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Impact of age on outcome in patients with advanced ovarian cancer treated within a prospectively randomized phase III study of the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group (AGO-OVAR)☆

Pauline Wimberger [a,*], Nils Lehmann [b], Rainer Kimmig [a], Alexander Burges [c], Werner Meier [d], Berit Hoppenau [a], Andreas du Bois [e] for the AGO-OVAR

[a] Department of Gynecology and Obstetrics, University of Essen, Hufelandstr. 55, D-45122 Essen, Germany
[b] Institute for Medical Informatics, Biometry and Epidemiology, University of Essen, Germany
[c] Department of Gynecology and Obstetrics, University of Munich-Grosshadern, HSK Dr. Horst Schmidt Klinik Wiesbaden, Germany
[d] Department of Gynecology and Obstetrics, Evangelisches Krankenhaus Düsseldorf, HSK Dr. Horst Schmidt Klinik Wiesbaden, Germany
[e] Department of Gynecology and Gynecological Oncology, HSK Dr. Horst Schmidt Klinik Wiesbaden, Germany

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Abstract

Objective. Ovarian cancer exhibits the highest mortality rate among gynecologic cancer and survival rates vary considerably by age. Therefore, we investigated impact of age on outcome in advanced ovarian cancer.

Methods. We performed a subgroup-analysis concerning influence of age classified according to three categories: younger patients (YP; <50 years) vs. middle-aged patients (MP; 50–65 years) vs. elderly patients (EP; >65 years). 686 patients with FIGO IIB–IV were treated within a prospectively randomized phase III study (AGO-OVAR 3) comparing cisplatin–paclitaxel vs. carboplatin–paclitaxel. This subgroup-analysis consisted of patients with homogeneous histology and complete surgical data.

Results. YP had statistically more often achieved no residual tumor after primary surgery than MP and EP ($P < 0.0001$) resulting in improved median overall survival: 60.7, 41.3, and 33.2 months for YP, MP, and EP, respectively. The survival advantage of YP compared to EP remained significant even in completely debulked patients. Multivariable analysis revealed age being an independent prognostic factor.

Conclusion. Reduced surgical radicality, that means both less optimal debulking and also less radical surgery, contributes to poorer outcome in elderly patients with advanced ovarian cancer. However, age-specific surgical approaches did only partially explain age-dependent outcome. Therefore, generalization of study results to all patient age groups might be limited and further studies should focus specifically on treatment in elderly patients.

Keywords: Ovarian neoplasm; Surgery; Age; Prognostic factor

Introduction

Ovarian cancer is the fifth leading cause of cancer related death in Germany and was responsible for approximately 5.850 fatalities in 1999 [1]. Initial debulking surgery followed by platinum-based chemotherapy was standard treatment in advanced disease [2] until the combination of cisplatin and paclitaxel showed superiority over platinum–cyclophosphamide and became generally accepted as standard regimen in the late nineties [3,4]. Improvement in quality of life was achieved by replacing cisplatin by carboplatin, the less neurotoxic, nephrotoxic, and emetogenic platinum analogue. Two prospectively randomized phase III studies, AGO-OVAR 3 and Gynecologic Oncology Group (GOG) protocol #158, com-

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* Corresponding author.
E-mail address: pauline.wimberger@med.uni-essen.de (P. Wimberger).

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pared cisplatin–paclitaxel and carboplatin–paclitaxel. Both trials showed comparable efficacy but improved tolerability, lower toxicity rates, and an easier mode of application, and, in addition, AGO-OVAR-3 showed carboplatin–paclitaxel being associated with significant advantages in quality of life [5,6]. Consequently, carboplatin–paclitaxel became the new standard treatment in advanced ovarian cancer in Germany [7].

However, more than two thirds of patients still relapse despite the progress that has been achieved. Surgical outcome has been described to be one of the most important prognostic factors [8,9]. Recommended standard surgery in primary ovarian cancer in Germany includes radical tumor debulking with vertical laparotomy, bilateral salpingo-oophorectomy (BSO), total hysterectomy (TAH), omentectomy, peritoneal debulking or biopsies, and, if necessary, tumor debulking including bowel surgery and other upper abdominal resections. Pelvic and paraaortic lymphadenectomy is recommended if optimal tumor debulking is achieved in the peritoneal cavity. However, not all institutions are capable of performing such extensive surgery [10]. Several factors influencing surgical outcome have been described: these are surgical training and experience [11], performance status, growth pattern, and expansion of disease [12,13]. In addition, patients' age has been reported to have a significant poor impact on surgical outcome [14].

Improvements in health care and nutrition, decrease in global mortality and increasing trends of mean-life expectancy result in humans getting older and less moribund compared to some decades ago, especially in developed countries. Nowadays, a person aged 70 years has a life expectancy of 14.2 years and in 2020 a 70 year old person will have a 72.5% probability of living for another 15 years [15–17]. Today, about half of all ovarian cancers occur in women over the age of 65 [18–20], but this percentage will steadily grow. Therefore, elderly patients will become more and more the majority thus indicating an increasing challenge for ovarian cancer surgeons to achieve the best results in this patient subgroup. This emerging aspect has not been sufficiently covered in the past. The improvement in survival rates observed in ovarian cancer in the last decades could not be shown for elderly patients and, in contrast, tumor related mortality has significantly increased in this age group [21]. A reason for suboptimal surgical treatment in elderly patients could be a fear of higher complication rates. However, less radical surgical management in elderly patients could be associated with a poorer outcome and survival. Therefore, we evaluated this possible relation between age, surgical radicality, and outcome within a population being treated within a prospectively randomized phase III in advanced ovarian cancer recruited between 1993 and 1995, the AGO-OVAR 3 protocol [5].

Patients and methods

Patients and study design

Patients with histologically confirmed International Federation of Gynecology and Obstetrics (FIGO) [22] stages IIB–IV ovarian cancer, age of 18 years or older (without upper age limit), and a performance status according to the Eastern Cooperative Oncology Group performance status (ECOG) of 0–2 were enrolled in this multicenter prospective randomized phase III study in first line treatment of primary ovarian cancer. Patients were randomly assigned to receive 6 courses of paclitaxel 185 mg/m^2 3 h iv plus either carboplatin AUC 6 (TC arm) or cisplatin 75 mg/m^2 (PT arm) every 3 weeks. Further details regarding inclusion and exclusion criteria and population characteristics were published elsewhere [5]. Standard surgery like exploration laparotomy with bilateral oophorectomy, hysterectomy, omentectomy, radical tumor debulking probably with bowel or urine bladder surgery, and in case of optimal tumor reduction also pelvic and paraaortic lymphadenectomy, was recommended according to German guidelines [7].

We performed an exploratory analysis evaluating the impact of age on surgical management in the study population. The following additional inclusion criteria had to be met for this exploratory subanalysis: information about surgical procedures had to be available (performance of hysterectomy, bilateral oophorectomy, omentectomy, radical tumor debulking, retroperitoneal lymphadenectomy) and residual tumor had to be documented.

Optimal debulking is defined as surgical outcome with no residual tumor after performance of total hysterectomy, bilateral oophorectomy, omentectomy, peritoneal stripping, and radical pelvic and paraaortic lymphadenectomy and if necessary resection of upper abdominal organs. The surgeons intraoperatively defined the amount of residual tumor and in case of measurable disease tumor measurements were performed by CT or MRT before and after chemotherapy.

We limited this analysis to patients with serous papillary, endometroid, mixed, and undifferentiated ovarian cancer. Mucinous tumors (37 patients, 4.7%) and other rare histological subtypes (60 patients, 7.6%) that include clear cell carcinoma were excluded to avoid a possible interaction between outcome and histology [23,24].

686 of the originally 798 randomized patients fulfilled the inclusion criteria and were divided in 3 groups of age: younger patients <50 years of age, middle-aged population with 50–65 years of age, and elderly patients who were older than 65 years. This classification was chosen according to published series [19,20].

Overall survival time was determined from the time of random assignment until death for any cause or to the date of last follow-up. Progression-free survival time was calculated from the time of random assignment until the date of documented disease progression or tumor related death. Overall and progression-free survival times were calculated using the Kaplan–Meier method [25] and hazard ratios were estimated using a Cox proportional multiple regression model [26], combined with a backward variable elimination procedure. Hazard ratios are given with their 95% confidence intervals. The log-rank test is applied to statistically evaluate differences in survival distributions across strata. Trends in proportions are assessed using Cochran–Mantel–Haenszel statistics. *P* values given are to be understood as strictly descriptive accounting for the retrospective explorative nature of this study. Calculations were performed using SAS software (version v8.2).

Results

686 of 798 (86%) originally included patients met our inclusion criteria. Patients were recruited from 137 participating centers and surgical outcome reflected the broad variety of hospitals participating in this study.

Age ranged from 20 to 83 years with a median age of 57.0 years. The study population defined by three groups of age comprised 22.4% younger patients (<50 years), 56.0% middle-aged patients (50–65 years), and 21.6% elderly patients, respectively. Another known important parameter for outcome in advanced ovarian cancer is the FIGO stage. As usual, and also in our study population, the majority of patients had macroscopic tumor spread beyond the pelvis and the most common stages were FIGO IIIB–IV (84.7%), whereas FIGO IIB–IIIA were reported in 15.3%. Complete removal of all visible tumor was achieved in 29.8% of all patients.