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Systematic Review

Efficacy and safety of stenting and additional oncological treatment versus stenting alone in unresectable esophageal cancer: A meta-analysis and systematic review

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ABSTRACT

Aim: To compare the efficacy and safety of stent insertion alone to stent insertion combined with any active oncological treatment in the palliative care of esophageal cancer.

Methods: A meta-analysis and systematic review were performed according to the PRISMA Statement. Comparative studies with patients receiving stent insertion alone (control group) were compared to patients receiving oncological therapy in addition to stent placement (intervention group). For mean dysphagia grade before stenting, weighted mean differences (WMD), for the complications of stenting, risk ratios (RR) were calculated, both were interpreted with 95% confidence intervals (CI). Whenever possible, subgroup analyses were performed for studies with irradiation stents as intervention. Survival, late dysphagia, esophageal perforation and medical costs were analyzed via systematic review. The protocol of the study was registered prior on PROSPERO.

Results: 17 studies with 1177 esophageal cancer patients were included in the final analysis, with 629 and 548 in the control and intervention groups, respectively. We found no significant difference in any complications of stenting between the two groups. 13 studies reported mean or median survival, and 8 found that combined therapy resulted in a significantly longer life expectancy. In the other 5 studies, there was no difference in survival between the two groups. Furthermore, additional treatment may be more effective in the long-term relief of dysphagia than stenting alone.

Conclusions: Irradiation stents may prolong survival, and stenting combined with oncological treatment does not increase the risk of complications as compared to stenting alone. However, further studies are warranted.

Core tip: Esophageal cancer is the eighth most common type of malignancy worldwide, and its prognosis is very poor. This suggests that palliative treatment modalities are paramount in its treatment. Self-expanding metal stents play an important role in the management of dysphagia caused by the tumor. However, it is unclear whether any additional oncological therapy should be administered to patients besides stenting. In this meta-analysis and systematic review, we evaluated the safety and efficacy of additional oncological therapies alongside stenting versus stenting alone in case of unresectable esophageal cancer.

Esophageal cancer is the eighth most common cancer worldwide with an estimated annual incidence and mortality above 572,000 and 508,000, respectively [1]. This makes it the sixth leading cause for cancer-related mortality [2]. Its five-year survival rate is estimated to be as low as 14% [3] and patients with metastatic disease have a median survival of less than one year if treated with chemotherapy [4].

Low survival rates are also explained by the fact that the majority of tumors are unresectable at the time of diagnosis [3]. In most cases the diagnosis is made after the onset of dysphagia, which indicates at least locally advanced cancer [5]. The most common symptom is dysphagia in 74% of patients at the time of diagnosis [6]. Absence of early symptoms and the lack of precancerous states make screening procedures difficult to organize effectively [3],

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with the exception of Barrett's esophagus, where surveillance is recommended [7].

Such high mortality rates underline the importance of palliative treatment options. Endoscopic stenting with metal stents plays an important role in the management of malignant dysphagia to achieve immediate dysphagia relief and quality of life improvement [8].

Currently, there are no clear guidelines on whether additional oncological treatment is required besides stenting in the palliative care of esophageal cancers [9]. Stenting may be combined with various types on oncological treatment, including photodynamic therapy, brachytherapy (irradiation stents), radiotherapy, chemotherapy, or chemo-radiotherapy. At present, the decision lies in the hands of individual clinicians, and is usually based on patient characteristics, such as performance status, presence of metastases, age and expected survival time [9].

Our study aims to quantitatively and qualitatively analyze the potential benefits, drawbacks and safety measures of oncological treatment administered in addition to palliative stenting for incurable esophageal cancer.

Methods

We conducted a meta-analysis and systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [10]. Our work was performed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [11]. The protocol was registered in PROSPERO under registration number CRD42018093921 [12].

Search

Two independent authors (BT and LS) carried out a comprehensive search using six electronic databases (PubMed, EMBASE, the Cochrane Library, Web of Science, clinicaltrials.gov, and the WHO Global Health Library) with the purpose of gathering all relevant articles on the topic of palliative stent therapy in esophageal cancer patients from inception until 10 February 2020.

Our PICO items were as follows: we looked for studies on patients with incurable esophageal cancer (P) that compare two palliative treatment modalities: stent insertion alongside any additional active oncological therapy (I) or stent insertion alone (C). The primary outcomes were mean survival time after stent insertion and the relief of dysphagia. Secondary outcomes were the complications of stenting (such as hemorrhage, deaths due to hemorrhage, chest pain requiring opiate analgesics, fever, stent migration, restenosis or obstruction, tracheoesophageal fistula formation, aspirational pneumonia and esophageal perforation) and the cost of the medical treatment (O).

The query "(esophagus OR oesophagus) AND ((malignan* OR cancer* OR carcinoma) AND (stricture OR stenosis OR obstruction OR blockage OR dysphagia)) AND (stent OR onco* OR radio* OR chemo* OR beam OR best supportive OR palliat*)" was used in all six databases. For a draft of our search strategy, see Supplementary 1.

The "human" filter was applied when searching in PubMed, EMBASE and the WHO Global Health Library. The "trials" and "completed" filters were used in case of the Cochrane Library and clincaltrials.gov, respectively. We imposed no language restriction to our search.

Inclusion and exclusion criteria

We included both observational and interventional studies except for case studies, case reports, editorials, comments, letters and reviews. Conference abstracts were included if they contained sufficient data for analysis. We included studies with either prospective or retrospective data collection, regardless of their primary objectives. In case of multiple publications on the same group of patients, the most recent record was chosen.

The inclusion criteria required patients to be over 18 years of age, with a diagnosis of incurable, late-stage esophageal cancer (of any histological subtype). An intervention and a control group both had to be present in the same study in order to provide comparability. The control group was defined as patients receiving any type of metallic stent implantation for palliative purposes, without the concurrent addition of other active treatment modality. The indication for stenting was malignant dysphagia. The intervention group consisted of those patients who received a metallic esophageal stent of any kind in combination with any type of active oncotherapy (radio-, chemo-, or photodynamic therapy) for palliative purposes. Insertion of irradiation stents was considered an intervention, as brachytherapy delivered by the stent is an additional active oncological treatment modality.

Screening and selection

Articles yielded by the initial search were imported into a reference management program (EndNote X7, Clarivate Analytics, Philadelphia, PA, USA). The same software was utilized for the removal of duplicates by searching for articles with overlapping publication year, authors or title.

After duplicate removal, two independent researchers (BT and LS) simultaneously screened all remaining articles against the pre-defined eligibility criteria first by title, abstract and then full text in order to find studies for inclusion. Reference lists of selected articles were searched to identify studies potentially missed by the electronic search. Any disagreements were resolved by arbitration by a third investigator (BE).

Data extraction

Two investigators separately extracted data from studies included and manually entered them on a Microsoft Excel 2016 sheet (Office 365, Microsoft, Redmond, WA, USA). Data were collected on first author, publication year, study type, geographical location, definition of control and intervention groups, demographical characteristics of patients included, and histological subtype of the tumors. Finally, data were collected on the aforementioned outcomes of interest. Differences in the data sheets were resolved by consensus.

Quality assessment and quality of evidence

We used a modified version of the Newcastle-Ottawa Scale (NOS) for the quality assessment of cohort studies included in our analysis [13]. Supplementary 2 shows the NOS Quality Assessment Form for Cohort Studies modified to fit the study design of the articles included. The Cochrane Risk of Bias Tool was used to assess the quality of the randomized-controlled trials [14]. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to rate the quality of evidence as high (level A), moderate (level B), low (level C) or very low (level D) [15].

Data synthesis and analysis

In case of the survival time and the dysphagia grade weighted mean differences (WMD) were calculated with their 95% confidence intervals (CI). In other comparisons, risk ratios (RRs) with 95% CI were calculated from the raw data extracted. Subgroup analyses were also performed by treatment type. Pooled estimates

were calculated with random effects model by using DerSimonian–Laird method [16]. Results of the meta-analysis were displayed graphically using forest plots. Heterogeneity was tested by using the Cochrane's Q and the I2 statistics, where I2 = 100% × (Q − df)/Q, and represents the magnitude of the heterogeneity (moderate: 30–60%, substantial: 50–90%, considerable: 75–100%) [11]. All meta-analytical calculations were performed by Stata v15.1 software (Stata Corp LLC, College Station, TX, USA).

Results

Our search yielded a total of 14,960 articles, 1226 in PubMed, 9505 in EMBASE, 355 in the Cochrane Library, 1503 in Web of Science, 2371 in the WHO Global Health Library, and 0 in clinicaltrials.gov. Four articles were identified by cross-referencing. After duplicate removal and three-step selection, a total of 40 articles were assessed for eligibility by their full text. Out of these studies, 23 were excluded for the following reasons: lack of intervention group (6 studies, [17–22]), lack of a control group (3 studies, [23–25]), insufficient outcome data (7 studies, [26–32]), use of non-metallic stents (2 studies, [33,34]), patients with curable cancer (2 studies, [35,36]) and curative intent (3 studies, [37–39]). For a summary of our search and selection, see Fig. 1: PRISMA flowchart of the study selection process.

Finally, 17 studies were deemed eligible for either qualitative or quantitative synthesis [40–56]. These included a total of 1177 subjects, out of which 629 and 548 patients received stent therapy alone (control group) or stent therapy supplemented by additional oncological treatment (intervention group), respectively. In case of 234 patients, brachytherapy with I^{125}-coated irradiation stents was the intervention method of choice, which provided basis for subgroup-analysis. Characteristics of studies included are shown in Table 1.

Tables 2 and 3 contain data collected on outcomes included in the meta-analysis, and Table 4 shows a summary of the results of the quantitative synthesis.

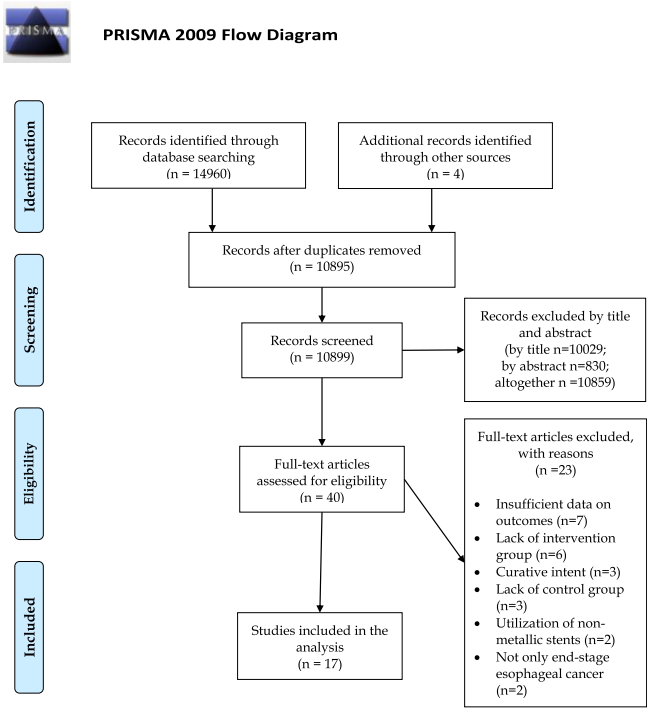

Fig. 1. PRISMA flowchart for the study selection process.

Complications of stenting. We found no significant association between additional oncological treatment and complications of the stenting procedure, such as chest pain requiring opiate analgesics (RR, 1.03; 95% CI, 0.84–1.26; I^2 0.0%; Supplementary 3), hemorrhage (RR, 1.32; 95% CI, 0.89–1.98; I^2 0.0%; Supplementary 4) and deaths due to hemorrhage (RR, 1.19; 95% CI, 0.67–2.11; I^2 0.0%; Supplementary 5). Neither increased risk of stent migration (RR, 0.96; 95% CI, 0.51–1.78; I^2 0.0%; Supplementary 6), nor stent restenosis or obstruction (RR, 0.62; 95% CI, 0.36–1.09; I^2 21.6%; Supplementary 7) were associated with additional treatment. Fistula formation and development of aspirational pneumonia and development of fever as complications of stenting also did not show association with additional active oncotherapy (RR, 1.62; 95% CI, 0.68–3.87; I^2 0.0%; RR, 0.76; 95% CI, 0.40–1.45; I^2 0.0%; RR, 1.24; 95% CI, 0.61–2.50; I^2 0.0%; Supplementary 8–10, respectively).

Subgroup-analyses of studies where irradiation stents were used [40,42,44,45,48,54,55] as intervention were performed whenever possible, showing no association with any of the complications examined (see Supplementary 3, 4, 6, 7, 8).

Dysphagia score before stenting and within 3 days of stenting. We found no significant difference between the two groups in dysphagia scores prior to and within 3 days of the stenting procedure (WMD, −0.03; 95% CI, −0.11–0.05; I^2 0.0%; WMD, 0.08; 95% CI, −0.01–0.17; I^2 0.0%; see Supplementary 11 and 12, respectively).

Table 5 demonstrates data extracted on outcomes analyzed in the systematic review section of our study.

Survival after stenting. 13 studies reported this outcome as mean or median survival time after stent insertion [40–46,48–51,54,55]. Out of the 13 articles, 12 compared the survival of patients in the two groups via log rank test [40–45,48–51,54,55]. These 12 articles included a total of 894 patients, out of which 473 and 421 belonged to the control and intervention group, respectively. The use of additional oncological treatment was associated with prolonged survival in 8 of these 12 studies [40,41,43,45,48,49,54,55] comparing a total of 542 patients, with 281 in the control group and 261 in the intervention group, respectively. The remaining 4 studies (352 total patients; 212 and 140 patients in the control and intervention group) found no significant difference between survival in the two groups [[42,44,50,51]]. No study showed significantly reduced survival time in patients that received stenting and additional oncological therapy as compared to stenting alone.

Regarding the sub-group of 7 articles (539 total patients, 254 and 285 patients in the control and intervention groups) where iodine-coated stents were used as intervention [40,42,44,45,48,54,55], 5 (345 total patients; 182 versus 163 patients in the control and intervention group) reported that that irradiation stents significantly prolong survival as compared to regular stents [40,45,48,54,55]. At the same time, 2 articles (194 patients, 72 in the control and 122 in the intervention group) found no significant difference between the two groups [42,44]. No articles suggested that irradiation stents are associated with reduced survival as compared to regular stents. Detailed results of this outcome in each study can be found in Table 6.

Late dysphagia. The studies contained insufficient data on dysphagia scores more than 3 days after the stenting procedure, therefore only quantitative synthesis was carried out in case of this outcome. 5 studies [40,42,48,49,57] of the included 17 contained data on the long-term improvement of dysphagia. Guo et al. found that dysphagia was equally well palliated in both groups up until the second month after treatment, where the intervention group had a significantly lower dysphagia score (exact dysphagia score values were not specified in the article, $p < 0.05$) [40]. Liu et al. concluded that there was no significant difference between dysphagia scores of patients in the control and intervention groups at 1 month after stenting (mean dysphagia score at 1 month 1.6 and 1.7 in the

Table 1
Characteristics of studies included.

Author (publication year)	Country	Design	Group definitions (C: Control; I: Intervention)	Patient Number (*n*)	Male (*n*)	Age (years, mean, SD)	Follow-up (months, mean)	Histology AC/SCC (*n*)
Bakheet (2019)	South Korea	Retrospective cohort	C: SEMS alone	41	38	67.7(11)		
			I: SEMS + chemotherapy	64	60	66.7(10.7)		
Tian (2016)	China	Cohort	C: SEMS alone	91	67	66.3 (9.4)	4 (median)	0/90
			I: I^{125}-coated Irradiation stent	40	30	66.9 (8.6)	4 (median)	0/41
Zhao (2016)	China	RCT	C: SEMS alone	25				0/25
			I: I125-coated Irradiation stent	18				0/18
Kim (2015)	South Korea	Retrospective cohort	C: SEMS alone	45				7/10
			I: SEMS + multiple modalities of oncological treatment	44				3/9
Liu (2014)	China	Cohort	C: Conventional SEMS	32	20	61.2	2.7	5/27
			I: I125-coated Irradiation stent	31	16	59.6	3.4	6/25
Zhu (2014)	China	RCT	C: SEMS alone	75	53	71(median)	4.1(median)	14/61
			I: I^{125}-coated irradiation stent	73	61	71(median)	5.7(median)	8/65
Zhongmin (2012)	China	Cohort	C: Covered stent alone	30	18	68.8(6.9)		12/18
			I: I^{125}-coated Irradiation stent	28	19	65(7.9)		8/20
Xu (2011)	China	RCT	C: SEMS alone	17				
			I: I^{125}-coated Irradiation stent	15				
Zhao (2011)	China	Cohort	C: SEMS alone I: I^{125}-coated Irradiation stent	25 18				
Burstow (2009)	Australia	Retrospective cohort	C: SEMS alone I: Adjuvant chemotherapy, radiotherapy, or both	67 23				
Guo (2008)	China	RCT	C: Conventional covered stent	27	20	69.54 (8.68)	3.3	6/20
			I: I^{125}-coated irradiation stent	26	19	72.19 (8.71)	7.2	5/22
Zhang (2005)	China	Cohort	C: Metal stent only	34	25	62.04		2/31
			I: Endoprothesis and external radiotherapy	33	26	60.17		2/30
Fu (2004)	China	RCT	C: SEMS alone	27	16	64.2 (14)		2/23
			I: Stent + external radiotherapy and/or chemotherapy	26	23	59.4 (9.6)		2/24
Javed (2004)	India	RCT	C: SEMS alone	37	27	58.1 (12.44)		6/31
			I: Stent + external beam radiotherapy	42	29	58.6 (12.13)		7/35
Zhong (2003)	China	Cohort	C: SEMS alone	18	13	64.6		0/18
			I: SEMS + external radiotherapy and/or chemotherapy	16	12	61.5		0/16
Ludwig (1998)	Germany	Cohort	C: Nitinol stent or wallstent	17	13	67 (median)		7/10
			I: stent combined with radiochemotherapy	12	11	57 (median)		3/9
Raijman (1997)	USA	Retrospective cohort	C: Coated expandable wallstent alone	21	10	66.8	6.4	8/13
			I: Stent + chemo/radio/both	39	29	64.7	5.9	12/14

control and intervention group, respectively, $p = 0.91$). At 3 months, however, the difference between the two groups became significant (mean dysphagia scores 2.6 vs 2.1 in the control and intervention groups, respectively, $p = 0.03$) [42]. In case of the article by Zhu et al., dysphagia was significantly lower in the intervention group as compared to the control group starting from 1 month after the procedure to the end of the follow-up [48]. Javed et al. states that the mean dysphagia score was comparable between the two groups up until 3 months post-treatment. Thereafter, dysphagia scores at 5 and 7 months were significantly lower in the intervention group [49]. Zhong et al. found that stenting dramatically improved dysphagia of patients, however patients in the control group had an increasing tendency of dysphagia grades 9 months after stent implantation (mean dysphagia in the control and intervention groups at 9 months after stenting; 1.75(±0.35) 4 and 1.58 (±38) respectively; statistical analysis not reported).

Perforation. 5 studies [42,45,47,49,53] on a total of 312 patients included data concerning esophageal perforation (or a lack thereof) as a complication of stenting. Perforation only occurred in two studies [42,53], with a combined rate of 6.1% (4/66) and 9.4% (6/64) in the control and intervention group, respectively. Out of the total 182 patients (83 in the control group and 99 in the intervention group) of the other 3 studies [45,47,49], no perforation was observed. None of the articles found a significant difference between the two groups ($p = 0.672$ in case Liu et al.).

Medical costs. Only one article out of 17 [44] assessed medical costs as an outcome. They reported that regular stent treatment received by the control group to be significantly cheaper than treatment with irradiation stent in the intervention group (7000 and 26,000 Chinese yuan, approximately 1000 and 3800 USD respectively, $p < 0.01$) [44].

Supplementary 16 and 17 represent the results of the quality assessment of the studies included.

Applying the GRADE approach to each of the outcomes assessed above resulted in a very low (D) level of evidence for every outcome.

Discussion

It is established knowledge that self-expanding metal stent insertion provides an acute relief of malignant dysphagia with an immediate success rate of 90–100% [57,58]. At the same time, recurring dysphagia within 4 to 10 weeks after stenting occurs in around 50% of patients [38,59]. On the other hand, radiotherapy exceeds at relieving long-term dysphagia [60], but the onset of its beneficial effects is slow, and may even worsen dysphagia early on due to radiation-induced swelling [49].

A randomized-controlled trial in 2005 demonstrated longer ongoing dysphagia relief with radiotherapy than stent alone [37].

Table 2
Data extracted on outcomes synthetized via meta-analysis, part 1.

Author (year of publication)	Group (C: control; I: intervention)	Patient Number (*n*)	Severe chest pain (*n*)	Hemorrhage (*n*)	Deaths due to hemorrhage (*n*)	Stent migration (*n*)	Restenosis/stent obstruction (*n*)
Bakheet (2019)	C	41				2	
	I	64				8	
Tian (2016)	C	91	16	6	6	5	4
	I	40	12	1	1	2	2
Zhao (2016)	C	25	3	0	0	0	3
	I	18	2	0	0	0	2
Kim (2015)	C	45					
	I	44					
Liu (2014)	C	32	9	7	3	4	
	I	31	8	11	4	3	
Zhu (2014)	C	75	15	5	5	0	
	I	73	17	5	6	0	
Zhongmin (2012)	C	30	24			2	2
	I	28	15			1	1
Xu (2011)	C	17	4	4			7
	I	15	3	4			3
Zhao (2011)	C	25	4	0		0	
	I	18	3	0		0	
Burstow (2009)	C	67					
	I	23					
Guo (2008)	C	27	7	7	7	3	6
	I	26	8	9	9	2	8
Zhang (2005)	C	34		3		3	7
	I	33		7		2	1
Fu (2004)	C	27	4	1			9
	I	26	7	2			1
Javed (2004)	C	37				0	9
	I	42				1	6
Zhong (2003)	C	18	1	2		1	
	I	16	0	3		0	
Ludwig (1998)	C	17					
	I	12					
Raijman (1997)	C	21	4	2			
	I	39	9	2			

Table 3
Data extracted on outcomes synthetized via meta-analysis, part 2.

Author (year of publication)	Group (C: control; I: intervention)	Patient Number (*n*)	Mean dysphagia grade before stenting[a]	Mean dysphagia grade within 3 days of stenting[a]	Fistula formation (*n*)	Aspirational pneumonia (*n*)
Bakheet (2019)	C	41	3.15	1.17		
	I	64	3.17	1.14		
Tian (2016)	C	91	3.27	0.20		
	I	40	3.28	0.38		
Zhao (2016)	C	25				
	I	18				
Kim (2015)	C	45				
	I	44				
Liu (2014)	C	32	3.03		1	3
	I	31	3.10		2	2
Zhu (2014)	C	75	3.40	1.30	5	14
	I	73	3.30	1.40	6	11
Zhongmin (2012)	C	30	3.40			
	I	28	3.43			
Xu (2011)	C	17				
	I	15				
Zhao (2011)	C	25				
	I	18				
Burstow (2009)	C	67				
	I	23				
Guo (2008)	C	27	3.12	1.04	0	2
	I	26	3.22	1.07	1	1
Zhang (2005)	C	34	2.15		1	
	I	33	2.18		3	
Fu (2004)	C	27				
	I	26				
Javed (2004)	C	37	3.22		0	
	I	42	3.10		0	
Zhong (2003)	C	18	3.11			
	I	16	3.06			
Ludwig (1998)	C	17				
	I	12				
Raijman (1997)	C	21	3.60	1.40		
	I	39	3.50	1.40		

[a] Measured on a 4-grade scale.

Table 4
Results of the meta-analysis.

	N of studies	RR or WMD	(95% CI)	I^2 (%)
Chest pain requiring opioids				
All studies[a]	12	1.03	(0.84–1.26)	0.0
Irradiation stent only	8	0.96	(0.84–1.26)	5.2
Other oncological treatment	4	1.03	(0.63–4.21)	0.0
Hemorrhage				
All studies[a]	11	1.32	(0.89–1.98)	0.0
Irradiation stent only	7	1.25	(0.79–1.97)	0.0
Other oncological treatment	4	1.62	(0.71–3.71)	0.0
Deaths due to hemorrhage				
Irradiation stent only[c]	5	1.19	(0.67–2.11)	0.0
Stent migration				
All studies[a]	11	0.96	(0.51–1.78)	0.0
Irradiation stent only	7	0.78	(0.35–1.71)	0.0
Other oncological treatment	4	1.34	(0.49–3.68)	0.0
Stent restenosis				
All studies[a]	8	0.62	(0.36–1.09)	21.6
Irradiation stent only	5	0.92	(0.51–1.66)	0.0
Other oncological treatment	3	0.29	(0.09–0.93)	39.7
Fistula formation				
All studies[a]	5	1.62	(0.68–3.87)	0.0
Irradiation stent only	3	1.47	(0.55–3.91)	0.0
Other oncological treatment	2	2.35	(0.34–16.10)	0.0
Aspirational pneumonia				
All studies[a]	3	0.76	(0.40–1.45)	0.0
Fever				
All studies[a]	3	1.24	(0.61–2.50)	0.0
Dysphagia grade before stenting				
All studies[a]	7	−0.03[b]	(-0.11–0.05)	0.0
Dysphagia grade after stenting within 3 days				
All studies[a]	4	0.08[b]	(-0.01–0.17)	0.0

OR: odds ratio; WMD: weighted mean difference.
[a] All studies where the corresponding outcome was reported.
[b] Weighted mean difference.
[c] Only studies with irradiation stents contained this outcome.

The complementary effects of the immediate relief from the stent insertion and the long term effect of brachytherapy make the combination of palliative stenting and radiotherapy a rational decision. Several individual studies suggest that brachytherapy using irradiation stents is associated with prolonged survival, in addition to the effective treatment of dysphagia (both acutely and on the long-term) [56,61].

Our meta-analysis did not find a significant difference in any assessed complications of stenting between the two groups, which suggests that active oncological therapy combined with stenting is non-inferior to stenting alone in terms of its safety. Our analysis did not cover the potential differences in quality of life between the two groups; however we believe this to be an important parameter to monitor, which should be taken into consideration when designing future trials.

Limitations and explanation of heterogeneity

While conducting the meta-analysis, we came across several limitations that may potentially impair the strength of our findings.

Regarding differences in patient populations, the tumor stage of involved patients varied from study to study. The articles reported this characteristic inconsistently, by describing the mean tumor stage [44,48,50], the number of patients with metastatic cancer [40,42,49,50], or the ECOG performance scale of the patients [48].

Methodological differences between studies include that the modality of active oncological treatment was not the same in every article. Most studies utilized I^{125}-coated irradiation stents in the intervention group [40,42,44,45,48,54,55]. In other cases, external radiotherapy, chemotherapy or both were applied in addition to stenting as intervention [41,43,46,47,49,50].

Statistical methods did not reveal the causes for heterogeneity among the included studies. The major confounding factors accounting for the heterogeneity are likely the differences between the populations (age, gender ratio, histological type of cancer) in the individual studies, the differences between the standard of palliative care. Chronological bias may be another important confounder as studies spread between 1997 and 2019.

Another methodological difference is the inconsistency of follow-up periods. Only 5 studies out of the analyzed 17 included data on the follow-up time of patients [40,42,44,47,48].

In case of two articles, patients were allowed to receive different treatment in addition to the treatment modalities of their assigned group. In Zhao et al., the use of alternative medicine and chemotherapy was allowed before, concurrently with, or after the assigned treatment [45]. In the study conducted by Guo et al., some patients received traditional Chinese medicine as well as their assigned treatment [40].

With regards to the outcomes assessed, we found slight differences in the definition of dysphagia between studies. Although every article that assessed dysphagia did so as a 0–4 scale, the definition of each value varied slightly.

Generalizability of the findings is questionable as the majority of studies are from China, some, from the same center, with squamous cell cancer as the predominant type of esophageal cancer. As environmental and genetic factors may be very different, the results above may not be reproducible in Western populations.

Table 5
Data extracted on outcomes synthetized via systematic review [a]measured on a 4-grade scale, [b]measure of effect not specified in the article.

Author (year of publication)	Group (C: control; I: intervention)	Patient Number (*n*)	Mean dysphagia grade after stenting at 1 month[a]	Mean dysphagia grade after stenting at 3 months[a]	Mean dysphagia grade after stenting at 5 months[a]	Fever (*n*)	Medical costs[b] (Chinese yuan)	Perforation (*n*)
Bakheet (2019)	C	41						
	I	64						
Tian (2016)	C	40					7000	
	I	91					26,000	
Zhao (2016)	C	25						0
	I	18						0
Kim (2015)	C	45						
	I	44						
Liu (2014)	C	32	1.60	2.60		4		3
	I	31	1.70	2.10		6		2
Zhu (2014)	C	75	1.76	2.56	2.65			
	I	73	1.74	1.85	1.87			
Zhongmin (2012)	C	30						
	I	28						
Xu (2011)	C	17				5		
	I	15				6		
Zhao (2011)	C	25						
	I	18						
Burstow (2009)	C	67						
	I	23						
Guo (2008)	C	27	1.17			3		
	I	26	1.22			1		
Zhang (2005)	C	34						1
	I	33						4
Fu (2004)	C	27						
	I	26						
Javed (2004)	C	37		1.27	2.55			0
	I	42		1.27	1.45			0
Zhong (2003)	C	18		1.36				
	I	16		1.29				
Ludwig (1998)	C	17						
	I	12						
Raijman (1997)	C	21						0
	I	39						0

Our meta-analysis found that stenting with additional active oncological therapy does not increase the risk for complications of stenting in case of patients diagnosed with unresectable esophageal cancer as compared to stenting alone. Furthermore, our systematic review strongly suggests that additional oncological therapy may prolong the survival of patients after stenting, and irradiation stents may be more effective in the relief of late dysphagia when compared to stenting alone.

However, due to the differences in study design, definition of outcomes and patient characteristics of the studies included, the quality of evidence remains very low. We believe that further large-scale, randomized-controlled trials are warranted to assess the effectiveness and safety of palliative treatment modalities in esophageal cancer.

Guarantor of the article

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Specific author contributions

Erőss B and Hegyi P conceptualized and designed the study in cooperation with Sarlós P; Tinusz B and Szakács Z constructed the search query and carried out the search process; Tinusz B, Szapáry L and Feczák D screened the articles for eligibility; Tinusz B and Szapáry L performed the data extraction; Tinusz B and Erős A conducted the quality assessment; Tinusz B and Erőss B wrote the article; Soós A carried out the statistical analysis; Márta K, Venglovecz V and Hegyi P provided valuable feedback after critically reviewing the first drafts of the manuscript. All authors reviewed and approved the final manuscript for publication.

PRISMA 2009 Checklist statement

The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised accordingly.

Statement of interests

1. Authors' declaration of personal interests:
   The authors declare no competing interests.
2. Declaration of funding interests:
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Table 6
Detailed data on the survival outcome of our systematic review; [1]mean, [2]median [3]confidence interval, [4]standard deviation, [5]range.

Author (year of publication)	Design	Group definitions (C: Control; I: Intervention)	Patient number (*n*)	Survival time (months)	*p* value of the long-rank test
Bakheet (2019)	Retrospective cohort	C I	41 64	4.4[1] (3.23–5.57)[3] 5.2[1] (4.4–6.0)[3]	0.592
Tian (2016)	Cohort	C I	40 91	4.2[1] (2.8)[4] 4.4[1] (2.4)[4]	0.752
Zhao (2016)	RCT	C I	25 18	4.8[1] (3.9)[4] 9.8[1] (4.3)[4]	<0.01
Kim (2015)	Retrospective cohort	C I	45 44	3,2[1] (3.0)[4] 5,6[1] (4.2)[4]	<0.001
Liu (2014)	Cohort	C I	32 31	3.1[1] (2.6–3.6)[3] 3.7[1] (3.1–4.3)[3]	0.064
Zhu (2014)	RCT	C I	75 73	4.9[2] (5.1–6.7)[5] 5.9[2] (4.1–5.7)[5]	0.0046
Zhongmin (2012)	Cohort	C I	30 28	4.9[2] (1–12)[5] 11[2] (3–18)[5]	<0.001
Zhao (2011)	Cohort	C I	25 18	4.8[1] (4.83–8.77)[3] 9.8[1] (9.43–12.83)[3]	<0.01
Guo (2008)	RCT	C I	27 26	3.5[1] (2.72–4.16)[3] 8.3[1] (6.36–10.21)[3]	<0.001
Fu (2004)	RCT	C I	27 26	8.17[1] (5.47–10.83)[3] 8.73[1] (6.97–11.5)[3]	0.813
Javed (2004)	RCT	C I	37 42	42 62	0.009
Ludwig (1998)	Cohort	C I	17 12	4.6[2] (0.85–25.7)[5] 8.0[2] (0.3–10.57)[5]	<0.05

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.05.015.

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