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RESEARCH ARTICLE



Predictive factors of surgery in metastatic colorectal cancer: a retrospective cohort study

Raffaele Calicis^{a*}, Antoine Dubois^{b,c,d*}, Christian Ritter^e, Nicolas Tinton^a, Benjamin Calicis^a, Yves Hoebeke^a, David Lepore^a, Francisco Da Rocha De Sousa^a, Emmanuel Cambier^a and Fabrice Corbisier^a

^aDepartment of Abdominal Surgery, Grand Hôpital de Charleroi, Charleroi, Belgium; ^bAbdominal Transplant Surgery & Transplant Coordination, University Hospitals Leuven & Department of Microbiology, Immunology and Transplantation, KU Leuven, Leuven, Belgium; ^cLeuven Intestinal Failure and Transplantation (LIFT), University Hospitals Leuven, Leuven, Belgium; ^dDepartment of Experimental Surgery and Transplantation (CHEX), University Hospital Saint-Luc, Brussels, Belgium; ^eStatistical Methodology and Computing Service, Université Catholique de Louvain, Louvain-la-Neuve, Belgium

ABSTRACT

Introduction: Current management of metastatic colorectal cancer is based on neoadjuvant chemotherapy. Few studies have reported on surgery procedures in patients with metastatic colorectal cancer. The objective of this study was to describe our institutional experience with emergency surgery performed in patients with metastatic colorectal cancer during chemotherapy.

Patients and methods: This was a retrospective cohort study including adult patients of ≤ 80 years with a metastatic colorectal cancer between 2017 and 2020 and undergoing surgery during chemotherapy. Statistical analyses were based on Kaplan–Meier's curve and Cox proportional hazard model. The surgery statistical risk during chemotherapy was studied through all tumor and patient's characteristics. Multivariable logistic regression models were used to identify predictive factors of emergency surgery in these patients.

Results: Seventy-two cases were identified and 60% patients undergone an emergency surgery. By Kaplan–Meier's analyses, intestinal surgery was much more frequent and early in patients who have severe stenosis (either blocking or only permeable using a gastroscope) at the time of diagnosis. Patients with severe malignant stenosis presented a 6.28 time higher surgery risk ($p < .0001$). The median time between admission and surgery was 54 days in patients with severe stenosis who were operated.

Conclusion: The degree of colorectal tumor stenosis measured by endoscopy was a risk factor for emergency surgery in patients with metastatic colorectal cancer during neoadjuvant chemotherapy. In this group of patients presenting low survival outcomes, further studies are needed to define the place of preventive surgery, avoiding emergency surgery and morbidity in such fragile patients.

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KEYWORDS

Metastatic colorectal cancer; surgery; colorectal tumor stenosis; colorectal cancer

Introduction

Colorectal cancer accounts for 10% of cancer-related deaths around the world is ranked third among malignant cancer worldwide [1]. Nowadays, 18–30% [2,3] of the patients may present metastases or locally advanced disease at the time of the diagnosis. In this specific patient group, colorectal obstruction and perforation are the most common life-threatening complications requiring emergency surgical procedures [4]. Indeed, colorectal obstruction is reported in 10–30% of the patients with metastatic colorectal cancer, being the major cause of emergency surgical management in these patients [3,5].

Emergency surgical procedures are associated with poor outcomes in these patients [6]. Previous studies reported a poor survival in patients undergoing emergency surgery for colorectal tumor obstruction and increased surgical complications rate are reported in these patients [7]. Colorectal malignant obstruction often presents with severe concomitant disease, worsened physical status, water-electrolyte disorder and higher malignancy degree, potentially explaining the higher rate of post-surgical complications [8].

However, position of surgery in the management of colorectal malignant obstruction remains controversial [9,10]. The current guidelines of the French National Society of Gastro-enterology [9]

CONTACT Raffaele Calicis ✉ raff219@hotmail.com 📍 Rue Marguerite Depasse 6, 6060 Charleroi, Belgium

*Both authors contributed equally to this work.

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emphasize the use of stent in malignant colorectal obstruction, admitting that the ulterior surgical procedures are often harder to manage after the use of a prosthesis. Colic stent results in a smaller stoma rate but remains a poor bridge to surgery, as highlighted in the guidelines of the World Society of Emergency [11]. Elective surgery in patients presenting a locally advanced disease may avoid the difficult bridge to surgery in case of tumor stenting and the comorbidities of an emergency surgical procedure [11]. Therefore, the aim of this study was to identify several risk factors for emergency surgery in patients with metastatic colorectal cancer during chemotherapy.

Materials and methods

Patients population and study design

Studied patients were identified from the hospital cancer registry in the Department of Abdominal Surgery at the Grand Hôpital de Charleroi. The patient was recorded in the database when presenting with a diagnosis of metastatic colorectal cancer initially treated by chemotherapy between January 2017 and July 2020. Exclusion criteria included patients <18 years and patients presenting missing data. This study was approved by the Grand Hôpital de Charleroi Institutional Research Ethics Board and was performed in accordance with STROBE guidelines for cohort studies [12].

Data collection

Patients baseline characteristics (sex, age at diagnosis, body mass index, presence of arterial hypertension, diabetes status, use of insulin and use of anticoagulant); anatomopathological tumor characteristics (adenocarcinoma, carcinoma, undifferentiated carcinoma, mucinous adenocarcinoma, neoplasm, nevi and melanoma and signet ring cell carcinoma); histological tumor grade (good differentiated, mild differentiated, low differentiated, undifferentiated/anaplastic; unknown); clinical stage (tumor, node, metastases (TNM)) and pathological stage (TNM) were recorded in an anonymous database. These data were extracted from the database for statistical analyses with the agreement of the local Institutional Research Ethics Board.

Definitions

The presence of arterial hypertension was defined as systolic blood pressure higher than 140 mmHg

and/or diastolic blood pressure of ≥ 90 mmHg during two measures of more with or without use of antihypertensive therapy. The presence of diabetes was defined as chronic hyperglycemia, following the criteria of the American Diabetes Association [13]. Clinical and pathological stages were defined according to the widely used TNM staging system from the American Joint Committee on cancer [14]. Four degrees for colorectal tumor stenosis were identified: none; tumor stenosis passed by classical endoscope; tumor stenosis passed by classical gastroscope and total tumor obstruction, impossible to pass by endoscopy.

Statistical analyses

Continuous descriptive characteristics were described as mean $\pm$ standard deviation (SD) or median (range), depending on the normality. Categorical descriptive characteristics were presented with count and percentages. Statistical analyses were based on Kaplan–Meier's curve and Cox proportional hazard model. The surgery statistical risk during chemotherapy was studied through all criteria recorded during data collection.

Results

One hundred and fourteen cases were identified from the database. As we restricted the main analysis to patients ≤ 80 years, 42 patients were initially excluded, leaving a total of 72 patients for final analysis. The outcomes of patients being >80 years is provided in the [supplemental material \(Table S1\)](#).

Patient's demographics

Baseline patient's characteristics are described in [Table 1](#). Mean age population was 71 years (± 15.9 years), with almost a ratio 1:1 between men and women (50.9% of men and 49.1% of women). More than 50% of the patients presented with arterial hypertension. The flowchart of the patients is represented in [Figure 1](#).

Table 1. Baseline patient's characteristics.

	N or median	% or mean standard deviation
Female	56	49.1
Male	58	50.9
Age at diagnosis (years)	71	15.9
Body mass index	25.6	5.6
Arterial hypertension	62	54
Diabetes	23	20
Insulin	4	4
Anticoagulant	7	6

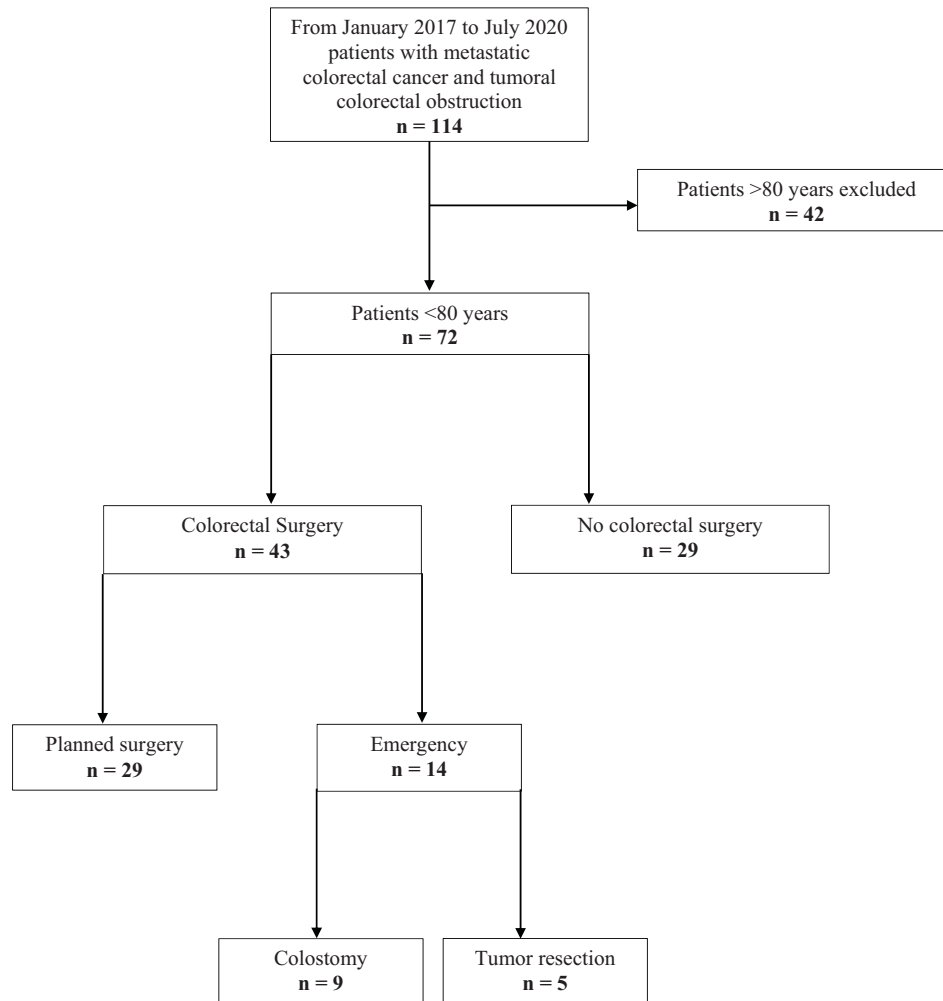


Figure 1. Flowchart of the patients included in the study.

Tumor's characteristics

Anatomopathological tumor's characteristics are described in Table 2. Histological tumor grade, clinical patient stage and pathological patient stage are described in Tables 3–5, respectively. Almost 90% of the tumor were adenocarcinoma and 5% of the tumors were mucinous adenocarcinoma. More than 50% of the tumor were histologically mild differentiated.

Predictive factors for surgery

Thirty-two patients presented with blocking stenosis. The percentage of operated patients remains high (five out of eight) among patients with severe stenosis which could be still passed through with a gastroscope. About 25% (eight out of 30) of patients who had no or mild stenosis had some intestinal surgery (Table 6). The Kaplan–Meier estimate of incidence curve of intestinal surgery shows that intestinal surgery is much more frequent and early in patients who have severe stenosis (either blocking or only permeable using a gastroscope) at the time of diagnosis (Figure 2).

With classification of the stenosis in two groups between severe (impassable or passage only with a gastroscope) and mild (non or penetrable with an endoscope), we found that the surgery risk is 6,8 times higher in the group with a severe stenosis ($p < .0001$) (Table 6). Also, the major part of the tumor was located at the sigmoid level (Table 7).

Time to surgery

For the 32 patients with severe stenosis who were operated, the median time between admission and surgery was 51 days (Table 6). Among these surgical interventions, 10 were urgent and three occurred in the month following the diagnosis. Regarding the eight patients with no or mild stenosis who were operated, the median time between admission and surgery was 263 days. The time to surgery was lower than one month in one patient but all others patients undergone a surgical procedure at more than 3 months. In total, 85% of the patients who had severe stenosis which could not even be passed through with a gastroscope

Table 2. Anatomico-pathological tumor's characteristics.

	N	%
Adenocarcinoma	101	89
Carcinoma	1	1
Undifferentiated carcinoma	1	1
Mucinous adenocarcinoma	6	5
Neoplasm	2	2
Nevi and melanoma	1	1
Signet ring cell carcinoma	2	2

Table 3. Histological tumor grade.

	N	%
Good differentiated	9	8
Mild differentiated	67	59
Low differentiated	24	21
Undifferentiated/anaplastic	3	3
Unknown	11	10

needed intestinal surgery later and many of them within 2 months.

Survival

The patients who had severe stenosis at diagnosis had better survival than those who had mild or no stenosis. However, this observation is not statistically significant since the difference in survival is not very big and the sample size is small (Figure 3).

Discussion

The main objective of this study was to identify predictive factors for surgical procedures in patients with colorectal cancer treated with chemotherapy. The analysis was restricted to the 75% of patients being ≤ 80 years. The main results may be summarized as follows: (i) no statistical significant difference of survival was shown between patients experiencing emergency surgery and those without interventions; (ii) the degree of tumor stenosis measured by endoscopy is a predictive factor for surgery in patients with colorectal cancer; and (iii) the risk for surgery is 6.28 times higher in the patients presenting a severe malignant stenosis degree.

In our retrospective cohort, there were no difference of survival between patients experiencing surgery and those without interventions. From previous literature, emergency surgical procedures such as colic derivation stoma or Hartmann procedure are often compared with colic stent placement in patients presenting malignant left colic obstruction [15,16]. Recently, a randomized control trial [15] found no difference in median survival between the stent placement strategy or emergency surgical procedure in these patients. However, as emphasized

Table 4. Clinical patient stage.

	N	%
Tumor (T)		
T1	1	1
T2	6	5
T3	68	60
T4	19	17
TX	18	16
Not available	2	2
Node (N)		
N0	21	18
N1	46	40
N2	2	2
NX	43	38
Not available	2	2
Metastasis (M)		
M1	18	16
M1a	50	44
M1b	36	32
M1c	10	9
Not available	0	0

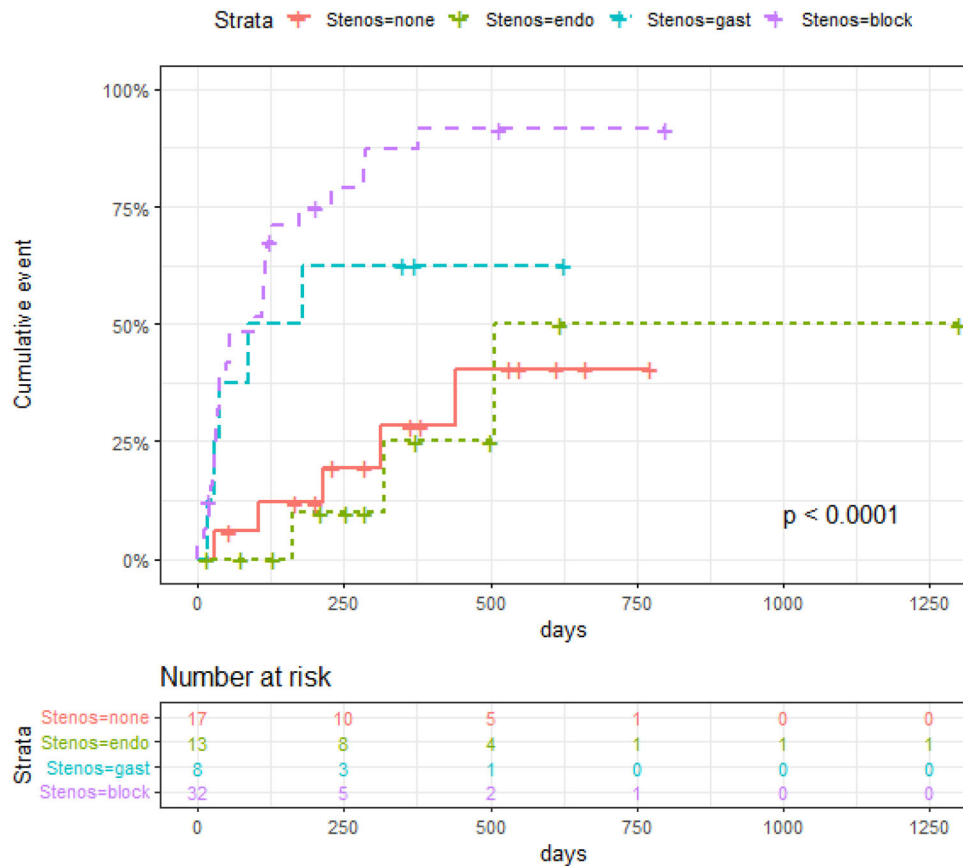
Table 5. Pathological patient stage.

	N	%
Tumor (T)		
T1	0	0
T2	2	2
T3	21	18
T4	3	3
T4a	10	9
T4b	1	1
TX	14	12
Not available	63	55
Node (N)		
N0	9	8
N1	4	4
N1a	5	4
N1b	6	5
N1c	1	1
N2	0	0
N2a	3	3
N2b	9	8
NX	15	13
Not available	62	54
Metastases (M)		
M1	14	12
M1a	7	6
M1b	2	2
M1c	4	4
MX	16	14
Not available	71	62

by the cost-effectiveness analysis of Xinopoulos et al. [16], the stenting palliation approach may provide a higher rate of local complications (as tumor perforation, tumor ulceration), complicating the bridge to surgery and often requiring an interruption in the chemotherapy. Despite a smaller rate of stoma after malignant tumor stenting [11] and an immediate improved quality of life assessment with respect to the surgical approach [17], the recent study of Nagula et al. [18] shows that up to one-fifth of the patients with primary stenting may be exposed to ulterior surgery, exposing these patients to a higher complications rate [11,16]. As the impact of primary management of colic malignant obstruction on the survival requires further investigation, surgery may be a safe option in these fragile patients.

Table 6. Relationship between tumoral stenosis and intestinal surgery.

Endoscopic stenosis characteristic	Stenosis characteristic divided in two groups	N (number of patients)	Emergency surgery (n, %)	Median days to surgery (n)	Surgery <60 days (n, %)
None	Mild	16	4 (25)	208	2 (12)
Passed by endoscope	Mild	13	3 (23)	319	1 (8)
Passed by gastroscop	Severe	8	5 (62)	39	3 (38)
Obstruction	Severe	31	26 (84)	54	15 (48)

**Figure 2.** Time to event to intestinal surgery among patients younger than 80 years who were not already operated as an emergency during the first three days following diagnosis.**Table 7.** Tumor localization.

Localization	N
Caecum	15
Hepatic angle	6
Splenic angle	2
Right colon	11
Left colon	7
Rectum	31
Sigmoid	34
Right transverse colon	4
Left transverse colon	1
Unknown	2

In this study, we found that the degree of tumor stenosis measured by endoscopy was a predictive factor for surgical procedure in patients with colorectal cancer. Some other studies analyzed the risk factors for presenting an emergency surgical procedure in case of colorectal cancer. In the cohort of Scott et al. [19], patients presenting a more advanced tumor (classified by Duke stages) were more likely submitted to emergency surgical procedures. Recent meta-analytic results also highlighted that a more advanced tumor stage and a

higher TNM sub-classification were both predictive factors for emergency surgery in patients presenting a metastatic colorectal cancer [20]. We can easily understand the underlying mechanism, as bigger tumor is reliable to anatomical impact, translating the higher risk for emergency procedure in these patients. Our findings are thus in accordance with the previous published literature [19,20].

This work highlights that the risk for emergency surgical procedure is 6.28 times higher in the patients presenting a severe malignant stenosis degree. Indeed, from our series of octogenarian patients, 84% of the patients having a block stenosis had some intestinal surgery later. A recent study from Norway [21] highlighted that in such selected patients, the 90-day mortality rate is high, but after this first period, the survival rate may be comparable to the younger patients. As the mid- and long-term survival in these patients remains controversial [15,16], it may be cautious to favor

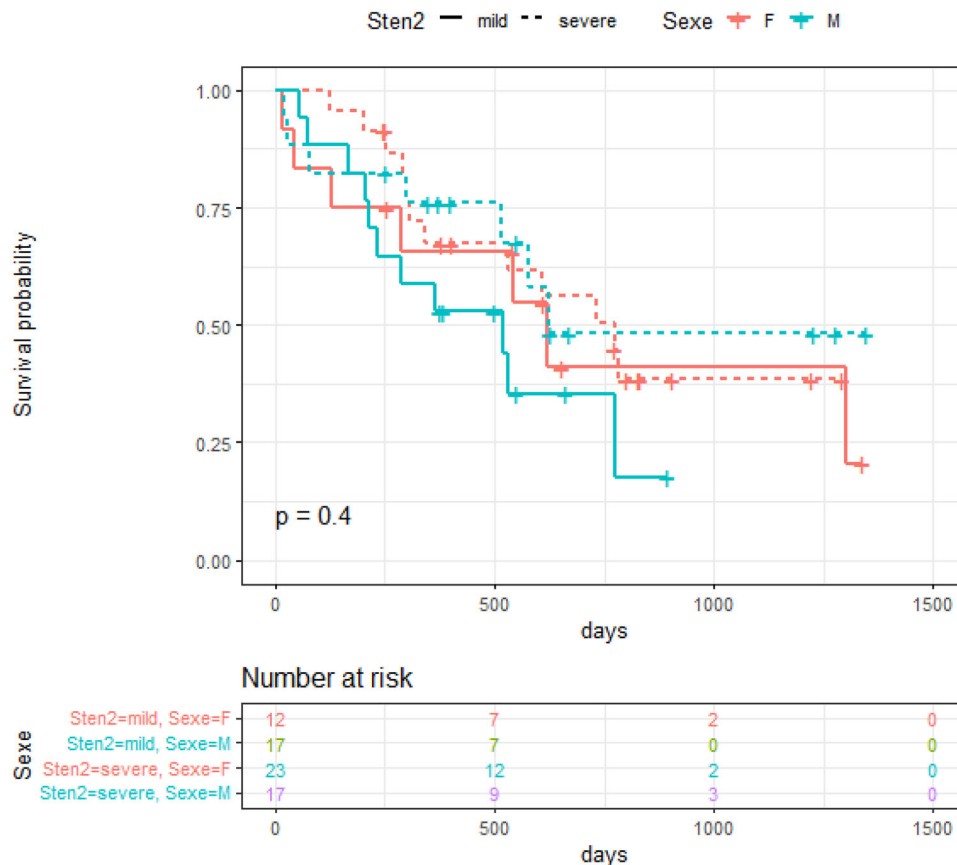


Figure 3. Survival times of patients by stenosis degree and sex among patients younger than 80 years who were not already operated as an emergency during the first three days following diagnosis.

the approach with the best oncological outcomes. A recent experimental study [22] showed that the stenting approach may result in a higher tumor dissemination rate. Actually, in patients eligible for some humanized monoclonal antibody therapy, tumor stenting is still not recommended [11,23]. As a ‘surgery-first’ approach may avoid the morbidity of an emergency surgical procedure and improve the oncologic outcomes, this perspective may be considered after careful multidisciplinary discussion with the patient, the oncologist and the surgeon.

This study presents several limitations. First, this a retrospective study, with the inherent bias to the retrospective series. We excluded patients >80 years from the main analysis, creating a possible selection bias. However, the patients being older than 80 years often go directly to the palliative care, following another care pathway. We also included only 68 patients, which is a low-sample cohort. Further trial and larger series are required to define the best management of such patients.

Conclusion

In this retrospective single-center cohort study analyzing a 43 patient undergoing emergency surgery for colorectal tumor obstruction, a predictive

factor for emergency surgical procedures has been found. The degree of colorectal tumor stenosis measured by endoscopy was a risk factor for emergency surgery in patients with metastatic colorectal cancer during neoadjuvant chemotherapy. No difference in terms of survival was found compared to patients without surgical interventions. The patients presenting a severe malignant stenosis degree had 6.28 times higher risk for emergency surgical procedure than the patients presenting a smaller malignant stenosis degree.

In this selected group of patients with malignant colic obstruction and low survival outcomes, further studies are needed to define the place of preventing surgery, avoiding emergency surgical procedures and morbidity in such fragile patients. Also, the role of surgery in the management of colorectal malignant obstruction, in the presence of others technologies as stent, has to be clarified.

Author contributions

Raffaele Calicis: conceptualization, methodology, investigation, writing, review and editing. Antoine Dubois: conceptualization, writing, review and editing. Christian Ritter: software, formal analysis, data curation and visualization. Nicolas Tinton: resources, investigation and visualization. Benjamin Calicis: resources, investigation and visualization. Yves

Hoebeker: resources, investigation and visualization. David Lepore: resources, investigation and visualization. Francisco Da Rocha De Sousa: resources, investigation and visualization. Emmanuel Cambier: resources, investigation and visualization. Fabrice Corbisier: conceptualization, methodology, review and editing, visualization and supervision.

Ethical approval

This study was approved by the Grand Hôpital de Charleroi Institutional Research Ethics Board. As the study is based on a retrospective anonymous database analyses, patient informed consent was waived by the ethical board due to the nature of the study.

Disclosure statement

The authors have no conflicts of interest to disclose.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author, R.F.

References

- [1] Bray F, Ferlay J, Soerjomataram I, et al. Global Cancer Statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394–424. doi:10.3322/caac.21492.
- [2] Siegel R, Naishadham D, Jemal A. Cancer Statistics, 2012. *CA Cancer J Clin.* 2012;62(1):10–29. doi:10.3322/caac.20138.
- [3] Law WL, Chan WF, Lee YM, et al. Non-curative surgery for colorectal cancer: critical appraisal of outcomes. *Int J Colorectal Dis.* 2004;19(3):197–202. doi:10.1007/s00384-003-0551-7.
- [4] Costi R, Leonardi F, Zanoni D, et al. Palliative care and end-stage colorectal cancer management: the surgeon meets the oncologist. *World J Gastroenterol.* 2014;20(24):7602–7621. doi:10.3748/wjg.v20.i24.7602.
- [5] Rosen SA, Buell JF, Yoshida A, et al. Initial presentation with stage IV colorectal cancer: how aggressive should we be? *Arch Surg.* 2000;135(5):530–534. doi:10.1001/archsurg.135.5.530.
- [6] Chen T-M, Huang Y-T, Wang G-C. Outcome of colon cancer initially presenting as colon perforation and obstruction. *World J Surg Oncol.* 2017;15(1):164. doi:10.1186/s12957-017-1228-y.
- [7] Ho YH, Siu SKK, Buttner P, et al. The effect of obstruction and perforation on colorectal cancer disease-free survival. *World J Surg.* 2010;34(5):1091–1101. doi:10.1007/s00268-010-0443-2.
- [8] Tentes A-AK, Mirelis CG, Kakoliris S, et al. Results of surgery for colorectal carcinoma with obstruction. *Langenbecks Arch Surg.* 2009;394(1):49–53. doi:10.1007/s00423-008-0307-5.
- [9] Lecomte T, André T, Bibeau F, et al. Cancer du côlon non métastatique. *Thésaurus National De Cancérologie Digestive*, France; 2021.
- [10] Van de Velde CJ, Boelens PG, Tanis PJ, et al. Experts reviews of the multidisciplinary consensus conference colon and rectal cancer 2012: science, opinions and experiences from the experts of surgery. *Eur J Surg Oncol.* 2014;40(4):454–468. doi:10.1016/j.ejso.2013.10.013.
- [11] Pisano M, Zorcolo L, Merli C, et al. 2017 WSES guidelines on colon and rectal cancer emergencies: obstruction and perforation. *World J Emerg Surg.* 2018;13:36. doi:10.1186/s13017-018-0192-3.
- [12] Von Elm E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ.* 2007;335(7624):806–808. doi:10.1136/bmj.39335.541782.AD.
- [13] American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2013;36(Suppl. 1):S67–S74.
- [14] Green FL, Page DL, Fleming ID, et al. *AJCC cancer staging manual*. 6th ed. New York: Springer Publishers; 2002.
- [15] Young CJ, De-Loyde KJ, Young JM, et al. Improving quality of life for people with incurable large-bowel obstruction: randomized control trial of colonic stent insertion. *Dis Colon Rectum.* 2015;58(9):838–849. doi:10.1097/DCR.0000000000000431.
- [16] Xinopoulos D, Dimitroulopoulos D, Theodosopoulos T, et al. Stenting or stoma creation for patients with inoperable malignant colonic obstruction? Results of a study and cost-effectiveness analysis. *Surg Endosc.* 2004;18(3):421–426. doi:10.1007/s00464-003-8109-x.
- [17] Watt AM, Faragher IG, Griffin TT, et al. Self-expanding metallic stents for relieving malignant colorectal obstruction: a systematic review. *Ann Surg.* 2007;246(1):24–30. doi:10.1097/01.sla.0000026112.72687.72.
- [18] Nagula S, Ishill N, Nash C, et al. Quality of life and symptom control after stent placement or surgical palliation of malignant colorectal obstruction. *J Am Coll Surg.* 2010;210(1):45–53. doi:10.1016/j.jamcoll-surg.2009.09.039.
- [19] Scott NA, Jeacock J, Kingston RD. Risk factors in patients presenting as an emergency with colorectal cancer. *Br J Surg.* 1995;82(3):321–323. doi:10.1002/bjs.1800820311.
- [20] Golder AM, McMillan DC, Horgan PG, et al. Determinants of emergency presentation in patients with colorectal cancer: a systematic review a meta-analysis. *Sci Rep.* 2022;12(1):4366. doi:10.1038/s41598-022-08447-y.
- [21] Hoydahl O, Edna T-H, Xanthoulis A, et al. Octogenarian patients with colon cancer – postoperative morbidity and mortality are the major challenges. *BMC Cancer.* 2022;22(1):302. doi:10.1186/s12885-022-09384-9.

- [22] Zhang A, Piccolo G, Cavallaro A, et al. A pilot study about the oncologic safety of colonic self-expandable metal stents (SEMS) in obstructive colon cancer: is occlusion always better than “silent” perforation? *Eur Rev Med Pharmacol Sci.* 2016;20(24):5242–5248.
- [23] Van Hooft JE, Van Halsema EE, Vanbiervliet G, et al. Self-expandable metal stents for obstructing colonic and extracolonic cancer: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. *Endoscopy.* 2014;46(11):990–1053. doi:[10.1055/s-0034-1390700](https://doi.org/10.1055/s-0034-1390700).