British Gynaecological Cancer Society recommendations for women with gynecological cancer who received non-standard care during the COVID-19 pandemic

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ABSTRACT
During the COVID-19 pandemic, pressures on clinical services required adaptation to how care was prioritised and delivered for women with gynecological cancer. This document discusses potential ‘salvage’ measures when treatment has deviated from the usual standard of care. The British Gynaecological Cancer Society convened a multidisciplinary working group to develop recommendations for the onward management and follow-up of women with gynecological cancer who have been impacted by a change in treatment during the pandemic. These recommendations are presented for each tumor type and for healthcare systems, and the impact on gynecological services are discussed. It will be important that patient concerns about the impact of COVID-19 on their cancer pathway are acknowledged and addressed for their ongoing care.

BACKGROUND
During the COVID-19 pandemic, there have been significant pressures on clinical services that required adaptation to how care was delivered for women with gynecological cancer.1 There have been occasions when it was necessary for treatment to deviate from what would be considered standard of care, due to clinical resource availability, increased risk from COVID-19 infection, and prioritization frameworks.2-7 In the international COVIDSurg study, 17% of 4722 women undergoing surgery for gynecological cancer had alteration in first-line treatment, including treatment delay or adaptation of surgery.8

In the UK, the COVID-19 pandemic severely impacted on gynecological cancer services resulting in the need for prioritization of care.1 There was a loss of anesthetic and intensive care availability with many centers having extremely limited or even no surgical capacity, while many staff members were redeployed to acute services. There was also national prioritization of radiotherapy and systemic therapy availability, with alteration of regimens to reduce the risks of COVID-19 infection when immunocompromised.

The British Gynaecological Cancer Society convened a multidisciplinary working group to develop recommendations for the onward management of women with gynecological cancer who have been impacted by a change in treatment. This document discusses ‘salvage’ measures based on expert opinion with recommendations presented by tumor type and for healthcare systems.

RECOMMENDATIONS ON DIAGNOSTIC PATHWAYS AND THE DUTY OF CANDOR
The COVID-19 pandemic has led to increased numbers of women presenting with advanced gynecological cancer, often as an emergency. This may have been due to a lack of medical access because of resource pressures, or due to a delay in presentation because of patient concerns about accessing medical care during the pandemic, which had a particular impact on frailter patients. While acknowledging their presentation may have been delayed, these women should be managed according to established national and international guidelines.

When there has been a delay or variation in treatment, there is a duty of candor to discuss with patients how their care varied from the normal pathway, whether this has potential impact on the survival benefits of treatment, and the implications for their ongoing care.9

RECOMMENDATIONS FOR OVARIAN CANCER
The COVID-19 pandemic led to significant issues in operating capacity, with many centers altering their ‘usual’ clinical practice according to COVID-19 infection rates and availability of high dependency units for post-operative care.

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Patients with Newly Diagnosed Ovarian Cancer

1. Due to reduced operating capacity, many centers deferred primary surgery and some women were not offered surgery either in the primary or interval setting. As a result, some women may have missed the opportunity to undergo cytoreductive surgery and their prognosis may have been impacted as a result.10
   - Although evidence is not available, it is recommended that women who did not have primary or planned interval surgery should be offered surgery after six cycles of treatment (or within 3 months of the last cycle of treatment). If currently receiving maintenance treatment, including poly ADP ribose polymerase (PARP) inhibitors or bevacizumab, treatment would have to be interrupted in the peri-operative period.
   - Women who started maintenance treatment after six cycles of chemotherapy and remain in remission should continue maintenance treatment and be considered for surgery at progression if an appropriate candidate.
   - Women who are on maintenance treatment and have residual disease can continue on maintenance treatment beyond 2 years until progression.
   - Women with asymptomatic disease should be considered for surgery or can continue maintenance treatment. If a patient has stable disease on treatment, careful consideration should be given before stopping the maintenance drugs.
   - Women with a symptomatic pelvic-abdominal mass should be considered for surgery regardless of the time from chemotherapy.
   - Additional post-operative chemotherapy following delayed surgery (after six cycles of neoadjuvant chemotherapy) is not routinely recommended, but may be considered depending on the time from last platinum-based chemotherapy, tumor burden at surgery, residual disease, pathologic response scores, and chemotherapy toxicity. An ongoing study looking at the timing of interval cytoreductive surgery (after three or six cycles) will provide more evidence and help with the decision-making process (NCT 03579394).

2. Due to lack of intensive care availability, patients assessed as frail or high risk for peri-operative morbidity (as per local guidelines and practice) may not have been offered surgery during the surges of the pandemic. It is recommended that these patients be re-evaluated for fitness to undergo radical surgery when the COVID-19 prevalence changes. Once vaccination is established and infection rates drop, the concomitant risk of COVID-19 related morbidity from surgery should also reduce.11 Age alone should not be a deciding factor for surgery regardless of COVID-19.

3. Many centers altered their systemic therapy schedules due to the potential risks for patients in the post-operative and neo-adjuvant settings. For example, some women stopped chemotherapy after four cycles and others were not offered maintenance treatment with bevacizumab. These changes might impact overall survival, particularly for women with stage IV or bulky residual disease. It is advised that women who discontinued chemotherapy after four cycles should continue on routine follow-up. Eligible women who have not been offered maintenance bevacizumab or PARP inhibitors should continue with routine surveillance and be considered for PARP inhibitors, where appropriate at relapse.

Patients with Recurrent Ovarian Cancer

1. During the COVID-19 pandemic some women with recurrent disease missed the opportunity to undergo secondary surgery which may have an impact on their survival.12 13 Women with operable disease who did not have secondary debulking surgery should be considered for surgery at a further relapse if deemed an appropriate candidate. Secondary surgery after three cycles of chemotherapy should not be routinely offered, as there are no prospective randomized data supporting this approach. Such surgery should be considered on an individual basis where the treating team considers there is a clear benefit. For patients who did not have surgery at diagnosis, the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) and iMODEL scores, used to predict operability at first recurrence of ovarian cancer, do not apply and will not be accurate tools to identify surgical candidates at relapse.14 15

2. Systemic therapy for relapsed ovarian cancer remains platinum-based chemotherapy (at least four cycles) followed by a PARP inhibitor for responders.16 In the UK, funding criteria during the COVID-19 pandemic did allow the use of PARP inhibitors without prior chemotherapy in exceptional circumstances. If patients were using PARP inhibitors as a treatment as opposed to a maintenance therapy, this should be continued for as long as deemed clinically appropriate. Similarly, if patients were on bevacizumab maintenance they should continue for as long as they benefit or the treatment is funded. Chemotherapy can then be considered in the event of future progression.

3. Women with low grade ovarian cancer who had surgery deferred should be offered debulking surgery if deemed appropriate surgical candidates. Where possible these women should be managed as per established guidelines.

4. Some women have been treated on the basis of ‘positive’ peritoneal cytology instead of a biopsy. In some cases, this approach might have led to a mis-diagnosis and/or a delay in determination of BRCA status. A biopsy remains the gold standard, but in certain cases it is acceptable to use a cell block to obtain a diagnosis, including immunophenotyping where there is no easily accessible tissue to biopsy. Somatic testing for BRCA variants or homologous recombination deficiency testing should be considered either on a biopsy or surgical specimen, but in selected cases may be possible where there is adequate DNA in the cell block.

RECOMMENDATIONS FOR UTERINE CANCER

1. Low-grade, early-stage endometrial cancer was categorized as a lower priority for surgery during the pandemic, since a delay of more than 4 weeks in treatment initiation was unlikely to have an impact on survival.17 When operating room capacity was limited, women were commenced on progestogen therapy until surgery was possible. However, in some patients there might have been inadequate tumor response or progression, or there may have been non-concordant histological findings between a low-grade endometrial sample and a high-grade tumor on the definitive surgical specimen.
   - Women who commenced endocrine therapy due to a lack of surgical availability should have definitive surgery ideally within 3 months of starting hormonal therapy or as soon as surgical...
capacity allows. There should be clinical review and repeat imaging after a maximum of 3 months, with non-responders prioritized for surgery.

► There should be a robust failsafe system for ensuring all patients who had surgery deferred are tracked.
► Once surgical treatment is complete, there should be no change to standard ongoing management with adjuvant therapy based on the final histopathological findings. Molecular classification, if available, may help to identify patients with low risk tumors who may avoid adjuvant treatment.18

2. Many women with endometrial cancer have co-morbidities that put them at a higher risk of mortality from COVID-19, including obesity, diabetes, and cardiovascular disease.19 20 Surgery may have been contra-indicated or deferred during the pandemic, particularly when high dependency availability was very limited and there was less support for optimizing patients including bariatric and pre-treatment optimization services.

► Re-evaluation of disease status should be undertaken, including imaging to assess whether there has been disease progression.
► Women who commenced progestogen therapy due to co-morbidities that contra-indicated surgery should be reviewed to assess whether optimization for surgery is possible or whether definitive radiotherapy is an option.

3. Due to the need to prioritize surgical time, there may have been a reduction in the number of patients who underwent surgical staging of lymph nodes. While this may have been a change in practice for some centers which would have resulted in an increase in the use of pelvic radiotherapy, established adjuvant treatment algorithms are based on whether nodal status is known or unknown.16 Therefore, no change from standard ongoing management is recommended.

4. Adjuvant treatment may have been omitted when it was unlikely to impact on overall survival, and, in particular, vaginal brachytherapy was not available in some centers. Patients may also have decided not to have adjuvant therapy due to concerns about having additional treatment during the pandemic. Therefore there will be a cohort of women who are at higher risk of relapse, particularly of loco-regional recurrence if vaginal vault brachytherapy or external beam radiotherapy was omitted.21 22 Whereas low-grade, low-risk endometrial cancer most frequently recurs in the vaginal vault within the first 2 years, loco-regional recurrence including lymph node metastases may occur later in intermediate and high-intermediate risk tumors.23 24

► Patients at increased risk of local recurrence should have regular clinical review with the aim of detecting a salvageable asymptomatic recurrence. They should not be recommended for patient-initiated follow-up.
► Surveillance imaging at 6 months and 18 months post-surgery should be considered for women with high-intermediate and high-risk disease who have not had external beam radiotherapy or nodal staging.

RECOMMENDATIONS FOR CERVICAL CANCER

Patients with Early-stage Cervical Cancer

In the UK, there was suspension of the cervical screening program during the initial phase of the COVID-19 pandemic. Delayed assessment may have resulted in women presenting with symptomatic or more advanced stage of disease. Surgery for early cervical cancer remained a high priority throughout the pandemic.1 However, some women who had local excision of early-stage disease had completion surgery delayed or modified due to the increased risk of peri-operative mortality from major procedures when COVID-19 infection rates were high.25

► When surgical management including lymph node assessment varied from usual care pathways, closer surveillance should be considered with MRI imaging for 2 years.

Patients Treated with Radiotherapy

Definitive radiotherapy for cervical cancer involves a course of external beam radiotherapy followed by intrauterine brachytherapy. Lack of resources, including anesthetic support or operating room capacity, may have necessitated changes to the intrauterine brachytherapy treatment pathway, using altered fractionation or referring to another hospital. Delays may have occurred due to lack of brachytherapy availability or to patients having COVID-19 infection. It may even have been necessary to use additional external beam radiotherapy in place of brachytherapy.1 There would be no significant impact to patient outcome if the change in brachytherapy fractionation still delivered treatment doses that met the Groupe Européen de Curiethérapie Committee of the European Society for Radiotherapy & Oncology (GEC-ESTRO) dose tolerances for tumor and organs at risk.26 27 A prolonged total treatment time with significant delay between external beam radiotherapy and brachytherapy will have a higher risk of persistent or recurrent disease, while omitting brachytherapy further reduces cure rates.28–30 For patients with this higher risk of local recurrence, surveillance including MRI imaging may detect salvageable persistent or recurrent disease.31

► No change to standard ongoing surveillance is required if the total tumor dose was consistent with GEC-ESTRO guidelines.
► Where there was a long gap with a total treatment time greater than 56 days, when lower tumor doses were delivered or when adjuvant radiotherapy was omitted, increased surveillance with MRI imaging 6 monthly over the following 2 years is recommended.
► It is recommended that patients in whom intrauterine brachytherapy was omitted or who had incomplete treatment should be evaluated by an examination under anesthetic and biopsy for consideration of completion surgery if there is persistent disease at 12–14 weeks after completing radiotherapy (subject to surgical capacity), provided there are no distant metastases on imaging.

RECOMMENDATIONS FOR VULVAL CANCER

Initial Treatment

Apart from seeing more delayed diagnoses and more advanced presentation of vulval carcinoma during the COVID-19 pandemic, most gynecological cancer centers in the UK maintained standard management of this disease. However, some hospitals may have encountered difficulty in accessing nuclear medicine resources for technetium-99m sentinel lymph node procedures for small (<4 cm) tumors without clinical lymphadenopathy. Centers may also have proceeded with radical vulval surgery, but omitted systematic inguino-femoral lymphadenectomy for larger tumors in order to reduce surgical morbidity and COVID-related peri-operative risks.
As a consequence, there may be some women with vulval cancer who did not undergo standard surgical lymph node staging.

Groin node recurrence risk is greatest in the first 2 years after diagnosis, particularly during the first 12 months. Therefore, the morbidity associated with delayed surgical inguinal lymph node staging, performed some months after primary vulval surgery, may outweigh the benefit of the diminishing probability of early diagnosis of nodal involvement. One study suggested that 3 monthly ultrasound of the groins for 2 years following negative sentinel node dissection was cost-effective in the detection of lymph node metastasis following sentinel lymph node assessment.32

 Patients whose surgery excluded surgical lymph node staging may therefore be monitored with at least 3 monthly clinical and ultrasound review until 12–24 months following surgery, aimed at early detection of nodal metastases.

Surveillance
The lack of clinical capacity and the risk to patients of in-person appointments during peak periods of the pandemic resulted in some patients missing follow-up appointments or having virtual consultations.

 Due to the field change effect of predisposing conditions, in-person follow-up with vulvoscopy/visual inspection should be re-instated as soon as possible.33 34

 Patients should be encouraged to self-manage and report new lesions or, in those with lichen sclerosus, new symptoms or lesions that do not start to respond to daily clobetasol propionate 0.05% ointment within 2 weeks. Patients should be reviewed urgently in these situations.

RECOMMENDATIONS FOR GYNECOLOGICAL CANCER FOLLOW-UP
Due to the need to reduce in-person hospital attendances, alternative follow-up models were introduced with increased use of remote consultations and patient-initiated follow-up.34 This was a necessary change during the pandemic and a positive consequence has been more widespread experience of these models of care. However, the need for rapid change in practice may have meant there was a loss of risk stratification and some women were not included in the decision to have ongoing patient-initiated follow-up. Patients have reported feeling abandoned by the sudden change and many have had a long period without face-to-face review.

There is a particular risk that there has been reduced detection of additional needs for vulnerable patients or safeguarding issues, and there have been increased numbers of patients who have been lost to follow-up.

 Ongoing development of patient-initiated and remote consultation models should be supported.

 Centers should ensure women are appropriately selected and counseled for their ongoing follow-up plan.

RECOMMENDATIONS ON COVID-19 VACCINATION
Vaccination significantly reduces the risks of infection and should be encouraged for all women planned for and undergoing cancer treatment.35 37 When national vaccination programs have a longer interval between vaccinations, clinicians may expedite the second dose of vaccine for patients undergoing treatment for cancer.38 A third vaccination may be indicated for patients who were previously immunocompromised depending on national policy.

SUPPORTIVE CARE AND PATIENT PERSPECTIVES
The challenges delivering care during the COVID-19 pandemic have had a profound impact on holistic and psychological support for patients and their families. At a time of high uncertainty and anxiety for women with gynecological cancer, the necessary reduction in direct patient contact will have affected their relationship with the clinical team. Many women had their care managed by a different team, or even in a different center, and there may have been challenging palliative care decisions. This will impact on our ongoing rapport and communication with patients and it is essential to prioritize reinstatement of supportive care services.

Patient Perspectives
COVID-19 has significantly affected cancer patients and family members. In a study including 1251 patients from 16 countries, the European Society of Gynecological Oncology-European Network of Gynecological Cancer Advocacy Groups (ENGAGE) found women were more fearful of cancer progression (71%) than developing COVID-19. Many patients, however, had high level anxiety that the disruption and uncertainty resulting from the pandemic would lead to changes in their cancer treatment, with 33% reporting modification to their treatment or follow-up.39

Studies have reported high levels of patient anxiety and a perception of medical abandonment during the pandemic.40 41 A qualitative analysis of 800 online forum posts with UK gynecology cancer charities shows that patients are extremely anxious about the impact of these changes on their current and future cancer care and contacted cancer charities to avoid burdening healthcare staff (S Sundar, personal communication, June 2021). It will be important for healthcare professionals to acknowledge and address these concerns as services recover so they may provide reassurance and appropriate care to their patients.

Clinical Nurse Specialists
Significant changes in care occurred when many nurse specialists were redeployed to support the general nursing demands of the pandemic, leaving women without appropriate essential support. The clinical nurse specialist will be pivotal to drive and support an effective ‘restart and recovery’ agenda, delivering effective remote assessment, helping patients navigate new technology, and advocating for patients.44 45 The nurse specialist workforce is highly skilled, often with a deep understanding of the needs for individual patients. Educating patients about the benefits of therapeutic well-being events and support groups as well as referral to specialist psychological support should help to address aspects of psychological distress.46

 Centers should recognize the need for additional clinical nurse specialist and holistic support resources for patients and carers in the recovery period.

IMPLICATIONS FOR GYNECOLOGY ONCOLOGY SERVICES
Once hospitals start to recover from the acute pressures of the pandemic, there will be a significant backlog of patients awaiting investigations and surgery.47
There is likely to be a surge of referrals for patients who have deferred presentation, and a higher proportion with advanced disease. Due to clinical pressures, there may have been delay or even cessation of screening and surveillance programs, while prophylactic surgery was deferred. Centers should aim to reinstate these preventative services as soon as possible.

The alteration in clinical pathways and working practices may have had an impact on team dynamics, with a risk of increased stress, anxiety, and sickness. Workforce planning and holistic support to staff should be prioritized during the recovery period. It is likely that training will have been impacted with many trainees redeployed to alternative roles, and it will be important to optimize ongoing training opportunities.

GYNECOLOGICAL CANCER RESEARCH

At the beginning of the pandemic, most UK sites paused active trial recruitment with research staff redeployed to COVID-19 wards. There were amendments to many trials to allow for remote monitoring and consent. After the pandemic, there will be residual clinical pressures with significant pressure on the availability of imaging and research biopsies. Currently, COVID-19 studies remain prioritized with resources diverted away from cancer research. The immediate priorities should include resource-sparing trials including chemotherapy-sparing regimens, de-escalation radiotherapy schedules, and registration, data collection, and bio-bank studies.

CONCLUSIONS

COVID-19 has resulted in unprecedented disruption to cancer care, requiring rapid and flexible adaptation to our delivery of care for women with gynecological cancer. Almost no evidence exists on how best we can restore outcomes for women adversely impacted when care deviated from standard practice. With new coronavirus variants rapidly evolving, there may need to be future adaptation to these recommendations. We hope that our consensus document will help guide women and clinicians on best options for ‘salvage’ and follow-up. Careful data collection into outcomes will provide insight into how these measures work in practice and provide valuable learning for future surges.

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REFERENCES

Consensus statement