Review Article
Epithelial Ovarian Cancer : Prognostic factors

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Summary

Epithelial ovarian cancer is the most lethal of gynecologic malignancies. In multivariate analysis only the tumor grade and the type of staging were significant independent prognostic factors for both disease free and overall survival. With neoadjuvant chemotherapy only 30% could achieve complete remission with progression free survival of 29% in 3 years. This result suggests that, in addition to volume of the disease, other unknown biological factors influence survival in patients with locally advanced disease. Recent advances in molecular biology e.g. ploidy analysis, image cytometry etc. offer the promise of improved understanding and insight into the development of this disease and so the prognosis.

Epithelial ovarian cancer: Prognostic Factors

Epithelial ovarian cancer is the most lethal of gynecologic malignancies. Despite advances in surgical techniques and chemotherapeutic agents over the past decades, there has been little improvement in the overall survival rates of women with this disease. Comprehensive surgical staging laparotomy accurately determines the stage (Table I) of the patient, thus allows evaluation of clinicopathologic prognostic variables (Table II) and assignment of appropriate adjuvant therapy based on individual patient risk. Multiple factors have been identified to have independent prognostic value in ovarian cancer. These various prognostic factors are discussed below.

Table I: Surgical staging procedure for early stage ovarian carcinoma
Midline Abdominal Incision
Multiple cytological washings
Intact tumor removal
Methodical exploration of abdomen and pelvis
Removal of remaining ovaries, uterus, tubes
Excision or biopsy of suspicious lesions
Biopsy of diaphragm, paracolic gutter, pouch of Douglas
Intracolic omentectomy
Appendectomy
Ipsilateral selective pelvic and aortic node sampling

Table II: Clinocopathologic Prognostic factors
FIGO stage
Histologic subtype
Histologic grade
Factors associated with tumor dissemination
  Malignant ascites
  Malignant peritoneal washing
  Tumour excrescences on ovarian surface
  Ruptured capsule
  Dense ovarian adhesions
  Volume of residual disease following extent factor of surgery

Tumour stage

The thoroughness of the staging has a significant

impact on survival particularly in poorly differentiated carcinomas. Tumour size, bilaterality and cytological negative ascites have no prognostic significance. Rupture of capsules, positive peritoneal cytology and dense adhesions are unfavourable characteristics. Patients with stage I disease with these poor prognostic features are termed as early stage disease with unfavourable characteristics and included in treatment protocols for patients with stage II disease. The 5-year survival of patients with ovarian cancer is directly correlated with the tumor stage. Patients with unfavourable characteristics have 5 year survival of 80% (Young et al 1990) and for stage II, III, and IV; reported 5 year survival is 0 to 40%, 15 to 20% and 5% respectively (Yancik, 1993).

Status of tumour capsule

Conventional criteria suggest worse prognosis of an ovarian cancer, if tumour has breached the tumour capsule, producing surface excrescences, adherent to adjacent structures or tumour rupture. However these factors may be related to other poor prognostic factors such as histologic degree of differentiation and may not impart a poor prognosis per se. Only tumour adherence was related to worse survival (Dembo et al, 1990). Among the patients with tumour removed intact and those with puncture and aspiration the survival rates were 89% and 83% respectively, compared to 60% in patients with inadvertent rupture during tumour removal (Purola & Nieminen). Anecdotal reports of tumour metastasis within incision, drain tracts and laproscopic instrument tract producing subcutaneous implants of ovarian carcinoma are of concern (Kohler et al 1991, Dobronte et al 1978 and Stockdale & Pocock 1985). For all these reasons intact removal of an early ovarian malignancy is considered optimal surgical management.

Ascites and malignant peritoneal cytology

A relatively poor survival for patients with early ovarian cancer who present with ascites or positive peritoneal cytology, has been noted. Although peritoneal cytology has poor sensitivity for detecting histologically confirmed peritoneal metastasis (Buchsbaum et al, 1989), identification of malignant cells in peritoneal washings is highly suggestive of occult peritoneal metastasis, particularly in patients who have not undergone comprehensive surgical staging.

Volume of residual disease

The volume of residual disease following cytoreductive surgery is directly related to survival. Patients who have been optimally cytoreduced have a 22 months improvement in median survival. The size of the largest residual mass has been believed to be the primary factor correlating with prognosis earlier but recently it has been demonstrated that the number of residual masses are also an important prognostic factor (Heintz et al, 1988). Patients who have only a single residual mass following cytoreductive surgery have a significantly greater chance of achieving a surgically confirmed complete remission, compared with those patients with multiple small nodules, even though each nodule is less then 2 cm in size. Patients who present with small volume disease that is optimally cytoreduced following hysterectomy, oophorectomy and omentectomy have disease that is biologically less aggressive than that in patients who are anatomically cytoreduced to the same amount of residual disease but require a maximal tumour reduction with removal of bulky disease throughout the peritoneal cavity (Ozols & Young, 1984). Optimal cytoreduction (less then 2-cm residual tumour masses) was possible in 87% of patients with stage III and IV disease (Piver et al, 1988).

Histologic Subtype and Grade

Tumor grade is the single most important biological prognostic factor in early ovarian cancer. Stage I patients with well or moderately differentiated tumour have a greater then 90% 5 year survival when treated with surgery alone (Young et al, 1990). In contrast, patients with stage I disease with poorly differentiated or clear cell tumour have 35 to 63% 5 year survival and postoperative therapy is indicated (Rubin et al, 1993). In advanced stage where patient is treated with cisplatin based chemotherapy, most studies have failed to demonstrate a significant relation between histologic grade and survival (Friedlander & Dembo, 1991).

The histologic subtype has less prognostic significance. Patients with mucinous adenocarcinoma and endometroid carcinoma have better survival in comparison to those with serous adenocarcinoma as this presents with lower histologic grade and stage. Poorly differentiated endometroid carcinoma cannot be differentiated with ease from poorly differentiated serous tumors and are generally classified as serous. Ovarian clear cell ademocarcinoma are more aggressive than the other common epithelial malignancies and have 60% 5 year survival for stage I and 12% for all other stages.

CA-125 Levels.

The serous histology subsets of epithelial ovarian cancer has > 85% elevated levels of CA125 whereas mucinous tumors are associated with low incidence of abnormally elevated serum CA125 levels. Serum CA 125 levels reflect the volume of the disease (Makar et al, 1992

and high levels may predict unresectability and inferior survival. Serum CA125 levels after 3 cycles of chemotherapy are accurate predictors of probability of a patient achieving complete remission. CA 125 levels are useful for predicting group outcome, but they do not have the predictive power to guide treatment decisions in individual patients.

With neoadjuvant chemotherapy only 30% could achieve complete remission with progression free survival of 29% for 3 years. This suggests that, in addition to volume of the disease, other unknown biological factors influence survival in patients with locally advanced disease (Piver et al, 1988).

Investigational Progonostic Factors:

Biological markers of tumour differentiation will prove more useful than conventional histologic grading to predict the presence of occult metastasis or to predict the need for post operative adjuvant therapy. A series of new molecular factors (Table III) have been proposed to have prognostic significance in ovarian cancer (Bookman Ozols 1996, van der Zee et al 1995 and van der Zee et al 1995). Most of these factors have been identified in retrospective studies and are not routinely used to select therapy in patients with ovarian cancer. Details of important ones are described.

Table III: Experimental prognostic factors in ovarian cancer

Morphometry
DNA ploidy and S-phase fraction
Drug resistance marker
  P-glycoprotein immunoreactivity
  Glutathion S transferase pi
  c-erbB 2
  Multidrug resistance protein (Lrp)
  Nucleotide excision DNA repair genes ERCC1 and XPAC
Oncogene
  Mutant p53 expression
  AKT 2
Markers of proliferation
  Ki67
  Proliferating cell nuclear antigen
Markers of tumor spread
  Metastasis-related genes (mm23-H1)
  Cathepsin D
  Urokinase-type plasminogen activators
  CSF-1
  CD44 molecules
  Cytokines levels and other active proteins
  Heat shock protein
  Interleukin 6
  Platelet derived growth factor

Ploidy Analysis

Ploidy analysis appears to be an independent prognostic factor. DNA content is aneuploid more commonly in higher than in lower stage tumor (Stage III IV are 50 to 80% aneuploid; Stage I to II 10 80%) and correlate with the degree of differentiation (grade). Whether DNA ploidy analysis has prognostic value in early stage disease and whether this technique might help to identify those patients at significantly higher risk of recurrence and those who might benefit from adjuvant therapy, is a highly debated subject. (Gajewski et al 1994 and Trope & Kaern 1994). At ten year follow up the survival was 100% for patients with diploid tumours and 58% for those with aneuploid tumours. Ninety four percent of positive second look operation were aneuploid, in contrast to only 47% where the operation was negative (53% diploid). There were no recurrences with diploid tumour in advanced stages, ploidy analysis offers information regarding degree of aggressiveness, with 5 year survival of about 45% for diploid tumours and 20 for aneuploid neoplasm. Majority of borderline tumour are diploid and aneuploidy was associated with adverse outcome (Kaern et al, 1990).

Image Cytometry

It is used to measure DNA content (ploidy analysis); has the ability to locate specific areas of interest and then quantify the stained tissue and is generally considered superior to flow cytometric methods. Image cytometry, while still considered investigational, has also improved in recent years to permit the analysis of cells at levels ranging from subcellular particle to the architectural organization of tissue. Morphometry which is defined as the quantification of morphologic features, can be used to measure many features, including mean nuclear area (MNA), mitotic index (MI) and volume percentage of epithelium (VPE) which is the percentage of epithelial tumour cell compared to stromal tissue. For patients with stage I ovarian cancer, 5 year survival rates were 91% for patients with low MI and VPE, 67 for tumours with high MI and VPE. Morphometric analysis is useful also in distinguishing among lesions that are normal, have borderline or dysplastic morphology and cancer. MNA in serous adenocarcinoma is twice that of borderline tumours (63um^2 vs. 30um^2) (Hytroglou et al, 1992). The serous adenocarcinoma are further segregated by degree of differentiation; the MNA in grade 1, 2 and 3 tumours is 45um^2, 67um^2, 79um^2 respectively. Additional discriminating feature include agyrophilic nucleolar organizer regions (AGNORs) and profiles of nuclear texture (Deligdisch et al 1993).

Genetic and Biologic Factors

Alteration in proto-oncogenes and suppress genes, particularly p53, is relatively common in epithelial

ovarian cancer. Increased level of p53 may be associated with an unfavourable prognosis in advanced disease (Hartmann et al, 1994). Overexpression of p53 is infrequently (40%) detected in borderline tumors. Expression of p53 was detected in early disease and associated with inferior survival (Hartmann et al, 1994). Growth factor receptors may prove to be clinically useful prognostic factor. Epidermal growth factor receptor (EGF-R) were detected in 54% of primary ovarian cancer. In a multivariate analysis, EGF-R expression was significantly associated with a high risk progression (Reed et al, 1987). The ERBB2 gene encode a cell surface protein that is similar in structure to EGF-R (Salmon et al, 1989). Initial study suggested an important correlation between amplification / expression of ERBB2 and progression in ovarian cancer patients (Salmon et al, 1989). Other studies have failed to confirm the prognostic significance of ERBB2 expression in advanced ovarian cancer (Rubin et al 1993; van der Zee et al, 1995).

Differing mechanisms of resistance to natural products and alkylating agents have been identified in ovarian cancer (Hamilton, 1992). Amplification and expression of the multidrug resistance gene (mdr) and enzyme associated with glutathione metabolism and DNA repair are associated with resistance to natural product (e.g. paclitaxel, doxorubicin, vinblastine) and alkylating agents and platinum compounds respectively. Increased levels of p-glycoprotein were detected in a minority of ovarian cancer samples from patients treated with doxorubicin (Fojo et al, 1987). More recently, utilizing more sensitive PCR methods, expression of mdr-1 was detected in 65% of specimen from untreated patients (Holzmayer et al, 1992). However the expression of mdr-1 has not been shown to be of prognostic value (van der Zee et al, 1995). Similarly while glutathione-s transferase was found to be abundant by immunostaining in 89% of untreated ovarian cancer, no relationship could be demonstrated with survival and response to chemotherapy. Increased DNA repair is associated with cisplatin resistance, (Chu, 1994) and a recent study has demonstrated that tumor from clinically resistant ovarian cancer patients had greater levels of expression of the repair enzyme ERCC-1 (Dabholkar et al 1992).

Platinum – DNA Adduct Levels

Platinum complexes are among the most active group of chemotherapeutic agents currently available for patients with ovarian cancer. After intravenous cisplatin or carboplatin, platinum DNA adducts can be measured using an ELISA assay in the DNA of peripheral white blood cells and in tumour specimens. It has been demonstrated that the extent of platinum DNA adduct formation in the DNA from white blood cells is statistically related to the likelihood of a response in patients treated with either single agent cisplatin or carboplatin (Reed et al, 1987). A retrospective assessment was performed to determine the relationship between likelihood of response to therapy and platinum DNA adduct formation in white blood cell DNA and eight other prognostic variables (Reed et al, 1993). Univariate analysis indicated that platinum adduct level more closely related to disease response than other previously identified prognostic variables. The complexity of the assay has limited large scale confirmation trials.

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