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# Comparison of Long-Term Outcomes of Colonic Stent as "Bridge to Surgery" and Emergency Surgery for Malignant Large-Bowel Obstruction: A Meta-Analysis

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### ABSTRACT

**Background.** The short-term safety and efficacy of insertion of a self-expandable metallic colonic stent followed by elective surgery, bridge to surgery (BTS), for malignant large-bowel obstruction (MLBO) have been well described. However, long-term oncological outcomes are still debated. Hence, this study is conducted to evaluate long-term outcomes of colonic stent insertion followed by surgery for MLBO.

**Methods.** A comprehensive electronic literature search through May 2014 was performed to identify studies comparing long-term outcomes between BTS and emergency surgery for MLBO. The main outcome measures were overall survival (OS), disease-free survival (DFS), and recurrence. A meta-analysis was performed using random-effects models to calculate risk ratios (RRs) with 95 % confidence intervals (95 % CIs).

**Results.** There were 11 studies that matched the criteria for inclusion, yielding a total of 1136 patients, of whom 432 (38.0 %) underwent BTS and 704 (62.0 %) underwent emergency surgery. In OS analyses of all patients and patients who underwent curative resection, BTS was similar to emergency surgery [(RR = 0.95; 95 % CI 0.75–1.21; P = 0.66) (RR = 0.96; 95 % CI 0.67–1.37;

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A. Matsuda, MD e-mail: a-matsu@nms.ac.jp P = 0.82), respectively]. DFS (RR = 1.06; 95 % CI 0.91– 1.24; P = 0.43) and recurrence (RR = 1.13; 95 % CI 0.82–1.54; P = 0.46) did not differ significantly between the BTS and emergency surgery groups.

**Conclusions.** Results of this meta-analysis on long-term as well as well-described short-term outcomes suggest that BTS could be a promising alternative strategy for MLBO patients.

Approximately 10 % of patients with colorectal cancer initially present with large-bowel obstruction, which in turn accounts for 85 % of colonic emergencies.<sup>1,2</sup> The standard for management of malignant large-bowel obstruction (MLBO) is emergency surgery, which frequently requires stoma creation. However, emergency colorectal surgery continues to be associated with significant mortality and morbidity.<sup>3</sup> Furthermore, patients who undergo emergency surgery are reported to have poorer oncological prognoses than those who undergo elective surgery, even for equivalent disease stages.<sup>4,5</sup> Dohmoto first described the placement of a self-expandable metallic colonic stent (SEMS) for the relief of colonic obstruction in 1991.<sup>6,7</sup> The SEMS is now considered to be a safe and effective alternative modality for decompressing MLBO, as several meta-analyses have demonstrated favorable short-term outcomes of SEMS insertion followed by surgery, "bridge to surgery (BTS)," compared with emergency surgery.<sup>8–10</sup> Preoperative SEMS insertion can prevent high-risk emergency surgery and may allow elective radical surgery following full preoperative staging, screening for synchronous proximal lesions, and appropriate bowel preparation.<sup>11–13</sup>

In theory, SEMS insertion could have deleterious effects on both tumor progression and metastasis, but the effect of

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SEMS on the long-term oncological outcome of patients whose disease is potentially curable is still unclear.<sup>14,15</sup> Until very recently, studies evaluating long-term oncological effects of BTS were sparse; however, several long-term studies were published after 2013 and have become drivers of further debate.<sup>16–20</sup> We have therefore conducted a meta-analysis that includes very recent studies and a large sample size (n = 1136) to provide a conclusive assessment of the effect of BTS for MLBO on long-term oncological outcomes.

# METHODS

This meta-analysis was performed in accordance with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009.<sup>21</sup>

## Literature Retrieval and Study Selection

A systematic review of literature in MEDLINE, Pub-Med, Google Scholar, and the Cochrane Database was performed to identify relevant studies published through May 2014. The search terms used were "colorectal cancer," "stent," "large bowel obstruction," "surgery," and "survival" as key words. The related article's function was used to broaden the search. Of those identified as potentially relevant, complete articles were retrieved and formally evaluated for inclusion. References from all relevant papers were hand-searched for additional studies.

#### Inclusion and Exclusion Criteria

We defined inclusion and exclusion criteria a priori. To be included in our meta-analysis: (1) a study had to be an randomized controlled trial (RCT) or other comparative study evaluating predefined outcomes in subjects who underwent BTS or emergency surgery for MLBO and (2) predefined outcomes had to be analyzed using more than 3 years of oncological data, including overall survival (OS) and/or disease-free survival (DFS) and/or recurrence. Articles written in any language were considered eligible. Studies were excluded if: (1) predefined outcomes were not reported for the two techniques or it was impossible to extract the number of events of outcomes from the published results, and (2) SEMS insertion was performed only with the intent of palliation (i.e., without being followed by surgery).

#### Data Extraction

Each retrieved publication was evaluated independently by 2 investigators (A.M. and T.K.) for inclusion or exclusion. Data reviewed included the primary author's name, the year of publication, the country in which the study was performed, the design and duration of the study, and the number of included subjects and their characteristics, including age, sex, tumor-related variables, surgery-related variables, follow-up period, and all available long-term outcomes.

## Data Synthesis and Statistical Analysis

Dichotomous variables were analyzed 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 RR < 1 favored the BTS group, and the point estimate of the RR was considered statistically significant at the P < 0.05 level if the 95 % CI did not include the value 1. The pooled RR was calculated using the Mantel-Haenszel method to combine RRs for outcomes of interest. Considering the between-study heterogeneity, a "random-effects" metaanalytical technique was applied, making the calculated RR more conservative than with a fixed-effects model.<sup>22</sup> Meta-analysis was performed using Review Manager (RevMan) Version 5.1 for Windows" (Nordic Cochrane Centre, Cochrane Collaboration; Copenhagen, Demark; http://www.cc-ims.net/RevMan). Cochran's Chi squarebased Q statistic test was applied to assess between-study heterogeneity.  $I^2$  was used to test the heterogeneity between the included studies. Study heterogeneity was measured using the  $\chi^2$  and  $I^2$  statistics, with  $\chi^2 P < 0.05$ and  $I^2 \ge 50$  % indicating heterogeneity.<sup>23</sup> Publication bias was assessed by visual examination of a funnel plot, with asymmetry formally assessed with Egger's linear regression test and the rank correlation test (Begg's test) using "WINPEPI" software (available at http://www. brixtonhealth.com/pepi4windows.html).24,25

### RESULTS

# Study Selection, Patient Characteristics, and Short-Term Outcomes

The electronic literature search yielded 497 hits. Of these, we excluded 430 studies based on title and abstract review; six were added from the related article's function or a manual search. Of 73 full-text articles evaluated, 62 were excluded after full-text article review. The 11 remaining studies, published between 2003 and 2014, matched our inclusion criteria for this meta-analysis (Supplementary Fig. 1).<sup>16–20,26–31</sup> The basic characteristics of the 11 included studies are shown in Table 1. There were 10 studies published in English <sup>16–20,26–30</sup> and 1 in Chinese.<sup>31</sup> There

	BTS		E Surg	ery		Risk Ratio			Risk R	atio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	N	I-H, Randoi	n, 95% Cl	í
5-year											
Choy et al.	1	60	7	180	1.2%	0.43 [0.05, 3.41]	2014	•	•		
Kim et al.	8	25	27	70	7.7%	0.83 [0.44, 1.58]	2013			_	
Tung et al.	12	24	18	24	10.6%	0.67 [0.42, 1.06]	2013				
Sabbagh et al.	36	48	15	39	11.2%	1.95 [1.27, 3.00]	2013				
Alcantara et al.	6	15	4	13	4.2%	1.30 [0.47, 3.62]	2011		-+	•	
Xu et al.	24	62	82	186	12.6%	0.88 [0.62, 1.25]	2010		-	-	
Dastur et al.	14	19	14	23	11.3%	1.21 [0.79, 1.85]	2008		+		
Saida et al.	26	44	22	40	12.2%	1.07 [0.74, 1.56]	2003		-	_	
Subtotal (95% CI)		297		575	71.0%	1.05 [0.80, 1.37]				•	
Total events	127		189								
Heterogeneity: Tau <sup>2</sup> =	0.07; Chi	<sup>2</sup> = 14.	55, df = 7	(P = 0.	04); I <sup>2</sup> = 5	2%					
Test for overall effect:	Z=0.34 (	P = 0.7	'3)								
3-year											
Quereshy et al.	18	28	22	39	11.9%	1.14 [0.77, 1.68]	2014		_		
Gianotti et al.	9	45	22	47	7.4%	0.45 [0.23, 0.87]	2014	_			
Gorissen et al.	18	62	19	43	9.7%	0.66 [0.39, 1.10]					
Subtotal (95% CI)	10	135	15	129	29.0%	0.73 [0.41, 1.28]	2013		-		
Total events	45		62		2010/1						
Heterogeneity: Tau <sup>2</sup> =	1	$r^{2} = 7.2$		P = 0.0	(3): $ ^2 = 72$	%					
Test for overall effect:					-,						
Total (95% CI)		432		704	100.0%	0.95 [0.75, 1.21]			•		
Total events	172		251			국가 전 두 두			1		
Heterogeneity: Tau <sup>2</sup> =		<sup>2</sup> = 23.	restant over 1	0 (P = 1	0.008); I <sup>2</sup> :	= 58%		H + -			-
Test for overall effect:	아이지 여기가 안 다니?		CARL STRONG CONTRACTOR					0.1 0.2	0.5 1	2	51
								-	s BTS Fav		

3	BTS E Surgery			<b>Risk Ratio</b>			Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H,	Random, 95% (	CI		
5-year						a))						
Choy et al.	1	56	9	174	2.7%	0.35 [0.04, 2.67]	2014	· · ·				
Kim et al.	3	20	20	60	7.2%	0.45 [0.15, 1.36]	2013					
Tung et al.	9	22	7	13	12.0%	0.76 [0.37, 1.55]	2013	_	•			
Sabbagh et al.	20	29	9	28	14.2%	2.15 [1.19, 3.87]	2013					
Alcantara et al.	6	15	4	13	7.9%	1.30 [0.47, 3.62]	2011		•	-		
Dastur et al.	5	10	6	15	9.6%	1.25 [0.52, 3.00]	2008					
Saida et al.	17	37	14	32	15.4%	1.05 [0.62, 1.78]	2003					
Subtotal (95% CI)		189		335	69.0%	1.07 [0.71, 1.60]			+			
Total events	61		69									
Heterogeneity: Tau <sup>2</sup> =	0.11; Chi	= 10.0	09. df = 6	(P = 0.)	12); $ ^2 = 4$	1%						
Test for overall effect:	Z = 0.32 (	P = 0.7	'5)		5.869 <b>8.8</b> 900 - 59							
3-year												
Quereshy et al.	18	28	22	39	18.2%	1.14 [0.77, 1.68]	2014					
Glanotti et al.	9	45	21	47	12.8%	0.45 [0.23, 0.87]	2013					
Subtotal (95% CI)		73		86	31.0%	0.74 [0.28, 1.95]						
Total events	27		43									
Heterogeneity: Tau <sup>2</sup> =	0.42: Chi	= 6.3	7. df = 1 (	P = 0.0	1); I <sup>2</sup> = 84	%						
Test for overall effect:			Carl Sol and a second second									
Total (95% CI)		262		421	100.0%	0.96 [0.67, 1.37]			-			
Total events	88	202	112	421	100.070	0.00 [0.01, 1.01]			T			
Heterogeneity: Tau <sup>2</sup> =		2-17		/D - 0	021-12-6	200		1				
Helerodenelly, 1911=	0.14; Chi	-= 17.	12, at = 8	(P = 0.	03); 1= 5	3%						
Test for overall effect:	7 0 00							0.1 0.2 0	.5 1 2	5 10		

**FIG. 1** a Meta-analysis of overall survival between bridge to surgery and emergency surgery for malignant large-bowel obstruction. **b** Meta-analysis of overall survival between bridge to surgery and emergency surgery for malignant large-bowel obstruction in the population that underwent curative resection. *BTS* bridge to surgery, *E Surgery* emergency surgery, *M*–*H* Mantel–Haenszel, 95 % *CI* 95 % confidence interval

TABLE 1	Basic (	characterist	TABLE 1 Basic characteristics of the 11 included studies	included	studies								
Reference	Year	Country	Reference Year Country Institutions Study design		Study period	Total Age cases (mea	Age (mean)	Male (%)	Male Location of (%) cancer	Type of stent	Type of surgery Matching	Matching	ITT Analysis
Quereshy	2014	2014 Canada	Single	RS	1998–2008	67	73.8	76.0	76.0 Lt-sided	NA	0, L	a, b, c, d, e	No
Choi	2014	Korea	Single	RS	2005-2011	240	64.9	67.9	Lt and Rt-sided	Lt and Rt-sided NA (uncovered)	NA	a, b, c, d, f, g	No
Gorissen	2013	UK	Single	PS	2006-2012	105	71.2	53.3	Lt-sided	Wallflex stent	0, L	a, b, c, d, e, g	No
Sabbagh	2013	France	Two	RS	1998-2011	87	72.0	56.3	Lt-sided	Wallflex stent	0, L	a, b, e, g	Yes
Gianotti	2013	Italy	Single	PS	2004-2011	92	70.5	59.0	Lt and Rt-sided	Hanaro stent	0, L	a, b, c, d, e, f, g	No
Kim	2013	Korea	Single	RS	1996-2007	95	61.7	65.2	Lt-sided	NA	0, L	a, b, c, d, g	No
Tung	2013	China	Single	RCT	2002-2005	48	66.5	58.3	Lt-sided	Wallflex stent	0, L	a, b, d, g	Yes
Alcantara	2011	Spain	Single	RCT	2004-2006	28	71.5	42.9	Lt-sided	Wallflex stent Hanaro stent	NA	a, b, c, d, e	Yes
Xu	2010	China	Single	RS	2000-2008	248	63.3	60.5	Lt-sided	Nitinol stent	NA	a, b, c, d	No
Dastur	2008	UK	Single	RS	1997–2004	42	71.2	57.1	Lt-sided	Wallflex stent Memotherm stent	NA	a, b, c, d, e	Yes
Saida	2003	Japan	Single	RS	1986-2001	84	63.9	51.1	Lt-sided	Z-stent	0	a, b, e, f, g	No
RS retrospoint $d = stage$ ,	sctive st e = An	udy, PS pr terican So	ospective stuc ciety of Anesi	dy, <i>RCT</i> 1 thesiolog	randomized $cc$ y score, $f = c$	omorbi	d trial, $O$ dity, $g =$	open su chemot	Irgery, L laparosco therapy administra	Rs retrospective study, PS prospective study, RCT randomized controlled trial, O open surgery, L laparoscopic surgery, NA not applicable, Matching: $a = age$ , $b = sex$ , $c = tumor$ location, $d = stage$ , $e = American Society of Anesthesiology score, f = comorbidity, g = chemotherapy administration, ITT intention-to-treat$	atching; a = age, b	o = sex, c = tumc	r location,
)			•	•	•								

were six studies that originated from Western countries  $^{17-20,26,27}$  and five from Asia.  $^{16,28-31}$  These 11 studies consisted of 2 RCTs,  $^{26,30}$  two prospective reviews,  $^{17,18}$  and seven retrospective reviews.  $^{16,19,20,27-29,31}$  One study was a multi-institution study,  $^{20}$  and the other ten were single-institution studies.  $^{16-19,26-31}$ 

The detailed characteristics and short- and long-term outcomes of the 11 included studies are presented in Supplementary Table 1. The number of patients in each study had a range of 28–248. Of the 1136 patients included in this meta-analysis, 432 (38.0 %) underwent BTS and 704 (62.0 %) underwent emergency surgery. Administration rates of adjuvant chemotherapy in each group were described in seven studies, and no significant differences were observed in all seven studies.<sup>16–18,20,28–30</sup> There were ten studies that mentioned median follow-up periods, with a range of 21–86 months.<sup>16,18–20,26–31</sup>

## Long-Term Outcomes

Of the 11 studies included in the meta-analysis, OS was evaluated as an endpoint in all 11 studies, DFS was evaluated in six,<sup>16,19,20,28–30</sup> and recurrence in eight.<sup>16,18–20,26,28–30</sup> If the study provided only a survival curve and not a survival rate, we obtained the rate by extracting data as accurately as possible from the figure and thereafter calculated the number of events.

Data on 5-year OS were available in eight studies, with the overall rate being 63.8 %.<sup>16,20,26–31</sup> The 5-year OS rates in the BTS and emergency surgery groups of these eight studies were 57.2 and 67.1 %, respectively. There were three studies that reported 3-year OS data; rates in the BTS and emergency surgery groups were 66.7 and 51.9 %, respectively.<sup>17–19</sup> The relatively short-term oncological outcomes of these three studies <sup>17–19</sup> were integrated into the data of the other eight studies <sup>16,20,26–31</sup> for final metaanalysis to increase the sample size to 1,136. Pooled together, meta-analysis of 11 studies investigated OS between BTS and emergency surgery groups and found no significant difference (RR = 0.95; 95 % CI 0.75-1.21; but the results were heterogeneous P = 0.66), $(\chi^2 = 23.79; P = 0.008; I^2 = 58 \%)$  (Fig. 1a). Visual inspection of the funnel plot for OS did not suggest the presence of publication bias (Supplementary Fig. 2), and no significant publication bias was observed on either the Egger (P = 0.592) or rank correlation (P = 0.697) test.

Considering the significant prognostic impact of residual cancer after surgery, which can negate the potential oncological influence of SEMS, we conducted an additional analysis investigating OS in the population of patients who underwent curative resection. A total of nine studies contributed the analysis and demonstrated no significant difference between the BTS and emergency surgery groups

BTS E Surgery			егу		<b>Risk Ratio</b>		Risk Ratio							
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	Λ	I-H, Ran	dom, 95%	CI			
5-year DFS														
Choy et al.	12	60	54	180	7.4%	0.67 [0.38, 1.16]	2014			+				
Sabbagh et al.	37	48	27	39	33.5%	1.11 [0.86, 1.44]	2013			-				
Tung et al.	11	22	7	13	5.3%	0.93 [0.48, 1.79]	2013			•				
Kim et al.	10	25	28	70	7.2%	1.00 [0.57, 1.75]	2013		_	+				
Saida et al.	29	37	21	32	24.8%	1.19 [0.88, 1.62]	2003							
Subtotal (95% CI)		192		334	78.2%	1.05 [0.87, 1.27]				٠				
Total events	99		137											
3-year DFS														
Quereshy et al.	20	28 28	26	39 39	21.8% 21.8%	1.07 [0.78, 1.48]	2014		-	+				
Subtotal (95% CI)	20	20	26	29	21.070	1.07 [0.78, 1.48]								
Total events Heterogeneity: Not ar	oplicable	·	0720											
Test for overall effect:	2=0.42	(P = 0.0	)8 <b>)</b>											
Total (95% CI)		220		373	100.0%	1.06 [0.91, 1.24]				•				
Total events	119		163											
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Ch	i² = 4.3	2, df = 5 (	P = 0.5	0); I <sup>2</sup> = 09	6		$\vdash$		+ +		-		
Test for overall effect:	Z = 0.79	(P = 0.4)	(3)					0.1 0.2	0.5	1 2	5	1		

FIG. 2 Meta-analysis of disease-free survival between bridge to surgery and emergency surgery for malignant large-bowel obstruction. BTS bridge to surgery, E Surgery emergency surgery, M-H Mantel-Haenszel, 95 % CI 95 % confidence interval

(RR = 0.96; 95 % CI 0.67–1.37; P = 0.82), but the results were heterogeneous ( $\chi^2 = 17.12$ ; P = 0.03;  $I^2 = 53$  %) (Fig. 1b).<sup>16,17,19,20,26–30</sup>

Also, five studies evaluated 5-year DFS, with the overall rate being 55.1 %.<sup>16,20,28–30</sup> The 5-year DFS rates in the BTS and emergency surgery groups of these 5 studies were 48.4 and 59.0 %, respectively. With an integration of 3-year DFS data by Quereshy et al., pooled analysis in a total of 593 patients demonstrated no significant difference between the BTS and emergency surgery groups in DFS (RR = 1.06; 95 % CI = 0.91–1.24; P = 0.43) with no significant heterogeneity ( $\chi^2 = 4.32$ ; P = 0.50;  $I^2 = 0$  %) (Fig. 2).<sup>19</sup>

Of the included studies, eight assessed the effect of BTS on recurrence in a total of 672 patients.<sup>16,18–20,26,28–30</sup> Metaanalysis of recurrence showed no significant difference between the BTS and emergency surgery groups (RR = 1.13; 95 % CI 0.82–1.54; P = 0.46) with no significant heterogeneity ( $\chi^2 = 8.81$ ; P = 0.27;  $l^2 = 21$  %) (Fig. 3).

#### Sensitivity Analysis

Sensitivity analyses address the robustness of the findings obtained from meta-analysis. They involve comparing the results of two or more meta-analyses calculated using different assumptions; i.e., they test whether the assumptions or decisions made during the course of the review have a major effect on the results. To identify potential moderator variables, sensitivity analyses across seven variables, including study design, region of study, number of cases, type of stent, surgical procedure in the BTS group, presence or absence of intention-to-treat analysis, and success rate of SEMS insertion, were performed (Table 2). Across all analyses involving different study/patient characteristics, the BTS group continued to be similar to the emergency surgery group in OS, with  $\chi^2 P$  and  $I^2$  continuing to indicate significant heterogeneity in the seven subgroups.

#### DISCUSSION

This systematic review and meta-analysis of 11 studies, which included 1,136 patients, evaluated the long-term oncological outcomes of BTS for MLBO compared with emergency surgery. The results of this meta-analysis show that BTS was oncologically comparable to emergency surgery with respect to OS, DFS, and recurrence. These results document the oncological safety of BTS and add to those of previous studies showing that SEMS insertion provides time for patient stabilization, staging workup, screening of synchronous proximal lesions, and appropriate bowel preparation and short-term safety and feasibility, in terms of morbidity, stoma creation, primary anastomosis, and length of hospital stay.<sup>8–10,32</sup>

	BTS	S	E Surg	егу		<b>Risk Ratio</b>			Ri	sk Rati	0	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	1	M-H, Ra	ndom,	95% CI	
Quereshy et al.	10	28	16	39	17.9%	0.87 [0.47, 1.62]	2014		-	-		
Choy et al.	10	60	46	180	18.1%	0.65 [0.35, 1.21]	2014		-	•		
Gorissen et al.	19	60	11	39	17.9%	1.12 [0.60, 2.09]	2013				-	
Tung et al.	11	22	3	13	7.4%	2.17 [0.74, 6.36]	2013			+	•	
Kim et al.	7	20	21	60	15.5%	1.00 (0.50, 1.99)	2013		-	+		
Sabbagh et al.	16	48	8	39	14.0%	1.63 [0.78, 3.39]	2013			+		
Alcantara et al.	8	15	2	13	4.9%	3.47 [0.89, 13.51]	2011			+		_
Saida et al.	3	15	3	21	4.3%	1.40 [0.33, 6.01]	2003		_	<b>-</b>		
Total (95% CI)		268		404	100.0%	1.13 [0.82, 1.54]				•		
Total events	84		110									
Heterogeneity: Tau <sup>2</sup> =	0.04; Chi	i <sup>2</sup> = 8.8	1, df = 7 (	P = 0.2	7);  2 = 21	%		<u> </u>				
Test for overall effect:	Z=0.75	(P = 0.4	6)		00052			0.05	0.2	1	5	20
		52 	2072					Fav	ours BTS	Favou	irs E Sur	gery

FIG. 3 Meta-analysis of recurrence between bridge to surgery and emergency surgery for malignant large-bowel obstruction. BTS bridge to surgery, E Surgery emergency surgery, M-H Mantel-Haenszel, 95 % CI 95 % confidence interval

In contrast to the well-defined short-term benefits of BTS, oncological outcomes of BTS continue to be discussed but are as yet undetermined. Saida et al. first demonstrated long-term outcomes of BTS retrospectively, reporting no significant difference in 5-year OS compared with emergency surgery (44 vs. 40 %, respectively).<sup>29</sup> Thereafter, Zhang et al. first reported results of meta-analysis in 2012 with regard to oncological outcomes and showed that BTS did not adversely affect long-term survival compared with emergency surgery.<sup>32</sup> However, this result seems inconclusive because this study analyzed survival in a relatively small number of studies and samples (4 studies and 390 cases). In addition, a recent retrospective study by Gianotti et al. demonstrated a survival benefit of BTS strategy over emergency surgery.<sup>17</sup>

Historically, the negative oncological impact of SEMS insertion has been of concern. The enforced radial dilatation by SEMS suggests the possibility of increased risk of perforation and tumor manipulation that can induce dissemination of cancer cells into the peritoneal cavity, surrounding lymphatic vessels, and bloodstream. A study by Maruthachalam et al. supported this theory by showing a significant increase of cytokeratin 20 mRNA expression in peripheral venous blood following SEMS insertion compared with staging colonoscopy.<sup>15</sup> In 2013, Sabbagh et al. reported a notable negative oncological impact of BTS compared with emergency surgery by showing 5-year OS data of 25 versus 62 %, respectively, although this study was retrospective but using a propensity score analysis to eliminate selection biases.<sup>20</sup> In a subsequent report, the authors also indicated that SEMS insertion in BTS caused higher rates of tumor ulceration, peritumor ulceration, perineural invasion, and lymph node invasion than did emergency-surgery groups and that these pathological alterations may partially explain the negative oncological impact of BTS.<sup>33</sup>

BTS strategy is currently becoming a more frequent treatment modality for MLBO based only on short-term benefits, but the contrary opinions should not be ignored and the oncological influence of BTS should be assessed by multicenter RCTs. However, seven previous multicenter RCTs investigating the efficacy of BTS have been closed prematurely because of a high rate of SEMS-related complications, including insertion failure and perforation.<sup>34,35</sup> Given the requirement of a very large sample size (more than 1,000 patients), its emergency setting, and the difficulty of technical standardization with SEMS insertion and surgery, such an RCT does not seem feasible.<sup>20</sup> Therefore, the results of our meta-analysis comprising 11 studies, with a relatively large sample size (n = 1136), are clinically meaningful.

The current meta-analysis demonstrates that BTS was similar to surgery without SEMS insertion with respect to oncological outcomes. Furthermore, the OS analysis of only those patients with curative resection, with the intention of eliminating the effect of residual tumor on survival, was also consistent. A plausible pathophysiological reason for SEMS insertion not adversely influencing oncological outcomes would be the reductive effect of BTS on morbidity. Among all 11 studies included in the current study, six demonstrated a significant reduction in morbidity for the BTS group (Supplementary Table 1). Major surgery induces a certain degree of systemic proinflammatory response, including release of proinflammatory cytokines, and subsequent postoperative complications cause further exaggerated proinflammatory responses.<sup>36–38</sup> Studies have

Variable	Subgroup	No. of studies	No. of cases	RR	95 % CI	Р	Heterogeneity			
							$\chi^2$	$I^{2}$ (%)	Р	
Study design	RCT	2	76	0.80	0.44–1.44	0.45	1.42	30	0.23	
	Non-RCT	9	1060	0.97	0.75-1.27	0.84	20.75	61	0.008	
Region of study	Western countries	6	421	1.02	0.68-1.54	0.91	18.43	73	0.002	
	Asia	5	715	0.87	0.71-1.08	0.20	2.99	0	0.56	
No. of cases	>80	7	951	0.89	0.62-1.28	0.54	19.24	69	0.004	
	<80	4	185	1.01	0.75-1.37	0.94	4.41	32	0.22	
Type of stent	Only Wallflex	3	240	0.96	0.46-2.00	0.91	14.85	87	0.0006	
	Not only Wallflex	8	896	0.96	0.78-1.19	0.71	9.26	24	0.23	
Surgical procedure in BTS group	Only LAP	2	143	0.72	0.49-1.05	0.08	0.31	0	0.58	
	Not only LAP	9	993	1.00	0.76-1.32	0.98	20.43	61	0.009	
Analysis	ITT	4	205	1.19	0.71-1.98	0.51	11.34	74	0.01	
	Non-ITT	7	931	0.85	0.68-1.08	0.19	8.95	33	0.18	
Success rate of	>90 %	5	540	0.83	0.60-1.14	0.24	7.64	48	0.11	
SEMS insertion	<90 %	5	356	1.09	0.76-1.56	0.63	12.29	67	0.02	

 TABLE 2
 Sensitivity analyses of overall survival between bridge to surgery and emergency surgery for malignant large-bowel obstruction

*RR* risk ratio, *CI* confidence interval, *RCT* randomized controlled trial, *LAP* laparoscopic surgery, *ITT* intention-to-treat, *SEMS* self-expandable metallic colonic stent

shown that a proinflammatory milieu can promote cancer progression and lead to poor prognosis in colorectal cancer patients.<sup>39–41</sup> In addition, the occurrence of postoperative complications can delay or omit the induction of adjuvant chemotherapy because of a patient's poor health condition. A longer interval from surgery to adjuvant chemotherapy has been reported to be associated with worse survival in colorectal cancer patients.<sup>42</sup> Taken together, the lower rate of morbidity in the BTS group may have compensated for the possible oncological deteriorations associated with SEMS insertion.

This study involves several other limitations that must be taken into account. As with all systematic reviews, the strength of our conclusions depends on the quality of the primary studies. Indeed, only two of the studies included in this meta-analysis are RCTs, one of which has closed prematurely because of the high rate of anastomotic leakage in the emergency surgery group.<sup>26</sup> The indication for SEMS insertion before surgery was not clear in any of the retrospective studies. However, as mentioned previously, considering the obstacles, such as the requirement of very large sample size, emergency setting, and the difficulty of technical standardization, pursuing a multicenter RCT on this topic does not seem feasible. The differences in selection criteria, sample size, type of SEMS, and technical quality of procedures, and other factors among the studies might be responsible for the high heterogeneity observed across studies. Calculations using the random-effects model for estimation of overall incidence might have minimized, but did not eradicate, this significant heterogeneity.

In conclusion, this study suggests that BTS, SEMS insertion followed by surgery, has no adverse influence in terms of patient oncological outcomes, including OS, DFS, and recurrence, compared with emergency surgery. Thus, results of this meta-analysis on long-term as well as well-described short-term outcomes suggest that BTS could be a promising alternative strategy for MLBO patients.

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# REFERENCES

- Deans GT, Krukowski ZH, Irwin ST. Malignant obstruction of the left colon. Br J Surg. 1994;81:1270–6.
- Yeo HL, Lee SW. Colorectal emergencies: review and controversies in the management of large bowel obstruction. J Gastrointest Surg. 2013;17:2007–12.
- Tekkis PP, Kinsman R, Thompson MR, Stamatakis JD, Association of Coloproctology of Great Britain I. The Association of Coloproctology of Great Britain and Ireland study of large bowel obstruction caused by colorectal cancer. *Ann Surg.* 2004;240:76–81.
- Korenaga D, Ueo H, Mochida K, Kusumoto T, Baba H, Tamura S, et al. Prognostic factors in Japanese patients with colorectal cancer: the significance of large bowel obstruction–univariate and multivariate analyses. *J Surg Oncol.* 1991;47:188–92.
- Runkel NS, Schlag P, Schwarz V, Herfarth C. Outcome after emergency surgery for cancer of the large intestine. *Br J Surg.* 1991;78:183–8.
- 6. Dohmoto M. New method: endoscopic implantation of rectal stent in palliative treatment of malignant stenosis. *Endosc Dig.* 1991;3:1507–12.

- 7. Dohmoto M, Hunerbein M, Schlag PM. Palliative endoscopic therapy of rectal carcinoma. *Eur J Cancer*. 1996;32A:25–9.
- 8. Cirocchi R, Farinella E, Trastulli S, Desiderio J, Listorti C, Boselli C, et al. Safety and efficacy of endoscopic colonic stenting as a bridge to surgery in the management of intestinal obstruction due to left colon and rectal cancer: a systematic review and meta-analysis. *Surg Oncol.* 2013;22:14–21.
- Huang X, Lv B, Zhang S, Meng L. Preoperative colonic stents versus emergency surgery for acute left-sided malignant colonic obstruction: a meta-analysis. *J Gastrointest Surg*. 2014;18:584–91.
- Tan CJ, Dasari BV, Gardiner K. Systematic review and metaanalysis of randomized clinical trials of self-expanding metallic stents as a bridge to surgery versus emergency surgery for malignant left-sided large bowel obstruction. *Br J Surg.* 2012;99:469–76.
- 11. Khot UP, Lang AW, Murali K, Parker MC. Systematic review of the efficacy and safety of colorectal stents. *Br J Surg.* 2002;89:1096–102.
- Saida Y, Sumiyama Y, Nagao J, Takase M. Stent endoprosthesis for obstructing colorectal cancers. *Dis Colon Rectum*. 1996;39:552–5.
- Vitale MA, Villotti G, d'Alba L, Frontespezi S, Iacopini F, Iacopini G. Preoperative colonoscopy after self-expandable metallic stent placement in patients with acute neoplastic colon obstruction. *Gastrointest Endosc*. 2006;63:814–9.
- Koch M, Kienle P, Sauer P, Willeke F, Buhl K, Benner A, et al. Hematogenous tumor cell dissemination during colonoscopy for colorectal cancer. *Surg Endosc.* 2004;18:587–91.
- Maruthachalam K, Lash GE, Shenton BK, Horgan AF. Tumour cell dissemination following endoscopic stent insertion. *Br J Surg.* 2007;94:1151–4.
- Choi JM, Lee C, Han YM, Lee M, Choi YH, Jang DK, et al. Long-term oncologic outcomes of endoscopic stenting as a bridge to surgery for malignant colonic obstruction: comparison with emergency surgery. *Surg Endosc.* 2014;28:2649–55.
- 17. Gianotti L, Tamini N, Nespoli L, Rota M, Bolzonaro E, Frego R, et al. A prospective evaluation of short-term and long-term results from colonic stenting for palliation or as a bridge to elective operation versus immediate surgery for large-bowel obstruction. *Surg Endosc.* 2013;27:832–42.
- Gorissen KJ, Tuynman JB, Fryer E, Wang L, Uberoi R, Jones OM, et al. Local recurrence after stenting for obstructing leftsided colonic cancer. *Br J Surg.* 2013;100:1805–9.
- Quereshy FA, Poon JT, Law WL. Long-term outcome of stenting as a bridge to surgery for acute left-sided malignant colonic obstruction. *Colorectal Dis.* 2014; doi:10.1111/codi.12666. [Epub ahead of print].
- 20. Sabbagh C, Browet F, Diouf M, Cosse C, Brehant O, Bartoli E, et al. Is stenting as "a bridge to surgery" an oncologically safe strategy for the management of acute, left-sided, malignant, colonic obstruction? A comparative study with a propensity score analysis. *Ann Surg.* 2013;258:107–15.
- 21. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–88.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–60.
- Egger M, Davey Smith G, Schneider M, Minder C. Bias in metaanalysis detected by a simple, graphical test. *BMJ*. 1997;315:629–34.
- Abramson JH. WINPEPI updated: computer programs for epidemiologists, and their teaching potential. *Epidemiol Perspect Innov.* 2011;8:1.
- Alcantara M, Serra-Aracil X, Falco J, Mora L, Bombardo J, Navarro S. Prospective, controlled, randomized study of intraoperative colonic lavage versus stent placement in obstructive left-sided colonic cancer. *World J Surg.* 2011;35:1904–10.

- Dastur JK, Forshaw MJ, Modarai B, Solkar MM, Raymond T, Parker MC. Comparison of short-and long-term outcomes following either insertion of self-expanding metallic stents or emergency surgery in malignant large bowel obstruction. *Tech Coloproctol.* 2008;12:51–5.
- Kim HJ, Choi GS, Park JS, Park SY, Jun SH. Higher rate of perineural invasion in stent-laparoscopic approach in comparison to emergent open resection for obstructing left-sided colon cancer. *Int J Colorectal Dis.* 2013;28:407–14.
- Saida Y, Sumiyama Y, Nagao J, Uramatsu M. Long-term prognosis of preoperative "bridge to surgery" expandable metallic stent insertion for obstructive colorectal cancer: comparison with emergency operation. *Dis Colon Rectum*. 2003;46:S44–9.
- Tung KL, Cheung HY, Ng LW, Chung CC, Li MK. Endo-laparoscopic approach versus conventional open surgery in the treatment of obstructing left-sided colon cancer: long-term follow-up of a randomized trial. *Asian J Endosc Surg.* 2013;6:78–81.
- 31. Xu K, Zhang H, Feng Y, Cong JC, Chen CS, Liu EQ. Comparison of the outcomes of preoperative stent insertion and emergency surgery in the treatment of obstructive left-sided colorectal cancer: an analysis of 248 cases (in Chinese). *Shijie Huaren Xiaohua Zazhi*. 2010;18:736–40.
- 32. Zhang Y, Shi J, Shi B, Song CY, Xie WF, Chen YX. Selfexpanding metallic stent as a bridge to surgery versus emergency surgery for obstructive colorectal cancer: a meta-analysis. *Surg Endosc.* 2012;26:110–9.
- 33. Sabbagh C, Chatelain D, Trouillet N, Mauvais F, Bendjaballah S, Browet F, et al. Does use of a metallic colon stent as a bridge to surgery modify the pathology data in patients with colonic obstruction? A case-matched study. Surg Endosc. 2013;27:3622–31.
- Pirlet IA, Slim K, Kwiatkowski F, Michot F, Millat BL. Emergency preoperative stenting versus surgery for acute left-sided malignant colonic obstruction: a multicenter randomized controlled trial. Surg Endosc. 2011;25:1814–21.
- 35. van Hooft JE, Bemelman WA, Oldenburg B, Marinelli AW, Lutke Holzik MF, et al. Colonic stenting versus emergency surgery for acute left-sided malignant colonic obstruction: a multicentre randomised trial. *Lancet Oncol.* 2011;12:344–52.
- 36. Lundy J, Ford CM. Surgery, trauma and immune suppression. Evolving the mechanism. *Ann Surg.* 1983;197:434–8.
- 37. Matsuda A, Furukawa K, Suzuki H, Kan H, Tsuruta H, Matsumoto S, et al. Does impaired TH1/TH2 balance cause postoperative infectious complications in colorectal cancer surgery? J Surg Res. 2007;139:15–21.
- Matsuda A, Matsutani T, Sasajima K, Furukawa K, Tajiri T, Tamura K, et al. Preoperative plasma adiponectin level is a risk factor for postoperative infection following colorectal cancer surgery. J Surg Res. 2009;157:227–34.
- 39. Matsuda A, Matsumoto S, Seya T, Matsutani T, Kishi T, Yokoi K, et al. Does postoperative complication have a negative impact on long-term outcomes following hepatic resection for colorectal liver metastasis?: a meta-analysis. *Ann Surg Oncol.* 2013;20:2485–92.
- 40. Mirnezami A, Mirnezami R, Chandrakumaran K, Sasapu K, Sagar P, Finan P. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. *Ann Surg.* 2011;253:890–9.
- Platt JJ, Ramanathan ML, Crosbie RA, Anderson JH, McKee RF, Horgan PG, et al. C-reactive protein as a predictor of postoperative infective complications after curative resection in patients with colorectal cancer. *Ann Surg Oncol.* 2012;19:4168–77.
- 42. Biagi JJ, Raphael MJ, Mackillop WJ, Kong W, King WD, Booth CM. Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. JAMA. 2011;305:2335–42.