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*Review*

# Endoscopic Stenting and Palliative Chemotherapy in Advanced Colorectal Cancer: Friends or Foes? An Analysis of the Current Literature

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**Abstract.** *Background/Aim: Chemotherapy offers a clear benefit in terms of survival rates of stage IV metastatic colorectal cancer (CRC) patients, but this advantage might be mitigated by the theoretical risks of short- and mid-term complications in the cases of contextual self-expandable metal stent (SEMS) positioning, which might also affect survival rates. Materials and Methods: We reviewed all available literature from Medline and Scopus databases to study the role of chemotherapy with or without the simultaneous administration of targeted therapy in increasing the risk of the complications after SEMS positioning and, eventually, in affecting the survival rates. Results: Thirteen retrospective studies and 1 randomized controlled trial (RCT) were eligible for the present analysis. The study group consisted of a total of 682 patients. A total of 305 patients were treated with conventional chemotherapy, 212 with conventional chemotherapy also containing targeted therapy, and 165 with no chemotherapy administration. Chemotherapy administration did not increase the rate of SEMS-related complications and these complications did not affect the overall survival rates. Conclusion: Chemotherapy administration is not associated with a higher risk of SEMS-related complications and a reduction in the survival rates.*

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Colorectal cancer (CRC) presents as an unresectable metastatic disease (stage IV) in 20% to 30% of patients, and sub-occlusive or occlusive symptoms are present in 10-30% of these patients (1-3). Surgical resection is a valid palliative treatment in the latter patients, even though complications are relatively frequent 25.5% (range=8.1-40.7%) and mortality rates reach 9.4% (range=3.7-25.8%) (4-8). Conversely, self-expandable metal stent (SEMS) positioning might be an alternative approach and it can be chosen as the first line of treatment for palliation of sub-obstructive or obstructive CRC. SEMS positioning shows, in fact, a technical success rate ranging from 88% to 100%, a shorter hospitalization, lower risk of stoma formation, lower costs, and shorter time to initiation of chemotherapy compared to surgery (9).

Despite these results, a risk of complications of SEMS positioning ranging from 34% to 44% has been reported, which can be theoretically exacerbated by the simultaneous administration of chemotherapy (10-12). Studies on the safety of palliative stenting for occlusive stage IV CRC during conventional chemotherapy or biological therapies are lacking. However, the introduction of the new cytotoxic agents has prolonged survival up to 2 years as compared with supportive care alone, which is associated with an overall survival of 5 months (1, 13). The use of chemotherapy seems to increase the risk of mid-term complications (such as stent migration resulting from tumor response or late perforation) in these patients (14, 15). Furthermore, bevacizumab has been associated with 1-2% of gastrointestinal perforations (16), apparently due to the necrosis of the tumor that has invaded the gastrointestinal serosa, or to local ischemia or delayed ulcer healing process (17). Therefore, the association of bevacizumab and SEMS might increase the risk of colonic perforations. Van Halsema *et al.* (18) in a relatively recent metanalysis, analyzed the risk factors of stent-related perforations and reported an increased risk of perforations in

80 patients treated with bevacizumab when compared with 578 patients treated with conventional chemotherapy (12.5% *vs*. 7%, respectively). However, these data are inconclusive because of the heterogeneity of the population, the inclusion of extracolonic cancers (associated with poorest outcome when compared to CRC) and the use of chemotherapy with no palliative intent (18).

The role of chemotherapy with or without the simultaneous administration of targeted therapy in increasing the risk of the complications after SEMS positioning and in affecting the survival rates of patients with symptomatic stage IV CRC was reviewed.

## Materials and Methods

The literature search was performed using Pubmed and Scopus, to identify all eligible studies. The last search was performed on February 1, 2022. No restrictions were applied. The following key words were used in the research process: "colorectal cancer", "colon" or "large bowel" and "obstruction" or "stenosis", "metastatic" or "IV stage", "chemotherapy" or "bevacizumab", "SEMS" or "stent". The search was supplemented with the bibliography section of each paper and other published reviews. No language restrictions were applied. Titles, abstracts, and subsequent full-text articles were independently scanned for eligibility by two reviewers (GBS and PS).

*Criteria for inclusion and exclusion*. Inclusion criteria included: randomized controlled trial (RCT), prospective and retrospective studies. Types of participants included patients affected with symptomatic CRC, inoperable or incurable owing to tumor metastases (stage IV).

Type of treatment included SEMS positioning followed by chemotherapy with or without targeted therapy, or no chemotherapy. Exclusion criteria included: Patients affected with other causes of colonic obstruction rather than CRC.

*Outcomes*. (i) The role of chemotherapy with or without the simultaneous administration of targeted therapy in increasing the risk of SEMS-related complications.

(ii) The influence of SEMS-related complications in survival rates.

## Results

The PRISMA (19) flow chart is schematically reported in Figure 1. The literature search yielded 348 studies, 14 met the inclusion criteria, and, therefore, were included in the present review.

*Characteristics of the studies*. Five (29%) studies specifically investigated the safety and efficacy of the concomitant use of palliative chemotherapy and SEMS positioning (12, 14, 15, 20, 21). The majority of the studies was performed in Europe (8 studies: 303 patients, 44%), 5 in South Korea (292 patients, 43%), and 1 in Canada (87 patients, 13%). The studies were published between 1996 and 2020. Five studies were multicentric (12, 14, 20-22). Thirteen studies were

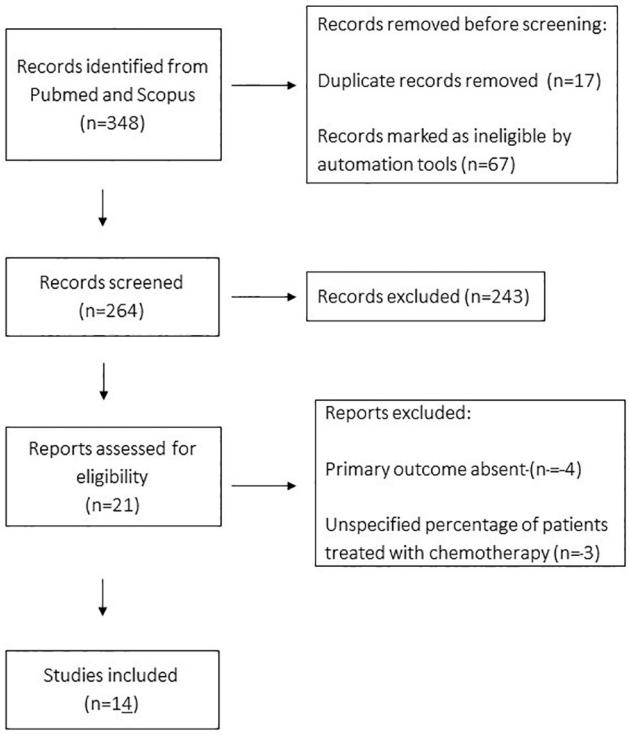


Figure 1. *PRISMA flow diagram*.

retrospective, and 1 was a RCT (Table I); the latter prematurely terminated for an unacceptable high rate of complications of SEMS positioning (22).

A total of 305 patients were treated with conventional chemotherapy (Group 1), 212 with targeted therapies (Group 2), and 165 had no chemotherapy administration (Group 3).

*Demographics*. Baseline characteristics are reported in Table I. Tumor location was not reported in 2 (14%) studies (23, 24). In 6 (43%) studies the tumors were in the colon (8, 12, 14, 20, 27, 29), but 4 (29%) included also the rectum (15, 21, 26, 28), in 1 (7%) the left colon and the rectum (25), and in 1 (7%) the left colon (22). In 6 (47%) studies an uncovered stent was used (8,14,22,24,25,29), covered, partially covered or uncovered in 4 (24%) (15, 21, 26, 27), and not reported in 4 (29%) (12, 20, 23, 28).

*SEMS-related complications*. Table II describes the rate of complications of the three groups of patients. When retrievable from the studies included in our literature search, overall, there were 95 (31%) complications in patients treated with conventional chemotherapy, 42 (20%) in the group of patients who underwent also targeted therapies, and 36 (22%) in the group of patients who had no chemotherapy. Complications included: 19 (25.7%) perforations, 38 (51.3%)

Table I. *Selected studies on palliative chemotherapy and SEMS positioning.*

| Author and year | Country | Type of study | SEMS | SEMS+Cht | SEMS+Ab | Age (median) | Female sex (%) | Follow-up (median) | Type of stent | Site of stenosis |
|---|---|---|---|---|---|---|---|---|---|---|
| Seoane *et al*. 2020 (25) | Spain | Retrospective | 0 | 0 | 6 | 76* | | | U | Left colon rectum |
| Pacheco-Barcia *et al*. 2019 (20) | Spain | Retrospective | 31 | 31 | 16 | | 63 | | | Colon |
| Park *et al*. 2019 (26) | South Korea | Retrospective | 0 | 0 | 96 | | | | U, C, PC | Colon rectum |
| Bong *et al*. 2019 (23) | South Korea | Retrospective | 0 | 0 | 23 | | | | | NR |
| Cezè *et al*. 2016 (14) | France | Retrospective | 0 | 38 | 0 | 65 | 53 | 15 | U | Colon |
| Imbulgoda *et al*. 2015 (12) | Canada | Retrospective | 30 | 47 | 10 | 75 68 55* | 50 40 50 | | | Colon |
| Han *et al*. 2014 (15) | South Korea | Retrospective | 42 | 27 | 3 | 71 60 NR | 45 30 NR | | U, C | Colon rectum |
| Fuccio *et al*. 2014 (21) | Italy | Retrospective | 9 | 37 | 45§ | 65 | 33 | 8.4* | U, C, PC | Colon rectum |
| Lee *et al*. 2012 (28) | South Korea | Retrospective | 0 | 32 | 3 | 60.3 | 39 | | | Colon rectum |
| Lee *et al*. 2011 (27) | South Korea | Retrospective | 20 | 41 | 5 | 64.1 | 34 | 9.6 | U, C | Colon |
| Karoui *et al*. 2010 (29) | France | Retrospective | 15 | 19 | 0 | | | | U | Colon |
| vanHooft *et al*. 2008 (22) | Netherlands | RCT | 2 | 6 | 1 | 59 | 78 | 12 | U | Left colon |
| Cennamo *et al*. 2009 (24) | Italy | Retrospective | 7 | 5 | 4˚ | | | 2.8 | U | NR |
| Karoui *et al*. 2007 (8) | France | Retrospective | 9 | 22 | 0 | 72* | 52 | | U | Colon |

SEMS: Self-expandable metal stent; Cht: conventional chemotherapy; Ab: chemotherapy with targeted therapy: bevacizumab, §11 patients treated with cetuximab and ˚2 patients treated with panitumumab; C: covered; U: uncovered; PC: partially covered; NR: not reported.
In the age column, the numbers with the asterisk symbol (*) indicate the mean.

obstructions, 2 bleedings (2.7%), and 15 (20.3%) stent migrations in patients treated with conventional chemotherapy; 26 (63.4%) perforations, 12 (29.3%) obstructions, 2 bleedings (4.9%), and 1 (2.4%) migration in the group of patients who underwent targeted therapies; and 10 (29.4%) perforations, 16 (47.1%) obstructions, 1 bleeding (2.9%), and 7 (20.6%) migrations in the group of patients who had no chemotherapy administration. Clinical appearance of complications ranged from 1 to 4.9 months after SEMS positioning and the initiation of chemotherapy. Targeted therapy consisted of bevacizumab in 199 (93.9%), cetuximab in 11 (5.2%), and panitumumab in 2 (0.9%) patients. Due to the association with chemotherapy, a specific influence of targeted therapy in increasing the risk of SEMS-related complication cannot be drawn.

*Differences in survival after chemotherapy administration.* Survival rates are reported in Table II. Survival ranged between 18 and 20 months in the group treated with conventional therapy, between 12.8 and 43 months in the group of patients who underwent also targeted therapy, and between 4.6 and 11 months in the group of patients not treated with adjuvant chemotherapy. According to the studies included in our literature search, the higher incidence of specific SEMS-related complications in the groups of patients analyzed did not affect overall survival rates.

## Discussion

In this study, we observed an extremely important finding, *i.e.,* the SEMS-related complications observed in patients who undergo chemotherapy are comparable to those of patients who had no adjuvant therapies.

Lee *et al*. (27) revealed that palliative chemotherapy was an independent risk factor for late complications in patients with SEMS (odds ratio=10.4; 95%CI=1.7-62.4; $p$=0.01). Conversely, Han *et al*. (15) reported that chemotherapy increases the rate of SEMS migration; however, reducing the risk of occlusion. Bong *et al*. (23) observed 7 (30.4%) perforations in 23 patients who had SEMS positioning and

Table II. *Complication and survival rates.*

| | Number of patients | | | Complications (%) | | | Survival (Months) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Author and year | SEMS | SEMS+Cht | SEMS+Ab | SEMS | SEMS+Cht | SEMS+Ab | SEMS | SEMS+Cht | SEMS+Ab | Overall |
| Seoane *et al*. 2020 (25) | 0 | 0 | 6 | | | 0 (0) | | | | |
| Pacheco-Barcia *et al*. 2019 (20) | 31 | 31 | 16 | 8 (26) | 13 (42) | 6 (38) | 11 | 20 | 43 | |
| Park *et al*. 2019 (26) | 0 | 0 | 96 | | | 7 (7) | | | 19.5 | |
| Bong *et al*. 2019 (23) | 0 | 0 | 23 | | | 7 (30) | | | | |
| Cezè *et al*. 2016 (14) | 0 | 38 | 0 | | 10 (26) | | | 18 | | |
| Imbulgoda *et al*. 2015 (12) | 30 | 47 | 10 | 5 (17) | 13 (28) | 5 (50) | 3.4* | 9.2* | 7.5* | |
| Han *et al*. 2014 (15) | 42 | 27 | 3 | 6 (14) | 11 (41) | 1 (33) | 4.6 | | | |
| Fuccio *et al*. 2014 (21) | 9 | 37 | 45 | 3 (33) | 6 (16) | 12 (27) | | | 12.8 | |
| Lee *et al*. 2012 (28) | 0 | 32 | 3 | | 8 (25) | 0 (0) | | | | 7.6 |
| Lee *et al*. 2011 (27) | 20 | 41 | 5 | 2 (10) | 21 (51) | 1 (20) | | | | 10.9 |
| Karoui *et al*. 2010 (29) | 15 | 19 | 0 | 2 (13) | 6 (32) | | | | | |
| vanHooft *et al*. 2008 (22) | 2 | 6 | 1 | 2 (100) | 4 (67) | 1 (100) | | | | 12 |
| Cennamo *et al*. 2009 (24) | 7 | 5 | 4 | 0 (0) | 0 (0) | 2 (50) | | | | 2.8 |
| Karoui *et al*. 2007 (8) | 9 | 22 | 0 | 8 (73) | 3 (14) | | | | | |
| Total | 165 | 305 | 212 | 36 (22) | 95 (31) | 42 (20) | | | | |

SEMS: Self-expandable metal stent; Cht: conventional chemotherapy; Ab: chemotherapy with targeted therapy. In the survival column, the numbers are reported as median, and those with the asterisk symbol (*) indicate the mean.

targeted therapy with bevacizumab. The Authors postulated that SEMS positioning without primary tumor removal was a risk factor for complications in patients treated with bevacizumab. Conversely, Imbulgoda *et al*. (12) showed that chemotherapy plus bevacizumab did not have a higher perforation rate when compared to the conventional chemotherapy (20% *vs*. 6%). Park *et al*. (26) reported in 96 patients who had SEMS positioning and received bevacizumab, a perforation rate of 7.3% (7/96 cases), not significantly different from the non-bevacizumab-users, in which immunotherapy was 7% (18/257, *p*=NS). Pacheco-Barcia *et al*. (20) observed that patients receiving systemic chemotherapy (with or without bevacizumab) were almost twice as likely to develop SEMS-related complications, with no difference between chemotherapy alone and bevacizumab-based regimens. Finally, in an Italian multicenter study including 91 patients, the complications occurred in 6/37 (16.2%) of patients who had chemotherapy alone, in 12/45 (26.7%) of those who received biological therapy and in 3/9 (33.3%) of those who received no chemotherapeutic treatment. No correlation between chemotherapy with or without biological therapy, K-ras status, and risk of SEMS-related complications was observed (21).

These contradictory data should be well interpreted, and the increase in survival rates of patients who underwent adjuvant therapies might be negatively counterbalanced by the risk of developing SEMS complications. It is, in fact, well known that SEMS positioning should be preferentially chosen in specific settings such as emergency operations and tertiary referral hospitals, as a bridge before surgery. Theoretically, the use of different types of stents might influence their complication rates (30). Han *et al*. (15) used covered and uncovered SEMS, and late obstruction occurred more frequently in patients with uncovered stents; however, late migration occurred more frequently in patients with covered (*p*=NS). Park *et al*. (26) reported that covered and partially covered stents significantly affected the complication rates (HR=1.73; 95%CI=1.144-2.624; *p*=0.009), and partial-covered stents were associated with a higher complication rate (HR=1.988; 95%CI=1.132-3.493; *p*=0.017). Cezè *et al*. (14) observed that the length and type of stent had no influence on complication rates. Finally, Lee *et al*. (27) found that a stent diameter of less than 20 mm was an independent risk factor for late complications.

Our study demonstrated a clear advantage of adjuvant chemotherapy over no chemotherapy in increasing the survival rates of patients. Pacheco-Barcia *et al*. (20) observed that patients receiving systemic therapy (chemotherapy alone or bevacizumab-containing regimens) had a significant increase in overall survival (27 months *vs*. 11 months) as compared to patients who had no treatment (*p*<0.001). Fuccio *et al*. (21) found that patients treated with biological therapy survived longer than those untreated (12.8 *vs*. 8 months, RR=0.5; 95%CI=0.3-0.9; *p*=0.020). Park *et al*. (26) observed that chemotherapy (HR=0.464, *p*<0.001), administration of targeted agents (HR=0.626; *p*=0.001), operation (HR=0.255; *p*<0.001), and re-obstruction (HR=0.651; *p*=0.004) were associated with a decreased mortality.

This study has several limitations, including the retrospective nature of all but one study included in our

analysis, the small numbers of patients included in the studies used for the present analysis, the extreme variability in the primary outcomes, and the lack of comprehensive data. Specifically, there was variability in the type of SEMS, chemotherapeutic agents, time to administration, indication for SEMS positioning (occlusion or subocclusion), and emergent or elective treatment.

Although we are confident to affirm that the association of chemotherapy and SEMS placement in the palliative treatment of obstructive CRC does not increase the risk of SEMS-related complications, we believe that prospective and larger studies are required to analyze the mid- and long-term outcomes of the association of chemotherapy and SEMS placement in the treatment of advanced non-metastatic CRC.

## Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

## Authors' Contributions

Giorgia Burrelli Scotti: Conception, design and writing the manuscript; Paolo Sapienza: Conception, design and writing the manuscript; Daniele Crocetti: Conception and design; Pierfrancesco Lapolla: Analysis and interpretation of data; Gioia Brachini: Conception and writing the manuscript; Mariarita Tarallo: Collection of data; Andrea Mingoli: Conception and design; Enrico Fiori: Conception, design, and data analysis.

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