Cohort Study

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Bowel obstruction in advanced tubo-ovarian cancer: a retrospective cohort study

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Background: Ten to fifty percent of women with advanced or recurrent ovarian cancer develop malignant bowel obstruction (MBO). We described the management and examined the complications and survival of MBO in primary epithelial tubo-ovarian cancer patients.

Materials and methods: The authors conducted a retrospective monocentric cohort study of tubo-ovarian cancer patients diagnosed with MBO between January 1st, 2011 until August 31st, 2017 at the University Hospitals Leuven, Belgium.

Results: Seventy-three patients with a total of 165 MBO episodes (median 1/patient; range 1–14) were included. The median time interval between cancer diagnosis and first MBO episode was 373 days (range 0–1937). The median time interval between MBO episodes was 44 days (range 6–2004). Complications were bowel perforation ($n = 5$; 7%) and bowel ischemia ($n = 1$; 1%). Conservative treatment was applied in 150 (91%) episodes, including gastrostomy in 4 (2%) episodes and octreotide in 79 (48%) episodes. Surgery was necessary in 15 (9%) episodes. Total parenteral nutrition was administered in 16 (22%) patients. During the study period 62 (85%) patients died (median 167 days since first MBO; range 6–2256). A significant difference in survival was found regarding the tumor marker CA 125 at cancer diagnosis, the use of palliative chemotherapy after the first episode of MBO and palliative surgical treatment for MBO in a group of well selected patients.

Conclusion: Tubo-ovarian cancer patients with MBO have a poor prognosis: 85% of the study population died within a relatively short time interval since the first MBO. In our study population, the majority of patients with MBO were treated conservatively. Both palliative chemotherapy and palliative surgical management are considerable treatment options depending on the individual patient profile.

Keywords: cohort studies, complications, intestinal obstruction, ovarian neoplasms, patient care management, survival analysis

Introduction

Ovarian cancer is the most aggressive type of gynecological cancer and has a poor prognosis[1]. The mortality rate is high with a 5-year survival of around 37%[2]. Worldwide, the age-standardized incidence of ovarian cancer is estimated 6.1 per 100 000 women, with mainly peri- and postmenopausal women affected[1,3]. The relapse rate in patients with early-stage disease is 10–30%[3]. Most patients remain asymptomatic until advanced-stage disease, with 75% of patients diagnosed with stage III or IV cancer, resulting in the name of 'silent killer'[3,4].

Malignant bowel obstruction (MBO) is a frequent and distressing complication in advanced and recurrent ovarian cancer, occurring in up to 50% of patients, and often a sign of progressive disease[4–9]. In 8–30% of patients, MBO is the presenting symptom of ovarian cancer and may be an indicator of a short progression-free and overall survival[10,11].

HIGHLIGHTS

- It is estimated that 10–50% of women with advanced or recurrent ovarian cancer develop malignant bowel obstruction (MBO), which is a presenting symptom of ovarian cancer in 8–30% of cases.
- Tubo-ovarian cancer patients with MBO have a poor prognosis. Eighty-five percent of our study population died within a median time interval of 167 days since the first episode of MBO.
- Depending on the individual patient profile both palliative chemotherapy and palliative surgical management are considerable treatment options for MBO in our tertiary center.

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In the recurrent disease setting, most patients die 65.5 days after MBO diagnosis, which is described as the main cause of death in this group of patients[4–6,12–15].

MBO can be caused by peritoneal carcinomatosis or an intra-abdominal tumoral mass[5–8]. Up to 54% of MBO is located in the small bowel, 31.7% in the large bowel and in 14.3% both the small and large bowel are affected[4]. MBO typically develops subacute and progressively causes symptoms such as nausea, vomiting, anorexia, abdominal pain, and distension as well as the absence of defecation and flatus in combination with absent or high-pitched bowel sounds[7,16,17].

A plain abdominal radiography is an efficient initial examination. Characteristic radiographic features are pathological dilatation of the bowel loops and pathological air-fluid levels[18,19]. When detailed imaging is needed, a computed tomography scan of the abdomen is considered the golden standard for diagnosis of MBO[17,18].

There is no consensus about the best treatment for MBO and studies focusing on survival have contradictory results[16,17,20]. The choice of treatment is therefore often based on clinical and prognostic factors[3]. Conservative management consists of stopping all oral intake, often in combination with a nasogastric tube or gastrostomy tube, intravenous fluids, and pharmacological treatment including steroids, antiemetics, analgesics, anticholinergics, and antisecretory drugs such as octreotide[3,4,7,8,16,17]. Interventional therapy includes adhesiolysis, stenting, bowel resection with either re-anastomosis, a stoma, or an enteric bypass[5,7,8]. Another possibility is palliative chemotherapy, which helps overcome MBO in 4 out of 10 patients[3].

The objective of this study is to describe our experience with the management, complications, and outcome of MBO in our tertiary center. We aim to guide practitioners in the treatment of this major clinical challenge.

Material and methods

A retrospective monocentric cohort study of tubo-ovarian cancer patients diagnosed with MBO between January 1st, 2011 until August 31st, 2017 was performed at the University Hospitals Leuven, Belgium. This study was reviewed and approved by the Ethics Committee Research UZ/KU Leuven (MP001927) on August 8th, 2018. Informed consent was not obtained from each individual patient in line with the recommendation of our Ethical Committee for retrospective research. All patients were able to refuse/withdraw the use of data according to hospital policy. The work has been reported in line with the strengthening the reporting of cohort, cross-sectional and case-control studies in surgery (STROCSS) criteria[21]. Our study was registered in the Research Registry.

Inclusion criteria

Primary epithelial tubo-ovarian cancer patients with MBO, documented by imaging, and treated at the University Hospitals Leuven were included. Patients with bowel obstruction due to fecal impaction, postoperative ileus, or with abdominal complications due to bevacizumab were excluded. We also excluded patients with another simultaneous primary malignancy. A flowchart detailing in- and excluded patients can be found in Figure 1.

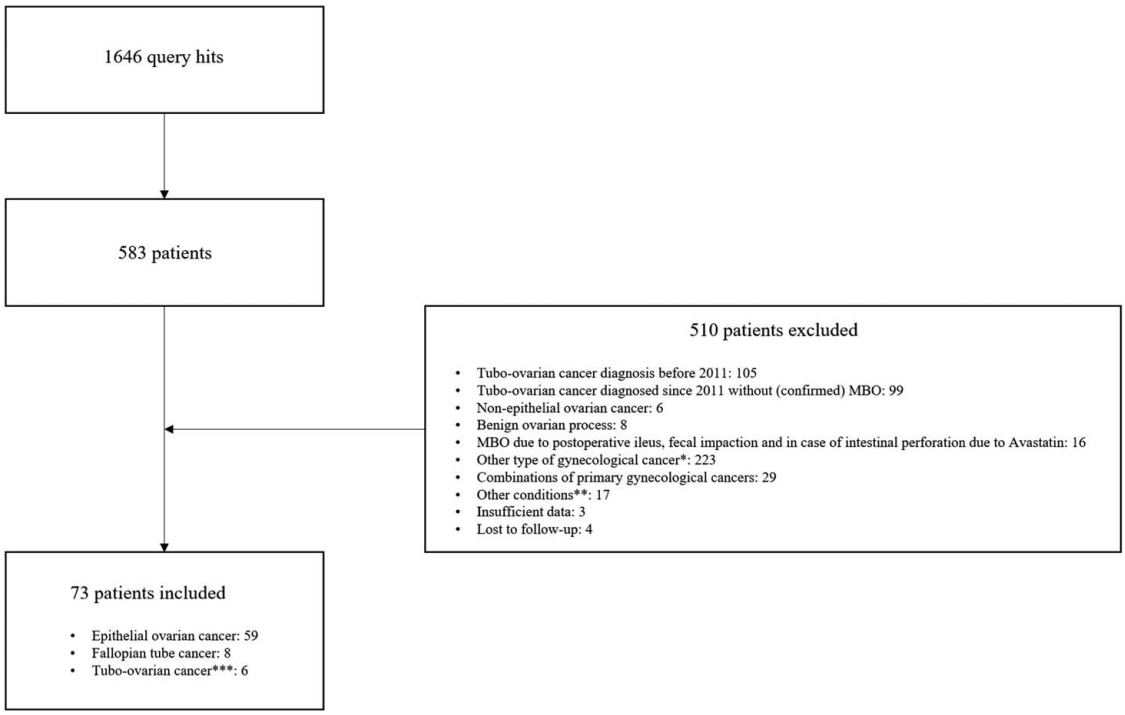

Figure 1. Flowchart detailing in- and excluded patients. MBO, malignant bowel obstruction. * (Metastatic) cervical cancer: 78; (metastatic) endometrial cancer: 60; uterine carcinosarcoma: 8; leiomyosarcoma: 7; (metastatic) vaginal cancer: 6; (metastatic) vulvar cancer: 9; (metastatic) breast cancer: 53; malignant trophoblastic disease: 2. ** Endometriosis: 3; nongynecological malignancies: 11; Morbus Crohn: 1; ovarian torsion: 1; e causa ignota: 1. *** Not further specified in patient files.

Treatment protocol

The University Hospitals Leuven protocol of management for MBO can be found in Supplemental Figure S1, Supplement Digital Content, http://links.lww.com/MS9/A120.

Data collection and statistical analysis

An electronic patient file query was performed within the department Gynecological Oncology of the University Hospitals Leuven with the search terms 'subobstruction' or 'obstruction' or 'Sandostatine'.

Data collection included: age, cardiovascular comorbidities, BRCA status, FIGO stage, tumor histology and grade, presence of ascites, and tumor marker CA 125 at the time of diagnosis. The number of MBO episodes per patient, timing of these episodes, and hospitalization time per episode were noted. Furthermore, data on symptoms, radiographic imaging modalities for diagnosis, site of bowel obstruction, and presence of progressive disease at the time of MBO, complications, treatment strategy, and administration of total parenteral nutrition (TPN) were noted. Before, during and after MBO the number of lines of chemotherapy were noted.

When exact dates were not available, the first day of the abstracted month was imputed.

A statistical analysis was performed using JMP® Pro 15.2.0 software. Absolute frequencies and percentages were used for qualitative variables, and median and range for quantitative variables. An exception was made for the tumor marker CA 125, since it was considered a qualitative variable, as these measurements were sometimes unknown or described as 'greater than'. Survival curves were constructed using the Kaplan–Meier method. Survival time was calculated from the first episode of MBO to death. The Log Rank test and Wilcoxon test were used to compare survival between groups of patients: the Log Rank test has a higher power to detect late differences while the Wilcoxon test has a higher power to detect early differences. A *P*-value of less than 0.05 was considered statistically significant.

Table 1

Characteristics of the study population of patients with MBO.

Characteristic	Number ($n=73$)
Age at tubo-ovarian cancer diagnosis, years	
Median (range)	63 (30–80)
Comorbidity	*n* (%)
None	53 (73)
Hypercholesterolemia	3 (4)
Hypertension	10 (14)
Diabetes Mellitus	0 (0)
Hypercholesterolemia AND Hypertension	5 (7)
Hypercholesterolemia AND Hypertension AND Diabetes Mellitus	2 (3)
BRCA	*n* (%)
BRCA1 +	7 (10)
BRCA2 +	0 (0)
BRCA –	41 (56)
Unknown	25 (34)
FIGO stage at diagnosis	*n* (%)
Ic	3 (4)
II	2 (3)
III	33 (45)
IV	35 (48)
Ascites at diagnosis	*n* (%)
Yes	54 (74)
No	11 (15)
Unknown	8 (11)
Bowel obstruction at diagnosis	*n* (%)
Yes	11 (15)
No	56 (77)
Unknown	6 (8)
Tumor histology and grade	*n* (%)
Clear cell	1 (1)
Serous, high grade	64 (88)
Serous, low grade	4 (5)
Serous, grade unknown	3 (4)
Transitional cell carcinoma	1 (1)
CA 125 at diagnosis, kU/l	*n* (%)
0–200	13 (18)
201–500	21 (29)
501–2000	17 (23)
> 2001	14 (19)
Unknown	8 (11)

Results

Patient characteristics

Five hundred eighty-three patients' medical records were reviewed, from which 73 patients were included (Fig. 1). Table 1 summarizes the baseline characteristics of the study population. A total of 165 MBO episodes were registered. Presenting symptoms of MBO were: nausea and vomiting ($n=61$; 84%), difficult or no oral intake ($n=42$; 58%), weight loss ($n=12$; 16%), absence of defecation and/or flatus ($n=21$; 29%), diarrhea ($n=16$; 22%), abdominal pain ($n=45$; 62%), abdominal distension ($n=34$; 47%), hypo- or aperistalsis ($n=7$; 10%), and hyperperistalsis ($n=4$; 5%). Acute abdomen as presenting symptom was not reported. The characteristics of the MBO episodes together with an overview of performed surgeries for MBO are shown in Table 2.

In 111 (67%) MBO episodes the diagnosis was confirmed using a plain abdominal radiography, in 48 (29%) episodes a computed tomography scan was used, in 2 (1%) episodes an abdominal ultrasound was performed, in 1 (1%) episode whole body MRI was used and in the remaining 3 (2%) episodes the imaging technique was unknown due to a diagnosis in another hospital.

The location of the obstruction was most often in the small bowel ($n=149$; 90%), followed by both the small and large bowel ($n=10$; 6%), and large bowel only ($n=3$; 2%). No specific localization of MBO was mentioned in the imaging protocol in 3 patients (2%). Disease progression was also found during 70 (42%) MBO episodes, in the majority no disease progression was reported ($n=95$ episodes; 58%).

Management

Conservative treatment was used in 150 (91%) episodes, including gastrostomy in 4 (2%) episodes. Octreotide (Sandostatin®) was administered in 79 (48%) episodes with a median hospitalization time of 9 days (range 3–67). In the latter group 2 (3%) patients died during hospitalization and 13 (18%) were palliatively discharged to receive outpatient supportive care. When no octreotide was administered, the median

Table 2

Characteristics of MBO and overview of performed surgeries for MBO in the study population.

Characteristic	Number
Time interval between diagnosis and first MBO episode, days	
Median (range)	373 (0–1937)
Episodes of MBO	*n* (%)
1	38 (52)
2	11 (15)
3	9 (12)
4	9 (12)
5	4 (5)
8	1 (1)
14	1 (1)
MBO episode per patient	
Median (range)	1 (1–14)
Time interval between MBO episodes, days	
Median (range)	44 (6–2004)
Hospitalization time per MBO episode, days	
Median (range)	10 (1–72)
Overview of performed surgeries	
Exploratory laparoscopy	
Adhesiolysis	1
Colostomy	1
Exploratory laparotomy	
Exploratory	1
Ileo-ascendostomy	1
Loop transversostomy	2
Gastro-jejunostomy and entero-enteric anastomosis	1
Adhesiolysis	3
Low anterior resection and colostomy	1
Ileotransverso anastomosis and loopcolostoma	1
Ileocolic resection	1
Ileosigmoidanastomosis	1
Hemicolectomy and ileostomy	1

hospitalization time was 12.5 days (range 1–72). Nine (12%) patients were palliatively discharged to receive outpatient supportive care, and eight (11%) patients died during hospitalization. TPN was administered in 22 (13%) episodes. Up to a maximum of 6 lines (median 1; range 0–6) of chemotherapy were administered after the first episode of MBO.

Surgery was performed in 15 (9%) episodes (Table 2).

Complications

Two types of MBO complications were registered: bowel perforation in 5 (7%) patients and bowel ischemia in 1 (1%) patient. Only one case of staple line leakage after surgery was reported.

Survival

At the end of the follow-up period, 11 (15%) patients were still alive. Sixty-two (85%) patients died during follow-up (median time interval of 167 days; range 6–2256).

We performed a survival data analysis using Kaplan–Meier estimates. The patients who presented with MBO as the first symptom of disease and thus did not receive chemotherapy prior to MBO ($n = 10$; 14%), had a median survival of 381 days (range 39–2256), counting from tubo-ovarian cancer diagnosis. The patients who had received treatment for tubo-ovarian cancer prior to their first MBO episode ($n = 52$; 71%) had a median survival of 155 days (range 6–2093). We found no significant difference in survival between both groups (Log Rank P-value = 0.0673; Wilcoxon P-value = 0.1278).

Regarding the use of palliative chemotherapy after the first episode of MBO, a significant difference in survival was found (Log Rank P-value = 0.0033; Wilcoxon P-value = 0.0055) (Fig. 2 plot 1). Patients receiving chemotherapy after the first episode of MBO had a median survival of 203 days (range 8–2256) whereas those who did not receive chemotherapy had a median survival of 60.5 days (range 6–491).

Patients receiving surgical treatment (Table 2) for MBO had a median survival of 395.5 days (range 175–2093) in comparison with a median survival time of 105 days (range 6–2256) in the group of patients with nonsurgical treatment. According to both the Wilcoxon test (P-value = 0.0069) and the Log Rank test (P-value = 0.0185) this difference in survival is significant (Fig. 2 plot 2).

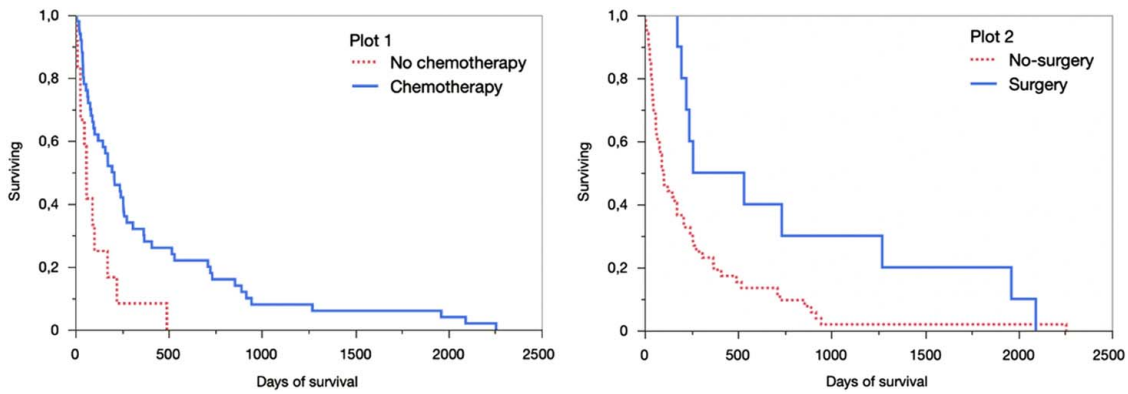

Figure 2. Survival in days from the first episode of malignant bowel (sub)obstruction to death. Plot 1: Survival in days from the first episode of malignant bowel (sub) obstruction to death according to the use of chemotherapy after the first episode of MBO. Plot 2: Survival in days from the first episode of malignant bowel (sub) obstruction to death according to surgery versus no-surgery for MBO.

A Log Rank and Wilcoxon test were also used to compare survival considering other variables (Supplemental Table S1 , Supplement Digital Content, http://links.lww.com/MS9/A120).

Discussion

Summary of main results

In this study, we registered a total of 165 MBO episodes in 73 patients. Tubo-ovarian cancer patients with MBO have a poor prognosis, the majority of the study population died within a relatively short time interval since the first MBO. Most MBO cases were treated conservatively, with TPN used in only 16 patients, and with few complications reported.

We presume that more difficult cases requiring specialized treatment are overrepresented in our tertiary center. Therefore, it was difficult to calculate the MBO rate in our study population considering the risk of miscalculation. In the available literature several obstruction rates have been cited, ranging from 5–42%[16].

Results in the context of published literature

Management: octreotide

Octreotide (Sandostatin®) is a somatostatin analog, that has a theoretical capacity to reduce gastrointestinal secretions and decrease intestinal motility, thereby decreasing MBO-related symptoms[22,23]. Due to the retrospective nature of this study, no specific report on the efficacy of octreotide can be provided. However, there was a higher rate of palliative discharges in the group of patients who received octreotide. When no octreotide was administered during a MBO episode, we found a longer hospitalization period and a higher patient mortality. The systematic review by Mercadante and Porzio found a therapeutic octreotide success rate of 60–90% ($n=281$ patients)[24]. Furthermore, Currow *et al*. concluded that there was no significant decrease in the amount of days free of vomiting at 72h after octreotide use from their double blind randomized controlled trial in which octreotide or placebo was associated with standard supportive therapy in 87 patients with advanced cancer and inoperable MBO with vomiting. Additionally, they found a greater need to treat colic pain in the octreotide group[22]. The first systematic review of 420 studies comparing the efficacy of somatostatin analogs with placebo and other pharmacological treatment in patients with inoperable MBO in terms of diminution of vomiting, abdominal distension, and pain found there was only low-level evidence of benefit with somatostatin analogs in comparison with placebo and more studies were needed[7]. Thus, the exact benefit of octreotide is not clear yet.

Management: total parenteral nutrition

The use of TPN in ovarian cancer patients with MBO is controversial[5,25]. In our hospital, TPN is not a standard part of the conservative treatment policy. Administration of TPN could have a life-prolonging effect, but this may not be desirable in view of the poor quality of life (QOL)[17]. There were only a few patients who received TPN in our study population. In these patients, with a longer life expectancy, it was found useful to bridge a temporary obstruction episode when oral intake was not or hardly possible. However, there was no survival benefit for these patients. This is in concordance with various randomized clinical trials, in which no benefit of TPN was found in patients with incurable malignant disease[5].

Regarding QOL, TPN is associated with a risk of complications such as infection, abdominal cramps, and diarrhea[26]. Additionally, Naghibi[27] conducted a cost analysis of home parenteral nutrition in 437 patients in a palliative setting with inoperable MBO and concluded a high cost for little benefit. Although TPN can be useful in a subgroup of patients with a relatively good performance status and prognosis, standard use in advanced- or end-stage ovarian cancer patients is not recommended[17,25,28].

Survival

Patients with tubo-ovarian cancer and MBO have a poor prognosis. We found that 85% of our study population died within a median time interval of 167 days since the first episode of MBO, while the literature available states that most patients die 65.5–105 days after MBO diagnosis in the recurrent disease setting[4,29]. The survival data concerning palliative surgical treatment in our study population also seemed to be better in comparison with the median survival time of patients receiving surgery for MBO versus those receiving nonsurgical treatment as described in the meta-analysis performed by Jin *et al*.[30] (Table 3).

Palliative surgical management of MBO is indicated for a highly selected group of patients. We considered surgery in case of mechanic bowel obstruction at only one level and depending on the patients' general condition and disease prognosis. This decision was made after multidisciplinary deliberation. Palliative chemotherapy was often given to resolve MBO, this also led to a longer survival when compared with patients who did not receive chemotherapy.

In the present paper, there was no significant difference in survival between patients presenting with obstruction and those without obstruction at the time of cancer diagnosis, while a survival benefit is described in the literature for patients with no MBO at the time of initial presentation[10,11]. However, it is difficult to compare exact survival data since most findings in the literature are based on patients in the recurrent disease setting[4–6,12].

Strengths and weaknesses

The strength of this study lies in its strict exclusion criteria and the inclusion of newly diagnosed primary epithelial tubo-ovarian

Table 3

Characteristics of studies included in the meta-analysis performed by Jin et al.[30] and results of the current study.

References	Number of patients surgery/nonsurgery	Median survival surgery/nonsurgery
Mooney[16]	373/1145	162/98
Suidan[20]	562/154	159/36
Chi[13]	14/12	191/78
Mangili[31]	27/20	74/60
Daniele[32]	22/18	408/171
University Hospitals Leuven	13/60	395.5/105

cancer patients in order to obtain a homogeneous study population.

This study is a retrospective data collection from a single center. Therefore, there is a possible under- or overreporting of outcomes due to the inclusion of patients that received prior care at other hospitals, patient selection due to our tertiary hospital setting and the difference in follow-up period. Also, this may limit the generalizability of the findings.

As this was a retrospective study, we could not investigate QOL. It is well known that QOL is greatly impaired in patients with MBO. Anxiety, worry, and distress levels are high, even after improvement of physical symptoms[33]. Psychological and palliative support should be offered as they are associated with better QOL and fewer readmissions[29].

To date, the literature on intestinal obstruction in ovarian cancer patients is generally focused on MBO in patients with relapsed disease[34]. Our study population includes both patients with newly diagnosed tubo-ovarian cancer and patients with relapsed disease.

Occasionally, only patients older than 65 years are included in previous studies[16,20]. In our study, age was not an inclusion criterion.

Furthermore, complications of MBO in tubo-ovarian cancer patients were considered a secondary endpoint in our study, while they are described poorly in previous literature.

Implications for practice and future research

Both palliative chemotherapy and palliative surgical management are considerable treatment options for MBO, depending on the individual patient profile.

Further studies should focus more on supportive and palliative measurements and its effect in this patient population.

Conclusion

Primary epithelial tubo-ovarian cancer patients with MBO suffer from few complications and are usually treated conservatively. Eighty-five percent of our study population died within a relatively short time interval after their first MBO. Although, there is no consensus concerning the best treatment for patients with MBO, our experience with the management and survival outcome of MBO in our tertiary center learns that both palliative chemotherapy and palliative surgical management are considerable treatment options depending on the individual patient profile.

Ethical approval

This study was reviewed and approved by the Ethics Committee Research UZ/KU Leuven (MP001927) on August 8th, 2018.

Patient consent

This was a retrospective study and informed consent was not obtained from each individual patient in line with the recommendation of our Ethical Committee. All patients were able to refuse/withdraw the use of data according to the hospital policy and information to the patients.

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This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author contribution

Jo.J. acquired and analyzed the data, wrote the manuscript, and revised it for final publication; Je.J. analyzed the data and revised the manuscript for final publication; S.N.H. provided scientific expertise, guidance, and support in the manuscript writing and revised it for final publication; E.V.N. approved the version to be published; E.O. revised the manuscript for final publication; P.N. approved the version to be published; I.V. provided scientific expertise and revised the manuscript for final publication; A.W. approved the version to be published.

Conflicts of interest disclosure

E. Oldenburger declares Varian Research Grant outside the submitting work. Vergote I. declares outside the submitting work Consulting Fees from Agenus, Akesobio, AstraZeneca, Bristol Myers Squibb, Deciphera Pharmaceuticals, Eisai, Elevar Therapeutics, Exelixis, F. Hoffmann-La Roche, Genmab, GSK, Immunogen, Jazzpharma, Karyopharm, Mersana, MSD, Novocure, Novartis, Oncoinvent, OncXerna, Regeneron , Sanofi, Seagen, Sotio, Verastem Oncology, Zentalis; Contracted research (via KU Leuven) from Oncoinvent AS; Corporate sponsored research from Amgen, Roche; accommodations and travel expenses from Karyopharm, Genmab, Novocure. All other Authors declare that they have no conflicts of interest.

Research registration unique identifying number (UIN)

1. The unique identifying number (UIN) is researchregistry8757
2. (https://www.researchregistry.com/browse-theregistry#home/registrationdetails/640e3375cf8f67002815f027/).

Data sharing

An electronic patient file query was performed within the department Gynecological Oncology of the University Hospitals Leuven with the search terms 'subobstruction' or 'obstruction' or 'Sandostatine'. A statistical analysis was performed using JMP® Pro 15.2.0 software. Survival curves were constructed using the Kaplan–Meier method. The Log Rank test and Wilcoxon test were used to compare survival between groups of patients.

Provenance and peer review

Not commissioned, externally peer reviewed.

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