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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**

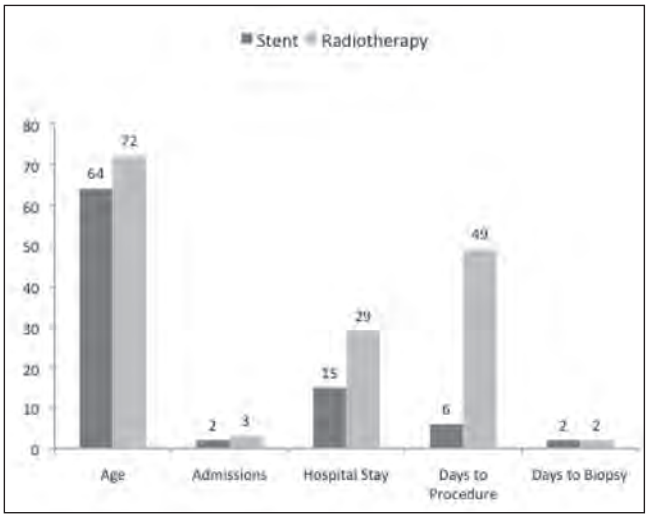

Fig. I. Median values for different outcomes.

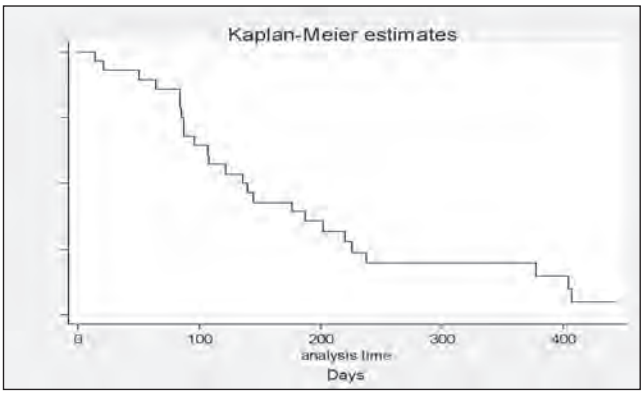

Fig. 2. Survival (days) from when first seen to death.

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).

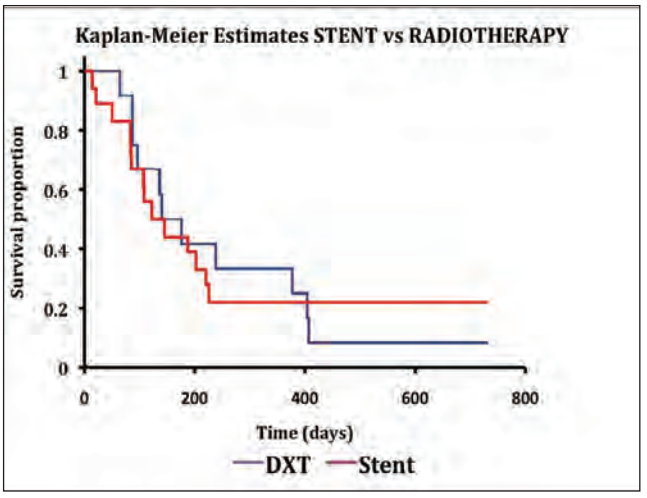

Fig. 3. Survival (days) from when first seen to death, stent v. radiotherapy groups.

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**

*A *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.

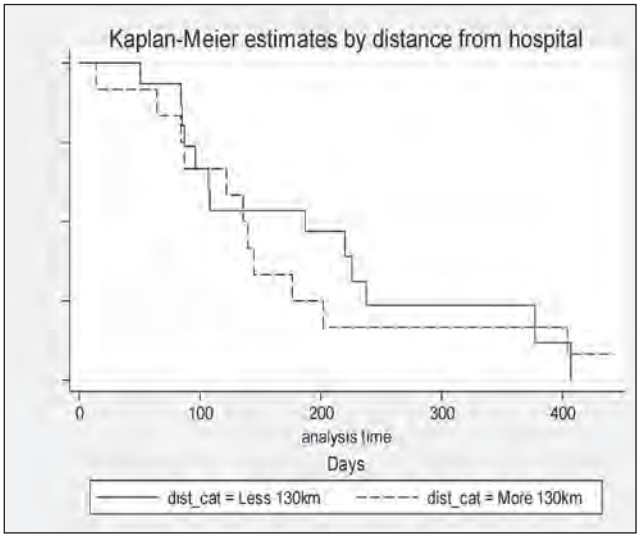

Fig. 4. Survival according to distance >130 km v. distance <130 km between patients' homes and hospital.

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.

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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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