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Impact of adjuvant therapy on recurrence patterns in stage I uterine carcinosarcoma

Koji Matsuo [a,*], Kohei Omatsu [b], Malcolm S. Ross [c], Marian S. Johnson [d], Mayu Yunokawa [e], Merieme M. Klobocista [f], Dwight D. Im [g], Stephen H. Bush [h], Yutaka Ueda [i], Tadao Takano [j], Erin A. Blake [k], Kosei Hasegawa [l], Tsukasa Baba [m], Masako Shida [n], Shinya Satoh [o], Takuhei Yokoyama [p], Hiroko Machida [a], Sosuke Adachi [q], Yuji Ikeda [r], Keita Iwasaki [s], Takahito M. Miyake [t], Shiori Yanai [u], Masato Nishimura [v], Tadayoshi Nagano [w], Munetaka Takekuma [x], Satoshi Takeuchi [y], Tanja Pejovic [z], Mian MK Shahzad [h], Frederick R. Ueland [d], Joseph L. Kelley [c], Lynda D. Roman [a]

[a] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Southern California, CA, USA
[b] Department of Gynecology, Cancer Institute Hospital, Tokyo, Japan
[c] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Magee-Womens Hospital, University of Pittsburgh, PA, USA
[d] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Kentucky, KY, USA
[e] Department of Breast and Medical Oncology, National Cancer Center Hospital, Tokyo, Japan
[f] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Albert Einstein College of Medicine, Montefiore Medical Center, NY, USA
[g] The Gynecologic Oncology Center, Mercy Medical Center, Baltimore, MD, USA
[h] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Moffitt Cancer Center, University of South Florida, FL, USA
[i] Department of Obstetrics and Gynecology, Osaka University, Osaka, Japan
[j] Department of Obstetrics and Gynecology, Tohoku University, Miyagi, Japan
[k] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Colorado, CO, USA
[l] Department of Obstetrics and Gynecology, Saitama Medical University International Medical Center, Saitama, Japan
[m] Department of Obstetrics and Gynecology, Kyoto University, Kyoto, Japan
[n] Department of Obstetrics and Gynecology, Tokai University, Kanagawa, Japan
[o] Department of Obstetrics and Gynecology, Tottori University, Tottori, Japan
[p] Department of Obstetrics and Gynecology, Osaka Rosai Hospital, Osaka, Japan
[q] Department of Obstetrics and Gynecology, Niigata University, Niigata, Japan
[r] Department of Obstetrics and Gynecology, The University of Tokyo, Tokyo, Japan
[s] Department of Obstetrics and Gynecology, Aichi Medical University, Aichi, Japan
[t] Department of Obstetrics and Gynecology, Kawasaki Medical School, Okayama, Japan
[u] Department of Obstetrics and Gynecology, Kurashiki Medical Center, Okayama, Japan
[v] Department of Obstetrics and Gynecology, Tokushima University, Tokushima, Japan
[w] Department of Obstetrics and Gynecology, Kitano Hospital, Osaka, Japan
[x] Department of Obstetrics and Gynecology, Shizuoka Cancer Center, Shizuoka, Japan
[y] Department of Obstetrics and Gynecology, Iwate Medical University, Iwate, Japan
[z] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Oregon Health & Science University, OR, USA

HIGHLIGHTS

- Stage I uterine carcinosarcoma (UCS) has a high incidence of distant recurrence.
- Adjuvant chemotherapy may be effective to decrease both local/distant recurrences.
- Adding radiotherapy to chemotherapy may be effective if tumor has ≥2 risk factors.

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ABSTRACT

Background. To examine recurrence patterns in women with stage I uterine carcinosarcoma (UCS) stratified by adjuvant therapy pattern.

* Corresponding author at: Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Southern California, 2020 Zonal Avenue, IRD520, Los Angeles, CA 9033, USA.
E-mail address: koji.matsuo@med.usc.edu (K. Matsuo).

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Methods. We examined 443 cases of stage I UCS derived from a retrospective cohort of 1192 UCS cases from 26 institutions. Adjuvant therapy patterns after primary hysterectomy-based surgery were correlated to recurrence patterns.

Results. The most common adjuvant therapy was chemotherapy alone (41.5%) followed by chemotherapy/radiotherapy (15.8%) and radiotherapy alone (8.4%). Distant-recurrence was the most common recurrence pattern (5-year cumulative rate, 28.1%) followed by local-recurrence (13.3%). On multivariate analysis, chemotherapy but not radiotherapy remained an independent prognostic factor for decreased risk of local-recurrence (5-year cumulative rates 8.7% versus 19.8%, adjusted-hazard ratio [HR] 0.46, 95% confidence interval [CI] 0.25–0.83, $P = 0.01$) and distant-recurrence (21.2% versus 38.0%, adjusted-HR 0.41, 95%CI 0.27–0.62, $P < 0.001$). The chemotherapy/radiotherapy group had a lower 5-year cumulative local-recurrence rate compared to the chemotherapy alone group but it did not reach statistical significance (5.1% versus 10.1%, adjusted-HR 0.46, 95%CI 0.13–1.58, $P = 0.22$). Radiotherapy significantly decreased local-recurrence when tumors had high-grade carcinoma, sarcoma component dominance, and deep myometrial tumor invasion (all, $P < 0.05$); and combining radiotherapy with chemotherapy was significantly associated with decreased local-recurrence compared to chemotherapy alone in the presence of multiple risk factors (5-year cumulative rates, 2.5% versus 21.8%, HR 0.12, 95%CI 0.02–0.90; $P = 0.013$) but not in none/single factor ($P = 0.36$).

Conclusion. Adjuvant chemotherapy appears to be effective to control both local- and distant-recurrences in stage I UCS; adding radiotherapy to chemotherapy may be effective to control local-recurrence when the tumor exhibits multiple risk factors.

1. Introduction

Uterine carcinosarcoma is a rare but aggressive high-grade endometrial cancer, representing a biphasic tumor with the sarcoma element being dedifferentiated from the carcinoma component [1–6]. The majority of uterine carcinosarcomas are diagnosed as stage I disease, and surgery with total hysterectomy, salpingo-oophorectomy, and lymphadenectomy remains the standard primary treatment approach [7,8]. Due to poor survival outcome even in stage I disease [9,10], adjuvant therapy after primary surgical treatment is an important consideration in the management of uterine carcinosarcoma [7,8].

Various studies have demonstrated the effectiveness of postoperative systemic chemotherapy for early-stage uterine carcinosarcoma [11,12]. This approach is based on the rationale that stage I disease can develop substantially high incidence of distant-recurrence in the absence of adjuvant chemotherapy [12]. A large-scale nation-wide study has shown a recent increase in the use of chemotherapy and chemo-radiotherapy for early-stage uterine carcinosarcoma [13]. This study also demonstrated that chemotherapy and chemo-radiotherapy were associated with improved survival compared to no treatment for early-stage uterine carcinosarcoma; however, no direct comparison was performed between chemotherapy alone and chemo-radiotherapy, making it difficult to evaluate the role of adding radiotherapy to chemotherapy in the management of stage I uterine carcinosarcoma [13].

Because the role of adjuvant radiotherapy is questionable for early-stage uterine carcinosarcoma in controlling local recurrence in women who also receive chemotherapy [11,13–18], identifying the predictors of radiotherapy response will be useful to maximize the benefit of radiotherapy and minimize the adverse effects related to this treatment modality. The objective of the study was to examine recurrence patterns and survival outcome of women with stage I uterine carcinosarcoma who received adjuvant therapy with chemotherapy and radiotherapy.

2. Patients and methods

2.1. Eligibility

We utilized the previously organized dataset for uterine carcinosarcoma from a multi-center international study that was conducted in 26 academic and/or regional cancer centers in the United States and Japan [19,20]. In this large-scale multicenter collaboration, consecutive cases of stages I–IV uterine carcinosarcoma were retrospectively reviewed for histopathology findings. We obtained Institutional Review Board approval at each participating institution. Inclusion criteria were consecutive cases of stage I uterine carcinosarcoma that underwent primary hysterectomy-based surgical treatment with available adjuvant therapy information between 1993 and 2013. Exclusion criteria included stages II–IV disease, neoadjuvant radiotherapy or chemotherapy, no hysterectomy status, incorrect diagnosis, and absence of archived histopathology slides for evaluation. The STROBE guidelines were consulted to outline the results of retrospective cohort studies [21].

2.2. Clinical information

We abstracted the following information from archived medical records for the eligible cases: patient demographics, histopathology results, treatment type, and survival outcomes. For patient demographics, patient age at surgery, country, ethnicity, body mass index (BMI), parity, and preoperative CA-125 level were collected. Histopathologic findings included carcinoma type, sarcoma element, dominant histology component, cancer stage, tumor size, lymphovascular space invasion (LVSI), and depth of myometrial tumor invasion. Treatment information abstracted included: use of neoadjuvant therapy, and surgical details regarding hysterectomy and pelvic/para-aortic lymphadenectomy, and type of postoperative adjuvant therapy. Adjuvant radiotherapy type included whole pelvic radiotherapy (WPRT) and intracavitary brachytherapy (ICBT). Adjuvant chemotherapy information included type and number of administered cycles. For survival outcomes, disease-free survival (DFS) and overall survival (OS) were recorded. Among recurrent cases, anatomical locations of the first recurrent site were abstracted.

2.3. Histologic evaluation

Gynecologic pathologists reviewed the archived histopathology hematoxylin-eosin and where available immunohistochemically stained slides at each participating institution to evaluate the histologic subtypes of carcinoma and sarcoma components [19]. We grouped the carcinoma components into low-grade (grades 1–2 endometrioid) and high-grade (grade 3 endometrioid, serous, clear cell, undifferentiated, and mixed histology) subtypes, and grouped the sarcoma components into homologous (endometrial stromal sarcoma, leiomyosarcoma, fibrosarcoma, and undifferentiated sarcoma) and heterologous (rhabdomyosarcoma, osteosarcoma, chondrosarcoma, and liposarcoma) subtypes. We examined the proportions of carcinoma and sarcoma components in a semi-quantitative fashion within the primary tumor site in the hysterectomy specimen.

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