CLINICAL PROGNOSTIC FACTORS IN PRE- AND POST-MENOPAUSAL WOMEN WITH OVARIAN CARCINOMA

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Abstract

Aims. To assess the impact of prognostic factors on the outcome of ovarian carcinoma (OC) and to determine the difference between pre and postmenopausal patients.

Design. Retrospective cohort, single centre study

Subjects and Methods. One-hundred-sixty patients with stage IC-IV OC diagnosed between 2004-2016 were included. Treatment consisted in primary surgery followed by adjuvant chemotherapy (n=127, 79.4%), neoadjuvant chemotherapy followed by surgery (n=27, 16.9%) and chemotherapy alone (3.7%).

Results. At diagnosis 62 patients (38.8%) were premenopausal. Most patients presented with advanced OC (stage III/IV, 63.1%). After a median follow-up of 60 months, median progression free survival (PFS) for all stages was 36 months and median overall survival (OS) was 96 months. Postmenopausal patients had a poorer oncologic outcome compared with pre-menopausal women (PFS 24 vs. 72 months, p=0.0001, HR=2.32). Other clinical prognostic factors identified were performance status 1 vs. 0 (p=0.0001), ascites (p=0.027). Pathology prognostic factors were tumour grade (G1 vs. G2 and G3, p=0.0001) and endometrioid subtype compared to serous (p=0.008). Patients with residual disease after surgery had an increased risk of recurrence and death (HR=6.1, p=0.0001 and HR=4.2, p=0.0001).

Conclusion. Premenopausal patients had a better oncologic long-term outcome and stage, ascites, grading, residual disease, were independent prognostic factors.

Key words: prognostic, menopause, residual disease, ovarian carcinoma.

INTRODUCTION

Worldwide, epithelial ovarian adenocarcinoma is the commonest cause of gynaecological cancer associated death, with the highest case-fatality ratio and the fifth cause of cancer in women (1). Because there are no screening methods and the symptoms are

not specific, the diagnosis of the disease is delayed and more than 75% of the women presented in advanced stages, when the disease is metastasised to the abdomen (2;3). Patients with ovarian cancer benefit from multidisciplinary treatment. Surgery plays an important role in diagnosis, correct staging, treatment of early disease and cytoreduction in advanced stage or recurrence (4). Most of the tumours are initially sensitive to chemotherapy with platinum salts (5). Unfortunately, after initial response, most of the tumours relapse, and additional treatment has to be administered. It is of extremely importance to identify prognostic factors in ovarian cancer in order to maximize the treatment and to offer the best survival chance with a good quality of life (6).

OBJECTIVE

The objective of the study was to evaluate the results of multimodality treatment (chemotherapy, surgery) in patients with ovarian carcinoma, to assess the impact of significant clinico-pathological prognostic factors on progression free survival rates, overall survival rates and to assess patients' outcome according to menopausal status and body mass index at presentation.

PATIENTS AND METHODS

The study includes 160 consecutive patients diagnosed with epithelial ovarian cancer treated in our institute between 2004-2016. Medical files of these patients were retrospectively analysed. Inclusion criteria consisted in: histopathological confirmation of ovarian adenocarcinoma, stage IC to IV, with a good performance status (ECOG 0-2) with acceptable hematologic, liver and renal function, fit and willing

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Table 1. Patients' characteristics

Patients characteristics	N
Age (median)	53.05±10.4
Stage distribution	
IC n(%)	19 (11.9%)
IIA n(%)	21 (13.1%)
IIC n(%)	19 (11.9%)
IIIA n(%)	4 (2.5%)
IIIB n(%)	3 (1.9%)
IIIC n(%)	69 (43.1%)
IV n(%)	25 (15.6%)
ECOG	
0 n(%)	100 (62.5%)
1 n(%)	58 (36.2%)
2 n(%)	1 (0.7%)
Pathology	
Serous	70.1%
Endometrioid	14.3%
Mucinous	14.9%
Clear Cell	0.6%
G	
G1	11.9%
G2	43.7%
G3	44.4%
CA125 (U/mL)	543.9±719
Tumour dimension (mm)	90.3±49.7

to undergo multimodality treatment. Patients' characteristics are summarised in Table 1.

Median age at diagnostic was 53 years, range 18-78.

The patients underwent either primary debulking surgery followed by adjuvant chemotherapy or neo-adjuvant chemotherapy and interval debulking surgery. Surgery consisted in bilateral salpingo-oophorectomy and hysterectomy and omentectomy ± para-aortic lymphadenectomy, bowel, diaphragm, hepatic resection, appendectomy, partial cystectomy, metastasectomy if these structures were involved and the surgeon tried to obtain no residual disease. Chemotherapy consisted in at least 4 cycles of platinum-based regimens (paclitaxel 175 mg/m² and carboplatin AUC = 5, or cisplatin 75 mg/m², or cyclophosphamide 600 mg/m² and cisplatin 75 mg/m²).

All eligible patients were included in the statistical analysis. The statistical analysis was performed using SPSS 23.0 for Windows. The following endpoints were analysed: progression free survival (PFS), defined as the interval between the date of diagnosis and first progression of the disease or death by any cause; and overall survival (OS), defined as the interval from date of diagnosis until the date of death by any cause. Survival data were calculated using the Kaplan-Meier method. Relevant parameters were

studied for influence on survival by univariate analysis using the log-rank test. A multivariate analysis was performed using stepwise cox proportional hazards model to identify independent prognostic factors. Results were considered significant at the 0.05 level.

RESULTS

According to menopausal status at diagnosis, 62 (38.8%) patients were premenopausal and 98 (61.2%) were postmenopausal. In our cohort, the incidence of nulliparity in women with ovarian cancer is 13.1%

Clinical status of the patients was assessed using ECOG status. At diagnostic 62.7% of patients presented with good clinical status ECOG 0 (fully active, able to carry on all pre-disease performance without restriction), 36.6% with ECOG 1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature) and 0.65% with ECOG 2 (ambulatory and capable of all self-care but unable to carry out any work activities).

Stage distribution was as followed: stage IC - 11.9% (12 patients were premenopausal and 7 postmenopausal), stage IIA 13.1% (7 premenopausal, 14 postmenopausal), stage IIC 11.9% (8 premenopausal, 11 postmenopausal), stage IIIA 2.5% (all

premenopausal), stage IIIB 1.9% (1 premenopausal, 2 postmenopausal), stage IIIC 43.1% (20 premenopausal and 49 postmenopausal), and stage IV was diagnosed in 15.6% (11 premenopausal, 14 postmenopausal). So, almost two thirds of patients (63.1%) were diagnosed with advanced stage and metastasis to the abdomen. Patients presented with large tumours, mean dimension of ovarian tumours being 90.3 mm, median 80 mm, (range 10-250 mm). CA125 level at diagnostic was elevated in 79% of the patients and mean value was 543.9 U/mL (range: 4-3520 U/mL). Ascites were present in a quantity of more than 500 mL (imagistic or surgery protocol) in 35.8% of patients.

Pathology confirmed epithelial ovarian adenocarcinoma in all patients: 70.1% were papillary serous subtype, 14.3% were endometrioid, 14.9% were mucinous and 0.6% were clear cell carcinoma. Regarding the differentiation of the tumour, 44.4% were poorly differentiated tumours G3, 43.7% were moderately differentiated G2 and only 11.9% were well differentiated G1. Serous histology was much more frequent in postmenopausal women (63.8%), and mucinous and endometrioid incidence was almost similar between the two groups.

Treatment strategy consisted in primary surgery followed by adjuvant chemotherapy in 127 patients (79.4%), neoadjuvant chemotherapy followed by surgery in 27 (16.9%) and only chemotherapy in 3.7% of patients because of poor performance status and comorbidities of the patients.

CA125 levels and dimensions of tumours were similar in pre and post-menopausal women.

After a median follow-up of 60 months (range 7-216), median estimated PFS for all stages was 36 months and median OS was 96 months (Fig. 1). For

stage IIIC median progression free survival was 21 months and overall survival was 51 months. For stage IV median PFS was 17 months and overall survival was 48 months.

In premenopausal women, PFS was significantly higher than in postmenopausal ones (72 vs. 24 months, $p=0.0001$) and OS was not reached for premenopausal and 60 months for postmenopausal patients ($p=0.0001$). Multivariate analysis confirmed that the postmenopausal status is an independent adverse prognostic status, with a higher risk of relapse, HR = 2.3, with 95% CI 1.4-3.6 (Fig. 2).

PFS was similar in patients who received surgery followed by adjuvant chemotherapy and in those who received neoadjuvant treatment followed by surgery (40 vs. 36 months, $p=ns$); there was a trend to a better overall survival in first surgery group, but it did not reach statistical significance (100 vs. 60 months, $p=0.154$). The worst outcome was in patients treated only with chemotherapy, with a progression free survival of just 10 months. There were no statistically significant differences between the treatment strategy regarding PFS and OS.

Clinical prognostic factors analysed were performance status, stage of the disease, histologic subtypes, treatment, and residual disease after surgery.

In our series, there was a significant advantage regarding PFS for patients with ECOG 0 vs. 1 and 2 (70 vs. 24 vs. 20 months, $p=0.0001$ for both). The presence of ascites was a poor prognostic factor, PFS for patients with ascites was 23 months as compared to no ascites 36 months ($p=0.027$) and overall survival was 60 months vs. 108 months in favour of patients without ascites at diagnosis ($p=0.005$) (Fig. 3).

Regarding the histological subtype, there was

Figure 1. Median estimates progression free survival (A) and overall survival (B) for studied patients.

Figure 2. Long term oncologic outcome PFS (A) and OS (B) in pre and postmenopausal women.

a clear advantage for endometrioid ovarian carcinoma compared to mucinous and serous (PFS does not reach for endometrioid vs. 27 months for serous $p=0.008$).

Almost half of the patients presented with poor differentiated tumours and this was associated with a poor outcome. PFS in G3 tumour compared to G2 was 20 vs. 70 months ($p=0.0001$) and OS was 44 months as compared to 120 months ($p=0.0001$).

According to their body mass index at presentation, 7% of studied women were underweight (BMI less than 18.5 kg/m^2), 37.3% were normal weight (BMI= $18.5\text{--}24.9 \text{ kg/m}^2$), 31.7% were overweight (BMI= $25\text{--}29.9 \text{ kg/m}^2$) and 25% were obese (BMI $> 30 \text{ kg/m}^2$). Best OS was for normal weight (median OS not reached, PFS 36 months) and overweight patients (OS 96 months, PFS 60 months) and the worst for obese patients (PFS 32 months, OS 62 months) and underweight (PFS 17 months, OS 50 months).

One of the most important prognostic factors was the presence of residual disease after surgery. The presence of residual disease after surgery was associated with a shorter PFS (156 vs. 15 months $p=0.0001$) and OS (not reached vs. 38 months, $p=0.0001$). The risk of recurrence and death in patients with residual disease was significantly higher (for PFS HR= 6.1, 95% CI 3.7–9.7 and for OS HR=4.2 95% CI 2.4–7.2). Moreover, the amount of residual disease is a prognostic factor. In our series, there was a significant difference in PFS and OS in patients with no residual disease, in patients with residual disease less than 1 cm and in patients with residual disease more than 1 cm (as quantified by post-surgery computed tomography or magnetic resonance imaging). For patients with no residual disease estimated PFS was 156 months, for patients with less than 1 cm residual disease, PFS was 20 months and for patients

with more than 1 cm residual disease the estimated PFS was only 13 months. Median OS for patients with no residual disease was not reached, for patients with less than 1 cm residual disease estimated OS was 65 months, and for patients with more than 1 cm residual disease OS was only 32 months (Fig. 3).

DISCUSSION

Ovarian cancer is a heterogeneous disease and unfortunately the vast majority of patients were diagnosed in advanced stage. Menopausal status is a well-known risk factor for ovarian cancer and more than 65% of patients diagnosed with ovarian cancer were postmenopausal (7). There were few data regarding ovarian cancer in premenopausal patients and this is contributing to the late diagnosis of the disease. In our series, there was a predominance of postmenopausal status (61.2% vs. 38.8%), similar with the literature (8). A recent study including 496 malignant epithelial tumours found an increase of incidence of ovarian cancer with age and postmenopausal status. There was an increase of endometrioid tumours as well in young patients, similar with our series (9).

Despite the biggest incidence of epithelial ovarian cancer was in postmenopausal women, the most important risk factors for developing this type of cancer were related to reproduction characteristics, such as nulliparity or low parity or contraceptive use (10). The most important pathogenic hypothesis for epithelial ovarian cancer is “incessant ovulation” hypothesis that postulates that the rupture and subsequent rapid proliferation of the ovarian surface epithelium with ovulation may lead to malignant transformation of ovarian epithelium (11). Most epidemiological studies

Figure 3. Overall survival in patients with ovarian cancer according to (A) BMI, (B) ECOG, (C), Ascites, (D) grading, (E) complete resection (F) amount of residual disease in cm (no residual disease, disease between 1 and 10 mm and disease more than 1 cm).

showed a nulliparity is a well-established risk factor, parous *versus* nulliparous women had a reduced risk of all ovarian cancer subtypes, relative risk [RR]=0.69, $p<.001$, especially for clear cell carcinomas (RR= 0.35;

95% CI= 0.27 to 0.47), whereas serous cancers had the least risk reduction (RR= 0.81; 95% CI=, 0.73 to 0.90) (12). High incidence of nulliparity in our study (13.1%) was consistent with these literature findings.

In this series of patients, median follow-up was 60 months (range 7 to 216 months); to our best knowledge, this is one of the longest follow-up periods, to assess such long-term oncologic outcome of pre and post-menopausal patients with epithelial ovarian cancer. In our series of patients, there was a statistical better PFS and OS in favour of premenopausal women even if they had similar stage distribution, dimension of the tumour and the same levels of CA125.

If the treatment of patients with advanced epithelial ovarian cancer should start with surgery or chemotherapy is still a matter of debate. Vergote *et al.* included 632 patients with epithelial ovarian cancer stage IIIC and IV and randomised them to neoadjuvant chemotherapy followed by interval debulking surgery or surgery followed by adjuvant chemotherapy. The study proved that the neoadjuvant chemotherapy followed by surgery is not inferior to surgery followed by adjuvant chemotherapy (PFS was 12 months in both arms and OS was 29 months and 30 months respectively, HR=1.01 (90% CI, 0.89 to 1.15) but the rate of residual tumour less than 1 cm was bigger in neoadjuvant arm (13). A second study published in 2013 included 276 and 274 patients in each arm and proved the same equivalence between the two treatment modalities with 3 years survival rate of 32% and 34%, respectively (14). The studies were criticised for low survival rate reported. To make the problem even more difficult, a recent study published in 2016 showed an advantage for primary surgery treatment compared to neoadjuvant chemotherapy, with median survival reported of 71.6 vs. 42.9 months (15). In our series of patients, there was no significant difference between patients treated in the two modalities in terms of PFS and OS.

It is of extreme importance to identify the prognostic factors in oncologic patients in order to choose correctly the treatment strategy and to identify the risk of progression and death. In our series, stage of the disease, performance status ECOG 1 or 2 vs. 0, presence of ascites, grading, serous histology vs. non-serous histology were independent prognostic factors. The most robust data regarding prognostic factors came from 3 prospective European randomised trials with similar inclusion criteria, which included 3126 patients, that proved that in univariate and multivariate analysis age, ECOG 2 vs. 0 or 1 FIGO IIIC-IV vs. IIB-IIIB, grading G2/3 vs. G1, mucinous vs. serous histology, ascites > 500 mL yes vs. no were statistical significant prognostic factors for PFS and OS (16). Another American trial included 1895 stage III patients with ovarian cancer and concluded that age, performance

status, tumour histology, and residual tumour volume were independent predictors of prognosis (17).

The most important prognostic factor was the presence of residual disease after surgery. The best outcome was for patients without residual disease after surgery, and more than that it was a statistical difference in progression free survival and overall survival between no residual disease, residual disease between 1 mm and 10 mm and residual disease more than 10 mm. In the American study, patients with stage III and no residual disease, patients with 0.1 to 1.0 cm and more than 1.0 cm residual disease had an increased risk of recurrence (HR = 1.96; 95% CI, 1.70 to 2.26; and HR = 2.36; 95% CI, 2.04 to 2.73, respectively) and death (HR = 2.11; 95% CI, 1.78 to 2.49; P = .001; and HR = 2.47; 95% CI, 2.09 to 2.92, respectively) (17). For stage IV disease, survival benefit was greatest for patients with complete resection, and patients with residual disease less than 10 mm had a smaller benefit compared to patients with residual disease more than 10 mm (18).

A recent study randomised the patients according to age (less and more than 40 years old) and found that patients less than 40 years had a better PFS and OS compared to those older than 40 years (PFS was 28.9 vs. 18.1 months and the median OS was 75.3 vs. 45.7 months). In our series, premenopausal women had a better PFS and OS compared to postmenopausal women (19).

Body mass index had emerged as a major threat by increasing the incidence and mortality of different types of cancer (colorectal, uterine cancer, pancreas and renal cell carcinoma) (20, 21).

The problem is even more complex considering the high incidence of obesity in our country (22).

A recent review of 43 studies, including 3491943 participants, found a statistically significant positive association between ovarian cancer risk and higher body mass index in 14 studies; 26 studies found no significant association, and 3 studies found a negative association between ovarian cancer risk and higher body mass index (23). Similarly to data reported in the literature, in our series obese and underweight women had the worst prognostic.

In conclusion, despite combined therapies, the outcome of patients with OC remains poor especially in patients with advanced disease. The optimal strategy and sequence of different treatment should be defined. Optimal cytoreduction is the most important prognostic factor and no residual tumor should be the goal of the surgery. Menopausal status, ECOG, grading, histopathological subtype, and residual tumour volume

were important prognosis factors. Much attention should be considered in diagnosing the patients in an early stage and at a younger age, because this provides the best prognostic for the patients. Other new immuno-histochemical, serologic and molecular markers are needed for predicting the recurrence and prognosis of epithelial ovarian cancer.

Conflict of interest

The authors declare that they have no conflict of interest.

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