

## Cytoreductive surgery in advanced endometrial cancer: the impact of optimal cytoreduction and adjuvant treatment method

İleri evre endometrium karsinomunda sitoreduktif cerrahinin yeri

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### ABSTRACT

**Aim:** To identify important prognostic variables and evaluate the contribution of cytoreductive surgery on survival in advanced endometrial carcinoma.

**Materials and Methods:** The files of patients with endometrial cancer admitted to İzmir Ege Maternity and Gynecology Training and Research Hospital between January 1995 and December 2009 were reviewed. Sixty-one patients with advanced stage (Stage 3 and Stage 4) endometrial carcinoma were included in the study. Important prognostic variables in advanced endometrial carcinoma were determined and the contribution of cytoreductive surgery on survival was evaluated. The staging was performed according to the FIGO surgical staging system.

**Results:** The study included 61 patients. All patients underwent primary cytoreduction. The mean age of the patients at the time of diagnosis was 58 years. 18% of the patients were premenopausal and 82% were postmenopausal. The histologic types were endometrioid (78.7%), serous (11.5%), adenosquamous (6.6%), clear cell (1.6%), and epithelial (1.6%). Surgical staging revealed that the most common sites of metastasis were lymph node (52.4%), pelvis (45.9%), omentum (8.1%), upper abdomen (8.1%), and extra-abdominal (8.1%). The endometrioid type was found to have a longer survival than other histologic types. The mean survival was 119 ± 10 months in patients with optimal cytoreduction and 22 ± 6 months in patients with suboptimal cytoreduction.

**Conclusion:** In our study, optimal cytoreduction was defined as residual disease with a tumor size of 1 cm or less. Accordingly, there is a significant correlation between optimal cytoreduction and survival.

**Keywords:** Endometrial carcinoma, advanced stage, cytoreductive surgery

### ÖZ

**Amaç:** İleri evre endometrium karsinomunda önemli prognostik değişkenleri belirlemek ve sitoreduktif cerrahinin sağ kalım üzerine katkısını değerlendirmek.

**Gereç ve Yöntemler:** Ocak 1995 – Aralık 2009 yılları arasında İzmir Tepecik Doğumevi'ne başvuran endometrium kanserli olgulara ait dosyalar incelendi. İleri evre (Evre 3 ve Evre 4) endometrium kanseri olan 61 olgu çalışmaya dahil edildi. İleri evre endometrium karsinomunda önemli prognostik değişkenler belirlenerek, sitoreduktif cerrahinin sağ kalım üzerine olan katkısı değerlendirildi. Evreleme FIGO cerrahi evreleme sistemine göre yapıldı.

**Bulgular:** Çalışmaya 61 hasta dahil edildi. Tüm hastalara primer sitoreduksiyon uygulandı. Hastaların tanı anındaki yaş ortalaması 58'di. Hastaların %18,03'ü premenopozal, %81,07'si postmenopozal dönemde olduğu görüldü. Çalışmada histolojik tipler; endometrioid (%78,7), seröz (%11,5), adenoskuamoz (%6,6), clear cell (%1,6) epitelial (%1,6) olarak saptandı. Cerrahi evreleme sonucunda, en sık metastaz alanları lenf nodu (%52,4), pelvis (%45,9), omentum (%8,1), üst abdomen (%8,1), ekstra abdominal (%8,1) olarak saptandı. Endometrioid tipin diğer histolojik tiplere daha uzun bir sağ kalımı olduğu tespit edildi. Optimal sitoreduksiyon uygulanan hastalarda ortalama sağ kalım 119+10 ay, suboptimal sitoreduksiyon uygulanan hastalarda 22+6 ay olarak bulundu. Optimal sitoreduksiyon, hastalara 97 aylık bir sağ kalım avantajı sağlamaktadır. Ayrıca; 24 ay sonunda optimal sitoreduksiyon uygulanan hastaların %72'si hayatta iken, suboptimal sitoreduksiyon uygulanan hastaların %22'si hayatta kaldı.

**Sonuç:** Çalışmamızda optimal sitoreduksiyon; tümör boyutu 1 cm ve altında rezidüel hastalık olarak kabul edilmiştir. Buna göre; optimal sitoreduksiyon ile sağ kalım arasında anlamlı bir bağlantı vardır. Bu bilgi literatür bilgisiyle uyumlu olarak bulunmuştur. Geniş vaka serileri ile yapılacak çalışmalarla bu konu hakkında daha net fikirler elde edilebilir.

**Anahtar Kelimeler:** Endometrium karsinom, ileri evre, sitoreduktif cerrahi

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## INTRODUCTION

Gynecologic cancers constitute approximately 13% of all cancers seen in women.<sup>1</sup> In developed countries, endometrial cancer is the most common cancer in the female genital system. Every year, 142000 women are diagnosed worldwide and 42000 women die from this disease.<sup>2</sup> Endometrial cancer is the fourth most common cancer in women after breast, bowel, and lung cancer. The average incidence is 24.7 per 100,000 women. The cumulative risk of endometrial cancer in a 75-year-old woman is 1.7%. Despite its high incidence and the lack of an effective screening test, it ranks low among the causes of death due to its early symptoms and treatment options and is the 8th most common cause of cancer-related deaths.<sup>3</sup> According to data from the Ministry of Health, it ranks 2nd among malignancies of the female genital system in Turkey.<sup>4</sup>

According to histologic features, endometrium cancer is divided into type 1 and type 2. Type 1 endometrial carcinoma is seen in 80% of cases. They are endometrioid adenocarcinomas (or adenosquamous, mucinous, villoglandular) showing good or moderate differentiation and limited to the uterine corpus at the time of diagnosis. Type 2 endometrial carcinoma is seen in 15-20% of cases. They are high-grade carcinomas such as clear cell and serous carcinomas showing nuclear atypia. These tumors usually invade the myometrium and spread outside the uterus during hysterectomy. Since the prognosis of the second group is worse, the pathologist who makes the diagnosis becomes more important in planning the patient's treatment.

Endometrial carcinoma is a cancer that has been surgically staged since 1988 according to the decision of the International Federation of Gynecology and Obstetrics (FIGO). The conventional surgical approach includes midline abdominal incision followed by peritoneal washing and cytology collection, total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy in selected high-risk cases, pelvic and paraaortic lymphadenectomy.<sup>5</sup>

The incidence of endometrial carcinoma is increasing and it is rapidly climbing up the list of gynecological cancers. For this reason, serious research is being carried out to find out the risk factors, screening methods for early diagnosis, factors affecting prognosis, and the most effective treatment methods on life expectancy. Although in the vast majority of patients, the carcinoma is confined to the uterus, in approximately 20% the tumor metastasises to pelvic lymph nodes and more distant organs. The surgical management of early-stage endometrial cancer has been clearly defined, but metastatic and recurrent disease has a poor response to current treatment regimens and the optimal management of these patients

is still to be determined.

Advanced endometrial cancer poses a problem from a clinical point of view. The reason for this is the lack of consensus on the most effective treatment method and the poor survival data of the disease to date. Especially stage 3 and stage 4 patients are responsible for 50% of endometrial cancer-related deaths. In stage 4 disease, 5-year survival is around 10-20%.<sup>6,7</sup> Therefore, the role of radical surgery in the management of patients with advanced endometrial carcinoma is increasing, especially in the management of patients who are expected to benefit from adjuvant radiotherapy or chemotherapy.

This study aimed to determine important prognostic variables in advanced endometrial carcinoma and to evaluate the contribution of cytoreductive surgery on survival.

## MATERIAL AND METHODS

In this retrospective study, the files of patients with endometrial cancer admitted to Izmir Ege Maternity and Gynecology Training and Research Hospital between January 1995 and December 2009 were analyzed. Seventy-four patients with advanced stage (Stage 3 and Stage 4) endometrial cancer were identified. Due to incomplete files, 13 cases were excluded from the study and 61 cases were included in the study. All patients underwent primary cytoreduction.

The contribution of cytoreductive surgery on survival in advanced endometrial carcinoma was evaluated by determining important prognostic variables. The staging was performed according to the FIGO surgical staging system. SPSS (Statistical Package for Social Sciences) for Windows 16.0 program was used for statistical analysis. All data are summarized in tables. Study

In addition to descriptive statistical methods (mean, standard deviation, percentage, minimum, and maximum value), the log-rank method was used for univariate analyses and the Cox proportional hazards regression test for multivariate analyses for intra- and intergroup comparisons of quantitative data. Pearson's chi-square and Fisher's chi-square tests were used to compare qualitative data. The results were evaluated at a 95% confidence interval and significance level  $p < 0.05$ .

## RESULTS

The age distribution of the patients at the time of diagnosis was between 32 and 77 years with a mean of 58 years. 77% of the

patients were younger than 65 years and 23% were older than 65 years. 18.03% of the patients were premenopausal and 81.07% were postmenopausal. The histologic types were endometrioid (78.7%), serous (11.5%), adenosquamous (6.6%), clear cell (1.6%), and not specified (malignant epithelial) (1.6%), respectively. Pathology results were grade 3 (poorly differentiated) in 14 cases, grade 2 (moderately differentiated) in 28 cases, and grade 1 (well differentiated) in 11 cases. In 8 cases, the reason for not specifying grade was serous and clear cell histology. When the cases were evaluated according to their stages; Stage 3a (n=20), Stage 3b (n=2), Stage 3c (n=35), Stage 4a (n=1), and Stage 4b (n=3) cases were detected.

All 61 patients underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, staging surgery, and maximal cytoreduction by explorative laparotomy. Hysterectomy was performed in 100% of the patients (61/61). 39 patients underwent type 1 hysterectomy, 6 patients underwent type 2 hysterectomy, and 16 patients underwent type 3 hysterectomy. 20 patients underwent omentectomy, 54 patients underwent lymph node dissection and 12 patients underwent appendectomy. Optimal cytoreduction was

defined as a residual tumoural disease with a maximum diameter of less than 1 cm. Optimal cytoreduction was performed in 86.9% and suboptimal cytoreduction in 13.1% of the patients. Abdominal wash cytology revealed 72.1% benign cytology, 24.6% malignant cytology, and 3.3% suspicious cytology. Abdominal wash cytology was not included in survival analyses because it has no prognostic significance in the 2009 FIGO staging system. Demographic and disease-related characteristics of the research sample are summarized in Table 1.

A total of 43 patients (41%) received postoperative chemotherapy. These patients received cisplatin alone or a combination of cisplatin with doxorubicin, cyclophosphamide, and paclitaxel. Radiotherapy was given additionally in 36 of these patients. 18 patients received radiotherapy only. Radiotherapy was administered as whole abdomen radiotherapy or brachytherapy.

In the calculation of survival for all patients who participated in the study, median survival could not be calculated because there were not enough patients in the ex-group, and mean survival was calculated instead. The mean survival of all patients participating in the study was  $111 \pm 10$  months. When the patients were evaluated

**Table 1.** Demographic and disease-related characteristics of the study sample

	<b>N</b>	<b>%</b>
<b>Age (mean, yrs)</b>	58 (range 32-77)	
<b>Menopausal status</b>		
Pre-menopausal	11	18.0%
Post-menopausal	50	82.0%
<b>Histologic Types</b>		
Endometrioid	48	78.7%
Serous	7	11.5%
Adenosquamous	4	6.6%
Clear Cell	1	1.6%
Not specified (malignant epithelial)	1	1.6%
<b>Grade</b>		
Low grade (G1)	11	18.0%
Intermediate grade (G2)	28	45.9%
High grade (G3)	22	36.1%
<b>Disease Site (Anatomic localization)</b>		
Lymph node	32	52.4
Pelvis	28	45.9
Omentum	5	8.1
Upper abdomen	5	8.1
Extra-abdominal	5	8.1
<b>Peritoneal cytology (fluid/washing)</b>		
Benign	44	72.1%
Malignant	15	24.6%

according to age groups, although patients younger than 65 years had longer survival, there was no statistically significant difference between them and patients older than 65 years ( $p=0.95$ ). When the cases were evaluated according to histological subtypes, it was found that the endometrioid type had a longer survival than other histological types ( $p=0.001^*$ ). There was no statistically significant difference between tumor grade and survival. When stage 3 patients were compared within themselves, there was no significant difference in survival between the group with lymph node involvement and the group without lymph node involvement ( $p= 0.49$ ).

Cases were compared in terms of residual disease volume and the mean survival was  $119 \pm 10$  months in patients with optimal cytoreduction (1 cm or less residual tumor) and  $22 \pm 6$  months in patients with suboptimal cytoreduction. This difference is statistically significant ( $p= 0.009^*$ ). It is seen that optimal

cytoreduction provides a 97-month survival advantage to patients. Furthermore, 72% of patients with optimal cytoreduction were alive at 24 months, compared to 22% of patients with suboptimal cytoreduction. The procedures, surgical optimality and adjuvant treatment methods are summarized in Table 2.

When the cases were evaluated according to metastasis and disease extent; there was no statistical difference in survival between disease limited to the pelvis and disease spread outside the pelvis ( $p= 0.997$ ). When Stage 3 cases were evaluated according to treatment modalities, it was observed that only chemotherapy or radiotherapy+chemotherapy combination had no significant contribution to survival. However, it was found that 18 patients who received radiotherapy alone had a survival of  $141 \pm 16$  months and had a better survival than the group of patients who received chemotherapy alone  $35 \pm 14$  months ( $p= 0.015^*$ ). However, there was no superiority to the radiotherapy+chemotherapy group.

**Table 2.** Procedures, surgical optimality and adjuvant treatment methods

	N	%
<b>Procedures performed</b>		
TAH-BSO	61*	100%
Omentectomy	20	32.8%
RPLND	54	88.5%
Appendectomy	12	19.7%
Rectosigmoid resection	1	1.6%
Visceral/Parietal peritonectomies**	5	8.2%
<b>Surgical Optimality</b>		
Optimal cytoreduction	53	86.9%
Suboptimal cytoreduction	8	13.1%
<b>Perioperative Morbidity &amp; Unintended Events</b>		
Blood product transfusion	4	6.5%
Bladder injury	1	1.6%
Re-exploration due to hemorrhage	1	1.6%
Delayed (>72 hrs) ICU stay	1	1.6%
Deep venous thrombosis	1	1.6%
Atelectasis	1	1.6%
Wound infection (superficial)	2	3.2%
Urinary tract infection	1	1.6%
<b>Adjuvant treatment</b>		
Chemotherapy	7	11.5%
RT	18	29.5%
Chemo-RT***	36	59.0%

TAH-BSO: Total abdominal hysterectomy and bilateral salpingo-oophorectomy, RPLND: Retroperitoneal Lymph Node Dissection, ICU: Intensive care unit, RT: Radiotherapy

\*: Two of which include Type 2 Hysterectomy

\*\* : Pelvic, anterior abdominal wall, diaphragma

\*\*\*: sequential or sandwich method

## DISCUSSION

Patients with advanced endometrial cancer constitute approximately 15-20% of all newly diagnosed patients, but more than half of all deaths due to endometrial cancer occur in this group. Prognostic variables and effective management strategies for patients in this group have not been determined until recently. In this study, the effect of residual disease volume on survival and other variables affecting survival in advanced endometrial cancer were analyzed.

To date, there are conflicting data in the literature about the effect of age on survival. Many researchers have found that age has no prognostic significance.<sup>8,9</sup> In a study by Pliskow et al. evaluating prognostic factors in 41 patients with advanced endometrial cancer, no significant association was found between age and survival.<sup>9</sup> However, in a study by Okuma et al. involving 111 patients with advanced endometrial cancer, survival was found to be longer in patients aged 60 years and younger.<sup>10</sup> Furthermore, Yutaka et al. evaluated the prognostic significance of cytoreductive surgery in 33 patients with stage 4 endometrial carcinoma and found that patients aged 70 years and younger had longer survival.<sup>11</sup> Similarly, in our study, survival was found to be longer in patients under 65 years of age, but it was not statistically significant.

Similar to previous studies, no significant correlation was shown between survival and tumor grade, and metastasis distribution in our study.<sup>12</sup> Bristow et al. performed cytoreductive surgery in 65 advanced endometrial carcinomas and published the results. In their study, the sites of metastasis were the pelvis (75.4%), omentum (49.2%), and retroperitoneal lymph node (38.5%), respectively. In our study, the most common sites of metastasis were the retroperitoneal lymph node (52.4%), pelvis (45.9%), and omentum (8.1%). Although there are proportional differences in other studies, the sites of metastasis are similar.<sup>13</sup>

No significant association was found between tumor histology and survival in previous studies. In the GOG study of 1203 patients in which McMeekin et al. investigated histological type and response to chemotherapy in advanced endometrial carcinoma, no difference was found between histological type and response to chemotherapy.<sup>14</sup> In their study, although survival was found to be shorter in patients with serous histology, it was not found to be statistically significant since this patient group constituted a small portion of the whole group. In a study conducted by Yutaka et al. in 33 patients with advanced-stage endometrial carcinoma, although a longer survival was found in patients with endometrioid histology, it was not statistically significant.<sup>11</sup> In our study, when tumor histology was evaluated independently of other factors, survival

was found to be significantly higher in the patient group with endometrioid histology compared to the patient group with other histologies. The mean survival was  $128 \pm 11$  months in the patient group with endometrioid histology and  $24 \pm 4$  months in the patient group with other histologies. The association between endometrioid histology and prolonged survival persisted in multivariate analyses. It is possible that the fact that our patient group with endometrioid histology was more numerous than the patient group with other histologies may have led to this result.

There is no comprehensive study on the prognostic value of general conditions in endometrial cancer. Recent studies have shown a link between preoperative general condition and survival as an independent factor. These data suggest that patients who are healthier and have a higher performance scale tolerate extensive cytoreductive surgery better, resulting in optimal cytoreduction and postoperative adjuvant therapy. Since GOG performance was not evaluated in our hospital files, this parameter was not studied.

Confirming previous investigators, treatment modality could not be shown to contribute to survival as an independent variable in our multivariate analysis.<sup>15</sup> Marcus et al. compared the efficacy of whole abdominal radiotherapy with doxorubicin+cisplatin chemotherapy in 423 patients with advanced endometrial carcinoma treated with optimal cytoreduction and published their results (GOG 122). In their study, they found that chemotherapy had a longer disease-free period and a longer survival compared to radiotherapy. Barlin and Bristow performed a meta-analysis of 14 studies evaluating 672 patients with advanced primary and recurrent endometrial carcinoma who underwent cytoreduction and published their results. According to this meta-analysis, each 10% increase in the proportion of patients receiving postoperative radiotherapy leads to an 11-month increase in survival, while each 10% increase in the proportion of patients receiving chemotherapy leads to a 10.4-month decrease in survival.<sup>16</sup> Interestingly, in our study, when evaluated alone, the patient group receiving radiotherapy alone had an increased survival compared to the group receiving chemotherapy alone. When evaluated together with other variables (age, general condition, surgical status), radiotherapy loses this importance. This may be because younger, more functional patients tolerate aggressive surgery better. On the other hand, since the patients in our study who received chemotherapy had more widespread and extensive metastases, the choice of chemotherapy as treatment may lead to shorter survival. This idea is supported by the fact that stage 4 patients have a shorter survival.

In the GOG 28 and 48 studies, no difference was found between combination chemotherapy and single-agent chemotherapy in terms of survival. In the study of Thigpen et al. comparing

combination and single-agent chemotherapy in advanced endometrial carcinoma, no difference was found between single-agent doxorubicin and doxorubicin+cisplatin chemotherapy, but combination chemotherapy was found to be better in terms of disease-free period.<sup>17</sup> In our study, no such comparison was made between patients in the chemotherapy group. However, the contribution of postoperative treatment modality on survival in selected patients with advanced endometrial cancer may be better demonstrated in future studies.

Developing standard treatment protocols in advanced metastatic endometrial cancer is difficult due to the limited therapeutic efficacy of radiotherapy, chemotherapy, and hormonotherapy on large tumor burden.<sup>18,19</sup> Therefore, achieving minimal residual disease with cytoreductive surgery has greater therapeutic importance. In this study, tumor size was one of the two most important predictive factors for survival. This importance persists in multivariate analyses. Although young age and good general condition are associated with improved survival, the only prognostic factor that can be directly influenced by the surgeon is the amount of residual tumor. Extensive literature shows that less residual tumor burden is associated with better survival in advanced ovarian cancer treated with cytoreductive surgery.<sup>20</sup> However, the literature showing the importance of cytoreductive surgery in advanced endometrial cancer is more limited. Goff et al. performed cytoreductive surgery in 29 of 47 patients with advanced endometrial cancer and no bulky residual disease was left behind.<sup>12</sup> Unfortunately, the residual tumor size was not specified in cm in their study. Bristow et al. performed cytoreductive surgery in all 65 patients with advanced endometrial carcinoma and performed optimal cytoreduction in 36 and suboptimal cytoreduction in 29 of these patients. In their study, they accepted 1 cm as the limit for residual tumor size. In our study, all patients who participated in the study underwent cytoreductive surgery. Optimal cytoreduction was performed in 86.9% and suboptimal cytoreduction in 13.1% of the patients. Optimal cytoreduction was defined as residual tumor less than 1 cm was accepted as optimal cytoreduction. Survival of patients who underwent optimal cytoreduction was found to be significantly better than patients who underwent suboptimal cytoreduction.<sup>13</sup> This information clearly demonstrates the prognostic value of an optimal cytoreduction with minimal residual disease, although its real contribution to survival cannot be fully determined due to the type of surgery performed.

Greer and Hamberger applied postoperative whole abdomen radiotherapy to 31 patients with advanced endometrial cancer and found a 5-year survival rate of 70% in patients with residual tumors less than 2 cm. In our study, it was found to be similar to

the literature with 63%. This study shows that adjuvant therapy in both stage 3 and stage 4 patients is much more successful in patients with minimal residual disease.<sup>21</sup> Chi et al. published the results of a study in which they performed cytoreductive surgery in 55 patients with advanced endometrial cancer. In this study, they found a significant correlation between the size of cytoreductive surgery and survival. In patients with tumors smaller than 2 cm, the median survival was 31 months. This indicates that optimal cytoreduction patients who underwent suboptimal cytoreduction had a longer survival compared to those who underwent suboptimal cytoreduction (median survival 12 months).<sup>8</sup>

In a study conducted by Ayhan et al. in 37 patients with advanced endometrial carcinoma, median survival was 25 months in patients with optimal cytoreduction and 10 months in the suboptimal group. The median survival was 48 months in patients with no remaining microscopic tumor tissue. The majority of the patients consisted of endometrioid adenocarcinoma. In univariate analyses, extra abdominal metastasis, suboptimal cytoreduction, macroscopic residual tumor size, pelvic and paraaortic lymph node metastasis, and cervical involvement were found to be poor prognostic factors. In multivariate analyses, optimal cytoreduction was found to be associated with prolonged survival.<sup>22</sup> Lambrou et al. performed primary cytoreduction in 85 patients with advanced stage (66 stage 3, 19 stage 4) endometrial adenocarcinoma and found that survival was shorter and morbidity increased in patients who underwent suboptimal cytoreduction. They found that survival was 17.8 months in patients with optimal cytoreduction and 6.7 months in patients with suboptimal cytoreduction.<sup>23</sup>

A meta-analysis of 14 studies by Barlin et al. showed that optimal cytoreduction had a significant contribution to median survival. According to this study, each 10% increase in the proportion of patients undergoing optimal cytoreduction leads to a 9.3-month survival increase. According to this study, the aim of advanced-stage endometrial carcinoma should be the resection of all visible tumorous tissues.<sup>16</sup>

In our study, median survival could not be calculated because the number of patients who died was not sufficient; instead, mean survival was used. Optimal cytoreduction was accepted as residual disease of 1 cm or less. Accordingly, mean survival was  $119 \pm 10$  months in patients with optimal cytoreduction and  $22 \pm 6$  months in patients with suboptimal cytoreduction was found. These data show that patients with optimal cytoreduction have better survival than patients with suboptimal cytoreduction, which is consistent with the literature. This significance was maintained in multivariate analyses.

## CONCLUSION

In our study, optimal cytoreduction was defined as residual disease with a tumor size of 1 cm or less. Accordingly, there is a significant correlation between optimal cytoreduction and survival. This information was found to be consistent with the literature. Further studies with large case series may provide a clearer idea about this issue.

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