International Journal of Colorectal Disease (2019) 34:1827–1838
https://doi.org/10.1007/s00384-019-03372-5

REVIEW

Long-term tumour outcomes of self-expanding metal stents as 'bridge to surgery' for the treatment of colorectal cancer with malignant obstruction: a systematic review and meta-analysis

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Accepted: 23 August 2019 / Published online: 12 September 2019

Abstract

Purpose To explore the long-term oncological results of self-expanding metal stents (SEMS) as a surgical transition compared with those of simple emergency surgery.

Methods A systematic review of studies involving long-term tumour outcomes comparing SEMS with emergency surgery was conducted. All studies included information on 3-year and 5-year survival rates, 3-year and 5-year disease-free survival (DFS) rates, and local and overall recurrence rates; the results were expressed as odds ratios.

Results Overall, 24 articles and 2508 patients were included, including 5 randomised controlled trials, 3 prospective studies, and 16 retrospective studies. The 3-year survival rate (odds ratio (OR) = 0.88, 95% confidence interval (CI) 0.69–1.12, $P = 0.05$), 5-year survival rate (OR = 0.91, 95% CI 0.70–1.17, $P = 0.67$), 3-year DFS rate (OR = 1.14, 95% CI 0.91–1.42, $P = 0.65$), 5-year DFS rate (OR = 1.35, 95% CI 0.91–2.02, $P = 0.17$), overall recurrence rate (OR 1.04, 95% CI 0.77–1.41, $P = 0.14$), and local recurrence rate (OR 1.37, 95% CI 0.84–2.23, $P = 0.92$) were determined. There was no significant difference between the randomised and observational studies in the subgroup analysis, and the 5-year survival rate was higher in studies with a stent placement success rate of ≥ 95%.

Conclusion SEMS implantation was a viable alternative in malignant left colon obstruction as a transition to surgery; its long-term survival results, including 5-year DFS and overall survival, were equivalent to those of emergent surgery.

Keywords Self-expanding metal stents · Emergency surgery · Colorectal cancer · Malignant obstruction · Long-term oncological results

Introduction

Colorectal cancer is currently one of the most common malignant tumours, ranking third in incidence and second in mortality. According to incomplete statistics, there are more than 1.8 million new cases and 881,000 deaths are estimated to occur in 2018 [1]. Acute intestinal obstruction is a common complication of abdominal tumours. It is estimated that 7% to 29% of all colorectal cancer patients have partial or complete intestinal obstruction, and about 70% of cases occur in the left colon [2, 3]. If not treated in time, fatal complications are likely to occur [3–6]. In case of acute obstruction, the traditional treatment method is emergent ostomy or intraoperative intestinal lavage after preventive ostomy, followed by radical resection or ostomy reversion surgery. Compared with elective colorectal surgery, the complications and mortality of patients are very high due to the poor patient condition and high surgical risk [7, 8]. In the early 1990s, Dohmoto first proposed the use of self-expanding stents as a new method for the treatment of malignant colonic obstruction. Tejero et al. reproted the initial experience with self-expanding metal stents (SEMS) to relieve obstruction in advanced colon cancer, which opened a new chapter in the treatment of colorectal cancer complicated with malignant obstruction [9, 10]. SEMS placement can effectively relieve obstruction and be used both as emergency and elective surgery, allowing patients with optimised clinical conditions to undergo selective

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laparoscopic resection to avoid stoma [11]. If a thorough evaluation after stent placement indicates the presence of an irresectable tumour, a surgical procedure would therefore be avoided. A number of prospective controlled studies and meta-analyses have shown that SEMS has a good short-term effect as a bridge to surgery (BTS) compared with emergency surgery [12–14]. Although the short-term benefits of SEMS as a BTS have been established in recent years, the promotion of metastasis caused by stent implantation remains suspected due to blood dissemination produced by tumour compression [15]. In case of perforation, the increase in peritoneal implantation is also plausible. The long-term survival results remain controversial [15–21]. This systematic review aims to explore the long-term oncological results of SEMS as a surgical transition compared with simple emergency surgery.

Methods

Search strategy and study selection

This study was approved by the Ethics Committee of the Tongji Medical College, Huazhong University of Science and Technology. A systematic literature search was conducted in the databases of Medline (PubMed), Embase (Ovid), and Cochrane libraries until January 2019. The following terms were used in conjunction or in combination: colonic stents, self-expanding stents, stents as a bridge to surgery, malignant intestinal obstruction, acute intestinal obstruction, and long-term tumour outcomes.

Inclusion/exclusion criteria and data extraction

The titles and abstracts of all retrieved references were independently reviewed by two investigators. Titles and abstracts identified as potentially relevant were included in the full-text analysis and selected if they met the inclusion criteria.

Studies that met the following criteria were considered eligible for inclusion: a comparative study of SEMS and emergency surgery; reporting at least one long-term tumour outcome measure (overall survival rate, disease-free survival rate, or any type of relapse rate); all patients involved in the study must have resectable tumours; and an average follow-up time of at least 3 years. Studies with the following features were excluded: written in a language other than English; comparing BTS and emergency surgery in both the left and right colon; unable to extract accurate measurement data; simple rectal cancer obstruction and palliative treatment; case reports, letters, and reviews.

Firstly, randomised trials and prospective or retrospective comparison cohort studies were selected to maximise patient numbers. For each study, the name of the lead author, the year of publication study, design, duration, number of participating centres, number of patients, median follow-up, and baseline characteristics were retrieved.

The primary outcome was overall survival at 3 and 5 years; secondary outcomes were 3-year and 5-year disease-free survival, total recurrence, and local recurrence. If the study only provided a Kaplan-Meier survival curve rather than an absolute survival rate, we estimated the incidence from the survival curve with the highest accuracy and then calculated the number of events, and the subgroup analysis should include study location, number of participants, year of publication, and other indicators [22]. Data were extracted by a researcher (YH C) to improve standardisation and reviewed by a second researcher (JN G) to resolve differences until a consensus was reached; if there was a disagreement, the third author (KL C) would make the final decision.

Statistical analysis

Pooled odds ratios (OR) with 95% confidence intervals (95% CI) for local and overall recurrence, 3-year and 5-year survival rates, and DFS were calculated using a random effects model. A meta-analysis was performed using Review Manager (RevMan) Version 5.3 for Windows (the Cochrane Collaboration 2012, Denmark). Dichotomous variables were analysed by assessing the risk ratio (RR) of an adverse event occurring with BTS compared with the emergency surgery group along with 95% confidence intervals (95% CIs). An OR < 1 favoured the SEMS as BTS group. The point estimate OR was considered statistically significant when the p value was < 0.05 and the 95% CI did not include the value 1. Heterogeneity among the included studies was assessed using graphical exploration of funnel plots, the Cochrane Q-statistic ($p < 0.1$ was considered representative of statistically significant heterogeneity) and the I^2 statistic ($I^2 >$ 50% was considered to represent substantial heterogeneity). In addition, sensitivity analysis on 5-year overall survival across six variables was conducted in order to investigate the robustness of the findings of this meta-analysis.

Results

Research characteristics

A preliminary search found 2180 related articles. After deleting duplicates, 1958 studies remained, of which 1923 were excluded based on the title or abstract. Finally, the full text of 35 articles was evaluated; 11 of these were further excluded. The reasons for exclusion were as follows: article content [23–26] ($n = 4$), no comparison study [27–30] ($n = 5$), non-English language ($n = 1$), and insufficient follow-up time ($n = 1$). A total of 24 articles were included in the study, including 5 randomised controlled trials [31–35], 16 retrospective studies [18, 19, 36–49], and 3 prospective studies [17, 50, 51] (Fig. 1). The features of included studies are shown in Table 1.

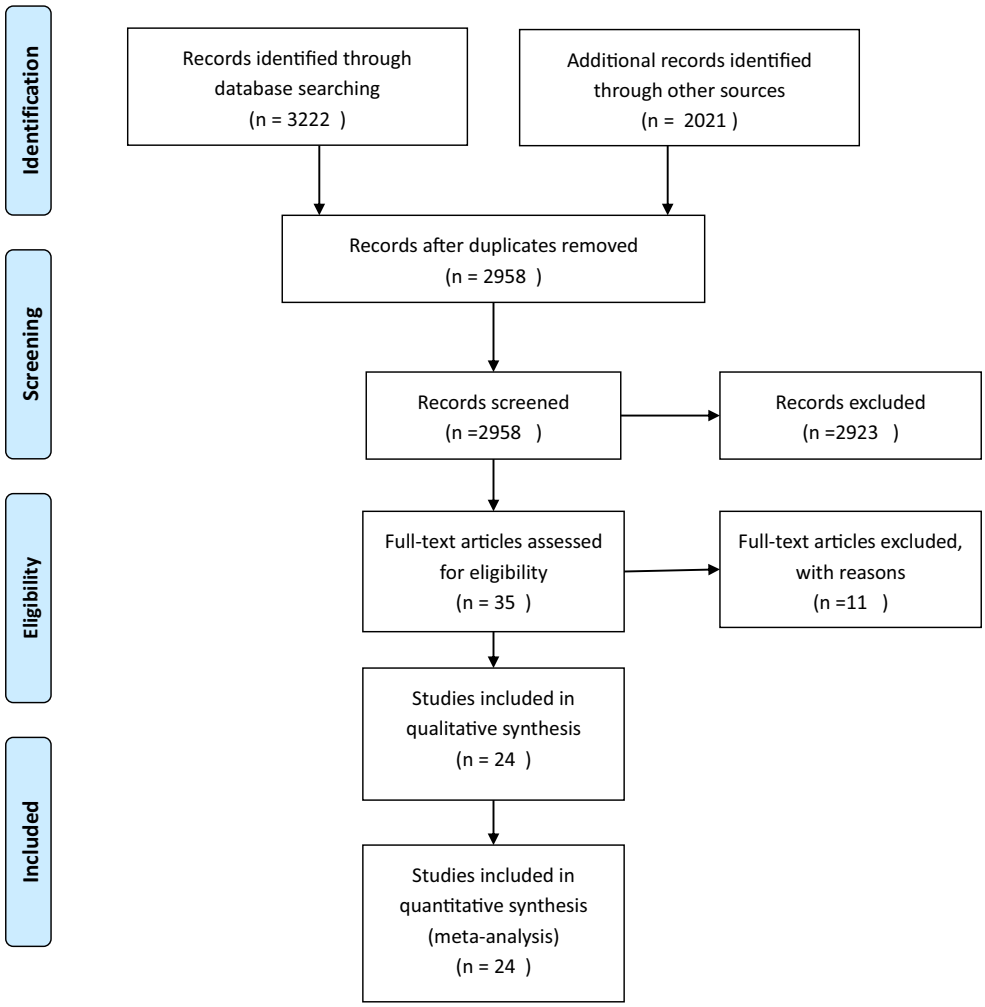

Fig. 1 Flowchart of document retrieval

Risk of bias and research quality

The systematic review was carried out in accordance with the Cochrane Handbook [52]. For randomised controlled trials, Cochrane collaborative tools were used to assess risk of bias [50] (Fig. 2a). For prospective and retrospective cohort studies, we used the methodological index for non-randomized studies (MINORS) to assess bias [53]. The level of evidence was based on the National Health and Medical Research Council's classification[54]. According to the Cochrane Collaboration Tool, all included non-randomised controlled trials were judged to have a low risk of bias (Fig. 2b).

Three-year survival rate

In the 24 studies included, only Amelung et al. did not report overall survival rate [42], and the remaining 23 studies compared the 3-year survival rates between the stent as a bridge to surgery (SBTS) and emergency surgery groups. A total of 2365 patients were included in the studies. The results showed the survival rates of the two groups were 62.8% and 59.1% respectively (OR = 0.88, 95% CI 0.69–1.12). There was no significant difference between the two groups ($P = 0.05$, $I^2 = 35\%$) (Fig. 3). The funnel plot did not show the presence of significant deviations (Fig. 9a).

Five-year survival rate

The 5-year overall survival rates of the two groups were obtained. A total of 1426 patients were included in the studies. The results showed that the survival rates of the two groups were 62.6% and 57.2%, respectively (OR = 0.91, 95% CI 0.70–1.17, $P = 0.67$). There was no statistically significant difference between the two groups ($P = 0.67$, $I^2 = 0\%$, Fig. 4). The funnel plot showed no significant deviation (Fig. 9b).

Three-year disease-free survival rate

A total of 14 studies reported the 3-year disease-free survival rate, with a total of 1658 patients enrolled in the studies. The 3-year disease-free survival rates in the

Table 1 Basic characteristics of the included studies

Author	Age	Country	Design	Center	Totlal	SEMS	ES	Tendency	Time	SEMS	ES	Ending	recurrence	Stent type	Risk score
Alcantara	2011	Spain	RCT	1	28	15	13	Yes	2004–2006	37	37	OS	Yes	Wallflex/Hanaro	Medium
Tung	2013	China	RCT	1	35	22	13	Yes	2002–2005	32	65	OS	Yes	Wallflex	Low
Ghazal	2013	Egypt	RCT	1	60	30	30	Yes	2009–2012	18	18		Yes	NA	Low
Sloothaak	2014	the Netherlands	RCT	25	58	26	32	Yes	2010	41	45	OS	Yes	Wallstent/Wallflex	Low
Arezzo	2017	Italy	RCT	5	115	56	59*	Yes	2008–2015	16	16	OS	Yes	NA	Low
Quereshy	2014	China	PS	1	67	28	39	No	1998–2008	26.5	31.3	OS	Yes	Wallstent	17
Gorissen	2013	UK	PS	1	105	62	43	No	2006–2012	32	33	OS	Yes	Wallflex	17
Gianotti	2013	Italy	PS	1	100	49	51	Yes	2004–2011	NA	NA	OS	NO	Hanaro	16
Saida	2003	Japan	RS	1	84	44	40	No	1986–2001	84	84	OS	Yes	Z-stent	14
Dastur	2008	UK	RS	1	26	11	15	Yes	1997–2004	21	30	OS	NO	Wallstent/Memotherm	18
Kim	2013	South Korea	RS	1	95	25	70	No	1996–2007	43	54	OS	Yes	NA	20
Sabbagh	2013	France	RS	2	87	48	39	Yes	1998–2011	30	37	OS	Yes	Wallflex	13
Kavanagh	2013	Ireland	RS	1	49	23	26	No	2005–2011	27.4	26	OS	Yes	Wallflex	18
Choi	2014	Korea	RS	1	240	60	180	No	2005–2011	41.4	45	OS	Yes	NA	16
Kim	2016	Korea	RS	6	168	112	56	Yes	2004–2010	45	49	OS	Yes	Hanaro/Niti-S	18
Amelung	2016	the Netherlands	RS	1	88	51	37	Yes	2004–2013	36	29	OS	Yes	Wallflex/Wallstent/Evolution	18
Li	2016	China	RS	1	171	120	51	No	2010–2014	29	29	OS	NO	NA	17
Kwak	2016	Korea	RS	1	84	42	42	Yes	2005–2011	42.1	52.8	OS	NO	NA	18
Ho	2017	China	RS	1	102	62	40	Yes	2006–2014	21	25.5	OS	NO	Niti-S/Evolution	18
Gibor	2017	Israel	RS	1	64	21	43	No	1999–2013	NA	NA	OS	Yes	NA	17
Yan	2017	China	RS	1	60	27	33	Yes	2007–2012	NA	NA	OS	NO	NA	17
Kang	2018	South Korea	RS	5	335	226	109	Yes	2004–2011	NA	NA	OS	NO	NA	20
Park	2018	Korea	RS	1	111	94	17	Yes	2006–2013	58.2	54	OS	Yes	Hanaro/Niti-S/WallFlex	18
Rodrigues	2019	Porto	RS	1	94	48	46	No	2010–2017	37	55	OS	Yes	Hanaro	18

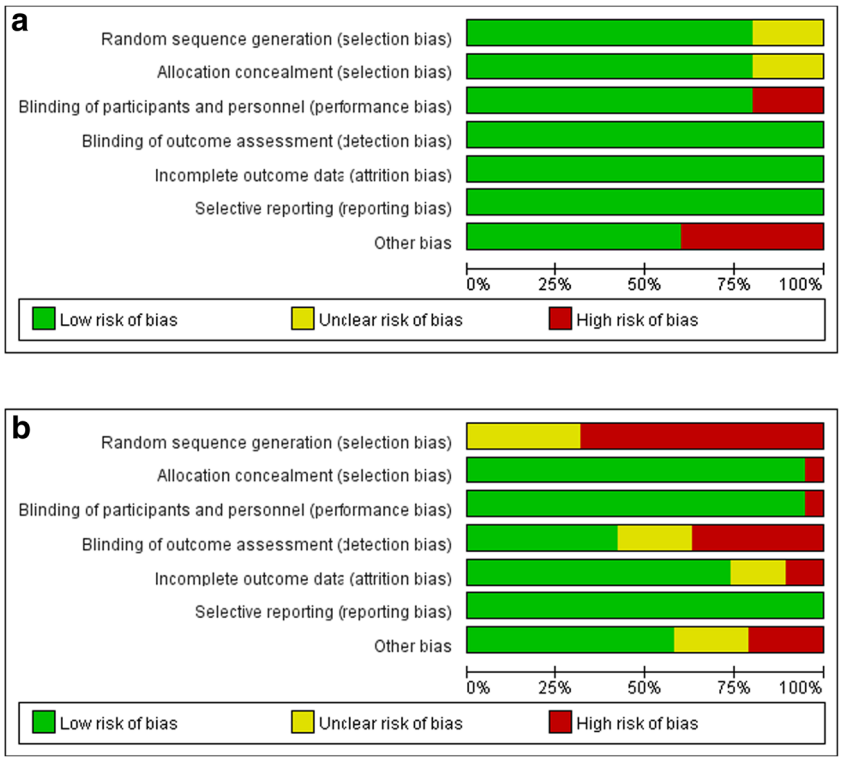

Fig. 2 **a** Risk of bias assessment of RCT included. **b** Quality assessment of non-randomised studies included (using the ROBINS-I tool for assessment of risk of bias)

SEMS and emergency surgery groups were 59.6% and 58.8%, respectively (OR = 1.14, 95% CI 0.91–1.42). There was no significant difference between the two groups ($P = 0.65$, $I^2 = 36\%$, Fig. 5), and the funnel plot did not show the presence of publication bias (Fig. 9c).

Five-year disease-free survival rate

Five-year disease-free survival was obtained from six studies, and a total of 1001 patients were included in the studies. The meta-analysis showed that the 5-year disease-free survival in

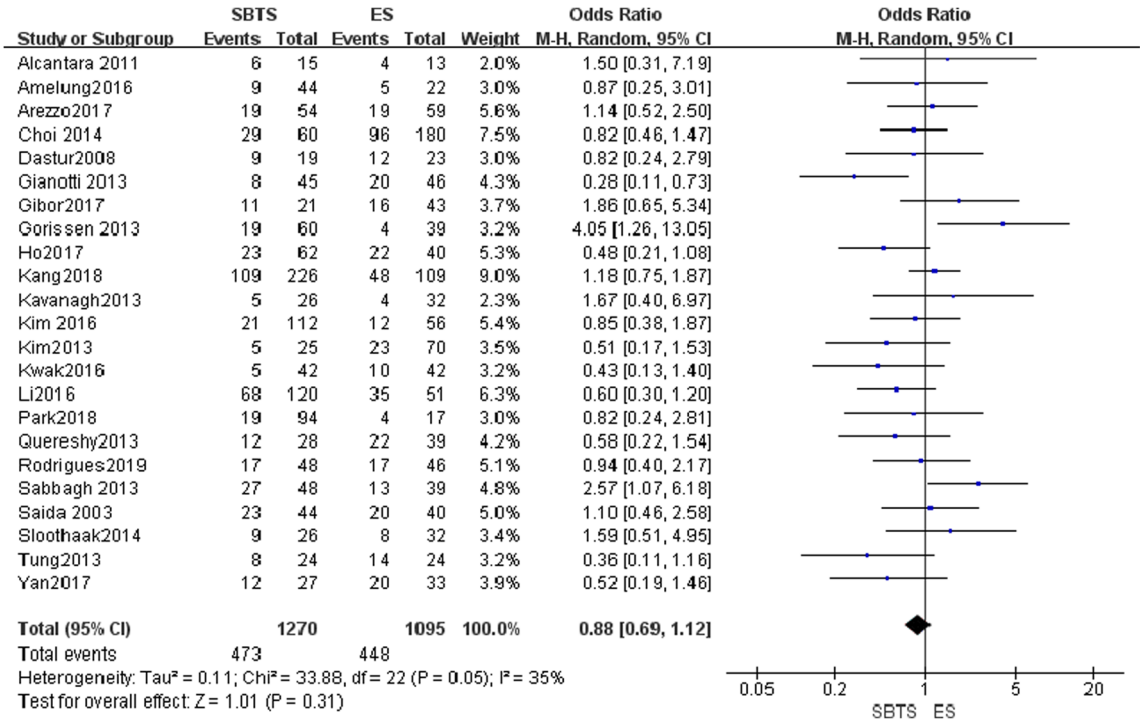

Fig. 3 Forest plot of 3-year OS between patients treated with SBTS or ES for MCO

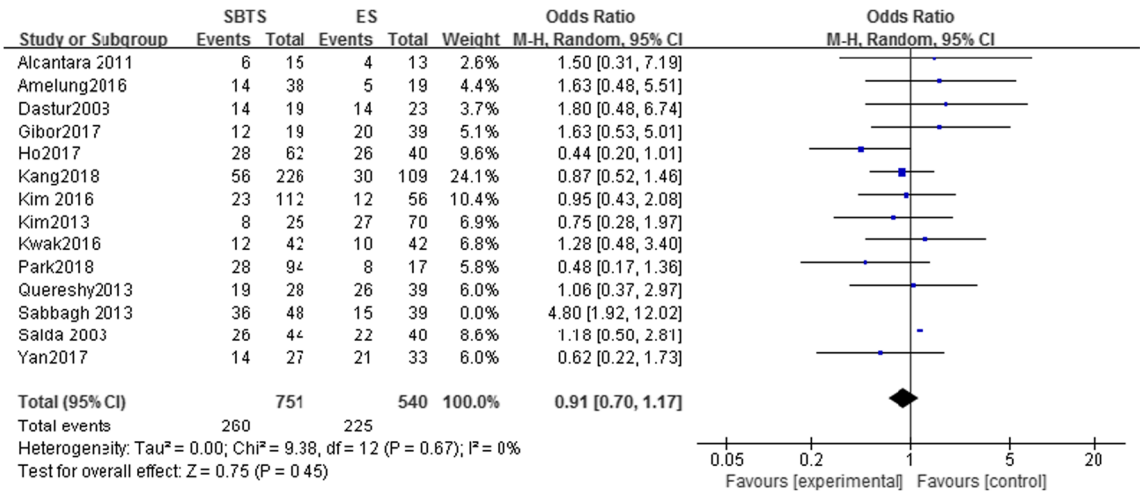

Fig. 4 Forest plot of 5-year OS between patients treated with SBTS or ES for MCO

the SEMS and emergency surgery groups was 43.7% and 44.0%, respectively (OR = 1.35, 95% CI 0.91–2.02). There was no statistically significant difference between the two groups ($P = 0.17$, $I^2 = 0\%$, Fig. 6). In addition, the funnel plot showed no significant deviation (Fig. 9d).

Local recurrence

The local recurrence rate in the SEMS and emergency surgery groups was 8.8% and 5.7%, respectively (OR = 1.37, 95% CI 0.84–2.23), with no significant difference between the two groups ($P = 0.92$, $I^2 = 0\%$, Fig. 7). The funnel plot did not show the existence of a publication bias (Fig. 9f).

Overall recurrence

A total of 17 studies on recurrence rates, including 13 cases of local recurrence, were included in this meta-analysis. The results showed an overall recurrence rate of 28.7% and 27.5% for the SBTS and emergency surgery groups, respectively (OR = 1.04, 95% CI 0.77–1.41). There was no significant difference between the two groups ($P = 0.14$, $I^2 = 28\%$) (Fig. 8). The funnel plot did not show the existence of publication bias (Fig. 9e).

Sensitivity analysis

With regard to the 5-year survival rate, sensitivity analyses were performed on 6 different variables included in 15 studies, including study type, study area, total number of patients, number of patients receiving stents, technical success rate, and publication year (Table 2).

Subgroup analysis of 2 randomised studies showed low heterogeneity, and there was no significant decrease in survival in the SEMS group (OR = 0.66, 95% CI 0.16–2.67, $P = 0.56$, 39 vs. 37); these results were contrary to non-randomised studies with a high degree of heterogeneity (OR = 0.88, 95% CI 0.65–1.19, $P = 0.4$, 781 vs. 562).

Subgroup analysis of the study region between Europe and Asia showed a similar result in the 5-year survival rate (OR = 0.76, 95% CI 0.58–1.0, $P = 0.05$, 684 vs. 470; and OR = 1.61, 95% CI 0.94–2.74, $P = 0.08$, 136 vs. 129), with low heterogeneity ($I^2 = 26\%$, $P = 0.28$).

For the year of publication, a subgroup analysis showed that the heterogeneity was low between years after 2015 and before, studies after 2015 (OR = 0.85, 95% CI 0.61–1.19, $P = 0.34$, 628 vs. 326), studies before 2015 (OR = 0.86, 95% CI 0.48–1.52, $P = 0.60$, 192 vs. 237); there was no significant difference in the 5-year survival rate between the two subgroups.

The subgroup analysis for the total number of patients (≥ 70 and < 70) and the number of patients receiving stents (≥ 30 and < 30) revealed that all studies showed low heterogeneity and similar results for 5-year overall survival.

When assessing the potential impact of SEMS surgery, studies with a success rate of ≥ 90% had a higher heterogeneity, but had a significant survival benefit (OR 0.65, 95% CI 0.45–0.94, $P = 0.02$, 424 vs. 262).

Discussion

The current systematic review and meta-analysis showed that the use of SEMS as a surgical transition in malignant obstructions caused by colorectal cancer might not lead to a negative impact on the long-term prognosis of the tumour compared with ES. The prognosis was similar between the two groups in 3-year and 5-year survival rates, and there were no significant differences in local or systemic recurrence.

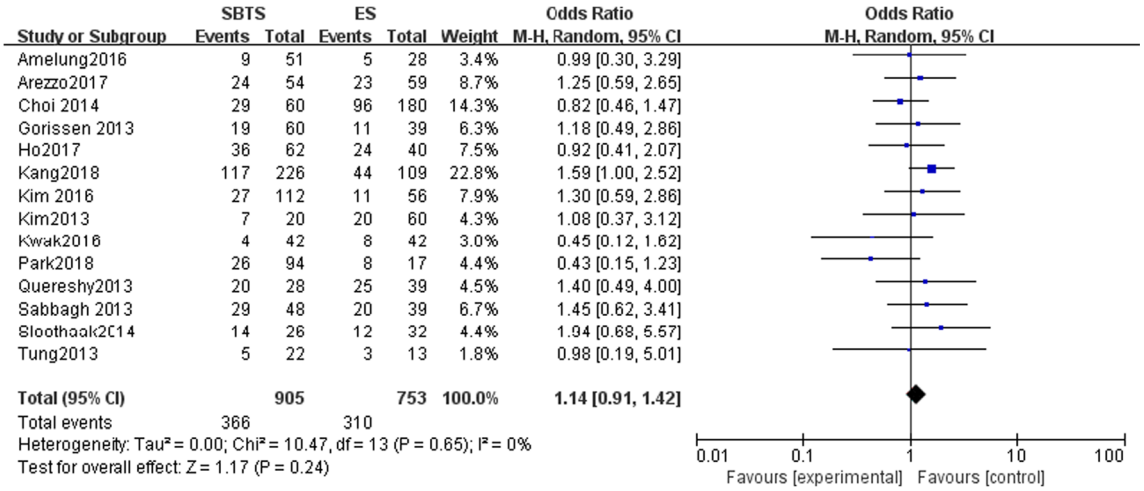

Fig. 5 Forest plot of 3-year DFS between patients treated with SBTS or ES for MCO

Patients with colorectal cancer complicated with acute intestinal obstruction were usually in a poor general condition and might have various problems such as dehydration, anaemia, metabolic disorders, malnutrition, and acid-base imbalance. The use of SEMS as a transition to surgery can alleviate these acute risks. Converting emergency surgery to elective surgery resulted in a more meticulous evaluation and treatment, as shown by the better short-term results [55]. At the same time, however, stent mechanical stress might cause long-term effects on tumour cell spreading; therefore, the debate on BTS persists [15, 19, 24, 34, 35, 56]. Related studies have shown that mechanical friction of the colonoscope and guidewire, mechanical expansion after stent release, and stent-related perforation during stenting can lead to the localised spreading of tumour cells and dissemination through blood and lymphatic vessels [57, 58]. Sterne et al. found that the expression of cytokeratin 20 was significantly increased in peripheral venous blood after stent implantation [59], and Maruthachalam et al. demonstrated that the circulating levels of CEA and CK20 mRNA were significantly increased after colon stenting [15]; Higgins-Julian and Kim et al. found that the invasion rate of nerves and lymph nodes increased after implantation of SEMS, but no difference in survival rate was found compared with emergency surgery. Moreover, no studies have demonstrated a relationship between stent placement and tumour recurrence. In addition, the oncological significance of these pathological results remains unclear [18, 21]. Gorissen et al. showed that patients with BTS had an increased local recurrence rate, especially in younger subjects; however, in multivariate analysis, stent placement was not associated with an increase in local recurrence rate and had no effect on overall survival [17]; Cao et al. found that in perforations caused by colonic stenting, there was no significant increase in abdominal or distant metastasis during long-term follow-up. A phase III clinical trial conducted by Gietelink et al. confirmed that there was no significant correlation between the presence of circulating tumour cells in the blood of patients with colorectal cancer and decreased survival [60]. Although evidence has shown that tumour cells can spread or metastasise during stent implantation, the current systematic review shows that BTS has no negative effects on long-term survival and prognosis. However, we still needed further relevant clinical trials to verify this conclusion.

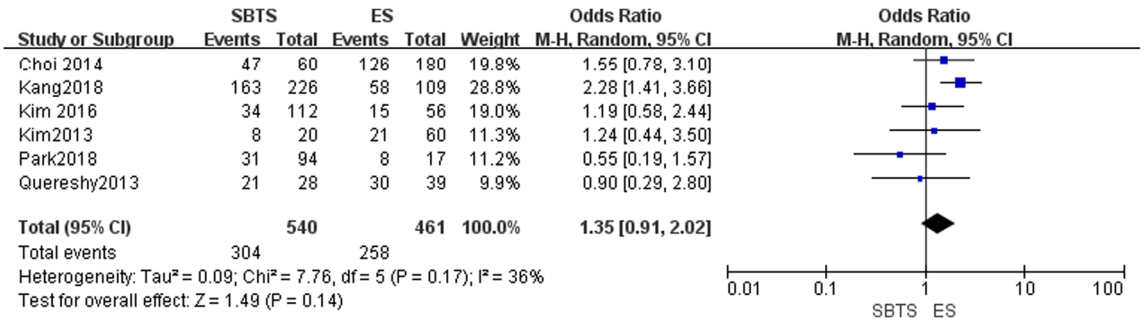

Fig. 6 Forest plot of 5-year DFS between patients treated with SBTS or ES for MCO

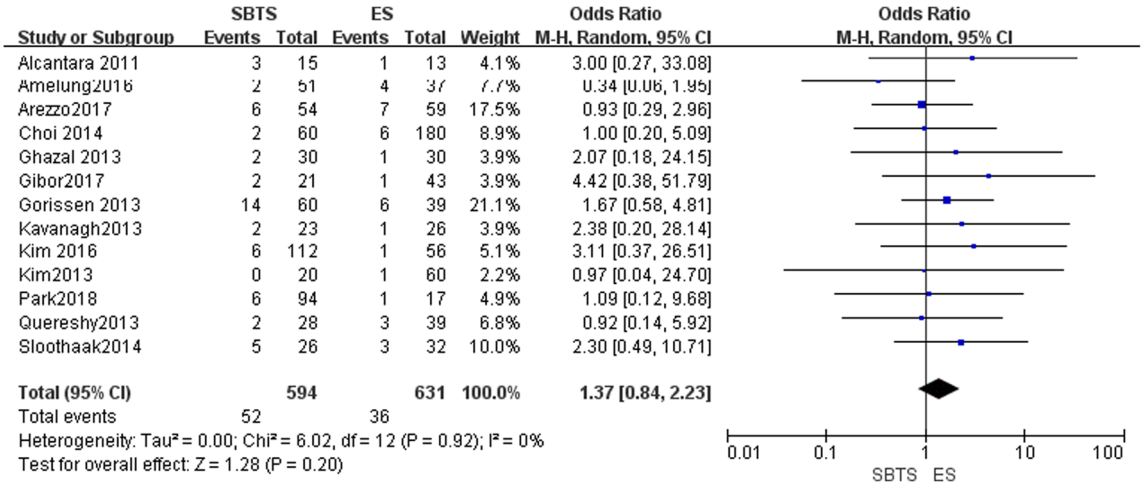

Fig. 7 Meta-analysis of local recurrences between patients treated with SBTS versus ES for MCO

Ceresoli et al. compared long-term oncologic outcomes of SBTS and ES in malignant left-sided colonic obstructions, and they thought there were no significant differences reported in local and overall recurrence rates [61]. Amelung et al. compared procedure-related mortality and morbidity rates between primary resection and stent placement as a bridge to surgery followed by elective resection for patients with acute right-sided colonic obstruction (RSCO), and they thought primary resection for patients with acute RSCO seems to be associated with higher mortality and major morbidity rates than stent placement and elective resection [62]. Other meta-analyses compared the long-term outcomes of stents as BTS and emergency surgery and found that BTS was oncologically comparable with emergency surgery with respect to OS, DFS, and recurrence, and there was no difference in long-term tumour outcomes [22, 63–66]. The results of 24 studies included in our systematic review also confirmed previous findings, and although the number of studies had increased, more randomised studies are still recommended to draw a better conclusion in this topic.

Artinyan et al. believe that postoperative complications of SEMS might have a negative impact on long-term oncologic outcomes and survival rates [67]. The most common complications of colon stenting were perforation, displacement, and re-obstruction. Perforation was the

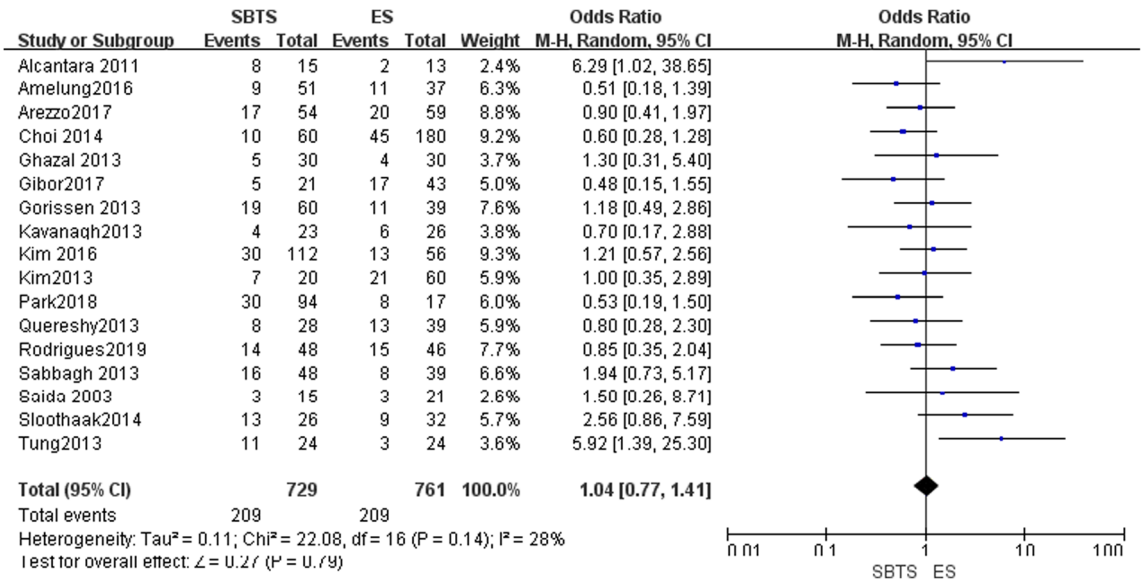

Fig. 8 Meta-analysis of overall recurrences between patients treated with SBTS versus ES for MCO

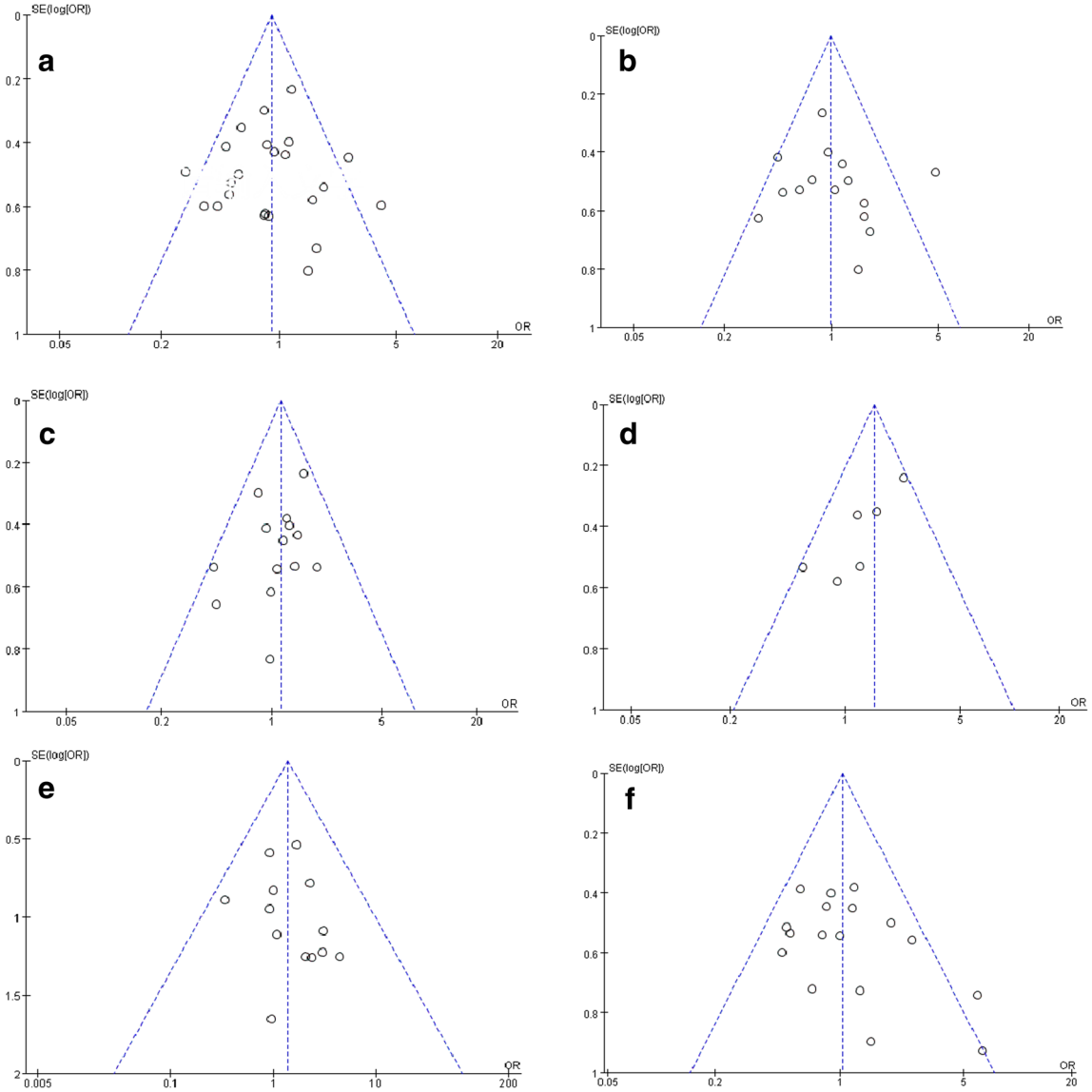

Fig. 9 Funnel plots were plotted of all studies that reported on 3-year overall survival (**a**), 5-year overall survival (**b**), 3-year DFS (**c**), 5-year DFS (**d**), local recurrences (**e**), and overall recurrences (**f**)

most life-threatening complication, with a reported incidence of 0–16% [68–70]; Higgins and Kwakn suggested that an increase in perforation rate might increase local recurrence rates and consequently affect long-term survival outcomes [43, 52]. In fact, stent-related perforation may be decreased to a very low extent. Avoiding adjuvant bevacizumab treatment or balloon dilatation during stent implantation might significantly reduce stent-related perforation [32]; in addition, the skills of endoscopists also have an important role in preventing stent perforation. Bridoux et al. and ESGE guidelines recommend that at least 20 cases are treated to overcome the learning curve.

This meta-analysis provides a contribution to highlight the alternative role of SEMS, since previously published meta-analyses did not focus on the long-term oncological effects of SEMS. We included more studies than the previous reviews or meta-analyses, with a corresponding sample size increase, and now the stratification of stenting success rate showed a different result from previous reviews. However, there were still limitations due to the shortage of studies on long-term tumour outcomes, especially randomised studies. Different choices of surgical procedures in emergency surgery (e.g. routine intraoperative lavage decompression vs. preventive ostomy) might also limit the reach of the conclusions.

Table 2 Sensitivity analysis of 5-year survival rate between SBTS and ES groups

Variable	Subgroup	Number	Number of cases	OR	95% CI	*P*	Heterogeneity *P*	I^2
Years	≥ 2015	8	1000	0.85	0.61–1.19	0.34	0.33	13%
	< 2015	7	429	0.86	0.48–1.52	0.6	0.10	44%
Area	Asia	10	1154	0.76	0.58–1.0	0.05	0.41	4%
	Europe	5	265	1.61	0.94–2.74	0.08	0.46	0%
Type of study	RCT	2	76	0.66	0.16–2.67	0.56	0.15	52%
	Non-RCT	13	498	0.88	0.65–1.19	0.4	0.19	25%
Total number of patients	≥ 70	9	1132	0.91	0.64–1.3	0.56	0.16	32%
	< 70	6	287	0.72	0.42–1.24	0.24	0.3	17%
Number of SEMS	≥ 30	8	955	1.07	0.77–1.47	0.69	0.37	8%
	< 30	7	464	0.64	0.42–0.98	0.04	0.34	12%
SEMS success rate	≥ 95%	7	686	0.65	0.45–0.94	0.02	0.88	0%
	< 95%	5	350	1.21	0.56–2.27	0.54	0.15	41%

Conclusion

The results of this meta-analysis suggest the long-term oncological outcome of SEMS placement and second stage surgery is comparable with that of emergency surgery. High success rate of stent implantation might lead to better outcomes. An alternative role of BTS was reinforced by this analysis and a higher technical success rate is important in clinical practice quality control. We also believe that there will be more relevant studies to confirm our conclusions, which will benefit more patients.

Author contributions Yinghao Cao, Junnan Gu, Shenghe Deng, Jiang Li, Ke Wu, and Kailin Cai meet all the criteria for the definition of authorship and contributed substantially to the manuscript. Yinghao Cao, Junnan Gu, and Shenghe Deng contributed equally to this work and they were considered co-first authors. Ke Wu and Kailin Cai are the correspondent authors.

Funding information This study was financially supported by grants from the Science and Technology Department of Hubei Province (no. 2018CFC884), the Wu Jieping Medical Foundation of China (no.320.2710.1843), and the Clinical Research Physician Program of Tongji Medical College, HUST.

Compliance with ethical standards

This study was approved by the Ethics Committee of the Tongji Medical College, Huazhong University of Science and Technology

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

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