Role of surgical staging and adjuvant treatment in uterine serous carcinoma

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Summary

Purpose of investigation: This study evaluates the association of clinical and pathologic characteristics of patients with uterine serous carcinoma (USC) with disease recurrence. *Materials and Methods:* Surgically-staged patients with USC at a single institution were identified and clinical and pathologic variables were compared. *Results:* Of the 51 patients included in this analysis, 75% percent received adjuvant chemotherapy, 51% received radiation therapy, and 47% received both. After a median follow-up of 33 months, 42% of patients had disease recurrence. On multivariable analysis, positive pelvic lymph nodes were associated with a shorter interval between surgery and recurrence: 13.6 months progression-free survival (PFS) with positive vs 17.2 months with negative lymph nodes ($p = 0.05$). Patients with early-stage disease who did not receive any adjuvant treatments had a significantly greater risk of disease recurrence (44.4% vs 7.70%, $p = 0.043$). *Conclusion:* In this population of surgically-staged patients with USC, pelvic lymph node metastases were predictive of a shorter PFS.

Key words: Uterine serous carcinoma; Surgical staging; Adjuvant therapy.

Introduction

Endometrial cancer is the most common gynecologic malignancy in the United States with approximately 40,000 new cases diagnosed each year [1]. Endometrial tumors are divided into type I and type II malignancies, a dualistic classification based upon distinct molecular features, pathogenesis, and clinical outcomes. Type I malignancies are endometrioid tumors that are driven by estrogen and generally diagnosed at an early stage, while type II malignancies have high-grade serous or clear cell features, often present at advanced stages at the time of diagnosis, and are associated with poor prognosis [2].

Uterine serous carcinoma (USC), the most common of the type II endometrial cancers, was described as a distinct entity from endometrioid endometrial cancer (EEC) in 1982 [3]. USC is histologically similar to serous epithelial ovarian cancer with a propensity for peritoneal spread and approximately 40% chance of being diagnosed at Stage III or IV disease. Stage for stage, USC is associated with worse prognosis as compared to EEC [4]. While representing less than ten percent of all endometrial cancer cases, USC accounts for 40% of all endometrial cancer-related deaths [5, 6]. Comprehensive surgical staging as per the International Federation of Gynecology and Obstetrics (FIGO) guidelines is indicated in patients with USC [7]. Many gynecologic oncologists have adopted staging and debulking procedures similar to ovarian cancer and routinely perform peritoneal biopsies and omentectomy. Given the relatively high risk of both local and distant relapse in USC, the National Comprehensive Cancer Network treatment guidelines advocate a combined modality approach with chemotherapy and radiation therapy [8].

In USC in contrast to EEC, the risk of extrauterine spread remains high despite the absence of traditional risk factors such as deep myometrial invasion or lymphovascular space invasion [9]. Elevated serum CA125 has been shown to correlate with metastatic disease, but its use in USC as a biomarker has not been validated in prospective studies [10, 11]. It remains unclear whether prognostic variables for recurrence in type I endometrial tumors, such as age, myometrial invasion, lymphovascular space invasion (LVSI), tumor size, disease stage, and type of therapy are relevant in type II endometrial disease [12]. This study examines the demographic and clinical variables of USC patients to determine if any significantly impact disease recurrence or progression-free survival (PFS).

Materials and Methods

A retrospective clinical review was conducted of patients undergoing surgery for endometrial cancer between 2002 and 2008 at a single, urban, university hospital. Patients with Stage I-IV USC who had undergone complete surgical staging at the present institution were included. Patients who had undergone neoadjuvant chemotherapy and those diagnosed with synchronous gynecologic malignancies were excluded. Approval for this study was obtained from the Institutional Review Board.

Clinical and pathologic variables were abstracted from hospital medical records and the pathology database. The following clinical information was extracted for all patients undergoing surgical staging for USC: age at diagnosis, gravidy, parity, body mass index (BMI), FIGO disease Stage, adjuvant

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chemotherapy, radiation therapy, and time to progression. Pathology outcomes collected included depth of myometrial invasion, LVSI, positive pelvic cytology, extension to the cervix, ovaries, fallopian tubes, omentum, appendix, and pelvic and para-aortic lymph nodes, and number of pelvic and para-aortic lymph nodes harvested.

Data were analyzed using IBM SPSS Statistics 19. Kolmogorov-Smirnov test was used to examine outcome variable distributions for normality. Clinical and pathologic variables were compared using independent sample t-tests for normally distributed continuous data and Mann-Whitney U tests for non-normally-distributed continuous variables. Chi-squared and Fisher's exact test were used for categorical variables. Multiple logistic regression was used to assess disease recurrence with the odds ratio, 95% confidence interval, and *p* value reported for each variable. Multiple linear regression was used to assesses PFS, which was defined as the time interval from the date of surgery to the date of the documented first recurrence or progression of disease. For linear regression analysis unstandardized B, *p* value and 95% confidence interval are reported. The unstandardized B represents the effect of an independent variable on the dependent variable, statistically controlling for the effects of the other independent variables. Type I error threshold was set at a *p* value of less than 0.05 for all tests.

Results

Sixty-five patients with USC were identified during the study period from hospital databases. Fourteen patients had incomplete medical records or primary surgery performed at an outside institution and were excluded from further analysis. The remaining 51 patients are included in this analysis. Disease distribution was as follows: 22-Stage I, 5-Stage II, 16-Stage III, and 8-Stage IV. The mean age at diagnosis was 67 years. Patient demographic variables are presented in Table 1. Thirty-eight (75%) patients received adjuvant chemotherapy, 82% of which received a regimen of combined carboplatin and paclitaxel. Twenty-six (51%) patients received postoperative radiation therapy (10% external beam pelvic radiotherapy, 18% vaginal brachytherapy, and 24% both). Twenty-four patients (47%) received combination chemotherapy and radiation therapy. Three patients (6%) received neither adjuvant chemotherapy or radiation therapy. After a median follow-up of 33 months, 42% of patients had disease recurrence. The median time to recurrence was 14 months (range 1.6 - 53.8).

Stage of disease was found to significantly affect disease recurrence. Seventy-three percent of patients with Stage III or Stage IV disease recurred (median 15.3 months) vs 21% for patients with Stage I or Stage II disease (median 26.6 months) ($p < 0.001$). Univariate analysis demonstrated multiple pathologic features that were predictive of disease recurrence, including LVSI ($p = 0.03$), positive pelvic cytology ($p = 0.05$), disease extension to serosa ($p = 0.004$), adnexa ($p = 0.001$), omentum ($p < 0.001$), and appendix ($p = 0.03$). Furthermore, three pathologic features were significantly associated with a shorter PFS, the presence of LVSI (17.9 vs 18.2 months, $p = 0.03$), disease extension to the serosa (12.4 vs 15.2 months, $p = 0.04$), and positive cytology (12.0 vs 23.5 months, $p = 0.05$).

Table 1. — *Patient demographics.*

Age at diagnosis (mean, standard deviation)		67 (13)
Body mass index (mean, standard deviation)		28 (7)
Stage no. (%)	I	22 (43)
	II	5 (10)
	III	16 (31)
	IV	8 (16)
Depth of invasion (mm) (mean, standard deviation)		44 (35)
Sites of extrauterine disease, no. (%)	Myometrial invasion	42 (84)
	Lymphovascular space invasion	30 (59)
	Cervix	18 (35)
	Ovaries	13 (26)
	Fallopian tubes	13 (26)
	Omentum	8 (15)
	Appendix	4 (8)
	Pelvic lymph nodes	8 (16)
	Para-aortic lymph nodes	2 (4)
# Total lymph nodes		12.7 (14.2)
	# Pelvic lymph nodes (mean, SD)	11.5 (12.6)
	# Para-aortic lymph nodes (median, range)	1.2 (0-10)
Adjuvant chemotherapy, no. (%)		38 (75)
	Paclitaxel/carboplatin	31 (61)
	Paclitaxel/cisplatin	1 (2)
	Doxorubicin/cisplatin	1 (2)
	Carboplatin	2 (4)
	Cyclophosphamide/cisplatin	1 (2)
	Unknown	2 (4)
Adjuvant radiation therapy, no. (%)		26 (51)
	External beam	5 (10)
	Vaginal brachytherapy	9 (18)
	External beam and vaginal Brachytherapy	12 (24)

On multivariable analysis, there were no independent significant predictors of disease recurrence; however the presence of LVSI approached significance ($p = 0.066$). Patients with LVSI were approximately 11 times more likely to recur than those without LVSI (Table 2). On multivariable analysis of PFS, only positive pelvic lymph nodes were associated with a shorter interval between surgery and recurrence: 13.6 months PFS with positive lymph nodes vs 17.2 months PFS with negative lymph nodes ($p = 0.046$, Table 3).

Finally, the role of adjuvant treatment in this cohort of patients was examined. Among patients with both early Stage (Stages I/II) and advanced disease (Stages III/IV), the authors found no difference in disease recurrence or PFS for patients who received chemotherapy or radiation therapy. The only significant finding among the adjuvant therapy data was that patients with early-stage disease who received neither radiation therapy nor chemotherapy had a significantly greater risk of disease recurrence (44.4% vs 7.70%, $p = 0.043$).

Table 2. — *Multivariable analysis of disease recurrence.*

	Odds ratio (95% CI)	*p* value
Depth of invasion	1.0 (0.8 - 1.1)	0.8
Disease extension		
Lymphovascular space	11.3 (0.9 - 150.2)	0.1
Serosa	229.5 (0.4 - 144619.2)	0.1
Cervix	1.0 (0.1 - 9.3)	1.0
Adnexa	0.9 (0.0 - 17.6)	0.9
Pelvic lymph nodes	32.9 (0.5 - 2303.4)	0.1
Adjuvant chemotherapy	0.4 (.02 - 6.4)	0.5
Adjuvant radiation therapy	0.4 (0.0 - 5.0)	0.5

Multiple logistic regression analysis of disease recurrence using adjusted odds ratio, 95% confidence interval, and *p* value to demonstrate significance.

Table 3. — *Multivariable analysis of progression-free survival (months).*

	Unstandardized B (95% Confidence Interval)	*p* value
Depth of invasion	1.0 (-0.7 - 2.8)	0.2
Disease extension		
Lymphovascular space	4.0 (-26.4 - 34.4)	0.7
Serosa	1.7 (-35.3 - 38.7)	0.9
Cervix	-6.5 (-36.8 - 23.7)	0.5
Adnexa	-11.9 (-58.5 - 34.8)	0.5
Pelvic lymph nodes	-28.8 (-56.7 - -0.9)	< 0.05
Adjuvant chemotherapy	-6.5 (-38.8 - 25.9)	0.6
Adjuvant radiation therapy	7.0 (-17.5 - 31.4)	0.4

Multivariable linear regression analysis of months of progression-free survival using unstandardized B, 95% confidence interval and *p* value to demonstrate significance. The unstandardized B represents the effect of an independent variable on the dependent variable, statistically controlling for the effects of the other independent variables. An unstandardized B less than 0 (negative number) indicates that the variable is associated with a shortening of the progression-free survival.

Discussion

USC is an aggressive subtype of endometrial cancer with a propensity for intra-abdominal spread and distant metastases [4]. Despite multiple proposed treatment strategies, including pelvic radiation therapy, whole abdominopelvic radiation therapy, single agent or combination chemotherapy, or combination chemo-radiation, the optimal management after surgery remains unclear [13]. Due to the high-risk of metastatic disease even in the absence of deep myometrial invasion, comprehensive surgical staging is recommended. Christman *et al*. discovered that 50% of USC cases were upstaged after surgical staging was performed [14].

Despite the trend towards comprehensive staging in USC, there is currently inadequate data to use pathologic information to guide adjuvant treatment or to develop a prognostic prediction model. It is well-established from retrospective studies that patients with advanced-stage disease have higher risks of recurrence and disease-related mortality [4]. However, even patients with early-stage disease or disease limited to the uterus have significant risks of recurrence. In the present study, 21% of patients with Stage I or II disease recurred in a median time of 26.6 months. The established risk-assessment models used in type I endometrial cancers to guide adjuvant chemotherapy and/or radiation therapy are less effective in USC. Prior studies suggest that increasing age, Stage of disease, depth of myometrial invasion, and LVSI may be pathologic determinants of poor prognosis in USC [15, 16]. The present study confirmed some of these risk factors in addition to positive pelvic cytology. On multivariable analysis, positive pelvic lymph nodes were independently associated with a shorter PFS. This highlights the importance of complete surgical staging in this disease subtype even in the absence of high-risk uterine features.

Adjuvant therapy remains a controversial topic in USC without adequate prospective data to guide practice patterns. Due to the poor survival outcomes and the high-risk of extrapelvic recurrence [8], many gynecologic oncologists recommend adjuvant treatment after surgery. Chemotherapy with radiotherapy (external beam and/or vaginal brachytherapy) is routinely offered in the adjuvant setting to patients with newly diagnosed USC at the present institution. In this study, the authors were unable to demonstrate a benefit in the rate of recurrence or PFS with chemotherapy or radiation therapy alone or in combination. It is interesting to note that patients with Stage I/II disease who did not undergo adjuvant treatment had a significantly higher risk of disease recurrence.

The optimal treatment of USC remains unclear as currently there are no randomized studies, and the existing retrospective studies are limited by a heterogeneous patient population and diverse adjuvant therapy protocols [13]. Some groups have demonstrated a response to platinum-based chemotherapy in USC [15, 17, 18]. Whole abdominal radiation therapy was first proposed in the 1980s but resulted in severe toxicities with minimal evidence of response [19-22]. Pelvic external-beam radiation therapy with or without vaginal brachytherapy has shown to decrease pelvic recurrences in single-institution studies [23]. More recently, a single-institution, Phase II study of multimodality treatment in USC patients with no visible residual disease after surgery showed a significantly increased three-year survival in low (Stage I/II) and high (Stage III/IV) stage patients as compared to historical controls. “Sandwich” therapy comprising of carboplatin and paclitaxel for three cycles followed by radiation followed by another three chemotherapy cycles was overall well-tolerated in this patient population [24].

Conclusion

The authors acknowledge the limitations of the current study, including the retrospective study design and small number of patients. Both limit the ability to draw definitive conclusions about the prognostic variables and the role of adjuvant treatments. However, despite the limited sample size, this study further highlights the aggressive clinical course of patients with USC. Known prognostic variables for EEC have limited validity in patients with USC and are not as helpful in guiding treatment decisions or discussions of prognosis with patients. More scientific studies are needed to identify the biological mechanisms that portend

a more aggressive course for this disease. In addition, multi-center prospective studies that include only patients with USC are urgently needed to identify chemotherapy and biologic agents that will affect recurrence and overall survival in this patient population.

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