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Expert Opinion

British Gynaecological Cancer Society (BGCS) ovarian, tubal and primary peritoneal cancer guidelines: Recommendations for practice update 2024

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NACT
Cytoreductive surgery
Chemotherapy

Introduction, methodology (evidence hierarchy and development process)

Grades of recommendations

Recommendations are graded as per the Royal College of Obstetricians and Gynaecologists document, Clinical Governance Advice No. 1: Guidance for the Development of RCOG Green-top Guidelines, available on the RCOG website at (see Supplementary Tables 1 and 2 below and at www.rcog.org.uk/rcog). Definitions for certainty of evidence based on formal GRADE assessment within systematic reviews are given in Supplementary Table 3 [677].

This guideline is for healthcare professionals who care for women, non-binary and trans people with different types of tubo-ovarian cancer. Within this document we use the terms woman and women's health. However, it is important to acknowledge that it is not only women for whom it is necessary to access women's health and reproductive services in order to maintain their gynaecological health and reproductive wellbeing. Gynaecological services and delivery of care must therefore be appropriate, inclusive and sensitive to the needs of those individuals whose gender identity does not align with the sex they were assigned at birth [1].

Guideline development process

The guideline development process is detailed below:

- Chair, officers, council and guidelines committee (GC) nominated a lead for each guideline topic;
- Lead then identified a team called the guideline team (GT) to develop the 1st draft;
- 1st draft was submitted to the GC;
- GC approved draft and recommended changes;
- Changes were accepted by the GT who produced the guidelines;
- 2nd draft was then submitted to council members and officers;
- Council and officers approved 2nd draft and recommended changes;
- Changes were then accepted by GC and GT;
- 3rd draft was sent to BGCS membership, national and international peer review and to public consultation, including relevant charities and patient support groups;
- GT then made changes based on peer review comments;
- Final draft approved by council and officers.

Ovarian cancer epidemiology

Ovarian cancer remains the 6th most common cancer in females in the UK with 7,495 new cases annually (2016–18), equating to a lifetime risk of 1 in 50 UK females [2]. The crude all-age incidence rate is 22.8/100,000 (2016–18). However, changes in the age of the population at diagnosis has resulted in the peak age incidence rising from 60-64 years to 75–79 years. Ovarian cancer incidence rates have been falling over the past decade, with the greatest fall being seen in the 60 to 69-year-old population, falling from 60.7/100,000 in 2001–3, to 46.7/100,000 in 2016–18. No clear differences have been identified in incidence with deprivation [3]. The incidence of ovarian cancer appears to be lower in Asian, Black and Mixed/Multiple ethnicity populations as compared to the White ethnic group [4].

Along with changing incidence rates, ovarian cancer mortality has also changed over time. The peak age for ovarian cancer mortality is 85–89 years, and nearly half of all ovarian cancer deaths occur in patients over the age of 75 years (2017–19). Mortality rates have decreased by 23 % over the past five decades, and have accelerated in the past few years and are now at 12.2/100,000 for 2017–19, equating to 4142 deaths annually (2017–19), and are projected to fall even further [5]. The greatest fall in mortality rates is seen in the age 60–69-year age group, from 42.2/100,000 (1988–90) to 24.5/100,000 (2017–19).

Many factors have been reported to contribute to the changing ovarian cancer landscape, for example increasing contraception use, risk-reducing surgery and evolving treatment options; these will be discussed in the subsequent chapters. There is a great need for accurate Cancer Registry data, without which it would not be possible to explore and understand the trends in ovarian cancer care within the UK as exemplified in the BGCS, Target Ovarian Cancer and Ovarian Cancer Action NCRAS Ovarian Cancer Audit Feasibility Pilot [6].

Surveillance and prevention (high/low risk populations)

Recommendations

There is currently no role for screening women considered at low or population level risk of development of ovarian cancer. (Grade A)

The role of ovarian cancer surveillance in women at high risk of ovarian cancer has shown good performance characteristics and significant downstaging. However, there is no available information demonstrating a survival benefit. Although surveillance is not an alternative to risk-reducing surgery in high risk women, there may be a potential role for considering four-monthly surveillance using a longitudinal biomarker algorithm, as an interim risk management strategy in women delaying risk-reducing surgery, following careful counselling. (Grade C)

Women who carry a pathogenic or likely pathogenic variant in a high to moderate risk ovarian cancer susceptibility gene (BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2) should be offered informed counselling for bilateral risk-reducing salpingo-oophorectomy (RRSO) for ovarian cancer prevention, once their family is complete. (Grade A)

Women with Lynch syndrome should be offered risk-reducing surgery in the form of a bilateral salpingo-oophorectomy and total hysterectomy to reduce their risk of ovarian and endometrial cancer. The timing of surgery should be individualised, based on the gene-specific risk, once their family is complete. (Grade A)

Risk-reducing early salpingectomy and delayed oophorectomy (RRESDO) as a two-stage surgical prevention procedure in women at increased risk of ovarian cancer should only be undertaken within the context of a research trial. (Grade C)

Women with a lifetime risk of ovarian cancer equal to or above 4–5 % can be offered surgical prevention in the form of bilateral risk reducing salpingo-oophorectomy (RRSO). (Grade B)

All women being offered surgical prevention should be reviewed by a specialist, with the support of a multidisciplinary team, to discuss risk reducing surgery. (Grade B)

A SEE-FIM protocol should be used for histopathological assessment for women undergoing RRSO. (Grade A)

Women diagnosed with a STIC or invasive cancer on histology should be referred to a specialist gynaecological cancer MDT for consideration of treatment options. (Grade A)

If isolated STIC is diagnosed at bilateral early salpingectomy alone, cytology is negative and imaging normal, completion bilateral oophorectomy is strongly advised. (Grade C)

For women undergoing prophylactic oophorectomy, consideration should be given to HRT, and consultation of the joint BGCS/British Menopause Society guidelines is recommended.

Women without a personal history of breast cancer (or contraindications to the use of HRT) who undergo risk-reducing surgery that leads to an iatrogenic menopause should be offered HRT till the average age of the natural menopause. Maintaining HRT compliance is necessary to minimise the detrimental consequences of premature menopause. (Grade B).

HRT is usually contraindicated in women with a personal history of breast cancer and should avoided in women with ER + or PR + breast cancer. (Grade B)

Some women at increased risk of ovarian cancer may not be at increased risk of breast cancer (e.g. *BRIP1*/Lynch syndrome). HRT use beyond the age of the natural menopause in these women may be governed by the same principles as women at population-based risk. (Grade C).

Opportunistic bilateral salpingectomy may be considered at the time of intra-abdominal surgery for women who have completed their family. (Grade C)

Women undergoing opportunistic salpingectomy should be recruited to prospective studies with long-term follow up. (Grade D)

Screening

The aim of a screening program is to identify individuals with a condition, or at an increased risk of a condition or health problem, at a time point whereby a timely intervention can be offered to make informed decisions to improve health outcomes [7]. Screening can be universal, whereby an ill-defined population (for example females over a certain age) is enrolled or can be case finding in which only those with defined risk factors are screened [8]. The principles of a screening programme were formalised by Wilson and Jungner in 1968 [9]. The UK National Screening Committee (UK NSC) have also established clear criteria and guidance for evaluating a population screening program [10].

Risk factors for ovarian cancer

Hereditary

Twin studies suggest that inherited genetic factors contribute around 22 % towards ovarian cancer risk [11]. *BRCA1/BRCA2* genes account for most of the known inheritable component of risk of ovarian cancer. Around 15–22 % of ovarian cancers are caused by pathogenic or likely pathogenic variants (called 'pathogenic variants' or 'PVs') in cancer susceptibility genes (CSGs) [12,13]. These include *BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2* and MMR (mismatch repair) genes. Together these PVs account for up to 40 % of the inheritable component of ovarian cancer risk. However, these data are from majority Caucasian populations. Lynch syndrome, an inherited deficiency within the mismatch repair system, also leads to an increased lifetime risk of ovarian cancer [14], and it is the second most common hereditary cause of ovarian cancer being associated with around 0.5–2 % of cases [15,16]. Of note, the biology of Lynch syndrome-associated ovarian cancer is different and it is often diagnosed at an earlier stage and may be less likely to metastasise [17]. A list of common CSGs associated with ovarian cancer risk are summarised in Table 1. In addition to moderate/high penetrance CSGs, a number of common genetic variants called SNPs may be associated with ovarian cancer risk with odds ratios (OR) varying from 0.8 to 1.4. Around 36 validated SNPs have been identified for ovarian cancer through Genome-wide association studies (GWAS). These explain around 6 % of heritability of ovarian cancer [18]. Multiple SNPs can be combined into a polygenic risk score (PRS) which can be used to refine risk stratification, both in general population women and in women with high-risk CSGs, leading to improved risk estimation and

Table 1
Cancer susceptibility genes, cancer risks, and recommended risk reducing surgery.

	Gene	Ovarian Cancer risk (CI)	Breast Cancer risk	Endometrial Cancer risk	Recommended risk reducing surgery	Age of surgery (years)	Evidence	Reference (s)
HBOC or HOC	*BRCA1*	High 44 % (36–53 %)	High		RRSO	≥35-40	Strong	[26]
	BRCA2	High 17 % (11–25 %)	High		RRSO	≥40	Strong	[26]
	PALB2	Moderate ~5% (2–10 %)	High		RRSO	>45–50	Moderate	[27]
	RAD51C	Moderate- High 11 % (6–21 %)	Moderate		RRSO	>45	Strong	[28]
	RAD51D	Moderate- High 13 % (7–23 %)	Moderate		RRSO	>45	Strong	[28]
	#*ATM*	Low 3–4 %	Moderate		Not recommended	NA	Insufficient	[29–32]
	BRIP1	Moderate 6–8 %	Low		RRSO	>45	Strong	[33]
Lynch Syndrome	*MLH1*	Moderate- High11% (7.4–19.7 %)		High	RRSO and Hysterectomy	>35–40	Strong	[34,35]
	†*MSH2*	High 17.4 % (11.8–31.2 %)		High	RRSO and Hysterectomy	>35–40	Strong	[34,35]
	MSH6	Moderate- High10.8 % (3.7–38.6 %)		High	RRSO and Hysterectomy	>35–40	Strong	[34,35]
	**PMS2*	Low 3 % (0.5—–43.3 %)		Moderate	Hysterectomy only*	>45–50	Moderate	[34,35]
Family history or model based risk		>4–5 %	Low	Low	RRSO	≥50	Strong / Moderate	[23,24,32]

HBOC: history of breast and ovarian cancer; HOC; history of ovarian cancer; RRSO: risk-reducing salpingo-oophorectomy.
*Routine bilateral salpingo oophorectomy is not recommended in women with PMS2 as these women are at low risk of ovarian cancer. However, opportunistic BSO may be considered at time of hysterectomy in post-menopausal women after careful counselling or pros can cons if surgery is undertaken after menopause.
#Risks associated with ATM on its own lie below the current thresholds for surgical prevention and RRSO is not currently recommended. Family history plays an important part in decision making. Cases with a family history of ovarian cancer should be discussed with a specialist with greater expertise.
†EPCAM deletion can result in silencing of the MSH2 gene. It is hypothesized that ovarian cancer and endometrial risks may be similar to MSH2 carriers but this is dependent on the type of EPCAM deletion. These cases should be discussed on an individual basis with a clinical geneticist, to confirm whether the variant is associated with increased endometrial cancer/ovarian cacner risks.
In cases where ovarian cancer risk assessment appears complex or difficult, it is important that advice from a specialist with greater expertise like a clinical geneticist or gynaecologist/gynae-oncologist with special interest in genetic risk assessment or hereditary cancer risk management is sought.

more informed decision making with respect to targeted prevention [19–22]. Having a family history of ovarian cancer is a strong factor affecting ovarian cancer risk. Having a first degree relative (FDR) with epithelial ovarian cancer can increase the risk of developing ovarian cancer by around threefold [23]. Higher relative risks are reported for women with two or three FDRs with ovarian cancer [24]. Epigenetics too may play a role in the future. Recently, a DNA methylation signature obtained from cervical cells has been shown to predict future ovarian cancer risk [25].

Environmental / epidemiologic

Environmental factors that increase the number of lifetime ovulations are considered risk factors for ovarian cancer [36]. These include nulliparity, early menarche and late menopause. Factors that reduce ovulation, such as oral contraceptives, have been shown to reduce ovarian cancer risk [37,38]. Increasing parity, breast feeding and a later age at births are also important protective factors against ovarian cancer [37,39]. Tubal ligation [40,41] and salpingectomy have been shown to reduce the risk of ovarian cancer [42–44]. Case control studies have explored the impact of benign gynaecological conditions and the risk of ovarian cancer. Endometriosis is associated with an increased risk of low grade serous, endometrioid and clear cell ovarian cancers [45–47]. Case control studies have found an association between pelvic inflammatory disease and borderline ovarian tumours, but not invasive cancers [48–50]. The presence of a community type O cervicovaginal microbiota was recently reported as a possible risk factor for ovarian cancer [51]. On balance, data from the Collaborative Group on Epidemiological Studies on Ovarian Cancer suggests the use of HRT increases an individual's risk of ovarian cancer, especially the serous and endometrioid histotypes [36,52]. However, data from the Ovarian Cancer Association Consortium (OCAC) found an increased risk with oestrogen alone rather than continuous combined oestrogen and progestogen preparations [53,54]. Height is an independent risk factor for ovarian cancer, and some studies suggest that BMI may [55] or may not be an independent risk factor [56]. IVF may be associated with an increased risk of borderline but not invasive ovarian cancers [57]. A *meta*-analysis has found smoking increases the risk of invasive mucinous ovarian cancer [58]. Additionally, exposure to asbestos is thought to increase an individual's risk of ovarian cancer, although the evidence for talcum powder is less conclusive [36].

Chemoprevention

Although the combined oral contraceptive pill (COCP) reduces ovarian cancer risk it has never been routinely prescribed just for primary prevention. The COCP is associated with a 29 % (95 % CI 23 to 34 %) reduction in ovarian cancer risk in low-risk women per five years of use [38], and an approximately 50 % reduction in ovarian cancer risk in high-risk women i.e. those with an inherited pathogenic variant in *BRCA* (33 % to 80 % for *BRCA1* carriers and 58 % to 63 % for *BRCA2* carriers) [59]. Benefits persist for up to 30 years after stopping the COCP, but decrease with time. COCP use in low-risk women is associated with a transient increase in breast cancer risk, although the absolute risk is small. Data in high-risk women have some uncertainty with case control studies showing no increase in breast cancer risk but cohort studies showing an increase in breast cancer risk in *BRCA* carriers [59]. A recent modelling study indicates that oral contraceptive use in *BRCA* carriers in the short-term was associated with an increase in breast cancer incidence but in the long-term led to a decrease in ovarian cancer incidence and overall cancer incidence [60]. These benefits are also impacted by future risk-reducing surgery choices. Women who are at high risk for ovarian cancer should receive informed counselling regarding the pros and cons of the oral contraceptive pill and alternative options. The other drug that has been associated with a potential reduction in ovarian cancer risk is aspirin, with a number of studies suggesting a reduction in OC risk [61–63]. However, a reduction in associated mortality was not found [64].

Population screening for ovarian cancer

Randomised control trial (RCT) data do not currently support population-level screening for ovarian cancer. Three RCTs have investigated screening for ovarian cancer in low-risk postmenopausal women. These include the Japanese Shizuoka (n = 82,400) (65), the USA PLCO (Prostate Lung Colorectal and Ovarian-cancer Screening) (n = 78,216) [66] and the UKCTOCS (United Kingdom Collaborative Trial on Ovarian-Cancer Screening) (n = 202,000) trials [67]. The Japanese and PLCO studies used a combination of annual ultrasound and absolute CA125 value to screen for ovarian cancer. The Japanese trial reported a non-significant stage shift, with a higher proportion of stage-I ovarian cancers (63 %) in the screened arm versus the control arm (38 %), but did not report on mortality [65]. Both the PLCO and UKCTOCS trials reported mortality outcomes of screening for ovarian cancer. The PLCO trial found no mortality benefit (mortality risk ratio of 1.18 (95 % CI 0.82 to 1.71), identified only 28 % early-stage ovarian cancers in the screened arm with no stage shift, and reported a high complication rate of 15 % from bilateral salpingo-oophorectomy (BSO) undertaken in screen positives [66]. UKCTOCS investigated a multimodal sequential longitudinal CA125 biomarker-based screening strategy called the Risk of Ovarian Cancer Algorithm (ROCA) along-with an annual ultrasound-based screening strategy in a 1:1:2 randomised design. ROCA based screening was found to have high sensitivity (84 % to 85.9 %), high specificity (99.8 %), an acceptable 3 operations per case detected and a 3.1 % complication rate [68,69]. Long-term follow-up data were recently reported. ROCA based multimodal screening was associated with a statistically significant stage shift, with a 39·2% (95 % CI 16·1% to 66·9%) higher incidence of stage I/II disease and 10·2% (–21·3% to 2·4%) lower incidence of stage III/IV disease in the screening arm [70]. Women in the screened group had a 24.5 % lower incidence of stage IV and 47.2 % higher incidence in stage I cancers. However, despite a significant down-staging of disease, and a higher rate of achieving no macroscopic residual disease (NMRD) at primary cytoreductive surgery (PCRS) for screen detected cancers, long-term follow-up data demonstrated no mortality benefit [71]. Primary analysis showed no reduction in ovarian/tubal cancer deaths in either the ROCA/multimodal (296 deaths, P = 0·58) or ultrasound-based screening (291 deaths, P = 0·36) groups compared with controls (619 deaths) [70]. Secondary analysis of all data from 2001 to 2020 too found no mortality benefit with a hazard ratio = 0.96 (95 % CI 0.83 to 1.10). Results showed that the stage I cancers found in the screened group proved to be more fatal than those in the non-screened group (case fatality rate 14.8 % versus 9.4 %). It is likely that the natural history or biology of many ovarian cancers is poor/lethal, and, despite cancers being identified earlier in the screened group, no additional lives were saved. Parallel evaluation of psychological outcomes showed that while screening did not raise anxiety, it was associated with increased psychological morbidity and sexual dysfunction in women needing repeat screens or those diagnosed with cancer [72,73].

Based on available data, general population screening for ovarian cancer in average risk women cannot be recommended as there is no mortality benefit. Women should be encouraged to seek medical review if they develop symptoms suggestive of ovarian cancer, for facilitating early diagnosis [74].

Surveillance in high-risk groups

Ovarian cancer surveillance in high-risk groups is not recommended, but is an option for those declining or delaying risk reducing surgery, after explanation that this is not a alternative and there is "little evidence that this leads to improved outcomes and saves lives" [75].

The current evidence base is focused on women with an increased ≥ 10 % life-time risk of familial ovarian cancer, based on family history

(including ethnicity), carrying a PV in *BRCA1/BRCA2* or MMR genes or a close family member. Annual screening for ovarian cancer using an absolute CA125 and an ultrasound scan was evaluated in the UK Familial Ovarian Cancer Screening Study (UKFOCSS) Phase-1 study, and not found to be effective [76]. Hence, annual screening is not advocated.

A more frequent (3–4 monthly) longitudinal CA125 ROCA-based screening strategy in high-risk women > 35 years was evaluated in the UKFOCSS Phase-2 study (4,348 women; 13,728 women screen years) in the UK [67] as well as the USA Cancer Genetics Network (CGN) and Gynecological Oncology Group (GOG) studies (3692 women; 13,080 women screen years) [77,78]. Screening was performed using a four-monthly ROCA and annual ultrasound scan across 42 sites in the UK. Results from the UKFOCSS Phase-2 study demonstrate good modelled sensitivity of 94.7 % (95 % CI 74.0 % to 99.9 %), PPV of 10.8 % (95 % CI 6.5 % to 16.5 %), and NPV of 100 % within one year of screening. In total 162 women underwent screen positive surgery; of these 13 had a cancer. Five (38.5 %; 95 % CI 13.9 % to 68.4 %) of the 13 screen-detected ovarian or tubal cancers were early stage I/II disease. Within a year of a screening test, six women were found to have an occult cancer (microscopic disease found at risk reducing surgery), however, none were found to have an interval cancer. Screening was associated with a significant stage shift. Seven of the 19 (36.8 %) women diagnosed with cancer within one year of last screen had stage IIIB/IV disease, compared with 17/18 (94.4 %) of those diagnosed more one year after the last screen (P = 0.001). Additionally, 95 % of women with screen-detected cancers had no macroscopic residual disease (NMRD) after cytoreductive surgery. Similar findings were reported in the CGN/GOG studies. The Avoiding Late Diagnosis of Ovarian Cancer (ALDO) study demonstrated real-world implementation of four-monthly ovarian cancer surveillance in high risk women with similar performance characteristics to UKFOCSS [79]. Down-staging from screening will avoid PARP-inhibitor treatment costs. However, whether any potential survival benefit (currently unknown) from earlier stage disease, will offset the potential survival benefit from PARP-inhibitor treatment remains unaddressed.

There were a limited number of women with Lynch syndrome in these studies, with the majority being *BRCA* PV-carriers. Lynch syndrome ovarian cancer is biologically different form *BRCA*-related cancers [80] and are more likely to be clinically diagnosed as early (stage I/II) disease [17]. However, the evidence-base for ovarian cancer screening in female Lynch syndrome carriers is small, and screening for endometrial cancer is inconclusive [81]. Routine ovarian cancer screening is not recommended in women with Lynch Syndrome [82].

As encouraging as some of the findings from cohort studies seem, these are non-randomised and should be considered with a degree of caution. These studies do not show that screening high-risk women saves lives. Unfortunately, these studies are not designed to address the impact on survival. Also, despite good screening performance in terms of sensitivity, specificity, PPV and NPV, a significant stage shift towards early-stage disease, as well as a higher NMRD rates, the RCTs in low-risk women using the ROCA based screening strategy did not show a mortality benefit. Therefore, risk-reducing surgery remains the mainstay of ovarian cancer prevention and management in high-risk women.

Further information about risk and counselling, and when to offer risk-reducing surgery, is available in the recent NICE guidance (NG241) [75]. Four-monthly surveillance with serum CA125, using a longitudinal algorithm to analyse results of, and an annual review to discuss the ongoing recommendation for risk-reducing surgery, can be offered as an interim risk management strategy in women delaying risk-reducing surgery following careful counselling. Women should be aware that this is not an alternative to risk-reducing surgery and that there is a risk of false-positive and false-negative tests. Decision for surveillance should be discussed through a familial ovarian cancer multidisciplinary team and only be considered in those in the following groups who choose to delay or wish not to have risk-reducing surgery:

- over 35 and have a *BRCA1* pathogenic variant; or
- over 40 and have a *BRCA2* pathogenic variant; or
- over 45 and have *RAD51C*, *RAD51D*, *BRIP1* and *PALB2* pathogenic variants.

Future screening strategies

Although there is currently no evidence to support screening for ovarian cancer in the general population, as technologies develop this may be an option in the future. While a comprehensive discussion about these potential technologies is beyond the remit of this guideline, the authors recognise that advances in screening strategies and biomarkers such as DNA methylation [25], cell free DNA [83], novel biomarkers [84], use of multi-marker longitudinal algorithms, and multi-cancer early detection biomarker strategies, may play a role in the future. Additionally, it is critical that for any biomarker-based ovarian cancer screening strategy to be effective, gynaecologists/gynae-oncologists/multi-disciplinary teams (MDTs) would need to be willing to operate on the basis of a rising biomarker without radiological corroboration of any abnormality, balanced against the morbidity associated with the proposed staging procedure. Moreover, it is clear that any future general population ovarian cancer screening strategy needs to be evaluated in a robust RCT with mortality as the primary outcome, because secondary or surrogate outcomes, such as stage shift (as demonstrated in UKCTOCS), are inappropriate in the context of ovarian cancer. Hence, any future screening programme is at least a decade away. These guidelines should be regularly reviewed and meaningful research into this area should be supported and prioritised.

Ovarian cancer prevention: risk ascertainment in the general population

It is increasingly important to maximise identification of those who are at increased risk of ovarian cancer so that they can be counselled and offered targeted prevention strategies [75]. Clinicians should take a three-generational family history routinely to identify pedigrees and women at an increased risk of ovarian cancer. Women with a strong family history of cancer should be referred to their regional genetics service for risk assessment. Individuals who have a 10 % probability of carrying a *BRCA* PV are offered genetic testing. A number of risk assessment tools are available to help identify these women [85]. Most commonly used are the Manchester scoring system for BRCA testing [86,87] and the BOADICEA or CANRISK model [21,88,89] in the UK and BRCAPRO in the USA [90,91].

Up to to 20 % of ovarian cancers in the general population and 40 % of ovarian cancers in the Jewish population are caused by an ovarian cancer-associated cancer susceptibility gene and are therefore preventable. Identification of unaffected women at increased risk is therefore critically important. One in 40 Ashkenazi Jewish (AJ) individuals carry one of three Jewish *BRCA* founder-mutations. Sixty percent of BRCA carriers are missed by a clinical criteria or family history-based testing approach [92]. A population-based approach to *BRCA* testing (irrespective of family history of cancer) is now recommended for the following populations (with at least 1 grandparent from the respective population): Ashkenazi Jewish; Sephardi Jewish; Greenlander [75].

Population-based testing in the broader general population, remains a matter of ongoing research [93]. This approach has been shown to be cost-effective for a range of cancer susceptibility genes and can prevent thousands more cancers than the current approach [94,95]. Complex ovarian cancer risk models incorporating multiple risk factors including genetic (cancer susceptibility genes and a polygenic risk score), family history, epidemiologic, hormonal and reproductive factors are now becoming available and can be used to predict a personalised ovarian cancer risk [21,22,96]. A pilot study shows high acceptability, feasibility, high satisfaction and reduced cancer worry with population genetic testing for personalised ovarian cancer risk prediction [97]. Future research is required to focus on large studies evaluating personalised

ovarian cancer risk prediction and population stratification for targeted prevention in general population women.

Ovarian cancer surgical prevention in women at increased risk of ovarian cancer

Risk-reducing salpingo-oophorectomy

Surgical prevention is the key strategy to reduce ovarian cancer risk in the absence of an effective screening programme. The most clinically effective method of preventing ovarian cancer in high-risk women is bilateral risk-reducing salpingo-oophorectomy (RRSO). This is usually undertaken through minimal access surgery once the woman's family is complete. It has been shown to reduce ovarian cancer risk by 80–97 % in *BRCA* carriers [98–102] although a small residual risk of high-grade serous cancer remains [100,102]. RRSO also reduces ovarian cancer and all-cause mortality [98]. Oophorectomy has also been shown to reduce ovarian cancer risk by 94 % in women at average or population-level risk of ovarian cancer [103]. While earlier studies suggested RRSO is associated with a reduction in breast cancer risk, recent studies correcting for earlier biases suggest this is not the case [104–106]. RRSO has been shown to be cost-effective at 4–5 % lifetime ovarian cancer risk thresholds [107–109]. RRSO should be offered to women at $\geq$ 4–5 % lifetime risk of ovarian cancer, as recommended by a scientific impact paper from the Royal College of Obstetricians and Gynaecologists (RCOG) [110] and the UK Cancer Genetics Group [111]. Another USA review has suggested a lower 3–4 % risk threshold [112].

In addition to the standard *BRCA1* and *BRCA2* genes, RRSO can be offered to women with PVs in moderate risk cancer susceptibility genes including *RAD51C*, *RAD51D, BRIP1, PALB2* (5–13 % lifetime ovarian cancer risk) [27,28,33], and selected women with a significant family history of ovarian cancer (e.g. one or two first-degree relatives with ovarian cancer) who are at intermediate risk (5–10 % lifetime risk) [23,24]. Family history should be incorporated into the individualised risk assessment process for all women. Decision-making to undergo RRSO is a complex and dynamic process which can change with time [113]. It requires informed counselling of advantages and disadvantages with patients managed within a multi-disciplinary team framework [114]. RRSO is associated with a 3–5 % complication rate [115]. The timing of surgery is individualised, taking into account personal preferences and clinical factors. It may vary according to age, menopausal status, type of cancer susceptibility gene, personal history of breast or other cancer and personal preference. Table 1 provides guidance on timing of RRSO according to risk and cancer susceptibility gene [110].

RRSO involves removal of both tubes and ovaries (usually via minimal access surgery), as well as peritoneal cytology or washings. Hysterectomy is not currently recommended in *BRCA*-carriers or women at increased risk of ovarian cancer alone, unless there is another gynaecological indication. While some recent papers suggest an increase in serous endometrial cancer risk with *BRCA1* PV-carriers (also referred to as *BRCA1*mut) [116–118], other studies have not found this association [119,120]. Serous endometrial cancers remain a small proportion (7 %) of endometrial cancers and studies indicate that the overall risk of endometrial cancer is not increased. Currently there is insufficient evidence to recommend routine hysterectomy for prevention in *BRCA1*-mut-carriers. Hysterectomy is recommended in women with Lynch Syndrome, as they also have an increased risk of endometrial cancer. Diathermy injury to the fimbrial end creates heat artefacts which reduce the odds of identifying occult cancers or STIC lesions, and hence, should be avoided [121]. It is essential that a strict surgico-pathological protocol involving serial sectioning of the tube called a 'SEE-FIM' (Sectioning and Extensively Examining the FIMbria) protocol is used for histopathological assessment, and pathologists should be alerted to the indication for BSO on the pathology request form [122]. A UK-wide protocol for this has been published recently [123]. Five percent of high-risk women have an occult microscopic *in situ* (called serous tubal intraepithelial carcinoma (STIC)) or invasive cancer identified at histological assessment [115,124]. Seventy percent of occult lesions are tubal rather than ovarian in origin [124] and these lesions may be missed if a SEE FIM protocol is not used. Women diagnosed with a STIC or invasive cancer at histology following RRSO should be referred to a gynaecological cancer MDT for further management (see Table 2 for management details) [123,125].

Premenopausal RRSO leads to an iatrogenic early menopause and incurs the associated detrimental sequelae to long-term health. It is associated with vasomotor symptoms, hot flushes, mood swings, reduced libido, vaginal dryness, dyspareunia, sexual dysfunction, higher risk of heart disease, increased risk of cardiovascular mortality (without HRT), osteoporosis, and neurocognitive decline [110,126]. HRT is recommended in women undergoing premature surgical menopause following early oophorectomy, provided there is no other contraindication. For women undergoing RRSO alone, with an intact uterus, oestrogen combined with progestogen HRT (E + P-HRT) is recommended. In women with Lynch Syndrome who also undergo a hysterectomy, oestrogen-only HRT (E-HRT) is advocated. A detailed description on HRT management following RRSO is provided in a recent RCOG Scientific Impact Paper [110]. A joint BGCS/British Menopause Society Consensus document detailing this further is due for publication shortly [127].

Early salpingectomy and delayed oophorectomy

The increasing evidence base and wide acceptability of the central role of the fallopian tubes in the aetiopathogenesis of ovarian cancer, coupled with the detrimental consequences of early menopause, has led to the proposition of a two-step surgical prevention strategy involving an initial risk reducing early salpingectomy, followed by delayed oophorectomy (RRESDO) at a later date, to avoid detrimental consequences of early menopause [125]. However, the precise level of risk-reduction obtained, and the impact on menopause is unknown. RRESDO has been shown to have high acceptability amongst patients and clinicians [114,128,129]. Prospective, ongoing studies in the UK, Netherlands and USA are evaluating acceptability, safety, quality of life, impact on menopause and cost-effectiveness of this strategy [123,130,131]. Initial data suggest, early salpingectomy is associated with better sexual function and menopause symptoms compared to standard RRSO [130], and has high acceptability and satisfaction [114]. RRESDO is currently only recommended in the context of a research study. The TUBA-WISP-II, SOROCk and PROTECTOR Phase-2 trials will report on ovarian cancer risk reduction in the coming years.

Ovarian cancer surgical prevention in women at population level risk

Opportunistic bilateral salpingectomy (OBS)

Following widespread acceptance of the tubal hypothesis,

Table 2
Management of occult *in situ* or invasive malignancy following RRSO histology.

	Staging CT Chest, abdomen, pelvis	Surgical staging*
Isolated STIC with positive cytology	Yes	Yes
Isolated STIC with negative cytology	Yes	Not indicated unless abnormality on CT suggesting otherwise
Isolated STIC with missing cytology	Yes	Not indicated unless abnormality on CT suggesting otherwise
Microscopic invasive cancer	Yes	Yes

Anyone diagnosed with STIC should be discussed at a gynaecological oncology MDT. If isolated STIC is diagnosed at bilateral early salpingectomy alone, cytology is negative and imaging normal, completion bilateral oophorectomy is strongly advised. Undertake genetic testing (as in women with high grade epithelial ovarian cancer) for patients with isolated STIC if not already done [123,125]. STIC- Serous tubal intraepithelial carcinoma, RRSO- risk reducing salpingo oophorectomy. *see below

Opportunistic Bilateral Salpingectomy (OBS) at routine gynaecological surgery has been proposed as a strategy to prevent ovarian cancer. Emerging data particularly from North America, have demonstrated it is safe, has acceptable morbidity, takes minimal additional time and is not associated with an increased postoperative complication rate, although analgesic requirement is increased [132,133]. There is an increased risk of haemorrhage (odds ratio (OR) 1.24, 95 % CI 1.15 to 1.33) and blood transfusion has been reported if performed at the time of caesarean section, although the absolute increase is small [134]. This has led to an increasing uptake of OBS in practice. Two large retrospective studies from Denmark and Sweden reported a 42 % (OR 0.58, 95 %CI 0.36 to 0.95) [44] and 65 % (hazard ratio (HR) 0.35, 95 % CI 0.17 to 0.73) ovarian cancer risk reduction following bilateral salpingectomy, respectively [42]. However, systematic reviews highlight the poor quality of evidence from these studies in relation to level of risk reduction [135,136]. These studies are retrospective, suffer from confounders, and indication and detection biases. Additionally, the procedures evaluated were not 'opportunistic' salpingectomies, the number of ovarian cancers were few, and the comparator in both these studies is no intervention at all rather than the standard surgical procedure. A follow-up study from the Swedish cohort which adjusted for the confounder of pelvic inflammatory disease (PID), subsequently found a much lower benefit of ovarian cancer risk reduction of 28 % (HR 0.72, 95 % CI 0.56, 0.93) from bilateral salpingectomy [43]. Additionally, the impact on long-term endocrine function is unknown. Recent, short-term RCTs show no detrimental impact on ovarian function [137]. However, these data in the literature are limited by small sample sizes, younger ages, use of surrogate markers and short follow-up. These results are not predictive of onset of menopause [138]. Long-term longitudinal assessment of hormonal function and menstrual cycle is essential to address the true association with premature menopause. A recent study reported OBS at hysterectomy was associated with longer hospital stay and an increased risk of menopausal symptoms at one year follow-up (RR 1.33, 95 % CI 1.04 to 1.69) [139]. Long-term prospective studies are needed to address the precise level of ovarian cancer risk reduction and long-term impact.

Diagnosis and staging

Recommendations

CA125 and pelvic ultrasound scan (+/- TVS as indicated) is recommended in the initial investigations for post-menopausal women presenting with signs or symptoms of ovarian cancer. (Grade A)

Cancer Unit leads, and their equivalents in the devolved nations, are encouraged to work with primary care providers to agree diagnostic pathways such that patients with physiological ovarian cysts can be managed within primary care (with secondary care support and safety-netting in place). (Grade C)

BGCS strongly encourages all cancer care providers to be aware of local pathways for vague non-specific symptoms and support Rapid Diagnostic Clinics. It is likely that these will improve cancer diagnostic access for women. (Grade C)

One-stop cancer exclusion clinics can streamline referrals and improve time to treatment and should be implemented. (Grade C)

The RMI should be discontinued as a triage test in clinical practice. Choice between ROMA (threshold 29.9 %) and IOTA-ADNEX (threshold 10 %) as a replacement test will depend on cost effectiveness and local resource implications. (Grade A)

Approximately 7,500 women are diagnosed with ovarian cancer annually in the UK, and five-year overall survival is around 45 %, lower than comparable European countries [140]. Ovarian cancer incidence is projected to increase by 15 % by 2035, due to ageing and increase in prevalence of risk factors [5].

Ovarian cancer has high case fatality in the first year, highlighting that improved diagnostics may be critical to improve outcomes: 32 % women diagnosed will die within the first 12 months; 14 % within the first two months [6]. Twenty-two percent of women with ovarian cancer in England will not receive any anticancer treatment, likely due to poor performance status at diagnosis and 26 % of women are diagnosed following an emergency presentation [141].

Ovarian cancer is frequently diagnosed at advanced stages (FIGO stages III and IV). Stage I cancer has a 90 % five-year survival, compared to ~ 15 % at Stage IV. The proportion of ovarian cancer diagnosed at stage I ranged from 10.0 % to 47.9 % across England; concomitantly five-year survival from ovarian cancer varies between 28 % to 49 % across England, revealing huge variation and inequalities [6]. The National Cancer Diagnosis Audit found that women diagnosed with ovarian cancer have a longer median diagnostic interval (time from presentation to diagnosis) of 55 days, compared to median of 40 days for all types of cancer [6]. Unfortunately, once referred to secondary care, median time to start treatment is 69 days; one of the longest of all cancers. Substantial room for improvement exists in the diagnostic pathway, from community through to tertiary care [142].

Symptom-triggered testing for ovarian cancer

Ovarian cancer is associated with symptoms in both early- and late-stage cancer [143]. Unfortunately, symptoms are vague and non-specific and frequently mis-attributed to several more common conditions, including irritable bowel syndrome, menopausal changes, and endometriosis. Symptoms include bloating, abdominal discomfort/pain, early satiety, change in bowel and urinary habit, back pain, vaginal bleeding, tiredness. Women with ovarian cancer usually have symptoms and report them to primary care, sometimes months before diagnosis [144–146]. NICE guidance recommends that women contact primary care if they experience these symptoms frequently (roughly 12 or more times a month) [147].

Community diagnosis

A 'Be Clear on Cancer' awareness campaign was successful in raising awareness of symptoms of ovarian cancer, with increased numbers of women visiting their GP with bloating (ranging from 14 – 30 % based on age), but it did not impact the number of ovarian cancers diagnosed, nor the stage of disease at diagnosis, although these were short term pilot studies [148].

Charities, such as Ovacome, Target Ovarian Cancer and Eve Appeal, have helplines and information sources that can be accessed if people are worried about symptoms. The CLOCS case-control pilot study, using analysis of supermarket loyalty card data, demonstrated that women with ovarian cancer are more likely to purchase non-pharmacy prescriptions, such as pain killers and indigestion medicines, than controls in the few months prior to diagnosis [149]. If validated in a large cohort study, this could be an important observation.

Primary care diagnosis

NICE guidance advocates sequential testing with CA125 and ultrasound for women who present to their GP with non-specific symptoms on a frequent basis or persistent basis, especially if more than 12 times a month [147]. If CA125 is > 35 IU/ml and the GP considers the ultrasound to be abnormal, referral to secondary care is mandated. An urgent referral to gynaecological cancer service is recommended if physical examination identifies ascites and/or a pelvic or abdominal mass (not obviously caused by fibroids). Women with normal CA125, but persistent symptoms, or elevated CA125 but normal ultrasound, should be assessed carefully for other clinical causes and kept under review in primary care, with repeated samples and referral for further investigations if rising, without other obvious cause.

Substantial variation in practice exists in the use of this pathway and GPs are more likely to refer, based on an abnormality in either test. NICE

guidance does not specify what constitutes an abnormal ultrasound, resulting in many referrals for physiological cysts. Post-COVID and with the increasing use of virtual clinics, it is likely that many women with symptoms will not receive a physical examination prior to referral. The impact of this on outcomes is not yet known. This has resulted in a large year-on-year increase in referrals for suspected ovarian cancer, with impact on conversion rates to ovarian cancer less clear cut [150]. Unfortunately, current diagnostic tests (CA125 and ultrasound) are neither highly sensitive, nor specific. CA125 is elevated in many conditions, including during menstruation, fibroids, endometriosis, whereas CA125 is only elevated in 50 % of Stage I cancers. Ultrasound invariably picks up normal physiological ovarian cysts in premenopausal women and up to 20 % postmenopausal women will have benign ovarian cysts. Ultrasound scoring systems can be complex, are not used routinely in primary care, and the quality of ultrasound in primary care is highly variable.

Making a diagnosis of ovarian cancer in primary care is challenging and one-third of women present to primary care with relevant symptoms three or more times before specialist referral. The average GP will see a new diagnosis of ovarian cancer once every five years and UK GPs have a lower readiness to refer patients on to specialists, compared to other countries [144–146].

A dual-testing approach where an abnormality in either test warrants referral (as already performed in Scotland and some Integrated Cancer Boards), maybe more sensitive for earlier diagnosis and is being proposed by cancer charities and the NHS cancer programme.

Organisation of primary care pathway

Rapid Diagnostic Clinics and Community Diagnostic Hubs offer non-specific symptom pathway routes for patients who do not fit into site-specific faster diagnosis pathways and may support the faster diagnosis of ovarian cancer for those without a raised CA125.

Diagnostic tests

A significant proportion of women with high CA125 levels have other cancers. A high incidence (12.3 %) of non-ovarian cancers were found in women with elevated CA125 levels (20 % of women aged $\geq$ 50 years with a CA125 $\geq$ 35 IU/ml), particularly for undiagnosed lung and pancreatic cancer. Over a third (38 %) of patients diagnosed with a lower gastrointestinal (GI) cancer, which has overlapping symptoms with ovarian cancer, had CA125 levels > 35 IU/ml [151]. This suggests referral to a 'vague symptoms pathway', where investigations are performed for multiple cancers simultaneously, could facilitate cancer diagnosis.

Funston *et al.* demonstrated that age-specific thresholds for CA125 (as discussed in NICE guidelines for ovarian cancer section above), can provide an individual ovarian cancer risk score for patients, which may provide a model for referral pathways. Acceptability amongst patients and primary care providers will need to be understood prior to implementation. The SONATA study is funded by the NHS cancer program and investigates a triaging strategy using ROMA in place of CA125 for women with symptoms in primary care.

Younger women are more likely to have rarer tumour types, including germ cell tumours, so women under 40 should also have beta-human chorionic gonadotropin (β-hCG), alpha-fetoprotein (AFP), lactate dehydrogenase (LDH) performed if a suspiscious mass is seen on pelvic ultrasound scan [152].

Other ovarian tumor markers may include inhibin, carcinoembryonic antigen (CEA), CA 19–9, and HE4). Serum levels can be elevated in patients with rarer ovarian cancer types (e.g., mucinous or endometrioid) or secondary ovarian malignancies/other primary tumours (e.g., appendiceal, colorectal and upper gastrointestinal tumours). Measurement of these markers prior to surgery can help avoid inappropriate treatment for other tumour types, if histological confirmation is not obtained prior to surgery, and for future monitoring after treatment in patients who do not have elevated serum CA-125 at baseline [153].

Secondary care

Organisation of diagnostic pathway

NHS England published guidance that sets out how a diagnosis within 28-days can be achieved for the suspected gynaecological cancer pathway, supporting the on-going improvement effort to shorten diagnosis pathways, reduce variation, improve patient experience of care, and meet the Faster Diagnosis Standard [154]. One-stop clinics for suspected ovarian cancer referrals hope to streamline referrals, reduce the substantial variation in imaging availability, and reduce time to biopsy if CT/ultrasound is required. In addition, biopsy slots can be aligned to these clinics. One-stop clinics are also integral to improving secondary care ultrasound, and allow iterative learning and implementation of ultrasound models, such as the International Ovarian Tumor Analysis (IOTA) score [155,156]. Ongoing quality improvement projects investigate whether frailty assessments, same day imaging/biopsy and prehabilitation efforts can be implemented in these clinics [157].

Diagnostic tests

Previous NICE and RCOG guidance recommend the use of the Risk of Malignancy Index I (RMI) in secondary care for triage into tertiary care [158,159]. However, the RMI has poor sensitivity and specificity for premenopausal women and these guidelines are now outdated, with new evidence to support better models. The Risk of Ovarian Malignancy Algorithm (ROMA) model combines the serum levels of He4 and CA125 in an algorithm [160]. Test thresholds vary based on test provider (Abbott versus Roche) with comparable test performance across both providers. The IOTA ADNEX score combines ultrasound characteristics with CA125 and age [161]. A recent Cochrane review analysed 58 studies (30,121 patients, 9061 cases of ovarian cancer). Prevalence of ovarian cancer ranged from 16 to 55 % in studies reflecting highly selected/pre-triaged populations. For premenopausal women, ROMA at a threshold of 13.1 (+/−2) and ADNEX at a threshold of 10 % (post-test probability of ovarian cancer of 10 %), demonstrated higher sensitivity compared to RMI > 200 (ROMA = 77.4 %; ADNEX = 95.5 %; RMI = 57.2 %) but lower specificity (ROMA = 84.3 %; ADNEX = 77.8 %; RMI 92.5 %). For postmenopausal women, ROMA and ADNEX demonstrated higher sensitivity compared to RMI (ROMA = 90.3 % versus ADNEX = 97.6 % versus RMI = 78.7 %). Specificity of ROMA was comparable with RMI, (ROMA = 81.5 % versus RMI = 85.4 %), whilst the specificity of ADNEX was lower compared to RMI (ADNEX = 55.0 %) [162].

ROMA is not currently available routinely within the NHS, due to lack of He4 testing. The ROCkeTS study evaluated RMI versus ROMA versus IOTA models in a prospective diagnostic test accuracy study recruiting mainly from secondary care rapid access clinics with ultrasound performed mainly by NHS sonographers, results have been presented but not yet published [156,163]. They found that IOTA ADNEX (>10 %) had the highest sensitivity but lower specificity, and ROMA (>29.9 %) had marginal improvement of sensitivity over RMI > 250 but with reduction in specificity. ORADS had little advantage over RMI [156]. They recommended that IOTA ADNEX (at 10 % threshold) in real-world NHS practice has highest sensitivity and should replace RMI as the new standard of care diagnostic test in ovarian cancer for postmenopausal women.

The Ovarian-Adnexal Reporting and Data System (O-RADS) lexicon for ultrasound was published in 2018, providing a standardized glossary that includes all appropriate descriptors and definitions of the characteristic ultrasound appearance of normal ovaries and various adnexal lesions [164]. Data are still accruing and given the considerable overlap between ORADS and the IOTA terminology, this guideline will adhere to the IOTA model as it has more supporting evidence. The use of ORADS lexicon by NHS sonographers is not recommended until further prospective evidence is available.

Implementation of IOTA ADNEX at 10 % will require skilling-up of NHS sonographers, ideally in the context of a one-stop clinic to support

skill acquisition and retention. Efforts are underway by the ROCkeTS team on resources to train up NHS sonographers. Two strategies may mitigate the impact of a reduction in specificity from use of IOTA ADNEX to triage patients in secondary care: (1) The use of a two step strategy of characterising ovarian lesions with simple descriptors to exclude patients with obviously benign ovarian masses followed by IOTA ADNEX [165]; and (2) Use of MRI for women with scores of 1–10 % to characterise lesions may be needed.

MDT referral and decision-making

Recommendations

All patients with suspected ovarian cancer, irrespective of fitness, should be discussed at a specialist MDT prior to a decision about mode and location of treatment. (Grade D)

Standardised ultrasound reporting models, combining both morphological and Doppler waveform analysis, such as the IOTA ADNEX ultrasound scoring system are encouraged. (Grade A)

Women with an IOTA ADNEX score of ≥ 10 % (or RMI of ≥ 200) should have further investigations and be referred to the specialist gynaecological centre MDT. (Grade A)

Women with lower scores in whom the clinical suspicion is high (e.g., due to family history), may also be referred for MDT consideration. (Grade D)

People with suspected ovarian cancer should undergo surgery at a cancer centre by RCOG subspecialty trained surgeons who are core members of a specialist MDT. (Grade B)

Patients with ovarian cancer should have accurate recording of FIGO stage at diagnosis, WHO performance status, and clinical frailty score at diagnosis. These data should be submitted to national registries where applicable. (Grade D)

Size and sites of residual disease following cytoreductive surgery should be recorded within the MDT discussion. (Grade D)

Patients requiring chemotherapy should be treated by a medical or clinical oncologist who is a core member of a specialist MDT. (Grade D)

Affected patients should have an identified key worker and responsible clinician. (Grade D)

Treatment summaries, including symptoms of recurrence, should be provided to all women on completion of each episode of treatment and on discharge to primary care. (Grade D)

Patients recruited into clinical trials should have record of this in MDT discussions. (Grade D)

Women with suspected ovarian cancer should be referred to gynaecological oncology centres for treatment. A *meta*-analysis of retrospective studies assessing over 9000 women suggested that treatment of women in institutions with gynaecological oncologists may prolong survival, compared to community or general hospitals (HR 0.90, 95 % CI 0.82 to 0.99) [166]. This supports data from the UK and guidelines on Improving Outcomes in Gynaecological Cancers [167–171].

There is substantial variability in rates of surgical and chemotherapy treatment for ovarian cancer across England, from a national ovarian cancer audit, suggesting significant variability in patient selection for cytoreductive (CRS) surgery [6]. The National Ovarian Cancer Audit Feasibility Pilot (OCAFP) found that one in four women with advanced ovarian cancer did not receive any anticancer treatment (surgery or chemotherapy) and less than half received standard of care treatment i.e., the combination of surgery and chemotherapy. What was apparent from these data was that women diagnosed in a cancer centre were more likely to receive surgery than those diagnosed in a unit, although surgery for those with ovarian cancer is centralised. As a result, the BGCS published a "call to action" and developed key performance indicators following a consensus meeting [172]. In order to improve identification of reasons for suboptimal management, and poor survival outcomes, the MDT plays an important role in recording patient factors and surgical outcomes. Completeness of information for regional and national audits is reliant on accurate recording of information and decision-making. The rationale for several of the recommendations in this section are set out in this document and targets for key performance indicators were agreed at this meeting [173].

Ultrasound is useful for determining the site of origin of a pelvic mass and to characterize the features of the mass and the likelihood of malignancy [174]. The use of standardised ultrasound reporting models, combining both morphological and Doppler waveform analysis, such as IOTA ADNEX ultrasound scoring system, are encouraged, in order to provide consistency in interpretations, standardisation of lexicon, lesion risk stratification and management [155,161,175].

In 2021 The European Society of Gynaecological Oncology (ESGO), the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), the International Ovarian Tumour Analysis (IOTA) group, and the European Society for Gynaecological Endoscopy (ESGE) jointly endorsed the use of the IOTA ADNEX for characterising adnexal masses on ultrasound followed by the use of the O-RADS score to direct further management [176]. Patients with an IOTA-ADNEX threshold of > 10 % should have further investigations and be referred to the specialist gynaecological centre MDT [175–177].

Histological diagnosis

Recommendations

Image-guided biopsy

As per the recommendation in ESGO Ovarian Cancer guidelines a histological diagnosis should be sought prior to cytoreductive surgery if there is doubt about the diagnosis. (Grade D)

Ascitic or pleural sampling and drainage

Ascitic or pleural drainage should be considered for patients requiring symptomatic relief. (Grade D)

Whenever possible, histology is preferred to cytology for diagnosis prior to neo-adjuvant chemotherapy. (Grade D)

If pleural cytology is positive accurate recording of FIGO stage within the MDT should be made. (Grade D)

Laparoscopic biopsy

If an image-guided biopsy is not feasible due to low volume disease, or disease location, consideration should be given to laparoscopic biopsies in order to confirm histological diagnosis, if primary cytoreductive surgery is not otherwise planned. (Grade D)

If laparoscopy is being performed for histology, assessment of operability with visualisation of potential sites of unresectable disease should be considered, understanding the limitations of laparoscopy to visualise the diaphragmatic peritoneum, Morrison's pouch and nodal areas. (Grade D)

Staging

Imaging

Recommendations

Computerised tomography (CT) of the chest, abdomen and pelvis, without the need for ultrasound, is advised for patients in whom there is a high clinical suspicion of advanced ovarian cancer. (Grade D)

Radiological staging with contrast enhanced CT of the chest, abdomen and pelvis is advocated in all patients with presumed ovarian cancer. (Grade D)

MRI should not be routinely used for the staging of ovarian cancer, but MRI with diffusion weighted sequences (DWI-MRI) can be used as an adjunct to CT staging, and can be considered in patients who have had an unenhanced CT scan. (Grade D)

MRI has a role in the characterisation of indeterminate adnexal masses identified on ultrasound in secondary care, if it is deemed

that further imaging will direct management, especially in patients who would prefer a fertility-sparing approach. (Grade A)

PET-CT is not recommended for routine preoperative staging. (Grade C)

Post-contrast CT of the chest, abdomen and pelvis is advocated as the first-line imaging investigation in patient with suspected ovarian cancer recurrence. (Grade B)

DWI-MRI and PET-CT for the assessment of disease recurrence is not routinely indicated but may be considered if this will alter the patient's management. (Grade B)

CT has significant value in excluding distant macroscopic disease spread, including intraparenchymal liver or lung metastases, and lymph node involvement, and in excluding synchronous cancers from other sites. CT is also able to detect other findings that may alter management, such as the presence of bowel obstruction, secondary cancers, hydronephrosis or pulmonary emboli. In addition, it may facilitate image-guided biopsy to enable histological confirmation of diagnosis. CT also allows identification of calcified peritoneal deposits (psammoma bodies), which are not readily identified on MRI [178,179].

CT imaging of the thorax, abdomen and pelvis is recommended to help define the extent of disease and to aid in surgical planning. However, retrospective data have shown that CT cannot accurately predict fine nodule peritoneal carcinomatosis, and therefore mitigate against suboptimal cytoreduction [180]. A review comparing 11 studies that used CT-based models to assess residual disease showed that CT had a poor discriminatory capacity, with sensitivity ranging from 15 to 79 % and specificity from 32 to 64 % [181]. In particular, CT has a low sensitivity (25 to 30 %) for detecting peritoneal tumour $<$ 10 mm [182,183], with sensitivity falling to 11 % for peritoneal deposits $<$ 5 mm [184]. The underestimation of peritoneal disease on CT in this study resulted in unnecessary surgery in 6 to 45 % of cases [185–187].

Currently, two large multi-centre trials (MROC and MRStagingOC) are ongoing to consider whether MRI can accurately select patients for whom cytoreductive surgery to achieve no macroscopic residual disease (NMRD) or no tumour deposits $>$ 1 cm (small volume residual disease (SVRD)) is feasible. In a prospective study of 161 patients comparing DWI-MRI to CT for the pre-operative assessment of incomplete cytoreduction with residual disease of any size, Whole-Body DWI-MRI showed significantly higher sensitivity (94 % versus 66 %), specificity (97.7 % versus 77.3 %) and accuracy (95.7 % versus 71.3 %) compared to CT [188].

MRI also has a high accuracy for predicting the Peritoneal Cancer Index (PCI) preoperatively compared with the PCI at surgery. Low et al. demonstrated no statistic difference between MRI PCI and surgical PCI and also demonstrated that MRI had an anatomical site-specific accuracy of 84 % for detecting peritoneal disease compared to 63 % for CT [189,190].

Approximately 18 %-31 % of adnexal lesions are classified as indeterminate on transvaginal ultrasound [191]. A multi-centred prospective cohort study confirmed the performance of a 5-point scoring system (O-RADS MRI), following the acquisition of a multi-parametric MRI scan, in assessing 1130 women with an indeterminate adnexal lesion on ultrasound. The study confirmed a strong concordance of the positive likelihood ratio of malignant neoplasms for each score category [191]. A study assessing semi-quantitative MRI perfusion parameters in women with complex adnexal masses demonstrated a significant difference in several perfusion parameters between benign and borderline/invasive malignant groups. Using a cut-off wash-in rate (WIR) $\geq$ 9.5 l/s had a specificity of 88 % and positive predictive value of 86 % for predicting malignancy, significantly better than conventional MRI (62 %, $P <$ 0.01). WIR $<$ 8.2 l/s had a negative predictive value of 94 % [192]. For more information, the role of advanced MRI techniques in identifying adnexal masses see the review by Thomassin-Naggara et al. [193].

18FDG PET-CT has a high diagnostic accuracy for the detection of retroperitoneal adenopathy in ovarian cancer (87–96 %), compared with CT (71 %) [194,195] and may provide a greater diagnostic accuracy for the detection of supra-diaphragmatic disease [196,197]. 18FDG PET-CT, however, is limited in its ability to identify $<$ 10 mm peritoneal disease, leading to false negative rates of 10 %. A large number of mis-registrations can also occur as a result of the physiological uptake in bowel and bladder, also contributing reducing diagnostic accuracy [198]. PET-CT does not seem to be a relevant additional diagnostic modality for the true extent of peritoneal spread of ovarian cancer, specifically bowel and mesenteric serosa, and therefore fails to predict resectability in those key sites, especially in the presence of low-volume, or low-grade disease [195].

The diagnostic performance of PET-CT can also be impacted negatively by certain tumour histological subtypes, due to lower fluorodeoxyglucose uptake in clear cell and mucinous invasive subtypes [176]. A Cochrane review of 18FDG PET-CT and MRI for assessing tumour resectability in advanced epithelial ovarian/fallopian tube/primary peritoneal cancer concluded that in a hypothetical group of 1000 women with an incomplete cytoreduction prevalence of 62 %, in 211 women, surgery would be incorrectly considered feasible (false negative) according to PET-CT, compared to 37 women according to DWI-MRI; 46 women would be incorrectly classified as having residual disease after surgery (false positive) according to PET-CT, compared to 8 women according to DWI-MRI [199]. A more recent clinical study in 20 women with HGCS, comparing CT with PET-CT, found that PET-CT had a lower sensitivity, detecting fewer disease sites than CT, especially in the upper abdomen and along the gastrointestinal tract [200].

Several studies, including systematic reviews and *meta*-analyses, comparing the different imagining modalities in the assessment of ovarian cancer recurrence demonstrated pooled accuracy of 94 % for MRI; 88–95 % for PET-CT and 76–79 % for CT [201–205]. Magnetic resonance imaging was more sensitive than PET-CT for detecting local pelvic recurrence and peritoneal lesions of recurrent ovarian tumours.

Laparoscopic assessment

Recommendaton

If laparoscopy is performed to obtain histology, documentation of the extent of disease should be made available for the MDT to allow informed treatment-planning. (Grade D)

A Cochrane systematic review of 18 studies of laparoscopy to determine operability and optimal resection in advanced stage ovarian cancer noted heterogeneity of included studies, precluding *meta*-analysis [206]; only two studies operated on all women, independent of laparoscopic findings, and provided data to calculate sensitivity and specificity. These two studies found that no women had a laparoscopy indicating unresectable disease and then went on to have only SVRD remaining after surgery (false positive). Laparoscopic assessment suggested that surgery could achieve NMRD or SVRD residual disease (negative predictive values) in 54 to 96 % of women who had NMRD after primary cytoreductive surgery, and in 69 to 100 % of women who had SVRD or less after primary cytoreductive surgery.

If performing laparoscopy to obtain histology, consideration could be given to using a quantitative validated scoring tool (e.g., Fagotti score – see supplementary materials below) [207]. A Fagotti predictive index score $\geq$ 8 identifies patients undergoing suboptimal surgery with a specificity of 100 and enables assessment of operability, including inspection of omental cake, peritoneal carcinomatosis, diaphragmatic carcinosis, mesenteric retraction, bowel and/or stomach infiltration, and liver metastases.

Pathology, molecular and genetic testing for epithelial tubo-ovarian/primary peritoneal cancers

Recommendations

The provision of a minimum set of clinical information on the histopathology request form is crucial to ensure a histopathology report of high quality for the accurate diagnosis and appropriate management. (Grade D)

Frozen section may be performed, if the result will alter the intra-operative management although there are limitations to the technique. (Grade B)

The Royal College of Pathology guidelines for reporting ovarian carcinomas mandate the provision of minimum clinical details to include demographics, clinical presentation, results of previous biopsies, radiological investigations for tumour staging, previous chemotherapy treatment, and details of the surgical procedures performed. It is desirable to include details of any family history of cancer and relevant hormonal therapy. The nature of surgical specimens from multiple sites should be carefully recorded and the specimen pots labelled to correspond to the specimen details on the request form and appropriately labelled as to site of origin. This section refers to high grade epithelial cancers. Histology specific to other cell types is described with the relevant sections.

High grade serous carcinoma

Primary site assessment

The origin of high-grade serous ovarian carcinoma (HGSC) has been the subject of intense study. The distal fallopian tube has emerged as the likely site of origin for most HGSC. This observation is, in great part, attributable to the use of sampling protocols that thoroughly examine the distal fallopian tube and also due to the reporting by greater number of specialist pathologists with a sub-specialty interest in gynaecological pathology. The discovery of serous tubal intraepithelial carcinoma (STIC) in women with *BRCA1* or *BRCA2* pathogenic variants following risk-reducing salpingo-oophorectomies (RRSO) and in women with advanced ovarian carcinoma led to the hypothesis that the natural history of HGSC might involve an origin in most cases at the distal fimbria of the fallopian tube. Identification of STIC in 18 % to 60 % of cases of advanced/symptomatic HGSC supports this assertion. STIC lesions are characterized by DNA damage, *TP53* mutation, and progressive molecular abnormalities that are also seen in high-grade serous carcinoma. An origin from epithelial inclusion cysts in the ovary has been proposed as a potential explanation as site of origin in the cases where complete examination of the fallopian tube does not reveal STIC. A consensus statement on primary site assignment in tubo-ovarian HGSC has been made (see Table 3) [208].

Morphology and immunohistochemical features of HGSC

HGSC of tubo-ovarian and peritoneal origin have similar morphological and immunohistochemical features. HGSC can be arranged in papillary, glandular or solid architecture. HGSC exhibits moderate to marked nuclear atypia and typically show greater than 12 mitoses per 10 high power fields. Necrosis and multinucleate cells are often present. The distinction between low-grade and high-grade serous carcinoma is based on cytological, not architectural, features. Homologous recombination deficient tumours frequently display SET (solid, endometrial-like, transitional) patterns. These tumours often show geographic necrosis and a prominent lymphocytic infiltrate.

On immunohistochemistry, HGSC of tubo-ovarian and peritoneal origin are typically positive for CK7, WT1, PAX8, oestrogen receptor and CA125. They do not express CK20, CEA and CDX2. Aberrant expression of p53 is a reliable method of identifying the underlying *TP53* mutation in 96 % of cases. In 4 % of cases, a wild-type pattern of staining may be observed despite an underlying loss of function (LOF). Immunohistochemistry for p53 should not be reported as positive or negative, but as aberrant/mutant or wild-type. In the majority, the aberrant staining is a mutant over expressed pattern characterised by diffuse strong positive nuclear staining in contrast to the wild-type staining observed in background normal tissues (e.g., fat, stroma). In a minority, there is complete absence of staining, reported as a null mutant pattern, or least frequently, a mutant cytoplasmic pattern. Especially in the latter two patterns, the wild-type staining observed in the internal control serves to confirm that the aberrant staining is genuine. In most cases, there is diffuse positivity for p16, a protein that has an important role in cell cycle regulation. Unlike in cervical adenocarcinomas, diffuse p16 positivity in HGCS is unrelated to an HPV aetiology.

Genetics

p53. As stated above, in > 95 % of cases, immunohistochemistry is reliable in detecting the presence of an underlying *TP53* mutation, the driver event in pathogenesis. In nearly all cases of HGSC, a combination of morphology and immunohistochemistry is sufficient for diagnosis. However, there may be rare cases where morphology is equivocal and the staining pattern of p53 is wild-type, where *TP53* mutational analysis helps distinguish HGSC from low grade serous carcinoma.

Homologous recombinant deficiency (HRD)

As described above, pathogenic variants in homologous recombinant (HR) genes result in an inability to repair breaks in double stranded DNA and increases the risk of developing tubo-ovarian/peritoneal HGSC. HR deficient tumours show increased sensitivity to platinum therapy and PARP inhibitory therapy. *BRCA1/2* genes are the most commonly affected, but less frequently, pathogenic variants may occur in other HR genes such as *BRIP1*, *RAD51C*, and *RAD51D* [209]. Furthermore, homologous recombination deficiency may be caused by epigenetic events, including *BRCA* methylation which won't be identified by genomic sequencing. Although mostly germline, HRD may less frequently result from somatic mutations in *BRCA* 1/2 and other HR genes, confined to tumour tissue only. Testing performed on tumour tissue detects somatic mutations and germline mutations. However, as germline *BRCA* variants with large genomic rearrangements are not captured by targeted next generation sequencing used for tissue *BRCA* (t*BRCA*) testing, the latter does not replace the need for germline testing. The NICE approval in March 2021 of maintenance olaparib (PARP inhibitor) therapy in advanced (FIGO stages III or IV), HR deficient, high grade epithelial ovarian, fallopian tube or primary peritoneal cancer, irrespective of the *BRCA* status, has led to routine HRD testing on tumour tissue in such cases. However, as per national test directory, tumour *BRCA* testing is performed in all cases of HGCS irrespective of FIGO stage. These tests are routinely requested by the pathologists on the tissue biopsy or resection specimen and occasionally on cytology cell block samples (if histology tissue sample is not available) provided patient consent has been obtained.

Women with HGSC or G3 endometrioid ovarian adenocarcinoma have > 10 % risk of an underlying *BRCA* mutation and should be offered genetics counselling and testing.

The BAGP/BGCS recommendations for tumour and germline *BRCA* and testing are as follows [210]:

- Patients with non-mucinous high-grade tubo-ovarian carcinoma are offered testing as early in their care pathway as possible.
- Clinicians must communicate to the pathologist that the patient has been consented, prior to testing being initiated.
- Tumour and germline (usually blood) testing should be undertaken in parallel.

Chemotherapy response score

Neoadjuvant chemotherapy (NACT) is increasingly used in advanced HGSC. The chemotherapy response score is based on omental examination of the interval debulking specimen and provides histological assessment of the NACT effect. It stratifies patients into complete/near complete response (CRS 3), partial response (CRS 2) and no or minimal response (CRS 1). As it correlates with progression free survival and has good reproducibility [211,212]; it is recommended by International Collaboration on Cancer Reporting (ICCR), and Royal College of Pathologists (RCPath) as a prognostic tool to guide further treatment in cases when there is poor response to NACT. At present there is no clinical

evidence that would recommend changing the standard adjuvant treatment approach based on CRS.

Clear cell adenocarcinoma

Ovarian clear cell carcinoma (CCC) accounts for approximately 10 % of epithelial ovarian cancer, with a higher prevalence in East Asia. These tumours are usually unilateral and are commonly associated with endometriosis. CCC is the most likely component to be part of a mixed carcinoma [213]. The majority of women present with early-stage disease, but due to relatively low chemosensitivity, prognosis is typically poor when presenting at higher stages (III-IV).

CCC typically displays a tubulocystic, papillary and/or solid architecture, with a single layer of tumour cells, which show hobnailing. Hyaline globules may be present. The tumour cells have uniform nuclear atypia, although areas of pleomorphism may be present, and mitotic rates are usually relatively low. While the cytoplasm is often clear, it may be eosinophilic (oxyphilic variant) and this may represent a pitfall in frozen section assessment.

CCC is generally positive for PAX8 by IHC and negative for ER. The majority of cases show wild-type p53 immunoreactivity, but a subset (reported incidence varying from 7-20 %) shows an aberrant/mutant p53 staining pattern corresponding to driver mutations in *TP53* and which is an independent poor prognostic factor [214–217]. IHC markers helpful for diagnosis in difficult cases include Napsin A, HNF1β and AMACR, all of which are variably positive in CCC; however, Napsin A is the least specific and may also be expressed in endometrioid ovarian carcinoma, while AMACR is specific, but not sensitive, and may only stain approximately half of CCC cases [218].

CCC is characterised predominantly by mutations in the *ARID1A* or *PIK3CA* genes [219,220], although a minority harbour a *TP53* driver mutation. A lower proportion of ovarian CCC shows mismatch repair deficiency than their endometrial counterpart or the endometrioid subtype within the ovary (reported rates vary from 2-7 %) [216,217,223–225], but given that approximately 12–14 % of Lynch syndrome-associated ovarian cancers are of CCC subtype [223], it seems reasonable to recommend universal MMR immunohistochemical testing on these tumours. Those with MMR deficiency often have a greater number of tumour-infiltrating lymphocytes and are enriched for *ARID1A* mutations [221]. A small number of studies have attempted to classify ovarian CCC according to TGCA and have demonstrated a very low number of *POLE* mutations (<1%) in this tumour type [217,221].

Ovarian endometrioid adenocarcinoma

Ovarian endometrioid carcinoma (OEC) accounts for approximately 10 % of epithelial ovarian cancer and has a more favourable prognosis than high grade serous, mucinous and clear cell carcinomas stage for stage [224]. OEC typically presents at an early-stage with low-grade tumours. Grade 3 endometrioid carcinomas of the ovary are much rarer than their endometrial counterparts. OEC has similar morphological features to that seen in the uterus, with low-grade tumours displaying a glandular architecture, often with cribriforming or papillary architecture, composed of columnar cells with mild to moderate cytological atypia and scattered mitotic figures. Squamous and/or mucinous differentiation is common. Other less common patterns include sex cord-stromal/sertoliform morphology [225], which mimic sex cord-stromal tumours and a spindled cell component or corded and hyaline features (CHEC); in these variant patterns, the recommendation is that grading is based on areas of conventional endometrioid morphology. A recently-described pattern is that resembling pilomatrix carcinoma with high-grade features, which is clinically aggressive [226]. Some cases give rise to a malignant squamous component and other rare cases are associated with somatically-derived yolk sac tumours. Cases associated with an undifferentiated component are termed dedifferentiated carcinoma, analogous to their endometrial counterpart. Ovarian adenocarcinomas previously falling into the category of seromucinous carcinoma are now also included in this histotype [227].

By immunohistochemistry, OEC is usually positive for PAX8 and ER, shows a wild-type p53 staining pattern, mosaic p16 staining and is negative for WT1. However, OEC have a higher propensity for WT1 expression than in the endometrium and, while often focal, even diffuse WT1 staining with typical endometrioid morphology should not deter pathologists from diagnosing as such [226,228]. In addition, there may be loss of PAX8 expression in the spindled or CHEC areas in these variants.

OEC often arises within a background of endometriosis, although other precursor lesions, such as endometrioid adenofibroma/endometrioid borderline tumour, may be present without definite endometriosis. Given their association with endometriosis, appropriate sampling is required to exclude a mixed carcinoma with a higher grade (usually clear cell) component. Approximately 10 % of patients presenting with OEC will have a synchronous endometrial endometrioid primary; although these may be clonally related, they are for clinical purposes regarded as discrete primaries due to their excellent prognosis and often the presence of precursor lesions at both sites (atypical hyperplasia in the endometrium, endometriosis in the ovary). Therefore, endometrial sampling is paramount in cases of fertility-preserving surgery for an endometrioid ovarian primary to exclude concurrent hyperplasia or overt malignancy.

OEC have similar mutation profiles to those in the endometrium, although have been shown to have lower rates of *PTEN* mutations and microsatellite instability than their endometrial counterparts and conversely higher rates of *CTNNB1* mutations [229,230]. While the rates of mismatch repair deficiency are lower than in the endometrium, immunohistochemistry for mismatch repair proteins is recommended in all cases of OEC to avoid missing a diagnosis of Lynch syndrome, in addition to the potential for immunotherapeutic options in relapsed or advanced disease. However, as in the endometrium, the majority of mismatch repair deficiency in OEC is sporadic in nature. Some studies have been performed to investigate The Cancer Genome Atlas molecular subgroups as described in endometrial endometrioid carcinomas; overall the rates of *POLE* mutation are slightly lower in the ovary than in the endometrium and an increased proportion of cases fall into the no specific molecular profile group. While numbers are small, a *meta*-analysis has demonstrated similar outcomes to those described in the endometrium when ovarian endometrioid carcinomas are categorised in this manner, with the most favourable prognosis seen in *POLE*-mutated tumours and the poorest outcomes in the p53-abnormal group [231,232].

Mucinous adenocarcinoma

See separate section below.

Low grade serous ovarian adenocarcinoma

See separate section below

Other rarer histological subtypes

About 10 % of all ovarian tumours can be classified as rare tumours [233]. Germ cell tumours, sex cord stromal tumours, low grade serous ovarian carcinoma and borderline tumours are discussed in separate sections below. Rarer epithelial subtypes are discussed here.

Mesonephric-like carcinoma

These tumours generally occur in postmenopausal women [234] and tend to be confined to the ovary at presentation. Abdominal or pelvic pain is the common mode of presentation. Diagnosis is made by histology. Morphological features include glandular, ductal and solid patterns. Intra-luminal eosinophilic colloid-like material may be seen. No squamous or mucinous differentiation is noted. These carcinomas are

regarded as high grade. On immunohistochemistry, the cells are typically negative for hormone receptors and WT1. They are positive for GATA3, TTF1, luminal CD10 and PAX8 [235]. Background endometriosis may be present. Targeted genomic profiling reveals activating *KRAS* mutations and *PIK3CA* mutations [236].

Undifferentiated and dedifferentiated carcinomas

These are tumours of *peri*-menopausal women. They are high grade tumours that are constituted by cells that are typically discohesive and arranged in sheets. Tumour infiltrating lymphocytes are often a feature [237]. Mitotic activity is high, and necrosis is not uncommon. There may be a well-differentiated component, and, in these instances, these are regarded as dedifferentiated carcinomas. The cells are usually negative for PAX8, ER, PR and WT1. EMA staining is usually focal and p53 wild type. Loss of SMARCA4 (BRG1), SMARCA2 (BRM), SMARCB1 (INI1), or ARID1A and loss of mismatch repair proteins are common [238,239].

Small cell carcinoma of the ovary, hypercalcemic type

This is a malignancy that occurs in young women with a median age of 25 years. Presenting symptoms are those of a pelvic or abdominal mass; up to two-thirds of the patients have serum hypercalcaemia at presentation. On microscopy, these are undifferentiated tumours composed of monomorphic cells with round nuclei, vesicular chromatin and brisk mitotic activity. They are mostly arranged in sheets with typical scattered follicle like spaces [240]. On immunohistochemistry, the tumours are positive for WT1, p53, and p16 with variable expression of SALL4, keratins, EMA, CD10, calretinin, all neuroendocrine markers, and PTHrP. Inhibin and TTF1 are typically negative. Almost all tumours show loss of *SMARCA4* (and *SMARCA2*) expression. Molecular testing shows somatic or germline inactivating mutations in *SMARCA4* [241]. Histogenesis of these tumours is still undecided. Their molecular profile raises the consideration that they belong to a family that includes malignant rhabdoid tumours [242]. Cases with scattered mucinous glands are seen. This raises the possibility that they may be associated with teratomas and may represent germ cell tumours. Prognosis is poor in cases presenting with spread outside the ovary.

Mixed carcinomas

With increased understanding of ovarian cancer morphology and molecular pathology, the category of mixed carcinoma is rare. At least two histological types must be clearly recognizable on H&E-stained sections. The different histological components should be confirmed by ancillary testing when appropriate. Any percentage of a second histological type that can be confidently demonstrated is sufficient to label the tumour as mixed. The types present and their percentages should be stated in the diagnostic report. The most common mixed tumour is endometrioid and clear cell carcinoma [213]. A combination of Napsin A (expressed in the clear cell component) and hormone receptor immunohistochemistry (expressed in the endometrioid component) can be used to distinguish between the two types of carcinomas.

Solid pseudopapillary tumour

This is a rare tumour, which has been most commonly recognised in the pancreas. Morphologically they typically show solid nests and pseudopapillary structures. These lack vascular cores. The cells are typically polygonal [243]. There may be an antipodal distribution of the nuclei at the base of the papillae. Tumour cells are usually positive for vimentin, CD10, CD56, CD99, WT1, and β-catenin (nuclear and cytoplasmic). Chromogranin, calretinin, and inhibin are negative [244]. The typical finding on DNA sequencing is an activating mutation of *CTNNB1* [245]. Although originally considered benign, there are increasing numbers of reports of aggressive behaviour.

Patient optimisation — Frailty, Prehabilitation, and enhanced recovery after surgery (ERAS)

This section outlines the role of prehabilitaiton for patients with ovarian cancer. Please see the recommendations from the BGCS prehabillitation consensus meeting (February 2024) for further details (manuscript in preparation).

Recommendations

General

Recognised clinical frailty scores (such as the Rockwood Clinical Frailty Score) are a useful way to identify patients who may benefit from referral to a care of the elderly service and can identify those at increased risk of treatment-related morbidity. (Grade D)

Optimisation of health from presentation to primary care with symptoms is feasible and has allied health benefits. (Grade D)

Prehabilitation programs should start at the earliest opportunity on the patient journey with clear goal-orientated milestones. (Grade D)

In order to optimise prehabilitation, gynae-oncology teams should look to adapt structured, but individualised programmes to include: nutritional and co-morbidity optimisation; increase in exercise tolerance; management of psychological stressors; social support, including financial and peer support. (Grade D)

Clinical Nurse Specialists and Cancer Support Workers are ideally placed to help facilitate and deliver effective prehabilitation programs. (Grade D)

Healthcare providers should promote physical activity and exercise guidelines through their incorporation into standard cancer care. (Grade B)

Nurse-led assessment & education clinics are a useful adjunct to improve patients' length of stay. (Grade B)

Chemotherapy

Patients with ovarian cancer undergoing neoadjuvant chemotherapy should be offered prehabilitation at the earliest opportunity, to optimise nutritional status, and reduce intraoperative surgical complications at interval surgery. (Grade C)

Oncology teams should encourage patients with advanced ovarian cancer to exercise during chemotherapy, due to reported high motivation and willingness. (Grade C)

Exercise during chemotherapy is safe and has beneficial effects on quality of life (QoL), physical functioning and completion of chemotherapy. (Grade B)

Surgery

Prehabilitation programs are feasible in abdominal cancer surgery and may improve surgical outcomes. In particular, multimodal prehabilitation programmes in major cancer surgeries are recommended to positively impact patient outcomes. (Grade B)

Prehabilitation may achieve cost-savings by lowering complication rates and decreasing care facility requirements. (Grade C)

Preoperative carbohydrate drinks should be considered to reduce length of hospital stay in adult patients undergoing elective surgery. (Grade B)

Continuing with physical activity post-surgery is associated with positive functional outcomes. (Grade C)

Medically frail patients, as assessed by clinical frailty scores, e.g. the Rockwood Score [246], experience higher complications, readmissions, and mortality rates from surgical procedures [247–249]. Frailty may occur across the age spectrum of ovarian cancer patients since it is defined as including chronic co-morbidities, not necessarily exclusive to increasing age, that affect both physiologic resilience and response to stressors [250]. Up until now, research in prehabilitation has been largely limited to pilot studies. These studies have demonstrated decreased length of hospital stay, decreased rates of post-operative complications and a quicker return to baseline performance status [251,252] as well as decreased healthcare costs [253].

Optimising fitness prior to any ovarian cancer treatment is a

challenge. Many women present with disease at an advanced stage and are likely to be physically compromised by the time they are first seen in a clinical setting. How best to optimise fitness at all levels requires new ways of thinking (and further research). Any intervention requires effectiveness within a short timeframe. Studies in both colorectal and thoracic care, emphasise that prehabilitation must start on first seeing patients with interventions in both nutritional and exercise tolerance status [254].

Many women undergoing abdominal surgery will be at high risk of postoperative complications and significant decline in physical function [255].

Prehabilitation for patients undergoing treatment

The recent Ovarian Cancer Audit Feasibility Pilot [6] demonstrated that, amongst women with stage II-IV and unknown stage ovarian cancer, fewer than half received standard management with a combination of surgery and chemotherapy. Additionally, 26.2 % of women were not offered any treatment. This may be due to poor fitness levels as reported in a previous study [256]. The rapidity of instigating investigations and appropriate treatment therefore become critical before the woman becomes too clinically weak and unwell for treatment. Prehabilitation is an integral part of this process, as part of a continuum of preventative, restorative, supportive and palliative rehabilitation; and even without *peri*-operative complications, surgical stress is associated with a 20–40 % decrease in functional capacity [257,258].

Use of physical activity and exercise science principles is recognised as being important [259]. In addition, use of behaviour change strategies may be considered. A systematic review [260] examined exercise training interventions in people with cancer undergoing adjuvant cancer treatment following surgery, however, due to the lack of adequately powered RCTs, it remained unclear whether exercise training in this context improved clinical outcomes, other physical fitness and health related quality of life (HRQoL).

In a systematic review of patients undergoing major abdominal cancer surgery and gynaecological surgery, five studies of prehabilitation programs in gynaecology (three RCTs, one study protocol, one pilot study) were identified [261]. Study protocols were heterogenous, but showed improvements in both physical and psychological parameters. Most studies showed improvement in complication rate and shorter length of hospital stay.

Multimodal prehabilitation programs may include exercise, nutritional counselling (e.g., protein supplementation), psychological support (e.g., stress-reducing strategies), and strategies to optimise underlying conditions and promote cessation of negative health behaviours such as smoking and alcohol consumption [262]. These interventions have been associated with reduced treatment associated morbidity and mortality, reduced length of hospital stay, improved cardiorespiratory fitness, nutritional status and mobility, as well as improvement in neuro-cognitive function [263]. The positive effect of these interventions can be seen in as little as two weeks, with the effects being maximised the longer they are continued [264]. Active participation of both healthcare providers and patients leads to better outcomes [265].

Miralpeix et al. 2019 suggest a safe, reproducible, functional, and easy-to-apply multimodal prehabilitation program for gynaecological oncology practice. A suggested interval for delivery is shown below (Fig. 1; image adapted [254] with permission):

A Cochrane review demonstrated that preoperative carbohydrate treatment was associated with a small reduction in length of hospital stay when compared with placebo or fasting in patients undergoing elective surgery [266], but should either be avoided or administered with caution in patients with diabetes.

Prehabilitation in the elderly

Older women are commonly seen as unable to tolerate extensive surgery and an increase in referral for neoadjuvant chemotherapy is seen in women over the age of 65 years of age [267]. Bias against surgery for women over 75 years of age is also demonstrated by exclusion from clinical trials [268]. The concept of frailty has already been discussed and frailty, rather than chronological age, should be considered in treatment decision-making. In a prospective study [254,269] of women over 75 years with newly-diagnosed ovarian cancer, patients were referred to a Care of the Elderly clinic for evaluation before cytoreductive surgery. Although there were no statistical differences in outcomes between women treated with surgery who did and did not have a preoperative geriatric evaluation, there were two deaths in the group that did not undergo evaluation and more unplanned ICU admissions (6 versus 1).

Timing and delivery of prehabilitation

Recommendations

Community-delivered prehabilitation

In a prospective cohort study, 189 patients underwent an ‘optimisation bundle’ assessment which aimed to identify opportunity to improve anaemia, smoking and alcohol behaviour, diabetes, hypertension, existing comorbidities, low BMI, and physical activity levels [270]. Of the 15 patients diagnosed with cancer, eight (53.3 %) underwent potentially curative surgery, of whom seven (87.5 %) required optimisation. None suffered significant therapy-related complications.

Prehabilitation before neoadjuvant chemotherapy

Miralpeix et al. conducted a retrospective observational pilot study of patients with advanced ovarian cancer treated with NACT and ICS [271]. The prehabilitation group received a structured intervention based on physical exercise, nutritional counselling, and psychological support. The prehabilitation group had higher mean total protein levels in both preoperative (7.4 vs. 6.8, $P = 0.004$) and postoperative (4.9 vs. 4.3, $P = 0.005$) assessments, with fewer intraoperative complications (40 % vs. 14.3 %), and lower requirement of intraoperative blood transfusion (14.3 % vs. 53.3 %, $P = 0.027$). The day of the first ambulation, rate of postoperative complications, and length of hospital stay were similar between the groups.

Timing and delivery of assessment of prehabilitation optimisation

Fang Huang et al. reported the success of an Advanced Practitioner Registered Nurse-led preoperative assessment and education (APAE) clinic which ran alongside the Gynaecological Oncology clinic where patients with gynaecological cancer were seen at first visit when planned for surgery. This study demonstrated clinical impact by influencing patients’ expectations about what they could anticipate before and after surgery and making appropriate home care arrangements earlier [272].

Prehabilitation validated in patients with ovarian cancer and peritoneal carcinomatosis

Unlike other disciplines in which prehabilitation has been well studied through a well-structured multimodal prehabilitation program, there are few studies published on prehabilitation programs in gynaecological surgery, and even fewer in gynaecological oncology patients [273]. There have been few studies on the benefit of prehabilitation programmes in patients with ovarian cancer undergoing surgery, and so the evidence is lacking.

Prehabilitation and impact on completion of treatment

A systematic review of randomised trials of adult patients undergoing chemotherapy, comparing an exercise intervention with standard care showed that aerobic exercise improved, or at least maintained

fitness during chemotherapy [274]. Moderately intense exercise, up to 70–80 % of maximum heart rate, was safe. Adherence was good (median 72 %). Exercise improved QoL and physical functioning, with earlier return to work.

Two out of four studies reported improved chemotherapy completion rates. Four out of six studies reported reduced chemotherapy toxicity. There was no evidence that exercise reduced myelosuppression or improved response rate or survival.

Enhanced recovery after surgery (ERAS)

Prehabilitation and enhanced recovery often overlap and the terms are used interchangeably. Generally, prehabilitation occurs well before surgery and enhanced recovery around the time of and after surgery. Enhanced recovery after surgery (ERAS) is a multidisciplinary, multimodal approach to the care of the surgical patient [275]. The ERAS society have published guidelines (part 1 and part 2) for gynaecologic oncology surgery in 2016 [276,277] and then updated guidelines in 2019 [278].

Enhanced recovery aims to improve post-operative outcomes and hasten functional recovery through a reduction in stress levels by attenuating the metabolic response to major surgery. It begins with pre-operative education and psychological preparation which has been shown to improve post-operative pain and nausea, reduce anxiety and increase patient satisfaction [261,279,280]. One RCT demonstrated written information in the form of a pre-operative leaflet was superior to oral information [281] although both is best practice.

Bowel preparation prior to major gynaecologic oncology surgery has been given assuming there is a reduction in post-operative infections and anastomotic leak following colonic resection, although several *meta*-analyses from colorectal surgery have not demonstrated a reduction following mechanical bowel preparation [282,283]. Furthermore, mechanical bowel preparation can lead to dehydration and electrolyte imbalances that can lead to poorer outcomes and worse patient satisfaction. However, one *meta*-analysis showed a combination of oral antibiotics and mechanical bowel preparation was associated with a lower rate of surgical site infection overall (7.2 % vs 16 %, $P < 0.001$) and incisional site infections (4.6 % vs 12.1 %, $P < 0.001$) with comparable organ space infections (4 % vs 4.8 %, $P = 0.56$) [284]. Although no randomized controlled trials have compared oral antibiotics alone to mechanical bowel preparation, several retrospective studies have suggested the antibiotics alone reduce post-operative infections [285,286].

Other recommendations for enhanced recovery include pre-operative carbohydrate drinks, avoidance of hypothermia and hyperglycaemia, avoidance of pre-operative sedative, avoidance of drains/nasogastric tubes, reduction of opioid analgesics, antimicrobial and venous thromboembolism prophylaxis, regular diet within 24 h, removal of catheter within 24 h and early mobilisation [278,287].

Data suggest that ERAS pathways can reduce complications by 10–20 % and save money [288–290] but unfortunately implementation and dissemination can be slow. Two new studies are underway which combine prehabilitation and ERAS which evaluate patient outcomes to determine if further improvements can be made for patients undergoing complex gynaecologic oncology surgery [261,291].

High grade epithelial ovarian cancer

First-line treatment – surgery

The following sections apply to high grade serous epithelial tubo-ovarian cancer (EOC), although parallels to these guidelines may apply to other histological subtypes and will be discussed in relevant sections where they differ.

Surgical management of suspected or confirmed early-stage epithelial ovarian cancer

Recommendations

Surgery

The aim of surgery for early-stage ovarian cancer (FIGO stage I and II) is to remove all visible disease and perform staging to tailor adjuvant treatment options. (Grade D)

Patients suitable for fertility-sparing surgery should be identified by the MDT and the advantages and disadvantages of this discussed with them, so that they can make an informed choice. (Grade D)

Early-stage disease may be an unexpected post-operative histological finding. Cross-sectional imaging and a re-staging procedure by a gynaecological oncologist may be indicated. The numbers of re-staging procedures may be reduced through careful case selection and the use of frozen section and intra-operative decision-making. (Grade C)

Staging surgery for apparent early-stage ovarian cancer includes peritoneal washings/ascitic sampling taken prior to manipulation of the tumour, bilateral salpingo-oophorectomy, hysterectomy, peritoneal biopsies, omental biopsy/ omentectomy. (Grade C)

Pelvic and bilateral *para*-aortic lymphadenectomy up to the level of the insertion of the renal vessels can be considered in the absence of peritoneal dissemination for prognostic purposes, or, if knowing the nodal status is likely to helpfully inform the choice of adjuvant therapies. (Grade C)

Frozen section analysis of the primary tumour is recommended when pelvic and *para*-aortic lymphadenectomy is planned, to confirm diagnosis of likely malignancy, prior to proceeding with lymphadenectomy. (Grade C)

Pelvic and *para*-aortic lymphadenectomy can be considered as a secondary staging procedure (after malignancy has been confirmed) for prognostic purposes, or, if knowing the nodal status is likely to helpfully inform the choice of adjuvant therapies. (Grade C)

Surgical staging of non-bulky lymph nodes is prognostic, but has not been shown to improve progression-free survival and may or may not improve overall survival. (Grade B)

The rates of positive lymph nodes in expansile type mucinous and low-grade endometrioid cancers are very low and systematic lymphadenectomy is not warranted. (Grade C)

Appendicectomy can be considered where a mucinous tumour is suspected, although pick up rates of a related abnormality are low, if the appendix appears macroscopically normal. (Grade C)

Routine excision of a macroscopically normal appendix should be avoided if a mucinous tumour is not suspected. (Grade C)

Surgical staging

Treatment for presumed early-stage epithelial ovarian cancer (EOC) should aim to remove all visible tumour deposits. Surgical staging traditionally has included peritoneal washings, total abdominal hysterectomy (TAH), BSO, omentectomy, systematic pelvic and *para*-aortic lymphadenectomy and blind peritoneal sampling [292].

Depending on the histological grade and subtype, up to 30 % of patients with apparent early-stage EOC will be upstaged after comprehensive surgical staging [293,294]. A retrospective study of 96 patients with grade 3 tumours, and gross disease confined to one ovary, found that 15 % had microscopically positive lymph nodes [295]. In a prospective study of participants with ovarian cancer, 15/111 participants (13.5 %) had lymph node metastases, of whom 13 had *para*-aortic node involvement (86.6 %) [296]. Lymphadenectomy-related complications (lymphocyst formation and lymphorrhoea) were found in 14.4 % patients.

Surgical staging may provide useful prognostic information and may inform subsequent adjuvant treatment, especially with regard to access

to targeted agents. The survival benefit of full surgical staging in apparent stage I ovarian cancer has largely been extrapolated from data from retrospective sub-group analysis of RCTs performed to assess the benefit of adjuvant chemotherapy in early-stage disease. In the initial sub-group analysis of the patients allocated to observation only, full surgical staging was associated with an improvement in OS and PFS over those without lymph node and blind-peritoneal sampling (HR 1.75, 95 % CI 1.04 to 2.95; P = 0.03 and HR 1.78, 95 % CI 1.15 to 2.77; P = 0.009, respectively) [297]. An updated Cochrane review, of ten-year follow-up data, could "neither confirm nor exclude survival benefits in lower risk disease or in optimally staged disease", and judged them to be of very low certainty [298].

A prospective RCT of systematic lymphadenectomy versus node sampling, in 268 participants with EOC clinically confined to the pelvis, found that positive nodes were detected more often in patients undergoing systematic lymphadenectomy, compared to those who underwent node sampling (22 % vs. 9 %; P = 0.007). The confidence intervals were very wide, with very low certainty in the results. A recent systematic review of the role of lymphadenectomy in EOC found one RCT in early-stage disease [299,300]. They noted significant biases in the study design, including no assessment for surgical quality and unilateral lymphadenectomy was allowed in unilateral tumours. Most importantly, the primary endpoint of the study was the prevalence of patients with positive nodes. At a median follow-up of 87.8 months, the adjusted risks were HR 0.72 for PFS (95 %CI 0.46 to 1.21, P = 0.16) and HR 0.85 for OS (95 %CI 0.49 to 1.47; P = 0.56). They concluded that "lymphadenectomy was not associated with improved OS" [300]. When the RCT was combined with data from four retrospective studies, lymphadenectomy was not associated with improvement in PFS (HR 0.71, 95 % CI 0.47 to 1.07). Combining the RCT and retrospective studies demonstrated in improvement in OS (HR 0.74, 95 % CI 0.68 to 0.82, and without SEER study; HR 0.64, 95 % CI 0.42 to 0.97). However, as only one study was an RCT (with little to no difference in OS), and all of the retrospective studies were at high risk of bias, the evidence is very uncertain. The authors concluded that the effect of lymphadenectomy on survival is unknown and, as the results of the LION study [301] in advanced ovarian cancer demonstrate that micro-metastases should be treated with chemotherapy, rather than surgical excision, the "main purpose of systematic lymphadenectomy is to identify the patients who can avoid or benefit from adjuvant chemotherapy and could be omitted with improvements in diagnostic imaging or with sentinel lymph node biopsy" [300]. As discussed above, even those with early-stage ovarian cancer may benefit from chemotherapy [298], and therefore, given the higher rate of short- and long-term adverse events with lymphadenectomy, this may not be of benefit unless knowledge of occult nodal involvement would affect access to targeted agents, such as PARP inhibitors, so can be considered where nodal involvement would change adjuvant treatment options.

Several studies have shown that the rate of positive lymph nodes in stage I mucinous cancer and low-grade endometrioid ovarian cancer are extremely low and therefore there is no benefit to lymph node sampling [302–306].

Diagnostic accuracy rates for frozen section analysis (FSA) of ovarian masses are high for malignant and benign ovarian tumours, but lower for borderline tumours, mucinous tumours and larger ovarian lesions [307]. A pooled analysis of 14 observational retrospective studies demonstrated sensitivity of 99 % and 94 % for benign and malignant tumour, respectively [308]. The corresponding false positive rate for malignancy was 0.23 % and the false negative rate 1.3 %. The pooled sensitivity for borderline and benign ovarian tumours was lower at 66 % due to an increased incidence of false-negative results [309]. A Cochrane diagnostic test accuracy review of 38 studies included a subset of 3953 participants with intraoperative frozen section and either borderline or invasive cancer, based on final diagnosis of malignancy [309]. If a positive test indicates invasive cancer and negative test indicates either a borderline or benign tumour (i.e. lymph node sampling not indicated), sensitivity was 90.0 % (95 % CI 87.6 % to 92.0 %) and specificity was 99.5 % (95 % CI 99.2 % to 99.7 %). Due to the relatively large size and heterogeneity of mucinous tumours, FSA is prone to misdiagnosis and this should be considered to prevent under-treatment, although, mucinous tumours have low positive node rates, so differentiating between a benign, borderline or invasive mucinous tumour is less important [302–305,307,310]. FSA is less reliable at determining tumour subtype and endometrioid, intestinal mucinous, and clear cell tumours are particularly prone to frozen section misdiagnosis [307,310]. Nevertheless, as FSA is used for guiding intraoperative management and final diagnosis, and subsequent management is based on formalin-fixed, paraffin embedded samples with immunohistochemistry, FSA remains an invaluable tool for the identification of malignancy in suspected early-stage disease, and can be used to limit the need for invasive and morbid staging procedures.

Confirmation of malignancy allows for full staging surgery to be undertaken at the time of the diagnostic laparotomy, according to pre-operative consent, avoiding the need for second dedicated staging procedures and subsequent delay in access to adjuvant treatment. Optimal assessment of frozen section histology depends on the following: (1) clinical information including tumour markers, radiology and intra-operative findings; (2) careful and thorough gross examination with judicious selection of the best areas for sampling: (3) accurate interpretation of frozen section histology and intraoperative cytology: (4) an effective and clear communication between surgeon and pathologist. Discordant results between frozen section and final diagnosis are often due to sampling or interpretation errors [311,308,312–318].

A further challenge to the pathologist lies in the discrimination between borderline and malignant ovarian tumours at frozen section. In contrast to the situation described above, intra-operative diagnosis of borderline tumour carries a higher risk of discordance with the final histological diagnosis [307,318–323]. De Decker et al. conducted a systematic review and *meta*-analysis of eight studies of borderline tumours and found that 41 % of women diagnosed with at least borderline on frozen section were found to have invasive carcinoma upon final diagnosis when compared with 9.7 % of women with a straightforward borderline frozen section diagnosis [323]. They recommend full staging surgery upfront in cases of 'at least borderline' to avoid a second surgical procedure.

Fertility-sparing surgery

Young women who wish to preserve their fertility, with apparent early-stage EOC, can be considered for fertility-sparing surgery. This requires careful counselling about the potential risk of recurrent epithelial ovarian cancer and need for further treatment. Patients with grade 1 or 2 mucinous, serous, endometrioid, or mixed histology and FIGO stage IA or stage IC with unilateral ovarian involvement may be considered for unilateral salpingo-oophorectomy in combination with surgical staging. In a large retrospective study, women with G3 disease, or stage IC3 with clear cell histology, had a higher risk of recurrence, but this mainly related to the higher incidence of occult extra-ovarian spread, rather than to a higher relapse rate in the preserved ovary [324]. Therefore, these patients should also be carefully informed about their prognosis, to enable them to make an informed choice about fertility-sparing surgery.

Routine appendicectomy in ovarian cancer

Appendiceal involvement in either mucinous borderline or invasive ovarian cancer is rare, unless there is clinically apparent disease [305,325]. In one case series of 309 women with mucinous ovarian tumours, 197 (64 %) were benign, 68 (22 %) borderline, and 44 (14 %) were invasive. Appendicectomy was performed in 155 women; there was only 1 metastatic low grade mucinous appendiceal tumour, and this was in a grossly abnormal appendix. A systematic review of 12 non-randomised studies in borderline mucinous ovarian tumours, included 667 patients with borderline ovarian tumours. Appendicectomy was

performed in 232 patients and only two (0.86 %) appendiceal carcinomas were found on histology, both of which were abnormal clinically [325]. In addition, increasing evidence from national case control studies suggests the appendix may not be vestigial and appendicectomy has been linked to an increased risk of Clostridium difficile infection, sepsis, and colorectal cancer [326,327]. Appendicectomy should not therefore be considered as being without long-term consequence.

Surgical management of suspected or confirmed advanced-stage primary ovarian cancer

Recommendations

Approach to surgery

All patients with FIGO Stage II to IV, or unstaged, ovarian cancer should be considered for *a combination of* cytoreductive surgery and chemotherapy by a specialist gynaecological cancer MDT. (Grade D)

The aim of cytoreductive surgery (CRS) should be to achieve no macroscopic residual disease (NMRD), as this is associated with improved survival. (Grade C)

A maximal cytoreduction approach to achieve no macroscopic residual disease (NMRD) can be safely delivered in appropriately selected patients and is associated with improved survival (compared to low complexity surgery) and no detriment in quality of life in those deemed suitable for this approach. (Grade C)

All women should be considered for CRS, even those not suitable for high complexity surgical approach. (Grade C)

Systematic lymphadenectomy should not be performed in the absence of bulky lymph nodes, and only those nodes that appear involved by disease should be removed. (Grade A)

Timing of Surgery

Timing of surgery depends of careful consideration of patient and disease factors. The key should be to achieve combination chemotherapy/surgical treatment, regardless of in which order, with least volume of residual disease remaining following surgical treatment. (Grade A)

Neoadjuvant chemotherapy (NACT) with interval CRS (ICRS) after three cycles of platinum-based chemotherapy is non-inferior to primary CRS (PCRS) and adjuvant platinum-based chemotherapy in terms of OS and should be considered for those in whom PCRS is unlikely to achieve NMRD or who are not suitable for the extent of surgery required to achieve this. (Grade A)

NACT reduces operative morbidity, lower rates of stoma formation, and reduced 30- and 90-day post-operative mortality and may be the preferred option for patients unfit for PCRS or in whom PCRS is unlikely to achieve NMRD. (Grade A)

All patients receiving neoadjuvant chemotherapy (NACT) should have joint surgical gynaecological oncologist and oncologist review in an MDT meeting after 3–4 cycles of chemotherapy, prior to decision-making for their further therapeutic steps, i.e., continuing with chemotherapy or proceeding to interval cytoreductive surgery. (Grade D)

Non-standard surgery

A second attempt at CRS during first-line treatment, after PCRS by a gynaecological oncologist, does not improve PFS or OS. However, ICRS after diagnostic-only, or surgery without cytoreductive intent by a non-gynaecological oncologist, lengthens PFS and OS in patients with advanced disease. (Grade A)

Documentation and governance

Cancer centres performing CRS should have the infrastructure to support this with appropriate governance and audit of the service provision. (Grade C)

Cytoreductive surgery should be undertaken with an appropriately trained sub-specialty gynaecological oncologist as the lead surgeon. (Grade B)

Collaboration between surgeons of appropriate expertise, such as colorectal, upper gastro-intestinal and hepato-pancreato-biliary should ideally be planned in advance and the specific surgeon responsible for each element of a resection should be discussed and agreed in advance within the team. (Grade D)

Patients with ovarian cancer undergoing cytoreductive surgery (CRS) should have the degree of residual disease recorded. (Grade D)

There should be an appropriate governance structure to manage post-operative complications and morbidity related to the procedure. (Grade D)

Any patient who is returned to theatre should be managed in line with the National Emergency Laparotomy Audit. (Grade D)

Rationale for cytoreductive surgery. The aim of surgery in advanced EOC is the removal of all visible disease to leave no macroscopic residual disease (NMRD). Several studies have demonstrated an inverse correlation between the amount of residual disease and survival [328–332]. A recent Cochrane prognostic review found 46 retrospective studies that met their inclusion criteria and examined results separated by timing of surgery (PCRS and ICRS) [329]. In PCRS, women with visible deposits < 1 cm (small volume residual disease (SVRD)) had more than twice the risk of death compared to women with NMRD (HR 2.03, 95 % CI 1.80 to 2.29; moderate-certainty evidence) [329]. This was similar to the ICRS-setting. Women who had any amount of visible RD after ICRS (SVRD and large volume RD (LVRD; >1 cm) had more than twice the risk of death compared to women with NMRD (HR 2.19, 95 % CI 1.06 to 4.52: very low-certainty evidence). However, these results are from retrospective analyses and the achievement of NMRD is dependent upon a range of patient, tumour and surgical factors and are not able to tell us whether there is no value in attempting surgical debulking, if NMRD or near-optimal debulking is not likely to be achieved. Results of other studies suggest there is value to surgical intervention even in these circumstances, as discussed below.

CRS for EOC includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy ± removal of bulky lymph nodes ± localised colonic resection ± diaphragmatic peritoneal stripping ± diaphragmatic resection ± extensive peritonectomies ± multiple bowel resections ± liver resection ± partial gastrectomy ± cholecystectomy ± splenectomy ± excision of porta hepatis and coeliac lymph nodes ± resection of tail of pancreas ± removal of extra-abdominal disease, such as paracardiac or inguinal lymph nodes, partial pleura resection [333,334].

Variations in surgery for advanced EOC therefore include degree of radicality employed to achieve NMRD, timing of surgery (PCRS versus ICRS after NACT), and patient eligibility for surgical effort. The OCAFP found that only half (51 %) of women with Stage II-IV and unstaged ovarian cancer received surgery and in four out of the 19 Cancer Alliances the rates were more than two standard deviations (SD) below average [6].

In a retrospective cohort study of 249 women treated in two neighbouring cancer centres in London, after a mean follow up period of 24 months, OS was 37 months (95 % CI 33.17 to 40.8 months) at centre A compared to 36.5 months at centre B (95 % CI 31.8 to 41.1 months; P = 0.517) [335]. Any attempt at CRS (whether PCRS or ICRS) was associated with improved OS compared with chemotherapy alone (HR 0.31 (95 % CI 0.19 to 0.52) for ICRS and HR 0.39 (95 % CI 0.22 to 0.67) for PCRS), even after adjustment for other prognostic factors. However, these are non-randomised data, so represent association, not causation, and it is unclear to what extent patient selection may have in this effect.

A cohort study from Sweden found that altering the surgical paradigm to maximal cytoreductive surgery, with supra-centralisation, did not confer an overall survival benefit to the population presenting with advanced ovarian cancer in their region (HR 1.03, 95 % CI 0.87 to 1.22; P = 0.75) [336]. This was despite an increase in achieving NMRD (37 % versus 67 %; P < 0.001), and an increase in the rate of PCRS with the systematic switch to maximal effort surgery (41 versus 62 %; P ≤ 0.001).

However, their surgical paradigm included a preference for PCRS and a significant reduction in rates of neoadjuvant chemotherapy (NACT) before interval CRS (ICRS) from 34 % to 4 % (P < 0.001). Interestingly, the switch to a primary maximal cytoreductive surgical approach was also associated with an 11 % decrease in surgically-treated patients (75 % versus 66 %; P ≤ 0.001), and consequently an increase in non-surgically treated patients (24 % versus 33 %; P ≤ 0.001). They concluded that an all or nothing approach to residual tumour is not valid and patient selection for those who might benefit from maximal cytoreductive surgery must be individualised beyond stage and performance status. These findings align with the Hall et al. study [335].

Aletti et al [337,338] in retrospective cohort studies combining data from "aggressive" cancer centres in the US argue that two factors, age and co-morbidities, as measured by either performance status or ASA grade, are associated with adverse outcomes the more complex the surgery being undertaken, as measured by Surgical Complexity Score (SCS) [337,338]. This system assigns points to individual procedures to determine an overall degree of surgical extent (see Table 7 and Table 8 for details). An overall SCS of ≤ 3, ≥4-7 or 8 aligns with low, intermediate and high complexity surgery, respectively. Pre-op albumin levels less than 35 g/L, ASA grade 3/4 and surgical complexity were all positively correlated with 30-day post-operative mortality. Three-month post-operative mortality was positively correlated with age and ASA status [337,338].

SOCQER2 was a prospective, multi-national observational study, which reported quality of life scores for 247 women with stage III or IV ovarian cancer undergoing surgery defined as of low, intermediate or high complexity, as measured according to the SCS classification [334,337,338]. There were no clinically or statistically meaningful differences in quality-of-life (QoL) score at 6 week, 6 months and 12 months regardless of the three grades of surgical complexity. There were small statistically significant improvements in QoL over time in all patients, regardless of SCS. Physical and emotional function were lower in the group of women with high SCS at 6 weeks post-surgery, but by 12 months there were no differences between each of the three groups. Further population-level data from centres involved in the SOCQER2 study, including all those with Stage III-IV or and unstaged disease, demonstrated a difference in overall survival between those centres that had low SCS, versus those with high SCS (median OS low SCS = 17.9 months (95 % CI 15.7 to 20.1) versus high SCS = 23.1 months (95 % CI 19.0 to 27.2); P = 0.043) [339]. Median OS in intermediate SCS (Int SCS) was 22.0 months (95 % CI 17.6 to 26.3) and did not differ significantly from high SCS centres. Treatment in a low SCS centre was associated with a higher risk of death than a high SCS (HR of 1.21 (95 % CI 1.03 to 1.40)) when adjusted for age and deprivation. Interestingly, combined surgery and chemotherapy rates were 39.2 % versus 51.8 % versus 38.3 % in low SCS, Int SCS and high SCS centres, respectively (P < 0.0001). This difference in treatment was attributed to differences in rates of surgical treatment (surgery rates 43.2 % versus 58.4 % versus 60.9 % in low SCS, Int SCS and high SCS centres, respectively (P < 0.001). It is therefore difficult to determine whether the degree of radicality or rate of surgery is the most important, or whether low SCS is a marker of lower overall quality of care and willingness to offer surgical treatment; data from the OCAFP suggest that rates of surgical treatment are associated with survival outcomes [6]. NICE guidance on high complexity CRS now considers maximal cytoreductive surgery as safe in standard care in the UK [340].

Lymphadenectomy in advanced EOC. The LION study randomised 647 women with stage IIb-IV EOC intra-operatively to either systematic lymphadenectomy or no lymphadenectomy after all other visible disease had been removed and lymph nodes were found to be not clinically enlarged [301]. There was no survival benefit conferred (PFS or OS) to women who underwent systematic lymphadenectomy, despite microscopic lymph node metastases being present in 55.7 % of the patients in the lymphadenectomy group. Women in the lymphadenectomy group had more repeat laparotomies for complications (12.4 % versus 6.5 %; P = 0.01) and an increase in 60-day mortality (3.1 % versus 0.9 %; P = 0.049). Addition of systematic lymphadenectomy increased *peri*-operative complications (duration of surgery (340 mins versus 280 mins; P < 0.001), median blood loss (650 ml versus 500 ml; P < 0.001), and requirement for blood transfusion (63.7 % versus 56 %; P = 0.005); increased admission rates to an intermediate or intensive care unit (77.6 % versus 69 %; P = 0.01)). An observational study of 381 patients found no benefit to systemic lymphaedenctomy in patients with rarer epithelial histological subtypes (OS, HR 0.96, 95 % CI 0.69 to 1.35) [341].

In a systematic review, 82 % of enlarged cardiophrenic nodes were involved with metastatic disease, and are associated with poorer survival outcomes (PFS, HR 2.14, 95 % CI 1.82 to 2.52) [342]. However, non-randomised evidence is inconclusive and does not demonstrate any significant impact on survival in those who have cardiophrenic lymph node resection [342–345].

Timing of primary cytoreductive surgery. The aim for primary treatment of EOC should be combination treatment with surgery and chemotherapy to achieve NMRD, some patients may do better with surgery first then chemotherapy and others with chemotherapy first, to shrink disease and make them better able to tolerate surgery. Careful patient selection is the key to optimise outcomes, although we do not yet have robust tools to accurately select patients for PCRS or to support patients to make informed choices.

An updated Cochrane systematic *meta*-analysis of four RCTs [268,346–349], comparing PCRS (also referred to as upfront debulking or primary debulking surgery) followed by adjuvant chemotherapy with NACT before ICRS in advanced EOC (Stage III-IV), found little to no difference in terms of OS (HR 0.96, 95 % CI 0.86 to 1.08; high-certainty evidence) or PFS (HR 0.98, 95 % CI 0.88 to 1.08; moderate-certainty evidence) [350]. In addition, NACT likely decreased *peri*-operative mortality (0.6 % in NACT group, versus 3.6 % in PCRS group (risk ratio (RR) 0.16, 95 % CI 0.06 to 0.46; high-certainty evidence), and the risk of grade ≥ 3 serious adverse events (RR 0.22, 95 % CI 0.13 to 0.38; moderate-certainty evidence). NACT probably had a large reduction in the need for a stoma (5.9 % versus 20.4; RR 0.29, 95 % CI 0.12 to 0.74; moderate-certainty evidence), and probably reduced the risk of bowel resection at the time of CRS (13.0 % versus 26.6 %; RR 0.49, 95 % CI 0.30 to 0.79; moderate-certainty evidence) [350].

A recent retrospective North American cohort study, of over 39,000 women, compared those treated in centres with either low (22.5 % of patients) or high use of NACT (42.2 %) after the results of the first RCT demonstrating non-inferiority of NACT in 2010 [349,351]. High NACT-use centres, compared to those that did not change practice from routinely offering PCRS, had greater improvements in OS (6.3-month improvement, 95 % CI 4.2 to 8.3 months), as well as 6-month (−2.3 %, 95 % CI −3.2 to −1.3 %) and 12-month mortality (−2.1 %, 95 % CI −3.7 % to −0.5 %). The Falconer study results also suggest that reducing NACT/ICRS rates too far, may be detrimental [336].

This remains a highly contentious area, and the applicability of the previous RCTs, to more modern surgical approaches, is contested [352]. While it is evident that patients with extensive and inoperable disease patterns, those with high frailty/ poor performance status or significant comorbidities will benefit from NACT; the question regarding the oncologic non-inferiority of NAC in fit and otherwise healthy patients with operable disease is the subject of currently ongoing clinical trials [353,354]. The new ESGO-ESMO consensus statement recommend PCRS as the preferred option, if NMRD after surgery seems achievable in suitably fit patients [355]. Patients with seemingly operable disease should be offered the risks and benefits of both approaches, so that they can make an informed decision about their treatment pathways. Decision aids, based on predictive factors, may help with shared decision-making [356].

Delayed primary surgery/timing of ICRS. As per the National Comprehensive Cancer Network guidelines, ICRS after three to four cycles is preferred [153]. However, if patients aren't fit enough to consider surgery at three cycles, and delay may be in the patient's best interest (e.g., acute venous thrombolic event), surgery may be reconsidered after four to six cycles. Studies comparing different timings of ICRS are ongoing [357].

Second-attempt at cytoreductive surgery in first-line treatment. The 1995 EORTC trial, by van der Burg et al. randomised 319 patients to further surgery versus no further surgery after three cycles of platinum-based chemotherapy after initial surgery by a non-gynaecological oncologist or diagnostic surgery only [358,359]. A Cochrane review, which included this and two other RCTs, found that repeat CRS in first-line treatment lengthened PFS and OS only in those who had not had maximal surgical effort at initial surgery by a subspecialist gynaecological oncologist; the risk of death was reduced by one third in this subgroup (HR = 0.68, 95 % CI 0.53 to 0.87) [360]. However, those who had had LVRD following initial CRS, despite maximal surgical effort, did not benefit from a repeat cytoreductive surgical procedure in the first-line treatment setting.

Governance. When maximal cytoreductive surgery is undertaken it should only be undertaken in centres with a regular practice of this type of surgery with appropriate governance, and audit of the service provision should take place [361]. Two models of delivery of maximum cytoreduction surgery exist with one model where the gynaecological oncologists perform all maximum cytoreduction surgery procedures and the other whether the gynaecological oncologist delivers this as the leader of a multi-surgeon team; both models are safe [362,363]. As per the joint statement of The Association of Coloproctology of Great Britain and Ireland (ACPGBI), Association of Surgeons of Great Britain and Ireland (ASGBI), Association of Upper Gastrointestinal Surgery of Great Britain and Ireland (AUGIS) and BGCS, collaboration between surgeons of appropriate expertise, such as colorectal, upper gastrointestinal (GI) and hepato-pancreato-biliary (HPB), should be formally recognised in job plans, and attendance of other specialities should ideally be planned in advance [364]. This joint statement recommends that the specific surgeon responsible for each element of a resection should be agreed in advance within the local team and that there should be an appropriate governance structure around the team to manage post-operative complications and morbidity related to the procedure. If a woman is returned to theatre her case should be managed in line with the National Emergency Laparotomy Audit (www.nela.org.uk). Morbidity and mortality meetings should involve the whole team, and, in sub-specialist training centres, the sub-speciality gynaecological oncology trainee should have at least one colorectal surgeon formally involved in their colorectal training.

The role of minimal access surgery for CRS is yet to be established. Non-randomised data, from carefully selected patients undergoing ICRS after NACT, with pelvic masses < 8 cm, suggest this may have a role, but more robust evidence is required and should not be considered standard care until evaluated in RCTs [365].

First-line treatment – systemic therapy

First-Line chemotherapy – early-stage disease

Recommendations

Adjuvant platinum-based chemotherapy should be considered and offered in all cases of early-stage ovarian cancer (stage I – IIB) except for completely staged patients with low grade FIGO IA/IB cancer; FIGO IA grade 1 and 2 endometrioid or expansile (or grade 1 and 2) mucinous cancer. (Grade A)

The benefit of adjuvant chemotherapy is less certain but can be considered as an option in patients with clear cell (stage IA and IB), Grade 1 and 2 endometrioid (stage IB/C); low-grade serous stage IB/C; expansile (Grade 1 and 2) mucinous stage IC; infiltrative mucinous stage IA. (Grade C)

For patients with early-stage disease who require adjuvant chemotherapy, either carboplatin alone 6 cycles (Grade A) or carboplatin/paclitaxel (Grade B) can be considered.

There is a lack of evidence supporting the value of targeted therapies, such as bevacizumab and PARP inhibitors, in early-stage ovarian cancer treatment and these treatments should not be offered outside clinical trials. (Grade D)

Adjuvant platinum-based chemotherapy has been shown to significantly prolong overall survival (OS) and progression free survival (PFS) in women with early-stage epithelial ovarian cancer (EOC) in two randomised, prospective trials, the ACTION and ICON1 trials. These trials included early-stage patients with grade 2/3 stage IA/B and all stage IC/IIA. The primary analysis of ICON1, with a median follow-up of four-years, demonstrated a significant improvement in both relapse-free survival (RFS) (HR 0.65, 95 % CI 0.46 to 0.91, P = 0.01) and OS (HR 0.66, 95 % CI 0.45 to 0.97; P = 0.03) in favour of adjuvant chemotherapy with six cycles of single agent carboplatin (AUC 5/6) [366]. Similar findings were reported in the ACTION trial in which the majority of patients received platinum-based combination chemotherapy [367]. Recent ESGO guidelines recommend six cycles of carboplatin-paclitaxel chemotherapy, or carboplatin alone, for those with stage I-IIB HGSC and high-grade epithelial cancer [292].

A Cochrane *meta*-analysis of five large prospective clinical trials concluded that chemotherapy is more beneficial than observation in patients with early stage ovarian cancer [368]. Patients who received platinum-based adjuvant chemotherapy had a better OS (HR 0.71, 95 % CI 0.53 to 0.93] and PFS (HR 0.67, 95 % CI 0.53 to 0.84) than patients who did not receive adjuvant treatment. However, approximately two thirds of the cases were sub-optimally staged and 30 % of women with presumed stage I disease may have had undetected stage III disease, and it may be that chemotherapy compensated for a lack of complete surgical staging. A Cochrane analysis of 10-year data from ACTION and ICON1 suggested that the difference between optimally and sub-optimally staged subgroups, in terms of deaths from ovarian cancer, was not significant (Test for subgroup differences: Chi^2 test = 2.75, df = 1, P = 0.10). Benefit for chemotherapy, even in optimally staged patients, could not be excluded. Adjuvant chemotherapy should therefore be discussed with all patients with high-risk, early-stage ovarian cancer [298].

Histological subtype may determine benefit from adjuvant chemotherapy. The response rate to chemotherapy in patients with non-serous epithelial ovarian carcinoma, including clear cell and mucinous tumours, is poor and the effectiveness of adjuvant chemotherapy in early-stage disease in these groups may be less than high-grade serous cancers. In grade 1 and 2 endometroid carcinoma a large SEER series did not show a benefit from adjuvant therapy [369]; a retrospective clear cell cancer series in an Asian population did not show a benefit for chemotherapy in early-stage disease (stage IA to IC1) [370]; and in expansile or grade I infiltrative mucinous cancer adjuvant chemotherapy could be avoided due to their excellent outcomes from surgery alone [371].

Patients with early-stage disease requiring chemotherapy, can be considered for either platinum alone or combination therapy with carboplatin and paclitaxel [372]. The standard recommendation is for 6 cycles of platinum-based chemotherapy. Shorter regimens of three cycles of carboplatin and paclitaxel chemotherapy may be appropriate for non-serous subtypes only based on a GOG trial that compared 3 versus 6 cycles of chemotherapy [373]. However, for patients with early-stage high grade serous ovarian cancer the recommendation is for 6 cycles of doublet chemotherapy [374].

First-Line chemotherapy – advanced stage (III and IV) disease

Recommendations

A combination of cytoreductive surgery and platinum-based

chemotherapy and consideration of maintenance therapy is recommended for all patients with stage III and IV EOC following first-line treatment. (Grade A)

Weekly paclitaxel 60–70 mg/m^2 and carboplatin AUC 2 could be considered in frailer patients unable to tolerate three-weekly treatment. (Grade B)

Inpatient chemotherapy in unwell, treatment-naïve, previously fit patients should be considered, even if it requires short-term parenteral nutrition. This may be time-critical and should be delivered as soon as possible, in those suitable for active treatment. (Grade D)

Bevacizumab (7.5 mg/kg for 12 months or 15 mg/kg every 3 weeks for 15 months) in addition to carboplatin and paclitaxel can be considered in patients with advanced (stage III + macroscopic disease or stage IV) ovarian cancer. (Grade A)

If bevacizumab is given in a NACT setting, it should be omitted for the cycles before and after surgery to reduce the risk of fistula formation. (Grade D)

Suitability for PARP inhibitors maintenance treatment following a response to first-line chemotherapy should be considered in patients with stage III–IV ovarian cancer. (Grade A)

PARP inhibitor (olaparib) maintenance therapy in combination with bevacizumab (15 mg/ kg) should be considered for patients with HR deficient and BRCA mutant stage III and IV high grade ovarian cancer. (Grade A)

The standard chemotherapy option is for six cycles of carboplatin AUC 5–6 and paclitaxel 175 mg/m^2 intravenously (i.v.) every 3 weeks [375]. Treatments in excess of six cycles or including additional agents have not been shown to improve outcomes [376]. For those patients who are intolerant of, develop allergies or significant side effects such as neuropathy, paclitaxel can be replaced by docetaxel [377] or pegylated liposomal doxorubicin (PLD) [378].

Dose dense chemotherapy protocols (weekly rather than three-weekly schedules) have been shown to improve PFS and OS in JGOG3016, a Japanese study [379,380], but are generally not recommended as the GOG-262 [381], ICON 8 [382] and MITO-7 [383] trials (predominantly Caucasian populations) did not confirm a benefit. The MITO 7 trial did demonstrate activity and improved tolerability of the regimen of weekly paclitaxel 60 mg/m^2 and carboplatin AUC 2, and therefore this schedule could be considered in frailer patients [383]. A recent study, ICON 8B [384], showed an improvement in PFS in favour of a weekly dose-dense chemotherapy (paclitaxel 80 mg/m^2 and carboplatin three-weekly AUC 5/6) in combination with bevacizumab 7.5 mg/kg (HR 0.75, 95 %CI 0.62 to 0.90, P = 0.002) and improvement in OS (HR = 0.77, 95 % CI 0.62 to 0.96, P = 0.02) for women in high risk of relapse with stage III (residual disease > 1 cm diameter after primary surgery or requirement for primary chemotherapy) and stage IV EOC.

Maintenance systemic treatment after first-line chemotherapy

Maintenance anti-angiogenic therapy after first-line chemotherapy. The monoclonal antibody targeting vascular endothelial growth factor (VEGF), bevacizumab in combination with chemotherapy and as single agent maintenance for up to 12 months (ICON 7) [385] or for 15 months (GOG 218) [386] prolonged PFS in patients with advanced disease HR 0.81, CI 95 % 0.70 to 0.94) and [HR 0.71, CI 95 % 0.62 to 0.82) respectively, although there was no benefit in OS. However, ICON7 retrospective *post hoc* analysis suggested a four-month benefit in OS in the high-risk subgroup (stage III patients with LVRD or stage IV patients) [387]. Currently there is no evidence that a longer bevacizumab schedule (30 rather than 15 months) improves PFS [388]. A recent Cochrane review demonstrated likely little to no difference in OS for bevacizumab maintenance treatment with and following first-line treatment compared to chemotherapy alone (HR 0.97, 95 % CI 0.88 to 1.07; moderate-certainty evidence) [389]. The evidence for PFS was very uncertain (HR 0.82, 95 % CI 0.64 to 1.05; very low-certainty evidence), although bevacizumab resulted in a slight reduction in global quality-of-life (QoL) (mean difference (MD) −6.4, 95 % CI −8.86 to −3.94; high-certainty evidence). Bevacizumab likely increased grade ≥ 3 adverse events (RR 1.16, 95 % CI 1.07 to 1.26; moderate-certainty evidence) and may result in a large increase in grade ≥ 2 hypertension (RR 4.27, 95 % CI 3.25 to 5.60; low-certainty evidence).

Other anti-angiogenic agents, including the oral tyrosine kinase inhibitors (TKIs) pazopanib and nintedanib, have also been shown to increase PFS, but not OS [390,391]. There are currently no licensed oral anti-angiogenic agents for use as maintenance therapy in ovarian cancer. The recent Cochrane review of anti-angiogenesis treatment found that TKIs given with first-line chemotherapy and continued as maintenance, likely resulted in little to no difference in OS (HR 0.99, 95 % CI 0.84 to 1.17; moderate-certainty evidence) and likely increased PFS slightly (HR 0.88, 95 % CI 0.77 to 1.00; moderate-certainty evidence) [389]. TKIs likely reduced QoL slightly (MD −1.86, 95 % CI −3.46 to −0.26; moderate-certainty evidence), increased grade ≥ 3 adverse events slightly (RR 1.31, 95 % CI 1.11 to 1.55; moderate-certainty evidence) and may cause a large increase in hypertension (grade ≥ 3) (RR 6.49, 95 % CI 2.02 to 20.87; low-certainty evidence).

PARP inhibitor maintenance therapy after first-line chemotherapy. Poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi) exploit the DNA repair vulnerabilities of ovarian cancer cells due to deficient homologous recombination repair (HRR) pathways. Hereditary mutations in *BRCA* 1/2 genes (*BRCA*mut) are present in approximately 20 % of patients. In addition tissue *BRCA*mut, mutations in genes such as *RAD51C, RAD51D*, and *PALB2*, epigenetic silencing via hypermethylation of *BRCA1* promoter and deficiency in other proteins and HR pathways lead to deficient HRR in up to 50 % of high grade serous ovarian cancers [32]. In patients with stage III–IV high-grade ovarian cancer, PARPi are routinely considered as maintenance treatment following chemotherapy. The studies have demonstrated a spectrum of benefit based on the *BRCA*mut and homologous recombination deficiency (HRD) status of patients. PARPi currently licensed in the UK include: olaparib in women with *BRCA*mut cancer; and niraparib in women regardless of their *BRCA*mut/HRD status. In addition, rucaparib was granted a first-line maintenance licence by the UK's Medicines and Healthcare products Regulatory Agency (MHRA) on 15 January 2024.

The SOLO1 trial [392] evaluated the role of 2 years of maintenance olaparib therapy following a response to platinum-based chemotherapy in patients with *BRCA*mut advanced EOC. Initial results demonstrated a benefit in the risk of relapse or death (HR 0.3, CI 95 % 0.23 to 0.41) in the women treated with olaparib compared to placebo. Mature results after a longer follow-up have confirmed a sustained benefit with 48 % of patients on Olaparib and 21 % on placebo progression-free at five years [393].

The PRIMA/ENGOT-OV26/GOG-3012 trial [394] evaluated the role of three years of another PARPi, niraparib, versus placebo in women with higher-risk high grade EOC regardless of their *BRCA*mut status. There was an improvement in PFS in the overall patient population receiving niraparib following a response to platinum-based chemotherapy (HR 0.62, 95 % CI 0.50 to 0.76), with the greatest benefit in those with HRD disease (HR 0.43, 95 % CI 0.31 to 0.59). Pre-planned molecular analysis demonstrated that patients with *BRCA*mut (HR 0.40, 95 % CI 0.27 to 0.62) and *BRCA*wt/HR-deficient tumours (HR 0.50, 95 % CI 0.31 to 0.83) benefitted the most, but even patients who had negative HRD tests had a 32 % improvement in PFS compared to the placebo group (HR 0.68, 95 % CI 0.49 to 0.94).

The randomised phase III trial, PAOLA1 [395] compared two years of maintenance olaparib and bevacizumab (15 mg/kg) versus placebo/bevacizumab treatment in stage III and IV high-grade EOC following a response to first line platinum-based chemotherapy. The trial demonstrated a benefit in PFS in the overall population (HR 0.59; 95 % CI 0.49

to 0.72). Pre-planned HR analysis by the Myriad My Choice assay demonstrated a clear benefit in PFS only in the group who had HR deficient tumours (HR 0.33, 95 % CI 0.25 to 0.45) compared to the HR negative/unknown group (HR 0.92). The combination of olaparib and bevacizumab (15 mg/kg) is now licensed for maintenance therapy only in women with HR deficient disease.

A recent Cochrane review included 15 studies of PARPi in EOC (6109 participants); four (3070 participants) with newly-diagnosed, advanced EOC and 11 (3039 participants) with recurrent EOC [396]. Most participants had BRCA mutations, either in their tumour (s*BRCA*mut) and/or germline (g*BRCA*mut), or tumour HRD. Two studies compared PARPi maintenance with placebo after first-line chemotherapy in EOC. The data demonstrated that PARPi may increase PFS (HR 0.42, 95 % CI 0.19 to 0.92; low-certainty evidence), but there may be an increase in the risk of experiencing any grade ≥ 3 adverse events (PARPi (54 %) versus placebo (19 %)(RR 2.87, 95 % CI 1.65 to 4.99; very low-certainty evidence. There is probably a slight reduction in QoL with PARPi, although this may not be clinically significant (MD −3.00, 95 %CI −4.48 to −1.52; moderate-certainty evidence). The Cochrane review found that PARPi probably resulted in little to no difference in OS (two studies, 1124 participants; HR 0.81, 95 %CI 0.59 to 1.13; moderate-certainty evidence) (alive at 12 months 68 % with PARPi versus 62 % for placebo). More mature OS data for olaparib have become available since the Cochrane review was published, demonstrating improved OS in the PARPi arm (HR 0.55, 95 % CI 0.40 to 0.76; P = 0.0004) [397], although these data did not meet the prespecified criteria for significance. There is a concern that PARPi may increase the risk of secondary cancers, especially myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML) from observational studies [398]. The longer term SOLO1 data (7-year follow-up) found four (1.5 %) cases of MDS/AML in the olaparib group and one (0.8 %) in the placebo group. New primary cancers were reported in 14 (5.4 %) participants in the olaparib arm versus and eight (6.2 %) in the placebo arm [397]. However, relatively small single RCTs are unlikely to be the best trial design to determine relatively rare harms. A *meta*-analysis of RCTs of PARPi for a variety of cancers found 18 placebo-controlled RCTs (n = 7307 patients) with adverse event data [398]. Their *meta*-analysis concluded that PARP inhibitors significantly increased the risk of MDS/AML compared with placebo treatment (OR 2.63, 95 % CI 1.13–6.14; P = 0.026). Potential adverse events and potential for negative effects on QoL therefore should be discussed with and balanced against benefits on OS and PFS.

Intra-peritoneal chemotherapy and hyperthermic intraperitoneal perioperative chemotherapy (HIPEC)

Recomendations

Intraperitoneal (i.p.) chemotherapy is not a standard first-line therapy option. (Grade B)

Hyperthermic intraperitoneal chemotherapy (HIPEC) could be considered at the time of interval cytoreduction for patients with newly diagnosed ovarian cancer, as per NICE interventional procedure guidance. However, it should only be undertaken in highly specialised centres by clinicians with specialist expertise and specific training in cytoreduction surgery and HIPEC. Special arrangements for clinical governance should in place and NICE recommends further research in the form of randomised controlled trials. (Grade B)

Direct administration of chemotherapy within the peritoneal cavity results in a significant increase in tumour exposure to high concentrations of cytotoxic drugs compared to the i.v. route (to a relatively shallow depth of tumour nodule penetration), while reducing systemic side-effects [399–401]. Several randomised trials found that the use of intraperitoneal (i.p.) cisplatin following primary cytoreductive surgery for advanced ovarian cancer was associated with longer OS [402–404]. A *meta*-analysis of the data from randomised trials found that use of i.p. chemotherapy improved PFS (HR 0.78, 95 % CI 0.70 to 0.86) and OS (HR 0.81, 95 % CI 0.72 to 0.90) compared with i.v. chemotherapy [405] and another *meta*-analysis of five RCTs showed OS and PFS benefit in patients with NMRD/SVRD after surgery [406].

However, a subsequent RCT (GOG252) comparing dose-dense weekly paclitaxel and carboplatin with two i.p. regimens, where all three arms received bevacizumab, showed no difference in PFS or OS between i.v. and i.p. chemotherapy [407,408]. Patients receiving i.p. chemotherapy are more likely to experience morbidity from infections, catheter-related pain and gastrointestinal toxicity [405]. Intraperitoneal (i.p) administration of chemotherapy is therefore not currently recommended outside of clinical trials due to the negative results of the GOG252 [407].

Hyperthermic i.p. chemotherapy (HIPEC) involves administration of a single treatment of heated chemotherapy at the time of completion of cytoreductive surgery. HIPEC has been evaluated in the first-line setting in the phase III OVHIPEC trial that evaluated the role of HIPEC (cisplatin 100 mg/m^2) after surgery for patients with stage III ovarian cancer who in whom cytoreduction to less than 10 mm residual disease following three cycles of NACT was thought feasible [409]. Patients undergoing surgery plus HIPEC had improvements in PFS (HR 0.66, 95 % CI 0.50 to 0.87; P = 0.003; 14.2 months versus 10.7 months, respectively) and OS (HR 0.67, 95 % CI 0.48 to 0.94; P = 0.02; 45.7 months versus 33.9 months, respectively) compared to those who had surgery only. There was no difference between the two groups in the percentage of patients experiencing grade ≥ 3 adverse events, although median length of surgery was significantly increased (surgery alone = 192 min (interquartile range (IQR), 153 to 251 min); surgery + HIPEC = 338 min (IQR 299 to 426 min). In a second RCT, women with stage III and IV ovarian cancer who had at most SVRD after PCRS or ICRS, were assigned to receive either HIPEC with cisplatin at a dose of 75 mg/m^2 or no intervention (control group) [410]. There was no difference in median PFS (19.8 months versus 18.8 months, respectively) and OS (69.5 months versus 61.3 months, respectively) between women receiving HIPEC and the control group. In the subgroup of women that underwent ICRS, administration of HIPEC was associated with an improvement in PFS (17.4 months versus 15.4 months, respectively) and OS (61.8 months versus 48.2 months, respectively) compared to the control group.

HIPEC is not currently regarded as a standard first-line therapy option at the time of PCRS and the results of ongoing trials are awaited [292,411]. NICE guidelines support controlled use of HIPEC at ICRS, recognising the “frequent and serious but well-recognised complications” and “vidence on its efficacy is limited in quality”. They recommend HIPEC “should only be used with special arrangements for clinical governance, consent, and audit or research” [412]. Further recommendations are that it should be limited to “highly specialised centres by clinicians with specialist expertise and specific training in [CRS] and [HIPEC]”. National Comprehensive Cancer Network guidelines from the USA state that “HIPEC with cisplatin (100 mg/m^2) can be considered” at ICRS for those with stage III disease [153]. The joint European Society of Gynaecological Oncology (EGGO), European Society for Medical Oncology (ESMO) and European Society of Pathology consensus guidelines were unable to come to a consensus on the use of HIPEC during ICRS [355].

The value of HIPEC in relapsed ovarian cancer has been assessed in an RCT and HIPEC with carboplatin was well tolerated, but did not improve survival [413]. This study does not support the use of HIPEC with carboplatin during secondary cytoreductive surgery for platinum-sensitive recurrent ovarian cancer and for that reason HIPEC is not part of the international treatment guidelines for relapsed disease [292].

Recurrent EOC

Secondary cytoreductive surgery (SCRS) for recurrent EOC

Recommendations

Secondary cytoreductive surgery (SCRS) may be considered for selected patients who have relapsed at an interval longer than 6 months from their first-line platinum-based treatment (with NMRD

after first-line CRS) and have no or little ascites at relapse. Patients should be fit enough for surgery and have fully resectable disease, since survival improvement is confined to those with NMRD following surgery. (Grade C)

Patients should be aware that the disease is incurable at relapse, even if NMRD is achieved at surgery, and that they will need systemic postoperative treatment. (Grade A)

The role of surgery at relapse has long been under debate. Retrospective data demonstrated that achieving NMRD at SCRS was associated with improved OS and PFS [414,415]. However, it was unclear whether this was correlation or causation and whether this was due to NMRD being associated with favourable tumour biology. A *meta*-analysis [416] of 36 studies from 80, largely retrospective and single-arm, included studies demonstrated that surgery was correlated with improvement in OS in participants with platinum-sensitive relapse. Heterogeneity between the studies was high, reflecting the differing designs and patients included in the studies.

However, three prospective RCTs (GOG 213 [417], SOC-1 [418], and DESKTOP III [419]) assessed the value of SCRS, comparing chemotherapy alone versus surgery and chemotherapy. These studies enrolled highly selected patients, with varying criteria, so the results are not applicable to all those with relapsed disease [420]. The development of valid tools and algorithms to accurately predict operability is essential to avoid unnecessary morbidity and mortality. The European/British DESKTOP III trial based selected participants based on the AGO-score, based on: performance status; residual disease at primary surgery; and presence of ascites at relapse [421,422]. The SOC-1 study used the i-model for participant selection, which combines FIGO stage, residual disease at primary debulking, length of platinum-free interval, ECOG performance status, CA125 level at recurrence, and presence of ascites [418,419]. GOG213 study did not have selection criteria for the identification of the ideal surgical candidates and selection was based each investigator believing that disease was operable [417], although the inclusion of patients with peritoneal carcinomatosis was discouraged. Only 5 % of the GOG213 patients had peritoneal carcinosis, a significantly lower number compared to the other two studies (~40 %) [417–419].

The GOG213 and the DESKTOP III study demonstrated opposing results. In DESKTOP III, the median OS was 53.7 months in the surgery/chemotherapy group and 46.0 months in the chemotherapy-only group (HR 0.75, 95 % CI 0.59 to 0.96; P = 0.02). Patients in whom NMRD was achieved after SCRS had a median OS of 61.9 months. Quality-of-life measures did not differ between the two groups [419].

In contrast, GOG213 did not demonstrate an improvement in OS (HR 1.29, 95 % CI 0.97 to 1.72; P = 0.08) with a median OS of 50.6 months (surgery/chemotherapy) and 64.7 months (chemotherapy only), respectively [417]. This was true even for the subgroup in whom NMRD was achieved. PFS was also not improved significantly (HR 0.82, 95 % CI, 0.66 to 1.01) with median PFS of 18.9 months (surgery/chemotherapy) and 16.2 months (chemotherapy only), respectively). Importantly, the rate of surgical morbidity was 9 %, and one of 240 (0.4 %) participants in the surgery arm died from postoperative complications. After a period of recovery from SCRS, there was no significant decrease in quality-of-life outcomes.

Mature OS data from the SOC-1 study are awaited [418], although interim OS data demonstrated median OS of 58·1 months (95 % CI not estimable) in the surgery arm and 53·9 months (95 % CI 42·2 to 65·5) in the no surgery arm (HR 0·82, 95 % CI 0·57 to 1·19) [418]. Nine of the 172 participants (5 %) had grade 3–4 surgical morbidity by 30 days post-surgery, with no deaths by 60 days post-surgery in either group. Eleven of 175 participants (6 %) in the no surgery arm had SCRS during second-line treatment, and 48 of 130 participants (37 %) who had disease progression had surgery at a subsequent recurrence.

A *meta*-analysis of patients in these studies found that secondary cytoreductive surgery, resulting in NMRD, prolongs OS in platinum-sensitive recurrent ovarian cancer with the median OS time increased by 9 % and 7 % when the NMRD and SVRD proportion increased by 10 %, respectively, after adjusting for other variables, although achievement of NMRD is post-treatment prognostic indicator [416]. The differences between the studies emphasise the need for robust selection algorithms and stratification criteria at relapse to identify those most likely to benefit from SCRS. Of note, PET CT was not routinely used to determine operability, relying on conventional imaging, such as CT or MRI [417].

The major challenge is how to incorporate surgical effort at relapse with all novel systemic approaches. Many studies that address the value of SCRS have been prior to the routine use of anti-angiogenic agents and PARP-inhibitors, although maintenance bevacizumab was given to 84 % of the participants in GOG213. In GOG213 those who received bevacizumab had similar survival in the surgery/no surgery groups, whereas those who had surgery and opted not to have bevacizumab had reduced OS compared to those receiving chemotherapy alone [417].

Tertiary CRS and palliative surgery at relapse

Recommendations

There is no prospective evidence of survival benefit from tertiary CRS. Retrospective evidence suggests that there might be survival benefit in highly selected patients in whom NMRD can be achieved at surgery. (Grade C)

Selection criteria from the secondary setting may be used to guide decision making to offer surgery in the tertiary setting. (Grade D)

Palliative surgery for bowel obstruction could be considered after failure of conservative treatment, but requires careful consideration of the overall prognosis, quality of life, previous treatments, future therapeutic options, performance status and co-morbidities. (Grade C)

Iatrogenic induced short bowel syndrome with the necessity of long life total parenteral nutrition should be avoided and plans for surgery should be agreed within a specialist MDT. (Grade C)

There are no prospective data to assess the value of tertiary CRS for the second or subsequent relapse of EOC. Numerous retrospective multicentre and monocentric analyses have shown that achievement of NMRD at surgery is a positive prognostic indicator for PFS and OS [423–429]. However, these data are retrospective, at critical risk of bias, based on post-surgical, post hoc subgroup analyses, and have no direct comparison to chemotherapy alone. The largest retrospective study for tertiary debulking evaluating 406 patients from multinational centres, demonstrated that even in the tertiary setting achievement of NMRD was associated with improved OS and PFS [430]. Presence of peritoneal carcinomatosis did not retain any prognostic significance after controlling for residual disease status, although it should be recognised that residual disease is an outcome of surgery and not a pre-surgical prognostic indicator. Postoperative systemic chemotherapy was associated with a significant improvement in OS, emphasizing the importance of combination modality treatment in the advanced setting. The challenge with all the above trials is that they are all retrospective and have no control arm of no surgery, involving all the inherited bias of such studies.

A follow up study of participants who were randomized to the chemotherapy-only arm of the DESKTOP III trial looked at outcomes of 32 of 171 participants who underwent cytoreductive surgery at a subsequent relapse [431]. NMRD was achieved in 19 participants (60 %); five had SVRD or LVRD and for eight patients, data were missing. Interestingly, only 16 (50 %) started chemotherapy within 90 days of surgery. Median OS was 54.0 months (95 %CI 39.8 to not estimable) and one- and two-year OS rates were 91 % (95 % CI 81 % to 100 %) and 84 % (95 % CI 72 % to 98 %), respectively. This suggesting that CRS in selected patients at third relapse can be considered in highly selected patients [431].

Patients with relapsed EOC frequently present with symptoms of acute or sub-acute bowel obstruction at relapse, often attributable to

diffuse peritoneal dissemination of recurrent tumour, rather than a single point of obstruction. The implementation of novel targeted therapies with anti-angiogenic potential may favour fistula formation, or intestinal perforation, and so recurrent EOC, with the potential to be complicated by such severe and acute events, constitutes a therapeutic dilemma [432]. A systematic review identified no RCTs comparing surgical and medical management, and evidence that showed a benefit to surgery over octreotide was of low quality [433]. In a retrospective study of 90 patients with bowel obstruction due to relapsed EOC, successful palliation (adequate oral intake at least 60 days postoperative) was achieved in two thirds, and absence of ascites was a predictor for successful palliation ($p = 0.049$) [434]. The median overall survival (OS) was 90.5 days (range, <1 day to 6 years). Neither elective versus emergency surgery, platinum-sensitivity nor achievement of optimal debulking (SVRD or NMRD) predicted OS or successful palliation from surgery ($p > 0.05$). Any perceived benefits should be carefully balanced against the risks for each individual patient and factors, such as co-morbidities, baseline quality of life, previous response to chemotherapy, length of treatment intervals, subsequent systemic options, and patient wishes, are likely to be crucial. The management of these cases should be led by specialist gynaecological multidisciplinary teams, including palliative care input at an early stage. If surgery is planned, intra-operative input from gynaecological oncologists is important, since they can evaluate the entire journey of the patient and how this impacts intraoperative decisions.

Endoscopic techniques, such as placement of intestinal stents and percutaneous endoscopic gastrostomy, may allow the palliation of gastrointestinal symptoms with reduced procedure-related morbidity in selected patients.

Surgical intervention should be restricted to cases where there is a distal mechanical bowel obstruction and where the formation of a proximal high output small bowel stoma is not likely to be necessary, as such high output stomas significantly reduce quality of life and require permanent total parenteral nutrition (TPN). Pre-operative imaging demonstrating the most proximal point of bowel obstruction should be used to identify patients with a level of obstruction at high risk of iatrogenic short bowel syndrome.

In cases where surgical intervention is not likely to relieve bowel obstruction, further chemotherapy, typically as an inpatient, can be considered if the patient has (partially) platinum sensitive disease. This can be supported with i.v. nutrition for three to six weeks, after which resolution of ongoing bowel obstruction is no longer likely. Management of patients with bowel obstruction should ideally happen within multidisciplinary teams with experience in managing such cases [435].

Systemic therapy for recurrence of EOC

Recommendations

In patients with longer treatment free intervals (TFI) (>6 months) or significant response to last platinum-based treatment, combination therapies with platinum re-challenge are recommended. (Grade A)

For patients who did not receive a PARPi in the first line setting and who have a subsequent response to platinum-based chemotherapy in the relapsed setting, PARPi maintenance should be considered. (Grade A)

In patients with short treatment-free intervals (<6 months), single agent chemotherapy is equally effective and less toxic than combination chemotherapy. The addition of bevacizumab to chemotherapy improves outcomes, but is not universally funded in the UK. (Grade A)

A number of factors inform the choice of chemotherapy for relapsed EOC, including patient preference and performance status, residual toxicities and prior hypersensitivity reactions, the TFI and platinum-free interval (PFI) and degree of response to prior platinum-based treatment. The conventional definition of 'platinum sensitivity' is a PFI of greater than six months after cessation of the last platinum-based chemotherapy course, and was based on the likelihood of disease response to platinum re-treatment in older studies [375,436]. However, in an era of more accurate imaging techniques and maintenance regimens, the definition of platinum sensitivity is more complex and in the absence of validated predictive biomarkers, should be less rigid for determining the next line of cytotoxic chemotherapy for an individual woman [437].

While the duration of response to platinum is important, retrospective data also suggest that seeking to extend the platinum-free interval itself may also help improve the patient's subsequent response to platinum re-treatment and there are now several studies supporting this concept [438,439].

Platinum-sensitive relapsed EOC. In patients with platinum-sensitive (PS) or partially platinum-sensitive (pPS) EOC recurrence (6–12 months PFI) published clinical evidence reports response rates to second-line therapy ranging between 27 % and 33 %, regardless of whether platinum-based or non-platinum drugs are used. However, benefit may be better expressed in terms of PFS and combination therapy (such as carboplatin / paclitaxel, carboplatin / liposomal doxorubicin or carboplatin / gemcitabine) would be recommended as this improves PFS and OS in this group of patients [436,440,441]. Trabectedin and pegylated liposomal doxorubicin (PLD) have been shown to be more beneficial compared with PLD alone, especially in the group of patients with pPS disease and may be an alternative to carboplatin with PLD in some circumstances [442,443].

The addition of bevacizumab to chemotherapy for women with PS relapse and as maintenance afterwards also increases PFS compared with combination carboplatin/gemcitabine alone [377,444]. However, no OS advantage has been demonstrated as yet, possibly due to a high rate of cross-over in the placebo group with later treatment lines, and bevacizumab is not routinely funded in this setting in the UK. A recent Cochrane review included three studies with 1564 participants who had relapsed PS EOC [389]. Bevacizumab with chemotherapy, and continued as maintenance, likely resulted in little to no difference in OS (HR 0.90, 95 % CI 0.79 to 1.02; moderate certainty evidence), but likely improved PFS (HR 0.56, 95 % CI 0.50 to 0.63; moderate certainty evidence). Bevacizumab slightly increased the risk of grade ≥ 3 adverse events (RR 1.11, 1.07 to 1.16; high-certainty evidence), and there was an almost 6-fold increase in the risk of hypertension (grade ≥ 2) (RR

Table 3
Criteria for primary site assignment in high-grade serous ovarian carcinoma (HGSC) .

Criteria	Primary site	Comment
Presence of serous tubal intraepithelial carcinoma (STIC)	Fallopian tube	Irrespective of ovarian and peritoneal involvement of any size
Invasive carcinoma involving the tubal mucosa with or without STIC	Fallopian tube	Irrespective of ovarian and peritoneal involvement of any size
Fallopian tube partial or completely incorporated in the tubo-ovarian mass	Fallopian tube	Irrespective of ovarian and peritoneal involvement of any size
Macroscopic or microscopic ovarian carcinoma in absence of STIC or mucosal tubal involvement	Ovary	Both tubes should be visible and examined by SEE-FIM protocol. Irrespective of peritoneal involvement of any size.
Bilateral tubes and ovaries free of HGSC after macroscopic and microscopic examination in the presence of peritoneal involvement by HGSC.	Peritoneal	Only in primary debulking surgery specimens prior to chemotherapy.
HGSC diagnosed on omental/ peritoneal biopsy	Tubo-ovarian	Endometrial serous carcinoma has been excluded.
Post-chemotherapy with no residual carcinoma	Site assigned as above	

adapted from [208]

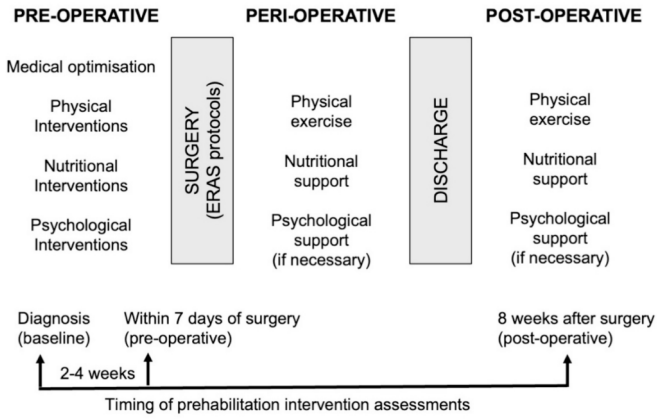

Fig. 1. Study design of the prehabilitation programme combined with an ERAS approach for gynaecological oncology patients. ERAS = enhanced recovery after surgery. Image adapted from [254] with permission.

5.82, 95 % CI 3.84 to 8.83), although no change in QoL (MD 0.8, 95 % CI −2.11 to 3.71; low-certainty evidence).

There are currently three PARPi approved for use in the UK as maintenance in PS recurrent EOC where there has been no prior PARP inhibitor. Olaparib has been shown to increase the PFS in both *BRCA*mut and wild type *BRCA* (*BRCA*wt) platinum-sensitive relapsed ovarian cancer [445,446]. In patients with *BRCA*mut a median overall survival benefit of 12.9 months over placebo is seen with olaparib maintenance [446,447]. Significantly improved PFS is also seen with maintenance niraparib for both germline *BRCA*mut and non-germline *BRCA*mut-associated relapsed platinum-sensitive ovarian cancer (those with tissue *BRCA* mutations and *BRCA*wt) [448]. Similarly, there is a significant PFS advantage with maintenance rucaparib in platinum-sensitive relapse for all women (*BRCA*mut, *BRCA*wt/HRD and *BRCA*wt/HRP tumours) [449]. With all PARP inhibitors, the greatest PFS advantage appears to be for *BRCA*mut disease, germline or tissue. Crucially, all three PARP inhibitors provide longer time without significant symptoms and quality-of-life-adjusted PFS compared with placebo. The Cochrane review of PARPi included four studies (1677 participants) of PARPi with chemotherapy and then as maintenance treatment [396]. PARPi resulted in a large PFS (HR 0.34, 95 % CI 0.28 to 0.42; high-certainty evidence; no evidence of disease progression at 12 months 37 % with PARPi versus 5.5 % for placebo), but may be at the cost of an increase in grade ≥ 3 adverse events (51 %) compared with placebo (19 %)(RR 2.62, 95 % CI 1.85 to 3.72; low-certainty evidence), although there may be little or no change in QoL (MD 1.20, 95 %CI −1.75 to 4.16; low-certainty evidence). As yet data have shown little to no difference in OS (HR 0.88, 95 %CI 0.65 to 1.20; moderate-certainty evidence; percentage alive at 36 months 21 % with PARPi versus 17 % for placebo), although these data were from only two of the studies and may change as data mature.

There are data to support PARP inhibitor monotherapy treatment as an alternative to platinum-based chemotherapy in women with PS disease recurrence, in *BRCA*mut-associated disease in particular, but this is not routinely funded in the UK [450,451]. A Cochrane review, which included three studies compared PARPi monotherapy with chemotherapy alone [396]. PARPi may result in little to no difference in OS (HR 0.95, 95 %CI 0.62 to 1.47; low-certainty evidence) (percentage alive at 36 months 18 % with PARPi versus 17 % for chemotherapy). Evidence for PFS was very uncertain (HR 0.88, 95 %CI 0.56 to 1.38; very low-certainty evidence)(no evidence of disease progression at 12 months 26 % with PARPi versus 22 % for chemotherapy) and there may be little to no difference in rates of grade ≥ 3 adverse events with PARPi (50 %) than chemotherapy alone (47 %) (RR 1.06, 95 %CI 0.80 to 1.39; low-certainty evidence).There are also emerging data to support consideration of PARP inhibitor re-challenge in select patients with platinum-sensitive ovarian cancer [452,453].

Platinum-resistant and platinum-refractory relapsed EOC. In the platinum-refractory (PRef)/platinum-resistant (PR) setting there does not appear to be any advantage in using combination therapies, which are associated with higher rates of adverse events. In the PR setting, second-line single-agent chemotherapy with non-platinum drugs (such as PLD, weekly paclitaxel, etoposide or topotecan) results in short-lived response rates of approximately 10 % to 25 % and PFS of 4–5 months and OS of one year [440,454,455] Carboplatin in combination with gemcitabine is also used in selected patients [456,457]. Metronomic oral cyclophosphamide or anti-oestrogen therapy, e.g., letrozole are also options for selected patients [458–460].

However, the addition of bevacizumab to conventional chemotherapy has been shown to increase PFS to 6.7 months, with OS of 16.6 months compared to monotherapy (PLD, weekly paclitaxel or topotecan) and may improve patient-related outcomes in a carefully selected population [455,461]. In a Cochrane *meta*-analysis, which included five studies and 778 participants, bevacizumab with chemotherapy and continued as maintenance increased OS (HR 0.73, 95 % CI 0.61 to 0.88; high-certainty evidence) and there was a large increase in PFS (HR 0.49, 95 % CI 0.42 to 0.58; moderate-certainty evidence). Bevacizumab may result in a 3-fold increase in hypertension (grade ≥ 2) (RR 3.11, 95 % CI 1.83 to 5.27; low-certainty evidence) and the rate of bowel fistula/perforation (grade ≥ 2) may be slightly higher (RR 6.89, 95 % CI 0.86 to 55.09).

If the patient cannot tolerate chemotherapy and/or symptoms are not requiring a rapid response to chemotherapy, then hormonal treatment could be an alternative, although evidence for benefit is limited [462,463]. Palliative radiotherapy may have a role in highly selected situations (see below).

Radiotherapy for EOC

Recommendations

There is no role for whole abdominal radiotherapy as adjuvant/consolidation treatment of EOC. (Grade A)

Definitive treatment using intensity-modulated radiotherapy or stereotactic radiotherapy may be considered for loco-regional recurrence or oligometastatic disease where surgery is not an option. (Grade D)

Palliative radiotherapy should be considered for symptomatic disease including vaginal bleeding, localised pain and brain metastases. (Grade D)

Prior to platinum-based chemotherapy, whole abdominal radiotherapy (WAR) was used as adjuvant or consolidation treatment following surgery for EOC. However, the toxicity of WAR and the development of new systemic therapies have limited the use of radiotherapy in this situation. Nowadays the role of radiotherapy in EOC is largely restricted to the treatment of selected patients with localised or oligometastatic recurrent disease and patients requiring palliation of specific symptoms where surgical resection is not an option. For recurrent EOC, the indications for definitive radiotherapy have been expanded by advanced radiotherapy techniques such as intensity modulated radiotherapy (IMRT) and stereotactic radiotherapy.

Adjuvant or consolidation radiotherapy

Whole abdomino-pelvic radiotherapy was replaced by adjuvant chemotherapy due to the higher toxicity profile with radiotherapy, although survival outcomes were similar [464–466]; in the Swedish-Norwegian Ovarian Cancer Study Group 10 % of patients receiving radiotherapy had severe late intestinal radiation reactions [465].

There may be an option for adjuvant pelvic radiotherapy when patients are unable to receive chemotherapy, or for histological subtypes for which adjuvant chemotherapy is less effective.

Clear cell carcinoma of the ovary

The role of adjuvant radiotherapy for clear cell carcinoma remains uncertain, but it may be of benefit for selected patients with Stage IC and Stage II disease. Retrospective analysis of large cohort studies with whole abdominal pelvic radiotherapy have reported improved overall and disease-free survival compared to chemotherapy-only groups [467,468].

In a more recent retrospective study of 163 patients with stage I and II clear cell carcinoma, adjuvant radiotherapy was not significantly associated with increased progression-free or overall survival, although there may have been more treatment selection based on patient risk factors in this later study [469].

Small cell of the ovary of hypercalcaemic type

The prognosis for patients with small cell of the ovary of hypercalcaemic type is poor, and multi-modality treatment is recommended. In a GCIG cohort study of 17 patients, the majority of long-term survivors received whole abdominal-pelvic or pelvic radiotherapy. This included five of the six patients with stage one disease who received radiotherapy achieving long term control, compared to only one of four who did not receive radiotherapy [470]. Adjuvant pelvic radiotherapy may be considered for ovarian small cell carcinoma of hypercalcaemic type and for selected patients when systemic therapy is not feasible or less effective.

Radiotherapy for recurrent disease

Although chemotherapy is the mainstay of treatment for recurrent ovarian cancer, patients with limited recurrent disease may achieve long-term disease control with radiotherapy where surgery is not an option. Newer targeted radiotherapy approaches including intensity modulated radiotherapy (IMRT) and stereotactic radiotherapy can achieve a higher radiotherapy dose to the target volume whilst sparing organs at risk compared to more conventional radiotherapy techniques. There are no published randomised trials comparing radiotherapy to chemotherapy in recurrent ovarian cancer [471–475].

Involved field radiotherapy

Radical radiotherapy may be an effective treatment for localised disease, with better outcomes reported in selected patients with small volume pelvic or nodal recurrence, platinum-sensitive disease and good performance status, although data are limited to non-randomised studies [471,472,476]. Fujiwara *et al.* prospectively evaluated the effects of local radiation therapy on patients with relapsed ovarian cancer after a median of two previous chemotherapy treatment. The patients received 52.3 +/- 8.3 Gy. The authors observed that smaller lesions and lymph nodes demonstrated the best responses, and they concluded that local radiation therapy may be a treatment option for relapsed or refractory but localised ovarian cancer, particularly when the tumour is small and/or located in the lymph nodes [473].

Two groups assessed predictive factors of disease control with radiotherapy for localised disease; one of 33 patients and found that cytoreductive surgery prior to radiotherapy was associated with recurrence-free survival, whereas BRCA1 status and being of African American race were negatively correlated with local control [474]. Another study, of 48 patients found no prognostic factors on multivariate analysis, however univariate analysis showed tumour size of less than 3 cm and objective tumour response were associated with overall and disease-free survival [475].

Stereotactic radiotherapy

For patients with brain metastases, stereotactic radiosurgery (SRS) is an effective treatment [477]. Stereotactic body radiotherapy (SBRT), which is also referred to as stereotactic ablative radiotherapy (SABR), is increasingly being used for oligometastatic extra-cranial disease including lung, liver and lymph node metastases. Several case series have demonstrated that SBRT is well tolerated with good local control for patients with oligo-metastatic and oligo-progressive ovarian cancer [478–481]. Pooled data from 15 centres, including 449 treated lesions in 261 patients, reported 65 % complete response and 82 % two-year local control. There was no grade 3–4 late toxicity and only 5 % grade one toxicity [480]. The radical treatment of oligo-metastases could potentially defer the need to commence or change systemic therapy.

Palliative radiotherapy

Short-course radiotherapy can provide useful palliation for patients with recurrent or metastatic ovarian cancer [482,483]. Indications for treatment include vaginal bleeding, localised pain and brain metastases. Typical dose-fractionation regimens for extra-cranial sites include 8–10 Gy in a single fraction, 20 Gy in 5 fractions or 30 Gy in 10–15 fractions. Patients with brain metastases that are not suitable for SRS may receive whole brain radiotherapy with 20 Gy in 5 fractions or 25–30 Gy in 10 fractions.

Follow-up and monitoring for recurrence

Recommendations

A careful history, assessment of new and potentially tumour-related symptoms and clinical examination is essential at follow up visits. (Grade C)

CA125 measurement is not mandatory and has not been proven to be of survival benefit. (Grade A)

Longer follow-up and surveillance for recurrence should be considered for *BRCA* carriers who have been shown to have improved 5-year overall survival. (Grade B)

Patients should have the contact details of their key worker so that they access an early review for unexpected symptoms. (Grade D)

Follow-up along a traditional hospital-based model provides opportunities to assess the risk and/or presence of recurrence and to assess patients holistically for the presence of on-going physical, psychological, emotional, financial and sexual survivorship issues related to their cancer treatment. If the history, physical exam or raised tumour markers suggest disease recurrence a CT scan should be performed. The intervals between follow-up visits vary according to local practice, but commonly consists of follow-up every 3 months for the first 2 years and then every 6 months up to 5 years after end of treatment, despite a lack of randomised trial data illustrating a benefit of strict follow-up protocols over an individualized patient- and symptom-led approach. However, data show that telephone follow-up is acceptable to patients [484], and patient-initiated follow up could also be considered, in line with BGCS guidelines [485].

Increases in CA125 may herald progressive disease in patients who achieve a normal CA125. A prospectively randomised MRC/EORTC trial demonstrated no difference in overall survival after a median follow-up of 56.9 months (HR 0.98, 95 % CI 0.80 to 1.20; $P = 0.85$) between patients who received chemotherapy based on a rising CA125 and those who did not receive chemotherapy until they were symptomatic [486]. Treatment based on an abnormal CA125 led to early treatment by a median of 4.8 months [486,487]. Interestingly, those in the arm where treatment was initiated on CA125 rise had a shorter interval to deterioration in global health score or death (HR 0.71, 95 % CI 0.58 to 0.88; $P < 0.01$). This finding led to many questioning the clinical and cost-effectiveness of routine CA125 measurements in follow-up. However, these data pre-date greater use of maintenance treatment and secondary cytoreductive surgery, as discussed previously, some patients may wish to know what might lie ahead and for others it may trigger imaging that will determine timing and value of further treatment [454]. Participation in first-line trials usually requires regular post-treatment CA125 measurements for trial end points. However, it is now accepted that a rising CA125 alone, without clinical or radiographic evidence of recurrence, should not be routinely be used as an indication to commence

systemic chemotherapy.

BRCA carriers and survival

It has been demonstrated that *BRCA* mutation carriers have improved long term survival and therefore extended follow up (beyond 5 years) may be considered, together with breast clinic/screening referral.

A pooled analysis of 1213 women with EOC and pathogenic germline mutations in *BRCA1* (n = 909) or *BRCA2* (n = 304) and 2666 non-carriers, noted an improved 5-year overall survival among *BRCA*mut carriers with ovarian cancer [488]. Reports have also noted improved survival specifically in *BRCA2*mut carriers [489]. A more recent report of 15-year survival of patients with *BRCA*mut EOC suggest that the survival benefit noted appears to be within the first 5 years and decreases over time [490]. The recent data from the SOLO1 trial demonstrated five-year OS rates of 67 % in women with newly-diagnosed EOC who have a *BRCA*mut, and received 2 years of maintenance Olaparib, compared with 46.5 % in the placebo arm. This suggests that longer term follow up should be considered for *BRCA*mut carriers [491].

Low-grade serous ovarian carcinoma (LGSC)

Recommendations

Surgery is the most effective management for LGSOC, which has a lower response rate to chemotherapy than HGSOC. (Grade B)

There is a 25 % response rate seen with a platinum-taxane regimen in LGSOC and given the lack of a superior alternative chemotherapy regimen, this can be offered in patients with advanced disease. (Grade B)

There is a 26 % response rate with trametinib in the advanced/recurrent setting compared with second line chemotherapy or endocrine treatment (6 %) and this should be considered in those with prior chemotherapy. (Grade B)

LGSC pathology

LGSC is the commonest of the 'rare' ovarian tumours. It constitutes about 5 % of all ovarian tumours. Patients with LGSOC are usually a decade younger than those with a diagnosis of a high-grade serous carcinoma. They often present with advanced stage disease and have a protracted clinical course. Architecturally, papillae and glands are frequently seen. The cellular morphology (mild to moderate atypia, less than three-fold variation in nuclear size, low mitotic activity [492]) is the key morphological feature that sets LGSC apart from high grade serous carcinoma. On IHC the cells are PAX8, CK7, WT1 and ER positive. They show wild type p53 expression [493,494]. LGSC has a high prevalence of activating somatic mutations in mitogen-activated protein kinase pathway genes. The most commonly mutated genes are *KRAS*, *BRAF* and *NRAS* [495]. Although standard of care is still cytoreductive surgery with platinum-based chemotherapy, targeted treatment with mitogen-activated protein kinase kinase enzyme (MEK) inhibitors is under the spotlight.

LGSC treatment

The management of LGSOC is predominantly surgical. Primary cytoreductive surgery aims to leave NMRD and may be considered again at relapse. A large *meta*-analysis showed a response rate to platinum-based chemotherapy of approximately 24 % in patients with advanced primary low grade advanced ovarian cancer after primary CRS, and hence lower than for their high-grade serous counterparts [496]. The authors concluded that HGSC and LGSOC differ with respect to chemosensitivity, chemotherapy being of considerably less benefit in patients with LGSOC than patients with HGSC, growth pattern and outcome following surgery. Hormonal maintenance strategies in LGSOC after completion of platinum-based chemotherapy seem to have a survival benefit in retrospective series [497].

Recent studies have focused on inhibitors of MEK or RAF/MEK, as these pathways are active in many LGSOC. A study of trametinib in the relapsed/metastatic setting, with objective response rates of 26 %, and prolonged stable disease rates of a further 59 % [498]. This compared to standard of care chemotherapy or endocrine treatment, with ORR ranging from 0 % to 11 % for the control arms. This could be considered for patients with relapsed/metastatic disease who have had platinum-based chemotherapy.

International multicentre studies are currently ongoing with combined RAF/MEK inhibitors but further trials are urgently needed to assess other biomarkers. Recruitment to these is important, as is registration of cases onto rare tumour databases to facilitate the study of this rare condition [499].

Mucinous cancers

Recommendations

True advanced mucinous tumours of primary ovarian origin are rare and effective systemic management / treatment strategies are limited. (Grade B)

Ovarian metastases from primary mucinous tumours of other organs, such as GI tract, are more common should be actively excluded. (Grade B)

If pseudomyxoma is suspected at the time of staging laparotomy, surgery should be limited in its extent and the patient referred to a national pseudomyxoma centre for further treatment. (Grade B)

Mucinous adenocarcinoma pathology

Mucinous histology accounts for 3 – 5 % of all ovarian carcinomas. Primary mucinous ovarian cancers are typically confined to the ovary at presentation, are large and show a continuum of architectural features including benign, borderline and malignant areas. Confluent and expansile patterns of invasion are often seen, but when an infiltrative pattern is present, the pathologist must be alert to the possibility of a metastatic carcinoma from another site. Invasive mucinous carcinoma with an infiltrative pattern has a more aggressive course than mucinous carcinoma with an expansile pattern. Mucinous carcinomas of the ovary usually exhibit a CK7+/CK20-/CDX2- immunohistochemistry profile. Advanced mucinous tumours, with intra-peritoneal involvement, are unlikely to be of ovarian origin as these are rare [500]. Many of these are Krukenberg tumours or arise from other organs, such as the appendix and gastro-intestinal (GI) tract origin, should be excluded, with bidirectional GI endoscopy, and referral to a GI MDT considered. Ovarian tumours metastatic from appendiceal primaries may have morphological features of mucinous borderline tumours and the presence of dissecting mucin in the peritoneal cavity (pseudomyxoma peritonei) favours this diagnosis. Rarely advanced mucinous tumours can arise from an ovarian teratoma.

Mucinous ovarian cancer treatment

If appendiceal pseudomyxoma is found at staging laparotomy, surgery should be limited to appendicetomy (+/- partial caecectomy) and BSO. A colonoscopy should be arranged urgently postoperatively, if not performed prior to surgery, in parallel with referral to a national pseudomyxoma centre. More extensive surgery with peritoneal stripping should be avoided, if possible, since this can compromise subsequent surgical treatment and HIPEC.

For primary ovarian malignancies where a GI primary is excluded, surgery with adequate peritoneal staging is the standard treatment for the majority of primary mucinous ovarian tumours. Fertility-sparing surgery should be considered in young women with unilateral disease.

The management of advanced true primary ovarian mucinous tumours is challenging, as they are not particularly chemo-responsive. The collection of pathological and clinical data from patients with these rare tumours is vital to allow progress to be made in determining appropriate therapeutic strategies [501]. Patients with advanced disease are usually treated with carboplatin and paclitaxel, although these tumours respond less well to this combination than the more common non-mucinous tumours. mEOC (NCT01081262), a randomised trial comparing carboplatin and paclitaxel, oxaliplatin and capecitabine +/- bevacizumab (a regimen used in gastrointestinal tract cancers) closed early due to poor recruitment with one conclusion being that primary ovarian mucinous tumours were rarer than previously thought [502].

Published evidence suggested equivalence between the carboplatin and oxaliplatin based arms [503]. Further work on molecular profiling has shown a number of patients have over-expression of HER2, and small series have shown good responses to HER-2 directed therapy, with regimens including weekly paclitaxel, trastuzumab+/- pertuzumab, although this has not been assessed in formal trials to date. Around half of patients with mucinous ovarian cancer have *KRAS* mutations, and trials are in set up to assess *KRAS*-directed targeted treatments in these patients. Further studies of molecular drivers and targeted treatments are urgently needed in these patients.

Where metastasis from the gastro-intestinal (GI) tract must be excluded, bidirectional GI endoscopy should be performed and referral to a GI MDT should be considered.

Borderline tumours

Recommendations

Patients aged between 18 and 24 should be managed jointly between the gynae MDT and the teenage and young adult MDT. (Grade D)

Where possible, a conservative surgical strategy is recommended to preserve fertility in women of childbearing age. (Grade C)

Appendicectomy is recommended only if the appendix is macroscopically pathological. (Grade C)

Routine hysterectomy is not recommended, unless the uterus is macroscopically involved and fertility is not a concern. (Grade C)

Referral to a fertility specialist should be offered to patients with a BOT and of childbearing age. (Grade D)

Follow-up beyond 5 years is recommended due to the long median time to recurrence. If either CA125 or CA19-9 are raised at presentation, these may be useful in follow up. (Grade D)

Hormonal contraception after serous or mucinous BOT is not contraindicated. (Grade C)

For women aged under 45 years with mucinous BOTs, who become menopausal as a result of treatment, given the lack of hormone-sensitivity, HRT should be recommended in the absence of other contraindications. (Grade C)

For serous BOTs there is the potential that they may be hormone sensitive and risks and benefits of HRT should be discussed. (Grade D)

Early-stage serous BOT

In case of bilateral serous early-stage BOT treatment and treatment to preserve fertility and/or endocrine function is desired, bilateral cystectomy can be performed. (Grade C)

In serous BOT diagnosed after cystectomy, restaging surgery for adnexectomy is not recommended in the absence of pathological high-risk features and/or suspicious residual lesions at the time of surgery and/or postoperative imaging (USS or pelvic MRI), if fertility/endocrine function is a concern. (Grade C)

Restaging surgery is recommended for serous BOTs with micropapillary features where there is no evidence of satisfactory inspection of the abdominal cavity during initial surgery. (Grade C)

Early-stage mucinous BOT

In early-stage mucinous BOT if cystectomy has been performed, unilateral adnexectomy is recommended. (Grade C)

Restaging surgery is recommended in mucinous BOT if a cystectomy has been performed or if the appendix has not been evaluated at initial surgery. (Grade C)

Early stage serous and mucinous BOT

Laparoscopic surgery is the preferred surgical route, if the tumour can be removed without risk of rupture. (Grade C)

Measures should be taken to avoid rupture, including conversion to laparotomy. (Grade D)

Extraction of the surgical specimen should be performed using an endoscopic bag to avoid unnecessary intracorporal tumour spill/rupture. (Grade D)

BSO is recommended for postmenopausal women with suspected unilateral or bilateral BOT prior to surgery. (Grade C)

Lymphadenectomy is not recommended, even in advanced disease, unless clinically bulky. (Grade C)

Frozen section can be useful to guide intra-operative treatment, although is more limited compared to invasive malignancy. (Grade B)

It is safe for young patients with BOT to receive fertility-sparing surgery but given the higher risk of relapse within any remaining ovarian tissue, regular sonographic follow up is recommended. (Grade C)

Advanced or recurrent BOT

Complete macroscopic tumour resection should be the aim of surgery for advanced or recurrent BOT. (Grade B)

There is no evidence-based indication for cytotoxic chemotherapy in BOT. (Grade B)

Ovarian epithelial tumour classification is characterised by its unique category of borderline tumours. Although the morphology of these tumours includes no invasive characteristics, clinically their behaviour is not always entirely benign.

Pathology

Borderline ovarian tumours (BOTs), despite varying grades of architectural complexity and cytological atypia, do not show features of frankly invasive malignancy. BOTs are staged according to the FIGO staging system of ovarian, fallopian tube and primary peritoneal carcinoma. Most BOTs tend to present as stage I disease and show benign behaviour, with only a small percentage of some subtypes showing extra-ovarian spread at presentation, recurrence and/or progression to invasive malignancy [504].

As some ovarian tumours may show the spectrum of benign, borderline and malignant features in the same tumour, BOTs should be sampled thoroughly at 1 block per cm of tumour maximum dimension. In tumours showing features raising the suspicion of invasive malignancy (e.g., marked cytological atypia) and in large tumours (e.g., mucinous tumours more than 10 cm), extra blocks should be taken, up to 2 blocks per cm of tumour maximum dimension [504]. Serous and mucinous BOTs represent the commonest types of BOTs and share some features/principles.

In tumours showing a spectrum of benign and borderline changes, the tumour is classified as BOT if the borderline features are seen in more than 10 % of the epithelial volume for a tumour. Otherwise the consensus is that it should be classified as benign cystadenoma / cystadenofibroma with focal epithelial proliferation [505]. Foci of stromal invasion < 5 mm in greatest dimension in any single focus are classified as microinvasion, and in their presence the tumour would still be classified as BOT [506,507].

Patients with stage I disease have an OS that is not significantly different from the general population, but patients with advanced stage disease have higher likelihood of tumour recurrence/progression and lower OS [508,509].

Serous borderline ovarian tumour (SBOT)

SBOTs histologically show hierarchical papillary architecture with the papillae having stromal cores and covered by epithelium showing stratification, and a degree of cytological atypia. Some tumours include a micropapillary / cribriform component, where the micro papillae arise directly from large papillae, lack stromal cores, are at least 5 times longer than wide, and / or interlink forming a cribriform pattern. If such a component measures more than or equal to 5 mm, the tumour is classified as SBOT of the micropapillary / cribriform subtype, which is more likely to be associated with aggressive behaviour [508].

In most studies, stromal microinvasion has not been shown to negatively affect outcome. However, if the morphology resembles low grade serous carcinoma (LGSC), the tumour is to be classified as microinvasive LGSC [510].

Extra-ovarian tumour deposits of SBOTs may be non-invasive to underlying tissue, and are classified as implants or showing invasion and hence classified as extraovarian LGSC, where the latter is a significantly adverse prognostic factor. Some implants may be difficult to classify and these are designated as indeterminate [508].

Lymph node deposits of SBOT can be found in some cases, but are rare and routine lymph node staging is not recommended [504].

Mucinous borderline ovarian tumour (MBOT)

MBOT is a non-invasive mucinous neoplasm of gastrointestinal type differentiation showing architectural complexity and varying degrees of cellular crowding / stratification, cytological atypia and mitotic activity [504]. The presence of focal marked cytological atypia and mitotic activity, warrants a diagnosis of intraepithelial carcinoma, which does not adversely affect overall survival. However, if these features are encountered in foci of microinvasion the tumour is best classified as microinvasive carcinoma [511]. Mural nodules may be present and show features of sarcoma / sarcoma like foci, anaplastic carcinoma, or show mixed features. Cases with anaplastic carcinoma, may be associated with aggressive behaviour [512]. MBOTs may develop in association with Brenner tumour or teratomas. Tumours arising in teratomas show significant morphological and immunophenotypic similarities to lower gastrointestinal tract mucinous tumours and may be associated with pseudomyxoma peritonei and extraovarian spread [513].

Rare types of borderline ovarian tumours

These include seromucinous, endometrioid and clear cell BOTs, which are usually associated with endometriosis. Endometrioid BOTs show crowded endometrioid glands, but lack confluent growth patterns and destructive invasion. Clear cell BOTs are extremely rare and thorough sampling is essential to exclude this being part of a clear cell carcinoma (which is the much commoner scenario), and densely crowded glands, and typically tubulocystic and papillary growth patterns should not be present in a clear cell BOT. Seromucinous BOTs are composed of an admixture of Mullerian-type epithelia, showing complex architecture, but no confluent or invasive growth patterns. Another uncommon type is borderline Brenner tumour, which resembles low grade papillary urothelial carcinoma, and areas of benign Brenner tumour are always present [504].

Clinical management

Patients with BOTs are younger and future fertility may be a concern; in a prospective study of 339 women, the median age was 39 years [514]. Not all had early-stage disease and 83.4 % were diagnosed with stage I disease, 7.9 % stage II, and 8.5 % stage III. In the presence of peritoneal implants, excision of involved peritoneum, with preservation of at least one ovary and tube and uterus, can be performed. Higher stage, incomplete staging, residual tumour and fertility-sparing surgery were independent prognostic factors for recurrence in two retrospective studies [515–517]. Surgery, even fertility-sparing, should include peritoneal staging (inspection, washings for cytology, peritoneal biopsies, omental biopsy/omentectomy, visualisation of the appendix and removal if macroscopically abnormal). However, the diagnosis is often made retrospectively following surgery by a non-gynaecological oncologist. In a French multi-centre retrospective study, 54 of 360 women with BOTs underwent a restaging operation, as disease was not expected at the time of initial surgery [518]. With adjustment for risk factors, recurrence rates were compared between those restaged (n = 54) and those who did not (n = 244). Eight (14.8 %) women had their disease upstaged, of which four had ovarian disease and four women had disease beyond the ovary. This was more common in those with serous BOTs (P = 0.06) and in those with a cystectomy at initial surgery (P = 0.008). These was no difference in recurrence rate between those restaged and those who were not. Patients should therefore be informed about the risks and benefits of completion staging after simple cystectomy or USO with an incidental finding of BOT. Those who might benefit most include: those who had a cystectomy (for completion oophorectomy), especially with a mucinous tumour; patients with mucinous tumours in whom the appendix was not inspected (if not already removed); those with serous tumours with micropapillary changes or did not have adequate peritoneal inspection, as per evidence and recommendations in the French national guidelines (see Fig. 2) [519–521].

Overall, prognosis is good, with disease-free survival of 99.6 % in stage I patients, 95.8 % in stage II, and 89 % in stage III over a median 70 month follow up [514]. Simple cystectomy in an ovary with BOT carries a higher risk of relapse and so should be considered only for fertility-sparing reasons and after thorough informed consent [522]. Longer-term, the risk of malignant transformation was low overall (~2%), but

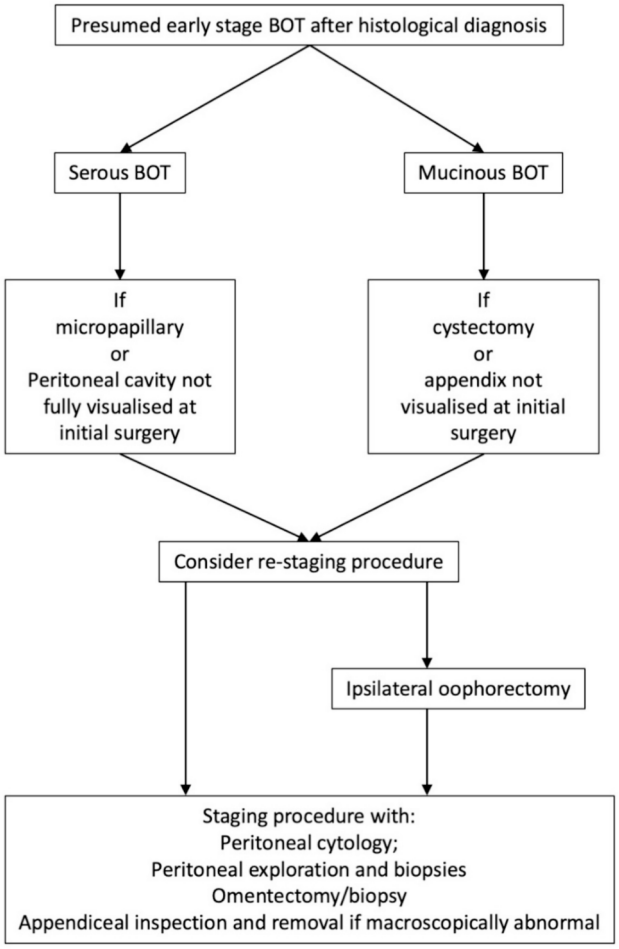

Fig. 2. Management of presumed early-stage BOT diagnosed after initial surgery.
Adapted from [521]

was found in 30 % of those with relapsed disease, although was much less frequent in women under 40 years of age at original diagnosis, compared to those aged over 40 years (12.0 % versus 66.7 %, P < 0.001). A French observational study devised a scoring system to determine risk of relapse, based on a series of 360 women (Table 5) [523]. Risk was associated with age < 45 years, preoperative CA125 > 150 IU/mL, serous histological subtype, stage other than IA, and ovarian surgery other than BSO. From their data, risk of recurrence was 11.8 % [35/297] for those with a score < 8 and 58.7 % (37/63) ≥ 8 points, respectively (see Table 4). After conservative surgery for fertility-preservation, completion surgery could be considered once women have finished their families. As the risk of recurrence is several-fold higher in studies where USO (11 %) is performed, compared to BSO (1.7 %), BSO should be recommended for postmenopausal women [524].

In early-stage BOT, with small volume masses, and in the absence of extensive peritoneal implants, laparoscopic management is as safe as laparotomy from an oncological point of view [525–527]. A retrospective observational study of 687 patients who underwent laparoscopy (n = 312) or open surgery (n = 375) for BOTs found that the rate of recurrence did not differ, despite lower rates of surgical radicality and staging in the laparoscopic group, over a median follow up of 41.8 months [525]. However, recurrence is associated with *peri*-operative cyst rupture, with one study demonstrating increased recurrence rates for those with intra-operative rupture (P = 0.04) [524]. In a Norwegian retrospective study, those who had stage I BOT measuring > 10 cm in diameter had an increased risk of intra-operative rupture during laparoscopic surgery compared with laparotomy (5/8 versus 9/44, P = 0.014) [528].

Hysterectomy has no value in complete staging of a patient with BOT, although hysterectomy should be considered, if the patient wishes, or for cytoreduction, if the uterus is involved with invasive disease [515]. There is no value in lymph node sampling or dissection in BOT and this should therefore not be routinely performed, although, if bulky lymph nodes are present, they should be removed. Frozen section of an ovarian mass can help determine the extent of surgery; a diagnostic test accuracy systematic review found that, if frozen section was used to differentiate between cancer and benign/borderline, sensitivity was 90.0 % (95 % CI 87.6 % to 92.0 %), and specificity was 99.5 % (95 % CI 99.2 % to 99.7 %) [318].

There is no proven value of cytotoxic chemotherapy in patients with BOT [515,529].

BOTs can relapse decades after the initial diagnosis, and is uncommon in those who have had both ovaries removed. Follow-up with ultrasound scan in patients after fertility-sparing surgery is advisable. In an observational study of 164 women who had fertility-sparing surgery for BOT, 28 (17 %) women had recurrence of a BOT (14 %) or carcinoma (3 %), over a median follow up period of 71 months [530]. USS detected recurrence due to an adnexal mass (23/24) or free fluid (1/24) for those with complete follow up data, whereas CA125 was elevated in only a third (8/24). The value of USS to monitor cysts in those treated with fertility-conserving surgery was also seen in a smaller follow up study of 34 patients who had a suspicious recurrent lesion [531]. There may be less value in routine serum tumour marker measurement in follow up for BOT patients, although it may be useful if CA125 or CA19-9 were raised at diagnosis [515]. Another study of 68 patients with BOT recurrence found that three-quarters (48/68; 74 %) had CA125 within the normal range (<35 IU/L) at recurrence [532].

In the Swedish Observational study of HRT and ovarian cancer, there were 150 women who had been treated for BOT [533]. With a median 5-year follow-up, 51 % of the women with BOT used HRT after diagnosis. There were only three deaths due to ovarian cancer and none of these women had used HRT before or after diagnosis. The French national guidelines concluded that neither assisted reproduction techniques nor HRT were contraindicated in BOT and actively encouraged the use in those with mucinous BOTs under the age of 45 to prevent the adverse health effects of premature menopause [519].

Recurrent BOT should be treated surgically, if feasible, since response to chemotherapy is poor.

Table 4
The Gynecologic Cancer Intergroup (GCIG) [437] categorisation of patients based on the length of remission following platinum-based chemotherapy. The platinum-free interval is however somewhat theoretical and in real-life exists as a spectrum.

Classification	Definition
Platinum Sensitive (PS)	Progression with an interval of > 12 months after completion of chemotherapy
Partially PS (pPS)	Progression with an interval of between 6–12 months after completion of chemotherapy
Platinum Resistant (PR)	Progression with an interval of less than 6 months after completion of chemotherapy
Platinum Refractory (PRef)	Progression during, or within 4 weeks after completion of chemotherapy

Table 5
Risk scoring system for recurrence of BOT. Adapted from [523] with permission. Low risk (11.8 % recurrence) score < 8; high-risk (58.7 %) score ≥ 8.

Factors Scoring	Scoring				
	0	1	2	4	6
Age (years)	≥45	<45			
FIGO stage	IA	≥IB			
CA125 (IU/mL)	<150		≥150		
Histological subtype	Mucinous		Serous		
Surgery type	BSO			USO	Cystectomy

Germ cell tumours

Recommendations

Patients aged between 18 and 24 should be managed jointly between the gynae MDT and the teenage and young adult MDT. (Grade D)

If GCT is suspected on markers or other imaging, CT scan of thorax, abdomen, and pelvis is recommended for pre-operative staging. (Grade D)

Cytoreductive surgery may be the treatment of choice for first-line treatment in those with surgically resectable disease, but should be discussed with a specialist germ cell centre MDT before proceeding. (Grade C)

Fertility-sparing surgery (FSS) should be offered to those with presumed early-stage disease who wish to retain their fertility. (Grade C)

Patients with stage IA dysgerminoma and stage I, grade 1 immature teratoma should be treated with staging surgery alone. (Grade C)

Selected patients with stage I GCT other than stage IA dysgerminoma and stage I, grade 1 immature teratoma can be considered for active surveillance following appropriate surgical staging. (Grade C)

Patients with stage II or higher GCT should be offered post-operative BEP chemotherapy. (Grade C)

Unresectable ovarian GCT should be offered primary chemotherapy followed by surgery. (Grade C)

Primary chemotherapy may also be considered for those with advanced germ cell tumours where debulking surgery may not conserve fertility. (Grade D)

All ovarian GCT should be monitored for recurrence for 10 years. (Grade C)

Patients should be counselled regarding fertility post-treatment and advised to avoid pregnancy for 2 years after treatment. (Grade D)

Recurrent ovarian GCT should be offered further chemotherapy +/− surgery as determined by an MDT specialising in the management of such tumours. (Grade C)

Germ cell tumour pathology

WHO classification of germ cell tumours (WHO 2020) [534]

Germ cell tumour.

- Dysgerminoma
- Embryonal carcinoma
- Yolk sac tumour
- Non-gestational choricoarcinoma
- Mature teratoma
- Immature teratoma
- Mixed germ cell tumour

Monodermal teratomas and somatic-type tumours arising from a dermoid cyst.

- Struma ovarii (benign and malignant)
- Ovarian carcinoid
- Neuroectodermal type tumours
- Monodermal cystic teratomas
- Somatic neoplasms arising from teratoma

Germ cell-sex cord stromal tumours.

- Gonodoblastoma
- Germ cell-sex cord stromal tumours (unclassified)

Clinical presentation of malignant ovarian germ cell tumours

These usually present in young females, most are under the age of 30 years [535]. The commonest presenting symptoms are abdominal pain and a palpable pelvic or abdominal mass (85 %), while a few (10 %) may present with acute symptoms due to ovarian torsion, haemorrhage, or rupture. A small proportion may exhibit isosexual precocity or false positive pregnancy test, due to human chorionic gonadotropin (hCG) production by the tumour. These tumours may demonstrate biologic activity with the production of excess endogenous hormones, most common being LDH, AFP and hCG [536]. Other uncommon serum markers include CA19-9, CA125 and SCC antigen. These can be helpful from a diagnostic standpoint, but also help monitor response and for post-treatment surveillance.

Macroscopic examination and histological sampling of MOGCT

Malignant ovarian germ cell tumours (MOGCT) are usually large tumours (average diameter 15 cm) and may be completely solid or may have cystic component/variegated appearance. These tumours should be extensively sampled (1 block/10 mm) and all the different areas, including necrotic areas need sampling. Most are unilateral, but dysgerminomas and teratomas may be bilateral.

Morphology and immunohistochemical features of dysgerminoma

Dysgerminomas, in addition to above clinical findings may presents with elevated serum LDH or hCG levels. Rarely paraneoplastic hypercalcemia may be seen. Most tumours are unilateral, but 5–15 % may be bilateral and the possibility of gonadal dysgenesis needs to be excluded [537]. Histology is characteristic with large and monotonous tumour cells, separated by fibrous septae showing infiltration by chronic inflammatory cells, mainly lymphocytes. The tumour cells are seen in sheets and nests, pseudoglandular or corded/trabecular pattern (mimicking carcinoid). These have well-defined cell borders, large 'squared-off' nuclei with prominent nucleoli and numerous mitoses. Variations in morphology may include extensive granulomatous septal inflammation, presence of hCG positive syncytiotrophoblasts among the tumour cells or scant inflammation.

On IHC, tumour is positive for OCT-3/4, SALL-4, NANOG, PLAP, CD-117, LIN28 and D2-40. Focal cytokeratin expression may be seen but EMA is negative. It is negative for glypican-3, CD30 and AFP [538–541].

C-KIT mutation is present in a third to half of dysgerminomas and chromosome 12 abnormalities may be seen in up to 80 % of the cases.

Morphology and immunohistochemical features of Embryonal carcinoma

EC is extremely rare as a pure MOGCT and is uncommon component of mixed GCT. Most frequently it is seen in association with YST or gonadoblastoma but can be seen with other components. This occurs mainly in children and young females (average age 14 years) and presents as palpable mass or pain, precocious puberty, menstrual abnormalities or false-positive pregnancy test. Serum AFP and hCG levels may be raised.

On microscopy, the tumour cells are arranged in solid sheets, nest, pseudoglandular/ papillary arrangements and cleft like spaces lined by undifferentiated polygonal to cuboidal cells. Loose myxoid, fibrous or cellular spindle stroma with prominent blood vessels may be seen around the tumour cells. Syncytiotrophoblastic giant cells (STGC) may be seen associated to tumour cells or isolated in the stroma. Necrosis and haemorrhage are usually seen. IHC is positive for AE1/3,CD30, OCT-3/4, SALL-4 and LIN28, and may show positive staining with SOX2, hCG (in STGC) and AFP. IHC is negative for EMA, CD117 and D2-40; i(12)p or 12p amplification are commonly seen in EC.

Morphology and immunohistochemical features of yolk sac tumour (YST)

Yolk sac tumours (YST) occur mainly in children and young females. Most patients are in their second to third decade and is rare in women over 40 years. Presentation is commonly with abdominal pain, abdominal/pelvic mass or with symptoms of an acute abdomen secondary to torsion. Serum AFP and CA-125 levels are raised in most patients.

YST are characterized by wide multitude of histological patterns (Microcystic/reticular, endodermal sinus/ festoon, solid, alveolar-glandular, parietal, papillary, polyvesicular vitelline, hepatoid, myxomatous) within the same tumour, causing potential diagnostic difficulties. Tumour cells are cuboidal with clear or amphophilic cytoplasm, hyperchromatic small- to medium-sized primitive appearing nuclei, usually prominent nucleoli and abundant mitotic activity. Eosinophilic PAS positive, diastase resistant hyaline globules and Schiller-Duval Bodies (glomeruloid structures) are prominent, although not characteristic, findings in YST.

On IHC, YST are positive with broad spectrum cytokeratin and are usually negative with CK7 and EMA. YST are usually diffusely positive for Glypican-3 and SALL-4 and focally with AFP. Lin28, CD117 and IMP-3 are expressed in varying percentages. Endodermal (somatic) differentiation may show CDX-2 (intestinal), TTF-1 (respiratory/ foregut) and Hepar-1 (hepatoid) positivity. Endometrioid glandular differentiation, however, is negative for ER and PR. CD30, NANOG and OCT-3/4 are usually negative.

Rarely, in older women, YST can be seen in association with somatic malignancies, mainly endometrioid, clear cell or mucinous neoplasms [542,543]. In this setting the YST is usually somatic and not germ cell in origin.

Morphology and immunohistochemical features of immature teratoma (IT)

IT usually present in first three decades of life and rarely occur in postmenopausal women. Most are unilateral and present as pelvic mass. 10–15 % may coexist with a contralateral mature cystic teratoma. Serum AFP may be elevated in tumours with a hepatoid component. These may produce LDH and rarely steroid hormones.

The tumour is usually large (average diameter 18 cm) and predominantly solid and fleshy, with variable cystic, necrotic and haemorrhagic component. Foci of cartilage, bone, hair and cysts filled with seromucinous, colloid or fatty material may be seen in the background. These

tumours are prone to perforate through the capsule.

Histology shows haphazard admixture of mature and immature elements, with the former usually predominating. Amongst the immature elements, neuroectodermal tissue (tubules, trabeculae, rosettes or sheets and nests of neuroblasts) is essential for diagnosis and grading, although immature mesodermal, and less commonly ectodermal, tissue may accompany. Two methods of grading exist based on the aggregate amount of the immature neuroectoderm in any given slide. The grading system also applies to metastatic sites. These can be graded as Grade 1–3, or as low grade (G1) and high grade (G2 and G3) [544].

Diagnosis of IT is mainly morphological and there is no specific IHC marker. However, neuroectoderm may stain positive for SOX-2, SALL-4, glypican and CD99. SALL-4 and AFP staining can be seen in 'enteroblastic' glands. Glial differentiation can be highlighted by GFAP and immature cartilage usually stains with CD34 and bcl-2 [538,539,545].

Molecular genetic: most pure IT typically do not exhibit i(12p) or gain of 12p while this is often present in IT component of mixed GCT [546].

Morphology and immunohistochemical features of non-gestational choriocarcinoma

NG-CC is seen mainly in children and young adults who present with symptoms similar to Embryonal carcinoma. Clinically, ectopic pregnancy may be a consideration in view of hCG production, positive pregnancy test and absence of intra-uterine conceptus.

NG-CC is a haemorrhagic and necrotic tumour composed of two cell population. These include mononuclear (cyto and intermediate trophoblast) and multinucleate syncytiotrophoblast giant cells (STGC) with IHC positive for cytokeratin, inhibin, GATA-3, CD10 and hCG. Intermediate cytotrophoblast may express Mel-CAM (CD146), hPL and less commonly p63 and PLAP [547].

Molecular genetics: molecular genotyping of short tandem repeat (STR) DNA sequences is the gold standard for differentiating NG-CC from gestational choriocarcinoma, as the genome in NG-CC reflects that of the host and no non-maternal/paternal component is identified.

Morphology and immunohistochemical features of mixed germ cell tumours

Most mixed tumours (80 %) contain two malignant germ cell components, while the rest may show three or more. There is no minimum amount or cut-off percentage for second component. The most frequent components of mixed GCT include dysgerminoma and YST followed by IT, choriocarcinoma and embryonal carcinoma. It is important to mention any mixed components and estimate their relative percentages, as the presence of more malignant components affects the therapeutic approach and the prognosis. A detailed and thorough examination of all GCTs should be performed and the right panel of immunocytochemistry is directed on areas with different morphological appearances. A significant proportion of mixed GCT show abnormalities of chromosome 12 or may arise in dysgenetic gonads with abnormal karyotype.

Morphology and immunohistochemical features of mature teratoma

Mature teratoma account for 20 % of all ovarian neoplasms encountered in pathology and mostly occur in women of reproductive age. These are essentially benign and in rare cases may be associated with malignant transformation.

Most are cystic although rarely these may be solid. Solid areas must be thoroughly sampled to exclude malignant transformation. Histologically, these show derivatives of ectoderm, mesoderm and endoderm. Some mature teratomas with prominent glial component may be associated with anti-NMDAR encephalitis, which should be surgically removed for treatment.

Morphology and immunohistochemical features of Monodermal teratoma and somatic type tumour arising from a dermoid cyst

Monodermal teratomas are solely or predominantly (>50 % of the teratoma) composed of one single type of tissue. The various types of monodermal teratomas include:

1. *Struma ovarii:* composed entirely/ predominantly of thyroid tissue. This is the most common type of monodermal teratoma. Most are clinically benign but rarely these may undergo malignant transformation (papillary, follicular or anaplastic thyroid carcinoma) or may be associated with carcinoid tumour.
2. *Ovarian Carcinoid:* these are well-differentiated neuroendocrine tumours and have an uncertain malignant potential. Most are seen in post-menopausal women [548]. Most are solid, but some may appear as a solid nodule within a cystic teratoma. Histology shows mainly four subtypes: insular, trabecular, stromal, and mucinous carcinoid. The cells have salt-and-pepper chromatin, with or without cytoplasmic granules and stromal hyalinisation. These characteristically express neuroendocrine markers. The prognosis is usually excellent except for poorly differentiated mucinous and insular carcinoids.
3. *Neuroectodermal type tumours:* these are malignant tumours, typically seen in younger patients (median age 23 years), are frequently associated with a teratoma [549]. Histologically the tumours are characterised by proliferation of small blue round cells with variable neural/ glial differentiation. Some tumours may be differentiated (central-type tumours) while others are less differentiated. Differentiated tumours (e.g. ependymoma, astrocytoma, oligodendroglioma, or neurocytoma) have a better prognosis than less differentiated (medulloblastoma, ependymoblastoma, medulloepithelioma, or glioblastoma) tumours.
4. *Monodermal cystic teratomas:* These are composed of either ectodermal or endodermal derivatives excluding the above three and are usually benign.
5. *Somatic neoplasms arising from teratoma:* These are malignant tumours and typically occur in older women (average age 55 years). Any somatic tumour (benign or malignant) may originate in a mature teratoma. Amongst the malignant transformations seen, cutaneous tumours (squamous cell carcinoma, melanoma, basal cell carcinoma, adnexal tumours etc) are the most frequent, followed by adenocarcinomas and sarcomas [550–554]

Primary treatment of GCT

Prior to surgery, patients should undergo a CT scan of thorax, abdomen, and pelvis, if GCT is suspected on markers or other imaging.

GCT surgery

Primary cytoreductive surgery is the mainstay of diagnosis and treatment of early-stage disease; for higher stage disease, delayed primary surgery has not been evaluated and should not be considered unless the disease is unresectable at diagnosis (see below). Given the age distribution of GCT, most patients are likely to not have completed their family, and FSS should be offered. This includes USO, omentectomy, peritoneal sampling (or excision of all visible disease) [555]. Retroperitoneal lymph nodes should only be dissected if macroscopically abnormal [556]. For patients whose family is complete, contra-lateral salpingo-oophorectomy and hysterectomy can be offered in addition. Given the high chemo-sensitivity of GCT, where the contra-lateral ovary is involved, but the patient wishes to retain fertility, a careful discussion of fertility options should be had; this should include leaving at least part of the affected ovary.

GCT systemic therapy

Patients with stage IA dysgerminoma and stage I, grade 1 immature teratoma have an excellent prognosis without adjuvant chemotherapy, and surgery as the sole modality has been the standard of care for many years [557]. The risk of recurrence is 15 % for stage IA dysgerminoma and 17 % for stage I grade 1 immature teratoma, these patients are typically cured at recurrence [558]. The prognosis of most other stage I GCT is also excellent, and cure rates at recurrence during surveillance is

high. In addition, immature teratoma does not appear particularly chemosensitive and outcomes are not influenced by grade [558,559]. Data from paediatric patients with female GCT also suggest that stage I GCT can be managed with surgery and active surveillance, reserving chemotherapy for disease recurrence [560]. Therefore, with the exception of non-gestational choriocarcinoma, a discussion about the benefits and toxicities of 3 cycles of adjuvant BEP compared to surveillance is warranted in all patients with stage I GCT.

If patients opt for active surveillance, this requires frequent attendances and tests (see below). Patients who might struggle to adhere to this intensive active surveillance strategy may be better served by treatment with adjuvant BEP.

BEP has been the mainstay of therapy in these patients for many years, many cohort studies demonstrating high activity [557], although randomised data are lacking. The optimal number of cycles has not been established, but three cycles of adjuvant therapy are recommended, where NMRD remains after surgery, for those with stage II disease, and low risk stage III and IV disease defined by the International Germ Cell Cancer Collaborative Group prognostic model, modified for ovarian GCT [561].

Typically, BEP is given over 5 days; a 3-day version has been described [562], but should only be given if compliance is thought to be an issue as it has not been directly compared to standard BEP. Patients over 40 years or those with pre-existing lung disease should be offered four cycles of EP due to the known pulmonary toxicity of bleomycin. Patients with dysgerminoma who are not suitable for cisplatin could receive carboplatin etoposide [563].

The standard of care chemotherapy for patients with unresectable disease at diagnosis remains BEP for four cycles. Based on data from male germ cell cancers, the addition of high-dose chemotherapy and autologous hematopoietic stem-cell rescue is not recommended in this setting [564]. Patients with resectable residual disease post chemotherapy should be offered resection, especially if markers have normalised on chemotherapy. Given the high chemosensitivity of ovarian GCT, in patients with potentially resectable advanced disease can be considered for primary chemotherapy if primary surgery has a high chance of removing fertility and where the patient wishes to retain this. Firm data for this approach are lacking and decisions about sequencing of therapy in any setting should be made in conjunction with a germ cell MDT.

GCT follow-up

Due to the potential for cure even in recurrent ovarian GCT, all patients should be closely monitored for disease recurrence. In the lack of a robust evidence base to support any particular schedule, patients should be followed clinically, supported by AFP, hCG and LDH measurements with a traditional follow-up schedule (every three months for two years, every six months for three years, and then annually for ten years). Not all GCT produce all markers, testing all in every GCT patients ensures the appropriate test is always performed.

Additional imaging can aid the detection of recurrence, particularly in patients with normal markers at diagnosis, but the risk of ionising radiation to a young, likely cured patient needs to be considered.

For patients treated with adjuvant BEP:

- CT scan of abdomen and pelvis at 12 and 24 months. A further CT scan at six months for patients who had a high burden of disease at presentation can be considered.
- No data exist to support the utility of routine chest radiographs (CXR) in in the surveillance of GCT in women. In men, the detection of recurrent GCT by CXR alone when it was not obvious clinically, from markers or routine surveillance scanning, is low at best [565] and CXR should not be routinely performed in female GCT.
- Patients treated with fertility sparing surgery should also be offered a pelvic ultrasound six-monthly for three years for surveillance of the remaining ovary.

For stage I patients not treated with adjuvant therapy:

- These patients should be seen more frequently in the 1st year, we recommend two-monthly with tumour markers.
- Patients with marker negative disease, should have a CT scan of abdomen and pelvis at three months in addition to the CT scan of abdomen and pelvis at 12 and 24 months.
- No routine CXR as above.
- Patients are typically treated with fertility sparing surgery and should be offered a pelvic ultrasound six-monthly for three years.

Patients treated with FSS and adjuvant BEP have a high chance of returning the same pre-chemotherapy menstrual pattern (above 90 %) [566] and the rate of pregnancy is 75 % in those attempting conception [567]. Despite this, where time allows, patients should be offered referral to a fertility service to discuss options. The risk of recurrence appears highest in the first 2 years [555,568] and patients should be counselled against falling pregnant in this time.

Treatment of recurrent GCT

There is no standard therapy for relapsed disease, and entry into a clinical trial should be offered if appropriate. Those with platinum sensitive disease should be re-challenged with platinum containing chemotherapy, options include TIP (paclitaxel, ifosfamide, cisplatin), VIP (etoposide, ifosfamide, cisplatin), although many regimens are recognised [569]. High-dose therapy with stem cell rescue may offer improved outcomes over standard chemotherapy at first relapse [536]; a re-challenge with BEP or EP seems to be less effective at achieving cure in this setting [561]. In platinum-resistant disease, therapy with VAC (vincristine, dactinomycin, cyclophosphamide) [570] or gemcitabine and oxaliplatin [571] can be considered.

Sex-cord stromal tumours

Recommendations

Patients aged between 18 and 24 should be managed jointly between the gynae MDT and the teenage and young adult MDT. (Grade D)

SCST should be classified according to the WHO classification system. (Grade D)

SCST should be considered as a rare cause of any abnormal vaginal bleeding in younger women. (Grade D)

A combination of serum AMH and inhibin B should be used for diagnosis. (Grade D)

Consideration should be given to assessment of endometrial thickness and investigated as per BGCS uterine cancer guidelines. (Grade D)

Patients with Sertoli Leydig Cell tumours should be referred to genetics to exclude DICER1 syndrome. DICER1 and FOXL2 tumour testing could be considered prior to germ line testing, where available. (Grade D)

Adequate staging, with or without fertility preservation, should be carried out in all cases of SCST. (Grade D)

Routine use of adjuvant chemotherapy is not recommended for patients with adequately staged early-stage disease. (Grade D)

There is no role for endocrine therapy in the adjunctive setting. (Grade D)

The role of adjuvant radiotherapy remains poorly defined and is not advised outside of clinical trials. (Grade D)

Surgery remains the mainstay of treatment for advanced or recurrent disease. (Grade D)

Acceptable regimens for systemic therapy may include both CP and BEP. (Grade C)

Aromatase inhibitor therapy is an acceptable treatment for advanced and recurrent recurrent adult granulosa cell tumours

that cannot be treated surgically. (Grade C)

Radiotherapy may have a role for palliation of disease that is not amenable to surgical resection. (Grade D)

Targeted agents may have activity in the treatment of recurrent disease. (Grade C)

Follow-up schedules should be personalised. (Grade D)

Sex cord stromal tumours (SCST) represent a relatively uncommon group of ovarian tumours which span the spectrum from indolent benign lesions to highly malignant neoplasms. They tend to present in a younger age group than other ovarian tumours and are often characterised by symptoms related to excessive hormonal production.

The majority of the evidence available relates to the commonest subtype of SCST, granulosa cell tumours, and care should therefore be taken when extrapolating guidance to other rarer subtypes.

Although SCST can affect women under the age of 18, this guidance relates specifically to women over the age of 18. Young women (aged 18 to 25 years) should ideally be managed with the support of the tumour of young adult (TYA) MDT.

Sex-cord stromal tumour pathology

Sex cord-stromal tumours constitute a heterogeneous group of benign and malignant neoplasms [572,573]. Sex cord-stromal tumours represent approximately 7 % of all primary malignant ovarian tumours [574], which are usually diagnosed at an early stage, and may have late recurrence, as late as 30 years, after the initial diagnosis and treatment. The most important prognostic factor for sex cord-stromal tumours are The International Federation of Gynecology and Obstetrics (FIGO) stage, and tumour rupture [575].

According to the WHO classification [576], these tumours are classified into three main groups; pure stromal tumours, pure sex cord tumours, and mixed sex cord-stromal tumours. Pure stromal tumours include fibromas, thecomas, sclerosing stromal tumours, microcystic stromal tumours, Leydig cell tumours, and steroid cell tumours. Pure sex cord tumours, include granulosa cell tumours, Sertoli cell tumours, and sex cord tumours with annular tubules [572]. Mixed-sex cord-stromal tumours include Sertoli-Leydig cell tumours and sex cord-stromal tumours that have not otherwise been specified [504]. Some sex cord-stromal tumours may have clinical signs of hormone production, including menstrual changes, precocious puberty, hirsutism, and/or virilisation [577].

Pure stromal tumours

Fibroma and fibrosarcoma. Fibromas are typically benign tumours, and this includes cellular fibromas and mitotically active cellular fibromas that may show brisk mitotic activity, but no notable cytological atypia. Some fibromas that show rupture or surface adhesions may be associated with local recurrence [578].

Ovarian fibrosarcoma is an extremely rare and aggressive neoplasm with poor prognosis [578]. Ovarian fibrosarcomas may be associated with naevoid basal cell naevus syndrome or Maffuci syndrome [579]. One case was reported to be associated with DICER1 syndrome [580].

Luteinised thecoma associated with sclerosing peritonitis. Luteinised thecoma with sclerosing peritonitis usually leads to morbidity and mortality caused by intestinal obstruction due to the sclerosing peritonitis, and not due to the ovarian tumour [581].

Sclerosing stromal tumour. Sclerosing stromal tumours represent less than approximately 5 % of all sex cord-stromal tumours, [572] and 70 % are diagnosed in young women of 14–29 years [582]. There is one report of a sclerosing stromal tumour that showed recurrence. This tumour was reported to have capsular breach and significant mitotic activity and necrosis [583].

Microcystic stromal tumour. Microcystic stromal tumours are very rare and present in patients between the ages of 20 and 60 years [584]. There is one case report of tumour recurrence [585].

On immunostaining, microcystic stromal tumours are negative for sex-cord stromal markers (α-inhibin and calretinin) [586], but characteristically show nuclear expression of β-catenin, reflecting somatic exon 3 missense *CTNNB1* mutation, which is a hallmark of most ovarian microcystic stromal tumours [587]. Microcystic stromal tumours may also be associated with familial adenomatous polyposis [582].

Steroid cell tumour. These are tumours composed of steroid cells which show malignant behaviour in approximately one third of cases. Factors predicting malignant behaviour include size > 7 cm, significant mitotic activity, necrosis, haemorrhage, and significant nuclear atypia [588].

Thecoma, signet ring stromal tumour and Leydig cell tumour. Thecoma, signet ring stromal tumour and Leydig cell tumour are almost always benign tumours [504].

Pure sex cord tumours

Granulosa cell tumours. Granulosa cell tumours account for 2–5 % of all ovarian tumours [589,590]. There are two clinically and histologically distinct types of granulosa cell tumours, which are adult granulosa cell tumours and juvenile granulosa cell tumours [591].

Adult granulosa cell tumours. Adult granulosa cell tumours account for approximately 95 % of all granulosa cell tumours, with a peak incidence in women aged 50–55 years [592]. Adult granulosa cell tumours are the most common malignant ovarian tumours that secrete hormones, mainly oestrogen, that may result in endometrial hyperplasia and endometrial carcinoma [593,594]. These tumours are usually considered low-grade malignant tumours with an indolent clinical course and possibility of late relapse [595]. Approximately 70–97 % of adult granulosa cell tumours have a somatic c.402C>G missense point mutation in the *FOXL2* gene [596,597], and which is rather specific marker for adult granulosa cell tumours, that helps in the distinction from other sex cord-stromal tumours [598].

Juvenile granulosa cell tumours. Juvenile granulosa cell tumour represents about 5 % of all granulosa cell tumours [599,600], and usually present in women younger than age 30 (mean age of 13 years) [601]. Clinical presentations of juvenile granulosa cell tumours include precocious pseudopuberty, irregular menstruation, and rarely virilisation [600]. Juvenile granulosa cell tumours have a relatively favourable prognosis [602].

Sex Cord-Stromal tumours with annular tubules. Sex cord-stromal tumours with annular tubules represent 1.4 % of all sex cord-stromal tumour [603], and may be sporadic or associated with Peutz-Jeghers syndrome [604]. Sex cord-stromal tumours with annular tubules associated with Peutz-Jeghers syndrome are mostly benign, while sporadic sex cord-stromal tumours with annular tubules may have malignant potential [605].

Sertoli cell tumours. These are usually benign tumours [504].

Mixed sex Cord-Stromal tumours

Sertoli-Leydig cell tumour. Sertoli–Leydig cell tumours represent less than 0.5 % of all ovarian tumours, [606] and usually present in women under 30 years of age [607]. Sertoli–Leydig cell tumours are associated with both somatic and germline *DICER1* mutations [587]. These tumours may be well, moderately or poorly differentiated. Moderately

and poorly differentiated tumours show malignant behaviour in 10 % and 60 % of cases respectively [608].

Sex cord stromal tumour NOS. Sex cord stromal tumour NOS is a tumour that show no features of one of the definitive tumour types. Some of these tumours are reported to show malignant behaviour [609].

Gynandroblastoma. This is a tumour that shows components of female and male differentiation, most commonly juvenile granulosa cell tumour and Sertoli-Leydig cell tumour. Most are benign, with rarely reported recurrences have been reported [610].

Presentation and diagnosis

Abnormal vaginal bleeding is the commonest single symptom of SCST, often associated with pain, and a palpable abdominal mass [611]. Hirsutism is a less common symptom but should also raise the possibility of SCST, particularly in pre-menopausal women. A significant proportion of cases will be asymptomatic and only diagnosed as an incidental finding.

CA125 is raised in a proportion of cases, most commonly in juvenile type granulosa cell tumours [611]. Despite this the RMI may not be elevated in many cases of SCST and clinical suspicion should override RMI in this situation in determining management.

Studies to assess the performance of imaging modalities for SCST are limited by numbers and the wide variety of tumours seen. There are no head-to-head comparisons of imaging modalities. The addition of colour Doppler appears to improve diagnostic accuracy for ultrasound [612], whilst the combination of T2, DCE and DW imaging provides the greatest MRI resolution [613].

SCST commonly secrete hormones, including oestrogen, which can lead to atypical endometrial hyperplasia and endometrial cancer. Imaging or sampling of the endometrium should be considered if the diagnosis of SCST is suspected and particularly in those women who are considering fertility preserving surgery with conservation of the uterus [614].

Somatic and germline *DICER* mutations are present in up to 60 % of Sertoli Leydig cell tumours [615]. Although reflexive testing is not currently available through the Genomics Test Directory, genetic referral to look for the familial DICER1 cancer predisposition syndrome is recommended [616].

Management of suspected early-stage disease

Surgical staging for SCST should include peritoneal washings, abdominal hysterectomy, bilateral salpingo-oophorectomy and infra colic omentectomy; retroperitoneal lymphadenectomy is not indicated, as there is a low incidence of nodal involvement [617]. Consideration of fertility preservation should be given to all juveniles and women of child-bearing age. Preservation of the uterus and contralateral ovary is considered safe in cases of stage IA disease however cystectomy should be avoided as it appears to be associated with worse outcome than oophorectomy [618]. Fertility-preserving surgery (FSS) for stage IC2 and IC3 disease remains controversial. However, data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database identified 255 adult women with stage I malignant SCST between 1984 and 2013, of whom 161 (63.1 %) underwent FSS, whereas 94 (36.9 %) had definitive surgery (BSO and hysterectomy). Cancer-specific survival ($P = 0.015$), but not overall survival ($P = 0.76$) was superior for women who had definite surgery over a median follow-up period of 104 months [619]. FSS is therefore an option with appropriate counselling and close follow-up. No RCTs have examined the role of minimal invasive surgery, but retrospective series suggest comparable outcomes between a laparoscopic and an open approach [620].

Data are limited, but retrospective series appear to show no benefit to the use of chemotherapy in the adjuvant setting, including stage IC disease [621,622]. Exceptions may include grade 2–3 Sertoli-Leydig cell tumours where limited data suggest there may be benefit to chemotherapy [623] and stage IC2 juvenile granulosa cell tumours. No studies have addressed the role of endocrine therapy as an adjuvant treatment and this can therefore not be recommended.

A single retrospective study suggests a survival benefit associated with the use of adjuvant radiotherapy for patients with granulosa cell tumours [624]. The potential risk of bias for this study is high [625] and further studies are required to confirm this finding and assess toxicity before radiotherapy can be recommended.

Management of advanced-stage and recurrent SCST

Given the relative indolent nature of many SCST, secondary cytoreductive surgery, with the aim of removing all macroscopic disease, remains the most effective management of advanced or recurrent disease. Surgery may need to be repeated on multiple occasions. No benefit has been demonstrated in the use of postoperative adjuvant chemotherapy for granulosa cell tumours [626].

Both paclitaxel/carboplatin (CP) and bleomycin/etoposide/cisplatin (BEP) regimens have been used for the treatment of SCST with evidence of activity for each regimen. Publication of the results of a randomised comparison of the two regimens is awaited, although data for the 63 participants are available on clinicaltrials.gov [627]. These demonstrate median PFS of CP was 27.7 months (95 % CI 11.2 to 41.0 months) compared with BEP of 19.7 months (95 % CI 10.4 to 52.7 months), although serious adverse events were more common in the BEP arm (CP = 34.38 % versus BEP 19.35 %). A single, phase II study, which recruited 36 patients, reported a response rate of 16.7 % and a stable disease rate of 77.8 % to treatment with bevacizumab with acceptable toxicity [628].

Many SCST express hormone receptors and multiple case series have described activity of hormonal agents, specifically aromatase inhibitors (AI). However, the only prospective phase II trial to date reported a high rate of clinical benefit (79 %), but low rate of objective response, suggesting hormonal therapy is a cytostatic agent [629].

Case reports [630] and small case series [631] describe response to radiotherapy for advanced or recurrent disease, which cannot be treated surgically, but no prospective series have been described.

Follow-up of SCST

Given the wide range of clinical manifestations of SCST, variability in malignant potential, and the variety of treatment options, follow up schedules should be personalised, but could range from regular consultant-led hospital follow-up, through nurse-led follow-up, patient-initiated follow-up to discharge. SCST are not currently included in the UK (BGCS) guidance for patient-initiated follow-up [485], but this regimen could be considered for tumours with low risk of recurrence. Factors which should be used to determine the follow-up schedule include grade and stage of the primary tumour, extent of initial surgery, likelihood of treatment related side effects, and patient wishes. Patients who have undergone FSS with conservation of one ovary could be considered for annual transvaginal ultrasound to monitor the remaining ovary. Follow-up can include the use of inhibin B, and AMH (if available), particularly if these were raised preoperatively [632]. European Society of Medical Oncology Guidelines suggests follow up with tumour markers (e.g., inhibin B, AMH) every 6 months starting from the third year, maintained indefinitely, although recognises that the evidence for efficacy is limited [633]. They also generally recommend pelvic ultrasound every 6 months in those patients who have undergone fertility-sparing surgery and note that more complex cross sectional imaging (CT or MRI) should be carried out if clinically indicated, based on symptoms or increase in tumour markers.

There is no direct evidence to support or refute the long-term

negative effect of HRT on granulosa cell tumour survivors, but considering the endocrinologically active character of these tumours, it may be safer not to initiate HRT in those with advanced disease [634].

Frailty, supportive care and survivorship

Recommendations

Interventions based on assessment of patient frailty may improve tolerability and outcome of any medical and surgical intervention. (Grade C)

All ovarian cancer patients should undergo a Health Needs Assessment and End of Treatment summary at each stage of their ovarian cancer treatment. (Grade D)

Frailty

The term frailty describes a distinctive health state which results from ageing associated with a decline in the body's physical and psychological reserves across multiple systems. Around 10 % of people aged over 65 years have frailty, rising to between a quarter and a half of those aged over 85 years [635]. Older people living with frailty are at risk of decompensation and adverse outcomes affecting their physical and mental wellbeing after a stressor event which challenges their health. This is of particular relevance following a diagnosis of cancer and when considering treatment options. Frailty, although distinct, may overlap with disability and co-morbidity.

Multiple tools and indices have been studied to measure frailty in clinical trials [636]. Comprehensive geriatric assessment (CGA) is a multi-system review of frailty, comorbidities, geriatric syndromes, mental health, functional difficulties and social circumstances. It is a four-part clinical process of screening, assessment, intervention and follow-through which has been shown to detect more co-morbidities and functional issues than the standard oncological assessment of performance status.

The time taken to perform a geriatric assessment (GA) in the oncology clinic setting is a practical issue and hence there has been much interest in the development of abbreviated and screening tools. The SIOG consensus on GA states that the key domains in a GA considered to be important are: functional status, fatigue, comorbidities, cognitive impairment and mental health status, social support, nutrition and the presence of geriatric syndromes such as falls. To date, there is no one GA tool that has been recommended over another to reliably predict tolerance to cancer therapy or clinical outcomes. Assessment tools available include patient-completed questionnaires, healthcare professional-led questionnaires and biological factors such as albumin, haemoglobin levels and renal function.

Examples of tools used to measure frailty include the Phenotype Frailty Index, Rockwood Frailty Index and the Clinical Frailty Scale. Abbreviated tools more commonly used in older cancer patients include G8, VES13 and the Edmonton Frailty Scale. Patient self-completed tools include CGA-GOLD [637] and CARG [638]. Further tools that can give more in-depth assessment of specific issues include Charlson Comorbidity Index, Timed up and go test (TUG), mini nutritional assessment, cognitive tests (e.g. clock drawing test, MMSE), mood assessment (e.g. Hospital Anxiety and Depression Scale).

The findings from frailty assessment tools are important to identify patients in need of interventions. Interventions can be introduced by oncology, including review of medication, anaemia treatment, physiotherapy, occupational therapy, dietician referrals. Ongoing clinical trials (NCT04300699; NCT06298877) aim to evaluate frailty assessments in patients with ovarian cancer [639,640].

The geriatric vulnerability score (GVS), validated in an international population, has been shown to be prognostic for overall survival in patients with advanced ovarian cancer [641]. The EWOC-1 randomised trial (80 participants) shows that compared with three-weekly or weekly carboplatin-paclitaxel combination regimens, single-agent carboplatin had poorer survival outcomes in vulnerable (GVS score 3 or higher) older patients (≥70 years) with ovarian cancer [642]. The median PFS was 12.5 (95 % CI, 10.3 to 15.3) months in the carboplatin-paclitaxel three-weekly arm, 4.8 (95 % CI 3.6 to 15.3) months with single-agent carboplatin, and 8.3 (95 % CI 6.6 to 15.3) months with weekly carboplatin–paclitaxel. Median OS was not reached (95 % CI 21.0. to 32.2 months) in the carboplatin-paclitaxel three-weekly arm, 7.4 (95 % CI 5.3 to 32.2) months with single-agent carboplatin, and 17.3 (95 % CI 10.8 to 32.2) months with weekly combination therapy. However, this is a small study and should not be overinterpreted.

Survivorship

Survivorship has been defined by as "living with and beyond cancer" [643]. Women are considered ovarian cancer survivors from the time of diagnosis to the end of life [644]. It has long been recognised that Clinical Nurse Specialists (CNSs) have a pivotal role in supporting patients with many aspects of living with their disease from diagnosis to best supportive care and end of life.

According to Cancer Research UK data, 35 % of women diagnosed with ovarian cancer between 2013 and 2017 are expected to survive 10 years or more [645]. However, the majority of clinical and research focus is on early diagnosis and treatment, not on supportive care and survivorship. Ovarian cancer patients often do not fit neatly into the traditional definition of survivorship. Equally, there has been little distinction as to what survivorship may mean, and the differences in need between patients at different ages and stages of life. Consideration should also be given to individuals from different ethnic and socio-economic backgrounds.

Since ovarian cancer is not a single disease entity, people also may have different supportive care needs depending on their tumour type. Those with advanced stage cancers may need differing support to those with more indolent tumours, such as low-grade cancers or those with borderline ovarian tumours.

Those under 18 years should be managed by paediatric oncology teams, with gynaecological oncology surgeons providing surgical expertise. Close working between MDTs allows personalisation of care and access to all relevant expertise, including support services where necessary.

Determining appropriate strategies for supporting cancer survivorship should be based on three key elements: physical, psycho-social and psychosexual. Evidence suggests, cancer survivorship programmes have proven effective in improving physical function, fatigue, anxiety and depression [646]. The challenge remains to implement this effectively in ovarian cancer where the disease is often multi-faceted. Missing cancer survivorship care dialogues with an unclear purpose of the cancer survivorship care needs assessment can lead to lack of a clear pathway for women who have completed treatment for ovarian cancer.

It is recognised that there are potential cost savings if survivors are effectively able to self-manage, reducing the overall burden on the healthcare system [647].

Since longer-term survivorship care is becoming increasingly important in the overall well-being of people with ovarian cancer, effort should be made to introduce nurse-led survivorship clinics to support holistic and individualised approaches [648].

Lack of an interactive survivorship discussion allows those with ovarian cancer to decide how much they wish to participate with regard to ongoing communication and interactions. Without this dialogue any approach will remain unclear with patients unfamiliar with what support (however, this meets their needs) exists.

Physical impacts

Impact of disease and treatment can have profound and long-lasting effects on women with ovarian cancer. This requires adjustment and ongoing re-adjustment. Physical effects can include bowel and bladder

issues, pelvic pain and menopausal symptoms amongst many. Successful survivorship programs should have a pro-active and patient guided approach to improving quality of life (QoL) with women having guidance to recognise concerning symptoms, supported by a responsive healthcare practitioner, allowing and enabling women to be more active participants in their care and management rather than passive recipients of a traditional clinical follow-up only approach [649].

Treatment-induced menopause may have a significant impact on women with ovarian cancer, not only at a physical level but menopause should be considered at the psychological and psycho-sexual levels when managing ovarian cancer survivors.

Abrupt onset of menopausal symptoms consequent to hypoestrogenemia after cytoreductive surgery or gonadotoxic chemotherapy can induce hot flashes, mood changes, and vaginal dryness or atrophy [650]. While systemic hormone therapy may improve many of the issues, this treatment is not appropriate for all patients given their action on oestrogen receptors. However, other non-hormonal treatments exist, including selective serotonin reuptake inhibitors, antiepileptics, natural remedies, and pelvic floor physical therapy [651].

It is recommended that all ovarian cancer patients should undergo a Health Needs Assessment and End of Treatment summary at each stage of their ovarian cancer treatment. Survivorship should be seen as proactive assessment and management by follow-up care providers, including primary care. In order for this to be meaningful, this assessment should not be seen as tokenistic form filling, but part of a living, active plan to support individual needs [652].

Many women will experience late effects of their cancer treatment which will require continuous and new information about how to best manage them. The challenge is for providers to offer innovative ways of offering such services to those with ovarian cancer, whilst meeting information needs for the whole population, not just English-speaking, computer literate patients. Consideration should be given to online clinics, webinars and face-to-face clinics delivered by CNSs and Cancer Support Workers.

Psycho-Social impact

As far back as 1999, the NHS Executive recognised that there were two key elements to managing individuals with ovarian cancer [168]. This comprised the early detection of recurrent disease, but equally the management of physical and psychological morbidity.

There are many ways in which cancer centres and units should look to meet these needs. There is an increasing emphasis on self-management, but for many people with ovarian cancer this may often feel too remote.

Ovarian cancer survivors often have high levels of depression and anxiety, commonly identifying fear of cancer recurrence (FCR) among their top concerns [653–661]. Ovarian cancer patients have historically been concerned about taking up too much time at clinic appointments with emotional concerns and the literature supports the view that CNSs are supportive with appropriate skills, knowledge and time to help address their needs [657].

Consideration should be given to implementing telephone clinics to support psychological management, although face-to-face appointments may be preferred, especially for those from hardly-reached groups (language and social barriers). Evidence has suggested this should be undertaken by an experienced clinician [484] so as to begin the process of offering personalised, tailored care as is the ambition of the call for evidence in the 2022 NHS Cancer Plan [658].

Cancer units and hubs should seek to implement CNS review (face-to-face and telephone), tailored to patients' individual needs [659]. CNSs with level 2 counselling skills are ideally placed to support patients for assessment and initial management of psychological morbidity [660]. Evidence from breast cancer studies show that in traditional clinical follow-up there is often little time to meet information and psychosocial needs [661]. Nurse-led review can form part of the on-going, iterative process of HNA between both CNS and Cancer Support Worker.

Consideration should be given to aligning with third sector organisations to help support survivorship programmes.

Sexuality/Sexual morbidity impact

Psychosexual issues following ovarian cancer are a common side effect, including increased vaginal dryness, dyspareunia, reduced arousal and desire, altered orgasm and sexual satisfaction, and reduced pleasure [662,663]. Women also can experience psychological challenges around their sexuality in relation to altered body image, femininity, loss of role and infertility [651,664].

Information on possible physical/psychological changes due to surgery and chemotherapy should be given to the patient prior to treatment, and this should include the subject of sexuality, with details of further information resources should the patients need to seek further information if difficulties occur [665,666].

As sexual difficulties may have multifaceted causes including physiological/biological, psychological, interpersonal and socio-cultural factors a joint approach to addressing problems should be adopted, having a multi-disciplinary approach will hopefully allow clinicians the safety to address this topic and refer to on if the issues are beyond their comfort or expertise [663,667].

Assessment and identification of sexual issues by clinicians can be performed efficiently and easily with short validated tools using a style of inquiry which starts by acknowledging how common sexual dysfunction is amongst cancer survivors rather than asking direct questions [667]. Assessment tools/patient reported outcome measures (PROMS) can help to identify sexual difficulties, promote discussions and management of sexual issues [668–675].

If sexual difficulties are present these should be addressed and where possible specific suggestions given, e.g. psychosexual education, use of lubrication during intercourse or vaginal moisturiser [662,663,671–673]. Where available, patients with ongoing difficulties should be referred to psychosexual services especially in women when sexual difficulties are persistent despite appropriate interventions and where there are high levels of individual/couple distress, pre-existing sexual problems and psychological vulnerability prior to diagnosis.

Research priorities

The former NCRI Gynaecological group updated its priorities for gynaecological cancer: https://www.ncri.org.uk/wp-content/uploads/NCRI-Gynaecological-Group-strategic-priorities_FINAL.pdf.

Key areas of interest include:

- Early detection and prevention of ovarian cancer in the general population
- Improved biomarker led treatment options, particularly for the cohort of patients who do not have homologous recombination deficiency and have poorer overall outcomes and reduced responsiveness to PARP inhibitors.
- Therapy options following prior treatment/ progression on a PARP inhibitor.
- The role of immunotherapy in the treatment of ovarian cancer also remains to be clearly defined, and alternative strategies, such as vaccines, are being trialled.
- Platinum resistant ovarian cancer remains an area where improved, less toxic therapies are required.

Research questions in prehabilitation and rehabillitation

An expert consensus group [674] recommended the following areas to advance research in surgical prehabilitation by identifying the role of exercise, nutritional optimization, and psychological stress reduction in

order to increase physiologic reserves in anticipation of surgery:

1. Determine the impact of prehabilitation on physical and psychological health in patients with cancer
   a. which patients are most likely to benefit.
   b. whether prehabilitation can increase surgical candidacy in high-risk patients.
2. Determine the impact of prehabilitation on
   a. health care utilization
   b. perioperative complications.
   c. the metabolic response to surgery.
   d. physical functioning.
   e. timing of recommended oncologic treatment.
   f. adherence to recommended oncologic treatment.
3. Characterize the performance of measures to assess baseline status and evaluate effectiveness of prehabilitation.
4. Identify procedure-specific prehabilitation assessments and interventions for specific patient populations.

The World Health Organization (WHO) defines rehabilitation as a set of measures that assist individuals, who experience or are likely to experience disability, to achieve and maintain optimum functioning in interaction with their environments [675].

Recent research has demonstrated that there is a huge unmet need for rehabilitation programs along the continuum of the cancer trajectory [676].

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Declaration of competing interest

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Appendix A. FIGO ovarian, fallopian tube, and peritoneal cancer staging system 2021

Table 6
FIGO ovarian, fallopian tube, and peritoneal cancer staging system 2021..

Stage	Description	
I	Tumour limited to the ovaries or fallopian tubes	
	IA	Tumour limited to one ovary (capsule intact) or fallopian tube; no tumour on ovarian or fallopian tube surface; no malignant cells in ascitic fluid or in peritoneal washings
	IB	Tumour limited to one or both ovaries (capsule intact) or fallopian tubes; no tumour on the surface of ovary or fallopian tube; no malignant cells in ascitic fluid or in peritoneal washings
	IC	Tumour limited to one or both ovaries or fallopian tubes, plus any of the following:
	IC1	Surgical spill
	IC2	Capsule ruptured before surgery or tumour on the surface of the ovary or fallopian tube
	IC3	Malignant cells in ascitic fluid or in peritoneal washings
II	Tumour involving one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer	
	IIA	Extension and/or implants on the uterus, fallopian tubes, and/or ovaries
	IIB	Extension and/or implants on other pelvic intraperitoneal tissues
III	Tumour involving one or both ovaries or fallopian tubes or peritoneal cancer with microscopically confirmed peritoneal metastases outside the pelvis and/or metastasis to the retroperitoneal lymph nodes	
	IIIA1	
	Positive retroperitoneal lymph nodes only (histologically proved)	
	IIIA1(i)	Metastasis $\leq$ 10 mm in largest dimension
	IIIA1(ii)	Metastasis $>$ 10 mm in largest dimension
	IIIA2	Microscopic extrapelvic (beyond the pelvic brim) peritoneal involvement, with or without positive retroperitoneal lymph nodes
	IIIB	Macroscopic peritoneal metastases that extend beyond the pelvis and that are $\leq$ 2 cm in largest dimension, with or without positive retroperitoneal lymph nodes
	IIIC	Macroscopic peritoneal metastases that extend beyond the pelvis and are $>$ 2 cm in largest dimension, with or without metastasis to retroperitoneal lymph nodes (includes extension of tumor to the capsule of the liver and spleen without parenchymal involvement of either organ)
IV	Distant metastases excluding peritoneal metastases	
	IVA	Pleural effusion with positive cytology
	IVB	Parenchymal metastasis and/or metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity)

Adapted from [678]

16.3. Adjusted Aletti surgical complexity score (SCS)

Table 7
Adjusted Aletti surgical complexity score (SCS) procedure score. .

Procedure	Score*
Total hysterectomy, bilateral salpingo-oophorectomy	1
Omentectomy	1
Pelvic lymphadenectomy	1
Para-aortic lymphadenectomy	1
Pelvic peritoneum stripping	1
Abdominal peritoneum stripping 1	1
Recto-sigmoidectomy with anastomosis (anterior resection)	3
Large bowel resection	2
Diaphragm stripping/resection 2	2
Splenectomy 2	2
Liver resection/s 2	2
Small bowel resection/s 1	1
Groin lymphadenectomy 1	1
Nephrectomy 1	1
Partial Gastrectomy 1	1

*Points only achieved in the context of systematic regional treatment.
Adapted from [337,338]

Table 8
Adjusted Aletti surgical complexity score (SCS) groups. .

Complexity score groups Group	Overall surgical complexity	SCS total score
1	Low	≤3
2	Intermediate	4–7
3	High	≥8

Adapted from [337,338]

OVARIAN CANCER - OPERATIVE REPORT

Date of Surgery:		**1st Surgeon:**	
Duration of the procedure (minutes):		**2nd Surgeon:**	
Estimated Blood Loss (cc):		**3rd Surgeon:**	
Nº RBC units transfused:		**Anaesthetist:**	

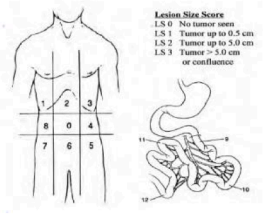
Type of Tumour:	Primary/ Recurrent	**Aim of Surgery:**	Cytoreduction/ Diagnosis/ Staging/ Emergency/ Palliative
Ca-125 UI/ml at Surgery:		**Performance Status:**	
Suspected stage IV?	Yes/ No	**If Yes, please select:**	Pleura/Lung/ Skin/Extra abdominal lymph nodes/ Abdominal wall/ Liver Parenchyma/ Spleen Parenchyma/ Other

Surgical Approach and Findings

Approach:	Open (Y75.2)/ laparoscopic (Y75.2)	**Type of procedure:**	Primary CRS/ further first-line CRS after recent primary surgery/ Primary Surgical Staging/ Re-staging after previous surgery/ Interval CRS after NACT/ 2ry CSR/ 3rd CRS/ 4th CRS/ Diagnostic procedure-biopsies/ Emergency procedure
Volume of Ascites:	No ascites/ <500 ml/ >500 ml	**Frozen Section Diagnosis:**	
Frozen Section:	Yes/ No		

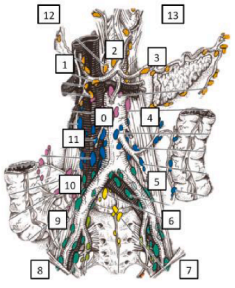
Tumour involvement

Right ovary		Uterus		Right gutter		Small bowel mesentery		Liver parenchymal		Celiac nodes	
Left ovary		Bladder/ ureter		Left gutter		Large bowel mesentery		Lesser omentum		Abdominal wall	
Right tube		Sigmoid-Rectum		Small bowel		Paraaortic nodes		Stomach		Skin	
Left tube		Recto-vaginal septum		Omentum		Right diaphragm		Pancreas		Pericardio-phrenic nodes	
Douglas		Pelvic wall		Large bowel		Left diaphragm		Spleen		Inguinal nodes	
Vagina		Pelvic nodes		Appendix		Liver surface		Hepatic hilum nodes			
Specify other:											



PERITONEAL CANCER INDEX

	Pre	Post
0 Central		
1 Right upper		
2 Epigastrium		
3 Left upper		
4 Left flank		
5 Left lower		
6 Pelvis		
7 Right lower		
8 Right flank		
9 Upper jejunum		
10 Lower jejunum		
11 Upper ileum		
12 Lower ileum		
PCI		



+: Suspicious or Positive
R+: Residual disease
R0: No residual disease

	+	R+	R0
0 Interaortocava / preaort.			
1 Porta Hepatis			
2 Celiac Axis			
3 Suprarenal/ Splenic			
4 Left aortic			
5 Left common iliac			
6 Left ext iliac			
7 Left inguinal			
8 Right inguinal			
9 Right ext iliac			
10 Right common iliac			
11 Pre-Paracava			
12 Right cardio phrenic			
13 Left cardio phrenic			

Surgical Procedures (Complexity score) (OPCS Code 4.2)

Hysterectomy (1) (Q07.4)		Pelvic nodes (1) (T87.9)		Resection lesser omentum (T36.1)		Liver capsule resection (J02.9)	
Unilateral salpingo oophorectomy (1) (Q23.1)		Peritonectomy gutters (1) (T31.8, Y05.2, Z53.7)		Partial gastrectomy (G28.9)		Atypical Liver resection (2) (J02.9)	
Bilateral salpingo oophorectomy (1) (Q22.1)		Paraaortic nodes (1) (T87.5)		Celiac axis (T87.5)		Partial hepatectomy (2) (J02.9)	
Small bowel mesentery (T38.1)		Small bowel resection (1) (G69.3)		Hepatic hilum nodes (T87.9)		Cholecystectomy (J18.3)	
Ureteral resection (M18.9)		Large bowel resection (2) (H08.1)		Diaphragmatic stripping (2) (T31.8, Y05.2, Z53.7)		Peritonectomy POD (1) (T31.8, Y05.2, Z53.7)	
Colorectal resection (H12.2)		Appendicectomy (H02.4)		Diaphragmatic resection (T17.9)		Inguinal nodes (T85.5)	
Partial cystectomy (M35.9)		Infracolic omentectomy (T36.1)		Splenectomy (2) (J69.9)		Pericardiophrenic nodes (T87.9)	
Pelvic peritonectomy (1) (T31.8, Y05.2, Z53.7)		Radical omentectomy (T36.1)		Partial pancreatectomy (J57.9)		Abdominal wall resection (T31.8, Y05.2, Z53.7)	
Rectosigmoidectomy (H33.5)		Rectosigmoid anastomosis (3) (H33.6)		Other colonic anastomosis (H08.1)			
Other:							

Fig. 3. Standard intra-operative reporting tool (adapted and with thanks to Phil Rolland and Jonathan Frost).

No. Anastomoses		Residual small bowel (cm):		Type:	End colostomy (H15.2)	
		Stoma Formation: Yes / No			Loop colostomy (H15.1)	
					Ileostomy (G74.2)	

Any comment that has not been specified:

Surgical complexity scoring (Only count TAH or USO/ BSO not both)					
1 (low) 3 or fewer		2 (intermediate) 4-7		3 (high) 8 or more	

Residual Disease		
Residual disease (*Intra-abdominal*):	NMRD/ SVRD (0.1-0.5 cm)/ SVRD (0.6-1 cm)/LVRD (>1 cm)	**Location/size of residual disease:**
Residual disease *(Extra-abdominal):*	NMRD/ SVRD (0.1-0.5 cm)/ SVRD (0.6-1 cm)/LVRD (>1 cm)	**Reason of Residual:**

Post Operative Care

Severe complications during the operation: None
ICU Admission: Yes/ No
Drain/s: (number and location)

Post Operative Plan

Date of completion of this operative report:
Operative Report filled by

Fig. 3. (*continued*).

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejogrb.2024.06.025.

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Glossary of abbreviations

AFP: alpha fetoprotein
AI: aromatase inhibitor
AMH: anti-mullerian hormone
APAE: Advanced Practitioner Registered Nurse-led preoperative assessment and education clinic
BEP: bleomycin 30 mg (d2, 9, 16), etoposide 500 mg/m^2 and cisplatin 100 mg/m^2, given over 5-days
BRCA: breast cancer gene
BOT: Borderline ovarian tumours
BSO: bilateral salpingo-oophorectomy

CA125: cancer antigen 125
CA19-9: Carbohydrate antigen 19–9
CCC: clear cell carcinoma
CGA: Comprehensive geriatric assessment
CNS: clinical nurse specialist
COCP: combined oral contraceptive pill
CRS: cytoreductive surgery
CSG: cancer susceptibility gene
Cytoreduction: surgery to remove visible tumour deposits – also called 'debulking' since a true R0 resection (>1 mm tumour-free margin) is not possible in advanced ovarian cancer
EOC: epithelial ovarian cancer
EP: etoposide 500 mg/m^2 and cisplatin 100 mg/m^2, given over 5-days
ERAS: enhanced recovery after surgery
FCR: fear of cancer recurrence
FDR: first degree relative
FSA: frozen section analysis
FSS: Fertility-sparing surgery
GCT: germ cell tumour, includes dysgerminoma and non-dysgerminoma
hCG: human chorionic gonadotrophin
HGSC: high grade serous cancer
HRT: hormone replacement therapy
IVF: in vitro fertilisation
LVRD: large volume residual disease (visible residual disease deposits over 1 cm diameter – often referred to as 'sub-optimal' cytoreduction)
ICRS: interval debulking surgery – surgery after a period of NACT
IFRT: involved field radiotherapy
IMRT: intensity modulated radiotherapy
IP: intra-peritoneal
LDH: Lactate dehydrogenase
LGSOC: Low Grade Serous Ovarian Cancer
MDT: multi-disciplinary team
MOGCT: Malignant ovarian germ cell tumours
MMR: mis-match repair
NACT: neoadjuvant chemotherapy
NG-CC: Non-Gestational choriocarcinoma
NICE: National Institute of Health and Care Excellence
NMRD: no macroscopic residual disease (often erroneously referred to as R0 or complete cytoreduction)
OBS: opportunistic bilateral salpingectomy
OCAC: Ovarian Cancer Association Consortium
OCAFP: National Ovarian Cancer Audit Feasibility Pilot
OEC: Ovarian endometrioid carcinoma
OS: overall survival
PARP: Poly (ADP-ribose) polymerase
PCRS: primary cytoreductive surgery (a.k.a primary or upfront debulking surgery – PDS)
PFI: platinum-free interval
PFS: progression free survival
PID: pelvic inflammatory disease
PRS: polygenic risk score
PV: pathogenic variant
QoL: quality of life
RCOG: Royal College of Obstetricians and Gynaecologists
RCT: randomised controlled trial
RMI: risk of malignancy index
ROCA: Risk of Ovarian Cancer Algorithm
RRESDO: Risk reducing early salpingectomy and delayed oophorectomy
RRSO: risk reducing salpingo oophorectomy
SBRT: Stereotactic body radiotherapy
SCRS: Secondary cytoreductive surgery
SCS: Surgical complexity score
SCST: Sex cord stromal tumours
SDS: secondary debulking surgery (a.k.a. secondary CRS)
SEE-FIM: Sectioning and Extensively Examining the FIMbria
SEER: National Cancer Institute Surveillance, Epidemiology, and End Results database
SNP: single nucleotide polymorphism
SRS: stereotactic radiosurgery
STIC: serous tubal intraepithelial carcinoma
SVRD: small volume residual disease (visible residual disease with deposits up to 1 cm diameter – often referred to as 'optimal' cytoreduction)
TAH: total abdominal hysterectomy
TFI: treatment free intervals
UCRS: upfront cytoreductive surgery (a.k.a upfront debulking surgery – UDS)
USO: unilateral salpingo-oophorectomy
WAR: whole abdominal radiotherapy
YST: yolk sac tumour