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Long-term survival in advanced ovarian carcinoma following cytoreductive surgery with standard peritonectomy procedures

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Abstract. Tentes A-AK, Mirelis CG, Markakidis SK, Bekiaridou KA, Bougioukas IG, Xanthoulis AI, Tsalkidou EG, Zafiropoulos GH, Nikas IH. Long-term survival in advanced ovarian carcinoma following cytoreductive surgery with standard peritonectomy procedures. *Int J Gynecol Cancer* 2006;**16:**490–495.

The impact of cytoreductive surgery with standard peritonectomy procedures has not been extensively assessed in the treatment of advanced ovarian cancer. The aims of the study are to report the long-term results of patients with advanced ovarian cancer undergoing cytoreductive surgery with standard peritonectomy procedures and to identify the prognostic indicators that may affect outcome. The records of 74 women with advanced ovarian cancer were retrospectively reviewed. Clinical indicators were correlated to survival. The hospital mortality and morbidity rates were 13.5% and 28.4%, respectively. Complete or near-complete cytoreduction was possible in 78.4% of the patients. Overall 10-year survival rate was 52.5%. Complete cytoreductive surgery, small-volume tumor, low-grade tumor, the absence of distant metastases, the use of systemic adjuvant chemotherapy, performance status >70%, and limited extent of peritoneal carcinomatosis were favorable indicators of survival. Complete cytoreduction ($P = 0.000$) and treatment with systemic chemotherapy ($P = 0.001$) independently influenced survival. Recurrence was recorded in 37.8% of the patients and was independently influenced by the tumor grade ($P = 0.037$). Cytoreductive surgery with standard peritonectomy procedures followed by adjuvant chemotherapy offers long-term survival in women with advanced ovarian cancer who have limited peritoneal carcinomatosis and no distant and irresectable metastases.

KEYWORDS: cytoreductive surgery, ovarian cancer, standard peritonectomy procedures.

Optimal cytoreduction is the cornerstone of treatment of epithelial ovarian cancer[1]. The role of cytoreductive surgery is to make possible maximal tumor reduction with minimal residual disease. Optimal cytoreduction is not precisely defined, and the residual tumor does not seem to be an absolute indicator of survival[2].

Complete cytoreduction with standard peritonectomy procedures is used in the treatment of nongynecological carcinomas with peritoneal spread and offers long-term survival in properly selected patients[3]. The completeness of cytoreduction (CC) score is a clinical indicator strictly defining the residual tumor[4].

In ovarian cancer, standard peritonectomy procedures have been rarely used[2]. The rates of optimal cytoreduction have been significantly improved with the use of aggressive surgery[5]. The impact of standard aggressive surgery on survival in patients with ovarian cancer has not been extensively investigated.

The aims of the study are to report the long-term results of patients with advanced primary and recurrent ovarian cancer who undergo cytoreductive surgery with standard peritonectomy procedures and to identify the prognostic indicators that may affect outcome.

Materials and methods

The records of women with FIGO stage III and IV ovarian epithelial cancer, treated from 1990 to 2003 in a single institution, were retrospectively reviewed. Clinical indicators were correlated to survival. Hospital morbidity, hospital mortality, recurrences, and failure sites were recorded and analyzed.

The Karnofsky performance scale was used for the assessment of the physical status. Metastases to lymph node groups that had no anatomical relation to the primary site were considered as distant.

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Two transverse and two sagittal planes were used to divide the abdomen in nine regions. The upper transverse plane was the lowest part of the costal margin and the lower plane the anterior iliac spine. The sagittal planes divided the abdomen into three equal sectors. The small bowel was assessed as a separate entity, divided into four different parts (upper and lower jejunum, upper and lower ileum).

The extent of prior surgery was assessed using prior surgery score (PSS)[6]. The score was defined as PSS-0 if no surgery had been performed, as PSS-1 if biopsy only or surgery in one abdominopelvic region had been performed, as PSS-2 if surgery in two to five regions had been performed, and as PSS-3 if surgery in more than five regions had been performed.

Tumor volume was assessed as LS-0 if no visible tumor was detected, as LS-1 if tumor nodules were <0.5 cm, as LS-2 if tumor nodules were 0.5–5 cm, and as LS-3 if tumor nodules were >5 cm in their largest diameter. LS-0, LS-1, and LS-2 were considered small-volume tumors and LS-3 as large-volume tumor. The extent and distribution of peritoneal dissemination was assessed by the calculation of the peritoneal cancer index (PCI)[6], which was the sum of the tumor volume in each one of the 13 abdominopelvic regions.

The completeness of cytoreduction was indicated by CC-0 to CC-3. A CC-0 indicated a resection if no visible tumor was left behind. A CC-1 indicated that residual nodules <0.25 cm in their largest diameter were left behind. A residual tumor >0.25 and <2.5 cm indicated a CC-2 cytoreduction, and a CC-3 indicated that nodules >2.5 cm were detected in the operative field after the completion of the operation. CC-0 and CC-1 surgeries were considered as complete or near-complete cytoreductions. CC-2 and CC-3 were considered as incomplete cytoreductions[6].

Low-grade tumors were considered the well-differentiated (G_1) ones with no evidence of tissue invasion. High-grade tumors were considered the undifferentiated ones or those with moderate differentiation (G_2 or G_3) with evidence or proven tissue invasion.

All the patients with epithelial ovarian cancer FIGO III and IV stages were included for treatment and analysis regardless of age and physical status.

Physical examination, hematologic–biochemical examinations, tumor markers, and whole-body computed tomography (CT) scan made possible the diagnosis and staging of the disease.

The patients were followed up in 6-month intervals with physical examination, hematologic–biochemical examinations, tumor markers, and CT scan. The recurrences and the failure sites were recorded and analyzed.

Treatment

The patients underwent surgery with the intention of performing a complete cytoreduction. The standard peritonectomy procedures used for maximal reduction of the tumor load were greater and lesser omentectomy, resection of the omental bursa, right and left subdiaphragmatic peritonectomy, and pelvic and parietal peritonectomy[7]. Resection of other organs, small and/or large bowel, gallbladder, spleen, and stomach, were performed if necessary for complete cytoreduction.

From 1990 to 1999, only systemic chemotherapy (platinum combined with taxanes) was used as an adjuvant treatment. After 1999, selected patients were treated with early postoperative intraperitoneal chemotherapy (EPIC) during the first 5 postoperative days. The ethical committee of the hospital approved the study concerning the use of EPIC, and the included patients gave written consent. 5-fluorouracil (5-FU) was used in patients with recurrent disease, who had been treated in the past with aggressive systemic chemotherapy, and taxotere was used in patients with primary ovarian cancer. The selection criteria for EPIC were a) acceptable physical status (Karnofsky performance status $>70\%$), b) normal liver and renal function, c) normal hematologic profile, and d) no evidence of other malignancy at risk for recurrence, except for basal cell carcinoma or *in situ* cervix cancer.

Statistical analysis was possible using SPSS (Statistical Package for Social Sciences). The study of relationships between variables was made using χ^2 (Pearson's correlation). Survival analysis was performed using the Kaplan–Meier method and comparison of curves with the log-rank test. Cox regression analysis made possible multiple analysis of survival. Logistic regression analysis was used to calculate the clinical factors related to recurrence and hospital morbidity. P values ≤ 0.05 were considered significant. The postoperative deaths were not excluded from the survival analysis. The end point of the study was survival.

Results

The records of 74 women with primary or recurrent ovarian cancer, mean age 64 ± 10 (42–86) years, were retrospectively reviewed. The characteristics of the patients are shown in Table 1. Twenty-five women were older than 70 years and 49 less than 70 years. Sixty-eight women were at stage III (92.9%) and 6 at stage IV (7.1%) diseases. Fifty-eight patients had primary ovarian cancer with no previous treatment. The other 16 patients had recurrent ovarian cancer and had been treated with cytoreduction and aggressive systemic

Table 1. General characteristics

	No. of patients	%
Physical status		
90–100%	64	86.5
70–80%	7	9.5
50–60%	2	2.7
20–40%	1	1.4
Tumor volume		
Small volume	18	24.3
Large volume	56	75.7
Tumor grade		
High grade	62	83.8
Low grade	12	16.2
PSS		
PSS-0	58	78.4
PSS-1	4	5.4
PSS-2	8	10.8
PSS-3	4	5.4
CC score		
CC-0	37	50
CC-1	21	28.4
CC-2	8	10.8
CC-3	8	10.8
Ascites present	41	55.4
Distant metastases	8	10.8
Histology		
Endometrioid	10	13.5
Mucinous cystadenocarcinoma	1	0.1
Serous cystadenocarcinoma	31	43.1
Clear cell	2	2.7
Serous papillary	22	29.7
Others	8	10.8
PCI		
PCI<13	43	58.1
PCI>13	31	41.9

chemotherapy (first and/or second line). Sixteen patients had undergone in the past cytoreductive surgery (Table 1). The majority of patients (96%) were in acceptable physical status (Karnofsky performance scale >70%). Forty-one patients had large-volume ascites and 8 had distant and irresectable metastases. One patient had multiple irresectable liver lesions, another had splenic parenchymal metastases, and four had pleural effusion with positive cytologic examination. Two more patients had cancer invasion at lymph nodes at the periaortic area from the level of the celiac axis below to the pelvis that could not be resected. Small-volume disease was present in 18 patients and low-grade tumor in 12. Limited peritoneal spread with a PCI not exceeding 13 was present in 43 patients. The performed peritonectomy procedures are shown in Table 2. Complete and near-complete cytoreductive surgeries (CC-0 and CC-1) were possible in 37 (50%) and in 21 (28.4%) patients, respectively. Complete or near-complete cytoreductions comprised 78.4%. A CC-2 operation was performed in eight (10.8%) patients.

Table 2. Peritonectomy procedures

Procedure	No. of patients	%
Pelvic peritonectomy	67	90.5
Greater omentectomy + splenectomy	21	28.4
Greater omentectomy	45	60.8
Right subdiaphragmatic peritonectomy	23	31.1
Left subdiaphragmatic peritonectomy	10	13.5
Parietal peritonectomy	17	23
Subtotal colectomy	9	12.1
Total gastrectomy	1	2.3
Antrectomy	5	6.8
Cholecystectomy + resection of the omental bursa	13	15.6
Intestinal resection	8	10.8
Lesser omentectomy	4	5.4
Colectomy other than low anterior resection	3	4.1

The remaining eight patients underwent palliative surgery (CC-3) with subtotal colectomy, pelvic peritonectomy, greater omentectomy, and splenectomy. In three of them, large tumor volume was left behind on the peritoneal surfaces of the small bowel and in five patients in lymph nodes located at distant sites that had no anatomical relation to the primary site. A CC-0 score was possible in 32 patients with a PCI <13 and only in 5 patients with a PCI >13. The completeness of cytoreduction was independently influenced by the PCI ($P = 0.021$, hazard ratio (HR) = 6.091, 95% confidence interval [CI] = 1.312–28.28) and by the tumor volume ($P = 0.006$, HR = 39.526, 95% CI = 3.917–535.562). Additional treatments included the use of EPIC in 15 cases and systemic chemotherapy in 55 cases. Four patients denied any other treatment than surgery.

Morbidity–mortality

Twenty-two patients (28.4%) were complicated in the immediate postoperative period (Table 3). By univariate analysis, it was shown that hospital morbidity was related to the extent of the peritoneal malignancy and

Table 3. Postoperative complications

Complication	No. of patients	%
Respiratory	6	8.1
Urinary infection	3	4.1
Anastomotic failure	2	2.7
Prolonged ileus	2	2.7
Trauma related	2	2.7
Pulmonary embolism	1	1.4
Renal failure	1	1.4
Postoperative pancreatitis	1	1.4
Adult Respiratory Distress Syndrome	1	1.4
Cardiac failure	1	1.4

to EPIC. The PCI ($P = 0.003$, HR = 1.122, 95% CI = 1.04–1211) and the use of EPIC ($P = 0.016$, HR = 0.194, 95% CI = 0.051–0.736) independently influenced morbidity. The hospital mortality was 13.5% (ten patients). Patients with poor performance status ($P = 0.012$) or extensive peritoneal seeding in whom a complete cytoreductive operation was not possible ($P = 0.007$) had higher mortality.

Survival

Overall 10-year survival rate was 52.5% (Fig. 1). The survival rate for complete or near-complete and incomplete cytoreductions was 64% and 0%, respectively (Fig. 2). Mean survival for complete or near-complete and incomplete cytoreductions was 89 ± 9 and 19 ± 9 months, respectively. Mean survival for CC-0, CC-1, CC-2, and CC-3 surgeries was 115 ± 6, 34 ± 6, 29 ± 9, and 7 ± 2 months, respectively. No difference in survival was found between patients with primary and patients with recurrent ovarian cancer (Fig. 3) ($P < 0.05$). By univariate analysis, it was demonstrated that the completeness of cytoreduction, the tumor volume, the tumor grade, the absence of distant metastases, the treatment with adjuvant systemic chemotherapy, the performance status, and a limited extent of the peritoneal spread (PCI < 13) were favorable indicators of survival (Table 4). The completeness of cytoreduction ($P = 0.000$, HR = 36.598, 95% CI = 7.269–183.4) and treatment with systemic adjuvant chemotherapy ($P = 0.001$, HR = 9.683, 95% CI = 12.648–35.399) independently influenced survival.

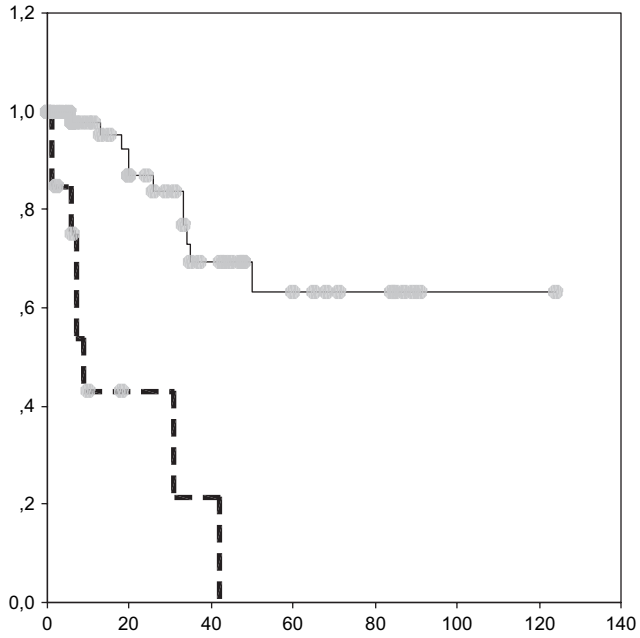

Figure 2. Ten-year survival rate for complete or near-complete (dashed line = 58 patients) and incomplete (dotted line = 16 patients) cytoreductions.

Follow-up

Mean follow-up time was 38 (7–124) months. No patient was lost during follow-up. Recurrence was

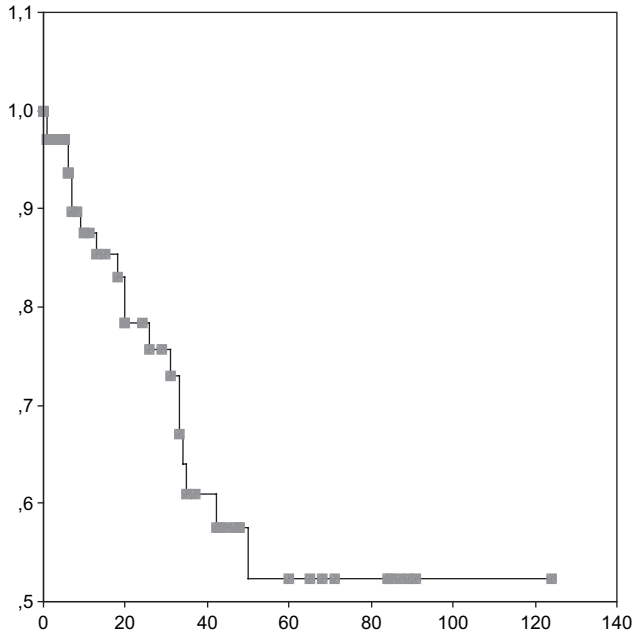

Figure 1. Overall 10-year survival rate.

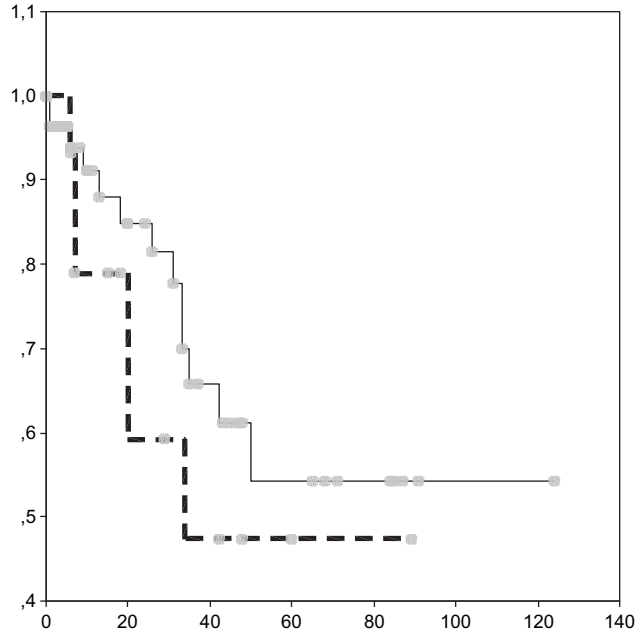

Figure 3. Ten-year survival rate for patients with primary (dashed line = 58 patients) and recurrent tumors (dotted line = 16 patients).

Table 4. Univariate analysis of survival

Indicator	*P* value
CC score	0.0001
Performance status	0.0001
PCI	0.0017
Tumor grade	0.0244
Tumor volume	0.039
Adjuvant chemotherapy	0.0407
Distant metastases	0.0464
PSS	0.0894
Age	0.2062
Ascites	0.0835

recorded in 29 (37.8%) women. Eight women developed distant and 21 locoregional metastases. Only one patient with low-grade tumor during initial diagnosis developed locoregional recurrence and underwent complete secondary cytoreduction. The patient is disease free 3 years following secondary surgery. The tumor grade ($P = 0.037$, HR = 9.533, 95% CI = 1.152–78.895) was the single factor independently influencing recurrence. Currently, 38 patients (51.4%) are alive and 24 of them are disease free. Nineteen patients (25.7%) died of recurrence and 7 (8.8%) of other causes.

Discussion

Optimal cytoreduction is possible in 40–80% of advanced ovarian cancer and is associated with prolonged survival[8]. It is obvious that the size of the residual tumor has a profound impact on survival[9,10], although no prospective study has proved it. The CC score is a valuable tool for the assessment of nongynecological tumors with peritoneal carcinomatosis as well as an independent prognostic indicator of survival[3]. It has rarely been used in ovarian cancer surgery[11–13], but in these cases, it has been a reliable prognostic indicator. The rates of optimal cytoreduction are significantly increased if standard peritonectomy procedures are used[5]. The systemic use of these procedures has made possible the performance of complete or near-complete cytoreduction (CC-0 and CC-1) in 78.4% of the patients. Aggressive cytoreductive surgery combined with systemic chemotherapy has made possible a 10-year survival rate more than 50% and a recurrence rate less than 40%. More than 80% of ovarian carcinomas are chemoresponsive and achieve complete remission[9]. Despite advances in systemic chemotherapy, recurrence is recorded in approximately 80% of the patients[10], and 5-year survival rate is limited only to 25–30%[9]. The completeness of cytoreduction and systemic chemotherapy has been identified as the two most important prognostic indicators of survival[14]. Complete cytoreduction has not been possible in those patients with extensive seeding of the small bowel or cancer invasion at lymph nodes with no anatomical relationship to the primary site that were irresectable. The difference in survival between complete or near-complete and incomplete cytoreductions has been identified as significant. The mean survival of patients with colorectal cancer with peritoneal carcinomatosis following aggressive palliative surgery in combination with intraperitoneal chemotherapy has been found to be 41.8 months[15]. The mean survival of patients with ovarian cancer undergoing palliative aggressive surgery is not comparable, but these patients have not been properly selected. Studies with large numbers of properly selected ovarian cancer patients, undergoing aggressive palliative surgery, are required for comparison. Systematic pelvic and periaortic lymph node resection is not generally considered a part of cytoreductive surgery for ovarian carcinoma[16] and has not proved to be related to survival[17,18]. Therefore, the presence of metastatic disease in lymph node groups in remote sites that are not resected during surgery is an unfavorable prognostic indicator.

The tumor grade has not been firmly established as an independent prognostic indicator because of high degree of variability[14]. The results of the study have shown that tumor grade is related to survival and is an independent indicator of survival. It is well known that low-grade tumors do not metastasize at distant sites unless they are transformed to high-grade tumors after repeated surgery[4].

The PCI is calculated intraoperatively but may be approximately estimated preoperatively by CT scan[4]. The PCI is of prognostic significance for nongynecological tumors[3,6]. In a few reports about ovarian cancer with small numbers of patients, the PCI has been verified as a prognostic indicator[11–13]. The PCI is an independent indicator of the completeness of cytoreduction because in invasive cancer, a high PCI makes impossible a complete cytoreduction. The reports about irresectability or incompleteness of cytoreductive surgery are conflicting. The presence of ascites, the presence of palpable abdominal tumor on physical examination, and the presence of tumor in Douglas' cul-de-sac have been reported as indicators of irresectability[19]. Large-volume tumor in a limited number of abdominopelvic regions does not make the tumor irresectable because the PCI is low and complete or near-complete cytoreduction is possible.

Complete resection of distant metastases in combination with complete cytoreduction offers the patients a significant survival benefit[20]. The complete resection

of distant metastases (located in the splenic parenchyma) was possible only in one patient. However, even if complete resection of metastatic lesions is possible, the presence of metastatic disease in remote sites remains an unfavorable prognostic indicator[7].

The tumor volume is a reliable indicator of survival in patients with peritoneal mesothelioma[21], with colorectal cancer with peritoneal spread[3], and with advanced ovarian cancer[12,13]. The performance status has been documented as a prognostic indicator[14] and has been verified in this study. Poor performance status is generally the result of extensive and long-standing disease. These patients cannot tolerate extensive surgery, they have a high mortality rate, and, if they survive surgery, they do not have long survival[11].

Although PSS is a prognostic indicator of survival for intracelomic tumors[3,11,21,22], it has not been verified in this study. The presence of ascites[9,14], advanced age[14,23], and histopathologic subtype[9,14] have been reported as prognostic indicators in a few studies, but these have not been confirmed in this study.

The effect of intraperitoneal chemotherapy cannot be assessed in this study because only a small number of patients received EPIC. However, although it has been demonstrated to offer a significant survival benefit either in patients with gastrointestinal tumors and peritoneal seeding[3,22] or even for advanced ovarian cancer[11,12], it is not still in use extensively. No definitive results have been reported about intraperitoneal chemotherapy, and large prospective studies are required to document its effect.

Maximal cytoreductive surgery is associated with a high morbidity rate[24]. The more extensive the peritoneal carcinomatosis, the higher the morbidity is. The data confirmed that the PCI independently influenced morbidity. The hospital mortality was high because no patient was excluded from treatment. The patients who died in the immediate postoperative period were either in a poor performance status or had undergone incomplete cytoreduction.

Conclusions

Complete cytoreductive surgery with standard peritonectomy procedures in combination with adjuvant chemotherapy in primary and recurrent advanced ovarian cancer is possible and safe in women who are in acceptable physical condition and have limited peritoneal seeding, without distant and irresectable metastases. These patients may be offered a significant survival benefit.

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