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Jeene, P.M.; Vermeulen, B.D.; Rozema, T.; Braam, P.M.; Lips, I.; Muller, K.; ... ; POLDER Study Grp

ORIGINAL ARTICLE

Short-Course External Beam Radiotherapy Versus Brachytherapy for Palliation of Dysphagia in Esophageal Cancer: A Matched Comparison of Two Prospective Trials

Paul M. Jeene, MD,[a,f,*] Bram D. Vermeulen, MD,[b] Tom Rozema, MD,[c] Pètra M. Braam, MD, PhD,[d] Irene Lips, MD, PhD,[e] Karin Muller, MD, PhD,[f] Daphne van Kampen, MD,[g] Marjolein Y. V. Homs, MD, PhD,[h] Vera Oppedijk, MD,[i] Maaike Berbée, MD, PhD,[j] Peter S. N. van Rossum, MD, PhD,[k] Sherif el Sharouni, MD, PhD,[k] Peter D. Siersema, MD, PhD,[b] Maarten C. C. M. Hulshof, MD, PhD[a]; On behalf of the POLDER Study Group

[a]*Department of Radiation Oncology, Amsterdam University Medical Centers, Amsterdam, The Netherlands*
[b]*Department of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen, The Netherlands*
[c]*Instituut Verbeeten, Tilburg, The Netherlands*
[d]*Department of Radiotherapy, Radboud University Medical Center Nijmegen, The Netherlands*
[e]*Department of Radiotherapy, Leids University Medical Centre, Leiden, The Netherlands*
[f]*Radiotherapiegroep, Deventer, The Netherlands*
[g]*Zeeuws Radiotherapeutisch Instituut, Vlissingen, Roosendaal, The Netherlands*
[h]*Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands*
[i]*Radiotherapeutisch Instituut Friesland, Leeuwarden, The Netherlands*
[j]*MAASTRO Clinic Maastricht, GROW School for Oncology and Developmental Biology, Maastricht University Medical Centre, The Netherlands*
[k]*Department of Radiotherapy, University Medical Center Utrecht, Utrecht, The Netherlands*

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ABSTRACT

Introduction: Short-course external beam radiotherapy (EBRT) and intraluminal brachytherapy are both accepted treatments for the palliation of dysphagia in patients with incurable esophageal cancer. We compared the effects of both treatments from two prospective studies.

Methods: We performed a multicenter prospective cohort study of patients with metastasized or otherwise incurable esophageal cancer requiring palliation of dysphagia from September 2016 to March 2019. Patients were treated with EBRT in five fractions of 4 Gy. Data were compared with all patients treated with a single brachytherapy dose of 12 Gy in the SIREC (Stent or Intraluminal Radiotherapy for inoperable Esophageal Cancer) trial, both between the original cohorts and between 1:1 propensity score–matched cohorts. The primary end point was an improvement of dysphagia at 3 months without reintervention. The secondary end points included toxicity and time-to-effect.

Results: A total of 115 patients treated with EBRT and 93 patients who underwent brachytherapy were eligible for analysis. In the original cohorts, dysphagia improved after EBRT in 79% of patients compared with 64% after brachytherapy ($p = 0.058$). Propensity score matching resulted in 69 patients in each cohort well-balanced at baseline. Improvement of dysphagia was observed in 83% after EBRT versus 64% after brachytherapy ($p = 0.048$). In responding patients, improvement of dysphagia at 2 weeks was observed in 67% after EBRT compared with 35% after brachytherapy, and the maximum effect was reached after 4 weeks in 55% and 33%, respectively. Severe toxicity

***Corresponding author.**

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Address for correspondence: Paul M. Jeene, MD, Department of Radiation Oncology, Amsterdam University Medical Centers, Meibergdreef 9, B0-107, Amsterdam AZ 1105, The Netherlands. E-mail: p.m.jeene@amsterdamumc.nl

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occurred in 3% of patients after EBRT compared with 13% after brachytherapy.

Conclusions: Short-course EBRT appears at least as effective as brachytherapy in the palliation of dysphagia in patients with esophageal cancer.

Keywords: Dysphagia; Esophageal cancer; Palliation; Brachytherapy; External beam radiotherapy

Introduction

Annually, approximately 572,000 patients are diagnosed with esophageal cancer worldwide.[1] In the Netherlands, the overall 5-year survival is approximately 22%.[2] The poor prognosis is mainly the result of a high incidence of distant metastasis at the time of diagnosis. For incurable patients, palliation of symptoms is the key to maintaining an acceptable quality of life. The predominant debilitating symptom of an advanced esophageal tumor is dysphagia, with 80% to 90% of all patients experiencing difficulties with swallowing at some point during their clinical course.[3,4] With a median life expectancy between 4 and 10 months in these patients, palliative treatment should be short, rapidly effective, and minimally invasive.[5-7]

Different types of treatment are available for dysphagia relief, including stenting, laser therapy, external beam radiotherapy (EBRT), and intraluminal brachytherapy. Determining the optimal strategy for treating dysphagia remains a challenge, mainly owing to a lack of evidence regarding one modality over the other.[8] In the SIREC trial (Stent or Intraluminal Radiotherapy for inoperable Esophageal Cancer), patients were randomized between a single dose of 12 Gy brachytherapy and self-expanding metal stent placement.[9] Although the effect of brachytherapy was longer-lasting, patients who received a stent experienced a quicker relief in dysphagia; thus, the latter should be reserved for patients with very short life expectancy. Furthermore, a recent meta-analysis revealed that single-dose brachytherapy was superior to fractionated brachytherapy in terms of the onset of toxicity; although fractionated brachytherapy led to a higher cumulative dose and yielded improved dysphagia-free survival rates.[10] Given the results of these studies (among others), the European Society of Gastrointestinal Endoscopy and Dutch guidelines recommend stent placement for patients with a life expectancy of fewer than 3 months.[11,12] For patients with a relatively longer life expectancy, single-dose brachytherapy is recommended.

Despite these guidelines, a recent study revealed a wide variation in palliative treatment modalities in the Netherlands, with EBRT being used far more frequently than brachytherapy.[11,13] The authors stated that although clinical decision-making is largely based on patient-related and disease-related characteristics, it is also associated with the hospital of diagnosis.

Given the generally poor survival of these patients, treatment needs to be widely available and rapidly effective, with the burden of toxicity being minimal. Furthermore, the duration of the palliative effect should be long in relation to their prognosis. Therefore, a shortcourse EBRT should be preferred over a more fractionated course. The literature on the use of EBRT in the palliative setting is scarce. A few retrospective series reveal fairly good results with a wide range of radiotherapy schedules.[14,15] To date, no prospective data exists that evaluated the efficacy of short-course EBRT in the palliation of dysphagia. There is a surplus of evidence on the use of brachytherapy compared with the use of EBRT, yet EBRT is applied more often. Hence, a randomized study comparing both modalities would be desirable. However, owing to the paucity of the actual use of brachytherapy, a randomized trial between brachytherapy and EBRT is no longer considered feasible.

Therefore, we performed a multicenter prospective registration trial to investigate the effectiveness of EBRT in five fractions of 4 Gy. Inclusion criteria and end points were similar to those of the SIREC study, enabling a direct comparison with the original data from the brachytherapy results of the SIREC trial. We hypothesized that EBRT would be at least as effective as brachytherapy for palliation of dysphagia caused by incurable esophageal cancer.

Materials and Methods

We performed a nationwide, multicenter, prospective cohort study of patients with metastasized or otherwise incurable esophageal cancer requiring palliation of dysphagia (Netherlands Trial register NL7198). All patients were treated with EBRT in five fractions of 4 Gy. This cohort was compared with the patients in the SIREC trial who were treated with single-dose brachytherapy of 12 Gy. Details of the SIREC trial were reported previously.[9] The study was approved by the Medical Ethics Review Committee of the Academic Medical Center and the Institutional Review Boards of all participating centers. All participating patients provided written informed consent.

Study Population

Inclusion criteria were based on the inclusion of the SIREC study. Eligible for inclusion were patients with

metastatic esophageal cancer or patients who were no longer candidates for curative locoregional treatment and were being referred for radiotherapy to relieve dysphagia.

Dysphagia grade greater than or equal to 2 according to the Ogilvie scale was mandatory before the start of EBRT.[16] Histologic confirmation of a squamous cell carcinoma, adenocarcinoma, or large-cell undifferentiated carcinoma of the esophagus or esophagogastric junction was required. A computed tomography (CT) of the chest and abdomen not more than 3 months old had to be available. The maximum tumor length was set at 12 cm, and the extension into the cardia of the stomach had to be less than 5 cm. Exclusion criteria were the presence of an esophageal stent, (suspicion of) tumor growth into the tracheal lumen, a life expectancy of fewer than 3 months, previous esophagectomy, previous radiotherapy to the mediastinum to a radiobiologic equivalent dose of greater than 20 Gy, and chemotherapy administered from 1 week before EBRT to 1 week after radiotherapy.

Radiotherapy

EBRT was given with a dosage of 20 Gy in five fractions of 4 Gy. Radiation was delivered using a linear accelerator with a photon energy of 6 to 18 MV. The gross tumor volume (GTV) consisted of the primary tumor plus the direct adjacent pathologic lymph nodes that could be (partly) responsible for the obstructive effect. No elective volume was delineated. The clinical target volume (CTV) was defined as the GTV plus 1 cm in craniocaudal direction and 0.5 cm in a lateral and anteroposterior direction. If organs at risk were not involved in the tumor process, they were excluded from the CTV. The planning target volume (PTV) was CTV plus 1 cm in all directions. In the case of online cone-beam CT-verification, a reduction in CTV-PTV margin was allowed on the basis of local practice. The radiation therapy required at least a three-dimensional planning technique. The prescription dose was defined according to the International Commission on Radiation Units and Measurements 83 criteria.[17] If lung tissue was overlapping with the PTV, an 85% isodose coverage in that area was accepted. Brachytherapy was prescribed as a single dose of 12 Gy at 1 cm from the source axis of the applicator. The standard active length of the application was the tumor length plus 2 cm extra at both ends of the tumor.[9]

Outcome Measures

The primary end point was an improvement of dysphagia score at 3 months without reintervention according to the Ogilvie score by greater than or equal to one point.[16] Dysphagia was scored as follows: score 0, ability to eat a normal diet; score 1, ability to eat some solid food; score 2, ability to eat some semisolids only; score 3, ability to swallow liquids only; and score 4, complete obstruction.

The secondary end points were time to maximum effect, duration of dysphagia relief, and overall survival (OS). The first improvement of dysphagia and time to the maximum effect was assessed at 2 weeks, 1 month, 2 months, and 3 months after treatment. Subgroup analyses were performed for the effectiveness of EBRT on the basis of histology or baseline dysphagia score. Survival was calculated from the first day of radiotherapy until death. Toxicity greater than or equal to grade 3 according to Common Terminology Criteria for Adverse Event version 4.0 was scored for each patient. The progression of dysphagia for which reintervention was indicated was considered as treatment failure.

Follow-Up

Baseline characteristics, including dysphagia scores, were retrieved before the start of the study. In the EBRT cohort, patients received a diary in which they scored dysphagia every week until the first 8 weeks after treatment. Diaries were retrieved by the investigators after 3 months. Follow-up was mandatory at 3, 6, 9, and 12 months after treatment. Follow-up by telephone was permitted if a hospital visit was no longer possible. In the brachytherapy cohort, patients were prospectively followed up by home visits by one of six specially trained research nurses at 14 days, 1 month, and then monthly until 1 year after treatment. Patients received a diary in which they scored dysphagia every day for 1 month and every week thereafter. Toxicity and reinterventions were scored at each visit. A reintervention for dysphagia was considered as a study end point, after which no further dysphagia was registered.

Statistical Analysis

In univariable analyses, we used the chi-square test and t test to assess baseline and outcome differences between patient groups in categorical and continuous data, respectively. Survival was calculated from the date of the first radiotherapy to the date of death or last follow-up, plotted using Kaplan-Meier curves and compared using a log-rank test.

We used propensity score matching to adjust for imbalances in baseline characteristics between the two groups. A propensity score was generated using logistic regression on the basis of the covariates age, sex, WHO performance score greater than or equal to 2, previous chemotherapy, tumor characteristics (histology, tumor location, and tumor length), and reason for palliation (i.e., metastasized or inoperable esophageal cancer).

Subsequently, nearest neighbor matching without replacement (1:1) was performed to generate matched pairs of cases in which the within-pair difference was minimized by setting a caliper of 0.1 of the SD of the logit of the propensity score.

The primary and secondary outcomes were compared both between the original (nonmatched) cohorts and between the propensity score–matched cohorts.

A two-tailed p value of less than 0.05 was considered significant in all statistical analyses. SPSS version 25.0 (IBM Corp, IBM SPSS Statistics for Windows, Armonk, NY) was used for study analyses.

Results

A total of 124 patients were included in the EBRT group. Data were compared with all 101 patients randomized to brachytherapy in the SIREC trial (Fig. 1). At the time of analyses, all patients treated with brachytherapy, and 95 of patients treated with EBRT had died. A minimum follow-up of 5 months was available for all patients.

Patient- and tumor-related characteristics were comparable between the two groups (Table 1). Mean tumor length was larger in the brachytherapy cohort than the EBRT cohort (7.4 versus 5.9 cm, respectively, $p < 0.001$). In the brachytherapy group, 14% of patients had involvement of the esophagogastric junction versus 34% in the EBRT group ($p = 0.001$). WHO performance status was generally higher in the brachytherapy group than in the EBRT group. However, WHO performance status greater than or equal to 2 was comparable with 29% versus 31%, respectively ($p = 0.73$). After propensity score matching, 138 patients (69 in each group) were selected for comparative analyses. No significant differences in baseline characteristics remained.

Improvement in Dysphagia Score

In the original cohorts, 55 patients (59%) in the brachytherapy group were available for analyses of the primary end point at 3 months and 67 patients (58%) in the EBRT group (Fig. 1). Improvement in dysphagia by greater than or equal to one point after 3 months occurred in 35 patients (64%) after brachytherapy and

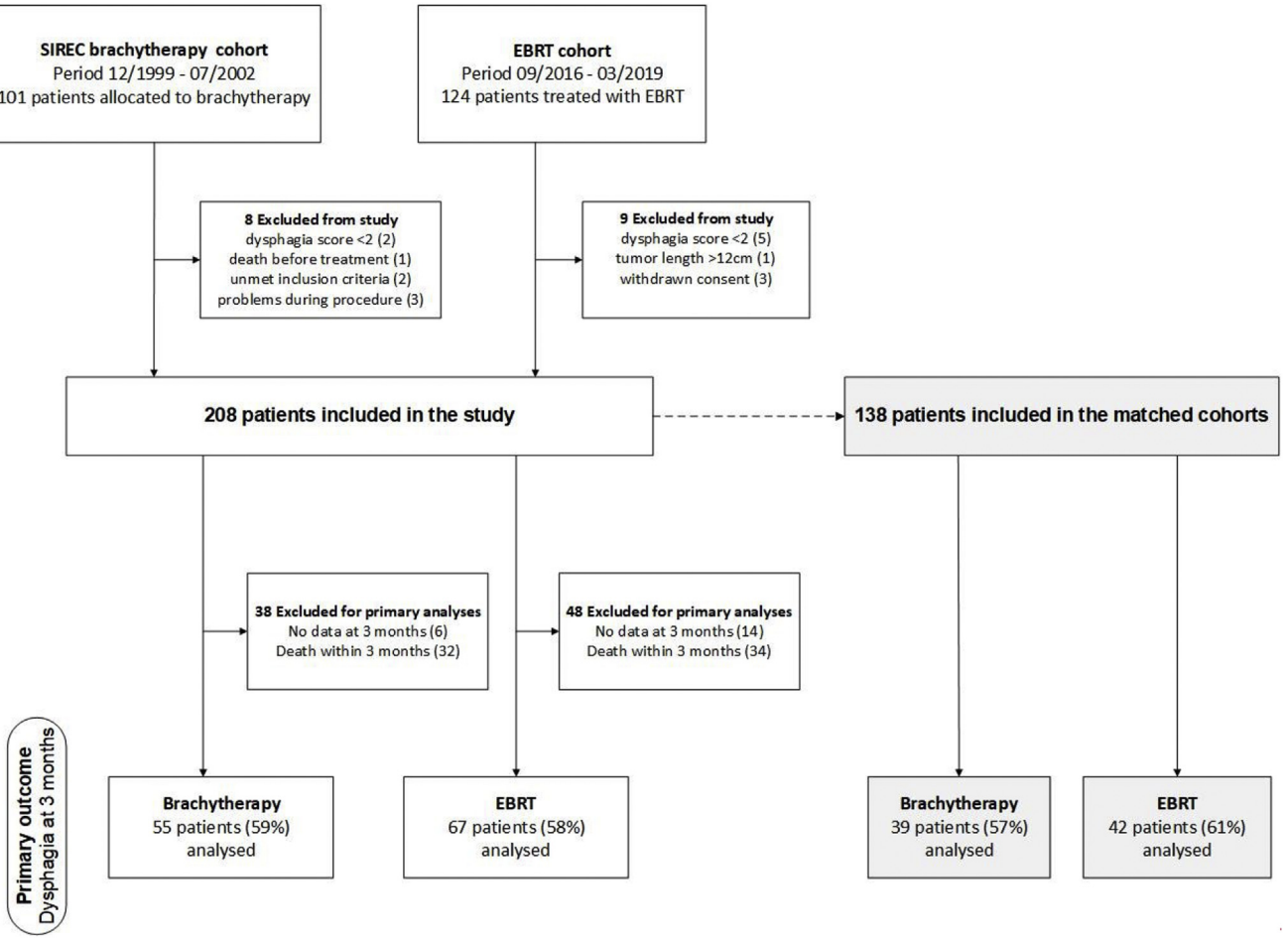

Figure 1. Study profile. EBRT, external beam radiotherapy; SIREC, Stent or Intraluminal Radiotherapy for inoperable Esophageal Cancer.

Table 1. Baseline Characteristics of Original Cohorts and After Propensity Score Matching

	Original Cohorts			Matched Cohorts		
	Brachytherapy (n = 93)	EBRT (n = 115)	*p* Value	Brachytherapy (n = 69)	EBRT (n = 69)	*p* Value
Age, y (mean ± SD)	69 (12)	72 (9)	0.038	70 (13)	70 (9)	0.84
Male sex, n (%)	69 (74)	91 (79)	0.40	50 (73)	52 (75)	0.70
Tumor type, n (%)			0.10			0.75
Adenocarcinoma	63 (68)	91 (80)		47 (68)	51 (74)	
Squamous cell carcinoma	27 (29)	22 (19)		21 (30)	17 (25)	
Other	3 (3)	1 (1)		1 (1)	1 (1)	
Tumor length, cm (mean ± SD)	7.4 (2.5)	5.9 (2.7)	**<0.001**[a]	6.8 (2.5)	6.5 (2.5)	0.46
Tumor location, n (%)			**0.001**[a]			0.83
Esophagus	80 (86)	76 (66)		56 (81)	57 (83)	
Esophagogastric junction	13 (14)	39 (34)		13 (19)	12 (17)	
Reason for palliative treatment, n (%)			0.09			0.37
Metastases	72 (77)	97 (87)		55 (80)	59 (86)	
Inoperable	21 (23)	15 (13)		14 (20)	10 (14)	
Previous chemotherapy, n (%)	11 (12)	8 (7)	0.26	7 (10)	6 (9)	0.81
WHO performance, n (%)			**<0.001**[a]			**0.038**[a]
0	31 (34)	16 (15)		21(30)	12 (17)	
1	34 (37)	58 (54)		28(41)	38 (55)	
2	16 (18)	30 (28)		12(17)	17 (25)	
3	10 (11)	3 (3)		8(12)	2 (3)	
WHO performance WHO, n (%)			0.73			0.85
0-1	65 (71)	74 (69)		49 (71)	50 (72)	
≥2	26 (29)	33 (31)		20 (29)	19 (28)	
Dysphagia score before treatment, n (%)			0.36			0.14
2	38 (41)	56 (49)		26 (38)	36 (52)	
3	36 (39)	42 (37)		28 (40)	25 (36)	
4	19 (20)	16 (14)		15 (22)	8 (12)	
Dysphagia score at 3 mo available, n (%)	55 (59)	67 (58)	0.99	39 (57)	42 (61)	0.73

[a]Statistically significant.
EBRT, external beam radiotherapy.

in 53 patients (79%) after EBRT ($p = 0.058$). In the matched cohorts, 39 patients (57%) in the brachytherapy group were available for analyses of the primary end point at 3 months and 42 patients (61%) in the EBRT group ($p = 0.73$). Improvement of dysphagia greater than or equal to one point after 3 months occurred significantly more frequently in the EBRT group than the brachytherapy group (83% versus 64%, respectively; $p = 0.048$).

In the original cohorts, time to the improvement of at least one point and time to maximum effect was significantly shorter after EBRT than brachytherapy. In the patients treated with EBRT, the first improvement of dysphagia was observed after 2 weeks in 67% compared with 36% after brachytherapy, and 87% versus 60%, respectively at 4 weeks ($p = 0.01$, Fig. 2). More than half of patients (55%) with an improvement of dysphagia reached their maximum effect within 4 weeks after EBRT compared with 33% after brachytherapy ($p = 0.021$, Fig. 3).

Duration of Effect

Persistent improvement of dysphagia was analyzed in the original cohorts. At 6 months after treatment, persistent improvement of dysphagia was present in 27 of 38 surviving patients in the brachytherapy group compared with 18 of 28 surviving patients in the EBRT group ($p = 0.56$). At 9 months after treatment, these numbers were 16 of 22 versus 10 of 13 patients, respectively ($p = 0.78$).

Survival

On comparison of the original cohorts, median OS was 5.1 months in the brachytherapy group (95% confidence interval [CI]: 3.9–6.3 mo) and 4.4 months in the EBRT group (95% CI: 2.8–6.0 mo, $p = 0.8$) (Fig. 4).

After matching, OS was 4.8 months in the brachytherapy group (95% CI: 3.2–6.5 mo) and 5.3 months in the EBRT group (95% CI: 3.1–7.5 mo, $p = 0.25$).

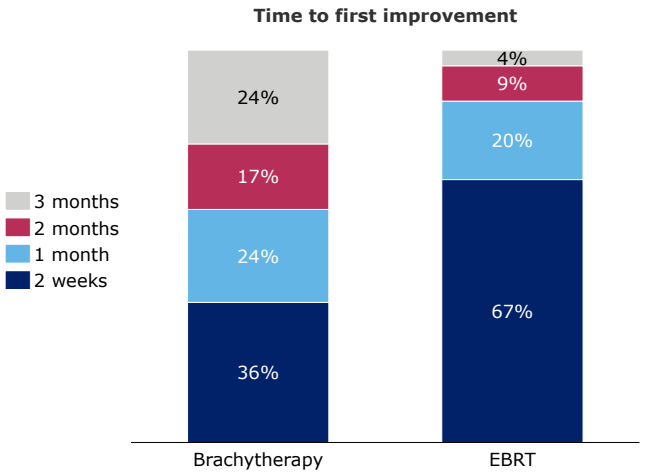

Figure 2. Time to improvement of dysphagia by at least one point after treatment. Results are revealed in percentages for patients with improvement of dysphagia and available data at 3 months after treatment. EBRT, external beam radiotherapy.

Reinterventions

In the original cohorts, similar reintervention rates for dysphagia were observed between the brachytherapy and EBRT groups (28% versus 25%, $p = 0.61$). Median time to reintervention was 3.2 months in the brachytherapy group (95% CI: 0.5–5.9 mo) compared with 3.7 months (95% CI: 2.5–5.0 mo) in the EBRT group ($p = 0.78$), and after matching, 3.2 months (95% CI: 0.23–6.1 mo) versus 4.6 months (95% CI: 1.7–7.4 mo), respectively ($p = 0.26$). Reinterventions after brachytherapy included stent placement (73%), repeated brachytherapy (12%), or removal of food impaction (12%). After EBRT, reinterventions included stent placement (54%) or repeated EBRT (35%).

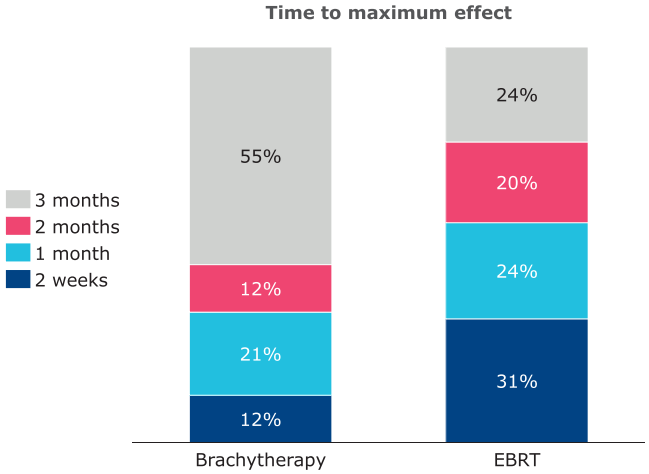

Figure 3. Time to maximum improvement of dysphagia after treatment. Results are revealed in percentages for patients with improvement of dysphagia and available data at 3 months after treatment. EBRT, external beam radiotherapy.

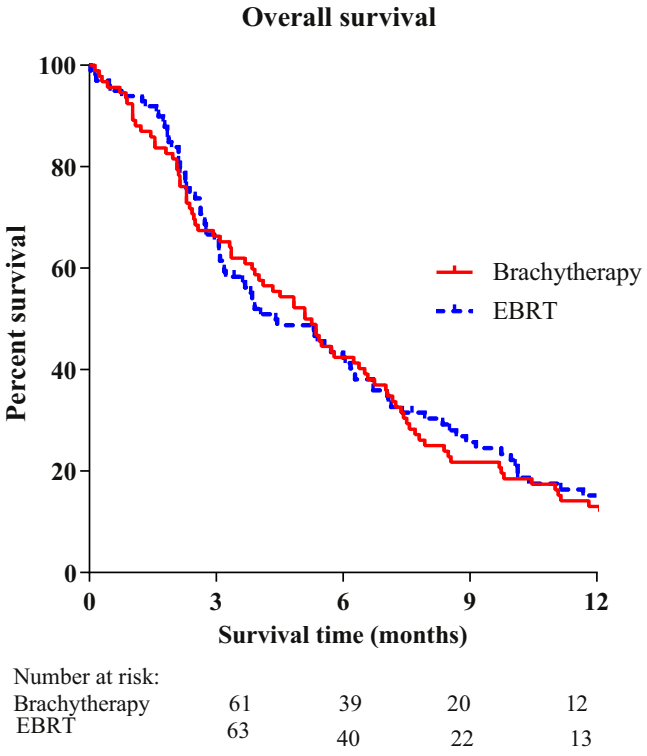

Figure 4. Overall survival according to treatment group. EBRT, external beam radiotherapy.

Toxicity

In the original cohorts, grade greater than or equal to 3 toxicity after EBRT occurred in 3% of patients. At 3 months, one patient (1%) experienced grade 3 pneumonia, one patient (1%) experienced grade 3 radiation-induced esophagitis, and one patient (1%) developed a fistula 5 months after treatment. One patient (1%) had grade 3 gastrointestinal toxicity 6 months after treatment but was also treated with systemic therapy at that time. Grade greater than or equal to 3 toxicity occurred in 13% of patients after brachytherapy, as reported previously.[9]

Subgroup Receiving EBRT

In the original cohort of patients treated with EBRT, we determined the effect of histology. For patients with adenocarcinoma, improvement of dysphagia of greater than or equal to one point after 3 months occurred in 82%, whereas for patients with a squamous cell carcinoma, 64% ($p = 0.30$). When patients were analyzed in subgroups on the basis of dysphagia score before treatment, response rates were 74%, 89%, and 83% for patients with dysphagia scores 2, 3, and 4, respectively ($p = 0.43$).

Discussion

Dysphagia is the most frequent symptom in patients with metastasized or otherwise incurable esophageal cancer. We compared the effect of EBRT and brachytherapy for improvement of dysphagia greater than or equal to one point at 3 months. Brachytherapy was effective in 64% of patients compared with 79% after EBRT ($p = 0.058$). After propensity score matching, improvement of dysphagia occurred in 64% after brachytherapy and in 83% patients after EBRT ($p = 0.048$). Dysphagia also improved more rapidly after EBRT than after brachytherapy. Thus, short-course EBRT appears at least as effective as brachytherapy in the palliation of dysphagia in patients with esophageal cancer.

The likelihood of improvement of dysphagia after EBRT was not dependent on the severity of dysphagia at presentation. More specifically, patients with a dysphagia score of 4 (complete obstruction) had similar effects compared with patients with a lower dysphagia score before treatment. This in contrast to patients treated with brachytherapy, in whom an initial dysphagia score of 4 was prognostically unfavorable, as reported previously.[18] However, as numbers are very small for these subgroups, no definitive conclusions should be drawn other than the finding that EBRT seems to be also indicated in this subgroup. We found no difference in effect between adenocarcinoma and squamous cell carcinoma, suggesting that histology should not influence the choice for EBRT.

Reported toxicity in brachytherapy was higher than the EBRT group. In the SIREC trial, grade greater than or equal to 3 complications were observed in 13%.[9] A recent meta-analysis found severe adverse events in 23% of treated patients, mostly including brachytherapy-related stenosis (12%) and fistula formation (8%).[10] The higher reported toxicity in the brachytherapy series might be explained by the much higher dose at the esophageal mucosa. The biologically equivalent dose at the reference point is fairly similar between five times 4 Gy and a single dose of 12 Gy.[19,20] However, the dose distribution in brachytherapy is very inhomogeneous. A dose of nearly 200% of the prescribed dose is delivered at the surface of the esophageal wall, dropping to 100% at 5 mm into the esophageal wall, and to less than 50% at 20 mm. Thus, a tumor with a thickness of more than 1 cm will be underdosed in the deeper parts. As this is a fundamental aspect of intraluminal brachytherapy more modern brachytherapy techniques using advanced image guidance cannot compensate for this effect. In contrast, EBRT has a very homogeneous dose distribution over the GTV, with the target volume received between 95% and 107% of the prescribed dose.[17] We speculate that the superior effect of EBRT can well be explained by a better dose coverage of the entire tumor compared to brachytherapy. The higher dose in the mucosa when using brachytherapy might also be a cause of more edema resulting in prolonged dysphagia.

In our study, a short-course EBRT regimen was chosen to minimize the patient burden. Murray et al.[15] retrospectively analyzed 148 patients who had been treated with palliative radiotherapy for esophageal cancer, mostly with five fractions of 4 Gy. Most patients had dysphagia (93%). Response was defined as any degree of patient-reported improvement of dysphagia at 4 to 6 weeks after completion of radiotherapy or thereafter. In line with our results, they found an improvement of dysphagia in 75% of patients, and toxicities were mild with a total grade 3 toxicity rate of only 3%. No grade 4 or 5 toxicities were seen. A recent retrospective study investigated the effect of EBRT up to total doses of 20, 30, or 39 Gy. The authors observed improvement of symptoms in 72% of patients without differences between radiotherapy schedules.[14] A phase I–II study from 2008, using 40 Gy in 20 fractions with two fractions per day, reported a response rate of 69% in dysphagia relief with a median response duration of 5.5 months.[21]Similar results were found by others after 30 to 35 Gy in 10 to 15 fractions.[22,23] Taken together, a short-course of EBRT seems equally effective as a more protracted course and is, therefore, preferable.

Logistics for EBRT are generally more convenient than for brachytherapy. EBRT can be applied at every normally equipped radiation department, whereas brachytherapy requires special equipment and treatment rooms, and also educated personnel for proper monitoring of the patient in case of mild sedation. The procedure requires the presence of a gastroenterologist, a radiation oncologist, an imaging technician, and staff for anesthesia and endoscopy assistance all at the same time. These logistics can be challenging, often causing a delay in the start of treatment. In contrast, EBRT requires a planning-CT scan and five brief (10 min) timeslots on a linear accelerator, does not require the presence of a radiation oncologist, and is regular treatment at a radiation oncology department. However, EBRT requires five visits to the clinic, whereas brachytherapy can be administered in only 1 day.

The main strengths of our study are the following: (1) the prospective multicenter design of both compared studies, (2) the treatment being uniform within each treatment group, and (3) the similar inclusion criteria for both treatment groups. Patients treated with brachytherapy were treated 15 years before those treated with EBRT; hence, we cannot exclude the possibility that this affected the results. However, OS was similar between

groups and, in general, has not substantially improved in this period for these patients.[2] To compensate for possible differences, propensity score matching was performed to further create comparable groups. However, it is not a randomized study, and the effects of differences in diagnosis, staging, and treatment have undeniably evolved over the past 15 years. Therefore, bias through potential unknown confounders cannot be excluded.

Conclusions

On the basis of this matched analysis of two prospective studies, short-course EBRT appears at least as effective as brachytherapy in the palliation of dysphagia in esophageal cancer. Dysphagia improved more often and more rapidly after EBRT than after brachytherapy. Considering the limited toxicity and advantages in logistics, EBRT should be the preferred treatment for the relief of dysphagia. This is true for both adenocarcinoma and squamous cell carcinoma, and also for all grades of dysphagia.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394–424.
2. van Putten M, de Vos-Geelen J, Nieuwenhuijzen GAP, et al. Long-term survival improvement in esophageal cancer in the Netherlands. *Eur J Cancer*. 2018;94:138–147.
3. Dai Y, Li C, Xie Y, et al. Interventions for dysphagia in esophageal cancer. *Cochrane Database Syst Rev*. 2014;10:CD005048.
4. Watkinson AF, Ellul J, Entwisle K, Mason RC, Adam A. Esophageal carcinoma: initial results of palliative treatment with covered self-expanding endoprostheses. *Radiology*. 1995;195:821–827.
5. Frenken M. Best palliation in esophageal cancer: surgery, stenting, radiation, or what? *Dis Esophagus*. 2001;14:120–123.
6. Hanna WC, Sudarshan M, Roberge D, et al. What is the optimal management of dysphagia in metastatic esophageal cancer? *Curr Oncol*. 2012;19:e60–e66.
7. Vermeulen BD, Jeene PM, Sijben J, et al. Low dose versus high dose radiotherapy for the palliation of dysphagia from esophageal cancer: a multicenter retrospective cohort study [e-pub ahead of print]. *Pract Radiat Oncol*. https://doi.org/10.1016/j.prro.2019.10.010. Accessed June 8, 2020.
8. van der Bogt RD, Vermeulen BD, Reijm AN, Siersema PD, Spaander MCW. Palliation of dysphagia. *Best Pract Res Clin Gastroenterol*. 2018;36–37:97–103.
9. Homs MY, Steyerberg EW, Eijkenboom WM, et al. Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from esophageal cancer: multicenter randomised trial. *Lancet*. 2004;364:1497–1504.
10. Fuccio L, Mandolesi D, Farioli A, et al. Brachytherapy for the palliation of dysphagia owing to esophageal cancer: a systematic review and meta-analysis of prospective studies. *Radiother Oncol*. 2017;122:332–339.
11. Dutch National Guidelines Esophageal Cancer. www.oncoline.nl/oesofaguscarcinoom. Accessed June 8, 2020.
12. Spaander M, Baron T, Siersema P, et al. Esophageal stenting for benign and malignant disease: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy*. 2016;48:939–948.
13. Opstelten JL, de Wijkerslooth LRH, Leenders M, et al. Variation in palliative care of esophageal cancer in clinical practice: factors associated with treatment decisions. *Dis Esophagus*. 2016;30:1–7.
14. Walterbos NR, Fiocco M, Neelis KJ, et al. Effectiveness of several external beam radiotherapy schedules for palliation of esophageal cancer. *Clin Transl Radiat Oncol*. 2019;17:24–31.
15. Murray LJ, Din OS, Kumar VS, Dixon LM, Wadsley JC. Palliative radiotherapy in patients with esophageal carcinoma: a retrospective review. *Pract Radiat Oncol*. 2012;2:257–264.
16. Ogilvie AL, Dronfield MW, Ferguson R, Atkinson M. Palliative intubation of esophagogastric neoplasms at fibreoptic endoscopy. *Gut*. 1982;23:1060–1067.
17. The International Commission on Radiation Units and Measurements. *J ICRU*. 2010;10:1–2.
18. Homs MYV, Steyerberg EW, Eijkenboom WMH, Siersema PD, Dutch SIREC Study Group. Predictors of outcome of single-dose brachytherapy for the palliation of dysphagia from esophageal cancer. *Brachytherapy*. 2006;5:41–48.
19. Barendsen GW. Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. *Int J Radiat Oncol Biol Phys*. 1982;8:1981–1997.
20. van Leeuwen CM, Oei AL, Crezee J, et al. The alfa and beta of tumours: a review of parameters of the linear-quadratic model, derived from clinical radiotherapy studies. *Radiat Oncol*. 2018;13:96.
21. Kassam Z, Wong RKS, Ringash J, et al. A phase I/II study to evaluate the toxicity and efficacy of accelerated fractionation radiotherapy for the palliation of dysphagia from carcinoma of the oesophagus. *Clin oncol (R Coll Radiol)*. 2008;20:53–60.
22. Penniment MG, De Ieso PB, Harvey JA, et al. Palliative chemoradiotherapy versus radiotherapy alone for dysphagia in advanced esophageal cancer: a multicenter randomised controlled trial (TROG 03.01). *Lancet Gastroenterol Hepatol*. 2018;3:114–124.
23. Suzuki G, Yamazaki H, Aibe N, et al. Palliative radiotherapy in the local management of stage IVB esophageal cancer: factors affecting swallowing and survival. *Anticancer Res*. 2017;37:3085–3092.