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A RETROSPECTIVE STUDY COMPARING EXPANDABLE METAL STENTING WITH RADIATION THERAPY IN ADVANCED OESOPHAGEAL CARCINOMA IN A REGIONAL SOUTH AFRICAN HOSPITAL

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A research report submitted to the Faculty of Medicine, University of the Witwatersrand, in partial fulfillment of the requirements for the Degree of Master of Medicine in the division of General Surgery.

Johannesburg 2012

DECLARATION

I, Dimitri Liakos, declare that the contents of the paper are all work of the author. It's being submitted for the degree of Master of Medicine, in the division of General Surgery, at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

This research report is based on this work, which has been published in the South African Journal of Surgery.

- Liakos D, Dower DWR, Florizoone M, Bizos, DB. Is oesophageal stenting for cancer the answer? A report from a secondary hospital in the developing world. **SAfr J Surg**. 2010; 48:43-49.

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Nineteenth day of April 2012

LETTER SIGNED BY CO-AUTHORS

SAJS. 2010; Vol 40: 43-49

Is oesophageal stenting for cancer the answer? A report from a secondary hospital in the developing world

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CONGRESS PRESENTATIONS ARISING FROM STUDY

Liakos D, Dower DWR, Florizoone M, Bizos, DB. Is oesophageal stenting the answer? A report from a secondary hospital in the developing world. **SAfr J Surg**. 2010; 48:43-49 (Appendix A).

- Presented to the Bert Myburgh Surgical Symposium in November 2008, Johannesburg, South Africa.

- Presented to the Surgical Research Society of Southern Africa in June 2009, Johannesburg, South Africa.

- Poster presentation to the Faculty of Health Sciences Research Day, University of the Witwatersrand in August 2008, Johannesburg, South Africa (Appendix B).

ABSTRACT

Introduction

Oesophageal cancer causes much morbidity and mortality in South Africa.

This disease has a 5-year survival of less than 10% despite improvements in therapy. Most patients present with advanced disease and are suitable only for palliative care. Current standard of palliative care for patients with end-stage oesophageal cancer that present with dysphagia include brachytherapy and stenting. Brachytherapy improves survival and has a more stable quality of life in the long term when compared to stenting. Conversely stenting has a more acute relief of dysphagia. In South Africa many patients with malignant dysphagia face socio-economic constraints that cause delays in therapy, especially in patients from rural areas.

Many prospective randomized trials of palliative treatment have been done in the developed world, not taking into account socio-economic constraints. We present a study from Tshepong Hospital (Klerksdorp, North West province), a secondary hospital in South Africa.

The aim of the dissertation was to compare radiation therapy versus stenting for the palliative treatment of advanced oesophageal cancer with malignant dysphagia in the South African context, especially looking at the impact of socio-economic constraints on patient management.

Patients and methods

We retrospectively reviewed the data on 30 patients seen between February 2005 and January 2008. All patients presented with inoperable oesophageal cancer and were palliated with either radiotherapy (*N*=12) or stenting (*N*=18).

Due to delays in treatment with radiotherapy, stenting was introduced in the unit as an alternative treatment option. Radiotherapy included either external beam radiotherapy or brachytherapy. We compared the number of admissions, length of hospital stay and time from when first seen to intervention as primary outcomes.

Results

Patients presented with either grade III or IV dysphagia. The median age was 64 in the stent group and 72 in the radiotherapy group. The majority of patients were male in both groups. All patients had confirmed squamous cell carcinoma. The number of admissions, length of hospital stay and days to procedure were significantly lower in the stent group ($p=0.018$, $p=0.0072$ and $p=0.0108$ respectively). The time before intervention was 6 days in the stent group versus 49 in the radiation therapy group. No major complications as a result of brachytherapy were reported. Conversely, complications in the stent group included chest pain, tumour overgrowth, stent migration and death.

Conclusion

Patients with malignant dysphagia have a limited lifespan and focus should be on improving the quality of life in these patients. Patients undergoing radiotherapy have a significantly longer hospital stay and longer wait to treatment. With socio-economic constraints imposed upon the health sectors of the developing world, we conclude that stenting is a feasible option in this situation. Adopting a prognostic score might help in identifying patients with a poor prognosis. Either the situation should be improved or stenting should become the preferred treatment.

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1. INTRODUCTION AND LITERATURE REVIEW

Seventy years ago oesophageal squamous cell carcinoma (OSCC) was a rare disease in the South African population (1). It has become endemic in some rural areas of South Africa like the Transkei, posing a major health concern (2). This devastating disease has a 5-year survival of less than 10% despite improvements in therapy (3). Due to advanced disease at presentation, over 50% of patients are only suitable for palliative care (4), and due to the advanced stage of disease there is no prospect for cure (5).

Patients with advanced disease usually present with dysphagia and the primary goal is to alleviate the dysphagia quickly, permanently and with minimal morbidity with the aim of restoring some quality of life to the patient. Common palliative treatment modalities include placement of expandable metal stents and radiation therapy (RT). Many clinical trials (6,7) (8) comparing the treatment modalities of palliative therapy have been done in First World countries and their outcomes may not be applicable in a developing country due to socio-economic constraints.

During this study, most patients with malignant dysphagia seen at our hospital (Tshepong Hospital, Klerksdorp, North West, South Africa) were from distant rural areas and needed to be referred to tertiary centers for RT (external beam RT or brachytherapy). A number of problems were encountered during the referral of these patients, including logistic delays, resource constraints and poor follow-up, which led to prolonged hospital stays and increased morbidities.

This led to the introduction of stenting as an alternative option for these patients seen at our institution, thereby reducing hospital stays. The following literature review focuses on OSCC and the palliative therapy thereof.

1.1. INCIDENCE AND DEMOGRAPHICS

Oesophageal cancer is the eighth most common cancer worldwide, with OSCC being the most prevalent (9). In contrast to oesophageal adenocarcinoma (OAC), which is more common in Western countries, OSCC predominates in developing countries (9).

South Africa has some of the highest reported cases of OSCC in the world, with incidences reaching 100/100000 cases per year (10).

In black South Africans it is the second most common cancer in males and the forth most common cancer in females. In the black male population it comprises 13 % of all cancers reported (11). Furthermore (3), there is a three- to four-fold increased risk in males compared to females for developing OSCC. The most prevalent age group for the development of oesophageal cancer is above 40, beyond which the incidence rises after each decade.

1.2. PATHOPHYSIOLOGY AND RISK FACTORS

Although the etiology of OSCC is unknown, there is a strong association with alcohol consumption and smoking (12). The risk of OSCC increases with the dose and duration of tobacco smoking (13); patients who smoked more than 20 cigarettes for more than 35 years had an odds ratio of 10.4 of developing OSCC. The latter study also described an increased risk if heavy alcohol consumption was combined with tobacco smoking. A snuff preparation of tobacco did not have a statistical increase in the risk for OSCC. Heavy alcohol consumption (12), of more than 3 drinks per day, has been shown to be independently and significantly associated with an increased risk of developing OSCC.

In contrast to the strong association of tobacco smoking with OSCC, this was not a strong risk factor for OAC and neither was alcohol consumption (13).

Nutritional deficiencies (3) may also play a role in the development of OSCC. These deficiencies include vitamins A and -C and zinc. Generally these deficiencies are associated with diets rich in carbohydrates and low in proteins and green vegetables. The commonly consumed diet in rural areas, such as the Transkei, comprises mostly of the staple cereal, maize, which represents such a diet.

There has been controversy about an association between achalasia of the oesophagus and an increased risk of OSCC. Streitz's group (14) described an increased risk of 14.5 times for the development of OSCC in patients with achalasia when compared to an age-adjusted and sex-adjusted control population.

Other conditions that have been associated with OSCC include tylosis (15), a rare autosomal dominant condition of abnormal keratinisation, Plummer-Vinson syndrome, Zenker's diverticulum of the pharyngo-eosophagus and previous radiation exposure to the oesophagus.

According to the literature (16,17), the major risk factors for the development of OAC are gastro-oesophageal reflux disease (GORD) and Barret's oesophagus. A study by Lagergen *et al* (18) showed that a high BMI (>30kg/m^2) was also associated with OAC, but not with OSCC.

OSCC is usually located in the middle third of the oesophagus compared to OAC in which the lower third may invade the gastric cardia. Early lesions of OSCC appear small and grey-white with plaque thickenings which may become raised or ulcerate. They eventually become large tumorous masses that may encircle the whole lumen of the oesophagus and eventually occlude it. Most OSCCs are moderately to well differentiated. Histological variants include verrucous carcinoma and carcinosarcoma (spindle cell carcinoma) (19).

Molecular genetics also play a role in the development of OSCC and OAC. The p53 gene, which is required for normal cell apoptosis, was associated with mutations in both OSCC and OAC that result in continued cell growth (15). Also, there has been much interest in the over-expression of certain growth factors (20), like epidermal growth factor (EGF) and transforming growth factor beta (TGFß), in OSCC. It was suggested that EGF interferes with the effects of the adhesion molecule, E-cadherin, and thereby changes the behaviour of the squamous cell to a more aggressive phenotype with increased invasive properties.

1.3. INVESTIGATIONS AND STAGING

On presentation all patients suspected of having oesophageal cancer should have a thorough clinical examination, history taking and medical fitness assessment for a surgical procedure, chemotherapy, RT or a combination of treatments. Patients should undergo routine blood and radiological investigations (chest radiograph). A contrast swallow may also be performed before endoscopy (21) with the rationale that a barium swallow radiograph can reveal any contour and motility abnormalities such as strictures and achalasia, and exclude the presence of airway fistulas.

Endoscopy should be performed and a histological diagnosis of malignancy confirmed. The staging of oesophageal cancer should include depth of local invasion, regional lymph node involvement and presence of metastatic disease.

Staging is important for the appropriate management of patients. Patients with oesophageal cancer should be staged according to the TNM classification developed by the American Joint Committee on Cancer (22), as shown in Table Ia, Ib and Ic.

Computed tomography (CT) is the initial investigation of choice (23) for determining if the patient has a resectable tumor and whether lymph node or distal metastasis is present. According to the literature, endoscopic ultrasound (EUS) is useful for determining the depth of invasion of the tumor and the presence of loco-regional lymph node involvement. EUS (24) is also able to determine lymph node involvement reasonably accurately using size and morphology of lymph nodes.

Ultrasonographic features, which suggest malignant lymphadenopathy, include lymph nodes that are homogeneous, hypoechoic (dark), rounded as opposed to elliptical, have well demarcated borders and are larger than 10 millimeters. EUS has a sensitivity of 89.1% and a specificity of 75% in predicting the presence of malignant lymph nodes. Furthermore (25) the size and proximity of lymph nodes to the primary tumor also predicted the presence of malignant lymph nodes. When fine needle aspiration (FNA) is combined with EUS (EUS-FNA), the accuracy of determining lymph node involvement is increased (26,27).

Table Ia. TNM Classification for Oesophageal Cancer (2010 American Joint Committee on Cancer)

Category	Description
Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia (HGD)
T1	Tumors invade lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumors invade muscularis propria
T3	Tumors invaded adventitia
T4	Tumors invade adjacent structures
T4a	Resectable tumor invading pleura, pericardium, or diaphragm
T4b	Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.
Regional Lymph Nodes (N)	
NX	Lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-2 lymph nodes
N2	Metastasis in 3-6 lymph nodes
N3	Metastasis in seven or more regional lymph nodes
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant Metastasis

Table Ib. Histologic Grade (G) of Oesophageal Cancer

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Table Ic.
Anatomic Stage/Prognostic Groups for Squamous Cell Carcinoma

Stage	***T***	***N***	***M***	***Grade***	***Tumor location****
0	Tis (HGD)	N0	M0	1, X	Any
IA	T1	NO	MO	1, X	Any
IB	T1	N0	M0	2-3	Any
	T2-3	N0	M0	1, X	Lower, X
IIA	T2-3	N0	M0	1, X	Upper, Middle
	T2-3	N0	M0	2-3	Lower, X
IIB	T2-3	N0	M0	2-3	Upper, Middle
	T1-2	N1	M0	Any	Any
IIIA	T1-2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
IIIB	T3	N2	M0	Any	Any
IIIC	T4a	N1-2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
IV	Any	Any	M1	Any	Any

**Location of the primary cancer site is defined by the position of the upper (proximal) edge of the tumor in the oesophagus.*

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer-Verlag New York, www.springer.com (22).

In a study conducted by the Mayo clinic, comparing spiral CT, EUS and EUS-FNA (28) for the lymph node staging of patients with oesophageal cancer, the results showed increased sensitivity of EUS-FNA when staging lymph node involvement compared to the other modalities. Furthermore (28), EUS-FNA results altered the management plan in 77% of patients and significantly altered therapy by correcting the CT-tumor stage.

Concerns when using EUS as a modality is the risk of perforation (29) in patients that present with malignant dysphagia, and therefore these patients would have to undergo serial dilatations of the oesophagus before intervention. Thin EUS probes that can be passed through the endoscope can overcome the risk of perforation.

Also, patients that presented with malignant dysphagia had a high probability of having advanced (stage III/IV) disease.

1.4. TREATMENT MODALITIES

1.4.1. Curative therapy

Stage I-III can be assumed to be resectable disease. Surgery is the mainstay of treatment for resectable disease. Perioperative chemotherapy substantially improved survival (30), and a combination of chemotherapy with RT followed by surgery resulted in higher median survival times (31). Neo-adjuvant chemoradiotherapy (CRT) (32) is now the mainstay of treatment for resectable oesophageal tumors.

1.4.2. Palliative therapy

1.4.2.1. Selection of patients for palliative therapy

After careful staging of the disease, patients' fitness for treatment should be assessed. In general, patients who are not fit enough for surgery will not be fit enough for radical RT or chemotherapy (15). Treatment options should be discussed with the patient and psychological well-being should be addressed.

Once all these issues have been resolved the palliative treatment of choice should be offered to the patient. It should be noted that the median survival in patients with advanced disease is poor at 120 days (33).

1.4.2.2. Mechanical endoscopic methods for relieving obstruction

Mechanical methods for relieving obstruction include dilatation only and dilatation followed by stenting of the oesophagus.

Intubation of the oesophagus for the treatment of malignant strictures of the oesophagus has been described as early as 1887 (34). Advances of oesophageal intubation saw the Celestin tube (plastic tube) being introduced as palliative therapy for malignant dysphagia (35); the insertion of this tube, however, required laparotomy for insertion and had many complications, including high perforation rate, hemorrhage and need for gastrostomy.

In 1980 Procter (36) described the advantages of the Procter-Livingstone tube, which did not require a laparotomy and, due to its shorter length, did not cause erosions and bleeding of the gastric mucosa.

Plastic stents, although they provide quick, inexpensive and long-term palliation in patients with malignant dysphagia, are not without complications. Procedure-related complications include oesophageal perforation, bleeding, pain and dislodgement post intubation.

In 1973 Didcott (37) described the Didcott Dilator (a metal stent), which was used for the slow dilatation of the oesophagus due to benign strictures. This dilator was the forerunner to the current self-expandable metal stent (SEMS). The mortality rate associated with the intubation of plastic stents may be as high as 8% (38) (39) and in a prospective study comparing plastic stents to SEMS, plastic stent insertion was associated with higher complications and mortality rates. Although perforation and bleeding are also complications of SEMS, they occur at a lower rate compared to plastic stents. Other complications in the SEMS group included tumor in-growth and lumen obstruction by impacted food causing recurrent dysphagia and reflux oesophagitis. The median survival time (38), however, was equal between the two (De Palma 1996). These findings were similar to those reported by (40). Conversely, O'Donnell (41) found an increase in survival in the SEMS group, with a median survival in the SEMS group of 102 days versus 62 days in the plastic stent group.

SEMS are effective, easy to use, and have fewer complications and lower mortality rates compared to plastic stents. SEMS seem to be the preferred choice over plastic stents. However, the costs of SEMS are substantially more than plastic stents. A group from Natal (42), South Africa, compared plastic stents to SEMS and investigated the cost-effectiveness of SEMS. They reported that the cost of the stent, including hospital stay, amounted to R 4123 in the SEMS group versus R 2146 in the plastic endoprosthesis group, making the SEMS group 1.9 times more expensive. Nevertheless, the clear advantages of SEMS constitute them the mainstay of stent therapy in malignant dysphagia.

The initial, so-called first generation SEMS were uncoated, but concerns of recurrent dysphagia, due to tumor in-growth and lumen obstruction with impacted food, prompted the use of coated metal stents to be introduced. The rates of recurrent dysphagia were found to be less in a prospective study when coated metal stents were used compared to uncoated metal stents (43). Completely covered metal stents, however, had an unacceptably high rate of migration due to the inability of the stent to integrate into the wall of the oesophagus (44). The development of a so-called second generation, partially covered SEMS had more promising results subsequently (45).

A few years later, a randomized, controlled trial (46) compared partially-covered SEMS to uncovered-SEMS and found that 27% of the patients in the uncovered stent group needed re-intervention due to tumor in-growth, as opposed to none of the patients in the partially-covered stent group.

This difference was found to be statistically significant. Food impaction causing obstruction was seen more frequently in the uncovered stent group whereas stent migration was more frequent in the partially-covered stent group; both these outcomes did not reach statistical significance.

Therefore while uncovered stents have less chance of migrating, the chance of obstruction due to tumor in-growth and/or food impaction is higher when compared to covered stents. The partially covered stent has the proximal and distal edges exposed to allow for mucosal in-growth, which prevents stent migration (a problem with the completely covered SEMS).

The remaining bulk of the stent is covered to prevent tumor in-growth. Two commonly used second generation SEMS, the Flamingo Wallstent (Boston Scientific, Natrick, MA, USA) and the Ultraflex stent (Boston Scientific, Natrick, MA, USA) were compared by Sabharwal (47), looking at dysphagia scores, migration of stent, severe reflux and other complications. Outcomes were similar between the 2 groups and the authors state the Flamingo Wallstent however allows more accurate placement. Two patients with the Ultraflex stent presented with stent migration compared to one patient with a Wallstent.

Furthermore, a prospective trial involving 100 patients (48) compared the Ultraflex stent, the Flamingo Wallstent, and the covered Z-stent (Wilson-Cokk Medical, Winston-Salem, NC, USA). There were no significant differences in the improvement of dysphagia or the recurrence of dysphagia or complication rates between the 3 different covered metal stents.

If the SEMS are placed across the gastro-oesophageal junction, gastro-oesophageal reflux becomes problematic. Reflux may also cause dyspnoea

due to micro-aspiration of gastric contents, which occurs especially at night. An attempt to overcome this complication was the development of the anti-reflux stent.

SEMS with a dual anti-reflux valve (Wilson Cook Medical, Winston-Salem, North Carolina) was compared to a standard SEMS with no difference in complications, dysphagia score, survival and global health score (49). Reflux symptoms were also not improved with the use of the anti-reflux stent but some improvement was seen with dyspnoeic symptoms. Of note is that assessment of reflux in the preceding study was based on symptoms alone.

A more scientific approach was used to assess the effectiveness of an anti-reflux valve by 24-hour pH monitoring in a study by Homs (50). They reported no decrease in reflux or acidic environment with the use of the anti-reflex valve in SEMS.

Furthermore, anti-reflux stents are not effective against preventing reflux but may reduce symptoms of dyspnoea.

In a meta-analysis by Sgourakis (51), looking at 16 randomised controlled trials comparing different SEMS to each other and SEMS to loco-regional palliative treatment modalities. These loco-regional treatment modalities included laser, thermal ablation, radiation therapy and argon plasma coagulation. They found no superiority of anti-reflux stents over standard SEMS. Furthermore the Flamingo stent had a better overall dysphagia score at 4 weeks and the Ultraflex stent was found to be the most inferior with regard to bolus occlusion.

Analysis of the current data reveals minor differences exist between the different types of SEMS available for use and choice should be dependant on tumor location, anatomy and cost.

1.4.2.3. Non-mechanical endoscopic methods for relieving obstruction

Other methods have been described for the palliation of malignant dysphagia, including thermal ablation using laser therapy, photodynamic therapy (PDT) and injecting of the tumor with sclerosants like ethyl alcohol.

Laser therapy uses neodynium ytrium aluminium garnet laser (Nd:YAG) to ablate the tumor and PDT involves injecting the tumor with porfimer sodium and then treatment with red light of 630nm wavelength (52).

Complications of laser therapy include pain, perforation, bleeding, repeated hospital admissions due to tumor overgrowth and fibrotic strictures. Complications of PDT include photosensitivity that may last up to 6 weeks after treatment, perforation, fistula formation and oesophagitis causing pain and fibrosis (15).

A large, multicenter, randomized trial was performed comparing PDT to laser therapy (52). Both modes of therapy had an average palliation failure time of 1 month and a quarter of the patients in both groups had no change in the dysphagia score after therapy. PDT had more adverse effects than laser therapy, which included sunburn, nausea, fever and asymptomatic pleural effusions. On the other hand laser therapy had more severe adverse affects which included a 7% perforation rate compared to 1% in the PDT group .

In a smaller study, the durability of palliation was longer at 84 days in the PDT group compared to 57 days in the laser group, p=0.008 (53).

Furthermore laser therapy was not effective in long tumors, or very narrow tumors or where tumors were not exophytic (54) (55).

Although there are benefits of laser therapy in rapid alleviation of dysphagia in patients with advanced oesophageal cancer, the main problem with laser therapy is the need for repeat sessions every 4-6 weeks to maintain patency of the oesophagus. Sargeant (56) looked at combining laser therapy with external beam RT (30 Gy in 10 fraction) to reduce the frequency of laser treatments. Time to laser was increased from 5 weeks to 9 weeks, but with a higher complication rate in patients being exposed to RT. These patients developed oesophageal strictures and had a higher rate of perforations and fistulae formations.

In a randomized study by Spencer (57), laser therapy was combined with brachytherapy and compared to laser therapy alone. Brachytherapy was give as a single fraction. There was a statistically significant difference with regard to mean time to recurrence of dysphagia in favour of the laser/brachytherapy combination group.

In the laser therapy alone group time to recurrence was 5 weeks whereas in the bracytherapy and laser therapy combination group the mean time to recurrence was 19 weeks. There was no difference in the mean survival time between the 2 groups. The median survival was 20 weeks in the laser alone group and 26 weeks in the combination treatment group.

In a small clinical trial laser therapy was compared to brachytherapy as sole modality treatment options (58).

Laser therapy versus brachytherapy confirmed that brachytherapy had a better long-term patency of palliative therapy than laser therapy however initial relief of dysphagia was slightly better in the laser group.

When laser therapy was compared to SEMS in a randomized trial (59), it was found that the relief of dysphagia (which was poor in both groups) was similar in both groups but the laser group had a higher survival time of 125 days compared to 68 days in the SEMS group. The authors did mention that the population group included old, frail patients with co-morbidities. Recurrent dysphagia was also higher in the laser group, 7 patients compared to 4 in the SEMS group. The authors also described a longer hospital stay and cost in the laser group.

In contrast to the above study, Adam (60) found a better initial relief of dysphagia when using SEMS compared to laser ablation therapy.

Conflicting results exist between laser therapy and SEMS. Initial relief of dysphagia seems to be similar between the 2 groups but with an increased rate of tumor recurrence in the laser group.

Endoluminal YAG-laser ablation therapy is a feasible option for the palliation of malignant dysphagia however, its durability is its shortfall with combination RT needed to extend the duration of palliation and an experienced endoscopist with laser therapy is needed (61).

PDT although has a longer durability, is easier to perform and has a lower perforation rate than laser therapy, its costly and has excessive adverse effects to patients.

New advances in metallic stent technology render them safe and simple to use with less adverse effects than laser therapy or PDT with shorter hospital stay (61), however complications of stent migration and hemorrhage can be problematic (62). In addition, results have shown that the use of SEMS after radiation and/or chemotherapy is safe, but with an increased risk of retrosternal pain (63).

Despite reports of effective results comparable to laser therapy with the use of ethyl alcohol injections (15) to induce chemical necrosis of the tumor with the aim of relieving dysphagia, it comes with considerably more pain. The use of ethanol injections has not become widespread.

1.4.2.4. Radiation therapy and chemoradiotherapy

RT includes both external beam RT (EBRT) and intra-luminal brachytherapy. EBRT requires considerably more therapy sessions with higher complications than brachytherapy due to the damaging of normal surrounding tissue.

Work has been done on EBRT as palliative treatment in malignant dysphagia. Complications of RT include oesophagitis, ulcerations of the oesophagus, fistula formation and hemorrhage (15).

The role of EBRT in malignant dysphagia is to shrink the tumor enough to allow for intra-luminal brachytherapy to be delivered, and not as a sole modality for palliative therapy (64). When EBRT was compared to brachytherapy, it was clear that brachytherapy was a better option for palliative therapy than ERBT alone (65).

Brachytherapy was first used as a booster to EBRT with promising results (66). Brachytherapy delivers high doses of RT to the lumen of the oesophagus with rapid shrinkage of the tumor. One of the main complications is the formation of strictures after treatment. These strictures were successfully managed with the Didcott Dilator.

Brachytherapy can be given in different doses and much work has been done looking at which is the most effective dose with the least morbidity by Sur in South Africa. In a small study (67) different doses of high dose rate (HDR) brachytherapy were compared. It was a small study with 25 patients. The authors concluded that 12-15 Gy given as a single fraction, was effectively the best dose for the relief of dysphagia with the least morbidity; this however was just a preliminary report.

A larger study (68) looked at 172 patients, divided into 3 groups. The groups received different doses of HDR brachytherapy, 12Gy/2 fractions, 16 Gy/2 fractions and 18 Gy/3 fractions. The fractions were given on a weekly basis. Patients that received the highest dose of HDR brachytherapy (16 Gy/2 fractions and 18 Gy/3 fractions) had the longest median survival and the longest dysphagia free survival.

Sur (69) then followed up with a large, prospective, randomized trial that involved 232 patients. All patients were diagnosed with OSCC. Patients were divided into 2 treatment arms, delivery of HDR brachytherapy at 16Gy in 2 fractions (group A) or 18Gy in 3 fractions (group B).

Statistically there were no differences between the 2 treatment groups regarding all outcomes and the dysphagia-free survival was 7.8 months in group A and 6.3 months in group B.

Overall survival in both groups was 7.9 months. Stricture rates were 10.7% versus 10.8% in groups A and B respectively. Fistula rates were also similar at 9.8% and 10% respectively.

Homs (70) reported less impressive results with the use of single-dose HDR brachytherapy. In their retrospective study 137 (92%) patients received 15 Gy in a single fraction but the dysphagia score improved in only 51% of their patients, and after 6 weeks the mean dysphagia improved from a score of 3 to 2. Mean survival was 160 days and 34/149 patients required stenting for persistent dysphagia.

Brachytherapy and SEMS placement are the most widely used forms of palliation for malignant dysphagia. The SIREC study (6) (a large, Dutch, multicenter, randomized trial) compared single-dose brachytherapy to stent placement primarily looking at dysphagia relief, median survival and quality of life scores.

Single-dose brachytherapy (12 Gy as a single fraction) had a better dysphagia score at 30 days than the stent group but the initial relief of dysphagia was better in the stent group. Furthermore the brachytherapy group had more days with almost no dysphagia (grade 0 or 1, Table II) (71) at 115 days versus 82 days in the stent group. Overall median survival was also slightly longer in the brachytherapy group at 155 days versus 145 days in the stent group and a better quality of life score was seen in the brachytherapy group.

Table II. Degree of dysphagia in patients with inoperable carcinoma of the oesophagus	
Symptom	Degree of dysphagia
No dysphagia	**0**
Dysphagia for solids	**I**
Dysphagia for semi-solids	**II**
Dysphagia for liquids	**III**
Complete dysphagia	**IV**

A further look into the health-related quality of life scores (HRQoL) revealed that initial scores were stable in both the brachytherapy and stent groups, however on 3-month follow-up there was deterioration in both groups but more so in the stent group (72).

Another randomized, controlled trial (33) from the Netherlands comparing stenting to brachytherapy revealed that stenting provided a more instant relief of dysphagia over brachytherapy, however brachythearpy offered a more stable HRQoL in the long run. Quality of health scores are calculated based on physical, emotional, social, cognitive and functioning of the patient. Overall median survival was comparable in both groups (around 120 days). Brachytherapy was given as 7 Gy in 3 fractions in contrast to a single dose of 12 Gy in the SIREC study (6).

Wenger (73) randomized 30 patients to receive 7Gy in 3 fractions of brachytherapy and 30 patients into the stent group.

The results in the study compared to other studies. After 1 month dysphagia scores were better in the stent group but after 3 months dysphagia scores were better in the brachytherapy group. Additionally 8 patients in the stent group required intervention in a median 83 days and in the brachytherapy group seven patients required intervention in a median 225 days due to progressive tumor overgrowth. Interestingly, the patients in the brachytherapy group that required re-intervention were stented. Median survival was similar in both groups at 158 days in the stent group and 162 days in the brachytherapy group.

Brachytherapy whether given in a single fraction or higher doses in 2 or 3 fractions provides longer relief of dysphagia compared to stenting and provides a longer median survival in advanced cancer of the oesophagus.

In the meta-analysis of 16 randomized controlled trials (RCT's) by Sgourakis (51), they compared median survival of patients undergoing primary stenting versus patients undergoing other loco-regional treatment modalities including brachytherapy and radiation therapy. Their results suggest a shorter median survival at one year in the stent group, however a higher re-intervention rate in the group undergoing other loco-regional treatment (these include laser, thermal ablation, radiation therapy and argon plasma coagulation).

Zhang (74) from China suggested in an editorial in The Lancet that patients with short survival expectancy (3 years) should be initially treated with stenting, due to its initial rapid relief of dysphagia, and then possibly followed by brachytherapy.

It would then seem that the ideal management of these patients would be the combination of stenting for the initial superior relief of dysphagia, followed by brachytherapy.

In another study from China, Guo (75) compared SEMS to ^{125}I coated SEMS with primary outcomes being dysphagia relief and survival time. Their dysphagia scores were similar at 1 month in both groups, however after 1 month dysphagia scores were better in the ^{125}I coated SEMS group. Median survival time was 7 months in the ^{125}I coated SEMS group compared to 4 months in the SEMS group. These results were statistically significant.

Health economic costs between stenting and brachytherapy were evaluated. Stenting was cheaper than brachytherapy overall, due to the longer hospital stay in the brachytherapy in a study from Sweden (73), and in another study carried out in the Netherlands stenting and brachytherapy costs were similar (8). It has to be noted however that the Swedish study 3 fractions of brachytherapy were given compared to a single-dose in the Dutch study.

Table III summarizes the randomized trials used in the literature review.

1.4.2.5. Chemotherapy

Chemotherapy or combined chemoradiotherapy has been described for the palliative management of malignant dysphagia, however comparative studies are few.

In a prospective cohort study (76) evaluating primarily the dysphagia relief in patients with advanced disease, the authors described CRT as effective in the management of malignant dysphagia.

They reported 78% of patients as having improved swallowing, and 41% of patients returning to normal swallowing. 14% of patients had no improvement in the dysphagia score. The mean survival in these patients was 7 months and tolerance to the treatment was acceptable. These patients received 35 Gy in 15 fractions of RT with one cycle of cisplatin and 5-fluorouracil.

These findings were similar in another study by Harney et al (77).

In a comparative study by Wong (78), the author's retrospectively compared CRT to stenting as palliative therapy in malignant dysphagia. There were 36 patients in each group. The dysphagia scores were similar after treatment and 8 patients in the CRT group need re-intervention by stenting at a median 4.5 months. Median survival was also longer in the CRT group at 10.8 months compared to 4 months in the stent group. Of note is CRT therapy consisted of cisplatin and 5-fluorouracil infusions, with concurrent radiotherapy of 50 to 60 Gy in 25 to 30 fractions over a period of 5 to 6 weeks.

Chemotherapy alone (79) may be considered for palliative treatment in patients that are medically fit enough. Dysphagia should be relieved before chemotherapy is commenced. The disadvantage of stent placement is the risk of migration into the stomach after chemotherapy and subsequent tumor shrinkage.

It should be noted that Sur (80) looked at 200 patients that received either brachytherapy alone or were first chemosensitized with 5-FU then followed by brachytherapy. He reported an increased rate of stricture formation due to fibrosis with the need for dilatation.

This occurred possibly because chemotherapy induces more mucosal damage, which is then potentiated by brachytherapy followed by fibrotic healing causing strictures. The dysphagia-free median survival times were similar between the 2 groups after 6 months, but after 1 year they were better in the group that did not receive prior chemotherapy.

Nevertheless, CRT has shown promising results with regard to median survival, and should be considered if patients are fit enough to undergo treatment.

1.4.2.6. The role of surgery

Surgery has little role to play in the palliative treatment of patients with oesophageal cancer. In the presence of advanced disease transtumoral resections are associated with poor survival rate and should be avoided as much as possible (81).

In a comparative retrospective study between surgery and other treatment modalities (chemotherapy, RT or both) in patients with T4 disease, the results show no survival benefit in the surgery group (82).

Palliative oesophagectomy can be considered for specific patients who develop resectable disease after CRT, without the presence of distant metastasis (83).

Bypass surgery has now largely been replaced by other more effective methods of palliation. Gastostomy feeding tubes have some role to play in palliation when other means of dysphagia relief have failed.

1.4.2.7. Fistula management

Fistulas can be formed most commonly between the oesophagus and the respiratory tract due to advanced disease, or due to complications of laser therapy, RT or stent placement (79). Patients usually present with coughing after drinking or eating, dyspnoea and recurrent chest infections. The mainstay of treatment is the placement of covered SEMS to occlude the fistula, with no clear differences between the different covered metallic stents available (84).

Table III: Summary of Randomized Trials

Study	Group	N	Histology		Tumor site (oesophagus)	Dysphagia Relief	Median Survival	Cost/pt	HRQL	Complications (number of patients)
			AC	ESCC						
Bergquist et al (33)	Stent	34	13	15	*	Superior at 1/12	149 days	*		TOF (2), Bleeding (2)
	Brachy (7Gy x 3)	31	13	11		Superior after 1/12	157 days		Better overall	TOF (1), Perforations (2)
Sur et al (69)	Brachy (16Gy x2)	118	-	118	Majority	No difference	207 days	-	-	Stricture (12), TOF (11)
	Brachy (18Gyx3)	104	-	104	Middle 1/3	No difference	273 days	-	-	Stricture (13), TOF (12)
Homs et al (6)	Stent	108	68%	29%	Middle1/3,	Superior at 1/12	145 days	8215€	Brachy more stable	TOF (3), Perforations (2)
	Brachy (12Gy single)	101	69%	27%	Lower 1/3	Superior after 1/12	155 days	8135€	long term	TOF (2), Perforations (1)
Wenger et al (73)	Stent	28	13	13	Mainly middle	Superior at 1/12	158	24564€**	*	
	Brachy	24	17	16	and distal 1/3	Superior 2/12-3/12 (equal after that)	162	35414€**		
De Palma et al (38)	Plastic stent	20	*	*	*	Grade 3 to 1	6.2 months	*	*	Perforations (3), Bleeding (1)
	Metal stent	19				Grade 2.9 to 0.5	6.6 months			Perforations (0), Bleeding (0)
O'Donnell et al (41)	Plastic stent	25	14	10	Middle	Equal at 1/12	62 days	*	Superior with metal stent	Re-interventions (8); Failed placement (2); Re-interventions (10)
	Metal stent	25	12	13	oesophagus	Superior at 2/12	107days			
Vakil et al (46)	Covered stent	32	27	*	Gastro-oesophageal	Grade 3 to 1 at 1/12	Equal	*	*	Tumour ingrowth (1); Stent migration(4)
	Uncovered	30	25		junction	Grade 3 to 1 at 1/12	Equal			Tumour ingrowth (9) ; Stent migration(1).

Table III: Summary of Randomized Trials (cont.)

Study	Group	N	Histology		Tumor site (oesophagus)	Dysphagia Relief	Median Survival	Cost/pt	HRQL	Complications (number of patients)
			AC	ESCC						
Siersema et al (48)	Ultraflex stent	34	21	13	Middle, distal oesophagus and cardia	Grade 3.3 to 0.5	104 days	*	*	Major complications (8); Recurrent dysphagia(9)
	Flamingo wall stent	33	21	11		Grade 3.2 t0 0.5	113 days			Major complications (6); Recurrent dysphagia(9)
	Gianturco-Z stent	33	25	7		Grade 3.2 to 0.7	110 days			Major complications(12); Recurrent dysphagia(5)
Sabharwal et al (47)	Flamingo Wallstent	22	*	*	Lower 1/3, Gastro-oesophageal junction	Grade 2. 9 to 0.9	4 deaths at 30 days	*	*	Migration (1); Severe reflux (1)
	Ultraflex stent	32				Grade 2.7 to 1	5 deaths at 30 days			Migration (2); Severe reflux (2)
Wenger et al (49)	Dua anti-reflux stent	19	13	4	Oesophagus (61%) and cardia (39%)	Similar improvement in both groups	58 days	*	Equal symptoms of reflux,	Perforation (0); Severe reflux (2)
	Z-stent	22	18	4			68 days		Dyspnoea symptoms improved in anti-reflux stent group	Perforation (2); Severe reflux (2)
Homs et al (50)	Anti-reflux stent	15	12	3	Distal oesophagus/ cardia (80/20%)	Grade 3 to 1 at 2/52	107 days	*	3 patients complained of reflux	23% increased acid levels on 24-hor pH monitoring
	Standard stent	15	12	3		Grade 3 to 0 at 2/52	87 days		2 patients complained of reflux	10% increased acid level on 24-hour pH monitoring
Lightdale et al (52)	PDT	118	52%	48%	Upper, middle and lower 1/3	Equal relief at 1/12	123 days	*	*	Sunburn (19%); Perforations (1%) ; Termination: serious adverse events (3%)
	Nd: YAG	118	50%	50%		Equal relief at 1/12	140 days			Sunburn (0%); Perforation (7%); Termination: serious adverse events (19%)
Spencer et al (57)	Nd:YAG	11	11	0	Distal 1/3 and cardia	Dysphagia palliation of 5/52	80 days	*	*	Re-interventions (5)
	Nd:YAG + Brachytherapy		11	0		Dysphagia palliation of 19/52	104 days			Re-interventions (2)

Table III: Summary of Randomized Trials (cont..)

Study	Group	N	Histology		Tumor site (oesophagus)	Dysphagia Relief	Median Survival	Cost/pt	HRQL	Complications (number of patients)
			AC	ESCC						
Dallal et al (59)	Thermal tumor ablation	34	23	10	*	Median change in dysphagia score at 1/12 was 0	125	6235 £	Overall better	Perforations (2); TOF (3); Recurrent dysphagia(7)
	Stent	31	19	10		Median change in dysphagia score at 1/12 was 0	68	3378 £	Overall worse	Perforations (0); TOF (0); Recurrent dysphagia(4)
Adam et al (60)	Laser	18	13	4	Middle and upper 1/3: 6; Lower 1/3: 12	2 (grade of dysphagia after treatment)	56	*	*	Re-intervention (100%)
	Stent uncovered	19	12	6	Middle and upper 1/3: 10; Lower 1/3: 9	1 (grade of dysphagia after treatment)	60			Re-intervention (26%)
	Stent covered	23	15	6	Middle and upper 1/3: 9; Lower 1/3: 14	1 (grade of dysphagia after treatment)	48			Re-intervention (43%)
Harvey et al (76)	Chemo-radiotherapy	106	51	50	Upper 1/3: 12 Middle 1/3: 30 Lower 1/3: 64	49%: grade 0 dysphagia after treatment 78%: at least 1 grade improvement 14%: no improvement	7 months	*	*	Treatment- related deaths: 6 (7%)

* Not stated, ** Total lifetime costs per patient, PDT (photodynamic therapy), Nd:YAG (neodynium ytrium aluminium garnet laser), TOF (trache-oesophageal fistula)

2. AIM OF STUDY

The aim of the retrospective study was to compare RT (EBRT or brachytherapy) versus stenting for the palliative treatment of advanced oesophageal cancer with malignant dysphagia in the South African context.

The primary outcomes included:

- Hospital stay (in number of days)
- Number of hospital admissions
- Number of days from day first seen to either stenting or RT
- The determining of hazard ratio (mortality risk) for patients residing further than 130 km from a secondary hospital

Secondary outcomes included:

- Number of days from intervention to biopsy
- Procedure related complications
- Median survival in both groups

3. PATIENTS AND METHODS

3.1. Patients

Between February 2005 and January 2008 the records of a total of 66 patients who presented with dysphagia grade III-IV (Table II) were evaluated. Of the 66 patients, 30 were included in the study of which 18 patients made up the stent group and 12 patients the RT group. Inclusion criteria included all patients that presented with malignant dysphagia and where inoperable oesphageal cancer was diagnosed. Patients who received combined treatment (i.e. Stent and brachytherapy) or feeding gastrostomies as palliation therapy were excluded from the study.

3.2. Methodology

Tshepong Hospital is a secondary hospital that drains a large portion of the population in the North-West Province. Although the hospital facilities include a surgical department that offers oesophageal stenting under screening, it does not offer radiation therapy. Imaging facilities include computer tomography (CT) scanning, ultrasound (US) evaluation and barium swallow.

Patients were evaluated with standard laboratory investigations, which included a full blood count, urea and electrolytes, liver function tests and calcium, magnesium and phosphate levels.

Radiological investigations included a chest X-ray, abdominal US, barium swallow and CT scan. Patients with severely poor general health and deemed not fit for any surgery did not undergo a CT scan and were assumed to have metastatic disease.

Patients either underwent stenting or RT. Due to the prolonged delays in patients receiving RT, stenting was introduced in the unit. At the time stenting was introduced, all patients with malignant dysphagia were subsequently stented according to unit policy.

All patients in the RT group were initially sent to an academic hospital for brachytherapy. The decision to give external beam RT was made by the radiation oncologists if the lumen of the oesophagus was too narrow for brachytherapy. Patients were dilated where required by the surgical department at Tshepong Hospital, however this was not adequate in some instances.

After treatment dysphagia was assessed clinically (see table II) after 2 weeks, and then monthly. Median survival was determined in both groups. In patients that were lost to follow-up, the death certificates were retrieved from the central department of home affairs to determine the date and cause of death.

3.3. Procedures

Before stenting or RT, all strictures were dilated to at least 12 mm with a Savary dilator over a guidewire. Gastroscopy with dilatation and stent placement was done under general anaesthesia (hospital policy).

Eighteen patients were stented with a self-expandable, coated, metallic stent (Ultraflex esophageal covered stents, Boston Scientific, Natrick, MA, USA) under fluoroscopic guidance.

Of the 12 patients who received RT, 5 received brachytherapy and 7 received external beam RT.

Patients undergoing RT either received brachytherapy or external beam RT (EBRT). EBRT was chosen if brachytherapy was unsuccessful due to advanced stenosis of the oesophagus.

3.4. Data Analysis

Patient records and surgical records were analysed. Patients that were still alive (37%) were followed up at the outpatients department.

Results were tabulated and statistically analysed using the Kruskal-Wallis test with a 95 % confidence interval, and $p<0.05$ was regarded as statistically significant. Median survival was determined using Kaplan-Meier estimates and the log-rank test.

The hazard ratio of patients living further than 130 km from a secondary hospital was determined using Cox regression analysis adjusted to treatment.

3.5. Ethics approval

Ethical approval was obtained from the Human Research Ethics Committee (M071109) in February 2008 (Appendix C).

No consent was required from patients and the data was coded and remained anonymous.

4. RESULTS

Of the 66 patients evaluated during the study period, 33 patients did not fulfill the criteria to be included in the study, as they did not receive any palliative therapy (i.e. stent insertion or RT). Reasons included lost to follow-up (n=10), death awaiting treatment (n=9), gastrostomy tube was inserted (n=3), refusal of hospital treatment (n=1), other malignancies causing dysphagia (n=3), benign oesophageal strictures (n=4) and inflammatory/infective causes of dysphagia (n=3).

Of the remaining 33 patients, 3 patients received both RT and stent insertion, and were therefore also excluded from the study.

The 30 remaining patients included in the study comprised of 21 males and 9 females. Median age was 64 in the stent group and 72 in the RT group (Table III).

All patients were black Africans. Only 14 of the patients had contact details, and most patients were referred from peripheral hospitals. All patients were inoperable at time of presentation due to advanced disease and/or were in poor general health. Patients presented with dysphagia grade III-IV (Table 2). The degree of dysphagia on presentation could not be ascertained in 2 of the stented patients. Most patients presented with middle third tumors. In the stent group 10 patients presented with middle third, 5 patients presented with distal third and 2 patients presented with upper third oesophageal tumours. In one patient the tumour site could not be determined.

In the RT group 8 patients presented with middle third, 2 patients presented with distal third and 1 patient presented with upper third oesophageal tumours. In 1 patient the tumour site could not be determined.

All patients included in the study had a poor nutritional status ascertained clinically (wasted), and with a history of excessive weight loss. One patient in the stent group was known with HIV and pulmonary tuberculosis. ECOG or Karnofsky perfomance scores were not determined in the study patients.

Histology examination revealed squamous cell carcinoma in all the patients.

In 9 cases stenting was done at initial gastroscopy on the clinical basis of malignancy of the oesophagus; the remaining 9 patients were stented following histological confirmation of the disease. There was a bias toward the stenting group as these patients were stented within 8 days of presentation to hospital on clinical grounds of carcinoma, thereby avoiding the delay of histological confirmation and hence decreasing the number of days from intervention to management in the group. Cancer was confirmed

histologically after stenting. The remaining patients from both groups were treated only once cancer was confirmed histologically.

In the RT group the patients needed to be sent to an academic hospital where this service was available (a distance of >120 km away). On arrival at the academic institution, patients would receive an appointment to have RT in 1 to 2 weeks time, after which they were sent back to their referring hospital.

The median number of admissions was 2 in the stent and 3 in the RT groups. This difference between the two groups was mainly due to the need for repeated cycles of EBRT. Hospital stay and time from first seen to treatment was also significantly shorter in the stent group.

Biopsy was done within 3 days of first presentation in 69% of the patients (n=20). The median number of days from presentation to biopsy did not differ between the two groups.

Outcomes are depicted in table IV.

Table IV: Comparison of outcomes between the patients receiving palliative treatment with stenting and those receiving radiotherapy			
Variables	Stent group (n=18) Median (Range)	Radiotherapy group (n=12) Median (Range)	*p- value
Gender **Females** **Males**	**5** **12**	**2** **10**	
Age	**64 (39-85)**	**72 (45-81)**	**p= 0.21**
Number of admissions†	**2 (1-4)**	**3 (2-7)**	**p=0.0180**
Hospital stay†	**15 (1-89)**	**29 (11-63)**	**p=0.0072**
Days to procedure†	**6 (0-104)**	**49 (35-377)**	**p= 0.0108**
Days to biopsy	**2 (0-43)**	**2 (1-19)**	**p=0.71**
**A p-value of <0.05 is statistically significant* *†Primary outcomes*			

A number of patients in both groups had excessively high values for various outcomes (number of admissions, hospital stay and time to intervention), which caused considerable delays in treatment. These delays were mainly caused by repeated cycles of EBRT, administrative and logistic delays, defaulted treatment by patients and technical factors, which include faulty gastroscope and EBRT machine.

Table V lists the causes for excessive hospital duration, admissions and time to intervention in 18 patients in both the stent and RT group. Delays were seen in both groups. In the RT group the main causes of delay were repeat cycles of RT and defaulted treatment. Due to multiple admissions required for RT, and long distances to be travelled especially in patients from rural areas, the risk of defaulted treatment was higher.

Four patients in the RT group re-obstructed after treatment, 3 patients who received brachytherapy and 1 patient who received EBRT. Two patients obstructed within 3 months and 2 patients obstructed within 4 months.

Three patients in the stent group re-obstructed due to tumour over-growth. One patient obstructed within 2 months and 2 patients obstructed within 4 months.

Table V: Upper range values of 18 patients in different outcomes with causes in both groups

OUTCOME	GROUP	PATIENT	UPPER RANGE VALUES IN PATIENTS	CAUSES
Admissions	Stent	1	**Number of admissions 3**:	**D**ehydration and lung abscess
		2	**Number of admissions 4**:	**T**echnical factors
	RT	3	**Number of admissions 5**:	**R**epeated cycles of EBRT
		4	**Number of admissions 6**:	**R**epeated cycles of EBRT
		5	**Number of admissions 7**:	**R**epeated cycles of EBRT
Hospital Stay (days)	Stent	6	**89 days**:	**A**waiting faulty EBRT machine, developed TOF, stented
		7	**36 days:**	**D**ehydration and lung abscess
		8	**34 days:**	**T**reatment for dehydration and lung abscess
	RT	9	**63 days**:	**R**epeated cycles of EBRT
		10	**58 days**:	**T**ransport problems
Time to Intervention (days)	Stent	11	**104 days**:	**A**dministrative delays awaiting brachytherapy, therefore stented
		12	**86 days:**	**R**epeat biopsy, histology results delay
		13		
		14	**70 days:**	**D**efaulted treatment
		15	**62 days:**	Repeat biopsy, histology results deay
			57 days:	**D**efaulted treatment
	RT	16	**377 days:**	**D**efaulted treatment
		17	**131 days:**	**D**efaulted treatment
		18	**98 days:**	**D**efaulted treatment

The median survival of patients in both groups was 129 days from the date first seen to death, survival ranging from 14 to 407 days. One patient was still alive at the time of writing, and the records of 4 patients could not be found; they were presumed to have died (Fig. 1). The median survival curves comparing the RT group with the stent group are depicted in Fig. 2.

The hazard ratio for living a distance >130 km from a secondary hospital adjusted to treatment was 1.34 (p=0.497). The distance curve shows an increase in risk of death at a distance of >130 km from a secondary hospital, however this did not reach statistical significance (Fig. 3).

7 patients in the RT and 6 patients in the stent group lived at a distance further than 130 km from the secondary hospital.

5 patients in the RT defaulted treatment, which caused considerable delays in management. 1 patient in the RT group died in hospital due to advanced disease after treatment and another patient in the RT group needed repeated cycles of RT resulting in multiple admissions and delays to treatment.

In the stent group there was delay to treatment in 1 patient due to no stock of stents. In the remaining patients in the stent group living further than 130 km from a secondary hospital there were no delays to treatment.

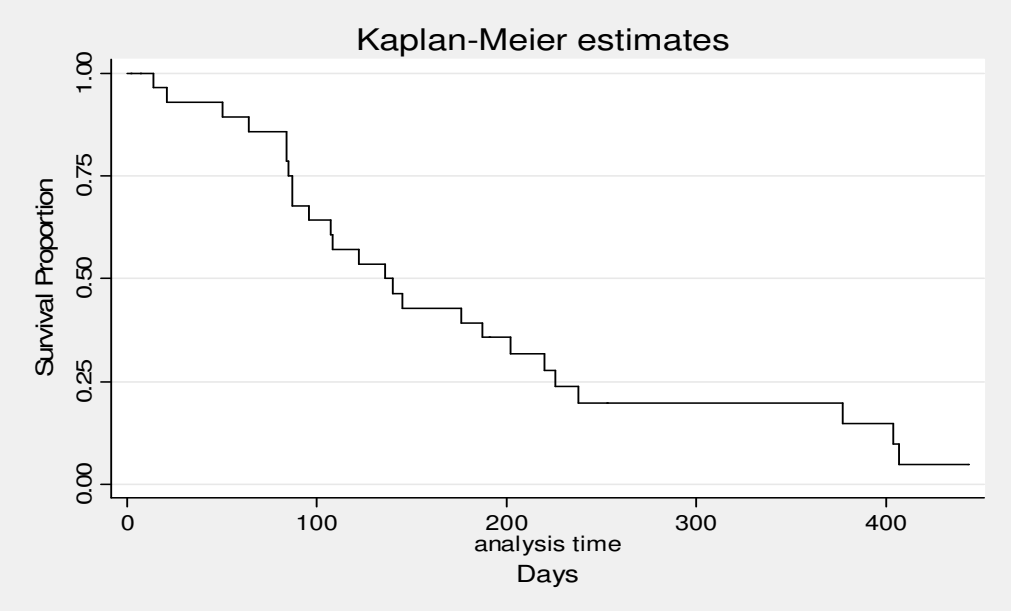


Figure 1. **Survival curve of all patients in both groups. The x-axis depicts the number of days and the y-axis depicts the proportion of patients that have survived.**

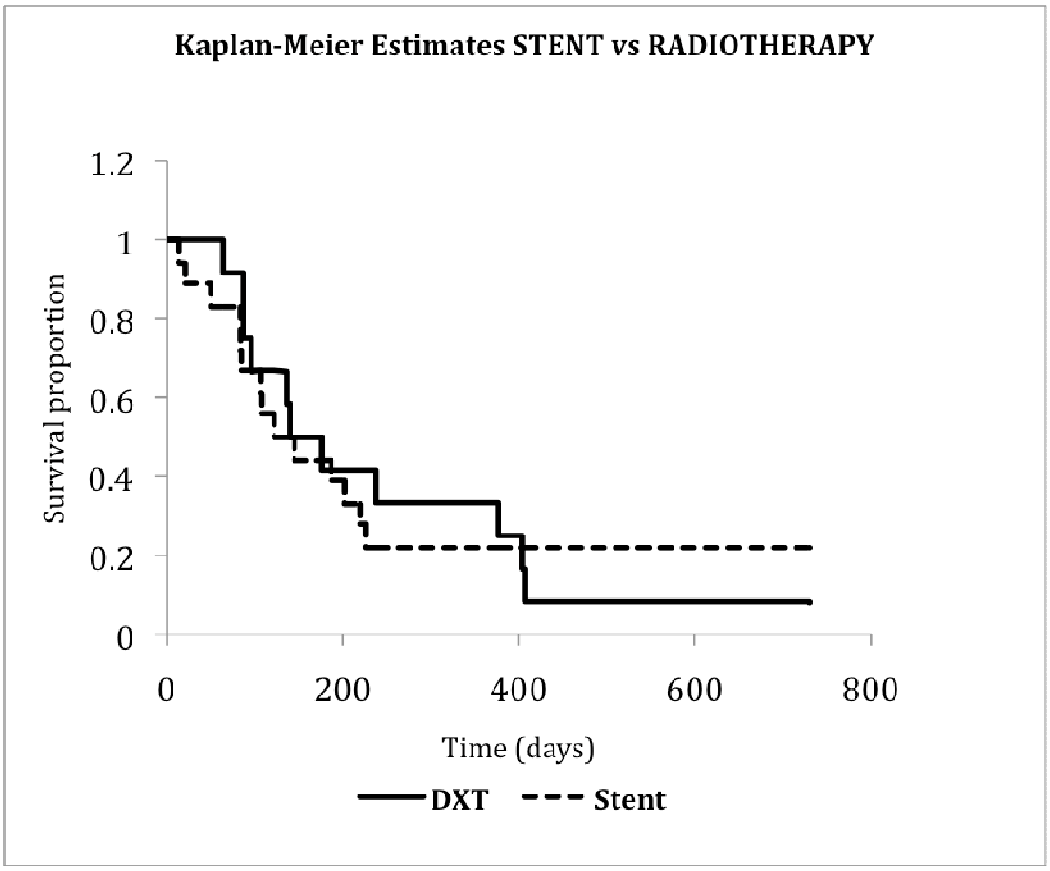


Figure 2. **Median survival curves between the stent and radiotherapy groups. The x-axis depicts the number of days and the y-axis depicts the proportion of patients that survived.**

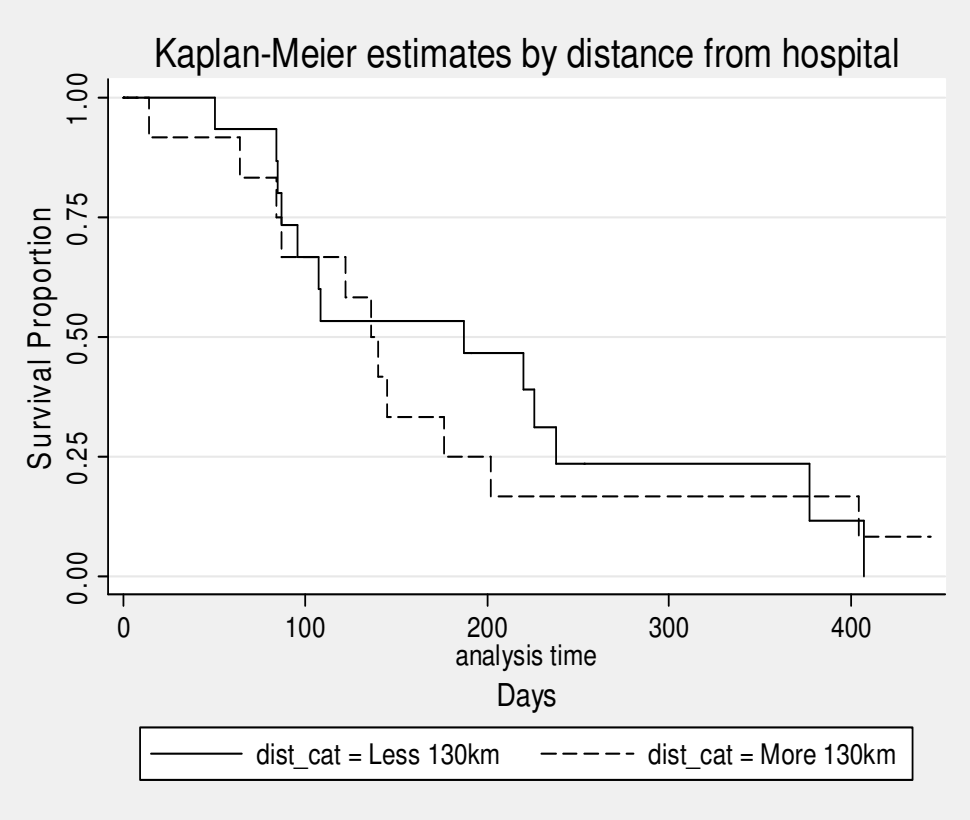


Figure 3. **Survival curves between patients that reside >130 km and patients that reside<130 km to a secondary hospital. There is a survival advantage in patients that reside <130 km from a secondary hospital, this difference did not reach statistical significance.**

Procedure related complications were noted in 4 patients in the stent group: stent migration (n=1); stent overgrowth (n=1); failure of stent to deploy completely (n=1); and death in theatre during stenting (n=1).

There were no major complications reported in the RT group.

5. DISCUSSION

Many studies have been done comparing stenting to RT in the palliative treatment of esophageal cancer. Many of these studies have been done in a first world setting and are therefore not subject to many of the socio-economic constraints present in the developing world. Many advances have been made with regards to palliation of malignant dysphagia and most commonly used methods include stent insertion and brachytherapy.

With all these advancements in treatment, our patients nevertheless present late and/or are faced with other socio-economic constraints and may not benefit from the longer lasting effect of brachytherapy alone or in combination with chemotherapy.

There was a significant increase in hospital stay, number of days from first seen to intervention and number of admissions in the group of patients who received RT. This was attributable to a number of factors. The majority of patients were referred from smaller peripheral hospitals to Tshepong Hospital. After admission, gastroscopy and biopsy was performed. Patients were then discharged and a follow up date given for histology results.

After confirmation of malignancy on histology they were then referred to an academic institution for brachytherapy or external beam RT.

Due to the high patient volume in these centers, patients were given an appointment for treatment, usually in 1 to 2 weeks time, and returned to Tshepong Hospital with an appointment date.

The fact that most patients were from distant rural areas, meant that transport problems were a significant factor in delaying treatment. The fact that they needed more than 1 session of RT also exacerbated the situation. Furthermore, Sur (69) described that the most effective course of brachytherapy was delivered in 2 or 3 fractions which would mean further admissions to hospital, longer hospital stays and an increased risk of default for patients.

Administrative problems including patients being referred with no results or incorrect results, was also a reason for delay and increased hospital stay.

Patients in both groups defaulted treatment and were lost to follow-up, however in the stenting group the patients were either stented on initial presentation or after histological confirmation of malignancy with a decreased number of admissions and therefore less chance of defaulting treatment due to socio-economic reasons.

Patients that were stented immediately had a dramatic decrease in hospital stay and had immediate relief from dysphagia.

Our study focuses on the short median survival of patients with end-stage esophageal cancer and it has been shown previously that patients receiving brachytherapy or stenting have a median survival of 120 days (33).

Median survival times in our study were 140 days in the RT group and 105 days in the stent group (Fig. 2), although patients in both groups presented with equally advanced local disease and high-grade dysphagia. One patient in the stenting group was known with HIV and pulmonary tuberculosis, which could have impacted on the median survival of the group.

The combined median survival time of both the stenting and radiotherapy groups was 129 days (Fig 1).

Although health-related quality of life scores are more stable in patients receiving brachytherapy (33,72), our study emphasizes on delays in receiving brachytherapy as palliative treatment. From the results it can be seen that the median number of days to intervention in the RT group was 49 compared to 6 days in the stenting group. Quality of life is the mainstay of palliative treatment in patients with end-stage cancer irrespective of the median survival. Invariably less time to treatment is required for stenting.

Therefore despite the median survival being better in the RT group, these patients were delayed in treatment and invariably had a shorter quality of life and dysphagia-free survival.

There was no significant difference in the number of days from presentation to time of biopsy. This is important as it indicates that there was no bias to either group with regards to initial work-up, in other words the significant difference in time to intervention between RT and stenting is the delay from initial work-up to final management.

A prognostic model published from the results of the SIREC trial shows that patients with a poor prognosis fare better with stenting than brachytherapy with regards to median survival and dysphagia-adjusted survival (85).

They describe male gender, age more than 70, tumour length of more than 10 cm, presence of distant metastases and a worse WHO performance score as poor prognostic factors. The majority of the patients in our study were males, above the age of 70 and had distant metastases on presentation.

Unfortunately the tumour length and performance scores were not documented. Furthermore in a study by Berquist (86) in 2011 they described the importance of HRQL questionnaires as important predictors of outcome in these types of patients. These HRQL questionnaires and determining of perfomance scores should become standard in all hospitals across the country when managing patients that present with oesophageal cancer.

In addition, the distance a patient resides from a secondary hospital is an important factor when assessing these patients. A distance of 130 km was chosen, as most of the rural areas were an average of 130 km away from a secondary hospital. The hazard ratio in these patients living further than 130km was 1.34. A criticism of the latter is the small sample size and values did not reach statistical significance, however it did have clinical significance and distance should always be considered when managing these patients.

Patients especially from distant rural areas have more of a chance of delay in treatment due to a lack of an efficient transport system and therefore might not be able to follow-up for further treatment.

An adequate history should be taken to determine whether transport to hospital and therefore follow-up might become an issue.

When distances are long, patients tend to fall in the poor prognosis group.

In these cases it might be more appropriate to stent these patients.

Patients with moderate or good prognosis can then be treated with single-dose brachytherapy and benefit from the long-term dysphagia-free effect of this treatment.

Efforts could also be focused on efficiently alleviating many of the socio-economic hurdles described, specifically aimed at time from first seen to RT.

Ideally patients with a poor prognosis should be admitted to hospital, a biopsy taken on initial presentation and kept in hospital until the biopsy results confirm malignancy – after this the patient should be stented. This avoids prolonged hospital stay and decreases the likelihood of defaulting treatment because of socio-economic constraints, which in many cases are currently unavoidable.

Four of the 12 patients in the RT group re-obstructed within 4 months. These patients were then dilated to relieve the obstruction. A better option for these patients would be stenting over serial dilatations.

Furthermore, with a nationwide effort in an attempt to overcome the socio-economic constraints that affect the delivering of adequate treatment to our patients, another option in the management of these advanced patients from rural areas is the combination of single-dose brachytherapy and stenting, adding a prolonged dysphagia-free survival to these patients.

6. CONCLUSIONS AND RECOMMENDATIONS

A comparative study between oesophageal stent insertion and RT for the palliative treatment of patients with advanced oesophageal cancer in a peripheral South African Hospital showed the following:

- Patients presenting with malignant dysphagia have a limited lifespan and focus should be on improving their quality of life.
- Patients undergoing RT have a significantly longer hospital stay and longer wait to treatment.
- Any unnecessary increases in hospital stay impacts negatively on quality of life.

- With socio-economic constraints imposed upon the health sectors of the developing world, we conclude that stenting is a feasible option in this situation.
- We have adopted this treatment because it is easier and more convenient for rural patients with a limited lifespan.
- Major problems seem to be associated with giving these patients RT at secondary hospitals.
- Either this situation must be improved, or stenting should become the preferred treatment.

Recommendations are as follows:

- Units treating patients with inoperable oesophageal cancer should audit their results before determining the optimum treatment for these patients.
- There should be close collaboration between all departments that are managing these patients and between hospitals. This will allow any effective overcoming of any hurdles that are faced during the management of patients.
- Brachytherapy and EBRT may be introduced to a number of secondary hospitals, which will take off some of the burden faced at major academic centers, if this is feasible.
- Possibly an introduction of a taskforce that specifically looks into the administrative and logistic constraints faced when managing these patients. This could identify more closely the problems that need to be addressed effectively and efficiently.

7. LIMITATIONS OF THE STUDY

Due to the retrospective nature of the study, important information regarding tumour and patient characteristics could not be determined. Tumour characteristics include tumour length, axial deviation and radial extension. Patient characteristics include ECOG and Karnofsky perfomance status scores. All these factors play an important role in determining overall prognosis in these patients.

Without complete data information an unbiased comparison between stenting and RT is not entirely possible. However, the aim of the study was mainly to compare the path to treatment and the constraints faced by our patients rather than the efficacy of these treatments in an ideal setting.

Although a prospective study would have been more accurate, the study revealed a problem that exists in the management of these patients. Efforts should now be made on alleviating the problems. Furthermore due to the small sample size, statistics did not reach statistical significance and are prone to type II error.

Nevertheless, the numbers show a trend that clinically have an impact and cannot be ignored.

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APPENDIX A: Reprint of article from SAJS

SAJS
General Surgery

Is oesophageal stenting for cancer the answer? A report from a secondary hospital in the developing world

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Summary

Introduction. Oesophageal cancer causes much morbidity and mortality in South Africa. Social and economic constraints further impact on the management of these patients. Many prospective randomised trials of palliative treatment have been done in the developed world, not taking into account these socio-economic constraints. We present a study from Tshepong Hospital, a secondary hospital in South Africa, comparing stenting with radiation therapy in the palliative treatment of oesophageal cancer.

Patients and methods. We retrospectively reviewed the data on 30 patients seen between February 2005 and January 2008. All presented with inoperable oesophageal cancer and were palliated with either stenting (*N*=18) or radiotherapy (*N*=12). We compared number of admissions, length of hospital stay and time from when first seen to intervention as primary outcomes.

Results. The number of admissions, length of hospital stay and days to procedure were significantly lower in the stent group. No major complications resulting from brachytherapy were reported. Complications in the stent group included chest pain, tumour overgrowth, stent migration and death.

Discussion. Studies have shown the superiority of brachytherapy over stenting with regard to long-term palliation and number of complications. In our setting, however, socio-economic constraints result in a delay in treatment. Given the short survival expected in these patients, stenting may be a reasonable option to consider given the decreased time to final intervention and hospital stay in patients with a poor prognosis. Adopting a prognostic score can help in identifying these patients.

Seventy years ago squamous cell carcinoma of the oesophagus was a rare disease in the South African population, which is predominantly a black population.[1] Currently it is the third most common cancer in males and the fourth most common in females (of all races) in South Africa.[1] It is most common in black men, comprising 13% of all cancers reported in this group.[2]

Major risk factors for oesophageal squamous cell carcinoma include smoking, alcohol, and diets low in vitamins A and C, magnesium and riboflavin. Maize, a common food in rural areas especially Transkei, a region in the Eastern Cape, represents such a diet.[2]

Despite improvements in care, the 5-year survival rate for oesophageal carcinoma is still well below 20%, with over 50% of patients eligible for palliative care only because of advanced disease at presentation.[3] Dilatation of the oesophagus became a recognised form of palliative treatment as early as 1973, when Didcott reported on use of the Didcott dilator for slow dilatation of the oesophagus.[4] This was a forerunner to the metal expandable stent.

In 1980 Procter described the use of the Procter-Livingstone endo-oesophageal tube (plastic stent) as a permanent form of palliative therapy in patients with oesophageal cancer.[5]

Self-expandable metal stents have been shown to be superior to plastic stents because they are associated with lower rates of complications such as oesophageal perforation and haemorrhage and lower mortality rates.[6-9]

The Stent or Intraluminal Radiotherapy for Inoperable Esophageal Cancer (SIREC) study found that although stenting produced immediate relief of dysphagia, brachytherapy offered a more durable result with fewer complications, especially after 3 months, and was recommended over stenting.[10] Following on from this finding, a prognostic score was developed which suggested that patients with a poor prognosis may benefit from stenting over brachytherapy.[11]

There have been conflicting data on the health economics of each method, with the SIREC study[10] finding no difference in cost between stenting and radiotherapy, and a study from Stockholm, Sweden, finding a marked difference in favour of stenting.[12]

Many of these studies were done in a First-World setting and were not subject to many of the socio-economic constraints faced in the developing world. Most patients with malignant dysphagia seen at our hospital (Tshepong Hospital, Klerksdorp, North West) were from distant rural areas and needed to be referred to tertiary centres for radiation therapy. A number of problems were encountered, including logistic delays, resource constraints and poor follow-up, which led to prolonged hospital stay and increased morbidity. Our institution therefore introduced stenting as an alternative option for these patients, with the aim of decreasing morbidity. A retrospective review was done comparing stenting with radiation therapy with multiple end-points. We aimed to find out whether stenting is a feasible option in these patients, who already have a poor prognosis.

Patients and methods

Between February 2005 and January 2008, the records of a total of 66 patients who presented with dysphagia due to malignant stenosis of the oesophagus were evaluated. Thirty patients were included in the study, 18 in the stent group and 12 in the radiotherapy group.

Before stenting or radiotherapy all strictures were dilated to at least a 12 mm diameter with a Savary dilator over a guidewire. Gastroscopy with dilatation and stent placement was done under general anaesthesia (hospital policy).

In all 18 patients who were stented, a self-expandable, coated metallic stent (Ultraflex Esophageal Covered Stents, Boston Scientific) was introduced under fluoroscopic guidance. In 9 cases this was done at initial gastroscopy on the basis of clinical features of carcinoma of the oesophagus, and in the remaining 9 cases the stent was placed after histological confirmation of the disease.

Of the 12 patients who received radiotherapy, 5 received brachytherapy and 7 external-beam radiotherapy. These patients needed to be sent to an academic hospital where this service was available (a distance of >120 km away). On arrival there, the patients were given an appointment for radiotherapy in 1 - 2 weeks' time and then sent back to the referring hospital.

Primary end-points in the study included number of hospital admissions, total number of days in hospital, number of days from intervention to either stenting or radiotherapy, and determining the hazard ratio (mortality risk) in patients residing further than 130 km from a secondary hospital. Secondary end-points included number of days from intervention to biopsy, procedure-related complications and median survival from initial intervention. There was a bias towards the stenting group; 9 patients in that group were stented within 8 days of presentation to hospital on clinical grounds of carcinoma, thereby avoiding the delay of histological confirmation and hence decreasing the number of days from intervention to management in the group. Cancer was confirmed histologically after stenting. The remaining patients in both groups were treated only once cancer was confirmed histologically.

Results were tabulated and statistically analysed using the Kruskal-Wallis test with a 95% confidence interval, and $p<0.05$ was regarded as statistically significant. Median survival was determined using Kaplan-Meier estimates and the log-rank test.

The hazard ratio of patients living further than 130 km from a secondary hospital was determined using Cox regression analysis adjusted to treatment.

Results

Of the 66 patients evaluated during the study period, 33 did not fulfil the criteria to be included in the study, as they did not receive any palliative therapy (i.e. stent insertion or radiotherapy). Reasons included loss to follow-up (N=20), death while awaiting treatment (N=9), gastrostomy tube insertion (N=3), and refusal of hospital treatment (N=1). Of the remaining 33 patients, 3 received both radiotherapy and stent insertion.

The 30 remaining patients included in the study comprised 21 males and 9 females. All were black Africans. Only 14 patients had contact details, and most were referred from peripheral hospitals. In all cases the lesion was inoperable at time of presentation because of advanced local disease and/or poor general health of the patient. All had grades III - IV dysphagia (Table I). Histological examination revealed squamous cell carcinoma in all patients.

The median number of admissions in the stent group was 2 compared with 3 in the radiotherapy group. The difference between the two groups was mainly due to the need for repeated cycles of deep X-ray therapy. Hospital stay and time from when first seen to treatment were significantly shorter in the stent group (Fig. 1, Table II).

Ranges in the values for outcomes are set out in Table II. A number of patients in both groups had excessively high values for various outcomes, which caused considerable delays in treatment (Table III). In 9 patients a stent was inserted on initial gastroscopy following biopsy of the tumour. This caused a considerable decrease in all primary outcomes.

The median survival of patients in both groups was 129 days from the date first seen to death, survival ranging from 14 to 407 days. One patient was still alive at the time of writing, and the records of 4 patients could not be found; they are presumed to be alive (Fig. 2). The median survival curves comparing the radiotherapy group with the stent group are depicted in Fig. 3.

The hazard ratio for living a distance of >130 km from a secondary hospital adjusted to treatment was 1.34 (p=0.497). The distance curve shows an increase in risk of death at a distance of >130 km from a secondary hospital (Fig. 4).

TABLE I. DEGREE OF DYSPHAGIA IN PATIENTS WITH INOPERABLE CARCINOMA OF THE OESOPHAGUS

Symptom	Degree of dysphagia
No dysphagia	**0**
Dysphagia for solids	**I**
Dysphagia for semi-solids	**II**
Dysphagia for liquids	**III**
Complete dysphagia	**IV**

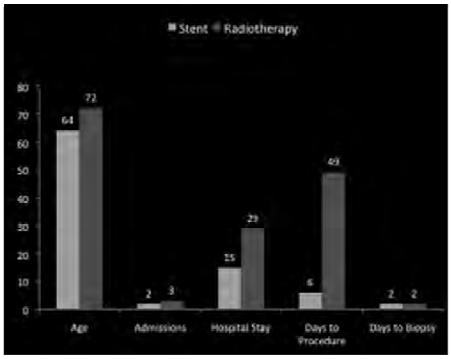


Fig. I. Median values for different outcomes.

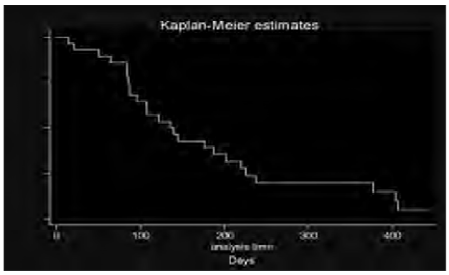


Fig. 2. Survival (days) from when first seen to death.

Procedure-related complications were noted in 4 patients in the stent group. These were stent migration (*N*=1), stent overgrowth (*N*=1), failure of stent to deploy completely (*N*=1) and death in theatre during stenting (*N*=1). No major complications were reported in the radiotherapy group.

Biopsy was done within 3 days of first presentation in 69% of the patients (*N*=20). The median number of days from presentation to biopsy did not differ between the groups (*N*=2).

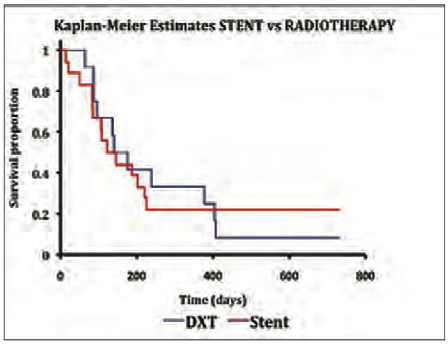


Fig. 3. Survival (days) from when first seen to death, stent v. radiotherapy groups.

Discussion

Many studies have compared stenting with radiotherapy in the palliative treatment of oesophageal cancer. Sur *et al.* and Didcott described the effectiveness of slow dilatation and brachytherapy in increasing survival and quality of life in these patients.[13,14] Newer studies have shown brachytherapy to be superior to stenting in the long-term management of inoperable oesophageal cancer, with longer relief from dysphagia and fewer complications.[10,15]

Other publications support the findings in the SIREC study, indicating the superiority of brachytherapy in the long-term management of this disease; however, initial relief of dysphagia is more effective with stenting, with no significant difference in median survival times.[11,15]

Patients who receive combined chemoradiotherapy have an increased median survival time compared with patients who receive either stenting or brachytherapy alone.[16] Furthermore a review on cancer of the oesophagus suggests that the palliative treatment of choice is combined chemoradiation therapy.[17] Not all patients can tolerate combined chemoradiotherapy, however, especially those with poor general health, where stenting becomes a feasible option.

Targeted therapy has gained much interest as a treatment modality and clinical trials are underway.[18] Many of these

TABLE II. COMPARISON OF OUTCOMES BETWEEN THE PATIENTS RECEIVING PALLIATIVE TREATMENT WITH STENTING AND THOSE RECEIVING RADIOTHERAPY

Variables	Stent group (*N*=18) (median (range))	Radiotherapy group (*N*=12) (median (range))	*p*-value*
Age	**64 (39 - 85)**	**72 (45 - 81)**	***p*=0.21**
Number of admissions†	**2 (1 - 4)**	**3 (2 - 7)**	***p*=0.0180**
Hospital stay†	**15 (1 - 89)**	**29 (11 - 63)**	***p*=0.0072**
Days to procedure†	**6 (0 - 104)**	**49 (35 - 377)**	***p*=0.0108**
Days to biopsy	**2 (0 - 43)**	**2 (1 - 19)**	***p*=0.71**

*^*p*-value of <0.05 is statistically significant.
†Primary outcomes.

TABLE III. UPPER RANGE VALUES FOR DIFFERENT OUTCOMES WITH CAUSES IN THE TWO PATIENT GROUPS

Outcome	Group	Excessive values and causes
No. of admissions	**Stent**	**3: dehydration and lung abscess** **4: technical factors**
	Radiotherapy	**5: repeated cycles of DXT** **6: repeated cycles of DXT** **7: repeated cycles of DXT**
Hospital stay (days)	**Stent**	**89: during wait for DXT due to faulty DXT machine developed TOF, then stented** **36: treatment for dehydration and lung abscess** **34: repeat biopsy, transfer to academic institution for stent due to faulty gastroscope at secondary hospital**
	Radiotherapy	**63: repeated cycles of DXT** **58: transport problems**
Time to intervention (days)	**Stent**	**104: administrative delays while awaiting brachytherapy, therefore stented** **86: repeated biopsies and delay in getting histology results** **70: patient defaulted treatment** **62: repeated biopsies and delay in getting histology results** **57: defaulted treatment**
	Radiotherapy	**98: defaulted treatment** **131: defaulted treatment** **377: defaulted treatment**

DXT = deep X-ray therapy; TOF = tracheo-oesophageal fistula.

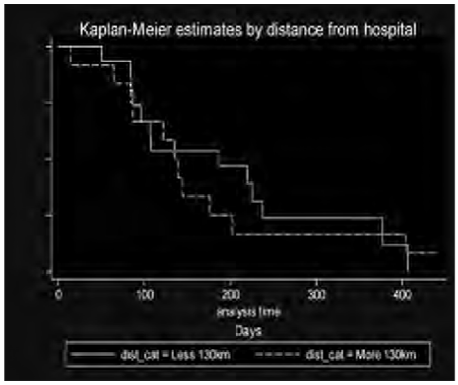


Fig. 4. Survival according to distance >130 km v. distance <130 km between patients' homes and hospital.

studies have been done in a First-World setting and are therefore not subject to many of the socio-economic constraints typical of the developing world.

A study done in Johannesburg, India and Poland showed a longer dysphagia-free time when using high-dose-rate (HDR) intra-luminal brachytherapy (ILBT) compared with other treatment modalities.[19] This study, although done in a developing world setting, was conducted in a major academic centre.

With all these advances in treatment, our patients nevertheless often present late and/or are faced with other socio-economic constraints and may not benefit from the longer-lasting effect of brachytherapy, alone or in combination with chemotherapy.

Our study showed a significant increase in hospital stay, number of days from first seen to intervention and number of admissions in the patients who received radiotherapy. This was attributable to a number of factors. The majority of patients were referred from smaller peripheral hospitals to Tshepong Hospital. After admission, gastroscopy and biopsy were performed. Patients were then discharged and a follow-up date given for histology results. After confirmation of malignant disease on histology they were then referred to an academic institution for brachytherapy or external beam radiotherapy. Owing to the high patient volume in these centres, they were usually given an appointment for treatment, usually in 1 - 2 weeks' time, and returned to Tshepong Hospital with an appointment date. The fact that most patients were from distant rural areas meant that transport problems were a significant factor in delaying treatment. The necessity for more than one session of radiotherapy also exacerbated the situation.

Administrative problems, including patients being referred with no results or incorrect results, was also a reason for delay and increased hospital stay.

Patients in both groups defaulted treatment and were lost to follow-up. In the stenting group, however, the patients were either stented on initial presentation or after histological confirmation of malignant disease. The decreased number of admissions meant less likelihood of defaulting treatment for socio-economic reasons.

Patients who were stented immediately had a dramatic decrease in hospital stay and obtained immediate relief from dysphagia.

Our study focuses on the short median survival of patients with end-stage oesophageal cancer, where it has been shown that patients who receive brachytherapy or stenting have a median survival of 120 days.[15] Median survival times in our study were 140 days in the radiotherapy group and 105 days in the stent group. The median survival time for the two groups combined was 129 days.

Although health-related quality of life scores are more stable in patients receiving brachytherapy,[15,20] our findings emphasise that in our setting delays tend to be associated with brachytherapy as palliative treatment. Our results show that the median number of days to intervention in the radiotherapy group was 49 days, compared with 6 days in the stenting group. Quality of life is the main concern of palliative treatment in patients with end-stage cancer, irrespective of the median survival. Invariably less time to treatment is required for stenting.

There was no significant difference in the number of days from presentation to time of biopsy. This is important, as it indicates that there was no bias with regard to initial work-up; in other words, the significant difference in time to intervention between radiotherapy and stenting is the delay from initial work-up to final management.

A prognostic model published from the results of the SIREC trial[10] shows that patients with a poor prognosis fare better with stenting than brachytherapy with regard to median survival and dysphagia-adjusted survival.[21]

The distance a patient lives from a secondary hospital is an important factor when assessing patients with oesophageal cancer. The hazard ratio in those living further than 130 km away was 1.34. This figure can be criticised on the grounds of small sample size; however it is representative, and distance should always be considered when managing these patients. When distances are long, the patient will tend to fall into the poor prognosis group. Patients with a moderate or good prognosis can then be treated with single-dose brachytherapy and benefit from the long-term dysphagia-free effect of this treatment. Efforts could also be focused on efficiently alleviating many of the socio-economic hurdles described, aiming specifically at time from when first seen to radiotherapy.

Ideally patients with a poor prognosis should be admitted to hospital on initial presentation, a biopsy taken, and the patient kept in hospital until the biopsy results confirm malignancy – after this the patient should be stented. This avoids prolonged hospital stay and decreases the likelihood of defaulting treatment because of socio-economic constraints, which in many cases are currently unavoidable.

Conclusion

Five-year survival in patients with inoperable oesophageal cancer is dismal.[19] Any unnecessary increase in hospital stay therefore impacts negatively on quality of life. With the socio-economic constraints imposed upon the health sectors of the developing world, we conclude that stenting is a feasible option in this situation, and have adopted this treatment because it is easier and more convenient for rural patients with a limited lifespan.

Major problems seem to be associated with giving these patients radiotherapy (brachytherapy) at secondary hospitals. Either this situation must be improved, or stenting should become the preferred treatment.

A prognostic score can be adopted with the aim of helping to determine the patient's prognosis. This should include the distance of the patient's home from the secondary hospital.

We thank Dr G. Candy (Ph.D.) and Dr P. J. Becker (Ph.D.) for their input with regard to the statistical analysis.

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Invited comment

The treatment of advanced oesophageal cancer in a resource-constrained clinical setting is difficult and frustrating, and the authors are to be congratulated on documenting their experience. Nevertheless, the conclusion they present is based on a small retrospective series, and this does not trump the evidence of a large prospective randomised trial. I accept that the logistic conditions, nutritional status and even the advanced stage of the cancer (as shown by the larger-bore catheter used by the Dutch investigators compared with what is used in Johannesburg), and our lower mean survivals, are worse in South Africa, but given that intraluminal HDR brachytherapy is available in tertiary hospitals, is relatively complication free, and only incurs additional transport and hospital stay costs, its benefits, namely prolonged dysphagia-free survival (a mean of 7.1 months was reported in the IAEA trial, including South African patients), should not be denied to patients as a matter of course.

I agree with the authors that a prognostic index needs to be developed to determine which patients will benefit from intraluminal brachytherapy. It is important for a South African trial to be set up in this regard, so that the competing modalities of stenting versus HDR brachytherapy can be compared under local conditions, and a locally validated prognostic index can be developed. With regard to delay in implementing treatment, it should be noted that stenting does not preclude subsequent HDR, and early stenting followed by delayed HDR brachytherapy for selected patients needs to be one of the options to consider.

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APPENDIX B: Poster presentation

IS OESOPHAGEAL STENTING THE ANSWER? A report from a secondary hospital in the developing world

D Liakos[1], DWR Dower[1], M Florizoone2
[1]Department of Surgery, WITS University, South Africa
[2]Department of Surgery, Tshepong Hospital, Northwest Province, South Africa

INTRODUCTION

Seventy years ago squamous cell carcinoma was a rare disease in the South African population, predominantly in the black population. It is increasing at an alarming rate in South Africa with it being the 3rd most common cancer in males and the 4th in females.
Despite improvements in care the 5 year survival rate still lies well below 20% with over 50% of patients eligible only for palliative care.
The SIREC study showed that single-dose brachytherapy is superior to stenting as palliative therapy in end-stage oesophageal cancer(4).
Following on this data a prognostic score suggested that stent placement is preferred in patients with poor prognosis.
Many patients that present with malignant dysphagia at secondary hospitals are faced with many socio-economic constraints resulting in prolonged hospital stays and increased morbidities.

Is stenting a more feasible option in these patients who already have a poor prognosis?

PATIENTS AND METHODS

Between February 2005 and January 2008 a total of 29 patients who presented with dysphagia due to malignant stenosis of the oesophagus were included in the retrospective study.
The patients were included in 2 groups:
- •Radiotherapy group (n=12) or stenting group (n=17)
- •All patients presented with dysphagia grade III-IV
- •All patients had confirmed squamous cell carcinoma on histology

Primary end points in the study include:
- •Number of hospital admissions
- •Total number of days in hospital
- •Number of days from intervention to either stenting or radiotherapy (pt were stented with self-expandable metal stents)

Results were tabulated and statistically analysed using the Kruskal-Wallis Test with a 95% confidence interval and a $p<0.05$ was regarded as statistically significant.

CONCLUSION

5-year survival in these patients is dismal. Therefore any unnecessary increase in hospital stay impacts negatively on quality of life.
With the socio-economic constraints imposed upon the health sectors of the developing world, we propose stenting as a feasible option for palliative treatment in patients with short life expectancies with a view to improving quality of life.

RESULTS

From the results it can be seen that there is a significant decrease in the number of admissions **(p=0.02)**, hospital stay **(p=0.01)** and days from intervention to procedure **(p=0.01)** in the stent group.
Our study focuses on the short median survival of patients with end-stage oesophageal cancer, where it has been shown that patients receiving brachytherapy or stenting have a median survival of 120 days.(1) Health-related quality of life scores are more stable in patients receiving brachytherapy(2), however our study emphasizes on delays in receiving brachytherapy as palliative therapy with increased morbidity.

Variables	Stent group (n=17) Median (Range)	Radiotherapy group (n=12) Median (Range)	*P- value
Age	65 (39-85)	72 (45-81)	p= 0.23
**Number of admissions	2 (1-4)	3 (2-7)	p=0.0221
**Hospital stay	15 (1-89)	29 (11-63)	P=0.0109
**Days to procedure	6 (0-104)	49 (35-377)	p= 0.0108

Comparative look at outcomes between the 2 groups.

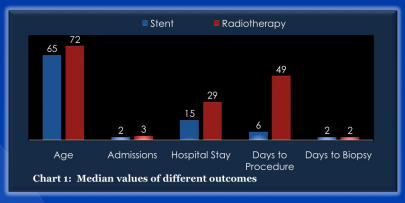


Chart 1: Median values of different outcomes

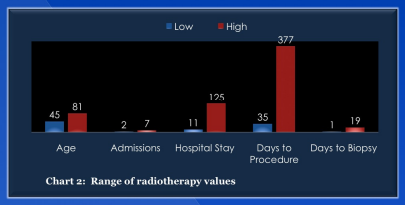


Chart 2: Range of radiotherapy values



Chart 3: Range of stent values

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Appendix C: Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dower/Liakos

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M071109**
PROJECT	The Value of Oesphageal Stenting Compared to Dilatation and Brachytherapy in a Secondary Hospital Setting in South Africa
INVESTIGATORS	Drs D/D Dower/Liakos
DEPARTMENT	Department of Surgery
DATE CONSIDERED	07.11.30
DECISION OF THE COMMITTEE*	APPROVED UNCONDITIONALLY

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 08.01.30 **CHAIRPERSON** .....
(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor :

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES