

## OVARIAN CANCER: NATURAL HISTORY AND METASTATIC PATTERN

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### 1. ABSTRACT

Ovarian cancer begins at a molecular level, however to date, our knowledge of genetic changes and mechanisms of ovarian tumorigenesis is limited. The natural history of ovarian cancer may depend on different anatomo-clinical and biological factors. In the life history of ovarian cancers the stage, histology, tumor grade, age of the patient and gene abnormalities, both oncogenes (c-myc, H-ra, new) and oncosuppressor genes (p53, in particular), DNA ploidy and steroid receptor status have important prognostic significance. Residual disease, when less than 1 cm, is another important prognostic factor, being significantly associated to the survival and, progression free, improvement in the survival. In the low stage ovarian cancer (Stage IA, IB, IAI,IBII,IC,IIA,IIB,IIC), adjuvant treatment seems not to influence Disease Free Survival (DFS) or Overall Survival (OS) The exception to this rule is when cisplatin regimen is assessed, as it can highly reduce the relapse rate while the survival is not significantly influenced. Ovarian cancers disseminate, primarily by continuity. Lymphatic dissemination to the pelvic and para-aortic lymph nodes (40% of patients at stage III-IV disease) as well as to the peritoneum is common. At the time of diagnosis, bone or brain metastases are rarely present and their presence is not related to the histology or grading of the tumor.

### 2. DISCUSSION

Epithelial carcinomas of the ovary are thought to arise from neoplastic transformation of the surface epithelium. Although the exact mechanism of ovarian carcinogenesis is unknown, some risk factors

exist. It has been hypothesized that continuous ovulation causes entrapment of the germinal epithelium within the stroma, resulting in the formation of an epithelial inclusion cyst. Subsequently, genetic changes in cancer-related genes produces malignant transformation. Whether this benign epithelium proceeds directly to invasive carcinoma or passes through an intermediate phase of benign and/or borderline neoplastic epithelium, is unknown. Hereditary factors and age may also be involved in this process (1). Early diagnosis is rare: up to 60% of cases are diagnosed at an advanced stages (stages III-IV, according to FIGO classification) (2).

The main reasons for the inability for the early diagnosis of ovarian are either paucity of and insidious development of symptoms, or the absence of a suitable test which can be routinely used. Moreover, at the time of diagnosis, only 2% of patients are asymptomatic. The natural history of ovarian cancer is influenced by both anatomo-clinical and biological factors. Among anatomo-clinical variables, stage, histology, tumor grade, and age bear significant prognostic value. With regard to five-year survival rates by stage, Jacobs *et al*, demonstrated that in stage I, the five-year survival rate was about 67%, in stage III and IV, it was about 10% while in total of all stages, it was almost 30%. These data establish the role of anatomo-clinical stage as important prognostic factor in determining the survival (3).

Majority of malignant ovarian tumors are epithelial cancers (85-90%). Overall the five years survival of ovarian cancer is low. For example in papillary adenocarcinomas, the five year survival rate is about 15%, whereas in mucinous adenocarcinomas it is 75%. However, in low stage disease, the histological type of ovarian cancer plays an insignificant role (4). Sugurdsson and colleagues took in consideration the role of tumor grading as a

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prognostic factor. In univariate analysis, tumor grading showed to have a prognostic value. In fact, five-year cumulative survival related to G3 tumors was less than 20%, whereas in G1-G2 tumors, it was about 70%. Moreover, G1-G2 tumors had similar survival rates. However, in multivariate analysis, tumor grading showed no independent prognostic value (5). Hightower, in 1994, performed a comparative survival study according to age in more than 5000 patients. Bivariate analysis of the patients' age shows that, at the same stage, patients aged less than 80 years live an average of 18 months longer than patients aged 80 years or more (6). Moreover, some authors demonstrated that, at all stages, patients aged less than 50 years have a five-year survival rate of about 40%, compared to 15% for patients older than 50 years (7,8,9).

The natural history of ovarian cancer can also be influenced by some biologic factors such as gene abnormalities, DNA ploidy and steroid receptor status. Many authors have demonstrated oncogene abnormalities in ovarian cancer (10,11,12). To date, the most commonly reported abnormalities involve c-myc, H-ras, K-ras and neu oncogenes (13). In the majority of cases, the frequency of K-ras alteration is high (about 10%). However there appears to be no correlation between levels of the ras oncogene products (p21) and prognosis (14). The most frequently observed abnormality is amplification or overexpression of HER-2/neu oncogene which occurs in about 20% of cases (13). Gallion, in 1995, studied the HER-2/neu expression in 73 patients with ovarian cancer. The five year survival rate demonstrated that a better median survival (32 months) is related to normal HER-2 neu expression in comparison with HER-2 neu overexpression (16 months). It was also demonstrated that normal HER-2/neu expression is significantly related to a negative second-look (1). Levesque, in 1995, showed presence of p53 gene alterations in a series of 90 patients with ovarian cancer (15). p53 negative tumors had a significantly longer DFS ( $p=0.03$ ) than p53 positive tumors. A trend in favor of a better survival has been observed in p53 negative tumors. Although in univariate analysis, p53 overexpression was associated with worse prognosis, multivariate analysis indicated that residual tumor was the only significant prognostic factor associated with relapse and death ( $p < 0.01$  for both); multivariate analysis also showed that mutant p53 had no independent prognostic value (15). When we examined the role of DNA ploidy, similar results were observed (16). In univariate analysis, DNA aneuploidy or multiploidy were significantly related to poor prognosis ( $p=0.009$ ), but multivariate analysis showed that ploidy could not be used as an independent prognostic factor (16). The prognostic

role of progesterone receptor status has been studied by Leake in a series of 89 patients (17). Most authors conclude that progesterone receptor expression in ovarian cancer had a significant prognostic value (17). There is a significant survival advantage for patients whose tumors are progesterone receptor positive. In fact, the mean survival time for patients in the receptor negative group is 8 months, whereas that for the receptor positive group is  $> 18$  months (17). As it has already been pointed out, presence of residual disease is strongly associated with survival. Estimated 5 and 8 year survival rates are respectively, 50% and 42%, for the size of residual disease smaller than 1 cm, about 19% and 10% when the bulk of the residual disease is 1 to 2 cm and about 13% to 8% when the residuum is greater than 2 cm. It follows that the survival and progression-free survival significantly improve in patients with less than 1 cm of residual disease ( $p < 0.001$ ) (18). With regard to the adjuvant treatment in the early stage ovarian cancer, two prospective randomized trials which compared separate treatment approaches based upon clinico-pathologic prognostic factors have recently been completed in patients with localized disease (19). In patients with favorable prognosis (Stage IA, IB disease), subjects were received either no chemotherapy or melphalan. There were no significant differences in the two treatment groups with regard to the 5-year disease-free period or the overall survival. Patients with unfavorable prognosis (stage IAI, IBII, IC, IIA, IIB, IIC) were randomly treated with either melphalan or a single intraperitoneal administration of chromic phosphate ( $^{32}P$ ). There were no significant differences in the two treatment groups with respect to the 5-year disease-free period or the overall survival. These two trials demonstrate that these categories of patients, after surgical exploration, require no further therapy (19).

Bolis and colleagues performed two randomized trials on 271 patients with stage I ovarian cancer. The study was aimed at assessing the role of adjuvant chemotherapy after radical surgery in early stages of disease. Trial I compared the administration of cisplatin to no further therapy in FIGO stage Ia and Ib Grade II-III patients; trial II compared use of cisplatin to  $^{32}P$  in Stage Iaii, Ibi and Ic. Cisplatin highly reduced the relapse rate by 65% ( $p=0.028$ ) and as compared to chromic phosphate treatment, cisplatin reduced the relapse rate by 61% ( $p=0.007$ ). Survival was not significantly different in both the trials. (20)

Ovarian epithelial cancers disseminate primarily by surface shedding and by lymphatic spread. Spread occurs mainly by continuity, causing

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an intra-tansperitoneal dissemination and cells tend to follow the circulatory path of the peritoneal fluid. Ovarian cancer can exfoliate cells before its capsule is disrupted. For this reason, it is possible to find malignant cells in the ascites fluid. Haematogenous spread is uncommon. Lymphatic dissemination to the pelvic and para-aortic lymph nodes is common and occurs in almost 40% of patients at stage III and IV disease. Peritoneum is the most common site of metastases in the advanced disease and is involved in about 70% of cases at stage III and IV disease. Superficial liver metastases are detectable in 54% of cases at stage IV, isolated omental metastases are observed in about 46% of patients at stage III disease and, finally, hepatic metastases can be documented in 43% of cases at stage IV (21). The median time for the development of distant metastases after the diagnosis of stage I, II or III is about 15 months, with a range of 2 to 139 months (22). At the time of diagnosis, bone or brain metastases are never present and distribution of metastases is not related to the histology or grading of the tumor (22).

### 3. CONCLUSIONS

Ovarian cancer begins at the molecular level. Although our understanding of the genetic mechanisms of tumorigenesis is limited, ovarian cancer appears to be the end result of a complex series of genetic changes in cancer-related genes. Clinical-pathologic factors, such as stage, histology, residual disease after primary surgery are the most significant prognostic indicators. Some biological factors, such as genetic abnormalities, DNA ploidy, steroid receptors, affect the natural history of ovarian cancer. With regard to the metastatic pattern, intraperitoneal dissemination and lymphatic spread are the most common metastatic routes, while haematogenous dissemination is uncommon. Central nervous system metastases are rare and carry the worst prognosis.

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