Original Article

Patient-reported outcomes after external beam radiotherapy versus brachytherapy for palliation of dysphagia in esophageal cancer: A matched comparison of two prospective trials

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ABSTRACT

Background and purpose: A matched comparison of external beam radiotherapy (EBRT) versus brachytherapy recently demonstrated that EBRT appears at least as effective for palliating dysphagia in patients with incurable esophageal cancer. The aim of this analysis was to compare patient-reported outcomes (PROs) after EBRT versus brachytherapy.

Materials and methods: In a multicenter prospective cohort study, patients with incurable esophageal cancer requiring palliation of dysphagia were included to undergo EBRT (20 Gy in 5 fractions). This EBRT cohort was compared to the single-dose 12 Gy brachytherapy cohort of the previously reported SIREC-trial. Propensity score matching was applied to adjust for baseline imbalances. The primary endpoint of dysphagia improvement was reported previously. PROs were secondary outcomes and assessed at baseline and 3 months after treatment using EORTC QLQ-C30 and QLQ-OES18 questionnaires.

Results: A total of 115 enrolled EBRT patients and 93 brachytherapy patients were eligible. After matching, 69 well-balanced pairs remained. At follow-up, significant deteriorations in functioning (i.e. physical, role, social), pain, appetite loss, and trouble with taste were observed after brachytherapy. In the EBRT group, such deterioration was observed only for role functioning, while significant improvements in trouble with eating and pain were found. Between-group comparison showed mostly comparable PRO changes, but significantly favored EBRT with regard to nausea, vomiting, pain, and appetite loss.

Conclusion: Short course EBRT results in similar or better PROs at 3 months after treatment compared to single-dose brachytherapy for the palliation of malignant dysphagia. These findings further support its use and inclusion in clinical practice guidelines.

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The predominant debilitating symptom in patients with incurable esophageal cancer is dysphagia, occurring in 80–90% of all patients at some moment during the disease course [1]. Palliative treatment options aiming at dysphagia relief include stent placement, intraluminal brachytherapy, and external beam radiotherapy (EBRT) [2]. Due to a lack of strong evidence regarding one modality over the other, individual determination of the optimal approach for managing dysphagia remains challenging [3]. The landmark 'Stent or Intraluminal Radiotherapy for inoperable Esophageal Cancer' (SIREC) randomized controlled trial (RCT), published in 2004 and including 209 patients, compared self-expanding metal stent (SEMS) placement with a single-dose of 12 Gy brachytherapy [4]. Although dysphagia improved more rapidly after SEMS placement, this difference in efficacy diminished gradually over time and brachytherapy provided superior dysphagia relief after 3 months follow-up [4]. Moreover, brachytherapy was associated with a slight benefit in patient-reported outcomes (PROs) after 3 months and fewer major complications compared to SEMS placement [5,6]. Accordingly, the

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European Society of Gastrointestinal Endoscopy (ESGE) as well as the Dutch national guidelines recommend SEMS placement for patients with a life-expectancy <3 months, and single-dose brachytherapy for patients with a longer life-expectancy [7,8].

Despite the favorable evidence and recommendations for brachytherapy, multiple factors, such as fear of complications, limited expertise, and lack of availability in many countries [9–11], have limited widespread implementation. In fact, short course EBRT has been the most commonly applied treatment strategy in the Netherlands and other countries, possibly because it offers substantial logistical advantages [12]. Our recent 'Palliation of Obstructive Local Disease of the Esophagus by Radiotherapy' (POLDER) study comparing EBRT with brachytherapy using data from a contemporary prospective EBRT cohort and the brachytherapy-arm of the SIREC study was the first study to present prospective data on EBRT in this setting [13]. The 1:1 propensity score-matched analysis in 138 patients demonstrated that EBRT was at least as effective as brachytherapy with regard to the primary outcome measure of dysphagia improvement (83% after EBRT versus 64% after brachytherapy, p = 0.048) [13]. Also, severe toxicity was less and overall survival was not compromised after EBRT compared to brachytherapy [13].

Dysphagia, overall survival and toxicity are important efficacy and safety endpoints, but these endpoints are not the only measure of benefit. Patient-reported outcomes, reflecting patients' perspective on their symptoms, functioning, and health-related quality of life, provide important complementary information. Patient-centric approaches to evaluate treatment strategies is fundamental in the definition of value-based health care [14], as prioritized by ESTRO in the Vision 2030 statement [15]. Therefore, the aim of the current analysis was to evaluate the secondary endpoint of PROs between short course EBRT and brachytherapy for palliation of dysphagia in patients with incurable esophageal cancer.

Materials and methods

The SIREC trial was a multicenter RCT conducted at 9 treatment centers in the Netherlands and compared brachytherapy to SEMS placement in a 1:1 randomized fashion. The details of the SIREC trial were described previously [4]. POLDER was a contemporary multicenter prospective cohort study including patients with metastatic or otherwise incurable esophageal cancer requiring palliation of dysphagia (Netherlands Trial Register NL7198). This was a nationwide study, conducted at 10 cancer treatment centers in the Netherlands. All patients underwent EBRT in 5 fractions of 4 Gy to a total dose of 20 Gy. The POLDER cohort was compared to the individual data of the patients from the SIREC trial who received single-dose 12 Gy brachytherapy. Institutional review board approval was obtained in all participating centers and all patients provided written informed consent.

Study population

Patient eligibility criteria for POLDER were based on the SIREC trial and included incurable esophageal or esophagogastric junction cancer patients, i.e. with distant metastases or otherwise not suitable for locoregional treatment with curative intent, who were referred for radiotherapy to relieve dysphagia. Other inclusion criteria included a dysphagia score of 2–4 (i.e. ability to eat some semisolids only to complete obstruction [16]), histological confirmation of the tumor, availability of a CT scan of chest and abdomen <3 months old, a maximum tumor length of 12 cm, and an extension into the gastric cardia of <5 cm. Ineligibility criteria included a life-expectancy of <3 months, (suspicion of) tumor growth into the tracheal lumen, presence of an esophageal stent, prior esophagec-

tomy, prior mediastinal radiotherapy (to a radiobiological equivalent dose of >20 Gy), and administered chemotherapy from 1 week before EBRT to 1 week after EBRT.

Interventions

The EBRT was delivered to the primary tumor plus directly adjacent pathologic lymph nodes (that could contribute to the obstruction) using a linear accelerator with 6–18 MV photon energy beams. The planning technique was either 3D-conformal radiotherapy or intensity-modulated radiotherapy (IMRT). Details on definitions of the target volumes, organ-at-risk dose constraints, and position verification protocols were reported previously [13]. Intraluminal brachytherapy was performed by passing a flexible applicator with a diameter of 10 mm down the esophagus. A single dose of 12 Gy was prescribed at 1 cm from the source axis of the applicator, with a standard active application length including the tumor length plus 2 cm at the proximal and distal ends of the tumor. Further details on the brachytherapy procedure were reported previously [4].

Outcome assessment

The primary endpoint of the POLDER study was dysphagia improvement at 3 months. Secondary endpoints included time to maximum dysphagia palliation, duration of dysphagia palliation, toxicity, and PROs. The current analysis represents the report on the prespecified secondary endpoint PROs. PROs were assessed with paper-based questionnaires at the time of study inclusion (before treatment) and 3 months after completion of treatment. Symptoms, functioning, and global health status were evaluated with two questionnaires that were developed by the EORTC: the Quality of Life Questionnaire-Core 30 (QLQ-C30) version 3, and its esophageal cancer module, the Quality of Life Questionnaire-OESophageal cancer 18 (QLQ-OES18). In the SIREC study, patients were prospectively followed up by home visits by specially trained research nurses at 14 days, 1 month, and then monthly until 1 year after treatment. EORTC QLQ-C30 and QLQ-OES23 questionnaires assessing PROs were completed on the day of treatment and at every home visit. For the purpose of the current study QLQ-OES23 was reduced to the module of 18 items (EORTC QLQ-OES18) in accordance with EORTC recommendations [17]. One other questionnaire (EuroQol-5D) of the SIREC study was not used in the POLDER study, and therefore omitted in the current comparative study.

The EORTC QLQ-C30 is a 30-item core questionnaire consisting of 1 multiple-item global health status scale, 5 multiple-item functioning scales (i.e. physical, role, social, cognitive, emotional), 3 multiple-item symptom scales (i.e. fatigue, pain, and nausea or vomiting), and 6 single-item measures for dyspnea, loss of appetite, insomnia, constipation, diarrhea, and perceived financial difficulties [18]. The complementary EORTC QLQ-OES18 module focuses on symptoms associated with esophageal cancer and its treatment. The questionnaire consists of 1 multiple-item functional scale (i.e. dysphagia), 3 multiple-team symptom scales (i.e. trouble with eating, reflux, pain), and 6 single-item measures for trouble swallowing saliva, choked when swallowing, dry mouth, trouble with taste, trouble with coughing, and trouble with talking [17].

Statistical analysis

As described in the previous report on the efficacy and safety endpoints [13], propensity score matching was applied to adjust for imbalances in baseline characteristics between the two groups. A logistic regression model was performed to determine a propen-

sity score for each patient in which the variables age, sex, WHO performance score ≥2, previous chemotherapy, tumor histology, tumor location, tumor length, and reason for palliation (i.e. metastatic or inoperable esophageal cancer) were accounted for. Patients from the EBRT and brachytherapy groups were matched (1:1) according to nearest-neighbor matching on the logit scale without replacement. Within-pair difference was minimized by setting a caliper of 0.1 of the standard deviation of the logit of the propensity score.

Patient-reported outcome scores were calculated based on EORTC scoring manuals and ranged from 0 to 100. Higher scores on the global health status and functioning scales indicate better health or function, whereas higher scores on the symptom scales and items represent more severe symptoms. A 10-point change or more from baseline (either deterioration or improvement) in a scale or item was deemed clinically relevant [19]. Likewise, a between-group difference of 10 points was deemed clinically relevant. Baseline characteristics were compared between the two treatment groups in both the original cohorts and the propensity score-matched cohorts. The independent-sample T-test was used to compare continuous variables, while nominal and ordinal categorical variables were compared using chi-square and Mann-Whitney U tests, respectively. All subsequent analyses (on PROs) were performed in the propensity score-matched cohorts only. Descriptive statistics on PROs and their changes after 3 months were presented as mean ± standard deviation (SD). Within-group changes in PROs from baseline to follow-up at 3 months were tested using paired T-tests, while between-group differences were tested using independent-sample *T*-tests.

Missing outcome data was observed in both treatment groups. This data was considered to be 'missing at random', meaning that the propensity for the outcome data point to be missing was related to -or could be explained by- part of the observed data (e.g. performance status, baseline PROs). Primarily, the complete-case analyses were reported using observed data only. Subsequently, in order to study the potential influence of the missing data on the findings and conclusions from the complete-case analyses, a sensitivity analysis was performed using multiple imputation (20×) by chained equations to impute the missing outcome data [20]. Missing data at follow-up 3 months after treatment

was imputed only in patients who were alive at that time point. Similar to the complete-case analyses, the within-group changes and between-group differences were studied in the imputed datasets. SPSS version 25.0 (IBM Corp, IBM SPSS Statistics for Windows, Armonk, NY) was used for all analyses and a *p*-value <0.05 was considered statistically significant.

Results

Between December 1999 and July 2002, a total of 101 patients were randomly allocated to the brachytherapy-arm of the SIREC trial. Between September 2016 and January 2019, a total of 124 patients were prospectively enrolled in the POLDER study and underwent EBRT. Due to reasons reported in Fig. 1, 8 and 9 patients in the brachytherapy and EBRT group, respectively, were excluded for data-analysis. At the time of analysis, all 93 eligible brachytherapy patients and 95 (82.6%) of 115 eligible EBRT patients had died.

Some baseline imbalances were observed between the cohorts with slightly higher age, shorter tumor length, and more esophagogastric junction tumors in the EBRT group (Table 1). After propensity score matching, 69 matched pairs were selected who appeared well-balanced in baseline patient- and tumor-related characteristics. Also, among patients with both baseline and follow-up PROs available, no statistically significant differences in baseline PROs were observed, with the exception of baseline 'trouble with taste' scores (mean 9.4 in brachytherapy group vs. 28.4 in EBRT group, *p* = 0.013).

The baseline PROs and changes in PROs during follow-up *within* the treatment groups (among patients with both baseline and follow-up PROs available) are presented in Table 2. Compared to baseline, 3 months after treatment in the brachytherapy group clinically relevant and significant deteriorations in physical functioning (mean change −17.9, *p* = 0.002), role functioning (−23.1, *p* = 0.002), social functioning (−17.5, *p* = 0.013), dyspnea (+13.7, *p* = 0.019), appetite loss (+16.2, *p* = 0.033), and trouble with taste (+14.5, *p* = 0.022) were observed. An observed worsening in pain 3 months after brachytherapy was statistically significant according to both QLQ-C30 and QLQ-OES18 questionnaires, but clinically
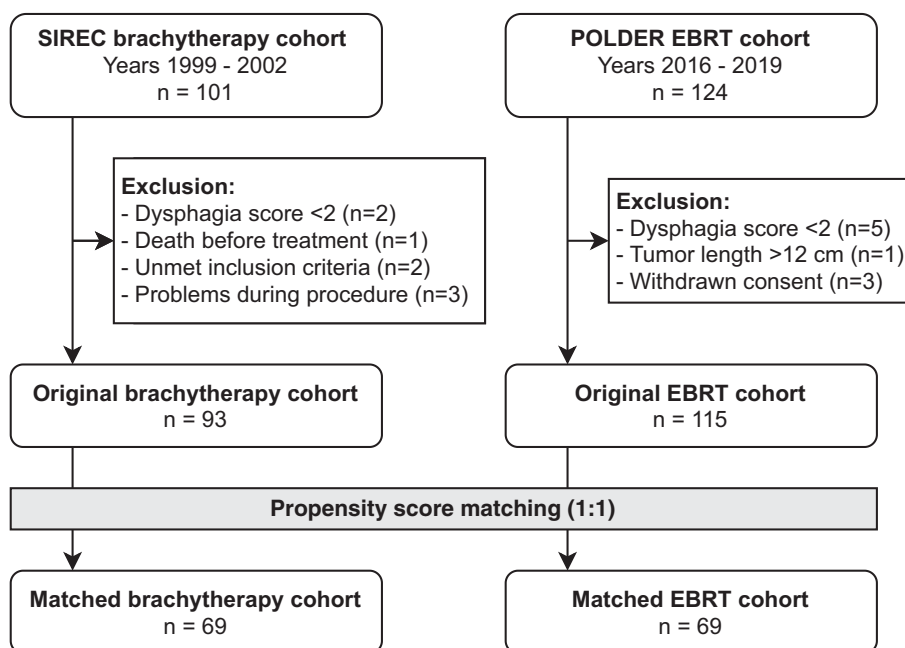

Fig. 1. Flowchart of study profile and patient selection.

Table 1
Baseline characteristics of the cohorts before 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 (mean ± SD)	69 (±12)	72 (±9)	0.04*	70 (±13)	70 (±9)	0.84
Male sex (%)	69 (74%)	91 (79%)	0.40	50 (73%)	52 (75%)	0.70
Tumor type (%)			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*	6.8 (±2.5)	6.5 (±2.5)	0.46
Tumor location (%)			0.001*			0.83
Esophagus	80 (86%)	76 (66%)		56 (81%)	57 (83%)	
Esophagogastric junction	13 (14%)	39 (34%)		13 (19%)	12 (17%)	
Reason for palliation (%)			0.09			0.37
Metastases	72 (77%)	97 (87%)		55 (80%)	59 (86%)	
Inoperable	21 (23%)	15 (13%)		14 (20%)	10 (14%)	
Previous chemotherapy (%)	11 (12%)	8 (7%)	0.26	7 (10%)	6 (9%)	0.81
WHO performance score (%)			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			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%)	

Table 2
Within-group changes in PROs from baseline to follow-up at 3 months among respondents in the matched cohorts of esophageal cancer patients.

	Brachytherapy				EBRT			
		Baseline	3 months			Baseline	3 months	
Domain	*n*	Mean (±SD)	Mean change (95% CI)	*p* value	*n*	Mean (±SD)	Mean change (95% CI)	*p* value
EORTC QLQ-C30								
Global health†	39	63.2 ± 20.7	−4.1 (−13.0; 4.8)	0.361	27	62.7 ± 24.4	4.3 (−4.8; 13.4)	0.339
Functional scales†								
Physical functioning	39	76.2 ± 19.8	**−17.9 (−28.8; −7.1)**	**0.002***	27	73.3 ± 30.0	−5.2 (−12.8; 2.4)	0.173
Role functioning	39	79.5 ± 28.5	**−23.1 (−37.0; −9.1)**	**0.002***	27	69.8 ± 32.7	**−16.0 (−27.7; −4.4)**	**0.009***
Social functioning	39	82.5 ± 27.8	**−17.5 (−31.2; −3.9)**	**0.013***	26	79.5 ± 23.3	−4.5 (−12.2; 3.3)	0.244
Cognitive functioning	39	86.8 ± 19.6	−7.3 (−16.4; 1.9)	0.117	26	81.4 ± 24.6	3.2 (−4.9; 11.3)	0.422
Emotional functioning	39	74.4 ± 24.4	−8.3 (−16.9; 0.2)	0.056	26	69.6 ± 20.1	6.7 (0.1; 13.3)	0.046
Symptom scales‡								
Fatigue	39	35.6 ± 27.0	7.7 (−3.2; 18.6)	0.161	28	36.9 ± 27.1	2.6 (−8.3; 13.5)	0.631
Nausea and vomiting	39	15.4 ± 20.2	11.5 (−0.2; 23.2)	0.053	27	19.1 ± 25.2	−8.0 (−18.1; 2.1)	0.114
Pain	39	15.0 ± 22.2	**21.8 (11.5; 32.1)**	**<0.001***	28	24.4 ± 27.0	−4.2 (−14.7; 6.3)	0.423
Dyspnea	39	12.0 ± 20.9	**13.7 (2.4; 25.0)**	**0.019***	27	12.3 ± 24.7	8.6 (−1.4; 18.7)	0.090
Insomnia	39	26.5 ± 31.7	5.1 (−4.6; 14.9)	0.295	28	27.4 ± 31.5	−4.8 (−16.3; 6.8)	0.404
Loss of appetite	39	30.8 ± 34.5	**16.2 (1.4; 31.1)**	**0.033***	26	35.9 ± 31.0	**−15.4 (−29.8; −1.0)**	**0.037***
Constipation	39	20.5 ± 32.1	3.4 (−10.3; 17.2)	0.618	25	22.7 ± 30.0	−2.7 (−16.9; 11.6)	0.703
Diarrhea	39	8.5 ± 21.2	−1.7 (−9.9; 6.5)	0.675	26	6.4 ± 16.4	10.3 (−0.4; 20.9)	0.058
Financial difficulties	39	0.9 ± 5.3	1.7 (−2.5; 6.0)	0.421	27	4.9 ± 20.1	3.7 (−4.7; 12.1)	0.376
EORTC QLQ-OES18								
Functional scales†								
Dysphagia	38	42.1 ± 25.1	**24.0 (7.7; 40.2)**	**0.005***	27	46.9 ± 26.2	**23.5 (7.5; 39.4)**	**0.005***
Symptom scales‡								
Trouble with eating	34	42.6 ± 25.4	5.6 (−5.9; 17.2)	0.327	24	42.7 ± 27.2	**−17.0 (−30.8; −3.2)**	**0.018***
Reflux	39	8.5 ± 21.2	−0.9 (−8.6; 6.9)	0.824	27	11.1 ± 17.9	−0.6 (−8.5; 7.2)	0.873
Pain	37	14.1 ± 20.4	9.0 (1.1; 17.0)	0.027	25	23.1 ± 19.5	**−15.6 (−24.3; −6.8)**	**0.001***
Trouble swallowing saliva	38	16.7 ± 32.7	−7.0 (−20.3; 6.3)	0.291	27	27.2 ± 30.7	−7.4 (−25.1; 10.3)	0.397
Choked when swallowing	37	8.1 ± 18.3	0.0 (−7.4; 7.4)	1.000	28	17.9 ± 23.1	7.1 (−5.7; 20.0)	0.264
Dry mouth	38	20.2 ± 30.5	8.8 (−3.9; 21.4)	0.169	28	25.0 ± 33.5	−1.2 (−11.4; 9.1)	0.813
Trouble with taste	39	9.4 ± 22.9	**14.5 (2.2; 26.9)**	**0.022***	27	28.4 ± 33.0	8.6 (−9.5; 26.8)	0.336
Trouble with coughing	39	17.9 ± 25.2	−0.9 (−12.9; 11.2)	0.886	28	26.2 ± 31.9	2.4 (−10.3; 15.0)	0.702
Trouble talking	39	4.3 ± 11.3	5.1 (−1.2; 11.5)	0.110	27	11.1 ± 24.5	−3.7 (−10.4; 3.0)	0.265

†: Score range 0–100; higher scores represent better quality of life or functioning. ‡: Score range 0–100; higher scores represent more severe symptoms. *: Clinically relevant (≥10 points) and statistically significant (*p* < 0.05) change. CI: Confidence interval. EBRT: External beam radiotherapy. SD: Standard deviation.

relevant according to the QLQ-C30 questionnaire only (+21.8, *p* < 0.001). In the EBRT group, a clinically relevant and significant deterioration was observed only in role functioning (mean change −16.0, *p* = 0.009). Significant improvements in dysphagia were similarly observed in both groups (after brachytherapy, mean change +24.0, *p* = 0.005; after EBRT, +23.5, *p* = 0.005). No other
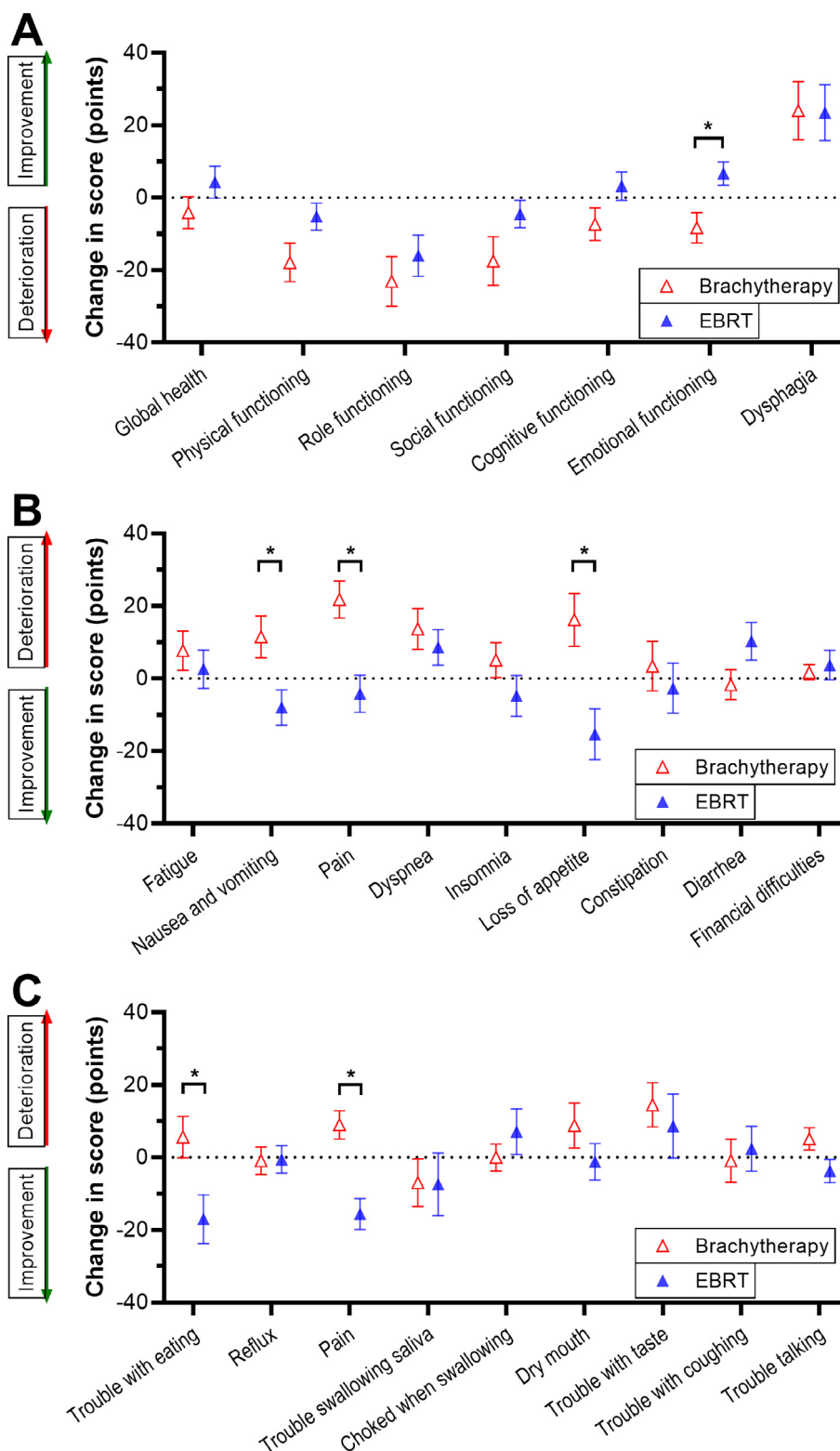
Fig. 2. Between-group differences in PRO changes from baseline to follow-up at 3 months in the matched cohorts of esophageal cancer patients for global health and functional scales (A), symptom scales of EORTC QLQ-C30 (B), and symptom scales of EORTC QLQ-OES18 (C). The symbols and error bars represent means and standard errors. *: Clinically relevant (≥10 points) and statistically significant (*p* < 0.05) difference.

significant PRO improvements were seen after brachytherapy, whereas after EBRT clinically relevant and significant improvements in appetite loss (mean change −15.4, *p* = 0.037), trouble with eating (−17.0, *p* = 0.018), and pain (QLQ-OES18; −15.6, *p* = 0.001) were observed.

The differences *between* the effect of brachytherapy and EBRT on changing PROs after 3 months compared to baseline are demonstrated in Fig. 2. Most effects on PROs were comparable between the two groups, but some clinically relevant and statistically significant differences were observed in favor of EBRT. After EBRT com-

pared to brachytherapy, observations included an average improvement rather than a deterioration in emotional functioning (mean difference 15.0, *p* = 0.006), nausea and vomiting (19.5, *p* = 0.018), pain (QLQ-C30, 26.0, *p* = 0.001; QLQ-OES18, 24.6, *p* < 0.001), appetite loss (31.6, *p* = 0.004), and trouble with eating (22.6, *p* = 0.013).

At baseline, PRO data was fully missing in 3 (4.3%) of 69 brachytherapy patients and in 23 (33.3%) of 69 EBRT patients. At follow-up at 3 months after treatment, 23 (33.3%) of 69 brachytherapy patients and 24 (34.8%) of 69 EBRT patients had died. Among the patients alive 3 months after treatment, PRO data was missing in 7 (15.2%) of 46 brachytherapy patients and in 16 (35.6%) of 45 EBRT patients. In the sensitivity analyses after multiple imputation, within-group changes over time were in line with the findings of the complete-case analyses (Appendix Table A). After brachytherapy a clinically relevant and significant deterioration of physical and social functioning, as well as increased pain, dyspnea and trouble with taste was found. Also, and in line with complete-case analyses, EBRT over time was associated with significantly less trouble with eating and pain. A significant deterioration in role functioning and improvement in dysphagia was observed in both groups. Furthermore, complete-case analyses results were confirmed in the between-group analyses across the imputed datasets with an average improvement rather than a deterioration in nausea and vomiting, pain, and appetite loss in favor of EBRT over brachytherapy (Appendix Fig. A).

Discussion

In this study, short course EBRT resulted in similar or better PROs at 3 months after treatment compared to single-dose brachytherapy for incurable esophageal cancer. Notably, clinically relevant benefits favoring EBRT compared to brachytherapy were observed in the domains of emotional functioning, nausea and vomiting, pain, appetite loss, and trouble with eating. Brachytherapy was not significantly superior to EBRT in any domain. As EBRT has inherent logistic benefits over brachytherapy, these findings further support the use of short course EBRT as preferred treatment option in this setting.

In the assessment of any treatment, the efficacy must be weighed against the risks of detrimental effects, which holds especially true for palliative treatments. To that regard, evaluation of adverse events and the effects of treatment on PROs is of importance. Although we previously reported short course EBRT for malignant dysphagia to be at least as effective for dysphagia relief as brachytherapy without comprising toxicity or overall survival [13], it is also important to evaluate the patients' perspective. The current analysis demonstrates that choosing EBRT over brachytherapy does not compromise PROs. The lack of any previous prospective PRO data in literature on this widely applied palliative strategy of short course EBRT further stresses the importance of this current report.

Similar or better PROs after EBRT may find its explanation in the superior homogeneous dose coverage of the entire tumor and relatively lower dose at the level of the mucosa compared to brachytherapy. Although the biologically equivalent dose at the reference point is similar between a single-dose of 12 Gy brachytherapy and an EBRT dose of 20 Gy in 5 fractions [21], brachytherapy is characterized by a very inhomogeneous dose distribution. For brachytherapy, the relative overdose (i.e. ~200% of the prescribed dose) at the superficial mucosal level may explain treatment-related stenosis (12%) and fistula formation (8%) as reported in literature, leading to severe (or grade ≥3) adverse event rates of up to 23% [4,22]. The relative mucosal overdose might also explain our observed inferiority of brachytherapy with

regard to pain outcomes through a possible increased risk of (prolonged) radiation-induced esophagitis. Furthermore, we speculate that the mucosal overdose with brachytherapy might be a cause of increased or prolonged edema resulting in more experienced trouble with eating during follow-up compared to EBRT.

After SEMS placement, brachytherapy is the second most studied approach for the palliation of dysphagia in esophageal cancer [1,22,23]. Besides the SIREC trial, head-to-head comparison between SEMS and brachytherapy (in 3 fractions of 7 Gy) has been performed in one other RCT in 65 patients, which confirmed improved rapid dysphagia relief with SEMS after 1 month, but not at ≥3 months [24]. After 3 months, many PROs deteriorated in the SEMS-group, but mostly remained stable in the brachytherapy-group [24]. Previous head-to-head comparisons between EBRT and brachytherapy include 2 retrospective studies which both had methodological limitations, such as unadjusted imbalances in baseline characteristics, and lacked assessment of PROs [25,26].

The results of this study should be interpreted with consideration of the following limitations. First, the two cohorts were 15 years apart with undeniable differences in staging and treatment (e.g. improvement in supportive care practice [27]), which may have influenced the results. However, time has likely not resulted in large differences as no significant changes in the prognosis of this patient group has been observed in this period in both our study and other studies [13,28]. Second, the acquisition method of PRO measurements was different between the two groups. In the brachytherapy cohort PROs were collected more frequently, and performed at home by a specialized nurse, whereas the EBRT cohort of patients completed the PRO questionnaires at home on paper without the presence of a health care professional. These differences in acquisition intensity could have resulted in a risk of bias in outcome assessment and are also likely the cause of the higher proportion of missing outcome data in the EBRT group.

Third, as this was not an RCT, residual unknown confounders may exist even after propensity score matching that was applied to adjust for known potential confounders. For example, the possibility of confounding from a difference in chemotherapy administration >1 week after EBRT or brachytherapy could not be excluded, as data on this variable was missing. Fourth, outcome data was partly missing which could have resulted in attrition bias. However, conducting PRO research in palliative care patients is known to be particularly challenging with a high number of missing data due to high mortality rates and symptom burden [29]. This issue was dealt with by studying the impact of the missing data on the findings of the complete-case analyses using sensitivity analyses that showed confirmative results. The study is strengthened by the prospective multicenter design of both cohorts, the similarity in inclusion criteria, the uniformity of treatment procedures within each group, and the use of similar PRO questionnaires.

In conclusion, short course EBRT compared to single-dose brachytherapy resulted in similar or better PROs at 3 months after treatment for incurable esophageal cancer. These findings further support the preference of short course EBRT over brachytherapy in this setting. Previous findings of similar or improved efficacy in dysphagia relief and limited toxicity rates [13], were reinforced by the current findings of similar or better PROs at 3 months after treatment. As such, inclusion of short course EBRT in clinical practice guidelines as standard treatment option for patients with a life expectancy of >3 months is recommended.

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Conflict of interest

The authors have no conflicts of interest relevant to this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.10.009.

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