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Original research

Survival impact of cytoreduction to microscopic disease for advanced stage cancer of the uterine corpus: A retrospective cohort study

Ioannis Alagkiozidis [a,*], Allison Grossman [b], Nancy Z. Tang [a], Jeremy Weedon [b], Benjamin Mize [a], Ghadir Salame [a], Yi-Chun Lee [a], Ovadia Abulafia [a]

[a] Department of Gynecologic Oncology, SUNY-Downstate Medical Center, Brooklyn, NY, USA
[b] Department of Epidemiology and Biostatistics, SUNY-Downstate Medical Center, Brooklyn, NY, USA

HIGHLIGHTS

- Optimal debulking is associated with improved survival in several malignancies.
- Optimal debulking is associated with improved survival in uterine cancer.
- The survival benefit is uniform among histologic types.
- There is no interaction between histologic type and feasibility of optimal debulking.

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ABSTRACT

Objective: To assess the impact of cytoreduction to no gross residual disease (R0) on overall survival (OS) in patients with stage III–IV uterine carcinosarcoma (CS), papillary serous/clear cell (UPSC/CC) and endometrioid carcinoma (EC).

Methods: We retrospectively identified 168 patients who underwent primary surgery for advanced uterine cancer between 1984 and 2009 in two teaching hospitals in Brooklyn, New York. Histology, stage, grade, residual disease (RD), adjuvant therapy, age, race and OS were collected. OS was calculated using the Kaplan–Meier method. Predictive factors were compared using the log-rank test and Cox regression analysis.

Results: Our cohort included 54 patients with CS (stage III, n = 32; stage IV, n = 22), 54 patients with UPSC/CC (stage III, n = 20; stage IV, n = 34) and 60 patients with EC (stage III, n = 45; stage IV, n = 15). R0 was achieved in 64% of patients with CS, in 53% of patients with UPSC/CC and in 68% of patients with EC. There was no interaction between histologic subtype and feasibility of complete cytoreduction ($p = 0.39$). R0 was associated with a median OS of 25 months (95% CI [18, 33]) versus 13 months (95% CI [8, 18]) in patients with gross RD ($p = 0.03$). This effect was uniform among histologic subtypes. On multivariate analysis, predictors of increased mortality were gross residual disease (HR = 2.0, 95% CI [1.1, 3.7], $p = 0.01$), stage IV (HR = 1.8, 95% CI [1.1, 3.1], $p = 0.02$) and age (HR = 1.04 per year of age, 95% CI [1.02, 1.07], $p = 0.002$).

Conclusion: Cytoreductive surgery to R0 is associated with improved OS in advanced uterine cancer. This effect is uniform among histologies. There is no interaction between histologic subtype and feasibility of complete cytoreduction.

1. Introduction

Uterine corpus cancer is the most common gynecologic malignancy in the United States and approximately 40,000 women are diagnosed each year. In the majority of cases, disease is confined to the uterus, but in approximately 20% of patients, tumor spreads to pelvic lymph nodes or distant sites. Patients with advanced disease have poor response rates to current treatment modalities and optimal management is ill defined [13]. Patients with Stage III–IV disease, more specifically, account for more than 50% of

* Corresponding author. 450 Clarkson Avenue, Box 25, Brooklyn, NY 11203, USA.
E-mail address: alagkiozidis@gmail.com (I. Alagkiozidis).

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uterine cancer-related deaths, with Stage IV disease being associated with five-year survival rates as low as 10%. Although an inverse correlation between diameter of residual disease and survival in ovarian cancer is well established, the benefit of aggressive cytoreductive surgery in uterine cancer is questionable [17]. Furthermore, complete gross cytoreduction often requires extensive surgical procedures that may lead to perioperative complications with negative impact on life expectancy and quality of life.

In theory, resection of large tumor mass facilitates tumor perfusion and drug delivery since smaller residual nodules are better vascularized. Reduction in tumor volume also decreases the possibility of mutations that promote drug resistance (Goldie–Coldman model). Furthermore, the population of residual cancer cells demonstrates increased growth fraction and is more sensitive to chemotherapy [1,2,18]. The goal of the current study is to investigate the survival benefit of complete gross cytoreduction (R0) in patients with advanced uterine cancer. The therapeutic effect of debulking surgery is linked to the sensitivity of cancer cells to adjuvant chemotherapy. The various histologic types of uterine cancer demonstrate distinct biology, patterns of spread and response to chemotherapy [9,11,12,14,19]. Interestingly, our patient cohort includes equal numbers of the three most common histologic types that account for more than 95% of uterine malignancies (Type I and II endometrial adenocarcinoma and CS). Therefore, an analysis of the interaction between histologic subtype and role of cytoreductive surgery is feasible.

2. Materials and methods

After IRB approval, we retrospectively identified 168 patients with FIGO 2009 Stage III–IV Type I and II endometrial and CS who underwent primary cytoreductive surgery between 1984 and 2009 in two major teaching institutions in Brooklyn, New York. Clinical characteristics including age at diagnosis, performance status (PS), race, tumor stage, tumor histology, and adjuvant therapies were abstracted from our chart review. Surgical characteristics including volume of residual disease and procedures performed were collected from the operative reports. Overall survival (OS) was defined as the interval from the date of primary surgery to the date of death or last follow-up.

Kaplan–Meier (KM) plots of survival stratified by residual disease status were constructed for all subjects and for each histologic subtype separately; log-rank tests of difference between RD categories were conducted. A test of homogeneity of survival differences among histologies was conducted. Proportional hazards (PH) regression (Cox analysis) was used to predict survival from disease stage (III v IV) & grade (1, 2 v 3), race (African American v other), adjuvant therapy, RD status, age and histologic subtype. Adjusted HRs are reported with 95% confidence intervals (CIs). Statistical analyses were performed using SAS (SAS Institute, Cary NC) Release 9.3.

In order to further delineate the independent effect of the surgical intervention, patients who underwent surgery after 2000, when a more comprehensive surgical approach was adapted in our institution, were compared to those that were operated before 2000. Operative, demographic and tumor characteristics between the two groups were compared (Chi-Square). OS was compared with the use of long-rank test.

3. Results

3.1. Patient characteristics

We retrospectively identified 168 patients who underwent primary surgery for advanced uterine cancer between 1984 and 2009 in two teaching hospitals in Brooklyn, New York.

All patients underwent a primary attempt for surgical cytoreduction. The median age of the patient population was 66 years (range 31–92 years). The majority of the study population was black (89%). 125 patients (74%) had a GOG performance status (PS) of 0 at the time of surgery, while 24 (14%) had a PS of 1, nine patients (5%) had a PS of 2 and three patients (2%) had a PS of 3. There was no interaction between PS and feasibility of complete gross cytoreduction (R0 in 64% of patients with PS 0 vs 58% of patients with PS 1–3, $p = 0.38$).

The histologic subtypes were as follows: EC, 60 patients; UPSC/CC, 54 patients; CS, 54 patients. Tumors were classified as Grade 3 (poorly differentiated) in 83% of the patients, Grade 2 (moderately differentiated) in 13% of the patients, and Grade 1 (well-differentiated) in 3% of the patients. The stage distribution was as follows: Stage III, 97 patients (58%); Stage IV, 71 patients (42%) (Table 1).

3.2. Surgical results

All 168 patients underwent primary surgical exploration. Hysterectomy was accomplished in 89% of patients (150/168). Seven patients underwent radical hysterectomy. Lymph node dissection, pelvic, para-aortic or both was performed in 114 patients. Omentectomy was performed in 98 patients. Among the procedures that were performed there were 20 bowel resections, one splenectomy, one resection of a liver segment and one diaphragmatic resection. Overall, 105 of 168 patients (63%) completed primary surgery with R0 status. For the suboptimally debulked patients, the most common sites of residual disease were the pelvis (61%), mid-abdomen (35%), and upper abdomen (35%) (Table 2).

3.3. Adjuvant therapy

A total of 95 patients (57%) received postoperative chemotherapy. A combination of paclitaxel and platinum was administered in 37 patients. Other chemotherapeutic agents were

Table 1
Patient and tumor characteristics.

Patient characteristics	N	%
All	168	100
Vital status		
Alive	43	25
Dead	125	75
Age at diagnosis		
Median	66	
Range	31–92	
Performance status (GOG)		
0	125	74
1	24	14
2	9	5
3	3	2
Grade		
=1	7	4
=2	22	13
=3	139	83
Stage		
III	97	58
IV	71	42
Histologic subtype		
Adenocarcinoma	60	36
MMMT	54	32
Serous/Clear cell	54	32
Adjuvant treatment		
Chemotherapy	95	57
Radiation	73	43
None	32	19
Unknown	7	4