Epithelial ovarian cancer in Southern Africa

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ABSTRACT

Introduction
Ovarian cancer is the eighth most frequently diagnosed cancer and currently is the leading cause of death from gynaecologic cancer. Globally, the five-year survival is only 15–20% for patients with clinically advanced ovarian cancer despite aggressive surgery and platinum based chemotherapy.[1] The poor overall prognosis is primarily due to the fact that the disease is almost invariably advanced when the diagnosis is made. In Africa the most common malignancies in females are cancer of the cervix (23.3%), breast cancer (19.3%), Kaposi's sarcoma (5.1%), liver cancer (5.0%), non-Hodgkin lymphoma (38%), and cancer of the ovary (3.7%).[1]

In South Africa, the National Cancer Registry reported 529 cases of ovarian cancer in 2001. Of these cases, 207 were in white patients, 225 in black patients, 69 in coloured patients and 16 were reported in the Asian community.[2] Known risk factors include age, primigravidity, history of breast, endometrial and colon cancer, intraperitoneal talc powder or vegetable fibre, ovarian hormonal hyperstimulation, delayed childbearing, high-fat diet, fertility drugs and the Lynch II syndrome. The use of the combined oral contraceptive pill, sterilisation and a previous hysterectomy appear to have a protective effect and decrease the incidence.[3]

Pathogenesis

Oncogenesis

Ovarian carcinogenesis is not well understood and there are several postulated mechanisms with a view to pathogenesis. One of these is the "incessant ovulation theory" whereby repeated damage and trauma to the ovarian epithelium is postulated during each ovulatory cycle. As a result there is an increased potential for genetic mutation and ovarian neoplasm during the process of repair.[4] Some epidemiological evidence is in support of this theory. It is known that with each full ovulation year, there is a 6% increase in risk of ovarian cancer. The highest risk seems to be in the 20 to 29 year age group, with a 20% increase in risk.[5] For every five years usage of the combined oral contraceptive pill there is a 60% decrease in incidence.[5]

Another possible model is that epithelial ovarian tumours are categorised into two types. Type I consists of low grade serous carcinoma, mucinous, endometroid and clear cell carcinoma and malignant Brenner tumour which arise in a step wise fashion from tumours of low malignant potential. Type II tumours consist of high grade serous, undifferentiated carcinomas and carcinosarcomas.[6] The precursor lesions of these tumours remain unidentified. Molecular genetic alterations separate the two types. Crum and colleagues suggest that type II epithelial cancers actually originate from the Fallopian tube. Of importance is the fact that a high incidence of histopathological and molecular genetic alterations are observed in women harbouring a BRCA mutation.[7]

Pattern of spread

The ovary is covered by a single surface layer of epithelium. Tumour cells from the affected epithelium are exfoliated and spread within the peritoneal fluid throughout the peritoneal cavity. This is aided by bowel peristalsis. The normal peritoneal fluid classically circulates upward from the right paracolic gutter to the right subdiaphragmatic space and crosses the midline and circulates downward to the left paracolic gutter and pelvis. The commonest site of detection of tumour deposits is the peritoneal reflections where the peritoneal fluid pools the longest. Infiltration of the omentum forms what is commonly called an "omental cake".

Local spread to the opposite ovary occurs in 6–13% of cases and to the uterus in up to 25% of cases. Metastases to other gynaecological organs are not common but they are described and include the vagina, cervix and vulva.[8] Ovarian lymphatic drainage occurs along three principal routes which need to be taken into account at surgery. Firstly they accompany the ovarian blood supply directly to the para-aortic nodes. The second pathway involves drainage into the lymphatics of the broad ligament and obturator nodes. There is a rich anastomotic network between the obturator, external iliac, common iliac and para-aortic basin. The third route is less significant but drainage may occur through the round ligament to the external iliac node and inguinal nodes.[9] Haematogenous spread is uncommon and hence metastases to brain, lung and bones are uncommon.

Staging

Ovarian cancer is staged surgically with pathological confirmation of disease. Imaging allows diagnosis of liver parenchymal and pulmonary metastases. Staging reflects both the patterns of spread and the prognosis. Surgical staging is based on the International Federation of Obstetrics and Gynecology (FIGO) classification system, first introduced in 1964 and revised in 1985. (See Table I.)

Table I: Ovarian cancer staging by FIGO criteria (1986)

I	Growth limited to the ovaries
Ia	Tumor limited to one ovary; capsule intact, no tumour on ovarian surface; no malignant cells in ascites or peritoneal washings
Ib	Tumour limited to both ovaries; capsules intact, no tumour on ovarian surface; no malignant cells in ascites or peritoneal washings
Ic	Tumour limited to one or both ovaries with any of the following: capsule ruptured, tumour on ovarian surface; malignant cells in ascites or peritoneal washings
II	Tumour involves one or both ovaries with pelvic extensions
IIa	Extension and/or implants on uterus and/or tube(s); no malignant cells in ascites or peritoneal washings
IIb	Extension to other pelvic tissues; no malignant cells in ascites or peritoneal washings
IIc	Pelvic extension with malignant cells in ascites or peritoneal washings
III	Tumour involves one or both ovaries with peritoneal metastasis outside the pelvis and/or retroperitoneal or inguinal node metastasis
IIIa	Microscopic peritoneal metastasis beyond pelvis
IIIb	Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension
IIIc	Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis
IV	Distant metastasis (excludes peritoneal metastasis) to liver parenchyma or malignant pleural effusion

Diagnosis

Ovarian cancer presents late and often with vague or gastro-intestinal symptoms. The disease is sometimes difficult to detect and enteroscopy, simple and advanced imaging and clinical examination can fail to reveal abnormality even in advanced disease stages. Many patients are diagnosed by non-gynaecologists and often only at the time of surgery. The difficulty to diagnose this disease is worsened by a low index of suspicion and the relatively low incidence of the disease. Ca 125 is elevated in almost all patients with late stage epithelial ovarian cancer.

Patients with a strong family history of breast, ovarian or colon cancer deserve special attention including a much higher index of suspicion, further investigation including risk evaluation and sometimes genetic testing. A cancer risk management plan can include prophylactic surgery, hormonal prophylaxis and screening. Inherited cancer risk and screening for ovarian cancer will be considered here.

Hereditary ovarian cancer in South Africa

Approximately 10% of epithelial ovarian cancers are thought to be related to a germline genetic mutation. Breast Cancer 1 (BRCA1) and Breast Cancer 2 (BRCA2) are the most commonly affected genes, accounting for approximately 90% of the mutations in hereditary ovarian cancer. These mutations are often unique to certain population groups. Despite increasingly sophisticated molecular and genetic analysis techniques, a thorough family history remains the cornerstone of the diagnosis of individuals who have Hereditary Breast Ovarian Cancer Syndrome. Inherited BRCA mutations are relatively rare, affecting approximately 1 in 500 individuals in the general population. The frequency of mutations in the different South African population groups is varying and not known.

The likelihood of a particular individual carrying a mutation increases with a high-risk family history. Amongst 90 South African families with breast and ovarian cancers who had gene screening, 20% where identified with BRCA disease-causing mutations. Four Ashkenazi Jewish families had a 185delAG mutation whereas two Afrikaner and one Ashkenazi Jewish family were found to harbour the 5382insC mutation. Five of the families (5.56%), all of whom are Afrikaners, were found to carry the novel E881X mutation.[11]

Hereditary ovarian cancer seems to behave differently to sporadic ovarian cancer. Although the distribution of stage, grade and histology are similar, the BRCA mutation carriers seem to have a better prognosis with regard to disease free and overall survival. The difference has been hypothesised to be due to an enhanced sensitivity to platinum.[12]

Screening for ovarian cancer

The accepted WHO criteria for disease screening are set out in Table II. Applying these criteria to currently available screening options for ovarian cancer, it is clear that many problems still exist. Ovarian cancer screening for the general population is not feasible at this point in time and screening does not safeguard the high risk patient sufficiently either.

Table II: WHO criteria for screening according to the Wilson-Jungner criteria [10]

1. The condition being screened should be an important health problem
2. The natural history of the condition should be well understood
3. There should be a detectable early stage
4. Treatment at an early stage should be of more benefit than at a later stage
5. A suitable test should be devised for the early stage
6. The test should be acceptable
7. Intervals for repeating the test are determined
8. Provision should be made for the extra clinical workload resulting from screening
9. The risks, both physical and psychological, should be less than the benefits
10. The costs should be balanced against the benefits

From an African and developing world perspective, the currently available modalities which include transvaginal ultrasound and serological CA125 estimates are unfortunately not affordable and feasible for the general population. If a screening test for ovarian cancer has a sensitivity of 80 percent, 6 000 tests would be required in women aged 45 to 75 years to find a single cancer. If it were 90 percent sensitive, 5 300 tests would be needed to identify one case.[13] If screening is done for a subgroup of women who have a particularly high risk, the yield and cost-effectiveness will be much more.

From a global perspective, two large-scale screening trials are underway namely the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial and the UK Collaborative trial of Ovarian Cancer Screening. The Prostate, Lung, Colorectal and Ovarian Screening Trial has randomised more than 39 000 women to receive screening with transvaginal ultrasonography (TVS) and CA125 or to no screen.[14] In the initial screening, 4.7% of the women had an abnormal TVS result, whereas 1.4% had an abnormal CA125 level. After further diagnostic testing, 29 neoplasms were identified, of which 20 were invasive. The positive predictive value for invasive cancer was 3.7% for an abnormal CA125 level only, 1.0% for an abnormal TVS result only, and 23.5% if both tests were abnormal. Follow up is ongoing to establish whether this is an effective method to reduce mortality.

The UK Collaborative Trial of Ovarian Cancer Screening is a multicentre randomised controlled trial (RCT) in which 200 000 women aged 50 to 74 are being randomised to no screening, screening with TVS, and screening with CA125. The trial is expected to end in 2010. Further information can be found on their website.[15]

A systematic review of 22 prospective studies (18 cohort and 4 RCTs) which investigated various methods of screening for ovarian cancer found that the multimodal approach, incorporating CA125 as a primary and TVS as a secondary test, seemed to be superior to other strategies.[16] None of these trials to date have demonstrated a reduction in mortality.

Imaging in ovarian cancer

Imaging in ovarian cancer has as primary role the determination of disease burden, the detection of distant metastases and at the same time providing some idea of whether resection is possible. It is important to bear in mind, however, that staging is determined surgically and operability is only truly appreciated at laparotomy. Ultrasonography, computer axial tomography (CAT) and magnetic resonance imaging (MRI) are the most commonly considered imaging modalities. In a local study, Guidozzi and Sonnendekker found that the addition of a CAT scan to the basic investigations of an abdominal pelvic ultrasound did not add benefit to assess resectability.[19] Internationally several studies have investigated and compared CAT to MRI, with neither being accurate in determining upper abdominal disease. Most mesenteric and small-bowel implants were not clearly detected and assessed appropriately with either CAT or MRI.[17]

In patients with indeterminate adnexal masses MRI is an excellent modality of imaging and may determine which patients are inoperable. While this modality is becoming more available in South Africa it still remains expensive and its precise role is not yet determined.[20]

The role of FDG PET in ovarian cancer has also been explored and numerous studies performed, most of them limited by small numbers and use of a PET scanner alone. Recently studies have been performed with PET/CT hybrid cameras that allow more accurate detection and localisation of lesions.[18] These investigations are expensive and not readily available.

In the opinion of the authors, the minimum pre-operative investigations should include a chest X-ray, abdominal and pelvic ultrasound, full blood count, urea and electrolytes, a Ca 125 and liver function tests. Determining the extent, localisation and operability of recurrent disease often requires advanced imaging modalities and this is an important potential place for both MRI and PET/CT.

Surgery for ovarian cancer

Primary cytoreductive surgery

Comprehensive staging and definitive surgical management at the time of the primary/initial laparotomy includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal washings, random sampling of multiple peritoneal sites (including pelvic sidewall, paracolic gutters, cul-de-sac, surface of bladder, rectum, diaphragm), and pelvic retroperitoneal lymphadenectomy.

The importance of cytoreductive surgery in the treatment of advanced stage ovarian cancer was first recognised in 1969 by Munnel.[21] In 1975, Griffiths was the first to show that residual disease was inversely proportional to survival.[22] The Gynaecology Oncology Group found a significant survival benefit in patients whom had ≤ 2 cm residual disease compared to those with ≥ 2cm of residual disease. There was however no difference in survival when comparing those patients with ≥ 2 cm of disease compared to those who had no surgery. The only benefit of surgery in those patients where optimal debulking is not possible is to relieve them of bowel obstruction and other symptoms. The value of surgical debulking is shown in Table III.

Table III: The value of surgical debulking

- Removal of resistant clones will decrease likehood of drug resistance
- Removal of large poorly vascularised tumours increases chemotherapy delivery
- Small lesions have higher growth factions, are better vascularised and are more chemosensitive
- Smaller lesions require less chemotherapy reducing development of drug resistance
- Enhances immune systems

One of the controversial issues in cytoreduction is the handling of diffuse small volume disease. The significance of the number of nodules on the overall benefit of aggressive surgery is unclear. Penetration of these nodules by chemotherapy is presumably optimal. Surgical strategies to manage this scenario could include the use of argon beam set at high power and low wattage which is presumably safe on bowel surfaces.[23] Use of the cavitational ultrasonic surgical aspiration (CUSA), which uses ultrasonic energy to selectively fragment tissue of high water and low collagen content whilst sparing tissue with higher collagen content has also been advocated.[24] Both of these strategies are rarely, if ever used, in South Africa.

The ability to achieve optimal debulking depends not only on the surgeon's surgical expertise and aggressiveness, but also on the volume and localisation of the tumour at the time of diagnosis. The larger the tumour bulk at the initial laparotomy, the less the likelihood of achieving optimal cytoreductive surgery. It appears that tumour biology may play an important role in being able to reduce tumour to < 2cm residual deposits. Tumours at the time of initial laparotomy with large confluent deposits are likely to be poorly differentiated and difficult to resect optimally.

It is widely accepted that optimal cytoreduction is much more likely if surgery is performed by a gynaecology oncologist.[25] In a study of 263 women undergoing surgery for advanced ovarian cancer the most significant predictor of survival was the presence of a gynaecology oncologist at the procedure.[26] The recommendation should therefore be very clearly that every woman suspected or diagnosed to have advanced ovarian cancer should be operated by an experienced gynaecology oncologist. Even though maximal surgery is the priority at the initial laparotomy, this type of surgery does have significant complications. Guidozzi and Ball found that 43% of patients developed serious post operative complications following maximal attempt at cytoreductive

surgery.[27] The incidence of complications reported in the literature varies according to definition, institution and surgeon.

Interval debulking for advanced ovarian carcinoma

Primary debulking surgery is the gold standard of care in epithelial ovarian cancer, but this may not be possible for all patients, particularly in some patients with advanced stage III and IV disease. Often the surgery will not result in optimal tumour debulking down to residual mass of 1 to 2 cm. In these cases, three cycles of neoadjuvant chemotherapy followed by interval debulking surgery and then another 3 cycles of chemotherapy, may be an alternative.

Interval surgery can follow induction chemotherapy (where no surgery was attempted or laparoscopic biopsy was done) or incomplete initial surgery (where surgery was abandoned due to technical difficulty or laparotomy by a non-appropriate surgical team). The precise role and potential advantage of this approach is still controversial, with most randomised trials showing similar results for survival, quality of life and adverse events in both arms.[28] Interval surgery offers an attractive opportunity for complete resection in patients who could not benefit from successful cytoreduction initially. It is clear, however, that patients receiving induction chemotherapy never followed by surgery have a much worse outcome than those with primary surgery followed by adjuvant chemotherapy.

Secondary cytoreductive surgery

Secondary cytoreductive surgery to reduce tumour burden following an optimal primary cytoreductive surgery attempt has no benefit in patients with persistant or progressive disease during initial chemotherapy, in patients with persistant disease at the end of initial chemotherapy or in patients with recurrent disease shortly after completion of therapy. Secondary surgery benefits patients with late recurrent disease (more than 12 months disease free) and single site or isolated pelvic recurrence most.[28]

Laparoscopic surgery in ovarian cancer

The value and place of laparoscopic surgery for ovarian cancer has been evaluated in a few studies. Potential roles include staging and resection of early stage ovarian cancer and the diagnosis and evaluation of the extent of the disease in late stage disease. Completion of staging after inappropriate surgery for apparent early stage disease can be done through laparoscopy and minimal access is ideal for the evaluation of chemo-response or evaluation and possible resection of recurrent disease. The most obvious concerns about laparoscopy in ovarian cancer include incomplete resection, rupture of a malignant cyst with dissemination of malignant cells and upstaging, spread of ovarian cancer cells facilitated by the use of CO2, port-site contamination and metastases. In general advanced laparoscopic surgery should only be attempted by experienced laparoscopic surgeons; oncologic surgery should be done by oncologists while in principle the type of access should not determine the type or extent of surgery. These principles limit the use of laparoscopy in ovarian cancer in Southern Africa to a few experienced centres and individuals.

The Cochrane review in 2008 found no evidence to quantify the value of laparoscopy for the management of early stage ovarian cancer as routine clinical practice.[30] Nezhat and colleagues evaluated the role of laparoscopic staging for ovarian cancer and found that it was a feasible option if performed by a gynaecology oncologist with advanced laparoscopic surgical skills. It did not appear to compromise survival in a follow up of 36 patients over 55,9 months.[31]

For the vast majority of patients who present with advanced disease, primary cytoreduction via laparotomy will be the obvious choice. As a rule we do not advocate primary laparoscopic surgery for a known case of ovarian cancer, particularly if there is clinical evidence of advanced disease. Several authors discourage laparoscopic surgery for advanced disease and believe that management of ovarian cancer mandates laparotomy as it is believed that adequate surgery may not be achieved via laparoscopy.[29]

Chemotherapy in ovarian cancer

First line chemotherapy

Without chemotherapy almost all patients with ovarian cancer will suffer disease relapse and progression after surgery, often within weeks to months. The first line regimens have evolved over the past three decades from single agent melphalan in the 1970s to combination platinum based therapy in the 1980s. In 1990, paclitaxel was shown to be an effective agent in patients with relapsed platinum refractory disease and this established the role of this drug in the treatment of ovarian cancer. Today, standard first line adjuvant chemotherapy is six cycles of paclitaxel and cis- or carboplatinum.[32-34]

The combined efforts of the ICON and the European Organisation for the Research and Treatment of Cancer (EORTC) have produced a combined analysis of adjuvant chemotherapy in 925 patients with early stage disease. They found that the overall survival improved significantly in the group given chemotherapy compared to the observed patients and this established adjuvant chemotherapy as the standard of care in all patients with high risk limited disease.[35] All patients with advanced ovarian cancer are offered adjuvant chemotherapy post operatively.

Most patients with advanced disease will have clinical and biochemical relapse during follow-up after chemotherapy. Second line chemotherapy will be the routine treatment for most of these patients and will be most beneficial to those who relapse later and to those who had good initial response. Drugs that have been shown to benefit also platinum refractory patients include liposomal doxorubicin, topetecan and gemcitabine. The choice of use depends on a number of factors and will not be discussed here.

Special considerations

Borderline ovarian tumours

Borderline ovarian cancers are associated with a better prognosis and constitute approximately 20% of all epithelial neoplasias. The histological criteria characterising the bordeline tumours can be summarised as follows:

- Stratification of the epithelial lining of the papillae
- Formation of microscopic papillary epithelial projections or tufts
- Epithelial pleomorphism
- Atypia
- Mitotic activity
- No stromal invasion present

In order to diagnose a borderline ovarian cancer, two of the above criteria need to be present.[36] Most patients are 10 to 15 years younger and generally present with stage I disease. Borderline tumours are either serous or mucinous. Serous tumours are frequently bilateral (25–60%) compared to mucinous tumours which are generally unilateral. Imaging and staging are the same as for epithelial malignancy. They should be treated surgically, usually with abdominal hysterectomy, bilateral salpingo-oopherectomy, omentectomy and washings. If the tumour is mucinous in type the appendix should be removed. If a patient desires fertility and conservative surgery is performed, these patients require close monitoring as the tumours may recur. Several investigators have attempted to correlate outcome with the type of peritoneal implants. These are assessed

as invasive or non-invasive based on histological appearance. The type of peritoneal implants will greatly impact on prognosis of women with stage II to IV disease. Women with stage II to IV disease associated with invasive implants will develop recurrence in 36% and 25% will die of their disease. Patients with non-invasive implants will develop fewer recurrences and only 6% will ultimately die of disease.[37]

Considerable controversy exists concerning the potential benefit of post operative chemotherapy for women with advanced stage borderline ovarian tumour. Several reports have been unable to demonstrate any benefit from treatment. Nevertheless it is still our policy to recommend post operative chemotherapy to all patients with invasive implants and those with non-invasive peritoneal implants and gross disease. Patients need to be informed about the gaps in our knowledge, lack of data, alternative strategies and potential acute and long term toxicities.[37] The incidence of recurrence or progression in these patients however is not different when the women who received chemotherapy were compared with those who were not treated.[38]

Fertility sparing surgery

About 14% of invasive epithelial ovarian cancer will occur in women younger than 40 years of age and of these 62% will be stage I–IIa. In these patients fertility may be a priority. Conservative primary cytoreductive surgery can be considered, whereby surgery that allows optimal removal of ovarian tumour and adequate staging but at the same time preserving reproductive potential may be performed. Fertility potential can be preserved without compromising curability. Patients for this management strategy would be young women with borderline ovarian tumours, germ cell tumours, stromal cell tumours and stage Ia epithelial ovarian cancer. Management would include peritoneal washings, careful inspection and exploration of all surfaces, either cystectomy or unilateral oopherectomy, omentectomy, pelvic and para-aortic lymphnode sampling and biopsy or resection of any adhesions or abnormal lesions. Unilateral adnexectomy is sufficient if the contralateral ovary has a normal appearance and wedge resection is not warranted.

Conclusion

Epithelial ovarian cancer still has a poor prognosis despite aggressive surgery and chemotherapy. This is most likely due to early spread of the disease, advanced stage at presentation and limited chemo-sensitivity. For the individual patient it is of importance to have appropriate early surgery followed by adjuvant chemotherapy as soon as possible. Ultimately the potential for improvement in prognosis of ovarian cancers lies with earlier diagnosis, identification of effective screening techniques and more effective systemic therapy.

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