Palliative care in patients with ovarian cancer and bowel obstruction.

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ABSTRACT

21

22 **Objective:** Bowel obstruction (MBO) is usually a pre-terminal event in patients with

23 ovarian cancer. However, because of the lack of data in literature, decisions around

24 surgical intervention, non resectional procedures or medical treatment of MBO in

25 patients with ovarian cancer can not be lightly undertaken. We analyzed medical and

26 surgical procedures, performance status, nutritional status, cachexia and their

27 prognostic value in this group of patients.

28 **Methods:** We retrospectively selected all consecutive patients with recurrent ovarian

29 cancer who received medical or surgical treatment for MBO between October 2008

30 and January 2014 at the Academic Department of Gynecological Oncology of

31 Mauriziano Hospital of Turin (Italy).

32 **Results:** We found 40 patients: 18 of them underwent medical treatment and 22 of

33 them were submitted to surgery. In the group of surgery, the hospitalization was

34 shorter (p: 0.02), the pain reduction was more effective (p: 0.001), the number of

35 chemotherapy lines was higher (p: 0.03) and re-obstruction was more rare (p: 0.02).

36 Between the two groups, we did not find any differences in post-palliation episodes

37 of vomit (p: 0.83), type of diet (p: 0.34), ability to return home (p: 0.72) and death

38 setting (p: 0.28). Median survival after palliation was longer in the group of surgery

39 (p: 0.025). Cachexia, low performance status and poor nutritional status were

40 significant predictors of worse survival after MBO, independently by the treatment.

41 **Conclusions:** Surgery has to be considered in patients without serious

42 contraindications, otherwise a medical protocol, including antisecretory drugs, is the

43 standard of care in frail patients.

44

INTRODUCTION

Bowel obstruction is defined as the situation in which the normal intestinal transit is abnormally delayed or completely stopped. It is a common complication in patients with end-stage cancer and it is estimated that malignant bowel obstruction (MBO) involves 3% of the patients admitted in Hospice. The reported frequency varies from 25% to 50% in patients with advanced ovarian cancer [1]. Survival is generally poor, with a reported median survival of 1-3 months, but some studies have demonstrated survival of up to 1 year.

In the patients with advanced ovarian cancer, more often the intestinal occlusion is due to the diffuse peritoneal carcinomatosis. MBO may be sometimes the consequence of the cancer treatment: adhesions from previous surgery, radiation enteritis, chronic ischemia, neurotoxicity from Vinca Alkaloids or narcotic intestinal syndrome from the use of opioids.

Bowel obstruction can be partial or complete and can occur at single or multiple sites. Small bowel obstruction is more common than large bowel obstruction (61 vs 33%) and both sites are involved in > 20% of patients [2].

Therapy directed at MBO must achieve certain goals, such as allowing the patient to return home, restoration of oral intake and relief of abdominal distension and pain. Once the obstruction is relieved, a small proportion of patients is suitable for further treatment with chemotherapy.

Although bowel obstruction in advanced ovarian cancer presents quite commonly, its management still remains a challenge, mainly because it has been the focus of very few clinical trials. Because of the lack of the evidences in literature, decisions around surgical intervention, non resectional procedures or medical treatment of malignant intestinal obstruction cannot be lightly undertaken. The survival benefit from the

70 different strategies is difficult to validate because of the heterogeneity of the

71 populations studied in various trials, particularly with respect to the primary cancer

72 type. Studies so far have measured perioperative mortality and morbidity but have

73 not taken the quality of life (QOL) into account when measuring the success of any

74 procedures [3].

75 The aim of the study was to compare the two different strategies, medical and

76 surgical, in the management of MBO in ovarian cancer patients. We evaluated if

77 operative and conservative approaches produce an effective and durable palliation in

78 terms of QOL and survival. Furthermore, we investigated the prevalence of low

79 performance status, poor nutritional status and cachexia in ovarian cancer patients

80 with MBO and whether the results correlated with overall survival.

81

82   **MATERIAL AND METHODS**

83 All consecutive patients with recurrent ovarian cancer who experienced bowel

84 obstruction between October 2008 and January 2014 at the Academic Department of

85 Gynecological Oncology of Mauriziano Hospital of Turin (Italy) were identified

86 through the discharging program of the Division. We excluded patients with MBO

87 for other gynecological malignancies, non-epithelial or borderline ovarian cancer,

88 patients with bowel obstruction for benign causes, patients with a history of previous

89 or concurrent malignancy and patients with concomitant recto-vaginal fistula.

90 The diagnosis of MBO was based on history, signs and symptoms, physical

91 examination and radiological findings. At the moment of hospital admission, all

92 patients underwent some laboratory tests and a chest-abdominal computed

93 tomography (CT) to identify the site of bowel occlusion and to restage the disease.

94   Because the location of the MBO can determine the treatment options, we

95   distinguished the site of obstruction in large, small and both small and large bowel.

96   The selected patients received medical or surgical treatment.

97   Medical management of the patients with MBO considered the following protocol:

98   - Morphine Sulphate 60 mg, Haloperidol 1.5 mg, Octreotide 0.3 mg [4]

99   through continuous subcutaneous pump infusion per day;

100   - Dexamethasone 8 mg intravenous per day;

101   - Stop oral intake;

102   - Parenteral liquids.

103   Surgical management consisted of the less invasive and most conservative

104   interventions to palliate symptoms and to restore intestinal function.

105   The significance of the palliative treatment was largely explained to the patients and

106   for the surgical procedures an informed consensus was signed by the patient and by

107   the surgeon. Patients and their families during the palliative care for the MBO were

108   followed by the team of gynecological oncology, a nutritionist, a palliative care

109   physician, a group of three colorectal surgeons and a nurse expert in ostomy

110   management. All patients were visited by all the specialists during the process of

111   care. At discharge, patients underwent chemotherapy, if indicated, or palliative care

112   at home or in hospice.

113   We collected the following data on the history of the patients relative to three stages:

114   I-   *Before MBO:* stage of the ovarian cancer at diagnosis (FIGO), date of the end

115   of the primary treatment, date of the recurrence, platinum sensitivity, number of

116   chemotherapy lines, secondary surgery and radiotherapy;

117   II-   *Time of MBO:* performance status (Karnofsky scale), nutritional status (PG-

118   SGA) [5-6], cachexia (CCSG) [7], body mass index (BMI - kg/m^2), comorbidities,

119   date of MBO, vomit, pain (NRS), palpable abdominal mass, CT scan findings

120   (peritoneal carcinomatosis, abdominal or extra-abdominal disease, ascites > 2 L and

121   the site of obstruction), serum sodium (mEq/L) serum kalium (mEq/l), calcium

122   (mg/dl), serum creatinin (mg/dl), total serum protein (g/dl), serum albumin (mg/dl),

123   haemoglobin (g/dl), C-reactive protein (mg/l), medical or surgical management, type

124   of surgical procedure, surgical morbidity and mortality, duration of the

125   hospitalization (days);

126   III-   *After MBO:* pain (NRS), vomit, type of diet at discharge (oral, oral and

127   parenteral or parenteral), ability to return home, accesses to emergency department

128   and re-hospitalization for re-obstruction and successive medical or surgical

129   intervention, number of chemotherapy lines, death setting (hospital, hospice or

130   home) and survival.

131   The range from the end of the primary treatment and the diagnosis of relapsed cancer

132   was defined disease free interval (DFI) and the recurrent disease was considered

133   platinum sensitive when it reappeared after a DFI > 6 months.

134   The study was approved by the Local Ethics Committee.

135

136   *Statistical analysis*

137   Differences in the groups were analyzed using the Student's t-test for continuous

138   variables or the U Mann-Whitney Test when a normal distribution was not assumed

139   (Non parametric test); the Pearson chi-square test was adopted to compare

140   frequencies. Overall survival curves were plotted according to the Kaplan–Meier

141   product limit method and analyzed by the Log-Rank test. Multivariate analysis was

142   performed using the Cox's proportional hazards logistic regression. Alfa level of less

143   than or equal to 0.05 were considered statistically significant.

RESULTS

Patients characteristics

Between October 2008 and January 2014, 53 patients were hospitalized in our division with the admission diagnosis of intestinal occlusion. Thirteen patients with MBO for endometrial, non-epithelial or borderline ovarian cancer, 5 patients with bowel obstruction for benign causes, 2 patients with a history of previous or concurrent malignancy and 3 patients with concomitant recto-vaginal fistula were excluded. Data from the remaining 40 patients with concomitant recurrent epithelial ovarian cancer and malignant bowel obstruction were collected. At ovarian cancer diagnosis, 4 patients were stage I-II and 36 patients were stage III-IV, according to FIGO. All patients underwent debulking surgery and all patients, except one, received neoadjuvant or first-line platinum based chemotherapy. Median DFI was 10 months (range 3 - 96 months). In three cases, the diagnosis of recurrent disease was concomitant to MBO. Before MBO, the median number of chemotherapy line was 3 lines (range 1 - 7). One patient was submitted to radiotherapy for a muscle-skeletal recurrence of the ileo-psoas region and one patient received radical secondary cytoreductive surgery. The median interval from the diagnosis of ovarian cancer to MBO was 26 months (range 3–149 months). The median age at first episode of MBO was 63 years (range 24 – 79 years). Nineteen patients suffered from at least one comorbidity and the most frequent was hypertension. Eighteen patients underwent medical treatment and 22 patients were submitted to surgery. Data of the patients at the moment of hospital admission for MBO are summarized in Table 1. We found 4 clinical factors, amongst the 12 analyzed, who resulted significantly different between the two groups: performance and nutritional status, pain (NRS $\geq$ 7) and ascites. Considering the laboratory tests, only the levels of serum albumin were

significantly higher in the group undergoing surgery (p: 0.01). At hospital admission, after the radiological restaging (chest-abdomen CT), thirty-two patients were classified stage FIGO III C (macroscopic peritoneal metastasis beyond the pelvis more than 2 cm), three patients were classified FIGO IV A (pleural effusion) and five patients were classified FIGO IV B (three patients with liver metastasis, one with pulmonary hilum lymph nodes metastasis and one with muscle-skeletal metastasis). On the basis of the FIGO staging, no difference has been found between the two groups.

Medical treatment

The medical protocol controlled symptoms within 4 days (range 1 – 9 days) and the median hospitalization duration was 8 days (range 3-25 days). No side effects were reported. Data about diet, re-obstruction, vomit and chemotherapy after MBO are reported in Table 2. Median survival after MBO for the group of medical treatment was 5.7 months (range: < 1 - 8.4 months). At the moment, 17 patients died, 4 (22.2%) in hospital, 3 (16.7%) in hospice, 10 (55.5%) at home and 1 patient is still alive with disease.

Surgical treatment

Surgical procedures included 4 (18.9%) bowel resection and anastomosis, 9 (40.9%) bowel resection and ostomy (2 colostomy and 7 ileostomy), 8 (36.4%) exclusive ostomy (1 colostomy and 7 ileostomy) and 1 (4.5%) positioning of colonic stent. One patient (4.5%), who underwent large bowel resection and anastomosis, had a postoperative recto-vaginal fistula and required a re-intervention and ileostomy. The mortality within 30 days from surgery was 4.5% (1 case), who died from progression of tumour. Five patients (22.7%) underwent surgery within 24 hours from the

194 hospital admission, but there were no more complications or longer hospitalization in

195 this group. Median hospitalization was 14 days (range 8 - 30 days). Data about diet,

196 re-obstruction, vomit and chemotherapy after MBO are reported in Table 2. The

197 median survival after MBO for the group of surgical treatment was 13.6 months

198 (10.1 – 17.0 months). Nineteen patients died of disease, 6 (27.3%) in hospital, 4

199 (18.9%) in hospice, 9 (40.9%) at home, and 3 (13.6%) patients are still alive with

200 disease.

201

202 *Comparison of treatments*

203 Median hospitalization was shorter for the medical than for the surgical treatment (p:

204 0.02). Pain reduction one week after palliation was significantly more effective in the

205 surgical group (p: 0.001). The number of accesses to emergency department and re-

206 hospitalization for re-obstruction was significantly higher in the group of medical

207 treatment and in these patients the medical protocol was applied or reapplied (p:

208 0.02) (Table 2). After intestinal occlusion, the number of chemotherapy lines was

209 higher in the surgical group (p: 0.03). Between the two groups we did not find any

210 difference in post-palliation episodes of vomit (p: 0.83), type of diet (p: 0.34), ability

211 to return home (p: 0.72) and death setting (p: 0.28). The median survival after

212 palliation was longer in the group of surgery (p: 0.025) (Fig. 1).

213 In the group of surgery, patients had a better performance and nutritional status, but

214 no differences were shown about cachexia (Table 1). Cachexia, defined by the CCSG

215 criteria, increased the risk of death with an odds ratio of 3.2 (95% C.I. 1.5-6.6) (p:

216 0.001), the performance status amplified the risk of death with an odds ratio of 2.3

217 (95% C.I. 1.4-3.7) (p: 0.0001) and having a poor nutritional status (SGA-C) enlarged

218   the risk of death with an odds ratio of 4.7 (95% C.I. 1.4-14.9) (p: 0.008), compared to

219   well nourished patients (SGA-A).

220   In the multivariate logistic regression analysis (Cox proportional hazard model),

221   including as co-variates all the considered variables, CCSG cachexia and

222   performance status resulted independent prognostic factors (p: 0.0001) (Table 3).

223

224   **DISCUSSION**

225
226   Bowel obstruction is usually a pre-terminal event in patients with ovarian cancer. For

227   this reason, the relief of symptoms is the first aim of the treatment of these patients,

228   but the clinical management is not completely defined. Many treatment options,

229   medical approaches, endoscopic procedures and surgical interventions have been

230   proposed, but current evidences do not provide a standard of care. Modern medical

231   protocols include the use of somatostatine analogs (Octreotide), that inhibits the

232   release of gastro-intestinal secretions and regularizes the intestinal motility [4].

233   Surgery remains a discussed issue in patients with advanced cancer.

234   In patients with MBO, the major perplexities concern the success of conservative

235   treatment and the safety of operative management. Tang et al. reported that only

236   3.8% of complete obstruction resolved with conservative management [8]. In a later

237   study, 43% of 329 patients were successfully treated conservatively but with a re-

238   obstruction rate of 40.5% [9]. On the other hand, palliative surgery was associated

239   with a reported morbidity of 5% – 49% and mortality of 5% – 15% [10-11-12].

240   Major operative complications are fistulas, anastomotic leaks and sepsis. In our

241   study, the post-operative morbidity and mortality were low (4.5% each). We

242   registered only 1 case of recto-vaginal fistula, who required a re-intervention and

243   ileostomy, and 1 case of death within 30 days from surgery due to tumour

244   progression. In similar recent studies, Kolomainen et al. found an operative mortality

245   and morbidity rate of 18% and 27%, respectively [13], and Perri et al. described a

246   mortality rate of 14.7% within 30 days[14]. Medina-Franco et al. described a hospital

247   mortality rate of 10.8% and a postoperative morbidity of 16.2%, and the factors

248   associated with a significant increase of surgical mortality were: advanced patient

249   age, hypoalbuminemia, ovarian neoplasms and poor performance status [14].

250   In patients with MBO and recurrent ovarian cancer, the reported median survival is

251   3–6 months after palliation [15-16]. More recent series reported a median survival of

252   11.4 – 12.6 months in patients undergoing surgery for MBO versus 3.7 – 3.9 months

253   for non-surgical patients [17]. In our study, the median survival after palliation was

254   13.6 months for the group of surgery and 5.7 months for the group of medical

255   treatment. Mangili et al. also found a longer survival in the surgical group [18] and

256   Kolomainen et al. reported a median overall survival after surgical management of

257   MBO around 3 months (range: 2 days – 6 years) [13]. Table 4 compares the reported

258   survival after palliation in the literature.

259   In the present study, amongst the analyzed factors, the two groups of treatment

260   showed 5 significant differences: performance status, nutritional status, pain, ascites

261   and albumin. There were not any differences between the two groups in terms of age,

262   FIGO stadiation, number of previous chemotherapy lines, DFI, time from ovarian

263   cancer diagnosis and MBO and time from the last chemotherapy infusion. In the

264   group of surgery, the number of chemotherapy lines after MBO was higher, 15

265   patients (68.2%) received at least one line and 5 patients (22.7%) completed more

266   than one line (p: 0.03).

267   In our series, many QOL criteria were considered in the analysis. Pain reduction was

268   more effective in the surgical group and re-obstruction was more frequent in the

269   group of medical treatment. Between the two groups we did not find any difference

270   in post-palliation episodes of vomit, type of diet and ability to return home. As

271   reported, 2 essential QOL factors, pain reduction and re-obstruction, were

272   significantly improved by surgical palliation. In case of re-obstruction, all patients

273   received medical treatment. Two reports, each describing a small series of ovarian

274   cancer patients who underwent exploratory laparotomy for recurrent bowel

275   obstruction, reported successful palliation in 30% of cases [2-3]. In accordance with

276   the cited studies, because of the high morbidity rate, the rapid development of

277   subsequent bowel obstructions and the limited survival, we agree that a non-surgical

278   approach is probably preferable for patients who experience repeated bowel

279   obstruction. Because of the retrospective design, we lack data from some overall

280   QOL questionnaires [18-19].

281   Considering some selection bias, our data suggest that patients who underwent

282   palliative surgery achieve more effective survival and QOL improvements, but

283   because of the reported implications, the decision to proceed with surgical palliation

284   in patients with ovarian cancer and MBO has to be carefully evaluated for each

285   individual patient.

286   Several studies have focused their attention to the identification of some prognostic

287   factors for the selection of patients who may benefit from surgery. Mangili et al.

288   suggested that the surgical approach seems to be useful for patients with life

289   expectancy greater than 2 months [20]. Studies identified age, ascites, previous

290   radiotherapy, multiple bowel obstructions, carcinomatosis, palpable masses and short

291   interval from diagnosis to obstruction as clinical indicators of poor prognosis after

292   surgery [13-21-22-23-24]. Henry et al. proposed a nomogram of 4 identified risk

293   factors: carcinomatosis on imaging, leukocytosis, normal albumin and non

gynecologic cancer, that revealed which patients with complete small bowel obstruction might benefit from surgery [25]. However, because only the 17% of the included patients had gynecologic malignancies, their findings might not be fully applicable to gynecological oncology. Finally, in the study of Perri et al., a 4-variable score was correlated with the 30 days and 60 days overall survival after surgical palliation for MBO in gynecologic malignancies: 2.7% and 5.4%, respectively (score 0-1), and 40% and 73.3%, respectively (score 3-5). The score includes age above 60, ascites of more than 2 L, non-ovarian primary tumor and albumin < 2.5 g/dl [3]. The first three factors were assigned a value of 1 if present and 0 if not. Albumin < 2.5 mg/dl was assigned a value of 2 if present and 0 if not. The proposed scoring system is easy to apply and might facilitate decision of the healthcare team and information of patients and families. The major limitation of this score is that it does not take into account information about performance status.

Different tools have been proposed for cancer malnutrition and wasting assessment. They have been largely confirmed in gastro-intestinal cancer patients, but they have never been validated in ovarian cancer neoplasm. We designed the second part of the study to identify the role of performance status, nutritional status and cachexia in ovarian cancer patients with MBO and their association with survival after palliation, independently by the treatment. Thirteen patients (32.5%) had a low performance status and, finally, in accordance with PG-SGA classification, 8 patients (20%) were "severely malnourished". Figures 2-3-4 show that low performance status, CCSG cachexia and poor nutritional status were all significant predictors of worse survival after MBO. To the best of our knowledge, the present study is the first that applied these assessment tools in such homogeneous group of patients with advanced ovarian carcinoma. The CCSG definition of cachexia was first introduced in a study of

319 patients with pancreatic carcinoma in which cachexia was found to be related to the

320 patients' survival [26]. In that study, 60% of the patients had cachexia and the HR for

321 overall survival was 2.23, close to our findings. These observations suggest that the

322 CCSG definition of cachexia should be applicable also in advanced ovarian

323 carcinoma. In this study, CCSG cachexia and low performance reached statistical

324 significance in both unadjusted and adjusted survival analyses and were the most

325 powerful predictors of survival. The sample size of the study was limited, and further

326 investigations are required to confirm the prognostic value of the nutrition and

327 cachexia assessments.

328 In our report, especially for the group of surgery, the long prognosis, the low rates of

329 postoperative morbidity and mortality and the high number of patients who received

330 chemotherapy after MBO probably reflect the good performance status of the

331 patients. Furthermore, previous reports date back several decades and so they do not

332 take into account the substantial improvements of the current medical protocols,

333 surgical techniques and anaesthesia. On the basis of our experience, we support the

334 hypothesis that performance and nutritional status and cachexia may address the

335 choice of the treatment.

336 All series, including ours, are retrospective and include a small numbers of patients,

337 but our study solely comprised ovarian cancer patients treated in a relatively short

338 period. In the analysis, we focused specific attention to QOL outcomes. Moreover,

339 our results come from a single institution and patients were assessed by a

340 multidisciplinary team.

341 In the setting of palliative care, a randomized trial is challenging [27]. A trial

342 comparing therapies for MBO will help to define therapy and identify selection

343 criteria. Untill now, no comparative trials have been performed on the role of the

therapeutic strategies for MBO. To prove the effects of any given treatment, hundreds of patients would need to be recruited. A trial in this scenery is hampered by many individual differences between patients and by the myriad of advanced medical and surgical protocols. Currently, in the absence of a shared protocol, it is our intention to validate our findings in a prospective study.

In conclusion, malignant bowel obstruction represents a common end-of-life event in ovarian cancer patients. Because of its complexity and frailty of involved patients, a multidisciplinary and collaborative approach is mandatory for an optimal clinical management and palliation of MBO. In a palliative setting, the most important goal is to identify the patient's expectations, because they are largely subjective for each individual patient [28]. For these reasons, patients, and eventually their families, must be informed about their health and life expectancy. Surgery has to be considered in patients without serious contraindications, otherwise a combination of opioids, anti-emetics, corticosteroids and antisecretory drugs is the mainstay in patients with poor general conditions.

369 **Conflict of interest**

370 Authors have no financial and personal relationships with other people or

371 organizations that could inappropriately influence this work.

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373 We have full control of all primary data and we agree to allow the journal to review

374 data if requested.

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