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Performance status as predective factor for response in ovarian cancer

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INTRODUCTION Of all gynecologic cancers, cancer of the ovary is the most common cause of death of the female genital tract. One particular type, celomic epithelial carcinoma of the ovary, accounts for the vast majority of all cases. More than two-thirds are stage III or IV disease.

Many studies concerning the use of chemotherapy in the management of patients with ovarian carcinoma have been reported and have demonstrated the efficacy of chemotherapy for short-term control and recurrence/death of most of these women over the long-term. The primary treatment of patients with early ovarian carcinoma (I and IIA) is surgical. The appropriate adjuvant treatment has been poorly defined and must be individualized. Chemotherapy or radiation therapy can be considered. In an advanced stage (IIB, III and IV), chemotherapy is the treatment of choice after appropriate cytoreductive surgery has been performed. The use of radiation therapy has remained a controversial subject.

At present, one of the leading issues in the treatment of ovarian cancer is the identification of subgroups of patients with good or poor prognosis. Increased attention is being directed to the delineation of prognostic features identifying those patients at greatest risk for recurrence. The assessment of prognosis is valuable not only in planning treatment for individual patients, but also for the stratification of patients in clinical trials.

Only 25% of epithelial ovarian carcinoma are diagnosed at an early stage. As a result, there are no prospective studies, which give sufficient information about the influence of different tumor characteristics on survival. Retrospective analysis shows that histologic grade, stage of disease, rupture of the tumor and age seem to have an influence on survival prognosis in early-stage ovarian cancer (1-3). However, in advanced ovarian cancer three major prognostic factors were identified in prospective studies as exerting an influence on patient outcome in the overall patient population: age, volume of residual disease and performance status (4).

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HOST FACTORS The success of the systemic therapies for cancer is clearly linked to a number of factors specific to the host organism bearing the tumor. Among these factors are nutritional status, functional capabilities and integrity of major organ systems. The effects of some of these factors on the success of chemotherapy are easily understood.

PERFORMANCE STATUS Less clear, but nonetheless important, are generalized host factors. The functional capability or performance status of a patient has been repeatedly shown to be of great prognostic importance in determining the outcome of a tumor and its treatment. Performance status is presumably a reflection of overall organ function integrity. Patients with poor performance status suffer greater toxicity with almost all forms of cancer therapy; they have shorter survival even when reasonable doses of therapy are administered and optimal supportive care is provided (5).

In 1949, *Karnofsky and Burchenal* (6) designed a performance scale with ten grades (*Table 1*) and in 1979, the *World Health Organization* (7) defined the performance status according to a 5-grade scale (*Table 2*).

ADVANCED OVARIAN CANCER Retrospective analyses of numerous trials suggest a relationship between patient outcome and volume of residual disease in patients with stage III ovarian carcinoma.

SMALL-VOLUME RESIDUAL DISEASE STATUS Small-volume residual disease status has been defined variously as consisting of disease confined to the peritoneal cavity with no nodule larger than 1, 2 or 3 cm remaining after surgical cytoreduction (4).

In GOG *Protocol 25* (4) patients with no nodule larger than 3 cm in diameter remaining after cytoreduction surgery were included and were treated with alkylating agents. In this trial the significant prognostic values were: number of residual lesions (0 or 1 versus multiple), tumor grade (1 versus 2 or 3), age (<55 years of age versus >55 years of age) and histologic type (endometrioid versus other). On the other hand, *Thigpen et. al.* (4) reported that in the GOG *Protocol 52* only patients with no nodule larger than 1 cm in diameter remaining after initial laparotomy were included and received a cisplatin-regimen. In this trial the significant prognostic

factors included age, residual disease, tumor grade and cell type. In these two *GOG trials* (4), including patients with small-volume residual disease treated with or without cisplatin, it seems that performance status does not play a significant role as a prognostic factor.

Table 1. Classification of performance status according to Karnofsky

100	Normal. Has no symptoms or signs of disease
90	Capable of normal activity. Minor symptoms or signs of disease
80	Normal activities with effort. Some symptoms or signs of disease
70	Cares for self. Unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most needs
50	Requires considerable assistance and frequent medical care
40	Disabled. Requires special medical care and assistance
30	Severely disabled. Hospitalization is indicated
20	Very sick. Hospitalization is necessary and active supportive treatment is required
10	Completely disabled. Rapid disease progression
0	Death

Table 2. WHO classification of performance status

0	Able to carry out all normal activity without restriction
1	Restricted in physical strenuous activity, but ambulatory and able to carry out light work
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair

LARGE-VOLUME RESIDUAL DISEASE STATUS On the contrary, an analysis of prognostic factors in patients with large-volume stage III and IV diseases, included in the *GOG Protocols 22 and 47* (4) treated with alkylating agents or with a cisplatin-regimen, emphasizes eight significant variables: performance status ($p < 0.001$), age ($p < 0.001$), cell type, FIGO stage, measurable disease, residual diameter, ascites and treatment. Associated with shorter survival were poor performance status, older age, mucinous or clear cell histology, lesions that were measurable, nodules with larger diameters, presence of ascites and regimen without cisplatin.

The data from two prospective randomized phase III trials that were initiated by the *West Midlands Ovarian Cancer Study Group* (WMOCSG) in 1981 and 1986 have been explored by *Warwick et al.* (8). A Cox proportional hazards model identified performance status ($p = 0.002$), residual disease ($p = 0.005$) and albumin level ($p = 0.04$) as independent prognostic factors. The risk of death for an individual with performance status >1 is 70% greater than that for an individual with performance status <1. These results are broadly in line with the findings of a similar study in the Netherlands.

In 1991, *Neijt et al.* (9) published the mature data from the *Netherlands Joint Study Group for Ovarian Cancer*. In two studies, 377 patients were treated for advanced epithelial ovarian cancer randomly receiving different regimens with or without cisplatin. Independent prognostic variables were identified: cisplatin-regimens, FIGO stage, size of residual tumor and performance status as measured by Karnofsky index *(Table 3)*.

Marsoni et al. (10) published the data on 914 patients enrolled in four Italian randomized trials, consecutively conducted between 1978 and 1986. Performance status was found as a strong independent factor affecting survival. The addition of this prognostic factor in the Cox model yielded a 1.5 relative risk of death for patients with a Karnofsky index below 90, while nullifying the influence of stage and age. The authors concluded: " ... this is not surprising since performance status could be a comprehensive marker of the same relationship between the patient's status and the extent of disease expressed by the combination of stage and age...".

Table 3. Advanced ovarian cancer: Karnofsky index as a prognostic factor (9)

Karnofsky index	Survival rates 1st study	Survival rates 2nd study	Survival rates 1st study	Survival rates 2nd study	Med. survival	Med. survival
	5y	10y	5y	10y		
100	26	18	39	31	2.2	3.3
90	35	19	34	29	2.6	1.9
80	26	22	25	6	1.9	1.8
70	21	8	9	9	1.3	1.0
=60	0	0	0	0	0.5	1.2

y years

The analysis of patient age as an independent prognostic factor for survival in a phase III study of cisplatin-cyclophosphamide versus carboplatin-cyclophosphamide in stage III (suboptimal) and IV of ovarian cancer was done by the *Southwest Oncology Group Study (SOGS)* (11). In this study, the multivariate regression analysis showed the following variables to be independent prognostic factors of survival: age ($p = 0.04$), performance status ($p = 0.004$), disease stage ($p = 0.03$) and race ($p = 0.05$). Patients under 65 years of age survived significantly longer than those 65 years or older, especially patients with a performance status of 2. Patients

with a baseline performance status of 0-1 survived longer than patients with a performance status of 2 *(Table 4)*. It is of interest in this study, that only 8% of the eligible patients 65 years of age and older were considered to have excellent performance status (PS = 0) before receiving the first therapy course. This percentage was significantly different from the 30% of patients under 65 years of age who had a performance status of 0.

Table 4. Advanced ovarian cancer: median survival (in months) of patients under 65 years of age versus 65 years or older according to performance status (11)

Performance status	<65 years	≥65 years
0	23.6	21.6
1	19.7	19.5
2	19.4	12.4

The relationship of residual disease status to Karnofsky index is illustrated in *Table 5* (12). There is a significant difference between residual disease <1 cm versus ≥1 cm with a worse performance status in patients with large-volume residual disease status.

Table 5. Advanced ovarian cancer: relationship of residual disease status to Karnofsky index (12)

Karnofsky index	<1 cm	≥1 cm
80-100	67.4%	32.6%
<80	27.9%	72.1%

CONCLUSIONS 1. In early-stage ovarian cancer patients and in advanced ovarian cancer patients with smal-volume residual disease treated with or without cisplatin, it seems that performance status doesn't play a significant role as a prognostic factor. 2. In advanced ovarian cancer patients with large-volume residual disease, performance status is one of the major independent prognostic factor.

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