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Acute malignant obstruction in patients with peritoneal carcinomatosis: The role of palliative surgery

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ABSTRACT

Introduction: Patients with peritoneal carcinomatosis who do not have curative treatment options often develop acute obstructive symptoms and when conservative management fails, surgical treatment is the remaining option. However, palliative surgery is associated with high morbidity and mortality and the chance of success is unclear. The aim of this study was to evaluate outcomes of palliative surgery and to provide guidance for surgeons, medical oncologists and patients in their decision-making.
Methods: All consecutive patients who underwent palliative surgery for acute obstruction caused by peritoneal carcinomatosis between January 2005 and October 2017 where identified.
Results: In total 148 patients underwent surgery. Primary malignancy was colorectal cancer (28.4%), neuroendocrine tumor (20.3%), ovarian cancer (14.2%) or 'other' (37.2%). Median length of postoperative hospital stay was 16 days (IQR 9–24). More than half (58.1%) of the patients developed postoperative complications, 29.1% developed ≥2 complications. In-hospital mortality was 8.8%. Readmission (56.1%) and re-obstruction (35.0%) were common. Median overall survival was 119 days (IQR 48–420). Patients with a neuroendocrine tumor had a significantly better overall survival compared to other primary malignancies ($p < 0.001$). Patients who developed an obstruction during or within 6 months after treatment with chemotherapy had a worse overall survival ($p < 0.001$), compared to patients treated with chemotherapy longer than 6 months ago, or patients not treated with chemotherapy.
Conclusion: Palliative surgery is associated with high rates of complications and readmission and re-obstruction are common. Comfort care is often a better option than surgery, especially in patients with disease progression under recent treatment with chemotherapy.

Introduction

Peritoneal carcinomatosis (PC) is a common evolution of abdominal cancers, like ovarian, colorectal or gastric carcinoma [1,2]. PC is associated with a poor prognosis and patients with extensive disease are often treated in a palliative setting with best supportive care or systemic chemotherapy [2,3].

Patients with PC who do not have curative treatment options often develop (acute) obstructive symptoms related to progression of the disease, such as abdominal pain, nausea and vomiting [4,5]. Treatment of choice is noninvasive management; for example with a nasogastric tube or endoscopic stents [6,7]. When noninvasive management fails, the only remaining treatment option is palliative surgery [3,8,9].

This presents the surgeon with a dilemma. Palliative surgery may relieve symptoms, but is also associated with high post-operative morbidity and mortality, especially when surgery is performed in an emergency setting [10,11]. The postoperative length of hospital stay is considerable and readmission and re-obstruction are common [4,5]. However, to decide to not operate in an acute situation is challenging, because this is often felt as "giving up". The patient, family and treating physicians have usually

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not been given time to accept that the problem cannot be solved and to consider stopping treatment. All are now forced to make an instant decision between acute palliative surgery or end-of-life comfort care.

The aim of this study is to gain more insight in the postoperative outcomes of acute palliative surgery and to identify possible risk factors that contribute to these outcomes. The main goal is to provide guidance for surgeons, medical oncologists and patients to assist in their decision-making.

Patients and methods

This retrospective cohort study was conducted in the Erasmus MC Cancer Institute, a tertiary referral center in Rotterdam, the Netherlands. All consecutive patients with acute obstruction caused by PC, in whom treatment with curative intent was not possible and who underwent palliative surgery between January 2005 and October 2017 were identified. Patient demographics, perioperative variables, tumor characteristics, short- and long-term outcomes, postoperative mortality and morbidity were extracted from medical records after formal approval by the institutional medical ethics committee was obtained (registration number MEC-2018-1319).

Statistical analysis

Continuous variables were presented as median with interquartile range (IQR). Categorical variables were presented as absolute numbers and percentages. The Kaplan-Meier method was used for survival analysis and comparisons between groups were made using log rank test. Overall survival (OS) was calculated from the date of surgery until death or last follow up. Patients were censored when alive at last follow up date. Median follow up of the survivors was calculated with the use of reversed Kaplan-Meier method; deaths were censored. Multivariable Cox proportional-hazards models were constructed to identify prognostic factors and hazard ratios (HR) and 95% confidence intervals (CI) for these factors were calculated. Two-sided p-values < 0.05 were considered statistically significant. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS), Version 24.0.0 for Windows (IBM Corporation, Armonk, NY, USA).

Results

Patient cohort

From January 2005 to October 2017, 148 patients with an acute obstruction and PC underwent palliative surgery in an emergency setting. Patients who were candidates for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy were excluded. Baseline characteristics are described in Table 1.

Most patients were female (n = 83, 56.1% vs male n = 65, 43.9%). Median age was 63 years (IQR 55–71). Primary malignancy was colorectal cancer (CRC) in 42 patients (28.4%), neuroendocrine tumor (NET) in 30 patients (20.3%), ovarian cancer in 21 patients (14.2%) and 55 patients (37.2%) were defined as “other”. Other malignancies included breast cancer, melanoma, sarcoma and appendiceal carcinoma. All 148 patients had peritoneal metastases, often in combination with systemic metastases. About half of all patients (n = 73, 49.3%) were previously treated with (palliative) systemic chemotherapy, while one-third (n = 50, 33.8%) received chemotherapy within the last 6 months before developing acute

Table 1
Baseline characteristics ($N = 148$).

	N	%
Age at operation	63	[55–71][a]
Gender		
Male	65	43.9
Female	83	56.1
ASA		
ASA 1	5	3.4
ASA 2	82	55.4
ASA 3	57	38.5
ASA 4	4	2.7
Primary cancer		
CRC	42	28.4
NET	30	20.3
Ovarian cancer	21	14.2
Other (i.e. Sarcoma, Breast, Melanoma, Appendix, Gastric)	55	37.2
Metastases (all patients had peritoneal metastases)		
Peritoneal only	50	33.8
Liver	51	34.5
Pulmonary	6	4.1
Liver and Pulmonary	14	9.5
Other multi organic metastases (i.e. Ovaria, pancreatic, adrenal gland)	27	18.2
Primary tumor in situ		
Yes	74	50.0
No	74	50.0
Prior treatment with chemotherapy		
No chemotherapy	75	50.7
<6 months	50	33.8
>6 months	23	15.5
Indication for surgery		
Acute obstruction	138	93.2
Bowel perforation	10	6.8
Type of surgery		
Laparoscopic	11	7.4
Laparotomy	137	92.6

[a] Median and interquartile range. *ASA* American Society of Anesthesiologists', *CRC* colorectal cancer, *NET* neuroendocrine tumor.

obstruction and undergoing surgery. Most patients were unsuccessfully treated non-invasively prior to undergoing acute paliative surgery.

Surgical procedure

The indication for surgery was acute obstruction in 138 patients (93.2%) and bowel perforation in 10 patients (6.8%). In 55 patients (37.2%) a stoma (colostomy, ileostomy, jejunostomy) was created, 40 patients (27.0%) received an intestinal bypass and in 5 patients (3.4%) both a bypass and a stoma were created. In 35 patients (23.6%) the obstructed part of the bowel was resected. Exploration only was performed in 8 patients (5.4%) because the surgeon felt perioperatively that given the situation, resection, bypass or stoma creation would not help the patient. Perioperative complications occurred in 13 patients (8.8%). All peri- and postoperative outcomes are described in Table 2.

Postoperative course

Median hospital length of stay after surgery was 16 days (IQR 9–24). More than half of all patients (n = 86, 58.1%) developed postoperative complications and 43 patients (29.1%) had ≥2 complications during their postoperative admission. Most common postoperative complications were persistent gastroparesis/paralytic ileus (n = 17, 11.5%), wound infection (n = 15, 10.1%), abdominal abscess (n = 11, 7.4%) high output stoma (n = 8, 5.4%), pneumonia (n = 7, 4.7%), delirium (n = 7, 4.7%) and urinary tract infection (n = 6, 4.1%). Most common life threatening complication was abdominal sepsis (n = 12, 8.1%), in 5 out of 12 cases caused by anastomotic leakage. In hospital mortality was 8.8% (n = 13) and 12 patients (8.1%) were discharged directly to a hospice for terminal care. Outcomes of patients discharged to their home or to a nursing home (n = 123) are described in Table 3. Re-obstruction occurred in 43 patients (35%). Readmissions where common (n = 69, 56.1%) and 43 patients (35%) were readmitted twice or more. Median length of hospital stay when readmitted was 5.7 days (IQR 3.5–9.1).

Table 2
Peri- and post-operative outcomes (*N* = 148).

	N	%
Duration of surgery (minutes)	97	[72–133][a]
Perioperative complications		
Serosal damage	7	4.7
Ureter injury	2	1.4
Iatrogenic perforation	3	2.0
Bleeding	1	0.7
Hospital length of stay (days)		
Overall	16	[9–24][a]
Days before surgery	3.5	[1–9][a]
Days after surgery	10	[6–14][a]
Number of postoperative complications		
1	43	29.1
2	27	18.2
3	10	6.8
4	5	3.4
5	1	0.7
Highest Clavien-Dindo score		
1–2	42	28.4
3a-3b	26	17.6
4a-4b	5	3.4
5	13	8.8
In hospital mortality	13	8.8
Discharged to hospice for terminal care	12	8.1
10 day mortality	13	8.8
30 day mortality	26	17.6
90 day mortality	63	42.6
Median Overall Survival (days)	119	[48–420][a]
Median Follow up (days)	747	[503–2513][a]

[a] Median and interquartile range.

Table 3
Patients outcomes after discharge (*N* = 123).

	N	%
Discharged to		
Nursing home	4	3.3
Home	117	95.1
Moved to other hospital	2	1.6
Ability to tolerate a diet		
Nasogastric tube feeding	6	9.9
Liquids only	7	5.7
Solids	80	65.0
Other	11	8.9
Not documented	19	15.4
Re-obstruction after discharge	43	35.0
Number of hospital readmissions		
1	26	21.1
2	23	18.7
3	10	8.1
4	8	6.5
5	2	1.6
Length of hospital stay when readmitted (days)	5.7	[3.5–9.1][a]
Visits to the emergency department after discharge		
1	28	22.8
≥2	5	4.1
Treatment after discharge		
None/Best supportive care	74	60.2
Chemotherapy	23	18.7
Radiotherapy	5	4.1
Chemoradiotherapy	1	0.8
Octreotide/Lutetium-177-octreotate	16	13.0
Other	4	3.3

[a] Median and interquartile range.

Survival

Median follow up was 747 days (IQR 503–2513). At last follow-up, 20 patients (13.5%) were alive. The 10-, 30- and 90-day mortality rates were 8.8% (n = 13), 17.6% (n = 26), and 42.6% (n = 63) respectively. Median overall survival (OS) after surgery was 119 days (IQR 48–420). Survival curves are shown in Fig. 1.

Median OS was calculated for each primary malignancy. Median OS of patients with a NET (562 days, IQR 133–1788), as primary malignacy was significantly better ($p < 0.001$) compared to other primary tumor groups (CRC = 108 days, IQR 53–304; Ovarian = 174 days, IQR 58–493; Other = 87 days, IQR 34–166).

Patients that were treated with chemotherapy within the last 6 months (CTx<6mo) had a worse prognosis ($p < 0.001$) compared to patients treated with chemotherapy longer than 6 months ago (CTx>6mo), and patients that did not receive chemotherapy (CTx-) (OS CTx<6mo = 71 days, IQR 32–166; OS CTx>6mo = 111 days, IQR 71–381; OS CTx- = 193 days, IQR 69–782).

No significant difference in OS was found between other baseline characteristics; i.e. gender, ASA-score, location of metastases (only peritoneal vs. peritoneal and systemic), primary tumor in situ (in situ vs. resected), and type of surgery (laparoscopic vs laparotomy).

To correct for possible confounding variables a multivariable analysis was performed, which confirmed the above; patients with peritoneal metastases caused by NET had a significantly better survival compared to other primary malignancies (HR = 0.46, 95% CI 0.25–0.86, p = 0.015) and patients who developed obstructive symptoms during or within 6 months after treatment with systemic chemotherapy had statistically significant worse survival (HR = 2.24, 95% CI 1.41–3.54, p = 0.001). Multivariable analysis is listed in Table 4.

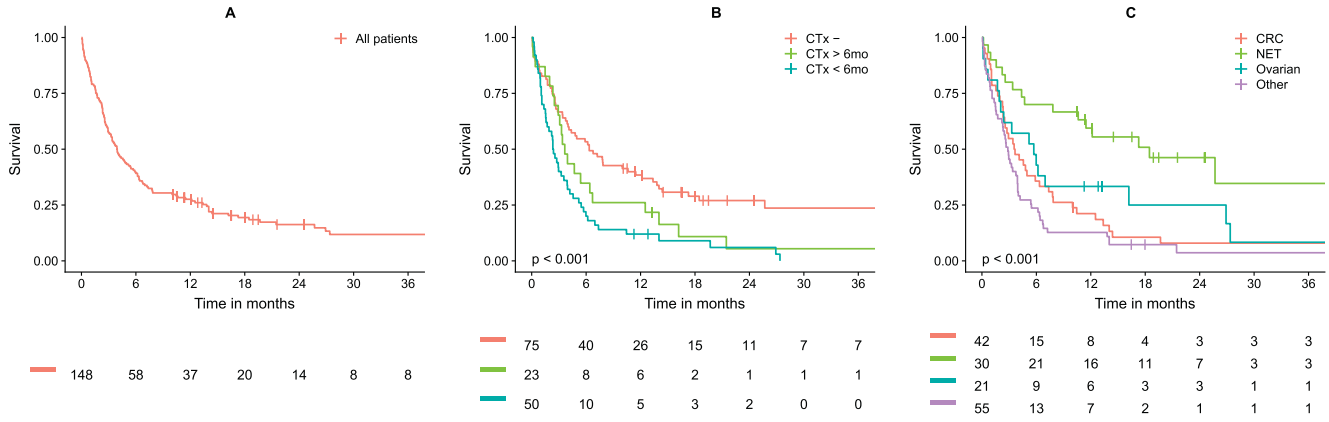

Fig. 1. Survival Curves. a) Overall survival (OS). b) OS for patients not treated with chemotherapy (CTx -), patients treated with CTx, last treatment longer than 6 months before surgery (CTx>6mo) and patients treated with CTx within the last 6 months (CTx<6mo) before undergoing surgery. c) OS for different primary malignancies; colorectal cancer (CRC), neuroendocrine tumor (NET), ovarian cancer, 'other'.

Table 4
Multivariable analysis of risk factors for mortality of any cause following acute palliative surgery.

Risk factor	HR [95%CI]	P-value
Gender		
Female	1.00	
Male	1.25 [0.84–1.85]	0.271
Age	1.01 [1.00–1.03]	0.195
Primary tumor		
CRC	1.00	
NET	0.46 [0.25–0.86]	0.015*
Ovarian cancer	0.67 [0.36–1.26]	0.216
Other	1.48 [0.97–2.26]	0.072
Chemotherapy		
No chemotherapy	1.00	
>6 months	1.38 [0.79–2.39]	0.254
<6 months	2.24 [1.41–3.54]	0.001*

HR hazard ratio, *CI* confidence Interval, *CRC* colorectal cancer, *NET* neuroendocrine tumor.

Remaining life spent in hospital

The percentage of remaining life spent in hospital after surgery was calculated for each patient using the OS (date of surgery until death or last follow up) and the days (re)admitted to the hospital. Patients with a NET spent a smaller percentage of their remaining life in the hospital (6.9%, IQR 1.3–21.9) compared to the other primary tumor groups; CRC 11.2% (IQR 6.2–33.7), ovarian 17.5% (IQR 5.7–51.0) and other 18.1%, IQR 10.0–29.4). Patients that were treated with chemotherapy within the last 6 months spent the highest percentage of their remaining life in the hospital (22.5%, IQR 9.7–47.1), when compared to patients treated with chemotherapy longer than 6 months ago (11.0%, IQR 6.3–18.1) and patients not treated with chemotherapy (8.1%, IQR 3.3–28.0).

Discussion

This study shows that the survival benefit of palliative surgery in patients with an acute bowel obstruction caused by PC is minimal, and that palliative surgery is associated with many postoperative problems. Mortality and morbidity rates are high, readmissions are common and many patients spend a significant part of their remaining life in hospital, dealing with postoperative complications and recurrent symptoms.

This study also shows that some patients are more likely to benefit from surgery than others. Patients with PC from a NET may undergo additional treatment (octreotide/lututetium-177-octreotate) after surgery: they have a significantly better overall survival and spent a smaller part of their remaining life in hospital. Patients with PC from CRC, ovarian cancer and other primary malignancies have a worse prognosis and surgery is unlikely to be a valuable contribution. In patients who develop symptoms despite recent treatment with chemotherapy, surgery appears to be futile.

The decision not to operate in acute situations is often a difficult one for medical oncologists, surgeons, patients and their family. Although most patients are aware their disease cannot be cured, they are often hopeful about the length of their remaining life. Previous studies showed that many patients have unrealistically positive expectations [12–16]. Even in acute situations, when death is imminent, patients are often hopeful about the impact of palliative surgery [13]. We think it is imperative to inform patients about the prognosis of their disease before problems presents itself. Moroever, patients should be informed about the consequences when problems arise. In case of peritoneal metastases, acute obstruction is common and when it occurs, the prognosis is dismal. With the exception of those patients with NET, patients should already be made aware that in case of an acute obstruction, there is a rather small chance that surgery will solve the problem, result in acceptable quality of life and lead to a worthwhile prolongation of their life. The result of surgery is often quite the opposite: more than 16% of patients die in hospital or in a hospice directly following discharge. For the other patients, a large part of their remaining life span will be spent in hospital, with the discomfort of postoperative complications, recurrent symptoms and the possibility of more interventions. Moreover, palliative surgery adds little with regard to extended survival.

Treatment focus in this end stage of disease should lie on comfort for the patient. It is important to discuss end-of-life topics, like ethical and religious issues, with patients and their family and coordinate the patients last wishes with treating physicians and general practitioners. Emphasis should lie on pain relief and symptom control, e.g. with anti-emetics or a nasogastric tube. This care, depending on the patient's condition and wishes, can be given at home, in the hospital or in an hospice.

This study has limitations. Because of the retrospective nature of this study, we were not able to quantitatively score the quality of life after surgery. Moreover, we have little data on symptom relief and recurrence of symptoms, because in a considerable amount of patients, the general practitioner provided supportive and terminal care. Other than the date of death, further data from these patients is not available.

Since we included patients with a variety of primary cancers, this is heterogenic study population. When compared to the most common malignancies causing PC, we included a large group of 'other' malignancies. However, all patients included where in the same end stage of disease, and had obstruction caused by PC without curative options. The goal of the study was to provide guidance to a range of different medical specialists treating PC and we believe these data provide valuable information for clinical decision making, regardless of the nature of the primary tumor. In addition, the patients included in this study were operated over a relatively large time span (2005–2017). However, during that period, little has changed in the treatment of this specific group of patients with PC without curative options.

Another limitation is the fact that we selected patients in whom the decision was made to perform surgery. Most likely, these were relatively young and fit patients. Therefore, the prognosis of all patients presenting with an acute obstruction and PC is likely to be worse. Studies comparing the outcome of palliative surgery with non-operative management or comfort care for acute obstruction are scarce. There are some that compared non-invasive management with palliative surgery in a less acute setting [1,3,17–19]. Patients in this study already had received maximum conservative treatment, after which acute obstuction or bowel perforation persisted or occurred.

Conclusion

With the exception of patients with NETs, it is highly questionable whether our results (poor survival benefit, high morbidity, high mortality, long hospital stay, high chance of recurring symptoms) warrants performing palliative surgery in patients with acute obstructions and peritoneal metastases. High quality comfort care may often be a better option than surgery. In patients who develop symptoms despite recent treatment with chemotherapy, surgery appears to be futile.

Declarations of interest

The authors declare no conflicts of interest.

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