Original Article

Long-term oncologic outcomes of stent as a bridge to surgery versus emergency surgery in malignant left side colonic obstructions: a meta-analysis

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Background: The placement of a metallic stent as a bridge to surgery (SBTS) could represents an option for the treatment of left-sided malignant colonic obstruction in centres with adequate skills. Several meta-analyses demonstrated better short-term outcomes after SBTS when compared with emergency surgery (ES); however, some studies reported a higher local recurrence rate. The aim of the present review is to investigate the long-term outcomes of stent bridge to surgery as compared to ES.

Methods: A systematic review was performed to retrieve studies comparing long-term oncologic outcomes of SBTS and ES. Local and overall recurrence rate, overall and disease-free survival were retrieved and results were expressed as risk ratios.

Results: Seventeen studies and a total of 1,333 patients were included in the analysis. No significant differences were reported in recurrence rate [risk ratio (RR) =1.11; 95% confidence interval (95% CI): 0.84–1.47, P=0.47], 3-year mortality (RR =0.90; 95% CI: 0.73–1.12, P=0.34) and 5-year mortality (RR =1.00; 95% CI: 0.82–1.22, P=0.99). There were no differences among randomized and observational studies.

Conclusions: SBTS has similar long-term oncologic outcomes to ES and in centres with appropriate skill should be considered the best treatment option for left-sided malignant colonic obstructions.

Keywords: Colonic stent; emergency surgery (ES); long-term outcomes; colonic obstruction

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Introduction

Colorectal cancer is the most common cause of large bowel obstruction, which represents the presentation of disease in about 10% of the patients (1). This condition requires an immediate treatment with surgical intervention, with related high morbidity and mortality (2,3). In the 90s the insertion of self-expandable metallic stents (SEMS) has been proposed as an alternative to surgery, both for palliation in advanced disease and as a stent as a bridge to surgery (SBTS) in order to solve the obstruction and to allow delayed elective surgery. Several randomized trials investigated this issue and were summarized in several meta-analyses: SBTS resulted in a lower morbidity, with more favorable short-term results (4-7). The World Society of Emergency Surgery (WSES) Guidelines on left-sided malignant colonic obstruction recommended SBTS as the better option when and where skills are available (8). SBTS developed a good diffusion as a treatment option due to favorable short-

term outcomes; however, the long-term prognosis of this treatment has not been well clarified.

Patients with colorectal obstructing cancer carry a worse prognosis as compared to elective patients without obstructive features (9,10). Moreover, concerns regarding the oncologic outcomes after the insertion of SEMS have been expressed: stenting is suspected to increase local and systemic neoplastic seeding. In particular, the direct effect of mechanical compression of the tumour could induce haematogenous spread and, in case of perforation, the risk of peritoneal involvement would be increased (11-16); however, the real effect on overall survival remains unclear, with contrasting results reported in literature.

The aim of this systematic review and meta-analysis is to investigate the long-term outcomes of SBTS as compared to emergency surgery (ES) in left-sided colorectal obstructing cancers, in order to clarify the real effect on disease free survival and overall survival.

Methods

Literature search and study selection

A systematic review was performed in Medline, Embase, PubMed, Cochrane Central Register of Controlled Trials (CCTR) and Cochrane Database of Systematic Reviews (CDSR) until 20th January 2017. The following terms were used combined with AND/OR: colonic stent, stent bridge to surgery, large bowel malignant obstruction, oncologic outcomes. All the titles and abstracts of retrieved references were reviewed independently by two researchers (M Ceresoli and N Allievi) and those identified as potentially relevant were included in the full-text analysis and then selected if they met the inclusion criteria.

Selection criteria

For the purposes of the current meta-analysis inclusion and exclusion criteria were defined as follows: full-text publications written in English reporting follow-up comparison between colonic SBTS and ES in left-sided and rectum obstructive cancer were selected. Either randomized trial and prospective or retrospective comparative cohort studies were initially selected, in order to maximize the number of patients. Studies were excluded if they regarded right side obstructive cancer or if they included no data about the long-term follow-up. Case series, letters, case reports and review were also excluded.

Data extraction, outcome measures

For each selected paper the following elements were retrieved: study protocol and design, period of study, number of participant centres, number of included patients and data about follow up including median follow-up, 3-year and 5-year mortality and recurrence rate, overall recurrence rate and local recurrence rate. Where available, data of subgroup of patients with potential curative resections were also analyzed. In case data about long-term outcomes were not available as proportion or percentages, we estimated the rate from the Kaplan-Meier survival curves with the highest possible accuracy and then the number of event were calculated.

Assessing risk of bias

For randomized controlled trials the risk of bias was assessed comprehensively according to the guidelines of the Cochrane Collaboration (17), attributing a judgement for the following items: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, assessment of incomplete data outcome, selective reporting and other source of bias. For the prospective and retrospective comparative cohort studies the quality of the included studies and the risk of bias were assessed using the MINORS score (18).

Statistical analysis

Data was analysed with Review Manager (RevMan) (Version 5.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Outcomes were expressed as risk ratio (RR) and 95% confidence interval (95% CI) and were calculated with the fixed-effect and random-effect models of the Mantel-Haenszel test (19,20); statistical heterogeneity was quantified using the I^2 inconsistency test and, when significant (P<0.1), the sole results of the random-effects model were reported.

Results

Selected studies

A total number of 1,083 abstract were retrieved and, after review of title and abstract, 25 were assessed for eligibility; there was good agreement between the two authors. Among them, after full text review, 17 studies were included for the analysis: 5 RCTs (21-25), 3 prospective comparative cohort

studies (16,26,27) and 9 retrospective comparative cohort studies (13-15,28-33). Five studies did not report follow-up data (34-38), 2 studies reported short-term outcomes of other included trials (39,40) and were also excluded. A retrospective comparative cohort study reported unclear data about long-term follow up, therefore it was decided to exclude it from the analysis (41).

Table 1 shows the characteristics of the included studies. See the PRISMA flow diagram in *Figure 1*.

All the included studies had similar study protocols, with the exception of the study design; all but two (26,32) reported the median follow-up, ranging between 16 and 84 months. Eleven studies reported the oncologic treatment and the pooled rate of patients receiving adjuvant chemotherapy after surgery was similar for both the groups (63% *vs.* 54%, RR =1.08; 95% CI: 0.95–1.23, P=0.26). *Table 1* shows the characteristics of included studies.

Risk of bias and quality of the studies

All the included RCT were judged as at low risk of bias, according to the Cochrane collaboration tool. Two trials were discontinued prematurely due to the high rate of anastomotic leak within the ES group (22) and to the high comorbidity rate in the stent group (SBTS) (24). Moreover, the trial by Ghazal did not report data as intention-to-treat analysis but as per protocol analysis (23) (*Table 2*).

The quality of comparative cohort studies was assessed using the MINORS score; no study obtained the maximum score (*Table 1*).

Overall and local recurrence

A total of 13 studies reported the recurrence rate and 1089 patients were included in the analysis: there were no significant differences between SBTS and ES (RR =1.11; 95% CI: 0.84–1.47, P=0.47). There were no differences among randomized and observational studies. Ten studies reported the rate of local recurrence and no significant differences were depicted (RR =1.41; 95% CI: 0.89–2.23, P=0.14). There were no differences among RCT and observational studies (*Figure 2*).

3-year mortality

Sixteen studies reported data about 3-year mortality and 1,274 patients were included in the analysis: there were no significant differences among the two groups (RR =0.90; 95% CI: 0.73–1.12, P=0.34) without differences among different study designs. Including only patients who underwent potentially curative resection, no differences were found (RR =1.04; 95% CI: 0.78–1.39, P=0.78) (*Figure 3*).

5-year mortality

A total of 865 patients from eleven studies were included in the analysis for 5-year mortality: extrapolated data showed no significant differences (RR =1.00; 95% CI: 0.82–1.22, P=0.99). Including in the analysis only patients with potentially curative resections, data from 8 studies were available and no significant differences were reported (RR =0.95; 95% CI: 0.53–1.69, P=0.86) (*Figure 4*).

3- and 5-year recurrence

Data regarding recurrence at three years was available from only seven studies: there was no significant difference among the two groups (RR =1.15; 95% CI: 0.95–1.39, P=0.14); data for the five-year outcome was available from six studies and no differences were found with the meta-analysis (RR =1.05; 95% CI: 0.88–1.25, P=0.59).

Discussion

The results of the present meta-analysis show that long-term oncological outcomes of patients treated with SBTS are comparable with those of patients treated with ES in case of left-sided malignant colonic obstruction. In particular, the pooled results of all the included studies did not show any differences in terms of local or systemic recurrence and no differences in 3- and 5-year survival.

The rationale of SEMS positioning as a bridge to surgery is to resolve the acute situation with colonic decompression, therefore transforming ES into scheduled or elective. The clinical success of the SEMS allows stabilization of comorbidities, improvement of nutritional status, accurate staging and definition of a tailored treatment for the patients, in the best conditions available. Patients with obstructing colonic tumour carry a worse prognosis than patients presenting without the obstructive picture (10). The increased interstitial pressure in the neoplastic mass can play a pivotal role in cells dissemination and it has been associated with cell shedding and tumour embolisation into lymphatic vessels (42,43).

The role of SEMS in neoplastic dissemination is an issue of great debate among surgeons, as demonstrated

Table 1 Characteristics of included studies

Study ID	Year of publication	Country	Study design	Included patients			Centres	Included patients characteristics	ITT analysis	Years of study	ACT (%)		Median follow-up		Risk of bias/ MINORS score
				Total	SBTS	ES					SBTS	ES	SBTS	ES	
Arezzo	2016	Italy, Spain	RCT	115	56	59	5	Only curative resections	x	2008–2015	66	70	16	16	Low
Alcantara	2011	Spain	RCT	28	15	13	1	Only curative resections	x	2004–2006	n/a	n/a	37	37	Medium
Ghazal	2013	Egypt	RCT	60	30	30	1	Only curative resections		2009–2012	100	100	18	18	Low
Sloothaak	2014	Netherlands	RCT	58	26	32	25	Only curative resections	x	2007–2009	50	46	41	45	Low
Tung	2013	Hong Kong, China	RCT	48	24	24	1	All patients	x	2002–2005	54	75	32	65	Low
Dastur	2008	UK	RC	42	19	23	1	All patients	x	1997–2004	n/a	n/a	21	30	18/24
Gianotti	2013	Italy	PC	91*	45*	46*	1	Subgroup analysis of curative resections for cancer		2004–2011	n/a	n/a	n/a	n/a	16/24
Gorissen	2013	UK	PC	105	62	43	1	Only curative resections	x	2006–2012	41	25	32	33	17/24
Ho	2016	Hong Kong, China	RC	102	62	40	1	Only curative resections	x	2006–2014	45	27	21	25.5	18/24
Kavanagh	2013	Ireland	RC	49	23	26	1	Only curative resections	x	2005–2011	n/a	n/a	27.4	26	18/24
Kim	2013	South Korea	RC	95	25	70	1	All patients		1996–2007	84	65	43	54	20/24
Kim	2016	South Korea	RC PS matched	168	112	56	6	Only curative resections	x	2004–2010	83	78	45	49	18/24
Kwak	2016	South Korea	RC PS matched	84	42	42	1	All patients	x	2005–2011	60	73	42.1	52.8	18/24
Quereshy	2014	Hong Kong, China	PC	67	28	39	1	Only curative resections	x	1998–2008	n/a	n/a	26.5	31.3	17/24
Sabbagh	2013	France	RC PS adjusted	87	48	39	2	All patients	x	1998–2011	56	43	30	37	13/24
Saida	2003	Japan	RC	84	44	40	1	All patients		1986–2001	66	53	84	84	14/24
Yan	2017	China	RC	60	27	33	1	All patients	x	2007–2012	70	45	n/a	n/a	17/24

*, subgroup analysis of cancer patients. ACT, adjuvant chemotherapy; PC, prospective cohort; RC, retrospective cohort; PS, propensity score.

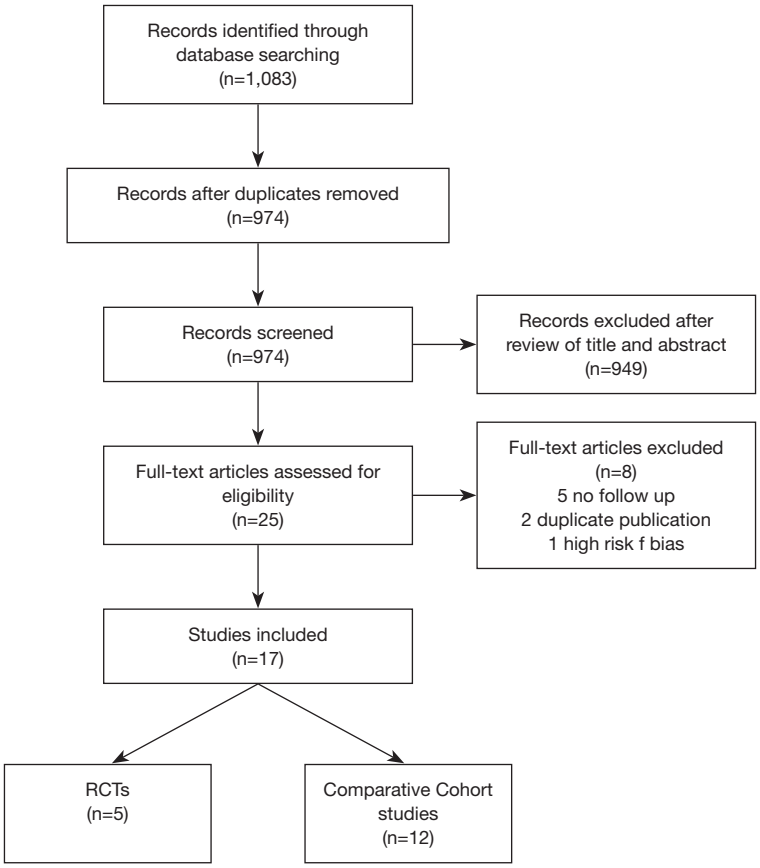

Figure 1 PRISMA flow diagram.

Table 2 Risk of bias assessment of RCT included

Study ID	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Alcantara 2011	Unclear	Unclear	Adequate	Adequate	Adequate	Adequate	Premature ending
Arezzo 2016	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	None
Tung 2016	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	None
Ghazal 2013	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	None
Sloothaak 2014	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Premature ending

by concerns raising from several published studies. Maruthachalam *et al.* (11) demonstrated that circulating mRNAs of CEA and CK20 were significantly higher after colonic stenting: the authors identified the tumor manipulation during guidewire insertion and the tumor dilatation during stent deployment as possible culprits of this phenomenon. Moreover, the dilatation and the manipulation could induce shedding and dissemination of cancer cells into the peritoneal cavity.

Gorissen *et al.* (16) reported a higher rate of local recurrence in patients treated with SBTS, especially in younger subjects (32% *vs.* 8%); however, at a multivariate analysis stenting was not correlated to this augmented local recurrence and no effect on overall survival was noted. Kim

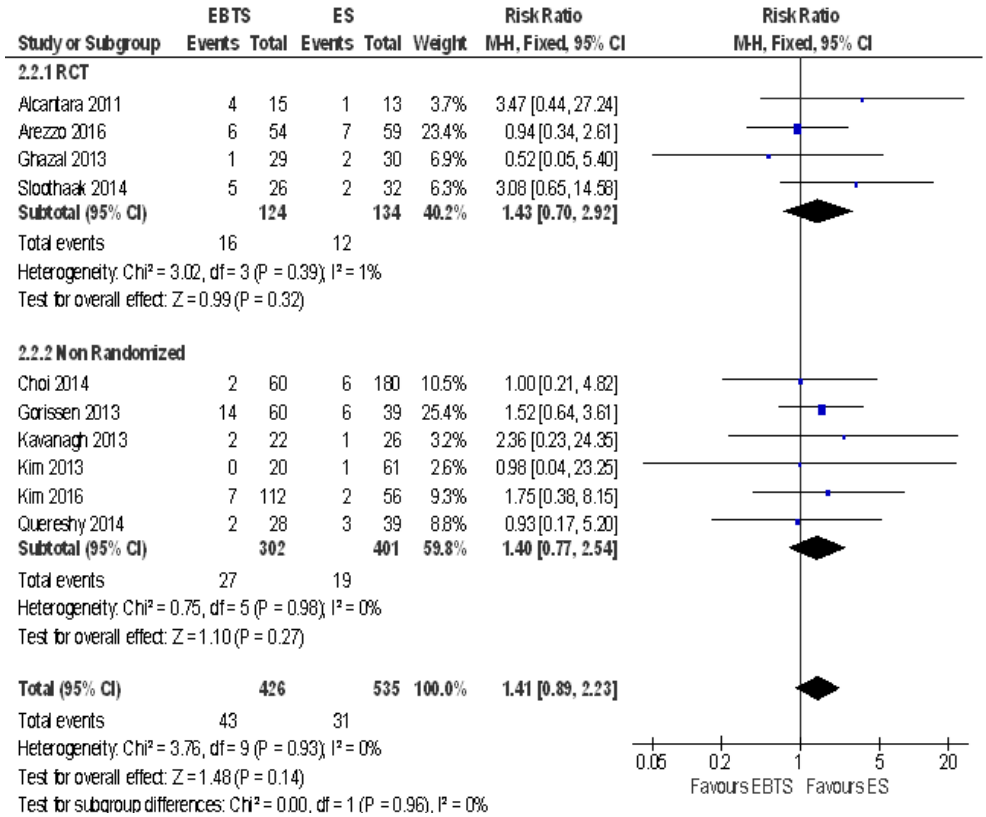

Figure 2 Forest plot of local recurrences between patients treated with SBTS or ES. SBTS, stent as a bridge to surgery; ES, emergency surgery.

et al. (14) demonstrated a higher rate of perineural invasion at histopathological examination of tumours treated with SBTS compared to those operated in emergency (76% *vs.* 51%): also in this case, no differences in survival rates were detected.

The role of circulating tumour cells still represents an issue of difficult interpretation with not clear results reported in the Literature: a large multicenter study demonstrated the presence of circulating cells in patients with stage III colorectal cancer but no clinical effects on long-term survivals and recurrences was detected (44). Despite the evidence of neoplastic cell spread from the primary site during the stenting procedure, the results of the current meta-analysis demonstrate that no clinical effects could be detected in long-term survival and prognosis and that SBTS did not affect negatively the oncological outcomes.

A hypothesis may be drawn to explain this phenomenon: post-operative complications affects negatively the oncologic outcomes and survivals (45). As previously demonstrated by several meta-analyses, SBTS has better short-term outcomes in term of post-operative morbidity (4-6); this could result in a higher rate of patients receiving full dose adjuvant chemotherapy with the appropriate timing, with better results in term of survival, as evidenced in the literature (46). Although not significantly, patients treated with SBTS had a higher rate of adjuvant chemotherapy, as compared to those treated with ES (63% *vs.* 54%) in the included studies of the present meta-analysis. Unfortunately, no data regarding the timing of chemotherapy and the adherence to the protocol is available, hindering definitive evidence-based judgement on this hypothesis.

The results of this meta-analyses should be interpreted at the light of a great limitation: none of the included studies was designed for long-term follow up. As a direct consequence, median follow up times were limited and heterogeneous and survival rates were estimated with the Kaplan Meier method rather than observed. Further accurate studies are needed to investigate the long-term outcomes with a proper design and number of included patients.

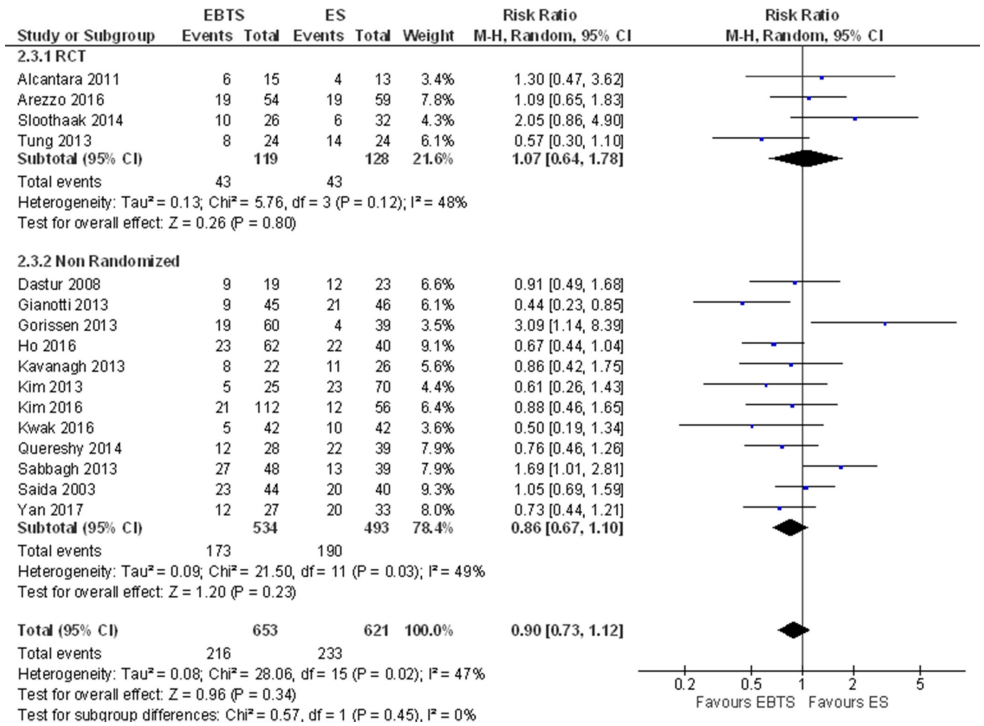

Figure 3 Forest plot of 3-year mortality between patients treated with SBTS or ES. SBTS, stent as a bridge to surgery; ES, emergency surgery.

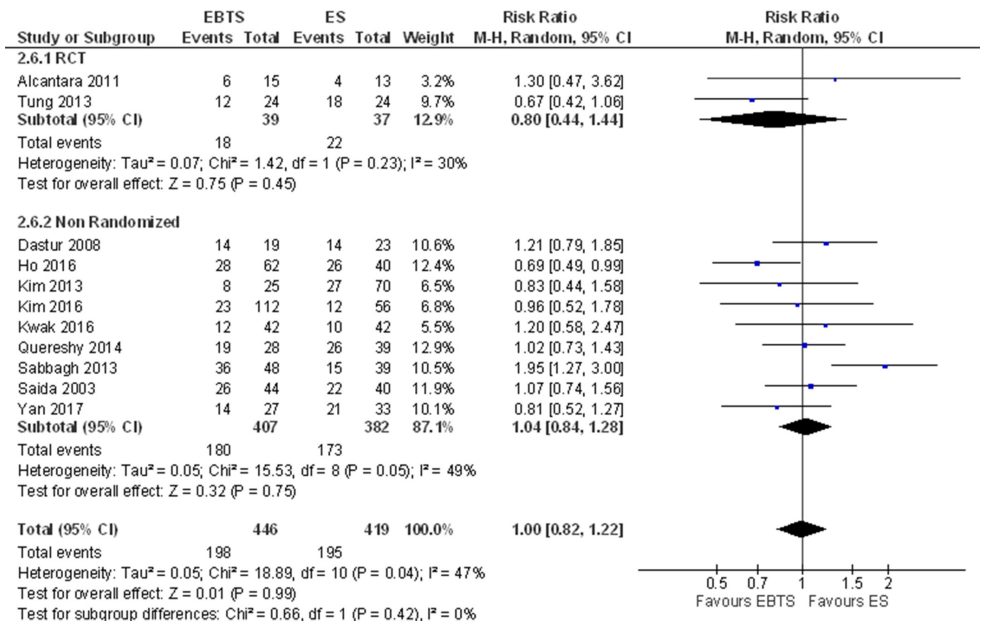

Figure 4 Forest plot of 5-year mortality between patients treated with SBTS or ES. SBTS, stent as a bridge to surgery; ES, emergency surgery.

Conclusions

The results of the present meta-analysis demonstrate that long-term oncologic outcomes are comparable in patients treated with SBTS or ES for left-sided malignant colonic obstructions. At the light of the favorable short-term outcomes and the absence of long-term clinical effects of the procedure, SBTS should be considered as a valid treatment option in centres with adequate technical skills.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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