

**Improving Ovarian Cancer Care
Along The Disease Trajectory:
From Prevention to Disease Management**

by

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i. Abstract

The overarching objective of this thesis was to investigate key clinical care questions along the ovarian cancer disease trajectory and formulate strategies to improve care provision. This thesis focused on three time points on the trajectory: *i*) cancer prevention; *ii*) tolerability of experimental treatment at disease recurrence; and *iii*) development of malignant bowel obstruction.

For women at high risk of developing ovarian cancer, such as those with a germline *BRCA1* or *BRCA2* mutation (*gBRCA1/2_{mut}*), risk-reducing salpingo-oophorectomy (RRSO) is the most effective preventative method and recommended by peak bodies. RRSO involves complete resection of the ovaries and fallopian tubes up to the insertion into the cornua of the uterus. The resection of the fallopian tubes is necessary as it is known that *BRCA1*- and *BRCA2*-associated gynaecologic cancers appear to originate in the fimbrial end of the fallopian tubes rather than the ovaries, even though they have been typically labelled as “serous ovarian cancer”. Previous research had raised concerns that the quality of RRSO surgery and associated pathology evaluation performed in Australasian women had been suboptimal prior to 2008. I therefore undertook an investigation of the quality of contemporary RRSO and compared it with data from the historical research, examining the clinical predictors of RRSO quality. Across 78 institutions in Australia and New Zealand, a total of 164 study participants had RRSO performed and the quality of RRSO, in particularly the related pathology examination, had improved significantly compared to the previous report. The proportions of women who received adequate surgery and pathology evaluation were 99% and 66% respectively, compared to 91% and 23%, respectively ($P < 0.001$) in the previous study. Implementable clinical strategies to potentially further improve quality were identified and included *i*) to direct RRSO referral to a gynaecologic oncologist (rather than general gynaecologist or general surgeon) and *ii*) to ensure the reporting pathologist is aware that the intent of surgery is risk-reduction in a high-risk woman, in order to prompt adequate processing and review of the RRSO specimens for occult cancer and pre-malignant lesions.

In women with *gBRCA1/2_{mut}* who undergo RRSO, whether hysterectomy should be performed at the time of RRSO to prevent uterine cancer was controversial. I therefore investigated the incidence of uterine cancer for Australasian *gBRCA1/2_{mut}* carriers. Of the 828 eligible women identified from a prospective multi-institutional follow up study (kConFab), there were five cases of uterine cancer. Compared to the expected incidence in the Australian population, the standardised incidence ratio (SIR) was 2.45 (95%Ci: 0.80-5.72; $P = 0.11$). All five cases were of

endometrioid adenocarcinoma histology and importantly, none had serous histology. Of those cases, three had a history of breast cancer and exposure to tamoxifen, a known risk factor for uterine cancer. Therefore, this finding did not justify the need for routine hysterectomy at the time of RRSO to reduce uterine cancer incidence in Australasian *gBRCA1/2_{mut}* carriers.

Disease progression in women with advanced ovarian cancer typically involves the omentum and peritoneum which causes abdominal symptoms. The goal of systemic treatment is to improve symptoms and delay further disease progression. Therefore, it is crucial that we consider the burden of treatment-related toxicities particularly in evaluation of novel drugs. Phase I clinical trials typically would include patients with different solid tumour types and are primarily intended to assess the safety and tolerability of investigational agents. Using the National Cancer Institute Phase I database, I performed a retrospective analysis of the adverse events (AEs) reported in women with gynaecological cancers compared to patients with other cancer types. Patients enrolled in the 150 phase I trials identified were divided into three groups to allow comparison; *i*) females with gynaecological cancers (n=685); *ii*) females with non-gynaecological cancers (n=1698); and *iii*) males with cancers (n=1886). Of those females with gynaecological cancers, the majority had ovarian cancer (n=527, 77%) followed by cervical cancer (n=76, 11%) and uterine cancer (n=72, 11%). Overall, females with gynaecological cancers were reported to have a significantly greater number of AEs during treatment (mean, 17.1 vs 14.7 vs 13.5, $P<0.001$), despite being similar at baseline (mean 7.0 vs 7.4 vs 7.0, $P=0.09$). In terms of AE severity, the main difference was a higher prevalence of grade 2 AEs reported in women with gynaecological cancers (mean 4.6 vs 3.9 vs 3.5). The five most prevalent AEs in women with gynaecological cancers were nausea (n=617, 90%), fatigue (n=587, 86%), anaemia (n=381, 56%), anorexia (n=357, 52%) and vomiting (n=355, 52%). These findings highlighted the need to improve the management for low-grade AEs in particular abdominal-related AEs for women with gynaecological cancers being treated on clinical trials. The inclusion of specific supportive care protocols/strategies into clinical trial protocols will better address symptom burden and improve quality of life.

Malignant bowel obstruction (MBO) is a common complication for women with recurrent ovarian cancer that causes protracted and debilitating symptoms. Recognising variation in clinical practice and the unmet need for evidence-based treatment, I conducted a literature review to summarise current treatment strategies for MBO in women with advanced gynaecological cancers from a multidisciplinary perspective. A pilot interprofessional MBO program was developed by the MBO

working group (which I co-led with Dr Stephanie Lheureux) and implemented in June 2016 at Princess Margaret Cancer Centre to support women who had, or were at risk, of developing MBO. The integrated model of care consisted of: *i*) standardised MBO symptom triage tools; *ii*) establishment of MBO multidisciplinary case conferences; *iii*) consensus on MBO care algorithms for in-patients and out-patients; *iv*) development of patient education materials for MBO; and *v*) prompt access to allied health professionals and supported advanced care planning.

To assess the impact of the interprofessional MBO program, I reviewed all consecutive patients presenting with MBO from April 2014 to March 2018 (i.e. before and after the implementation of the program) and compared their outcomes. Of the 169 patients included, the majority (n=124, 73%) had recurrent ovarian cancer. There were 106 patients admitted prior to implementation of the MBO program (*baseline group*) whilst 63 patients were managed under the MBO program (*MBO program group*). Overall, the MBO program group had a significantly shorter average accumulated hospital length of stay (LOS_{sum}) by 9 days (13 vs 22 days, adjusted P=0.006). Furthermore, their median overall survival post MBO diagnosis was approximately 5 months longer compared to the baseline group (243 vs 99 days, P=0.002). This retrospective, single institution study suggests a beneficial impact towards improving the complex care of women with advanced gynaecological cancers who developed MBO. Following on from this retrospective study, I developed a prospective MBO study incorporating patient reported outcomes to validate these findings, which is currently recruiting (MAMBO study, N=61/150 NCT03260647).

In conclusion, the body of academic work carried out in this thesis has addressed known clinical gaps in ovarian cancer care throughout the disease trajectory and generated specific care recommendations to guide risk-reducing surgery management, to improve symptom burden whilst undergoing cancer treatment, and to improve management of malignant bowel obstruction. Broadly, this research will help clinicians, peak bodies and health funders implement evidence-based care and institutional and national policies to facilitate better care provision for patients with ovarian cancer.

ii. Declaration

I declare that

- this thesis comprises only my original work towards the Master of Philosophy – MDHS (Medicine) except where indicated in the preface
- due acknowledgement has been made in the text to all other material used
- this thesis is fewer than the maximum word limit

Signed:

Yeh Chen Lee

iii. Preface

I, Yeh Chen Lee, was primarily and principally responsible for the following: development of the research proposal; selection of research methods; data analysis; interpretation of findings; and preparation of the thesis.

My supervisors Professor Kelly-Anne Phillips (Chapter 1-2) and Assistant Professor Stephanie Lheureux (Chapter 3-5) assisted with the concept of the projects, provided constructive feedback and critique throughout all stages of the projects, and reviewed multiple drafts of this thesis.

With regard to the publication titled “Improved quality of risk-reducing salpingo-oophorectomy in Australasian women at high risk of pelvic serous cancer”, the authors Peter Grant, Peter Russell, Belinda Kiely, Roger Milne, Sue-Anne McLachlan, Martha Hickey, Michael Friedlander and John Hopper contributed to the study design, data interpretation and manuscript writing. Charmaine Smith, Sandra Picken, and Stephanie Camm contributed to the data collection, data analysis and manuscript writing. Kelly-Anne Phillips and Mathias Bressel contributed to the study design, data collection, data analysis, data interpretation and manuscript writing.

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With regard to the manuscript in this submission titled “The evaluation of toxicities related to novel therapy in clinical trials for patients with gynaecologic cancers”, the authors Elise C. Kohn, Lawrence Rubinstein, S. Percy Ivy and Pamela Harris contributed to the study design, data interpretation and manuscript writing. Stephanie Lheureux and Lisa Wang contributed to the study design, data collection, data analysis, data interpretation and manuscript writing.

With regard to the publication titled “Malignant Bowel Obstruction in Advanced Gynecologic Cancers: An Updated Review from a Multidisciplinary Perspective”, the authors Catherine O’Brien, Tanya Chawla, Eran Shlomovitz, Sarah Buchanan, Jenny Lau, Jennifer Croke, Johane P. Allard, Preeti Dhar, Stephane Laframboise, Sarah E. Ferguson, Neesha Dhani, Marcus Butler, Pamela Ng, Terri Stuart-McEwan, Pamela Savage, Lisa Tinker, and Amit M. Oza contributed to the data review and manuscript writing. Stephanie Lheureux and Nazlin Jivraj contributed to the literature search, data review, data interpretation and manuscript writing.

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With regard to the publications titled "Improved quality of risk-reducing salpingo-oophorectomy in Australasian women at high risk of pelvic serous cancer" and "Risk of uterine cancer for *BRCA1* and *BRCA2* mutation carriers", I wish to thank Heather Thorne, Eveline Niedermayr, all the kConFab research nurses and staff, the heads and staff of the Family Cancer Clinics, and the Clinical Follow-Up Study for their contributions to this resource, and the many families who contribute to kConFab.

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vii. List of Abbreviations

Abbreviations	Terms
AE	Adverse event
ANZGOG	Australia New Zealand Gynaecological Oncology Group
ASCO	American Society of Clinical Oncology
CAHON	Chinese American Hematologist and Oncologist Network
CTCAE	Common terminology criteria for adverse events
DLT	Dose-limiting toxicity
ESMO	European Society for Medical Oncology
g <i>BRCA1/2</i> _{mut}	Germline <i>BRCA1</i> or <i>BRCA2</i> mutation
HGSOC	High grade serous ovarian cancer
kConFab	Kathleen Cuningham Foundation Consortium for Research in to Familial Breast Cancer
LOS _{sum}	cumulative length of stay
MBO	Malignant bowel obstruction
MTD	Maximal tolerated dose
NCCN	National Comprehensive Cancer Network
OCP	Oral contraceptive pill
PARPi	Poly (ADP-ribose) polymerase inhibitors
PDF	Portable document format
PRO	Patient reported outcomes
RDI	Relative dose-intensity
RRSO	Risk-reducing salpingo-oophorectomy
SEE-FIM	Sectioning and extensively examining the fimbriated end protocol
SIR	Standardized incidence ratio
STICs	Serous tubal intraepithelial carcinomas
TCGA	The Cancer Genome Atlas
TPN	Total parenteral nutrition

viii. Main Chapters

Introduction

Rationale for the Thesis

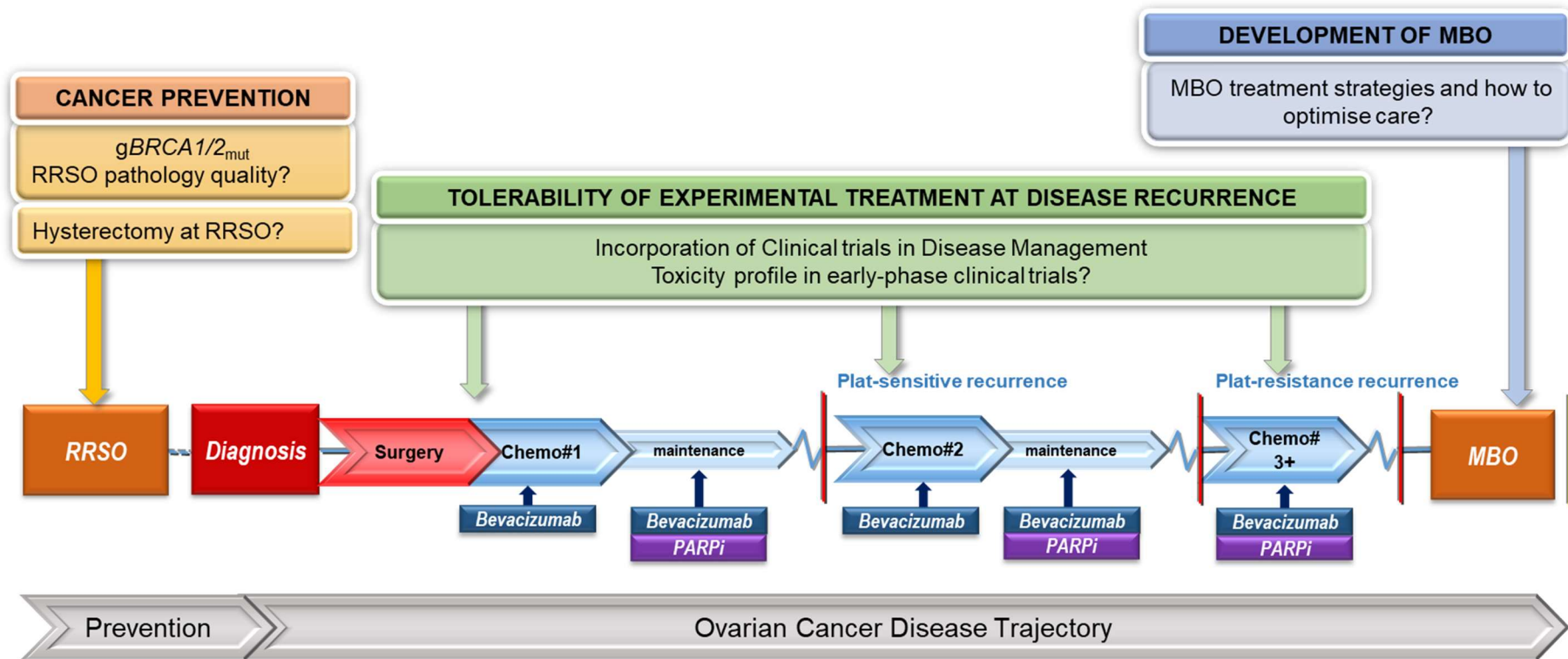
Every day in Australia, four women will be diagnosed with ovarian cancer and three will succumb to their disease.¹ High grade serous cancer is the most common ovarian cancer subtype and remains the most lethal of all gynaecological cancers - more than 50% of women will not survive beyond five years.¹ The poor survival rate is largely attributable to late-stage disease at diagnosis, high tendency for disease recurrence despite optimal first-line therapy (surgery and chemotherapy) and a paucity of effective novel agents. Almost 70% of women with ovarian cancer are diagnosed at stage III or IV disease when treatment options mainly involve cytoreductive surgery and platinum-taxane based chemotherapy.¹ The use of molecularly targeted agents, such as those targeting poly ADP-ribose polymerase (PARP) or angiogenesis, have changed the disease management paradigm in the treatment and maintenance phases,²⁻⁹ however, approximately 80% of women with advanced disease will experience disease relapse despite optimal first-line treatment.^{10,11} These episodes of disease recurrence eventually culminate in acquired chemo-resistance and often development of malignant bowel obstruction (MBO), the most frequent cause of death.^{10,12}

As shown in **Figure 1**, the research work in this thesis endeavoured to improve ovarian cancer care by focusing on current gaps in clinical practice along the disease trajectory:

- i) Cancer prevention: What was the quality of risk-reducing salpingo-oophorectomy (RRSO) in Australia and is concurrent hysterectomy at the time of RRSO warranted to reduce uterine cancer risk?
- ii) Tolerability of experimental treatment at disease recurrence: What is the toxicity profile for women with gynaecological cancers participating in early phase clinical trials in comparison to other cancer types and how might their symptom burden be improved?
- iii) Development of MBO: What are treatment strategies for MBO and how can we optimise care?

These arguably represent the most important points of disease impact for these women and thus focus on them might provide insightful knowledge for quality care provision and better outcomes.

Figure 1: Schematic presentation of the research work in this thesis to improve ovarian cancer care along the disease trajectory: from prevention to management of advanced disease



Abbreviations: *gBRCA1/2_{mut}*: germline *BRCA1* and *BRCA2* mutation carriers; RRSO: risk-reducing salpingo-oophorectomy; MBO: malignant bowel obstruction; chemo: chemotherapy; PARPi: Poly (ADP-ribose) polymerase inhibitor

Outline of Chapters

Chapter 1 focuses on ovarian cancer prevention and the quality of RRSO in Australasian women. The chapter includes a published manuscript reporting a study assessing the quality of contemporary RRSO in Australasian women at high risk of developing ovarian cancer. A total of 164 contemporary RRSOs were compared to the 201 historical RRSOs performed in the same prospective cohort study (kConFab) to evaluate whether there has been an improvement in the quality of RRSO performed over time. In addition, the clinical factors associated with improved RRSO quality were examined.

Chapter 2 reviews the risk of uterine cancer in *gBRCA1/2*_{mut} carriers and the role of concurrent hysterectomy at the time of RRSO. The chapter includes a published manuscript reporting a study investigating the risk of uterine cancer in Australasian women carrying *gBRCA1/2*_{mut} and if this risk justifies the recommendation of risk-reducing hysterectomy at the time of RRSO. A total of 828 women with *gBRCA1/2*_{mut} were prospectively followed in a large multicentre cohort study (kConFab) and the incident cases of uterine cancer were reported and discussed.

Chapter 3 reviews the role of clinical trials in assessing toxicity of novel drug therapy and evaluates the toxicity profile of women with gynaecological cancers. The chapter includes a manuscript reporting a study assessing the toxicities related to novel therapy in clinical trials for patients with gynaecological cancers. A total of 4269 patients enrolled in phase I trials from the National Cancer Institute Phase I database were analysed and their toxicity profiles were compared in three groups: *i*) females with gynaecological cancers; *ii*) females with non-gynaecological cancers; and *iii*) males with cancers.

Chapter 4 reviews what is known in the literature to guide the management of MBO. The chapter includes a published literature review of the management of MBO from a multidisciplinary perspective. It summarised therapeutic options for MBO including: surgical intervention, chemotherapy, pharmacological management, and the use of total parenteral nutrition for patients with MBO. The clinical review discussed current challenges faced in optimising treatment for MBO given the lack of quality of life data and clinical trials design that was suited to evaluate this vulnerable patient population.

Chapter 5 summarises the development of a pilot interprofessional MBO program at a large Canadian tertiary cancer centre. The program encompasses the overall setup of a dedicated MBO multidisciplinary case conference, inpatient and outpatient MBO symptom management algorithms and production of patient education materials focused on MBO. It includes a published manuscript of a study evaluating the outcomes of women with advanced gynaecological cancers who developed MBO, before and after implementation of a pilot interprofessional MBO program. A total of 169 women with MBO were evaluated to assess their overall length of stay in hospital for MBO management, MBO treatment received and overall survival post MBO diagnosis.

Chapter 6 summarises the principal findings of this thesis as a whole. It includes a general discussion of the research work undertaken, their implications for clinical practice and potential future research.

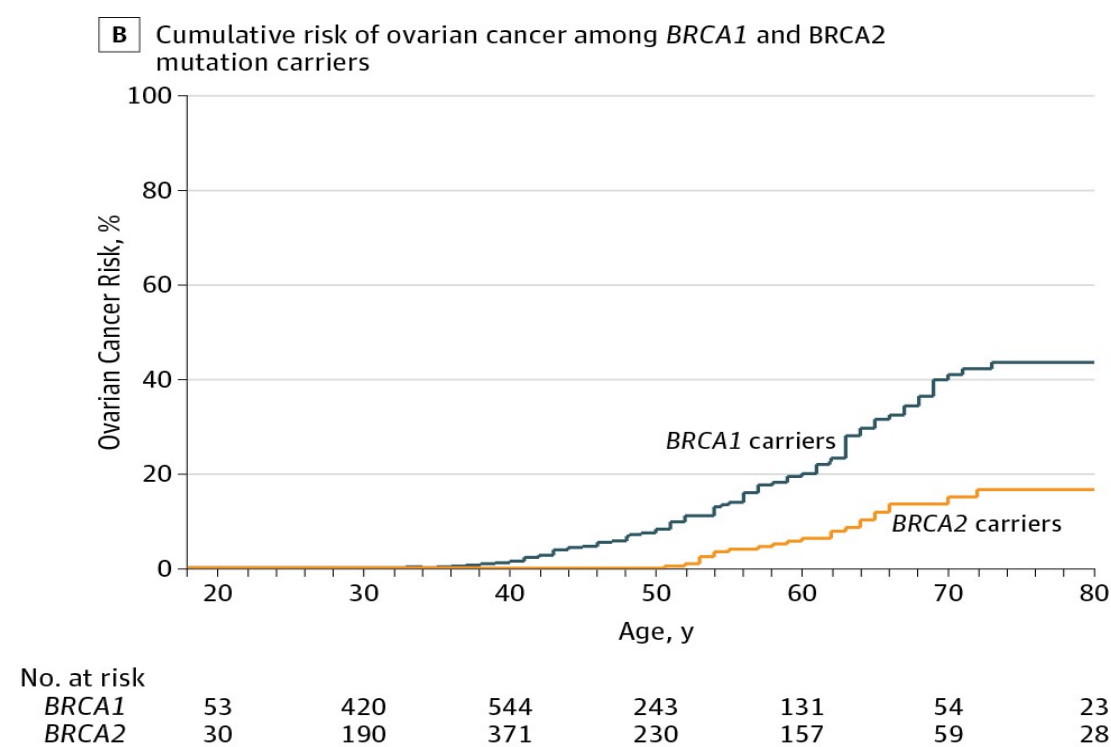
Chapter 1: Cancer Prevention - Risk-Reducing Salpingo-Oophorectomy in Women at High Risk

1.1 Ovarian Cancer Prevention

Women carrying a germline *BRCA1* or *BRCA2* mutation (*gBRCA1/2_{mut}*) are at high risk of developing high grade serous ovarian cancer (HGSOC), with an average lifetime cumulative risk of 44% and 17%, respectively.¹³ Similarly, women with a strong family history of HGSOC, but no identified *gBRCA1/2_{mut}* are also at increased risk of developing HGSOC, as compared to the general population ovarian cancer risk of approximately 1%.^{1,14}

Ovarian cancer screening is ineffective, potentially harmful, and not recommended in Australia even for women at high risk of the disease.^{1,15-18} Given the poor prognosis of HGSOC and the lack of effective screening strategies, prevention is critical.¹⁹ Risk-reducing salpingo-oophorectomy (RRSO) is the most effective method and is associated with a 79-85% reduction in ovarian cancer risk,²⁰⁻²² and is therefore recommended by the U.S. National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO) and Cancer Australia.^{15,18,23} This form of surgery, as its names implies, incorporates the removal of both ovaries and fallopian tubes up to their insertion into the cornua of the uterus. The recommended timing of RRSO is based on mutation profile and family history. The estimated cumulative risk of ovarian cancer is low up to age 40 years for *BRCA1* mutation carriers, and up to age 50 years for *BRCA2* mutation carriers (**Figure 2**).¹³ Cancer Australia recommends consideration of RRSO by *gBRCA1/2_{mut}* at around the age of 40 years and an individualized discussion for other women at high risk in the absence of a gene mutation.¹⁵ More recent recommendations from EviQ, ESMO and NCCN suggest RRSO from the age of 35 upon completion of childbearing for *BRCA1* mutation carriers, and between age 40 to 45 for *BRCA2* mutation carriers.^{16,18,23} The use of the oral contraceptive pill (OCP) is another risk-reducing method for women who elect against RRSO or to postpone it, however with a lower ovarian cancer risk reduction up to 50% and concern about the impact of the OCP on breast cancer risk in these high-risk women.²⁴⁻²⁷

Figure 2. Cumulative risk of ovarian cancer among germline *BRCA1* and *BRCA2* mutation carriers (Kuchenbaecker, JAMA 2017)¹³



As clinicians advocate the benefits of RRSO, it is equally important to ensure the surgery and associated pathology examination are performed in accordance with the recommended standard guidelines.^{15,28} Despite being a preventative procedure, occult cancers or precursor lesions can be detected in a subset of these women; highlighting the importance of comprehensive histopathologic assessment of these specimens. Cancer precursor lesions, called serous tubal intraepithelial carcinomas (STICs), and occult carcinomas can be detected at the time of RRSO; and have been reported to have a prevalence of 2-8% and 3-6%, respectively.²⁹⁻³³ The variation of the reported rates are likely due to the differences in underlying ovarian cancer risk of the study participants (such as proportions of g*BRCA1/2*_{mut} carriers or age), type of surgery and more importantly, variation in the extent of pathological evaluation of the RRSO specimen. As per the recommendation by Cancer Australia, the minimum pathological examination of RRSO specimens that might be considered adequate is the complete embedding of all excised ovarian and fallopian tube tissue.¹⁵ More recently, the use of the Sectioning and Extensively Examining the Fimbriated End Protocol (SEE-FIM) for RRSO is recommended as standard clinical practice by EviQ and NCCN.^{28,34} The SEE-FIM protocol stipulates that all tissue be serially sectioned and submitted, with particular examination to the fimbriated ends of the fallopian tube.^{34,35}

The quality of RRSO and associated pathology performed in Australasian women prior to year 2008 was reported to be suboptimal.¹⁷ In this prior study, 91% of women had adequate surgery and only 23% had adequate pathology according to the minimum definitions of Cancer Australia guidelines stated above.¹⁷ The study findings were likely to be representative of Australia-wide clinical practice as the study participants were enrolled via 24 Family Cancer Clinics across Australia and New Zealand in a prospective, multi-institutional study resource called the Kathleen Cuninghame Foundation Consortium for Research into Familial Breast Cancer (kConFab). Therefore, the research work described in this chapter aimed to investigate the quality of contemporary RRSO, using the kConFab study resource, to determine whether it had improved, and to identify clinical factors associated with adequate RRSO that might suggest interventions to further improve adequacy.

1.2 PDF of Manuscript 1: Improved Quality of Risk-reducing Salpingo-oophorectomy in Australasian Women at High Risk of Pelvic Serous Cancer

The research work for chapter 1 was presented as an oral abstract at the 6th International Symposium on Hereditary Breast and Ovarian Cancer (Montreal, Canada, 2016) and published in the peer-reviewed and indexed journal *Familial Cancer* (2017).³⁶ The manuscript has been distributed to all kConFab members.

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Improved quality of risk-reducing salpingo-oophorectomy in Australasian women at high risk of pelvic serous cancer

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Abstract

Objectives The quality of risk-reducing salpingo-oophorectomy (RRSO) performed in Australasian women was previously reported to be suboptimal. Here we describe the quality of RRSO performed since 2008 in women enrolled in the same cohort and determine whether it has improved.

Design Prospective cohort study of women at high risk of pelvic serous cancer (PSC) in kConFab. Eligible women had RRSO between 2008 and 2014 and their RRSO surgical and pathology reports were reviewed. “Adequate” surgery and pathology were defined as complete removal and paraffin embedding of all ovarian and extra-uterine fallopian tube tissue, respectively. Associations between clinical factors and “adequate” pathology were assessed using logistic regression. Data were compared with published cohort data on RRSO performed prior to 2008 using Chi square test.

Results Of 164 contemporary RRSOs performed in 78 centres, 158/159 (99%) had “adequate” surgery and 108/164 (66%) had “adequate” pathology. Surgery performed by a gynaecologic oncologist rather than a general gynaecologist [OR 8.2, 95%CI (3.6–20.4), $p < 0.001$], surgery without concurrent hysterectomy [OR 2.5, 95%CI (1.1–6.0), $p = 0.03$], more recent year of surgery [OR 1.4, 95%CI (1.1–1.8), $p = 0.02$], and clinical notation that indicated high risk [OR 19.4, 95%CI (3.1–385), $p = 0.008$] were independently associated with “adequate” pathology. Both surgery and pathology were significantly more likely to be “adequate” ($p < 0.001$) in this contemporary sample.

Conclusion The quality of RRSOs has significantly improved since our last report. Surgery by a gynaecologic oncologist who informs the pathologist that the woman is at high risk for PSC is associated with optimal RRSO pathology.

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Introduction

The increased risk of invasive pelvic serous cancer (PSC) of the ovary, fallopian tube or peritoneum in women carrying a germline mutation in the *BRCA1* and *BRCA2* cancer predisposition genes is well established, with a lifetime risk ranging from 31–54% and 6–27%, respectively [1–5]. The term “pelvic serous cancer” is used because the majority of *BRCA1*- and *BRCA2*-related gynaecologic cancers appear to originate in the fimbrial end of the fallopian tube rather than the ovary, although they have typically been labelled as “serous ovarian cancer” at diagnosis [6]. Women with a strong family history of “serous ovarian cancer”, but no identified *BRCA1* or *BRCA2* mutation in the family, also have elevated risks of PSC [7].

Given the poor prognosis of PSC and the lack of effective screening strategies [8], risk-reducing salpingo-oophorectomy (RRSO) is recommended by peak bodies, such as the U.S. National Comprehensive Cancer Network (NCCN) [9] and Cancer Australia [10], for all women at high risk of PSC. Cancer Australia recommends consideration of RRSO by *BRCA1* and *BRCA2* mutation carriers at around the age of 40 years and individualised discussion for other women at high risk in the absence of a gene mutation [10]. RRSO has proven efficacy, with a reduction in “ovarian cancer” risk of 79–85% [11–13], and it is associated with lower cancer-specific and all-cause mortality in *BRCA1* and *BRCA2* mutation carriers [13, 14]. This form of surgery, as its names implies, incorporates the removal of both ovaries and fallopian tubes up to their insertion into the cornua of the uterus.

Despite being a prophylactic procedure, occult carcinomas or cancer precursor lesions such as serous tubal intraepithelial carcinomas (STICs) are detected in a subset of RRSO specimens; between 2.6–6% [15–17] and 2–8% [18, 19], respectively. The variability between studies is likely due to differences in the underlying PSC risk of the study participants, extent of surgery undertaken and, importantly, variation in the extent of pathological evaluation of the RRSO specimen. The minimum pathological examination of RRSO specimens that might be considered adequate is the complete embedding of all excised ovarian and fallopian tube tissue [10]. Notably, a more detailed pathological examination protocol, such as the SEE-FIM protocol, results in an approximately fourfold increase in detection of precursor lesions or occult carcinoma [20]. More recently, the use of the SEE-FIM protocol for RRSO

specimens is recognised as the recommended standard clinical practice [9].

Our previous report on RRSOs, performed in 201 Australian women prior to the year 2008, found 91% had adequate surgery and only 23% had adequate pathology according to the minimum definitions above [21]. Here we aimed to determine the quality of contemporary RRSO surgery and pathology, performed between 2008 and 2014, to compare it with our previous findings, and to identify any factors associated with adequate RRSO. We hypothesised that, due to increased awareness of the issues discussed above, the adequacy of surgery and pathology would have improved.

Methods

Participants were a subset of females enrolled in the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab), a resource of data and biospecimens from multiple-case breast and ovarian cancer families [22]. Eligibility criteria for kConFab are available on the website [22]. Families are recruited via 24 Family Cancer Clinics (FCCs) in Australia and New Zealand. At enrolment, blood is drawn for possible future *BRCA1* and *BRCA2* mutation analysis. Epidemiology and family history questionnaires are also completed. A mailed, self-administered follow-up questionnaire is used to collect updated information on cancer events, epidemiological and lifestyle factors and uptake of preventative strategies on all female participants every 3 years [23]. Self-reported cancer events and surgeries, including risk-reducing surgeries, are verified with pathology and surgical reports obtained from the treating institutions. Notably, these institutions are often not linked with the FCC that the woman attended for her cancer risk assessment and genetic testing. All cohort participants provide written informed consent and the cohort study has ethics approval at all recruitment sites.

Women enrolled in kConFab were eligible for this study if they had RRSO performed between 2008 and 2014, had a deleterious mutation in *BRCA1* or *BRCA2* or, in the absence of a mutation, if they had a family history of PSC (limited to first- or second-degree relatives). Women were excluded if they were non-carriers within a *BRCA1* or *BRCA2* mutation-carrying family, if they had a personal history of gynaecological cancer or metastatic cancer or if their RRSO pathology report was not available.

Date of surgery, type of surgery, name of surgeon, whether clinical notes on the pathology report indicated the woman was at high risk of PSC and the extent of surgery and pathology were abstracted from the RRSO surgical and pathology reports, and supplemented by self-reported information from the 3-yearly follow-up questionnaire.

“Adequate” surgery was defined as complete removal of all ovarian and extra-uterine fallopian tube tissue, whilst “adequate” pathology was defined as paraffin embedding of all removed ovarian and tubal tissue. The same definition from the previous published study was used to allow direct comparison of the RRSO performed prior to 2008 to this study sample, however whether the pathology procedures reported were consistent with the SEE-FIM protocol [20] was also recorded. The presence of occult carcinoma and/or STIC at RRSO was also abstracted from pathology reports. The duration of follow-up was calculated from the date of RRSO to the date of death or last contact.

Surgeon type was determined using Australian Health Practitioner Regulation Agency (APHRA) data [24]. Clinicians were defined as general surgeons if they were registered fellows of the Royal Australasian College of Surgeons; general gynaecologists if they were registered fellows of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG), or gynaecologic oncologists if they also held certification in gynaecologic oncology of the RANZCOG. For New Zealand practitioners not listed on APHRA, categorisation was based on information from their institutional website profile.

All statistical analyses were performed in R (version 3.1.1; R Development Core Team 2009). Logistic regression was used to assess the association between adequacy of pathological examination of the RRSO specimen and the presence of clinical notes indicating high risk, year of surgery, surgeon type, history of breast cancer, risk status (family history vs. *BRCA* mutation), type of surgery (abdominal vs. laparoscopic) and hysterectomy. Published data for 201 RRSOs, performed between 1999 and 2008 in women in the kConFab cohort [21], were pooled together with data from this study population to examine the change in the prevalence of “adequate” surgery and pathology over this whole period. Chi square test was used to compare categorical variables and *t* test was used to compare age between the RRSOs performed before January 1st, 2008 and those performed after that date. All *p* values were two-sided, and those less than 0.05 were considered statistically significant.

Results

From January 2008 to December 2014, a total of 284 women from the kConFab follow-up study underwent RRSO. Of those, 120 women were excluded (37 had no documented gene mutation and no family history of PSC in a first or second-degree relative; 34 were non-carriers within a *BRCA1* or *BRCA2* mutation-carrying family; 24 carried a variant of uncertain significance in *BRCA1* or

Table 1 Characteristics of RRSOs performed in 2008–2014

Characteristic	Number (%) or median [range]
Risk status	
<i>BRCA1</i> mutation	80 (49)
<i>BRCA2</i> mutation	48 (29)
<i>BRCA1</i> and <i>BRCA2</i> mutation	2 (1)
Strong family history of ovarian cancer	34 (21)
Age at RRSO	
All participants	48.5 [30–77]
<i>BRCA1</i> mutation carriers	46.5 [32–73]
<i>BRCA2</i> mutation carriers	46 [30–77]
<i>BRCA1</i> + <i>BRCA2</i> mutation carriers	39.5 [39–40]
Strong family history of ovarian cancer	53.5 [39–70]
Location where RRSO was performed	
Australian Capital Territory	6 (4)
New South Wales	39 (25)
Northern Territory	1
Queensland	17 (10)
South Australia	36 (22)
Tasmania	5 (3)
Victoria	27 (17)
Western Australia	21 (13)
New Zealand	12 (7)
Prior history of breast cancer	
Yes	66 (40)
No	98 (60)

RRSO risk-reducing salpingo-oophorectomy

BRCA2; 20 had a previous history of gynaecological cancer or metastatic cancer; 4 carried a mutation in the *p53* or *ATM* genes; and for 1 the pathology report could not be obtained). Therefore, 164 women were eligible who underwent RRSO at 78 institutions across Australia and New Zealand; their clinical characteristics are shown in Table 1. Of those, 80 carried a *BRCA1* mutation, 48 carried a *BRCA2* mutation, 2 carried both a *BRCA1* and a *BRCA2* mutation, and the remaining 34 had a family history of PSC in a first or second degree relative but no *BRCA1* or *BRCA2* mutation. The median ages at RRSO for women carrying *BRCA1* or *BRCA2* mutation were 46.5 years and 46 years respectively. Whilst the median age at RRSO for women with family history of PSC was 53.5 years. Forty percent of women had a history of invasive breast cancer.

Surgical and pathological characteristics are detailed in Table 2. Most surgery was performed laparoscopically (74%). The majority of RRSOs were performed by gynaecologic oncologists (58%), or general gynaecologists (40%). In most cases, pathology laboratories (93%) were notified that this was an RRSO for a woman at high risk. Forty-five percent (*n* = 73) of the study participants had a

Table 2 Surgical and pathological characteristics of RRSOs performed in 2008–2014

Surgical and pathological characteristics	Number (%)
Year of surgery	
2008	44 (27)
2009	47 (29)
2010	22 (13)
2011	22 (13)
2012	14 (9)
2013	13 (8)
2014	2 (1)
Type of surgery	
Laparoscopic	118 (74)
Abdominal	34 (21)
Laparoscopic converted to abdominal	5 (3)
Vaginal	3 (2)
Unknown	4 ^a
Hysterectomy at time of RRSO	
Yes	73 (45)
No	91 (55)
Surgeon type	
Gynaecologic oncologist	94 (58)
General gynaecologist	65 (40)
General surgeon	3 (2)
Unknown	2 ^b
Clinical notes indicating high risk on pathology report	
Yes	153 (93)
No	11 (7)
Occult carcinoma at RRSO	3 (1.8)
Precursor lesion (STIC) at RRSO	2 (1.2)

RRSO risk-reducing salpingo-oophorectomy, STIC serous tubal intraepithelial carcinoma

^aFive surgical reports were unavailable but in one case the hospital discharge summary was available and provided detail about type of surgery

^bFive surgical reports were unavailable, but for three cases the surgeon name was available in self-reported information from the 3-yearly follow-up questionnaire

hysterectomy at the time of RRSO; of these most ($n=46$) indicated the intention of the procedure was to reduce uterine cancer risk, 11 indicated it was to treat benign issues such as fibroids or prolapse, 2 indicated it was because they planned to have tamoxifen for breast cancer treatment or prevention, and 14 did not provide a rationale.

All but one case (99%) were deemed to have had adequate surgery, whilst 66% of the pathological evaluations were deemed adequate. Compared to RRSOs performed prior to 2008 in women enrolled in the kConFab cohort study, where adequate surgery occurred in 91% cases and adequate pathology in 23% cases [21], there was significant improvement ($p<0.001$, Fig. 1). Of note, pathology

processing procedures consistent with the SEE-FIM protocol were reported in only eight cases. Personal and surgical characteristics were similar between RRSOs performed prior to 1st January 2008 and after, with the exception of the presence of clinical notes indicating high risk, which rose from 80 to 93% ($p<0.001$, Table 3).

The one case of inadequate surgery was performed in 2009 by a general gynaecologist. The patient carried a *BRCA1* mutation and she had bilateral oophorectomy but the left fallopian tube and part of the right fallopian tube were left in situ. Given that only one case had inadequate surgery, analysis for clinical predictors for adequate surgery was not undertaken.

From the multivariable model (Table 4), the presence of clinical notes to indicate the woman was high risk ($p=0.008$), surgery performed by gynaecologic oncologist ($p<0.001$), surgery without concurrent hysterectomy ($p=0.03$), and more recent year of surgery ($p=0.02$), were independent predictors of adequate pathology.

There were three cases (1.8%) of occult carcinoma identified at RRSO (Table 5). Two carried a *BRCA1* mutation and one carried a *BRCA2* mutation. They underwent RRSO at the age of 42, 53 and 63 years, respectively. No specific macroscopic findings were noted at surgery but microscopic cancer was found on pathology. Two proceeded to have formal staging laparotomy and were found to have Stage IA (serous adenocarcinoma) and Stage IIIA (mixed müllerian) cancers respectively; the latter went on to have chemotherapy and subsequently died 5 years later. The patient who did not undergo formal staging laparotomy had poorly differentiated adenocarcinoma involving the right ovary without capsular breach.

There were two cases (1.2%) of STIC found at RRSO (Table 5), both based on morphology, and immunostaining for p53 and Ki67 as recommended by Visvanathan et al. [25]. The first case was a *BRCA1* mutation carrier, age 61 years, whilst the second case was a *BRCA2* mutation carrier, age 56 years. The foci of STIC were found at the fimbrial end of the fallopian tube in both cases.

The median duration of follow-up after RRSO was 40 months (range, 1–82 months). Subsequent to RRSO, there was one reported case of primary peritoneal cancer 3 years later. She carried a *BRCA1* mutation and had RRSO performed in 2008. Surgical and pathology evaluation at RRSO for this case were classified as adequate according to the study definitions, but of note the SEE-FIM protocol was not used to examine the RRSO specimen.

Discussion

This is a prospective, multi-institutional study that investigated the practice of RRSO in Australasian women at high

Fig. 1 Quality of RRSO Performed in Australasian women at high risk of ovarian cancer before and after January 1st 2008

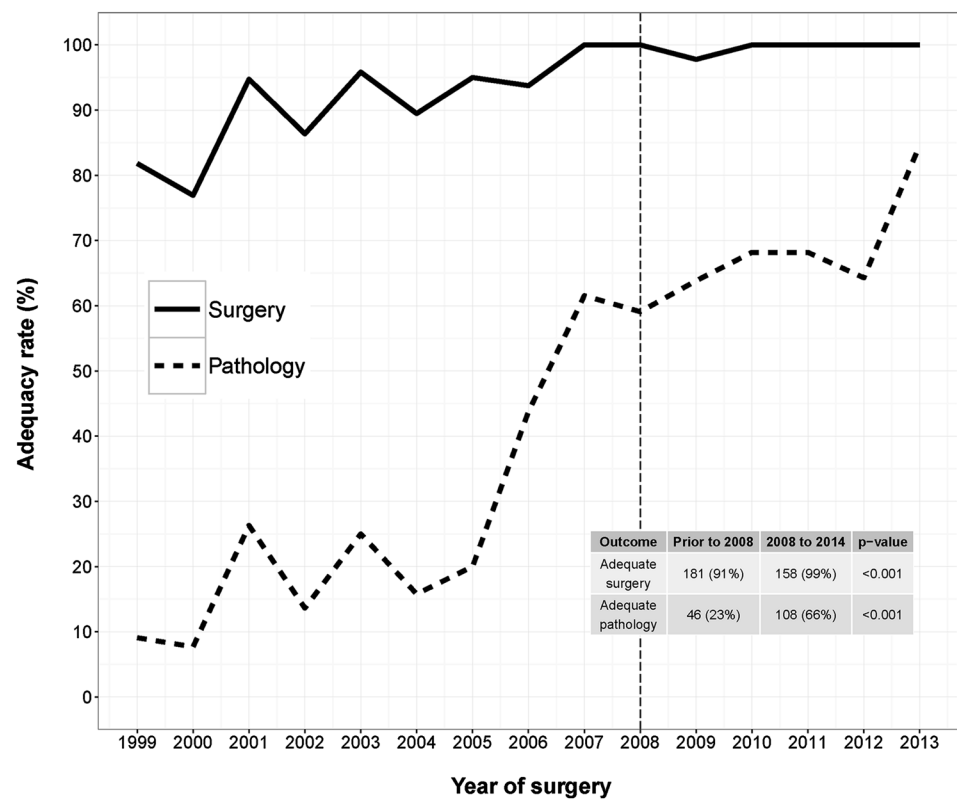


Table 3 Comparison of characteristics of RRSOs performed before and after 1st January 2008

Clinical variable	1998–2007 (n = 201)	2008–2015 (n = 164)	p value
Risk status			
BRCA1 mutation carrier	102 (50%)	80 (49%)	0.17
BRCA2 mutation carrier	71 (36%)	48 (29%)	
BRCA1 and BRCA2 mutation carrier	0 (0%)	2 (1%)	
Strong family history of PSC	28 (14%)	34 (21%)	
Age at completion of RRSO			
Mean (SD)	48.59 (8.79)	49.01 (9.66)	0.67
Median (range)	48 (30–77)	48.5 (30–77)	
Type of surgery			
Abdominal	53 (26%)	34 (21%)	0.30
Laparoscopic	137 (68%)	118 (74%)	
Hysterectomy			
No	108 (54%)	91 (55%)	0.79
Yes	93 (46%)	73 (45%)	
Surgeon type			
General surgeon	11 (6%)	3 (2%)	0.16
General gynaecologist	85 (42%)	65 (40%)	
Gynaecologic oncologist	105 (52%)	94 (58%)	
Unknown	0	2	
Clinical notes indicating high risk			
No	37 (20%)	11 (7%)	<0.001
Yes	151 (80%)	153 (93%)	
Pathology report unavailable	13	0	

RRSO risk-reducing salpingo-oophorectomy, PSC pelvic serous cancer

Table 4 Multivariable analysis of factors associated with adequate pathology

Variable	Statistic	Pathology evaluation		Univariable		Multivariable (full model)		Multivariable (final model)	
		Adequate	Inadequate	OR (95% CI)	p-value	OR (95% CI)	p value	OR (95% CI)	p value
History of breast cancer	No	67 (68%)	31 (32%)	1		1			
	Yes	41 (62%)	25 (38%)	0.8 (0.4–1.5)	0.41	1.3 (0.5–3.2)	0.59		
Clinical notes indicating high risk	No	1 (9%)	10 (91%)	1		1		1	
	Yes	107 (70%)	46 (30%)	23.3 (4.3–433)	0.003	10.5 (1.5–215.6)	0.04	19.4 (3.1–385)	0.008
Risk status	Family history	16 (47%)	18 (53%)	1		1			
	Mutation carrier	92 (71%)	38 (29%)	2.7 (1.3–6.0)	0.01	2.9 (0.9–9.3)	0.07		
Surgeon type ^a	General gynaecologist	29 (45%)	36 (55%)	1		1		1	
	Gynaecologic oncologist	79 (84%)	15 (16%)	6.5 (3.2–14.0)	<0.001	11.2 (4.3–32.5)	<0.001	8.2 (3.6–20.4)	<0.001
Year of surgery ^a	2008	26 (59%)	18 (41%)	1.20 (0.98–1.49) ^b	0.09	1.4 (1.0–1.8) ^b	0.03	1.4 (1.1–1.8) ^b	0.02
	2009	30 (64%)	17 (36%)						
	2010	15 (68%)	7 (32%)						
	2011	15 (68%)	7 (32%)						
	2012	9 (64%)	5 (36%)						
	2013	11 (85%)	2 (15%)						
Type of surgery	Abdominal	18 (53%)	16 (47%)	1		1			
	Laparoscopic	83 (70%)	35 (30%)	2.1 (1.0–4.6)	0.06	2.1 (0.7–6)	0.17		
Hysterectomy	Yes	44 (60%)	29 (40%)	1		1		1	
	No	64 (70%)	27 (30%)	1.6 (0.8–3.0)	0.18	2.7 (1.1–7.3)	0.04	2.5 (1.1–6.0)	0.03

^aAdequacy of surgeries performed by general surgeon ($n = 3$) and surgeries performed in 2014 ($n = 2$) were not assessed given small numbers^bOdds ratio per year**Table 5** Features of occult carcinomas and precursor lesions detected following RRSO

Age at RRSO (years)	Gene mutated	Surgery	Pathological findings			
			Extend of evaluation	Ovary	Fallopian tube	Other findings (peritoneum)
42	<i>BRCA1</i>	TAH+BSO	Adequate	2 mm invasive adenocarcinoma on right side	Benign	Benign
53	<i>BRCA1</i>	BSO	Adequate	Benign	2 mm invasive adenocarcinoma on left side	Small malignant deposit in paratubal soft tissue
63	<i>BRCA2</i>	LAVH+BSO	Adequate	Invasive mixed mullerian tumour in both ovaries	Invasive tumour on left side	Omental and pelvic side wall deposits Benign uterus findings No lymph node involvement (0/6) Peritoneal fluid cytology positive for malignancy
61	<i>BRCA1</i>	BSO	Adequate	Benign	STIC, focus at fimbria on left side	Benign
56	<i>BRCA2</i>	TAH+BSO	Adequate	Benign	STIC, <1 mm at fimbria on left side	Benign

TAH total abdominal hysterectomy, BSO bilateral salpingo-oophorectomy, LAVH laparoscopic-assisted vaginal hysterectomy, STIC serous tubal intraepithelial carcinoma

risk of PSC. Overall, the quality of contemporary RRSO has improved significantly since the period of our previous report ($p < 0.001$). Reassuringly, in this contemporary study, all women but 1 (99%) had adequate surgery, although only 66% had adequate pathological evaluation. The incidence of occult carcinoma (1.8%) and STICs (1.2%) was relatively low.

The improvement in the prevalence of adequate pathology, to 66% from 23%, likely reflects better awareness among the medical community. Three modifiable clinical factors were associated with adequate pathology. First, pathology evaluations completed on RRSOs performed by gynaecologic oncologists were more likely to be adequate. This may be related to the fact that most gynaecologic oncologists practice in tertiary centres where multi-disciplinary surgico-pathological meetings are the norm rather than reflecting differences in surgical expertise. Because of its subspecialist nature, gynaecologic oncologists usually practice in large hospitals with academic pathology departments or refer specimens to private laboratories with known gynaecological pathology expertise. Secondly, communication from the surgeon to the pathology department that the woman was at high risk of PSC was also independently associated with adequate pathology. Most women who undergo gynaecological surgery do so for benign gynaecologic reasons, so minimal pathology examination of their operative specimen sometimes occurs. Our finding highlights the importance of communicating to the pathologist that the specimen has been taken from a woman at high risk. Directing the specimen to be assessed by an experienced gynaecologic pathologist may also facilitate quality pathology processing. Our finding that women who did not have concurrent hysterectomy were more likely to have adequate pathology may suggest that, when there is a greater load of operative specimen, examination of the crucial components (tubes and ovaries) is less likely to occur. There remains uncertainty whether the risk of uterine cancer is higher than normal in mutation carriers [26, 27] and Australian guidelines are silent on the issue of risk-reducing hysterectomy in this setting [10]. In this study 45% of women having RRSO underwent concurrent hysterectomy and most indicated the intention of this procedure was to reduce uterine cancer risk.

The definition of adequate pathology in our study, although consistent with Cancer Australia guidelines [10], is very much a minimum standard for RRSO pathology assessment. Increasingly more detailed pathologic examination of RRSO specimens, such as the SEE-FIM protocol [20], is considered optimal. SEE-FIM stipulates that all tissue be serially sectioned and submitted and the fimbriated ends of the fallopian tube are sectioned parallel to the long axis of the fallopian tube to maximize the exposure of tubal epithelium available for histological examination.

In this study, very few RRSO specimens underwent the SEE-FIM protocol [20]. A finding of occult carcinoma is of clinical importance as it necessitates further management to ensure complete cancer staging and consideration of chemotherapy, whilst clinical management of STICs is more controversial [18]. The clinical importance of finding occult carcinoma also reinforces the commitment to detailed examination of the RRSO specimens in the laboratory. However, SEE-FIM is labour-intensive and therefore may be difficult to implement into practice in a nationwide setting. In our study, 164 RRSOs were performed at 78 centres across Australia and New Zealand; so most centres performed only 1–3 of the 164 study cases each, raising the question of whether this type of specialised surgery and pathology would be better centralised in higher volume, tertiary or academic centres. Centralisation of care would also potentially provide additional advantages with respect to optimal management of cases with occult carcinoma and STICs.

The incidence of occult carcinoma and STICs in our study was relatively low, 1.8% and 1.2%, respectively. These rates may be an underestimate as one-third of cases had inadequate pathology and even in the cases with adequate pathology, there would be variation in the extent of pathology assessment. One woman developed primary peritoneal cancer during follow-up, she was reported to have adequate surgery and pathology at RRSO. This is similar to the reported low rates in other series [12, 28]. Notably the median follow-up (40 months) of our study may be too short for cancers to manifest.

Three occult carcinomas were detected in women over 40 years old, consistent with prior data linking increasing age and risk [20]. Two cases of STICs and one case of occult carcinoma were found only within fallopian tubes, consistent with the fallopian tube being the origin for *BRCA1* and *BRCA2* mutation-associated tumours [6, 29].

Our study does have some limitations. Although the RRSOs and diagnoses of occult carcinomas/STICs were verified, we relied on the information detailed in operation and pathology reports to determine the adequacy of surgery and pathology. In cases where there was insufficient detail from the surgical report, we assumed that the tissue received by pathologist represented the tissue removed by the surgeon. We did not undertake central pathology review of RRSO specimens. In addition, we are unable to differentiate a gynaec-pathologist to a general pathologist.

This multicentre study is likely to provide a true reflection of current RRSO practice for high risk women in Australia and New Zealand. Women who elect RRSO deserve high quality surgery and pathology that will reduce their future risk of gynaecological cancer. Our study findings suggest that clinicians might consider referring their high risk women to a gynaecologic oncologist for their RRSO,

or at least should consider discussing the requirements for optimal pathology with the woman's chosen surgeon. Surgeons performing RRSO should inform the pathologist about the intent of surgery to prompt adequate processing of these specimens or even consider specifying an experienced gynaecologic pathologist to examine these specimens. RRSO is an effective way of preventing PSC in the vast majority of women who are identified to be at high risk of the disease, so further quality improvements should be a priority.

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Chapter 2: Cancer Prevention - Risk of Uterine Cancer for Germline *BRCA1* and *BRCA2* Mutation Carriers

2.1 Risk of Uterine Cancer for Germline *BRCA1* and *BRCA2* Mutation (g*BRCA1/2*_{mut}) Carriers

One finding from the research work in chapter 1 was that 45% (n=73/164) of women underwent concurrent hysterectomy with risk-reducing salpingo-oophorectomy (RRSO).³⁶ Further analysis of the reason for hysterectomy showed that most indicated that the intention was to prevent uterine cancer. At the time, there was ongoing debate whether hysterectomy to reduce uterine cancer risk should be performed at the time of RRSO, as the risk of uterine cancer associated with g*BRCA1/2*_{mut} was unclear with conflicting reports from various studies (**Table 1**).³⁷⁻⁴¹

Most studies have suggested a two-fold increase in uterine cancer risk compared to general population, and only two of these studies showed a statistically significant result.^{38,40,41} Retrospective data from the Breast Cancer Linkage Consortium showed an increased risk of uterine cancer for germline *BRCA1* mutation carriers (RR=2.65; 95%CI=1.69-4.16; p<0.001).³⁸ This finding was supported by prospective data from Segev *et al.*, showing a standardised incidence ratio (SIR) of 1.91 (95%CI=1.06-3.19; p=0.03) for germline *BRCA1* mutation carriers;⁴¹ however, there was a stronger association with a SIR of 4.14 (95%CI=1.92-7.78; P=0.001) when women were stratified according to tamoxifen use; a known risk factor for uterine cancer in postmenopausal women.⁴¹ A recent report by Shu *et al.*, suggested a much higher relative risk but only specifically of the serous uterine cancer subtype and the findings were statistically significant for germline *BRCA1* mutation carriers only; whilst the overall risk of uterine cancer for g*BRCA1/2*_{mut} following RRSO did not appear to be increased (p=0.06).⁴² Australian and international guidelines were silent on the issue of whether concurrent hysterectomy should be recommended,^{15,43} which prompted the research work outlined in chapter 2 investigating the risk of uterine cancer for Australasian g*BRCA1/2*_{mut} carriers compared with the general population. Performing abdominal hysterectomy at the time of RRSO increases peri-operative complications and morbidity, although the extent of this increase is difficult to define and is less with minimally invasive surgery.^{44,45} Therefore, better understanding of uterine cancer risk in the Australasian g*BRCA1/2*_{mut} carriers would help guide clinicians and their patients in the decision-making process weighing up potential benefits against the peri-operative risk.

Table 1. Risk of uterine cancer in germline *BRCA1* or *BRCA2* mutation carriers

First author (year of publication)	Number of mutation carriers	Number of uterine cancer cases	Risk of uterine cancer	Confidence interval; P value
Analysis of germline <i>BRCA1</i> and <i>BRCA2</i> mutation carriers combined				
Reitsma (2012) ⁴⁰	315	2	SIR 2.13	95%CI 0.24-7.69; P=0.27
Segev (2013) ⁴¹	4456	17	SIR 1.87	95%CI 1.13-2.94; P=0.01
Shu (2015) ⁴²	1083	8	O/E 1.9	lower 97.5%CI 0.82; one-sided P=0.07
Analysis of germline <i>BRCA1</i> mutation carriers only				
Thompson (2002) ³⁸	2245	11	RR 2.65	95%CI 1.69-4.16; P<0.001
Segev (2013) ⁴¹	3536	13	SIR 1.91	95%CI 1.06-3.19; P=0.03
Shu (2015) ⁴²	627	4*	O/E 22.6	lower 97.5%CI 4.92; one-sided P<0.0001
Analysis of germline <i>BRCA2</i> mutation carriers only				
BCLC (1998) ³⁹	471	5	RR 1.25	95%CI 0.46-3.37; P=NP
Segev (2013) ⁴¹	920	4	SIR 1.75	95%CI 0.55-4.23; P=0.2
Shu (2015) ⁴²	453	1*	O/E 6.5	lower 97.5%CI 0.2; one-sided P=0.14

*serous histology subtype only

Abbreviations: SIR, standardised incidence ratio; O/E, Observed to expected incidence ratio; RR, relative risk; CI, confidence interval; NP, not provided;

2.2 PDF of Manuscript 2: Risk of Uterine Cancer for *BRCA1* and *BRCA2* Mutation Carriers

The research work for chapter 2 was accepted as a poster presentation and awarded a merit award at the 2016 ASCO Annual Meeting (Chicago, United States). I was also invited to give an oral presentation of this research work at the 2017 Australia New Zealand Gynaecological Oncology Group (ANZGOG) Annual Scientific Meeting (Melbourne, Australia) and awarded the ANZGOG travel fellowship to attend the meeting. The research was subsequently published in the peer-reviewed and indexed journal *European Journal of Cancer* (2017).⁴⁶

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Original Research

Risk of uterine cancer for *BRCA1* and *BRCA2* mutation carriers



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KEYWORDS

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Abstract Background: Whether *BRCA1* and *BRCA2* mutation carriers have a clinically relevant elevated risk of uterine cancer has implications for risk-reducing surgery.

Aim: This multicentre, prospective cohort study assessed uterine cancer risk for mutation carriers compared with the general population.

Methods: Eligible mutation carriers were enrolled in the Kathleen Cunningham Foundation Consortium for Research into Familial Breast Cancer (kConFab) cohort study, had a uterus present and no history of uterine cancer at cohort entry. Epidemiological, lifestyle and clinical data were collected at cohort entry and updated three-yearly. Cancer events were verified using pathology reports. Follow-up was censored at death or last contact. Relative risk of uterine cancer was estimated using the standardised incidence ratio (SIR), with the expected number of cases determined using population-based data for Australia.

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Results: Of 1,111 mutation carriers in kConFab, 283 were excluded due to prior hysterectomy ($N = 278$), prior uterine cancer ($N = 2$) or being non-residents ($N = 3$). After a median follow-up of 9.0 years, five incident uterine cancers were reported in the 828 eligible women (419 had prior breast cancer and 160 had prior tamoxifen use), compared to 2.04 expected ($SIR = 2.45$; 95% confidence interval [CI]: 0.80–5.72; $P = 0.11$). In 438 *BRCA1* mutation carriers and 390 *BRCA2* mutation carriers, three and two incident cases of uterine cancer were reported, respectively, compared to 1.04 expected ($SIR = 2.87$; 95% CI: 0.59–8.43; $P = 0.18$) and 0.99 expected ($SIR = 2.01$; 95% CI: 0.24–7.30; $P = 0.52$), respectively. All cases were endometrioid subtype, International Federation of Gynaecology and Obstetrics stage I–II disease. No serous uterine cancers were reported.

Conclusions: Our findings are consistent with those from most other reports and do not support routine risk-reducing hysterectomy for *BRCA1* and *BRCA2* mutation carriers.

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1. Introduction

Women carrying a deleterious germline *BRCA1* or *BRCA2* mutation are recommended to undergo risk-reducing salpingo-oophorectomy (RRSO) by peak bodies, such as the United States National Comprehensive Cancer Network [1] and Cancer Australia [2]. This is due to the established elevated risk of high grade pelvic serous cancer in these women, with a lifetime cumulative risk ranging from 6% to 54% [3–6]. RRSO is associated with an 85% reduced risk of pelvic serous cancer in mutation carriers [7–9] and reduced cancer-specific and all-cause mortality [7,10]. The term ‘pelvic serous cancer’ is used because the majority of *BRCA1* and *BRCA2* mutation-associated gynaecologic cancers (ovarian, fallopian tube or primary peritoneal) appear to arise from the fallopian tube fimbriae rather than the ovary, although they have often been labelled as ‘ovarian cancer’ at diagnosis [11–13].

An ongoing area of controversy is whether risk-reducing hysterectomy should be performed at the time of RRSO [14,15]. The risk of uterine cancer for *BRCA1* and *BRCA2* mutation carriers remains unclear with conflicting findings in different studies possibly confounded by prior tamoxifen use. Although, most studies have suggested about a two-fold increase in risk relative compared to the general population [16–19], the findings were statistically significant in only two of these studies [16,17]. A recent study suggested a much higher relative risk (RR) but only when the analysis was limited to the serous uterine cancer subtype and the finding was only statistically significant for *BRCA1* mutation carriers [19].

Performing abdominal hysterectomy in conjunction with RRSO is associated with higher risk of complications compared to RRSO alone, although the complications are less with minimally invasive surgery [20,21]. Therefore, a more precise estimate of the incidence and RR of uterine cancer for *BRCA1* and *BRCA2* mutation carriers would help guide clinicians in weighing up risk-

reduction benefits against the peri-operative and long-term morbidity [22]. We sought to assess, using data from a prospective cohort study, whether *BRCA1* and *BRCA2* mutation carriers are at increased risk of developing uterine cancer compared to the general population. If mutation carriers are at significantly increased risk of developing uterine cancer, there may be an added benefit of prophylactic hysterectomy at the time of RRSO.

2. Patients and methods

2.1. Participants

Eligible women were a subset of females enrolled in the Kathleen Cuninghame Foundation Consortium for Research into Familial Breast Cancer (kConFab), a resource of data and biospecimens from multiple-case breast and ovarian cancer families [23–25]. Eligibility criteria for kConFab are detailed on the website [23]. Families are recruited via 24 familial cancer clinics in Australia and New Zealand. At enrolment, blood is drawn for *BRCA1* and *BRCA2* mutation analysis.

Women were included in this study if they were *BRCA1* or *BRCA2* mutation carriers, had a uterus present and no previous history of uterine cancer at cohort entry. Women were excluded if they did not reside in Australia or New Zealand.

2.2. Data collection

Information on cancer events, epidemiological and lifestyle factors, hysterectomy and uptake of cancer risk-reduction and screening strategies were collected by interview at cohort entry and then every 3 years using a mailed questionnaire [26]. Self-reported cancer events and surgeries, including risk-reducing surgeries, were verified using pathology reports obtained from the treating institutions. Information about date of surgery and histologic subtype of cancer were abstracted from

the pathology report. The International Classification of Disease for Oncology was used to classify the histologic subtype of uterine cancer.

2.3. Statistical analysis

Indirect standardisation was applied to calculate the standardised incidence ratio (SIR) for incident uterine cancer using all Australians as the standard population. The number of observed cases in the cohort was obtained for each 5-year age group and calendar-year for the period of interest. Person-years at risk of uterine cancer were calculated for each cohort member from the date of cohort entry to the date of death, date of last contact or date of hysterectomy for non-malignant reason. The expected number of cases for each 5-year age group, sex and calendar-year was calculated as person-years at risk multiplied by the incidence reported by the Australian Institute of Health and Welfare.

The SIR was calculated as the total number of observed cases divided by the total number of expected cases, where the total number was the summation over all age groups, sex and calendar-years. Exact 95% confidence intervals (CIs) were calculated based on assuming that the total number of observed cases is a Poisson count and the expected value is known without error. *P*-values were calculated as twice the one-sided Poisson probabilities of observing a more extreme count.

3. Results

A total of 1,111 *BRCA1* and *BRCA2* mutation carriers with systematic prospective follow-up were identified. Of those, 283 women (25%) were excluded as they had hysterectomy (for non-malignant reasons) before cohort entry (*N* = 278), prior history of uterine cancer (*N* = 2) or they did not reside in Australia or New Zealand (*N* = 3). The remaining 828 women, 438 (53%) *BRCA1* mutation carriers and 390 (47%) *BRCA2* mutation carriers, were prospectively followed from cohort entry for a median of 9.0 years.

Most women were Caucasian (97%) with a median age of 43 years (mean age 44 years, interquartile range [IQR], 34–52 years) and median body mass index (BMI) of 24 kg/m² (IQR, 22–28 kg/m²) at cohort entry, as shown in Table 1. Half of the women had a diagnosis of breast cancer and 19% had taken tamoxifen. Approximately one-quarter (26%) of the women had undergone hysterectomy after enrolment at a median age of 46 years (IQR, 41–54).

Five incident cases of uterine cancer were reported in *BRCA1* and *BRCA2* mutation carriers, compared to 2.04 expected, based on the incidence in the general population (SIR = 2.45; 95% CI: 0.80–5.72; *P* = 0.11), as shown in Table 2. Three *BRCA1* mutation carriers

Table 1

Sample characteristics (*N* = 828).

	<i>N</i> (%)
Mutation status	
<i>BRCA1</i> mutation	438 (53)
<i>BRCA2</i> mutation	390 (47)
Ethnicity	
Caucasian	801 (97)
Indian/Southern Asian/Chinese	9 (1)
Other/not reported	18 ^a (2)
Country of residence	
Australia	785 (95)
New Zealand	43 (5)
Age (years) at cohort enrolment	43 (34–52) ^b
BMI (kg/m ²) at cohort enrolment	24 (22–28) ^b
Breast cancer diagnosis	
Yes	419 (51)
No	409 (49)
Prior tamoxifen exposure	
Yes	160 (19)
No	668 (81)
Hysterectomy for non-malignant reason after enrolment	214 (26)
Age at hysterectomy	46 (41–54) ^b

Abbreviations: *N* = number; BMI = body mass index.

^a Includes four Aboriginal/Torres Strait islanders.

^b Median (interquartile range).

Table 2

Incidence of uterine cancer during prospective follow-up in *BRCA1* and *BRCA2* mutation carriers as compared to general population.

Mutation type	Number	Uterine cancer cases	Expected incidence	SIR	95% CI (<i>P</i> -value)
<i>BRCA1</i> or <i>BRCA2</i>	828	5	2.04	2.45	0.80–5.72 (<i>P</i> = 0.11)
<i>BRCA1</i>	438	3	1.04	2.87	0.59–8.43 (<i>P</i> = 0.18)
<i>BRCA2</i>	390	2	0.99	2.01	0.24–7.30 (<i>P</i> = 0.52)

Abbreviations: SIR = standardised incidence ratios; CI = confidence interval.

developed uterine cancer compared to the 1.04 expected (SIR = 2.87; 95% CI: 0.59–8.43; *P* = 0.18). Two *BRCA2* mutation carriers developed uterine cancer compared to 0.99 expected (SIR = 2.01; 95% CI: 0.24–7.30; *P* = 0.52).

Notably, all five cases of uterine cancer were of endometrioid subtype and International Federation of Gynaecology and Obstetrics Stage I–II disease: two cases of grade I, one of grade II and two cases of grade III disease (Table 3). For one of the cases with grade III disease, the pathology report specifically indicated no serous cancer component. No cases of serous uterine cancer were reported. Three cases were women carrying a *BRCA1* mutation and the remaining two cases carried a *BRCA2* mutation. Four of the five women were obese (BMI > 30 kg/m²) and developed uterine cancer after menopause. Three of the five women had been treated for breast cancer and all three had taken tamoxifen.

Table 3
Characteristics of uterine cancer cases ($N = 5$).

Mutation status	Ethnicity	Age at UC diagnosis	UC subtype	UC FIGO stage, grade immunohistochemistry	Breast cancer diagnosis (age)	Tamoxifen exposure	BMI (kg/m ²) at enrolment	F/U from enrolment (years)	F/U from UC diagnosis (years)	Status at last F/U
1 <i>BRCA1</i>	Caucasian	68	Endometrioid adenocarcinoma	Stage IA, grade III ER 33%, PR 33%	Yes (51)	Yes	32	15	4	Alive
2 <i>BRCA1</i>	Caucasian	57	Endometrioid adenocarcinoma	Stage II, grade III ^a ER/PR status NA	Yes (46)	Yes	24	12	9	Alive
3 <i>BRCA1</i>	Caucasian	53	Endometrioid adenocarcinoma	Stage IA, grade I ER 70%, PR 70%	No	No	53	9	3	Alive
4 <i>BRCA2</i>	Caucasian	71	Endometrioid adenocarcinoma	Stage IA, grade I ER/PR status NA	Yes (56)	Yes	31	6	2	Deceased
5 <i>BRCA2</i>	Caucasian	44	Endometrioid adenocarcinoma	Stage II, grade II ER >90%, PR>90%	No	No	43	12	7	Alive

UC, uterine cancer; BMI, body mass index; F/U, follow-up; FIGO, International Federation of Gynaecology and Obstetrics; ER, oestrogen receptor; PR, progesterone receptor; NA, not assessed.

^a Pathology report specified FIGO grade III endometrioid adenocarcinoma with no elements of clear cell or serous differentiation.

4. Discussion

Our study investigated the incidence of uterine cancer for *BRCA1* and *BRCA2* mutation carriers residing in Australia and New Zealand. Compared to the general population, women with a deleterious *BRCA1* or *BRCA2* mutation had about 2.5-fold increased risk of developing uterine cancer, although this was not statistically significant. More specifically the SIR was 2.87 for *BRCA1* mutation carriers and 2.01 for *BRCA2* mutation carriers. This finding is consistent with the literature which generally describes a two-fold increase in risk (Table 4). A large retrospective study from the Breast Cancer Linkage Consortium showed an increased risk of uterine cancer for *BRCA1* mutation carriers (RR = 2.65; 95% CI: 1.69–4.16; $P < 0.001$), but not

BRCA2 mutation carriers (RR = 1.25; 95% CI: 0.46–3.37; P -value not reported) [16,27]. Another retrospective study from the Netherlands reported an SIR for uterine cancer in *BRCA1* and *BRCA2* mutation carriers combined of 2.13 (95% CI: 0.24–7.69; $P = 0.27$) [18]. In a North American prospective study, *BRCA1* and *BRCA2* mutation carriers had a SIR for uterine cancer of 1.91 (95% CI: 1.06–3.19; $P = 0.03$) and 1.75 (95% CI: 0.55–4.23; $P = 0.2$), respectively [17]. The increased uterine cancer risk in *BRCA1* mutation carriers in that study was higher for women who had taken tamoxifen; the SIR was 4.14 (95% CI: 1.92–7.87) for women who received tamoxifen and 1.67 (95% CI: 0.81–3.07) for women who did not receive tamoxifen.

More recently, Shu *et al.* reported on uterine cancer risk in *BRCA1* and *BRCA2* mutation carriers followed

Table 4
Studies reporting incidence of uterine cancer in women carrying a *BRCA1* or *BRCA2* germline mutation.

Study	Number of women	Mutation status		Median/mean age at enrolment, (years)	Median/mean follow-up, (years)	Number of uterine cancer cases	Expected number of cases	Relative risk estimate
		<i>BRCA1</i>	<i>BRCA2</i>					
Shu <i>et al.</i> , 2016	1083 ^a	627	453	45.6 IQR 40.9–52.5	5.2	8	4.3	O/E 1.9 95% CI 0.8–3.7, $P = 0.09$
Segev <i>et al.</i> , 2013	4456	3536	920	42.7 IQR NR	5.7	17	9.06	SIR 1.87 95% CI = 1.13 –2.94, $P = 0.01$
Reitsma <i>et al.</i> , 2013	315	201	144	50 IQR 32–78	6	2	0.94	SIR 2.13 95% CI = 0.24 –7.69, $P = 0.27$
Thompson <i>et al.</i> , 2002	2245	2245	–	NR	NR	11	3.94	RR 2.65 95% CI = 1.69 –4.16, $P < 0.001$
The BCLC, 1999	471	–	471	NR	NR	5	3.35	RR 1.25 95% CI = 0.46 –3.37, P -value NR

IQR, interquartile range; O/E, Observed to expected ratio; SIR, standardised incidence ratio; RR, relative risk; NR, not reported; CI, confidence interval.

^a Three of 1083 women carried both a *BRCA1* and a *BRCA2* mutation.

prospectively after RRSO without hysterectomy. The observed to expected uterine cancer ratio was 2.1 (95% CI: 0.7–4.9; $P = 0.09$) for *BRCA1* mutation carriers and 1.6 (95% CI: 0.3–4.6; $P = 0.30$) for *BRCA2* mutation carriers [19]. However, when analysed by tumour subtype, there was a statistically significantly increased risk of serous carcinomas in *BRCA1* mutation carriers (observed to expected ratio of 22.2; 95% CI: 6.1–56.9; $P < 0.001$). Specifically, there were five incident cases of serous/serous-like endometrial carcinoma that occurred after RRSO in this cohort study of 1,083 women, four in *BRCA1* mutation carriers and one in *BRCA2* mutation carriers. In contrast, there were no incident cases of serous endometrial carcinoma in our study; all five cases of uterine cancer in our cohort of 828 women were endometrioid endometrial carcinomas. Similar findings were reported in a retrospective study from the Netherlands, which described two incident cases of endometrioid endometrial carcinoma and no incident cases of serous endometrial carcinoma in 345 *BRCA1* and *BRCA2* mutation carriers [18].

For post-menopausal women, tamoxifen is known to increase risk of uterine cancer [28], particularly high-risk subtypes of uterine cancer such as grade III endometrioid, serous or clear cell carcinoma [29–32]. This may explain the increased risk of serous endometrial carcinomas reported by Shu *et al.*, where three of the five serous carcinomas occurred in women with prior breast cancer who had used tamoxifen. Interestingly, three out of five cases of uterine cancer in our study occurred in women with prior breast cancer who had also used tamoxifen and two of these three developed grade III tumours, although none of the five uterine cancer cases were of serous histology. The two incident cases of uterine cancer reported by Reitsma *et al.* [18] were both endometrioid subtype, and among the small number of pathology reports (6/17) retrieved in the study by Segev *et al.* [17], all cases showed endometrioid histology. All of these studies included women with history of breast cancer and tamoxifen exposure. In these studies, the inclusion of women who have previously received tamoxifen complicates the interpretation of the results, as the SIRs are calculated based on the general population risk of uterine cancer, and in the general population a much smaller proportion of women would be expected to have been exposed to tamoxifen.

Our study, despite having a large number of mutation carriers being followed prospectively, had limited power due to the relatively small number of events observed. The mean age of uterine cancer diagnosis in the general population is approximately 70 years [33] so the relatively young age of the women in our cohort (mean, 44 years) was a contributing factor to this. However, the average age of women in our cohort is comparable to that of other studies (Table 4) and our study has longer median follow-up of 9 years [18,19]. In our single-arm

cohort study, we observe no serous cases among those diagnosed with uterine cancer. A case–control design may be required to overcome this limitation and better assess the previously reported association of *BRCA1* and *BRCA2* mutation and serous endometrial carcinoma. One of the strengths of our study is the systematic prospective follow-up of women after cohort enrolment and access to diagnostic pathology reports from treating institutions, although central pathology review was not performed.

The addition of concomitant abdominal hysterectomy to RRSO increases peri-operative complications and morbidity, although the extent of this increase is difficult to define and is less with minimally invasive surgery [34,35]. When considering whether to perform a hysterectomy at the time of RRSO in a *BRCA1* or *BRCA2* mutation carrier, there should be careful consideration of the potential risks and benefits, particularly given the low incidence of uterine cancer. One argument in favour is that concomitant hysterectomy facilitates the use of unopposed, oestrogen only hormone replacement therapy (HRT) after RRSO, if HRT is required. Women with an intact uterus require combination HRT because unopposed oestrogen increases uterine cancer risk, but combined HRT may further increase the risk of breast cancer [36] which is important for *BRCA1* and *BRCA2* mutation carriers who have a high-background breast cancer risk. Although hysterectomy eliminates the risk of uterine cancer in mutation carriers who choose tamoxifen for treatment or prevention of breast cancer, the use of an aromatase inhibitor instead of tamoxifen is an alternative approach and is not associated with uterine cancer [37–40]. Precisely estimating the true increased risk, if any, of uterine cancer in *BRCA1* and *BRCA2* mutation carriers will need a large multi-national study or meta-analysis; in the meantime, we do not believe that routine hysterectomy at RRSO is justified in the vast majority of *BRCA1* and *BRCA2* mutation carriers.

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Conflict of interest statement

None declared.

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Chapter 3: Tolerability of Experimental Treatment at Disease Recurrence

3.1 Improving Our Understanding of Toxicity Profile Specific to Women with Gynaecological Cancers

Systematic evaluation of novel therapeutic agents through clinical trials has enabled the development of effective cancer treatments that improve outcomes. Following the Cancer Genome Atlas (TCGA) molecular characterisation of solid tumours including gynaecological cancers, many different targeted therapies have been developed and some are now approved for use in routine treatment of gynaecological cancers, such as bevacizumab and poly ADP ribose polymerase (PARP) inhibitors.⁴⁷ To better understand the toxicity profile of these investigational agents, stringent protocols were in place to report all adverse events (AEs) that occurred in patients participating in all phases of clinical trials. Phase I clinical trials are primarily intended to assess the safety and tolerability of investigational agents.⁴⁸⁻⁵⁰ In addition, the value of phase I trials in predicting AEs and accurately defining drug-related toxicity profiles has been well documented.⁵¹

Patients with advanced gynaecological cancers enrolled in clinical trials may be at increased risk of certain toxicities given the extent of peritoneal disease and prior treatments (cytoreductive surgery, chemotherapy and radiotherapy). An archetypal example would be the phase II study investigating BKM120, a PI3K inhibitor, in endometrial cancer (NCT01397877) which was prematurely discontinued due to the unfavourable toxicity profile observed.⁵² Although BKM120 was established as tolerable with an acceptable safety profile at the estimated maximal tolerated dose (MTD) of 100mg/day in general tumour types, the same dose resulted in high toxicities in women with recurrent endometrial cancer.^{53,54} The safety profile of BKM120 was subsequently found to vary significantly depending on the primary tumour site and even histological subtype.⁵² Therefore, research work outlined in this chapter investigated AEs documented in phase I studies of patients across all tumour types, and compared the toxicity profile of patients with gynaecological cancers *versus* other tumour types. The aim of the study was to identify prevalent AEs experienced in women with gynaecological cancers and thereby inform the design of prospective studies and supportive care of these women in clinical practice.

As per the National Comprehensive Cancer Network, the best management for any cancer patient is in a clinical trial; participation in clinical trials is especially encouraged.²⁸ Systematic evaluation of new therapeutic agents through clinical trials has enabled the development of novel treatment agents to improve cancer outcomes and patient care. In addition to evaluating the therapeutic efficacy of the investigated agents, we gain insight into the associated toxicities and disease symptom burden using a standardised reporting tool known as the common terminology criteria for adverse events (CTCAE).

3.2 PDF of Manuscript 3: The Evaluation of Toxicities Related to Novel Therapy in Clinical Trials for Patients with Gynaecologic Cancers

The research work in chapter 3 was presented as a poster presentation at the 2018 ASCO Annual Meeting and I was awarded the Young Investigator Award by the Chinese American Hematologists and Oncologists Network (CAHON). The manuscript was subsequently published in the peer-reviewed and indexed journal *Cancer* (2020).

Manuscript

Lee YC, Wang L, Kohn EC, Rubinstein L, Ivy SP, Harris P, Lheureux S. Evaluation of toxicities related to novel therapy in clinical trials for patients with gynaecologic cancers. *Cancer*. doi.10.1002/cncr.32783. 2020.

Evaluation of Toxicities Related to Novel Therapy in Clinical Trials for Women With Gynecologic Cancer

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BACKGROUND: Women with gynecologic cancer may be at increased risk for adverse events (AEs) due to peritoneal disease burden and prior treatment (surgery, chemotherapy, and pelvic radiotherapy). This study compared the toxicity profiles of patients with and without gynecologic cancer enrolled in phase 1 trials. **METHODS:** This was a retrospective analysis of the National Cancer Institute phase 1 database for all trials enrolling 1 or more patients with gynecologic cancer over 2 decades (1995-2015). Clinical parameters collected included demographics, cancer history, trial information, AEs, and responses. AEs (according to the Common Terminology Criteria for Adverse Events) were documented for each patient during treatment, and they were counted once and analyzed on the basis of the highest grade and drug attribution. Multiple regression models were used to compare AEs at the baseline and during treatment. **RESULTS:** A total of 4269 patients enrolled in 150 trials were divided into 3 groups: 1) women with gynecologic cancer ($n = 685$), 2) women with nongynecologic cancer ($n = 1698$), and 3) men with cancer ($n = 1886$). The median age was 58 years. The mean number of total AEs reported during treatment was highest for women with gynecologic cancer (17.1 vs 14.7 vs 13.5; $P < .001$), even though they were similar at the baseline (7.0 vs 7.4 vs 7.0; $P = .09$). The mean number of drug-related AEs was also highest for women with gynecologic cancer (8.3 vs 6.9 vs 6.2; $P < .001$). Grade 3 to 5 AEs were similar (2.3 vs 2.3 vs 2.1); however, grade 2 AEs were more frequent in women with gynecologic cancer (4.6 vs 3.9 vs 3.5). Treatment discontinuations due to AEs were similar (9% vs 9% vs 10%). **CONCLUSIONS:** Women with gynecologic cancer experienced more frequent low-grade AEs during treatment, and this warrants attention to support their symptom burden. Study dose management should be considered for recurrent grade 2 AEs, particularly during continuous therapy. *Cancer* 2020;0:1-7. © 2020 American Cancer Society.

KEYWORDS: clinical protocols, drug therapy, ovarian neoplasms, toxicity.

INTRODUCTION

The systematic evaluation of therapeutic agents through clinical trials has enabled the development of effective cancer treatments that improve patient outcomes. Following The Cancer Genome Atlas molecular characterization of solid tumors, including gynecologic cancers, many different targeted therapies have been developed, and some, such as bevacizumab and PARP inhibitors, are now approved for use in the routine treatment of gynecologic cancers.¹ Stringent protocols are in place to report all adverse events (AEs) that occur in patients participating in all phases of clinical trials so that we can better understand the toxicity profiles of these investigational agents. Phase 1 clinical trials are primarily intended to assess the safety and tolerability of investigational agents.²⁻⁴ The value of phase 1 trials in evaluating AEs and accurately defining drug-related toxicity profiles has been well documented.⁵

Patients with advanced gynecologic cancers who are enrolled in clinical trials may be at increased risk for certain toxicities because of the extent of peritoneal disease and prior combined treatments, including extensive cytoreductive surgery, chemotherapy, and radiotherapy. An example would be the phase 2 study investigating BKM120, a PI3K inhibitor, for endometrial cancer, which was prematurely discontinued because of an unfavorable toxicity profile observed in this specific population.⁶ Although BKM120 was established as tolerable with an acceptable safety profile at the estimated maximal tolerated dose of 100 mg/d,^{7,8} the same dose resulted in toxicities for women with recurrent endometrial cancer that were not reported in the initial phase 1 trial. Depending on the primary tumor sites and even histological subtypes, the safety profile of BKM120 was found to vary significantly.⁶ Therefore, our study investigated AEs documented in phase 1 studies of patients across all tumor types, and we compared the toxicity profiles of patients with gynecologic cancers with those of patients with other tumor types. In addition, we explored whether there were sex differences in toxicity profiles.⁹ We aimed to identify the prevalent AEs experienced

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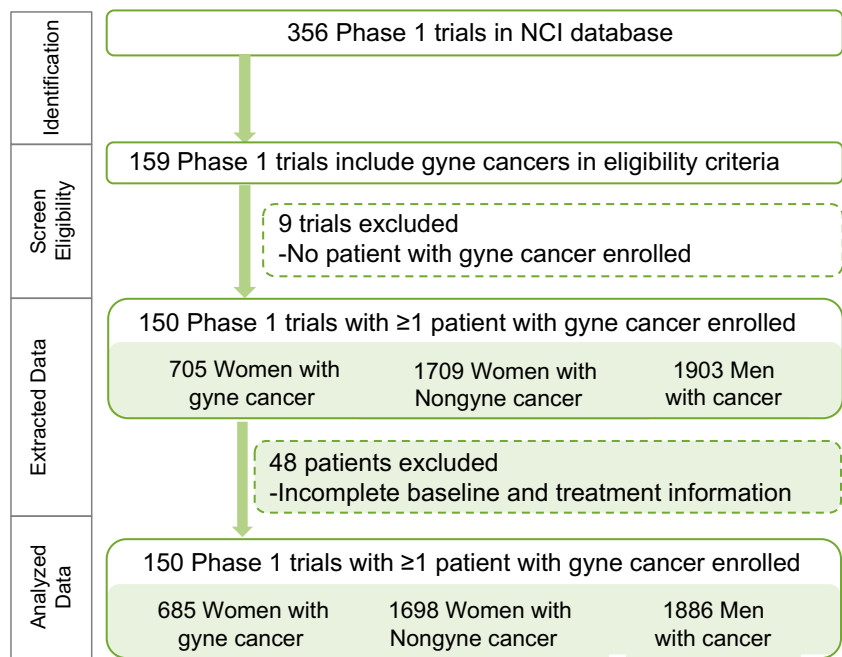


Figure 1. Study trial and patient selection flow diagram. Gyne indicates gynecologic; NCI, National Cancer Institute; nongyne, nongynecologic.

by women with gynecologic cancers and thereby inform the design of prospective studies and supportive care for these women in clinical practice.

MATERIALS AND METHODS

A retrospective review was conducted of all patients who participated in phase 1 studies from 1995 to 2015 via the National Cancer Institute (NCI) database. The NCI database includes each and every phase 1 trial conducted by NCI investigators since the inception of the database in the year 1995. The lead principal investigator and local investigators for each phase 1 trial registered in the database were responsible for enrolling patients who met the eligibility criteria. In this review, only trials that enrolled at least 1 patient with gynecologic cancer were selected to compare their toxicity profile with those of other cancer types. These patients had received at least 1 dose of the clinical trial drug, and their data entry was complete from the baseline to the end of trial participation. The unlinked data set was extracted by the NCI with unique patient number labeling. The study eligibility was determined and the data were analyzed by Y.C.L. and L.W. Senior authors E.C.K. and S.L. oversaw all study procedures and verified that the data presented were accurate. All selected patients were divided into 3 groups: 1) women with gynecologic cancers, 2) women with nongynecologic

cancers, and 3) men with cancers. Women with gynecologic cancers were defined as women who had ovarian/fallopian tube/peritoneal cancers, uterine cancers, cervical cancers, or vulvar cancers. All patients had been consented for data collection for their respective clinical trial and registered in the NCI database using an unlinked dataset. NCI consent templates have addressed future unspecified use of unlinked data. Accordingly, this research pertained to an NCI exempt research category.

Information on phase 1 trials, patient demographics, cancer histories, treatments, and AEs was extracted for analysis. Clinical data included the age at study enrollment, sex, primary cancer diagnosis, histological subtype, prior lines of treatment, treatment cycles, AEs, best treatment response, duration on trial, and reason for being off study. AEs at the baseline and during treatment for each patient were coded according to the trial’s protocol-designated versions of the Common Toxicity Criteria or Common Terminology Criteria for Adverse Events (CTCAE). All uncoded AEs (predominantly from earlier trials) were manually reviewed and categorized accordingly. Recurring AEs for each patient were counted as 1 AE for the whole duration of treatment and were analyzed on the basis of the highest grade and drug attribution.

TABLE 1. Patient Characteristics at Enrollment in Phase 1 Trials

Characteristic	Women With Gynecologic Cancer (n = 685)	Women With Nongynecologic Cancer (n = 1698)	Men With Cancer (n = 1886)
Age, median (range), y	56 (21-84)	56 (18-86)	60 (20-87)
Prior lines of therapy, No. (%)			
1	67 (10)	181 (11)	245 (13)
2-3	185 (27)	504 (30)	704 (37)
≥4	421 (61)	916 (54)	823 (44)
Investigated agents, No. (%)			
Targeted therapy	528 (77)	1259 (74)	1271 (67)
Cytotoxic	116 (17)	375 (22)	541 (29)
Immunotherapy	10 (1)	11 (1)	14 (1)
Other	31 (5)	53 (3)	60 (3)

Analyses were performed with SAS 9.4 (SAS Institute, Cary, North Carolina). Multivariable linear regression models were used to compare the averages of total AEs at the baseline and during treatment among the 3 groups, and they controlled for the number of treatment cycles and the year of treatment. All *P* values presented are 2-sided.

RESULTS

Patient Characteristics

A total of 356 phase 1 trials were identified in the NCI phase 1 database between 1995 and 2015; 159 of these trials included patients with gynecologic cancer in their eligibility criteria (Fig. 1). After data extraction, there were 150 trials with at least 1 patient with gynecologic cancer enrolled. A total of 4317 patients with baseline information were enrolled in these trials. There were 48 patients excluded because of incomplete treatment information. The remaining 4269 patients were divided into 3 groups: 1) women with gynecologic cancers (n = 685), 2) women with nongynecologic cancers (n = 1698), and 3) men with cancers (n = 1886).

The patient characteristics are displayed in Table 1. The median age of all patients at the time of study enrollment was 58 years (range, 18-87 years), and the top 6 primary cancers were gastrointestinal (n = 1153 [27%]), gynecologic (n = 685 [16%]), breast (n = 475 [11%]), hepatobiliary/pancreatic (n = 429 [10%]), lung (n = 349 [8%]), and genitourinary (n = 330 [8%]). The majority of gynecologic cancers were ovarian/fallopian tube/peritoneal cancers (n = 527 [77%]), which were followed by cervical cancer (n = 76 [11%]) and uterine cancer (n = 72 [11%]). The median number of lines of treatment before study enrollment for all patients was 4 (range, 1-20).

Trial Characteristics

Nearly all phase 1 studies (n = 145 [97%]) included patients with advanced cancers across multiple tumor sites. The remaining 5 trials recruited patients with

TABLE 2. Phase 1 Trial Characteristics and Classes of the Investigated Agents

Characteristic	Trials (n = 150), No. (%)
Trials by year	
1995-1999	49 (33)
2000-2004	38 (25)
2005-2009	29 (19)
2010-2015	35 (23)
Investigated agents	
Targeted therapy	
DNA damage repair pathway	29 (19)
Epigenetic modification	13 (9)
Cell cycle checkpoint regulators	10 (7)
VEGF/VEGFR inhibition	9 (6)
BRAF-MEK-ERK pathway	7 (5)
NF-κB signaling pathway	6 (4)
Notch signaling pathway	6 (4)
PI3K/AKT/mTOR pathway	4 (3)
Apoptosis pathway	4 (3)
Hormone receptor pathway	3 (2)
Protein kinase C pathway	3 (2)
EGFR inhibition	2 (1)
Hedgehog signaling pathway	1 (1)
Cytotoxic	
Microtubules	13 (9)
Topoisomerase inhibitors	10 (7)
Alkylating agents	6 (4)
Antimetabolites	2 (1)
HIF-1α	2 (1)
Platinum	1 (1)
Retinoid	1 (1)
Immunotherapy	
Vaccine therapy	8 (5)
Interleukin	3 (2)
PD-1	1 (1)
IDO1 inhibitor	1 (1)
Other	
Miscellaneous agents	5 (3)

gynecologic cancers only for a total of 49 study participants. As shown in Table 2, therapeutic agents were classified as targeted therapy (n = 97 [65%]), cytotoxic agents (n = 35 [23%]), or immunotherapy (n = 13 [9%]). Targeted therapy included DNA damage repair pathway modifiers (n = 29 [19%]) such as PARP inhibitors and heat shock protein inhibitors, epigenetic modifiers (n = 13 [9%]) such as histone deacetylase

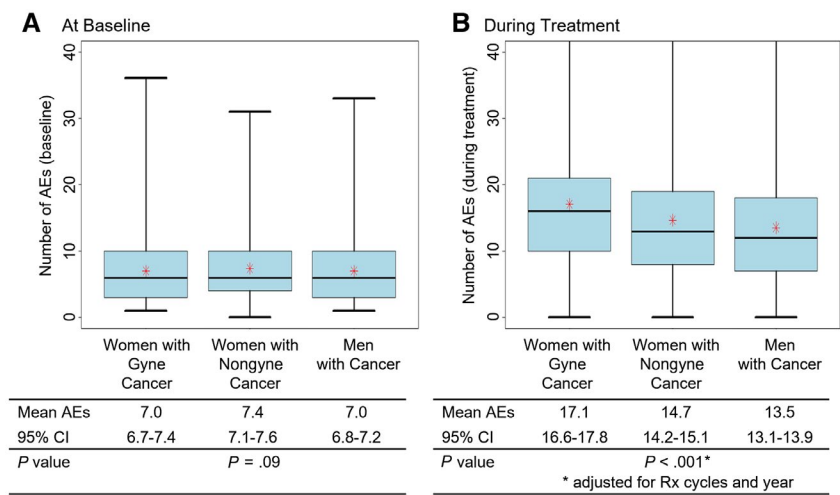


Figure 2. Number of AEs reported (A) at the baseline and (B) during treatment during participation in phase 1 trials. AE indicates adverse event; CI, confidence interval; gyne, gynecologic; nongyne, nongynecologic; Rx, treatment.

TABLE 3. Adverse AEs per Patient Reported During Treatment in Phase 1 Trials

Characteristic	Women With Gynecologic Cancer (n = 685)	Women With Nongynecologic Cancer (n = 1698)	Men With Cancer (n = 1886)
No. of AEs			
Average AEs at baseline	7.0	7.4	7.0
Average AEs on treatment	17.1	14.7	13.5
AEs (on treatment only)			
Attributable to drug	8.31	6.86	6.20
Not attributable to drug	8.76	7.79	7.32
Grade of AEs (on treatment only)			
1	10.13	8.41	7.89
2	4.64	3.95	3.51
3-5	2.30	2.30	2.10
Grade of AEs (on treatment only and attributable to drug)			
1	4.76	3.94	3.65
2	2.36	1.82	1.61
3-5	1.19	1.10	0.94
Categories of AEs (on treatment only)			
Abdominal-related AEs ^a	5.54	4.49	4.26
Myelosuppression	2.06	1.76	1.50
Electrolyte derangement (Na, K, Mg)	0.86	0.71	0.62
Liver enzyme derangement	0.83	0.95	1.00
Genitourinary AEs	0.54	0.32	0.39
Infection	0.52	0.38	0.34

Abbreviation: AE, adverse event.
^aThese AEs include nausea, vomiting, constipation, diarrhea, abdominal pain, and so forth.

inhibitors and DNA methyltransferase inhibitors, and cell cycle checkpoint regulators (n = 10 [7%]) such as cyclin-dependent kinase inhibitors and checkpoint kinase 1 inhibitors. The main cytotoxic agents investigated were microtubule inhibitors (n = 13 [9%]) and topoisomerase inhibitors (n = 10 [7%]), and the predominant immunotherapy agents were vaccine therapies (n = 8 [5%]).

Reports of AEs

The average numbers of total AEs reported at the baseline were similar across all 3 groups (7.0 for women with gynecologic cancer vs 7.4 for women with nongynecologic cancer vs 7.0 for men with cancer; $P = .09$). However, the average numbers of total AEs reported during treatment were significantly different in the 3 groups (17.1 vs 14.7 vs 13.5; $P < .001$) after we accounted for the

TABLE 4. Patient Characteristics During Treatment in Phase 1 Trials

Characteristic	Women With Gynecologic Cancer (n = 685)	Women With Nongynecologic Cancer (n = 1698)	Men With Cancer (n = 1886)
Treatment cycles received, mean	4.3	3.3	3.1
Reason off trial, No. (%)			
Disease progression	423 (62)	1150 (68)	1301 (69)
Adverse events	61 (9)	160 (9)	185 (10)
Death during treatment	15 (2)	41 (2)	76 (4)
Best response, No. (%)			
Complete response	12 (2)	14 (1)	4 (—)
Partial response	65 (9)	91 (5)	57 (3)
Stable disease	246 (36)	523 (30)	591 (31)
Progressive disease	257 (38)	782 (46)	947 (50)

number of treatment cycles and the year of treatment (Fig. 2). During treatment, the average number of total AEs attributable to the drug was also higher (8.3 vs 6.9 vs 6.2; $P < .001$; Table 3). Table 3 shows AE severity and drug attribution. The average numbers of all grade 3 to 5 AEs were similar across the 3 groups (2.3 vs 2.3 vs 2.1). There was a higher average number of grade 1 AEs reported in women with gynecologic cancer (10.13 vs 8.41 vs 7.89; $P < .001$). There was also a higher average number of grade 2 AEs reported in women with gynecologic cancer (4.6 vs 3.9 vs 3.5; $P < .001$). More specifically, the number of grade 2 AEs attributable to the drug on treatment was also higher (2.36 vs 1.82 vs 1.61). There was a numerically higher average number of total AEs for abdominal-related AEs and myelosuppression (Table 3).

The 5 most prevalent AEs in women with gynecologic cancer were as follows: nausea (n = 617 [90%]), fatigue (n = 587 [86%]), anemia (n = 381 [56%]), anorexia (n = 357 [52%]), and vomiting (n = 355 [52%]). For women with nongynecologic cancer, similar trends but lower rates of these symptoms were noted apart from anemia (n = 451 [27%]): nausea (n = 1373 [81%]), fatigue (n = 1372 [81%]), anorexia (n = 780 [46%]), and vomiting (n = 719 [42%]). Men with cancer reported similar rates of fatigue (n = 1625 [86%]) and anorexia (n = 902 [48%]) but much lower rates of nausea (n = 1385 [73%]), vomiting (n = 661 [35%]), and anemia (n = 624 [33%]).

Treatment Responses

Women with gynecologic cancer remained on treatment marginally longer (cycles, 4.3 for women with gynecologic cancer vs 3.3 for women with nongynecologic cancer vs 3.1 for men with cancer; $P < .001$) and achieved higher objective response rates (11% vs 6% vs 3%; $P < .001$; Table 4). The majority of patients discontinued treatment because of disease progression

(62% vs 68% vs 69%; Table 4). The treatment discontinuation rates due to AEs were similar (9% vs 9% vs 10%; Table 4). There was a higher percentage of death during treatment for men versus women (4% vs 2%; $P = .007$; Table 4).

DISCUSSION

This study reports an analysis of the toxicity profiles of women with gynecologic cancers participating in phase 1 studies across the United States and Canada. The NCI's collaborative network of multiple cancer centers has enabled better patient access to clinical trials and integration of research resources to advance the science and systematic investigation of novel therapeutics. We showed that women with gynecologic cancer experienced a greater number of AEs during treatment than patients with other cancer types. Specifically, they reported higher average numbers of total drug-related AEs and abdominal-related AEs, the majority of which were low-grade toxicities (grades 1 and 2). The most common AEs found in women with gynecologic cancer were abdominal symptoms, such as nausea, vomiting, anorexia, constipation, diarrhea, abdominal pain, and distension. There were also notable sex difference in the AE profile, with women being more likely to report nausea and vomiting despite similar rates of anorexia. Therefore, there should be specific consideration for trial safety monitoring and symptom management for women with gynecologic cancer.

Early-phase trial designs have become highly selective in their eligibility criteria as more targeted therapies are being examined in biomarker-specific populations; these designs often also use novel statistical methods to improve the efficiency of dose escalation to its maximal therapeutic dose.^{4,10,11} As the pace of drug development increases and becomes more complex, greater attention should be paid to monitoring the safety of patients. The assessment of AEs has been traditionally based on

the physician's assessment and the seriousness of the events. There is growing emphasis on the need to take into account repetitive grade 2 toxicity events observed during continuous dosing in the definition of dose-limiting toxicity (DLT).¹²⁻¹⁵ Information throughout the treatment cycles, specifically about intolerable clinical grade 2 toxicities leading to a reduction in patients' relative dose intensity, should be incorporated when the recommended phase 2 dose is determined for further studies.¹⁵ The low-grade AEs observed in this study, particularly those attributable to the investigated agent during treatment, seem to be more prevalent in women with gynecologic cancers and may not be recognized as problematic. Study dose modifications, such as changing continuous therapy to intermittent dosing, could be considered for study patients experiencing recurrent grade 2 AEs.

The integration of patient-reported outcomes into clinical trials may provide greater insight into regimen tolerability, patients' symptom burden, and the implications of AEs beyond the CTCAE grading by clinicians.¹⁶ A recent report by Henon et al¹³ showed that patients' most feared AEs, which they deemed intolerable even when they were low grade (grade 1 or 2), were gastrointestinal and neurological toxicities as well as personality changes; these AEs were different from physicians' most feared toxicities and the definition of DLT. To this end, the NCI has developed a patient-reported outcomes version of CTCAE for use in clinical trials and is actively addressing the operational concerns to allow its full integration into clinical trials in collaboration with the US Food and Drug Administration and the Office for Human Research Protection.¹⁷⁻¹⁹ In addition, fit-for-purpose patient-reported outcome measures, such as the Measure of Ovarian Symptoms and Treatment (MOST), can be used in clinical trials specifically for women with recurrent ovarian cancer.²⁰ The incorporation of patient-reported outcomes into trial assessments may uncover low-grade AEs that could be addressed early and allow a better assessment of a patient's toleration of the investigated drug.

Our large data set demonstrated that patients with gynecologic cancers in comparison with other cancer types had a higher average number of low-grade (grade 1 and 2) AEs and abdominal-related AEs, and this highlights the need to support their symptom profile and improve their quality of life. The most common AEs found were nausea, vomiting, anorexia, constipation, diarrhea, and abdominal pain and distension. In addition, fatigue was one of the most prevalent AEs reported among all groups of patients participating in

the trials. This symptom burden is consistent with the literature and is perhaps underestimated, as evidenced by Friedlander et al's report showing that almost half of patients with ovarian cancer reported a constellation of gastrointestinal symptoms contrary to their physician's account of their AEs.²¹ Adaptive development of digital health technologies, such as the use of a mobile application for regular monitoring of AEs and protocol-driven feedback interventions, may facilitate closer symptom management and early interventions to ameliorate the degree of toxicity experienced.²²

Effective novel agents are required to improve outcomes and to expand the existing limited therapeutic options for women with gynecologic cancers. Patients participating in phase 1 trials typically have progressed through multiple lines of treatment, with a median of 4 lines of treatment in our study. Their participation in clinical trials is often hindered by concerns about the high abdominal disease burden and their risk of developing malignant bowel obstructions or fistulas. The eligibility criteria in current trial protocols typically exclude patients with a recent history of bowel obstruction. Our study showed that the main difference in toxicity outcomes for women with gynecologic cancers was the incidence of repetitive moderate-grade AEs, which can be addressed by early management and supportive care. Specific supportive care strategies could be incorporated into clinical trial protocols to address these risks. These may include the following: 1) proactive screening and management of bowel function; 2) avoidance or reduction in the use of medications prone to altering bowel function, such as magnesium replacement, which causes diarrhea, or 5-hydroxytryptamine inhibitor anti-emetic agents, which cause constipation; 3) patient education to increase awareness as well as early recognition and reporting of abdominal symptoms to lead to early interventions; 4) screening for diet and nutrition; and 5) encouragement to exercise and take regulated rest periods to cope with cancer fatigue.

Our data set consists of large, comprehensive phase 1 trials that were rigorously conducted by the NCI at specialized cancer centers since 1995. The group analysis was intended to elucidate overall trends, and it would be difficult to account for individual nuances, such as changes in the nature of drug therapy from cytotoxic agents to targeted agents; it does not reflect patients on immunotherapy agents. The relatively short DLT evaluation period and generally short follow-up time of phase 1 trials limit the assessment of long-term toxicities. The collection of patient-reported outcomes in prospective clinical trials

may provide greater insight into the full impact of low- and intermediate-grade toxicities over time and add value beyond the initial close monitoring of DLT.

In conclusion, our large study highlighted the AE profiles of women with gynecologic cancers while they were participating in phase I studies. These women experienced greater low-grade AEs during treatment in comparison with women or men with other cancer types, so specific supportive care recommendations are warranted. Our findings also reaffirm the notion that novel therapeutics should be studied specifically for gynecologic cancers in early-phase trials to allow an in-depth understanding of drug tolerability and toxicity profiles.

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CONFLICT OF INTEREST DISCLOSURES

Stephanie Lheureux reports consulting for AstraZeneca, Merck, Roche, and GSK. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Yeh Chen Lee: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, validation, visualization, writing—original draft, and writing—review and editing. **Lisa Wang:** Conceptualization, formal analysis, investigation, methodology, software, validation, and writing—review and editing. **Elise C. Kohn:** Conceptualization, supervision, validation, visualization, and writing—review and editing. **Lawrence Rubinstein:** Methodology, resources, validation, visualization, and writing—review and editing. **S. Percy Ivy:** Methodology, resources, validation, visualization, and writing—review and editing. **Pamela J. Harris:** Methodology, resources, validation, visualization, and writing—review and editing. **Stephanie Lheureux:** Conceptualization, formal analysis, methodology, project administration, resources, supervision, validation, visualization, and writing—review and editing.

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Chapter 4: Development of Malignant Bowel Obstruction - Management from a Multidisciplinary Perspective

4.1 PDF of Manuscript 4: Literature Review of Malignant Bowel Obstruction in Advanced Gynaecologic Cancers

Malignant bowel obstruction (MBO) in women with advanced gynaecologic cancer is common, particularly in ovarian cancer, and is described by patients as the most devastating event experienced over their disease trajectory. Disease progression is inevitable for nearly all women with advanced high grade serous ovarian cancer and typically involves the peritoneum which eventually leads to MBO. This poses a particular clinical challenge as it limits therapeutic options and is associated with substantial symptoms such as the inability to maintain oral intake, vomiting and abdominal pain that lead to nutrient deprivation and related complications.

The optimal clinical management of MBO is not well-defined and thus represents an important area of unmet clinical and research need.⁵⁶⁻⁵⁸ Research activity in this setting has been limited due to the paucity of effective therapeutics and lack of standardisation of care. I performed a literature review for MBO management from a multidisciplinary perspective. The review was published in *Obstetrics and Gynecology International* (2018).

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Review Article

Malignant Bowel Obstruction in Advanced Gynecologic Cancers: An Updated Review from a Multidisciplinary Perspective

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Malignant bowel obstruction (MBO) is a major complication in women with advanced gynecologic cancers which imposes a significant burden on patients, caregivers, and healthcare systems. Symptoms of MBO are challenging to palliate and result in progressive decompensation of already vulnerable patients with limited therapeutic options and a short prognosis. However, there is a paucity of guidelines or innovative approaches to improve the care of women who develop MBO. MBO is a complex clinical situation that requires a multidisciplinary approach to ensure the appropriate treatment modality and interprofessional care to optimally manage these patients. This review summarizes the current literature on the different approaches targeting MBO management including surgical intervention, chemotherapy, total parenteral nutrition, and pharmacological treatment. In addition, the impact of MBO management on patients' quality of life (QOL) is examined. This article focuses on the challenges in developing evidence-based treatment guidelines for MBO and barriers in clinical trial design for MBO and proposes strategies to advance the MBO management. Collaboration is essential to design studies that may improve the overall care and quality of life for these patients. Prospective data are needed to inform clinical practice, establish a new benchmark for evidence-based MBO management, and better understand the biology of MBO.

1. Introduction

Malignant bowel obstruction (MBO) in women with advanced gynecologic cancer is common and a major clinical challenge as it is associated with protracted symptoms such as the inability to maintain oral intake, vomiting, and abdominal pain. Ovarian cancer is the dominant cause of MBO and the most lethal of all gynecologic malignancies [1–5]. In reported retrospective series, up to 51% of women [3–6] with recurrent ovarian cancer developed MBO and their median survival following MBO diagnosis ranged from 45 to 169 days [4, 5, 7–9]. Median survival was longer (124–408 days) [5, 7–10] for those selected patients who underwent palliative surgical intervention. Majority of these women would experience recurrent episodes of MBO over their short life expectancy [11].

Recognizing variations in clinical practice and the unmet need for evidence-based treatment, the International Conference on MBO and Clinical Protocol Committee established a unifying definition for MBO to advance research in this field [12]. The criteria to define MBO are (i) clinical evidence of bowel obstruction (history/physical/radiological examination), (ii) bowel obstruction beyond the ligament of Treitz, (iii) diagnosis of intra-abdominal cancer with incurable disease, or (iv) a diagnosis of non-intra-abdominal primary cancer with clear intraperitoneal disease [12].

Herein, we will examine recent advances in the literature targeting different modalities and aspects of MBO management, including palliative surgical intervention [13–28], chemotherapy [28–30], pharmacological management of symptoms [31–40], total parenteral nutrition (TPN) [30, 41–46], and quality of life (QOL) in patients with MBO.

2. Diagnosis of MBO

MBO can be partial or complete and can occur at single or multiple sites. Small bowel obstruction is more common than large bowel obstruction (61% versus 33%, resp.) [47, 48]. The majority of MBO occurs due to external compression or functional occlusion of the gastrointestinal tract from peritoneal carcinomatosis or tumor infiltration of bowel muscle/nerves [49]. In some cases, the etiology of bowel obstruction may be related to nonmalignant causes (albeit not the focus of this review) such as adhesions from previous surgery, intraperitoneal chemotherapy, radiation enteritis, or opioids [17, 48].

Patients with advanced gynecologic cancers may develop MBO at primary presentation or more commonly at the time of disease recurrence or progression. The timing of MBO presentation as well as the underlying disease histology and extent of cancer spread are important factors to consider in management decision. Presentation of MBO is often subacute with cardinal symptoms such as nausea, vomiting, pain, abdominal distention, and absence of stools or passage of gas [48]. These symptoms are a result of distention-secretion-motor activity of the compromised bowel perpetuating the process of MBO: (i) accumulation of gastric, pancreatic, and biliary secretions, (ii) reduced

absorption of water and salt from the intestinal lumen, and (iii) increased secretion of water and salt into the lumen [48, 50]. The cumulative impact of these events is the appearance of intestinal edema, dilated bowel loops with gas and fluid retention, and increased endoluminal pressure [48]. These episodes may be intermittent in cases of partial MBO, and patients may describe passage of liquid stools due to bacterial liquefaction of the digestive content and intestinal hypersecretion [48, 49].

The diagnosis of MBO is established on clinical grounds and confirmed with abdominal imaging. Typical findings on abdominal radiographs seen in the upright position include distention of bowel loops with air-fluid levels in the segment proximal to the occlusion, as well as reduction in gas and stools in the segment distal to the occlusion (Figure 1) [51–53]. Plain abdominal radiographs have moderate sensitivity, ranging 40–80%, for detecting small bowel obstruction [51]. The absence of radiologic findings despite clinical symptoms suggestive of obstruction should not deter the clinician from the diagnosis as they may have functional bowel obstruction secondary to disseminated disease infiltration of the mesentery. Contrast computed tomography (CT) is more valuable as it provides diagnostic precision in identifying the site, etiology, and extent of obstruction and can confirm complications such as superimposed ischemia and intestinal perforation (Figure 1) [51]. Oral contrast agent administration in cases of suspected MBO is controversial, and the use of iodinated contrast medium (gastrografin) is preferred over barium as it is absorbable and provides similar radiological definition [52].

3. Surgical Intervention for MBO

Surgical intervention can be successful in reestablishing bowel function for selected MBO patients with good functional status and treatment options for the underlying cancer [10, 18, 48]. Large bowel obstruction is associated with significant morbidity and risk of perforation and death, and conservative management is not usually appropriate in this setting. The predominant surgical approach to large bowel obstruction consists of diverting stoma rather than primary resection and anastomosis or bypass [1, 54]. Small bowel obstruction without strangulation is mainly treated with conservative measures as it often relates to multifocal small bowel involvement secondary to peritoneal carcinomatosis [1, 54]. Only a minority would be considered for small bowel resection with anastomosis or internal bypass [1].

A systematic review of 868 patients with MBO showed that surgery was able to palliate obstructive symptoms (32–100%), enable resumption of a modified diet (45–75%), and facilitate successful patient discharge to home (34–87%) [54]. Similar results were found in another study examining treatment outcome for MBO under a multidisciplinary care model [10]. Compared to patients who received medical treatment, the surgical group had longer median survival ($p = 0.025$), shorter hospitalization ($p = 0.02$), more effective pain reduction ($p = 0.001$), higher number of chemotherapy lines ($p = 0.02$), and lower reobstruction rate

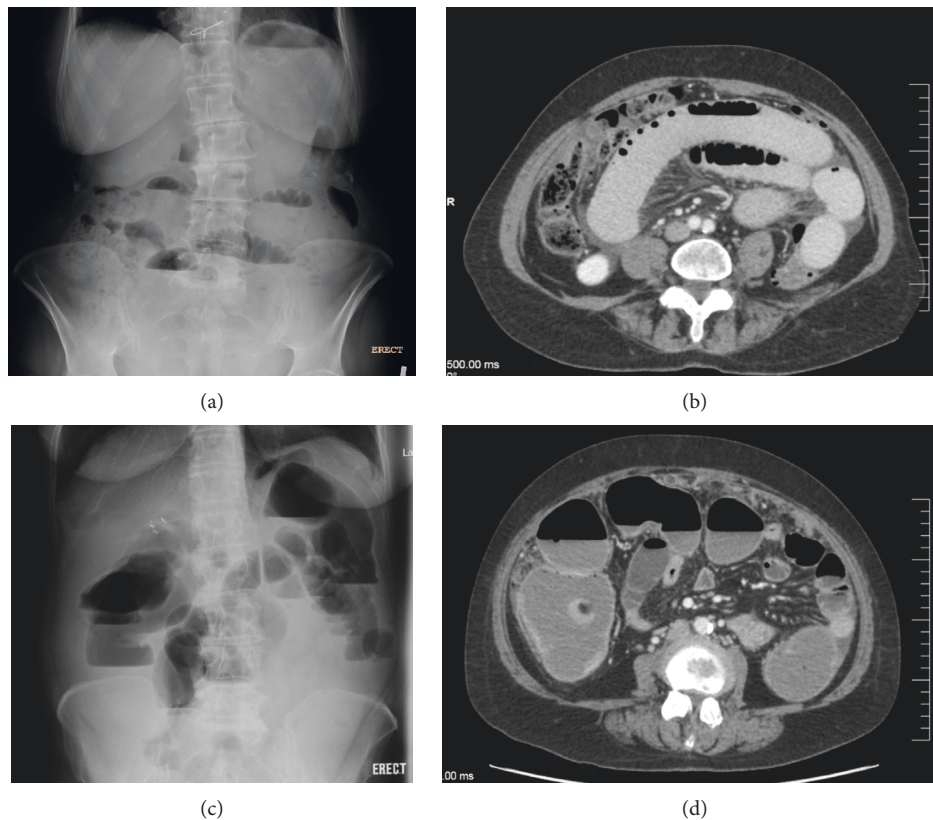


FIGURE 1: Radiographic images showing malignant bowel obstruction. (a) Abdominal radiograph in upright position showing multiple air-fluid levels consistent with small bowel obstruction (SBO). (b) Computed tomography (CT) confirms a high-grade SBO. (c) Abdominal radiographs in upright position showing large bowel obstruction (LBO). (d) CT demonstrates distended and fluid-filled large bowel loops concordant with LBO.

($p = 0.02$) [10]. A prospective outcome analysis was performed on 26 patients with ovarian cancer who had undergone palliative procedures, including bowel diversion surgery ($n = 8$), intestinal bypass/resection ($n = 6$), and endoscopic procedures ($n = 12$) [9]. The majority ($n = 23$, 88%) reported overall symptomatic improvement or MBO resolution within 30 days, and ongoing symptom control at 60 days was achieved in 16 patients [9]. These aforementioned studies favor consideration of palliative surgery in highly selected patients with certain clinical characteristics, including good performance status, longer treatment-free interval, absence/small volume ascites, single-site disease, and albumin level [28, 55]. This is also in concordance with the recommendation by the European Association for Palliative Care that surgery should not be undertaken routinely in patients with poor performance status, intra-abdominal carcinomatosis, and massive ascites [47]. Only few reported series have investigated these clinical variables with mixed results, and it appears that collective assessment of the clinical variables into a risk-score system may be predictive of surgical outcome [4, 10, 56–58].

It is critical that discussions about realistic goals and limitations of surgery occur as it confers significant risk, with the operative mortality rate ranging from 6 to 32% and morbidity rate ranging from 7 to 44%, depending on type and setting (emergency versus elective) of the surgery

[1, 13, 21, 22, 54]. There is also considerable risk of reobstruction (6–47%), hospital readmission (38–74%), and hospitalization for surgery which may consume a substantial portion of the patient's remaining life (11–61%) [54]. A Cochrane review examined the role of surgery in MBO secondary to advanced gynecologic and gastrointestinal cancer and included data from 43 studies with a total of 4265 participants [17]. No firm conclusion could be drawn due to the wide variability comparing different surgical procedures, the diverse definition of clinical outcome, heterogeneous clinical practice, and selection bias within these studies [17]. Therefore, the role for palliative surgery remains controversial and should only be considered in patients with more favourable disease factors and therapeutic options for their disease.

Less invasive approaches using self-expandable metallic stent (SEMS) for gastric outlet obstruction and left-sided colonic obstruction may be feasible in some cases of MBO. This procedure is less morbid compared to open surgery and is able to restore bowel function without the need of creating a stoma [22, 24]. The benefit of SEMS as a palliative procedure or as bridge to surgery has been well described with a lower overall morbidity and rate of temporary/permanent stoma [22–26, 59]. It was also recognized that the procedural success rate relied heavily on operator expertise and resources, and the overall complication rate can be as low as 3.4% for the risk of perforation and 0.5% for the risk of major bleeding [27].

For inoperable but symptomatic patients, venting gastrostomy may be placed to avoid the prolonged use of a nasogastric tube for digestive decompression, particularly in patients with protracted vomiting as their dominating symptom [20, 50, 60–62]. Placement of venting gastrostomy is shown to be feasible despite the inherently added risk of complications in patients with ascites [20, 60–62]. Prompt venting gastrostomy insertion can be advantageous in reducing the polypharmacy burden to control visceral symptoms, avoiding repeated hospital admissions for medical/nasogastric tube interventions, allowing consumption of modified diet for comfort, and facilitating sustained discharges to home or community palliative care unit [61].

4. Chemotherapy for MBO

The role of chemotherapy in MBO is to treat the underlying disease and requires careful consideration of the anticipated response and tolerability. There are very limited data in the literature given that patients with MBO are typically excluded from clinical trials. In addition, the majority of patients with MBO will have received multiple lines of chemotherapy and thus are unlikely to mount a clinically meaningful response resulting in the resolution of MBO [41, 46]. The type of chemotherapy prescribed for patients with advanced gynecologic cancers and MBO may include platinum-based therapy, taxane-based therapy, or gemcitabine [30]. Consideration of dose modification or a weekly regime is common as patients with MBO are at higher risk of toxicity and complications due to their general compromised nutritional state.

Two retrospective series investigated the provision of chemotherapy and TPN in patients with MBO and reported a median survival of 72 and 93 days, respectively [30, 41]. Patients who received chemotherapy and TPN following MBO diagnosis appears to have longer median survival compared to TPN alone [30, 41]. Chouhan et al. also reported resolution of small bowel obstruction in 10 of 82 patients, 5 of which were attributable solely to chemotherapy, and the remainder had received additional interventions such as surgery [30]. Of note, the study also included patients with advanced gastrointestinal cancer who were receiving first-line treatment for metastatic disease (albeit with chemosensitive disease). Overall, the currently available literature to support the use of chemotherapy in patients with advanced gynecologic cancers who developed MBO is still limited, and caution should be exercised when extrapolating data from larger MBO series that have a preponderance of nongynecologic cancers.

5. Total Parenteral Nutrition (TPN) in MBO

The use of TPN in patients with metastatic, incurable disease has been discouraged historically due to concerns regarding impact on QOL, increased risk of complications, and lack of proven benefit in the literature [30, 44, 45]. General guidelines have been established by expert committees, such as the European Society for Clinical Nutrition and Metabolism (ESPEN) and the American Society for Parenteral

and Enteral Nutrition (ASPEN), although recommendations for patients with MBO remain vague [63, 64].

Studies examining the use of TPN in patients with advanced gynecologic cancer and MBO reported short median overall survival of 40–93 days [30, 41, 42, 65, 66]. In these studies, the rate of complications was highly variable, ranging from 4 to 54% [30, 41, 42], and they included predominantly catheter-related infections and less commonly deep venous thrombosis and TPN-related liver disease [67].

Embedded within these reported studies, there is invariably a subgroup of patients who survive for an extended period (24% survival at 6 months and 8% survival beyond 1 year), presumably as a result of TPN and relative disease stability based on biology [30, 41, 66–70]. It is reasonable to postulate that certain disease histology/biology (such as low-grade serous ovarian cancer) and the absence of cancer spread to visceral organs may correlate with better survival. There is however limited information to identify the characteristics that may predict such a sustained benefit from TPN. Bozzetti et al. suggested that the Glasgow prognostic score (GPS) of zero, Karnofsky performance status (KPS) >50, and tumor spread (local-locoregional disease) were significant prognostic factors of survival beyond 3 months following TPN [66]. Combining these three clinical variables may distinguish a patient subgroup whose survival at 6 months was 43.7% compared to 5%. A nomogram based on these parameters was developed enabling estimation of expected survival (3- and 6-month survivable probability) and needs further validation. In parallel with better understanding the biology of MBO and disease evolution, this proposed nomogram could help facilitate a balanced discussion and decision making for both health professionals and their patients. More work is underway to improve the proposed nomogram with inclusion of additional predictors and to establish its clinical utility [71].

The economic impact or cost effectiveness for the utility of TPN in patients with MBO is lacking and needs to be considered [70]. One systematic review demonstrated that the incremental cost-effectiveness ratio (ICER) for TPN in patients with inoperable MBO was high at £176,587 per quality adjusted life year (QALY; equivalent to CAD 312,071) [70]. In Canada, an intervention with an ICER greater than CAD 100,000 is typically viewed as a poor use of resources, although the threshold values are frequently debated and do not represent widely accepted standards [72]. In addition, these threshold values do not take into account the disease biology, treatment response, and reversibility of bowel obstruction.

Whilst it remains unclear how to best select the small subgroup of patients who derive extended benefit from TPN, balanced in-depth discussions and realistic expectations must be set with patients and family members early on to emphasize the limitations of TPN use in MBO and situations when TPN should be discontinued. Data on QOL are required to better inform decisions about the value of TPN in patients with MBO and what would be the minimal length of survival needed before benefit is likely to be experienced.

6. Pharmacological Management of MBO

Medical management in MBO is directed at reducing inflammation and endoluminal pressure and secretions as well as relief of pain and distressing symptoms. Polymodal medical treatment based on the combination of glucocorticoids, opioid analgesics, antiemetics, and antisecretory drugs can achieve good symptomatic control for MBO [10, 35, 39, 48, 73]. Most patients with MBO cannot tolerate oral medications; therefore, alternate methods of drug administration are considered such as intravenous, subcutaneous, and transdermal. Doses and choice of drugs are highly personalized and variable [10, 35, 69]. It is also necessary to adjust the medication regimen periodically depending on the trajectory of MBO and treatment response. There are palliative care guidelines established, such as the National Comprehensive Cancer Network [74], to aid clinicians to make appropriate prescriptions.

There are few studies investigating the use of steroids [31–35], somatostatin analogues [35–38], and olanzapine [40] in relieving the symptoms of MBO. A study investigating the use of dexamethasone (at a dose ranging up to 16 mg) in 35 patients showed a higher rate of spontaneous resolution of MBO in patients on dexamethasone compared to placebo, 37% versus 22%, respectively [31]. Another study assessed the use of methylprednisolone (240 mg or 40 mg versus placebo for 3 days) in 52 patients and showed trend for symptom improvement in the methylprednisolone group (59% versus 33.5%, $p = 0.08$) [33]. Overall, there is a trend to support the use of steroids in MBO, and the side effects are generally well tolerated [34]. Concerns regarding prolonged use of glucocorticoids in this setting include infection risk, gastric ulceration, and mood swings and therefore should be rapidly tapered if minimal response is observed [73]. Recently, Obita et al. performed a systematic review on somatostatin analogues in the management of MBO and found no observed benefit of somatostatin analogues based on the highly variable primary outcome established by the seven eligible studies (a total of 427 patients) evaluated [36]. Nonetheless, somatostatin analogues appeared to be well tolerated with no dropouts due to toxicity as reported in the randomized controlled trials (RCTs) [36, 75].

Opioid analgesia is a common and effective medication used to palliate pain in advanced cancers, as supported by the WHO guidelines [76, 77]. Pain in MBO can be colicky (cramping and intermittent) or continuous in nature [12, 50]. There are very limited data on the optimal analgesic agent for MBO; however, experts favor the use of opioid analgesia given that it can be administered bypassing the oral route (intravenous, subcutaneous, sublingual, or transdermal) and the depressive effect on bowel motility may in fact relieve colicky pain [12, 50, 78].

7. Quality of Life (QOL)

Data on QOL and cost analysis were consistently lacking across the literature for MBO [26]. Such data are essential, particularly when the palliative management of patients with

advanced disease is assessed. The resolution of MBO has typically been used as a surrogate marker for improved QOL. Bowel function recovery, and its measure for QOL, has been evaluated among patients undergoing stent or diverting colostomy [79, 80]. Whilst both methods were found to be effective in palliating symptoms of MBO, stent placement was associated with improved QOL related to gastrointestinal function [81].

A prospective study assessed the changes of QOL over three months in 35 patients with nongynecological cancers following the diagnosis of MBO, as measured by the Edmonton Symptom Assessment Scale (ESAS) and Rotterdam Symptom Checklist (RSCL) [82]. This showed a poor overall baseline QOL and subsequent significant improvements in QOL on many parameters with therapy (surgical/chemotherapy/supportive care) by one week and one month ($p < 0.05$), except for activity level and psychological functioning [82]. The overall improvement in QOL score plateaued after one month and remained similar at three months [82]. It is noteworthy that psychological distress continued to rank highly at three months despite the improvement in overall QOL.

One US-based study investigated QOL, nutritional status, and functional outcomes of 52 advanced cancer patients receiving TPN using validated methods such as EORTC-QLQ-C30, KPS, and Subjective Global Assessment (SGA) [83]. All of these patients also received active treatment including chemotherapy, radiation, or hormonal therapy [83]. This study demonstrated that TPN was associated with significant improvement in global QOL (increase of 6.3 points, $p < 0.001$), nutritional status (weight 1.3 kg, $p = 0.009$), and functional status (KPS increase of 5.8, $p < 0.001$) each incremental month with the greatest benefit at three months [83].

8. Challenges in Optimizing Treatment for MBO

There is a paucity of RCT data for MBO due to inherent heterogeneity in the treatment paradigm in this already vulnerable patient population. Obtaining this level of evidence is challenging, and there are very limited clinical trials underway (Table 1). Most intervention studies reported were retrospective in nature targeting single modality of treatment within a specific MBO setting. Apart from confounding variables such as uncontrolled concurrent therapies, each intervention only targeted specific time points of a MBO episode and therefore did not inform the longitudinal MBO trajectory for these patients. One prospective study followed 35 patients with MBO for two years in a single institution and provided insight into the collaborative approach in multimodal interventions and symptom palliation over the multiple interjecting hospital admissions for these patients [69]. Yet, this study specifically excluded patients with gynecologic cancers [69]. Therefore, a prospective study examining the longitudinal MBO trajectory in advanced/recurrent gynecologic cancers is warranted.

Clinical trials designed for MBO have also proven to be difficult due to the complex nature of the clinical settings and

TABLE 1: Current active clinical trials investigating malignant bowel obstruction.

Trials identifier	Trial name	Design	Intervention
NCT03260647	Risk-stratified multidisciplinary ambulatory management of malignant bowel obstruction in gynecological cancers (MAMBO)	Prospective observational study	Multidisciplinary MBO care program
NCT02365584	Quality of life in Patients with inoperable malignant bowel obstruction (QOL in IMBO)	Phase II, multicentre, RCT	Lanreotide with standard care versus standard care alone
NCT02275338	Study to assess efficacy and safety of lanreotide autogel 120 mg in treatment of clinical symptoms associated with inoperable malignant intestinal obstruction (IMIO)	Phase II, multicenter open label study	Lanreotide
NCT02270450	S1316, surgery or nonsurgical management in treating patients with intra-abdominal cancer and bowel obstruction	Phase III, RCT	Surgery versus nonsurgical management
NCT03150992	EDMONd–elemental diet in bowel obstruction	Phase II, open-label study	Dietary supplement: elemental 028 extra liquid

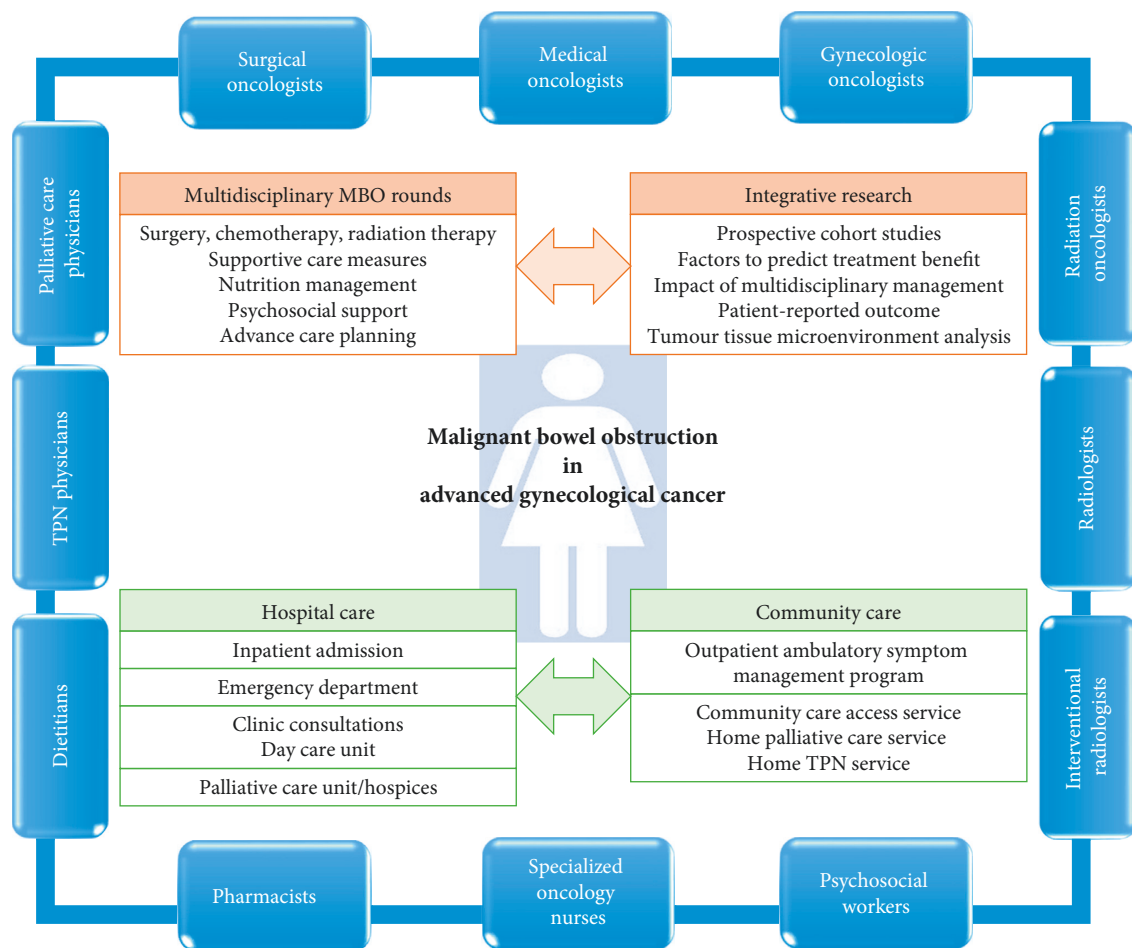


FIGURE 2: Interprofessional malignant bowel obstruction management team integrating clinical care and research.

variation in defining the primary outcome measure. There is an ongoing debate regarding what constitutes a clinically relevant study endpoint for symptom control in MBO. For instance, when should we expect to see the benefit of intervention, for how long should the benefit be sustained, and what magnitude of benefit would be considered clinically

relevant for patients and caregivers [36]? The subacute and recurrent nature of MBO has also hindered the ability to appropriately assess the effectiveness of therapy. Therefore, the conduct of prospective clinical trials for MBO is necessary and requires a multidisciplinary team effort to define the complex care approach and improve treatment strategy.

9. Conclusions and Perspectives

MBO is a challenging complication of advanced gynecologic cancers, particularly in ovarian cancer. Clinical decision making involves complex considerations of different approaches with limited guidance available from the current literature. Only a small subset of patients with MBO appears to benefit from surgical interventions, and there is ongoing controversy with the use of chemotherapy and TPN, highlighting the need for further investigation. The majority of patients with MBO are treated with the medical management focusing on symptom control and quality of life. Early integration of palliative care is essential in the management of MBO symptoms and facilitates discussions addressing treatment expectations and goals of care [55, 73, 84].

Patients with MBO can be managed in an out-patient setting by the hospital specialist team with the support from community care services, such as home palliative care services, community nursing care, and domestic care services. This ambulatory model of care appears feasible and allows patients to be supported at home [85]. Patients with MBO can be closely monitored by a team of physicians and nurses who can manage their symptoms accordingly, thereby alleviating unnecessary emergency department visits. Education about MBO is also the key to empower patients (and their caregivers) to be confident in managing their symptoms and when to seek help.

In this complex care, establishing a multidisciplinary care platform to build consensus treatment strategies as patients navigate through different healthcare providers seems a logical approach to improve the care of this population, particularly with the goal of out-patient management. This promotes an effective communication across disciplines and ensures that patients receive consistent plans of care. In addition, the multidisciplinary platform will foster collaboration in designing and implementing best practice institutional processes and research proposals for MBO (Figure 2). A prospective study examining the MBO disease trajectory in patients with advanced gynecologic cancers under a dedicated multidisciplinary team approach is currently underway (NCT03260647, Table 1). Embedded within the study is the assessment of the ambulatory MBO management approach and quality of life using patient-reported outcomes. In the challenges in optimizing care for patients with MBO, a collaborative approach among the gynecologic cancer groups would be instrumental to establish best practice guidelines and implement feasible MBO research studies to optimize care for patients with MBO.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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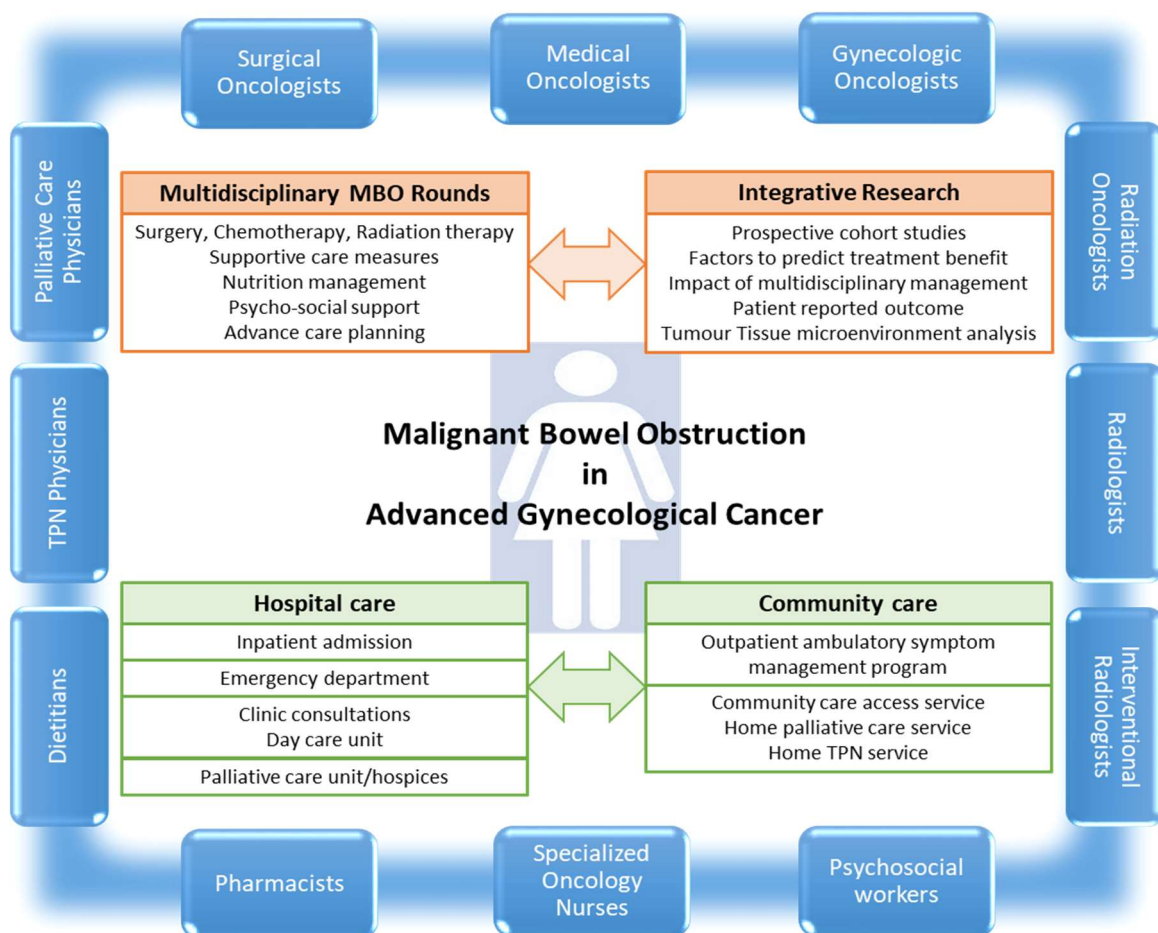
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Chapter 5: Management and Disease Characterisation of Patients with Gynaecological Cancers Who Developed Malignant Bowel Obstruction

5.1 The Development of A Pilot Interprofessional Malignant Bowel Obstruction Program

Incorporating knowledge of malignant bowel obstruction (MBO) from current literature as described in chapter 4, I developed and co-led a pilot interprofessional MBO program alongside Dr Stephanie Lheureux – principal investigator and Gynaecology Oncology Site Lead at Princess Margaret Cancer Centre, Toronto, Canada. The vision of the MBO program was to integrate interprofessional clinical care and research in MBO (**Figure 3**).

Figure 3. Interprofessional malignant bowel obstruction program integrating clinical care and research



The dedicated interprofessional MBO team consists of medical, surgical, gynaecologic, and radiation oncologists, palliative care physicians, diagnostic and interventional

radiologists, total parenteral nutrition (TPN) physicians, specialised oncology nurses, dietitians, pharmacists and social workers. The pilot MBO program was launched in June 2016 and consisted of the following integrated model of care: *i*) implement standardised MBO symptom triage and management tools (**Figure 4-5**); *ii*) establish the MBO multidisciplinary case conference (**Figure 6**); *iii*) consensus on MBO care algorithms for in-patients and out-patients (**Figure 7**); *iv*) develop patient education materials for MBO (**Appendix 1**); and *v*) prompt access to allied health professionals and supported advanced care planning.

In July 2016, the MBO working group implemented an innovative out-patient model of care that utilises a colour-coded MBO triage tool for patients with or at risk of MBO (**Figure 4**). This triage colour-coded system classifies patients according to MBO diagnosis or at risk of MBO and utilises a standardised approach to care management (**Figure 4-7**). According to the MBO management algorithm (**Figure 6-7**), patients who are suspected to have MBO will undergo prompt assessment and investigation to establish the diagnosis. In parallel to immediate MBO symptom management (bowel rest, parenteral rehydration and pharmacologic management), patients will be reviewed by MBO team members for consideration of surgical intervention, chemotherapy, TPN and best supportive care based on disease prognosis. Early discussions about goals of care and advanced care planning are incorporated. I was responsible for chairing the regular MBO multidisciplinary case conferences where the MBO team formally reviews MBO cases and develops consensus treatment recommendations. Once discharged from hospital, patients with MBO will be proactively followed by a team of specialised oncology nurses who coordinate their care between clinic consultations.

In more detail about the colour-coded MBO triage tool (**Figure 4**), patients with bowel symptoms are categorised to a colour code representing different management acuity and settings:

- i) Red: patients with active MBO requiring inpatient management
- ii) Orange: patients with active MBO suitable for outpatient management
- iii) Yellow: patients being investigated and found to have no MBO, however remain at risk of developing MBO
- iv) Green: patients with no bowel symptoms to suggest MBO
- v) Blue: patients with active MBO diagnosis and main treatment goal is for comfort care by palliative care team

Patients deemed suitable for out-patient management (Orange and Yellow code) are proactively followed by specialised oncology nurses through telephone consultations

between out-patient clinic appointments with their clinicians (Surgical, Medical or Palliative team). If their MBO resolves and they maintain symptom-free status for at least one month, patients will transition to a different colour code (Yellow or Green). All nurses in the gynaecological oncology outpatient clinic at Princess Margaret Cancer Centre are specialised oncology nurses who rotate through the gynaecological surgical, medical and radiation oncology clinics. They were trained to assess bowel symptoms using a standardised MBO assessment sheet (**Figure 5**), as well as recognising symptoms of surgical emergencies. The MBO assessment sheet (**Figure 5**) is a one-page questionnaire that enquires specifically about bowel function, such as bowel movement frequency and consistency, nausea, vomiting, passing flatus, abdominal pain, bloating, early satiety, fluid consumption, and medications taken (laxatives, opioid analgesia). Based on this MBO assessment and review of the disease factors that potentially put patients at risk of MBO, nurses would then consult with the clinician if they have alarming bowel symptoms. Patients are instructed to either present to emergency department or attend clinic for further assessment.

Figure 4. Malignant bowel obstruction (MBO) triage tool and nursing proactive ambulatory management according to the colour code system. MBO was defined using the following criteria: clinical evidence of bowel obstruction (history/ physical/ radiological examination; bowel obstruction beyond the ligament of Treitz, in the setting of a diagnosis of intra-abdominal cancer with incurable disease, OR a diagnosis of non-intra-abdominal primary cancer with clear intraperitoneal disease.

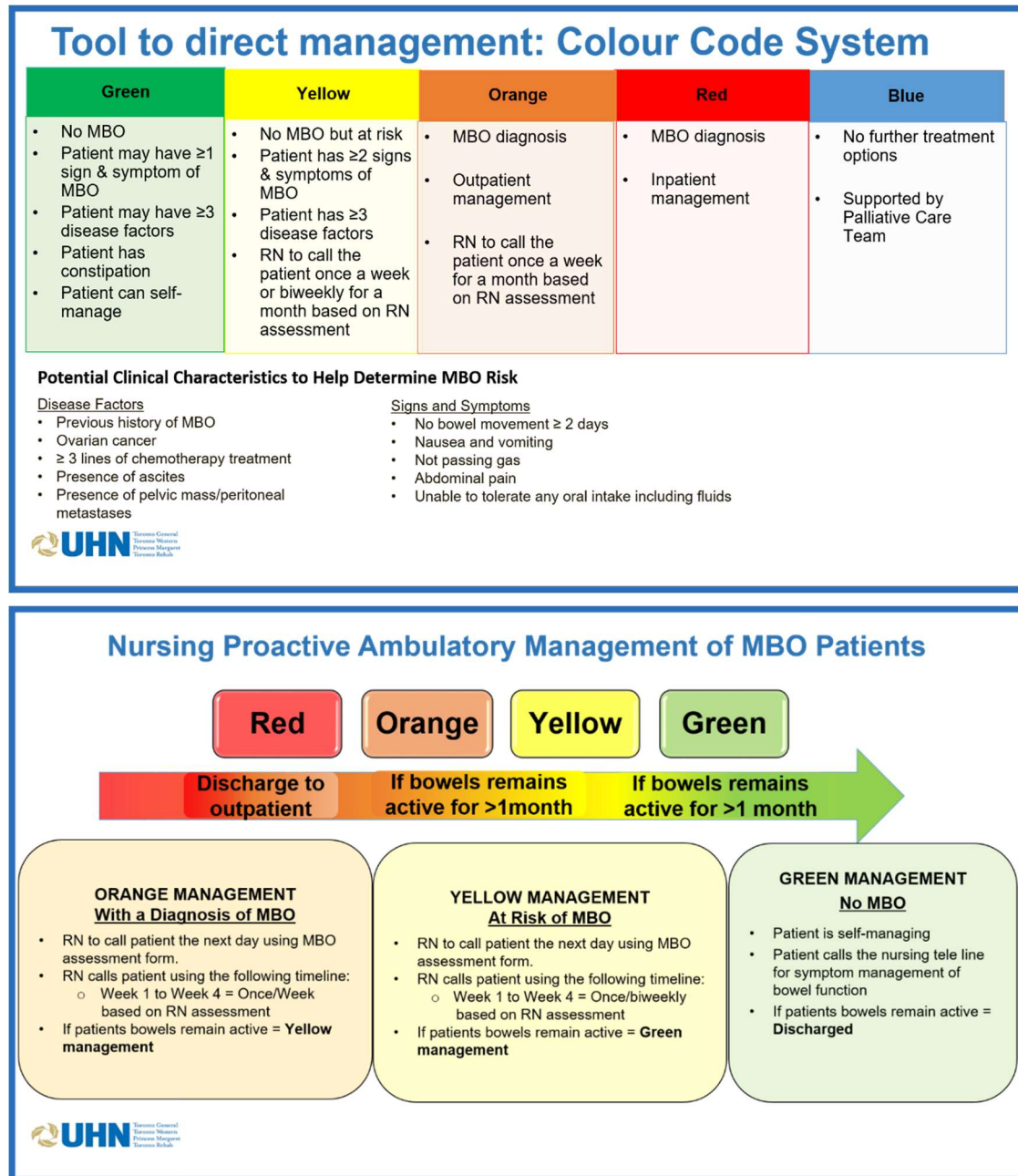


Figure 5. Malignant bowel obstruction assessment sheet for patients with advanced gynaecological cancer at Princess Margaret Cancer Centre.

Insert Patients Sticker

Gyne Patient's Bowel Function Assessment

To be completed for patients with a DART score of 3 or more for any of the following: Pain = _____ Appetite = _____ Nausea = _____

Please circle the number that best describes how you feel NOW:

No constipation 0 1 2 3 4 5 6 7 8 9 10 Worst possible constipation

No vomiting 0 1 2 3 4 5 6 7 8 9 10 Worst possible vomiting

No diarrhea 0 1 2 3 4 5 6 7 8 9 10 Worst possible diarrhea

1. Do you have an ostomy (a bag that collects the poo)? ☐ Yes ☐ No

2. When was your last bowel movement (poo)? _____

3. Look at the Bristol Stool Chart. What type was your last bowel movement (poo)?

Hard = ☐ Type 1 ☐ Type 2 Formed = ☐ Type 3 ☐ Type 4 ☐ Type 5 Loose = ☐ Type 6 ☐ Type 7

4. Have you taken any medications to help your bowels (poo) move? ☐ Yes ☐ No

☐ Colace® (docusate sodium) ☐ Senokot® (senna) ☐ RestoraLAX®/Lax-A-day® ☐ Lactulose

☐ Other _____

5. How many bowel movements (poo) did you have in the last 24 hours? _____

6. Are you passing gas? ☐ Yes ☐ No

7. Do you have nausea (feeling of wanting to throw up)? ☐ Yes ☐ No

8. Have you been vomiting (throwing up)? ☐ Yes ☐ No

➤ If yes, how many times did you vomit (throw up) in the last 24 hours? _____

9. How much fluid are you drinking in a day? Please check (✓)

☐ 0 glasses ☐ 1 glass ☐ 2 glasses ☐ 3 glasses ☐ 4 glasses ☐ 5 glasses ☐ more

10. Do you have pain in your tummy? ☐ Yes ☐ No

11. Are you taking any medications for your tummy pain? ☐ Yes ☐ No

➤ If yes, please check (✓) or write the name: ☐ Tylenol® (acetaminophen) ☐ Tylenol #3® ☐ Oxycodone®

☐ Morphine® ☐ Dilaudid® (hydromorphone) ☐ Other _____

12. Is your tummy bloated or swollen? ☐ Yes ☐ No

13. Does it take a small amount of food to make you feel full? ☐ Yes ☐ No

Figure 6. Overall management algorithm for malignant bowel obstruction (MBO) in patients with advanced gynaecological cancer. The colour code box within the figure represent a management algorithm for different MBO settings.

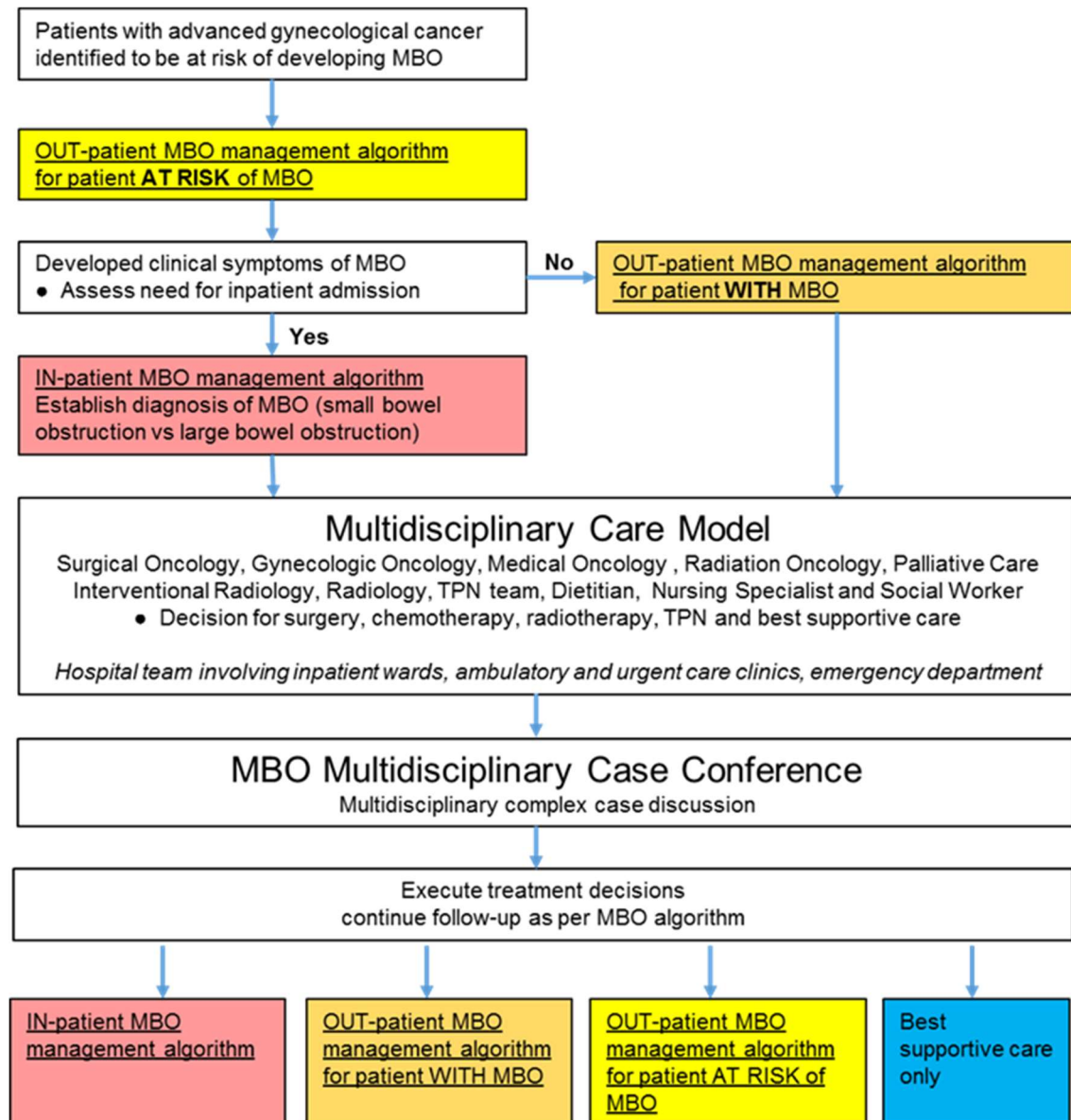
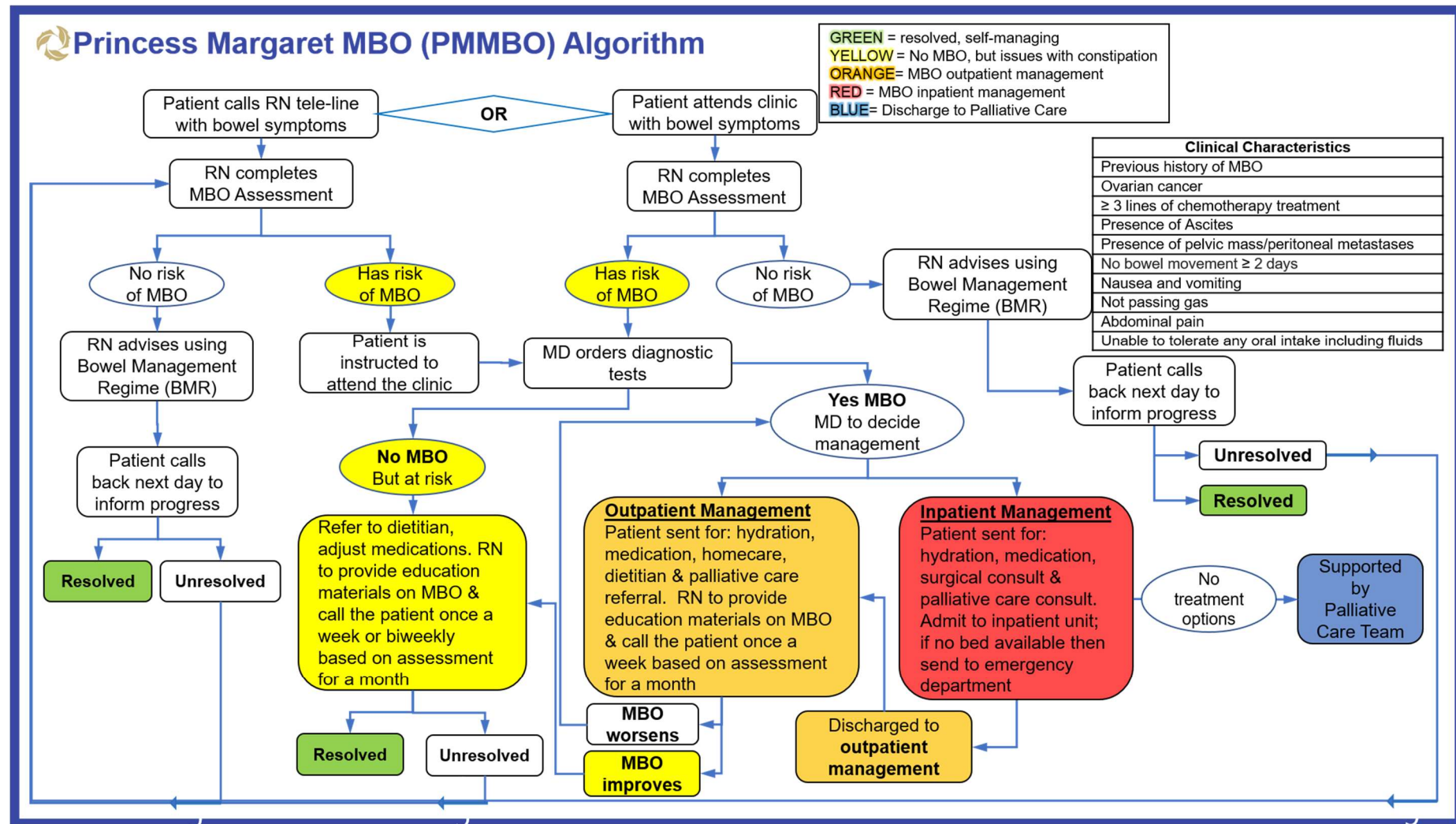


Figure 7. Princess Margaret Malignant Bowel Obstruction (PMMBO) algorithm



Written patient education materials including a “Know How to Maintain Good Bowel Function” pamphlet and low residue diet information were provided to all patients as part of the MBO program (**Appendix 1**). Ms Nazlin Jivraj (specialised oncology nurse) and I were awarded the inaugural Cancer Education Video Award (2017) to fund the development of a patient education video for MBO, to inform patients and create crucial awareness about MBO. I worked with Ms Nazlin Jivraj to produce five video clips which are now available on the Princess Margaret Cancer Centre Youtube site. These short video clips cover the common questions patients may have regarding bowel function and how to recognise symptoms of bowel obstruction (**Table 2**).

Table 2. Patient education video clip about malignant bowel obstruction

Video Title	Length	Youtube Link
1. Know What to do If You Have Bowel Obstruction	7:01	https://www.youtube.com/watch?v=4iYs14htuxg&list=PLaLgrtXadEF8JI-TtwYcaaYM1DnxksUI8&index=2&t=0s
2. Know How to Maintain Good Bowel Function	3:17	https://www.youtube.com/watch?v=EewrQceT27o&list=PLaLgrtXadEF8JI-TtwYcaaYM1DnxksUI8&index=2
3. Know About Medicines to Maintain Bowel Function	5:51	https://www.youtube.com/watch?v=TVziTNKJYr0&list=PLaLgrtXadEF8JI-TtwYcaaYM1DnxksUI8&index=3
4. Know If You Are at Risk for Bowel Obstruction	2:57	https://www.youtube.com/watch?v=1DLqGm9iLLU&list=PLaLgrtXadEF8JI-TtwYcaaYM1DnxksUI8&index=4
5. Know How Diet Can Help to Manage Bowel Function	4:35	https://www.youtube.com/watch?v=mPQf8-ZVzF0&list=PLaLgrtXadEF8JI-TtwYcaaYM1DnxksUI8&index=5

Research projects are integrated as part of the interprofessional MBO program. I performed a retrospective analysis comparing the outcomes of all consecutive patients admitted for MBO management before and after the implementation of the pilot MBO program. The research work is detailed in Chapter 5.2. In addition, I designed an MBO clinical trial (NCT03260647, MAMBO study), which was launched in October 2017 to prospectively assess and validate the efficacy of the implemented interprofessional MBO program (**Appendix 2**). The MAMBO study has incorporated systematic collection of patient reported outcomes and opportunistic tumour tissue collection for patients undergoing surgical intervention for MBO. This information is lacking in the current literature and therefore critical towards establishing new benchmarks for evidence-based MBO management.

The details of the interprofessional MBO program at Princess Margaret Cancer Centre were presented as a poster presentation at the 2017 Palliative and Supportive Care in Oncology Symposium (San Diego, US).⁵⁹ The interprofessional MBO program team (which I co-led with Dr Stephanie Lheureux) was awarded the 2018 Quality Award by the Cancer Quality Council of Ontario in recognition of the significant impact on patient experience and the sustainable systemic changes across the cancer program. The interprofessional MBO program has now been integrated as standard practice at Princess Margaret Cancer Centre.

5.2 PDF of Manuscript 5: Optimizing the Care of Malignant Bowel Obstruction in Patients with Advanced Gynaecologic Cancer

I performed a retrospective analysis comparing the outcome of all consecutive patients admitted for MBO management before and after the implementation of the pilot MBO program. The research work has been accepted for publication in the peer-reviewed and indexed journal *Journal of Oncology Practice*.

Publication citation

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Optimizing the Care of Malignant Bowel Obstruction in Patients With Advanced Gynecologic Cancer

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QUESTION ASKED: What is the impact of implementing a pilot interprofessional malignant bowel obstruction (MBO) program for the care of women with advanced gynecologic cancer?

SUMMARY ANSWER: After implementation of the MBO program, women admitted to hospital with bowel obstruction had shorter average cumulative length of stay in the hospital (13 v 22 days; adjusted $P = .003$) within the first 60 days of MBO diagnosis and improved median overall survival (99 v 243 days; $P = .002$, adjusted for initial cancer stage and lines of chemotherapy). They can be supported effectively within the community under the structured care of the interprofessional MBO team.

WHAT WE DID: A pilot interprofessional MBO program was implemented in a large Canadian cancer center to provide a systematic framework to coordinate care and consensus decision-making among different specialties relevant to MBO management. Specific highlights unique to this MBO program are the collaborative approach to MBO management and integrated outpatient model of care led by specialized oncology nurses through telephone consultations between clinic appointments. The interprofessional team reviews MBO cases and formulates treatment consensus and supportive care plans. Standardized clinical processes, assessment tools, and documentation in the electronic medical record are incorporated to facilitate seamless transition between in- and outpatient care. Patient educational materials have been developed to empower patients to recognize and effectively communicate their

symptoms. We performed a retrospective analysis to compare clinical outcomes of women with MBO before and after implementation of the MBO program.

WHAT WE FOUND: Compared with the baseline group (ie, before MBO program implementation), the MBO program group had a different treatment pattern and was more likely to receive two or more MBO interventions. The MBO program group had shorter hospital admission and seems to have better survival after MBO diagnosis.

BIAS, CONFOUNDING FACTORS, REAL-LIFE IMPLICATIONS:

There are no universal guidelines for optimal management of MBO and treatment approach varies based clinical factors and disease prognosis. A collaborative and programmatic approach to MBO management enabled efficient use of institutional resources to maximize patient outcome and better support their complex care needs. Importantly, the MBO program consists of a collective set of multidisciplinary interventions; therefore, it is not possible to reliably isolate the outcomes of each intervention (eg, surgery, chemotherapy, total parenteral nutrition, and supportive care). The recurrent and progressive nature of MBO may inherently hinder the ability to appropriately assess the effectiveness of MBO interventions. Education about MBO was also critical for empowering patients and their caregivers to confidently manage their symptoms and know when to seek help. The principles of this interprofessional MBO program can be adopted by other oncological disciplines or cancer institutions.

Author affiliations and disclosures are available with the complete article at jop.ascopubs.org.

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Optimizing the Care of Malignant Bowel Obstruction in Patients With Advanced Gynecologic Cancer

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abstract

PURPOSE Malignant bowel obstruction (MBO) is a common and distressing complication in women with advanced gynecologic cancer. A pilot, interprofessional MBO program was launched in 2016 at a large Canadian tertiary cancer center to integrate these patients' complex care needs across multiple disciplines and support women with MBO.

METHOD Retrospective analysis to evaluate the outcomes of women with advanced gynecologic cancer who were admitted to hospital because of MBO, before (2014 to 2016: baseline group) and after (2016 to 2018) implementation of the MBO program.

RESULTS Of the 169 women evaluated, 106 and 63 were in the baseline group and MBO program group, respectively. Most had ovarian cancer ($n = 124$; 73%) and had small-bowel obstruction ($n = 131$; 78%). There was a significantly shorter cumulative hospital length of stay (LOS_{sum}) within the first 60 days of MBO diagnosis in the MBO program group compared with the baseline group (13 v 22 days, respectively; adjusted $P = .006$). The median overall survival for women treated in the MBO program was also significantly longer compared with the baseline group (243 v 99 days, respectively; adjusted $P = .002$). Using the interprofessional MBO care platform, a greater proportion of patients received palliative chemotherapy (83% v 56%) and less surgery (11% v 21%) in the MBO program group than in the baseline group, respectively. A subgroup of women ($n = 11$) received total parenteral nutrition for longer than 6 months.

CONCLUSION Implementation of a comprehensive, interprofessional MBO program significantly affects patient care and may improve outcomes. Unique to this MBO program is an integrated outpatient model of care and education that empowers patients to recognize MBO symptoms for early intervention.

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INTRODUCTION

Malignant bowel obstruction (MBO) is a common occurrence in women with advanced gynecologic cancer, particularly ovarian cancer.¹⁻³ Previous retrospective series reported that MBO developed in up to 51% of women with recurrent ovarian cancer and median survival after MBO diagnosis ranged from 45 to 169 days.²⁻⁵ The development of MBO is typically subacute and progresses to distressing symptoms such as inability to eat, vomiting, and abdominal cramps and distension.^{6,7} MBO management often mandates extended hospital admission. Despite initial interventions, most of these women will experience recurrent episodes of MBO over time, which negatively affects their quality of life.¹ Although MBO is a frequent complication, there are no guidelines on MBO treatment approaches.

Pilot MBO Program

Optimal and efficient management of MBO is an unmet clinical need.² To address this complex clinical challenge, a pilot MBO program with an integrated outpatient model of care was launched in June 2016 at a large Canadian tertiary cancer center. The dedicated interprofessional MBO team consists of medical, surgical, gynecologic, and radiation oncologists, palliative care physicians, diagnostic and interventional radiologists, total parenteral nutrition physicians, specialized oncology nurses, dietitians, pharmacists, and social workers. After review of literature, the MBO working group developed the following: (1) expert consensus MBO clinical care algorithms for inpatients and outpatients; (2) patient education materials; (3) standardized MBO symptom triage and management

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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tools; and (4) guidance on advanced care planning and involvement of palliative care (Data Supplement).

Using the MBO program framework, patients suspected of having MBO underwent prompt review to establish a diagnosis, were triaged according to the standardized MBO assessment tool, and treated on the basis of the Princess Margaret Cancer Centre MBO algorithm (Data Supplement). The MBO assessment tool is a one-page questionnaire focused solely on bowel function, such as bowel movement frequency, stool consistency, nausea, vomiting, flatus, abdominal pain, bloating, early satiety, fluid consumption, and medications taken (eg, laxatives, opioid analgesia). Patient undergo additional radiological imaging on the basis of symptoms. Once diagnosed with MBO, patients receive immediate MBO symptom management (ie, bowel rest, parenteral rehydration, and pharmacologic management) and are reviewed by MBO team members for consideration of surgical intervention, chemotherapy, total parenteral nutrition (TPN), and best supportive care on the basis of disease prognosis. Early discussions regarding goals of care and advanced care planning are incorporated. Patient care is systematically documented in the electronic medical record to ensure effective communication within the interprofessional network.

Patients known to the MBO program are categorized according to a color-code system: (1) red for patients with active MBO requiring inpatient management; (2) orange for patients with active MBO suitable for outpatient management; (3) yellow for patients with no MBO but who are at risk for development of MBO; (4) green for patients with no bowel symptoms to suggest MBO; and (5) blue for patients with active MBO diagnosis and whose main treatment goal is for comfort care by the palliative care team (Data Supplement). Patients deemed suitable for outpatient management (orange and yellow codes) are proactively followed by specialized oncology nurses through telephone consultations between outpatient clinic appointments with their clinicians (surgical, medical or palliative care teams). If MBO resolves and patients are symptom free for at least 1 month, they transition to different color code (yellow or green). Written patient-education materials including a “Know How to Maintain Good Bowel Function” pamphlet and low-residue diet information were provided to all patients as part of the MBO program.

All MBO cases are discussed at the regular MBO multidisciplinary case conference to review radiological imaging and consensus treatment recommendations. Treatment plans are documented particularly if a patient is deemed not suitable for surgery and thereby will be cotreated by medical oncology and palliative care teams.

METHODS

Since June 2016, a pilot, interprofessional MBO program with an integrated outpatient model of care was launched at

the Princess Margaret Cancer Centre. A retrospective analysis was performed to evaluate the impact of the MBO program on cumulative hospital length of stay (LOS_{sum}) for MBO management for all consecutive patients who presented with bowel obstruction (*International Classification of Diseases, Tenth Revision*, code: K56 or K91.3) at the Princess Margaret Cancer Centre and/or the affiliated Toronto General Hospital from April 2014 to March 2018 (based on fiscal year). Patients were identified using data from the National Ambulatory Care Reporting System, which captured patient information on hospital admission, emergency department visits, and community-based ambulatory care. Chart reviews were conducted to select patients with MBO who met the following criteria: (1) clinical evidence of bowel obstruction (history, physical, and radiologic examination); (2) bowel obstruction due to malignant deposits beyond the ligament of Treitz; and (3) diagnosis of advanced gynecologic cancer. These criteria are aligned with the definition of MBO set by the International Conference on MBO and Clinical Protocol Committee.⁸ We excluded patients who presented with MBO at the time of initial diagnosis of ovarian cancer, as well as patients with bowel obstruction due to noncancer-related etiologies, such as adhesion incarcerated hernia, sigmoid volvulus, and radiation stenosis.

For all eligible patients, a detailed chart review was conducted and reviewed by at least two authors (Y.C.L., K.N., and S.C.). The following data fields were extracted and recorded: patient demographics, tumor characteristics (ie, primary tumor site, histopathology, cancer stage, *BRCA1/2* mutation status, presence of ascites), treatment history (ie, dates, types and lines of treatment), nutritional markers (ie, albumin, height, weight), and MBO management and treatment outcome. Patients with ovarian cancer who underwent chemotherapy were classified according to their antecedent treatment-free interval at the time of MBO diagnosis as either platinum sensitive (longer than 6 months) or platinum resistant (6 months or shorter).

Statistical Analysis

The primary objective of this study was to compare the cumulative days of hospitalization for the first 60 days of MBO diagnosis before and after implementation of the MBO program. The difference between groups was estimated using the general linear model, controlled for age, histology, and platinum-sensitivity status. Survival outcomes were compared using the Kaplan-Meier method and log-rank test, with censoring at date of last follow-up in May 2018.

All *P* values were two-sided, and *P* < .05 was considered statistically significant. Descriptive summaries included mean and confidence intervals for quantitative measures and case numbers and percentages for qualitative measures.

RESULTS

A total of 312 patients were identified from hospital records using the aforementioned selection criteria. Of those, 143 were excluded for the following reasons: bowel obstruction due to postoperative ileus ($n = 86$), adhesions ($n = 40$), incarcerated hernia ($n = 5$), sigmoid volvulus ($n = 3$), radiation stenosis ($n = 2$), and MBO at the time of initial ovarian cancer diagnosis ($n = 7$). The remaining 169 patients were divided into two groups for comparison: the baseline group (preimplementation of MBO program) and MBO program group (postimplementation of the MBO program).

Clinical Characteristics of Patients With MBO

The clinical characteristics of the 169 patients are listed in [Table 1](#). Overall, median age at MBO diagnosis was 62 (range, 31 to 91) years. The predominant primary cancer diagnoses were ovarian cancer ($n = 124$; 73%), uterine cancer ($n = 30$; 18%), and cervical cancer ($n = 15$, 9%). Most patients ($n = 134$; 80%) had stage III-IV disease at the time of diagnosis. The median duration from initial cancer to MBO diagnosis was 35 (range, 3 to 205) months. At initial MBO diagnosis, most patients presented with small-bowel obstruction ($n = 131$; 78%). On imaging, approximately half of all patients had a single transition point ($n = 83$; 50%) and low-grade obstruction ($n = 89$; 53%).

Hospital Admission Due to MBO

The average cumulative LOS (LOS_{sum}) in hospital within the first 60 days of MBO diagnosis was significantly shorter in the MBO program group (13 days [95% CI, 10 to 16] v 22 days [95% CI, 18 to 26]; $P = .006$, adjusted for age, histology, platinum sensitivity, and surgery; [Fig 1A](#)). This magnitude of difference was similar when comparing the mean LOS_{sum} for the first 90 days and 180 days of MBO diagnosis. For the first 90 days of MBO diagnosis, the mean LOS_{sum} was 14 days (95% CI, 11 to 17) versus 23 days (95% CI, 18 to 27; adjusted $P = .006$; [Fig 1B](#)). Expanding to the first 180 days of MBO diagnosis, the mean LOS_{sum} was 15 days (95% CI, 11 to 19) versus 23 days (95% CI, 15 to 31; $P = .113$; [Fig 1C](#)). Since the initial diagnosis of MBO, patients had a median of two hospital admissions (range, 0 to 8) and the median time interval between MBO-related admissions was 26 (range, 1 to 880) days.

The median overall survival (OS) for all patients with MBO was 141 (95% CI, 100 to 189) days. Notably, patients treated under the MBO program lived longer compared with the baseline group: median OS compared with baseline group: 243 (95% CI, 142 to 323) days versus 99 (95% CI, 79 to 133) days; $P = .002$, adjusted for initial cancer stage and lines of chemotherapy; [Appendix Fig A1](#), online only).

MBO Intervention and Outcome

The palliative care team contributed to the care of women with MBO, and their involvement was similar in both the

MBO program group and the baseline group (81% v 82%, respectively). Compared with the baseline group, patients in the MBO program group received less palliative surgery (11% v 21%, respectively) but more chemotherapy (83% v 56%, respectively; [Table 2](#)). The proportions of patients who received TPN (27% v 23%), stent procedure (8% v 5%), or radiation therapy (5% vs 4%) were relatively similar between the MBO program and baseline groups, respectively. Of note, the proportion of patients who received two or more interventions was higher in the MBO program group (42% v 33% of baseline group).

Just above half ($n = 37$ of 63; 59%) of the patients in the MBO program group would recover from the first episode of MBO ([Table 2](#)). Of those, most ($n = 25$ of 37; 68%) subsequently had another episode of MBO. Similarly, half of the patients ($n = 54$ of 106; 51%) in the baseline group recovered from the first episode of MBO and of those, 31 of 54 (57%) had recurrent MBO episodes. Complications that occurred due to MBO included bowel perforation (MBO program group v baseline group: 13% v 5%) and fistulizing disease (MBO program group v baseline group: 6% v 12%).

Of the 111 patients who received chemotherapy at the time of MBO, approximately 33% ($n = 37$ of 111) subsequently received up to three additional lines of chemotherapy at the time of disease progression.

Forty-one patients (24%) received TPN for a median duration of 69 (range, 9 to 739) days. At baseline, the median body mass index was 22 (range, 14 to 38) kg/m^2 and serum albumin level was 33 (range, 23 to 44) g/L. Of those, nine patients were able to resume oral diet as they responded to treatment (two underwent diverting stoma surgery and all had chemotherapy). A subgroup of 11 patients (27%) received TPN for longer than 6 months, up to 2 years. The complication rate related to line sepsis was 24% ($n = 10$ of 41) in patients who received TPN.

Cost Analysis for Hospital Admission

The cost per hospital admission (in Canadian dollars) for patients treated as part of the MBO program (mean, \$12,284; median, \$8,810; range, \$840 to \$42,179) was less than for the baseline group (mean, \$18,934; median, \$12,800; range, \$978 to \$138,556). Similarly, the cost per patient, including multiple episodes of hospital admissions, in the MBO program group (mean, \$17,358; median, \$15,032; range, \$1,523 to \$84,106) was less than that in the baseline group (mean, \$24,885; median, \$17,871; range, \$2,506 to \$138,556).

DISCUSSION

To our knowledge, this is the first study to demonstrate the benefit of an interprofessional MBO program toward improving the complex care of patients with MBO secondary to gynecologic cancer. Patients who were treated under the MBO program were discharged sooner from hospital and supported as outpatients than those treated before

TABLE 1. Clinical Characteristics of Patients With Advanced Gynecologic Cancer Who Developed Malignant Bowel Obstruction

Characteristic	Baseline Group (n = 106)	MBO Program Group (n = 63)
Age at MBO diagnosis, median (range), years	63 (31-84)	60 (33-91)
Time from initial cancer to MBO diagnosis, median (range), months	31 (3-205)	37 (5-124)
<i>BRCA1/2</i> mutation carrier		
Yes	18 (17)	10 (16)
No	33 (31)	27 (43)
Variant of unknown significance	2 (2)	5 (8)
Primary cancer and histologic type		
Ovarian cancer		
High-grade serous carcinoma	69 (65)	44 (69)
Low-grade serous carcinoma	2 (2)	4 (6)
Other subtype*	4 (4)	1 (2)
Uterine cancer		
High-grade serous carcinoma	6 (6)	4 (6)
Endometrioid adenocarcinoma	5 (5)	5 (8)
Other subtype†	9 (8)	1 (2)
Cervical cancer		
Squamous cell carcinoma	7 (7)	2 (3)
Adenocarcinoma	4 (4)	2 (3)
Platinum sensitivity of ovarian cancer at MBO diagnosis		
Sensitive	15 (14)	10 (16)
Resistant	59 (56)	38 (60)
FIGO stage at initial cancer diagnosis		
I-II	7 (21)	9 (15)
III-IV	83 (79)	50 (80)
Characteristics at first MBO diagnosis		
Site of MBO		
Large bowel only	19 (18)	10 (16)
Small bowel only	81 (76)	50 (79)
Large and small bowel	6 (6)	3 (5)
No. of transition point of MBO		
None	25 (24)	9 (14)
Single	53 (50)	30 (48)
≥ 2	27 (25)	24 (38)
Grade of MBO		
Low grade	58 (55)	31 (49)
High grade	44 (42)	32 (50)
Presence of other cancer characteristics at MBO diagnosis		
Ascites	49 (46)	32 (51)
Intra-abdominal mass > 5 cm	38 (36)	16 (25)
Extra-abdominal disease	39 (37)	14 (22)
Serum albumin < 30 g/L	29 (27)	7 (11)

NOTE. Data are reported as No. (%) unless otherwise indicated.

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; MBO, malignant bowel obstruction.

*Includes endometrioid, mucinous, clear cell, and granulosa cell histologic types.

†Includes carcinosarcoma, sarcoma, and leiomyosarcoma histologic types.

implantation of the MBO program. In addition, they were more likely to receive multimodality interventions (MBO program group v baseline group, 43% v 33%) under a collaborative multidisciplinary care platform and had a longer median survival of approximately 5 months.

In our study, most women with MBO had recurrent ovarian cancer and, unfortunately, had recurrent MBO episodes requiring ongoing management. This finding is in keeping with those reported by Martinez Castro et al¹ that women with MBO and ovarian cancer have a median of three episodes of MBO before death; the median time interval between each episode is 17 (range, 1 to 727) days. The mean LOS was 13 days for each MBO episode in the aforementioned study.¹ In comparison, our study captured the accumulated LOS_{sum} within the first 60 to 180 days to include the recurrent admissions for each patient. The significant improvement in LOS_{sum} from 22 to 13 days (within the first 60 days of MBO diagnosis) is evidence for the positive impact of our MBO program in augmenting and sustaining the delivery of high-quality care support in the outpatient setting.

Unique to this MBO program is an integrated outpatient model of care and emphasis on patient education. The MBO program connects the inpatient and outpatient care teams using existing hospital resources and infrastructure. Using standardized triage and assessment tools we developed, patients' symptoms were followed proactively by specialized gyne-oncology nurses for early intervention and support. The program also connected patients with community care services, such as home palliative care services, community ambulatory nursing care, and domestic care services, to maximize patient support at home without incurring extra costs to the hospital system. Education about MBO was also critical for empowering patients and their caregivers to confidently manage their symptoms and know when to seek help, particularly given the high risk of MBO recurrence. Patients were provided teaching and

written information packages about MBO so they could effectively communicate their symptoms and participate in decision-making. This study demonstrated how adopting measures such as standardized proactive assessments and education tools can evolve the previous inpatient model of care toward a sustainable, safe, and efficient ambulatory model of care.

The MBO program group has demonstrated a significant survival advantage of approximately 5 months compared with the baseline group. The median OS in the baseline group was comparable with that reported in previous studies, ranging from 45 to 169 days.^{1,4,5,9,10} The clinical and MBO characteristics were similar between the two groups (Table 1). We hypothesize that this survival advantage is due to the overall impact of the MBO program in early identification of symptoms, tailored treatment intervention (before onset of complications), and best supportive care adapted specifically for women with MBO secondary to gynecologic cancer. A core feature of the MBO program is that patient cases were reviewed at the dedicated MBO multidisciplinary case conferences. This interdisciplinary approach likely accounts for the differences in treatment pattern between the two groups and provides an explanation of why patients in the MBO program were more likely to receive multimodal intervention. The integration of management algorithms eased patients' transition from hospital to home. After discharge, patients were proactively followed by specialized gyne-oncology nurses and community services. In addition, patients were screened and referred promptly to allied health professionals, such as dietitians for nutrition assessment and low-fiber diet education. All these measures would collectively enable early intervention for patients who developed or were at risk for developing another episode of MBO.

There is ongoing controversy regarding the use of TPN in patients with incurable cancer who develop bowel

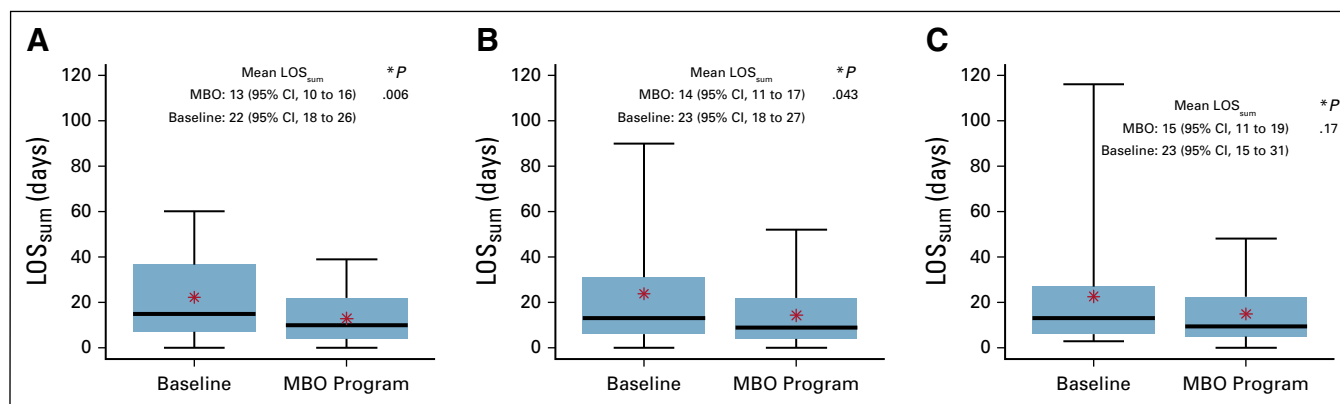


FIG 1. Box plots of accumulated hospital length of stay (LOS_{sum}) before and after implementation of the malignant bowel obstruction (MBO) program. (A) First 60 days after MBO diagnosis. (B) First 90 days after MBO diagnosis. (C) First 120 days after MBO diagnosis. (*) Adjusted for age, histology, platinum-sensitivity status, and surgery.

TABLE 2. Care Management of Patients With MBO Before and After Implementation of MBO Program

Type of Care	Baseline Group (n = 106)	MBO Program Group (n = 63)
Hospital admission		
Length of stay in first 60 days of MBO, median (95% CI), days	22 (18 to 26)	13 (10 to 16)
No. of admission episodes per patient, median (range)	2 (0-7)	2 (0-8)
No. emergency department episodes, median (range)	1 (0-8)	1 (0-9)
No. of ICU admission episodes	5	1
MBO intervention		
Palliative care team involvement	87 (82)	51 (81)
Surgery	22 (21)	7 (11)
Diverting stoma, No.	16	6
Bypass surgery, No.	3	0
Bowel resection, No.	1	0
Exploratory laparotomy, No.	2	1
Stent	5 (5)	5 (8)
Chemotherapy	59 (56)	52 (83)
Platinum-based doublet or single agent, No.	21	22
Taxane-based agent, No.	29	24
Liposomal doxorubicin, No.	17	16
Other single agents, No.*	8	14
Clinical trial agent, No.	6	5
Hormonal therapy, No.	2	2
Radiation therapy	4 (4)	3 (5)
Total parental nutrition	24 (23)	17 (27)
Patients receiving two or more interventions	35 (33)	27 (43)
Outcome		
MBO resolution		
Resolution from first episode of MBO	54 (51)	37 (59)
Progressive MBO	52 (49)	26 (41)
Recurrent MBO episodes	31 (29)	25 (40)
Complications due to MBO		
Bowel perforation	5 (5)	8 (13)
Fistulizing disease	13 (12)	4 (6)

NOTE. Data reported as No. (%) unless otherwise indicated.

Abbreviations: ICU, intensive care unit; MBO, malignant bowel obstruction.

*Includes gemcitabine, cyclophosphamide, topotecan, and trabectedin.

obstruction. Prior studies investigating the use of TPN in patients with advanced gynecologic cancer and MBO invariably reported short median OS of 40 to 93 days, with concerns of complication rates up to 54%, such as catheter-related infection.¹¹⁻¹⁵ However, embedded within these studies was a subgroup of patients who survived for extended periods (24% survival at 6 months and 8% survival beyond 1 year).^{11-13,16-18} The predictive factors of who would benefit from TPN for an extended period are still unclear. Similarly, we found that 27% of patients receiving TPN seemed to derive extended benefit, surviving beyond 6 months and up to 2 years. Owing to the availability of

a home TPN service at our center, patients who were deemed suitable for TPN would commence TPN in the hospital and, in parallel, would be trained to self-manage their TPN before being discharged. Once discharged, they would be followed by the home TPN program and be supported to self-administer TPN overnight at home. The catheter complication rate for our patients receiving TPN was 24%, likely attributed by the frequent use of a central catheter for an extended period.

This study is subject to limitations, given the retrospective analysis of this single-institution study. This pilot MBO program requires additional validation to determine

whether it can be adopted by other institutions. The broad integration of this MBO program will depend on the organization, infrastructure, and resources available within the local health care system. Given the inherent limitation of the retrospective study, it is not possible to distinguish improvement in survival related to lead time bias, because of early recognition of MBO and measuring survival from an earlier time point, or true improvement in survival because of greater opportunity for therapy and intervention on the basis of defining impending bowel obstruction and managing it more effectively. Prospective confirmation of survival improvement requires randomized evaluation with a cluster randomized clinical trial. There is also ongoing debate as to what constitutes a clinically relevant study end point for symptom control in MBO. The recurrent and progressive nature of MBO may inherently hinder

the ability to appropriately assess the effectiveness of MBO interventions. A prospective clinical trial (Risk Stratified Multidisciplinary Ambulatory Management of Malignant Bowel Obstruction [MAMBO] Program for Women With Advanced Gynecological Cancers study; ClinicalTrials.gov identifier: [NCT03260647](https://clinicaltrials.gov/ct2/show/study?term=NCT03260647)) is currently underway, integrating the assessment of quality-of-life measures in patients with MBO and qualitative interviews to evaluate their care needs.

In conclusion, a collaborative approach is instrumental in optimizing care of patients with MBO and improving patient outcomes. The implementation of an interprofessional MBO program may reduce duration of hospitalization and support and empower patients in an outpatient setting without adding additional financial or infrastructure strain to a specialized cancer center.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI <https://doi.org/10.1200/JOP.18.00793>.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Optimizing the Care of Malignant Bowel Obstruction in Patients With Advanced Gynecologic Cancer

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APPENDIX

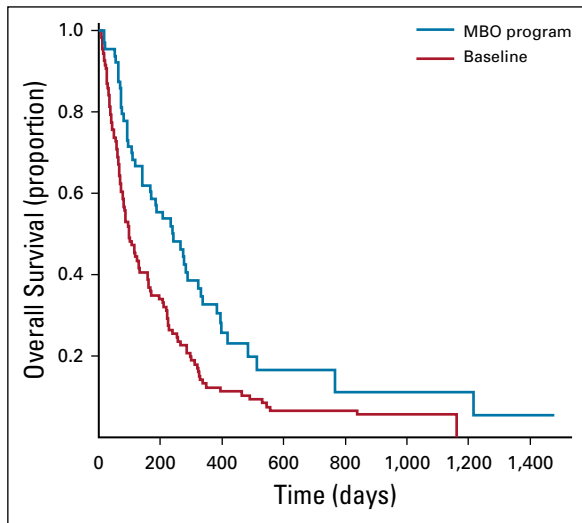


FIG A1. Overall survival of patients with advanced gynecologic cancer who developed malignant bowel obstruction (MBO), before and after implementation of MBO program.

Chapter 6: Discussion and Concluding Remarks

6.1 Overview

This chapter brings together the work in this thesis and considers it as a whole. The theme of this thesis is to improve the care of women with ovarian cancer by focussing on current clinical gaps over important time points during their disease trajectory. The principal findings of each research study performed will be presented followed by their implications to clinical practice and recommendations for future research directions.

6.2 Summary of Principal Findings and Implications to Clinical Practice

6.2.1 Cancer prevention: The quality of risk-reducing salpingo-oophorectomy (RRSO) in Australasian women at high risk of developing ovarian cancer has improved over time and there are implementable strategies to further improve quality.

The research work is an analysis of prospective data from a national cohort study – kConFab, which is a unique multi-disciplinary research co-operative with a well-structured database of families with strong history of breast and ovarian cancer. These families were recruited via 24 Family Cancer Clinics in Australia and New Zealand. Therefore, the findings of the research work are likely to be representative of current RRSO practice for high risk women in Australia and New Zealand.

Overall, 158/159 (99%) had “adequate” surgery and 108/164 (66%) had “adequate” pathology. Compared to the published series of RRSOs performed prior to 2008 in women enrolled in the same cohort, where “adequate” surgery occurred in 182/201 (91%) cases and “adequate” pathology in 46/201 (23%) cases, there had been a significant improvement ($p < 0.001$) in this contemporary sample. The statistically significant improvement in the prevalence of adequate RRSO pathology, from 23% to 66% ($p < 0.001$), between this contemporary study sample and previously published data from women enrolled in the same cohort study may reflect better clinician awareness of the importance of detailed pathology examination of RRSO specimens. However, the definition of “adequate” pathology in this research work would be the minimum requirement for RRSO pathology assessment, although in adherence to the Cancer

Australia guidelines at the time.¹⁵ Furthermore, there is definitely room for further improvement in quality of RRSO pathology evaluation. The emerging gold standard for RRSO pathology evaluation is to apply the SEE-FIM protocol and this is supported by the recent updates to the EviQ and NCCN guidelines.^{16,23} Even as a mandatory requirement in the clinical trial setting, there appear to be multiple barriers to conforming to these standards, as exemplified by the 85% compliance rate in the GOG-0199 study.³⁰ Similarly, a more recent preliminary report investigating compliance with RRSO surgical guidelines in 10 hospitals, within a large metropolitan area in United States, showed compliance rate of 69%.⁶⁰

Of note, the 164 RRSOs evaluated in our study were performed at 78 centres across Australia and New Zealand, ranging from regional to academic centres. Only 37% (N=61/164) of RRSOs were performed in tertiary academic centres. Among the 103 RRSOs performed in non-tertiary centres, 52% (n=54/103) were performed in private hospitals by gynaecologic oncologists who were also affiliated with a tertiary academic centre. Although the SEE-FIM protocol has been adopted by tertiary centres in Australia in recent years, it is unclear if the same practice has been widely implemented in a nationwide setting. Future studies relevant to the work presented here should include further elucidation of the extent of implementation of the SEE-FIM protocol in Australian practice and the optimal management for occult carcinomas or precursor lesions (STICs) found at the time of RRSO.

The median ages at RRSO in this study were 46.5 years and 46 years for *BRCA1* and *BRCA2* mutation carriers respectively, which was higher than the recommended age of the NCCN guidelines. This is consistent with the findings in other countries, where the adherence to recommended age for RRSO were generally low.^{61,62} Therefore, it is reasonable to anticipate that the potential of detecting precursor lesions or occult ovarian cancer to be higher, coinciding with their age-related risk. Whilst efforts are made to increase awareness of the optimal age recommendations for RRSO in g*BRCA1/2* mutation carriers, it is equally important to emphasise that detailed RRSO pathology assessments are performed on these specimens.

Three pertinent clinical factors were associated with adequate pathology suggesting changes to clinical practice that might further improve quality. Firstly, optimal pathology evaluation was more likely if RRSOs were performed by a gynaecologic oncologist, rather than a general gynaecologist (OR 8.2; 95%CI [3.6–20.4]; p<0.001). This may be related to the fact that most gynaecologic oncologists practice in a tertiary centre in

Australia, where multi-disciplinary surgico-pathological meetings are the norm, rather than reflecting differences in surgical expertise between these two clinician groups. A recent multicentre study in the United States investigating RRSO quality reported similar findings that surgery performed by a gynaecologic oncologist compared to obstetrician/gynaecologist are associated with higher compliance to RRSO surgical and pathology processing protocols.⁶⁰ Secondly, in our study, communication from the surgeon to the pathology department that the patient was at high risk of OC was also independently associated with adequate pathology (OR 19.4; 95%CI [3.1–385]; $p=0.008$). In the general population, most women who undergo gynaecological surgery do so for benign gynaecologic reasons, so limited pathology examination of their operative specimen sometimes occurs. Our finding highlights the importance of communicating to the pathologist that the specimen has been taken from a woman at high risk of ovarian cancer. Advance direct communication to pathology colleagues about the intention of the procedure will ensure that the specimen is marked for a detailed pathologic examination (such as using the SEE-FIM protocol). Given that a proportion of RRSOs will be performed at regional centres, advance communication would also allow an opportunity for the specimens to be directed to tertiary centres within each state for central pathology processing and review. Last but not least, women who did not have concurrent hysterectomy were more likely to have adequate pathology (OR 2.5, 95%CI [1.1-6.0], $p=0.03$). This finding may suggest that, when there is a greater load of operative specimen, examination of the crucial components (tubes and ovaries) is less likely to occur.

The findings of this research contributed to the published literature providing further evidence to support stronger recommendations for pathology evaluation of RRSO specimens, as reflected in the updated EviQ guidelines.¹⁶ The manuscript has been distributed to all Family Cancer Centres and kConFab members (surgeons, clinicians, pathologists and consumers) to increase awareness of the importance of detailed RRSO pathological evaluation.

6.2.2 Cancer prevention: The risk of uterine cancer in Australasian gBRCA1/2_{mut} carriers does not justify the recommendation for routine hysterectomy at the time of risk-reducing salpingo-oophorectomy

Of the 828 women identified and prospectively followed for a median of 9 years, a total of five incident cases of uterine cancer were reported among gBRCA1/2_{mut} carriers residing in Australia and New Zealand. Relative to the expected incidence of 2.04 cases

for the general population, the SIR was 2.45 (95%CI: 0.80-5.72; P=0.11). Despite being the largest cohort of *gBRCA1/2*_{mut} carriers available in Australia and New Zealand, this study had limited power due to the relatively small number of events observed. The finding of the approximately two-fold increase in risk of uterine cancer in *gBRCA1/2*_{mut} carriers, SIR of 2.45, was consistent with the other studies in the literature.³⁸⁻⁴² Therefore, the findings of this study (5 incident cases of uterine cancer among *gBRCA1/2*_{mut} carriers and SIR of 2.45) do not justify the recommendation for routine prophylactic hysterectomy at the time of RRSO. This conclusion is consistent with the current literature and international guidelines recommending against prophylactic hysterectomy on the basis of uterine cancer risk-reduction alone.^{16,23,63}

Of note, all uterine cases in this study were of endometrioid adenocarcinoma subtype and none had serous subtype. Tamoxifen exposure is a known risk factor for uterine cancer and thereby also a confounding factor to this study. Three out of five cases of uterine cancer in this study had history of breast cancer and were treated with tamoxifen. The lack of serous subtype cases in this study is of particular importance, as this finding is in contrast to the study by Shu et al, suggesting an increased risk of specifically serous uterine cancer in *BRCA1* mutation carriers.⁴² A recent meta-analysis suggested a link between *gBRCA1/2*_{mut} carrier and serous uterine cancer, however this finding was driven by Shu et al's study and has not been seen in other prospective studies, including ours.⁶⁴ The risk of serous uterine cancer in *BRCA1* mutation carriers still requires further evaluation in collaboration with international databases and resources before more definitive recommendations can be made.

The decision for hysterectomy at the time of RRSO in a *gBRCA1/2*_{mut} carrier may still be considered for reasons other than risk-reduction. One may choose to have hysterectomy in order to facilitate the use of unopposed oestrogen-only hormone replacement therapy, which may reduce the long-term impact of surgical menopause and appears to be more favourable for breast cancer risk profile, compared to the combination of oestrogen and progesterone.⁶⁵⁻⁶⁸ A prospective, longitudinal cohort study reported that the 10-year actuarial risk of breast cancer was significantly lower for *BRCA1* mutation carriers who used oestrogen-alone compared to those who used combination oestrogen and progesterone (12% versus 22%; p=0.04).⁶⁷ For each year of oestrogen-containing hormone replacement therapy, there was an 8% reduction in breast cancer risk (HR 0.92; 95% CI 0.83-1.01; p=0.07); these associations were stronger for women who underwent RRSO prior to age 45.⁶⁷ Tamoxifen use is a known risk factor for development of uterine cancers.^{41,69} Hence, other reasons to consider hysterectomy at the time of RRSO include

to facilitate the use of tamoxifen in mutation carriers who choose tamoxifen for treatment or prevention of breast cancer; or to treat benign gynaecological conditions such as menorrhagia.

The findings of this research contributed to the literature regarding the risk of uterine cancer in g*BRCA1/2*_{mut} carrier within the Australasian population, as reflected in the updated EviQ risk management guidelines that the decision to perform hysterectomy at the time of RRSO should be individualised and not justified for uterine cancer prevention alone.^{16,17} The increased expense and morbidity of hysterectomy may be appropriate in some patients for reasons other than risk-reduction, but requires careful consideration and individual counselling. The manuscript has been distributed to all Family Cancer Centres and kConFab members to improve understanding of uterine cancer risk in g*BRCA1/2*_{mut} mutation carriers to aid decision making regarding hysterectomy at the time of RRSO.

6.2.3 Tolerability of experimental treatment at disease recurrence: Women with advanced gynaecological cancers experienced greater low grade adverse events compared to other cancer types, thus warranting specific attention to support their symptom burden

A total of 4,269 patients, enrolled in the 150 phase I trials from the National Cancer Institute database, were divided into three groups to allow comparison of their toxicity profile: *i*) females with gynaecological cancers (n=685); *ii*) females with non-gynaecological cancers (n=1698); and *iii*) males with cancers (n=1886). The median age of all patients at the time of study enrolment was 58 years (range, 18-87) and patients had a median of 4 lines of prior therapy (range, 1-20). The top three primary cancers represented were gastrointestinal (n=1153, 27%), gynaecological (n=685, 16%) and breast (n=475, 11%). The main therapeutic agents investigated were targeted therapies (n=97/150, 65%), cytotoxic agents (n=35/150, 23%) and immunotherapies (n=13/150, 9%).

Comparing the three groups, the average of total AEs reported during treatment were significantly different (17.1 vs 14.7 vs 13.5, adjusted $P < 0.001$) despite being similar at baseline (7.0 vs 7.4 vs 7.0, $P = 0.09$). In terms of AE severity, the main difference was that females with gynaecological cancer had greater average of total grade 2 AEs reported compared to other groups (4.6 vs 3.9 vs 3.5), but was similar in terms of grade 3-5 AEs (2.3 vs 2.3 vs 2.1). There was also greater average of total drug-related AEs in

females with gynaecological cancer (8.3 vs 6.9 vs 6.2). The five most prevalent AEs in females with gynaecological cancer were nausea (n=617, 90%), fatigue (n=587, 86%), anaemia (n=381, 56%), anorexia (n=357, 52%) and vomiting (n=355, 52%).

Women with gynaecological cancer experienced more grade 2 AEs whilst participating in clinical trials. There is now growing recognition to incorporate grade 2 AEs into consideration of DLT definition given its impact on patients' quality of life and drug tolerability in the long term.⁷⁰⁻⁷³ Information throughout the treatment cycles, specifically intolerable clinical grade 2 toxicities leading to a reduction in patients' relative dose-intensity (RDI) should be incorporated when the recommended phase 2 dose is determined for further studies.⁷³ The low grade AEs, which are observed in this study, seem to be more prevalent in women with gynaecologic cancers and may not be recognised as problematic. Study dose modifications, such as changing continuous therapy to intermittent dosing, should be made if study patients are experiencing recurrent grade 2 AEs.

Integration of patient-reported outcomes (PRO) into clinical trials may provide greater insight on regimen tolerability, patient symptom burden and implications of AEs beyond the CTCAE grading by clinicians.⁷⁴ It is known that the AEs considered intolerable by patients differ from those that are of concern to clinicians or meet the definitions of DLT.⁷¹ The most feared AEs by patients are typically symptoms that directly impact their quality of life such as fatigue, nausea, anorexia and vomiting, highlighting the importance of incorporating supportive care strategies to improve their symptom burden.⁷¹ Furthermore, it is also known that there is a discrepancy between AEs assessed by clinicians and the patient reported outcomes (PRO).⁷¹ Hence, it is possible that the AE rates shown in this study may be underestimated.

To this end, the NCI has developed the patient-reported outcomes version of CTCAE (PRO-CTCAE) for use in clinical trials and is actively addressing the operational concerns to allow its full integration in clinical trials in collaboration with the U.S. Food and Drug Administration and the Office for Human Research Protection.⁷⁵⁻⁷⁷ In addition, fit-for-purpose PRO measures, such as MOST – Measure of Ovarian Symptoms and Treatment, can be used in clinical trials specifically for women with recurrent ovarian cancer.⁷⁸ Incorporation of PRO into trial assessments may uncover low grade AEs that could be addressed early on and allow better assessment of patients' tolerability to the investigated drug.

6.2.4 Development of malignant bowel obstruction (MBO): Implementation of a comprehensive interprofessional MBO program has a significant impact to improve the outcome of women with advanced gynaecological cancer who developed bowel obstruction

In this retrospective analysis, the cumulative length of stay (LOS_{sum}) of 169 patients presenting with MBO were compared before and after the implementation of the multidisciplinary MBO program. Patients in the MBO program group were reported to have a significantly shorter average LOS_{sum} in hospital within the first 60 days of MBO diagnosis, 13 vs 22 days (adjusted P=0.003). The same findings remained even after expanding to the first 90 and 180 days of MBO diagnosis. Furthermore, the median overall survival of patients in the MBO program group was significantly longer compared to the baseline group, at 243 vs 99 days (P=0.002). Given the difference in LOS, it is not surprising that the costs for patients in the MBO program group were less than the baseline group with a mean of \$12,284 vs \$18,934 CAD per hospital admission.

The median age at MBO diagnosis was 62 years (range, 31-91) and the majority of patients had ovarian cancer (n=124, 73%). Since the initial diagnosis of MBO, patients had a median of two hospital admissions (range, 0-8) and the median time interval between MBO-related admissions was 26 days (range, 1-880). These clinical characteristics were in line with existing literature,^{56,79,80} and provided further insights given its larger sample size and the direct comparison of their MBO care before and after implementation of a comprehensive interprofessional MBO program in the same institution under the same team of health professionals. Therefore, the overall reduction in hospital LOS_{sum} reflects the effectiveness and efficiency of the systematic MBO care pathway implemented through the pilot interprofessional MBO program. The MBO program has also improved cost-effectiveness by reducing unnecessary hospitalisation; and patient experience by shifting and sustaining their care to an out-patient model (reduced hospital cost and patient costs such as transportation and parking).

The key to the successful delivery of high-quality care support in the out-patient setting lies in the proactive standardised triage and assessment by specialised gynaecological-oncology nurses and the emphasis on patient education to promote awareness and early intervention to bowel function derangement (constipation or partial bowel obstruction). The program also connected patients with community care services, such as home palliative care services, community ambulatory nursing care, and domestic care services to maximise patient support at home without incurring extra costs to the hospital system.

In patients with bowel obstruction and a single transition point, our data suggested that the care provision in the MBO program group had enabled considerations for less invasive and better selection of treatment approach without necessarily compromising outcome. For patients with large bowel obstruction, a higher proportion of patients in MBO program group were offered a colonic stent procedure (63% vs 19%) instead of open surgery (25% vs 63%); both groups achieved an equivalent success rate of 75% in resolving bowel obstruction. In addition, for patients with small bowel obstruction, there appeared to be better selection of patients suited for surgery in the MBO program group; all 3 patients who were offered surgery had successful resolution of bowel obstruction, compared to 4 out of 7 patients in the baseline group.

The palliative care team contributed to the care of women with MBO and their involvement was similar in the MBO program group and the baseline group (81% vs 82%). Of note, patients under the MBO program group were more likely to receive two or more interventions (42% vs 33%). The MBO program group received less palliative surgery (11% vs 21%) but more chemotherapy (83% vs 56%) and the proportion of patients who received TPN (27% vs 23%), stent procedure (8% vs 5%) or radiation therapy (5% vs 4%) were relatively similar. As part of the MBO program, all new MBO cases were discussed in the MBO multidisciplinary meeting. The integration of the interprofessional team model has allowed provision of multimodal MBO treatment plans for patients and undoubtedly improved communication among the disciplines.

The findings of this study added to the limited existing literature regarding the use of chemotherapy and TPN in patients with MBO. Approximately 32% (n=37/115) who received chemotherapy after MBO diagnosis subsequently received up to three further lines of chemotherapy at the time of disease progression. Conversely, 24% (n=41/169) of patients in this study received TPN for a median duration of 69 days (range, 9-739). Of those, nine patients were able to resume oral diet as they responded to treatment intervention (2 had diverting stoma surgery and all had chemotherapy). A small subgroup (n=11/41, 27%) received TPN for a duration beyond six months, up to two years. Despite the controversy regarding the use of chemotherapy and TPN in patients with incurable cancer who developed bowel obstruction, the findings in this study add to the body of the literature demonstrating a small subpopulation of patients who appears to benefit from these interventions. However, there are no established predictive factors to guide the selection of these patients at this stage. Therefore decision-making to initiate TPN requires careful consideration and patients should also be counselled about the realistic

goals of TPN and more importantly, limitations of care including situations when TPN would be ceased (if no longer responding to systemic treatment or deterioration in health status). Further studies of the role of palliative chemotherapy and TPN in the setting of MBO and how to best select patients that would benefit from these interventions is warranted.

The prospective study (MAMBO study, NCT03260647) incorporating patient reported outcome measures will help inform practice and establish new benchmarks for evidence-based MBO management. As of August 2019, a total of 61 patients have been enrolled in the MAMBO study.

The implementation of an interprofessional MBO program can reduce duration of hospitalisation, support and empower patients in an out-patient setting without adding additional financial or infrastructure strain to a specialised cancer centre. A collaborative approach is instrumental in optimising care of patients with MBO and improving patient outcomes. The pilot interprofessional MBO program has now been incorporated as part of standard of care for patients with gynaecological cancers at Princess Margaret Cancer Centre. There is provincial support by the Cancer Council of Ontario to gradually roll out the MBO program in other cancer centres within Ontario. The MBO program may also be generalisable to patients with gastrointestinal cancers who are also at risk of developing MBO.

6.3 Conclusion

The research work carried out in this thesis has addressed key clinical gaps along the ovarian cancer trajectory that are of significant impact to our patients. Based on the body of work, practical care recommendations have been generated to guide clinicians on risk-reducing surgery management, how to improve symptom burden for women undergoing cancer treatment, and how to improve their care for malignant bowel obstruction. Furthermore, the research work has generated informative data to use as an evidence base for national guidelines and institutional policies towards better care provision for our patients.

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x. Appendices

Appendix 1. Education Materials Developed for Patients with Malignant Bowel Obstruction (MBO) or At Risk of MBO

1.1 Patient Pamphlet: Know How to Maintain Good Bowel Function (7 pages, only front page presented here)

Patient Education
Improving health through education



Know how to maintain good bowel function

Princess Margaret

For women who have gynecologic cancer

Read this pamphlet to learn:

- What is the bowel
- What is good bowel function
- What is constipation
- What is a bowel obstruction
- What should I do if I think I have a bowel obstruction
- What can I do to help prevent a bowel obstruction

Please visit the UHN Patient Education website for more health information: www.uhnpatienteducation.ca
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Toronto General
Toronto Western
Princess Margaret
Toronto Rehab

1.2 University Health Network (UHN) Stool Chart

 UHN Stool Chart			
Consistency HARD (H)	Type 1		Separate hard lumps, like nuts (hard to pass)
	Type 2		Sausage-shaped but lumpy
FORMED (F)	Type 3		Like a sausage but with cracks on surface
	Type 4		Like a sausage or snake, smooth and soft
	Type 5		Soft blobs with clear-cut edges (passed easily)
LOOSE (L)	Type 6		Fluffy pieces with ragged edges, a mushy stool
WATERY (W)	Type 7		Watery, no solid pieces. Entirely liquid

Constipation



MOST COMMON

Diarrhea

1.3 Bowel Medication to Help Manage Bowel Function

Bowel Medications to Help Manage Bowel Function	
	Some examples of Medications
Docusate Sodium (Colace/Soflax): This medication adds oil to your stool (poo) to make it 'soft'. It does not cause cramping; the pills are red in colour.	
Senokot(Senna): This medication is a laxative; it pushes the stool (poo) out. It can cause some cramping; the pills are often brown in colour	
Bisacodyl (Dulcolax): This medication is a laxative; it pushes the stool (poo) out. It can cause some cramping; the pills are often yellow in colour.	
Polyethylene Glycol (PEG) or (RestoraLAX / LaxAday): This medication is a laxative that takes water from the body to soften the stool which makes it easier to pass.	
Lactulose: This medication is laxative syrup that takes water from the body to soften the stool which makes it easier to pass.	
*Please note there are many different brands that these medications come in, the photos are provided as examples for your reference. Please ask your pharmacist if you have any questions. *	

1.4 Diet Guidelines for People with Bowel Narrowing (Phase 1 – Most Restrictive)

<u>PHASE 1 - MOST RESTRICTIVE</u>		
<u>FOOD GROUP</u>	<u>FOODS ALLOWED</u>	<u>FOODS TO AVOID</u>
VEGETABLES	all vegetable juices	All other vegetables (raw, cooked or pureed)
FRUITS	all fruit juices except prune juice	All fresh, frozen, canned or pureed fruit; prune juice
BREADS, CEREALS & GRAINS	Breads: white, egg, French, Italian, English muffins, tea biscuits, crumpets, scones (without raisins)	Breads: whole grains like whole wheat, pumpernickel, rye or those with nuts, seeds or dried fruits, high fat breads like croissants and donuts
	Cereals: Cheerios, Rice Krispies, Cornflakes, Special K, Crispix, Triples, cream of wheat	Cereals: Bran Flakes, All Bran, Bran Buds, Shredded Wheat, Red River, Oatmeal, Fruit & Fibre, Meuslix, granola
	Grains: white rice, pasta noodles, plain cookies (ie. social tea, gingersnap, digestive), plain crackers (saltine, melba toast, rice cakes), plain muffins made with white flour (ie. lemon)	Grains: egg noodles, brown or wild rice, barley, whole grain crackers (ie. Rye Crisp), cookies (ie. Oatmeal, fig bar) all other muffins (ie. bran, banana, oatmeal, apple, orange)
HIGH PROTEIN FOODS	eggs, milk, cheese, yogurt (plain, vanilla, cappuccino), strained cream soups, pudding, custard, ice cream, sherbet, ovaltine, nutritional supplements (ie. Ensure, Boost, Carnation, Instant Breakfast)	all meat, poultry, fish, peanut butter (smooth or chunky), legumes (ie. kidney beans, split peas), fruit bottom yogurt, cream soups not strained, dairy products containing nuts or dried fruits
MISCELLANEOUS	clear broth, broth with noodles, tea, coffee, soda pop (flat), Postum, jello, popsicles, pretzels, honey, jelly, fats as tolerated (ie. butter, oil)	nuts, seeds, coconut, jam, marmalade, pickles, popcorn, taco chips

1.5 Diet Guidelines for People with Bowel Narrowing (Phase 2 – Moderately Restrictive)

PHASE 2 - MODERATE RESTRICTION

<u>FOOD GROUP</u>	<u>FOODS ALLOWED</u>	<u>FOODS TO AVOID</u>
VEGETABLES	vegetable juices pureed vegetables * blenderized vegetable soups * cooked white potato without skin * If gas is a problem, avoid pureed "gassy" vegetables such as cabbage, broccoli, cauliflower and turnip.	all other raw or cooked whole vegetables
FRUITS	all fruit juices including prune juice (1/4 cup serving), pureed or baby fruits only	all other fruits (fresh, frozen or canned)
BREADS, CEREALS & GRAINS	Breads: whole wheat, white, egg, French, Italian, rye or pumpernickel (no seeds) Cereals: low in fibre (serving size unrestricted) - Rice Krispies, Cornflakes, Cheerios, Crispix, cream of wheat, Triples, Special K Moderate in fibre (3/4 cup or less) - oatmeal Grains: all pasta noodles, white rice crackers and cookies without nuts, seeds or dried fruit muffins with allowed ingredients (ie. plain oatmeal, apple, banana)	Breads: with nuts, seeds, dried fruits, added bran, cracked wheat or other coarse food particles Cereals: high in fibre - All Bran, Bran Buds, Grapenuts, Fibre One, wheat germ, Red River, 100% bran (unprocessed), Fruit & Fibre, Meuslix, granola Moderate in fibre - Bran Flakes, Shredded Wheat, Corn Bran, Oat Squares, Shreddies, oatbran Grains: brown or wild rice, barley crackers and cookies containing nuts, seeds or dried fruit muffins with nuts, seeds and fruit 'not allowed' (ie. oatmeal with raisin, blueberry, bran)

<u>FOOD GROUP</u>	<u>FOODS ALLOWED</u>	<u>FOODS TO AVOID</u>
HIGH PROTEIN FOODS	poultry, fish, minced meats, eggs, smooth peanut butter, any pureed meats, fish or poultry milk, milkshakes, cheese, yogurt (plain, vanilla, cappuccino or peach), strained cream soups, pudding, custard, Ovaltine, ice cream, sherbet, nutritional supplements (ie. Ensure, Boost, Carnation, Instant Breakfast)	sliced meat, chunky peanut butter, legumes like kidney beans even if pureed due to gassy nature yogurt with seeds (strawberry, blueberry, raspberry), cream soups not strained, ice cream with nuts or fruit (ie. spumoni)
FATS	small amounts of all fats (ie. butter, margarine, vegetable oil, mayonnaise)	fats in large amounts (may cause stomach discomfort)
MISCELLANEOUS	tea, coffee, broth, Postum, soda pop, jello, snack foods and desserts without nuts or seeds, honey, jelly, mustard, ketchup	seeds, nuts, coconut, olives, pickles, radish, jam, marmalade, popcorn

NOTE:

If you feel gastrointestinal symptoms are getting worse, switch to the lighter, PHASE 1 diet guidelines.

1.6 Diet Guidelines for People with Bowel Narrowing (Phase 3 – Least Restrictive)

<u>PHASE 3 - LEAST RESTRICTION</u>		
<u>FOOD GROUP</u>	<u>FOODS ALLOWED</u>	<u>FOODS TO AVOID</u>
VEGETABLES	WELL COOKED vegetables only without seeds or skins: Asparagus tips, beets, carrots, eggplant, green or yellow beans, potato (white or sweet), squash, parsnip, pumpkin, turnip *, zucchini, tomato paste, tomato sauce, vegetable juices, blenderized vegetable soups * If gas is a problem, avoid these vegetables even if pureed.	all other raw or cooked vegetables (unless pureed): broccoli*, brussel sprouts*, cabbage*, cauliflower*, celery, corn*, cucumber, endive, escarole, green or red peppers, lettuce, onion*, okra, peas*, radish, spinach* soups containing chunky vegetables on the "avoid" list
FRUITS	Peeled Fresh Fruits: apple, ripe banana, ripe pear, peach, nectarine, cantaloupe, honeydew, watermelon Canned Fruit: peaches, mandarin oranges, pears, fruit cocktail All Fruit Juices: including prune juice	All Other Peeled Fresh, Frozen or Canned Fruits, Especially: oranges, grapefruit, pineapple, grapes, kiwi, cherries, rhubarb, berries, persimmons Dried Fruits: raisins, dates, figs, apricots
BREADS, CEREALS & GRAINS	Breads: whole wheat, white, egg, French, Italian, rye or pumpernickel (no seeds), plain pancakes, waffles, crepes Cereals: low in fibre (no limit to serving size) - Rice Krispies, Cornflakes, Cheerios, Crispix, cream of wheat, Triples, Special K Moderate in fibre (3/4 cup or less) - Bran Flakes, Shredded Wheat, Corn Bran, Oat Squares, Shreddies, oatmeal, oatbran	Breads: with nuts, seeds, dried fruits, added bran, cracked wheat or other coarse food particles Cereals: high in fibre - All Bran, Bran Buds, Grapenuts, Fibre One, wheat germ, Red River, 100% bran (unprocessed), Fruit & Fibre, Meuslix, granola

<u>FOOD GROUP</u>	<u>FOODS ALLOWED</u>	<u>FOODS TO AVOID</u>
BREADS, CEREALS & GRAINS	Grains: all pasta noodles, white rice crackers and cookies without nuts, seeds or dried fruit muffins with allowed ingredients (ie. plain oatmeal, apple, banana)	Grains: brown or wild rice, barley crackers and cookies containing nuts, seeds or dried fruit muffins with nuts, seeds and fruit 'not allowed' (ie. oatmeal with raisin, blueberry, bran)
HIGH PROTEIN FOODS	tender meats, fish, poultry, eggs, smooth peanut butter milk, milkshakes, cheese, yogurt (plain, vanilla, cappuccino or peach), strained cream soups, pudding, custard, ice cream, sherbet, Ovaltine, nutritional supplements (ie. Ensure, Boost)	tough or over-cooked sliced meat, chunky peanut butter, legumes (ie. split peas, kidney beans) yogurt with seeds (strawberry, blueberry, raspberry), cream soups not strained, ice cream with nuts or dried fruit (ie. spumoni)
FATS	small amounts of fats (ie. butter, margarine, vegetable oil, mayonnaise)	fats in large amounts (may cause stomach discomfort)
MISCELLANEOUS	tea, coffee, broth, Postum, soda pop, jello, snack foods and desserts without nuts or seeds, honey, jelly, mustard, ketchup	seeds, nuts, coconut, olives, pickles, relish, jam, marmalade, popcorn

NOTE:

If you feel gastrointestinal symptoms are getting worse, switch to the lighter, PHASE 1 or PHASE 2 diet guidelines.

Appendix 2. Synopsis of the MAMBO Protocol: Risk Stratified Multidisciplinary Ambulatory Management of Malignant Bowel Obstruction (MAMBO) Program for Women with Advanced Gynaecological Cancers

Clinical Protocol MBO
Version Date 22 Mar 2018

Risk stratified Multidisciplinary Ambulatory management of Malignant Bowel Obstruction (MAMBO) program for women with advanced gynecological cancers

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Interventional Radiologist:

Radiologist:

TPN Physician:

Professional Practice Director:

Clinical Director:

Nurse Specialist:

Dietitian

Dr Stephan Laframboise

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Dr Yeh Chen Lee

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Protocol Synopsis

Title	Management of Malignant Bowel Obstruction (MBO) in Patients with Advanced Gynecological Cancers
Primary Objectives	To optimize the multidisciplinary care management of MBO in patients with advanced gynecological cancer treated at University Health Network (UHN) including Princess Margaret Cancer Centre and Toronto General Hospital; which include in-patient and ambulatory management algorithm for MBO Measured by a ratio of days alive and out of hospital compare to days in hospital within the first 60 days after diagnosis of MBO
Secondary Objectives	- To evaluate the treatment outcomes of patients with MBO - Measured by resolution of MBO and overall survival - Measured by transition through specific bowel management colour code system - To evaluate the impact of MBO management on number of emergency room visits, hospital admission and number of days alive and outside of hospital within the first 168 days (6 months) after the diagnosis of MBO - To evaluate the impact of ambulatory MBO management on patient reported outcomes using Distress Assessment & Response Tool (DART) - To evaluate the nutritional status of patients with MBO - To evaluate the clinico-pathological factors that may predict benefit from palliative surgery, chemotherapy and total parenteral nutrition (TPN). - To improve patients' understanding and awareness of MBO with patient education material.
Exploratory Objectives	- To evaluate tumour microenvironment via molecular profiling on tissue obtained during palliative or therapeutic procedures or surgery - To explore the use of a mobile health application "Lifeguard Mobile" for symptom monitoring in the ambulatory care setting - To assess the feasibility of an ambulatory TPN program - To assess the use of a checklist of MBO risk factors as part of nursing assessment to identify patients at risk of MBO
Eligibility	- Histologically and/or cytologically confirmed gynecological cancer, including ovarian, fallopian tube, endometrial, cervical or primary peritoneal cancer - Deemed to be at risk of developing or have a clinical diagnosis of MBO