Review Article

Palliation of malignant dysphagia: stent or radiotherapy?

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Abstract: Palliation of dysphagia forms the cornerstone in treating incurable esophageal cancer. The ultimate goal is to provide rapid and sustained relief of dysphagia. Optimal management is however a challenge as a single modality providing both rapid and sustained relief is not readily available. The two most commonly used modalities for palliative treatment of dysphagia include esophageal stent placement and radiotherapy. Treatment choice primarily depends on life-expectancy and dysphagia severity. Radiotherapy is preferred in those with a life-expectancy of more than three months as it is superior to stent placement with regard to effect duration. Regarding the former, short cycle external-beam radiotherapy (EBRT) is currently preferred over single-dose brachytherapy (BT) because of better clinical outcomes, lower toxicity and easier application. In contrast, if life-expectancy is less than three months, immediate relief of dysphagia is important and self-expandable metal stent (SEMS) placement is the preferred treatment. Although combining these two treatment modalities seems promising, evidence to support this is lacking. Placement of an irradiation stent has been suggested for patients with a reasonable life-expectancy, although placement requires a specifically-designed unit and experienced personnel. The research agenda should focus on further improving radiotherapy techniques, stent design, and effectiveness of combination therapy aiming to provide rapid and sustained dysphagia relief while maintaining quality of life.

Keywords: Esophageal cancer; dysphagia; palliation; radiotherapy; self-expanding metal stent

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Introduction

The incidence of esophageal cancer is increasing rapidly (1). Currently, it is the seventh most frequent cancer with annually approximately 572,000 newly diagnosed cases worldwide (2). The majority of patients are diagnosed at an advanced stage and are confronted with palliative treatment options only (3). The initial step in palliation is to relieve dysphagia, which occurs in over 70% of patients and has substantial impact on quality of life (4,5). Unfortunately, optimal management of these patients is still not clear, which has resulted in large practice variation (6). As the median survival of these patients is only four to five months, treatment choice should depend on life-expectancy (as this influences the importance of effect duration and adverse events of a treatment) and severity of dysphagia (as this influences the importance of time until effect on dysphagia) (7). Stent placement and radiotherapy are the two most widely used treatment modalities for reducing and preferably resolving obstructive symptoms. Both have been proven effective and safe (8-11).

Rigid plastic tubes were first introduced for malignant dysphagia in the 1970s (12). Its placement required however esophageal dilatation before placement which was associated with an increased risk of hemorrhage and perforation. Self-expandable metal stents (SEMS) were introduced in the mid-1990s and soon replaced plastic tubes because of fewer stent-

related adverse events and better outcomes with regard to dysphagia improvement (13-16). SEMS placement has the advantage that it can almost always be performed under endoscopic and/or fluoroscopic guidance, without the need for prior esophageal dilation. Improvement of dysphagia after SEMS placement is seen directly after stent expansion and technical success rates are high (9,10,17). Nonetheless, adverse events are still seen in 40–50% of patients (10). The most common severe adverse events are hemorrhage, stent migration and retrosternal pain. Importantly, SEMS placement is associated with a relatively high rate of recurrent dysphagia (up to 31%) (10). Recurrent dysphagia is commonly seen after a median of two months and is mostly the result of stent migration or tumor/hyperplastic tissue in- or overgrowth, both of which are influenced by stent design. Whereas fully covered SEMS (fcSEMS) have been shown to have higher migration rates due to lack of anchoring capacity, partially covered SEMS (pcSEMS) are associated with increased tumor/tissue in- or overgrowth (18).

Radiotherapy is usually well-tolerated with only a few serious adverse events reported. It is known for a longer-lasting relief of dysphagia compared to stent placement, although it may take one to two weeks before it becomes clinically noticeable (11). It can be provided externally through external-beam radiotherapy (EBRT) or intraluminal as brachytherapy (BT) using an endoluminal applicator. Whereas EBRT is easier to perform than BT, the latter has gained interest because of a more focused application of radiation energy to the tumor site while sparing normal surrounding tissue. Nonetheless, the endoluminal applicator needs placing inside the esophagus using endoscopic guidance and optimal dosing and fractionation are not completely clear.

To combine advantages of both the SEMS and radiotherapy, an irradiation stent has been developed. This stent is loaded with iodine 125 (125I) beads, resulting in a prolonged local release of radiation in the esophagus while maintaining esophageal lumen patency with the stent. This technique is however not widely available and measuring and planning of the most accurate radiation dosimetry is still not completely elucidated. In line with the rationale of the irradiation stent, combining radiotherapy (EBRT or BT) and esophageal stenting has gained interest, but so far results of larger studies are to be awaited.

The aim of this review is to outline the current literature on stenting, radiotherapy and combination therapies as a palliative treatment of malignant dysphagia.

Methods

We systematically searched the literature on the treatment of malignant dysphagia using PubMed. The following search terms were included: [‘deglutition disorders’, ‘dysphagia’ or ‘esophageal stenosis’] AND [‘stent’, ‘radiotherapy’ or ‘brachytherapy’]. We excluded studies with treatment options other than stent placement or radiotherapy, animal studies and *in vitro* studies. Furthermore, studies were excluded when full text was not available in English, Dutch or Spanish. Title and abstract of all 2,087 studies published in the last 10 years were screened for eligibility. Full text of 69 studies was evaluated and reference lists of included studies were also screened.

Radiotherapy

Radiotherapy has a direct cytotoxic effect on tumor cells thereby providing palliation of dysphagia by shrinking the esophageal tumor. Retrospective studies on EBRT have shown that patients treated with EBRT had significant improvement of dysphagia in >70% with only limited toxicity reported (19-23). Two systematic reviews that assessed BT as palliative treatment in patients with malignant dysphagia showed a dysphagia-free survival rate of 87% after one month and a median duration of dysphagia relief of 99 days (24,25). However, severe adverse events were seen in 23% of patients, with BT-induced development of esophageal stenosis and fistula most commonly seen (24,25). When comparing dosages and fractions, patients treated with fractionated BT had an increased dysphagia-free period compared to those treated with only a single dose of BT (24).

EBRT *vs.* BT

Table 1 shows all studies comparing radiotherapy as palliative treatment of malignant dysphagia. Two studies compared EBRT with BT (26,27). A retrospective cohort study comparing EBRT (20–30 Gy in 5–10 fractions) *vs.* single-dose BT (12 Gy) showed no significant difference in dysphagia scores or adverse events between both groups (26). A recent multicenter non-randomized cohort study comparing short cycle EBRT (5 fractions of 4 Gy) performed in a prospective follow-up study *vs.* single-dose BT (12 Gy), obtained from a previous study in which BT randomly was

Table 1 Studies comparing radiotherapy as palliation for malignant dysphagia

Comparison	First author (year)	Study design	Interventions	N belonging to study arm			Efficacy				Safety
				1	2	3	Dysphagia relief (short term)	Dysphagia relief (long term)	Median survival (days)	QoL	Adverse events
EBRT *vs.* BT	Eldeeb (2012)	Retrospective	Study-arm 1: EBRT (20–30 Gy/5–10#), Study-arm 2: BT (1×12 Gy)	21	23	–	NS	NS	NR	NR	NS
	Jeene (2020)	Prospective	Study-arm 1: EBRT (5×4 Gy), Study-arm 2: BT (1×12 Gy)	69	69	–	67% *vs.* 36% after 2 weeks	83% *vs.* 64% after 3 months	NS	NR	3% *vs.* 13%*
BT/EBRT *vs.* BT + EBRT	Sur (2004)	RCT	Study-arm 1: BT (2×8 Gy), Study-arm 2: BT (2×8 Gy) + EBRT (30 Gy/10#)	30	28	–	NS	NS	NS	NR	NS
	Rosenblatt (2010)	RCT	Study-arm 1: BT (8 Gy), Study-arm 2: BT (8 Gy) + EBRT (30 Gy/10#)	109	110	–	67% *vs.* 83% after 100 days		NS	NR	NS
	Welsch (2016)	Retrospective	Study-arm 1: EBRT (30–40.5 Gy total, 2.5–3 Gy per fraction), Study-arm 2: BT (15–25 Gy total, 5–7 Gy per fraction), T3: EBRT (30–40.5 Gy) + BT (10–14 Gy)	65	46	28	Dysphagia free survival: 90% *vs.* 37% *vs.* 92% after 6 months		NR	NR	NS
	Vermeulen (2019)	Retrospective	Study-arm 1: EBRT (5×4 Gy), Study-arm 2: EBRT (10×3 Gy) + BT (1×12 Gy)	72	72	–	Persistent/recurrent dysphagia: 64% *vs.* 42% after 6 weeks		88 *vs.* 177	NR	NS

#, number of fractions; *P value not reported or not applicable. BT, brachytherapy; EBRT, external-beam radiotherapy; N, number of patients; NR, not reported; NS, not significant; QoL, quality of life; RCT, randomized controlled trial; SEMS, self-expandable metal stent.

compared with stent placement, demonstrated that short cycle EBRT was superior in relieving dysphagia (83% *vs.* 64%, P<0.05) (27). In addition, dysphagia improved more rapidly after EBRT. Survival rates were not different between both groups. Severe toxicity was more frequently seen in the BT group than the EBRT group (13% *vs.* 3%, P value not reported), which can possibly be explained by a higher radiation dose at the level of the esophageal mucosa resulting in stenosis and fistula formation.

EBRT combined with BT

Two randomized controlled trials (RCT) compared BT *vs.* BT combined with EBRT (28,29). One RCT, including a limited number of patients (n=59) reported no significant differences in dysphagia scores, survival or adverse events (29). The other RCT (n=219) showed improved long-term dysphagia scores in the combination therapy group (83% *vs.* 67%, P<0.05) (28).

A retrospective study that compared EBRT *vs.* BT *vs.* combination therapy of EBRT and BT also showed statistically significantly dysphagia free survival scores between groups (90% *vs.* 37% *vs.* 92% respectively, P<0.01) (30). Remarkably, dysphagia free survival scores of EBRT alone were comparable to combination therapy of EBRT and BT, suggesting that adding BT to EBRT did not affect outcome in this study. A multicenter retrospective study comparing EBRT (5 fractions of 4 Gy) with combined radiotherapy (10 fractions EBRT of 3 Gy and single-dose 12 Gy BT) however showed lower persistent/recurrent dysphagia rates (64% *vs.* 42% respectively, P<0.05) in the combination therapy group (31). Although

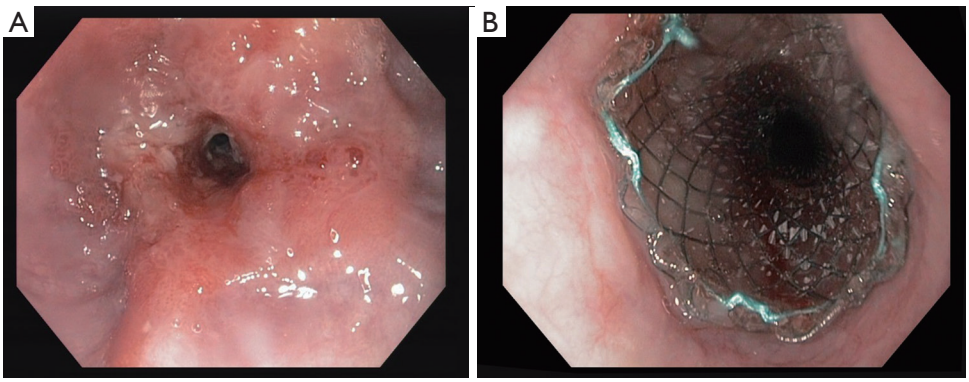

Figure 1 Stent placement for stenotic esophageal cancer. Stenotic esophageal cancer in a patient who also had liver metastases (A). A fully covered SEMS was placed that allowed the patient to resume an almost normal diet (B). SEMS, self-expandable metal stent.

dysphagia scores did not significantly differ between groups, a trend favoring combining EBRT and BT was seen (66% *vs.* 55% improvement, P=0.066). Furthermore, superior survival rates (177 *vs.* 88 days, P<0.001) were found in the combination therapy group and adverse event rates were not different between both groups. As all above mentioned studies used a higher radiation dose in the combination therapy group, the difference might well be explained by difference in dosage.

Stent placement

As stent placement does not directly affect tumor viability, its effect on reducing dysphagia is established by restoring luminal patency by mechanical force only (*Figure 1*). In general, SEMS placement is a relatively easy procedure providing rapid relief of dysphagia (8-10,17). Currently, two types of SEMS are available: pcSEMS and fcSEMS. Based on stent design (a smooth outer surface due to stent cover), higher stent migration rates were expected when using fcSEMS. A systematic review and meta-analysis comparing pcSEMS with fcSEMS showed however no difference in stent migration rates (32). Furthermore, no significant differences were seen between pcSEMS and fcSEMS with regard to reducing dysphagia or adverse events. Therefore, the choice for either pcSEMS or fcSEMS for palliation of malignant dysphagia is primarily based on non-stent related factors, such as pricing of the device, ease of placement and physician preference. Although manufacturers currently focus on developing improved stent designs that prolong palliation of dysphagia and reduce occurrence of adverse events, this seems hard to establish given the progressive course of esophageal cancer with stents having no effect on the natural history of the malignancy.

Stent placement *vs.* BT

Table 2 shows all studies comparing stent placement and BT or irradiation stent placement as palliative treatment of malignant dysphagia. Two RCTs have compared stent placement with BT (single-dose or fractionated) in a head-to-head design (33,34). One study clearly showed improved long-term (≥ three months) dysphagia relief in the BT group compared to stent placement (34). This was thought to be the result of a high early recurrence rate of dysphagia in the stent group caused by stent migration (17%), tumor/hyperplastic tissue in- and overgrowth (15%) and food-bolus obstruction (15%). As expected, patients treated with a stent had earlier symptom relief (33,34). In line with dysphagia scores, short-term quality-of-life (QoL) of patients was also in favor of the stent group, whereas long-term QoL showed a positive trend towards the BT group (33). For several QoL scales (among others dysphagia, emotional, cognitive and social functioning) these differences were statically significant within groups. The only statistically significant scales in the intergroup analysis were the dysphagia scale after 1 months in favor of the stent group and the trouble with speech score after 6 months in favor of the BT group (33). Survival was not significantly different between both groups (33,34). Whereas one RCT did not report differences in adverse events (33), the other RCT showed a higher adverse event rate in the stent group (33% *vs.* 21%, P<0.05) (34). The most frequent adverse events in the stent group included late hemorrhage (> seven days), tumor/tissue in- or overgrowth, stent migration and food bolus obstruction. In one of these studies pcSEMS, that are known for higher tumor ingrowth rates compared to fcSEMS, were placed (34). Remarkably, patients in the BT group showed even higher recurrent tumor growth rates in

Table 2 Studies comparing stent placement and brachytherapy or irradiation stent placement as palliation for malignant dysphagia

Comparison	First author (year)	Study design	Interventions	N belonging to study arm		Efficacy				Safety
				1	2	Dysphagia relief (short term)	Dysphagia relief (long term)	Median survival (days)	QoL	Adverse events
SEMS *vs.* BT	Homs (2004)	RCT	Study-arm 1: pcSEMS, Study-arm 2: BT (1×12 Gy)	105	95	NS	BT > SEMS after 30 days up till 350 days*	NS	NS	33% *vs.* 21%
	Bergquist (2005)	RCT	Study-arm 1: SEMS, Study-arm 2: BT (3×7 Gy)	28	24	NR		NS	Dysphagia scale SEMS > BT after 1 month, trouble with speech score BT > SEMS after 6 months	NS
SEMS *vs.* IS	Zhongmin (2012)	Prospective (IS) and retrospective (SEMS)	Study-arm 1: SEMS, Study-arm 2: IS	30	28	NS		147 *vs.* 330	NR	NS
	Tian (2016)	Prospective	Study-arm 1: SEMS, Study-arm 2: IS	91	40	NS	NS	NS	NR	NS
	Zhao (2017)	RCT	Study-arm 1: SEMS, Study-arm 2: IS	25	18	NS		Mean: 144 *vs.* 294	NR	NS
	Chen (2017)	Meta-analysis	Study-arm 1: SEMS, Study-arm 2: IS	6 studies including 539 patients		IS > SEMS after 3 and 6 months*		IS > SEMS (pooled weighted mean difference 2.7 months)	NR	NS

*P value not reported or not applicable. BT, brachytherapy; IS, irradiation stent; N, number of patients; NR, not reported; NS, not significant; OR, odds ratio; QoL, quality of life; RCT, randomized controlled trial; SEMS, self-expandable metal stent.

this study (26% in the BT group *vs.* 15% in the SEMS group). A cost-effectiveness analysis comparing SEMS placement and single-dose BT concluded that total costs of palliative treatment were equal, although the initial costs for SEMS placement were higher than for single-dose BT (35).

Stent placement *vs.* irradiation stent

A total of nine studies, four of them being RCTs, compared regular SEMS placement with placement of an irradiation stent (see *Table 2*) (36-39). All studies showed comparable results, including dysphagia relief in both groups. A systematic review and meta-analysis suggested that irradiation stents were superior over SEMS in terms of dysphagia relief at three and six months after placement (39). Performing a meta-analysis for dysphagia relief was not possible however due to limited data available (only mean dysphagia scores provided, no standard errors). All studies except one also showed a prolonged median survival in patients treated with the irradiation stent (ranging from 111–330 *vs.* 93–147 days; all P<0.05) (37-39). Adverse event rates were not different between both treatment groups in the meta-analysis (36-39). Non-surprisingly, medical costs were significantly lower in the regular SEMS-treated group, mainly because costs in the irradiation stent therapy group were approximately two-thirds higher compared to SEMS placement (36).

Stent placement combined with EBRT

Table 3 shows all studies comparing combination therapies as palliative treatment of malignant dysphagia. In total, five studies were found that combined stent placement with EBRT (40-44), with only one study randomizing patients between SEMS *vs*. SEMS followed by EBRT (30 Gy in 10 fractions) (41). Short-term dysphagia scores were similar for combination therapy compared to SEMS placement only. As expected, dysphagia relief persisted for a longer time in the group treated with EBRT after SEMS placement (7 *vs*. 3 months, P<0.05) (41). All studies except two also showed a survival benefit for combined therapy compared to stenting alone (median survival ranging from 161–237 *vs*. 91–169 days, all P<0.05) (40,41,44). One study showed however higher survival rates in the stent-only group, which could likely be explained by selection bias as this was a retrospective study that compared patients treated with a SEMS because of recurrent dysphagia after prior radiotherapy with curative or palliative intent with patients immediately treated with a stent when presenting with dysphagia (42). The effect of combined EBRT and stenting on adverse event rates is not completely clear. It has been suggested that EBRT after stent placement could increase adverse events up to 85%, specifically with regard to stent migration rates, due to tumor shrinkage as a consequence of radiotherapy (44). In one study more adverse events were seen when EBRT was performed before stent placement (42), specifically a higher incidence of gastrointestinal bleedings (42% *vs*. 9%, P<0.01) and pneumoniae were seen (56% *vs*. 9%, P=0.000). Mortality of major gastrointestinal bleeding was associated with a higher radiation dosage and female gender. In contrast, one RCT, one prospective and one retrospective study did not show significant differences in adverse event rates between groups (40,41,43).

Stent placement combined with BT

Three studies combined stent placement with BT, two of them being single-arm studies (45,46) and one RCT (47). A single-arm prospective study on single-dose BT (12 Gy) followed by biodegradable stent placement was prematurely terminated due to an unacceptably high adverse event rate of 89% (46). Adverse events included pain, vomiting, hematemesis and recurrent dysphagia. Although dysphagia scores improved in all patients, 37% of patients could not tolerate a normal diet due to pain and/or vomiting. Another single-arm prospective study in which SEMS placement was followed by single-dose BT (12 Gy) showed relief of dysphagia without the occurrence of major adverse events (45). The RCT comparing SEMS placement followed by BT to BT alone (3×8 Gy) included only a limited number of patients (n=41) (47). In this trial, a significant improvement of dysphagia scores was seen in the combined therapy group after three weeks of treatment (71% *vs*. 39%, P<0.05). However, this difference gradually diminished seven weeks after treatment. Survival was not different, and no severe adverse events were reported.

Discussion

Optimal management for palliation of dysphagia in patients with non-curable esophageal cancer remains a challenge. Stent placement and radiotherapy are the two most commonly used treatment modalities. Patients suffering from severe dysphagia or with a life-expectancy of less than three months, clearly benefit from SEMS placement. In case of more than three months life-expectancy, radiotherapy is preferred with short cycle EBRT being superior over single-dose BT. Upcoming therapies include placement of an irradiation stent and combination therapies. Irradiation stent placement appears superior over SEMS in terms of effect duration and could be considered as an alternative in patients with a longer lasting life-expectancy. Combining stent placement with EBRT or BT seem promising; however, adverse events rates are not uncommon and evidence in favor of combination therapy is lacking as only a few RCTs have been published. *Table 4* and *Figure 2* show characteristics and effect in time of stent placement and radiotherapy, respectively, in palliation of malignant dysphagia.

The European Society for Medical Oncology (ESMO) and the European Society of Gastrointestinal Endoscopy (ESGE) both recommend BT as palliative treatment of malignant dysphagia (48,49). BT clearly has shown longer-lasting dysphagia relief when compared to SEMS placement, which makes it a better choice for patients with a longer life-expectancy (> three months) (33,34). In contrast to current guidelines, it was recently shown that short cycle EBRT results in more frequent and faster relief of dysphagia and also showed increased survival rates compared to BT (27). It is thought that the superior results of EBRT are due to a better dose application to the entire tumor compared to BT. Nonetheless, performance of a 3D CT-based treatment planning compared to a 2D X-ray based planning has been suggested to improve BT results (50). In this way, BT

Table 3 Studies comparing combination therapies as palliation for malignant dysphagia

Comparison	First author (year)	Study design	Interventions	N belonging to study arm			Efficacy				Safety
				1	2	3	Dysphagia relief (short term)	Dysphagia relief (long term)	Median survival (days)	QoL	Adverse events
SEMS *vs.* SEMS + EBRT	Song (2002)	Retrospective	Study-arm 1: fcSEMS, Study-arm 2: EBRT + fcSEMS, Study-arm 3: fcSEMS + EBRT (details about EBRT unknown)	48	47	13	NR		Study-arm 1 *vs.* 3: 91 *vs.* 161, Study-arm 2 *vs.* 3: 70 *vs.* 161	NR	Study-arm 1 *vs.* 3: 21% *vs.* 85% Study-arm 2 *vs.* 3: 21% *vs.* 85%
	Rueth (2012)	Retrospective	Study-arm 1: SEMS, Study-arm 2: EBRT + SEMS, Study-arm 3: SEMS + EBRT (details about EBRT unknown)	20	16	8	NS		NS	NR	NS
	Eldeeb (2012)	Prospective	Study-arm 1: EBRT (20–30 Gy/5–10#), Study-arm 2: SEMS, Study-arm 3: EBRT (20–30 Gy/5–10#) + SEMS	30	35	26	NS		Study-arm 2 *vs.* 3: 169 *vs.* 237, other NSD	NR	NS
	Javed (2012)	RCT	Study-arm 1: SEMS, Study-arm 2: SEMS + EBRT (30 Gy/10#)	37	42	–	3 *vs.* 7 months of relief		120 *vs.* 180	Declined immediate after EBRT*	NS
	Qiu (2013)	Retrospective	Study-arm 1: SEMS, Study-arm 2: EBRT (median 60 Gy) + SEMS	35	57	–	NS		246 *vs.* 77	NR	GI bleeding (9% *vs.* 42%), pneumoniae (9% *vs.* 56%)
Stent + BT	Bergquist (2012)	Single-arm prospective	Study-arm 1: SEMS + BT (1×12 Gy)	11	–	–	90.9% after 1 month		198*	Dysphagia-related scores improved*	Only minor*
	Hirdes (2012)	Single-arm prospective	Study-arm 1: biodegradable stent + BT (1×12 Gy)	19	–	–	100% after 1 month		NR	NR	59% (47% major)*
BT *vs.* SEMS + BT	Amdal (2013)	RCT	Study-arm 1: BT (3×8 Gy), Study-arm 2: SEMS + BT (3×8 Gy)	20	21	–	39% *vs.* 71% after 3 weeks, NS after 7 weeks		NS	NR	NS

#, number of fractions, *P value not reported or not applicable. BT, brachytherapy; EBRT, external-beam radiotherapy; GI, gastrointestinal; N, number of patients; NR, not reported; NS, not significant difference; QoL, quality of life; RCT, randomized controlled trial; SEMS, self-expandable metal stent.

Table 4 Characteristics of stent placement and radiotherapy as palliation for malignant dysphagia

Variable	Stent placement	EBRT	BT	IS
Time until effect on dysphagia	Rapid (within 1 day)	Less rapid (in 1–2 weeks)	Less rapid (in 1–2 weeks)	Rapid (within 1 day)
Duration of dysphagia relief	Short (recurrence after 2–3 months)	Relatively long (>3 months)	Relatively long (>3 months)	Relatively long (>3 months)
Adverse event rate	Relatively high (40–50%)	Low (around 20%)	Low (around 20%)	Relatively high (equal to stent placement)
Survival	No effect on survival	No effect on survival*	No effect on survival*	Prolonged survival
Availability	Good	Good	Moderate + complex treatment planning	Moderate + complex treatment planning
Costs	Equal to BT	Insufficient evidence	Equal to stent placement	Two-thirds higher than stent placement

*, combination therapies including EBRT and/or BT have shown prolonged survival rates. BT, brachytherapy; EBRT, external-beam radiotherapy; IS, irradiation stent.

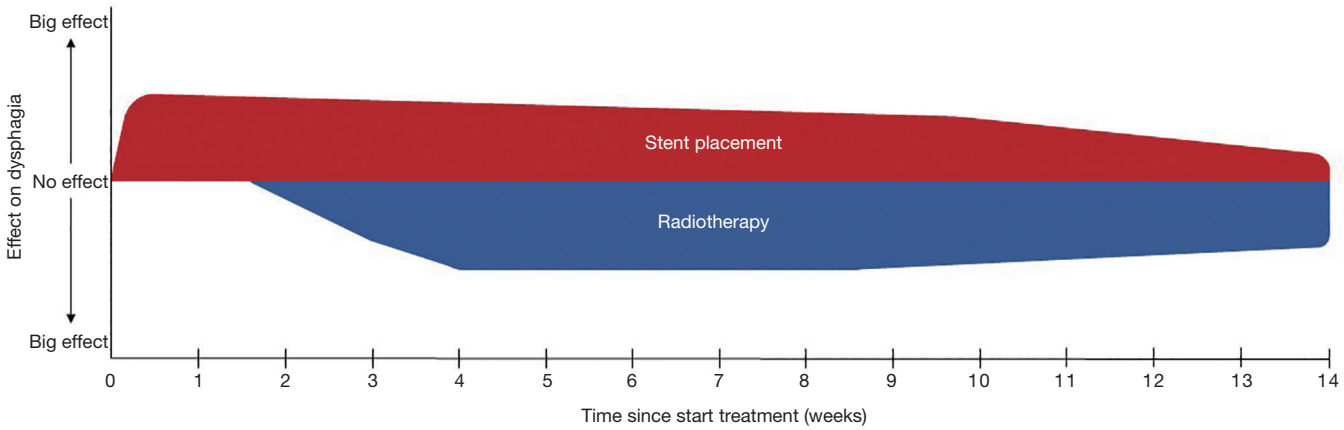

Figure 2 Effect of stent placement vs. radiotherapy on dysphagia in time.

isodose can be calculated on the full extent of the tumor and its distance to high-risk surrounding tissues. Although this seems promising, 3D treatment planning is complicated by logistics, complexity of treatment and lack of expertise. Even when radiation planning is optimized, it remains uncertain if BT can compete with EBRT. Logistics for EBRT are much less complicated as EBRT can be offered at almost each radiotherapy facility. Therefore, considering the better outcomes, lower toxicity and less complex logistics, we consider EBRT preferable over BT. Although no differences were found between EBRT schedules (19-23), a higher doses of radiotherapy seems favorable specifically in patients with a life-expectancy of more than six weeks (31). However, the most optimal radiation dosage and total number of fractionations for treatment in patients with incurable esophageal cancer remains to be established.

As stated before, stent placement has been shown to restore luminal patency and improve dysphagia scores within one day compared to only 50% relief of dysphagia within two weeks after radiotherapy, especially BT (17,51). The use of SEMS is largely limited by the high dysphagia recurrence rate as a result of stent migration and tumor ingrowth. Therefore, we consider SEMS placement as the treatment of choice in case of severe dysphagia in patients with a limited life expectancy (< three months).

Results of irradiation stents so far seem very promising, showing rapid and longer-lasting dysphagia relief and prolonged survival compared to SEMS (36-39). Most

important advantages include focused radiation to the inner part of an esophageal cancer, protecting surrounding tissues, and endured internal radiation up to 180 days (37). Disadvantages include the availability and the complexity of sophisticated tumor measurement and treatment planning. Although all published studies showed similar outcomes, some studies that did not have access to a dedicated treatment planning system (TPS) for luminal organs have reported uncertainties in these measurements and planning (36,52-54). An accurate measurement technique contributes to optimal calculation of the required number of 125I seeds and their distribution ratio of dosage. As this may affect outcomes, experience and a TPS for luminal organs is warranted. Until now, only studies comparing irradiation stents with regular SEMS with a small sample size and all coming from China have been published. Therefore, there is a need for larger studies comparing irradiation stent treatment with radiotherapy, SEMS placement or a combination of radiotherapy and SEMS in a more heterogeneous population.

Combining stent placement with EBRT has been suggested to provide a longer-lasting relief of dysphagia due to the effect of radiation therapy on the local tumor which may delay tumor ingrowth (40,41,43,44). Although SEMS combined with BT seems safe (45,47), safety outcomes are unclear in case of SEMS combined with EBRT (42,44). In addition, use of a biodegradable stent combined with BT is discouraged as this resulted in an unacceptable high adverse event rate (46). As only two RCTs have been published on combination therapies, results need to be interpreted with caution. Further studies should provide more information on efficacy and safety of combination therapies compared to stenting and/or radiotherapy alone.

The reported prolonged survival rates in favor of the irradiation stent compared to SEMS, combining EBRT and BT compared to EBRT alone and combining EBRT and SEMS compared to SEMS alone seem remarkable at first sight (31,37-41,44). The reason is that survival in incurable esophageal cancer mostly depends on progression of metastases and these treatment modalities probably only affect locoregional disease. Although better relief of dysphagia and subsequent improved nutritional status might contribute to survival rates, some concerns have been put forward that selection bias and/or confounding may have been involved in the favorable results. Moreover, an increase in survival has also been observed in a meta-analysis involving the use of chemotherapy (55). Although the evidence that shows that chemotherapy alone could improve dysphagia is scarce, palliative chemotherapy combined with radiotherapy could be considered in patients with an expected reasonable life-expectancy and good performance status (21,56).

As practice variation in palliative treatment of esophageal cancer has been noted, some guidance in choosing optimal palliative treatment seems warranted (6). A prognostic tool that may help deciding which patients will benefit from stent placement or BT has already been developed (57). This tool is able to differentiate between patients with a predicted poor *vs.* better prognosis, based on age, gender, tumor length, metastases and World Health Organization (WHO) performance score. More tools like this could contribute to more standardization and thereby improving palliative care in patients with malignant dysphagia.

Conclusions

Although individual patient-related factors should be taken into account when selecting optimal palliative treatment of malignant dysphagia, short cycle EBRT is nowadays the treatment of choice in patients with an expected survival of at least three months. SEMS placement might be reserved for patients with severe dysphagia and short life-expectancy (less than three months). More studies are needed to give irradiation stents and/or combination therapies an established position in the treatment algorithm.

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Footnote

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