Factors prognostic of survival in advanced-stage uterine serous carcinoma ☆

Laura L. Holman [a], Navdeep Pal [a], David A. Iglesias [a], Pamela T. Soliman [a], Nyla Balakrishnan [a], Ann Klopp [b], Russell R. Broaddus [c], Nicole D. Fleming [a], Mark F. Munsell [d], Karen H. Lu [a], Shannon N. Westin [a,*]

[a] Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, United States
[b] Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, United States
[c] Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, United States
[d] Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, United States

HIGHLIGHTS

- Retrospective review of 260 patients with stage III or IV uterine serous carcinoma
- Treatment group and stage were predictors of survival on multivariate analysis.
- The prognosis for women with advanced USC is poor regardless of treatment received.

ARTICLE INFO

ABSTRACT

Objectives. The study objective was to analyze the impact of prognostic factors, including treatment modality, on outcome in patients with advanced-stage uterine serous carcinoma (USC).

Methods. A retrospective review of patients diagnosed with stage III or IV USC between 1993 and 2012 was performed. Summary statistics were used to describe demographic and clinical characteristics. Overall survival (OS) and recurrence free survival (RFS) were estimated by Kaplan-Meier analysis. Cox proportional hazards regression was used to model the association of potential prognostic factors with OS and RFS.

Results. The study included 260 patients with median follow-up of 26.6 months (range 1–172.8). Median age was 63 years (range 30–88) and 52.3% had stage III disease. In all, 60% were treated with surgery followed by chemotherapy, 18.1% received surgery, chemotherapy, and radiotherapy, 11.5% had surgery and radiotherapy, and 10.4% had neoadjuvant chemotherapy. The overall complete response rate was 68.9%, and the cumulative incidence of recurrence was 82.7%. Treatment that included surgery, chemotherapy, and radiation and stage III disease were associated with improved RFS on multivariate analysis. For OS, therapy with surgery, chemotherapy, and radiation, mixed histology, and stage III disease were associated with better OS on multivariate analysis.

Conclusions. Patients with advanced-stage USC have a poor prognosis, regardless of clinical factors or treatment received. However, combination therapy that includes chemotherapy and radiation appears to be associated with improved survival in these women.

© 2017 Elsevier Inc. All rights reserved.

1. Introduction

Of the more than 60,000 new cases of endometrial cancer in 2016, approximately 10% were diagnosed with uterine serous carcinoma (USC) [1,2]. USC is a high-grade histologic subtype of endometrial adenocarcinoma characterized by its aggressive nature. While only 16% of endometrioid endometrial cancer cases are advanced stage at diagnosis, up to 38% of women with USC are stage III or IV. Even in cases with little or no myometrial invasion, extrauterine metastases are found at the time of surgery in up to 37% of patients [3,4]. For these reasons, this relatively rare tumor accounts for up to 50% of all endometrial cancer-related deaths [5,6].

Though women with USC are typically included in prospective endometrial cancer trials, they tend to make up only a small number of patients. This can lead to difficulty in making meaningful conclusions

regarding USC from the results of these studies. Additionally, the vast majority of USC-only studies are retrospective, with small numbers that include patients with all stages of disease. However, as with most malignancies, the prognosis for women with USC varies widely by stage. While the 5-year survival for patients with stage IA disease is 81.5%, it is only 19.9% for stage IV disease [3].

Several authors have attempted to evaluate how various clinical variables affect survival among women with advanced stage USC [7–9]. However, the majority of these studies were either small or included all stages of USC. The aim of the present study was to retrospectively assess potential prognostic factors among women with stage III or IV USC.

2. Materials and methods

A retrospective review was conducted of women with USC treated at The University of Texas MD Anderson Cancer Center between March 1993 and January 2012. This study was approved by the Institutional Review Board (IRB) of MD Anderson Cancer Center. As no data were collected prospectively, a waiver of informed consent was granted by the IRB.

To be included in the study, women must have had stage III or IV USC as defined by 2009 criteria published by the International Federation of Gynecology and Obstetrics (FIGO) [10]. For the purposes of this study, patients who were diagnosed prior to 2009 had their cancer re-staged. All pathology had been previously confirmed by a gynecologic pathologist at MD Anderson Cancer Center. Any tumor with >5% serous component was included. Women with inadequate data in the medical record, synchronous primary tumors, or carcinosarcoma were excluded.

Demographic information and medical history were abstracted from the medical record. Patients were divided into one of four groups based upon the primary treatment they received: 1) neoadjuvant chemotherapy, 2) surgery and chemotherapy, 3) surgery and radiotherapy, or 4) surgery, radiotherapy, and chemotherapy. Neoadjuvant chemotherapy was defined as women who received any chemotherapy immediately after diagnosis, with or without interval tumor reductive surgery. To be included in the surgery and chemotherapy group, women must have had primary tumor reductive surgery followed by any chemotherapy. Women in the surgery and radiotherapy group underwent primary tumor reductive surgery followed by radiation treatment with or without concurrent chemotherapy. The radiation may have included vaginal brachytherapy, whole pelvic radiation, or both. The surgery, radiotherapy, and chemotherapy group had primary surgery followed by treatment with any radiation with or without concurrent chemotherapy and adjuvant chemotherapy. A small number of women did not fall into any of the defined treatment groups as they did not receive any treatment ($n = 2$), underwent surgery alone ($n = 18$), or received radiation alone ($n = 2$) and were lost to follow-up. These women were excluded from the analysis. Patients were considered to have a recurrence if it was documented from physical examination or imaging findings. Complete response was defined as no evidence of disease by exam or imaging at the completion of therapy.

Summary statistics were utilized to describe demographic and clinical characteristics. Fisher's exact test was used to compare treatment groups with respect to categorical demographic and clinical characteristics. The Kruskal-Wallis test was used to compare medians of groups with respect to demographic and clinical characteristics measured on a continuous scale.

Time to recurrence (TTR) was defined as the time from the start of treatment to the date of recurrence. Patients were censored on the date of their last clinic visit, and death was considered a competing event. Cumulative incidence of recurrence was estimated using the methods of Gooley et al. [11]. The methods of Fine and Gray were used to model the cumulative incidence of recurrence as a function of treatment, with death as a competing event [12]. Overall survival (OS) was defined as the time from the date treatment started to the date of death or last contact. Patients alive at last contact were censored on that date. Recurrence-free survival (RFS) was defined as the time from the date treatment started to the date of recurrence, date of the last clinic visit, or the date of death. Patients were censored on the date of the last clinic visit. For RFS, recurrence and death from any cause were considered events. OS and RFS were estimated with the product-limit estimator of Kaplan and Meier [13]. Cox proportional hazards regression was used to model the association of potential prognostic factors with OS and RFS in a univariate fashion [14]. All factors with a p-value < 0.25 were then used in a saturated, multivariate model and backward elimination was used to remove factors one at a time until only those with a p-value of ≤0.05 remained. Type of adjuvant chemotherapy, CA125 at diagnosis, and platelet level at diagnosis were not considered in the multivariate models as there were too many missing values. All analyses were performed with SAS 9.3 for Windows (Copyright©

Table 1
Participant characteristics by treatment group.

	Neoadjuvant chemo % ($n = 27$)	Surgery/chemo % ($n = 156$)	Surgery/radiation % ($n = 30$)	Surgery/radiation/chemo % ($n = 47$)	p
Age					0.279
Median	66.3	63.2	65.5	60.0	
(Range)	(46–81)	(30–82)	(38–88)	(40–78)	
Race					**0.008**
White	29.6 (8)	71.2 (111)	76.7 (23)	72.3 (34)	
African-American	48.2 (13)	16.7 (26)	13.3 (4)	12.8 (6)	
Hispanic	14.8 (4)	6.4 (10)	10 (3)	8.5 (4)	
Asian	7.4 (2)	5.1 (8)	0 (0)	6.4 (3)	
Other	0 (0)	0.6 (1)	0 (0)	0 (0)	
BMI					0.216
Median	29.2	29.6	26.1	29.6	
(Range)	(18.1–68.8)	(17.5–105)	(18.7–39.9)	(17.8–45)	
Stage					**<0.001**
IIIA	0 (0)	6.4 (10)	13.3 (4)	19.2 (9)	
IIIB	0 (0)	1.3 (2)	0 (0)	8.5 (4)	
IIIC1	0 (0)	14.7 (23)	40 (12)	36.2 (17)	
IIIC2	0 (0)	21.2 (33)	30 (9)	27.7 (13)	
IVA	7.4 (2)	1.9 (3)	0 (0)	0 (0)	
IVB	81.5 (22)	54.5 (85)	16.7 (5)	8.5 (4)	
Unstaged	11.1 (3)	0 (0)	0 (0)	0 (0)	
Histology					**0.002**
Pure USC	70.4 (19)	36.5 (57)	23.3 (7)	31.9 (15)	
Mixed	29.6 (8)	63.5 (99)	76.7 (23)	68.1 (32)	

Significant p values are in bold.