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Phase III randomised trial

Palliative brachytherapy with or without primary stent placement in patients with oesophageal cancer, a randomised phase III trial

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ABSTRACT

Purpose: To investigate whether a combination of self-expanding metal stent (SEMS) and brachytherapy provided more rapid and prolonged effect on dysphagia without increased pain compared to brachytherapy alone in patients with incurable oesophageal cancer.
Methods: 41 Patients were randomised to SEMS followed by brachytherapy, 8 Gy × 3 (n = 21) or brachytherapy alone, 8 Gy × 3 (n = 20). Change in dysphagia and pain three and seven weeks after randomisation (FU1 and FU2) was assessed by patient-reported outcome. Dysphagia, other symptoms and health-related quality of life were assessed every four weeks thereafter. The study was closed before the estimated patient-number was reached due to slow recruitment.
Results: Patients receiving SEMS followed by brachytherapy had significantly improved dysphagia at FU1 compared to patients receiving brachytherapy alone (n = 35). Difference in pain was not observed. At FU2, patients in both arms (n = 21) had less dysphagia. Four patients in the combined treatment arm experienced manageable complications, no complications occurred after brachytherapy alone.
Conclusion: For the relief of dysphagia, SEMS followed by brachytherapy is preferable and safe for patients in need of immediate alleviation, while brachytherapy with or without preceding SEMS provides relief within a few weeks after treatment.

In patients with advanced cancer of the oesophagus, the poor prognosis is associated with advanced stage of the disease, reduced performance status (PS), and weight loss [1,2]. In a retrospective palliative study, the median survival was shorter for patients with WHO PS = 2 (three months) compared to patients with WHO PS 0–1 (six months) [3]. Such patients need palliative interventions with high efficacy, short treatment duration and few side effects.

Common treatments for the alleviation of dysphagia are stent placement, external radiotherapy, brachytherapy and chemotherapy, but the optimal intervention has yet not been established. Systematic comparisons of different modalities are rare [4,5]. In a trial of 209 patients, dysphagia improved more rapidly using self-expanding metal stents (SEMS) than with single dose brachytherapy (12 Gy). The effect, however, lasted longer with brachytherapy [6]. Similar results were obtained in another study ($n = 65$) of SEMS versus fractionated brachytherapy (7 Gy × 3) [7]. Both studies reported more complications with SEMS than with brachytherapy, and patients in the brachytherapy arm reported better quality of life after treatment.

At the Norwegian Radium Hospital, fractionated brachytherapy (8 Gy × 3) or SEMS placement was standard palliative treatment for oesophageal cancer patients with dysphagia and reduced PS. Applicators designed to be used inside stents, allowing central positioning of the radioactive probe, were available from 2008. Based on the two studies above, a randomised trial comparing SEMS followed by brachytherapy versus brachytherapy alone was initiated.

The primary aim was to assess by patient-reported outcomes (PROs) whether SEMS followed by brachytherapy gave patients improved dysphagia without more pain at the first follow-up three weeks after randomisation (FU1), compared to patients who received brachytherapy alone. Secondary aims were to explore differences between the treatment arms at the second follow-up, seven weeks after randomisation (FU2) in: dysphagia, pain, treatment feasibility, weight and selected health related quality of life (HRQL) parameters; global quality of life, emotional function, dysphagia, and eating restrictions.

Methods

Patients and study design

Patients from the south-eastern region of Norway, with incurable carcinoma of the oesophagus and dysphagia grade 1–4, who

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were not candidates for more aggressive palliative treatment, were eligible for inclusion (Fig. 1). Patients with residual or progressive disease after primary treatment were also candidates. Exclusion criteria were tumour located at the pharyngo-oesophageal junction or with the major component in the gastric cardia, and patients with contraindications for further radiotherapy or stent placement. Based on a previous study [3], we expected 30 eligible patients per year.

The design was a prospective, two-armed phase III trial. The patients were randomised by our Clinical Trials Unit using computer-based real time permuted block randomisation to either arm A: SEMS followed by brachytherapy (experimental arm) ($n = 21$) or arm B: Brachytherapy alone (standard arm) ($n = 20$).

The study was approved by the Regional Ethics Committee and the hospital's local authorities. Written informed consent and a completed patient questionnaire were obtained before randomisation.

Procedures

Stent placement

Covered SEMS were used in Arm A. The proximal and distal tumour margins were measured endoscopically and marked with metal pellets on the patient's skin guided by fluoroscopy. After the stent was inserted, the position was controlled endoscopically and with fluoroscopy.

Brachytherapy

A flexible applicator (Bonvoisin-Gérard Esophageal Applicator Set® Nucletron, Veenendal, The Netherlands) with a diameter (15 mm, 13 mm or 10 mm) that best fitted the stent diameter (Arm A) or oesophageal lumen diameter (Arm B) was introduced into the oesophagus. A metal wire with radiopaque markers at 1 cm interval was inserted into the applicator and the position of the applicator was adjusted by fluoroscopy. The treatment length included the tumour with an inferior and superior margin of one centimetre. In the radiotherapy department, the applicator was connected to a MicroSelectron® afterloading device with a stepping source of Iridium-192. A dose of 8 Gy was prescribed at seven millimetres depth from the surface of the applicator. The duration of radiation for each patient (5–25 min) depended on the source strength, the length of treatment volume and the applicator diameter. Three fractions of 8 Gy were given at one-week intervals. Brachytherapy started the week after stent insertion in arm A.

In a pilot study using three dimensional image guided brachytherapy, the precision of treatment was not improved and conventional treatment planning was used in this trial.

All patients received intravenous sedation and analgesics during the procedure. They were allowed to drink one hour after treatment. Most patients left the hospital within a few hours after the procedure.

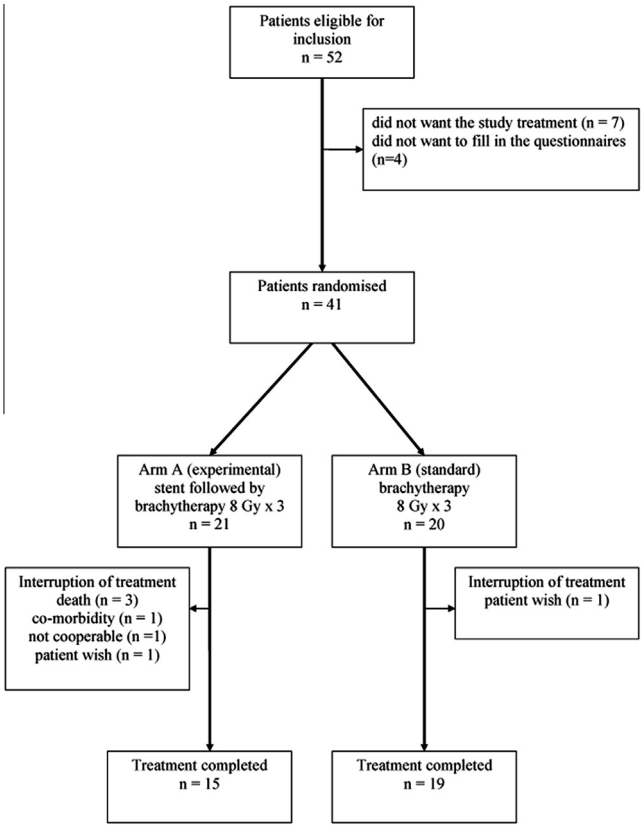

Fig. 1. Trial profile.

Clinical characteristics and observer-rated outcomes

Stage of disease was based on the TNM classification of malignant tumours [8]. The extent of disease, the WHO PS, weight change, use of analgesics and selected symptoms and signs according to the NCI-CTCAE [9] were recorded at the time of inclusion, FU1 and FU2. The dysphagia was scored as follows: score 0; ability to eat a normal diet without problems, score 1; ability to eat some solid food, score 2; ability to eat semisolid food, score 3; ability to drink only, score 4; complete dysphagia [10]. Complications requiring an intervention or prolonged stay in hospital were recorded for each treatment session.

All patients received weekly telephone-calls from the study coordinator or study nurse from the end of treatment to FU2, and thereafter every four weeks until death. At FU2, endoscopy was performed if needed. Patients in Arm B with persistent or increased dysphagia were offered SEMS at FU2, and if, at a later time point, they had relapse of dysphagia, they were offered a SEMS at their local hospital. Days in hospital from randomisation until death were registered.

Patient-reported outcomes (PROs)

A set of questionnaires consisting of a dysphagia grading scale, a symptom assessment scale and two HRQL questionnaires was completed by the patient at the hospital before randomisation and at FU1. Later, it was mailed to the patients every four weeks until death, withdrawal of consent for PRO-part of study or end of study.

The dysphagia grading scale [10] has been used as patient-reported measure of dysphagia [5]. The Edmonton Symptom Assessment Scale (ESAS) is developed to measure symptoms in palliative patient populations [11]. Aspects of HRQL for cancer patients in general is covered by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 version 3 (EORTC QLQ-C30) [12,13]. It comprises five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, nausea/vomiting and pain), six single items and a global quality of life scale. The EORTC oesophagogastric specific module (EORTC QLQ-OG25) contains six symptom scales (dysphagia, eating restrictions, reflux, odynophagia, pain and discomfort, and anxiety), and 10 single items. Both HRQL questionnaires are validated for use in oesophageal cancer patients [14].

Endpoints

Primary endpoints; change in patient-reported dysphagia and pain at rest measured by the dysphagia grading scale and ESAS from inclusion to FU1. Three weeks after inclusion was selected as FU1 in order to capture the maximum toxicity after SEMS and to measure effect while the compliance still was sufficient in a patient group with high attrition due to death. Secondary endpoints; change in patient-reported dysphagia (dysphagia grading scale) and pain at rest (ESAS) at FU2. Patient-reported change in emotional function and global quality of life measured by EORTC QLQ-C30 and dysphagia and eating restrictions measured by EORTC QLQ-OG25 were assessed. Differences in treatment feasibility and patients' weight change from baseline to FU2 were also explored. Other PRO data are presented of descriptive purposes.

Statistical methods

Descriptive statistics are presented as means or medians with ranges as appropriate. Differences between groups were tested by Chi-square tests (linear-by-linear associations).

Survival was calculated as the number of days from randomisation to death or censored on 01.08.2012 if alive. Survival was estimated using the Kaplan–Meier method and comparison of the two treatment groups was done by the log rank test.

In a sample size calculation, it was estimated that 64 patients were needed to detect a difference in change of dysphagia at FU1. This was based on the assumption that the expected proportion of patients with improved dysphagia was 90% in arm A and 60% in arm B (significance level: 0.05, power 80%). However, the study was closed before the estimated number of patients was included due to slow patient recruitment. Based on the small number of patients, only a limited number of tests have been performed and caution has been taken not to make strong conclusions based on non-significant results.

Standard algorithms provided by the EORTC Quality of life group [15] were used. The patients answered scales with Likert type response categories ranging from 1 (not at all) to 4 (very much) or from 1 (very poor) to 7 (excellent) (global questions 29 and 30). All scores were linearly transformed to a 0–100 scale where a high score represents a high degree of function or a high degree of side effects/problems. For every scale, the mean value was calculated. Clinically significant response on an EORTC scale is defined as a change of $\geqslant 10$, while the situation is said to be unchanged if the change is <10 [16]. Missing items were handled according to the EORTC QLQ-C30 scoring manual [15]. ESAS had response scales ranging from no (0) to the worst possible (10) problems, and for each score a change of two steps was considered clinically significant.

Results

The baseline characteristics of the two treatment groups SEMS followed by brachytherapy (arm A) and brachytherapy alone (arm B), were similar for most variables (Table 1).

Primary and secondary PRO

Significantly more patients in arm A (12/17) than in arm B (7/18) reported improved dysphagia without a significant difference

Table 1
Patient characteristics at baseline.

		Total $n = 41$	Stent + brachytherapy $n = 21$	Brachytherapy alone $n = 20$
Age (years)	Mean (range)	74 (47–91)	73 (59–90)	74(47–91)
Sex	Male/female	26/15	13/8	13/7
Stage of disease	Local (T1-T3N0)	2	1	1
	Locally advanced (T1-T4N1/T4N0)	39	20	19
	Distant metastases (M1)	18	9	9
Tumour length (cm)	Mean (range)	7 (3–13)	8 (5–13)	7 (3–13)
Tumour localisation	Proximal 1/3	2	1	1
	Middle 1/3	11	5	6
	Lower 1/3	27	15	12
	Overlap middle – lower	1	0	1
Histology	Adenocarcinoma	25	12	13
	Squamous cell carcinoma	14	7	7
	Carcinoma, unclassified	2	2	0
State of disease	Primary disease	35	17	18
	Relapse/progression	6	4	2
WHO performance status	0/1	14	4	10
	2	23	14	9
	3/4	4	3	1
Weight loss	$\leqslant$5%	9	4	5
	>5%	30	16	14
	Missing	2	1	1
Analgesics	None	22	11	11
	Non-opioids only	8	2	6
	Opioids+/−non-opioids	11	8	3
Patient reported outcomes				
Dysphagia (grading scale)	Normal diet (0)	0	0	0
	Discomfort (1)	9	3	6
	Soft diet (2)	17	8	9
	Fluids only (3)	12	8	4
	Full stop (4)	3	2	1
Pain at rest (ESAS)	None (0)	26	13	13
	Mild (1–3)	11	6	5
	Moderate (4–6)	4	2	2
	Severe (7–10)	0	0	0

Table 2
Change in patient-reported dysphagia and pain from baseline to FU1 (week 3) and from baseline to FU2 (week 7).[a]

FU1 evaluation		Change score	Stent + brachytherapy $n = 17$	Brachytherapy alone $n = 18$	p-Value[b]
Dysphagia	Mean change (range)		1 (−1, 3)	0 (−1, 1)	
Proportion of patients	Improved	3	1/17	0/18	
		2	4/17	0/18	
		1	7/17	7/18	0.02
	Unchanged	0	4/17	9/18	
	Worse or always full stop	−1	1/17	2/18	
Pain	Mean change (range)		1 (0, 9)	1 (−2, 3)	
Proportion of patients	Improved		0/17	1/18	
	Always no pain		7/17	7/18	0.3
	Unchanged		6/17	5/18	
	Worse		4/17	5/18	
FU2 evaluation		Change score	Stent + brachytherapy $n = 9$	Brachytherapy alone $n = 12$	
Dysphagia	Mean change (range)		1 (−1, 3)	1 (0, 4)	
	Improved	1–3	7/9	10/12	
Proportion of patients	Unchanged	0	1/9	2/12	
	Worse or always full stop	−1	1/9	0/12	
Pain	Mean change (range)		2 (−1,8)	1 (−1,4)	
	Always no pain		2/9	4/12	
Proportion of patients	Improved		0/9	0/12	
	Unchanged		3/9	5/12	
	Worse		4/9	3/12	

[a] Different populations due to attrition.
[b] Linear-by linear association (2-sided).

in the proportion of patients with increased pain at FU1 (Table 2). At FU2, most evaluable patients in both groups reported improved dysphagia (17/21) (Table 2). A corresponding clinically significant improvement was found for aspects of HRQL connected to eating measured by EORTC QLQ-OG25 (dysphagia scale, eating restriction scale) (Supplementary Table). No significant differences were found between the treatment arms for the EORTC HRQL scales explored (emotional function, global quality of life, dysphagia and eating restrictions) Odynophagia, eating in front of others and dryness of the mouth improved while most of the other aspects of HRQL deteriorated or remained low (Supplementary Table).

Compliance and patient-reported dysphagia

The number of patients/of those alive, filling in questionnaires at FU1, FU2, Week 11 and week 15, were 35/37, 21/32, 16/24 and 13/19 respectively. Most patients (33/41) continued to fill in the questionnaires near up to (last or second last FU) the time of death, but the short survival resulted in rapid attrition of patients (Supplementary Figure).The majority of patients (10/13 at week 15) with initial relief of dysphagia continued to have the effect of treatment close until death.

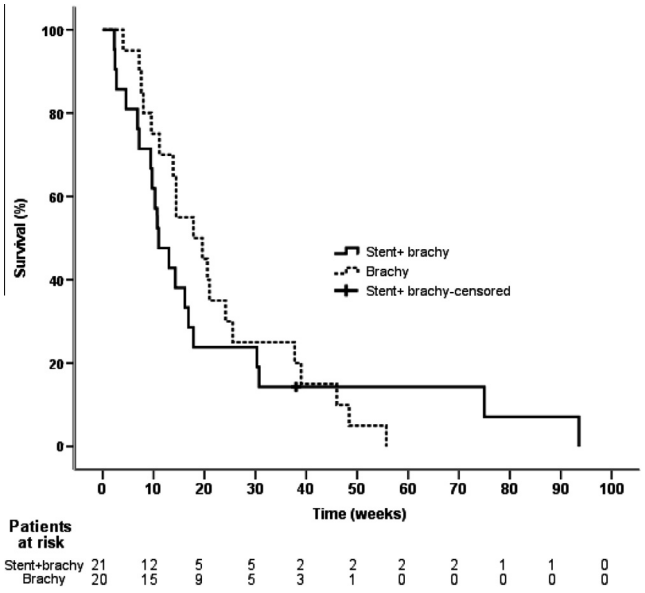

Fig. 2. Overall survival by treatment arm ($p = 0.6$).

Survival and treatment feasibility

Median survival was 14 weeks for the total group without statistical significant difference between patients in arm A (11 weeks) and arm B (18 weeks) (Fig. 2). One patient was alive and censored at the closure of study. All the others ($n = 40$) died of their index cancer.

The study treatment was completed by 34 patients; 15 in arm A and 19 in arm B (Fig. 1). Treatment was delayed for one patient due to fever and for three patients because of administrative reasons. Mean duration (range) of treatment was 20 days (14–24) for arm A and 14 days (11–20) for arm B. Half of the patients (17/34) completed the treatment as outpatients with three to four visits at the hospital. The procedure started after lunchtime and 10 patients had to stay overnight because of practical reasons.

Complications of treatment occurred in arm A only; aspiration pneumonia ($n = 2$), aspiration pneumonia and bleeding ($n = 1$) and stent dislocation during brachytherapy ($n = 1$). There were no perforation or fistula formations. All complications, except the stent dislocation, resulted in prolonged stay in hospital, but none were life-threatening and all were successfully treated. Symptoms at the end of treatment, (oesophagitis, heartburn, strictures, chest pain, nausea, vomiting, constipation, diarrhoea, cough and dyspnoea) were in general mild. However, 19 patients had grade 3 fatigue and 10 patients had grade 3 anorexia.

Clinical evaluation at FU2 and thereafter

More patients were available for the observer-rated evaluation ($n = 33$), than the patient-reported part ($n = 21$) of the study. Improved observer-rated dysphagia was found for 17 of the 33 patients while 13 patients were unchanged. Differences between groups were not observed. Chest pain increased from baseline for

13 patients, while five had less pain. All of them were treated with analgesics.

A large proportion of patients (23/33) had irreversibly reduced PS and 3/4 of the patients with PS 3 at baseline died before FU2. Body weight was available for 28 patients both at the baseline and FU2 and 16 had weight loss. Difference between the treatment arms was not seen.

Endoscopic evaluation at FU2 was performed in 14 patients in arm B; four of these were in need of SEMS. Another eight of the 20 patients in arm B, later received SEMS at median (range) 12 weeks (6–43) from the end of treatment. Eight patients never received a SEMS. In arm A, three patients needed a second SEMS, 12, 24 and 28 weeks after the end of treatment.

A total of 21 of the 33 patients did not need hospital admission between the end of treatment and FU2. After FU2, eight patients had no hospitalisation, seven had fewer than seven hospital days but six patients used more than ¼ of their remaining life time in hospital.

Discussion

This is the first randomised trial comparing SEMS followed by brachytherapy vs brachytherapy alone for relief of dysphagia in patients with oesophageal cancer. Such a trial has been asked for [17,18]. Despite reduced power in the study, a clinical and statistically significant difference between the arms was found for the primary endpoint in favour of SEMS followed by brachytherapy. We demonstrated that the immediate effect of SEMS could be combined with the more longstanding effect of brachytherapy. In accordance with others [17,19], we believe that this combination is feasible, safe and superior to brachytherapy alone in the initial relief of dysphagia. In accordance with these results, the clinical practise at our institution is now being changed.

Due to the toxicity of SEMS followed by brachytherapy, this treatment might be limited to patients who need immediate alleviation of dysphagia. The additional effect of SEMS was most prominent during the first weeks of treatment. For patients who are able to eat semi-solid food and can wait a few weeks for the effect, brachytherapy alone might be better. On the other hand, the five complications seen in four of the 21 patients in arm A had no serious implications.

It was reassuring that most patients living more than three months, had maintained improvement of dysphagia. The high proportion of patients in arm B later receiving a SEMS (12 of 20 patients) shows that brachytherapy alone has limitations. Therefore, regular clinical follow-ups are needed and patients with persistent or recurrent dysphagia should be offered a SEMS.

Median survival of our patients was shorter than in other brachytherapy trials [6,17] indicating that they had more advanced disease. Brachytherapy may be the treatment of choice for a larger group of patients with cancer of the oesophagus and dysphagia. In a trial published in 2010, brachytherapy (8 Gy × 2) followed by external radiotherapy (3 Gy × 10) was compared with brachytherapy alone (8 Gy × 2) [20]. The combination was superior in relief of dysphagia. The disadvantage of external radiotherapy is the length of the treatment period, and we are reluctant to believe that external radiotherapy is beneficial for patients with life-expectancy shorter than six months. We would rather suggest re-treatment of patients with persistent dysphagia due to tumour obstruction. Our patients spent a few days in hospital. A further reduction in treatment time by using a shorter brachytherapy schedule would be an advantage. Currently, there is no international consensus on the optimal fractionation. Two trials with a comparison of two fractionation regimens; 6 Gy × 3 vs 8 Gy × 2, showed similar efficacy in palliation of dysphagia [21,22]. The second regimen, shortened the time period by giving treatment on alternate days instead of weekly. Alternatively, single-dose brachytherapy, 12 Gy × 1, with one outpatient procedure, is efficient and safe [6,17]. The effect of fractionated brachytherapy vs single-dose brachytherapy has not been published [23].

It is difficult to distinguish between toxicity of treatment and symptoms of a progressive disease. Severe fatigue and appetite loss were frequently reported both at baseline and at the end of treatment. Many patients continued to lose weight despite relief of dysphagia and improved eating ability. The irreversibility of the weight loss, anorexia and fatigue suggest that these patients suffer from primary cachexia rather than undernutrition. Therefore, it is important to communicate to the patients that the planned treatment aims to relieve dysphagia, but will not necessarily improve weight loss, appetite or fatigue. Nevertheless, we believe that it is of value for the patients' general well-being to be able to swallow until death.

Corresponding results were found for HRQL. The improved aspects of HRQL were connected to eating while most of the other aspects of HRQL including anorexia and fatigue deteriorated irreversibly. This is in line with results found for similar patient groups [7,17].

In accordance with recommendations [24], predefined PRO was included both as primary and secondary endpoints. Survival was included as a secondary endpoint, in order not to miss a non-expected survival difference. A completed patient-questionnaire as one of the inclusion criteria ensured 100% compliance from start. Unfortunately, the rapid attrition of patients made it impossible to explore differences between groups over time.

The slow patient recruitment was due to more patients being treated at the radiotherapy units closer to home and reorganisation of our hospital. There was a shift in the multidisciplinary team's preference in favour of chemotherapy even though there are no publications comparing the effect of chemotherapy vs brachytherapy or other interventions for dysphagia [5]. A few phase II studies have reported relief of dysphagia after chemotherapy [25,26].

Conclusions

SEMS followed by brachytherapy is preferable and safe for patients in need of immediate alleviation of dysphagia. Brachytherapy with or without preceding SEMS provide relief of dysphagia within a few weeks. Improvement of aspects of HRQL not related to eating cannot be expected and patients should be informed thereof.

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2013.04.008.

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