Ovarian cancer
where are we now?

Ovarian cancer has a well deserved reputation as a disease with high morbidity and poor survival. Survival is improved by diagnosis at the earliest time, skilled staging and surgery, and individualised chemotherapy.

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Ovarian cancer is the second most common gynaecological cancer, behind cancer of the endometrium, but it has the highest death rate of all gynaecological cancers. Published figures from the NSW Central Cancer Registry showed that in 2001 there were 356 patients presenting with a new ovarian carcinoma (2.6% of all cancers in women that year). The lifetime risk of developing ovarian cancer in NSW is estimated at 1:128, with endometrial carcinoma at 1:88 and cervical cancer now at 1:177. The lifetime risk of dying from ovarian cancer is 1:204, compared with cancer of the endometrium at 1:641 and cervix at 1:527.

Epidemiology and risk factors

There is some difference in incidence rates of ovarian cancer among countries, but this is not nearly as marked as in the other gynaecological malignancies, such as those of the cervix or endometrium. The Scandinavian races have rates of ovarian cancer greater than those of Australians, who have rates greater again than those of the Asian races.

There is a weak correlation of increased risk of ovarian cancer with higher education and socio - economic status, but this has been attributed to lower parity.[1] It is now well established that pregnancy protects against ovarian epithelial tumours. The outcome of the pregnancies is unrelated, but the higher the gravidity the lower the risk. In keeping with this, infertility is also a risk factor.

Other factors that have been implicated in increasing risk include a history of breast cancer or mumps parotitis, Western dietary habits, exposure to ionising radiation and use of talc. There appears to be a protective effect against the disease from oral contraceptive use and previous hysterectomy (even with ovarian conservation). A very small percentage of women will have a family history of disease, and two genetic markers have

IN SUMMARY

- **Ovarian carcinoma is uncommon but is associated with poor survival.**
- **The majority of patients present with advanced disease, many having had nonspecific symptoms for some time.**
- **Primary treatment is usually surgery followed by chemotherapy.**
- **Certain tumours can now be treated with conservative surgery or chemotherapy alone in some instances, so preserving the reproductive potential of younger patients.**
- **Success in treating ovarian cancer depends on diagnosis at the earliest time, appropriate staging and surgery by skilled specialists, and the tumour's responsiveness to chemotherapy.**
- **The best survival figures are achieved when the primary management is by a multidisciplinary team at a recognised gynaecological oncology centre.**
- **While screening tests are available, their accuracy is poor and they are not cost effective.**

been identified (*BRCA1* and *BRCA2*). However, few (5 to 10%) women with ovarian cancer have either of these markers.

Presentation

Ovarian cancer is usually asymptomatic until metastases have occurred, most commonly within the peritoneal cavity initially. The majority of patients present with advanced disease (having epithelial tumours; Figure 1) – many of these women having had nonspecific symptoms for some time. A mass may be found when they are examined by their general practitioner, either for abdominal distension or discomfort, or as an incidental finding at a routine examination such as Papanicolaou smear. This is usually confirmed by ultrasound examination.

Unlike other gynaecological malignancies, the final diagnosis of ovarian cancer is rarely made until laparotomy and histopathological examination, either intraoperatively with the surgical findings or postoperatively with the final histopathology.

Because of the difficulties in making the diagnosis clinically, a potential ovarian malignancy should be considered in any woman with a complex adnexal mass seen on ultrasound. Obvious exceptions include young women with small adnexal masses (less than 8 cm in diameter) in whom clinical signs are strongly suggestive of benign disease (such as pelvic inflammatory disease, polycystic ovaries or a functional cyst).

Occasionally patients may present with symptoms from hormones produced by their tumour, the nature of the symptoms depending on whether the effect is oestrogenic or androgenic.[2]

The various tumour types are described in the box on this page. Generally speaking, the older the patient the more likely is her tumour to be epithelial in origin and malignant. Germ cell tumours (Figure 2), on the other hand, are far more likely to be found in girls and young women. The rate of malignancy of germ cell tumours rises as age falls, being 25% in those around 15 years old and rising to 84% in those less than 10 years old.[5] These factors should be taken into account when planning the management of any patient.

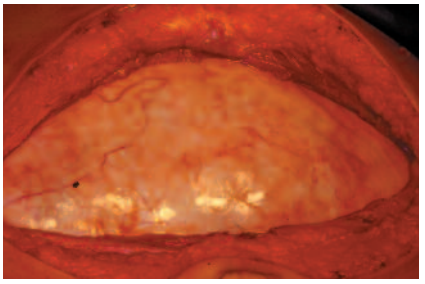

Figure 1. A huge proliferating mucinous tumour – an epithelial tumour.

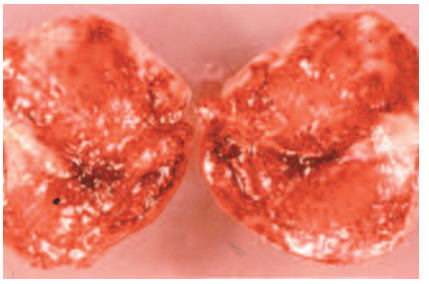

Figure 2. Dysgerminoma – a germ cell tumour.

Ovarian tumour types

There are three main types of ovarian tumours, derived from the three tissue elements in the ovaries:

- epithelial tumours – these are the most common, constituting over 50% of benign tumours and 85 to 90% of primary malignant disease
- germ cell tumours – these are rarely malignant; they are found in 25% of benign lesions but constitute only 3 to 5% of primary malignancy overall
- malignant sex cord stromal tumours – these are found in 7% of patients.

Epithelial tumours may occasionally contain sarcomatous elements (malignant mixed Müllerian tumours), which are believed to derive initially from epithelial cells rather than sarcoma *de novo*.[3] Some tumours contain mixtures of germ cell and sex cord elements.

Within the epithelial tumours, there is a subgroup called low malignant potential, proliferating or borderline tumours. These appear to behave in a much less aggressive fashion, although a percentage will still recur, often up to 10 years later. They are found in the younger age group and often are difficult for the pathologist to diagnose accurately.

There is a variant of serous carcinoma (peritoneal serous papillary carcinoma) that arises from peritoneal surfaces generally within the abdominal cavity without a dominant ovarian mass (Figure A).[4] This disease can arise in women who have had oophorectomy previously and behaves the same as serous carcinoma arising in an ovary.

Figure A. Primary peritoneal carcinoma showing huge omental cake and small ovaries.

From 10 to 30% of malignant ovarian tumours will prove to be metastases, usually from the breast, gastrointestinal tract or uterus.

Preoperative assessment

Because of the doubt about diagnosis before operation, all patients in whom there is suspicion of ovarian cancer should have a full preoperative assessment. This should include full blood count and biochemistry screen, tumour markers (carcinoembryogenic antigen, beta human chorionic gonadotropin, CA 125, alpha fetoprotein, CA 19.9) and chest x-ray.

Other tests may assist in the diagnosis or surgical management and may be indicated preoperatively. These include barium enema, abdominopelvic ultrasound, CT scan or intravenous pyelogram. Solid areas on ultrasound or CT scan or ultrasonic evidence of lowered blood flow resistance are highly suggestive of malignancy;[6] however, these investigations have a significant false negative rate (up to 27%). Fine metastatic spread to the omentum and peritoneum is particularly difficult to detect.

Before surgery, blood should be crossmatched and prophylactic antibiotics and a full bowel preparation given in case resection to remove metastases is necessary.

Any postmenopausal patient with a complex tumour, with bilateral tumours, in whom the CA 125 or other marker is elevated, or with any clinical suspicion of malignancy should have her primary treatment performed by a gynaecological oncologist.

Management of ovarian cancer

Success in treating ovarian cancer depends on:

- diagnosis at the earliest time
- appropriate staging and surgery in a centre with specialists skilled in ovarian cancer management
- the tumour's responsiveness to chemotherapy.

Ovarian cancer is best managed in a multidisciplinary department where specialists in gynaecological surgery, chemotherapy, radiotherapy, pathology and palliative care work in close liaison to provide optimal care for the patient.

A recent review of mucinous ovarian carcinoma (an epithelial tumour) by the Sydney Gynaecological Oncology Group (SGOG) found a significant disease-free survival advantage (survival, 89% for early and late stage borderline tumours and 88% for early stage invasive tumours) for patients being treated primarily by gynaecological oncologists compared with those having surgery by general gynaecologists and then being referral postoperatively (survival, 52 and 50% respectively). Several studies, including a recent one from Victoria,[7] have shown that adequate staging and surgery are more likely to be completed when they are performed by a gynaecological oncologist. This is associated with a survival advantage that we believe stems from more accurate staging and detection of occult disease leading to appropriate treatment for that stage of disease, rather than attempting salvage therapy when the disease recurs clinically.

Staging and surgery

The FIGO (International Federation of Gynecology and Obstetrics) staging is shown in Table 1; it is based on clinical examination (including x-ray and scanning procedures) and laparoscopy or laparotomy findings. The stage of any tumour is not finalised until the histology and cytology reports after surgery are received.

Table 1. FIGO staging of ovarian tumours

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

Subsequent therapy is planned according to the stage of disease,[8] the histopathology and the condition of the patient and, most importantly, for her to meet her goals in life. Accurate staging is essential to determine the best treatment for the patient.

Unfortunately many patients with apparent stage I to II disease will be shown at laparotomy to have occult abdominal or retroperitoneal metastases (and therefore will be upgraded to a higher stage). Accurate staging will alter the initially assigned tumour stage in over one-third of cases (stage I disease in 10 to 20% of cases and stage II disease in over 50 to 80% of cases). This has led to an apparent improvement in survival, because restaging and taking out the patients with occult changes who will have recurrent disease and die increases the overall survival figure for the remaining patients in that stage.

For epithelial disease that is obviously malignant and for a postmenopausal patient, the object is to remove all visible disease (Figure 3) and the likely sites for metastases. Thus surgery includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendicectomy and resection of any bulky disease that can be removed, including bowel resection, peritoneal resection and para-aortic and pelvic lymphadenectomy if indicated. The object is to leave only microscopic or minimal disease for the chemotherapy to eradicate.[9]

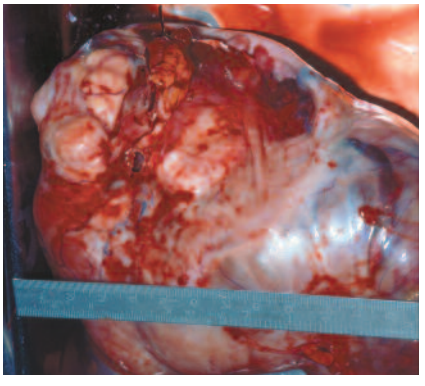

Figure 3. Primary ovarian carcinoma.

In younger patients wishing to conserve fertility, particularly those with apparent early stage disease, a more conservative approach may be followed. Many epithelial tumours in younger patients are early stage or low malignant potential (borderline) tumours with high survival rates. Germ cell tumours in younger patients are often chemosensitive, and we now believe that fertility-sparing surgery does not compromise survival.

Postoperative treatment

After surgery, adjuvant chemotherapy is given to eliminate residual disease, except to patients with stage IA disease and well differentiated tumours that have been fully staged. The recurrence rate in other stage I disease is high enough to warrant further treatment.

There must be individualisation of treatment according to the condition of the patient. Several chemotherapeutic agents have been shown to cause tumour regression in more than 50% of patients with ovarian cancer. A platinum-based drug and a taxane are now standard first line drugs. In patients unfit for such aggressive treatment, carboplatin alone appears to have equivalent response rates. In addition, alkylating agents, anthracyclines and endocrine agents have all demonstrated activity. Intraperitoneal chemotherapy has been used but with varying results.

Treatment is given for six courses. In this time, the patient's condition is closely monitored with physical examination and tumour markers, and psychological support for her and her family is offered as needed.

Subsequent treatment

If at the end of chemotherapy there is no clinical evidence of disease, tumour markers are negative and the CT scan is normal, the patient may be considered for further surgery to ascertain if there is any microscopic disease left and to debulk completely any tumour found. Positron emission tomography scanning may also be useful in this circumstance.

There is a small survival advantage if further disease is found and removed, compared with waiting for it to become evident clinically. The disadvantage is another surgical procedure for a patient who has just weathered chemotherapy.

A study by the Clinical Oncological Society of Australia (COSA) showed that 40% of patients who are disease free at re-exploration will develop recurrence and die within five years.[10] Additional therapy for this group, such as further chemotherapy or whole abdominal irradiation, may improve survival.

Free and Webb reviewed multiple series and found that 43 to 65% of 'second look' operations detected disease that had not been apparent, and that survival was low unless there was no disease or only microscopic residual disease, or debulking to these states was achieved at second look operation.[11]

When there is clinical, radiological or biochemical evidence of disease, re-exploration is not indicated unless debulking of a residual mass is considered feasible.

When primary surgery is not appropriate

Just as the management of a patient who has had surgery and chemotherapy is individualised, patients for whom primary surgery is not appropriate – because of poor general condition, disease that is not likely to be resectable or disease without any dominant mass to be removed – also need individualised management. In these patients, chemotherapy is commenced and the patient re-evaluated after three or six cycles of treatment. Those patients who have responded well are then offered surgery immediately to debulk disease prior to completing their chemotherapy. It is not yet known if this approach will give equivalent survival,

but it is under investigation. Given the poor overall survival rates with our current treatments, maintaining quality of life for these patients is paramount, and ascertaining what goals they have and working towards achieving them takes priority over treatment itself.

Prognosis and survival

The prognostic factors for ovarian cancer are listed in Table 2. These factors intermesh and should all be considered for prognosis.[1] A worse prognosis is seen in elderly patients with serous tumours, in stage III or IV disease, aneuploid tumours and disease that cannot be adequately debulked to nodules less than 2 cm.

The degree of the specialist's surgical training and exposure to patients with what appears to be extensive disease impacts upon the patient's survival, with many studies over the last 20 years showing improvement for those managed by a trained gynaecological oncologist.[12]

In the previously mentioned review from the SGOG database, few patients with early mucinous tumours treated primarily within the group have succumbed to disease in the last 20 years, with no deaths in those with borderline tumours. The same cannot be said for serous disease, where even apparent early invasive or borderline disease may harbour occult micrometastases that ultimately reveal themselves.

Thus even in adequately staged cases, the chance of recurrence for stage I disease is considerable (recurrence, 15 to 40%). Five-year survival for stage IA disease is 82%, whereas in stages IB and IC it is 75%. With modern staging procedures, stage II disease is relatively rare, constituting less than 15% of all ovarian cancers. Prognosis is dependent largely on the presence of residual disease and this is more likely in stage IIB to IIC (five-year survival, 52%) compared with IIA (61%).

The prognosis for later stage disease is dependent on reduction of the tumour and its subsequent response to chemotherapy. For stage III disease when bulk reduction is possible, a five-year survival rate of 25 to 30% has been reported, compared with 7 to 12% when reduction is not possible or is not undertaken. The latter figures are comparable to those for stage IV disease, which has a poor survival rate of only 5%.

The NSW Cancer Registry compared mortality rates in the 10 years leading up to 2000. Over that time there was a slight decrease (13%) in mortality, with no change in incidence.

Screening for ovarian cancer

Screening for ovarian cancer has been investigated extensively in the past 15 years. Ultrasound examination (abdominal and now transvaginal) has been the main tool used; it is more sensitive than manual pelvic examination but has a significant false positive rate. Better discrimination has been found if the serum CA 125 level and vaginal examination are used as well as ultrasound.

Routine screening is currently not recommended because the incidence of the disease is low, there are a significant number of false negative and false positive results, and it is not cost effective.

Recently there has been much interest in familial groupings of cancers, including ovarian cancer. With a single relative with breast or ovarian cancer, there is only a small increase in risk (5%), particularly if the relative developed her disease at an advanced age. When there is a family history of ovarian or breast cancer in two or more first or second degree relatives, there is an increased risk of up to 44%, especially if the relatives developed disease at age less than 50 years or there is a proven genetic abnormality. Patients with genetic abnormalities form a very small group within those developing ovarian cancer, but they are also at significant risk of breast cancer (56 to 87%). While genetic testing may identify such patients, we have no effective treatment that will totally preclude the subsequent development of ovarian or peritoneal disease.

Table 2. Prognostic factors for ovarian carcinoma

Patient's age
Patient's performance status
Histological type
Tumour grade
Stage of disease
Tumour ploidy (DNA analysis)
Size of largest metastasis
Residual disease after primary surgery
Response to primary chemotherapy
CA 125 level after three chemotherapy cycles
Surgeon's expertise

Where to now?

Future developments are mainly directed at new drug development or new combinations of drugs already known to have activity. There are also a number of trials being undertaken, predominantly overseas, to evaluate immune therapy, gene therapy and antiangiogenic factors, and SGOG is investigating the use of dendritic cell therapy after standard chemotherapy. However, all of these studies are relatively early and are still accruing patients. The Australia New Zealand Gynaecological Oncology Group (ANZGOG) is participating in a major epidemiological study of ovarian carcinoma, following successful studies from Queensland involving data and tissue collection for ongoing research into this difficult disease. MT

The list of references is available on request to the editorial office.

Further reading

1. Australian Cancer Network. Clinical practice guidelines for the management of epithelial ovarian cancer. Draft, February 2003 (www.cancer.org.au/guidelines). Highly recommended.

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