Editorial

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Staging of ovarian cancer: time to subdivide more?

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See accompanying article by Suh and colleagues on page 352.

Ovarian cancer is the leading cause of death among women with gynecologic cancer and the fifth leading cause of all cancer related deaths among women. In 2013, the estimated number of new cases of ovarian cancer in the USA is 22,240 with 14,030 deaths. In Europe, in 2012 there were 65,538 cases of ovarian cancer with 42,704 deaths corresponding to incidence rates of 13.1 and 7.6/100,000 women, respectively. The majority of cases of ovarian cancer are diagnosed in women over 55 years of age and the risk of ovarian cancer is particularly high in women who carry *BRCA1* and *BRCA2* gene mutations.

New therapies have improved disease-free survival in women with ovarian cancer; however there has been little real impact on overall cure rates. The International Federation of Gynecology and Obstetrics (FIGO) staging, last updated in 1988, has proved to be an important prognostic discriminator, with women with advanced disease having a significantly worse survival compared to early stage disease. Since 1988 there have been many advances in our understanding of the molecular and genetic profiles of ovarian cancer, which has in fact prompted the FIGO Gynaecology Oncology Committee to rework the staging of ovarian cancer, hence the article by Suh et al. [1] in this Edition of the Journal of Gynecologic Cancer has special relevance.

Suh et al. [1] present a retrospective review of 870 cases of epithelial ovarian, fallopian tube and primary peritoneal cancer between 1990 and 2011. They assigned stage 1 patients to three categories: 1) surgical or intraoperative spill (IC1), 2) preoperative rupture (IC2), and 3) ascites or peritoneal washes positive for malignant cells (IC3). The overall survival of stage 1 patients was 82.5%, for women with surgical spill only 92%, with preoperative rupture, 85% and with malignant ascites or washings 71%, p=0.004.

The FIGO staging of ovarian cancer to date has not distinguished intraoperative spill from preoperative rupture. It was traditionally believed that spill would lead to peritoneal metastasis due to release of tumor cells. The literature has given conflicting data on the prognostic significance of intraoperative or surgical spill. In a meta-analysis of intraoperative rupture of the ovarian capsule on prognosis, Kim et al. [2], out of a potential of 518 studies, selected 9 retrospective studies which included 2,382 patients. They found that preoperative rupture increased the recurrence rate when compared with intraoperative rupture (hazard ratio [HR], 2.63; 95% confidence interval [CI], 1.11 to 6.20), however there was no difference in progression free survival between intraoperative rupture and no rupture in patients who underwent complete surgical staging and adjuvant platinum-based chemotherapy (HR, 1.49; 95% CI, 0.45 to 4.95). Further patients with preoperative rupture had a poorer overall survival compared to those with no rupture or intraoperative rupture. These data support the findings of Suh et al., and subdividing stage 1C into the three categories described. The FIGO Gynecologic Oncology Committee will be publishing the new staging shortly and is likely to support this view. What is not clear from this publication is whether there was any difference according to site of origin of the cancer e.g., ovary, fallopian tube, and peritoneum and whether these factors were taken into consideration in the multivariate analysis.

Ovarian cancer is known to spread via the retroperitoneal lymphatic channels and para-aortic and pelvic lymph nodes are frequently involved with metastases, particularly in

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women with advanced disease. Spread through the lymphatic channels of the diaphragm, can result in metastatic spread above the diaphragm to involve the supraclavicular node. The 1988 FIGO staging of stage III disease assigned positive regional lymph nodes to stage IIIC, along with micro- and macro- intraperitoneal spread of disease. However, a number of studies noted that survival outcomes were better in women with metastatic disease confined to the retroperitoneal nodes without peritoneal metastases compared to those with peritoneal metastases. Onda et al. [3] showed that women without peritoneal metastases but positive retroperitoneal nodes had a similar survival to patients with pelvic disease and negative nodes. Kanazawa et al. [4] showed that women upstaged to IIIC based on positive lymph nodes were 58% compared to 18% for those women staged as IIIC based on intraperitoneal metastases. Suh et al. [1] support these findings in their study. The overall survival of women with stage IIIC disease (n=410) was 38.5%. The 5-year survival of women with retroperitoneal spread without intraperitoneal involvement was significantly better than patients with macroscopic intraperitoneal disease (66.3% vs. 35.8%; p=0.005) and better than women with microscopic intraperitoneal spread (57.5%). Further Suh et al. [1] compared women classified as stage IV by virtue of a positive supraclavicular node to women with distant metastases and showed that the 5-year survival was 52.0% and 28.0%, respectively, suggesting that women with only supraclavicular nodal involvement have a better prognosis that women with other distant metastases. There suggestion that stage I, III, and IV be subdivided as above is helpful as we await the final staging and publication from the FIGO Gynecologic Oncology Committee.

CONFLICT OF INTEREST

Lynnette Denny has received honoraria for appearing various speaker forums for Merck/MSD and GlaxoSmithKline on HPV Vaccination, and has received research support from both companies.

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