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Colonic stent for bridge to surgery for acute left-sided malignant colonic obstruction: A review of the literature after 2020

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Abstract

It has been found that 8%-29% of colorectal cancers are obstructive. The use of "stent as bridge to surgery" is one of the most debated topics in obstructive left-sided colorectal cancer management. The endoscopic placement of a self-expanding metallic stent as bridge to surgery (BTS) could turn an emergency surgery to an elective one, increasing the number of primary anastomoses instead of stoma and facilitating the laparoscopic approach instead of an open one. However, in recent years the possible risk of perforations and microperforations facilitating cancer spread related to the use of self-expanding metallic stent for BTS has been highlighted. Therefore, despite the useful short-term outcomes related to BTS, the recent literature has focused on long-term outcomes investigating the disease-free survival, the recurrence rate and the overall survival. Due to discordant data, international guidelines are still conflicting, and the debate is still open. There is not agreement about using self-expanding metallic stent for BTS as the gold standard.

Key Words: Colorectal cancer obstruction; Anastomosis; Laparoscopy; Recurrence rate; Overall survival; Guidelines

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Core Tip: The most recent articles (published after 2020) about self-expanding metallic stent as bridge to surgery in left-sided colorectal cancer obstruction were collected. Both the short-term and long-term outcomes were analyzed, focusing on the role of stent-related microperforations in worsening disease-free and overall survival rates. Despite the growing number of studies published in recent years, the use of self-expanding metallic stent as bridge to surgery is not considered the gold standard due to conflicting reports. Updating meta-analyses, randomized studies and reviews will help determine new international guidelines and a shared treatment flow-chart.

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INTRODUCTION

It is known that 8%-29% of colorectal cancers (CRC) are initially characterized by obstruction[1]. In the management of left-sided colonic obstruction there are two different options: emergency surgery (ES) and stent placement as bridge to surgery (BTS). Historically, an ES was first considered for distal malignant obstruction[2]. In this context, three different surgical options could be considered[3]: (1) Three-stage management, in which the first intervention is a proximal stoma formation, followed by colonic resection and stoma reversal; (2) Two-stage management (Hartmann's intervention); and (3) One-stage management that consists of resection and primary anastomosis. About 20 years ago the SEMS placement was first used to decompress neoplastic stenosis[4].

ES is often conducted with an open approach because a distended bowel may hamper laparoscopy [5]. In addition to that, ES frequently concludes with stoma formation that negatively impacts patient quality of life[6]. This is why the interest in BTS has become increasingly important. In fact, authors have primarily focused on short-term outcomes of using SEMS for BTS, such as anastomosis and stoma rate, laparoscopic and open approach and postoperative hospital stay. On the other hand, the recent BTS literature is focused on long-term outcomes, such as disease-free survival (DFS), overall survival (OS) and progression-free survival. Due to the length of time since the start of using SEMS for BTS, a multitude of data have been collected (Figure 1).

However, despite a growing number of articles about CRC obstruction, the use of SEMS for BTS is still debated. No uniform international guidelines have been published yet due to the hypothesized role of microperforations worsening the long-term outcomes of patients. The purpose of this review was to collect the latest (since 2020) research on SEMS for BTS use. In one of the more updated systematic reviews and meta-analyses[7], only two studies published after 2020 were included (Arezzo *et al*[8] multicentric study and Allievi *et al*[9] single center study). Both the international guidelines and the short-term/long-term outcomes focusing on the new data published after 2020 have been analyzed (the "update" part of each chapter).

GUIDELINES

In left-sided colonic obstructions, colonic stenting in a palliative setting is commonly accepted. However, the best treatment in a curative setting is still debated. There is still not agreement whether SEMS placement for BTS or upfront ES is better.

Some of the most important American guidelines recommend stent insertion as the first choice to solve colonic obstruction[10,11], while another considers both possibilities to be equally valid[12]. In general, the attitude of European guidelines is more moderate. No guidelines consider the insertion of a stent as the only option[13-15]. Both approaches are also considered in the World Society of Emergency Surgery[16]. Webster *et al*[17] analyzed high-quality international recommendations published between 2010 and 2019 and found that only two studies considered the use of a stent as the gold standard.

In this context, another discussed point is the "time to elective surgery," which is the time between stent insertion and elective surgery[18,19]. Theoretically a delayed interval between SEMS placement and definitive surgery could allow better recovery and improve nutritional status, but it could be burdened by a high rate of local tumor infiltration and fibrosis[20]. Not all guidelines indicate the ideal number of days between stent positioning and surgery. However, in the American Society for Gastrointestinal Endoscopy 6 d before elective surgery is considered the best interval. After the 6th day the risk of perforation is increased[10]. In the Eastern Association for the Surgery of Trauma an interval of 7 d is considered[21].

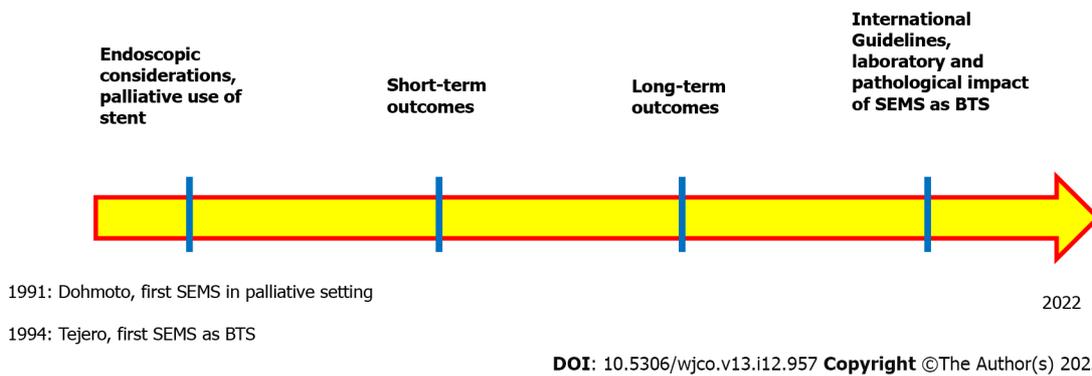


Figure 1 Self-expandable metallic stent as bridge to surgery timeline. Topic of interest of self-expandable metallic stent (SEMS) used as bridge to surgery from the initial use to current use. BTS: Bridge to surgery.

Update

Recently, the European Society of Gastrointestinal Endoscopy (ESGE) guidelines-Update 2020 has been published[22]. They strongly recommend with high quality of evidence that stenting for BTS as an option in patients with potentially curable left-sided obstruction, and it must represent a shared decision-making process. This main recommendation is different from the 2014 ESGE guidelines, which stated that the stent placement could be considered as an alternative only for patients with American Society of Anesthesiologists \geq III and/or age $>$ 70 years[23]. However, in the 2014 and 2020 editions, the most important recommendation to use SEMS for BTS should be reserved for patients without signs of perforation (always strong recommendation)[22]. In the recent ESGE guidelines a time interval of 2 wk until surgery is considered (weak recommendation, low quality evidence)[22].

ENDOSCOPIC CONSIDERATIONS

For patients suspected of having a neoplastic left-sided colonic obstruction, an urgent colonoscopy is usually performed[24]. It may be useful to identify other colonic lesions and to stage cancer with more accuracy[25].

The SEMS placement remains a challenging procedure. The technical success is defined as the endoscopic correct stent placement, while the clinical success is the resolution of the obstruction[26]. SEMS can be covered and uncovered. The uncovered SEMS can be divided into through-the-scope and non-through-the-scope[27]. The through-the-scope SEMS is inserted through a guidewire. The diameter of the SEMS is about 18-22 mm[24]. In the majority of studies[24,25] the WallFlex enteral colonic stent and the Niti-S enteral colonic stent were used.

SEMS placement for BTS has been extensively studied for left-sided colonic obstruction, while limited data have been collected for the right-sided obstruction[28].

Although severe endoscopic adverse events complicate $<$ 5% of procedures[10], early and late complications can sometimes occur[29]. Some early complications (within 30 d) are migration, perforation and bleeding, while some late complications (after 30 d) are a late obstruction, migration and perforation. The covered SEMS have a higher migration rate and lower obstruction rate, while uncovered SEMS have a lower migration rate[27]. Only a few studies investigated the predictors of technical failures, but it seems that a stenosis $>$ 8 cm may be associated with a higher rate of technical failure[30].

Update

A central part of the updated ESGE guideline is dedicated to endoscopic technical considerations. Colonic stenting should be performed directly or supervised by a medical figure both with colonoscopy and fluoroscopic expertise[22].

In 2021, a multicenter prospective cohort study affirmed that the WallFlex stent was the most used globally[31].

Some authors tried to compare the feasibility and safety of SEMS for BTS based on the grade of colonic neoplastic obstruction, classified 0 to 2 by the Colorectal Obstruction Scoring System. No differences were found in safety and short-term outcomes in patients classified as 0, 1 or 2[26].

An effort to standardize the SEMS placement has been made. It has likely contributed to excellent short-term outcomes, technical success and low perforation rate[31].

According to the most recent literature, colonic stenting should be performed by endoscopists who demonstrate a good expertise as it represent a challenging procedure. In some articles a minimum number of procedures is indicated[32]. If stenting expertise is not available, decompressing stoma as a

bridge to elective surgery should be considered[22].

It was shown that delaying surgery can lead to a significantly higher recurrence rate[33].

LABORATORY AND ANATOMOPATHOLOGICAL CONSIDERATIONS

In the last 2-3 years there has been a growing interest about the possible association between SEMS for BTS and worse long-term oncological outcomes, such as perineural invasion (PNI) and vascular and lymphatic invasion[34]. The presence of PNI seems to decrease long-term survival[34]. The PNI negatively impacts recurrence and survival in CRC. In some studies, there was no difference in perineural invasion between the ES group and the SEMS for BTS group[35]. The tumor stage and vascular invasion were found to be independent risk factors for PNI in patients with obstructing colonic stenting[36]. According to Wang *et al*[37], PNI may be associated with obstruction but not with stent insertion.

In other articles, laboratory elements, such as circulating cell-free DNA (cfDNA) and circulating tumor DNA (ctDNA), have been identified. cfDNA, which indicates cellular damage, is derived from apoptotic or necrotic cells. ctDNA indicates tumor-derived DNA possibly from apoptotic or necrotic cells, and it could contain gene mutations. During the endoscopic procedure of colonic stenting the manipulation of the tumor could increase plasma ctDNA and cfDNA[38]. Stent-induced neoplastic manipulation may lead malignant cells to local and distant invasion, worsening long-term outcomes [38].

Broholm *et al*[39] performed a gene expression analysis. The Nano String Counter Pan Cancer Immune Oncology Panel 360 gene expression was used. They observed that SEMS for BTS induced changes in gene expression in the neoplastic microenvironment, related to progression in CRC and may induce a more aggressive phenotype. These changes seemed to be caused by mechanical pressure of the cancer and the following inflammation of tissue. Six genes promoting angiogenesis were significantly upregulated. Tumor-promoting inflammation gene expression, such as *IL-6*, were involved. The use of anti-inflammatory drugs after stenting has been proposed[39].

SHORT-TERM OUTCOMES

In almost all studies postoperative complications are analyzed. Postoperative outcomes such as 30-d or 60-d mortality, anastomosis rate and laparoscopic rate are often considered.

The most important advantages of using a SEMS for BTS is transforming an urgent surgery to an elective one and maintaining bowel continuity by avoiding stoma creation[40,14]. In fact, a primary anastomosis can be created more safely in an elective setting than in an urgent or emergent setting. Wang *et al*[41] revealed in their meta-analysis that the use of colonic stenting could not increase the risk of anastomotic leakage incidence compared with emergency surgery.

Using a stent for BTS approach could be different as well. Donlon *et al*[42] reported a 78% rate of the laparoscopic approach. However, in the same year Boland *et al*[43] reported only three studies (41%) in which the laparoscopic approach was successfully completed after the stent insertion.

According to De Ceglie *et al*[44], postsurgical complications like infections were less frequent in patients undergoing urgent surgery. In the same article, the hospitalization rate was similar in the ES and BTS groups. On the other hand, Consolo *et al*[45] observed a different result, demonstrating a reduced hospital stay in the BTS group.

Arezzo *et al*[46] found in their high-quality meta-analysis published in 2017 a significantly lower rate of temporary and definitive stomas (33.9% vs 51.4%, $P < 0.001$ and 22.2% vs 35.2%, $P = 0.003$), while no difference in the 60-d mortality was observed.

Only a few studies analyzed the cost-effectiveness between using SEMS for BTS and ES[10]. Allievi *et al*[47] and Neo *et al*[48] concluded that more data about cost-effectiveness are needed.

Update

The updated review of Hiyoshi *et al*[49] demonstrated that the use of SEMS was associated with low hospital mortality, a higher rate of primary anastomosis and decreased stoma rate. For these reasons after colonic stenting for BTS, patients often have a better quality of life compared with immediate resection[50]. Better short-term outcomes of the BTS group were confirmed by Spannenburg *et al*[51]. Higher primary anastomosis, lower 30-d mortality rate, lower overall complications rate and shorter hospital stay were reported.

In June 2022, a study that compared BTS to diverting stoma was published[52]. Seven studies were included, and 1358 patient were recruited (646 in the first group and 712 in the second group). A lower Clavien-Dindo I/II complication rate was highlighted in the BTS group (8.68% vs 16.85%, $P = 0.004$), while the III-IV grade were similar (7.69% vs 8.79%, $P = 0.37$). There were no differences in short-term mortality, 3-year OS and permanent stoma rate.

LONG-TERM OUTCOMES

Even though SEMS for BTS short-term outcomes have been quite established, the long-term outcomes still remain uncertain. In the last few years, the literature on using SEMS for BTS focused on oncological outcomes. The DFS is the time between surgery and discovery of new cancer signs, while the OS is the time between surgery to death. In the early 2000s, Kim *et al*[53] suspected that SEMS insertion could negatively impact oncological outcomes.

Some authors tried to explain the mechanism. Some authors hypothesized that SEMS manipulation could cause a microperforation that may lead to peritoneal carcinomatosis. Other authors hypothesized that tumor compression was the cause of hematogenous diffusion[54]. Maruthachalam *et al*[55] found an increased expression of cytokeratin 20 mRNA (marker of tumor cells) in patients after stent insertion.

Amelung *et al*[56] found no significant differences in recurrence rate and 3-year and 5-year OS. Rodrigues-Pinto *et al*[57] also found no differences in tumor recurrence, recurrence-free survival and OS between the ES and BTS groups. The same result was also obtained by Matsuda *et al*[6] and Gibor *et al* [58].

These results were strongly supported by Arezzo *et al*[46] and Amelung *et al*[56]. The first was a multicentric prospective randomized trial conducted by the European Association for Endoscopic Surgery. The second was a meta-analysis in which no differences between the two groups in terms of 3-year and 5-year DFS and in 3-year and 5-year OS were confirmed.

However, a few studies showed differences in long-term oncological outcomes. In 2019 Foo *et al*[54] presented a higher distant recurrence rate in the BTS group (25.3% *vs* 15.0%, $P = 0.046$) and overall recurrence rate in the BTS group (37.0% *vs* 25.9%, $P = 0.049$). A 5-year follow-up is usually described in all studies, whereas Verstockt *et al*[59] presented a 1-year, 2-year, 3-year, 5-year and 10-year OS for all patients regardless of stage.

In recent literature, the cost-effectiveness has also been considered[60]. The American Society for Gastrointestinal Endoscopy guidelines considered the use of stent for BTS more cost-effectiveness than ES[10]. However, little data about this topic are available[47].

Update

According to Cirocchi *et al*[7], the overall recurrence and 3-year OS rates are similar for both the ES and BTS groups. In another recent study, 3-year and 5-year DFS and OS were not different despite a higher number of lymph nodes harvested in the BTS group than the ES group[51].

In the ESCO trial[8], neither OS nor DFS differed in the BTS and ES groups in a 36-mo follow-up study. However, as it has been reported in this paper, one randomized trial showed an increased rate of malignant recurrence[61]. The contradictory data need a well conducted prospective, randomized trial. The inclusion criteria used by ESCO were colonic cancer between the splenic flexure and 15 cm from the anal margin and diagnosed by computed tomography. Similar long-term oncological outcomes were observed. A significant time to progression was observed in the descending colon, possibly because it was the easiest endoscopic procedure (compared to flexure and sigmoid). No differences in terms of time to progression, DFS and OS were observed considering age, sex, body mass index and American Society of Anesthesiologists score[8].

In February 2022, a multicentric study[62] including 564 patients was published. The results showed the “non-inferiority” of BTS *vs* ES in terms of OS ($P = 0.012$). However, in another a recent study[63] considering only stage II and III patients, a higher frequency of distant metastatic recurrence was shown in BTS group than in the surgery alone group (30.4% *vs* 13.3%, $P = 0.035$).

In 2022, Yamada *et al*[64] tried to explain how tumor manipulation may worsen the prognoses in CRC patients after SEMS insertion. Seven days after stent insertion the cfDNA, ctDNA and serum lactate dehydrogenase levels were significantly higher. This indicated that SEMS injures cancer and spreads damage-associated molecular patterns released by necrotic cells that induce sterile inflammation. SEMS placement seems to induce unfavorable gene circulation, which results in a microenvironment associated with cancer progression. According to this last study, angiogenesis is also induced by cancer manipulation *via* miR-9 downregulation.

According to some authors, using a standardized and reproducible SEMS insertion method is essential for reducing the perforation rate[31].

Veld *et al*[65] compared SEMS for BTS with decompressing stoma bridge to resection instead of ES. The authors concluded that the two techniques have similar intermediate-term oncological outcomes [65].

A comprehensive literature review compared SEMS for BTS long-term outcomes with decompressing stoma for BTS and ES. The authors found that colonic stent and decompressing stoma may lead to better 5-year OS and DFS than ES. The decompressing stoma may have a better 5-year OS than the BTS strategy. According to these data, Tan *et al*[66] recommended decompressing stoma as the best choice for left-sided colonic obstruction.

CONCLUSION

In 2022, the BTS strategy is considered a safe strategy, and many studies have demonstrated better short-term outcomes than ES. By using a stent for BTS, it is possible to obtain an increased rate of primary anastomosis *vs* stoma rate, a laparoscopic approach *vs* open approach and a shorter post-operative stay.

The endoscopic stent placement is not a simple procedure, and it requires specific skills[57]. The most recent ESGE guidelines recommend that colonic stenting should be performed by an operator with competence both in colonoscopy and fluoroscopic technique[22]. The stent insertion could be followed by early (< 30 d) or late complications (> 30 d), such as migration, perforation, bleeding and obstruction. However severe adverse events only occur in < 5% of procedures[10]. Stents could be covered or uncovered, with covered stents having a lower obstruction rate[27].

The use of a stent for BTS changes an ES into an elective surgery. The role of BTS has been analyzed for both short-term and long-term outcomes. The short-term outcomes are represented by higher laparoscopic approaches *vs* open surgery[42,43], higher rate of anastomosis *vs* stoma rate[41,46,67], 30-d post-surgery complications and hospital stay[44]. The long-term outcomes include the DFS, the progression-free survival and OS.

Almost all articles about SEMS for BTS from the late 1990s to 2010 focused on the short-term outcomes. After stent placement in an elective setting, surgery can be completed with a laparoscopic approach. In addition, a higher rate of primary anastomosis and lower rate of temporary or definitive stoma rates improve patient quality of life[46].

Currently, more focus is being placed on long-term outcomes than short-term outcomes. Initially, gastroenterologists and surgeons were enthusiastic due to the excellent short-term results from the use of SEMS for BTS. However, conflicting data about the worsening of OS and DFS due to BTS curbed the initial enthusiasm[68]. Although there are many hypotheses, the exact biological mechanism has not been described. The use of a stent for BTS seems to be burdened by a higher rate of perforations and microperforations resulting in cancer spread[64]. Most articles only have 1-year to 3-year or 5-year follow-up. Some rare cases have longer periods[59].

Because of all these contrasting data, international guidelines do not agree about using a stent for BTS as the gold standard. The American guidelines suggest the use of a stent for BTS as the gold standard [10], while the European guidelines suggest the surgical resection and the use of SEMS for BTS as possible treatments in patients with left-sided obstructing colonic cancer[22].

Some of the most important topics for further studies are the national and international agreement on therapeutic algorithm of treatment for patients with left-sided obstructive colonic cancer and a more detailed cost-benefit analysis. Furthermore, considering literature after the 2020, it could be interesting to prepare a specific study to understand the impact of the COVID-19 pandemic impact on the use of SEMS for BTS.

FOOTNOTES

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