Ovarian Cancer Research Review™

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In this issue:

Abbreviations used in this review:

ADNEX = Assessment of Different NEoplasias in the adneXa; **BOTs** = borderline ovarian tumours; **CA 125** = cancer antigen125; **FDG** = fluorodeoxyglucose; **SUV** = standardised uptake value

Welcome to the fourth issue of Ovarian Cancer Research Review.

This edition includes the first population-based case-control study to look at the effect of different types of tubal sterilisation on the incidence of high-grade serous ovarian cancers. The study found that tubal sterilisation reduced the risk of serous ovarian or peritoneal cancers by 41%, and excisional tubal sterilisation reduced the risk by 65%. Further prospective studies in this area are currently being conducted in Canada.

An Australian cancer registry evaluated all 1192 women diagnosed with epithelial ovarian cancer in Australia in 2005 and reported the overall crude 5-year survival was 35%. Increasing age and stage were most strongly associated with poor survival. This study confirms the ongoing poor long-term prognosis for women with ovarian cancer and highlights the need for further research to find an effective screening test for early diagnosis.

Other findings reported in this edition include: advanced disease stage, old age, and microinvasion are risk factors for progression to invasive carcinoma in patients with borderline ovarian tumors; a review article reports HE4 showed better specificity than CA 125 in the diagnosis of ovarian cancer recurrences; and a multicentre, randomised phase III trial of weekly paclitaxel/carboplatin regimen for the treatment of ovarian cancer found there was no benefit in terms of OS, PFS or RR.

We hope you find the selection for this month's edition useful in your practice, and we look forward to receiving your comments or feedback.

Kind Regards,

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Effect of tubal sterilization technique on risk of serous epithelial ovarian and primary peritoneal carcinoma

Authors: Lessard-Anderson CR, et al

Summary: The authors performed a population-based case-control study using the Rochester Epidemiology Project to determine whether tubal sterilisation affected the subsequent development of serous epithelial ovarian or primary peritoneal cancer. They identified all patients with these two malignancies diagnosed between 1966 and 2009, and age matched each case to 2 controls without either diagnosis. There were 194 cases of serous ovarian or peritoneal cancer identified during this period. The study found that tubal sterilisation reduced the risk of serous ovarian or peritoneal cancers by 41%, and excisional tubal sterilisation reduced the risk by 65%. They concluded that prospective studies were needed and this is happening currently in Canada.

Comment: Epidemiological studies have shown for some time that tubal ligation or hysterectomy decreases the risk of ovarian cancer. This has been thought to be possibly related to an ascending carcinogen such as talc. Recent evidence that some of these tumours may originate from serous tubal intraepithelial carcinoma lesions in the fimbrial end of the tubes has given impetus to removal of at least the fimbrial end of each tube at the time of tubal ligation or hysterectomy. There is no doubt that prophylactic removal of both tubes and ovaries will markedly decrease the incidence of serous pelvic tumours in patients with a known BRCA1 or BRCA2 mutation, and it is tempting to speculate that removal of at least the tube may decrease the incidence of ovarian cancer while retaining ovarian function in premenopausal women. However reversal of sterilisation is impossible after salpingectomy, and more prospective data are needed before definitive recommendations can be made about the benefits of salpingectomy.

Reference: Gynecol Oncol 2014 Oct 11. pii: S0090-8258(14)01365-1

Abstract

Evaluating the risk of ovarian cancer before surgery using the ADNEX model to differentiate between benign, borderline, early and advanced stage invasive, and secondary metastatic tumours: Prospective multicentre diagnostic study

Authors: Van Calster B, et al

Summary: The Assessment of Different NEoplasias in the adneXa (ADNEX) to discriminate between benign, borderline, Stage I invasive, Stages II-IV invasive and secondary metastatic ovarian tumours was developed on 3506 patients recruited between 2000 and 2007. All patients underwent a standardised ultrasonic examination prior to surgery. There were 24 different centres performing the ultrasound in 10 countries. The model is complicated, and contains three clinical and six ultrasonic predictors. The authors concluded that the model discriminated well between benign and malignant tumours, and offered fair to excellent discrimination between four types of ovarian tumours.

Comment: This model may be academically interesting, but what is required in everyday practice is a simple system that allows triage of patients with an adnexal mass between a gynaecologist, a gynaecological oncologist or another surgeon, eg. a colorectal surgeon, if thought to be a metastatic bowel cancer. Taking a careful history and performing a thorough physical examination is the first step, with particular attention to any upper or lower gastrointestinal tract symptoms. At least 90% of adnexal masses will be gynaecological, and the Risk of Malignancy Index is an easily applied method with acceptable sensitivity and specificity. To determine the Risk of Malignancy Index, the absolute cancer antigen125 (CA 125) titre is multiplied by 3 if the woman is postmenopausal, and by 3 again if the mass is complex on ultrasound. A woman with a value greater than 200 should be considered to have an ovarian cancer until proven otherwise.

Reference: BMJ 2014 Oct 15;349:g5920
Abstract

Survival of Australian women with invasive epithelial ovarian cancer: A population-based study

Authors: Anuradha S, et al

Summary: This study evaluated all 1192 women diagnosed with epithelial ovarian cancer in Australia in 2005, using state-based cancer registries. There were no surprises in this study. The overall crude 5-year survival was 35% (95% CI, 33-38%), and increasing age and stage were most strongly associated with poor survival. After adjusting for these factors, survival was also worse for women with carcinosarcomas, clear cell and mucinous cancers compared to women with serous cancers. The presence of ascites at diagnosis and associated comorbidities also impaired survival, as did relative socio-economic disadvantage and regional – remote residence.

Comment: In a country such as Australia with a free universal health system, socio-economic disadvantage should not be a significant prognosis factor. However, many of these women are likely to be Aboriginal and Torres Strait Islanders, or culturally and linguistically disadvantaged women. These groups frequently do not access even local health facilities effectively or follow through on treatment recommendations. Patients in remote areas are also often reluctant to travel to gynaecological cancer centres to seek expert care, and this has recently been investigated for New South Wales in a paper by Elizabeth Tracey et al (Int J Gynaecol Cancer 2014; 24(7): 1232-40). Overall, the results highlight the need for further research to find an effective population screening test to allow early diagnosis of women with ovarian cancer.

Reference: Med J Aust 2014 Sep 1;201(5):283-8
Abstract

The effects of dexamethasone on the proliferation and apoptosis of human ovarian cancer cells induced by paclitaxel

Authors: Hou W, et al

Summary: Dexamethasone is routinely used as pretreatment in patients receiving paclitaxel for ovarian cancer, to decrease nausea and to prevent allergic present reactions. There is some evidence to suggest that paclitaxel induced apoptosis could possibly be inhibited by dexamethasone, which would be counter-productive.

Comment: Glucocorticoid receptor activation has been implicated in the initiation of antiapoptotic signalling pathways, but the evidence that this reduces the effectiveness of paclitaxel is limited. The authors used two human ovarian cancer cell lines to determine whether or not pretreatment with dexamethasone influenced paclitaxel induced apoptosis. Their results demonstrated that dexamethasone did decrease apoptosis rates in cancer cells. They postulated that dexamethasone could up-regulate the expressions of members of the anti-apoptotic Bcl-2 family and members of the IAP family (survivin). This information is of interest, but the practical implications are uncertain.

Reference: J Ovarian Res 2014 Sep 30;7:89
Abstract

The role of HE4 in ovarian cancer follow-up: A review

Authors: Piovano E, et al

Summary: A medline search identified 28 studies of HE4 for follow up of ovarian cancer, of which 7 were selected for review. Four of the studies were prospective, but all of them were based on a small number of patients (8-73 women). HE4 showed better specificity than CA 125 in the diagnosis of ovarian cancer recurrences, and also gave an earlier indication of relapse, with a lead time of 5 to 8 months.

Comment: These are preliminary data, and the authors suggest that the role of HE4 in ovarian cancer follow up deserves to be further investigated in prospective, randomised, multicentre studies. Their review also showed that HE4 showed better performance when used in association with other markers, such as CA 125 and CA 72.4. This only increases the cost of follow-up, at a time when some are questioning the value of any tumour marker follow-up of patients with ovarian cancer.

My own policy is to offer follow up with CA 125 titres every 3 months for 2 years, and every 6 months thereafter, beginning 6 months post chemotherapy. Most patients will be asymptomatic when CA 125 titres begin to rise, and imaging studies at this stage can sometimes identify disease which is amenable to secondary cytoreduction. Most patients are reassured by negative markers, and in my experience, very few patients want to wait until they are symptomatic before beginning investigations.

Reference: Int J Gynecol Cancer 2014 Oct;24(8):1359-65
Abstract

Long-term results of a randomised phase III trial of weekly versus three-weekly paclitaxel/platinum induction therapy followed by standard or extended three-weekly paclitaxel/platinum in European patients with advanced epithelial ovarian cancer

Authors: van der Burg ME, et al

Summary: The authors have reported a randomised, phase III trial of six cycles of weekly paclitaxel 90mg/m^2, cisplatin 70mg/m^2 or carboplatin (AUC 4) versus 3 cycles of paclitaxel 175 mg/m^2, cisplatin 75 mg/m^2 or carboplatin every 3 weeks, followed by either 3 or 6 cycles of 3 weekly paclitaxel/cis or carboplatin, for patients with FIGO stages IIB-IV epithelial ovarian cancer. There were 267 eligible patients, and not surprisingly, weekly cisplatin was less well tolerated than weekly carboplatin. After a median follow up of 10.3 years (range 7.1 to 14.8 years) there was no benefit in terms of overall or progression-free survival for a weekly regime, nor for extended chemotherapy, as first line therapy for epithelial ovarian cancer in European women.

Comment: The findings of this study are quite different to those of the Japanese study, which showed a significant benefit for weekly paclitaxel in women with advanced epithelial ovarian cancer. Unlike the Japanese study, this study also used weekly platinum, so the study designs were not strictly comparable. This leaves open the question of whether there is a significant survival advantage with the Japanese protocol, or whether Japanese women are inherently different to Caucasian women. This report does confirm earlier studies that have shown no advantage to extending first line chemotherapy beyond 6 cycles. These findings strongly support the importance of the ongoing ICON 8 trial. The latter is a randomised trial of standard 3 weekly carboplatin and paclitaxel versus carboplatin every 3 weeks and paclitaxel weekly (Japanese GOG protocol) versus weekly carboplatin (AUC 2) and paclitaxel 80 mg/m^2 for 18 weeks.

Reference: Eur J Cancer 2014 Oct;50(15):2592-601
Abstract

Independent commentary by Professor Neville F Hacker, AM is Director of the Gynaecological Cancer Centre at the Royal Hospital for Women in Sydney, and Professor of Gynaecological Oncology, Conjoint, at the University of NSW.

He is a former President of the International Gynaecological Cancer Society, and a current Member of the FIGO Cancer Committee. He has received many honours, including the inaugural Jeanne Ferris Award from Cancer Australia, and the inaugural Robert Sutherland AO "Making a difference" Award from the NSW Cancer Institute, both in 2013. He has written over 170 peer reviewed a rticles, over 30 book chapters, and edited two textbooks, both in their 5th editions.

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Maximum standardized uptake value of fluorodeoxyglucose positron emission tomography/computed tomography is a prognostic factor in ovarian clear cell adenocarcinoma

Authors: Konishi H, et al

Summary: Intracellular fluorodeoxyglucose (FDG) uptake is measured as the standardised uptake value (SUV) and differs depending on tumour characteristics. The authors investigated differences in maximum SUV (SUV max) according to histological type of epithelial ovarian cancer, and the relationship between SUV max and prognosis. The study included 80 patients with Stages I-IV epithelial ovarian cancer who had undergone PET/CT before treatment. The SUV max of primary lesions was compared for different histologic types, and the prognosis associated with different maximum uptakes was evaluated.

Comment: The median SUV max was lower in mucinous and clear cell carcinomas than in serous or endometrioid tumours. Overall, median SUV max was lower in clinical Stage I than clinical Stages III and IV although for both clear cell and endometrioid tumours, no difference was seen between stages. In clear cell carcinomas, the 5 year survival was significantly higher in the low – SUV max group (100%) than in the high – SUV max group (43%; p=0.009). The authors concluded that SUV max may represent a prognostic factor for clear cell carcinomas. The heterogeneity of epithelial ovarian cancers has been well documented in recent years. Compared to high grade serous cancers, clear cell carcinomas are more likely to be associated with endometriosis, to be confined to the pelvis at the time of diagnosis, and to be associated with preoperative thromboembolic events. The prognostic significance of low uptake of FDG in the primary tumour on a pre-treatment PET/CT scan appears to be another significant point of difference with other epithelial ovarian cancers

Reference: Int J Gynecol Cancer 2014 Sep;24(7):1190-4
Abstract

Laparoscopic and open abdominal staging for early-stage ovarian cancer: Our experience, systematic review, and meta-analysis of comparative studies

Authors: Bogani G, et al

Summary: The authors matched 35 patients undergoing laparoscopic staging for early ovarian cancer between 2003 and 2010 with a historical cohort of 32 patients undergoing open surgery. Baseline characteristics were similar between the groups, and spillage was not significantly different. As expected, the laparoscopic group experienced longer operative times, but shorter hospital stay and lower postoperative morbidity. The 4 year disease-free and overall survival was not influenced by the surgical approach. A pooled analysis of the literature corroborated their results.

Comment: Laparoscopy has been shown in randomised studies to be comparable to open surgery for survival of patients with endometrial cancer, and should be considered the treatment of choice. No randomised studies have been undertaken for patients with early ovarian cancer, but as long as spillage can be avoided, it is a reasonable option. Pelvic and paraaortic lymphadenectomy are required for full surgical staging of non-mucinous ovarian tumours, and the advent of safe laparoscopic approaches to the paraaortic area has meant that laparoscopic surgery has been increasingly used for these patients.

Surgical staging significantly influences the outcome of patients with early ovarian cancer, and the adequacy of the staging is much more important than the type of surgical approach that is used.

Reference: Int J Gynecol Cancer 2014 Sep;24(7):1241-9
Abstract

Correlation of pelvic magnetic resonance imaging diagnosis with pathology for indeterminate adnexal masses

Authors: Haggerty AF, et al

Summary: The authors used pelvic MRI to further characterise a cohort of 237 women who had an indeterminate ultra-sonic examination at a tertiary care institution in the United States. Surgical intervention was undertaken in 41.4% of cases. They reported that pelvic MRI had a sensitivity of 95% and specificity of 94.1% for differentiating between benign and malignant masses. The majority of the cohort (59%) were able to be managed expectantly based on the MRI results, and the authors concluded that this investigation allowed more detailed patient counselling, appropriate subspecialty referral, and reassurance to pursue conservative management in appropriate cases.

Comment: Determining the nature of an adnexal mass is a common problem for both primary care practitioners and gynaecologists. Most adnexal masses in reproductive aged women will be functional cysts, such as follicular or corpus luteal cysts, but if there has been haemorrhage into these cysts, they can look quite worrisome on ultrasound. Functional cysts need observation through two menstrual cycles, along with pain relief in some cases, and they will shrink, and eventually disappear. All of the remaining ovarian masses will be neoplasms, either benign or malignant, and an MRI is an expensive way to triage them. The Risk of Malignancy Index using the CA 125 titre, menopausal status and complexity of the mass on ultrasound, is a simple method of triage with similar sensitivity and specificity. Women in their teens and 20's should have serum alpha fetoprotein, serum human chorionic gonadotropin and lactate dehydrogenase titres done to exclude a germ cell malignancy. An MRI may help to differentiate ovarian from non ovarian masses in difficult cases.

Reference: Int J Gynecol Cancer 2014 Sep;24(7):1215-21
Abstract

Risk factors for progression to invasive carcinoma in patients with borderline ovarian tumors

Authors: Song T, et al

Summary: The authors retrospectively reviewed 364 patients treated and followed for borderline ovarian tumours (BOT's) between 1996 and 2011. Median follow up was 53.8 months and 31 patients (8.5%) developed recurrent disease. Twelve patients (3.31%) had invasive cancer at recurrence, and 19 (5.2%) had borderline histology. Disease related deaths (7 of 364; 1.7%) were observed only in patients with progression to invasive cancer. Independent risk factors for progression to invasive cancer were advanced stage disease (HR 5.59 p=0.005), age 65 years or older (HR 5.13; p=0.037), and the presence of microinvasion (HR 3.71; P=0.047).

Comment: This is a large series of borderline tumours of all stages, and confirms the generally excellent prognosis for these tumours. In fact, there were no deaths among patients whose recurrence was also of borderline histology. The only deaths were in patients who recurred with invasive cancer, and this was more likely in older patients with advanced disease, particularly if the original histology showed microinvasion.

Most series of borderline tumours examine recurrence rates in patients treated conservatively (with unilateral salpingo oophorectomy or cystectomy) in order to preserve fertility. Recurrence rates (almost always in the contralateral ovary) are higher in these patients, usually in the order of about 15%. The current study gives reassurance that removal of both tubes, ovaries and the uterus following completion of childbearing should ensure close to 100% survival for patients with disease confined to the ovaries.

Reference: Int J Gynecol Cancer 2014 Sep;24(7):1206-14
Abstract

