Screening tool for malignant bowel obstruction in relapsed, metastatic ovarian cancer

Robert D Morgan,1,2,3 Sofia Stamatopoulou,1 Nerissa Mescallado,1 Geoff Saunders,4 Richard Welch,5 Claire Mitchell,1 Jurjees Hasan,1 Andrew R Clamp,1,2,3 Gordon C Jayson1,2,3

ABSTRACT

Background Malignant bowel obstruction (MBO) is a common cause of morbidity and mortality in women diagnosed with ovarian cancer. Earlier detection of MBO may improve patient outcomes. There are currently no screening tools to assist detection.

Aim We report a screening questionnaire that can be used to detect MBO, and how the severity score for key clinical symptoms correlate with radiological evidence of MBO from ovarian cancer.

Design A case–control study in which patients with relapsed, metastatic ovarian cancer were asked to answer 10 questions related to key clinical symptoms associated with intestinal obstruction. The study group included women with CT-confirmed MBO, whereas the control group had no evidence of MBO. Patients scored each question according to severity from 1 (least severe) to 5 (most severe).

Setting/participants Between 1 June and 31 December 2016, 37 women completed the screening questionnaire.

Results Patients in the study group (n=17) reported significantly higher (ie, more severe) scores for abdominal pain, nausea, vomiting and constipation. In contrast, differences in severity scores between groups did not differ significantly in response to questions regarding abdominal swelling, borborygmi, diarrhoea or loss of appetite. All patients in the study group more frequently stated that their symptoms had deteriorated within the 2 months prior to completing the questionnaire.

Conclusion Here we report the key clinical symptoms associated with radiologically-confirmed MBO from ovarian cancer. We recommend healthcare practitioners focus on these specific symptoms during patient consultations in order to improve risk stratification of MBO.

INTRODUCTION

Ovarian cancer is the second most common gynaecological cancer and the sixth most common cause of cancer-related death in women in the UK, with around 7000 new cases diagnosed each year and >4000 attributable deaths.1 Unfortunately due to its insidious nature, most women diagnosed with ovarian cancer present with advanced stage disease (International Federation of Gynecology and Obstetrics (FIGO) stage 3 or 45) from which cure is unlikely.5 The most common anatomical sites where metastases are found include the serosal membrane lining the abdominopelvic cavity and viscera, as well as the peritoneal folds, omentum and mesentery.4 It is this predilection to metastasise to the peritoneum and peritoneal folds that means many women diagnosed with advanced stage or relapsed, metastatic ovarian cancer are at high risk of developing malignant bowel obstruction (MBO). Indeed, MBO is considered the most common cause of mortality in women diagnosed with ovarian cancer3,5 and is associated with a median overall survival of around 90 days.6–10

There are currently no standards of care/best clinical practice treatments for MBO.11–13
Although surgery is a potential option, its use often depends on a number of factors, such as a patient’s fitness for surgery, the anatomical level of obstruction and the extent of bowel involvement.\textsuperscript{8,11,14–18} Indeed, most women diagnosed with MBO due to ovarian cancer have multilevel obstruction; a clinical scenario in which surgical intervention is relatively contraindicated. Alternative invasive therapeutic options are aimed at gastrointestinal luminal decompression and/or recanalisation, including nasogastric suction, gastrostomy/jejunostomy and endoscopic stenting. These interventions are associated with variable outcomes and complication rates in small retrospective case series.\textsuperscript{7,19–25} Further, the use of palliative systemic anticancer therapy may be associated with extended inpatient stay and treatment responses that are heavily reliant on the chemo-resistant nature of the residual tumour.\textsuperscript{9,10,16} Other therapeutic options used to support patients with MBO include laxatives, analgesia, anti-emetics, anti-secretive drugs and steroids as well as parenteral nutrition and low-fibre diets.\textsuperscript{12,18,24–26}

Intestinal obstruction is believed to present with a myriad of symptoms, including abdominal pain, abdominal swelling, bloating, vomiting and a change in bowel habit (constipation and/or diarrhoea), and these symptoms are usually discussed during patient consultations. The clinical diagnosis is often confirmed using cross-sectional imaging, in particular CT.\textsuperscript{27} At present there are no screening tools that can assist healthcare practitioners in detecting prodromal symptoms that may exist prior to developing complete MBO. In this case–control study, we investigated the use of a simple screening questionnaire designed to score the severity of commonly explored symptoms of MBO in everyday clinical consultations (figure 1). We report our quantitative analysis of this screening tool and how these results correlate with radiologically-confirmed MBO in ovarian cancer.

**METHODOLOGY**

Patients were approached to answer the screening questionnaire at routine outpatient follow-up appointments (figure 1). The screening questionnaire was offered to any patients with relapsed, metastatic ovarian cancer who had CT-confirmed MBO (study group). CT-confirmed MBO included new and/or progressive dilated or distended loops of large or small bowel with or without collapse of proximal loops of bowel, considered by the reporting radiologists to represent intestinal obstruction; the cause of which was deemed most likely to be ovarian cancer and less likely non-malignant disease, for example, intra-abdominal adhesions. The screening questionnaire was also offered to patients with relapsed, metastatic ovarian cancer who had no evidence of MBO on their latest CT scan (control group). Patients recruited to the control group had no active disease at the time they completed the questionnaire, as determined by stable disease or an ongoing treatment response on their latest CT scan, and no evidence of progression disease according to the Gynecologic Cancer Intergroup (GCIG) CA-125 criteria.\textsuperscript{28}

The screening questionnaire specifically asked patients to score each symptom from 1 (least severe) and 5 (most severe) according to a severity scale (figure 1). The maximum total score was therefore 50 and the minimum score 10. All patients were specifically asked to score only recent symptoms that had occurred in the 4 weeks prior to completion of the questionnaire. To ensure that scores matched with CT findings (ie, MBO [control group] or no MBO [study group]), the screening questionnaire was offered to patients within 7 days of their latest CT scan. Moreover, the screening questionnaire was given to patients before they were informed of the CT result to avoid reporting bias. Finally, platinum sensitivity was defined according to progression-free interval following a patient’s latest line of platinum-based therapy.\textsuperscript{29}

In this study, categorical data were reported as number (percentage) and continuous data reported as mean (range) or median (range). A difference in severity scores between groups was assessed using Fisher’s exact test. A Mann-Whitney U test was used to assess the difference in mean total scores in the two groups. A p value of ≤0.05 was considered statistically significant.

**RESULTS**

Between 1 June 2016 and 31 December 2016, 37 women with ovarian cancer completed the screening questionnaire (table 1). All patients had been diagnosed with relapsed, metastatic ovarian cancer and treated with at least two lines of cytotoxic chemotherapy. All patients in the control group were considered to have inactive disease at the time of answering the questionnaire, evidenced by no radiological or biochemical evidence of progressive disease. The most common histological subtype was
Table 1  Demographic data

| Demographics                                      | Study group (N=17) | Control group (N=20) |
|---------------------------------------------------|--------------------|----------------------|
| Age in years at diagnosis, median (range)         | 62 (56–68)         | 64 (59–69)           |
| Morphological subtype, n (%)                      |                    |                      |
| Adenocarcinoma, not otherwise specified           | 1 (6)              | 2 (10)               |
| Clear cell                                        | 0 (0)              | 2 (10)               |
| Endometrioid*                                     | 1 (6)              | 1 (5)                |
| Serous— low-grade                                 | 1 (6)              | 1 (5)                |
| Serous— high-grade                                | 14 (82)            | 14 (70)              |
| FIGO stage at diagnosis, n (%)                    |                    |                      |
| Early stage disease (FIGO stage 1/2)              | 0 (0)              | 2 (10)               |
| Advanced stage disease (FIGO stage 3/4)           | 17 (100)           | 18 (90)              |
| Platinum-free interval, n (%)                     |                    |                      |
| Platinum-refractory (<4 weeks)                    | 1 (6)              | 0 (0)                |
| Platinum-resistant (1–6 months)                   | 8 (47)             | 8 (40)               |
| Partially platinum-sensitive (6–12 months)       | 6 (35)             | 9 (45)               |
| Platinum-sensitive (>12 months)                   | 2 (12)             | 3 (15)               |
| Prior lines of platinum-based chemotherapy, median (range) | 4 (2–6) | 3 (2–3) |
| Prior lines of chemotherapy, median (range)       | 4 (2–6)            | 3 (2–4)              |

*High-grade (poorly differentiated, grade 3) endometrioid ovarian adenocarcinoma

FIGO, International Federation of Gynecology and Obstetrics.

DISCUSSION

Despite the prevalence of, and the morbidity associated with MBO in advanced, recurrent ovarian cancer there remains very little research on the topic, globally. We therefore sought to define a simple questionnaire that could be used to identify patients at risk of developing MBO, so that future research and clinical trials could recruit patients with the prodromal clinical syndrome. Our data show that there are statistically significant differences in the responses of women with and without radiologically-confirmed MBO due to ovarian cancer. Our analysis specifically found that subjective reporting of four key symptoms including (1) abdominal pain, (2) nausea, (3) vomiting and (4) constipation correlated with the presence of radiologically-confirmed MBO due to ovarian cancer, and that these symptoms deteriorated in the preceding eight weeks. We therefore suggest that healthcare practitioners focus specifically on eliciting the severity and time course of these four key symptoms to improve detection and risk stratification for MBO.

Interestingly, in contrast, the differences in severity scores between groups of other commonly explored symptoms associated with intestinal obstruction were not significant, including (1) abdominal swelling, (2) borborygmi, (3) diarrhoea and (4) loss of appetite. We suggest that these findings may be due to the biological relevance of each symptom in relation to the development and progression of ovarian cancer and/or the non-specific nature of some symptoms. Indeed, abdominal swelling/bloating may be a late symptom associated with complete bowel obstruction or more prevalent in women who develop abdominopelvic ascites as opposed to MBO. Further, loss of appetite is often a symptom associated with systemic malignancy as opposed to localised bowel involvement. Moreover, diarrhoea is often variably described by patients and requires further direct questioning regarding frequency of stool motions, consistency and comparison to normal bowel habit; information that was not collected in our study. Finally, borborygmi is a non-specific symptom that can be present with normal bowel function.

It is noteworthy that the symptoms, and their severity, detected using our screening questionnaire were meant to reflect persistent symptoms over the course of the preceding weeks as opposed to any acute changes in bowel function. We added the adjective ‘persistent’ to the questionnaire to avoid patients referring to any short, brief episodes of symptoms that were due to an alternative aetiology such as acute infective gastroenteritis (figure 1). Despite this, we recognise that the data from our study is not able to determine the actual duration of symptoms prior to MBO, although longitudinal assessment with the bowel symptom screening questionnaire may help define this in the future.

The tumour biomarker CA-125 has been validated as a marker of disease activity in ovarian cancer, which can be used to guide management. In our study, a doubling
Table 2  Patient responses in the control and study groups to each screening question

| Screening questions | Severity score* |    |    |    |    |    |
|---------------------|-----------------|----|----|----|----|----|
|                     | Groups          | 1  | 2  | 3  | 4  | 5  | P value |
| Tummy pain          | Control         | 10 | 0.02 | 5 | 0.4 | 5 | 0.7 | – | 0.04 | – | 0.005 |
|                     | Study           | 2  | 2  | 3  | 4  | 4  | 6  |
| Tummy swelling/bloating | Control        | 11 | 0.04 | 4 | 0.66 | 2 | 0.4 | 1 | 0.2 | 2 | 0.4 |
|                     | Study           | 3  | 2  | 4  | 4  | 4  | 4  |
| Rumbling noises in your tummy* | Control        | 9  | 0.7 | 4 | 1.0 | 6 | 0.4 | 1 | 0.6 | – | 0.09 |
|                     | Study           | 6  | 3  | 3  | 2  | 3  | 3  |
| Feeling sick        | Control         | 13 | 0.007 | 3 | 1.0 | 1 | 0.08 | 3 | 0.2 | – | 0.005 |
|                     | Study           | 3  | 3  | 5  | –  | 6  |
| Being sick          | Control         | 18 | 0.003 | – | 0.2 | 2 | 0.6 | – | 1.0 | – | 0.01 |
|                     | Study           | 7  | 2  | 3  | –  | 5  |
| Constipation        | Control         | 10 | 0.02 | 2 | 1.0 | 3 | 0.3 | 5 | 0.4 | – | 0.005 |
|                     | Study           | 2  | 1  | 6  | 2  | 6  | 6  |
| Diarrhoea           | Control         | 17 | 0.4 | 1 | 0.6 | 2 | 1.0 | – | 0.5 | – | 1.0 |
|                     | Study           | 12 | 2  | 2  | 2  | 1 

Data reported as number of patients who answered with scores between 1 and 5 (1 = ‘not at all’, 2 = ‘very little’, 3 = ‘some’, 4 = ‘quite a lot’, 5 = ‘a lot’).

*Equivalent to borborygmi.

of CA-125 only occurred in less than half of patients prior to radiological confirmation of MBO, suggesting that a doubling of the CA-125 level is insufficiently sensitive to use in the assessment of MBO. These observations also suggest that subtle changes in the activity of the tumour, not evidenced by changes in the CA-125 levels, are associated with the development of MBO, and therefore also highlight the need for longitudinal utilisation of the screening questionnaire. In this regard, we recommend the screening tool is used at least as frequently as CA-125 tumour marker levels are investigated.

There are a number of limitations with our study. It is a case–control study and therefore associated with the bias common to this study type. Second, each group was relatively small, and therefore further assessment in larger populations is required prior to broader clinical applicability. Third, the data were gathered at one specific time point from each patient and we did not reassess the patient’s symptoms during treatment or as part of active surveillance. For these reasons, we are not, as yet, able to define a threshold for healthcare practitioners to use to guide earlier use of CT and/or treatments. This screening questionnaire will however be further investigated in a prospective clinical trial assessing the use of combinatorial systemic anti-cancer therapy to treat MBO.

In conclusion, the data reported in the study suggest that four deteriorating, clinical symptoms correlate with the presence of radiologically confirmed MBO due to ovarian cancer. It is envisaged that this tool may be used in the future to assess patients as part of routine outpatient clinic follow-up in order to identify those at low, moderate and high risk of MBO, thereby prompting earlier investigations and/or therapeutic intervention to abort the development of MBO and improve the morbidity associated with ovarian cancer.

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