 0.18	0.776
DS at time of RT	0.56	0.22 - 0.90	**0.001***
PS *(Ref: PS 1/2)*	-0.16	-0.59 - 0.27	0.465
Histology *(Ref: SCC)*	-0.12	-0.87 - 0.63	0.749
Site of tumour *(Ref: Upper 1/3)*			
Middle 1/3	-0.004	-0.58 - 0.58	0.990
Lower 1/3	0.16	-0.50 - 0.82	0.626
GEJ	-0.08	-0.98 - 0.81	0.854
RT fractionation sched *(Ref: 20.0Gy/ 5#)*			
18.4Gy in 4#	-0.17	-0.65 - 0.30	0.477
30Gy in 10#	-0.61	-1.44 - 0.22	0.147
Weight loss *(Ref: No)*			
Yes, ≤10%	0.32	-0.43 - 1.06	0.404
Yes, >10%	0.13	-0.47 - 0.74	0.663

The median OS of patients receiving RT was 150 days [IQR: 131 – 169]. The median OS in the RT patients without stents was 154 days [IQR: 99 – 211] while the median OS in the RT patients with stents was 136 days [IQR: 71 – 206]. The difference between these values compared by Mann Whitney U test was not statistically significant (p=0.387).

The median survival following RT in the study population was 95 days [IQR: 41-154]. In the stented group of patients, the median survival was 81 days [IQR: 30-135] compared to 123 days [IQR: 58-181] in the non-stented group of patients. The Mann Whitney U test was used to assess the correlation between post RT OS and stent insertion and showed that median survival post RT was significantly shorter in patients who had a stent insertion (p= 0.0482).

Simple regression analysis showed the only variables which significantly affected post RT OS were DS at presentation (p = 0.027), change in DS post RT (p = 0.006) and PS (ECOG) (p =

0.031) (Table 5). Using multiple linear regression, DS at presentation (p = 0.002) and change in DS post RT (p <0.0001) were found to be significantly associated with post RT OS. From this analysis, for every 1 unit increase in DS at time of RT, duration of post-RT survival decreases by 75 days, holding other variables constant and for every 1 unit increase in the change in DS, duration of post-RT survival increases by 56 days, holding other variables constant.

Table 5: Simple linear regression analysis for variables associated with post RT survival

	Simple linear regression analysis		
	Beta coeff.	**95% CI**	**p value**
Age category *(Ref: <60)*	-5.04	-57.67 - 47.60	0.849
DS at presentation	-30.52	-57.54 - -3.49	**0.027***
DS at time of RT	-43.85	-90.97 - 3.27	0.068
Change in DS	39.73	11.49 - 67.97	**0.006***
PS *(Ref: PS 1/2)*	-61.65	-117.67 - -5.69	**0.031***
Gender *(Ref: Female)*	-13.35	-66.10 - 39.41	0.616
Histology *(Ref: SCC)*	41.86	-67.11 - 150.83	0.447
Site of tumour *(Ref: Upper 1/3)*			
Middle 1/3	-3.64	-79.86 - 72.57	0.924
Lower 1/3	38.94	-48.48 - 126.38	0.378
GEJ	76	-41.29 - 193.29	0.201
RT fractionation sched *(Ref: 20.0Gy/ 5#)*			
18.4Gy in 4#	-30.11	-95.45 - 35.23	0.362
30Gy in 10#	-44.26	-156.77 - 68.24	0.436
Weight loss *(Ref: No)*			
Yes, ≤10%	46.73	-55.96 - 149.43	0.368
Yes, >10%	12.79	-71.97 - 97.54	0.765

Discussion

From our study, the median DPFS after palliative RT was 73 days; the median DPFS in patients without stent insertion was approximately one month longer than the stented subgroup of patients (83 days vs 54 days), however this result was not statistically significant

between the two groups (p=0.224). Patients having DS 1 or 2 at presentation or post RT or PS (ECOG) ≤2 had significantly better DPFS. No other variables were associated with DPFS. Due to the assumption that patients who died were considered to have progression of dysphagia at the time of death, the estimated value for median DPFS in our study represents the worst case scenario and is most likely to represent a minimum value as the cause of death may not be directly related to failure to swallow in these patients.

Following palliative RT, the median change in DS was 0 with most patients (57.8%) remaining unchanged following treatment. The mean objective change in DS was calculated as 0.45 ± 0.89 points. This value is much lower than described in studies examining the impact of stent insertion as the sole intervention[5] which suggests that patients receiving RT have a less dramatic improvement in dysphagia than patients who have stent insertion. Existing literature reports approximately 60-70% of patients have improvement in DS immediately following stent insertion[14, 21, 22]. The relief of dysphagia following RT is slower usually taking approximately 4-6 weeks post RT to improve[11, 23]. From our data, at six weeks post RT only 37.5% of patients reported improvement in DS thus supporting previous data that stenting provides a more rapid relief of dysphagia than RT.

In our study population, the median OS was 150 days, the median OS in the RT patients without stents was 154 days while the median OS in the RT patients with stents was 136 days. Previous data has suggested the median OS in patients with only covered stent insertion to be 62 days [10]. Thus, our data suggests that the RT with or without stenting leads to an improved median OS.

The median post RT survival in the study population was 95 days. The post RT survival was significantly longer in the non-stented group than in the stented group of patients (123 versus 81 days p= 0.0482). PS (ECOG ≤2) and DS ≤ 2 at presentation and after RT were significantly associated with improved median post RT survival on simple linear regression analysis. Using the DPFS curve for all patients who received radiation, at the time of 95 days (median post RT survival), 40% of patients still did not have any progression of dysphagia. This validates the use of RT as an effective method of palliation of dysphagia to ensure that most patients remain able to swallow at least liquids and soft diet until time of death.

Most patients who had stents inserted had worse DS at presentation which can be attributed to more advanced disease and possibly more aggressive tumour biology. Cumulatively, these factors could lead to decreased tumour response and control following palliative RT and hence account for the poorer response in all measured outcomes in the stented subgroup of patients in our study population. Other than DS and PS (ECOG), no other patient or tumour factors significantly affected the outcomes in our patients treated with palliative RT. As such, PS and DS at presentation can be used to guide patient selection for those who will benefit the most from palliative RT, which can be useful in the setting of limited resources. Additionally, the DS and mean objective change in DS after RT can also be used to determine which patients are likely to have a longer survival and hence may benefit from further palliative therapies.

A major problem in developing countries such as our setting, revolves around access to care and health education resulting in a high proportion of patients presenting late with advanced stage disease(24). In our study, approximately 75% of patients reported having symptoms for more than 3 months and almost 10% of patients had symptoms for more than a year. Approximately 70% of patients presented with PS (ECOG) ≥ 2 and more than 80% of patients presented with significant weight loss of more than 10% baseline body weight. This can be attributed to the advanced DS at presentation with more than 90% of patients having a DS at least grade 2. This affects nutritional status, PS (ECOG) and contributes to the poor general physical condition that precludes many oesophageal cancer patients from receiving radical treatment(6, 7).

When examining patient and disease characteristics, a male predominance is seen in our study (54.8%) with a higher incidence of squamous cell cancer (92.9%) and the predominance of tumours of the upper and middle oesophagus (70.3%). Previous data reports oesophageal cancers located in the upper oesophagus are primarily squamous cell cancers and are associated with lifestyle and cultural factors such as diet, smoking and heavy alcohol consumption(25) and generally tend to be more prevalent in lower socio-economic populations(2). These factors are also noted in a large proportion of our study population.

At our centre, the standard fractionation schedule used is 18.4Gy in 4 fractions which has the same EQD2 as 20Gy in 5 fractions, a frequently used palliative fractionation schedule(26). Notably, the fractionation schedule did not impact the objective response to RT. This is of significance in low- and middle-income countries where resources are scarce as a shorter

fractionation schedule (ie. 18.4 Gy in 4 fractions) can improve workflow. The acute toxicity and complication associated with this regimen from our experience is tolerable, however was not described in the study and hence further research is necessary to for comparison in this regard to other fractionation schedules.

A limitation of our study was that the impact of RT on the other symptoms associated with locally advanced oesophageal cancer such as odynophagia, pain and regurgitation was not assessed. Existing data suggests benefit of radiation for palliation of these symptoms but the duration of response is unknown[27]. In addition, there was an objective assessment of the DS following RT, however, the impact on nutritional status and weight gain was not assessed. These represent areas requiring further work in locally advanced and metastatic oesophageal cancer.

Conclusion

RT is beneficial in the palliation of dysphagia associated with locally advanced and metastatic squamous cell cancer of the oesophagus with respect to DPFS and improvement in DS. The median duration of DPFS following RT was 73 days; in relation to the post RT survival, this was effective in palliating dysphagia in approximately 60% of patients until time of death. Patients who have stent insertions had a shorter duration of response compared to patients without stent insertions. In the setting of patients with locally advanced and metastatic oesophageal cancer who are receiving palliative treatment, PS (ECOG) and DS at presentation can be used as a surrogate to determine which patients will benefit the most from RT. A short course of RT can be an effective method of palliation in these patients in a limited resource setting. Additional investigations on quality of life and impact of RT on relief of other symptoms may be beneficial to further quantify the magnitude of benefit in these patients.

Ethical considerations

The study proposal was approved by the Human Research and Ethics committee of the Faculty of Health Sciences at University of Cape Town.

Competing interests

The authors declare no competing interests. No funding or fees were received in any form in the preparation of this manuscript.

Authors Contribution

Dr Nazreen Bhim was responsible for the literature research, data analysis and write up of the manuscript. All authors were responsible for reviewing the manuscript prior to submission.

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APPENDIX

Table 1: DYSPHAGIA SCORE GRADING SYSTEM (Knyrim et al; 1993)

Grade 0	Able to eat all solids/ No dysphagia
Grade 1	Able to eat only some solid foods
Grade 2	Able to eat only soft foods
Grade 3	Able to drink liquids only
Grade 4	Complete dysphagia

Table 2: LIST OF ABBREVIATIONS

Abbreviation	Meaning
2D	Two-dimensional
BMI	Body mass Index
Co-60	Cobalt-60
DPFS	Dysphagia progression-free survival
DS	Dysphgia score
EBRT	External beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
EQD2	Equivalent dose in 2Gy fractions
GEJ	Gastro-oesophageal junction
IQR	Interquartile range
MV	Megavoltage
OS	Overall survival
PS	Performance Status
REDCap	Research Electronic Data Capture
RT	Radiation therapy
SCC	Squamous cell cancer

PART D: APPENDICES

(i)Data collection Instrument

Date of birth	_____
Age on enrolment (years)	_____
Age on enrolment (years) - calc	_____
Sex	◯ Female ◯ Male ◯ Other
Date of death	_____
Visit date (copy)	_____
Height (cm)	_____ (30-215)
Weight (kilograms)	_____ (0.35-200)
BMI	_____
Performance status	◯ PS=0 ◯ PS=1 ◯ PS=2 ◯ PS=3 ◯ PS=4 ◯ unknown
Dysphagia Score at presentation	◯ GRADE 1 ◯ GRADE 2 ◯ GRADE 3 ◯ GRADE 4 ◯ GRADE 5
Duration of Symptoms	◯ ◯ 1-3 months ◯ 3-6 months ◯ 6-12 months ◯ 1-2 years ◯ >2 years
Stent insertion	◯ YES ◯ NO
Date of Stent Insertion	_____
Weight loss	◯ Yes ◯ No

Date diagnosed	_____
Site of Cancer	◯ Upper 1/3 ◯ Middle 1/3 ◯ Lower 1/3 ◯ GEJ ◯ Unknown (free text)
Histology	◯ Squamous cell Cancer ◯ Adenocarcinoma ◯ Other ◯ Unknown (ICD10-CM)
Other histology	_____ (free text)
Stage	◯ I ◯ II ◯ III ◯ IV ◯ Unstaged
Sites of Metastases	☐ Liver ☐ Lung ☐ Lymph node ☐ Other (ICD10-CM)
Other site of metastases	_____
RT	◯ Yes ◯ No
Reason for no chemo	◯ Poor PS ◯ Died ◯ Chemo ◯ Declined ◯ Defaulted ◯ Other
Other reason for no RT	_____
Date of RT	_____
Dysphagia Score at time of RT	◯ GRADE 1 ◯ GRADE 2 ◯ GRADE 3 ◯ GRADE 4 ◯ GRADE 5
RT dose	◯ 8.0Gy/ 1# ◯ 20.0Gy/ 5# ◯ 18.4Gy/4# ◯ 30.0Gy/10# ◯ 50.00Gy/ 25#
Referred externally for follow-up	◯ Yes ◯ No

Date of post RT rv	_____
Dysphagia Score at post RT rv	◯ GRADE 1 ◯ GRADE 2 ◯ GRADE 3 ◯ GRADE 4 ◯ GRADE 5 ◯ defaulted
Calc improved DS	◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ -1 ◯ -2
Date of worsening dysphagia	_____
Censored by Death	◯ Yes ◯ No
Dysphagia Score at time of worsening dysphagia	◯ GRADE 1 ◯ GRADE 2 ◯ GRADE 3 ◯ GRADE 4 ◯ GRADE 5 ◯ unknown ◯ died
Calc decreased DS	◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4
Time frame (months) until worsening of dysphagia	◯ 1/52 ◯ 2/52 ◯ 3/52 ◯ 1/12 ◯ 2/12 ◯ 3/12 ◯ 3-6 months ◯ 6-9 months ◯ 9-12 months ◯ > 1 year ◯ Unknown
Duration of DFS	◯ 1/52 ◯ 2/52 ◯ 3/52 ◯ 1/12 ◯ 6/52 ◯ 2/12 ◯ 10/52 ◯ 3/12 ◯ 4/12 ◯ 5/12 ◯ 6/12 ◯ 7/12 ◯ 8/12 ◯ 9/12 ◯ 10/12 ◯ 11/12 ◯ 1 year ◯ >1 year ◯ unknown

Ethical Approval

UNIVERSITY OF CAPE TOWN
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Human Research Ethics Committee

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12 February 2018

HREC REF: 106/2018

Dr B Robertson
Department of Radiation Oncology
LE 34
GSH

Dear Dr Robertson

PROJECT TITLE: INVESTIGATING THE DYSPHAGIA PROGRESSION-FREE SURVIVAL IN OESOPHAGEAL CANCER PATIENTS POST PALLIATIVE RT- (MMeD-candidate-Dr N Bhim)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 28 February 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr N Bhim will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

signature removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC:106/2018

Hospital Approval

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
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Dr B. Robertson
Radiation Oncology

E-mail: Barbara.robertson@uct.ac.za. / nazeenbhim@gmail.com

Dear Dr Robertson

RESEARCH PROJECT: Investigating The Dysphagia Progression-Free Survival In Oesophageal Cancer Patients Post Palliative RT (MMed Dr Nazeen Bhim)

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **28 February 2019, subject to Professor J. Parkes approval.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) No additional costs to the hospital should be incurred i.e. Lab, consumables or stationary.
d) **No patient folders may be removed from the premises or be inaccessible.**
e) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
f) Confidentiality must be maintained at all times.
g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Kindly submit a copy of the publication or report to this office on completion of the research.

I would like to wish you every success with the project.

Yours sincerely

Signature Removed

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 24 December 2018

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2 March 2018

Dear Dr Nazreen Bhim

Permission is hereby granted to Dr Nazreen Bhim for the following research study to be conducted in the department of Radiation Oncology.

MMed Title: Dysphagia progression-free survival in locally advanced and metastatic oesophageal cancer following palliative radiation therapy.

Please note that permission is also required from the institutional research committee and from the ethics committee before commencing the research study.

Yours sincerely

Signature Removed

Professor Jeannette Parkes
Head of Division
Radiation Oncology Division

South African Journal of Oncology Criteria for submission

Original Research Article

An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format. Systematic reviews should follow the same basic structure as other original research articles. The aim and objectives should focus on a clinical question that will be addressed in the review. The methods section should describe in detail the search strategy, criteria used to select or reject articles, attempts made to obtain all important and relevant studies and deal with publication bias (including grey and unpublished literature), how the quality of included studies was appraised, the methodology used to extract and/or analyse data. Results should describe the homogeneity of the different findings, clearly present the overall results and any meta-analysis.

Word limit	3500-4000 words (excluding the structured abstract and references)
Structured abstract	250 words to include a Background, Aim, Setting, Methods, Results and Conclusion
References	60 or less
Tables/Figures	no more than 7 Tables/Figure
Ethical statement	should be included in the manuscript
Compulsory supplementary file	ethical clearance letter/certificate