Original Article

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Resumption of oncological therapy in patients with advanced cancer undergoing explorative laparotomy for bowel obstruction

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ABSTRACT

Introduction: Obstruction of the gastrointestinal tract is a frequent surgical emergency experienced by patients with advanced cancers. We aimed to evaluate factors associated with resumption of post-operative chemotherapy in patients with advanced cancer undergoing explorative laparotomy for bowel obstruction.
Methods: This retrospective cohort study was conducted between 2009 and 2013 at Herlev Hospital, Denmark. All patients with advanced cancer were identified from a local electronic database containing all emergency laparotomies. Adult patients with mechanical bowel obstruction were included if they had any kind of cancer and had been under active oncological treatment within the last eight weeks prior to surgery. Demographic, clinical, pre-, and post-operative data were collected and reviewed manually. Multivariate logistic regression analysis was performed to identify predictors for resuming oncological treatment.
Results: A total of 76 patients admitted with bowel obstruction and undergoing oncological treatment within eight weeks before surgery were included. Post-operatively, cancer treatment was resumed in 58% of patients. An American Society of Anesthesiologists (ASA) score < III (odds ratio = 12.6 (95% confidence interval (CI): 2.9-54.6); p = 0.001) and a performance status < 3 (odds ratio = 9.7 (95% CI: 1.4-67.2); p = 0.021) were associated with resuming post-operative cancer treatment.
Conclusions: We found that ASA score and performance status are associated with resumption of cancer treatment post-operatively and should be taken into consideration when considering the treatment strategy for patients with advanced cancer and malignant bowel obstruction.
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The incidence of cancer diagnoses is increasing; the development of new oncological treatments,

including palliative chemotherapy, has prolonged survival in patients with advanced cancer and might lead to cancer-related emergencies [1, 2]. One frequent surgical emergency experienced by cancer patients is obstruction of the gastrointestinal tract [3]. The prevalence of bowel obstruction is estimated to fall in the 3-15% range in these patients [4]. The effect of emergency surgery as a treatment for bowel obstruction in patients with advanced cancer is controversial, and the criteria for selecting patients for surgery remain unclear [5]. A number of studies have shown that cytotoxic chemotherapy and/or radiation therapy prolongs survival and quality of life in patients with, e.g., advanced colorectal, pancreatic and biliary cancer and lung cancer [6-8]. The rate of patients with advanced cancer resuming oncological cancer treatment after emergency surgery for bowel obstruction is largely unknown. The expected median survival of cancer patients with bowel obstruction is 1-3 months, unless chemotherapy is an option, which might prolong survival [9].

We aimed to investigate preoperative factors associated with resumption of post-operative oncological therapy in patients with advanced cancer undergoing explorative laparotomy for bowel obstruction.

METHODS

This was a retrospective cohort study. Patients were identified from a local electronic database containing all emergency laparotomies performed during the 2009-2013 period at Herlev Hospital, which is affiliated with Copenhagen University, Denmark. After identifying patients with advanced cancer who underwent acute exploratory laparotomy, medical records were reviewed manually. In the present study, advanced cancer is defined as follows: cancer that is unlikely to be cured or controlled with treatment. The cancer may have spread from where it initially started to nearby tissue, lymph nodes or distant parts of the body [10].

Adult patients with mechanical bowel obstruction were included if they had any kind of cancer and had been under active oncological treatment within the last eight weeks prior to surgery, regardless of previous surgical treatment. Demographic information was collected on underlying co-morbidities, such as cerebrovascular disease, cardiovascular disease, endocrine disorder, and pulmonary disease. The American Society of Anesthesiologists (ASA) physical status and performance status according to Zubroed/ the WHO classification were registered. Smoking and alcohol habits were registered. Information was obtained on cancer type, stage and preoperative oncological treatment – chemotherapy line and number of cycles and/or radiation therapy. Cancer stage was defined as follows according to the Tumour, Node, Metastasis (TNM) classification system: Stage II and III – locally advanced cancers. Stage IV – metastasised cancer, spread of tumour cells from the primary tumour to surrounding tissues and to distant organs [11]. Data on primary operation, post-operative complications and post-operative cancer treatment were collected. Post-operative complications were evaluated according to the Clavien-Dindo (CD) classification [12]. In brief, a CD score 1-2 was defined as complications requiring drug treatments,

blood transfusion, superficial wound infections or prolonged hospital stay. A CD score 3-4 was defined as complications demanding surgical, radiological or endoscopic interventions, and/or any complication requiring critical care management. Grade 5 was defined as death of the patient. For statistical analysis, descriptive statistics were used, and statistical analyses were performed using SPSS for Windows, Version 19.0. Frequencies and percentages were calculated, and the Chi-squared test was used to compare categorical variables. Multivariate logistic regression analysis was performed to estimate the most important factors associated with resuming oncological treatment after surgery. The variables included in the multivariable analysis were: gender, age, performance status, ASA score, cancer type and cancer stage. Listwise deletion was used to eliminate missing cases from analysis. Odds ratios with 95% confidence interval (CI) were given and considered statistically significant if $p < 0.05$. The Danish Data Protection Agency approved the study and data processing agreement, I-Suite no.: 06312 and ID-no.: HGH-2018-031. Under Danish law, registration with the Danish Ethical Committee was not required.

Trial registration: not relevant.

RESULTS

A total of 367 cancer patients underwent acute exploratory laparotomy during the 2009-2013 period. Overall, 76 patients met the inclusion criteria. Of 76 included patients, 62% were men, 80.3% were older than 60 years and 50% had one or more co-morbidities. Hypertension was the most frequently observed co-morbidity (26% of the patients), 53.9% of patients had an ASA score < III and 82.8% had a performance status < 3. A summary of demographic information is found in **Table 1.**

TABLE 1 / Demographic and co-morbidity characteristics of study population (N = 76).

	n (%)
Gender, men	47 (61.8)
Age, yrs	
⟨ 40	1 (1.3)
40-59	14 (18.4)
60-79	49 (64.5)
≤ 80	12 (15.8)
ASA score[a]	
I	19 (25)

II	22 (28.9)
III	16 (21.1)
IV	9 (11.8)
Missing	10 (13.2)
Performance[b]	
0	15 (19.7)
1	20 (26.3)
2	28 (36.8)
3	8 (10.5)
4	2 (2.6)
Missing	3 (3.9)
Smoker	
Yes	8 (10.5)
Missing	20 (26.3)
Alcohol	
> 7/14 U/wk[c]	7 (9.2)
Missing	22 (28.9)
Co-morbidity	
Diabetes	2 (2.6)
Thyroid disease	4 (5.3)
Cerebrovascular disease	2 (2.6)
Hypertension	20 (26.3)
Atrial fibrillation	2 (2.6)
Ischaemic heart disease	2 (2.6)
Obstructive pulmonary disease	6 (7.9)

ASA = American Society of Anesthesiologists.
a) The ASA physical status classification system.
b) WHO performance status.
c) A weekly intake of alcohol higher than recommended by the Danish Health Authority.

The most common types of cancer among patients were gastrointestinal cancer and gynaecological cancer found in 43.4% and 28.9% of the patients, respectively. Stage IV cancer was present in 77.6%. Cancer types and stages among patients are presented in **Table 2**; 68% of patients received first-line cancer treatment. Chemotherapy was received by 84% of patients, 6.9% of patients received radiation therapy, and 9.1% of patients received concomitant chemoradiotherapy. All patients underwent exploratory laparotomy, of whom 32.9% underwent enterostomy, 31.6% large bowel resection and colostomy, 14.5% adhesiolysis, 13.1% small bowel resection and 7.9% underwent an exploratory laparotomy without further intervention. Post-operative complications requiring surgical intervention (CD III-V) were found in 19.6%, among whom 5.3% had a rupture of the abdominal fascia. Severe medical complications (CD III-V) were found in 29% of patients. An overview of complications is shown in **Table 3**.

TABLE 2 / Tumour characteristics by stage and localisation according to the TNM classification (N = 76).

	n (%)
Gastrointestinal cancer	
Upper gastrointestinal tract	9 (11.8)
Lower gastrointestinal tract	24 (31.6)
Gynaecologic cancer	22 (28.9)
Urogenital cancer	10 (13.2)
Haematological cancer	4 (5.3)
Lung cancer	3 (3.9)
Breast cancer	2 (2.6)
Stage[a]: II/III/IV	2 (2.6)/15 (19.7)/59 (77.6)

TNM = tumour-node-metastasis.
a) Based on the TNM classification of malignant tumours [11].

TABLE 3 / Frequencies of medical and surgical complications according to the Clavien-Dindo (CD) classification (N = 76).

	n (%)
Post-operative complications, CD I-II/CD III-V[a]	
Cardiopulmonary	22 (28.9)/10 (13.2)
Gastrointestinal	14 (18.4)/5 (6.6)
Urogenital	6 (7.9)/6 (7.9)
Central nervous system	2 (2.6)/1 (1.3)
Surgical	16 (21.0)/1 (19.6)
Reoperation	15 (19.6)
Abdominal fascia rupture	4 (5.3)
Surgical site infection	2 (2.6)
Intra-abdominal abscess	2 (2.6)
Anastomosis leak	2 (2.6)
Bowel obstruction	1 (1.3)
Bleeding	1 (1.3)
Other	3 (3.9)

a) Based on the CD classification [10].

The 30-day mortality rate was 34.2%, 76% of whom had stage IV cancer, 20% had stage III cancer and 4% had cancer in stage II. The 90-day mortality rate was 50%, 81.1% of whom had stage IV cancer, 16.2% had stage III cancer, and 2.7% had stage II cancer. Post-operatively, cancer treatment was resumed in 58% of patients. Significant clinical variables such as sex, age, performance status, ASA score, cancer type and cancer stage were analysed to identify factors associated with resuming cancer treatment post-operatively. We found that an ASA score < III (odds ratio = 12.6 (95% CI: 2.9-54.6); p = 0.001) and a performance status < 3 (odds ratio = 9.7 (95% CI: 1.4-67.2); p = 0.021) were associated with resuming post-operative cancer treatment. There was no significant difference between sex, age, cancer type or stage and cancer treatment post-operatively. **Table 4** shows the multivariate logistic regression analysis.

TABLE 4 / Predictive factors for cancer treatment post-operatively, multivariate logistic regression analysis.

	Odds ratio (95% CI)	p-value
Gender	2.3 (0.5-10.1)	0.262
ASA[a] ≤ 3	12.6 (2.9-54.6)	0.001
Performance[b] ≤ 3	9.7 (1.4-67.2)	0.021
Age ≤ 60 yrs	2.7 (0.3-20.3)	0.310
Gastrointestinal cancer	0.4 (0.2-6.8)	0.545
Gynaecologic cancer	0.1 (0.004-2.29)	0.150
Urogenital cancer	1.4 (0.82-24.0)	0.815
Haematological cancer	2.5 (0.11-56.0)	0.549
Lung cancer	4.9 (0.064-373.4)	0.472
Breast cancer	4.0	1.000
Cancer stage		
II	0.0	0.479
III	0.0	1.000
IV	0.0	1.000

ASA = American Society of Anesthesiologists; CI = confidence interval.
a) The ASA physical status classification system.
b) WHO performance status.

DISCUSSION

Data on surgical emergencies experienced by patients with advanced cancer are very limited. Management of these patients and treatment strategy are often complex and controversial. More than half of all included patients resumed treatment with chemotherapeutic agents post-operatively. We found an ASA score below III (odds ratio = 12.6 (95% CI: 2.9-54.6); p = 0.001) and a performance status below three (odds ratio = 9.7 (95% CI: 1.4-67.2); p = 0.021) to be significantly associated with resuming cancer treatment. Several previous studies have identified factors associated with survival. The Eastern Cooperative Oncology Group (ECOG) performance status as well as albumin level, the P-POSSUM score, the WHO performance status and the Charlson score have all been proven to be associated with survival after cancer surgery. In some studies, an ASA

score of more than III was found to be a strong predictor of post-operative mortality in patients with cancer [13-16]. Our study confirms that an ASA score of more than III and a performance status of more than three are associated with a poor outcome. Interestingly, variables such as cancer type and cancer stage did not have a significant impact on cancer treatment post-operatively. Similar findings have been reported in other studies [17]. The present study also confirms the high risk associated with surgery performed in patients with advanced cancer. The thirty-day and 90-day mortality rates were 34% and 50%, respectively. These results are comparable to findings elsewhere when keeping in mind the target study population [18-20]. It is known that emergency surgery in patients with advanced cancer and active oncological treatment are associated with higher complication rates and mortality compared with the general population [21, 22]. Data from previous general population cohort studies demonstrated 30-day mortality rates after emergency laparotomy of 14-17% with considerably higher mortality rates of 24-50% in patients aged 80 years or older [23, 24].

The present study has several limitations that require reflection. First, retrospective analysis carries a potential for selection bias, and it is important to note that the present study does not present the outcomes of cancer patients who do not undergo an operation but follow a conservative treatment strategy for bowel obstruction. Second, our study was conducted at a single centre, which limits the generalisation of the results. Third, the present study cohort is relatively small and very heterogeneous. The study population consists of patients with different primary tumours and patients were included regardless of any previous surgical treatment. This reduces the power of the study and leads to a higher variability, which can cause bias. Another important limitation is that the ASA score was missing in ten (13.2%) patients. Unfortunately, the small sample size of the present study did not allow statistical adjustment for missing data and this may have had an impact on our results. Previous studies have described that the ASA score is strongly associated with clinical outcome in general [25, 26], and our results indicate, with the limitations described, that the same association is present in this population. It is important to note that operative procedures were not included in multivariate logistic regression analysis. All patients were treated for intestinal obstruction and were exposed to surgical stress and trauma imposed by explorative laparotomy. Finally, we did not analyse patient-reported outcomes, including quality of life and functional outcome after surgery.

In summary, we have demonstrated that an ASA score < III and a performance status < 3 are independently associated with resuming oncological cancer treatment in patients with advanced cancer after emergency surgery for bowel obstruction. We recommend that these variables be included as a part of the risk stratification when an operative or conservative management strategy of malignant bowel obstruction is considered in patients with advanced cancer.

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