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Editorial

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Surgical management of non-invasive uterine clear cell carcinoma

Toru Sugiyama, Satoshi Takeuchi, Hiroaki Itamochi

Department of Obstetrics and Gynecology, Iwate Medical University School of Medicine, Iwate, Japan

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Correspondence to
Toru Sugiyama
Department of Obstetrics and Gynecology, Iwate Medical University School of Medicine, 19-1 Uchimaru, Morioka, Iwate 020-8505, Japan.
E-mail: sugiyama@iwate-med.ac.jp

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ORCID iDs
Toru Sugiyama
https://orcid.org/0000-0002-2385-9040
Satoshi Takeuchi
https://orcid.org/0000-0001-8868-6462
Hiroaki Itamochi
https://orcid.org/0000-0002-7417-8595

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Uterine clear cell carcinoma (UCCC) is an uncommon and aggressive type II endometrial tumor that constitutes only 1%–6% of all endometrial carcinomas [1]. In 1976, its poor prognosis compared to endometrioid endometrial carcinoma was reported in a series of 21 cases by Kurman and Scully [2]. More recently, the International Federation of Gynecology and Obstetrics (FIGO) Annual Report 2006 indicated that the 5-year overall survival (OS) rate for UCCC was significantly lower than that for endometrioid carcinoma (62.5% vs. 83.2%) [3]. It is plausible that this difference in survival is related to the propensity of UCCC to spread to the uterus. For example, in a multi-institute review of patients with UCCC and no gross evidence of extrauterine disease, it was shown that 52% (39/69) had their disease upstaged at the time of surgery [4]. Similarly, Nguyen et al. [5] revealed that 46% (59/129) of patients with clinical stage I UCCC had extrauterine spread. These reports support the argument that UCCC can spread early, including to the lymph nodes and omentum.

Using the Surveillance, Epidemiology, and End Results (SEER) registry, the incidence of retroperitoneal lymph node involvement has been evaluated to identify the risk factors for lymphatic spread in patients with uterine papillary serous carcinoma (UPSC) and UCCC after complete surgical staging and lymph node dissection [6]. In this study, 29.0% (282/972) of patients had positive lymph nodes, of which 54.3% and 45.7% had pelvis-only lymph node involvement and para-aortic lymph node involvement, respectively. According to the FIGO 1988 criteria, the incidence of lymph node metastasis in early stage UCCC was 9.3% for stage IA disease, 12.8% for stage IB disease, and 39.2% for stage IC disease, and a lower 5-year OS rate was observed in patients with positive lymph nodes. These results suggest a potential role for therapy targeting lymph nodes in these patients.

Occult metastases of the omentum have been reported in patients with endometrial cancer that is grossly limited to the uterus [7]. Saygili et al. [8] found that 6% (6/97) of patients with clinical stage I endometrial carcinoma had omental metastasis. Of the 5 patients with UCCC included in their study, 2 (40%) had omental metastasis. By contrast, Thomas et al. [4] reported the absence of omental metastasis in a series of 99 patients with UCCC, although omentectomy was performed in 39 patients. In December 2014, a multidisciplinary meeting was held by the European Society for Medical Oncology (ESMO), European Society for Radiotherapy & Oncology (ESTRO), and European Society of Gynaecological Oncology

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(ESGO). Entitled "Consensus Conference on Endometrial Cancer," the outcome of discussion recommended that omentectomy should be employed for uterine serous carcinoma, but that it was not mandatory for UCCC or uterine carcinosarcoma [9]. Therefore, it is of debate whether omentectomy is a part of staging surgery in patients with UCCC.

In this issue of the *Journal of Gynecologic Oncology*, Sarı et al. [10] report the results of a multicenter, retrospective, departmental database review of patients with UCCC. The authors investigated the oncologic outcomes of patients surgically staged as having non-invasive UCCC (UCCC with no myometrial invasion) to assess the prognosis of those patients and the role of adjuvant therapy among them. In total, 7,495 women with uterine corpus cancer treated between 1997 and 2016 at 8 Gynecologic Oncology Centers were identified. Of these, 232 (3.1%) patients had pathologically confirmed UCCC (64 had non-invasive UCCC). Finally, 53 patients with non-invasive UCCC with complete surgical staging were included in the study. They found that 12 patients (22.6%) were upstaged at surgical assessment, with 5 patients upstaged to isolated omental metastasis and 3 patients upstaged to lymph node involvement. The 5-year disease-free survival (DFS) rate for patients who had extrauterine disease was significantly lower than that for those with no extrauterine disease (31.3% vs. 95.7%), and multivariate analysis revealed that positive peritoneal cytology and extrauterine disease were independent risk factors for DFS. Among a group of 41 patients who had disease limited to the endometrium, they found no significant difference in DFS between patients with and without adjuvant therapy. Therefore, the authors conclude that comprehensive surgical staging, including omentectomy, should be the standard of care for women with UCCC, regardless of the depth of myometrial invasion. In addition, they argue that observation might be a reasonable option when disease is truly confined to the endometrium alone.

Consistent with their study, the Society of Gynecologic Oncology (SGO) reviewed patients with UCCC subtype and recommended complete surgical staging, including omentectomy, for these patients [1]. Furthermore, the National Comprehensive Cancer Network (NCCN) guidelines regard all non-endometrial carcinoma subtypes, including UCCC, as being high risk, and therefore, recommends omentectomy as part of staging surgery [11]. Omentectomy is also recommended in the ESMO clinical practice guidelines and the Japan Society of Gynecologic Oncology (JSGO) guidelines 2013 for the treatment of uterine body neoplasms [12]. Therefore, the findings of Sarı et al. [10] could support the evidences of these clinical guidelines for the surgical management of UCCC.

Existing guidelines also recommend adjuvant treatments for early stage IA UCCC, though they also suggest that observation can be valid for these patients if there is no myometrial invasion [11,12]. In a retrospective review, a total of 77 patients with stage IA uterine serous carcinoma (USC) and UCCC were identified [13]. In that review, recurrence was observed in only 1 of 26 patients with tumors without myometrial invasion who received observation alone after surgery. Kim et al. [14] also reported that adjuvant radiation therapy had no influence on OS for patients with stage IA UCCC without myometrial invasion.

In summary, although the retrospective study by Sarı et al. [10] was the lack of comprehensive central pathology, their results highlight that extrauterine disease may occur in the absence of myometrial invasion in patients with UCCC and that the omentum appears to be the most common site of metastasis in these patients. Thus, total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, omentectomy, and peritoneal

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biopsies could be justified when treating of UCCC, regardless of the depth of myometrial invasion. However, further study is needed to clarify the need for adjuvant treatment in patients with non-invasive UCCC.

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