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ORIGINAL ARTICLE

Comparison of 125 Iodine Seed-Loaded Stents with Different Diameters in Esophageal Cancer: A Multicenter Retrospective Cohort Study

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Abstract

Currently, there are no recommendations or guidelines concerning the preferred diameter of esophageal stents for palliative treatment, owing to the lack of adequate evidence. We therefore conducted a retrospective cohort study to evaluate whether 18 mm stents would achieve a similar function of dysphagia relief with fewer complications and longer survival compared to 20 mm stents. Esophageal cancer patients who underwent 125 iodine seed-loaded stent placement with a diameter of either 18 mm ($n=103$) or 20 mm ($n=54$) were included at five hospitals in China. The stabilized inverse probability of treatment weighting (IPTW) was used to control potential confounding factors and bias that are inherent in a retrospective study. The primary endpoint was dysphagia relief. Stent-related complications and overall survival were assessed as the secondary endpoints. In the IPTW-adjusted analysis, no significant difference was found in the dysphagia score between the two groups either at 1 week after stent placement or at the last week before death. Despite a comparable rate of overall complications, there was a significantly lower incidence of severe retrosternal pain (15.4% vs. 32.7%, $p=0.013$) and a trend toward longer survival (median survival, 176 days [95% confidence interval (CI) 144 to 209] vs. 109 days [92 to 126], $p=0.057$) in the 18 mm group. An irradiated stent with a diameter of 18 mm showed a similar outcome of dysphagia relief to that achieved with a 20 mm diameter stent, but halved the incidence of retrosternal pain after stent placement.

Keywords Advanced esophageal cancer · Deglutition · Deglutition disorders · Stent diameter · Brachytherapy · Inverse probability of treatment weighting

Introduction

More than 70% of patients with esophageal cancer suffer from dysphagia which can lead to malnutrition [1]. Esophageal stent insertion, as a safe, effective, and quicker procedure to dysphagia relief [2], has been recommended by guidelines [3, 4]. For patients with unresectable esophageal cancer, esophageal stent placement may restore oral intake, improve nutritional status, and reduce hospital stay and costs [5–7]. Therefore, stent placement is an important clinical management strategy for esophageal cancer patients. However, no consensus has been reached regarding the key issue of stent diameter, owing to the theoretical dilemma that larger stents would achieve better esophageal patency and more sufficient esophageal decompression, but may increase the risk of stent-related complications.

Currently, the diameter of esophageal stents range from 16 to > 23 mm in different countries [8, 9]. One study

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conducted in 2007 compared 18 mm and 20 mm stents in malignant esophageal strictures [10]. The findings suggested that recurrent dysphagia from stent migration, tissue overgrowth, and food bolus obstruction were more frequent in patients with small diameter stents (18 mm, 21–42%) than in those with large diameter stents (20 mm, 10–15%). Increasing the diameter in some stent types may, however, increase the risk of hemorrhage, perforation, fistula, and fever. In 2015, a randomized trial compared the outcomes between small diameter esophageal stents (18 mm shaft/23 mm proximal flange) and a large one (23 mm shaft/28 mm proximal flange) for malignant esophageal obstruction [11]. It was observed that in addition to the similar palliation of dysphagia (38% vs. 47%, $p=0.23$) and the cumulative incidence of adverse events in both groups, trends toward more frequent gastrointestinal bleeding and esophago-respiratory fistulas were found in the large diameter group, while more frequent stent migration was observed in the small diameter group. In contrast, another study conducted in 2018 reported that a larger width stent (20 mm diameter) could be a risk factor for migration compared with a smaller stent (18 mm diameter) (OR 7.70, 95% CI 2.03–29.20, $p=0.003$) [12]. Thus, the effect of stent diameter on dysphagia relief and related complications in esophageal cancer patients remains unclear. Further evidence is needed to support the proper strategy in choosing the stent size for patients.

An esophageal stent loaded with iodine-125 (^{125}I) seeds, combining the advantages of stent placement and brachytherapy, has been developed by our team and applied to clinical practice in recent years in China. Our previous phase 2 and 3 trials showed that compared to the conventional, covered, self-expandable metallic stent (SEMS), patients treated with ^{125}I seed-loaded stents had a longer median survival (177 days [95% CI 153–201] vs. 147 days [124–170], $p=0.046$) and a better long-term performance status of esophageal patency ($p<0.05$), yet a comparable rate of major complications was observed between the two groups [13, 14]. However, no in-depth study has investigated the association between stent diameter and the clinical outcomes of this treatment strategy.

In addition, considering the difference in patients' body surface area in different regions, the outcome of esophageal stent placement with different diameters requires urgent observation. Therefore, the aim of this study was to observe the effect of different diameters of ^{125}I seed-loaded stents on clinical outcomes through a retrospective study. To reduce the impact of treatment selection bias and potential confounding factors inherent to a retrospective study, significant differences in patient characteristics, disease status, and symptom burden were rigorously adjusted using stabilized inverse probability of treatment weighting (IPTW) [15, 16].

Materials and Methods

Study Design and Patients

This is a multicenter, retrospective study comparing the palliative therapy of ^{125}I seed-loaded stents with 18 mm and 20 mm diameter in patients with malignant esophageal strictures. The inclusion criterion was patients with unresectable or postoperative recurrent esophageal cancer who underwent ^{125}I seed-loaded stent placement from June 2012 to March 2016 at five hospitals in China. The exclusion criteria included receiving radiotherapy or chemo-radiotherapy after ^{125}I seed-loaded stent placement and incomplete follow-up data. All five hospitals are public university hospitals. This study was approved by the clinical ethics committee of each participating hospital. The need for informed consent was waived because of its retrospective nature.

Stent Placement

Patients or their relatives provided written informed consent before stent placement. The ^{125}I seed-loaded stent was a combination of a fully covered SEMS (Nanjing Micro-Tech Co Ltd., Nanjing, China) and ^{125}I radioactive seeds (CIAE-6711; Chinese Atomic Energy Science Institution, Beijing, China) (Fig. 1) [14]. The location and length of the lesions were evaluated via endoscopy, and a stent 2 cm longer than the stricture at both the superior and inferior margins was selected. Calculations of the number, dosage, and distribution of ^{125}I seeds were completed by a treatment planning system (TPS, FTT Technology Ltd. Co, Beijing, China). A standard stent placement procedure was performed under the guidance of either fluoroscopy or endoscopy after topical anesthesia. Radiation safety and management were conducted according to the criteria from the International Commission on Radiological Protection [17].

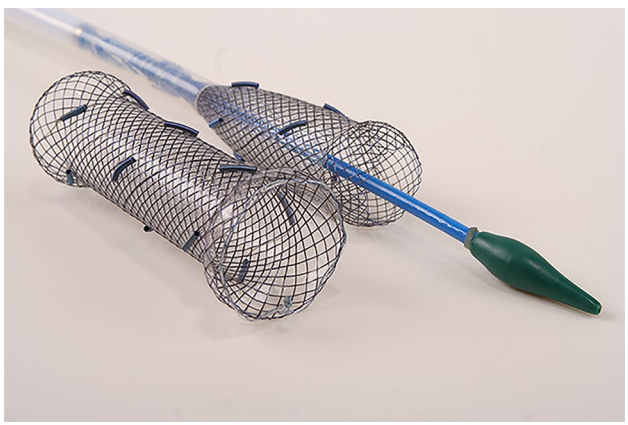

Fig. 1 The 125 iodine seed-loaded stent utilized in this study

Data Collection and Outcomes

Data were retrieved from medical records at each hospital with the assistance of a trained local coordinator or doctor and were supplemented with data for follow-up. The collected data included demographics and clinical characteristics before stent placement and the outcomes after the procedure.

The primary outcome was the relief of dysphagia after ^{125}I seed-loaded stent placement between the two groups. The relief of dysphagia was defined as a decrease in the dysphagia score (0 for nil, 1 for normal diet avoiding certain foods such as raw apple and steak, 2 for semisolid diet, 3 for fluids only, and 4 for complete dysphagia, even for liquids) [18] between the time of stent placement and the last week before death or the cutoff time of follow-up examinations (September 31, 2016).

The incidence of stent-related complications and overall survival were designed as the secondary endpoints. The complications, including hemorrhage, aspiration pneumonia, fistula formation, recurrent dysphagia, stent loss, and severe chest pain, were recorded according to the Common Terminology Criteria for Adverse Events (CTCAE 4.02) by experienced clinical doctors [19, 20].

Hemorrhage was defined as hematemesis after stent placement that required endoscopic intervention or rehospitalization. Fistula formation, stent loss, and recurrent dysphagia (due to the occurrence of tissue growth or overgrowth, stent migration, or food obstruction) were confirmed by endoscopy. Pain, as a stent-related complication, was defined as retrosternal pain that required an analgesic for relief or a numeric rating scale (NRS) score ≥ 7. Data on the use of analgesic drugs and the NRS scores (0 for nil, 1–3 for mild pain, 4–6 for moderate pain, and 7–10 for severe pain) [21, 22] were extracted from the medical records at five hospitals. Overall survival was defined as the time from the placement of the ^{125}I seed-loaded stent to death from any cause. If patients were alive, the endpoint was censored at the date of last confirmed contact (September 31, 2016).

Statistical Analyses

The balance of baseline characteristics was assessed between the two groups according to the diameter of the ^{125}I seed-loaded stent they received. To account for selection bias, differences in baseline characteristics were controlled by performing a stabilized IPTW analysis [15]. We calculated the probability of receiving the stent with a diameter of 18 mm (propensity score) for each patient using a logistic regression model. The model included the following independent variables: patient age, sex, tumor histology, tumor location, TNM classification, Eastern Cooperative Oncology Group (ECOG) performance status score, stent length, previous chemo-radiotherapy, and surgical resection. We calculated individual weights using the propensity score as follows: 1/propensity score for patients receiving the 18 mm stent, and 1/(1–propensity score) for the 20 mm stent.

To assess the baseline characteristics between the two groups, differences in quantitative variables were evaluated using Student's t-test or the Mann–Whitney U test if the distribution was abnormal, and differences in the numerical data were examined using the χ^2 test or Fisher's exact test. The means and standard deviations or median and interquartile ranges (IQRs) are reported for normally or non-normally distributed continuous variables, respectively. Categorical variables are presented as frequencies and proportions. We performed these tests before and after stabilized IPTW.

After IPTW adjustment, the Wilcoxon signed-rank test was used to compare the dysphagia score and the NRS score between the two groups that received either 18 mm or 20 mm diameter stents. A chi-square test or McNemar test was used to test stent-related complications between the two groups. Overall survival was estimated using the Kaplan–Meier method, and log-rank tests were performed to compare the differences between groups.

We performed all analyses using SPSS software version 18.0, and two-sided statistical significance was defined as $p < 0.05$.

Results

Patient Characteristics in the Unweighted and Weighted Populations

From June 2012 to March 2016, a total of 186 esophageal cancer patients were reviewed for eligibility, and 29 patients were excluded. The main reasons for exclusion were the administration of additional chemo-radiotherapy treatments after stent placement ($n = 16$) and loss to follow-up ($n = 13$). Finally, 157 patients were included in this analysis, with 103 patients in the 18 mm group and 54 patients in the 20 mm group.

The baseline characteristics of eligible patients were stratified according to the diameter of stent they received (Table 1). Five unweighted comparisons, including age, gender, segment, previous chemo-radiotherapy, and stent length, showed significant differences ($p < 0.05$) between the two groups, indicating that both treatment groups differed significantly with respect to demographic, clinical, and tumor characteristics. After stabilizing the IPTW adjustments, these factors were well balanced between the two groups, and the distribution of baseline characteristics was similar between the 18 and 20 mm diameter groups.

Table 1 Baseline characteristics of patients who underwent 18 mm diameter versus 20 mm diameter ^{125}I seed-loaded stent placement in unweighted and weighted study populations

Characteristics	Unweighted comparison ($n=157$)			Weighted comparison[b]		
	18 mm ($n=103$)	20 mm ($n=54$)	p value	18 mm	20 mm	p value
Age, years Mean (SD)	72.59 (11.33)	67.93 (9.94)	0.007	70.94 (12.08)	70.63 (9.81)	0.116
Sex, n (%)			0.015			0.544
Male	74 (71.84%)	48 (88.89%)		82 (78.1%)	41 (78.8%)	
Female	29 (28.16%)	6 (11.11%)		23 (21.9%)	11 (21.2%)	
Histology of tumor, n (%)			0.582			>0.999
Squamous cell carcinoma	76 (73.8%)	42 (77.8%)		80 (76.9%)	40 (76.9%)	
Adenocarcinoma	27 (226.2%)	12 (22.2%)		24 (23.1%)	12 (23.1%)	
Segment, n (%)			0.001			0.998
Superior segment	22 (21.36%)4	0		4 (3.8%)	2 (3.8%)	
Middle segment	40 (38.83%)54	27 (50%)		58 (55.2%)	29 (55.8%)	
Inferior segment	41 (39.81%)45	27 (50%)		43 (41.0%)	21 (40.4%)	
TNM classification, n (%)[a]			0.75			0.412
Stage II	39 (37.9%)	23 (42.6%)		38 (36.2%)	25 (47.2%)	
Stage III	24 (23.3%)	10 (18.5%)		24 (22.9%)	10 (18.9%)	
Stage IV	40 (38.8%)	21 (38.9%)		43 (41.0%)	18 (34%)	
Dysphagia score before treatment, n (%)			0.648			0.747
3	76 (73.79%)	38 (70.37%)		76 (73.1%)	40 (73.5%)	
4	27 (26.21%)	16 (29.63%)		28 (26.9%)	13 (24.5%)	
ECOG-PS, n (%)			0.705			0.960
0	3 (2.91%)	2 (3.70%)		3 (2.9%)	1 (1.9%)	
1	23 (22.33%)	10 (18.52%)		23 (21.9%)	10 (19.2%)	
2	44 (42.72%)	28 (51.85%)		46 (43.8%)	24 (46.2%)	
3	33 (32.04%)	14 (25.93%)		33 (31.4%)	17 (32.7%)	
Surgical resection			0.533			0.883
Yes	10 (9.71%)	7 (12.96%)		13 (12.4%)	7 (13.2%)	
No	93 (90.29%)	47 (87.04%)		92 (87.6%)	46 (86.4%)	
Previous chemo-radiotherapy, n (%)			0.049			0.209
Yes	47 (45.6%)	16 (30%)		45 (43.7%)	18 (33.3%)	
No	56 (54.5%)	38 (70%)		58 (56.3%)	36 (66.7%)	
Stent length, cm (mean, SD)	92.72 (18.48)	100.37 (13.17)	0.026	86.21 (16.97)	92.47 (13.50)	0.086
TP	64.82 (6.83)	65.48 (5.91)	0.107	65.19 (7.02)	65.30 (5.95)	0.923
ALB	36.92 (5.06)	37.28 (5.50)	0.331	37.12 (5.09)	37.29 (5.77)	0.849

Data are mean (SD) or n (%) and compared by the unpaired t-test or χ^2 test as appropriate

ECOG-PS Eastern Cooperative Oncology Group performance score, *TP* serum total protein concentration, *ALB* serum albumin concentration

[a]The American Joint Committee for Cancer TNM Classification for Esophageal Cancer (2010 version)

[b]Weighted by inverse probability of treatment weighting estimation to balance patient characteristics

Relief of Dysphagia in the Weighted Population

Dysphagia was relieved immediately after stent placement in all patients. The mean dysphagia scores decreased from 3.19 (95% CI 3 to 4) before stent placement to 2.01 (2 to 2) in the first week after stent placement and to 2.47 (2 to 3) in the last week before death or the last follow-up in 157 patients ($p<0.001$).

In the IPTW-adjusted analysis, no significant difference was found in the dysphagia score between the 18 and the 20 mm groups both in the first week after stent placement and in the last week before death or the last follow-up (2.02 vs. 2.00, $p=0.799$ and 2.59 vs. 2.34, $p=0.089$, respectively) (Fig. 2).

Until one week before death or the last follow-up, nine patients could eat normally without dysphagia (dysphagia score 0), ten patients could eat a normal diet avoiding certain foods such as raw apple and steak (dysphagia score 1), 62 patients could eat semisolid foods (dysphagia score 2), and 59 patients could only swallow fluids (dysphagia score

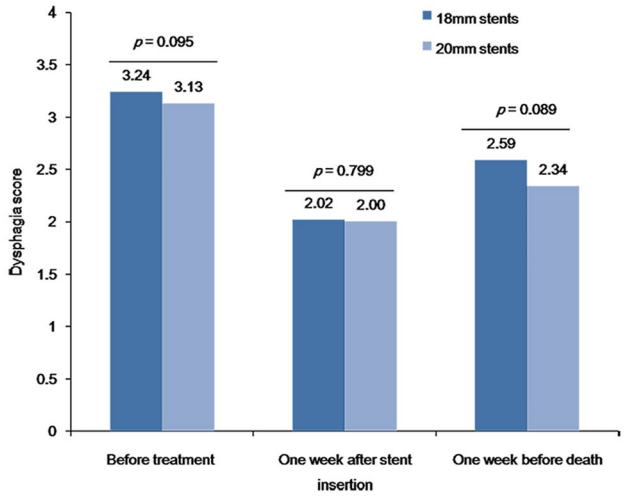

Fig. 2 Comparison of immediate and long-term relief of dysphagia between the 18 and 20 mm groups after stabilized inverse probability of treatment weighting. The Wilcoxon signed-rank test was used to compare dysphagia scores, and dysphagia scores at each time point were not different between groups

3). The remaining 17 patients were completely unable to swallow anything due to endoscopically confirmed recurrent dysphagia ($n=8$), fistula formation ($n=5$), or hemorrhage ($n=6$). Notably, despite adequate luminal patency, six patients declined to swallow anything due to retrosternal pain ($n=3$), vomiting ($n=1$), or aspiration pneumonia ($n=2$).

Complications After ^{125}I Seed-Loaded Stent Placement

Table 2 shows the complications noted in the 18 mm group versus the 20 mm group. In the weighted analysis, no significant differences were found in hemorrhage (8.7% vs. 9.6%, $p=0.843$), pneumonia (16.2% vs. 9.4%, $p=0.247$), fistula formation (7.7% vs. 5.8%, $p=0.658$), recurrent dysphagia (8.7% vs. 7.5%, $p=0.538$), or stent loss (4.8% vs. 5.86%, $p=0.534$) between the two groups. However, the incidence of severe retrosternal pain was significantly different after stent placement, with 15.4% (16/104) in the 18 mm group and 32.7% (17/52) in the 20 mm group ($p=0.013$). The pain in most patients could be controlled by an injection of dezocine. Five patients were given morphine injection at the first week after stent insertion (three in the 18 mm group and two in the 20 mm group), and two patients were given pethidine injection after 20 mm stent placement. Three patients were reluctant to eat because of pain, although patency of the esophagus had returned. Furthermore, according to the NRS score, the percentage of the most severe chest pain episodes (NRS ≥ 7) was significantly different between the two groups (1.9% vs. 9.3%, $p=0.010$) (Fig. 3).

Table 2 Complications after ^{125}I seed-loaded stent placement between the 18 mm and 20 mm groups in weighted study populations

Complications	18 mm group	20 mm group	*p* value
Severe chest pain	16 (15.4%)	17 (32.7%)	0.013[a]
Hemorrhage	9 (8.7%)	5 (9.6%)	0.843[a]
Pneumonia	17 (16.2%)	5 (9.4%)	0.247[a]
Fistula formation	8 (7.7%)	3 (5.8%)	0.658[a]
Recurrent dysphagia	9 (8.7%)	4 (7.5%)	0.538[a]
Stent migration	5 (4.8%)	3 (5.8%)	0.534[a]
Number of complications per patient			0.170[b]
0	65	23	
1	24	21	
2	9	8	
> 2	5	2	

Data are number (%)

[a] χ^2 test was used

[b] Kruskal-Wallis test was used

More than one complication occurred in 24 patients (14 in the 18 mm group and 10 in the 20 mm group). More than two complications were noted concurrently or successively in seven patients (five in the 18 mm group and two in the 20 mm group). During follow-up, six additional covered esophageal stents were inserted under fluoroscopy in six patients (three patients in each group) due to recurrent

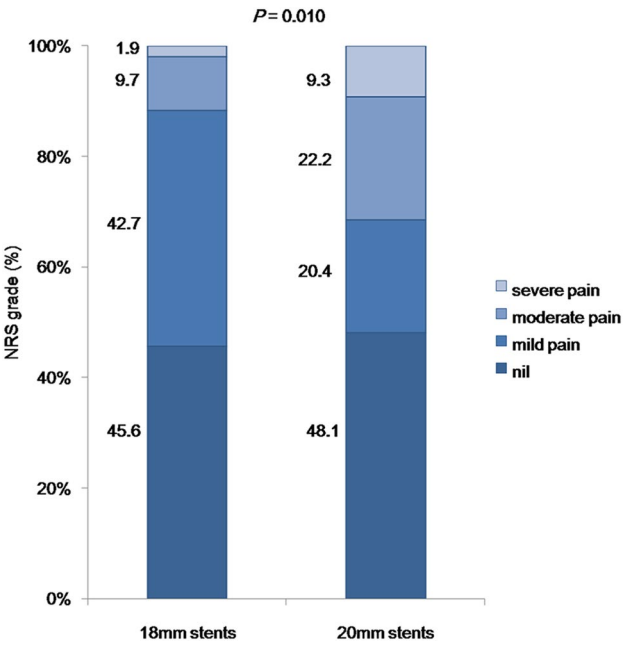

Fig. 3 Percentage bar chart of NRS grades. The percentage of the most severe NRS grade was compared with the Mann–Whitney U test and was significantly different between the two groups

dysphagia, and four ^{125}I seed-loaded stents were placed in four patients because of stent migration (three in the 18 mm group and one in the 20 mm group). Additionally, one covered stent was inserted because of an esophagotracheal fistula in a patient 6 months after 20 mm stent placement.

Survival Analyses

Of the 157 patients included in this analysis, 151 patients (96.2%) died during follow-up. The causes of death included cachexia or multiorgan failure related to disease progression ($n=102$ [67.5%]), hemorrhage ($n=3$ [2%]), pulmonary infection ($n=14$ [9.3%]), malnutrition due to recurrent obstruction of the stent ($n=11$ [7.3%]), and other unclear reasons ($n=21$ [13.9%]).

The median survival of the 157 patients was 148 days (95% CI 115–180). There was a trend toward longer survival in the 18 mm group (median survival, 176 days [95% CI 144–209] vs. 109 (92–126), $p=0.057$) (Fig. 4).

Discussion

The ideal stent diameter in esophageal stent placement should be sufficient to maintain esophageal patency, provide adequate relief of dysphagia, and equally, if not more importantly, avoid exposing patients to discomfort, such as severe retrosternal pain, thereby improving the quality of life in the terminal phases of illness. Our study suggests a favorable overall outcome with 18 mm ^{125}I seed-loaded stents and lends support to their use in patients with unresectable esophageal cancer for the relief of dysphagia with the following findings: (1) there were similar esophageal patency and overall complication rates with the 18 mm and 20 mm stents; (2) there was an advantage of 18 mm stents in reducing severe retrosternal pain; and (3) there was a trend of 18 mm stents in extending survival time after stent placement.

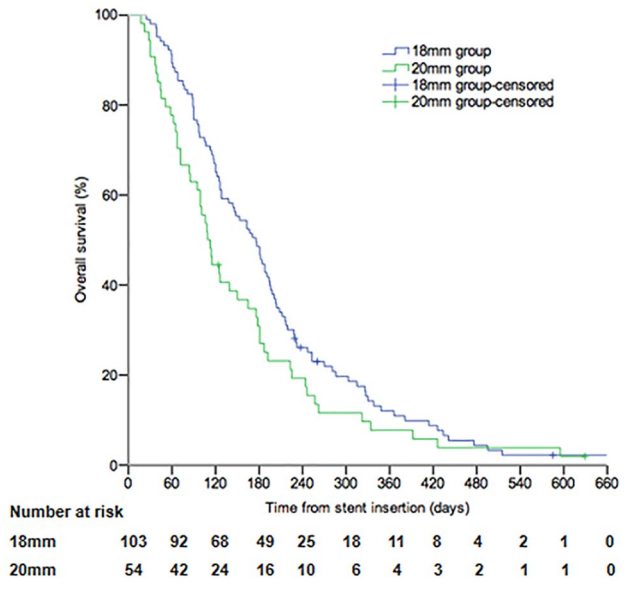

Fig. 4 Kaplan–Meier estimates of the overall survival period since the time of stent placement

The improvement of dysphagia with esophageal stent placement has been acknowledged [2, 3, 6]. The ^{125}I seed-loaded stent consisting of a metal stent and ^{125}I seeds has advantages of integrated stenting and brachytherapy, direct contact with the tumor surface, and a continuously low dosage and long-term exposure [13, 14]. This irradiation stent has been widely applied in recent years in China because of better survival benefits and long-term dysphagia relief compared to the conventional covered stent. The radioactivity emitted by each ^{125}I seed was 25.9 MBq, with a half-life of 59.4 days. The results from this analysis showed that the 18 mm stent did not compromise the relief of dysphagia, and the incidence of recurrent dysphagia was similar between the two groups (8.7% and 7.5%) yet was lower than that achieved with conventional stent placement (9.4%–39.3%), as reported in previous studies [19, 20, 23]. This finding may be due to the inhibition of tumor growth by ^{125}I seeds.

Researchers have reported that retrosternal pain, as a common and early stent-related complication, is up to 16–24.5% in the first 7 days after esophageal stent placement for malignant strictures [9, 14, 24, 25]. However, the incidence may be underestimated, and nearly 50% of patients may experience varying degrees of retrosternal pain after this palliative treatment. Stent-related severe chest pain, which is clearly of vital importance to cancer patients, should be evaluated accurately after the procedure because it directly affects the patients' comfort and even the end-stage quality of life. In this study, we combined the use of analgesic drug administration with NRS scores to define the incidence of severe pain and to fully reflect the adverse events caused by stent placement. Data from this analysis showed that the incidence rates of severe chest pain were 15.4% and 32.7% in the 18 mm and 20 mm groups, respectively ($p=0.013$), demonstrating a significant correlation between the retrosternal pain and stent diameters. This result may be attributed to the higher expansion force caused by the larger diameter stent. Except for cases that may improve spontaneously, patients with severe pain were treated with analgesics for 7–10 days after the procedure [26]. A recent study even revealed that 8% of cases of pain triggered stent removal after SEMS placement. In our study, three patients refused to swallow anything because of the severe retrosternal pain after stent insertion, even though their esophageal stricture had been resolved.

Our study has several limitations. First, although the imbalance of baseline characteristics was rigorously

adjusted by the stabilized IPTW analysis, the patency status of the stent could not be appraised directly due to the absence of endoscopic images in some patients who were home one week before death. Therefore, the relief of dysphagia was evaluated by the dysphagia score according to the follow-up data. Second, the stents used in this analysis were ^{125}I seed-loaded stent, but not the SEMS that has been used more widely in the world. However, because they were used in both groups, the type of stent may not influence the between-group comparisons. Third, the population included in the current study comprised Chinese patients whose body surface areas are smaller than that of other patient populations; hence, caution should be applied when extrapolating the results, and further investigations will be needed for other populations.

In conclusion, the present study suggests that compared to 20 mm diameter stents, 18 mm diameter ^{125}I seed-loaded stents may achieve a favorable clinical outcome with non-compromised dysphagia relief, nearly half the incidence of severe retrosternal pain, and a trend toward longer survival. Therefore, 18 mm ^{125}I seed-loaded stents should be favored for malignant esophageal strictures.

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Author Contributions GJT conceived the study and designed the main concept of the study. JQ, HDZ, TP, and JL analyzed the data. JQ and HDZ wrote the first version of the manuscript and edited the manuscript. JQ, HDZ, JHG, CFN, PW, HX, and AWM acquired the data and interpreted the results. GJT and HDZ critically revised the important intellectual content of the manuscript. All authors contributed to the discussion, reviewed the manuscript, and approved the final draft submitted.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval The current study is in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Clinical Ethics Committees of all participating hospitals.

Informed Consent Informed consent was waived because of the retrospective nature of this study.

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