ABSTRACT

Background

The palliation of dysphagia in metastatic esophageal cancer remains a challenge, and the optimal approach for this difficult clinical scenario is not clear. We therefore sought to define and determine the efficacy of various treatment options used at our institution for this condition.

Methods

We reviewed a prospective database for all patients managed in an esophageal cancer referral centre over a 5-year period. All patients receiving palliation of malignant dysphagia were reviewed for demographics, palliative treatment modalities, complications, and dysphagia scores (0 = none to 4 = complete). The Wilcoxon signed rank test was used to determine significance (p < 0.05).

Results

During 2004–2009, 63 patients with inoperable esophageal cancer were treated for palliation of dysphagia. The primary treatment was radiotherapy in 79% (brachytherapy in 18 of 50; external-beam in 10 of 50; both types in 22 of 50), and stenting in 21%. Mean wait time from diagnosis to treatment was 22 days in the stent group and 54 days in the radiotherapy group (p = 0.003). Mean duration of treatment was 1 day in the stent group and 40 days in the radiotherapy group (p = 0.001). In patients treated initially by stenting, dysphagia improved within 2 weeks of treatment in 85% of patients (dysphagia score of 0 or 1). However, 20% of patients presented with recurrence of dysphagia at 10 weeks of treatment. In the radiotherapy group, the onset of palliation was slower, with only 50% of patients palliated at 2 weeks (dysphagia score of 0 or 1). However, long-term palliation was more satisfactory, with 90% of patients remaining palliated after 10 weeks of treatment.

Conclusions

In inoperable esophageal cancer at our centre, radiation treatment provided durable long-term relief, but came at a high price of a long wait time for initiation of treatment and a long lag time between initiation of treatment and relief of symptoms. On the other hand, endoluminal stenting provided more rapid and effective early relief from symptoms, but was affected by recurrence of dysphagia in the long-term. It is now time for a prospective randomized trial to assess the safety and efficacy of combined-modality treatment with both endoluminal stenting and radiation therapy compared with either treatment alone.

KEY WORDS

Esophageal cancer, palliation, stents, radiation therapy

1. INTRODUCTION

Despite advances in cancer care, the prognosis in esophageal cancer remains poor, with overall survival rates approaching 10%–15% at 5 years. This poor prognosis is a result of the high rate of metastasis at initial presentation. For such patients, whose average survival ranges between 4 and 6 months, effective and timely palliation of the debilitating dysphagia associated with esophageal cancer is of paramount importance for ensuring adequate quality of remaining life.
Several treatment modalities are used for the palliation of dysphagia in patients with inoperable esophageal cancer, including radiotherapy (endoluminal and external-beam), endoscopic ablation (for example, by laser, cryotherapy, photodynamic therapy), endoluminal plastic and metallic stents, and resection or bypass surgery. Of those approaches, endoluminal stenting and radiation therapy are the ones most commonly used.

It has been suggested that endoluminal stenting provides early relief from dysphagia, but that the effects are short-lasting; complete resolution of symptoms is seldom achieved. Direct esophageal perforation from stent insertion is estimated to occur in about 1% of cases, with an equivalent rate of mortality directly related to the procedure. In a large retrospective series, Burstow and colleagues documented bolus obstruction, bleeding, and stent migration as relatively more frequent complications (in 12%, 11%, and 7% of patients respectively). Aspiration pneumonia after stent insertion was recorded in 3% of patients. Nevertheless, endoluminal stents have been shown to significantly enhance quality of life for esophageal cancer patients, with improvement in swallowing, appetite, insomnia, and overall well-being. However, it has been suggested that the positive effects of stent insertion are limited and tend to diminish with time because of stent migration, tumor ingrowth, and general deterioration of the patients.

On the other hand, radiation therapy (brachytherapy or external-beam) has been shown to provide more effective and longer-lasting relief, but with a much longer lag time between onset of treatment and amelioration of symptoms. In a prospective trial evaluating the effect of radiotherapy on dysphagia in esophageal cancer, Hayter et al. found that radiation treatments, regardless of modality, are usually very well tolerated, with serious side effects occurring extremely rarely. One third of patients experienced transient worsening of dysphagia because of radiation esophagitis immediately after treatment; however, 68% of patients experienced complete resolution of dysphagia—but only 7 weeks after the end of treatment.

Two recent randomized controlled trials comparing brachytherapy with endoluminal stenting have been undertaken. In a Dutch trial, Homs et al. were able to demonstrate more effective and more durable relief from dysphagia by brachytherapy compared to endoluminal stenting. However, patients who were treated with endoluminal stents had a clear advantage in terms of rapidity of symptom resolution. In a Swedish trial, Bergquist et al. showed that dysphagia scores (DS) and quality-of-life scores were better in the stent group than in the brachytherapy group at 1 month of follow-up. However, patients who survived more than 6 weeks showed far better outcomes with brachytherapy, especially in terms of recurrence of dysphagia, which was greater in the stent group because of migration and tumor ingrowth.

Considering the discrepancies, we chose to review our own experiences with the treatment of dysphagia in esophageal cancer, and to examine the potential advantages of a combined-modality treatment over those of stenting or radiotherapy alone.

2. METHODS

After Institutional Review Board approval, we completed a retrospective review of prospectively-entered databases for all patients who presented with advanced inoperable esophageal cancer at our institution between 2004 and 2009. All patients with dysphagia were identified, and data on demographics, DS, treatment modalities, duration of treatment, treatment complications, and whether more than one modality of treatment was used were collected.

The primary outcome was change in the DS before and after treatment. The DS was measured using a previously validated 4-point Likert scale: 0, no dysphagia; 1, dysphagia to solids; 2, dysphagia to semi-solids; 3, dysphagia to liquids; 4, dysphagia to own saliva. The DS was documented for every patient before onset of treatment and at 2-week intervals until the 10th week after initiation of treatment. Other outcomes of interest were time to achievement of best DS, time from diagnosis to onset of treatment, and total duration of treatment. The Wilcoxon rank test was used to determine statistical significance (p < 0.05).

Between 2004 and 2009 at our institution, 95 patients with inoperable esophageal cancer received treatment to palliate dysphagia. All patients were reviewed by our Esophageal Cancer Tumor Board before treatment. Of those 95 patients, 32 were excluded from the study because they were treated operatively (n = 9), had incomplete DS records (n = 12), or had been lost to follow-up (n = 11). The 63 included patients were stratified into two groups: an endoluminal stent group (ESG, n = 13) and a radiation therapy group (RTG, n = 50).

Patients were placed in the ESG if their primary and first treatment on record was an endoluminal stent. All ESG patients were treated with partially-coated self-expandable metallic stents (Ultraflex: Boston Scientific, Natick, MA, U.S.A.; or Esophageal Z-Stent: Cook Medical, Bloomington, IN, U.S.A.), with diameters ranging between 7 mm and 10 mm.
Patients were placed in the RTG if their primary and first treatment on record was either brachytherapy or external-beam radiation therapy (EBRT). The RTG was further stratified into three subgroups, depending on the primary modality of radiation treatment provided (Figure 1): brachytherapy alone \((n = 18)\), EBRT alone \((n = 10)\), or brachytherapy plus EBRT \((n = 22)\). The planned treatment dose of brachytherapy was 20 Gy in 5 fractions, which all the patients successfully completed. Although the total dose of EBRT varied at the discretion of the treating radiation oncologist, most patients received 30 Gy in 10 fractions. The addition of EBRT to brachytherapy occurred for multiple reasons, including patients being found to have slow or little relief of dysphagia with brachytherapy alone, recurrence of dysphagia, or complications from brachytherapy.

Intention-to-treat analysis was used regardless of whether any patient required further palliative treatment by additional stenting, additional radiotherapy, or palliative chemotherapy. Chemotherapy was not used for first-line palliation of dysphagia; rather, it was added to either stenting or radiotherapy.

### 2.1 Statistical Analysis

Data are expressed as mean ± standard deviation for parametric variables and as median and range for nonparametric variables. The statistical significance of between-group differences was determined using the Fisher exact test for categorical variables and the Mann–Whitney \(U\)-test for continuous variables. A difference was considered significant if a \(p\) value of less than 0.05 was obtained.

### 3. RESULTS

#### 3.1 Patient Demographics

There was no difference in median age between patients in the ESG and in the RTG (66 years vs. 77 years, \(p = 0.12\)). Compared with patients in the RTG, those in the ESG had a higher proportion of adenocarcinoma (72% vs. 44%), but the difference was not statistically significant \((p = 0.35)\). Overall, 51% of patients presented with an initial DS of 1; only 10% presented with an initial DS of 4. There was no significant difference in the median DS between the ESG and the RTG \([2 \text{ range: } 1–4] \text{ vs. } 1 \text{ range: } 1–4, \ p = 0.49\)\). However, strictly considering severe dysphagia (DS > 2), the ESG had a significantly higher incidence of patients with severe dysphagia (68% vs. 48% in the RTG, \(p = 0.03\), Table 1).

#### 3.2 Treatment Factors

“Time to initiation of treatment” was defined as the number of days between the date of pathology diagnosis and the date of stent insertion in the ESG or the date of the first radiation treatment in the RTG. For patients in the ESG, that interval was 22 days (range: 14–88 days). For patients in the RTG, the interval was significantly longer at 52 days (range: 39–91 days, \(p = 0.003\)). Treatment duration was defined as the number of days spent receiving treatment. Mean treatment duration was 1 day in the ESG and 40 days in the RTG \((p = 0.001)\).

<table>
<thead>
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<th>Variable</th>
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<th>(p) Value</th>
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<tr>
<td>Patients ((n))</td>
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</tr>
<tr>
<td>Median age (years)</td>
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</tr>
<tr>
<td>Adenocarcinoma (%)</td>
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<td>44</td>
</tr>
<tr>
<td>Dysphagia score</td>
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</tr>
<tr>
<td>Range ((1–4))</td>
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<td>(1–4)</td>
</tr>
<tr>
<td>Dysphagia score &gt; 2 (%)</td>
<td>68</td>
<td>48</td>
</tr>
</tbody>
</table>

NS = nonsignificant.
Among patients in the ESG, 61% received adequate palliation with the stent alone and did not require further local treatment. Initially unplanned palliative treatment in the form of brachytherapy (16%) or EBRT (23%) was required in 39%. Of all patients in the ESG, 28% received systemic treatment with palliative chemotherapy at our institution. Among patients in the RTG, 56% received adequate palliation with either brachytherapy alone (36%) or with EBRT alone (20%). The remaining 44% required both brachytherapy and EBRT to achieve adequate palliation. Of all patients in the RTG, 25% received systemic treatment with palliative chemotherapy.

### 3.3 Resolution of Dysphagia Over Time

When patients were considered overall, general resolution of dysphagia occurred over 10 weeks of treatment (Figure 2). Acceptable resolution of dysphagia was defined as achieving or maintaining a DS of 1 or 0 at the 10-week follow-up mark. At time of presentation, 51% of all patients had a DS of 1, and the remaining 49% had a DS of more than 1; at 10 weeks of treatment, 90% of patients had a DS of 1 or 0, and only 10% had a DS of more than 1 ($p < 0.001$).

When each of the treatment groups was considered separately, it became apparent that the timeline to achieving acceptable resolution of dysphagia was different between the ESG and the RTG (Figure 3). In the ESG, only 31% of patients had a DS of 1 at the start of treatment. Significant resolution of dysphagia was seen 2 weeks after stent insertion, with 85% of patients having achieved a DS of 1 or 0; only 15% remained at a DS of more than 1 ($p = 0.015$). Symptom relief was maintained until week 8, when some patients begin to experience an increase in DS, which is frequently caused by stent blockage, stent displacement, or tumor growth into the stent. By week 10, 62% of patients had a DS of 1 or 0, and 38% had a DS of more than 1 ($p = 0.002$). Overall, 54% of patients experienced an improvement of 1 point in their DS, 23% experienced an improvement of 2 points, and 15% experienced no improvement at all.

Within the RTG, 90% of patients achieved a DS of 1 or 0 at 10 weeks of follow-up. In 68% of patients, the DS improved by 1 point, and in 7%, by 2 points. In 14% no improvement at all was seen. In 4 patients (8%) who initially improved, dysphagia recurred. When the subgroups of the RTG were analyzed separately, their results were similar. In the subgroup that received brachytherapy alone, 50% of patients had a DS of 1 at presentation, and 50% had DS greater than 1. Those ratios held unchanged until the 8th week after initiation of treatment, when the proportion of patients with a DS of 1 or 0 abruptly rose to 82%. At week 10 of treatment, the proportion of patients with a DS of 1 or 0 rose from 50% to 86%, and the proportion of patients with a DS greater than 1 fell from 50% to 14% ($p = 0.02$). The same trend was seen in the subgroup of patients who were treated with EBRT alone. In that group, an abrupt resolution of dysphagia was seen by week 8 of treatment, and at week 10, the proportion of patients with a DS of 1 or 0 rose from 50% to 80%, and the proportion of patients with a DS greater than 1 fell from 50% to 20% ($p = 0.35$). In the subgroup of patients treated with both brachytherapy and EBRT, the resolution of dysphagia followed a more gradual course, starting at the 6th week after treatment initiation. By week 10, the proportion of patients with a DS of 1 or 0 rose from 62% to 96%, and the proportion of patients with a DS greater than 1 fell from 38% to 4% ($p = 0.005$).
4. DISCUSSION

Despite advances in cancer care, the optimal treatment regimen for palliation of dysphagia in metastatic esophageal cancer remains controversial. Although two randomized controlled trials comparing endoluminal stenting with brachytherapy have shown a certain advantage for brachytherapy in terms of long-term relief from dysphagia, those trials failed to address many important issues, including the lag time between diagnosis and treatment, the time spent in treatment, and the efficacy of combined-modality treatments with both stenting and radiotherapy. We undertook the present study to shed light on some of those issues and to attempt to identify an ideal approach to this difficult clinical scenario.

4.1 Time to Initiation and Duration of Treatment

Our study showed that, at our institution, outside the context of a clinical trial, the time from the date of histology diagnosis to initiation of treatment is, on average, 52 days for patients treated with radiotherapy as the primary modality. We recognize that by defining time to treatment in this manner (time of histology diagnosis to date of treatment initiation), many factors are included, some of which are independent of the treatment modality: for example, wait time for imaging, tests, and for referral to various medical specialists. However, to be able to standardize this interval for comparisons between the study groups, we elected to use the fixed date of histology diagnosis rather than the time of decision to intervene with a palliative modality. The long delay in the radiotherapy group could be attributed to the fact that radiation treatment requires consultation with a radiation oncologist, planning time, endoscopy time (in the case of brachytherapy), and a significant amount of organization and resource allocation. On the other hand, endoluminal stent insertion is frequently performed by the surgeon or gastroenterologist who initially saw the patient, is readily available in both the hospital and the outpatient endoscopy settings, does not always require imaging for planning; thus, it was associated with a considerably shorter interval (22 days) between pathology diagnosis and treatment. The study also showed that the average duration of treatment for patients receiving radiotherapy was 40 days, but that it was only 1 day for patients treated by stenting. Our data are consistent with those from the Dutch and Swedish trials, in that dysphagia improved more rapidly after stent placement, but long-term relief was better with radiotherapy. Although the Dutch trial commented on the costs of the various treatments, neither it nor the Swedish trial addressed the lag time between diagnosis and treatment, or the time spent in treatment under either modality. Although we did not demonstrate that dysphagia worsens when the patients are waiting for treatment, such worsening is highly likely given the progressive nature of this cancer.

4.2 Resolution of Dysphagia over Time

Our study shows that 85% of patients treated with endoluminal stents at our institution during 2004–2009 achieved a ds of 0 within 2 weeks of stent insertion. Adding that time to the 22-day average interval between the date of pathology diagnosis and treatment, it would be reasonable to conclude that a patient treated with a stent received adequate palliative treatment within 36 days of pathology diagnosis. Such palliation will last until the 8th week post-insertion, when roughly 20% of patients will experience an increased ds because of tumor overgrowth, stent migration, or blockage. Therefore, at the 10th week after stent insertion, the proportion of patients with an acceptable ds of 0 declines to 62% from 85% at 2 weeks. Indeed, 39% of patients in the esg required additional treatment in the form of brachytherapy (16%) and erbt (23%) to palliate recurrent dysphagia. In addition, 15% of patients required additional endoscopy to replace or unblock their initial stent.

The time to acceptable relief of dysphagia was significantly longer in rtg patients than in esg patients, because it took 6–8 weeks of treatment for 85% of patients to reach a ds of 1 or 0. When that interval is added to the time lag between the pathology diagnosis and treatment initiation, it effectively means that, compared with rtg patients, esg patients achieved an acceptable resolution of dysphagia at least 1 month earlier on average. Given the short median survival of patients with metastatic esophageal cancer, that difference is not only statistically significant, but also highly clinically significant. However, rapid relief of dysphagia with stenting comes at a cost, including a less durable effect, a high rate of recurrent dysphagia, and a lesser number of patients achieving complete dysphagia resolution (ds of 0).

4.3 Combined-Modality Treatment with Stenting and Radiotherapy

Given our findings of early relief of dysphagia with stent insertion, but more effective and longer lasting relief with radiotherapy, it would be intuitive to consider combined-modality treatment for patients with dysphagia resulting from inoperable esophageal
cancer. A stent could be inserted in the initial treatment phase, with the goal of minimizing the wait time and achieving rapid relief from dysphagia. Patients could then proceed to receive radiation therapy (brachytherapy or EBRT) to maintain relief and avoid the recurrence of dysphagia that is seen in patients treated with stenting alone. In our series, only 3 patients were treated with this combined modality, and therefore no real comment can be made on the safety or efficacy of such an approach. However, we are currently designing a prospective randomized controlled trial to compare combined-modality (stenting plus brachytherapy) with single-modality treatment (stenting), perhaps being able to establish a consensus on the best approach for palliative treatment of dysphagia in inoperable esophageal cancer.

5. CONCLUSIONS

Dysphagia from inoperable esophageal cancer is a common and complex management problem, and there is no consensus on the ideal treatment approach. Our retrospective review suggests that, although radiation treatment provides durable long-term relief, it comes at a high price: long waiting times for initiation of treatment, and long lag times between initiation of treatment and relief of symptoms. On the other hand, endoluminal stenting provides more rapid and effective early relief from symptoms, but comes with a higher recurrence of dysphagia in the long term. In our study, recurrences can in part be attributed to the selection of patients with a higher DS, but the inherent limitations of stenting also play a role. Further investigations, including randomized controlled trials exploring the toxicity and effectiveness of multimodality treatments with combinations of stenting, radiotherapy, and chemotherapy are required to address these unresolved issues and help to clarify management in this complex clinical scenario.

6. CONFLICT OF INTEREST DISCLOSURES

All authors have no financial conflicts of interest to disclose.

7. REFERENCES


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