Comparison of the Long-Term Oncological Outcomes of Stent as a Bridge to Surgery and Surgery Alone in Malignant Colonic Obstruction

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ABSTRACT: **Background:** Self-expanding metallic stents (SEMS) insertion is an alternative to emergency surgery in malignant colonic obstruction. However, the long-term oncological outcome of stents as a bridge to surgery is limited and controversial.

Objectives: To determine the long-term oncological outcome of stents as a bridge to surgery.

Methods: Data of patients who underwent emergency surgery and endoscopic stent insertion as a bridge to surgery due to obstructing colonic cancer at Soroka Medical Center during a 14 year period were collected retrospectively. Preoperative data, tumor staging, and oncological outcomes in terms of local recurrence, metastatic spread, and overall survival of the patients were compared.

Results: Sixty-four patients (56% female, mean age 72 years) were included in the study: 43 (67%) following emergency surgery, 21 stent inserted prior to surgery. A stent was inserted within 24–48 hours of hospital admission. The mean time between SEMS insertion and surgery was 15 days (range 0–30). Most of the patients had stage II (41%) and stage III (34%) colon cancer. There was no difference in tumor staging and localization between groups. There was no significant difference in disease recurrence between SEMS and surgery groups, 24% and 32%, respectively. Disease-free survival rates were similar between the SEMS group (23.8%) and surgery group (22%). Four year and overall survival rates were 52.4% vs. 47.6%, 33.3% vs. 39.5%, respectively.

Conclusions: SEMS as a bridge to surgery in patients with obstructing colon cancer provide an equivalent long-term oncological outcome to surgery alone.

IMAJ 2017; 19: 736–740

KEY WORDS: colon cancer, colonic obstruction, endoscopic stent, self-expanding metallic stents (SEMS)

Colorectal cancer presents as a large bowel obstruction in up to 30% of patients, about 70% of whom are in the left colon and represent a common cause of surgical emergency [1-3].

The traditional treatment for malignant large bowel obstruction has been surgery. However, that changed in the past decades with the introduction of self-expanding metallic stents (SEMS) in 1991. SEMS were first introduced as a palliative alternative for advanced cancer, and later as a bridge to surgery, with the presumed benefit of optimizing the patient's clinical conditions prior to surgery and thus, theoretically, providing less morbidity, lower mortality rates, and reduced need for stoma [2,4].

However, in recent years concerns have been raised regarding the complication of SEMS, which include bowel perforation, stent obstruction and migration, and bleeding. Of these, bowel perforation and micro-perforation are of greater concern due to the potential risk of metastatic spread [2,5]. Moreover, concerns have been raised over the association of SEMS insertion with local recurrence [1].

SEMS are used by surgeons and gastroenterologists to relieve malignant colonic obstruction. They can decompress the obstruction, provide an opportunity for bowel preparation, and make single-stage surgical resections possible. Moreover, use of SEMS is associated with a shorter hospital stay, less morbidity, lower mortality rates, and lower stoma formation rates than emergency surgery [9,10]. Clinical application of SEMS has changed dramatically in Europe.

After initial enthusiasm about SEMS, their use became controversial due to complications and was stopped in France, Sweden, Norway, and the Netherlands. But in the U.K., colonic stenting has been a standard surgical procedure. The consensus of a group of European multidisciplinary specialists recommended SEMS insertion as a bridge to surgery in elderly frail patients with a short stenosis, and suggested that acute resection should be the standard of care in healthy patients younger than 70 years of age without significant co-morbidities [11].

Since 2004, Soroka Medical Center started using SEMS for obstructing colonic tumors. We aimed to compare the results of SEMS vs. surgery alone in the setting of malignant large bowel obstruction, with regard to oncological outcomes including

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recurrence of the disease, metastatic spread, and survival of our patients.

PATIENTS AND METHODS

A retrospective comparative study was performed on patients who were admitted to Soroka Medical Center with obstructing colon cancer between 1999 and 2013.

Data were collected from patient medical charts. Diagnosis of an acute malignant colonic obstruction was made by abdominal X-rays, gastrografin enema (BerliMed S.A, Madrid, Spain), and/or abdominal computed tomography (CT) scan, and confirmed by histological examination. From 1999 to 2004, all patients with malignant colonic obstruction underwent emergency surgery. From 2004, we started using SEMS for the treatment of colonic obstruction. Decisions regarding patient management and stent insertion were made by the senior attending surgeon based on clinical signs of colonic obstruction, abdominal plain film, and findings of obstructing colon tumors on a CT scan. Peritoneal signs or cecal distension more than 8 cm on abdominal plain film or a CT scan were contraindications for stent insertion. Stent insertion was conducted by gastroenterologists. Patients with a failed stent underwent emergency surgery and were included in our surgery group. All patients underwent surgery and were divided into two groups:

- SEMS group: patients who underwent surgery only, including patients who were first allocated to the SEMS procedure but failed
- Surgery group: patients who underwent SEMS and then surgery

Elective surgery was performed a few days after SEMS insertion had relieved the colonic obstruction. Tumors were classified according to their location as right sided or left sided. Left-sided tumors were further divided into splenic flexure, descending colon, sigmoid, and rectosigmoid. Pathological tumor classification was conducted according to the American Joint Committee on Cancer (AJCC) TNM classification [9]. All patients underwent subsequent chemotherapy and were followed in our oncological facility after surgery. There was no difference in the oncological follow-up and treatment between the two groups. Patients were followed initially at 3 month intervals for 2 years and then every 4 months for the next 3 years. Follow-up examination included clinical history, physical examination, and carcinoembryonic antigen (CEA) level. Colonoscopy was performed between 6 and 12 months after surgery. Patients with elevated CEA levels underwent CT scans of the chest and abdomen. Overall and disease-free survival rates were measured from the time of surgery until December 2013.

STATISTICAL ANALYSIS

The data were coded and stored using Microsoft Excel 2011 (Version 2016) software (Microsoft Corp, USA), and then analyzed with SPSS 18.0 (SPSS, Chicago, IL, USA). We analyzed the data first using descriptive statistics (mean and standard deviation) and performed analytical statistics using chi-square tests for categorical variables and *t*-tests for quantitative variables, unless they did not meet the indications for parametric analysis, in which case a Mann–Whitney test was used. To evaluate the intra-rater reliability, we used Cohen's Kappa. Differences were considered statistically significant for *P* values less than 0.05.

Evaluation of survival was conducted using Kaplan–Maier procedures with a log rank test to evaluate the difference between survival of the groups analyzed.

RESULTS

Overall, 64 patients (56% females) with a mean age of 72 years were included in our study. Of these, 36 underwent emergency surgery. We attempted SEMS insertion as a bridge to surgery with 28. SEMS insertion failed in seven patients, and thus they were considered for an emergency operation and included in the surgery group.

The causes for the stent failure included technically impossible guide insertion through the narrowed bowel lumen in four patients and perforation during stent insertion in one case. In two cases the cause of failure was not explained in medical records. Thus, we included 43 patients in the surgical group and 21 in the stent group. Patient characteristics and background were similar in both groups [Table 1]. The stent was inserted 24

Table 1. Patients and tumor characteristics

Patient characteristic	SEMS (n=21)	Surgery (n=43)	*P*
Mean age, years (range)	74.14 (57–91)	71.16 (28–92)	0.317
Gender Female n (%) Male n (%)	 9 (43) 12 (55)	 27 (63) 16 (38)	0.131
Medical background n (%) IHD DM HTN	 2 (9) 8 (38) 12 (57)	 6 (28) 8 (38) 9 (43)	 0.238 0.999 0.355
Prior cancer n (%)	3 (16)	0 (0)	0.540
Tumor location* n (%)	13 (61)	25 (57)	0.799
Left hemicolectomy/+laparoscopic Right hemicolectomy	6/+2 (28/+10) 1 (5)	7 (16) 9 (21)	
Hartmann's procedure Loop colostomy	0 1(5)	10 (23) 0	
Sigmoidectomy/+laparoscopic	7/+3 (33/+14)	13 (30)	
Low anterior resection	1 (5)	0	
Subtotal colectomy	0	4 (10)	

SEMS = self-expanding metallic stents, IHD = ischemic heart disease, DM = diabetes mellitus, HTN = hypertension

*Tumor location: due to the low number of patients, we were unable to calculate proper statistics for every location and thus combined them in two main groups: sigmoid vs. other locations

to 48 hours after hospital admission. The mean time between SEMS insertion and surgery was 15 days (range 0–30). Most of the tumors were localized in the left colon (82.8%) with the majority (51.6%) in the sigmoid colon. There was no difference in surgery types in the groups. There were more laparoscopic colectomies performed after SEMS insertion. About one-quarter of patients in the surgery group underwent Hartmann's procedure and stoma formation. There was only one case of colostomy in the SEMS group. The cause of colostomy was stent migration with subsequent obstruction in an advanced sigmoid carcinoma. This patient underwent loop colostomy for palliation.

Table 2 shows the oncological outcome. Most patients presented with stage II (41%) and stage III (34%) colon cancer. There was no difference in tumor staging and localization between the groups. There was no difference in disease distant or local recurrence (disease-free survival) between SEMS and surgery groups, 32% and 40%, respectively, odds ratio (OR) was 1.458 and confidence interval (CI) was 0.6–3.5. Moreover, four of five patients who underwent laparoscopic surgery had recurrence of the disease (one local and three metastatic spread) without having an effect on survival rates. Analysis of the subgroup of patients who failed stent insertion did not show a difference in survival (overall, 4 year, and disease-free) compared with the surgery and SEMS groups. However, there were high failure rates for stent insertion in patients with advanced-stage disease ($P = 0.048$).

The four year survival rate was similar ($P = 0.722$) with 52.4% survival among SEMS vs. 47.6% in the surgery group. In addition, there was no difference in overall survival: 33.3% (median 56 months) in the SEMS group and 39.5% (77 months) in the surgery group [Figure 1]. Moreover, even when excluding stage IV, the disease-free survival of stages II + III showed no difference with an average of 74.4 months in the surgery group vs. 49.3 in the SEMS group ($P = 0.111$), with overall survival of 81 months on average in the surgery group vs. 58 months in the SEMS group ($P = 0.93$). Median survival showed a disease-free survival of 21 months in the surgery group compared to 28 months in the SEMS group, with overall survival of 52 months in the surgery group vs. 42 months in the SEMS group. These differences were not significant using the Mann–Whitney ranked test.

Table 2. Oncological outcomes

	SEMS (n=21) n (%)	Surgery (n=43) n (%)	*P*
TNM (classification of malignant tumors) staging			0.768
I n	0	0	
II n (%)	10 (48)	17 (40)	
III n (%)	6 (28)	16 (37)	
IV n (%)	5 (24)	10 (23)	
Recurrence n (%)	5 (32)	17 (40)	0.517
Local	2	1	
Distant	5	16	
Median disease-free survival, months (range)	28 (5–130)	21 (6–184)	0.428
Median overall survival, months (range)	42 (1–130)	52 (3–184)	0.419
4 year survival (%)	52.4%	47.6%	0.321
Median disease-free survival stages II + III, months (range)	40.5 (5–130)	46.0 (8–184)	0.376
Median overall survival stages II + III, months (range)	56 (5–117)	77.5 (11–184)	0.353

SEMS = self-expanding metallic stents

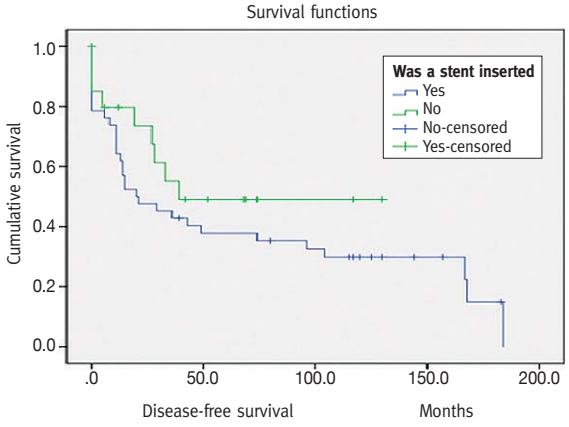
DISCUSSION

Our data are similar to published results [1,6-8]. SEMS, as a bridge to surgery, have the same overall oncological results as surgery alone. We did not find a statistical difference in the 4 year survival rate in the groups or a difference in the overall survival. However, a final conclusion regarding stent effects on oncological outcomes in any specific procedure and patient groups are still not encouraging or final. Thus, our study is important in this debate.

Frago and co-authors [3] in a systematic review of 59 studies including 34 using SEMS, found various alternatives and lack of high-grade evidence and considered an individually tailored approach to each patient with distal colonic obstruction. Maruthachalam and colleagues [12] found that tumor cells spread in blood samples following SEMS insertion in malignant colonic obstruction. Maruthachalam et. al [13] presented immediate results after SEMS only, without long-term oncological outcome, which weakens their conclusions.

However, concerns were raised regarding the long-term effects of SEMS usage, especially the oncological outcome [1,2,5]. Various researchers compared the effects of stent insertion on elective and emergency colonic resections in long-term outcome. Comparison of stent to elective surgery found better

Figure 1. Kaplan–Mayer overall survival comparison between the groups



Four year survival rate ($P = 0.722$), median = 56 months in the SEMS and 77 months in the surgery group

SEMS = self-expanding metallic stents

outcome toward the elective procedure [6]. Choi et al. [7] found similar overall and disease-free 3 and 5 year survival in patients with stents compared to emergency surgery. Knight and collaborators [13] considered the same 5 year survival in a group of 15 patients with stents compared to elective colectomies. Conversely, Sabbagh and colleagues [14] found worse patient outcome following stent insertion in 5 year disease-free and overall survival in similar groups. The main bias of these studies is that the surgeries (elective and emergency, one- and two-stage procedures, subtotal and total colectomies) are not similar.

Our study also confirmed reduced formation of stoma as in other literature reports [15-17] and the increased possibility for laparoscopic surgery after SEMS insertion [18,19]. The type of surgery following stent insertion is another variable. Recent studies demonstrated safety, feasibility, and effectiveness of laparoscopic surgery after SEMS [1,19-21]. In our study, most cases of laparoscopic resections had tumor recurrence. This recurrence can be the result of stent micro-perforations after insertion and during surgery following laparoscopic colonic dissection, and instrument handling in the tumor region can spread tumor cells in cases of advanced carcinoma. Stent itself results in specimen rigidity and cautionary specimen removal and wound protection prevent local spread in the wound. A recent study by Gorissen and co-authors [1] showed higher local recurrence rates without changes in survival following SEMS. However, other studies did not find a difference in local recurrence or in survival. In our opinion, accurate surgical techniques and less tumor handling during laparoscopic dissection may be effective to decrease a tumor local recurrence. One of the limitations of our study is the small sample size of patients who underwent laparoscopic surgery after stent insertion; however, most of the other studies also presented small patient groups.

Some authors have raised concerns regarding the risk of a higher recurrence rate following SEMS insertion [12,14], both local and metastatic. Our data indicate that there is no statistical difference in overall recurrence.

This study has several limitations. We conducted a retrospective study that included a small number of patients with obstructing colon cancer treated in our hospital by surgery alone and SEMS as bridge to surgery. Patients who had SEMS insertion had shorter follow-up due to later start using this technique in colonic obstruction.

We used 4 year survival due to short lengths of follow-up in SEMS patients. A longer period of time would have added additional power to our results.

We regarded recurrence as either local or distant and thus were unable to evaluate local recurrence with the stent which is an important aspect.

CONCLUSIONS

SEMS insertion as a bridge to surgery does not cause an adverse oncologic outcome compared with the treatment by surgery alone in patients with malignant colonic obstruction. Laparoscopic surgery is an available option for colonic resection in patients with colonic stent; however, there is a higher incidence of recurrence, and thus we advise considering colonic stents as a viable option. Our experience and this study have shown that this procedure can be conducted safely, with the patient having to undergo only one operation, and in most cases having it done laparoscopically instead of an open procedure, decreasing all the morbidity and mortality that resolve upon additional surgeries and an open approach.

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Capsule

Getting to the guts of mosquito control

Malaria persistently evades our best efforts to eliminate it. **Pike** and colleagues genetically modified malaria vector mosquitoes to be more immune-resistant to infection by the parasite, which altered the composition of the mosquitoes' gut bacteria. Genetically modified male (female) mosquitoes preferentially mated with wild-type females (males). Ten generations later, the genetically modified mosquitoes constituted 90% of a caged population without losing resistance to the malaria parasite. In an alternative strategy, **Wang** et al. engineered mosquitoes' gut bacteria. A strain of nonpathogenic bacteria, AS1, was both sexually and transgenerationally transmitted. The strain infected a laboratory population of mosquitoes and persisted for at least three generations. AS1 engineered to inhibit malaria parasite development in the midgut could do so without handicapping the mosquitoes.

Science 2017; 357: 1396 and 357: 1399

Eitan Israeli

Capsule

Synovial immunophenotype and anti–citrullinated peptide antibodies in rheumatoid arthritis patients

Serum anti-citrullinated peptide antibodies (ACPAs) may be present before the development of rheumatoid arthritis (RA) and may be predictive of more severe, erosive disease. **Orr** and colleagues examined the synovial tissue immunophenotype according to ACPA status in patients with RA, as well as the response to treatment and erosion status. In total, 123 subjects (78 ACPA+) were included. Compared to ACPA–RA patients, synovium from ACPA + RA patients was characterized by significantly higher levels of CD19+ B cells and CD3+ and CD8+ T cells (each $P < 0.05$), and CD19+ B cell levels were significantly higher in patients who were naive to treatment. The CD19+ B cell infiltrate level was higher in patients with erosions at follow-up ($P = 0.0128$). Levels of lymphoid aggregates of CD19+ B cells were significantly higher in ACPA+ patients ($P < 0.05$), and this was associated with increased serum CXCL13 levels. The EULAR response was significantly associated with the level of CD3+ T cell infiltrates ($P < 0.05$), while CD68+ macrophage and CD8+ T cell levels were predictive of the response to tumor necrosis factor inhibitors ($P < 0.05$). The results of this prospective study demonstrate that the levels of synovial B cell infiltrates and lymphoid aggregates were significantly higher in ACPA+ RA patients, especially those who were naive to treatment. In addition, ACPA+ subjects developed more erosions during progression of the disease and had higher serum levels of CXCL13. The EULAR response to therapy in ACPA+ RA patients was associated with increased levels of T cell and macrophage markers.

Arthr & Rheumatol 2017; 69: 2114

Eitan Israeli

"Medicine is aptly described as an art, not a science. To this end, four different doctors may have up to four different diagnoses or prescriptions"

Andrew Saul, (Born 1955), Editor-in-Chief of the *Orthomolecular Medicine News Service* and on the editorial board of the *Journal of Orthomolecular Medicine*. He has published more than 200 peer-reviewed articles and has written or coauthored 12 books

"History is a novel whose author is the people"

Alfred de Vigny, (1797–1863), French poet, playwright, novelist, and early leader of French Romanticism