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Overview

Brachytherapy in the Palliation of Oesophageal Cancer: Effective but Impractical?

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Abstract

Dysphagia in people with advanced oesophageal cancer can be treated by oesophageal stents, external beam radiotherapy (EBRT) and intraluminal brachytherapy. Despite guidelines recommending brachytherapy for patients with a predicted life expectancy exceeding 3 months, its uptake in the UK has been limited. Here we examine the strength of the evidence supporting the use of brachytherapy compared with oesophageal stents and EBRT and possible reasons for its limited uptake. Trials and observational studies suggest brachytherapy alone confers a benefit to patients, but its impact is less immediate than oesophageal stents; the evidence on effectiveness and value-for-money is limited. Moreover, stronger evidence will probably be insufficient to increase uptake, due to the extra complexity of delivery compared with stents and EBRT and a lack of experience among specialists.

Key words: Brachytherapy; dysphagia; oesophageal cancer; palliative care

Statement of Search Strategies Used and Sources of Information

The following databases were used to identify papers relevant to the topic: MEDLINE and Pubmed. The search terms: brachytherapy, oesophageal, esophageal, cancer, carcinoma and palliative were used in key word searches. The reference lists of selected papers were also used to find relevant literature.

Introduction

People with oesophageal cancer often have a poor prognosis because they are diagnosed with advanced disease or are too frail to undergo curative treatment. For these reasons, oesophageal cancer is the seventh most common cause of death due to cancer in the UK despite being the 13th most common type of tumour [1]. Most patients are unsuitable for curative treatment and the aim of their treatment is primarily either to extend life expectancy or reduce the impact of symptoms on quality of life, although the latter is perhaps the dominant consideration. Among patients with stage IV cancer, recent population-based figures show life expectancy remains poor, with 1-year relative survival rates of 25.3 and 21.3% for squamous cell and adenocarcinoma tumours, respectively [2].

Dysphagia is a common, debilitating symptom among patients with advanced oesophageal cancer and can present with various stages of severity, such as restricting patients to eating specific solids, to swallowing only liquids or preventing anything from being ingested orally. Various therapies are available to alleviate dysphagia, including oesophageal stent insertion, external beam radiotherapy (EBRT), brachytherapy, laser therapy, photodynamic therapy and argon plasma coagulation [3]. Oesophageal stents

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provide immediate relief, but the procedure can lead to adverse outcomes, such as significant postoperative pain, haemorrhage (occurring in 8% of cases) and stent migration (occurring in 7% of cases) [4]. In the longer term, tumour overgrowth around the stent (occurring in 14% of cases) can reduce its effectiveness [4]. In comparison, EBRT is able to give longer lasting relief, but is associated with a longer delay between the onset of treatment and symptom relief.

The 2014 Cochrane Review on 'Interventions for dysphagia in oesophageal cancer' concluded from its synthesis of evidence from randomised controlled trials (RCTs) that, compared with self-expanding metal stents, intraluminal brachytherapy provided a small improvement in long-term relief from dysphagia and possibly a better quality of life [3]. The evidence has informed recent clinical guidelines, which recommend brachytherapy as an alternative to oesophageal stents for the palliation of dysphagia in patients with advanced oesophageal cancer and a life expectancy exceeding 3–4 months [4–6]. However, brachytherapy is infrequently used to palliate dysphagia in the UK. The National Oesophago-Gastric Cancer Audit reported that the procedure was carried out at just six English National Health Service Trusts and Welsh Health Boards between 2014 and 2016 [7] and although over 2700 patients had a stent inserted, brachytherapy was received by only 47 patients during this period. In addition, the audit reported that 59% of patients who had a stent survived for longer than 3 months [7], suggesting that many patients might have been suitable candidates. Infrequent use of brachytherapy has also been observed in the USA [8] and Italy [9].

Here we consider whether brachytherapy should be more widely used in patients with oesophageal cancer. We evaluate the strength of the evidence on the potential benefits and harms of brachytherapy compared with other treatment options, its cost and anticipated variation in patient preferences, and consider both RCTs and cohort studies. We also examine potential practical reasons for its limited uptake.

The Clinical Evidence for Brachytherapy as a Treatment for Dysphagia

Brachytherapy for oesophageal cancer involves using endoscopic techniques to deliver radiotherapy in close proximity to the tumour. Two types of intraluminal brachytherapy can be delivered, low dose rate and high dose rate. The former involves placing radioactive sources near the tumour for several days, whereas the latter involves using a higher dose of radiation for a much shorter duration, usually a few minutes. Currently, high dose rate brachytherapy is most frequently used for oesophageal cancer, with a recommended dose of either 12 Gy in one fraction or 12–16 Gy in two fractions [10]. In comparison with EBRT, the duration of treatment is typically shorter, with EBRT often involving the delivery of 30 Gy in 10 fractions over 2 weeks [11].

In this section we review the current state of the evidence comparing brachytherapy to alternative palliative treatments. The studies were identified by searching for RCTs and cohort studies in MEDLINE and Pubmed that compared the effectiveness of brachytherapy, stent insertion and EBRT to palliate dysphagia among patients with advanced cancer. The key search terms were: brachytherapy, oesophageal, (o)esophageal, cancer, carcinoma and palliative. The reference lists of selected papers were also used to find relevant literature. Table 1 describes the characteristics of the studies included in the review. All studies reported improvement in dysphagia as an outcome, with this being the primary outcome in all but one. All measured symptom severity using the same five-point dysphagia scale (0 no dysphagia to 4 complete dysphagia) produced by Ogilvie *et al.* [12].

Brachytherapy versus Stenting

Two RCTs compared brachytherapy to stent insertion for relief of dysphagia. The Stent versus Intraluminal Radiotherapy for Inoperable Esophageal Carcinoma (SIREC) trial published in 2004 [13] was conducted in the Netherlands and compared Ultraflex metal stents to single dose (12 Gy) brachytherapy in 209 patients with inoperable cancer of the oesophagus or gastro-oesophageal junction and progressive dysphagia. It reported that patients who received stents had greater improvements in their dysphagia scores initially, but by 30 days, both treatments provided similar benefits. Beyond 30 days, brachytherapy was reported to be more effective and was associated with a longer period of dysphagia-adjusted survival (115 days versus 82 days, $P = 0.015$). Health-related quality of life (HRQL) scores also showed greater improvements in the brachytherapy group over time. Complications were more frequent in the stent group (33% versus 21%; $P = 0.02$) [13].

A second RCT of 65 patients conducted in Sweden enrolled a comparable patient cohort to the SIREC trial but compared metal stents to a different regimen of brachytherapy (three fractions of 7 Gy over 2–4 weeks) [14]. The study found no statistically significant differences in the distribution of dysphagia scores when measured at 1, 3 and 6 months in the two groups. However, changes in HRQL were reported on various subscales of the EORTC OES-18 instrument. Improvements in dysphagia-related HRQL scores were observed at 1 month for the stent group but these tended to deteriorate thereafter. Patients in the brachytherapy group had improved dysphagia-related HRQL scores by 3 months and these were maintained at 6 months [14].

Two more recent trials compared combined therapies (stents and brachytherapy) to either brachytherapy or stents alone for patients with inoperable oesophageal cancer [15,16]. The first study was a multicentre RCT with 160 patients, and found that patients with unresectable oesophageal cancer who received stents loaded with radioactive iodine (I-125) seeds had prolonged overall survival (median = 177 days; 95% confidence interval 153–201) compared with those patients who received conventional covered stents (median = 147 days; 95% confidence interval 124–170) [16]. The mean dysphagia score in the irradiated

Table 1
List of relevant studies that have compared brachytherapy to stents, external beam radiotherapy (EBRT) and combination treatments in patients with oesophageal and gastro-oesophageal junctional (GOJ) cancer

Reference	Study design No. patients Study period	Selection criteria	Interventions	Outcome
[13]	RCT $n = 209$ December 1999 to July 2002	Inoperable cancer of the oesophagus or GOJ due to metastases or medically unfit for surgery AND dysphagia grade 2–4	1: HDRBT 12 Gy in single dose 2: Partly covered Ultraflex stent	Dysphagia-adjusted survival better in brachytherapy group (115 versus 82 days, $P = 0.015$). Long-term relief of dysphagia better in brachytherapy group. Higher rate of complications in the stent group (33% versus 21%, $P = 0.02$). HRQL scores favoured brachytherapy. Median overall survival of 155 days in brachytherapy group (95% CI 127–183) versus 145 days in stent group (95% CI 103–187).
[14]	RCT $n = 65$ May 1999 to April 2002	Histologically proven cancer of the oesophagus or GOJ that has metastasised or T4 or medically unfit for radical treatment AND dysphagia grade 2–4	1: HDRBT 21 Gy in 3 fractions over 2–4 weeks 2: SEMS	At 1 month, the stent group had better HRQL scores for dysphagia than brachytherapy. At 3 months, both groups had improved dysphagia-related scores and the brachytherapy group had less deterioration thereafter. Difference in median overall survival (106 days in brachytherapy patients; 132 days in stent patients) not statistically significant.
[20]	Cohort $n = 139$ 1994–2014	Histologically proven SCC or adenocarcinoma of the oesophagus that is advanced or unsuitable for surgery AND dysphagia grade 1–4	1: HDRBT 15–25 Gy in 5 Gy per fraction/week 2: EBRT 30–40.5 Gy/2.5–3 Gy per fraction, 5 days weekly 3: EBRT 30–40 Gy plus 1–3 fractions brachytherapy (5–7 Gy/fraction/week)	At 6 months, proportion of patients with dysphagia-free survival were 37%, 90% and 92% for the brachytherapy, EBRT and combination treatment groups, respectively ($P < 0.001$). Median overall survival for all patients = 10 months
[15]	RCT $n = 41$ Period not stated	Incurable cancer of oesophagus and dysphagia grade 1–4	1: HDRBT 24 Gy in 3 fractions weekly 2: SEMS followed by HDRBT	At 7 weeks, change in mean dysphagia score was +1 for SEMS + HDRBT and +1 for HDRBT group. Median overall survival was 11 weeks for SEMS + HDRBT group and 18 weeks for HDRBT group
[16]	RCT $n = 160$ November 2009 to October 2012	Patients with unresectable oesophageal cancer (metastases or poor medical condition) and progressive dysphagia (grade 3 or 4) and ECOG 0–3	1: Stent insertion with ^{125}iodine radioactive seeds 2: Conventional covered stent	Median overall survival in the irradiated stent group was longer than in the conventional stent group (177 days versus 147 days, $P = 0.0046$). Mean dysphagia scores at baseline, at 1 day and at 6 months were 3.3, 1.4 and 2.6 in stent group and 3.4, 1.3 and 1.9 in the irradiated stent group

(*continued on next page*)

Table 1 (*continued*)

Reference	Study design No. patients Study period	Selection criteria	Interventions	Outcome
[17]	RCT $n = 60$ July 2000 to December 2000	Inoperable advanced oesophageal cancer, histologically proven SCC, no distant metastases and ECOG performance score 0–2	1: HDRBT 16 Gy in 2 fractions over 3 days 2: HDBRT followed by EBRT 30 Gy/10 fractions over 2 weeks	Comparable dysphagia-free survival rates in both groups at 6 months (>50% in both). Median overall survival was 7.2 months for HDRBT group and 7.5 months for HDRBT + EBRT group
[18]	RCT $n = 219$ March 2003 to June 2006	SCC oesophagus and dysphagia and one successful HDRBT insertion, ECOG performance score 1–2	1: HDRBT 8 Gy 2: HDRBT followed by EBRT 30 Gy in 10 fractions over 2 weeks	At 200 days, proportion of patients not experiencing dysphagia event was 51.8% for HDRBT and 69.6% for HDRBT + EBRT ($P < 0.001$) Median overall survival for all patients was 188 days; there was no difference between groups
[19]	RCT $n = 62$ July 2003 to December 2004	Patients aged 17–70 years with SCC oesophagus tumour ≥ 5 cm and surgically inoperable, Karnofsky performance score > 50, no prior malignancy	1: EBRT 30 Gy/10 fractions/2 weeks followed by HDRBT 12 Gy/2 fractions/weekly 2: EBRT 30 Gy/10 fractions/2 weeks 3: EBRT 20 Gy/5 fractions/1 week	Mean global QOL scores improved in all groups from baseline to 3 months. Mean dysphagia scores improved most for combination group and were maintained at 3 months.

Dysphagia was graded on the following scale: 0 = normal diet; 1 = able to eat some solids; 2 = able to eat semi-solids only; 3 = able to swallow liquids only; 4 = complete dysphagia [12].
HDRBT, high dose rate brachytherapy; GOJ, gastro-oesophageal junction; SCC, squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; RCT, randomised controlled trial; HRQL, health-related quality of life; CI, confidence interval; QOL, quality of life; SEMS, self-expanding metal stent.

stent group was lower than the mean in the control group at 1 month after treatment, and remained so at 3, 6 and 9 months. In contrast to other studies included in this review, this is the only study where brachytherapy was delivered via irradiated stents and the trial had comparatively high complication rates (about 56%) in both groups. The second RCT randomised 41 patients to receive either stent followed by brachytherapy or brachytherapy alone [15]. The 21 patients who received a stent and brachytherapy had earlier relief of dysphagia, but four patients experienced complications, all of which were manageable.

Brachytherapy versus External Beam Radiotherapy

No RCTs have directly compared the efficacy of brachytherapy to EBRT. The three trials involving both brachytherapy and EBRT have examined combinations of treatments – two compared a regimen of brachytherapy alone to brachytherapy followed by EBRT [17,18]; the other compared EBRT alone to EBRT followed by brachytherapy [19]. All three trials used similar EBRT regimens (typically 30 Gy in 10 fractions) but each used a different regimen of brachytherapy – the test interventions being 16 Gy in two fractions over 3 days [17], a single dose of 8 Gy [18] or 12 Gy in two fractions (after EBRT) [19]. The largest of the trials [18] enrolled 219 patients with incurable squamous cell carcinoma of the oesophagus, and reported that combination treatment was superior to brachytherapy alone in improving dysphagia relief (overall mean dysphagia scores for period 1–12 months after treatment were 1.23 for brachytherapy alone and 0.79 for combined treatment) and both interventions were well-tolerated. Overall survival was similar in both groups, with the median overall survival being 188 days for all patients. The other two trials [17,19] enrolled only around 60 patients and the outcomes achieved by patients receiving brachytherapy in combination with EBRT did not differ statistically from the outcomes in the brachytherapy-alone group.

A cohort study conducted in Germany by Welsch *et al.* in 2016 [20] retrospectively analysed data on 139 patients with advanced or recurrent oesophageal cancer (unsuitable for radical treatment) and dysphagia. The study compared three groups of patients: those who received EBRT alone, those who received brachytherapy alone and those who received a combination of both EBRT and brachytherapy. The authors reported that, the proportion of patients who were dysphagia-free at 6 months post-treatment was 92% for the combined group, 90% in the EBRT group and 37% in the brachytherapy group ($P < 0.001$). Patients in the brachytherapy group were significantly older and tended to have a worse performance status than patients in the EBRT and combination groups, but the authors did not report if

the analysis of outcomes included appropriate adjustments for these differences.

In all the studies described above, there were no significant differences in the rate of complications between patient groups that received combination treatment and those that received either brachytherapy or EBRT alone. However, the small sizes of the trials and the potential for selection bias in the cohort study means that strong conclusions cannot be reached on the benefits of either brachytherapy compared to EBRT or in relation to the combination of brachytherapy and EBRT.

Cost Comparison of Brachytherapy and Stent Insertion

There are currently no cost-effectiveness analyses comparing brachytherapy with metal stent insertion. To date, studies have only provided information on the costs involved in the delivery of brachytherapy and stents; cost comparisons of brachytherapy and EBRT have yet to be undertaken.

Polinder *et al.* [21] compared the direct and indirect costs of both treatments in the SIREC trial [13]. Patients were followed up for 1 year and the study reported that, although the initial cost of stent therapy was higher, primarily due to the cost of the Ultraflex stent, the annual costs of both procedures (including initial treatment, medical procedures during follow-up and the cost of intramural and extramural care) were similar in both groups.

Wenger *et al.* [22] used data from the RCT conducted in Sweden [14] to compare the costs of stent therapy to brachytherapy. Compared with the SIREC trial (which used a single dose of brachytherapy), patients in the brachytherapy group received three fractions of 7 Gy; Wenger *et al.* reported that the median lifetime cost of this brachytherapy regimen was nearly double the cost of stent therapy [22]. This was largely due to higher costs of initial therapy in the brachytherapy group.

Why is Brachytherapy so Infrequently Used and Should it be Used More?

In this section, we examine the possible reasons that might account for the infrequent use of brachytherapy among oesophageal cancer patients with dysphagia, given the moderately strong evidence that brachytherapy is an effective alternative to stents for alleviating dysphagia. First, there are various clinical scenarios in which using brachytherapy would be inappropriate. These scenarios include patients with tumours exceeding 10 cm in length, tumours with extra-oesophageal extension or regional lymphadenopathy and tumours involving the gastro-oesophageal junction or cardia. Absolute contraindications to using brachytherapy include complete luminal occlusion, oesophageal fistula and cervical oesophagus location [23].

A second reason is that clinicians judge the limited evidence on the comparative effectiveness of brachytherapy to be insufficient to change from their current treatment patterns and offer brachytherapy to patients. The trials have tended to be rather small and this means they produced imprecise estimates of the potential benefit and harms of brachytherapy. That trials have not been able to show the absence of clinically important differences in adverse effects is concerning because there are several known side-effects associated with brachytherapy. Long-term side-effects include chronic oesophagitis, ulceration ($\leq$30% of patients) and stricture and fistula formation [24]. Oesophageal stricture formation occurs in 5–30% of patients and can be treated with oesophageal dilation [24]. Fistula formation can occur after brachytherapy treatment, particularly when given as a boost to EBRT alongside chemotherapy in the curative setting [25]. Perforation and haemorrhage are rare side-effects [24]. Furthermore, although trials have shown a statistical improvement in dysphagia outcomes, the absolute benefits of brachytherapy have been modest, amounting to about a 30-day increase in dysphagia-free survival. Another challenge to interpreting the studies in Table 1 arises from the different approaches they used to report changes in dysphagia after treatment; some reported dysphagia-free survival [13,17,20], whereas others reported the change in dysphagia scores at particular time points [14–16]. More generally, the interpretation of the results from studies on interventions to alleviate dysphagia is hampered by the use of different dysphagia scales, such as the Swallowing Performance Status Scale and the Dysphagia Outcome and Severity Score [26].

A third reason might relate to the difficulty in selecting suitable patients. Guidelines recommend brachytherapy for patients who are expected to survive at least 3 months [6], but estimating the life expectancy of a patient with advanced oesophageal cancer is difficult for clinicians due to an absence of prognostic models for this patient group. A related challenge is the need to balance the different speed of relief each type of treatment offers. Stents may be chosen as the treatment option because they provide a greater guarantee of immediate relief of dysphagia, and this might be weighted more strongly than the longer-term effectiveness of brachytherapy when the duration of survival is uncertain. Furthermore, the median overall survival of patients in trials has been less than 6 months [13,14,16] and in many cases it may not be practical to arrange brachytherapy given the expected life expectancy of the patient.

A fourth reason for its lack of use might relate to the fact that the delivery of brachytherapy is more difficult than both stent insertion and EBRT. For patients, the typical brachytherapy regimens involve multiple visits to the radiotherapy centre (unlike stent insertion) and each visit might involve considerable effort for patients if travel times are long. Consequently, patient preferences could also be an important factor in the low uptake rates, but this has not been explored in any studies or surveys thus far. For clinicians, brachytherapy is a more complex procedure compared with EBRT, requiring endoscopy under sedation followed by the insertion of an applicator to deliver the radiotherapy dose. Thus, it requires greater co-ordination between specialists. Finally, the limited use of brachytherapy means that there is a lack of experience among staff in brachytherapy for oesophageal cancer.

Insight into how these potential challenges might affect the delivery of brachytherapy was provided by a survey of Italian radiotherapy centres in 2015–2016 [9]. The survey was comprised of seven questions pertaining to the availability and importance of brachytherapy in the management of oesophageal cancer and limitations to its use; responses were obtained from over 50% of radiotherapy centres in Italy. Lack of experience was the most frequently expressed reason for not performing brachytherapy for oesophageal cancer. Other common reasons cited by respondents included complexity, logistical problems and absence of an effective response. The authors of this study speculated whether palliative patients receive less input from the multidisciplinary team compared with patients being treated with curative intent and the impact this could have on adherence to current guidelines [9].

Conclusions and Recommendations

Various clinical guidelines recommend that clinicians consider the use of brachytherapy in the palliation of dysphagia in patients with oesophageal cancer who will probably live beyond 3 months. It may confer better long-term symptom control and dysphagia-free survival, but these benefits should be balanced against the potential risks of the procedure, patient choice, convenience (for example, distance from a brachytherapy centre and lost work productivity of patients and their carers) and the probable life expectancy of the patient. Furthermore, the speed of dysphagia progression should be considered; patients whose dysphagia becomes worse gradually may be better candidates for brachytherapy than patients whose ability to swallow is deteriorating quickly. Ideal candidates for treatment would have tumours located in the thoracic oesophagus and both squamous and adenocarcinomas are amenable to treatment.

Whether brachytherapy should be used in combination with either stents or EBRT to reduce the need for re-intervention is unclear, and there is a need for further research in this area. Indeed, the moderate evidence was insufficient for the National Institute for Health and Care Excellence (NICE) to recommend brachytherapy for dysphagia relief in their 2018 guideline on the treatment of oesophageal cancer [27] (in contrast to the other guidelines). Instead, the NICE guideline advises either self-expanding stents or radiotherapy, depending on the degree of dysphagia and its effects on nutritional status and quality of life of the patient.

However, it would appear that better evidence is not the only prerequisite for improved availability and uptake of brachytherapy in the UK. First, it appears necessary to address the logistical issues associated with its use and the unfamiliarity with the procedure. A minimum caseload of 10 patients per year per brachytherapy centre has been recommended to ensure quality standards are maintained [28], but this represents less than one patient per month on average. Commissioners and local cancer services might consider this an insufficient volume to justify the investment required for a viable service, given the specialist expertise required. To overcome this, the centralisation of brachytherapy services to tertiary centres within radiotherapy networks may be required before its use will expand.

Second, there needs to be a better decision tool to support the identification of patients who will probably live beyond 3 months. Two prognostic models have been developed to aid clinical decision making in patients with inoperable oesophageal cancer [29,30]. However, the performance of these models has not been externally validated and further work is required to evaluate the usefulness of such models in helping to select patients for appropriate palliative treatments.

Conflict of Interest

The authors declare no conflicts of interest.

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