EJGO European Journal of Gynaecological Oncology

Epithelial ovarian cancer and primary peritoneal carcinomatosis in the elderly: what is our clinical practice?

J.M. Mañé, B. Calvo, U. Aresti, S. Carrera, A. Sancho, E. Azkona, I. Marrodán, I. Ugalde, I. Rubio, G. López-Vivanco

Department of Medical Oncology, BioCruces Health Research Institute Cruces University Hospital, Basque Health Service (Osakidetza), Bizkaia (Spain)

Summary

Purpose of investigation: The aim of this study was to evaluate clinical practice and the prognostic variables related to survival in elderly people diagnosed with epithelial ovarian cancer (EOC) or primary peritoneal carcinomatosis (PPC). *Materials and Methods:* Fifty-three patients were included and they were divided into two groups, 65-75 years and over 75 years. The variables analyzed were PS, CA125, stage, metastases, cytoreductive surgery, quality of surgery, chemotherapy, and response to chemotherapy. *Results:* The median age of the patients was 73 years. Eighty-nine of the patients had EOC. The median overall survival was 30.5 months with no significant difference between the age groups. The statistical analysis showed no difference except among Stage III patients compared to IV in favor of the younger group ($p = 0.023$). In the multivariate analysis only the Eastern Cooperative Oncology Group (ECOG) score ($p = 0.001$) and response to chemotherapy ($p = 0.007$) significantly influenced survival. *Conclusion:* The specific assessment of elderly allows optimizing the results of cancer treatment in ovarian tumors.

Key words: Epithelial ovarian cancer, Primary peritoneal carcinomatosis, Elderly patients, Geriatric assessment.

Introduction

The incidence of cancer in elderly patients has increased over the last decades and almost 60% of the cases are diagnosed in people over 65 years of age [1]. Given the improvement of the quality of life in developed countries, along with life expectancy, cancer incidence increases. The rise in life expectancy is correlated to higher comorbidity, decreased functional reserve of different organs, and might entail changes in many pharmacokinetics and cross reactions due to the usual polypharmacy of these patients. The combination of all these facts supposes a challenge for oncologists when determining a correct medical approach in the treatment of cancer in elderly patients.

Epithelial ovarian cancer (EOC) represents a paradigmatic location to assess the management techniques employed for the treatment of this neoplasm in elderly people. On one hand, the commonly unspecific symptoms related to this disease can delay the diagnosis; on the other, the treatment involves a surgical debulking together with a polychemotherapy leading to a hardly manageable toxicity. In fact some publications in the literature reflect poorer survival among elderly patients compared to younger ones [2, 3]. Despite the fact that several papers deal with specific aspects of prognosis [4] or treatment [5] in ovarian cancer in older patients, the scientific evidence still remains limited.

Primary peritoneal carcinomatosis (PPC) is an entity characterized by abdominal carcinomatosis without ovarian involvement and no other primary identifiable. Usually clinical presentation and management is accepted to be similar for patients with ovarian cancer [6].

This work aimed to review retrospectively elderly women diagnosed with ovarian cancer or primary peritoneal carcinomatosis at the Cruces University Hospital - Medical Oncology Department, in order to assess the medical approach carried out according to the clinical characteristics and the outcome of these patients.

Materials and Methods

A retrospective analysis of elderly patients with the histological diagnosis of EOC or PPC treated in the Medical Oncology Department at Cruces University Hospital between January 2007 and December 2011 was performed. Patients with a time follow-up of less than one month were excluded. In order to compare clinical and therapeutical characteristics, patients were divided into two age groups: 65-74 and ≥ 75 years.

The therapeutic process was established by a multidisciplinary team that included at least one pathologist, a radiologist, a gynecologist specialized in cancer surgery, and a medical oncologist. Occasionally, the presence of a digestive surgeon was required. After a consensual decision, the patients were assessed again in

Revised manuscript accepted for publication April 5, 2016

7847050 Canada Inc.
www.irog.net

Table 1. — *Patient characteristics.*

Characteristics		n	%
Age (years)	65-74	31	58.5
	75-88	22	41.5
Entity	OC	47	88.7
	PC	6	11.3
ECOG	0	13	25.0
	1	18	34.6
	2	14	26.9
	3	4	7.7
	4	3	5.8
CA-125	Elevated	42	79.2
Stage	I	4	7.5
	II	5	9.5
	III	28	52.8
	IV	16	30.2
Metastases	Hepatic	7	13.2
	Pleural	5	9.4
	Splenic	1	1.9
	Lymph node	1	1.9
	Multiple	2	3.8
	No	37	69.8

**One ECOG report was unavailable.*

Table 2. — *Patient treatment and response.*

Treatment			n	%
Surgery	Yes	Initial	28	52.8
		Interval surgery	7	13.2
	No		18	34.0
Chemotherapy	Yes	Monotherapy	8	15.1
		Polychemotherapy	42	79.2
	No		3	5.7
Response to Chemotherapy	CR	9	25.7	
	PR	15	42.9	
	SD	9	25.7	
	PD	2	5.7	

CR: complete response; PR: partial response;
SD: stable disease; PD: progressive disease.
It was not possible to evaluate the response of 15 treated patients for different reasons (non-measurable disease or early death).

each of the specialities relevant to the therapeutic procedure. Therapeutic assessment included at least performance status according to Eastern Cooperative Oncology Group (ECOG) scale, and an internal simplified test (internal use) to appraise comorbidities and psychosocial aspects.

Performance status was assessed using the ECOG score, ranging from 0 (asymptomatic) to 5 (death). The following data were also gathered: entity (EOC *vs*. PPC), CA-125, stage, metastases, surgery (residual tumor less or more than one cm), chemotherapy regimen, response [complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD), and overall survival (OS)]. OS, from the first chemotherapy treatment to the patient's death or the date of last follow-up information for live patients, was estimated according to the Kaplan-Meier product limited method and compared using the log-rank test. Differences among distribution of qualitative variables in the different groups were analyzed by the χ^2 method.

Clinicopathological characteristics and outcomes were analyzed using a multivariable Cox proportional hazards model. This retrospective study was approved by the Cruces University Hospital Ethical Committee. The requirement for informed consent was waived.

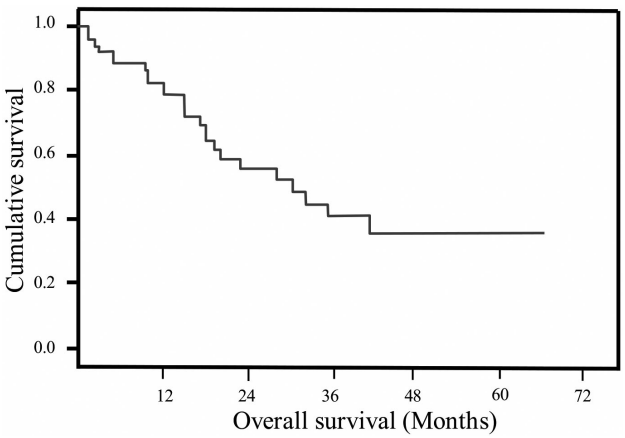

Figure 1. — The whole group survival.

Results

A total of 53 patients were included in the study. The main features at the time of diagnosis are summarized in Table 1. The age of the patients ranged between 65 and 88 years, with a mean and median age of 73 years and a mean follow-up of 23.37 months. Sixty-two percent of the patients were over 70 years of age and the mayority (89%) of them were diagnosed with ovarian cancer compared to 11% who were diagnosed with PPC.

The predominant histological variant was serous type adenocarcinoma (15%), but 5.7% were clear cell carcinomas, 2% mucinous carcinomas, and 2% carcinosarcomas. Fifty-two per cent of the patients were in Stage III and 30.2% of the patients presented metastatic disease at the time of diagnosis.

Regarding the treatment (Table 2), 66% of the patients underwent surgery and 94.3% received chemotherapeutic treatment. The most commonly used drug was platinum as the single agent or in combination with others. Eighteen percent of the patients who received chemotherapy were sensitive to platinum and were treated again with the same platinum based scheme. More than fifty per cent (56.4%) of the patients received more than one line of cytostatic treatment (between two and five). The response rate was 70.6%.

The median overall survival was 30.6 months (Figure 1). The age group of 65 to 74 years did not reach the median survival. The median of the oldest group (75−88 years) was 30.57 months (13.11−48.03) (Figure 2). No significant differences in survival between the two groups were observed.

Performance status analysis showed higher survival for those with better ECOG (0, 1) than those with ECOG 2-4

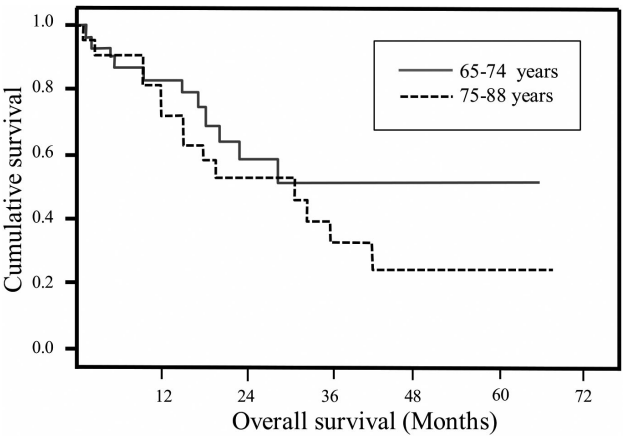

Figure 2. — Survival by age group.

($p < 0.0001$) and there was no difference between the two age groups.

Patients with metastases showed a lower survival than those who did not have widespread disease at diagnosis (median 19.6 and 35.7 months, respectively) although the difference was not significant ($p = 0.306$). In the latter group, there was a significant survival difference ($p = 0.023$) between the young patients (that did not reach the survival median) and the older patients (median 30.6 months). Patients with metastases did not show survival differences in the two age groups. Survival of patients who did not undergo surgery was 15.17 months, while patients that underwent surgery did not reach the median survival ($p = 0.00023$). No significant differences were observed when patients were stratified by age in the two considered groups.

Surgery was optimal for 17 patients (residual tumor < 1 cm) whereas 16 patients had suboptimal surgery (residual tumor > 1 cm). Evaluations of two patients were unknown. Patients with optimal surgery did not reach the median survival and those with suboptimal surgery showed a median of 28.23 months ($p = 0.047$). No differences in the two age groups were detected.

Responder (CR, PR) and non-responder (SD, PD) patient groups showed a median of 32.43 and 17.27 months, respectively. A significant difference was found in the survival between them ($p = 0.034$), however not in the age group distribution.

The multivariable Cox proportional hazards model analysis performed with the Stage (I, II *vs.* III, IV), ECOG (0, 1 *vs.* 2, 3, 4), tumor marker (elevated *vs.* normal), surgery, response to chemotherapy (CR, PR *vs.* ED, PD), and age (65-74 *vs.* ≥ 75) parameters showed that performance status ($p = 0.001$; Exp (B) = 6.6, 95% CI = 2.1−20.4) and response to treatment ($p = 0.007$; Exp (B) = 4.7, 95% CI = 1.5−14.3) were the main variables that affected survival.

All analyses were also performed stratifying patients into three age groups (65-69, 70-74, and ≥ 75 years), nonetheless the results did not show statistical significance (data not shown).

Discussion

Age is an important variable in the treatment of cancer. However, in elderly patients with cancer, chronological age is not an exclusive determinant. Falandry *et al.* [7] developed a geriatric vulnerability score (GVS) in elderly patients with ovarian cancer that included two dependent scores evaluating functionality (Activities of Daily Living, ADL and Instrumental Activities of Daily Living, IADL), two dependent biological values (albuminemia and lymphopenia) and assessment of emotional disorders, but not age. Mohile and Magnuson [8] underlined that a patient's chronologic age does not reflect their overall health status. In the present study, the results agree with this consideration.

As previous authors have stated, the evaluation of elderly patients should include other factors such as comorbidities, psychosocial aspects or specific conditions of old age, such as dementia or functional disability [9]. The present authors report that performance status (ECOG) is an instrument to be included in a geriatric screening tool in agreement with other authors [10, 11]. Nevertheless, some authors [12, 13] found that a percentage of patients showing good performance status had IADL limitations, and warn of its use [14]. Furthermore, current International Society of Geriatric Oncology (SIOG) guidelines recommend to evaluate different targets, besides ECOG, that allow to identify age dependent problems. Inclusion of all the aforementioned factors leads to a more complex and heterogeneous population that cannot be extrapolated to studies with younger patients, greatly hampering therapeutic decisions [15]. Furthermore, ovarian cancer is a tumor of great interest to evaluate the decision process in older patients as it requires a multidisciplinary team to integrate the need for a surgical approach with aggressive chemotherapy. In the present study, a multidisciplinary team planned the treatment based on the ECOG and a simplified score to assess comorbidities and psychosocial dependence.

Usually, in clinical practice, older patients with ovarian cancer are treated with established evidence of studies designed for younger patients. A "soft" or suboptimal implementation of treatment guidelines is most often used for elderly patients, but in some studies age is not itself an adverse prognostic factor [16, 17]. Undertreatment in elderly patients with cancer may be a primary reason for them having poorer outcomes than younger patients [18]. A uterine cancer study driven by Ahmed *et al.* [19] concluded that elderly patients had worse prognosis than younger ones, mostly because of decreased frequency of adequate surgical treatment. According to this, in the current study the authors observed a relationship between surgery and survival,

with better survival for patients that underwent surgery, regardless of age. However, it is difficult to establish an overall decision process designed exclusively for these patients.

The role of chemotherapy in some types of tumor deserves special consideration. The narrow therapeutic scope of many cancer treatments, particularly in palliative cases, may limit the use of these drugs, especially in older patients. In fact, these patients may be particularly vulnerable to certain toxicities and the ratio between effectiveness and toxicity has to be specially adjusted. Some researchers show that Geriatric Assessment (GA) could predict the toxicity of chemotherapy and thereby optimize treatment [5], but these factors are not widely agreed and implemented in daily clinical practice. In the current patient sample, when analyzing response to chemotherapy schedule (Table 2), 68.6% of patients showed a positive trend (CR or PR) although it was not significant in terms of OS when comparing with no-responder patients. Along this line, less time-consuming screening tools have been designed in order to determine which patients could require a GA. These tools also add a predictive/prognostic element for treatment toxicity. Although useful scales like G8 or Vulnerable Elders Survey-13 (VES-13) [20] do not substitute GA. However, GA is a topic with enhancing relevance in the literature of the recent years and in this way, SIOG [14, 21] and the National Comprehensive Cancer Network (NCCN) guidelines recommend using this assessment in order to properly select a suitable cancer treatment for elderly patients [15].

Although the present data are questionable because it is a retrospective study with simplified and not validated scales, in addition to a low statistical power caused by a small sample, the present authors believe that the results are suggestive and interesting due to the OS for the whole group and the absence of statistical differences between the two age groups. However, GA do not identify the best treatment for cancer in the elderly, although its application is associated in different publications with optimizing outcomes and improved survival [5, 22]. Nevertheless acceptance is difficult due to the heterogeneity of results in addition to the low quality of some scientific studies published on this topic [15]. On the other hand, some progress in this area has been achieved. For instance, in a study involving 375 elderly patients with cancer, after assessment by a mult-disciplinary team, the initial treatment was modified in 20-28% of the patients and generally by reducing the intensity of the treatment [23]. The ADL score and malnutrition were the independent variables associated with changes in treatment. The same authors published a review in 2014 with data of GA usefulness for predicting cancer treatment outcomes [24]. They observed that GA results influenced 21–49% of the treatment decisions and the factors that most often predicted mortality and chemotoxicity were functional impairment, malnutrition, and comorbidities. Kenis *et al.* [25] showed that in 25% of the cases, when the GA results were known, geriatric interventions were implemented to address these issues.

In conclusion, the specific assessment of elderly and proper evaluation of the benefits of any interventionist procedure is essential for improving the effectiveness of the treatment. The higher frequency of elderly patients in the subgroups of clinical trials as well as tests designed for this purpose can help answer these questions.

Acknowledgments

The authors acknowledge the Committee for Gynecologic Cancer of the Cruces University Hospital for its support and Ties Venema for the supervision of the manuscript.

This research was supported by a grant from the Medical Oncology Association of the Cruces University Hospital.

References

[1] Haddad A., Shepard D.: "Geriatric Oncology and Palliative Medicine". *Semin. Oncol*., 2011, *38*, 362.

[2] Petignat P., Fioretta G., Verkooijen H.M., Vlastos A.T., Rapiti E., Bouchardy C., Vlastos G.: "Poorer survival of elderly patients with ovarian cancer: a population-based study". *Surg. Oncol.*, 2004, *13*, 181.

[3] Fairfield K.M., Lucas F.L., Earle C.C., Small L., Trimble E.L., Warren J.L.: "Regional variation in cancer-directed surgery and mortality among women with epithelial ovarian cancer in the Medicare population". *Cancer*, 2010, *116*, 4840.

[4] Winter W.E. 3rd, Maxwell G.L., Tian C., Carlson J.W., Ozols R.F., Rose P.G., *et al.*: "Prognostic factors for stage III epithelial ovarian cancer: a Gynecologic Oncology Group Study". *J. Clin. Oncol.*, 2007, *25*, 3621.

[5] Freyer G., Geay J.F., Touzet S., Provencal J., Weber B., Jacquin J.P., *et al.*: "Comprehensive geriatric assessment predicts tolerance to chemotherapy and survival in elderly patients with advanced ovarian carcinoma: a GINECO study". *Ann. Oncol*., 2005, *16*, 1795.

[6] Bhuyan P., Mahapatra S., Mahapatra S., Sethy S., Parida P., Satpathy S.: "Extraovarian primary peritoneal papillary serous carcinoma". *Arch. Gynecol. Obstet*., 2010, *281*, 5561.

[7] Falandry C., Weber B., Savoye A.M., Tinquaut F., Tredan O., Sevin E., *et al.*: "Development of a geriatric vulnerability score in elderly patients with advanced ovarian cancer treated with first-line carboplatin: a GINECO prospective trial". *Ann. Oncol.,* 2013, *24*, 2808.

[8] Mohile S.G., Magnuson A.: "Comprehensive geriatric assessment in oncology". *Interdiscip. Top. Gerontol.*, 2013, *38*, 85.

[9] Brunello A., Sandri R., Extermann M.: "Multidimensional geriatric evaluation for older cancer patients as a clinical and research tool". *Cancer Treat. Rev*., 2009, *35*, 487.

[10] Carey M.S., Bacon M., Tu D., Butler L., Bezjak A., Stuart G.C.: "The prognostic effects of performance status and quality of life scores on progression-free survival and overall survival in advanced ovarian cancer". *Gynecol. Oncol*., 2008, *108*, 100.

[11] Owusu C., Koroukian S.M., Schluchter M., Bakaki P., Berger N.A.: "Screening older cancer patients for a Comprehensive Geriatric Assessment: A comparison of three instruments". *J Geriatr. Oncol.,* 2011, *2*, 121.

[12] Extermann M., Hurria A.: "Comprehensive geriatric assessment for older patients with cancer". *J. Clin. Oncol*., 2007, *25*, 1824.

[13] Repetto L., Fratino L., Audisio R.A., Venturino A., Gianni W., Vercelli M., *et al.*: "Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study". *J. Clin. Oncol.,* 2002, *20*, 494.

[14] Wildiers H., Heeren P., Puts M., Topinkova E., Janssen-Heijne M.L.G., Extermann M., *et al*. "International Society of Geriatric On-

cology Consensus on Geriatric assessment in Older patients with cancer*". J. Clin. Oncol.*, 2014, *32*, 2595.

[15] Puts M.T., Hardt J., Monette J., Girre V., Springal E., Alibhai S.M.H.: "Use of geriatric assessment for older adults in the oncology setting: a systematic review". *J. Natl. Cancer Inst.,* 2012, *104*, 1133.

[16] Trillsch F., Woelber L., Eulenburg C., Braicu I., Lambrechts S., Chekerov R., *et al.*: "Treatment reality in elderly patients with advanced ovarian cancer: a prospective analysis of the OVCAD consortium". *J. Ovarian Res*., 2013, *6*, 42.

[17] Hilpert F., du Bois A., Greimel E.R., Hedderich J., Krause G., Venhoff L., *et al.*: " Feasibility, toxicity and quality of life of first-line chemotherapy with platinum/paclitaxel in elderly patients aged > or = 70 years with advanced ovarian cancer - a study by the AGO OVAR Germany". *Ann. Oncol.,* 2007, *18*, 282.

[18] Dale D.C.: "Poor prognosis in elderly patients with cancer: the role of bias and undertreatment". *J. Support Oncol.*, 2003, *1*, 11.

[19] Ahmed A., Zamba G., De Geest K., Lynch C.F.: "The impact of surgery on survival of elderly women with endometrial cancer in the SEER program from 1992–2002". *Gynecol. Oncol.,* 2008, *111*, 35.

[20] Decoster L., Van Puyvelde K., Mohile S., Wedding U., Basso U., Colloca G., *et al.*: "Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations†". *Ann. Oncol*., 2015, *26*, 288.

[21] Hurria A., Cohen H.J., Extermann M.: "Geriatric Oncology research in the cooperative groups: a report of a SIOG special meeting". *J. Geriatr. Oncol*., 2010, *1*, 40.

[22] Maione P., Perrone F., Gallo C., Manzione L., Piantedosi F., Barbera S., *et al.*: "Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian lung cancer in the elderly study". *J. Clin. Oncol.,* 2005, *23*, 6865.

[23] Caillet P., Canoui-Poitrine F., Vouriot J., Berle M., Reinald N., Krypciak S., *et al.*: "Comprehensive geriatric assessment in the decision-making process in elderly patients with cancer: ELCAPA study". *J. Clin. Oncol*., 2011, *29*, 3636.

[24] Caillet P., Laurent M., Bastuji-Garin S., Liuu E., Culine S., Lagrange J.L., *et al.* : "Optimal management of elderly cancer patients: usefulness of the Comprehensive Geriatric Assessment". *Clin. Interv. Aging*, 2014, *9*, 1645.

[25] Kenis C., Bron D., Libert Y., Decoster L., Van Puyvelde K., Scalliet P., *et al.*: "Relevance of a systematic geriatric screening and assessment in older patients with cancer: Results of a prospective multicentric study". *Ann. Oncol*., 2013, *24*, 1306.

Corresponding Author:
J.M. MAÑÉ MARTÍNEZ, M.D.
Department of Medical Oncology
BioCruces Health Research Institute
Cruces University Hospital
Basque Health Service (Osakidetza)
Plaza Cruces 12
Barakaldo 48903, Bizkaia (Spain)
e-mail: juanmanuel.manemartinez@osakidetza.eus