Contemporary Issues in Cancer Imaging

Cancer of the Ovary



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Rodney H. Reznek

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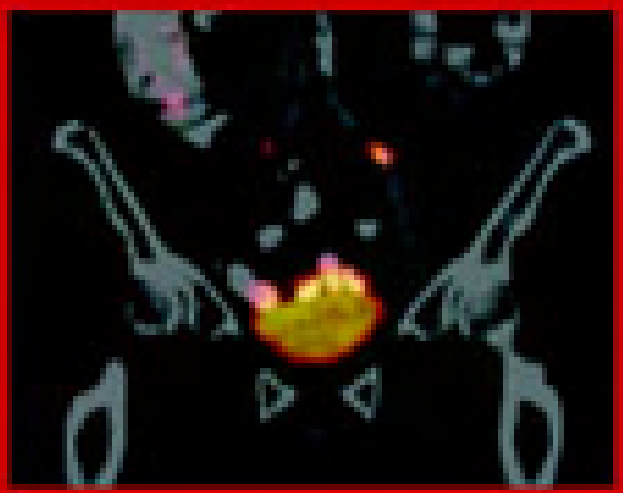

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Cancer of the Ovary

Ovarian cancer is not only the commonest but also the most lethal gynaecological malignancy, partly because the majority of patients present with advanced disease. Nevertheless, the management of patients with ovarian neoplasms has changed substantially recently, with improved survival due to better screening strategies, major advances in chemotherapy and the constantly evolving role of surgery.

Central to these advances has been the development and application of imaging in diagnosis, staging and follow-up. All forms of imaging play a critical role not only in the day-to-day management of the patient but also in the development of future strategies. This volume provides a detailed review of all relevant imaging modalities and treatment options, enhancing understanding of the role of imaging for all involved in patient care.

About the series

Each volume in *Contemporary Issues in Cancer Imaging – A Multidisciplinary Approach* is edited by an expert guest editor with contributions from all members of the multidisciplinary team, bringing together expertise from many specialities to promote the understanding and application of modern imaging in overall patient management.

Forthcoming titles in the series:

Colorectal Cancer
Lung Cancer
Carcinoma of the Kidney
Carcinoma of the Esophagus
Carcinoma of the Bladder

Contemporary Issues in Cancer Imaging

A Multidisciplinary Approach

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Series Foreword

Imaging has become pivotal in all aspects of the management of patients with cancer. At the same time it is acknowledged that optimal patient care is best achieved by a multidisciplinary team approach. The explosion of technological developments in imaging over the past years has meant that all members of the multidisciplinary team should understand the potential applications, limitations and advantages of all the evolving and exciting imaging techniques. Equally, to understand the significance of the imaging findings and to contribute actively to management decisions and to the development of new clinical applications for imaging, it is critical that the radiologist should have sufficient background knowledge of different tumours. Thus the radiologist should understand the pathology, the clinical background, the therapeutic options and prognostic indicators of malignancy.

Contemporary Issues in Cancer Imaging — A Multidisciplinary Approach aims to meet the growing requirement for radiologists to have detailed knowledge of the individual tumours in which they are involved in making management decisions. A series of single subject issues, each of which will be dedicated to a single tumour site, edited by recognised expert guest editors, will include contributions from basic scientists, pathologists, surgeons, oncologists, radiologists and others.

While the series is written predominantly for the radiologist, it is hoped that individual issues will contain sufficient varied information so as to be of interest to all medical disciplines and to other health professionals managing patients with cancer. As with imaging, advances have occurred in all these disciplines related to cancer management and it is our fervent hope that this series, bringing together expertise from such a range of related specialties, will not only promote the understanding and rational application of modern imaging but will also help to achieve the ultimate goal of improving outcomes of patients with cancer.

Rodney Reznek
London
Janet Husband
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Preface to Cancer of the Ovary

Ovarian cancer is not only the commonest but also the most lethal gynaecological malignancy, partly because the majority of patients present with advanced disease. Nevertheless, as is true for so many cancers, the management of patients with ovarian neoplasms has changed substantially over the years. Several factors have contributed to this: for example, major advances in chemotherapy have resulted in improved survival; the role of surgery is constantly evolving and being refined. Many challenges are being addressed in order to lessen the devastating effects of advanced disease: screening strategies are being introduced and detection of early stage disease may offer an opportunity to reduce mortality. Also, a better understanding of the interactions between environmental and molecular biological events that cause or protect against ovarian cancer may lead to clear clinical benefits in prevention, early detection and treatment of the disease.

There is little doubt, however, that central to these advances has been the development and application of modern imaging, whether it be in diagnosis, staging or follow-up. All forms of imaging, including ultrasound, MRI and CT, play a critical role not only in the day-to-day management of the patient but also in the development of future strategies. Position emission tomography may also in future play a role.

This issue of *Contemporary Issues in Cancer Imaging — A Multidisciplinary Approach* deals with all these important developments. Increasingly, there is a need for the radiologist to understand the clinical issues that prompt the need for imaging. Equally, it is essential that clinicians understand the contribution that imaging can make to the care of the patient. I hope that, in keeping with the ethos of this series, bringing together the contributions of experts in each of these disciplines will promote a better understanding of the role of imaging for all involved in the management of patients with ovarian cancer.

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Epidemiology of Ovarian Cancer

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Introduction

Primary carcinoma of the ovary is the fourth most common cancer among women in developed countries. In 1999, almost 7,000 new cases were reported in the United Kingdom, which equates to a lifetime risk for women of 2%. Ovarian cancer is also the most common cause of death from a gynaecological malignancy – there are about 4,500 deaths from the disease in the UK every year [1]. Worldwide, ovarian cancer incidence rates vary widely between different geographic regions and ethnic groups. The highest incidence is in Northern Europe; the lowest incidence is in Japan (Fig. 1.1). As with other cancers, there are notable increases in risk in populations that migrate from a country with low risk to a country of higher risk, indicating a possible role for dietary and environmental factors. The purpose of this article is to review the epidemiological, lifestyle and genetic factors that may be responsible for the variations in ovarian cancer risks.

Genetic Epidemiology

Familial Risks

The most significant risk factor for ovarian cancer is a family history of the disease. A meta-analysis of data from 15 case-control and cohort studies estimated that the relative risk of developing ovarian cancer for women with a single first-degree relative affected with ovarian cancer is 3.1 (95% CI = 2.6–3.7) [2]. Based on ovarian cancer incidence rates typical in northern Europe and North America,

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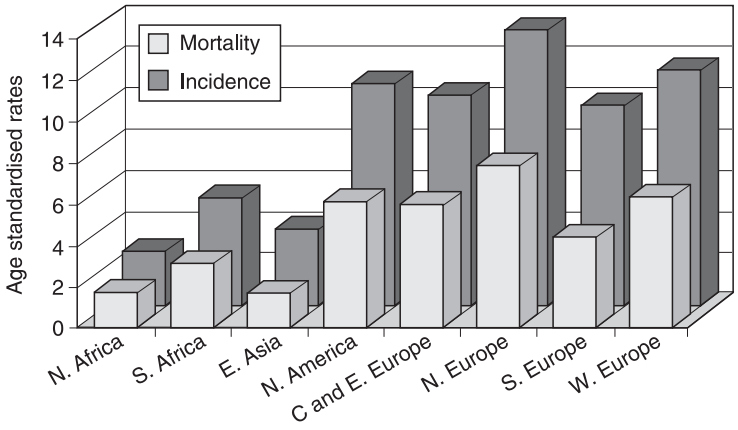

Figure 1.1 Geographical variation in incidence and mortality rates for epithelial ovarian cancer: data from the GLOBOCAN 2002 database project hosted by the Descriptive Epidemiology Group at the International Agency for Research on Cancer, Lyon, France http://www-dep.iarc.fr/.

this risk equates to a cumulative risk of 4% by age 70. This risk estimate represents an average across all ages. However, the familial risk may decline with the age at which the relative was affected and with the age of the at risk woman. In one study, the relative risk of ovarian cancer in sisters of a woman diagnosed with ovarian cancer before age 55 was 5.2 compared with 3.6 for sisters of women diagnosed after the age of 55, though this difference was not statistically significant [3].

There are varying estimates of the risks of ovarian cancer in women with two or more affected relatives. Using data from a population-based cohort study of women with two first-degree relatives with confirmed ovarian cancer, Easton *et al.* found the relative risk of death from ovarian cancer to be 24 (95% CI = 6.6–62) [4]. By contrast, Schildkraut and Thompson [5] found the relative risk of developing ovarian cancer to be 2.1 (0.20–13) for women with two affected relatives in a population-based case-control study [5]. A combined analysis of data from these studies estimated the relative risk of developing ovarian cancer to be 12 (5.3–26) for these women [2].

In another study based on women from 316 families with at least two first-degree relatives with ovarian cancer, the average relative risk of ovarian cancer was found to be 7.2 (95% CI 3.8–12). This risk declined from 16 (6.4–33) in women under 50 to 4.4 (1.6–9.5) in women 50 years of age and older, which corresponds to an absolute risk of ovarian cancer by age 70 of 11% [6].

Genetic Susceptibility to Ovarian Cancer

The two most plausible explanations for the observed association between family history and an increased risk of ovarian cancer are: (i) genetic susceptibility and (ii) environmental exposure. Despite this, family studies are not able to distinguish between genetic and non-genetic causes of familial aggregation. However, twin studies can compare the concordance of cancer between monozygotic and dizygotic twins, and have provided some information on the relative importance of genes and non-genetic factors to ovarian cancer.

The largest twin study of ovarian cancer included data on nearly 10,000 pairs of twins [7]. The ovarian cancer risk to a monozygotic twin of an affected woman was 6-fold greater, which is twice the sibling risk. This would be expected if most of the excess familial risk were due to genetic, rather than shared environmental factors.

Genetic models of familial cancer can be formally tested using segregation analysis (statistical assessment of patterns of transmission of disease within families). Such studies in ovarian cancer have provided evidence for different types of genetic effect. In one study, Houlston *et al.* analysed 462 pedigrees ascertained through an unaffected relative. They found the observed pattern of ovarian cancer was compatible with an autosomal dominant gene. The gene frequency of the abnormal allele was predicted to be 0.0015–0.0026 [8]. In contrast, an analysis of ovarian cancer families ascertained from a population-based series of ovarian cancer cases found evidence for a recessive gene [9].

High Penetrance Ovarian Cancer Susceptibility Genes

Ovarian cancer is part of the phenotype of two distinct familial cancer syndromes: hereditary breast/ovarian cancer syndrome and Lynch syndrome (hereditary non-polyposis colorectal cancer). No gene that confers increased susceptibility to ovarian cancer alone has yet been isolated, and so site-specific familial ovarian cancer and the hereditary breast ovarian cancer syndrome are considered to be part of the same spectrum.

Two genes have been identified that are responsible for most multiple case hereditary breast/ovarian cancer families: the *BRCA1* gene on chromosome 17q12–21 and the *BRCA2* gene on chromosomes 13q12–13 [10–12]. There have been many studies that have examined the contribution of *BRCA1* and *BRCA2* to hereditary breast and ovarian cancer families; but only two studies have analysed families ascertained primarily on the basis of a family history of ovarian cancer [13,14]. The largest of these was based on 112 families from the UK and suggested

that the proportion of families that were found to have a mutation varied according to the extent of the family history [13]. Mutations were present in the majority of families containing multiple cases ovarian cancer (≥3 cases) or ovarian and breast cancer (≥2 cases of both cancers), but in only 20% of families with two cases of ovarian cancer only.

There have been several studies reporting the prevalence of *BRCA1* mutations in ovarian cancer cases unselected for family history [14–18]; each study provides different estimates of mutation prevalence. In the first published study of 374 ovarian cancer cases from Southern England, 12 truncating mutations were identified (3%) [19]. A further, larger study reported a higher prevalence (8%) in 515 patients from Canada [18]. However, a substantial proportion of these mutations were in cases from the Ashkenazi Jewish or French-Canadian ethnic groups, in whom common founder mutations are known to be prevalent. In the 316 cases of British origin, only 8 (2.5%) were *BRCA1* mutation carriers. Less data are available for *BRCA2*, but the Canadian study reported 21 truncating mutations out of the total of 515 cases (4%) of which 7 occurred in the 316 cases of British origin (2.2% prevalence). The study reported by Rubin *et al.* found only one *BRCA2* mutation carrier in 116 cases [23].

The risks of developing ovarian cancer in *BRCA1/2* mutation carriers have been estimated from both familial studies and from the analysis of ovarian cancer cases unselected for a family history. For *BRCA1* carriers the lifetime risks are 16–44% and for *BRCA2* carriers 27% [19–22].

Clinical Features of BRCA1- *and* BRCA2-*Associated Ovarian Cancers*

The data looking at the association between patient outcome and *BRCA1/2* mutations status are conflicting. One study reported improved survival of *BRCA1*-associated ovarian cancer patients compared to sporadic controls [23] but was subsequently criticised for possible selection bias. Another study also reported improved survival for *BRCA1/2*-associated ovarian cancer patients presenting with stage III disease, though the result was no longer significant when early stage cases were included in a multivariate analysis that also adjusted for age at diagnosis [24]. Other studies have found no difference in survival of *BRCA1*-associated ovarian cancer in breast cancer families compared with population controls [25], and no survival difference in ovarian cancer patients from *BRCA1* and *BRCA2* ovarian cancer families compared to patients from families in which no mutation could be found [26].

Hereditary Non-Polyposis Colorectal Cancer

Hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome is characterised by marked susceptibility to malignancies of the large bowel but cancers in other organs, including the ovary, also occur frequently [27]. Cancer susceptibility in HNPCC families is the result of mutation in one of several genes that function in DNA mismatch repair pathway (*MSH2*; *MSH3*; *MLH1*; *PMS1*; *PMS2*). Mutations in *MSH2* and *MLH1* account for 70% of reported HNPCC cases with *PMS1*, *PMS2* and *MSH3* accounting for some of the rest [28]. The cumulative risk of colorectal cancer in *MMR* gene mutation carriers from *HNPCC* families is over 80%, and that of ovarian cancer 12% [29].

Low Penetrance Ovarian Cancer Susceptibility

The known ovarian cancer susceptibility genes explain approximately 10% of all ovarian cancer cases and <40% of the excess familial risks (Fig. 1.2). Thus, it is likely that other ovarian cancer susceptibility genes exist. Several genetic models may explain residual familial clustering but other highly penetrant genes are likely to be rare, because *BRCA1* and *2* are responsible for most families containing ≥3 ovarian cancer cases. Alternatively, several moderate risk genes with a combined frequency of 5% could account for the remaining excess familial risk, and for the remaining multiple case families. Finally, there may be multiple low risk (low penetrance) genes that confer relative risks of less than three.

The most widely used study design in the search for common, low-penetrance alleles is the genetic association study. The aim is to identify polymorphic genetic variants that have a direct causal effect on cancer susceptibility. There are several types of polymorphism in the human genome that may alter protein function in one of several ways; these include: (1) single nucleotide polymorphisms (SNPs) in the coding sequence of genes that lead to amino acid substitution in the protein

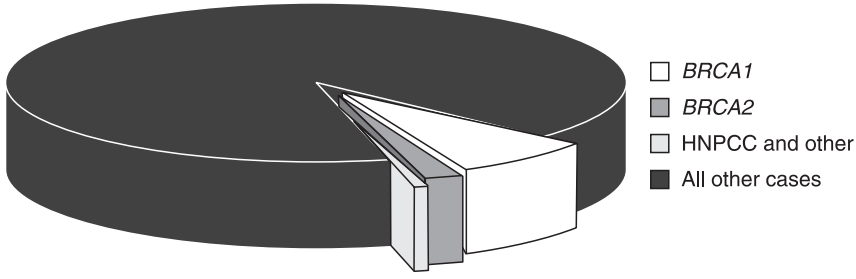

Figure 1.2 The contribution of high-risk susceptibility genes to epithelial ovarian cancer.

product and (2) polymorphisms in non-coding or regulatory sequences that may affect mRNA, expression, stability and translation.

Many candidate SNP/gene association studies for ovarian cancer have been published over the past few years; these include polymorphisms in the progesterone receptor gene (*PGR*) [30–34], the androgen receptor (*AR*) [35,36], *CYP17* [37,38], *TP53* [38–40], prohibitin [41], epoxide hydrolase [42,43], *GSTM1* *GSTP1* and *GSTT1* [44–46] and *HRAS1* [47]. Few of the published studies report results that are statistically significant; but few had sufficient statistical power to detect moderate risks even for common genetic variants. Furthermore, very few studies have used comprehensive tagging approaches to capture all the common variation in a gene. Where positive associations have been found, the case for a susceptibility allele remains unproven, due either to conflicting results from follow-up studies or because a positive result awaits confirmation in other ovarian cancer population studies. So far, positive associations include: an increased ovarian cancer risk reported for 2 *PROGINS* haplotypes [33]; a protective effect for the PGR promoter +331A allele in endometrioid ovarian tumours [34]; and an increased risk of borderline ovarian cancer associated with the pro72arg polymorphism in the *TP53* gene [41].

Reproductive and Hormonal Factors

Early Menarche and Late Menopause

There have been several epidemiological studies that have looked at age at menarche as a risk factor for ovarian cancer. In general, these have found no association [48–52].

Although no association has been found between age at menopause and ovarian cancer risk in most studies [50,53], a small number of studies have suggested that late menopause may increase risk with estimates ranging from a 1.5 to 2.9-fold increased risk in the oldest menopause groups compared with younger referents [49,52,54].

Parity

Epidemiological studies have continually shown that parity is protective against ovarian cancer. Whittemore *et al.* [50] reviewed 12 case-control studies and showed that parity had a significantly protective effect against ovarian cancer; there was an

approximately 40% reduction in risk with first birth and a further reduction of 10% with each subsequent birth.

There may also be an association with the age at first birth, although this is less clear. Some hospital-based studies suggest that an older rather than younger age at first birth is more protective [50,53,54]; but case-control studies with population-based controls indicate that the reverse is true [49,55,56].

Whilst the impact of full-term pregnancies on the ovarian cancer risk is clear, the effect of miscarriages, terminations and ectopics is not. A case-control study from Denmark found no relationship between ovarian cancer and pregnancies that fail to go to term [57]. However, other studies suggest that incomplete pregnancies confer some risk reduction, albeit a weaker protective effect than for full-term pregnancies [51,52,55].

Lactation

Most studies that have separated the effects of breast-feeding from pregnancy have demonstrated a small protective effect from lactation. Risk estimates range from between 0.6 and 0.9 in parous women who have breastfed their children compared with those who have never breastfed [50,55,57,58].

Oral Contraceptive Pill

Based on a large body of epidemiological studies, it is now accepted that the oral contraceptive pill (OC) protects against ovarian cancer. The cause of this protective effect has been put down to the cessation of ovulation and/or the decrease in gonadotrophin levels in mid-cycle. In case-control and prospective studies, 'ever' users of OCs have been shown to have a lower risk compared to never users [49–51,54,57,60,62]. The protective effect increases with duration of OC use; there is a 10–12% decrease in risk associated with a one-year OC use [62] and an approximate 50% decrease after 5 years of use [63]. The risk reduction associated with OC use continues for a long time after cessation of the OC; several studies showed a 40–70% risk reduction even 10 years after cessation of OC use [49,50,54,62]. One recent study even suggested a risk reduction after 25 years of OC use [61].

OCs confer a protective effect regardless of other known risk factors such as parity or age [60–62]. However, there does appear to be an additive effect for parity and OC use combined; Franceschi *et al.* found that women who have two children

and have taken the oral contraceptive pill for ≥5 years had a 70% risk reduction for ovarian cancer [63].

The risk reduction for OC use may also be associated with a different histological sub-type of ovarian cancer. In a case-control study that examined the effect of OC use on the risk of mucinous and non-mucinous ovarian cancer, Risch *et al.* found that the risk of mucinous ovarian cancer was not reduced in women on the combined oral contraceptive pill [64].

There is a wide variety of oral contraceptives with differing contents of oestrogens and progestins. The initial OCs of the 1960s were high-dose monophasic formulations. Hormonal doses were then reduced in the 1970s, and in the 1980s biphasic and triphasic formulations were introduced. The majority of studies showing the protective role of OCs were based on women using the early monophasic formulations. The protective effect appears to be present in newer formulations as well; use of one of two types of low-dose OC formulations (≤35 μg of ethinyl oestradiol) compared to never users was associated with a reduced relative risk of ovarian cancer of 0.7 and 0.4, respectively, and there was a risk reduction with multiphasic OCs as well [59]. In another study, in which both high and low-dose OCs reduced the risk of ovarian cancer, the high-dose regimen appeared slightly more effective [65].

A few studies that have evaluated the effect of progesterone-only contraceptives on ovarian cancer suggest a slight protective effect. In a study of 5,000 women receiving medroxyprogesterone injections with a follow-up of 4–13 years, there was an insignificant decrease in ovarian cancer risk (RR 0.8, 95% CI 0.1–4.6) [66].

The association between oral contraceptive use and ovarian cancer risk in women who are *BRCA* carriers has also been studied. In a population-based study, no association was observed between oral contraceptive use and risk reduction in high-risk women [67]. However, in a family-based study, a 60% risk reduction was observed in women with *BRCA* mutations who had been on the pill for 6 or more years [68]. More recently, in a study of 451 *BRCA1/2* mutation carriers, the odds-ratio for ovarian cancer associated with the use of oral contraceptives for 6 or more years was 0.62 (95% CI 0.35–1.09) after adjusting for parity [69].

Infertility

In 1992, a collaborative analysis of 12 US case control studies reported that the risk of ovarian cancer in nulliparous women who received fertility treatment was increased 27-fold. However, this finding should be treated with caution for

two reasons. First, the confidence intervals for this study were wide (95%, CI 2.3−315.6) [50]. Second, the individual studies that make up the collaborative analysis differ vastly in the depth with which the relevant information was collected; only 3 of the 12 studies contained results regarding infertility therapy. Since this report, a further 2 case-control studies have failed to find an association between fertility drug use and ovarian cancer [70,71]. A number of cohort studies of women undergoing fertility treatment have also failed to show an increased ovarian cancer risk associated with infertility [72−74]. In the largest of these studies, the excess risk of ovarian cancer was observed in women with unexplained infertility that had *not* had any fertility drugs [74].

There are several difficulties in study design that make this a hard question to address, and this may be responsible for some of the disparity observed between studies. For example, it is unclear whether the risk of ovarian cancer increases as women come to an age where ovarian cancer is more common or which coincides with the timing of infertility treatment. In addition, for case-control studies, there are problems associated with defining the 'infertility type', the different types of fertility drugs used and in the selection of an appropriate control group.

Hormone Replacement Therapy

Issues relating to the use of hormone replacement therapy (HRT) and its safety continue to challenge clinicians.

HRT initially contained oestradiol or conjugated oestrogens only. It then became apparent in the 1970s that the use of oestrogen therapy (ET) was associated with an increased risk of endometrial cancer. As a result, progestins were added to the ET in women with an intact uterus. ET, however, continues to be used in women who have undergone a hysterectomy.

Studies on the effect of ET/HRT on the risk of ovarian cancer are contradictory. In a recent cohort study that followed 44,241 menopausal women for approximately 20 years, a relative risk of 1.6 (95% CI 1.2−2.0) was observed among ever users compared with never users of ET [75]. The largest risk observed in this study was for women who used ET for 20 years or more: the relative risk was 3.2 (95% CI 1.7−5.7). In another study, there was an increased risk of ovarian cancer associated with ET of 10 or more years [76].

Until recently, many of the studies that examined the effect of combined HRT on ovarian cancer risk have been too small to draw firm conclusions. One such study suggested that HRT did not increase the risk of ovarian cancer if progestin was used

for more than 15 days per month [77]. The largest trial so far on the effect of HRT on ovarian cancer risk is the Women's Health Initiative (WHI) [78]. In this double-blind control trial approximately 17,000 women were randomised to either combined HRT or placebo. After an average 5.6 years of follow-up, there was a non-statistically significant increase in ovarian cancer risk in users of HRT compared to the placebo group (hazard ratio 1.58, 95% CI 0.77−3.24).

Other Factors

Age

There is a progressive increase in ovarian cancer incidence with age. For epithelial ovarian tumours, the risk of disease in women under the age of 30 is low, even in families where there is evidence of a hereditary basis for ovarian cancer. From 30 to 50 years of age, ovarian cancer incidence rises in a linear fashion. It then continues to increase, albeit at a lower rate, reaching a maximum incidence of 60.5 per 100,000 in the 75 to 79 years age group (data from the US Surveillance, Epidemiology and End Results, see Fig. 1.3).

Talcum Powder

There is some evidence to suggest that agents that irritate and inflame the ovarian epithelium promote ovarian carcinogenesis. This theory arose from

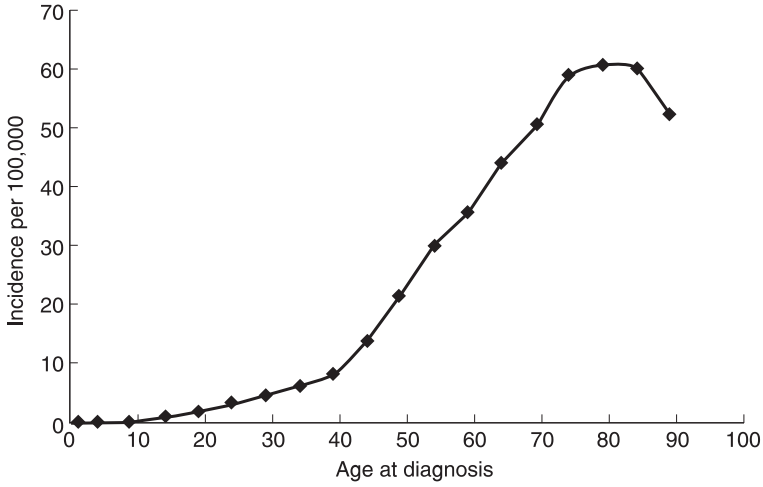

Figure 1.3 Age associated incidence of epithelial ovarian cancer.

observations that asbestos was associated with mesotheliomas in animals [79] and that particle passage from the vagina to the ovary was possible [80]. Talcum powder use in the genital area has been postulated to increase the risk of ovarian cancer by ascending the genital tract. This theory has been supported in a case control study [45,81] that gave an OR of 1.6 (95% CI 1.18–2.15) and suggested that talcum powder use was associated with serous and undifferentiated tumours.

Pelvic Surgery

The association between pelvic surgeries such as tubal ligation and hysterectomy and ovarian cancer has been reported in a number of epidemiological studies. Although the Oxford Family Planning Association study showed no association between sterilisation and ovarian cancer (OR 1.5, 95% CI 0.7–3.1) [82], the majority of studies support a protective effect with observed risk reductions from 10–80% [82–85].

A similar protective effect was observed in women who underwent hysterectomy, although the magnitude of protection appears to be lower than that of tubal ligation [82–85].

Both these operations provide closure of the ovaries to the external genital tract and it has been suggested that these operations reduce the risk of ovarian cancer by preventing carcinogens from ascending the genital tract. It is however interesting that the protective effect has been reported only up to 20 years after surgery.

Endometriosis

Pathology and epidemiological studies have consistently shown an association between endometriosis and ovarian cancer, particularly of the endometrioid [86,87] and clear cell [86] sub-types of ovarian cancer. Histopathology studies analysing large series of ovarian tumours have identified ovarian endometriotic lesions in 5–10% of cases. These were most commonly found in tumours of the endometrioid (up to 60%) and clear cell (up to 15%) sub-types, which is disproportionate to the expected frequencies of these sub-types of ovarian cancer (10–20% and 3–10%, respectively). In another study, endometriosis was found in 40% of women with stage I endometrioid or clear cell carcinoma, one third of which were carcinomas arising out of the endometriotic lesions. Two theories have been proposed for the transformation

of endometriosis to ovarian cancer. First, aberrant inflammation may serve to promote the growth and invasion of ectopic endometrium. Second, it has been postulated that the same balance of steroid hormones that has been shown to increase the severity of endometriosis may also enhance the occurrence of ovarian cancer.

Polycystic Ovarian Syndrome (PCOS)

Clinical features of PCOS commonly include obesity, infertility, menstrual abnormalities and hirsutism. In addition, PCOS is also characterised by a raised luteinizing hormone (LH) to follicle stimulating hormone (FSH), increased androgen production and abnormal oestrogen secretion. There is a well-established relationship between PCOS and endometrial cancer risk, but the risks associated with ovarian cancer are less clear. In a case-control study [88], the risk of ovarian cancer was increased in women with PCOS (OR 2.5; 95% CI 1.1—5.9) and the risk was greater in women who had not used the OC (OR 10.5; 95% CI 2.5—44.2). Other studies, however, found no association between PCOS and ovarian cancer [89].

Pelvic Inflammatory Disease (PID)

PID can arise as a complication of sexually transmitted diseases or after childbirth, terminations and gynaecological procedures. Whilst some studies have found a positive association between PID and the risk of ovarian cancer [90], others have not [51,83,91]. In a Canadian study, there was an increased risk of ovarian cancer with one episode of PID compared to those with none (OR 1.5, 95% CI 1.0—2.1). Risks were also greater if PID had occurred at an earlier age, if the women were nulliparous, infertile or had repeated episodes of PID [90]. Despite the association between human papilloma virus (HPV) and cervical cancer, no association has been found with ovarian cancer [92,93].

Diet

Diet may affect ovarian cancer risk but there appears to be no consensus about which dietary factors may be causative or protective. Several studies have suggested a link between one or more of lactose, animal fat, meat, egg and cholesterol intake with an increased risk of ovarian cancer [94,95]. A high

consumption of vegetables and olive oil on the other hand may decrease risk [96,97]. A systematic review of 11 population based case-control studies and 5 cohort studies [98] showed a positive association between body size and ovarian cancer risk, which is of course associated with dietary and calorific intake. These findings have been confirmed in more recent studies [99–103].

Conclusion

Based on several epidemiological studies, there is good evidence that increased parity, use of the oral contraceptive pill, tubal ligation and hysterectomy reduce the risk of ovarian cancer. Other factors such as lactation, age at menarche and age at menopause seem to have a weaker effect on risk reduction. The effects of endometriosis, infertility treatment and PCOS on ovarian cancer risk remain unclear.

The genetic basis of high penetrance susceptibility to epithelial ovarian cancer has been well characterised over the past decade. The identification of mutations in the *BRCA1* and *BRCA2* genes is now used in routine clinical practice for managing women that are at a high risk because of a family history of ovarian and/or breast cancer. The clinical options given to mutation carriers are currently limited to prophylactic surgery; oophorectomy and/or mastectomy.

However, there is still uncertainty about the absolute ovarian cancer risks that are associated with *BRCA1/2* mutations. Risk estimates derived from family-based studies appear to be somewhat higher than those derived from population-based studies, suggesting the risks of ovarian cancer may be modified by environment, lifestyle or additional genetic factors.

It will be a major challenge of future research to identify any gene–gene and gene–environment interactions that may exist, and then to characterise them to the extent that they can be used to improve clinical management and, ultimately, outcome of the disease. But such studies might also identify alternative non-surgical approaches to ovarian cancer management including chemo-prevention strategies.

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2

The Pathological Features of Ovarian Neoplasia

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Introduction

Ovarian neoplasms are common. Of genital tumours in women, ovarian cancer accounts for about a third, about the same proportion as carcinoma of the endometrium and cervix [1]. The incidence is highest in developed countries and is increasing [2]. About 70% of patients present with advanced ovarian cancer and the survival is consequently poor [3]. A screening test is being introduced that considers the results of tumour marker studies (particularly CA125) and transvaginal ultrasound imaging in a computer algorithm that indicates which women are at highest risk so that more concentrated imaging can be undertaken [4].

The WHO classification of tumours of the ovary is given in abbreviated form in Table 2.1. A radiologically more useful way of addressing the classification is given in Table 2.2, in which the macroscopical features of ovarian tumours that have a bearing on imaging are considered rather than simply the tissue type of the tumour.

Non-Neoplastic Cysts

The three principal types of so-called 'functional' ovarian cyst – that is, not neoplastic cysts – are surface inclusion cysts, follicle cysts (Graafian follicle cysts) and luteal cysts (corpus luteum cysts). Surface inclusion cysts are characteristically tiny, multiple and lined by nondescript low cuboidal or flattened cells. They are so common as to be considered normal and are unlikely to be a difficult radiological

Cancer of the Ovary, ed. Rodney Reznek. Published by Cambridge University Press.

Table 2.1. WHO classification of ovarian tumours

Surface epithelial tumours
Serous tumours: benign, borderline and malignant
Mucinous tumours: benign, borderline and malignant
Endometrioid tumours: benign, borderline and malignant
Clear cell tumours: benign, borderline and malignant
Transitional cell tumours (Brenner tumours): benign, borderline and malignant
Mixed and unclassified tumours
Germ cell tumours
Teratoma
benign polyphasic
benign monophasic such as struma ovarii
malignant
malignant element in a polyphasic teratoma
immature teratoma, in which all elements are malignant
Dysgerminoma
Yolk sac tumour
Choriocarcinoma
Gonadoblastoma
Sex cord stromal tumours
Granulosa cell tumours
Thecoma
Sertoli-Leydig cell tumours
Sex cord tumour with annular tubules
Steroid cell tumours other than above
Miscellaneous tumours
Wilms' tumour
Lymphoma
Small cell tumour with hypercalcaemia

Modified from [60].

diagnosis. A surface inclusion cyst rarely reaches 2.5 cm in diameter however long it lasts, unless neoplasia has supervened and the non-neoplastic surface inclusion cyst has become a serous cystadenoma. Changes in p53 protein and *c-erbB-2* gene expression have been demonstrated in atypical surface inclusion cysts [5–7].

Table 2.2. Classification of ovarian tumours by radiological and other imaging features

- Cystic tumours with no or few solid elements
  - containing serous fluid
    - follicular cyst
    - surface inclusion cyst
    - serous cystadenoma
  - containing mucinous fluid
    - mucinous cystadenoma
  - containing blood or altered blood
    - corpus luteum cyst
    - endometriotic cyst
    - any benign or non-neoplastic cyst into which haemorrhage has occurred as a secondary event
  - containing lipoid material
    - dermoid cyst (benign cystic teratoma): often associated with calcification
- Cystic tumours with some solid elements
  - containing serous fluid
    - serous tumour of borderline type
    - serous adenofibroma
  - containing mucinous fluid
    - mucinous tumour of borderline type
    - mucinous adenofibroma
  - containing blood or altered blood
    - endometrioid tumour of borderline type
    - endometrioid adenofibroma
    - any borderline cyst into which haemorrhage has occurred as a secondary event
  - containing lipoid material
    - dermoid cyst (benign cystic teratoma): often associated with calcification
- Predominantly solid tumours
  - epithelial
    - serous cystadenocarcinoma
    - mucinous cystadenocarcinoma
    - endometrioid cystadenocarcinoma
    - clear cell cystadenocarcinoma
    - Brenner tumour: benign, borderline or malignant
  - lipid containing
    - granulosa cell tumour
    - thecoma and other sex cord stromal tumours

(*continued*)

Table 2.2 (*cont.*)

dermoid cyst (benign cystic teratoma): often associated with calcification
other
fibroma
dysgerminoma
yolk sac tumour
lymphoma
metastatic tumours

Cystic Graafian follicles are normal and measure less than 2.5 cm in diameter, deriving from a maturing follicle that has failed to rupture or involute, and so is lined by granulosa cells surrounded by theca cells. The cyst content is thin clear fluid. Cystic follicles can remain the same size for about three months and then regress. They are characteristically unilocular but in conditions such as polycystic ovary syndrome can be multiple and so appear on imaging to be multiloculated [8]. A Graafian follicle cyst (that is, a true pathological cyst rather than a cystic normal structure) is 2.5 cm or more in diameter and persists for longer than 3 months. There is no evidence that a Graafian follicle cyst is preneoplastic but the diagnosis enters the differential for persistent ovarian cysts.

Cystic corpora lutea are normal and have the same characteristics of a cystic Graafian follicle in terms of size and persistence, but are lined by large luteinised granulosa cells and usually contain blood or altered blood rather than serous fluid. A corpus luteum cyst is a true pathological cyst rather than a normal structure and characteristically lasts for longer than three months on USS.

Endometriotic cysts were considered to be a variant of diffuse ovarian endometriosis and so not neoplastic, but solitary endometriotic cysts of the ovary have been shown to be monotypic and probably monoclonal, and so are considered to be neoplastic.

Ovarian Neoplasms

Ovarian masses were classically categorised into non-neoplastic cysts as above, and into benign and malignant neoplasms. The introduction of a new category of epithelial tumours of borderline type became necessary when it was realised that there is a distinct type of ovarian neoplasm, defined as having some or all of

the features of a malignant tumour but no stromal invasion – this definition holds even if there are extraovarian lesions of similar appearance [9]. These tumours behave clinically in a more aggressive way than a benign neoplasm but have a better prognosis than an invasive malignancy. Some classifications include borderline tumours as *in situ* carcinoma. Other terms for borderline ovarian tumours include 'tumours of low malignant potential', 'proliferating tumours', 'tumours with atypical proliferation' and 'tumours of low grade malignancy'. None of these are as cogent as 'borderline ovarian tumours' for several reasons [10].

Borderline tumours present in women about 15 years before invasive ovarian neoplasms, at about 45 years rather than 60 years. A further category of borderline tumour with microinvasion has been made as this also has a usefully different prognosis between that of borderline tumours and frankly invasive tumours [11].

The histogenesis of ovarian tumours mirror the various types of differentiation of which the epithelium covering the ovary is capable. Mullerian-duct-derived epithelium differentiates normally into the ciliated, columnar epithelium lining the Fallopian tube; into the cuboidal, glycogen-containing epithelium of the endometrium; and into the tall, 'picket-fence', mucin secreting epithelium of the endocervix. A neoplasm lined with Fallopian tube type epithelium will contain serous fluid similar to that secreted by the normal tube, and so is called a serous ovarian tumour. One lined by cervical epithelium is a mucinous ovarian tumour. One lined by endometrial epithelium is an endometrioid ovarian tumour.

Other neoplasms in the epithelial group include transitional cell tumours (with cells resembling the transitional cell epithelium of the urinary tract), such as transitional cell carcinoma and the range of Brenner tumours; clear cell tumours, almost all of which are malignant; and mixed tumour types, either mixed epithelial cell types or mixed epithelial and connective tissue malignancy – carcinosarcoma (Table 2.1).

Benign Epithelial and Mixed Ovarian Tumours

Serous Cystadenoma

The commonest benign ovarian neoplasm is a serous cystadenoma, which accounts for about 15% of all ovarian epithelial neoplasms. They can affect women at any age

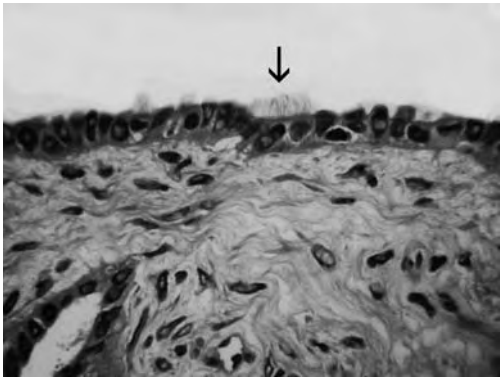

Figure 2.1 Ciliated simple columnar epithelium lining a serous cystadenoma. The epithelium is indistinguishable from normal Fallopian tube epithelium. A group of ciliated cells is marked.

but are usually found in women aged 50–70 years. About one-third are bilateral, but this may be metachronously, and are considered to be derived from surface epithelium or invaginations of it [12] (Fig. 2.1).

They tend to be unilocular or multilocular cysts with relatively thin walls and a smooth peritoneal surface. The size can vary from 5 cm to 35 cm in diameter. The contents are clear and straw-coloured but they may tort, when the contents would be bloodstained or frank blood. The cysts have papillary projections which are small and dense, usually with a maximum size of 2 cm. Solid areas with the density of fibrous tissue in the wall might mean that the tumour is a serous cystadenofibroma, a mixed epithelial/mesodermal benign neoplasm.

Mucinous Cystadenoma

These are the second commonest benign epithelial neoplasm of the ovary, affecting the same age range of women and with about the same incidence of bilaterality. Macroscopically they can resemble serous cystadenomas but tend to have thicker walls to the multiloculated cystic mass (Fig. 2.2). The contents are clear or white thick mucus unless tortion has occurred (Fig. 2.3). The size range is the same as for benign serous tumours.

Solid areas in the wall might be the result of the known association of mucinous tumours with Brenner tumours and with cystic teratomas of the ovary. Solid tissue could also be formed of reactive fibrous tissue around extravasated mucin (pseudomyxoma ovarii), though this is more commonly found in borderline mucinous tumours. Microscopically mucinous cystadenomas have mucin-secreting cells: some cysts are of typical cervical type and some are lined with epithelium of intestinal differentiation, with neuroendocrine cells.

Figure 2.2 A multiloculated mucinous cystadenoma. The thick clear mucinous contents have largely drained away.

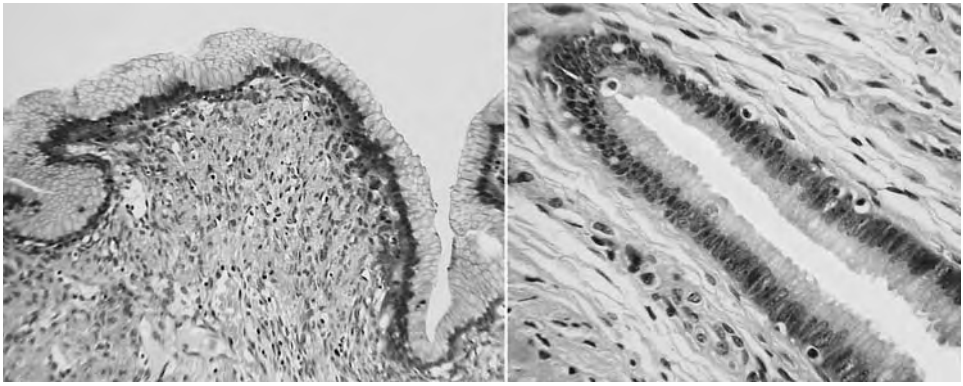

Figure 2.3 Mucinous cystadenoma lined by a single layer of tall, 'picket fence' mucus secreting cells (pictured on the left) similar to those of the normal endocervix (pictured on the right).

Endometrioid Cystadenoma

A solitary endometriotic cyst of the ovary is different from an endometrioid cystadenoma. The lining of an endometriotic cyst is of endometrioid glands *and adjacent stroma*, and these are relatively common lesions (Fig. 2.4). The term 'endometrioid cystadenoma' is reserved for the rare benign endometrioid neoplasms that are lined by endometrioid epithelium alone, without stroma.

These benign neoplasms tend to be smaller than the above types at presentation and are found surgically as smooth-surfaced or stuck-down silver cysts. The colour is because the presence of the endometrial tissues stimulate a brisk fibrous reaction, as with diffuse endometriosis of the female genital system.

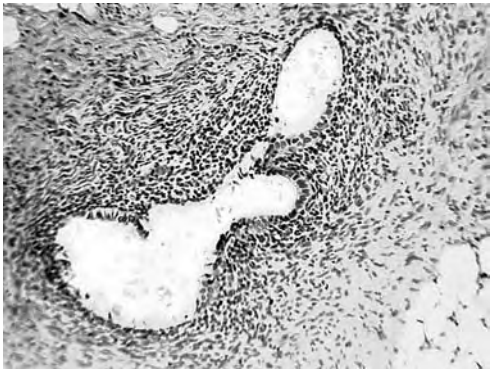

Figure 2.4 A cystic deposit of endometriosis in the peritoneum. The cyst is lined by endometrioid epithelium surrounded by endometrioid stroma (and not by the adipose tissue of the peritoneum, as would be the case in a metastatic deposit of endometrioid carcinoma of ovary).

They are called 'chocolate cysts' not because of the outside appearances but of the contents, which is denatured blood either lying free or within macrophages as haemosiderin.

Brenner Tumour

A benign ovarian tumour with two components: transitional cell epithelium in discrete islands with small cystic spaces; and a fibrous stroma which is part of the neoplasm. It can therefore be considered to be a mixed epithelial/mesodermal tumour. Most are discovered by chance in women aged 30–60 years. Only 7% are bilateral.

Brenner tumours are found in the wall of a mucinous ovarian tumour in 25% of cases of all Brenner tumours. More rarely, a Brenner tumour is associated with a benign cystic teratoma. The stromal component of a benign Brenner tumour can secrete oestrogens (and rarely other steroid hormones) and so the tumour can be associated with endometrial hyperplasia.

Borderline Epithelial Ovarian Tumours

Each of the classes above has a corresponding borderline and borderline-with-microinvasion class. The latter category has been in use only relatively recently; studies have shown that the prognosis is better than for frankly invasive carcinoma and worse than for borderline tumours without invasion. Sampling of large ovarian tumours is problematic and the possibility that an invasive component has not been examined by chance should always be borne in mind when considering histopathological reports of these tumours.

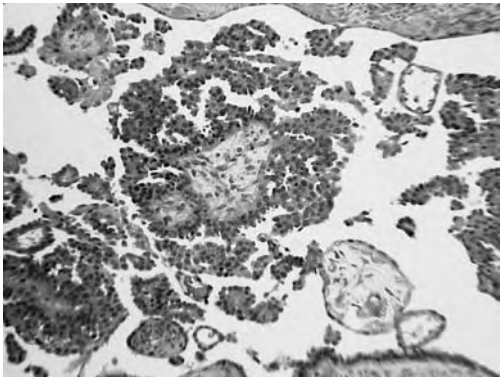

Figure 2.5 Fine papillary projections with complex architecture typical of tissue in a borderline serous ovarian neoplasm.

Borderline Serous Ovarian Neoplasia

The commonest borderline ovarian neoplasm is the serous type which affects women typically aged 45–60 years. About one-half are bilateral at presentation or metachronously. They are usually multilocular cysts in which there are fine papillary processes which can be endophytic or exophytic (Fig. 2.5). The size is variable but is usually within the range of benign tumours, about 10–25 cm diameter.

The cyst contents are the same as for the benign counterpart but may be turbid because of acute inflammation with a polymorph infiltrate, a feature more common in borderline and malignant tumours than benign. The papillary projections are different from those in a cystadenoma: they are finer, more complex, and have multilayering and budding off of the epithelial cells. The papillae are often multiple and can be much larger than in benign tumours. Surface involvement and the finding of atypical neoplastic cells on cytology of peritoneal washings at the time of operative surgery are associated with a worse prognosis.

The prognosis also depends on the clinical stage – stage I tumours do not progress and the patients have an excellent 5-year survival. Even in patients with stage III tumours and peritoneal implants the prognosis is up to 75% at 5 years.

Peritoneal implants (and lymph node implants) are collections of borderline ovarian tumour cells on the peritoneum, in the omentum, and in lymph nodes. They are of two types: non-invasive and invasive (though implants of both types may be found in the same patient, indicating the importance of extensive sampling). Non-invasive implants, which are well-defined, round or oval collections of neoplastic cells, have very little impact on prognosis.

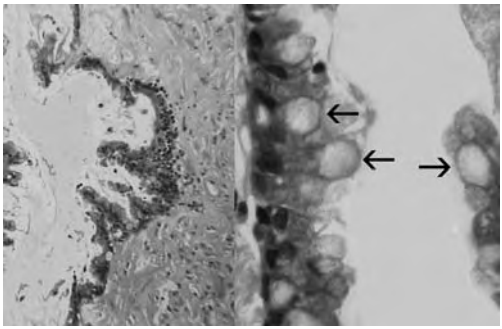

Figure 2.6 Borderline mucinous ovarian tumour of intestinal type. The high power view on the right shows obvious goblet cells which are marked.

Patients with invasive implants have a poor prognosis; about half have recurrences and their 10-year survival is overall half that of patients with non-invasive implants.

Flow cytometry can now assist with prognostication. Patients with borderline tumours that are diploid on the DNA histogram have a good prognosis: patients with an aneuploid borderline tumour have a poor prognosis. The same results apply to flow cytometry of implants, with non-invasive implants tending to be diploid and vice versa.

Borderline Mucinous Ovarian Neoplasia

Unlike their benign counterpart, borderline mucinous tumours are usually of intestinal type (85–90%). Bilaterality is uncommon. The rest are of endocervical type. The macroscopical appearances are of cysts forming large multilocular masses (occasionally unilocular, but this is rare) containing mucoid material which have papillary projections on the inner surface and occasionally on the peritoneal surface. The lining epithelium is like that of a serous borderline tumour – multilayered, atypical mucinous epithelium (either of intestinal or endocervical type) with mitoses and shedding of cells (''budding'') but no destructive stromal invasion (Fig. 2.6).

There is a strong association between a borderline mucinous tumour and a similar tumour involving the appendix as a mucocele or mucinous neoplasm. Borderline mucinous tumours are cytokeratin-7 positive (a marker of Mullerian differentiation) rather than cytokeratin-20 positive (a marker of colorectal differentiation) as for appendiceal tumours, so it is possible that there is a field change rather than metastasis.

As well as appendiceal disease, features that indicate aggressive behaviour include invasive implants and, to a lesser extent, pseudomyxoma peritonei. Differentiation

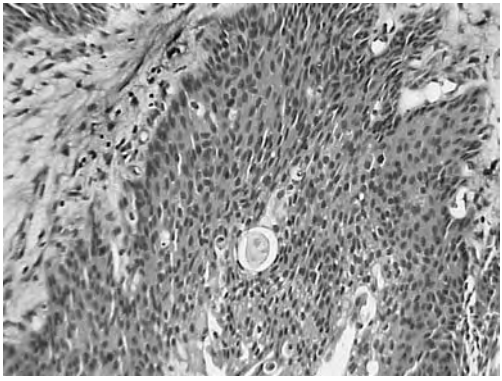

Figure 2.7 An atypically proliferating Brenner tumour composed of sheets of transitional cell epithelium surrounded by the specific Brenner stroma.

also has some effect on prognosis: tumours of endocervical type appear to behave more indolently than those of intestinal type, though the numbers studied are small [13].

Borderline Endometrioid Ovarian Neoplasia

These are rare. They may arise from the surface epithelium of the ovary or from deposits of endometriosis. The tumours may be of mixed glandular and fibrous type (adenofibromatous), papillary or villoglandular, or mixed. The prognosis does not seem to be affected by the cell type or types involved, and is usually excellent.

Borderline Ovarian Brenner Tumour

Borderline Brenner tumours are also rare. They are very similar to the benign counterpart but have mitoses, atypical cells and a more complex architectural arrangement (Fig. 2.7). By definition, there is no stromal invasion. Only 3% of all Brenner tumours are borderline. The prognosis is excellent.

Invasive Epithelial Ovarian Tumours

Ovarian cancer is staged as given in Table 2.3. About 70% of patients with ovarian cancer have disease that has spread beyond the pelvis at the time of diagnosis. Metastasis is through lymphatics, the peritoneal cavity (transcoelomic spread) and rarely through the bloodstream [14].

Patients with ovarian carcinoma have familial clustering. The relative risk to a woman of having a first-degree relative with ovarian carcinoma is about 2 but

Table 2.3. FIGO and TNM staging of ovarian tumours

FIGO stage	TNM stage	Extent of the ovarian neoplasm
I	T1	Neoplasm confined to the ovary or ovaries
IA	T1a	Neoplasm confined to one ovary, capsule intact, no involvement of ovarian suface, no neoplastic cells in peritoneal fluid or washings
IB	T1b	Neoplasm confined to both ovaries, capsules intact, no involvement of ovarian surface, no neoplastic cells in peritoneal fluid or washings
IC	T1c	Neoplasm confined to one or both ovaries with any of the following: capsules involved, involvement of ovarian surface, neoplastic cells in peritoneal fluid or washings
II	T2	Neoplasm involves one or both ovaries with extension into the true pelvic
IIA	T2a	Extension or implants, or both, to other pelvic tissues on the uterus or one or both tubes: no neoplastic cells in peritoneal fluid or washings
IIB	T2b	Extension or implants, or both, to other pelvic tissues; no neoplastic cells in peritoneal fluid or washings
IIC	T2c	Pelvic extension as either of the above two stages above with neoplastic cells in peritoneal fluid or washings
III	T3 $\pm$ N1	Neoplasm involves one or both ovaries with microscopically confirmed metastases to peritoneum outside the true pelvis, with or without regional lymph node metastasis
IIIA	T3a	Microscopic peritoneal metastases outside the true pelvis
IIIB	T3b	Macroscopic peritoneal metastases outside the true pelvis 2cm or less in greatest measurement
IIIC	T3c $\pm$ N1	Macroscopic metastases outside the true pelvis 2 cm or more in greatest measurement or regional lymph node metastasis, or both
IV	M1	Any of the above stages with distant metastases other than peritoneal metastases (including lymph node metastases beyond regional node involvement)

Modified from Sohaib and Reznek, Ovarian Cancer 2nd Edition, I. J. Jacobs, J. H. Shepherd, D. H. Oram, A. D. Blackett, D. M. Luesley, A. Berchuck, C. N. Hudson, eds., (Oxford University Press 2002) p. 262.

rises to 25 if there are multiple close female relatives affected [15]. Several genes have been identified as having a role in the genetic susceptibility to the disease. Most patients with familial breast cancer will have the *BRCA1* gene; a smaller percentage will have the *BRCA2* gene. *MLH1* or *MLH2* genes are also implicated but in much smaller numbers. The relative risk of a woman with ovarian cancer developing endometrial cancer is higher than by chance [16].

When women from families in which there is a high risk of ovarian carcinoma are studied genetically, there are three clinical patterns:

- hereditary ovarian cancer without an excess of breast cancer; this is an autosomal dominant condition and associated with *BRCA1* and *BRCA2* gene mutations
- hereditary breast and ovarian cancer; this is also autosomal dominant and associated with *BRCA1* and *BRCA2* gene mutations
- hereditary non-polyposis colorectal cancer; an autosomal dominant condition in which ovarian cancer is associated with early-onset colorectal cancer and endometrial cancer, and is associated with mutations of several mismatch repair genes [16].

BRCA1 and *BRCA2* genes are tumour suppressor (growth inhibitor) genes. The protein products of these genes are most abundant in the testis and thymus, and to a lesser extent in the ovary and breast [17]. The genes act with DNA repair genes and are involved in apoptosis [18]. Inactivation may therefore lead to an increased frequency of DNA aberrations that are permitted to multiply.

Serous Ovarian Carcinoma

This is an invasive neoplasm composed of cells resembling the Fallopian tube in well-differentiated areas and of anaplastic epithelial cells at the other extent of the range of differentiation. The tumour may be invisible to the naked eye (especially in intended prophylactic oophorectomy specimens in women with *BRCA1* or *BRCA2* genes or abnormalities of p53 gene) to 20 cm in diameter or more; serous cystadenocarcinoma is by far the most likely histological type to arise in a woman with such a genetic abnormality [19,20]. Serous cystadenocarcinomas and serous adenocarcinomas (the solid variant without recognisable cysts) are often bilateral — in some series in up to 66% of cases [14].

The tumours are more usually adherent to adjacent structures (Fig. 2.8) but it can be very difficult to diagnose invasive malignancy on naked eye examination. Histologically, the tumours vary in differentiation but are usually moderately or poorly differentiated. Psammoma bodies are commonly found; these are

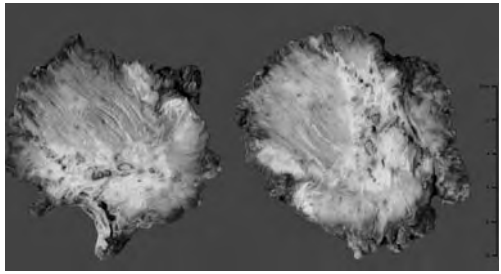

Figure 2.8 Serous adenocarcinoma invading skeletal muscle of the posterior pelvic wall. The invasive tumour tissue is almost white against the grey of the muscle fibres.

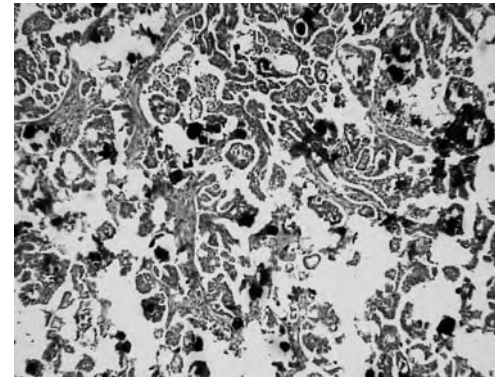

Figure 2.9 Serous cystadenocarcinoma with numerous psammoma bodies (calcispherites) forming dense, brittle nodules which shatter on sectioning.

concentric laminations of dystrophic calcification related to the papillary nature of the better differentiated elements of these tumours [21] (Fig. 2.9). Tumours with massive numbers of psammoma bodies have a favourable prognosis. The tumours are almost always CK 7 positive and CK 20 negative, and are negative for markers of mesothelium.

Mucinous Ovarian Carcinoma

Mucinous carcinomas are more likely than serous to be unilateral and multilocular. Malignancy is also more likely to be confined to one area of the tumour, with the rest showing benign or borderline features, and so sampling should be extensive [22]. The lining epithelium is usually recognisably mucus-secreting in all but the most poorly differentiated tumours (Fig. 2.10). The differential diagnosis is of any metastatic adenocarcinoma, especially one of gastric or large bowel origin. These tend to be bilateral and are often confined to the surface of the ovaries, especially in early deposits.

The prognosis of mucinous carcinoma of the ovary is better than that of serous carcinoma, though when there is extraovarian spread the prognosis is poor [23]. Grading has little to offer in prognostic terms as they are usually moderately or poorly differentiated. Expansile invasion has a better outcome than infiltrative invasion, and microinvasive tumours of 1 cm or less have a good prognosis [24].

In the staging of mucinous tumours the presence of pseudomyxoma peritonei should be regarded with caution. Clonality studies have shown the same mutations

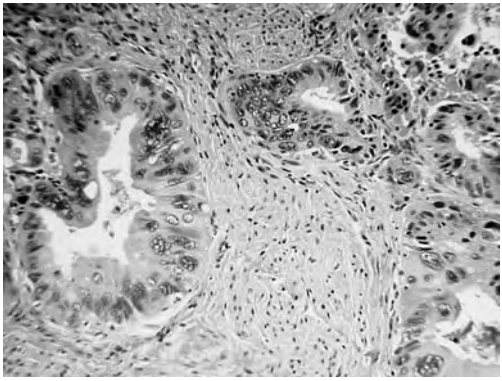

Figure 2.10 Mucinous adenocarcinoma with nuclear and cellular pleomorphism and an invasive pattern of growth. Mucin secretion is still evident.

in appendiceal and ovarian tumours; most mucinous tumours that have such mutations are considered to be metastatic to the ovary from the appendix or large bowel elsewhere. When staging a mucinous ovarian tumour, the stage should not be increased as if the appendiceal pseudomyxoma constituted evidence of metastasis from an ovarian primary [25].

Endometrioid Ovarian Carcinoma

An origin from a deposit of endometriosis or an endometriotic cyst was once required for the diagnosis of endometrioid ovarian carcinoma, but this is no longer the case: when the malignant cells have the staining and immunostaining characteristics of endometrium the term is now used irrespective of accompanying endometriosis Endometrioid carcinoma accounts for about 10% of all ovarian carcinomas and tends to affect postmenopausal women [26]. Almost half are associated with endometriosis in the same ovary or elsewhere [27]. Endometriosis is a common condition, affecting up to 10% of pre-menopausal women, and so the significance of this association is reduced [28,29].

Endometrioid carcinoma of the ovary is associated in about 20% of cases with endometrial carcinoma in the uterine corpus [30]. When the tumours are confined to the ovary and corpus only the prognosis is excellent, suggesting that these are therefore each stage I separate tumours rather than metastatic spread from one to the other [31]. Flow cytometric and loss-of-heterozygosity data can also help to differentiate a field change from metastatic disease, but the genetic profile can be identical in separate synchronous tumours in the ovary and endometrium and so is not foolproof [32]. When metastasis is suspected or established, it might be impossible to know whether the primary tumour was in the endometrium

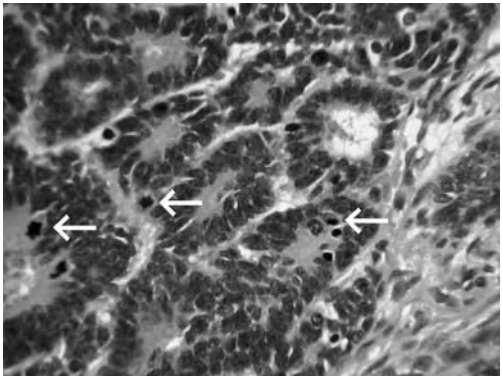

Figure 2.11 Endometrioid adenocarcinoma, composed of cuboidal, dark-staining endometrioid cells with numerous mitoses (marked).

or ovary: FIGO has decided that when there is doubt, the primary site should be determined by the initial clinical symptoms and signs.

The prognosis of endometrioid carcinoma of the ovary is best determined by stage, though women with well differentiated and moderately differentiated tumour have a better prognosis than those with anaplastic carcinoma, as would be expected [33] (Fig. 2.11). Squamous differentiation is common in these tumours and has no independent influence on prognosis: well-differentiated squamous epithelium is usually found in a well-differentiated adenocarcinoma and vice versa [34,35]. Conversely, a mixed endometrioid and serous carcinoma, or a mixed endometrioid and clear cell carcinoma, have a worse prognosis, which follows that of the admixed tumour cell type [36].

Carcinoma of endometrioid type is the one found in most cases of carcinosarcoma (malignant mixed Mullerian tumour, MMMT). These are usually partly cystic but mainly solid neoplasms with extensive haemorrhage and necrosis and a high prevalence of bilaterality. Metastasis or local extension has occurred by the time of presentation in most patients. MMMT are composed of epithelial and connective tissue elements, the latter being either homologous (smooth muscle, endometrial stroma) or heterologous (cartilage, skeletal muscle, bone). The prognosis is unaffected by this. The other types of mixed tumour are adenofibroma (both the epithelial and connective tissue elements are benign), adenosarcoma (in which the glandular element is apparently benign but there is fibrosarcoma, leiomyosarcoma of other connective tissue malignancy), and carcinofibroma, which is very rare.

Clear cell carcinoma is closely related to endometrioid carcinoma and similarly is associated with endometriosis [37]. Instead of polyhedral endometrioid cells, the tumour is composed of clear, glycogen-rich cells (Fig. 2.12) or so-called 'hob-nail'

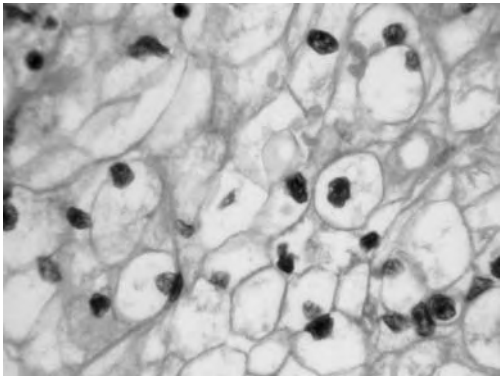

Figure 2.12 Clear cell carcinoma of ovary. The cells contain glycogen, which does not stain with H+E.

cells in which the nuclei project into the lumen on a drawn-out strand of cytoplasm. The tumour has a prognosis that is worse, stage-for-stage, than endometrioid carcinoma, and there is no evidence that the growth pattern, mitotic count, grade or predominant cell type affect prognosis [38]. The differential diagnosis is more difficult: this tumour can resemble a yolk-sac tumour, dysgerminoma and occasionally a steroid cell tumour of ovary, which a typical endometrioid carcinoma does not resemble.

Malignant Brenner and Transitional Cell Ovarian Carcinoma

These are rare. If there is a recognisable Brenner component with the biphasic pattern of epithelium and stroma, the invasive tumour is called a malignant Brenner tumour. If there is no stromal component the tumour is a transitional cell carcinoma, and the patient must be investigated for a primary bladder or other urothelial carcinoma. Ovarian transitional cell carcinomas have the histological but not immunostaining characteristics of a bladder transitional cell carcinoma, so it is usually possible to differentiate [39–41].

Germ Cell Tumours of the Ovary

These are classified into teratomatous and non-teratomatous. The latter include dysgerminoma, yolk-sac tumour (also called endodermal sinus tumour but human beings do not have endodermal sinuses), non-gestational choriocarcinoma and other rarer tumours. By far the commonest is the teratomatous type, of which almost all are benign cystic teratomas (mature teratomas, dermoid cysts of ovary).

Mature Teratoma

This is a tumour composed of mature, well-formed adult tissues, most commonly epidermis and adipose tissue. It is the third commonest ovarian tumour in women. It occurs at all ages and, though uncommon, is seen in pre-pubertal girls. It mainly affects younger women, with only 5% arising in post-menopausal women [42]. Bilaterality may be a feature but is uncommon. The origin is parthenogenetic: the tumours have no Y chromosome. They almost certainly arise from a post-meiotic germ cell — lymphoid infiltrates in a teratoma are heterozygous, from the patient's lymphoid system, while thymic tissue in a teratoma is homozygous suggesting origin from the neoplasm itself [42].

Usually there is a cystic component but occasionally a mature teratoma may be solid. When an ovarian cyst has only an epidermal element it is called an epidermal cyst; when there is epidermis and skin adnexal structures from the dermis, such as sebaceous glands, hairs and sweat glands, with an adipose tissue layer below as a 'subcutis', it is a dermoid cyst. Thyroid tissue, neural tissues, choroid plexus, cartilage and intestinal epithelium are commonly seen. Monophyletic dermoid cysts may be composed of skin, thyroid parenchyma or brain.

Malignancy in a Teratoma

Malignancy can arise in an element of the mature teratoma or be a focus or overgrowth of an immature teratoma in which all of the tissues are immature. Malignancies in monodermal teratomas include papillary carcinoma of thyroid, carcinoid tumour, ependimoma and glioma formation [43]. Rarer neoplasms include melanoma, retinal anlage tumour and sebaceous gland tumours.

Dysgerminoma

A dysgerminoma is a tumour of primitive germ cells without differentiation into mature or immature tissues. Occasionally other germ cell derived cells may be present, such as syncytiotrophoblast and yolk sac elements [44]. They are usually unilateral, solid and white or light brown in colour. Histologically in a typical dysgerminoma there are sheets and cords of large clear cells resembling the spermatogonial cells in the testis. An infiltrate of T lymphocytes is common. Immunostains for placenta-like alkaline phosphatase (PLAP) are positive in the tumour cells, and when there is syncytiotrophoblast, stains for βhCG are positive; the prognosis is unaffected by the presence of these cells and may in fact be

improved, as βhCG is a serum tumour marker [45,46]. The prognosis depends simply on stage as these tumours are very sensitive to radiotherapy and chemotherapy [35].

Yolk Sac Tumour

Yolk sac tumours are teratomatous tumours that recapitulate primitive gut structures such as secondary yolk sac vesicle, intestine and liver [47]. They are usually encapsulated and well defined. The cut surface shows a variegated appearance with areas of haemorrhage and necrosis. Cysts form but are usually small. Patients often have a benign cystic teratoma in the contralateral ovary.

Histologically, a yolk sac tumour has a myxoid stroma with microcystic spaces around clear tumour cells in a wide variety of patterns. Hyaline globules are common and stain for α-fetoprotein. Schiller-Duval bodies are often found in yolk sac tumours. These are papillary fibroepithelial bodies that are found classically in the endodermal sinuses of the placenta of the rat (hence the obsolete synonym for the neoplasm of 'endodermal sinus tumour': rats have endodermal sinuses but human beings do not) [48]. The prognosis is generally good: some tumours may be cured by surgery alone; others require adjuvant chemotherapy.

Sex Cord and Stromal Tumours of the Ovary

The primitive gonad, uncommitted to the sex of the woman at this early stage, has sex cords that extend from the ovarian surface and surround the early gamete cells. In males the sex cords persist as the seminiferous tubules and differentiate into Sertoli cells. In females the cords themselves degenerate but the cells surrounding the early oocytes remain and differentiated into granulosa cells. The cells in the immediately adjacent stroma differentiate into Leydig cells in men and theca cells in women. Sex cord and stromal cell tumours are essentially granulosa cell tumours, thecomas and related tumour cell types.

Granulosa Cell Tumours

These are classified into adult and juvenile types. Almost all cases are of adult type and affect women aged 50—70 years. About 5% of cases are juvenile type and affect women aged less than 30 years. Both types are characteristically

unilateral. Granulosa cell tumours account for 70% of malignant sex cord stromal tumours [49].

Adult granulosa cell tumours are solid, white or tan, bossellated tumours with a smooth contour. A small percentage have cysts. The tumour may have extensive lipid accumulation and be yellow, corresponding with the capacity for these tumours to secrete steroid hormones, especially oestrogens (with the resulting effects on endometrium of hyperplasia and occasionally neoplasia). The tumour cells microscopically are generally uniform, partly diffuse and partly arranged in a microcystic, rosette pattern as Call-Exner bodies. The nuclei have a characteristic longitudinal groove. Immunostains for inhibin and S100 protein are positive, and for CK7 and EMA are negative [50].

The behaviour of the tumour and its prognosis is impossible to predict from the histological features. The most reliable predictor is the stage of the tumour at operation. All of these tumours have the potential for aggressive behaviour. About 10% of patients have recurrences, which may be 30 years after the operative surgery.

The rarer form of granulosa cell tumour, the juvenile type, has a gross appearance that is similar to the adult variant, though cyst formation is commoner. Microscopically there are cysts of different sizes surrounded by more pleomorphic cells than in the adult type, with mitoses and bizarre forms. Despite this, only 5% behave aggressively and the overall prognosis is good [50].

Thecoma and Fibroma

Thecomas are derived from stromal cells and have the capacity to secrete steroid hormones, classically oestrogen. They are less common than granulosa cell tumours and usually affect post-menopausal women, often being discovered by chance or by the oestrogenic changes on the endometrium resulting in post-menopausal bleeding. The macroscopical appearances are of a dense, solid mass usually only a few centimetres across with a yellow cut surface and occasional cysts. The cells in a thecoma are uniform, plump and spindle shaped; oedema fluid may separate the cells. Thecomas are almost always benign [51].

Ovarian fibromas are related to thecomas. They are firm, white stromal tumours composed of slender spindle cells that do not excrete oestrogen or other steroids. They are usually small and discovered by chance but may be associated with ascites and a pleural effusion that resolve when the fibroma is removed (Meig's syndrome) [52]. They are also related to naevoid basal cell

carcinoma syndrome [53]. It is not known whether the rare ovarian fibrosarcoma arises from a pre-existing fibroma or not: when the malignancy is diagnosed the tumour has grown through the ovary and into adjacent structures, so it is impossible to know the previous pathology [54].

Sertoli-Leydig Cell Tumours

These are the equivalents of granulosa cell tumours and thecomas, though Sertoli cell tumours and Leydig cell tumours (and mixed forms) have the potential to be aggressive (as with granulosa cell tumours, it is not possible to label most of them malignant – some will behave indolently and others aggressively). They are rare, partly cystic but mostly solid, unilateral, large tumours of the ovary [55]. Histologically they are composed of sheets of tumour cells that in places resemble Sertoli cells and Leydig cells of the testis (Fig. 2.13). Poorly differentiated tumours may have very few recognisable cells and be diagnosed on immunochemistry alone [56].

Staging of Ovarian Neoplasms

The staging refers to the extent of spread of the neoplasm, and so applies only to neoplasms that might spread beyond the ovary (or ovaries, as benign neoplasms can be bilateral). The most used staging system is that of the International Federation of Gynecology and Obstetrics, FIGO. This recommends a laparotomy for complete staging, but imaging with CT and MRI can be contributory. Another staging system, used for all malignant neoplasms but modified for ovarian neoplasms, is the TNM staging method in which T refers to aspects of the tumour (site, size), N refers to *regional* lymph node metastases and M to distant metastases including lymph node metastases beyond regional lymph node involvement. Both staging systems are listed in Table 3 with a descriptor of each stage.

Tumours Metastatic to the Ovary

A Kruckenberg tumour is a signet-ring cell, mucin-secreting tumour that is metastatic from the gastrointestinal tract, pancreas, biliary system or elsewhere [50].

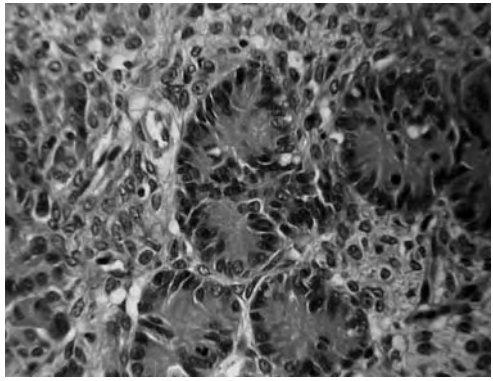

Figure 2.13 A Sertoli-Leydig cell tumour. The clearly demarcated islands of Sertoli cells are surrounded by plume spindle-shaped Leydig cells.

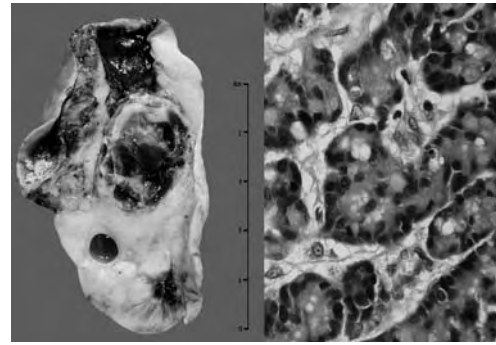

Figure 2.14 One of a pair of ovaries containing metastatic mucous-secreting adenocarcinoma (in this case from a colonic primary). The macroscopical specimen is on the left, showing a partly cystic and partly solid tumour mass greatly expanding the ovary. On the right are cells containing clear collections of mucin which stained positively for cytokeratin 20.

In his original paper, Kruckenberg did not specify a primary site [57]. Kruckenberg tumours are classically bilateral. Metastatic spread to the ovaries is common and is found in about one-third of women dying of cancer (Fig. 2.14). Most cases originate from cancers of the breast, colon, stomach and endometrium. In a patient with pseudomyxoma peritonei there is very often a tumour of the appendix or large bowel that would account for this. Diagnostic difficulty in telling metastatic large bowel mucinous carcinoma from primary ovarian mucinous carcinoma can be resolved in most cases by the use of CK 7 (positive in ovarian but not large bowel tumours) and CK 20 (vice versa).

Other rarer epithelial metastases in the ovaries include carcinoid tumour, melanoma, renal cell carcinoma, transitional cell carcinoma, thyroid carcinoma, bronchial carcinoma and adenoid cystic carcinoma [50]. Metastases from sarcomas and blastomas are very rare. They include leiomyosarcoma, endometrial stromal sarcoma, fibrosarcoma, osteosarcoma and rhabdomyosarcoma. Blastomas and other developmental tumours include hepatoblastoma, nephroblastoma, neuroblastoma, retinoblastoma and Ewing's sarcoma [50,58].

Involvement by lymphoma is also relatively common as secondary involvement in women with disseminated lymphoma and is bilateral in about half of cases [59]. Primary involvement by Burkitt's lymphoma accounts for half of cases of ovarian lymphoma in children in endemic areas, especially Africa [35].

Primary involvement by lymphoma results in large, nodular and smooth-surfaced ovaries with an intact capsule. On sectioning the tissues are solid, white or tan, and occasionally have foci of haemorrhage and necrosis. When the ovaries are involved secondary to disease in lymph nodes and bone marrow it may not be macroscopically detectable.

Conclusion

The typing of ovarian cancers has changed relatively little in recent years, but with the development of molecular pathology techniques for identifying abnormalities of p53 protein, *c-erb-B2*, loss of heterozygosity and other genetic abnormalities there is a good possibility that some reclassification will be called for. Until then, typing is essentially on histological appearances supported by immunostains for cytokeratins, inhibin, neuroendocrine markers and other cell components that assist histological diagnosis.

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3

Ovarian Cancer Screening

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Introduction

Ovarian cancer remains not only the commonest but also the most lethal gynaecological malignancy in the UK (Table 3.1 [1]).

Despite advances in molecular biology, surgery and chemotherapy, ovarian cancer remains a difficult condition to manage and long-term survival rates have hardly improved since the 1970s [2]. The poor prognosis of the disease is believed to be due to the fact that more than 70% of women present with disease spread beyond the ovaries (Table 3.2 [3]). This probably reflects the absence of major symptoms in early stage disease, due to the location of the ovaries, which results in little interference with surrounding structures until ovarian enlargement is considerable or metastatic disease supervenes. When symptoms occur, they may be non-specific, requiring frequent consultations with a GP before further investigation is prompted. However, it should be noted that most stage I ovarian cancers have an extremely good prognosis following surgery alone. Detection of early stage disease may therefore offer an opportunity to reduce mortality. However, so far, no screening protocol for ovarian cancer has been shown to achieve this aim. Nevertheless, developments in ultrasound and tumour marker technology, combined with more sophisticated approaches to interpretation have improved the performance of the potential screening strategies to levels which may reduce mortality. These strategies are currently being tested in two large randomised controlled trials of ovarian cancer screening; one in the UK [4] and one in the USA [5]. However, neither of these is expected to report before 2012.

Cancer of the Ovary, ed. Rodney Reznek. Published by Cambridge University Press.

Table 3.1. The 10 commonest female solid cancers in the UK in 1999–2001 [1]

Site	Average annual incidence 1999–2001	Mortality: incidence ratio
Breast	40,740	0.32
Lung	14,878	0.87
Colorectal	15,939	0.48
Ovary	**6,663**	**0.67**
Uterine corpus	5,490	0.18
Melanoma	3,833	0.19
Pancreas	3,637	0.99
Stomach	3,454	0.75
Bladder	3,302	0.55
Cervix	3,045	0.39

Source: Office of National Statistics (HMSO, London), 2001.

Table 3.2. Five-year survival rates by stage at presentation in 4004 women treated from 1996–1998 [3]

FIGO stage	Proportion of cases (%)	5-year survival (%)
IA	11.7	89.3
IB	1.4	64.8
IC	14.0	78.2
IIA	1.8	79.2
IIB	2.6	64.3
IIC	5.1	68.2
IIIA	3.0	49.2
IIIB	6.3	40.8
IIIC	41.3	28.9
IV	12.8	13.4

Source: FIGO (International Federation of Gynaecology and Obstetrics), 2003.

Screening Test Requirements

High sensitivity (the probability of the test being positive in individuals with the disease) and high specificity (the probability of the test being negative in individuals without the disease) are important requirements for any screening test. However, increasing the sensitivity of a test (e.g. by lowering the cut-off used for a tumour marker) tends to result in a reduction in specificity, and vice versa. Specificity is crucially important in ovarian cancer screening, because most women testing positive will require surgical intervention. Consequently, neither patients nor clinicians will accept large numbers of false positive screening results. Due to the relative rarity of ovarian cancer, even a test with 98% specificity would result in 50 surgical procedures for every case of ovarian cancer detected on screening the post-menopausal population. A screening test for this population requires 99.6% specificity to yield a positive predictive value (PPV) of 10% (i.e. 10 operations for each case of cancer detected) [6]. It should also be noted that lower specificity may be acceptable in higher risk populations (e.g. women with a strong family history of ovarian cancer), because their incidence of ovarian cancer will be higher. A variety of different modalities have been used to detect ovarian cancer in asymptomatic women. These will be considered individually, and then in combination, in the context of multimodal screening.

Screening Techniques

Vaginal Examination

Most investigators would agree that this modality lacks sufficient sensitivity and specificity for asymptomatic screening. Consequently, whilst vaginal examination remains important in the assessment of women presenting with gynaecological symptoms, it cannot be recommended as a first-line screening tool.

Tumour Markers

The ability to detect malignancy via a blood test has long been an objective in medical screening. The advantages of such an easy, relatively non-invasive and operator-independent test are self-evident. A variety of ovarian tumour markers have been studied. The most extensively investigated of these is CA125. This antigen was first recognised in 1981, using a murine monoclonal antibody

developed in response to immunological challenge with an ovarian cancer cell line [7]. Serum CA125 was elevated in 50% of stage I and 90% of stage II ovarian cancers [8], and retrospective analysis of 25% of 59 samples stored more than 5 years prior to diagnosis had elevated levels [9]. Whilst sensitivity for stage I disease using a simple cut-off of 30 iu/ml was limited, it was apparent that CA125 was able to detect ovarian cancer preclinically. Using CA125 with a cut-off of 30 iu/ml also lacks specificity, as many conditions are associated with raised levels (e.g. fibroids, endometriosis, menstruation, endometrial cancer, many non-ovarian malignancies, pancreatitis, colitis, pericarditis, diverticulitis, and SLE) [10]. Any condition which results in inflammation of a mesothelium-derived surface (pleura, peritoneum, pericardium, etc.) can cause an elevated CA125 level. Consequently, measuring CA125 in patients with ascites but no pelvic mass can result in an erroneous diagnosis of ovarian cancer [11]. Despite these limitations, CA125 has been used in prospective ovarian cancer screening trials, either alone, or combined with ultrasound (Table 3.3). The largest CA125-based trial to date suggests that using a simple CA125 cut-off as a first line test may improve survival in the screened population [12].

Recently progress has been made by a more sophisticated approach to interpretation of CA125 results, using an algorithm incorporating patient age, absolute level and, most importantly, rate of change of CA125 [13]. This algorithm utilises the fact that women with ovarian cancer have rising levels of CA125, whereas women without ovarian cancer have static or falling levels, even if the levels remain above 30 iu/ml. In a retrospective analysis, this algorithm yielded a sensitivity of 83%, a specificity of 99.7% and a PPV of 16% for predicting a woman's risk of developing ovarian cancer in the year following her last screen. Because this algorithm analyses rate of change of CA125 values, women with ovarian cancer can be recalled for an ultrasound scan before their CA125 level has reached 30 iu/ml, increasing sensitivity and facilitating earlier intervention. This 'risk of ovarian cancer' (ROC) algorithm is an important component of the UKCTOCS randomised controlled trial of ovarian cancer screening. The results of a prospective pilot study using the algorithm in over 13,000 post-menopausal women have confirmed the high PPV of the previous retrospective analysis [14].

The use of a combination of markers to improve sensitivity and specificity has been extensively investigated and some of the most promising include CA72-4 (TAG 72), M-CSF, OVX1, LPA, Prostacin, Osteopontin, Inhibin and Kallikrein [15]. Many of these exhibit complementarity to CA125 (e.g. mucinous tumours which tend not to produce CA125 do produce some of these markers). The use of

Table 3.3. Prospective ovarian cancer screening studies in the general population

Study	Population	Screening strategy	No. screened	No. of invasive EOC detected[a]	No. of positive screens	No. of operations/ cancer detected
CA125 alone						
Einhorn *et al.* 1992 [26]	Age >40 yr	CA125	5,550	6 2 stage I	175[b]	29[b]
Multimodal approach — CA125 (Level 1 screen), then USS (Level II screen)						
Menon *et al.* 2005 [14]	Age >50 yr postmenopausal	CA125 ROCA, TVS if ROC↑	6,532	3 (1) 2 stage I	16	5.3
Jacobs *et al.* 1999 [12]	Age >45 yr postmenopausal	RCT CA125 TAS/TVS, if CA125↑	10,958 3 annual screens	6 3 stage I	29	4.8
Jacobs *et al.* 1996 [27]	Age >45 yr postmenopausal	CA125 TAS, if CA125↑	22,000	11 4 stage I	41	3.7
Adonakis *et al.* 1996 [28]	Age >45 yr	CA125 TVS, if CA125↑	2,000	1(1) 1 stage I	15	15
Grover *et al.* 1995 [29]	Age >40 yr or FH (3%)	CA125 TAS/TVS, if CA125↑	2,550	1 0 stage I	16	16

(continued)

Table 3.3 *(cont.)*

Study	Population	Screening strategy	No. screened	No. of invasive EOC detected[a]	No. of positive screens	No. of operations/ cancer detected
USS-only approach — USS (Level 1 screen), then repeat USS (Level II screen)						
van Nagell *et al.* 2000 [30]	Age > 50 yr postmenopausal or > 30 with FH	TVS Annual screens Mean 4 screens/woman	14,469	11 (6) 5 stage I	180	16.3
Sato *et al.* 2000 [31]	Part of general screening programme	TVS TVS + markers at Level II	51,550	22 17 stage I	324	14.7
Hayashi *et al.* 1999 [32]	Age > 50 yr	TVS	23,451	3 (3) 2 stage I	258	13.6[c]
Tabor *et al.* 1994 [33]	Aged 46–65 yr	TVS	435	0	9	—
Campbell *et al.* 1989 [22]	Age > 45 yr or with FH (4%)	TAS (3 screens at 18-monthly intervals	5,479	2 (3) 2 stage I	326	163
Millo *et al.* 1989 [34]	Age > 45 yr or postmenopausal (mean 54)	USS (mode not specified)	500	0	11	—

Goswamy *et al.* 1983 [35]	Age 39–78 yr postmenopausal	TAS	1,084	1 1 stage I		
USS and CD (Level I screen)						
Kurjak *et al.* 1995 [36]	Aged 40–71 yr	TVS and CD	5,013	4 4 stage I	38	9.5
Vuento *et al.* 1995 [37]	Aged 56–61 yr	TVS and CD	1,364	(1)	5	—
USS (Level 1) and other test (Level II screen)						
Parkes *et al.* 1994 [38]	Aged 50–64 yr	TVS then CD if TVS positive	2,953	1 1 stage I	14[d]	9
Holbert *et al.* 1994 [39]	Aged 30–89 yr postmenopausal	TVS then CA125 if TVS positive	478	1 1 stage I	33[e]	11

N.B. some of these studies have previously been reported in earlier publications. In order to avoid duplication of data, these have not been included in this table.

EOC = epithelial ovarian cancer; FH = family history; RCT = randomised controlled trial; ROCA = risk of ovarian cancer algorithm; TAS = transabdominal ultrasound; TVS = transvaginal ultrasound; USS = ultrasound; CD = colour Doppler.

[a]Primary invasive epithelial ovarian cancers. The borderline/granulosa tumours detected are shown in parentheses.

[b]Not all of these women underwent surgical investigation as the study design involved intensive surveillance rather than surgical intervention.

[c]Only 95 women consented to surgery and there are no follow-up details on the remaining.

[d]86 women had abnormal USS prior to CD.

[e]Only 11 of these women underwent surgery.

a panel of markers in ovarian screening appears attractive. The power of this technique relies on interpretation of the pattern of different marker levels in relationship to each other, rather than the absolute levels of each marker. This can lead to observations which would be missed by less sophisticated analysis; for example, a fall in the level of marker A in relation to marker B may be associated with an increased risk of having a disease, whereas a rise in marker A may reduce the risk. This type of analysis is well within the capabilities of modern bioinformatics.

Recently, the use of mass spectrometry (MS) to analyse the serum proteome has been suggested as a possible means of screening asymptomatic women for ovarian cancer [16]. This technique involves using a laser to ionise the thousands of proteins contained in serum (the serum 'proteome') and separating them by their molecular weight using the principle that heavier ions take longer to travel a set distance than lighter ions. Whilst initial data [16] demonstrated the ability of MS to differentiate women with ovarian cancer from healthy controls on the basis of the pattern of different serum proteins, this data has subsequently been criticised for the following reasons. First, the technique of protein pattern recognition used was a 'black box' technology, i.e. the complex algorithm used to discriminate between cancer cases and controls was not transparent, and re-analysis of the raw MS data by other groups using independent algorithms has suggested that the differences identified may have been artefact [17]. Second, no specific proteins were identified as discriminating cancers from controls [18]. Third, the particular MS technique used was not considered to be the most sensitive for the detection of subtle changes in serum protein concentration and different MS techniques may be more appropriate [19]. Nevertheless, other groups have also used this technique to identify specific serum proteins in ovarian cancer [20,21]. The use of proteomic technology in screening for a variety of diseases is under investigation but has not yet been sufficiently validated for use in a prospective ovarian cancer screening trial. Fortunately, the use of the CA125-based ROC algorithm has already enabled the implementation of single marker serum screening into a randomised controlled trial.

Ultrasound

Various methods of ultrasonic ovarian assessment have been investigated. Transabdominal pelvic ultrasound [22] lacked sufficient specificity, as over 50 women underwent surgical investigation for each case of cancer detected. This was due to the relatively poor resolution of the older ultrasound machines

used and the difficulties of imaging pelvic anatomy through the abdominal wall. This problem has been overcome by the development of transvaginal scanning, which offers greater resolution by virtue of closer proximity of the probe to the ovaries. There have been attempts to improve sensitivity and specificity by use of a morphological index, so that ovaries can be scored for their risk of malignancy [23]. Such techniques have established a very low risk of ovarian cancer in simple cysts <10 cm in diameter [24]. Specificity has been further enhanced by colour flow Doppler imaging; the neovasculature, which arises in malignancies, contains less smooth muscle than its benign counterpart and therefore offers less resistance to blood flow. This can be measured as the pulsatility index of the vessel. This technique has also been used in a scoring system [25], which also incorporates the distribution of the vessels.

Other Modalities

Other methods used to image ovarian cancer include ultrasound using a variety of contrast agents, 3D ultrasound, computerised tomography, magnetic resonance imaging and radioimmunoscintigraphy. None of these can currently be advocated as a first-line test for population screening due to cost, availability, patient acceptability and/or radiation exposure. Nevertheless, these techniques may have a role in ovarian cancer screening; at the point at which first-line tests (tumour markers and/or standard transvaginal ultrasound) demonstrate that a patient is likely to have an ovarian malignancy, they may reduce the number of patients without cancer being referred for surgery.

Multimodal Screening

The results of general population screening using tumour markers and ultrasound individually, in combination and sequentially are shown in Table 3.3. These data suggest that the highest PPV is achieved with multimodal screening using CA125 as a first-line test, followed by ultrasound if CA125 is abnormal. However, the sensitivity of ultrasound as a first-line test for early stage ovarian cancer may be greater than that of CA125.

The use of multimodal screening has three advantages over strategies incorporating a single modality. First, using serum screening as a first-line test reduces cost. Second, reserving ultrasound as a secondary test reduces the number of women undergoing transvaginal assessment. Finally, combining different

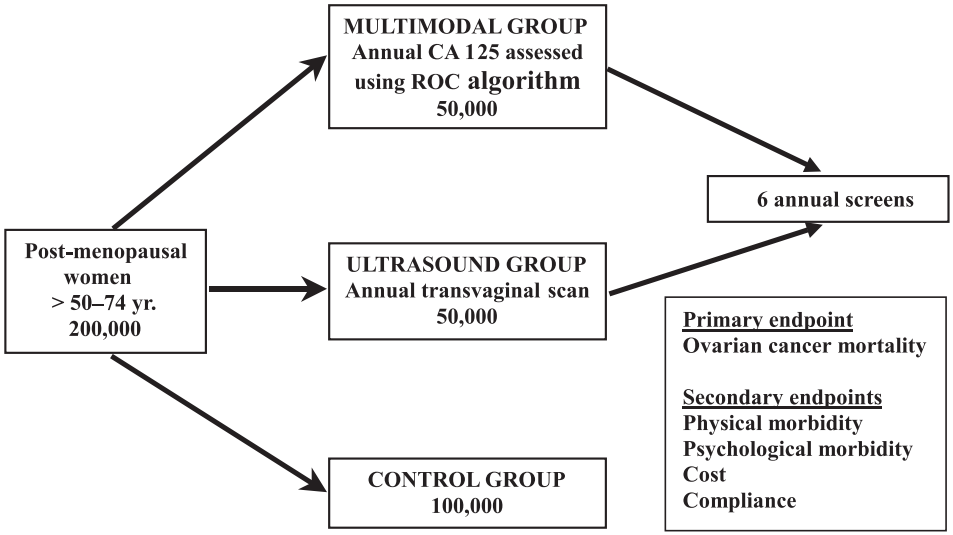

Figure 3.1 UKCTOCS trial design. All women will be followed up for 7 years via 'flagging' through the Office of National Statistics and via postal questionnaires.

modalities can achieve sensitivity and specificity comparable to that of the most sophisticated analyses utilising Doppler ultrasound and morphological indices. Nevetheless, it remains to be proven that CA125, even if used with the ROC algorithm, has adequate sensitivity for early stage disease and consequently the use of ultrasound as a first-line test is also being investigated in the UKCTOCS trial.

Two randomised controlled trials incorporating multimodal screening are currently underway. The first of these, the US NIH PLCO study [5], has randomised 78,000 women over 55 years old to a control group or screening with clinical examination, ultrasound and CA125. Any abnormal tests result in referral to a gynaecological oncologist for further investigation. The study duration to achieve 80% power for a 30% reduction in mortality is 16 years. The other study is UKCTOCS [4], which has recruited 200,000 postmenopausal women aged 50−74 years old (Fig. 3.1). These volunteers are being randomised to a control group or annual screening with CA125 or transvaginal ultrasound scanning (TVS). On the basis of the pattern of CA125 results analysed by the ROC algorithm, volunteers will be allocated to a low risk group (annual CA125), intermediate risk group (repeat CA125 sooner) or an elevated risk group (TVS). An abnormal scan triggers referral for surgery. This trial has 80% power to detect a 30% reduction in mortality and aims to report in 2012. In a recently completed pilot study of 6,532 women screened using the ROC algorithm [14], a specificity of 99.8% and PPV

of 19% were achieved, suggesting that this algorithm is suitable for assessment in the UKCTOCS trial.

Whatever the outcomes of these trials, it would appear that on present evidence, some form of multimodal screening will probably provide the most cost-effective and acceptable strategy (see below) for the detection of early ovarian cancer in the general population.

Test Acceptability

The successes of breast and cervical screening programmes have demonstrated that many women are willing to undergo uncomfortable, intrusive examination regularly in order to reduce their risk of dying from malignancy. Lower uptake rates in poorer socio-economic groups have provided cause for concern in breast and cervical screening programmes as the incidence of these cancers is inversely related to social class. However, ovarian cancer is more prevalent in professional classes [40]. In fact, employment was significantly associated with screening by ultrasound in women with a family history of ovarian cancer [41]. In this study, use of CA125 was associated with both an increasing number of affected family members and cancer worries. The latter also increased ultrasound usage in women with one affected relative. These data suggest that women's fear of cancer exceeds their fear of screening, particularly when they have personal experience of malignancy, and that screening may be more acceptable to a population at higher risk.

Further evidence of test acceptability comes from a large randomised trial of multimodal screening [12], in which compliance with annual screening only fell marginally from 79.7% at the first screen to 77.2% at the third screen. More recently, our group performed a pilot study comparing venepuncture, cervical smears, mammography and TVS amongst 100 randomly selected women aged 50–80 years, who had taken part in an ovarian screening trial and had experienced all four screening techniques (Menon U., personal communication). Over 80% of the 91 women returning the questionnaire rated venepuncture as their preferred screening method and the acceptability of transvaginal scanning was comparable to that of cervical cytology and mammography. A similar study of 54 women in another ovarian screening trial found TVS significantly less uncomfortable than smears or mammograms [42]. Recent evidence [43] found that compliance with 6-monthly screening in 292 average to intermediate risk women fell from 97% to 64% over 18 months, and compliance with CA125 was better than that with

TVS. In conclusion, it would appear that current methods used for ovarian screening are largely acceptable to the majority of women, but if a reduced screening interval is required, compliance may fall.

Target Populations

As the incidence of a disease decreases, the specificity required to achieve a given positive predictive value increases. Thus a test which lacks the specificity required for screening the general population may be suitable in a high-risk population.

The 'High-Risk' Population

The results of screening studies in high-risk populations are summarised in Table 3.4. These data suggest that screening the high-risk population with current techniques has an acceptable PPV. A recent meta-analysis [44] of familial ovarian cancer screening studies has raised concerns that screening on an annual basis may not be adequate to detect early stage disease and may result in large numbers of interval cancers (cancers which present clinically between screens). However, when corrected for cases which occurred following the last screen, rather than between screens, the number of true interval cancers in the meta-analysis was only two, giving an apparent sensitivity for detection of ovarian cancer at one year follow-up of 94% [45]. This is, however, subject to the important caveat that follow-up in many of the studies analysed was incomplete. In addition, when a correction is made for the inadvertent inclusion of 7 cases reported twice in separate publications, 14/31 cases detected were stage I or II (45%). The recent meta-analysis [44] also suggested that screen-detected familial ovarian cancers are not usually high-grade serous carcinomas, which carry a poor prognosis, but rather better prognosis of histologic types. If this is correct, then screening this population using current strategies may not reduce mortality, and consequently prophylactic oophorectomy on completion of childbearing may be a safer option. Nevertheless, there is a dearth of good quality data in this area and there remains a need to offer screening to women unwilling or not ready to undergo such surgery. Because an optimal screening strategy has yet to be defined, Cancer Research UK and the US NCI are supporting the UK Familial Ovarian Cancer Screening Study (UKFOCSS) to establish the optimum screening regimen in women with a $>10\%$ lifetime risk of ovarian cancer. As it is considered unethical to randomise this

Table 3.4. Prospective ovarian cancer screening studies in women with family history of ovarian or breast cancer or personal history of breast cancer

Study	Population	Screening protocol	No. screened (% premenopausal)	No. referred for diagnostic tests (%)[a]	No. of invasive EOC detected (borderline tumours)	Cancers in screen negative women
Weiner *et al.* 1993 [46]	PMH of BC	TVS and CD	600	12 (2)	3 1 stage I	Not stated
Muto *et al.* 1993 [47]	Aged >25 yr FH of OC	TVS and CA125	384 (85)	15 (4)	0	Not stated
Belinson *et al.* 1995 [48]	Aged >23 yr (mean 43 yr) FH of OC	TVS and CD and CA125	137	2 (2)	1	Not stated
Menkiszak *et al.* 1998 [49]	Aged >20 yr FH of BC/OC	TVS and CA125 (6-monthly)	124	Not available	1 (3)	Not available
Karlan *et al.* 1993 [50]	Aged >35 yr FH of	TVS and CD and	597[b] (75)	10 (2)	0 (1)	Not stated
Karlan *et al.* 1999 [51]	OC, BC, endometrial or colon cancer, PMH of BC	CA125 (6-monthly until 1995, then annually)	1261	Not stated	1 EOC, 3 PP (2) 1 stage 1	4 PP (5, 6, 15, 16 months)
Dorum *et al.* 1996 [52]	Aged >25 yr	TVS and CA125	180[b]	16 (9)	4 (3)	2[c]
Dorum *et al.* 1999 [53]	(mean 43 yr) Strict criteria for FH of BC/OC		803	Not stated	16 (4)	Not stated

(continued)

Table 3.4 *(cont.)*

Study	Population	Screening protocol	No. screened (% premenopausal)	No. referred for diagnostic tests (%)[a]	No. of invasive EOC detected (borderline tumours)	Cancers in screen negative women
van Nagell *et al.* 2000 [30]	FH of OC	TVS then CD and CA125	3299	Not stated	3 (1) 2 stage I	2 (12, 14 months)
Taylor and Schwartz, 2001 [54]	Aged >30 yr FH of OC	TVS and CD and CA125	252 (83)	3 (1)	1	1 (12 months)
Scheuer *et al.* 2002 [55]	Aged >35 yr BRCA1/2 mutation carriers	TVS and CA125 (6-monthly)	62	22 (36) 10 had surgery	4 EOC, 1 PP 3 stage I	0[d]
Laframboise *et al.* 2002 [56]	Aged >22 yr (mean 47 yr) Strict criteria for FH of BC/OC	TVS and CA125 (6-monthly)	311	9 (3)	1 stage I	Not stated
Liede *et al.*[e] 2002 [57]	Mean age 45 yr Jewish	TVS and CD and CA125	290	Not stated	1 EOC, 2 PP	1 EOC (2 months)

	FH of OC/BC	(6-monthly until 1995, then annually)			1 stage I	4 PP (1–17 months)
Tailor *et al.* 2003 [58]	Aged >17 yr (mean 47 yr) FH of OC	TVS then CD	2500 (65)	104 (3)	6 (4) 4 stage I	2 – PP (20–40 months) 7 – EOC (9–46 months)
Fries *et al.* 2004 [59]	Aged >28 yr (mean 53 yr) FH of OC/BC	TVS and CA125 (6-monthly)	53	3[f](6)	0	Not stated
Stirling *et al.* 2005 [60]	Strict criteria for FH of BC/OC or mutation carriers	TVS and CA125 (annually)	1110	39 (4)	9 (1) 2 stage 1	3 (2, 4, 12 months)

(continued)

Table 3.4 *(cont.)*

Study	Population	Screening protocol	No. screened (% premenopausal)	No. referred for diagnostic tests (%)[a]	No. of invasive EOC detected (borderline tumours)	Cancers in screen negative women
Olivier *et al.* 2005 [61]	Strict criteria for FH of BC/OC or mutation carriers	TVS and CA125 (annually)	312 (176)	10 (3)	3 1 stage 1	1 (2 months)

N.B. some of these studies have previously been reported in earlier publications. In order to avoid duplication of data, these have not been included in this table. PMH = personal history, FH = family history, OC = ovarian cancer, BC = breast cancer, EOC = epithelial ovarian cancer, PP = primary peritoneal cancer, TVS = transvaginal ultrasound scan, CD = colour flow Doppler.

[a]Following positive secondary screens.

[b]incorporated in reference below.

[c]Further 13 women underwent oophorectomy for BC, 2 had EOC not detected by TVS.

[d]2 women who opted for oophorectomy with normal scans and CA125 had Stage 1 EOC.

[e]sub-cohort of Karlan *et al.* (1999) followed up more recently.

[f]All three had surgery.

high-risk group to a non-screening arm, all volunteers are having annual CA125 and TVS. They are also providing 4-monthly serum samples for storage and retrospective analysis for novel tumour markers. A familial risk of ovarian cancer index will be calculated retrospectively, based on marker levels and scan results, combined with the knowledge of whether or not an individual developed ovarian cancer in the year following each screen. Cancer Research UK have recently agreed to continue funding the study until 2011, which will facilitate the use of prospective 4-monthly serum CA125 screening, analysed using the ROC algorithm, which has now been adapted for use in the premenopausal as well as postmenopausal population. It is hoped that this strategy will facilitate the introduction of a validated screening programme for the high-risk population.

The General Population

The two randomised controlled trials of general population screening, described above, both involve postmenopausal women only. The reasons for choosing the postmenopausal population are three-fold. First, the incidence of epithelial ovarian cancer increases rapidly beyond 50 years, such that the rate more than doubles in the 60–64 years age group as compared to 45–49 years [1]. Under 15% of ovarian cancers occur in women under 50 years and many cancers in the youngest age groups are non-epithelial, and are therefore either not amenable to screening by CA125 or carry an excellent prognosis irrespective of stage at presentation. Consequently, screening younger age groups with a low incidence of ovarian cancer will reduce the specificity and hence the PPV of screening. Second, many of the conditions associated with raised CA125 (e.g. menstruation, endometriosis and fibroids) occur either exclusively or more commonly in premenopausal women. Third, if pre-menopausal women were to be scanned, a variety of physiological and benign pathophysiological conditions of the ovary (e.g. functional cysts, endometriomas, etc.) would result in a greater number of 'abnormal' ultrasound scans and possibly higher rates of unnecessary surgical intervention in an age group with a lower incidence of cancer.

The Cost of Screening

In the absence of completed definitive trials of ovarian cancer screening, computer modelling has been used to estimate the cost of screening [62]. Whilst there are limitations to such techniques, it was concluded that even if the variance of rate

of disease progression was higher than that used in an initial model, the cost of ultrasound lower, or only 80% of tumours produced CA125 (instead of the 95% used in the initial analysis), then a multimodal approach was still the most cost-effective method of mass screening. A cost of less than $100,000 per year of life saved was achieved using annual CA125 screening as a first-line test, prompting TVS only if the value doubled since the previous screen or was >35 iu/ml. More reliable information on cost will be available following completion of the UKCTOCS and PLCO trials. This data is extremely important as it will be required to convince governments and health insurers that ovarian screening is cost-effective. It should be noted that UK health insurance companies are not currently recommending or funding ovarian screening as it has yet to be proven effective.

Conclusions

Ovarian cancer screening remains a great challenge. Advances in tumour marker and ultrasound technology, combined with sophisticated statistical analysis, have facilitated two large adequately powered randomised controlled trials of screening, the results of which are eagerly awaited. In the meantime, further efforts are being directed towards the discovery of even more sensitive and specific techniques for screening. Serum proteomics holds great promise in this respect, but requires rigorous validation before it can be used in clinical trials.

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4

Surgical Management of Patients with Epithelial Ovarian Cancer

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Introduction

Ovarian cancer constitutes the leading cause of gynaecological cancer mortality in the industrialised countries. The American Cancer Society reported an estimated 25,580 newly diagnosed ovarian cancer cases and 16,090 deaths caused by ovarian cancer in 2004 in the United States. According to Cancer Research UK, 6,880 women were newly diagnosed with ovarian cancer, and 4,600 women died of the disease in 2001 in the United Kingdom [1]. The disease is frequently called 'the silent killer' as approximately 75% of the patients with ovarian cancer have advanced (stages III–IV, disseminated) disease at the time of the diagnosis, with an overall 5-year survival of 30–40%. The mainstay of the primary treatment for patients with ovarian cancer is still surgery with chemotherapy; however, the sequence of treatment modalities has become a matter of scientific debate during the past decade.

Our aim with this review is to summarise the current state of the surgical management of patients with epithelial ovarian cancer.

Staging Laparotomy

According to the International Federation of Gynaecology and Obstetrics (FIGO), patients with ovarian cancer have to be staged surgically: staging is of importance in planning therapy and assessing prognosis. The main goal of the procedure is to estimate the extent of the disease while, ideally, achieving macroscopic clearance with a so-called maximal or optimal debulking procedure. Table 4.1 shows the key

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Table 4.1. The key elements of surgical staging for ovarian cancer

• Midline incision (extended above the umbilicus if necessary)
• Peritoneal washings from diaphragm, left and right paracolic gutters, pelvis
• Complete staging – palpation and visualisation of abdominal and pelvic organs
• Total abdominal hysterectomy and bilateral salpingo-oophorectomy
• Cytoreduction in case of disseminated disease
• Infracolic omentectomy
• Random blind biopsies of normal peritoneal surfaces
• Removal of bulky pelvic and para-aortic lymph nodes
• Excision and biopsy of any suspicious lesions, adhesions, masses
• Appendectomy for mucinous tumours

elements of the surgical staging procedure for ovarian cancer patients according to FIGO [2].

Appropriate staging plays an important prognostic, diagnostic and therapeutic role in the management of ovarian cancer. Patients with adequately staged, FIGO stage IA grade 1 ovarian cancer confined to one ovary do not need further chemotherapy. However, a significant proportion of apparent, but incompletely staged, stage I ovarian cancers are upstaged to stage IIIc following a full staging procedure and will benefit from adjuvant chemotherapy [3–6]. According to Morice *et al.*, 13% of macroscopic stage IA, 33% of stage IB and 38% of stage IC ovarian cancers have either pelvic and/or para-aortic lymph node metastasis, and therefore are upstaged to FIGO stage IIIC [6]. These figures emphasise the need for proper staging, especially in young patients who wish to conserve fertility by undergoing fertility-sparing surgery, i.e. unilateral salpingo-oophorectomy for early stage ovarian cancer. In the case of positive para-aortic lymph nodes, the left para-aortic lymph nodes above the level of the inferior mesenteric artery are most frequently involved, indicating that a staging laparotomy for apparent early stage ovarian cancer should involve complete pelvic and para-aortic lymphadenectomy up to the level of the renal hilum [6]. Inaccurate staging in these cases results in undertreatment in patients who may benefit from the adjuvant chemotherapy.

In 1990, the European Organisation for Research and Treatment of Cancer (EORTC) initiated a prospective randomised trial named ACTION (Adjuvant ChemoTherapy in Ovarian Neoplasm) comparing platinum-based adjuvant chemotherapy with observation only following staging laparotomy in stage

IA-IIA (except IA grade 1) ovarian cancer. Trimbos *et al.* in their summary concluded that patients, who were in the observational arm and were optimally staged, achieved significantly improved, overall, disease-free survival over those with suboptimal staging in the same arm, indicating the impact of proper staging on survival [7].

Primary Cytoreductive Surgery

The most widely accepted surgical intervention for ovarian cancer is *primary debulking* or *cytoreductive surgery*, which was first introduced by Meigs in 1934 and has been widely used as the cornerstone in the management of ovarian cancer patients since the publication of Griffiths *et al.* in 1975 [8]. Apart from proper staging of the cancer, the intention of this procedure is to remove the tumour bulk, which can eliminate poorly vascularised, therapy-resistant tumour mass and may increase the number of proliferating tumour cells. This can make the tumour cells more sensitive to chemotherapy. By removing the tumour bulk, patients may require fewer cycles of chemotherapy with less chance of developing drug-induced resistance; the host immunocompetence can also be enhanced. However, at this time there is no prospective randomised study supporting the beneficial role of primary cytoreductive surgery in ovarian cancer, although studies, e.g. CHORUS (CHemotherapy OR Upfront Surgery) and EORTC are ongoing to investigate this issue.

The cytoreductive procedure is called *complete* if there is no macroscopic residual tumour left during surgery, *optimal* if the tumour residuum is less than 1 cm, and *suboptimal* if larger than 1 cm. However, it is very difficult to estimate such residual tumour foci. Prefontaine *et al.* studied interobserver variability in tumour measurement and found that the size of the tumour tended to be underestimated [9].

Since the seminal work of Griffiths *et al.* there have been numerous publications indicating that there is an inverse relationship between the residual tumour size and survival, as complete and optimal cytoreduction is related to improved 5-year survival when compared to suboptimal debulking [8,10]. Two large meta-analyses on debulking surgery by Hunter *et al.* and Bristow *et al.*, however, drew conflicting conclusions. Reviewing 6,962 patients with advanced ovarian cancer Hunter *et al.* concluded that primary debulking surgery had no significant impact on survival [11]. Bristow *et al.* reviewed 81 cohorts including 6,885 patients with stage III–IV

ovarian cancer who underwent cytoreductive surgery between 1989 and 1998, and concluded that the strongest predictor of survival was optimal surgical debulking [12].

Although the main goal in the surgical management of ovarian cancer is to achieve complete or at least optimal debulking, there is a wide disparity in surgical success rates, with a proportion of completely cytoreduced patients reported as 42% only [12]. The real explanation of this poor success rate is unknown, but the extent of the cytoreduction basically depends on the institutional philosophical approach, personal experience, and skill of the operating surgeon. Several studies have confirmed that patients operated on by gynaecological oncologists achieve better survival than those operated on by general surgeons or general gynaecologists [18–20]. The multidisciplinary approach also has a positive impact on the outcome of ovarian cancer patients; therefore, all patients with ovarian cancer should undergo treatment in gynaecological oncology centres under the care of a multidisciplinary team [21,22].

Some authors question the justification of suboptimal or perhaps even optimal cytoreduction in the management of ovarian cancer as opposed to a complete surgical resection of all tumour. Eisenkop *et al.*, in their series of 163 patients with FIGO stage IIIC and IV ovarian cancer, achieved complete cytoreduction in 85.3% and observed significant difference (52% vs. 29%) in 5-year survival between completely and optimally debulked patients [13]. They advocated a highly radical surgical approach including diaphragm-stripping or resection, en bloc tumour resection with bowel resection or modified pelvic exenteration, pelvic and para-aortic lymph node dissection, and the use of an argon beam coagulator or a cavitron ultrasonic aspirator (CUSA), with an acceptable rate of serious postoperative complications. They performed a significant number of radical excisions as 52% of their patients underwent modified posterior pelvic exenteration and 20% extrapelvic bowel resection. They concluded that achieving a high rate of complete cytoreduction is possible, whilst avoiding significant morbidity and mortality.

In advanced ovarian cancer, 40% of patients with stage II and 55% of those with stage III and IV disease have positive retroperitoneal nodes [6]. Whether a complete retroperitoneal lymphadenectomy should be performed therapeutically in patients with advanced ovarian cancer, however, is still a matter of debate. Retrospective analyses found a therapeutic benefit for lymphadenectomy [14–16]. Nevertheless, Benedetti-Panici *et al.*, in their recent prospective randomised study of advanced ovarian cancer, compared the survival of patients after systematic

lymphadenectomy with removal of bulky lymph nodes only, and found no overall survival benefit. However, the progression-free survival was significantly improved in the systematic lymphadenectomy group [17].

However, controversy exists regarding the actual effect of the aggressiveness of the surgical cytoreduction on survival, with some authors suggesting that the aggressive biological behaviour of the neoplasm rather than the aggressiveness of the surgeon is responsible for the irresectability of an ovarian cancer [23]. This latter concept may be supported by the low percentage of patients in whom complete cytoreduction is achieved during primary cytoreduction. According to the studies of Hacker *et al.* and Hoskins *et al.*, despite optimal cytoreduction, those patients with initial large intra-abdominal metastases had worse survival rates than those patients with small lesions, suggesting that the biological aggressiveness of the tumour plays a major role in the outcome of the primary cytoreduction [24,25]. This was supported by Crawford *et al.* who analysed the surgical aspect of the SCOTROC-1 (SCOTtish Randomised trial in Ovarian Cancer) trial on primary cytoreduction followed by combination chemotherapy, and concluded that the maximal benefit of complete primary cytoreduction seemed to be in those patients with initially less extensive disease [26,27].

Many question the tradition of surgical management in advanced ovarian cancer and, in future, we may consider patients with stage IIIC ovarian cancer as non-surgical candidates and, therefore, more suitable for primary chemotherapy: similar to other disseminated intra-abdominal neoplasms, such as lymphomas or male germ cell tumours, from which surgery has long receded [23]. Selection of patients for optimal debulking surgery can be done by imaging and assessing preoperative CA-125 levels [28].

Delayed Primary Surgery following Neoadjuvant Chemotherapy

As Bristow *et al.* reported in their meta-analysis, two-thirds of patients are not candidates for optimal primary cytoreduction. However, others have achieved better results using more extended surgery [12,13]. The argument as to whether suboptimal cytoreduction is the consequence of a more aggressive tumour or a less aggressive surgical approach still exists. This significant subset of patients undergoing suboptimal debulking will not derive any benefit from this procedure, but will suffer the morbidity of such an intervention. The alternative to primary

surgery in patients with an unresectable tumour or poor performance status is *neoadjuvant chemotherapy*.

Retrospective studies have shown comparable survival results in patients undergoing neoadjuvant chemotherapy, and reported significantly higher rates of subsequent optimal surgical cytoreduction and less postoperative morbidity [29–36].

The EORTC is conducting a prospective, randomised study comparing primary tumour debulking surgery followed by chemotherapy with neoadjuvant chemotherapy prior to surgery in patients with stage IIIC or IV ovarian cancer (protocol 55971). The primary objectives of the study are to compare the overall and the progression-free survival, the quality of life, and the complications of the different methods. The Royal College of Obstetricians and Gynaecologists (RCOG) has also set up a phase II/III randomised feasibility study named *CHORUS* (CHemotherapy OR Upfront Surgery) to assess the timing of surgery and chemotherapy in treating patients with newly diagnosed advanced ovarian epithelial, fallopian tube, or primary peritoneal cavity cancer. These two randomised studies may determine the real role of neoadjuvant chemotherapy and surgery in the management of ovarian cancer.

Criteria for selecting patients for primary cytoreductive surgery should be clearly defined, as no reliable preoperative strategy for predicting the resectability of a disseminated ovarian cancer has yet been decided universally. Laparoscopic staging can be a proper tool for selecting those patients who are more suitable for neoadjuvant chemotherapy followed by interval debulking. Balanced against this is the concern that in animal models and in vitro studies CO_2-pneumoperitoneum was shown to facilitate tumour cell growth [37]; however, Abu-Rustum *et al.* in their series failed to prove the adverse effect of pneumoperitoneum on survival [38,39]. As the use of laparoscopy in ovarian cancer patients can be associated with port site metastasis [40], delay in commencing neoadjuvant chemotherapy after laparoscopy has to be avoided [38,41].

Computed tomography (CT) and magnetic resonance imaging (MRI) have been extensively investigated in selecting patients for primary chemotherapy [42–47]. Imaging-guided biopsy and histopathologic verification of the ovarian cancer are advisable prior to neoadjuvant chemotherapy. This is not always possible in cases where cytology of aspirated ascetic fluid and appropriate imaging may have to suffice prior to neoadjuvant treatment.

Interval Debulking following Induction Chemotherapy

Interval cytoreductive surgery is usually performed after three cycles of induction chemotherapy in patients with primarily suboptimally debulked ovarian cancer. The aim of this approach is to remove the remaining tumour mass following chemotherapeutic shrinkage.

To determine the effect of such secondary debulking surgery on survival, EORTC initiated a phase III randomised study in 1987 [48]. Patients with residual disease of more than 1 cm after primary debulking were eligible for the study; after three cycles of cisplatin-cyclophosphamide induction chemotherapy those patients who responded to chemotherapy underwent interval debulking followed by three more cycles of chemotherapy. Patients with progressive disease were removed from the study, which provoked some criticism. Van der Burg *et al.* found that debulking surgery for primarily suboptimally debulked (>1 cm residual disease) patients who did not progress during induction chemotherapy significantly prolonged progression-free and overall survival, with a difference in median survival of 6 months. A similar phase III randomised study by the Gynecologic Oncology Group (GOG152) using paclitaxel/cisplatin combination, however, failed to prove any benefit of secondary debulking surgery on progression-free or overall survival [49]. There were differences between the two studies in the selection criteria of patients; most importantly the GOG152 study selected more patients with less residual disease, suggesting that those patients who underwent less successful initial debulking may benefit from the interval debulking following induction chemotherapy.

Cytoreductive Surgery for Recurrent Ovarian Cancer

The place of surgery in the management of recurrent ovarian cancer has not thus far been fully defined. The endpoint of such surgery is unclear as the idea of complete/optimal/suboptimal cytoreduction has been applied to the primary cytoreductive surgical effort. No randomised study has indicated which subpopulation of patients with recurrence can achieve complete cytoreduction and, more importantly, whether complete resection automatically results in survival benefit. The only phase III randomised study on chemotherapy alone versus chemotherapy followed by secondary cytoreductive surgery in patients with recurrent ovarian cancer launched by EORTC (55963 — Larocson study) has been closed due to

failure to recruit patients [50]. The retrospective studies published on secondary cytoreductive surgery have been controversial as the selection criteria and the surgical approach have differed widely. However, several of them reported that complete surgical clearance has provided significant survival benefit compared to optimal or suboptimal secondary debulking [50].

The question of which patients can achieve complete surgical cytoreduction has been addressed in the retrospective DESKTOP study (AGO-OVAR) including 268 patients with recurrent ovarian cancer. Harter *et al.* found that factors indicating a higher probability for complete cytoreduction in a multivariate analysis were good performance status, small volume ascites (<500 ml), no residuum after primary cytoreductive surgery, and no evidence of peritoneal carcinomatosis on imaging prior to operation. Complete cytoreduction was possible in 81% of those patients with these four variables present, and only 43% of those patients with less than four factors [50]. Desktop-II study will be conducted to evaluate these variables prospectively. Eisenkop *et al.*, in their series of 106 patients with recurrent ovarian cancer, have identified smaller tumour size (<10 cm), good performance status, and no salvage chemotherapy prior to operation as good predictors for complete cytoreduction [51].

Until results from prospective randomised trials are available no proper answer can be given on the role of cytoreductive surgery in the management of recurrent ovarian cancer.

Palliative Surgery for Recurrent Ovarian Cancer

The majority of patients undergoing repeat explorative laparotomy will do so for symptomatic control of intestinal obstruction. Retrospective studies estimated that bowel obstruction occurs in up to 50% of patients with ovarian cancer [52,53]. Most of these patients underwent previous complex treatment including surgery, several lines of chemotherapy, or radiotherapy. Therefore, the main outcome measure of treatment is to improve the quality of life in a patient with limited life expectancy.

The median survival is 3 to 6 months in patients who have developed bowel obstruction due to recurrent cancer. Therefore, the quality of life for patients after surgery for obstruction, the risk of recurrent obstruction (up to 50%) eligibility for salvage chemotherapy, as well as the rates of perioperative mortality (up to 30%) and morbidity, have to be considered in the decision-making process [54,55].

The role of surgery for recurrent ovarian cancer-related bowel obstruction has remained controversial. As these clinical situations must be assessed individually, each involving the gynaecological surgeon, medical oncologist, palliative care team and, most importantly, the patient and her family, there is little chance to conduct prospective randomized studies. Retrospective analyses revealed that those patients who have undergone optimal primary cytoreduction respond significantly better to a conservative approach than those with suboptimal primary surgery. Age, malignant cause of obstruction, an advanced stage at presentation and shorter interval time from the primary surgical intervention are all adverse prognostic factors; a single site of obstruction and a benign cause are good prognostic measures. Most bowel obstructions are caused by the tumour itself; however, 30% of gastrointestinal obstruction in ovarian cancer are of non-malignant pathology.

To better define patients who would benefit from surgery, in 1983 Krebs and Gopelrud developed a prognostic model based on age, nutritional and tumour status, presence of ascites, previous chemotherapy and radiotherapy. They reported that 84% of patients with a score ≤ 6 survived at least 60 days post-surgery, while only 20% with a score ≥ 7 survived [56].

It is crucial that the patient and her family have to be fully informed and aware of the clinical situation, the palliative nature of the management and the results, as well as complications of the available procedures. A multidisciplinary review between surgeon, medical oncologist and palliative physician is critical in order to select which patients may benefit from palliative diversion or bypass if a bowel resection is not feasible.

Conclusion

The conflicting data quoted in this review raises a controversial question as to whether ovarian cancer should be treated surgically or medically. The answer from prospective randomised studies may not be forthcoming and so the management of ovarian cancer patients needs to be more individualised. Some cases may require the traditional approach of combined surgical and medical treatment, while others will be treated solely by chemotherapy. Conversely, we must not forget the two major factors in determining management of women with ovarian cancer. Firstly, *quality of life* is an important endpoint of management, as well as *5-year survival* [57]. All those treating patients afflicted by this dreadful

disease must be able to balance the likelihood of response to treatment and cure against important quality of life issues.

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5

Medical Treatment of Ovarian Carcinoma

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Introduction

Ovarian cancer is a very chemosensitive tumour with a number of classes of drugs showing activity. Major advances in treatment of newly diagnosed ovarian cancer have improved survival but most patients relapse and require further treatment and only a minority of patients with advanced disease achieve long-term survival. Research is directed towards finding new effective agents and regimes with minimum toxicities.

Chemotherapy in Early Stage Disease

Two prospective, randomised trials of patients with stage Ia or Ib disease with well or moderately differentiated cancers demonstrated a 5-year survival of over 90% with surgery alone. 81 patients were randomized after surgery to receive oral melphalan (0.2 mg/kg/day for 5 days) or no further treatment. There were no significant differences between the no chemotherapy and the melphalan arms with respect to either 5-year disease-free survival (91% vs. 98%; $p = 0.41$) or overall survival (94% vs. 98%; $p = 0.43$). In the second trial, 141 patients with poorly differentiated stage I or stage II disease received either melphalan (as above) or a single intraperitoneal dose of P^{32} at the time of surgery. The outcomes for the two treatment groups were similar. 5 year disease-free survival (DFS) was 80% in both groups and overall survival was 81% with melphalan versus 78% with P^{32}; $p = 0.48$ [1]. An Italian group studied 271 patients with moderate or poorly differentiated stage Ia, b and c disease. Patients were randomised to Cisplatinum

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(50 mg/m^2 with repeated courses every 28 days for 6 cycles) versus observation versus P^{32}. Cisplatinum significantly reduced the relapse rate by 65% and 5-year survival was 88% vs. 82% vs. 79%, respectively, but was not significantly different. There was, however, crossover to Cisplatinum at the time of relapse [2].

Two European studies of 923 patients with stage Ia, b and c disease were randomised to platinum-based chemotherapy versus observation. The 5-year DFS was 76% vs. 65% and 5-year survival 82% vs. 75%. There was a 28% reduction in the odds of death in the treatment arm with similar benefit across age, stage and differentiation [3]. The ICON I (International Collaboration on Ovarian Neoplasms) trial has defined the new standard of care in early stage ovarian cancer and has established the role of adjuvant therapy in this group of patients.

In localized ovarian cancer, comprehensive staging at the time of surgical resection can serve to identify those patients who can be followed without adjuvant chemotherapy. The remaining patients with localized ovarian cancer should receive adjuvant therapy.

Chemotherapy in Advanced Disease

Systemic Chemotherapy

The current management of advanced ovarian cancer (stages III and IV) involves cytoreductive surgery, where possible, and cytotoxic chemotherapy. Cisplatin was discovered in the 1970s and it became clear that it was a very effective drug in ovarian cancer [4]. Most randomised studies show superior response rates and progression-free survival with cisplatin-based regimes [5,6]. By the late 1980s platinum-based combination therapy was the international gold standard. In 1971 paclitaxel, extracted from the bark of *Taxus brevifola* (Pacific yew tree), was identified [7] and subsequently found to be active in women who had progressed following platinum therapies [8]. Two broadly similar studies investigated the role of paclitaxel in combination first-line therapy. They strongly supported the use of cisplatin/paclitaxel chemotherapy with significantly improved response rates by up to 14%, progression-free survival (PFS) by up to 5 months, and overall survival by up to 14 months [9,10]. Given the improved safety profile of carboplatin, several studies were performed that confirmed carboplatin-paclitaxel was as effective as cisplatin-paclitaxel [11,12].

However, these apparently clear benefits of the addition of paclitaxel have been contradicted in two further studies [13,14]. In the first study, the paclitaxel-only arm was clearly inferior but there was no significant difference between single-agent cisplatin and cisplatin-paclitaxel in terms of response rate (67% vs. 67%), PFS (16.4 vs. 14.1 months) and overall survival (30.2 vs. 26.0 months). ICON3 was a much larger trial that found no significant difference between carboplatin or cyclophosphamide, doxorubicin and cisplatin combination versus carboplatin-placlitaxel. Also, the single agent carboplatin was better tolerated, producing less toxicity, such as alopecia and peripheral neuropathy. It is not clear whether the carboplatin arm in ICON3 did better than expected or whether carboplatin-paclitaxel performed worse. The two earlier, positive studies were both large and produced highly significant results, which one would not expect to occur by chance. There is, however, clear heterogeneity between the trials discussed. The data clearly demonstrates that cisplatin-paclitaxel is superior to cisplatin-cyclophosphamide, and that carboplatin-paclitaxel gives similar efficacy with less toxicity. Paclitaxel is an active drug in platinum-resistant patients but appears to add little to carboplatin and may even be antagonistic. Carboplatin-paclitaxel has become the standard of care but the ICON3 data show that single-agent carboplatin is a reasonable alternative, particularly in less fit patients.

Other Treatment Approaches

The biology of ovarian cancer, with most patients having disease confined to the abdomen and pelvis, has made intraperitoneal therapy an attractive area for research. This modality allows for dose escalation in the tumour environment with less systemic toxicity and has been explored in patients with small volume disease. Two randomised studies have shown a statistically significant improvement in median survival for patients receiving intraperitoneal therapy as well as systemic chemotherapy, but the practical difficulty of administering this therapy and the fact that it is only applicable to the small cohort of patients with small-volume residual tumour has meant that it has not become widely used [15,16]. A recent study of over 400 patients with optimally debulked stage III ovarian cancers showed a significant increase in progression-free (23.8 vs. 18.3 months) and overall survival (65.6 vs. 49.7 months) for patients receiving intraperitoneal paclitaxel and cisplatin plus intravenous paclitaxel compared to those having intravenous paclitaxel and cisplatin alone [17].

Relapsed Ovarian Cancer

Chemotherapy

Paclitaxel, etoposide, topotecan, gemcitabine, liposomal pegylated doxorubicin, oxaliplatin, capecitabine and vinorelbine are all active as single agents in relapsed disease with overall response rates of 15–30% and median response duration of 6–8 months.

Paclitaxel

Paclitaxel promotes microtubule assembly and blocks depolymerization producing non-functional microtubules. Several studies showed activity in patients with relapsed disease. A study of 45 patients who had previously received platinum-based treatment had an overall response rate of 37% [18]. A large group of patients who had received at least three lines of prior chemotherapy had an objective response of 22% with single agent paclitaxel [19]. The findings of the ICON4 trial suggest the combination of platinum and paclitaxel on recurrent platinum-sensitive patients is superior to platinum alone [20]. High-dose paclitaxel (250 mg/m^2) with GCS-F (granulocyte colony stimulating-factor) support resulted in an overall response rate of 48% [21]. Patients who have not received paclitaxel in the first-line should be offered it at relapse but this situation is becoming increasingly uncommon as mentioned previously.

Etoposide

Etoposide is a topoisomerase II inhibitor with a response rate of approximately 15–20% in recurrent ovarian carcinoma. It is a convenient option as it may be administered in the oral form and it is well tolerated. In one phase II study using 50 mg oral etoposide twice daily for up to 14 days of a 21-day cycle as tolerated showed an overall response rate of 24% and 22% of patients had stable disease [22]. In a larger study 50 mg/m^2 daily for 21 of a 28-day cycle, a response rate of 28% was found in platinum-resistant patients but 34% in those previously sensitive to a platinum agent. Myelotoxicity with this regime, however, was significant and unpredictable [23].

Topotecan

Topotecan is a topoisomerase I inhibitor with single agent activity in platinum-resistant ovarian carcinoma. Overall response in second or third line ranges

from 13.7 to 33% and median duration of response of 11.2 to 21.7 months [24–26]. When topotecan was compared with paclitaxel in patients who progressed during or after one platinum-based regimen the response rate in the topotecan arm was 20.5% compared with 13.2%, but this was not significant ($p = 0.138$). Median time to progression was 23 weeks (14 weeks for paclitaxel, $p = 0.002$), showing that topotecan is at least as effective in this setting [27]. The crossover effect was later reviewed in a subset of 110 of these patients and failed to demonstrate that the two drugs have a degree of non-cross-resistance. Patients failing to respond to one drug may go on to respond to the other [28]. The standard dosing schedule of topotecan is a daily intravenous dose for 5 consecutive days, which is not very practical, and the drug is associated with significant myelosuppression. Various dosing schedules and methods of administration have been studied with variable success. It appears to have significant activity in the oral preparation with possibly less toxicity [29].

Gemcitabine

Lund *et al.* used a regime of gemcitabine (a nucleoside analogue) given intravenously at 800 mg/m^2 weekly for 3 weeks followed by a 7-day break to 50 patients [30]. There was a response rate of 19% and median response duration of 8 months, but there was significant myelotoxicity. When used at higher doses, response rates of 13 to 18% were seen [31,32], confirming a modest level of activity as a single-agent platinum and taxane-resistant disease.

Anthracyclines

Liposomal doxorubicin (Caelyx) is a formulation of the anthracycline that results in a small volume of drug distribution, slower plasma clearance, prolonged plasma half-life [33] and higher tumour concentrations than in normal tissue. This results in reduced side-effects, including cardiac toxicity, which previously limited the use of doxorubicin [34]. Thirty-five patients with platinum/paclitaxel resistance received single agent Caelyx 50 mg/m^2 every 3 weeks with an overall response rate of 25.7%, PFS 5.7 months and overall survival 11 months [35]. A later, larger phase II study, with the same dose every 4 weeks, showed an overall response rate of 16.9% with a median time to progression of 19.3 weeks [36]. There was no significant difference in progression-free and overall survival between caelyx and topotecan in 474 patients who had platinum-refractory disease. Caelyx caused more palmar-plantar erythema but topotecan was more myelosuppressive [37]. When compared with paclitaxel in a large study of paclitaxel-naïve patients, who had progressed either during or after first-line platinum regimens, overall

response was 17.8% in the caelyx group and 22.4% in the paclitaxel arm ($p = 0.34$); thus caelyx has comparable efficacy to paclitaxel in relapse after platinum therapy [38]. Epirubicin is another anthracycline that is less commonly used in ovarian carcinoma.

Other Platinum Agents

Oxaliplatin

Oxaliplatin is a third generation platinum analogue, which has a relative lack of cross-resistance with cisplatin and carboplatin, and is not associated with nephro- or ototoxicity. It is administered as an intravenous infusion and is active in recurrent ovarian cancer with response rates of 16 to 29% as single agent in patients who have previously received a platinum agent. The main toxicity of this drug is peripheral neuropathy but it is a reasonable treatment option in this setting [39,40].

Vinorelbine

This drug, also known as Navelbine, is a vinca-alkaloid that is currently administered by a short weekly intravenous infusion that produces response rates of up to 29% [41]. It is commonly used in non-small-cell lung and breast cancers and the toxicity is usually mild and most commonly haematological.

Capecitabine

This is an oral fluoropyrimidine that is used in colorectal and breast malignancies, and has been evaluated recently in recurrent ovarian carcinoma. It shows some activity in heavily pre-treated patients with small phase II studies demonstrating response rates of up to 32% [42]. Toxicities most commonly encountered with this agent include diarrhoea and palmar-plantar erythema.

Combination versus Single-Agent Therapy

Studies so far have shown that while toxicity is greater with combination therapy, especially myelotoxicity, few have demonstrated superiority over single agent regimes. An international 5-arm randomised trial of paclitaxel and carboplatin versus triplet or sequential doublet combinations (ICON5) is currently ongoing.

Response Prediction

The interval between completion of first-line therapy and relapse has been shown to be strongly predictive of response to subsequent therapies [43,44]. Patients who have a treatment-free interval of less than 6 months have a significantly poorer response rate to salvage therapy and a reduced median survival. Response rates at relapse to platinum-based treatment for patients with treatment-free intervals of 5–12 months, 13–24 months and more than 24 months were 27, 33 and 59%, respectively [45]. All three studies suggest that patients should be rechallenged with a platinum agent if disease relapse occurs after a significant time-interval.

When should Treatment be Started?

Despite the treatment advances in newly diagnosed disease most patients do relapse and require salvage therapy. These patients are incurable and, therefore, treatment goals are effective symptom control and increased survival. The decision as to when to commence treatment can be difficult as a rising CA125 tumour-marker may predate clinical relapse by several months [46,47]. Most oncologists would recommend observing a rising marker level and deferring treatment until a patient was symptomatic, but not all patients find this acceptable. There are no data at present that demonstrate a survival advantage to either approach, but a randomised MRC trial of early second-line treatment based on CA125 levels alone versus delayed second-line treatment based on conventional clinical indications is currently looking at this problem [48].

Other Treatment Approaches

Endocrine Therapies

Ovarian tumours may frequently express hormone receptors but receptor status has not shown to be predictive of response to endocrine manipulation therapy. Most trials have been retrospective and small. Tamoxifen and progesterones have been used in pre-treated relapsed ovarian carcinoma with a response rate of about 10% [49]. GnRH agonists have been used in the treatment of advanced, recurrent, or persistent ovarian carcinoma. The combined results have shown a 12% response rate with 30% stable disease [50].

Novel Therapies

New platinum analogues and taxanes are being evaluated with some success and further evaluation is ongoing. There is rapid development of various new drugs with differing modes of action throughout oncology and this is likely to increase further the number of therapeutic options available to patients with epithelial ovarian cancer. These approaches include oral tyrosine kinase inhibition and monoclonal antibodies targeting both the epidermal growth factor receptor and vascular endothelial growth factor receptor. A number of these agents, such as Bevacizumab, are already available in clinical practice [51].

Telcyta (TLK286) is a molecule that is activated by glutathione S-transferase P1−1 (GSTP1−1). This is overexpressed in many cancer cells, but not in normal cells, and overexpression is associated with chemotherapy resistance. When activated, Telcyta initiates cellular death predominantly only to tumour cells, resulting in minimal side-effects. As a single agent it appears to produce responses and stabilize cancer progression in patients with ovarian cancer that has stopped responding to standard chemotherapy [52].

Conclusion

Various different cytotoxic drugs show activity in ovarian cancer. In early stage disease adjuvant platinum agents may increase the 5-year disease-free survival by over 10% and increase the overall survival post-surgery. Platinum also has superior response rates in most randomised studies and carboplatin with paclitaxel is now the standard of care. In relapsed ovarian cancer paclitaxel, etoposide, topotecan, gemcitabine, liposomal pegylated doxorubicin, oxaliplatin, capecitabine and vinorelbine are all active as single agents with overall response rates of 15 to 30% and median response duration of 6−8 months. Patients who have not received paclitaxel should be offered it in the second-line setting. Combination therapies show greater toxicity without any significant superiority compared with single-agent treatments. The interval between completion of first-line treatment and relapse is strongly predictive of subsequent response and survival. Endocrine therapies have a role to play and novel therapies are being assessed. Difficulties exist regarding whether to reinstitute treatment based on a rising CA125 tumour marker alone. There are no data currently to support this approach. There are a number of ongoing trials which should serve to aid management decisions further.

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6

Ultrasound in Ovarian Carcinoma

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Ultrasound is the first imaging test used in most patients with an adnexal mass, and the great majority of adnexal masses are benign. Ultrasound has been shown to have a high sensitivity for detecting malignancy, but this is countered by a much lower specificity. In this chapter the ultrasonic features which suggest a malignant diagnosis and the wide differential diagnosis which often has to be considered are summarised. The performance of ultrasound in detecting malignancy in adnexal masses and its role in the diagnosis of ovarian cancer are then discussed.

Ultrasonic Technique

The patient's clinical presentation, age, menstrual status and CA125 level are all important factors influencing the differential diagnosis when the ultrasonic assessment is made.

Morphological Assessment

Most adnexal masses are assessed transvaginally because the resolution which can be obtained with high frequency transvaginal transducers (6–10 MHz) is superior to that obtained transabdominally, scanning at frequencies of 3–5 MHz. Transvaginal ultrasound is limited by a maximum depth of view of 5–6 cm and this makes it unsuitable for full examination of larger masses which have to be evaluated transabdominally. However, even when the mass is large, it is often worth doing

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a transvaginal examination because this allows high resolution visualisation of the inferior part of the mass and because it may be the only way to identify normal pelvic structures displaced by a large mass. The key elements of the morphological assessment are identification of the normal uterus and ovaries, so that the site of origin of the mass can be determined, and detailed characterisation of the internal structure of the mass. Identification of normal ovarian tissue stretched at the margin of a mass (ovarian crescent sign) identifies the site of origin of the mass and suggests that invasive malignancy is less likely [1].

When the pelvic ultrasound examination suggests that malignancy is possible, the whole abdomen should be examined to check for other features which may suggest malignancy. These include ascites, evidence of peritoneal disease – either nodules or larger masses such as the typical omental cake of advanced disease, liver metastases, enlarged nodes or renal obstruction.

Doppler Examination

Doppler examination is widely used to look for features suggestive of tumour neovascularity. Vascularity is sought in solid masses and in the complex areas of cystic masses, such as septa, nodules or thickened areas of the wall. Power Doppler appears to be more sensitive than conventional velocity Doppler [2]. When vessels are seen, a spectral trace can be obtained to look for the typical low impedance arterial flow associated with tumour neovascularity [3]. Both the pulsatility index (PI) and resistance index (RI) typically decrease in areas of malignancy neovascularity. A PI of less than 1.0 and an RI of less than 0.4 are described as indicating 'malignant' flow [3–5]. The limitations of Doppler ultrasound and its diagnostic role are considered later in the chapter.

New Developments

It has recently been suggested that 3D ultrasound combined with power Doppler improves the diagnosis of malignant masses [6] but others have found the performance of 3D power Doppler to be no better than that of conventional 2D power Doppler [7]. Different patterns of enhancement with ultrasonic contrast media in malignant and benign ovarian masses have been described [8–10], but the clinical importance of these observations remains to be evaluated.

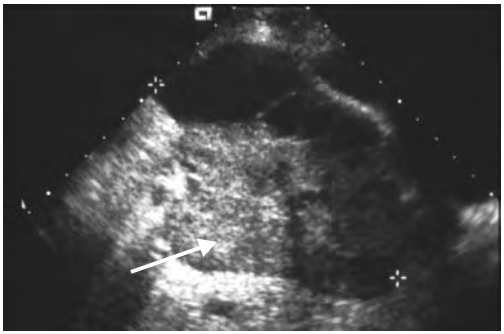

Figure 6.1 Poorly differentiated adenocarcinoma, diameter 11 cm (transabdominal scan). Note the large solid area (arrowed) and cystic area containing fine septa.

Ultrasonic Diagnosis of Malignancy

Tumours of surface epithelial origin account for approximately 90% of primary ovarian malignancy. Serous ovarian tumours are the most common, accounting for up to 40%, followed by endometrioid, mucinous, undifferentiated and clear cell tumours in decreasing order of frequency [11]. Metastases account for 5–10% of all ovarian tumours. In this section the ultrasonic findings which suggest malignancy are summarised, and the features which may be used to make a more specific diagnosis among the primary ovarian tumours or to diagnose metastatic ovarian malignancy are then considered.

Malignant Features

A malignant diagnosis is suggested by a mass greater than 6 cm in diameter. However, cystic masses greater than 10 cm in diameter are often benign. Bilaterality also raises the suggestion of malignancy. Morphological features which suggest malignancy are solid areas (Fig. 6.1), solid areas containing fluid (which may indicate necrosis) (Fig. 6.2) and complex cystic masses. Complex cystic masses contain papillary or nodular solid projections, have septa or walls greater than 3 mm in thickness, and are frequently multilocular [12,13] (Figs. 6.3 and 6.4).

Ultrasonic Features of Primary Malignancies

Serous Tumours

Serous tumours are usually predominantly cystic and are multilocular. Papillary solid projections into the cysts are typical (Fig. 6.3). Microscopic calcifications

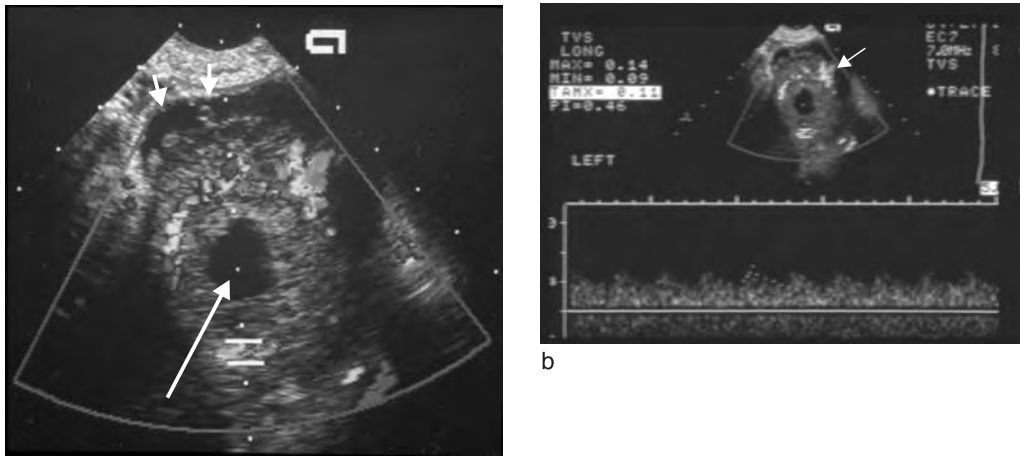

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Figure 6.2 Endometrial carcinoma, diameter 5 cm (transvaginal scans). (a) Solid mass with central necrosis and fluid (long arrow). Note small peritoneal nodules on tumour surface (short arrows) surrounded by ascites. (b) Doppler examination shows bright signal of vascularity (arrowed) and spectral trace with high diastolic flow, PI = 0.46.

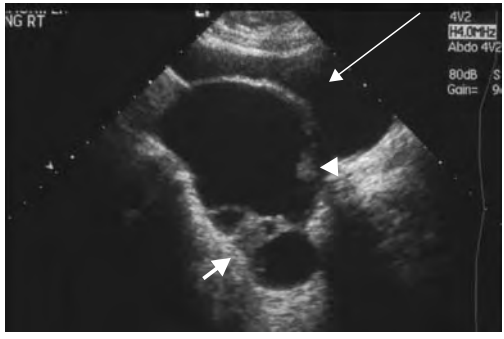

Figure 6.3 Serous cystadenocarcinoma, diameter 10 cm (transabdominal scan). Predominantly cystic mass deep to bladder (long arrow) contains a solid nodule (arrowhead) and solid area adjacent to septa (short arrow).

(psammoma bodies) occur in up to one third of tumours but are not detectable with ultrasound [14].

Mucinous Tumours

Mucinous tumours are also predominantly cystic and typically multilocular (Fig. 6.4). Malignancy is more usually indicated by solid areas and thickened walls or septa than by papillary projections. The contained fluid may show low-level echoes indicating mucin or blood.

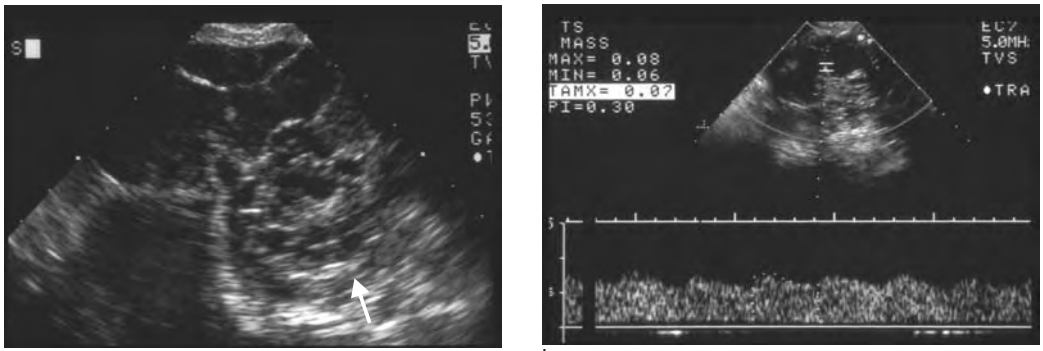

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Figure 6.4 Mucinous cystadenocarcinoma, diameter 15 cm. (a) Transabdominal scan shows cystic mass with multiple septa, reflective material in fluid and solid area (arrowed). (b) Transvaginal Doppler examination shows spectral trace with high diastolic flow, PI = 0.30.

In both serous and mucinous tumours there is a continuum of disease from benign cystadenoma to malignant cystadenocarcinoma, which may make precise identification of malignancy difficult. Multilocularity alone does not necessarily indicate malignancy in serous and mucinous tumours.

Endometrioid Carcinomas

Endometrioid carcinomas are usually solid and may contain fluid or necrotic areas (Fig. 6.2). In up to one third of patients there may be endometrial hyperplasia or carcinoma [14].

Clear Cell Tumours

Clear cell tumours are often cystic with a nodular or mass-like solid component [14].

Epithelial Tumours of Low Malignant Potential (Borderline Tumours)

Epithelial tumours of low malignant potential (borderline tumours) mimic other epithelial tumours and are usually impossible to identify with certainty by imaging (Fig. 6.5). Papillae have been described as being a diagnostic feature [15–17] but also occur in true malignancy.

Germ Cell Tumours

Germ cell tumours (dysgerminomas) are typically solid tumours containing fluid areas of necrosis. Immature teratomas are usually large and contain coarse calcification and small areas of fat [5].

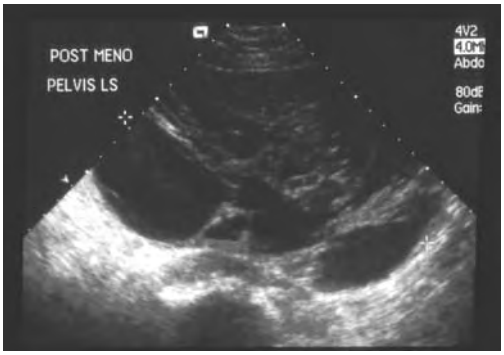

Figure 6.5 Borderline mucinous cystadenoma, diameter 19 cm. Transabdominal scan shows complex mass with multiple septa, some thick, and solid areas.

Ultrasonic Features of Metastatic Malignancy

Metastatic ovarian tumours may be predominantly fluid-containing, mixed solid and fluid, or solid [18]. On their ultrasonic appearance they are often indistinguishable from primary ovarian malignancy (Fig. 6.6), although multilocularity appears to favour a diagnosis of primary ovarian cancer [19]. Pointers to the diagnosis are current or previous primary malignancy elsewhere (especially colon, breast, stomach or pancreas) and bilaterality.

Differential Diagnosis of Adnexal Masses

The differential diagnosis of a possibly malignant adnexal mass is wide and includes a variety of benign ovarian cysts, benign ovarian tumours, uterine and tubal pathology as well as a number of non-gynaecological diagnoses.

Simple Ovarian Cysts

Simple ovarian cysts contain clear fluid with good posterior acoustic enhancement, have a thin wall and no complex features (Fig. 6.7). In premenopausal women these are often functional follicular cysts which resolve spontaneously. In postmenopausal women, simple cysts may occur in up to 18% [20]. They have a low risk of malignancy and many resolve spontaneously [21,22].

Benign Cystadenomas

Benign serous and mucinous cystadenomas may be seen ultrasonically as simple cysts. However, they may attain a large size and may show a variety of complex

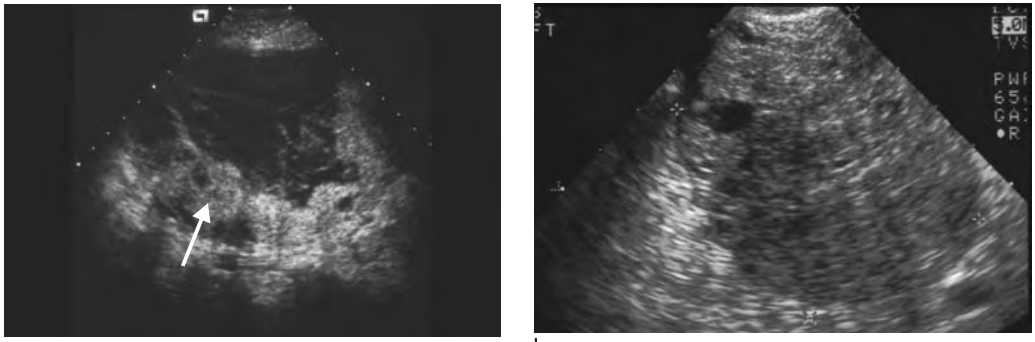

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Figure 6.6 Ovarian metastases. (a) 13 cm cystic mass with septa and peripheral solid component (arrowed) (transabdominal scan). (b) 6 cm predominantly solid mass in the contralateral ovary (transvaginal scan).

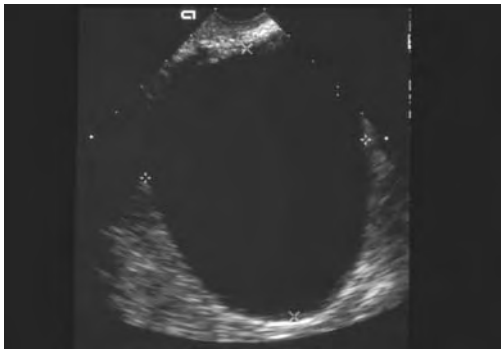

Figure 6.7 Simple ovarian cyst, diameter 7.5 cm. Transvaginal scan shows simple fluid collection.

features, making them indistinguishable ultrasonically from malignant tumours. Typically serous cystadenomas show small papillary excrescences (Fig. 6.8) and mucinous cystadenomas may be multilocular and contain reflective material representing mucin within the fluid (Fig. 6.9).

Haemorrhagic Functional Cysts

Haemorrhagic functional cysts occur when there is haemorrhage into the corpus luteum. They have a complex ultrasonic appearance with echoes within the cyst which may have a reticular or lace-like pattern (Fig. 6.10), or with a solid nodule representing retracting clot. Haemorrhagic cysts may mimic malignant cysts. This diagnosis should always be considered in a premenopausal female and can be

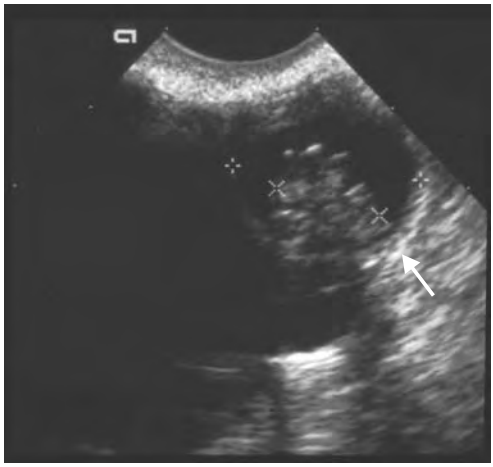

Figure 6.8 Serous cystadenoma, diameter 4 cm (transvaginal scan). Note 1.7 cm solid nodule (arrowed) and fine septum.

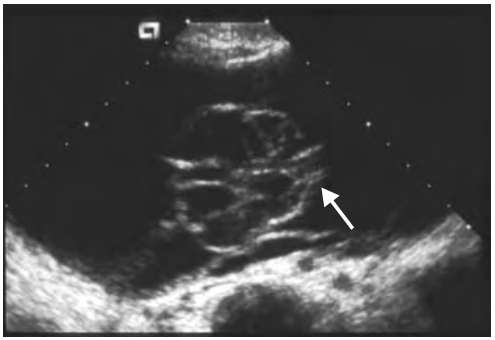

Figure 6.9 Mucinous cystadenoma, diameter 16 cm (transabdominal scan). Predominantly cystic mass with a complex multiseptate area posteriorly (arrowed). (By permission of Clinical Radiology.)

established when the cyst resolves at follow-up. Unlike a tumour nodule, retracting clot does not show vascularity on Doppler examination.

Mature Cystic Teratoma of the Ovary

Mature cystic teratoma of the ovary can have a wide variety of ultrasonic appearances which may mimic malignancy [23,24]. An area of focal high reflectivity (more reflective than adjacent myometrium) occurs where there is solid fat (Figs. 6.11 and 6.12). A highly reflective focus with acoustic shadowing may arise from calcification or hair in a Rokitansky nodule. Hair within the mass gives rise to reflective lines and dots (Fig. 6.13). A variety of fluid-fluid levels of different reflectivity may occur between sebum and serous fluid (Fig. 6.14) [25] and there may be a floating mass on the fluid.

Endometriomas

Endometriomas may also mimic ovarian malignancy. The most typical appearance is a mass with diffuse low level echoes (less reflective than normal myometrium) and good through transmission of sound (Fig. 6.15). This pattern occurs in 95% of endometriomas [26]. Other findings include small peripheral, highly reflective foci, multilocularity and fluid-fluid levels [26,27] (Fig. 6.16). Thus endometriomas and dermoids have some features in common.

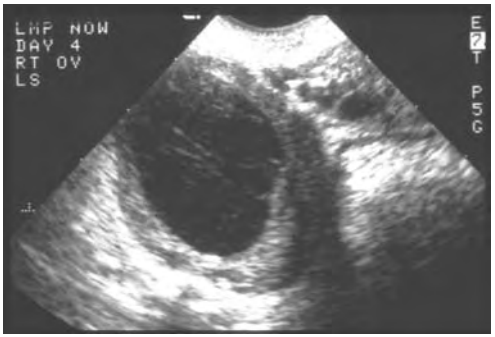

Figure 6.10 Haemorrhagic functional cyst, diameter 3 cm. Transvaginal scan shows typical central lacelike reticular pattern.

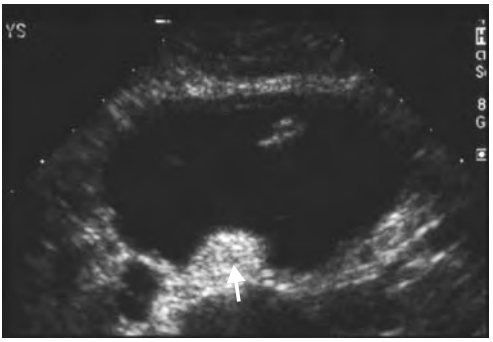

Figure 6.11 Mature cystic teratoma, diameter 6 cm (transvaginal scan). Cystic mass with a highly reflective nodule (arrowed) on posterior wall, shown on MR to contain fat. (By permission of Clinical Radiology.)

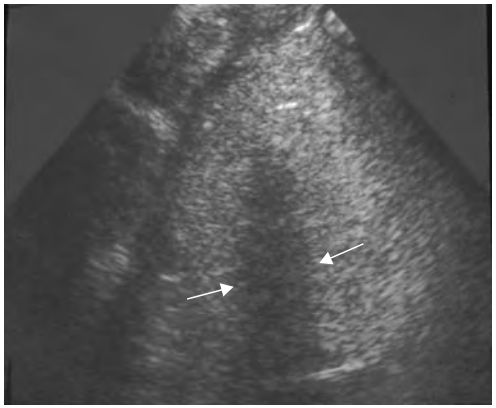

Figure 6.12 Mature cystic teratoma, diameter 7 cm (transvaginal scan). Mass shows increased reflectivity with acoustic shadowing (arrowed) arising from its centre.

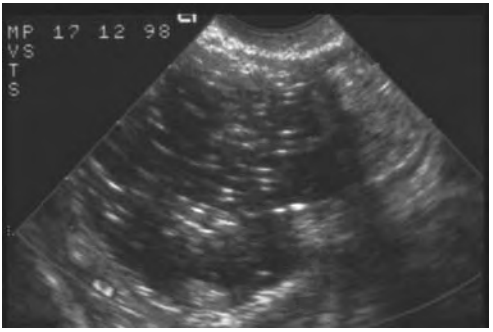

Figure 6.13 Mature cystic teratoma, diameter 3 cm (transvaginal scan). Mass contains multiple reflective lines and dots caused by hair.

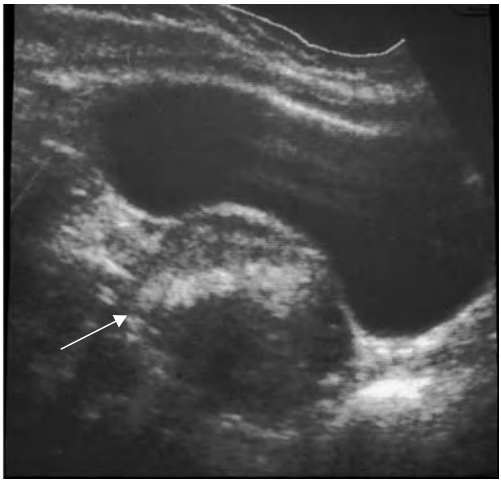

Figure 6.14 Mature cystic teratoma, diameter 5 cm (transabdominal scan). Mass contains a fluid level (arrowed).

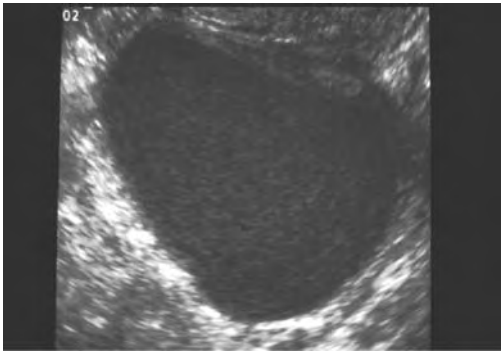

Figure 6.15 Endometrioma, diameter 6 cm (transvaginal scan). Diffuse low level echoes fill the cystic mass.

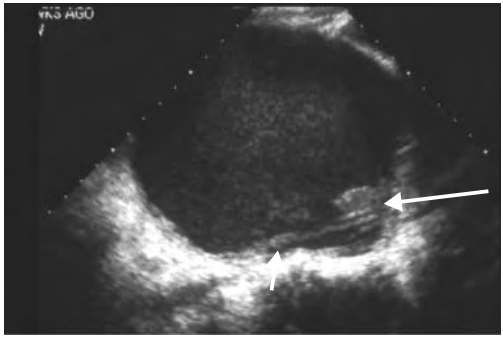

Figure 6.16 Endometrioma, diameter 15 cm (transabdominal scan). Note septum (short arrow) and nodule (long arrow) in addition to diffuse low level echoes.

Ovarian Fibromas and Thecomas

Ovarian fibromas and thecomas are solid tumours which may be homo- or heterogeneous on ultrasound and typically attenuate the sound beam in the absence of a strongly reflective focus [28–30] (Fig. 6.17).

Granulosa Cell Tumours

Granulosa cell tumours are usually solid and have no ultrasonic features that distinguish them from other ovarian tumours [31], although the association with endometrial hyperplasia may suggest the diagnosis.

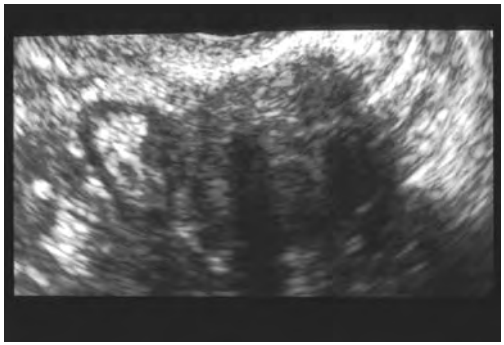

Figure 6.17 Ovarian fibroma, diameter 2.5 cm (transvaginal scan). Solid mass with acoustic shadowing arising from it.

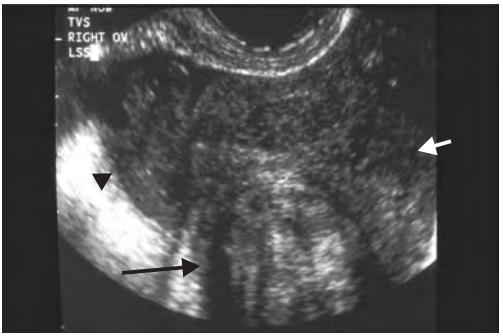

Figure 6.18 Uterine fibroid, diameter 4.5 cm (transvaginal scan). Heterogeneous solid mass (long arrow) arising from uterus (short arrow) with the ovary lying adjacent (arrowhead).

Brenner Tumours

Brenner tumours are small solid homogeneous masses which may contain dense calcification [14].

Uterine Fibroids

Uterine fibroids are solid myometrial masses which transmit sound poorly and may contain areas of calcification or fluid which indicates necrosis (Figs. 6.18 and 6.19). Continuity with the myometrium is an important diagnostic criterion for the diagnosis of a fibroid. However, it may not be seen with pedunculated fibroids, and large complex or necrotic fibroids may also give rise to diagnostic difficulties with ultrasound.

Masses of Tubal Origin

Masses of tubal origin are often elongated rather than rounded, and contain fluid in which the folds in the tubal wall may be seen. If the ovary is seen separate to the mass, a tubal origin is suggested but with large and complex tubal masses it may be impossible to identify the ovary.

Peritoneal Pseudocysts

Peritoneal pseudocysts are fluid-containing masses which may be multilocular and which follow previous surgery or pelvic inflammatory disease. The diagnosis is suggested in the appropriate clinical setting when normal ovaries are seen separate to the mass, and when the fluid in the mass is seen to surround rather than arise from pelvic structures.

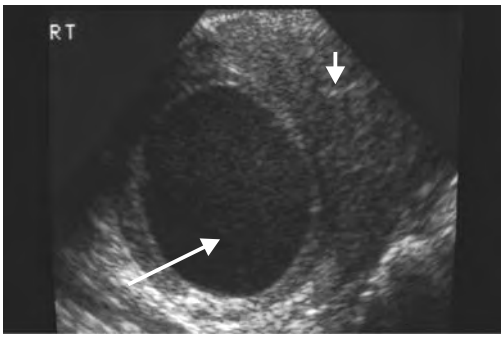

Figure 6.19 Necrotic uterine fibroid, diameter 4.5 cm (transvaginal scan). Mass arising from the uterus has a fluid centre with reflective material in it (long arrow). Short arrow indicates endometrium.

Other Pelvic Masses

Other pelvic masses which may have to be included in the differential diagnosis of ovarian carcinoma [32] are listed in Table 6.1.

Performance of Ultrasound in Detecting Malignancy

Morphological Ultrasound

The many studies evaluating the performance of ultrasound in detecting malignancy based on morphological features have all shown good sensitivity, in the range 88–100%, but less satisfactory specificity, in the range 39–87% [33–40]. A corollary of the high sensitivity is a high negative predictive value for malignancy, an important feature in a test being used to triage for malignancy.

Table 6.1. Pelvic masses which may simulate gynaecological pathology

1. Gastrointestinal:	Perforated sigmoid carcinoma
	Diverticular abscess
	Perforated appendix abscess
2. Peritoneal pseudocyst	
3. Extraperitoneal tumours:	Presacral teratoma
	Ganglioneuroma
	Soft tissue sarcoma
4. Lymphocoele	
5. Bladder diverticulum	
6. Lymphadenopathy, e.g. lymphoma	

Several factors contribute to the less than optimal specificity of ultrasound morphological assessment. The continuum of morbid anatomy from benign to malignant among the epithelial neoplasms leads to difficulty. Thus, papillary projections are a sign of malignancy, but one or two small projections may be seen in benign serous cystadenomas. Benign mucinous cystadenomas are often multilocular with echoes within the fluid giving a complex appearance. Another problem relates to the complex features shown on ultrasound in a number of the common benign ovarian lesions, particularly mature cystic teratomas, haemorrhagic functional cysts and endometriomas.

Doppler Ultrasound

Early results with Doppler ultrasound indicated that measurement of RI was associated with high sensitivity and specificity for detecting malignancy – for example Kurjak [41] obtained a sensitivity of 96% and specificity of 95%. Subsequent studies produced variable and less favourable results with sensitivity varying from 18–100% and specificity from 46–98% [34,36,42]. False positive Doppler results are particularly likely in premenopausal females where follicular development is normally associated with low impedance ('malignant') flow patterns. Many benign tumours, cysts and inflammatory masses may also show low impedance flow. Equally, many malignant tumours may not show typical 'malignant' flow [43,44].

Combined Morphology and Doppler

A number of studies have indicated that combining the morphological and Doppler findings leads to improved sensitivity and specificity [38,45–47] and this suggestion was confirmed by a meta-analysis of 46 studies with 5,159 subjects [48]. Thus, while the major part of the ultrasound assessment is morphological, evaluation of vascularity in complex areas combined with measurement of Doppler indices may improve diagnostic accuracy.

Ultrasound-guided Biopsy in Advanced Disease

The majority of patients with ovarian cancer present with advanced disease, with evidence of peritoneal spread. If chemotherapy is planned before surgical debulking, ideally a histological diagnosis should be obtained before chemotherapy. A histological diagnosis may be particularly important if there is doubt about

the site of the primary tumour, or if the patient is unfit for surgery. Ultrasound-guided core biopsy of omental cake, other peritoneal masses or an adnexal mass can relatively non-invasively provide a histological diagnosis [49].

Ultrasound Staging of Ovarian Cancer

Ultrasound examination of the whole abdomen to check for metastatic spread is often undertaken when an adnexal mass has features suggesting that it may be malignant. However, ultrasound is less accurate than CT or MR for detecting peritoneal metastases, especially in the subdiaphragmatic and subhepatic spaces [50]. Also, CT and MR are more sensitive for detecting liver metastases and lymph node involvement. Formal staging is therefore usually undertaken using CT (or MR).

Screening for Ovarian Cancer (See chapter 3)

The late presentation of many patients with advanced ovarian cancer has led to interest in screening to detect early disease. Some studies have used ultrasound alone and have achieved high sensitivity [51]. However, this has often been at the expense of lower specificity. An alternative multimodal approach using CA125 first and transvaginal ultrasound when the CA125 was raised achieved better specificity [52]. At present, there are major studies underway in the UK (200,000 subjects) and US (74,000 subjects) to assess the value of multimodal screening [53]. Currently, ultrasound screening for ovarian cancer is not recommended for the general population.

Conclusion

The high sensitivity and high negative predictive value of combined morphological and Doppler ultrasound assessment makes it an ideal first imaging test for possible ovarian malignancy. The less than ideal specificity of ultrasound necessitates further imaging evaluation in a proportion of patients in whom the ultrasound is equivocal or suggests malignancy in a clinical setting where benign disease is likely. In such patients, MR usually readily identifies benign pathology such as mature cystic teratoma, haemorrhagic functional cyst, endometrioma or uterine fibroid [40,54]. Where ultrasound gives an unequivocal malignant

diagnosis and this is supported by CA125 and clinical assessment, full staging necessitates CT (or MR) [50]. In advanced disease a histological diagnosis may be obtained before chemotherapy using ultrasound-guided biopsy of peritoneal, omental or adnexal masses [49]. Ultrasound screening of the general population for ovarian cancer is not currently recommended [53].

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7

MR Imaging in Ovarian Cancer

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Introduction

MR imaging is increasingly being used in gynaecological and pelvic imaging due to its high contrast resolution compared to CT and ultrasound. As MR imaging techniques continue to improve, its role continues to evolve. Consequently, MRI is proving useful in characterising adnexal masses and may have a role in defining the extent of disease in ovarian cancer.

Technique

Optimal imaging in ovarian cancer requires a high-field system with good gradients in order to obtain rapid and high-resolution images. Imaging acquisition is further enhanced by the use of phased-array coils that are compatible with parallel imaging techniques. These techniques use some of the spatial information contained in the individual elements of a radiofrequency (RF) receiver coil array to increase imaging speed [1].

For characterisation of adnexal masses, images should be obtained in at least two planes to assist in determining the organ of origin of the mass. Both T1- and T2-weighted images are important for pelvic anatomy and in tissue characterisation. The use of small field of view high-resolution images improves the delineation of small structures such as papillary projections. Fat-suppression sequences help to distinguish fatty from haemorrhagic masses. Fat-saturated chemical shift techniques are preferable to STIR sequences. This is to avoid confusion between fat and haemorrhagic lesions, as haemorrhagic lesions may have the same T1 relaxation time as fat on the STIR sequence. Gadolinium-enhanced

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fat-suppressed T1-weighted images improve lesion characterisation by increasing the conspicuity of nodules and septa in complex adnexal masses [2–5]. Contrast-enhanced scans also improve detection of peritoneal and omental implants, and bowel wall infiltration. The value of dynamic contrast-enhanced imaging with gadolinium has not been established but preliminary reports are encouraging in this regard [6]. Limited experience in small series with diffusion-weighted imaging have shown that malignant and benign ovarian cystic fluid cannot be differentiated based on findings on echo planar diffusion weighted imaging (EPDWI) or apparent diffusion coefficient (ADC) value [7].

When MR is used for defining the extent of ovarian cancer, the whole abdomen and pelvis should be imaged. Coronal sequences are helpful for examining spread to the liver surface, diaphragm and pelvic sidewall. Sagittal images in the pelvis outline the relationship of the ovarian neoplasm to the uterus, bladder and rectum. We believe that contrast medium-enhanced, fat-suppressed, T1-weighted images are essential in the characterisation and staging of ovarian cancer. Administration of an antiperistaltic agent to reduce bowel motility is also recommended.

Characterisation and Diagnosis of a Pelvic Mass

Role of MRI in the Characterisation of Adnexal Lesions

Adnexal masses are a common clinical problem with an estimated 5–10% of women undergoing surgery for a suspected adnexal mass. However, in less than 25% of them does the mass prove to be malignant [8,9]. Accurate evaluation of such lesions is important as it affects subspecialty referral and surgical decisions. Ultrasound (abdominal, transvaginal, and Doppler), CT, MRI and radionuclide imaging have all been used to characterise adnexal masses.

Studies that have directly compared ultrasound and MRI have shown that both techniques are highly sensitive in characterising the masses, but MR imaging is substantially more specific than ultrasound [10–13]. This greater specificity of MRI is due to its ability to identify dermoids, endometriotic cysts and fibroids, which may appear malignant or indeterminate on ultrasound [10]. It is also in part due to its superior contrast resolution [10]. A recent meta-analysis showed that in women with an indeterminate ovarian mass at grey-scale

ultrasound, MRI contributed to a change in probability of ovarian cancer in both pre- and post-menopausal women more so than CT or combined grey-scale and Doppler ultrasound results [14].

Ultrasound with Doppler techniques is preferred as the initial investigation for a clinically suspected adnexal mass. In our practice, no other imaging is required if the mass has features clearly indicating that it is benign or if the ultrasound findings, together with tumour marker and clinical assessment, strongly indicate malignancy. However, if the ultrasound features are suspicious for malignancy or equivocal, but the patient is young or the CA 125 is normal or minimally elevated, then the patient should have further evaluation with contrast-enhanced MRI because of its higher specificity compared to ultrasound [10]. If the MRI findings allow a definitive diagnosis of a benign lesion, such as dermoid (Fig. 7.1) or endometrotic cyst (Figs. 7.2 and 7.3), the patient can be managed accordingly. Frequently, particularly in young patients, the preoperative distinction of a benign from a malignant lesion allows conservative rather than radical surgery to be planned. MR imaging often provides valuable additional information regarding the lesion's location, extent and relationship to adjacent anatomic structures.

MRI Features of Malignant Ovarian Tumours

MRI has an accuracy of 60–95% in distinguishing a benign from a malignant lesion [2,6,15,16]. As with ultrasound and CT, MRI relies on morphological features to identify lesions as malignant. Findings suggestive of malignancy include the detection of solid masses and partially solid/cystic masses, as well as the presence of papillary projections into a cystic lesion and thick septa (Figs. 7.4, 7.5 and 7.6). Secondary features of malignancy such as pelvic side-wall invasion, peritoneal, mesenteric or omental involvement, and lymphadenopathy are readily detected indicators of malignancy. Analysis of the MR imaging features has shown that the characteristics most predictive of malignancy are vegetations in a cystic lesion (Fig. 7.4), presence of ascites, a maximal diameter greater than 6 cm, and necrosis in a solid lesion [6,17]. Although suggestive of malignancy, the finding of pelvic ascites is not specific and can also be seen in ovarian torsion, pelvic inflammatory disease and benign ovarian fibromas [18]. Abdominal ascites alone, or the finding of ascites anterior to the uterus, is highly suggestive for malignant ascites [18,19].

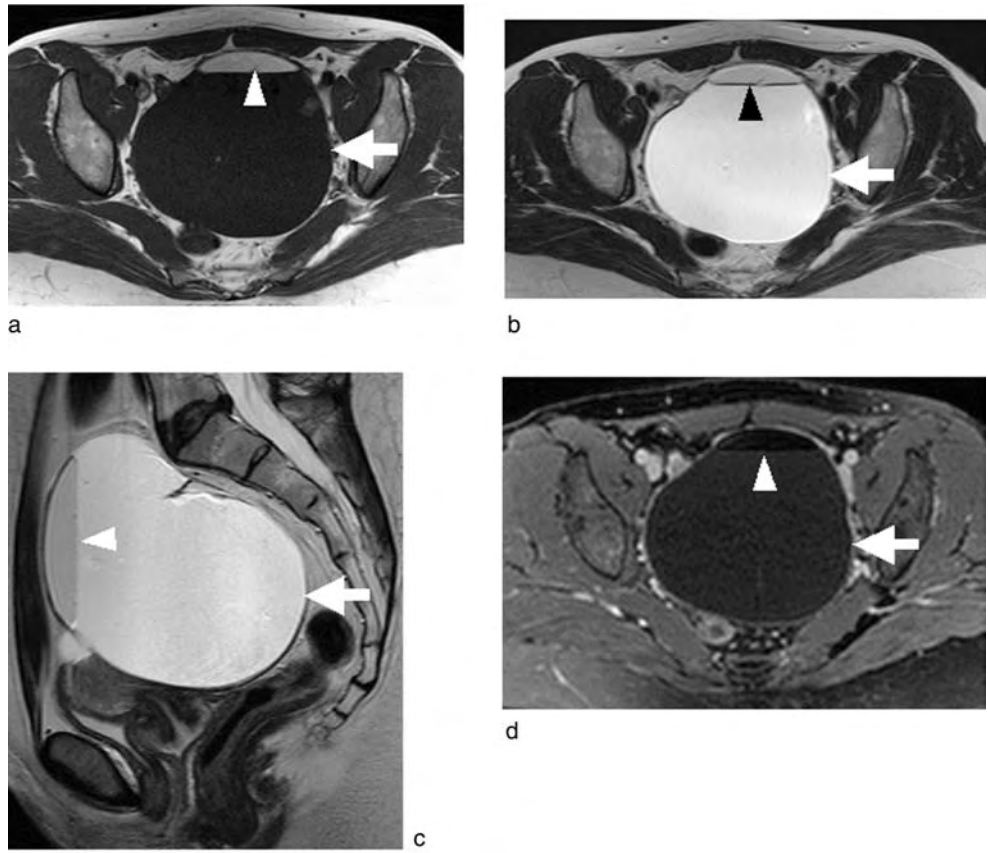


Figure 7.1 Benign cystic teratoma. (a) Axial T1-weighted, (b) axial and (c) sagittal T2-weighted, and (d) post-intravenous gadolinium-enhanced fat-suppressed T1-weighted images show a pelvic mass (arrows) lying above the uterus. The mass shows a fat-fluid level (arrowhead). The fat can be seen as high-signal intensity on both the T1- and T2-weighted scans and shows loss of signal on the fat-suppressed image, i.e. similar signal intensity to intrapelvic and subcutaneous fat.

MRI Characteristics of Ovarian Masses

General Features

The diverse histological types of ovarian cancer and the mixed cellularity of many tumours results in a wide range of appearances. Although accurate characterisation of the different ovarian masses usually cannot be made, certain features may suggest a particular pathology.

Several types of tissue and fluid can be distinguished from their signal intensity characteristics which depend upon the presence, type and proportion

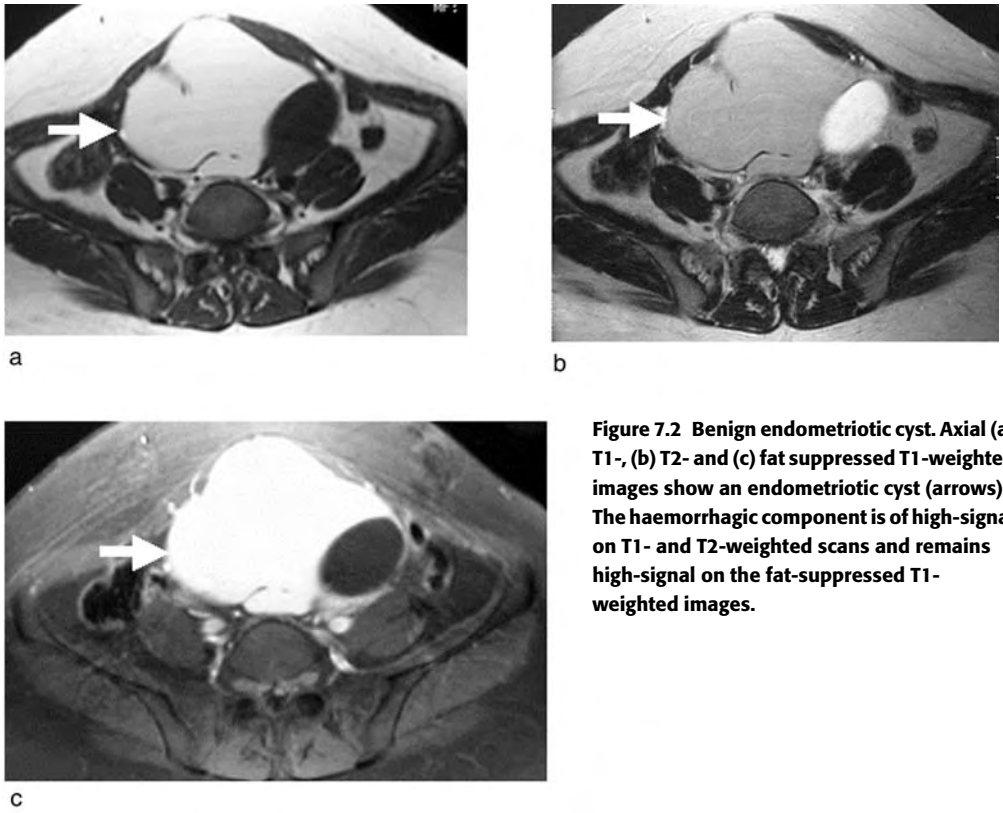


Figure 7.2 Benign endometriotic cyst. Axial (a) T1-, (b) T2- and (c) fat suppressed T1-weighted images show an endometriotic cyst (arrows). The haemorrhagic component is of high-signal on T1- and T2-weighted scans and remains high-signal on the fat-suppressed T1-weighted images.

of solid and fluid components of the mass. The soft tissue components are of intermediate or low signal intensity on T2-weighted images. Tumours with predominantly smooth muscle or fibrotic components, such as fibroma, fibrothecoma, cystadenofibroma, Brenner tumour and leiomyoma, all have low to intermediate signal on T2-weighted images [20,21]. Predominantly or uniformly low signal intensity within a lesion is therefore a feature of benign tumours [6].

The signal intensity of the cystic component of an ovarian neoplasm may vary depending upon its protein content. Such variations in signal intensity are commonly seen in mucinous tumours and cystic lesions containing haemorrhage and cellular debris. Fat, haemorrhage and some high viscosity, mucin-containing lesions usually have high signal on T1-weighted images (Figs. 7.1 and 7.2).

MRI is the most sensitive imaging technique for imaging blood-related products. Characteristically, endometriomas show very high signal on T1 and low signal on T2-weighted images. Togashi *et al.* [22] reported that low signal intensity on

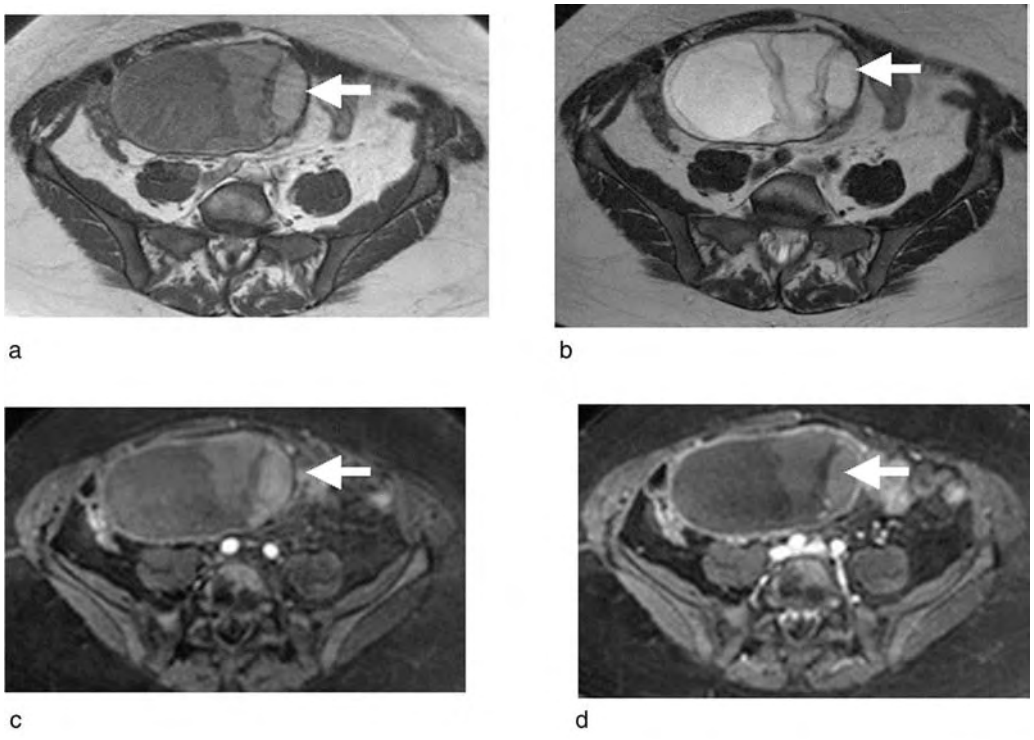


Figure 7.3 Benign endometriotic cyst. Axial (a) T1-, (b) T2- weighted images and (c) pre- and (d) post-intravenous gadolinium-enhanced fat-suppressed T1-weighted images show a pelvic mass (arrows). The appearances were complex on ultrasound and indeterminate. The MR images show no enhancing component suggesting a benign lesion and the high signal intensity on T1-weighted images would be compatible with some haemorrhagic component. Pathological examination following excision of the mass revealed this to be a benign endometriotic cyst.

T2-weighted images was noted in 55 (64%) of 86 benign endometrotic cysts. This intensity pattern is believed to be caused by a magnetic susceptibility effect generated by haemosiderin in old haemorrhage, densely concentrated fluid or fibrosis. Other signs on MRI of an endometrioma are thick low signal intensity wall, and adhesion to pelvic structures. Consequently, on endometrioma can be diagnosed with a high specificity [22]. However, the contents of some endometriomas may have a non-specific signal intensity and have to be distinguished from other cystic lesions, in particular haemorrhagic cyst lesions such as simple cysts, corpus luteal cysts, benign or malignant ovarian neoplasms. The same morphological criteria are used to distinguish benign from malignant tumours as for non-haemorrhagic cystic lesions.

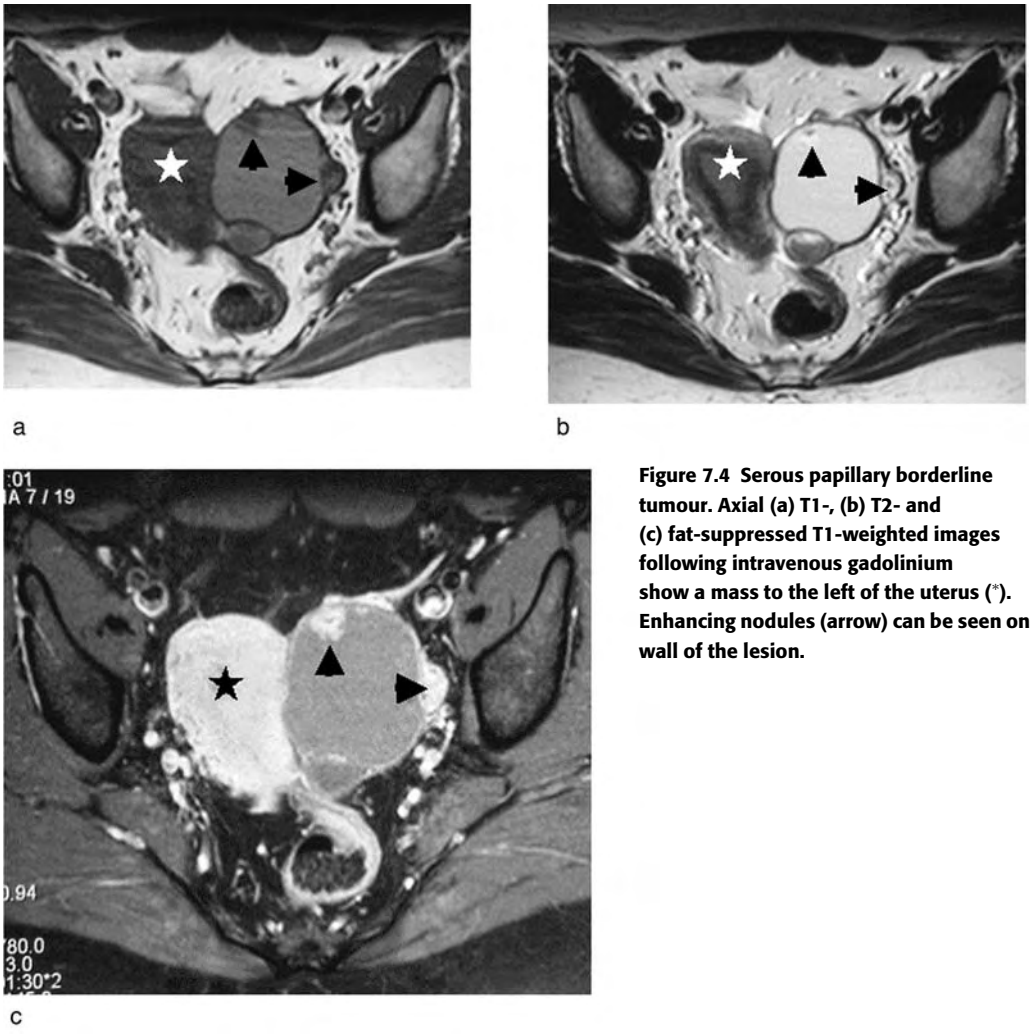
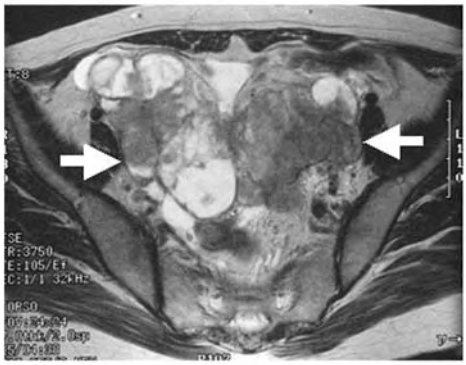


Figure 7.4 Serous papillary borderline tumour. Axial (a) T1-, (b) T2- and (c) fat-suppressed T1-weighted images following intravenous gadolinium show a mass to the left of the uterus (*). Enhancing nodules (arrow) can be seen on wall of the lesion.

Endometriosis is occasionally associated with malignant ovarian tumours, especially endometrioid and clear cell adenocarcinomas [23–25], although the incidence of malignancy in ovarian endometriosis is only 0.6–1.0% [23]. Conversely, the incidence of endometriosis in patients with ovarian cancer varies from 4.2 to 14.5% [23]. Endometriotic cysts with malignant transformation rarely show low signal intensity on T2-weighted images and usually have enhancing mural nodules. Because the enhancement of mural nodules is often difficult to evaluate on conventional T1-weighted images, dynamic post-contrast medium subtraction imaging can be valuable.



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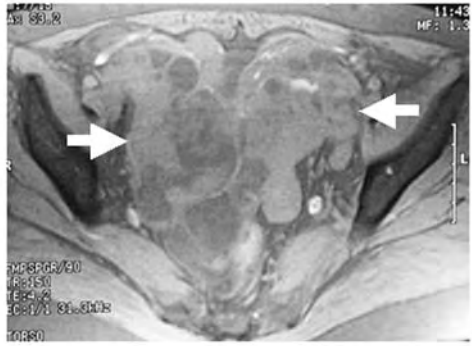

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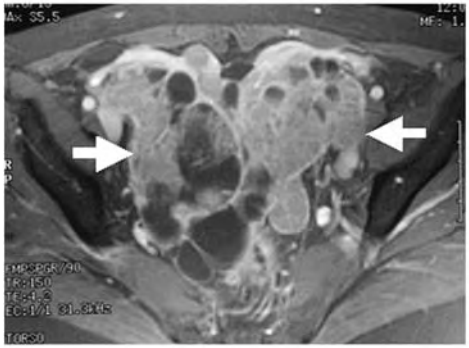

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Figure 7.5 Ovarian adenocarcinoma. Axial (a) T2-weighted and fat-suppressed T1-weighted images (b) before and (c) after intravenous gadolinium enhancement show a bilateral complex solid cystic ovarian mass (arrows).

Specific Features

Epithelial Tumours

Benign epithelial tumours, whether serous or mucinous cystadenomas, appear on MRI as thin-walled cystic lesions without evidence of any soft tissue components, irregular walls or papillary projections [18]. Serous cystadenoma are most commonly uni- or bilocular and may show plaque-like calcification. Mucinous cystadenomas are typically multilocular. Serous fluid on MRI is of high signal on T2-weighted and low signal on T1-weighted images. High signal intensity fluid on T1- and T2-weighted images indicates recent haemorrhage (especially in serous cystadenoma) or mucin (in mucinous cystadenoma). The specific features of benign epithelial tumours, such as thin walls, minimal septation and an absence of papillary projections, are often identified on T2-weighted sequences, but better seen with contrast-enhanced T1-weighted images [15,19].

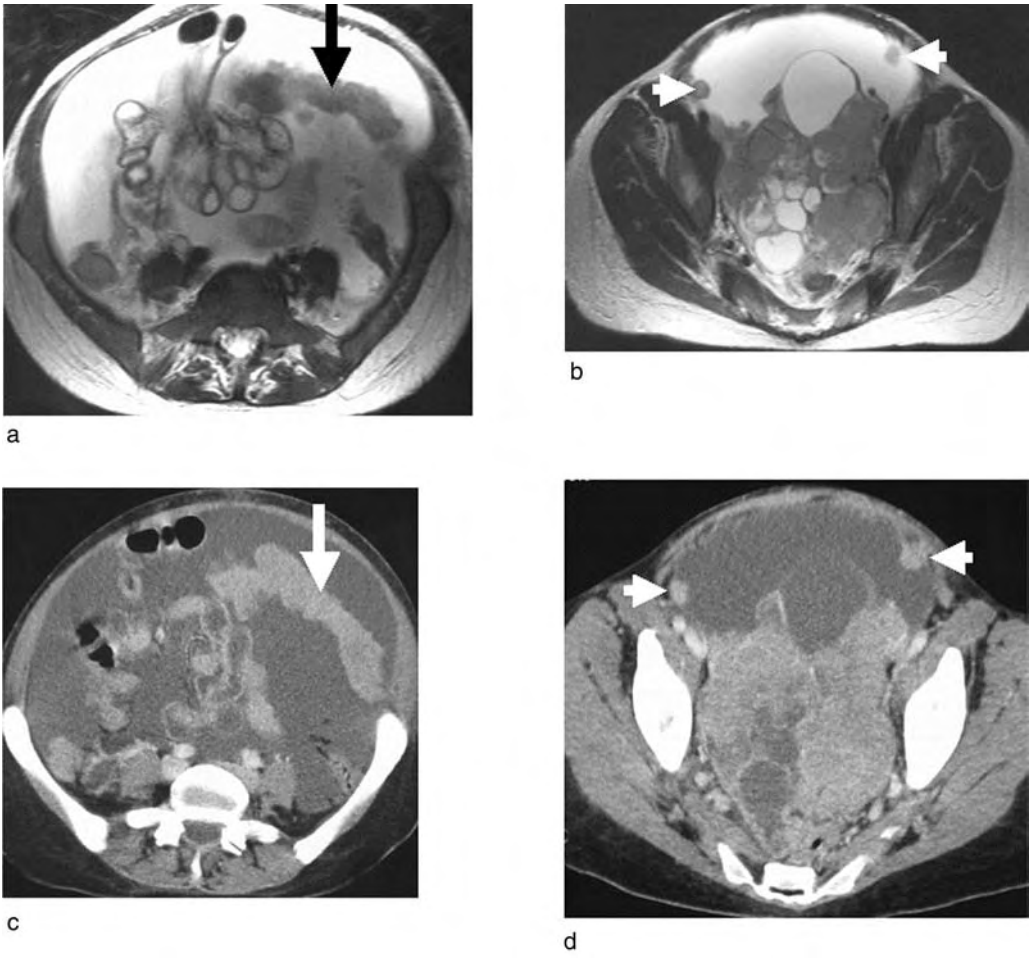

Figure 7.6 Ovarian adenocarcinoma. (a, b) Axial T2-weighted and (c, d) contrast-enhanced CT images show a complex solid and cystic mass in the pelvis with ascites. Peritoneal nodules (small arrows) and omental disease (long arrows) are well seen.

Malignant epithelial tumours have a more complex appearance with many features suggestive of the malignancy. Cystadenocarcinomas are usually larger, more complex, multilocular masses which contain soft tissue projections extending into the cystic spaces. Endometrioid tumours and clear cell carcinomas have a variable appearance on imaging, ranging from entirely cystic masses to complex masses with solid and cystic components. Brenner tumours may appear as solid masses with or without calcification. On MRI their signal intensity pattern is similar to fibroma, thecoma or uterine leiomyomas.

Borderline or tumours of low malignant potential are histologically characterised by epithelial anaplasia without stromal invasion (see Chapter 2). Most tumours are either serous or mucinous but other histological types are occasionally seen. Morphologically the features of these tumours are between those of the benign and their malignant counterpart (Fig. 7.4). In a comparison of borderline ovarian tumours with stage I cancers, the thickness of septations and the size of solid components were larger in stage I cancers. However, neither feature allowed confident differentiation between borderline tumours and stage I cancers [26].

Germ Cell Tumours

Germ cell tumours include teratoma, dysgerminoma, endodermal sinus (yolk sac) tumours, embryonal and choriocarcinomas. Ovarian cystic teratomas may contain sebum, hair, epithelium, calcium and other elements which give rise to their complex appearance. *Ovarian cystic teratomas* have characteristic features on MRI often permitting a definitive diagnosis on imaging such as a fat-fluid (Fig. 7.1) or hair-fluid level. Fat is of high signal on T1-weighted MR images. Fat on MRI is most effectively distinguished from high-signal blood-related products or proteinous material by frequency selective presaturation where loss of signal similar to abdominal fat is shown [27].

Mixed Germ Cell Tumours

Mixed germ cell tumours contain more than one germ cell component. The imaging features of mixed germ cell tumours are variable due to the diversity of their components. When a predominantly solid and heterogeneous ovarian tumour contains fatty areas or calcifications suggestive of a mature cystic teratoma, or when a mature cystic teratoma contains an enhancing solid portion, a diagnosis of a mixed germ cell tumour is possible.

A collision tumour is defined as a tumour with two adjacent but histologically distinct tumours without histologic admixture at the interface. Collision tumours involving the ovaries are rare. The most common type of ovarian collision tumour is composed of a mature cystic teratoma and a mucinous cystadenoma or cystadenocarcinoma [28]. Imaging studies of a collision tumour composed of a teratoma and a mucinous tumour show a typical multiloculated cystic mass with an internal locule filled with pure fat.

Malignancy associated with mature cystic teratoma is rare and occurs in 1–2% of reported cases [29]. It may occur either by malignant transformation of one of the pre-existing benign elements or may represent a malignant lesion

coexistent with a benign teratoma [30]. Malignant transformation usually occurs in post-menopausal women, in contrast to mature cystic teratoma, which is detected in women of reproductive age. In 85% of cases the malignant components are composed of squamous cell carcinoma arising from the squamous lining of the cyst wall [29,30]. On CT and MRI, ovarian teratoma with malignant transformation appears as a fat-containing tumour with an enhancing, irregularly marginated, solid component. The solid component tends to be relatively large and to show extensive transmural extension and direct invasion of neighbouring structures. The contrast enhancement of the Rokitansky protuberance should raise the possibility of malignant transformation [29,31]. The imaging findings of malignant transformation may be similar to those seen in mixed germ cell tumours. Elevated serum α-fetoprotein and human chorionic gonadotropin levels and younger age can help in the diagnosis of mixed germ cell tumours.

Dysgerminomas

Dysgerminomas are malignant solid masses, which may contain cystic areas representing haemorrhage or necrosis [32]. On MRI, these tumours appear as soft tissue masses, occasionally showing areas of high or low density/signal intensity due to fresh blood, the breakdown products of haemoglobin or fluid. A characteristic finding in a dysgerminoma is fibrovascular septa within a solid mass best seen on contrast enhanced CT and MRI [33]. The imaging appearances of endodermal sinus tumours are similar to those of dysgerminomas.

Sex Cord–Stromal Cell Tumours

Sex cord–stromal tumours of the ovary are rare ovarian neoplasms that arise from stromal cells and primitive sex cords in the ovary. They affect all age groups and account for most of the hormonally active ovarian tumours. Granulosa cell tumours are usually large multi-loculated cystic masses with variable solid portions [34,35]. The tumours are associated with endometrial abnormalities. Ovarian fibromas are well circumscribed solid tumours which demonstrate low signal intensity on both T1- and T2-weighted images, not unlike leiomyomas. Fibromas show minimal enhancement [36,37]. The multiplanar imaging on MRI allows one to differentiate an ovarian fibroma from an exophytic leiomyoma or other tumours [20,21]. Sclerosing stromal tumours show typical, early peripheral enhancement with centripetal progression [34]. Sertoli-Leydig cell tumours appear as well-defined, enhancing solid masses with variable-sized intratumoural

cysts [34]. Steroid cell tumours show a heterogeneous solid mass with internal areas of intracellular lipid [34].

Ovarian Metastases

Metastases to the ovary may be solid, partially solid and cystic, or rarely as a multiloculated cystic lesion. They are usually bilateral but on imaging alone they may be indistinguishable from primary ovarian tumours [38]. Kruckenberg tumours are ovarian metastases with mucin-filled 'signet ring' cells. They are usually bilateral and solid, and may have areas of haemorrhage and necrosis [37].

Defining Extent of Disease and Staging

For patients proceeding to a staging laparotomy the need for further imaging depends on individual surgical teams. Imaging cannot replace surgical staging: surgery continues to be the gold standard for defining the extent of disease and is far superior to any imaging techniques for the detection of peritoneal deposits. However, increasingly cross-sectional imaging is being used to plan surgery and to decide if optimal debulking is feasible, or whether the patient may benefit from initial chemotherapy. In most institutions this is done with CT rather than MR imaging.

On MR imaging the features of spread are similar to CT. As with CT, MRI can detect tumour involvement of many intra-abdominal and pelvic structures. These include small and large bowel, urinary tract, peritoneum and mesentery, liver, lymph nodes and ascites.

The accuracy for the detection of peritoneal tumour deposits is dependent on their location, their size and the presence of ascites, which increases their conspicuity. On CT/MRI peritoneal metastases may appear as rounded, 'cake-like', stellate or ill-defined masses (Figs. 7.6 and 7.7). These tumour deposits usually enhance following intravenous injection of contrast medium and appear as soft tissue nodules along the peritoneum, or the whole of the peritoneal surface may be thickened (Fig. 7.8). In ovarian cancer peritoneal infiltration is best seen in the right subphrenic space, the greater omentum and pouch of Douglas.

The sensitivity of CT and MRI are similar for the detection of peritoneal deposits >1 cm in diameter [15,39]. However, disease within the mesentery or implants on the wall of the small and large bowel are better detected by CT. Calcified deposits, which have a high conspicuity on CT, are very difficult to

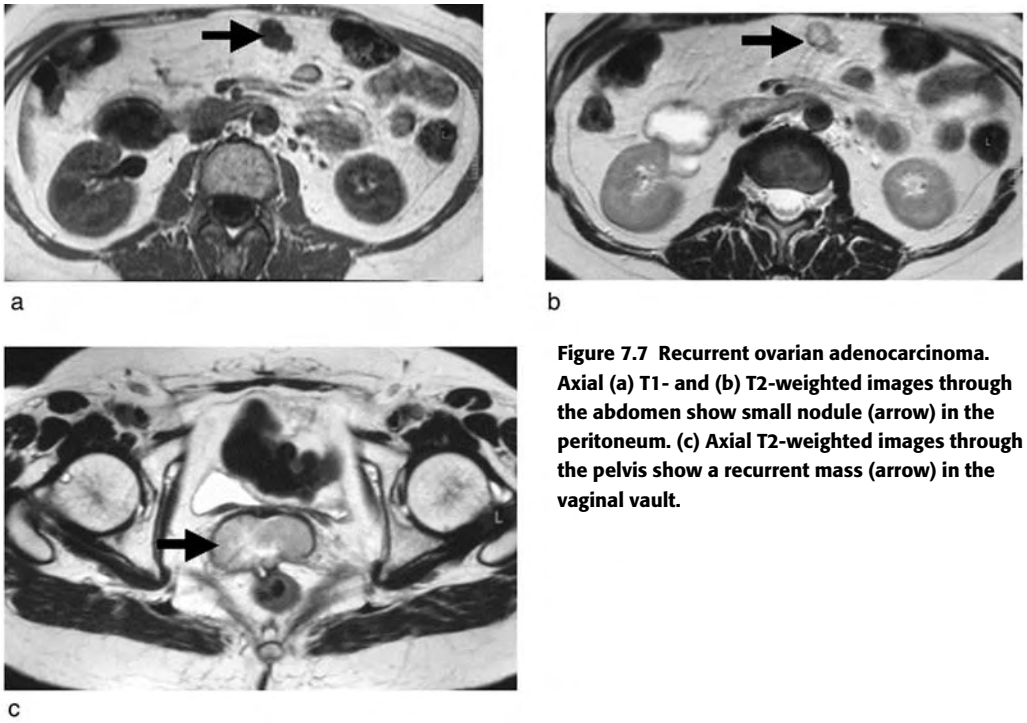

Figure 7.7 Recurrent ovarian adenocarcinoma. Axial (a) T1- and (b) T2-weighted images through the abdomen show small nodule (arrow) in the peritoneum. (c) Axial T2-weighted images through the pelvis show a recurrent mass (arrow) in the vaginal vault.

recognise on MRI, particularly in the subhepatic space [40]. An 'omental tumour cake' can be identified as an infiltrating mass lying deep to the abdominal wall, and fingerlike projections of tumour may be seen spreading into the surrounding fat. Omental disease also shows enhancement following injection of intravenous contrast medium. Fat suppression sequences increase the conspicuity of enhancing peritoneal tumour deposits and omental disease by suppressing the signal from hyperintense fat in the abdomen and pelvis (Fig. 7.8) [3]. The use of an oral contrast medium, such as supraparamagnetic iron oxide particles, may be helpful in the detection of peritoneal metastases, as it lowers the signal intensity of the bowel contents on T1-weighting, whereas enhancing tumour deposits have a high-signal intensity [41,42]. Nevertheless, contrast-enhanced MRI has a high false-positive rate in the detection of peritoneal tumour deposits due to enhancement of benign tissue such as granulation tissue and postoperative adhesions, and also has a high false-negative rate due to the difficulty in identifying small volume disease.

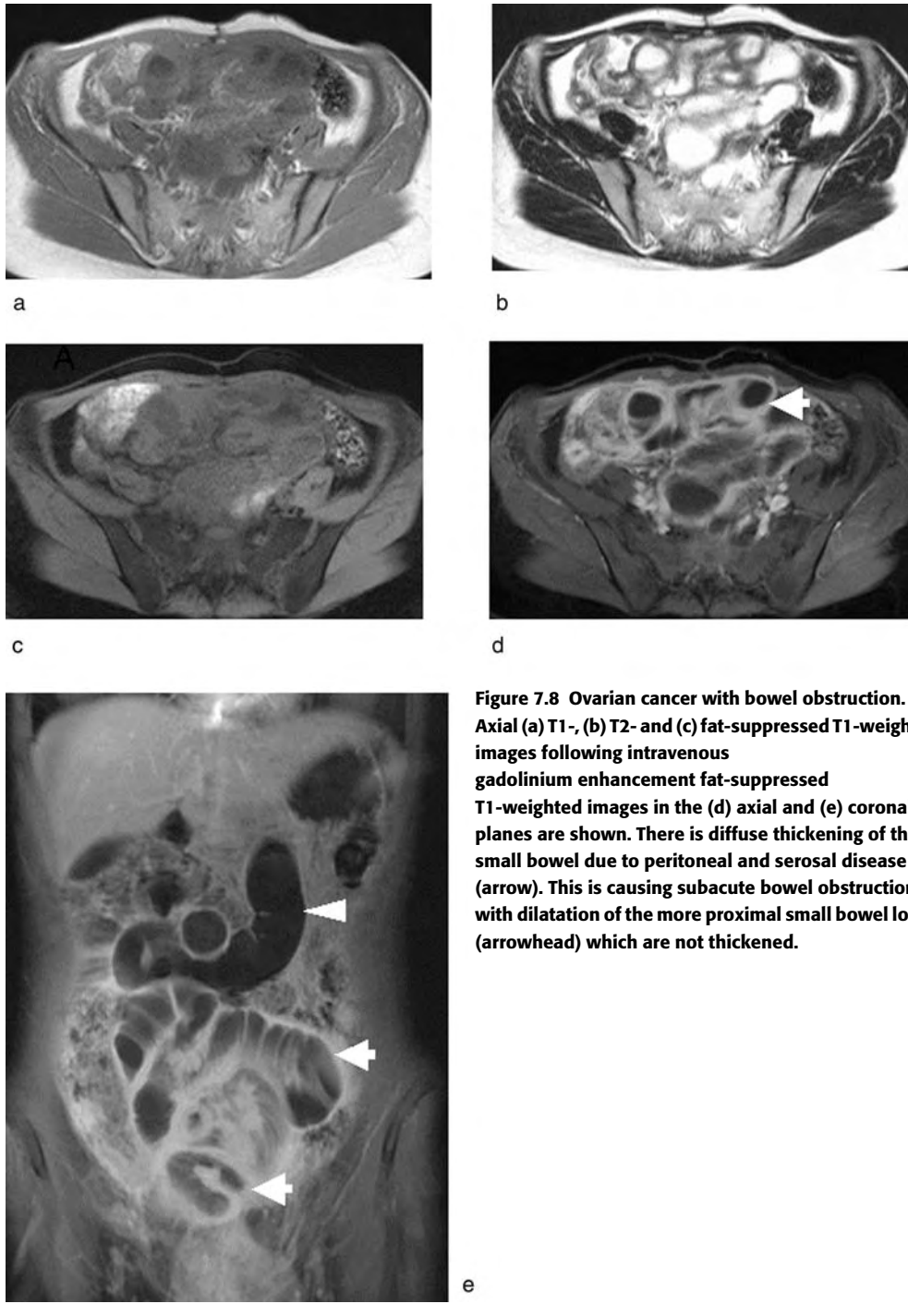

Figure 7.8 Ovarian cancer with bowel obstruction. Axial (a) T1-, (b) T2- and (c) fat-suppressed T1-weighted images following intravenous gadolinium enhancement fat-suppressed T1-weighted images in the (d) axial and (e) coronal planes are shown. There is diffuse thickening of the small bowel due to peritoneal and serosal disease (arrow). This is causing subacute bowel obstruction with dilatation of the more proximal small bowel loops (arrowhead) which are not thickened.

The spread of ovarian cancer into the uterus or adjacent organs such as the sigmoid colon, bladder and rectum may be better appreciated on MRI than on CT using a combination of T1- and T2-weighted sequences [43]. Pelvic organ invasion by ovarian cancer may be difficult to diagnose accurately as the mass or masses may abut adjacent structures, without necessarily invading them. This problem is often encountered in diagnosing uterine invasion as the parametrial fat planes may be lost in ovarian cancer without invasion of the uterine serosa [44]. Indeed, in patients with large ovarian masses it may be difficult to identify the uterus, which may be partially or completely surrounded by tumour. This is a common finding in post-menopausal women in whom the uterus is atrophied. Pelvic sidewall invasion should be suspected when the primary tumour lies within 3 mm of the pelvic sidewall or when the iliac vessels are surrounded or distorted by tumour [2]. Focal obliteration of the fat plane or tumour encasement of the bladder or rectosigmoid is highly suspicious of involvement of these structures [45].

Accuracy of Staging

Surgical staging is the gold standard for ovarian cancer but, even so, understaging due to inadequate exploration at surgery is common, occurring in 30–40% of cases. A frequent reason for understaging is that the preoperative diagnosis is that of a benign tumour resulting in an inappropriate abdominal incision which precludes the detection of upper abdominal disease. The staging accuracy of CT/MRI ranges from 70–90% [46–48] and although CT/MRI cannot replace appropriate staging laparotomy, it is a valuable procedure for postoperative staging in patients with irresectable tumour or multiple sites of disease where optimum cytoreduction cannot be achieved. Also, CT/MRI may identify disease missed at surgery, important sites being tumour deposits posteriorly in the right lobe of the liver or in a subcapsular location, and involved enlarged retroperitoneal and retrocrural lymph nodes [49,50].

According to the few studies where MRI and CT have been compared, these techniques appear to be equal for staging abdomino-pelvic disease, but the high cost and relatively long examination times of MRI precludes its routine use in most patients. Evaluation of disease within the pelvis is better demonstrated with MRI, but within the abdomen both techniques understage seedling tumour implants [2]. Sensitivity for the detection of enlarged retroperitoneal lymph

nodes is probably equal with CT and MRI. At present, therefore, CT is the recommended imaging modality of choice for staging ovarian cancer.

Tumour Resectability

Aside from staging ovarian cancer, pretreatment evaluation with CT or MRI may be helpful in identifying patients with irresectable disease or those patients who cannot undergo optimum cytoreduction. Criteria for non-resectable disease vary, but usually include tumour deposits larger than 2 cm in the porta hepatis, intersegmental fissure of the liver, diaphragm, lesser sac or gastrosplenic ligament; presacral extraperitoneal disease and lymph node enlargement at the level of the coeliac axis or above [2,51,52]. Both CT and MRI identify pathology in these sites extremely well and thus the accuracy of CT and MRI in predicting unresectability is 93–96% [16].

Assessment of Residual Disease, Tumour Response and Detection of Recurrent Disease

Cross-sectional imaging is frequently used to detect persistent or recurrent ovarian cancer and to document tumour response to chemotherapy. In most hospitals this is routinely assessed using CT. The MRI findings in recurrent ovarian cancer are similar to those of CT, hence similar difficulties are encountered. The presence of ascites improves the detection of peritoneal disease, as in the assessment of pre-treated disease. Comparisons of CT and MRI for restaging ovarian cancer are similar (Table 7.1). Certain areas are difficult to assess on CT. These include tumour deposits in the region of the vaginal vault, in the cul-de-sac and at the bladder base. These areas are better assessed with MR imaging (Fig. 7.8). In a retrospective study, Low *et al.* have shown that gadolinium-enhanced, spoiled gradient-echo MR imaging depicts residual tumour in women with treated ovarian cancer with an

Table 7.1. Comparisons of CT and MRI for restaging ovarian cancer

	Accuracy %	Sensitivity %	Specificity %	References
CT	66–85	40–67	93–100	[41,47,54–57]
MRI	59–90	62–91	40–93	[41,54,58,59]

accuracy that is comparable to laparotomy and superior to those of serum CA-125 values alone [53].

Conclusion

The role of MR imaging in the management of ovarian cancer continues to evolve. Ultrasound is the primary imaging modality in the detection and characterisation of an ovarian mass prior to definitive diagnosis at surgery. Compared to ultrasound, MRI has far greater specificity in the diagnosis of malignancy. Therefore, MRI should be used for the characterisation of masses in those patients where the results of ultrasound are equivocal, if the markers are normal, particularly in younger patients where conservative rather than radical surgery is contemplated.

Computed tomography (CT) is the major imaging modality for patients with established ovarian cancer, both for staging prior to treatment and for evaluating therapeutic response. Although MRI appears to be equally accurate to CT in the evaluation of ovarian tumour spread, it is currently seldom used in routine clinical practice.

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8

CT in Carcinoma of the Ovary

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Introduction

CT is used at all points along the patient pathway in ovarian cancer: (i) at initial diagnosis and in staging prior to debulking surgery or neoadjuvant chemotherapy; (ii) following debulking surgery and prior to chemotherapy; (iii) for assessment of treatment response during chemotherapy including those patients being considered for interval debulking surgery (IDS); (iv) for confirmation of remission; (v) at suspected relapse; (vi) to assess complications of the disease or its treatment including presentations with acute abdominal pain.

It is important to have a well understood protocol for the use of CT in routine clinical practice, where the likelihood of CT providing clinically useful information is the guide to its utility. However, there should be the flexibility to tailor imaging to individual needs. In the context of clinical trials, there are typically more rigid and exhaustive protocols prescribed. In problem cases multidisciplinary discussion should be used to define the clinical issues to be resolved by imaging.

CT at Initial Diagnosis and in Staging

Prior to Surgery or Neoadjuvant Chemotherapy

When faced with a woman with an ovarian mass the gynaecologist is required to make a judgement about the likelihood of malignancy. After clinical assessment, ultrasound and CA-125 estimation are the first-line investigations. Based on these three evaluations women can be divided into those with (1) an ovarian mass *and*

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evidence of peritoneal spread (the presence of ascites almost always indicates this) or (2) an ovarian mass but no clear evidence of spread.

For the first group of women believed to have peritoneal spread of cancer (and two-thirds of women with ovarian cancer present this way), CT has a central role. The key question is whether radical cytoreductive surgery is possible and appropriate. This is a judgement to be made in a multidisciplinary setting. Presuming a diagnosis of primary ovarian cancer, considerations include clinical issues regarding fitness for major abdominal surgery (performance status) and further imaging assessment of the pattern and extent of disease.

It is also necessary to question whether the patient might have disease metastatic to the ovaries from another site, e.g. the G-I tract or breast. Such metastases can have an identical presentation to primary ovarian cancer. This consideration becomes even more pertinent when a woman has a prior history of such disease, even many years after the initial presentation.

At the other end of the spectrum of ovarian cancer are women whose only abnormality is a complex ovarian mass. In some pre-menopausal women there are issues regarding future fertility since ovarian cancer surgery removes the uterus and contralateral ovary. CT may allow prediction of which women have confined (stage IA or IB) cancers so surgery can be limited to removal of the mass and biopsy of peritoneal and omental structures, limiting morbidity and, where appropriate, preserving fertility.

CT Technique

The standard CT technique for examining women with ovarian cancer includes the abdomen and pelvis. Patient preparation requires the patient to drink oral contrast for bowel preparation (5 ml of gastrografin diluted in 200 ml of water ideally 6 to 8 hours prior to examination) and to improve colonic opacification. For in-patients this is sent to the ward and for outpatients this is sent through the post in a small glass vial in a padded envelope with the patient information leaflet and appointment details. This dilute gastrografin is taken at bedtime for a next morning appointment and at breakfast time for an afternoon appointment. The patient fasts for 4 hours prior to the CT examination. On arrival in the CT department the patient is asked to drink slowly and steadily a further 1000 ml of 3% gastrografin over the hour prior to examination with the final 200 ml of this taken immediately prior to the examination in order to distend and opacify the stomach and duodenum. A vaginal tampon is used, when tolerated, to define

the vaginal vault. Intravenous contrast is routinely administered, typically 100 ml of a 300 mg iodine strength non-ionic agent at 3 ml/sec using a pump injector. A helical examination technique using a maximum of 5 mm collimation is recommended. The image acquisition is timed to coincide with maximal portal venous enhancement beginning at 65 seconds and covers from the domes of the diaphragm to the lower border of the pubic symphysis. With the advent of multidetector CT it is possible to reconstruct high quality reformatted images in the coronal and sagittal plane and imaging parameters should be chosen to allow this.

The examination is supervised to inspect the images prior to the patient leaving the department. Additional sections are obtained following a delay of 30 minutes, further oral contrast or in decubitus positions in selected cases to allow distinction of unopacified bowel from pelvic, peritoneal or omental masses. Inspection of images in other planes at the workstation may resolve these issues.

The chest is only examined in patients at initial staging when pleural effusion, lung metastasis or mediastinal lymphadenopathy are evident on baseline chest radiography and in a limited number of women with suspected relapse when the abdomen and pelvis show no evidence of this.

It is important to be aware of patients with renal impairment and to take measures to minimise contrast medium nephrotoxicity (CMN). These patients at risk should receive either non-ionic iso-osmolar dimeric or non-ionic low osmolar monomeric contrast medium and intravenous fluid. Intravenous infusion (1 ml/kg body weight/hour) of 0.9% saline starting 4 hours before contrast injection and continuing for at least 12 hours afterwards is effective in reducing the incidence of CMN.

CT Features of Untreated Ovarian Cancer

The CT features of epithelial ovarian cancer are those of the primary tumour(s) and those of the metastatic spread. A variety of 'typical' primary tumour patterns are seen which overlap with those of complex benign lesions: (a) a cystic mass with a solid mural nodule; (b) circumferential mural thickening and irregularity; (c) multilocularity with differing contents; (d) multiple irregular internal solid elements (Fig. 8.1). However, ovarian cancer may result in a predominantly solid mass with areas of necrosis (Fig. 8.2). Calcifications and contrast enhancement may be present in the cyst wall or within solid tumour components.

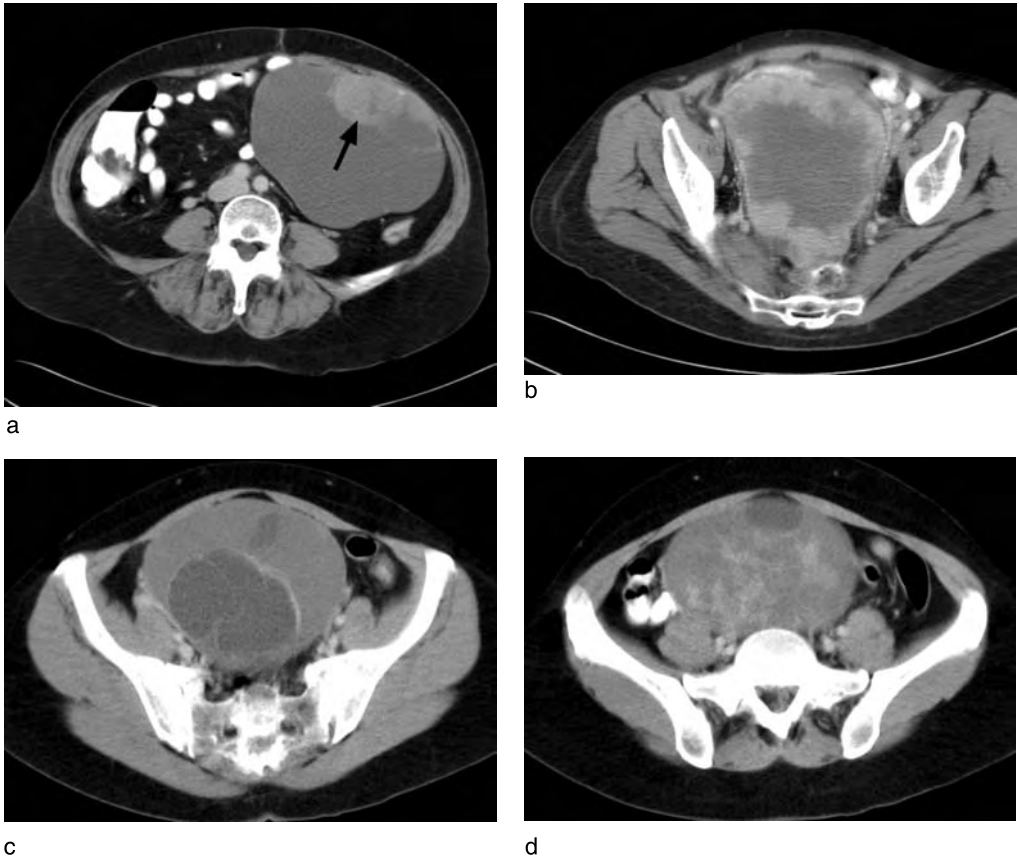
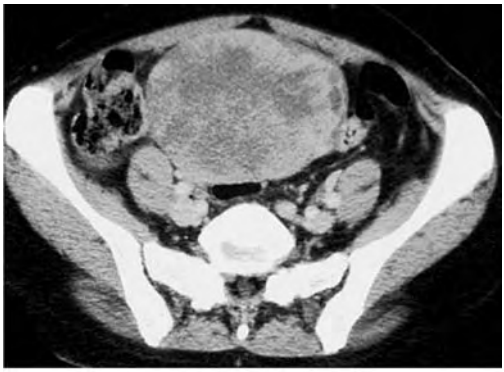


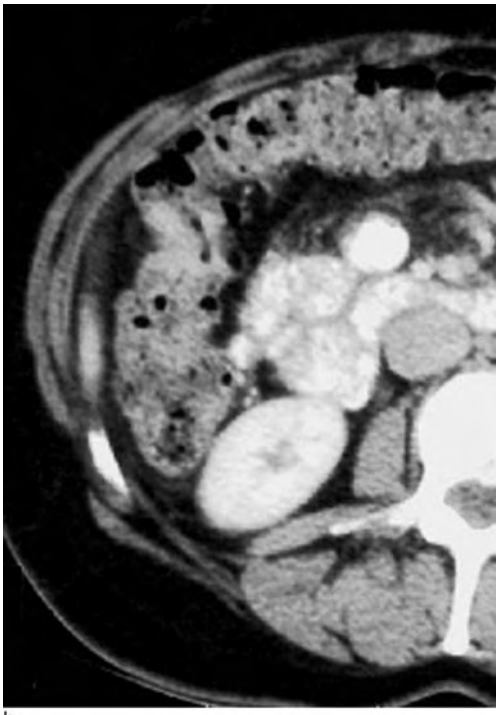
Figure 8.1 Appearances of primary ovarian cancers. (a) A cystic mass with a solid mural nodule (arrow); (b) circumferential mural thickening and irregularity; (c) multilocularity with differing contents; (d) multiple irregular internal solid elements.

The CT appearance of ovarian metastases may be indistinguishable from that of primary ovarian cancer (Fig. 8.2). Both may produce bilateral masses. In further analysis of the Radiological Diagnostic Oncology Group (RDOG) study, the only factor favouring primary ovarian cancer was multilocularity as shown by US or MR imaging. This was not a significant feature for CT [1]. The stomach, colon, appendix and pancreas are within the examination volume and should be inspected as potential primary cancer sites within the abdomen (Fig. 8.2).

Primary ovarian cancers are most frequently found in the adnexal region or pouch of Douglas (recto-uterine recess) displacing and compressing the uterus, bladder and rectum. If the ovarian mass continues to enlarge into the abdomen



a



b

Figure 8.2 Appearances of an ovarian metastasis from a right colon cancer. (a) A solid pelvic mass showing areas of necrosis; (b) a stenosing but non-obstructing tumour of the hepatic flexure of the colon.

it lies above the bladder displacing the pelvic small bowel. Eventually the mass may reach the undersurface of the liver. Metastatic spread is predominantly via the peritoneal cavity, usually with ascites, but also via lymphatics to the pelvic and para-aortic groups, and by haematogenous spread to the liver (Table 8.1). Patterns of spread identified within the pelvis (stage II) by CT are involvement of small and large bowel (Fig. 8.3), and the pelvic sidewall with encasement of the iliac veins leading to thrombosis, or of the pelvic ureter with resultant hydronephrosis. Hydronephrosis is, however, more commonly due to simple mass effect upon the pelvic ureter. Metastatic spread to the abdomen (stage III) may be manifest as peritoneal and mesenteric masses, and omental 'cakes', and there may be involvement of the abdominal wall (Fig. 8.4). Involvement of the surface of the liver and spleen is classified as stage III disease but parenchymal deposits within the liver upstage the patient to stage IV (Table 8.1, Fig. 8.4) [2].

Detection of peritoneal seedlings is easier in the presence of ascites due to increased contrast between enhancing peritoneal surfaces and adjacent fluid.

Table 8.1. FIGO staging classification for ovarian cancer

Stage	Characteristics
I	Growth limited to the ovaries
IA	Growth limited to one ovary; no malignant ascites; negative peritoneal cytology finding; no tumour on the external surface, capsule intact
IB	Growth limited to both ovaries; no ascites; negative peritoneal cytology finding; no tumour on the external surface; capsule intact
IC	Tumour either stage Ia or Ib, but with tumour on the surface of one or both ovaries; or with capsule ruptured; or with ascites present containing malignant cells; or with positive peritoneal washings
II	Growth involving one or both ovaries with pelvic extension
IIA	Extension or metastasis to the uterus, tubes or both
IIB	Extension to the pelvic tissues
IIC	Tumour either stage IIa or IIb, but with tumour on surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells; or with positive peritoneal washings
III	Tumour involving one or both ovaries with peritoneal implants outside the pelvis or a positive finding in retroperitoneal or inguinal glands; superficial liver metastases; tumour limited to the true pelvis but with histologically proven malignant extension to small bowel or omentum
IIIA	Tumour limited to the true pelvis, unaffected nodes but histologically confirmed microscopic seeding of abdominal peritoneal surfaces
IIIB	Tumour involving one or both ovaries with histologically confirmed implants on abdominal peritoneal surfaces, none exceeding 2 cm in diameter, nodes unaffected
IIIC	Abdominal implants greater than 2 cm in diameter or unaffected retroperitoneal or inguinal nodes
IV	Distant metastases; if pleural effusion is present there must be a positive cytology

However, CT can detect the calcified tumour implants containing psammoma bodies from serous cystadenocarcinoma of the ovary even in the absence of ascites. Conversely, densely calcified tumour implants from serous tumours may be mistaken for bowel containing oral contrast (Fig. 8.5). CT can detect 50% of implants that are 5 mm or more in size [3]. Detection of these and smaller peritoneal seedlings remains the province of surgery.

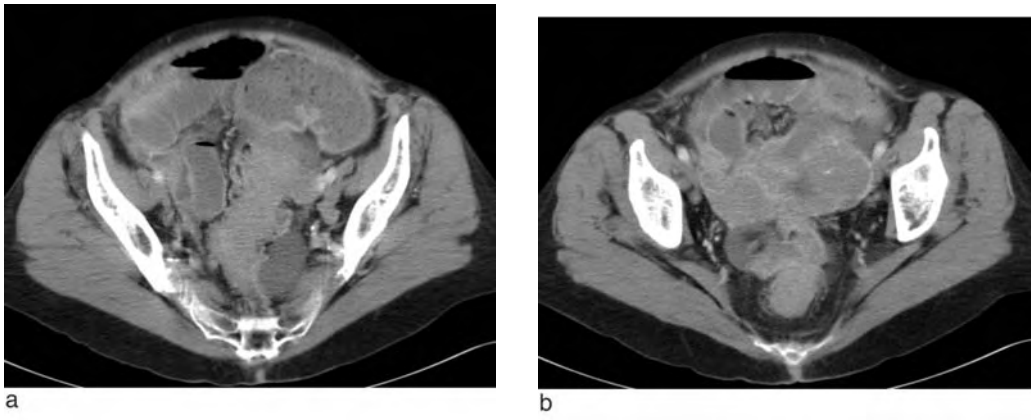


Figure 8.3 Stage II disease with (a) invasion and obstruction of the sigmoid colon from (b) bilateral ovarian cancers indicating a need for colostomy.

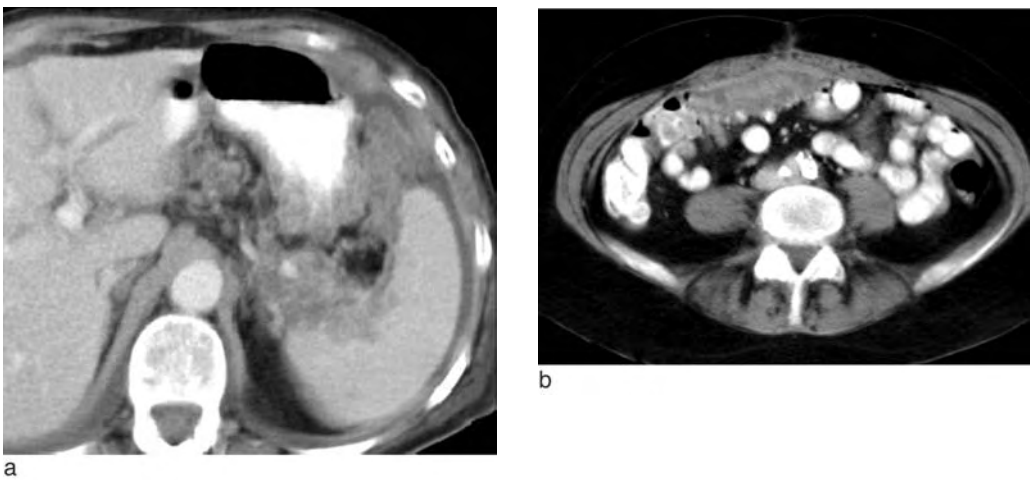


Figure 8.4 Contrast-enhanced CT of stage IIIC ovarian cancer. (a) Extensive left upper quadrant tumour invading the spleen and stomach and (b) omental tumour directly invading the anterior abdominal wall.

Current Best Evidence Regarding the Accuracy of Pre-surgical Imaging

Over the last decade the Radiology Diagnostic Oncology Group (RDOG) conducted a major multicentre diagnostic imaging study of women prior to ovarian cancer surgery and published its findings in three landmark papers [1,4,5]. These studies compared US, CT and MR imaging in 280 women, evaluating these

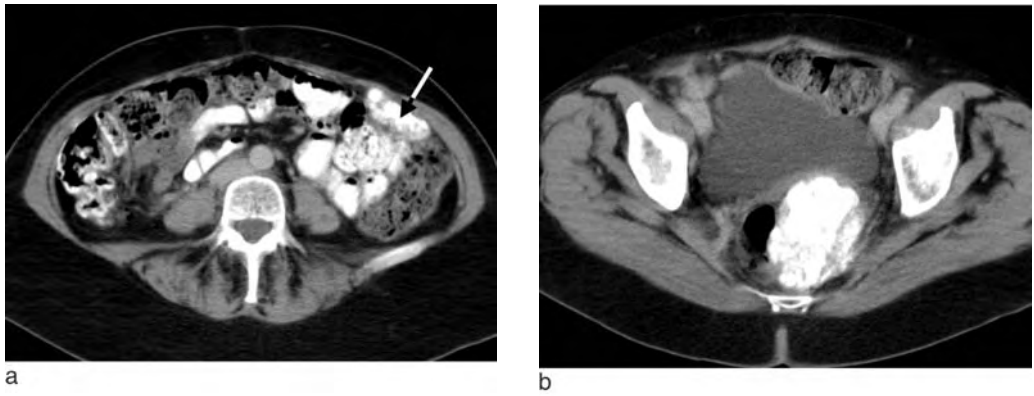


Figure 8.5 Heavily calcified ovarian cancer with (a) a left lower quadrant calcified omental cake mimicking opacified bowel (arrow) and (b) a similar primary tumour in the left pelvis.

modalities for cancer diagnosis and staging. In the study 189 women had unilateral masses and 91 had bilateral masses. Only 114 of the 280 women had ovarian cancer and of these 27 were not primary ovarian cancer but other malignancies metastatic to the ovary, some of which demand entirely different cancer management. Women with a history of malignancy were excluded so the risk of confusion between primary ovarian cancer and other cancers metastatic to the ovaries was less than in routine clinical practice.

A number of lessons have been learned and re-emphasised by these important studies. They have shown that both CT and MR imaging are superior to US in assessment of the nature of ovarian masses, with the highest accuracy for MR imaging [4]. In assessment of the stage of disease all had similar accuracy of 91% since the presence of ascites effectively predicted peritoneal spread of tumour. In determination of the sites and extent of this metastatic tumour US was inferior to both CT and MR imaging [5]. A particular problem for US was in depiction of peritoneal metastases. The ready availability of CT makes it the investigation of choice for planning surgery in women believed to have metastatic spread of ovarian cancer. CT can replace urography and barium studies for assessment of hollow organ involvement and, in most cases, is the only imaging study required to plan management.

CT remains inferior to surgical staging in detection of tiny peritoneal, omental and mesenteric nodules even with meticulous technique using multidetector CT technology not available at the time of the RDOG studies [3]. But this is not its role.

CT defines and alters patient care at the other end of the spectrum of ovarian cancer. In the presence of bulky metastatic tumour, CT predicts when cytoreductive surgery is likely to be incomplete by defining sites of unresectable tumour. CT indicates when the gynaecologist may require assistance from other surgical colleagues to achieve effective debulking when, for example, there is involvement of ureters, pelvic small bowel or colon. The need for colostomy may be highlighted (Fig. 8.3). Bulky disease in the supracolic compartment around the spleen and stomach, within suprarenal lymph nodes, and affecting the subdiaphragmatic recesses and parenchyma of the liver is usually beyond the scope of surgery. CT may highlight invasion of the abdominal wall, which may compromise or contraindicate attempts at resection (Fig. 8.4). CT provides the surgeon with the detail required to discuss surgical and other therapeutic options with the patient and her carers. A variety of schemes have been devised to judge the tumour extent at key sites [6].

Almost any amount of tumour can be resected, but at what cost? And with what benefit? Rather, the surgeon needs to be alerted to the actual extent of disease at key sites and the likelihood of success. CT can do this.

When radical cytoreductive surgery is not considered appropriate for women with bulky disease, with poor performance status or with a history of malignancy which can mimic primary ovarian cancer, CT can help further. Image-guided needle core biopsy (IGB) is an effective, safe and well-tolerated alternative to surgery (mini-laparotomy, laparoscopy) in providing a definitive histological diagnosis when cancer surgery is not considered appropriate [7]. There is current interest in neoadjuvant chemotherapy followed by intervention (interval) debulking surgery (IDS) for women with primary ovarian cancer unable to undergo radical surgery at initial diagnosis [8] (see Chapters 4 and 5). With this therapeutics approach primary chemotherapy is administered in the hope that the tumour, as monitored by serial CT examination, can be debulked and downstaged to allow subsequent surgery. The one virtue of attempting debulking surgery in such women was that at least it provided a confident histological diagnosis even if its primary aim was not achieved, i.e. an 'open and shut' laparotomy.

Thus IGB using CT or US guidance is a valuable and useful alternative to laparoscopy or exploratory surgery in the following circumstances:

1. in women believed to have ovarian cancer but with poor performance status or with advanced disease believed beyond the scope of primary cytoreductive surgery;
2. in women with a history of cancer whose metastases may mimic ovarian cancer (e.g. GI tract, breast, melanoma);

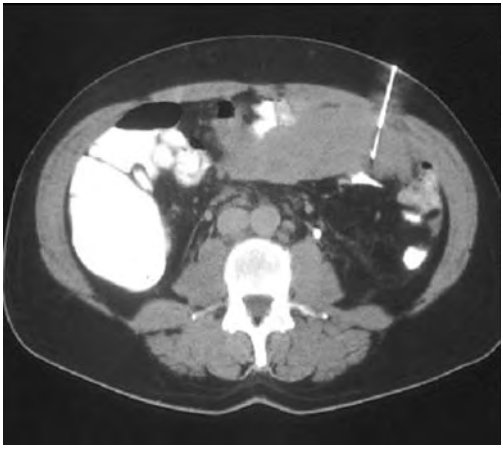


Figure 8.6 Omental biopsy in a woman with bilateral solid ovarian masses, extensive peritoneal tumour but minimal ascites. Tumour marker CA-125 was only minimally elevated. Diagnosis: non-Hodgkin lymphoma.

Table 8.2. Commonly used immunohistochemical stains to cytokeratins and tumour markers

CA-125	Mullerian duct epithelium (ovary)
Cytokeratin 7	Mullerian duct epithelium (ovary)
CEA	Colonic epithelium
Cytokeratin 20	Colonic epithelium
BRST-2	Breast epithelium

3. when there is diagnostic uncertainty, e.g. unusual imaging patterns of disease such as peritoneal carcinomatosis with bilateral solid ovarian masses or non-enlarged ovaries or with an unusual tumour marker profile (Fig. 8.6).

In a woman with undiagnosed peritoneal carcinomatosis, IGB should precede an exhaustive (and potentially hazardous and unpleasant) series of investigation of potential primary sites such as upper and lower bowel endoscopy. Its findings can focus the search for the primary tumour when appropriate. In the majority of women undergoing IGB standard haematoxylin and eosin (H&E) staining is diagnostic – and this can be compared with historical material in women with prior malignancy. In women with poorly differentiated tumours further special immunohistochemical stains may be required which identify specific tumour markers and other cellular proteins such as cytokeratins (Table 8.2). Management of such women is best discussed in a multidisciplinary setting.

One cause of diagnostic uncertainty recognised in recent years is primary peritoneal carcinoma (PPC), which arises from the peritoneal surfaces as a papillary serous tumour of Mullerian duct origin. This entity is managed in an identical manner to primary ovarian cancer with cytoreductive surgery and platinum-based chemotherapy, yet has some differences in imaging findings. The typical CT features of PPC are of ascites, omental and peritoneal masses, which may be calcified, but with *normal sized ovaries* [9,10]. PPC was initially recognised as a subset of women with peritoneal carcinomatosis whose prognosis was more favourable [11–13]. Median survival was 23 months with PPC compared with 3 to 4 months for peritoneal carcinomatosis related to non-gynaecological malignancy. The diagnosis of PPC was made at laparotomy in those series but it is a diagnosis which can be suggested on the basis of imaging and confirmed using image-guided needle core biopsy [5]. Both ovarian cancer and PPC may occur in women with the *BRCA1* and *BRCA2* gene mutations for breast cancer [14]. The treatment options and prognosis differ markedly between ovarian cancer/PPC and abdominal recurrence of breast cancer. In a woman with prior breast cancer with peritoneal carcinomatosis IGB allows this distinction to be made with confidence allowing comparison with tissue from the breast biopsy or specimen from the initial diagnosis [5].

Technique for CT-Guided Peritoneal Biopsy

Criteria for image guided biopsy are:

1. the presence of omental, peritoneal or pelvic mass allowing core biopsy on diagnostic imaging;
2. no bleeding diathesis with platelet count $>10 \times 10^9$/L and INR (International Normalised Ratio) <1.4; and
3. a decision made after multidisciplinary review that obtaining a definitive diagnosis by non-surgical means was required to plan further treatment.

The image-guided biopsy is performed as a separate procedure after multi-disciplinary review of the diagnostic studies. For the biopsy, CT is performed with only oral contrast preparation and after a limited number of localizing sections planned from the prior study. An 18G cutting needle using a spring-loaded device is used (Temno, Bauer Medical International SA, Dominican Republic). The number of needle passes made is judged by the supervising radiologist to provide the equivalent of two full needle cores of solid material for the pathologist. From a solid omental cake (Fig. 8.7) only two or three needle passes are required

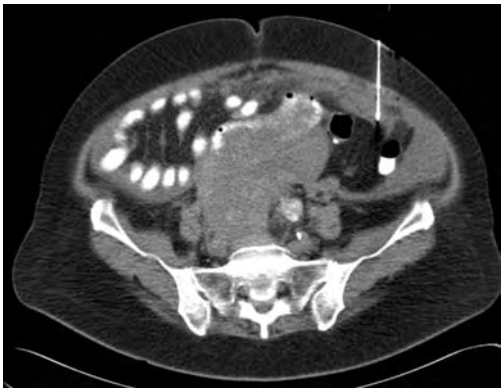


Figure 8.7 Omental biopsy from a solid infracolic omental cake. Diagnosis: Mullerian type (ovary or primary peritoneal) carcinoma.

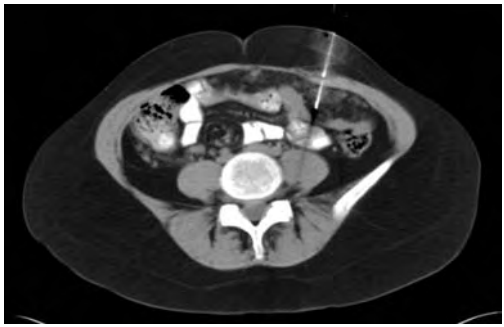


Figure 8.8 Omental biopsy from a whispy and nodular infracolic omental cake. Diagnosis: recurrent breast cancer.

but with more wispy or nodular infiltrates up to six passes may be required (Fig. 8.8). With such infiltrates the specimen may be predominantly fatty and float on the formalin in the specimen bottle.

The biopsy procedure typically lasts 15–20 minutes. Aftercare includes bed rest for 6 hours with measurement of blood pressure and pulse half-hourly for 2 hours and then hourly for 4 hours, after which the patient may eat and drink and become ambulant. The biopsy can be performed as a day case procedure. For in-patients the procedure may be combined with placement of an ascitic drain.

Needle core biopsies are formalin-fixed, embedded in paraffin wax and sections cut at 3 to 4 micrometer thickness. These are stained with haematoxylin and eosin (H&E). Further immunohistochemical analysis of the biopsy material is performed using the labelled streptavidin-biotin peroxidase system with monoclonal antibodies to CEA-M, cytokeratin 7 (CK7), CK20 (DAKO, Carpinteria, CA) and CA-125 (Novocastra, Newcastle, UK). In selected cases additional monocloncal antibodies are used at the discretion of the reporting pathologist in women with previous breast cancer for oestrogen receptors (M7047, DAKO, Denmark) and progesterone receptors (M3569, DAKO, Denmark) and to a breast marker, BRST2 (GCDFP-15, Signet Labs Inc, USA). Isotypes are lineage-specific and this characteristic is retained during malignant transformation and progression. Antibodies to CK7 react with ovarian epithelia but rarely with colonic; antibodies to CK20 react conversely [15–17]. Only strong and widespread positive staining is accepted.

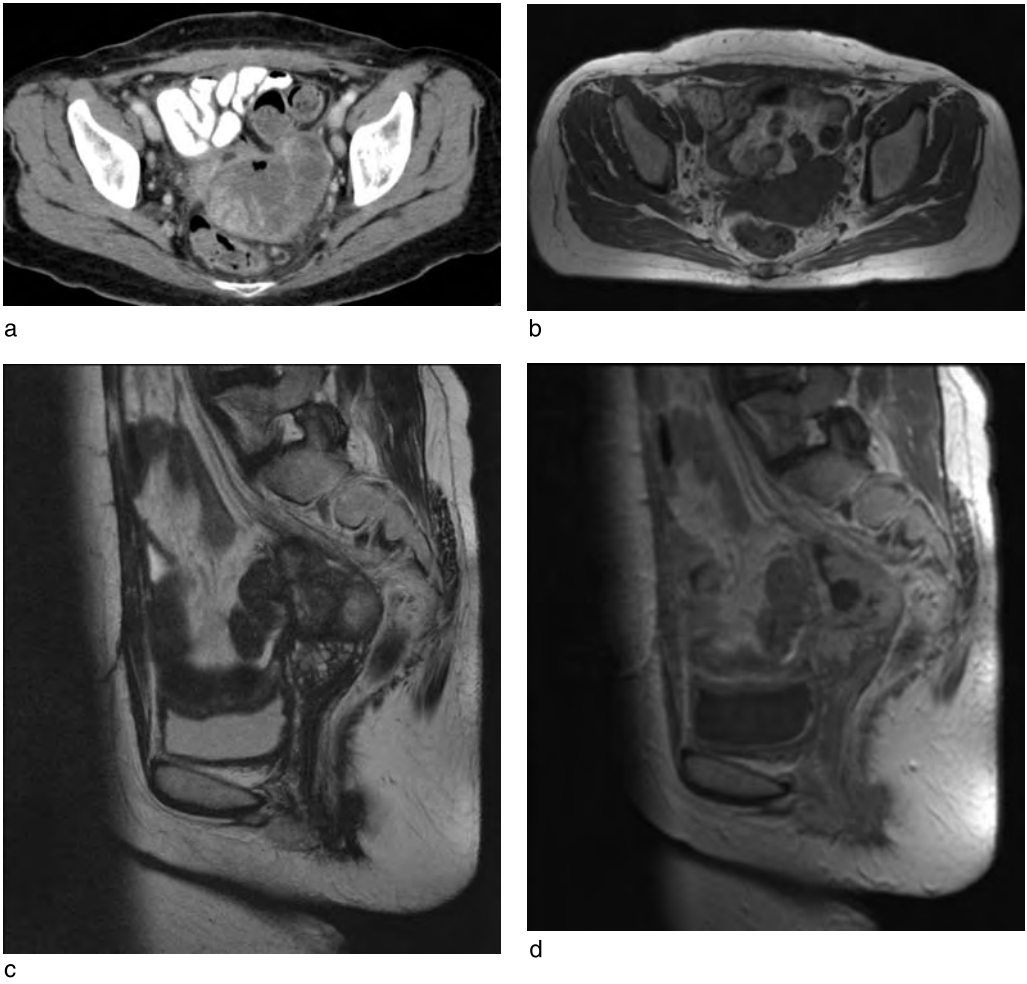


Figure 8.9 Baseline post-surgery pre-chemotherapy contrast enhanced CT showing (a) a complex pelvic mass ? haematoma ? abscess ? tumour and 3 weeks later into chemotherapy the MR images (b) axial T1-weighted showing no products of haemorrhage, (c) sagittal T2-weighted and (d) sagittal gadolinium-enhanced T1-weighted MR imaging showing a tumour deposit above a congested vagina.

CT following Debulking Surgery and Prior to Chemotherapy

After primary debulking surgery it is necessary to obtain a new CT baseline examination to assess the remaining bulk of disease. It is important to recognise post-surgical findings which may lead to diagnostic confusion and indeed mimic residual tumour (Fig. 8.9) [18]. There may be marked thickening at the vaginal vault and fluid collections may be seen here as well as at a variety of other

pelvic locations. Haematoma of the round ligament may mimic cystic tumour on the pelvic sidewall. MR imaging is a valuable problem-solving tool (Fig. 8.9). Ovarian vein thrombosis may also occur with the great majority of cases on the right. Characteristic CT findings are of a tubular retroperitoneal mass along the course of the vein from the pelvis to the infrarenal vena cava.

CT in Assessment of Treatment Response during Chemotherapy including those Patients being Considered for Interval Debulking Surgery (IDS)

Protocols for the use of CT differ between routine clinical practice and in the context of clinical trials. A well tested and pragmatic approach in the Leeds Cancer Centre is to make a judgement on the basis of the initial post-surgery baseline CT. If debulking was considered successful and CT shows no residual disease, no further CT is performed until the end of chemotherapy, when a new baseline is obtained. For women with CT-documented residue or who were incompletely debulked, an interval CT is also performed after three of the six planned cycles of chemotherapy to ascertain progress as the risk of progression is greater. This is also the protocol for patients being planned for IDS. Here it is important to pre-book the scan to be available for multidisciplinary discussion just prior to surgery between the 3rd and 4th cycles of chemotherapy. A new baseline examination is obtained post-IDS and then a further post-treatment CT at the end of chemotherapy which may extend to eight cycles.

In assessment of response a variety of criteria have been used. These criteria differ but categorise response either as complete response, partial response, stable disease or progressive disease. For many years the WHO criteria were used for assessment of treatment response [19]. These are well understood by radiologists and clinicians and it is entirely reasonable to use these in clinical practice. The WHO criteria use bidimensional measurements resulting in an area product:

- *complete response*: disappearance of all known sites of disease;
- *partial response*: residual mass of less than 50% pre-treatment size;
- *stable disease*: less than 50% reduction and less than 25% enlargement;
- *progressive disease*: more than 25% enlargement, new lesions, requirement for palliative treatment.

A *residual mass* is defined as a post-treatment mass of greater than 1 cm. A residual mass of less than 1 cm is considered a *complete response unconfirmed* (CRU).

More recently, the RECIST (response criteria in solid tumours) criteria have been devised [20]. The RECIST criteria are used in most clinical trials. These use long axis linear measurements of lesions and the product of up to 10 lesions and up to 5 in a single organ. Response is measured in the sum length of these measurements:

- *complete response*: disappearance of all known sites of disease;
- *partial response* with residual mass product of less than 70%;
- *stable disease*: less than 30% reduction and less than 20% enlargement;
- *progressive disease*: enlargement of lesions by 20%, new lesions, requirement for palliative treatment.

CT in Confirmation of Remission

In all clinical trials a further CT examination is prescribed at 28 days following an examination showing a complete or partial response to treatment to confirm its durability. This is not routinely performed in clinical practice.

Second-look laparotomy to confirm remission is no longer performed.

CT in Follow-up and at Suspected Relapse

There is no requirement for CT in routine clinical follow-up of women with treated ovarian cancer believed to be in remission.

CT is the investigation of choice to investigate suspected relapsing disease on the basis of rising CA-125 or clinical features.

These bland statements are based on extensive experience, clinical audit and expert advice. There is paucity of data regarding the use of imaging in assessment of treatment response and follow-up of women with ovarian cancer and this was not addressed in the RDOG studies. Expert advice from the National Cancer Institute (NCI) is for no follow-up imaging in women believed to be in remission with CA-125 estimation as the mainstay of follow-up [21].

Clinical audit supports this contention but suggests a possible role for CT in that 10–15% minority of women for whom CA-125 estimation is unhelpful, i.e. they have ovarian cancer without raised levels of CA-125 [22]. Relapse was first diagnosed by CT in these women as clinical signs were absent or misleading. CT defined the sites and extent of disease far better than clinical assessment,

thus planning therapeutic and interventional options [22]. CT also identified unsuspected treatment complications requiring intervention including subacute small bowel obstruction and asymptomatic hydronephrosis.

In the small proportion of patients with recurrent ovarian cancer considered for further cytoreductive surgery CT has also proved useful in defining sites and extents of tumour. Hydronephrosis and pelvic sidewall invasion were predictors of non-resectability [23].

CT examination of the abdomen and pelvis for assessment of suspected relapse based upon symptoms or elevated *CA-125* level may not provide an answer. CT has limitations. Vaginal vault relapse may be underdiagnosed and this requires expert clinical assessment. Small volume peritoneal disease may not be detected although recent studies of multidetector CT report detection of deposits well into the subcentimetre range [3].

The options for further assessment of women with no clinical or CT evidence of relapse are as follows:

1. to wait and watch;
2. to perform alternative or additional examinations;
3. to intervene, in this case to perform laparoscopy or laparotomy;
4. to institute treatment for relapsed disease on the basis of compelling clinical grounds and tumour marker data.

What data are available regarding other investigations might be helpful in this situation? Recent studies have indicated a limited role for chest CT. Two retrospective studies of the value of CT in follow-up found that supradiaphragmatic relapse in the absence of abdomino-pelvic disease was rare [24,25]. There was 'chest only' relapse in 3–4% of women in these studies. The commonest chest manifestation was pleural effusion seen in up to 40% of women at some point in their history [24]. Lung metastases were seen in 6% of women at some point but all had prior abdomino-pelvic disease [25]. These authors suggested examination by chest CT when abdomino-pelvic CT had failed to explain a tumour marker rise. Whilst lung metastasis and lymphangitis are rare, mediastinal lymphadenopathy is more common, particularly in women with previous retroperitoneal nodal disease.

Calcified mediastinal nodal disease from papillary serous ovarian cancers must not be dismissed as old tuberculous disease. It is important to check whether the patient is old enough to have encountered tuberculosis; and that the nodes are not enlarging [26]. Mediastinal, axillary and neck lymphadenopathy does occur with ovarian cancer and may even be its presenting feature. In everyday practice it is

reasonable to rely upon clinical examination and chest radiography to assess these areas at diagnosis. If there is pleural disease the chest should be included in the staging CT protocol. Pragmatically, once the effusion has resolved one can rely upon surveillance of the lung base on the abdominal CT in follow up unless there is an unexplained rise in CA-125.

Newer examinations such as MR imaging and PET require further evaluation and comparison with 'state of the art' CT. It is reasonable to ask why, if more accurate alternative investigations are potentially available, these are not used in preference to CT. The first consideration is one of coverage versus focus. When it is necessary to examine the chest, abdomen and pelvis, CT offers a more rapid and well-tolerated examination than MR imaging. The second consideration is availability of technology. The burden of imaging in treatment assessment and follow-up is huge when compared with that at diagnosis. Whilst it may be feasible to offer MR imaging at a single point in the pathway of the cancer patient, such as at initial diagnosis, to do so for the numerous subsequent visits poses a greater challenge. Finally, there are issues of expertise and familiarity with more sophisticated techniques following initial surgery. They are untested in any large comparative study such as the RDOG study for technical and diagnostic factors: reproducibility of technique; ease of scrutiny by off site radiologists after onward referral; definition of treatment response and recognition of treatment related complications.

More sophisticated techniques such as gadolinium-enhanced fat-suppressed abdomino-pelvic MR imaging and PET have been recently assessed both at initial presentation and at suspected relapse [27,28]. In the RDOG studies CT and 'standard' MR imaging was validated against surgical pathology at initial diagnosis with extensive surgery taking place within days or weeks of imaging. Dynamic gadolinium-enhanced MR imaging and PET have been validated only in small groups of women against surgical findings but not compared with 'state of the art' CT.

Patterns of Recurrent Ovarian Cancer at CT

The clinical and imaging patterns of relapsing disease differ from that at initial diagnosis. The ovaries, tubes, uterus and greater omentum have been removed. Ascites may be minimal. Relapse is often represented by small areas of thickening

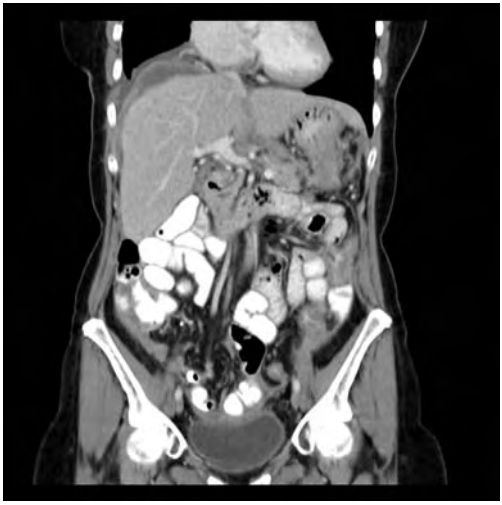


Figure 8.10 Coronal reconstruction from a 16-slice CT examination showing recurrent disease in the right subphrenic space, gastrosplenic and gastrocolic ligaments and *en plaque* disease in the lower paracolic gutters. Note there is minimal ascites and no omental cake.

on the peritoneal surfaces or the serosa of the bowel or small volume pelvic sidewall and retroperitoneal changes close to the bladder and ureters. Delineation of such small volume changes, characterisation and distinction from normal enhancement and from excreted contrast and isotopic agents provides a greater challenge than in the untreated patient for MRI and PET.

In the post-surgical patient there is no greater omentum and so omental masses are rarely seen. Recurrent tumour may involve other peritoneal recesses and reflections notably in the supracolic compartment around the spleen and stomach and in the ileocolic recess (Fig. 8.10). Unopacified bowel loops may mimic recurrent peritoneal tumour. Meticulous CT technique with thinner sections and optimal bowel contrast opacification increases the detection of recurrent disease. Adhesions from previous surgery, radiotherapy or tumour may impair bowel opacification and it can be useful to compare with previous CT studies to identify fixed loops of bowel.

Pelvic recurrence of ovarian cancer may be central at the vaginal vault associated with vaginal bleeding and discharge or lateral involving the pelvic sidewall with venous thrombosis or ureteric obstruction, often painless. Ascites may become loculated with displacement of adjacent organs and encysted lesser sac ascites may compress the stomach [29]. Lymphadenopathy may be pelvic, retroperitoneal or even involve the mediastinum or neck. With serous tumours this may be heavily calcified and be mistaken for granulomatous

lymphadenopathy [26]. Women with previous stage IV disease may relapse with pleural effusion.

Women with suspected relapsing disease present with clinical problems requiring clear delineation of cause and extent to plan treatment. Mere detection of recurrent tumour is not sufficient. Symptoms may reflect treatment-related complications rather than recurrent disease. Abdominal swelling could be due to ascites or bowel obstruction; loin or pelvic pain to urinary obstruction or lymphadenopathy; leg swelling to venous or lymphatic compromise; breathlessness to many potential causes. In such clinical situations the newer modalities are untested and for the moment CT is likely to remain the first-line investigation of symptomatic treated women.

CT and Unusual Sites of Recurrence and Metastasis

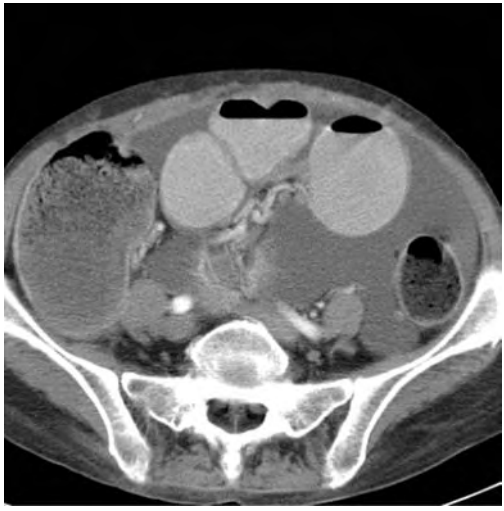
After surgery for ovarian cancer the pattern of disease is altered. With effective chemotherapy women may live much further into the natural history of the cancer. Sites and patterns of metastasis only seen in the hospice or at *post mortem* are being encountered in clinical practice with novel and surprising CT appearances. Metastases at sites such as bone, lung and brain are seen which are virtually never identified at presentation. Isolated brain metastasis may be seen and long disease-free survival may be seen after neurosurgical intervention [30].

CT in Assessment of Complications of the Disease or its Treatment including Presentation with Acute Abdominal Pain

Women with ovarian cancer may present with acute abdominal pain due to complications of the disease or its treatment, or from unrelated causes. The aim of imaging is to define the nature, site and extent of the cause notably to indicate when specialist surgery will be required involving a gynaecological oncologist.

Most common of these is acute intestinal obstruction which may result from either tumoural involvement of the bowel or from post-surgical adhesions (Fig. 8.11). CT has a central role in assessment:

- to confirm the diagnosis
- to determine if there is tumour or loculated ascites as its cause
- to look for signs of intestinal ischaemia which would contraindicate conservative therapy.



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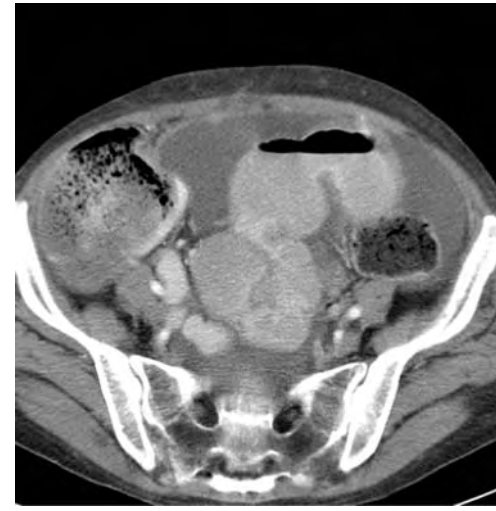

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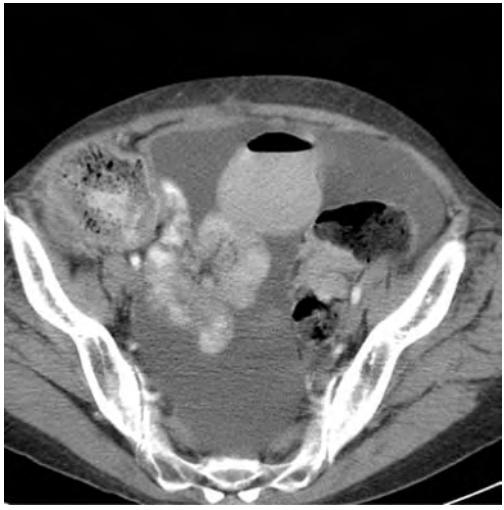

c

Figure 8.11 Two level intestinal obstruction shown by CT with (a) proximal contrast-filled small bowel, (b) a transition point and then (c) distal collapsed small bowel and an (a, b) obstructed dilated right colon due to (c) a stenosing serosal deposit on the sigmoid colon.

With evidence of high-grade obstruction on plain radiographs oral contrast material does not need to be administered. Whilst CT may provide sufficient information about the small bowel it does not tell the surgeon everything that is required to plan surgery. The preferred palliative procedure is ileo-colic anastomosis. Because the bowel is collapsed beyond the point of obstruction its patency may be uncertain. In such situations a water-soluble contrast enema is a valuable adjunct to CT.

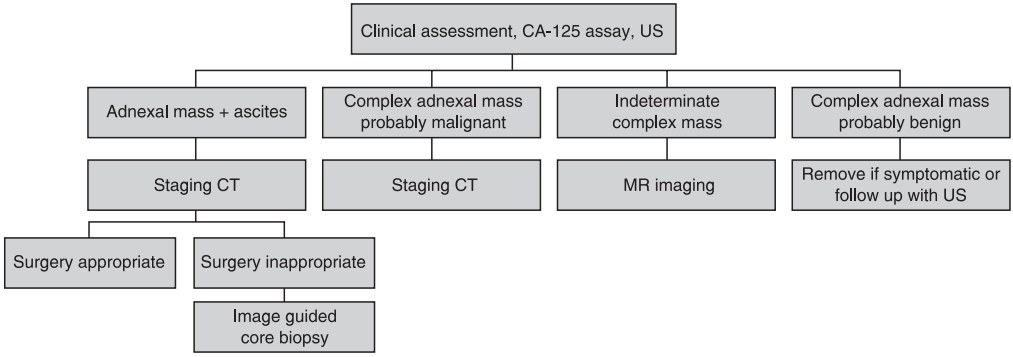

Figure 8.12 Pathway for imaging ovarian cancer at diagnosis.

Ascites may become loculated and cause symptoms due to compression and obstruction of vital structures. Image-guided drainage offers palliation. One unusual cause of bowel obstruction seen is the 'squashed stomach syndrome' in which ascites become entrapped in the lesser sac and the stomach and duodenum are compromised [29].

Other causes of an acute abdomen include unrelated but common benign conditions such as appendicitis and diverticulitis, complications of chemotherapy or, more rarely, of radiotherapy.

Summary and Recommendations for Use of CT in Ovarian Cancer

The role of CT in ovarian cancer is as follows:

- *At initial diagnosis and in staging prior to debulking surgery or neoadjuvant chemotherapy*: CT should not be used to characterise masses but is useful for staging and for image guided biopsy (Fig. 8.12).
- *Following debulking surgery and prior to chemotherapy: a new baseline CT should be obtained for assessment of treatment response during chemotherapy including those patients being considered for interval debulking surgery (IDS).* CT should only be used during therapy in patients with radiologically evaluable disease, or with concern for disease progression and then after treatment for a new baseline.

- *For confirmation of remission*: CT is only used in clinical trials.
- *At suspected relapse*: CT is of proven value.
- *To assess complications of the disease or its treatment including presentations with acute abdominal pain*: CT will provide valuable information.

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9

PET and PET/CT in Ovarian Cancer

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Positron Emission Tomography

Positron emission tomography (PET) is a non-invasive imaging technique that measures the distribution of positron emitting radiopharmaceuticals. Depending on the radiolabelled tracer used, PET can determine various physiological and biochemical processes in vivo [1]. PET is highly sensitive, with the capacity to detect nanomolar concentrations of radiotracer and provides superior image resolution to conventional gamma camera imaging. Currently, PET can target several biological features of tumours including glucose metabolism, cell proliferation, perfusion and hypoxia [2]. Most malignant tumours are characterized by elevated glucose consumption, which means that their uptake of the glucose analogue [F-18] fluorodeoxyglucose (FDG) increases. The uptake mechanism and biochemical pathway of the glucose analogue [F-18] fluorodeoxyglucose (FDG) has been extensively studied in vitro and in vivo. The transport of the radiotracer through the cell membrane via glucose transport proteins and subsequent intracellular phosphorylation by the enzyme hexokinase have been identified as key steps for subsequent tissue accumulation (for recent review see [3]). As FDG-6-phosphate is not a suitable substrate for glucose-6-phosphate isomerase, and the enzyme level of glucose-6-phosphatase is generally low in tumours, FDG-6-phosphate accumulates in cells and is visualized by PET.

PET imaging using FDG has been applied for staging of cancer patients for more than a decade now. It is generally accepted that imaging the metabolic activity of tumour tissue provides sensitive and specific information about the extent of disease for many types of tumours [4]. FDG-PET often provides additional

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and more accurate information about the presence of malignant disease than morphologic/anatomical imaging alone. The metabolic activity of cancer tissue offers further information about cancer biology and can also be used to determine tumour aggressiveness and to assess response to treatment.

General PET Imaging Procedures and Image Analysis

To ensure a standardized metabolic state, especially low plasma glucose and insulin levels, it is necessary that oncology patients have fasted for at least 4 to 6 hours prior to administration of FDG. The blood glucose level should be tested prior to tracer injection and should not exceed 150 mg/100 ml [5]. It is important to note that most studies published have excluded diabetic patients and the diagnostic performance of FDG-PET is generally lower in patients with elevated blood glucose levels. Intravenous administration of about 300–400 MBq (~10 mCi) F-18 FDG is used in most centres, although some inject more than 750 MBq (~20 mCi) specifically in larger patients. Most FDG is taken up by tissue within one hour after tracer injection and PET data acquisition should be started after approximately 60 minutes. Some studies found increasing target-to-background ratios over time suggesting benefits to longer waiting periods between tracer injection and data acquisition [6]. However, lower image quality, due to radionuclide decay, has to be taken into account. Attenuation correction is required for optimal tumour localization as well as subsequent quantification of regional tracer uptake. Using iterative reconstruction algorithms results in better image quality and has largely replaced filtered back projection.

Calculating standardized uptake values (SUV) by normalization of tumour FDG uptake to injected activity and body weight is the most common method for tumour quantification. Dynamic data acquisition allows calculation of the tracer influx constant, although this procedure is more complex and has not been shown to significantly increase the diagnostic accuracy of PET imaging. Visual image interpretation should include analysis of transaxial, coronal, and sagittal views. Cancer typically presents with focally increased FDG uptake, whereas benign tumours are generally negative in PET imaging. However, common pitfalls include increased FDG uptake in normal ovaries, e.g. during ovulation as well as normal physiologic activity in bowel, endometrium, and blood vessels and focal retained activity in ureters, bladder diverticula, pelvic kidneys, and urinary diversions [7,8]. Kim *et al.* found increased physiological FDG accumulation in the ovaries of premenopausal women around the time of ovulation and during the early luteal

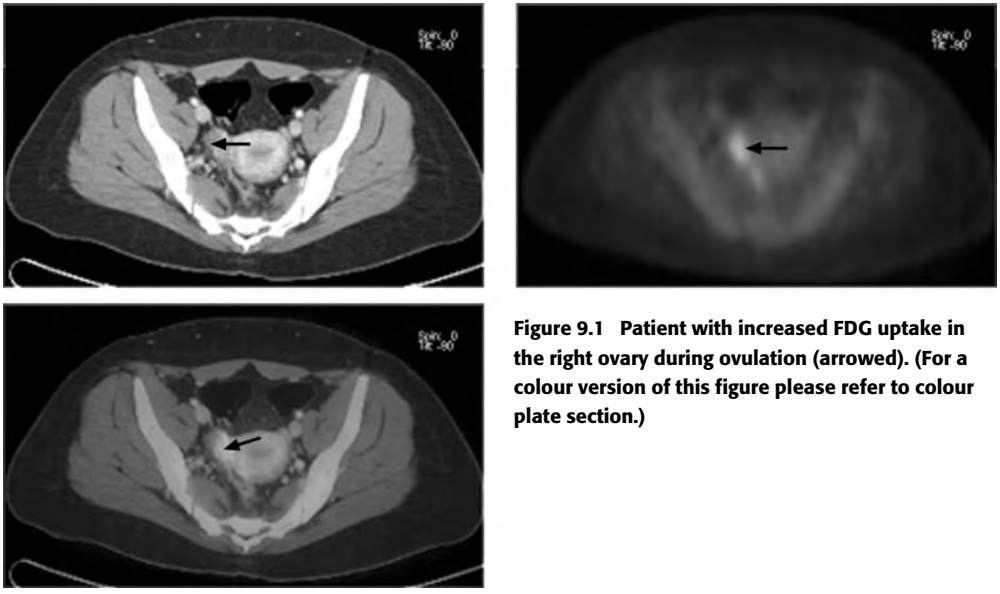

Figure 9.1 Patient with increased FDG uptake in the right ovary during ovulation (arrowed). (For a colour version of this figure please refer to colour plate section.)

phase of the menstrual cycle [9]. Whole-body imaging can be improved by intravenous injection of furosemide (20—40 mg) to reduce tracer retention in the urinary system and by *n*-butyl-scopolamine (20—40 mg) to reduce FDG uptake in the bowel [10]. For the imaging of the pelvic region, Rose *et al.* used continuous bladder irrigation and Sugawara *et al.* suggested additional postvoid imaging [11,12]. Many investigators have incorporated a technique of hydration, diuretic administration and pre-imaging voiding with success, avoiding invasive procedures such as bladder drainage.

FDG-PET Imaging of Primary Ovarian Cancer

The utility of FDG-PET has been evaluated in a large series of patients by Fenchel *et al.* [13,14]. Preoperative FDG-PET was compared to ultrasound and magnetic resonance imaging (MRI) in 101 patients with asymptomatic adnexal masses. Following surgery, 12 malignancies were discovered: 4 of these were tumours of low malignant potential (LMP), 7 were invasive ovarian cancers (3 stage I, 4 stage III) and one was metastatic breast cancer. Benign lesions included functional ovarian cysts, endometriomas and benign cystadenomas. FDG-PET correctly classified 7 of 12 asymptomatic adnexal masses as malignant and 66 of 87 as

benign, resulting in a sensitivity of 58% and a specificity of 80%. This compares with a sensitivity and specificity for ultrasound of 92 and 60%, respectively, and for MRI at 83 and 84%, respectively. When all three modalities were combined the sensitivity was 92% with a corresponding specificity of 85%. All false-negative results by FDG-PET imaging were either invasive stage I or tumours of low malignant potential (LMP). The authors concluded that the addition of MRI and/or FDG-PET may improve the diagnostic accuracy of ultrasound in the identification of ovarian cancer. However, in patients with an asymptomatic adnexal mass none of these imaging modalities can definitively rule out the presence of early-stage ovarian cancer or a borderline malignancy. An important finding in this and other studies is that tumours of low malignant potential (LMP tumours) are characterized by a low FDG uptake and can not reliably be detected by FDG-PET [15–17].

The accuracy of FDG-PET for the detection and evaluation of primary ovarian cancer may be improved by selecting patients who have a significantly increased risk for malignancy based on history, clinical examination, tumour markers or suspicious conventional imaging. An early study by Hubner *et al.* evaluated 51 patients with suspected primary ovarian cancer prior to surgery [18]. At surgical exploration, the overall incidence of pelvic malignancies in this population was 59% (30/51), half of which were ovarian primaries. In this series the sensitivity and specificity of FDG-PET for detecting primary ovarian malignancies was 93 and 82%, respectively. False-negative scans were seen in one LMP tumour and one ovarian adenocarcinoma imaged two days after chemotherapy. Similarly, Schroder *et al.* performed preoperative FDG-PET scans on 28 patients with a high clinical suspicion for primary ovarian cancer based on clinical examination and the results of ultrasound or CT examination [16]. Of these patients, 14 had a primary ovarian malignancy confirmed at laparotomy and FDG-PET correctly identified 10 of 11 invasive epithelial ovarian cancers, missing one stage I tumour, but identified only 1 of 3 borderline tumours of the ovary. Furthermore, the identified LMP tumour was detected only due to uptake in surrounding nodes, which was thought to have resulted from recent laparoscopic surgery several days before the scan. The only false positive in this series was a benign pelvic abscess [16]. A separate analysis was done for the detection of peritoneal carcinomatosis and nodal involvement in these 28 patients, together with 12 patients who were being evaluated for recurrent disease. In these 40 patients, the sensitivity and specificity for nodal involvement was 72.7 and 92.3%, respectively. Peritoneal carcinomatosis was detected with 71% sensitivity and 100% specificity.

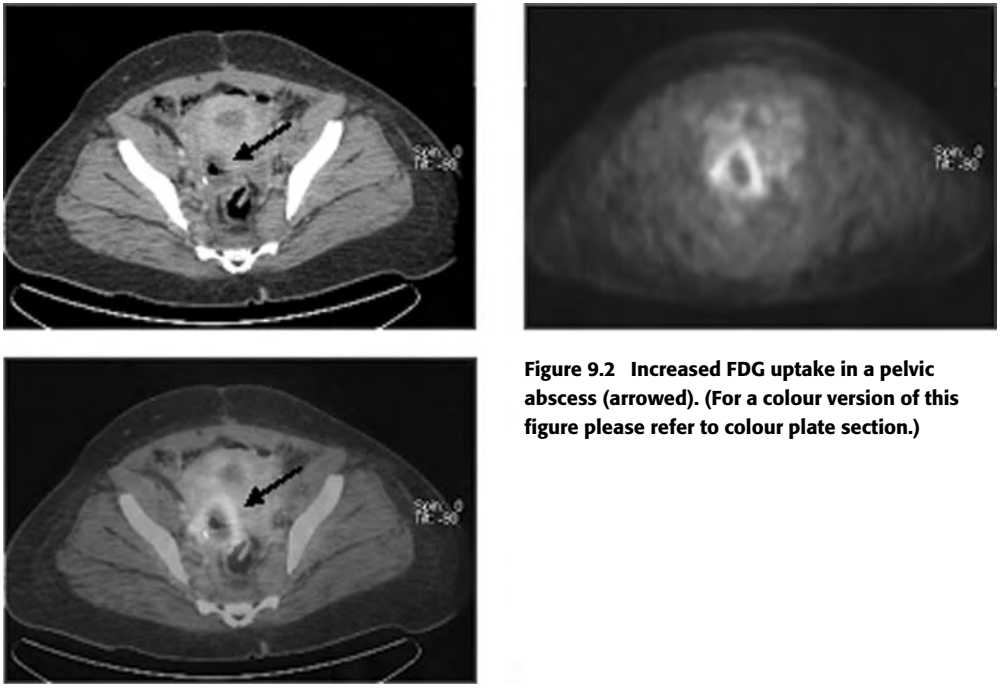

Figure 9.2 Increased FDG uptake in a pelvic abscess (arrowed). (For a colour version of this figure please refer to colour plate section.)

Similarly, in a study of 6 ovarian cancer patients and 13 benign tumours, all malignant tumours showed enhanced FDG uptake with the exception of one false-negative borderline (LMP) carcinoma [15]. However, 4 cases with inflammatory lesions as well as endometrial and follicular cysts also revealed high FDG uptake, resulting in a sensitivity of 83% and a specificity of only 54%. Disseminated peritoneal carcinomatosis was not detected in two patients, which is lower compared to other studies reporting sensitivities between 71 and 86% [15–17].

In conclusion, all series evaluating FDG-PET in primary ovarian cancers to date have very high detection rates for advanced stages of ovarian cancer, with most false negative cases representing tumours of low malignant potential (LMP) or stage I invasive tumours. Although FDG-PET is able to accurately identify the presence of advanced disease, the ability to specifically detect disseminated carcinomatosis or locate small tumour deposits (<1 cm) is lower, thus potentially limiting the ability of FDG-PET to provide accurate preoperative staging. False positive cases were due to benign lesions with a significant inflammatory component.

Diagnosis of Distant Metastases and Recurrent Disease

The majority of patients with advanced stage ovarian cancer will have persistent disease or develop recurrent disease, even after complete clinical response following primary therapy. A number of studies have been performed to address the ability of FDG-PET to detect recurrent ovarian cancer. Zimny *et al.* reported results of 106 FDG-PET scans in 54 patients performed in follow-up after surgery and chemotherapy [19]. Fifty-eight FDG-PET scans were performed in patients with suspected recurrence and 48 in patients who were clinically disease-free undergoing surveillance. FDG-PET correctly identified recurrent disease in 73 out of 88 cases and ruled out recurrent disease in 15 out of 18 cases. Thirty-seven had histologic confirmation and 66 had clinical follow up, for a median of 22 months in disease-free patients or 12 months in those with recurrent disease. The sensitivity and specificity for FDG-PET were 83 and 83%, respectively. An important finding of this study was that in patients with suspected disease, the sensitivity was 94% compared to only 65% in clinically disease-free patients. Similar findings have been reported in several smaller studies [20,21]. This finding is most likely explained by a low sensitivity of FDG-PET to detect microscopic disease and small tumour deposits [11,22]. While FDG-PET has limited sensitivity for detecting small-volume (<1 cm) metastatic disease, accurate identification of larger tumour nodules may have an impact on clinical management, e.g. for localizing discrete macroscopic tumour masses and selecting patients for radiation therapy or surgery.

In a subgroup of patients with rising CA-125 levels following primary surgery and chemotherapy, the sensitivity of FDG-PET to detect and localize tumour tissue is relatively high. Chang *et al.* performed FDG-PET scans in 28 patients with rising CA-125 levels and negative conventional imaging. Recurrent disease was correctly confirmed by histology or clinical follow up. FDG-PET correctly identified 19 out of 20 recurrences and 7 out of 8 benign lesions with a sensitivity and specificity of 95 and 87.5%, respectively [23]. Similarly, in another study of 14 patients with suspected recurrent ovarian cancer based on elevated tumour marker levels and normal or equivocal results in CT and MRI, FDG-PET correctly defined disease in 13 of the 14 patients, resulting in a diagnostic accuracy of 93% [24]. These findings have been confirmed by a number of different investigators [18,20,21,25–27]. The overall accuracy of FDG-PET in the diagnosis of recurrent ovarian cancer ranges from 79 to 93% [18,24–26,28]. In a recent study including 29 ovarian cancer patients the sensitivity, specificity, positive predictive value,

negative predictive value, and accuracy of FDG-PET were 84.6% (22/26), 100% (3/3), 100% (22/22), 42.9% (3/7), and 86.2% (25/29), respectively [29].

In summary, results obtained so far suggest that FDG-PET may be particularly helpful for staging in the setting of suspected recurrent disease when CA-125 is rising but CT findings are negative or equivocal, to identify clinically and radiographically occult but surgically resectable metastases. FDG-PET may also be particularly useful in detecting metastatic lesions intimately associated with the bowel wall that are difficult to distinguish on CT or MRI. As the treatment of recurrent ovarian cancer moves away from recurrent surgical debulking, FDG-PET may be useful in selecting patients for more disease-specific treatment. Those patients with focal disease may benefit from surgical debulking or focal radiation, followed by consolidation chemotherapy. Whereas those with a negative FDG-PET or diffuse milliary spread may not benefit from the added morbidity of surgical resection.

FDG-PET/CT in Ovarian Cancer

An important limitation of FDG-PET is the precise localization of abnormalities due to the lack of reliable anatomical landmarks and the limited spatial resolution of current PET scanner technologies. Metabolic FDG-PET imaging is particularly challenging in the neck, abdomen and pelvis due to variable physiologic FDG uptake in lymphatic, bowel and muscle tissue as well as by the renal excretion of the radiotracer which can confound image interpretation. Combined positron emission tomography and computed tomography (PET/CT) is a new imaging technology which has recently become available, merging the metabolic information from FDG-PET with the anatomical information from CT [30]. Combined PET/CT devices acquire PET and CT images that are concurrent and co-registered. The use of FDG-PET/CT has been shown to improve the diagnostic accuracy compared to the individual imaging procedures by localizing areas of increased FDG uptake with improved anatomic specificity and by also providing better characterization of suspicious morphological abnormalities [31].

There is limited information available so far describing the role of FDG-PET/CT in the follow up of ovarian cancer patients. A retrospective review compared FDG-PET/CT and conventional CT in eight patients with recurrent ovarian or fallopian tube cancer [32]. Five of eight patients were correctly identified with recurrent disease by FDG-PET/CT, while conventional CT identified only one of eight

patients. Nanni *et al.* recently evaluated 41 patients for ovarian cancer recurrence where 32 were positive on FDG-PET/CT (30 true-positive, 2 false-positive) and 9 were negative (5 true-negative, 4 false-negative) [33]. Overall, FDG-PET/CT provided a sensitivity of 88.2%, a specificity of 71.4%, and an accuracy of 85.4%, which is superior to that reported for conventional imaging. In another study, the results of second-look surgery were compared with FDG-PET/CT in 31 patients, 17 (55%) had persistent tumour, and 14 (45%) had no tumour recurrence [34]. A total of 41 lesions were tumour positive: 16 localized in lymph nodes, 21 in peritoneal lesions and 4 in the pelvis. The diameter of these lesions ranged from 0.3−3.2 cm with a mean size of 1.7 cm. The overall lesion-based sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of FDG-PET/CT were 78, 75, 77, 89 and 57%, respectively. A size threshold of 0.5 cm was identified for the largest lesion missed by FDG-PET/CT.

Thrall *et al.* found FDG-PET/CT most helpful in the clinical setting of rising CA-125 levels but negative or indeterminate on conventional CT imaging [35]. A total of 24 FDG-PET/CT were performed in 22 patients in which 18 (75%) correctly identified disease recurrence. These results compare favourably with a recent report evaluating FDG-PET/CT in 22 patients with suspected recurrent ovarian cancer [36]. All patients had subsequent surgical evaluation and FDG-PET/CT identified tumour lesions larger than or equal to 1 cm with a sensitivity of 83.3%. Another recent study included 19 patients with suspected ovarian cancer recurrence where FDG-PET, CT, and fused FDG-PET/CT were evaluated separately and imaging results compared with pathological findings and clinical follow-up [37]. In 8 of 11 patients, recurrence was identified by FDG-PET, CT, and fused FDG-PET/CT. In the remaining three patients, only FDG-PET, and FDG-PET/CT identified the recurrent tumour. Overall, 12 ovarian cancer deposits were detected by CT, 17 by FDG-PET and 18 by FDG-PET/CT. In three metastases at the level of the diaphragm, the spleen and the thoracic wall, respectively, the determination of the exact localisation was only possible by fused FDG-PET/CT.

Recently, a study assessed the value of FDG-PET/CT for identification of recurrent ovarian cancer in retroperitoneal lymph nodes [38]. Fourteen patients with rising serum CA-125 levels and negative or equivocal conventional CT imaging, identified as having recurrent disease limited to retroperitoneal lymph nodes by combined FDG-PET/CT, underwent surgical reassessment of targeted nodal basins [38]. There were 29 target nodes in 15 nodal basins identified with

increased metabolic activity on combined FDG-PET/CT. Eleven patients (78.6%) had tumour positive retroperitoneal lymph nodes targeted by FDG-PET/CT. Of 143 nodes retrieved, 59 contained recurrent ovarian cancer with a median nodal diameter of 2.5 cm ranging from 0.8 to 5.2 cm. The sensitivity, specificity and accuracy for recurrent ovarian cancer in dissected lymph nodes were 40.7% (24/59), 94.0% (79/84), and 72.0% (103/143). FDG-PET/CT failed to identify microscopic disease in 59.3% of pathologically positive nodes. The authors concluded that combined FDG-PET/CT demonstrates high specificity in identifying recurrent ovarian cancer in retroperitoneal lymph nodes when conventional CT findings are negative or equivocal.

The ability to identify the extent and exact location of recurrent ovarian cancer is important in the subsequent selection of therapeutic modalities. In the above mentioned study by Thrall *et al.*, FDG-PET/CT aided in the treatment planning of 14 patients with known disease recurrences who were considered for site-specific treatments [35]. It is important to note that in 4 (28.6%) of these 14 patients, FDG-PET/CT scans revealed unsuspected disease that was either outside of the abdomen or in surgically inaccessible areas. In summary, FDG-PET/CT provides improved diagnostic accuracy compared to the individual imaging procedures and appears to be specifically helpful for treatment stratification, providing important additional information which can be used in deciding between localized treatment and surgical procedures.

Therapy Monitoring

Anatomical imaging modalities, although providing accurate tumour size measurements, have distinct limitations, particularly for assessment of therapy response early in the course of treatment and in the assessment of novel biological therapies. The current endpoint for assessing response to therapy in solid tumours is by measuring the change in tumour size [39]. Anatomical imaging modalities, predominantly computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound (US) are used to obtain uni- or bi-dimensional measurements of reference tumour lesions from pre-treatment scans relative to follow-up. However, important limitations of anatomic imaging based assessment of treatment response have to be taken into consideration. Based on the WHO criteria, a tumour is classified as responding when the product of two perpendicular diameters has decreased by at least 50% [40]. More recently, response criteria have been changed

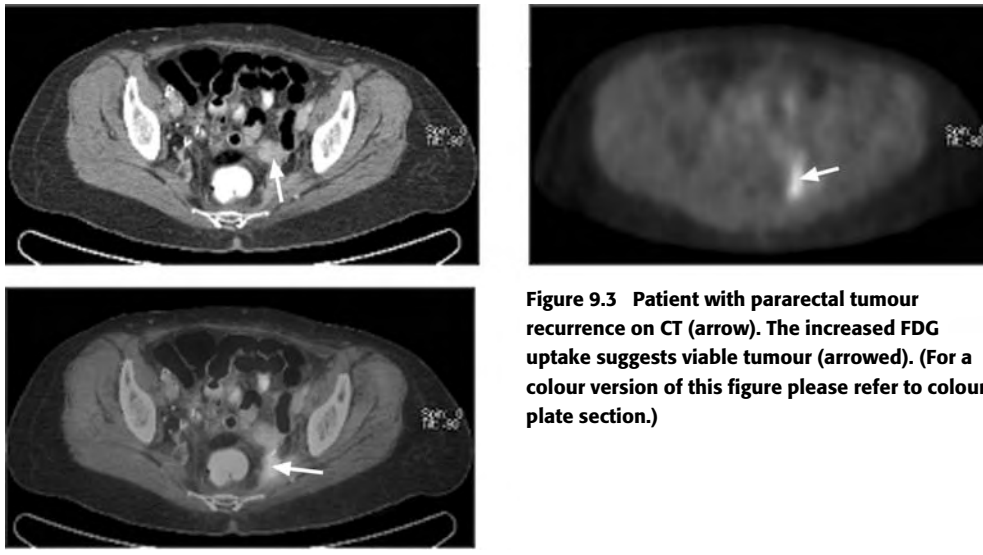

Figure 9.3 Patient with pararectal tumour recurrence on CT (arrow). The increased FDG uptake suggests viable tumour (arrowed). (For a colour version of this figure please refer to colour plate section.)

to uni-dimensional tumour diameter measurements. The new RECIST (response evaluation criteria in solid tumors) criteria define tumour response as a decrease of the maximum tumour diameter by at least 30% [39]. In ovarian cancer, serum levels of CA-125 are often used clinically to assess tumour response [41]. While CA-125 monitoring is non-invasive, CA-125 levels do not accurately reflect volume of residual disease and according to the *Guidelines to Evaluate the Response to Treatment in Solid Tumors*, CA-125 cannot be used alone to assess tumour response [39].

Response evaluation after completion of treatment can pose a challenge if a residual mass is present, since it is difficult to differentiate viable tumour tissue from post-treatment changes such as scarring and fibrosis. In a recent study by Thrall *et al.*, FDG-PET performed after completion of treatment allowed reliable identification of residual viable tumour. Eight FDG-PET/CT scans in five patients were performed for assessment of treatment response following chemotherapy or radiation therapy. All patients had a positive baseline FDG-PET/CT and imaging response corresponded well with clinical response in all patients. FDG-PET/CT was specifically useful in these patients as the disease was not clearly identified by conventional CT imaging at baseline. The higher diagnostic accuracy of FDG-PET/CT for identifying recurrent disease also seems to improve the ability to monitor treatment response.

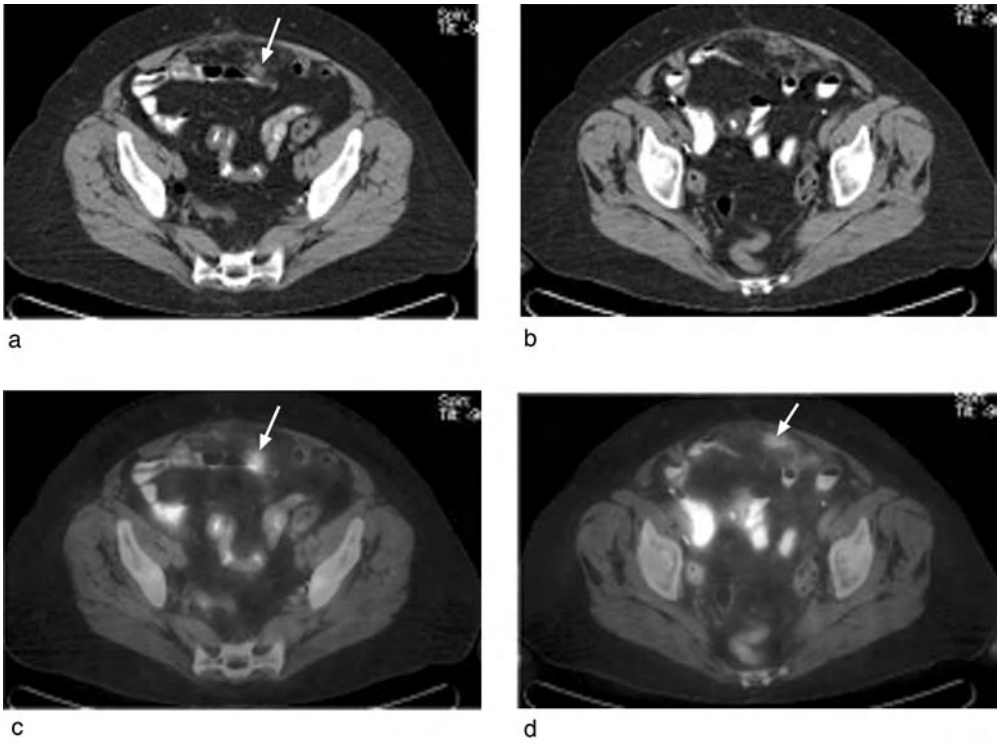

Figure 9.4 (a+b) Patient with omental tumour recurrence on CT (arrowed). (c+d) These multiple small omental masses demonstrate increased FDG uptake (arrowed). (For a colour version of this figure please refer to colour plate section.)

In ovarian cancer patients not responding to initial platinum/paclitaxel-based chemotherapy, the prognosis generally is poor [42]. As newer, effective alternate agents to platinum become available [43], it becomes increasingly important to identify non-responders to standard chemotherapy as early as possible in the course of disease so that ineffective therapy can be discontinued and more effective chemotherapy can be initiated. In particular, early identification of non-response is essential to avoid ineffective treatment, unnecessary side-effects and costs. Since therapeutic approaches are increasingly modified on an individual basis, there is a need for modalities that allow prediction of treatment response early in the course of therapy.

Dissolving and shrinkage of a tumour mass is the final step in a complex cascade of cellular and sub-cellular changes after initiation of treatment.

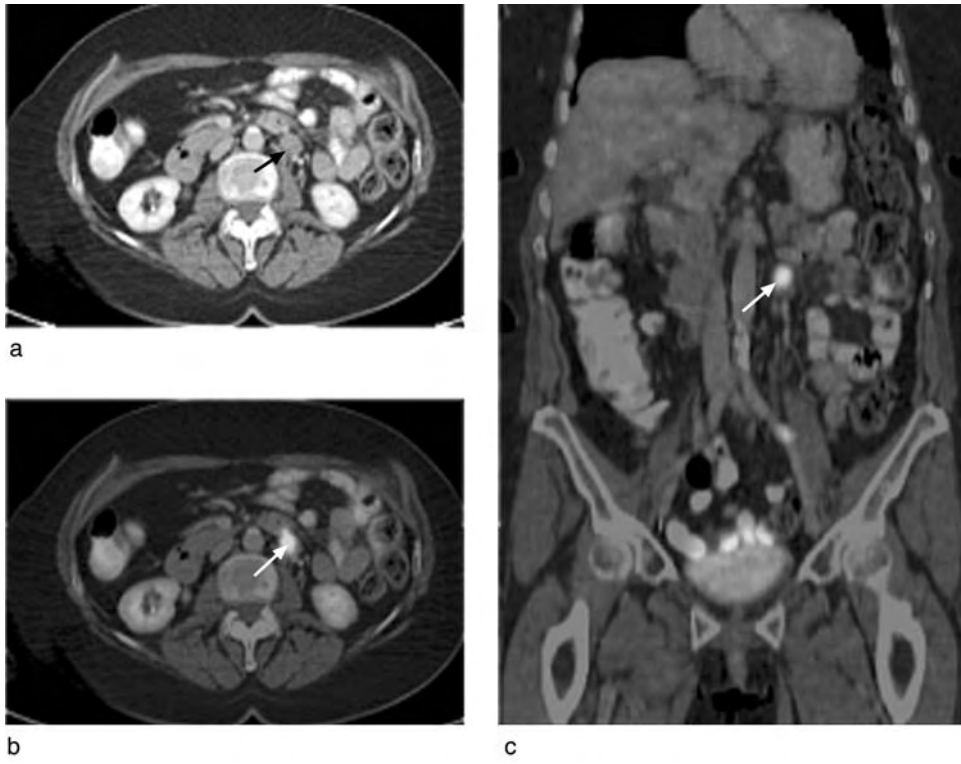

Figure 9.5 Patient with left para-aortic tumour recurrence. (a) The CT shows a small left para-aortic mass (arrowed). (b+c) Increased FDG uptake corresponding to a mass on CT (arrowed). (For a colour version of this figure please refer to colour plate section.)

Frequently, several cycles of chemotherapy or other treatments need to be applied before treatment response can be assessed by current anatomical imaging modalities. Metabolic FDG-PET imaging provides unique information about biological and pathophysiological behaviour of tumour tissue in vivo and is promising in the early identification of tumour response to therapy in ovarian cancer. Changes in glucose metabolism have been shown to precede changes in tumour size and to accurately reflect treatment response in various types of tumours [2,44–49]. These findings establish the basis for the future clinical application of sequential FDG-PET imaging as in vivo test for chemosensitivity, predicting response to treatment early after onset of chemotherapy.

A recent study in advanced stage ovarian cancer patients treated with neoadjuvant chemotherapy indicated that the metabolic information from

FDG-PET is superior to clinical response, changes in CA-125 levels, and histopathology [50]. Thirty-three advanced-stage (FIGO stages IIIC and IV) ovarian cancer patients received three cycles of carboplatin-based chemotherapy, followed by cytoreductive surgery. Quantitative FDG-PET of the abdomen and pelvis was acquired before treatment and after the first and third cycle of chemotherapy. A significant correlation was found between FDG-PET metabolic response after the first and third cycle of chemotherapy and overall survival. By using a threshold for decrease in SUV from baseline of 20% after the first cycle, median overall survival was 38.3 months in metabolic responders compared with 23.1 months in metabolic non-responders. At a threshold of 55% decrease in SUV after the third cycle median overall survival was 38.9 months in metabolic responders compared with 19.7 months in non-responders. There was no correlation between clinical response criteria or CA-125 response criteria and overall survival, and only a weak correlation between histopathologic response criteria and overall survival. This study confirmed a recently identified characteristic behaviour of malignant tumours, namely the close correlation between the early decrease in glucose metabolism measured by FDG-PET and treatment response. Further validation, however, is required to define the role of sequential FDG-PET for prediction of treatment response early in the course of therapy in ovarian cancer.

Summary

Positron emission tomography (PET) using F-18 fluorodeoxyglucose (FDG) has become an important diagnostic modality for imaging cancer patients and has also gained increasing importance in ovarian cancer. The application of FDG-PET for characterization of adnexal masses is limited by the increased FDG uptake in inflammatory processes and the inability to accurately differentiate such processes from ovarian cancer. FDG-PET does not currently provide sufficient sensitivity for detecting tumours of low malignant potential (LMP) or stage I invasive ovarian cancer. On the other hand, FDG-PET is highly accurate in localizing recurrent disease. Combined positron emission tomography and computed tomography (PET/CT) is likely to play an important role for localizing suspected recurrent ovarian cancer in the future. Assessment and prediction of treatment response is an exciting application of metabolic imaging, and the appropriate clinical use of FDG-PET in ovarian cancer requires further evaluation.

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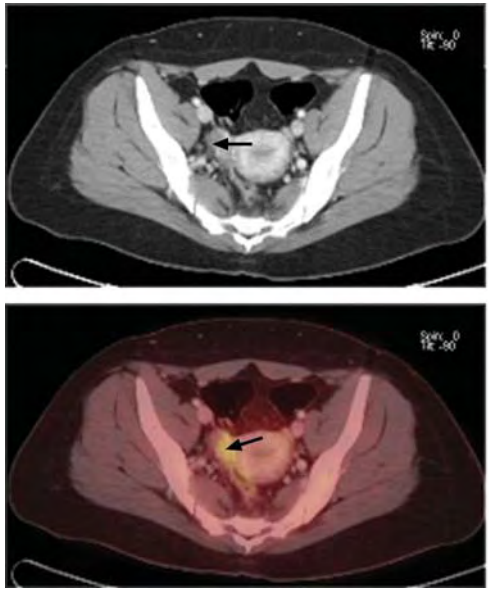


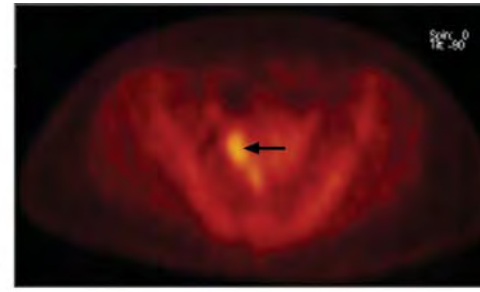
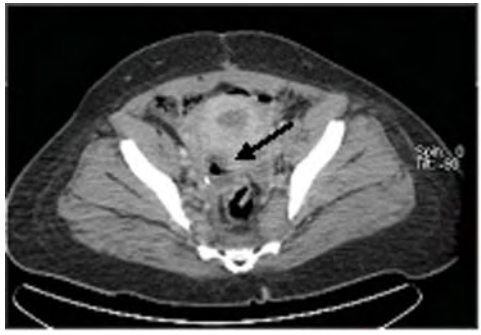
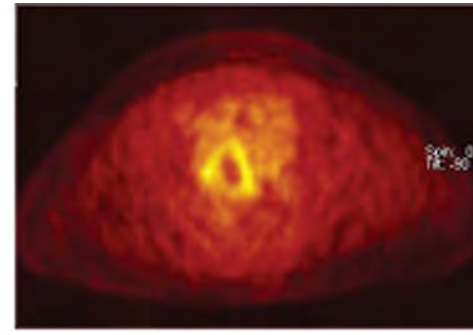


Fig 9.1 Patient with increased FDG uptake in the right ovary during ovulation (arrowed).





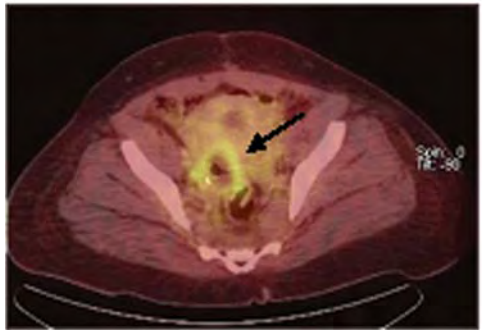


Fig 9.2 Increased FDG uptake in a pelvic abscess (arrowed).

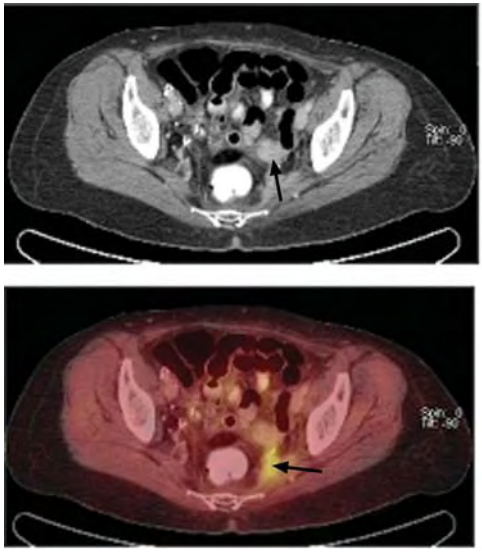


Fig 9.3 Patient with pararectal tumour recurrence on CT (arrow). The increased FDG uptake suggests viable tumour (arrowed).

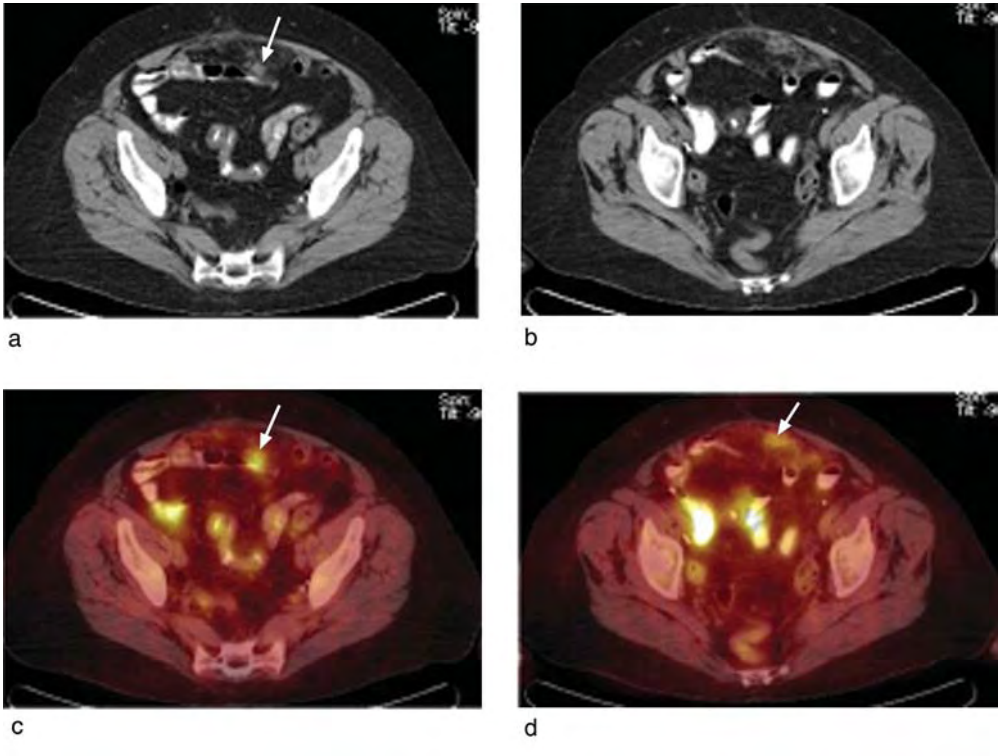


Fig 9.4 (a+b) Patient with omental tumour recurrence on CT (arrowed). (c+d) These multiple small omental masses demonstrate increased FDG uptake (arrowed).

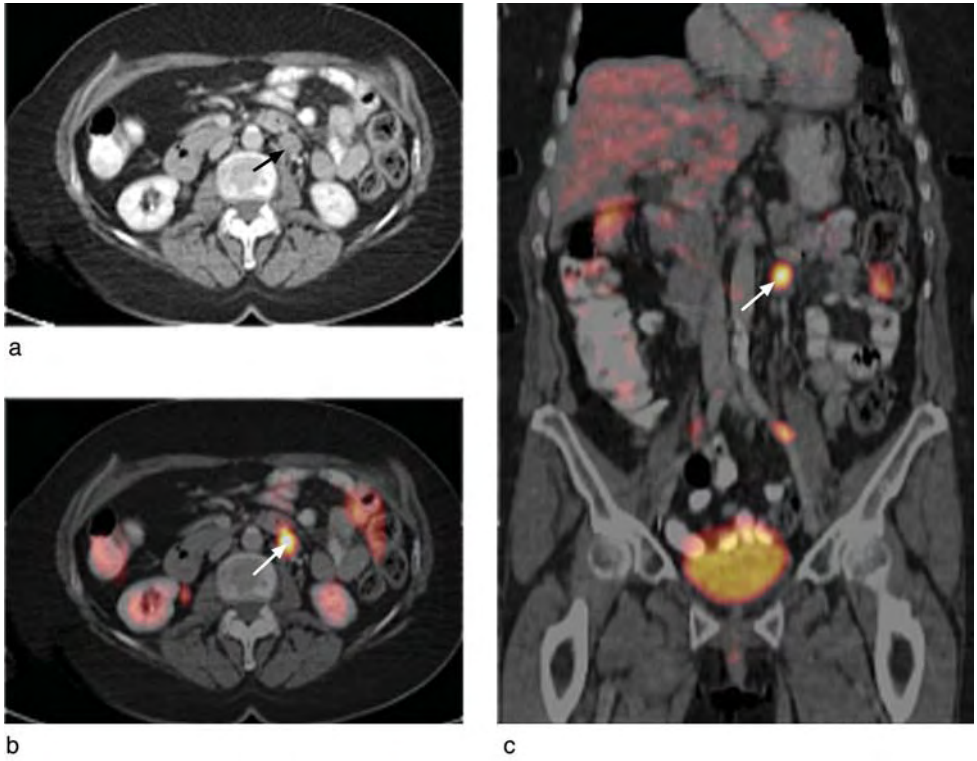


Fig 9.5 Patient with left para-aortic tumour recurrence. (a) The CT shows a small left para-aortic mass (arrowed). (b+c) Increased FDG uptake corresponding to a mass on CT (arrowed).