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EVIDENCE-BASED ONCOLOGY

Brachytherapy improved dysphagia more than stenting in people with inoperable oesophageal cancer

Abstracted from: Homs MYV, Steyerberg EW, Eijkenboom WMH, et al. Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: a multicentre randomised trial. Lancet 2004;364:1497–504.

Background

The prognosis of oesophageal cancer is poor (10–15% 5-year survival rate) and dysphagia is a common complication in advancing disease. Palliative therapy aims to relieve dysphagia and prevent fistulation. Brachytherapy (intraluminal radiotherapy) and stenting are two commonly used palliative techniques for relieving dysphagia. The relative effectiveness of these techniques is not known.

Objective

To compare the effectiveness of single-dose brachytherapy versus placement of metal stent for palliating dysphagia in people with inoperable oesophageal cancer.

Setting

Six general hospitals and three teaching hospitals in the Netherlands; recruitment from December 1999 to July 2002.

Method

Multicentre randomised controlled trial.

Participants

209 people (78% male; average age 69 years) with cancer of the oesophagus (179 people, 86%) or oesophagogastric junction (30 people, 14%). All participants were considered inoperable because of metastatic disease (134 people, 64%) or poor medical condition (51 people, 24%) or both (24 people, 12%) and a dysphagia score of 2–4 (mean 2.8). Thirty (14%) participants had received previous chemotherapy. People were excluded if they had: tumour length >12 cm; tumour growth within 3 cm of upper oesophageal sphincter; deep ulceration or trachea-oesophageal fistula; macroscopic or microscopic tumour extension into the tracheal lumen; a pacemaker; previous radiation treatment; previous stent placement.

Intervention

Participants were randomized to self-expanding metal stent placement or single dose brachytherapy. After endoscopy, the oesophagus was dilated and tumour margins were marked with radiographic contrast medium.

Stent placement: A partly covered stent was used (diameters: proximal 23 mm, distal 18 mm) and monitored using fluoroscopy. The stent was placed

so that it extended for at least an extra 15 mm either side of the proximal and distal tumour margins.

Brachytherapy: A 12 Gy dose of radiotherapy was administered with a flexible applicator (diameter 10 mm) along the length of the tumour and an additional 2 cm at either end. People in the brachytherapy group received sucralfate for 4 weeks after treatment to prevent odynophagia.

Main outcomes

Primary outcome was dysphagia score (as recorded by participants in a diary every day for 1 month following treatment and then weekly thereafter), recorded as: ability to eat normal diet (score 0); eat some solid food (score 1); eat semi-solids only (score 2); swallow liquids only (score 3); or the presence of complete obstruction (score 4). Secondary outcomes were quality of life (using oncology specific questionnaire EORTC-QLQ); adverse effects, and costs.

Main results

Benefits. Most results were reported graphically. Stent placement improved dysphagia score more

rapidly than brachytherapy (significance not reported). However, by the end of follow up, brachytherapy significantly increased the median number of dysphagia-free days compared with stenting (see Evidence Table 1). Over time brachytherapy was beneficial on most quality of life scales (results presented graphically). Survival was similar in both groups (see Table 1).

Adverse events. There were significantly more complications after stenting than after brachytherapy (see Evidence Table 2). After 390 days follow up, all but 16 participants had died. 158 deaths were due to tumour progression, seven were due to haemorrhage that may have been related to treatment. Three deaths were due to complications of perforation. The remaining 25 deaths were unrelated to tumour or treatment.

Authors' conclusions

Brachytherapy was more effective in relieving dysphagia at longer follow up times than using a metal stent; was associated with significantly fewer complications and led to slight improvement in participants' quality of life. There was no difference in recurrence or persistence of dysphagia.

Evidence Table 1 Evidence profile: benefits

Outcome	Brachytherapy (n = 101)	Metal stent placement (n = 108)	Difference (95% CI)	P value
Median survival in days	155 (95% CI 127 to 183)	145 (95% CI 103 to 187)	10 (not stated)	0.23
Days without dysphagia ^a	115	82	33 (1 to 64)	0.015

^a Defined as number of days rated grade 0 or 1 during follow up.

Evidence Table 2 Evidence profile: harms

Complications	Brachytherapy n = 101 (%)	Metal stent placement n = 108 (%)	Significance (P)
Minor complications ^a	8 (8)	16 (15)	0.08
Major complications ^b	13 (13)	27 (25)	0.02
Total complications	21 (21)	36 (33)	0.02
Persistent/recurrent dysphagia ^c	43 (43)	43 (40)	0.81

^a Not life threatening, e.g., mild pain and gastro-oesophageal reflux.

^b Life threatening, e.g., perforation, haemorrhage, fever, fistula formation, severe pain.

^c *Persistent*: symptom continuing 2–4 weeks after treatment and requiring a second treatment. *Recurrent*: tumour re-growth more than 4 weeks after treatment, stent migration or fracture, food obstruction.

Method notes

<i>Random error</i>	
Power calculation	90% power with 104 in each treatment group, assuming 89% improvement in dysphagia after stent placement and 70% improvement after brachytherapy, at a 5% level of significance using a two-sided test
<i>Bias</i>	
<i>Comparator bias</i>	
Was true uncertainty about relative effects of competing treatments acknowledged?	<i>Measures to prevent bias</i> Adequate: authors report that treatment with self-expanding metal stents and with single dose brachytherapy are commonly used and, though effective, their relative efficacy is not known
<i>Selection bias</i>	
Selection method	Adequate
Generation of allocation sequence	Adequate: randomization was performed centrally with stratification according to location of the tumour and whether chemotherapy was received before treatment
<i>Allocation concealment</i>	
Balanced groups	Adequate: well balanced with respect to age, sex, location of tumour, tumour histology and indications for palliative treatment
<i>Performance bias</i>	
Blinding	Neither treating physicians or participants were blinded to treatment
<i>Detection bias</i>	
Assessors blinded	Not clear
<i>Attrition bias</i>	
Withdrawals and dropouts described	Adequate
<i>Analysis</i>	
Intention to treat analysis	Yes
Other statistical methods used	Kaplan–Meier survival curves; log-rank test

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Commentary

Oesophageal cancer ranks eighth in frequency of malignancy worldwide, with overall mortality in the order of 80%.¹ Over 90% of patients will experience dysphagia at some stage of their illness and for many, this is the main source of morbidity for the remaining life span. Even for patients who are candidates for curative therapy, local recurrence is expected to occur in 30% of patients undergoing surgery, and 60% of patients treated with chemoradiotherapy.

Many therapeutic strategies for malignant dysphagia are in use. These can be broadly classified into mechanical versus antineoplastic strategies. Life expectancies, pattern of disease, and practical implications for patients are important factors that are often used to guide the choice of therapies. Much of the diversity in patterns of practice however, stems from the lack of high quality evidence. Methodological issues around measuring symptoms as a primary endpoint, and the high attrition rate typically expected from palliative trials has contributed to the paucity of high quality data in this area.

What is the existing effectiveness guiding the choice of localized therapy for the relief of malignant dysphagia? (Table 1)

External beam radiotherapy is commonly used for the relief of malignant dysphagia. Treatment regimen can range from single treatments, to hypofractionated regimen given over 5–10 days, to more protracted regimen. Many single arm series have been published demonstrating response rates of 30–80% with median duration of responses in the order of 5 months.^{2,3} Existing trials comparing external beam radiotherapy with mechanical forms of therapy have generally been of modest quality, limiting their power of inference. These include comparisons of external beam radiotherapy with rigid tubes,⁴ tube and best supportive care,⁵ dilatation,⁶ dilatation plus tube,⁷ and chemotherapy (Bleomycin and adriamycin).⁸ The addition of external beam radiotherapy typically provides more durable responses.

Table 1 Summary of available RCTs in the relief of dysphagia²²

	Stent	Brachytherapy	External beam XRT	External beam XRT + Brachytherapy	External beam XRT + Chemotherapy
Dilatation	–	–	6,7	–	–
Plastic stents	10–15	–	4,5	–	–
Laser	9	17 ^a 18,19	–	–	–
Stent	16	23,24	–	–	–
Brachy		20,21	–	–	–
External beam XRT			–	25 ^b	26 ^b

^a Laser vs. Laser and Brachytherapy.

^b Ongoing studies.

Among the mechanical forms of therapy, the superiority of flexible stents over plastic stents have been well established. Eight randomized trials have been conducted in this area.^{9–16} When considering durability of dysphagia relief, and toxicity assessment, flexible stents are more effective than plastic stents and have generally been accepted to be the treatment of choice. Perforation and stent migration occurs more frequently with plastic stents. No significant differences were found between ultraflex and wall stents in one study.¹⁶

Brachytherapy has very similar practical implications to flexible stents for patients. Both modalities require the malignant stricture to permit intubation and require the patient to undergo an endoscopic procedure, although for some regimen brachytherapy requires 2–3 applications to complete the treatment regimen. However, the mechanisms of action are obviously different. The only mechanical form of treatment brachytherapy has been directly compared to is laser therapy,^{17–19} with one out of three studies favouring brachytherapy for dysphagia-free duration.¹⁹ Two studies have been conducted by Sur et al.^{20,21} comparing different regimen of fractionated radiotherapy concluding similar efficacy for 16 Gy in two fractions and 18 Gy in three fractions with a median dysphagia free survival of approximately 7.1 months for a group of patients with a median survival of 7.9 months.

Contribution of the study

The current study by Homs et al.^{23,24} is the only study providing a direct comparison between stent

and brachytherapy. This is an elegantly conducted study. It makes a significant contribution to the literature in at least three ways.

First, the study provides a rich data set on the profile of dysphagia relief achievable by the two treatment modalities. Even though the primary endpoint, proportion of patients with dysphagia relief at 30 days, was not significantly different (73% vs. 76% for brachytherapy vs. stent, $p = 0.61$), the dysphagia score profile, dysphagia-free adjusted survival, quality of life data and economic analysis provides a much more refined picture of the relative merits to guide treatment decision making.

Second, the study illustrated the utility of a strategy of using trained research nurses to perform home visits to secure outcome data. This was supplemented by more conventional techniques including diaries and phone calls. The median survival for this sample was 20 weeks, although provision was made to follow patients for up to a year with this method. Of the expected questionnaires, response was more than 90% (681/724) which is an admirable response rate in the context of palliative trials.

Third, for many palliative trials, symptom score profile over time is perhaps more important than conventional outcomes such as proportion and duration of response, and mean scores at specified time points. The use of dysphagia score profile with spline function to provide a 95% CI limits, and symptom-free adjusted survival represent clinically meaningful methods of comparing the data to guide evidence-based practice. These methods of reporting should be considered by future researchers in this and other areas in symptom control and palliation.

Homs et al. provide compelling evidence of the relative merits of stent and brachytherapy. The benefits in dysphagia relief and quality of life were similar until around 150 days after which brachytherapy was superior to stents. Life expectancy is therefore a key factor for applying the results of this study. For patients with shorter life expectancy (e.g. 2–3 months), stent insertion provides rapid onset of dysphagia relief, although, accompanied by slightly more pain as measured by the VAS pain profile, and it should be the treatment of choice. For patients with an intermediate life expectancy, (e.g. >3 months), brachytherapy provides more durable benefits in dysphagia and quality of life and is the treatment of choice. For patients with longer life expectancies, tumor regrowth and direct invasion to surrounding structures is likely to have the greatest impact on dysphagia and quality of life. The relative merit of palliative external beam radiotherapy, plus or minus chemotherapy, may be an appropriate addition or alternative.

To establish the optimal role of external beam radiotherapy in this context, two large randomized trials are ongoing. An international collaboration between the Trans-Tasman Radiation Oncology Group (TROG) and the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) is examining the effectiveness of adding 5 FU/cisplatin to a palliative course of radiotherapy (30 Gy in 10 fractions to 35 Gy in 15 fractions).²⁶ The International Atomic Energy Agency is sponsoring an international trial to establish the effectiveness of adding external beam radiotherapy to brachytherapy.²⁵

The widespread application of the results from Homs et al. is likely to be limited only by accessibility to the expertise and resources necessary for its implementation.

Quality assessment (1 = fair, 4 = excellent)

Relevance	3
Validity	4
Applicability	2
Feasibility	3
Impact	4
Knowledge context	4

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