I-125 seed-loaded versus normal stent insertion for obstructive esophageal cancer: a meta-analysis

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Abstract

Introduction: Malignant esophageal obstruction is usually caused by esophageal and other chest cancers. More than 80% of cases of obstructive esophageal cancer (OEC) have lost the chance of curative resection. Stent insertion is a first-line palliative approach used to treat incurable OEC.

Aim: To gauge the relative clinical efficacy of I-125 seed-loaded stent (ISS) versus normal stent (NS) insertion as a treatment for OEC.

Material and methods: Querying of the PubMed, Embase, and Cochrane Library databases was conducted to find all relevant studies published up to November 2020. The meta-analysis was undertaken using RevMan v5.3.

Results: We identified 158 studies initially, eight (4 randomized controlled trials and 4 retrospective studies) of which were used in this meta-analysis. We found that the two groups exhibited the comparable pooled Δdysphagia scores (MD = 0.02; p = 0.80), stent restenosis rates (OR = 0.97; p = 0.89), stent migration rates (OR = 0.81; p = 0.63), severe chest pain rates (OR = 1.05; p = 0.81), hemorrhage rates (OR = 1.53; p = 0.16), aspiration pneumonia rates (OR = 0.72; p = 0.38), and fistula formation rates (OR = 1.47; p = 0.44). The pooled time-to-restenosis and survival were both significantly longer in the ISS group (p = 0.04 and < 0.0001, respectively). Significant heterogeneity was detected in the endpoints of Δdysphagia scores and survival (I² = 73% and 86%, respectively). Funnel plot analysis indicated an absence of publication bias related to the selected study endpoints.

Conclusions: For patients with OEC, our meta-analysis indicated that ISS insertion could provide longer stent patency and survival than NS insertion.

Key words: I-125, seed, stent, esophageal cancer.

Introduction

Malignant esophageal obstruction is usually caused by esophageal and other chest cancers [1–4]. More than 80% of cases of esophageal obstruction were caused by esophageal cancer [2]. When patients are diagnosed with obstructive esophageal cancer (OEC), more than 80% of cases have lost the chance of curative resection [5]. In addition, patients with OEC also have a poor quality of life because of the dysphagia.

Stent insertion is a first-line palliative approach used to treat incurable OEC [1–4]. Like most malignant luminal obstruction, normal stent (NS) insertion does not directly treat the causes of obstruction [5–10]. To extend the stent patency and survival, several researchers have developed a novel I-125 seed-loaded stent (ISS) for patients with inoperable OEC [11–18].
The ISSs not only can effectively relieve the dysphagia, but also can provide the brachytherapy to the tumor [11–18]. The results from a single study can be influenced by many factors; a meta-analysis should be carried out to decrease the bias and increase the statistical power of the small sample study.

Aim

To make a definite conclusion on the efficacy of esophageal ISS, the present meta-analysis was performed to gauge the relative clinical value of ISS and NS insertion as a means of treating patients with OEC.

Material and methods

Study selection

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [19] was used to guide the present meta-analysis. The Medline, Cochrane Library, and Embase databases were queried for relevant studies published until November 2020 as follows: (((SEMS [Title/Abstract]) OR (stent [Title/Abstract])) AND (((radioactive [Title/Abstract]) OR (seed [Title/Abstract])) OR (irradiation [Title/Abstract])) OR (iodine [Title/Abstract])) OR (I [Title/Abstract])) AND ((esophagus [Title/Abstract]) OR (esophageal [Title/Abstract])).

Study inclusion criteria:
(a) type of study: comparative studies (randomized controlled trials [RCTs] and retrospective studies);
(b) disease: patients with OEC;
(c) types of intervention: ISS versus NS insertion;
(d) language: English.

Study exclusion criteria:
(a) non-comparative studies;
(b) case reports;
(c) animal or other preclinical studies;
(d) review articles.

Data extraction

Data from all included studies were independently extracted by two researchers, while discrepancies were resolved through discussion with a third author. Extracted items included: study baseline data, patient baseline data, and treatment-associated data.

Quality and bias assessment

The Cochrane risk of bias tool was used to gauge potential bias in included RCTs, which were evaluated for their risk of bias associated with selection, detection, performance, reporting, attrition, and other biases.

All studies which were not RCTs were assessed using the 9-point Newcastle-Ottawa scale [20], with scores of $\geq 7$, 4-6, and $< 4$ corresponding to low, moderate, and high bias risk, respectively.

Endpoints

The primary endpoint for this meta-analysis was survival, while secondary endpoints included clinical effectiveness, stent patency, and complications. Clinical effectiveness was evaluated by comparing the dysphagia score before and after stent insertion. Stent patency included the items of stent restenosis, time-to-restenosis (TTR), and migration. Complications included severe chest pain, hemorrhage, aspiration pneumonia, and fistula formation.

Statistical analysis

RevMan v5.3 was used to analyze data. The Mantel-Haenszel method was used to measure pooled odds ratios (ORs) and 95% confidence intervals (CIs) for dichotomous variables, and continuous variables were assessed through mean differences (MDs) and 95% CIs. Hazard ratios (HRs) with a 95% CI were used to measure pooled survival. Study heterogeneity was gauged via $\chi^2$ and $I^2$ tests, with $I^2 > 50\%$ indicating significant heterogeneity. Fixed-effects models were used for analyses when significant heterogeneity was not detected, whereas random-effects models were otherwise used. Causes of heterogeneity were assessed through subgroup and sensitivity analyses, whereas risk of bias was examined using funnel plots.

Results

Study characteristics

We initially identified 158 possibly relevant studies. Among them, four RCTs [11, 12, 17, 18] and 4 retrospective studies [13–16] were incorporated into this meta-analysis (Figure 1). Two RCTs had unclear risk of random sequence generation and allocation concealment [11, 17]. All RCTs were open label with the unclear risk of other bias (Figure 2). The Newcastle-Ottawa scale of the 4 retrospective studies ranged from 7 to 8 (Table 1).

These 8 studies included a total of 288 patients with OEC who had undergone ISS insertion and 352
who had NS insertion (Table I). All studies used metal stents. Two studies only included patients with esophageal squamous cell carcinoma [13, 15]. The baseline data were comparable between ISS and NS groups in all included studies. The outcome data are shown in Table II.

**Clinical effectiveness**

The data of improvement of dysphagia score could be extracted from 4 studies [12, 13, 16, 18]. We found that the two groups exhibited comparable pooled Δdysphagia scores (MD = 0.02; 95% CI: −0.11, 0.14; \( p = 0.80 \), Figure 3). We observed significant heterogeneity among these studies (\( I^2 = 73\% \)). The significant heterogeneity disappeared (\( I^2 = 37\% \)) when the Guo et al. [12] study was removed. Under this condition, the two groups still exhibited comparable pooled Δdysphagia scores (MD = −0.03; 95% CI: −0.12, 0.06; \( p = 0.54 \)).

**Stent patency**

The stent restenosis rates could be extracted from 7 studies [11–13, 15–18]. We observed comparable pooled stent restenosis rates between the groups (18.9% vs. 17.1%, OR = 0.97; 95% CI: 0.62–1.52; \( p = 0.89 \), Table III). No significant heterogeneity among these studies was observed (\( I^2 = 0\% \)).
### Table I. Characteristics of the included studies

| Study/year/country/design | Stent type | EC types | TS | Groups | Sample size (M/F) | Age [years] | NOS |
|---------------------------|------------|----------|----|--------|------------------|------------|-----|
| Dai/2013/China/RCT [11]   | Metal      | Multiple | Not given | ISS    | 31 (26/5) | 68 | – |
|                           |            |          |         | NS     | 36 (28/8) | 71 | – |
| Guo/2008/China/RCT [12]   | Metal      | Multiple | Not given | ISS    | 27 (19/8) | 72 | – |
|                           |            |          |         | NS     | 26 (20/6) | 70 | – |
| Li/2020/China/Re [13]     | Metal      | SCC      | III, IV | ISS    | 42 (25/17) | 63 | 8 |
|                           |            |          |         | NS     | 39 (24/15) | 63 | – |
| Liu/2014/China/Re [14]    | Metal      | Multiple | Not given | ISS    | 29 (Not given) | 60 | 8 |
|                           |            |          |         | NS     | 30 (Not given) | 61 | – |
| Tian/2016/China/Re [15]   | Metal      | SCC      | III, IV | ISS    | 40 (30/10) | 67 | 7 |
|                           |            |          |         | NS     | 91 (67/24) | 66 | – |
| Zhongmin/2012 China/Re [16] | Metal   | Multiple | II–IV  | ISS    | 28 (19/9) | 65 | 8 |
|                           |            |          |         | NS     | 30 (18/12) | 69 | – |
| Zhao/2016/China/RCT [17]  | Metal      | Multiple | III, IV | ISS    | 18 (Not given) | 70 for all | – |
|                           |            |          |         | NS     | 25 (Not given) | – | – |
| Zhu/2014/China/RCT [18]   | Metal      | Multiple | II–IV  | ISS    | 73 (61/12) | 71 | – |
|                           |            |          |         | NS     | 75 (53/22) | 71 | – |

EC – esophageal cancer; RCT – randomized controlled trial; Re – retrospective, SCC – squamous cell carcinoma, TS – tumor stage, M – male, F – female, NOS – Newcastle-Ottawa scale.

### Table II. Characteristics of the treatment outcomes

| Study     | Groups | Restenosis | Migration | Severe chest pain | Hemorrhage | Aspiration pneumonia | Fistula formation | Survival |
|-----------|--------|------------|-----------|-------------------|------------|----------------------|-------------------|----------|
| Dai [11]  | ISS    | 11/31 (35.5%) | Not given | Not given | Not given | Not given | Not given | 145 d    |
|           | NS     | 16/36 (44.4%) | Not given | Not given | Not given | Not given | Not given | 90 d     |
| Guo [12]  | ISS    | 8/27 (29.6%) | 2/27 (7.4%) | 8/27 (29.6%) | 9/27 (33.3%) | 1/27 (3.7%) | 1/27 (3.7%) | 8.3 mo |
|           | NS     | 6/26 (23.1%) | 3/26 (11.5%) | 7/26 (26.9%) | 7/26 (26.9%) | 2/26 (7.7%) | 0/26 (0%) | 3.5 mo  |
| Li [13]   | ISS    | 4/42 (9.5%) | 1/42 (2.4%) | 8/42 (19.0%) | 7/42 (16.7%) | Not given | Not given | 187 d   |
|           | NS     | 5/39 (12.8%) | 0/39 (0) | 5/39 (12.8%) | 7/39 (17.9%) | Not given | Not given | 145 d   |
| Liu [14]  | ISS    | Not given | 3/29 (10.3%) | 8/29 (27.6%) | 11/29 (38%) | 2/29 (6.9%) | 3/29 (10.3%) | 3.7 mo  |
|           | NS     | Not given | 4/30 (13.3%) | 9/30 (30%) | 7/30 (30%) | 3/30 (10%) | 2/30 (6.7%) | 3.1 mo  |
| Tian [15] | ISS    | 2/40 (5%) | 2/40 (5%) | 16/40 (40%) | 1/40 (2.5%) | Not given | Not given | 4.4 mo  |
|           | NS     | 3/91 (3.3%) | 5/91 (5.5%) | 16/91 (17.6%) | 6/91 (6.6%) | Not given | Not given | 4.2 mo  |
| Zhongmin [16] | ISS   | 1/28 (3.6%) | 1/28 (3.6%) | 15/28 (53.6%) | Not given | Not given | Not given | 11 mo   |
|           | NS     | 2/30 (6.7%) | 2/30 (6.7%) | 24/30 (80%) | Not given | Not given | Not given | 4.9 mo  |
| Zhao [17] | ISS    | 2/18 (11.1%) | 0/18 (0%) | Not given | 0/18 (0%) | Not given | Not given | 9.8 mo  |
|           | NS     | 3/25 (12%) | 0/25 (0%) | Not given | 0/25 (0%) | Not given | Not given | 4.8 mo  |
| Zhu [18]  | ISS    | 21/73 (28.8%) | Not given | 17/73 (23.3%) | 5/73 (6.8%) | 11/73 (15.1%) | 6/73 (8.2%) | 177 d |
|           | NS     | 20/75 (26.7%) | Not given | 15/75 (20%) | 5/75 (6.7%) | 14/75 (18.7%) | 5/75 (6.7%) | 147 d  |

d – days, mo – months.
The data of TTR could be extracted from 2 studies [12, 13]. The pooled TTR was significantly longer in the ISS group (MD = 1.85; 95% CI: 0.09–3.61, p = 0.04, Table III). No significant heterogeneity among these studies was observed ($I^2 = 50\%$).

The stent migration rate could be extracted from 6 studies [12–17]. We observed comparable pooled stent migration rates between groups (4.9% vs. 5.8%, OR = 0.81; 95% CI: 0.34–1.92; p = 0.63, Table III). No significant heterogeneity among these studies was observed ($I^2 = 0\%$).

**Survival**

The data of survival could be extracted from all studies. The pooled survival duration was significantly longer in the ISS group (HR = 1.53; 95% CI: 1.26–1.85, p < 0.0001, Figure 4). We observed significant heterogeneity among these studies ($I^2 = 86\%$). The significant heterogeneity disappeared ($I^2 = 50\%$) when the Tian et al. [15] study was removed. Under this condition, the ISS group still exhibited significantly longer pooled survival duration (MD = 1.61; 95% CI: 1.38–1.87; p < 0.0001).

**Complications**

The severe chest pain rates could be extracted from 6 studies [12–16, 18]. We observed comparable pooled severe chest pain rates between the two groups (27.6% vs. 26.1%, OR = 1.05; 95% CI: 0.70–1.58; p = 0.81, Table IV). No significant heterogeneity among the included studies was observed ($I^2 = 30\%$).

The hemorrhage rates could be extracted from 6 studies [12–15, 17, 18]. We observed comparable pooled hemorrhage rates between the two groups (14.4% vs. 9.1%, OR = 1.53; 95% CI: 0.85–2.75; p = 0.16, Table IV). We did not observe significant heterogeneity ($I^2 = 11\%$).

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Table III. Meta-analytic pooled results of the stent patency

| Variable         | Number of studies | OR/MD (95% CI), p | Heterogeneity | Favor |
|------------------|------------------|------------------|---------------|-------|
| Restenosis       | 7                | 0.97 (0.62–1.52), 0.89 | 0.89 | $I^2 = 0\%$ – |
| Time-to-restenosis| 2                | 1.85 (0.99–3.61), 0.04 | 0.00 | $I^2 = 50\%$ ISS |
| Migration        | 6                | 0.81 (0.34–1.92), 0.63 | 0.00 | $I^2 = 0\%$ – |

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Figure 3. The pooled Δ dysphagia scores were comparable between the two groups

Figure 4. The pooled survival duration was significantly longer in the ISS group
The aspiration pneumonia rates could be extracted from 3 studies [12, 14, 18]. We observed comparable pooled aspiration pneumonia rates between the two groups (10.9% vs. 14.5%, OR = 0.72; 95% CI: 0.34–1.51; p = 0.38, Table IV). We did not observe significant heterogeneity (I² = 0%).

The fistula formation rates could be extracted from 3 studies [12, 14, 18]. We observed comparable pooled fistula formation rates between the two groups (7.8% vs. 5.3%, OR = 1.47; 95% CI: 0.56–3.90; p = 0.44, Table IV). We did not observe significant heterogeneity (I² = 0%).

Subgroup analyses

Subgroup analyses were performed based on the studies which focused on esophageal squamous cell carcinoma [13, 15]. Five endpoints could be pooled (Table V). We observed that the pooled restenosis rate (p = 0.91), migration rate (p = 0.81), chest pain rate (p = 0.16), hemorrhage rate (p = 0.74), and survival (p = 0.74) were all similar between groups. Significant heterogeneity was found in the endpoints of hemorrhage rate (I² = 74%) and survival (I² = 83%).

Publication bias

No potential publication bias pertaining to selected study endpoints was detected in funnel plot analyses.

**Table IV.** Meta-analytic pooled results of the complications

| Variable               | Number of studies | OR/MD (95% CI), p       | Heterogeneity | Favor |
|------------------------|-------------------|-------------------------|---------------|-------|
| Severe chest pain      | 6                 | 1.05 (0.70–1.58), 0.81  | I² = 30%      | –     |
| Hemorrhage             | 6                 | 1.53 (0.85–2.75), 0.81  | I² = 11%      | –     |
| Aspiration pneumonia   | 3                 | 0.72 (0.34–1.51), 0.38  | I² = 0%       | –     |
| Fistula formation      | 3                 | 1.47 (0.56–3.90), 0.44  | I² = 0%       | –     |

OR – odds ratio, MD – mean difference.

**Table V.** Meta-analytic pooled results based on the studies regarding squamous cell carcinoma

| Variable    | Number of studies | OR or HR (95% CI), p | Heterogeneity | Favor |
|-------------|-------------------|----------------------|---------------|-------|
| Restenosis  | 2                 | 0.94 (0.31–2.86), 0.91 | I² = 0%       | –     |
| Migration   | 2                 | 1.19 (0.29–4.96), 0.81 | I² = 0%       | –     |
| Chest pain  | 2                 | 1.66 (0.81–3.41), 0.16 | I² = 0%       | –     |
| Hemorrhage  | 2                 | 1.66 (0.08–32.82), 0.74 | I² = 74%     | –     |
| Survival    | 2                 | 1.28 (0.81–2.02), 0.74 | I² = 83%     | –     |

OR – odds ratio; HR – hazard ratio.

Discussion

Herein, we evaluated the safety, clinical effectiveness, and long-term effects of ISS and NS insertion in OEC patients. Firstly, we found that the pooled dysphagia scores were similar between the 2 groups (p = 0.80). This result indicated that both ISS and NS can rapidly alleviate OEC patient symptoms.

While short-term clinical benefit can be achieved with different types of stents, stent restenosis remains the major problem which limits the long-term outcome in patients with OEC [11–18]. The major causes of stent restenosis are tumor growth, followed by fibroepithelial hyperplasia and food debris obstruction [11–18]. Several therapeutic approaches have been conducted to try and decrease rates of restenosis [5–7]. Compared to the traditional external beam radiation, I-255 seed brachytherapy better shields surrounding tissues, more precisely targeting radiation to the tumor site [21].

In this meta-analysis, the stent restenosis rates were similar between groups (p = 0.89). This result might be attributed to the fact that ISS could only decrease the cancer-specific restenosis rate. However, the TTR was significantly longer in the ISS group (p = 0.04). Although ISS cannot prevent stent restenosis, it was able to inhibit tumor growth and to thereby prolong stent patency in treated patients.

Another problem regarding stent dysfunction is migration. Stent migration usually occurred due to tumor shrinkage after anticancer treatment. Howev-
er, the stent migration rates were only observed as 4.9% and 5.8% in ISS and NS groups, respectively \((p = 0.63)\). These results might be attributed to the anti-migration design of the esophageal stents. The esophageal stents were usually designed as a tubular configuration with a drum structure at double ends \([1]\). The bilateral drum structure can help to fix the stent to the esophageal wall.

The pooled HR value indicated that ISS can significantly improve patients’ survival. This result is consistent with findings from other meta-analyses regarding ISS insertion for malignant biliary obstruction patients \([22–24]\).

The major complications of esophageal stent included severe chest pain, hemorrhage, aspiration pneumonia, and fistula formation \([11–18]\). We found that ISS did not increase such complications when compared to NS. These results showed that ISS insertion was safe for palliative management for OEC patients.

We conducted a subgroup analysis of esophageal squamous cell carcinoma patients \([13, 15]\). In this analysis, we found that ISS might have no effect on prolonging survival for patients with esophageal squamous cell carcinoma. In the Li et al. \([13]\) study, survival was significantly longer in the ISS group (187 days vs. 145 days, \(p = 0.011\)). However, Tian et al. found that the overall and cancer-specific survival were both comparable between 2 groups \([15]\). In research by Tian et al. \([15]\) hemorrhage and tumor metastasis were the primary causes of death, and while inhibition of tumor growth was possible, ISS did not prevent either of these causes of mortality. Furthermore, there was significant heterogeneity in the points of survival \((I^2 = 83\%)\). Therefore, more studies should be added to investigate the clinical effectiveness of ISS for patients with esophageal squamous cell carcinoma.

There are some limitations to the results of our study. For one, most included studies were retrospective and may thus be prone to bias. Second, patients enrolled in the included studies suffered from OEC associated with a variety of tumor subtypes, potentially limiting the reliability of our results. Future research will thus be required to evaluate these endpoints in the context of specific cancer subtypes. Third, there is a lack of studies regarding ISS versus NS with other type of radiation therapy; therefore, we cannot compare the clinical effectiveness between brachytherapy and other types of radiation therapy. Last, all included studies were performed in China. Future work will thus be required to assess the validity of these findings in other populations.

**Conclusions**

We found that ISS can extend stent patency and OEC patient survival as compared with NS insertion.

**Conflict of interest**

The authors declare no conflict of interest.

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