Keywords

Adjuvant Therapy, Cervical Adenocarcinoma, Cervical Adenosquamous Carcinoma, Lymph Node Metastasis, Prognostic Factors

1. Introduction

Adenocarcinoma/adenosquamous carcinomas (AC/ASC) are relatively uncommon histological subtypes of cervical cancer. Recently, AC/ASC has accounted for approximately 20% of all cervical cancer cases [1]-[3]. In general, the prognoses of patients with cervical AC/ASC are poorer than those of patients with cervical squamous cell carcinoma (SCC), because AC/ASC is more likely to grow aggressively and metastasize [4] [5]. This may be partly due to the lack of consensus on the optimal treatment for cervical AC/ASC [6]. The first-line treatment for AC/ASC is similar to that for SCC [7] [8]; cervical cancer patients with AC/ASC that are classified as stage IB-IIB by the International Federation of Gynecologists and Obstetricians (FIGO) are often treated with radical hysterectomy [9]. However, there are conflicting reports about whether the prognoses of AC/ASC patients who undergo surgery or radiotherapy are worse than those of SCC patients [5] [10]-[13].

To help resolve this issue, we aim to identify outcomes and prognostic factors in early-stage cervical AC/ASC patients who are treated with radical hysterectomy and adjuvant therapy. This information may be useful in optimizing the treatment of these patients.

2. Patients and Methods

After obtaining approval from the Institutional Review Board of Niigata University Hospital, we retrospectively reviewed the medical records of 26 patients with FIGO stage IB-IIB cervical AC/ASC who were treated with radical hysterectomy and adjuvant therapy between January 2001 and April 2013. Fifteen patients received neoadjuvant chemotherapy with at least one cycle of cisplatin (10 mg/body on days 1 - 10 every four weeks) and 5-fluorouracil (250 mg/body on days 1 - 10 every four weeks) [14]. One patient received a cycle of paclitaxel (175 mg/m^2 on day 1every three weeks) and cisplatin (75 mg/m^2 on day 1every three weeks) [15]. The remaining patients did not receive any neoadjuvant therapy. All patients underwent type III Piver-Rutledge radical hysterectomy [16] and systematic pelvic lymphadenectomy.

Approximately four weeks after surgery, all patients received radiotherapy (RT), chemotherapy (CT), or concurrent chemoradiotherapy (CCRT) as adjuvant therapy. RT consisted of external whole pelvic irradiation with 50.4 Gy in 28 fractions. CT (docetaxel: 70 mg/m^2 on day 1; carboplatin: area under the curve = 5 on day 1) was administered for at least three cycles at three-week intervals. CCRT consisted of concurrent RT and cisplatin alone (30 - 40 mg/m^2 weekly) or cisplatin (50 mg/m^{2}every three weeks) plus paclitaxel (50 mg/m^2 weekly). The differential indications for these therapies were based on the presence or absence of risk factors for postoperative recurrence, such as lymph node metastasis, parametrial invasion, positive surgical margin, large tumor size (≥4 cm), lymphovascular space invasion (LVSI), and deep stromal invasion (≥2/3 thickness). For example, among patients without lymph node metastasis, five received CCRT and eight received either RT or CT alone. On the other hand, among patients with lymph node metastasis, four received CCRT and nine received either RT or CT alone.

Survival outcomes were examined using the Kaplan-Meier method and compared using the log-rank test. Multivariate analyses of overall survival (OS) and progression-free survival (PFS) were performed with the Cox proportional hazards regression model to determine the prognostic significance of clinical features. A p-value of less than 0.05 was considered statistically significant.

3. Results

Patient characteristics are shown in Table 1. The median age at the start of treatment was 48.0 years (range: 29 - 69 years). For all patients, the estimated five-year OS rate was 49.5% and the estimated five-year PFS rate was 36.5%. Disease recurrence occurred in 12 patients (46.2%) with a median time of 11 months (range: 2 - 57 months). All patients except one had at least one risk factor for postoperative recurrence. However, the patient

Table 1. Clinicopathological characteristics of the 26 patients with cervical adenocarcinoma/adenosquamous carcinomas in this study.

Clinical stage (FIGO)	Number of patients	Percentage
IB1	7	27
IB2	13	50
IIA2	1	4
IIB	5	19
Age (years)		
20 - 39	9	35
40 - 49	4	15
50 - 59	7	27
60 - 69	6	23
Histological subtype		
Adenocarcinoma	23	88
Adenosquamous carcinoma	3	12
Adjuvant therapy		
Concurrent chemoradiotherapy	9	35
Cisplatin	5	
Paclitaxel + Cisplatin	4	
Radiotherapy alone	3	11
Chemotherapy alone	14	54
Docetaxel + Carboplatin	13	
Paclitaxel + Cisplatin	1	

who did not have any risk factors still received adjuvant RT because cervical adenocarcinoma has a high risk of recurrence.

As shown in Table 2, lymph node metastasis was a significant prognostic factor for both OS and PFS. In addition, LVSI was a significant prognostic factor for only OS and parametrial invasion was a significant prognostic factor for only PFS. When these prognostic factors were further assessed using the Cox multivariate proportional hazard model, lymph node metastasis was identified as an independent predictor of PFS ($p = 0.021$, risk ratio = 6.47, 95% confidence interval: 1.33 - 31.43).

The effects of different types of adjuvant therapy in patients with and in those without lymph node metastasis on OS and PFS are shown in Figure 1. In patients with lymph node metastasis, relapses occurred in 10 patients (seven who did not receive CCRT and three who received CCRT). Compared with CT or RT alone, the effects of CCRT on OS and PFS were not significant. In patients without lymph node metastasis, relapses only occurred in two patients who did not receive CCRT. However, compared with CT or RT alone, the effects of CCRT on OS and PFS were not significant.

4. Discussion

In this study, we demonstrated that lymph node metastasis is an independent predictor of PFS in patients with cervical AC/ASC who are treated with radical hysterectomy and adjuvant therapy. This result is consistent with several other studies that show that lymph node metastasis in patients with cervical AC/ASC is an independent predictor for survival [9] [17] [18]. However, the type of adjuvant therapy did not make any significant difference on either OS or PFS, regardless of lymph node metastasis.

Table 2. Multivariate analysis of survival for patients with cervical adenocarcinoma/adenosquamous carcinomas.

Covariate		*n*	OS					PFS				
			Estimated 5-year survival (%)	Univariate p-value	RR	95% CI	Multivariate p-value	Estimated 5-year survival (%)	Univariate p-value	RR	95% CI	Multivariate p-value
Age	<50 years	13	61.4	0.904				42.1	0.982			
	≥50 years	13	40.0					34.6				
Stage	IB	20	53.8	0.188				35.5	0.597			
	IIA+IIB	6	40.0					40.0				
NAC	Received	15	51.3	0.510				31.4	0.717			
	Not received	11	(60.0)*					(72.7)*				
Adjuvant therapy	Concurrent chemoradiotherapy	9	(57.1)*	0.543				(63.5)*	0.424			
	Radiotherapy alone	3	100.0					100.0				
	Chemotherapy alone	14	46.9					25.6				
Lymph node metastasis	Negative	13	80.0	0.023	7.21	0.89 - 58.46	0.064	65.6	0.0027	6.47	1.33 - 31.43	0.021
	Positive	13	30.0					17.1				
Parametrial invasion	Negative	19	54.1	0.158				60.4	0.0158	2.68	0.83 - 8.66	0.099
	Positive	7	33.3					0				
Surgical margin	Negative	25	52.2	0.207				38.4	0.097			
	Positive	1	0					0				
Maximum tumor diameter	<4 cm	9	60.0	0.259				44.4	0.291			
	≥4 cm	17	46.2					30.9				
LVSI	Negative	13	75.0	0.035	4.41	0.89 - 21.98	0.070	37.7	0.126			
	Positive	13	25.6					36.1				
Deep stromal invasion	Negative	8	83.3	0.371				65.6	0.256			
	Positive	18	41.9					26.0				

Abbreviations: OS: overall survival, PFS: progression-free survival, LVSI: lymphovascular space invasion, RR: risk ratio, CI: confidence interval.
*Parenthetical values indicate that all cases were assessed before year 5.

Since there is no agreement about the optimal treatment for cervical AC/ASC, patients with AC/ASC tend to be treated similarly to those with SCC, namely, radical hysterectomy followed by adjuvant therapy [13]. Rotman *et al.* [19] suggested that postoperative adjuvant therapy, particularly RT, may be more beneficial for AC/ASC than for SCC. However, there are conflicting reports in the literature about the effect of CCRT on cervical AC/ASC. Some studies have shown that CCRT is beneficial for cervical AC/ASC [20]-[23], while other studies have reported that CCRT does not improve the survival of patients with risk factors, such as lymph node metastasis [22] [23]. In this study, we showed that CCRT did not improve the survival of patients compared with either RT or CT alone, regardless of lymph node metastasis (**Figure 1**). However, our small sample sizelimits the statistical power of this study. As a result, a larger study is needed to confirm the generality of this conclusion.

These results suggest that other adjuvant therapeutic strategies may be needed to improve the survival of patients with cervical AC/ASC. For example, Park *et al.* [24] suggested that adjuvant therapy should be tailored

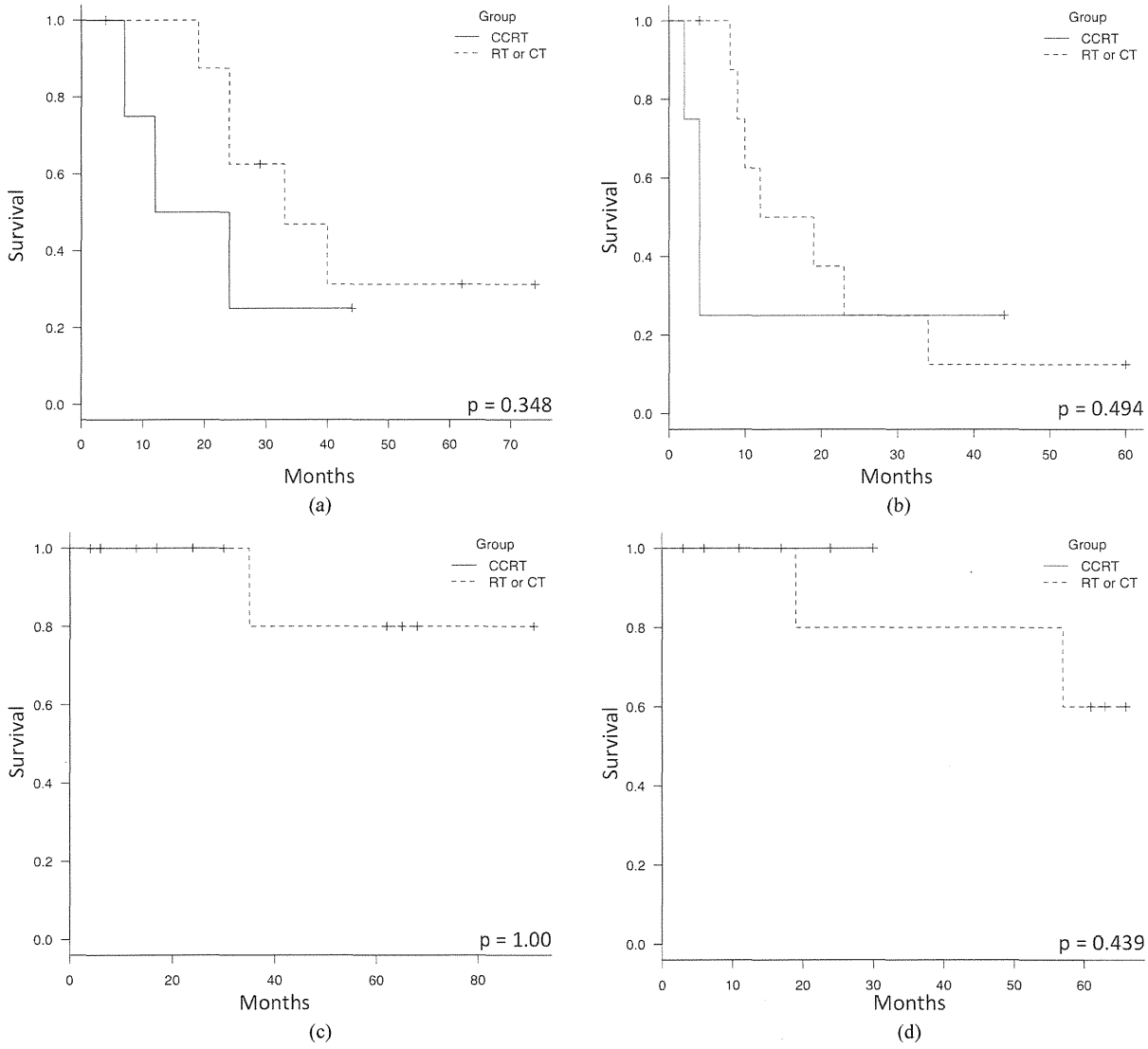

Figure 1. Kaplan-Meier analysis comparing the effects of adjuvant radiotherapy, chemotherapy, or concurrent chemoradiotherapy in patients with cervical adenocarcinoma/adenosquamous carcinomas. (a) Overall survival of patients with lymph node metastasis; (b) Progression-free survival of patients with lymph node metastasis; (c) Overall survival of patients without lymph node metastasis; (d) Progression-free survival of patients without lymph node metastasis.

according to postoperative risk factors in patients with early stage adenocarcinoma. Since CCRT has many adverse effects [15] [20], personalizing adjuvant therapydepending on the presence or absence of lymph node metastasis to reduce adverse effectsmay be worth considering.

5. Conclusion

In conclusion, we found that lymph node metastasis was an independent prognostic factor for poor survival in cervical AC/ASC patients treated with radical hysterectomy and adjuvant therapy. In this study, CCRT does not improve patient survival, regardless of lymph node metastasis, which suggests that novel or personalized adjuvant therapeutic strategies with fewer adverse effects than existing strategies are needed.

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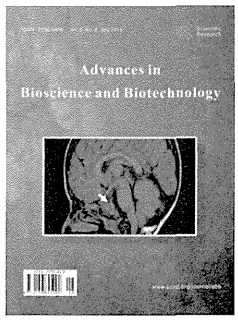

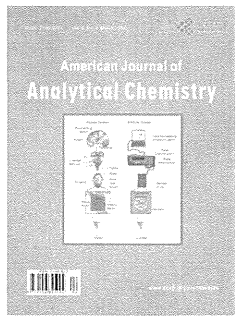

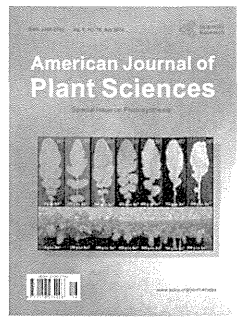

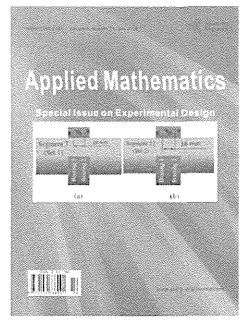

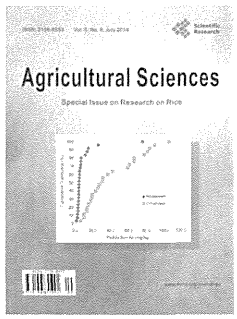

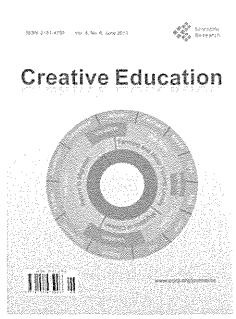

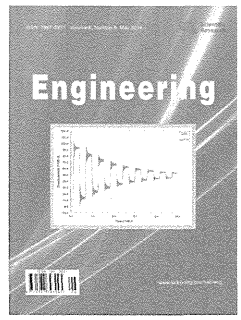

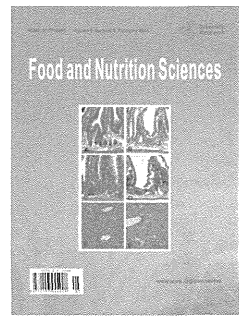

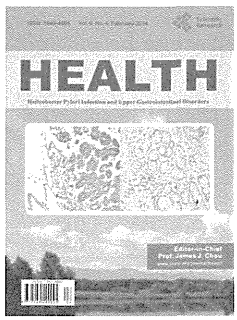

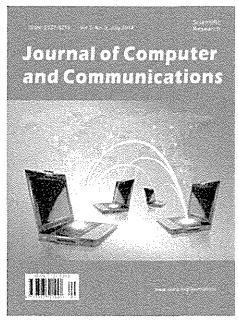

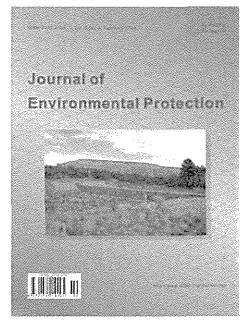

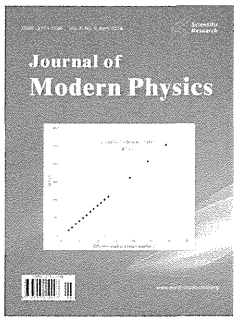

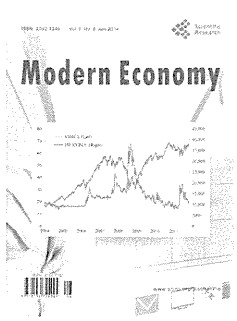

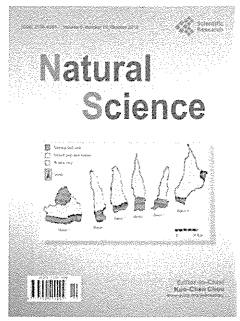

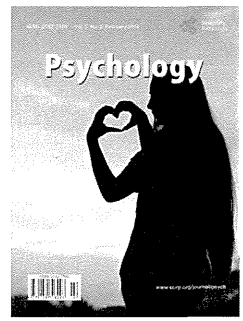

Preoperative Ultrasound-Guided Needle Biopsy of 63 Uterine Tumors Having High Signal Intensity Upon T2-Weighted Magnetic Resonance Imaging

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Objective: The differential diagnosis between uterine sarcoma and benign leiomyoma is difficult when made only by magnetic resonance imaging (MRI); it usually requires an additional preoperative diagnostic procedure. We report our results using ultrasound-guided needle biopsy for these types of uterine tumors.

Methods: Ultrasound-guided needle biopsy was performed on 63 patients with uterine smooth muscle tumors suspected of malignancy by MRI. We compared the results of presurgical biopsy against the postsurgical pathology of the tumor.

Results: Among 63 patients with a high signal intensity of the uterine tumor on T2-weighted MRI (1 case was undetermined), 12 cases (19.3%) were diagnosed by the needle biopsy as malignant, and 51 cases (80.6%) were benign. Among the 12 diagnosed as malignant tumors, 11 had surgery performed, and one was treated with chemotherapy. Among the 51 patients diagnosed with a benign tumor, 27 had surgery performed, and 24 were put on a wait-and-see clinical follow-up schedule. One of the 27 surgical patients with a benign tumor had a postsurgical diagnosis of a low-grade endometrial stromal sarcoma. In the 38 cases where surgery was performed, we found the sensitivity, specificity, and the positive and negative predictive values of the needle biopsy were 91.7%, 100%, 100%, and 96.2%, respectively.

Conclusions: Ultrasound-guided needle biopsy may be a reliable preoperative diagnostic procedure for uterine tumors with suspected malignancy.

Key Words: Uterine tumor, Needle biopsy, Sarcoma, Leiomyoma, Diffusion-weighted MRI

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Uterine sarcomas are relatively rare, accounting for only 3% to 8% of uterine cancers, and approximately 1 of every 800 smooth muscle tumors of the uterine is a leiomyosarcoma (LMS).[1,2] Magnetic resonance imaging (MRI) is 1 of the most useful imaging modalities, but even with MRI, it is difficult to distinguish between malignant LMSs and benign leiomyomas. There are reports that the use of gray scale and Doppler sonographic findings can be helpful,[3] with similar findings for the use of positron emission tomography using 2-[18F] fluoro-2-deoxy-D-glucose (PET-FDG)[4]; there is not at present an established practice for making an accurate presurgical differential diagnosis of these 2 tumor types. Recently, Yoshida et al[5]

TABLE 1. MRI appearance of 63 patients who underwent needle biopsy

MRI Appearance	n	Malignant Tumor
High signal on T2WI	46	2 (4.3%)
High signal on T2WI + necrosis or irregular margin	16	10 (62.5%)
Undetermined on T2WI (with irregular margin)	1	1 (100%)

T2WI, T2-weighted image.

reported that 16α[18F] fluoro-17β-estradiol PET was effective for differentiating uterine sarcomas from benign leiomyoma; however, in the 24 cases they studied, they had 2 false positives (a leiomyoma with adenomyosis and a hemorrhagic cellular variant leiomyoma) and 2 false negatives (a low-grade endometrial stromal sarcoma and an LMS).

The most reliable preoperative diagnostic method has been found to be a biopsy of the tumor. Because an LMS arises within the uterine smooth muscle, a biopsy of the endometrial malignant tissue is difficult to perform, and in many cases, the tumor is found only at surgery. Various authors have reported that LMS may be present in the submucosa of the uterus in 30% to 50% of patients, but even in such cases, the biopsy diagnosis is not easy.[1] Although past reports have demonstrated the usefulness of a needle biopsy for uterine tumors,[6,7] the use of the biopsy option has generally not gained widespread acceptance. To support its wider use, we report our experience with the ultrasound-guided needle biopsy for uterine tumors.

MATERIALS AND METHODS

We enrolled patients who had unusual MRI findings, in particular, those with a higher intensity tumor image than normal myometrium (50% or higher on T2-weighted images). In addition, we considered whether the patient had evidence of hemorrhagic necrosis (indicated by high signal intensity on T1-weighed image and nonenhancement in the same area) or irregular margins. From January 2005 to August 2012, we obtained informed consent from 63 patients to perform an ultrasound-guided needle biopsy of their uterine mass suspected by MRI of being a malignant tumor. This is a retrospective study, and the exact number of uterine tumors during that period with high or undetermined T2-weighed MRI signal is unclear. However, about 10% of the patients with uterine tumors met our eligibility to perform needle biopsy. Some patients desire surgery without performing preoperative needle biopsy, and others desire regular follow-up without performing needle biopsy. Needle biopsy was mainly performed to the cases that did not desire the surgery immediately but were suspected malignancy rather than typical leiomyoma.

The median patient age was 47.0 years (range, 21–83 years). The solid part of the mass was characterized as having a high signal intensity on a T2-weighted MRI (ie, the mass had a high signal intensity on a diffusion-weighted image [DWI] and a low apparent diffusion coefficient [ADC] map) and was specified in 3 dimensions. We evaluated MRI with DWI and ADC in 18 patients.

The biopsy was performed, without general anesthesia, using a Bard Magnum biopsy system (C. R. Bard, Inc, Murray Hill, NJ), with an automatic cutting needle (30 cm long, 18 gauge, with a 19-mm notch). The biopsy needle was inserted through a sterile needle guide that was attached to the ultrasound transducer. The ultrasound transducer was manipulated to position the uterine tumor along a line on the screen. After the tip of the needle was within the uterine tumor, the biopsy gun was fired, and a core of tissue was obtained. We performed 3 biopsies to reduce sampling error. A 50-mg diclofenac sodium suppository was administered before conducting the needle biopsy. All patients took a cephem antibiotic for 3 to 5 days after the needle biopsy. There were no cases that required post-biopsy hospitalization.

We recommended surgery for all cases diagnosed by biopsy with malignant tumors. In the cases diagnosed with benign tumors, we either observed or operated, depending on any myoma-related symptoms, infertility, or the patient's desire to undergo surgery. In the operative cases, we compared the results of the needle biopsy and the results of the surgical specimen. The patients who did not undergo surgery were regularly followed at the hospital and have had no outcome event suggestive of malignancy at 4 to 81 months of follow-up (median, 41 months) after the needle biopsy.

RESULTS

Table 1 shows the MRI appearance of the 63 patients who underwent a needle biopsy. Among the 46 patients who had solid parts with high signal intensity on T2-weighted MRI, there were 2 atypical malignant cases. One case had a well-defined cystic area that was suspected of being a leiomyoma with degenerative liquefaction; the other had a nodule with a high-signal T2-weighed image on MRI typical of a leiomyoma. Among 16 patients who had a mass with an MRI pattern of hemorrhagic necrosis and/or an irregular margin, there were 10 malignant tumors by biopsy. We could not determine the T2-weighted image signal ratio in 1 case because we could not find any normal myometrium for comparison.

Figure 1 shows the outcomes of 63 patients with uterine tumors, with a high signal intensity or an undetermined ratio (1 patient), on T2-weighted imaging, which we preoperatively performed an ultrasound-guided needle biopsy on. Among the 63 patients, malignant tumors were identified by biopsy in 12 cases (19%), and benign tumors were diagnosed in 51 cases (81%). Table 2 shows the characteristics of patients with a malignant tumor.

Of 12 patients with the diagnosis of a malignant tumor by needle biopsy, 11 had surgery performed, and 1 was treated with chemotherapy because it was an advanced case. Two advanced cases were treated with surgery after chemotherapy. Surgery specimens were classified as LMS (n = 10) and endometrial stromal sarcoma (n = 1). Of 51 patients with the diagnosis of benign tumors, 27 underwent a hysterectomy or myomectomy. After the surgery, the condition of 1 of the

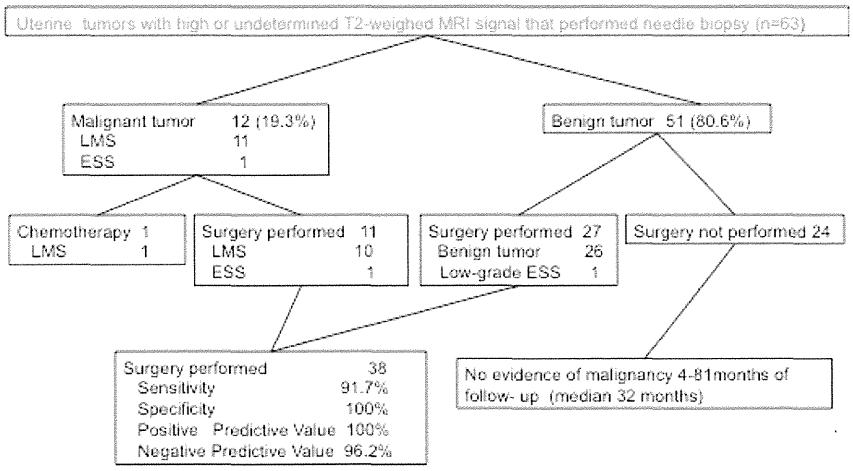

FIGURE 1. Outcomes of 63 patients with uterine tumor with high signal intensity or undetermined (single patient) on T2-weighted image. Data are shown as the number of patients.

27 patients was diagnosed with a low-grade endometrial stromal sarcoma, and the other 26 were diagnosed with a leiomyoma.

Twenty-four patients were managed conservatively, being observed every 3 months according to their symptoms. Tumor and uterine sizes were measured by ultrasonography at each visit. These 24 patients lacked any evidence of uterine malignancy during subsequent follow-ups.

In the 38 cases where surgery was performed, the sensitivity and specificity of the biopsy diagnosis was 91.7% and 100%, respectively. The positive predictive value of the biopsy was 100%, and the negative predictive value was 96.2%. We had 2 cases of infection that needed surgery to control. Both cases were LMS with widespread necrosis. Other than these 2 cases, no major complications, such as intraperitoneal hemorrhage or injury to adjacent structures that required surgery, were observed.

CONSIDERATION

To treat a uterine tumor properly without doing unnecessary surgery, differentiating uterine sarcomas from benign leiomyomas is very important. The MRI is an important tool for diagnosing uterine tumors. The typical MRI appearance of an LMS reveals a heterogeneous appearance with intermediate to high signal intensity on T2-weigted images and enhances well. In a typical case, MRI reveals high intensity on T1-weigted images with coagulated tumor necrosis.[8] Confeld et al[9] reported finding a distribution of imaging criteria between leiomyoma and other mesenchymal neoplasms. Objective criteria included T1 and T2 signal characteristics, enhancement pattern, the presence of cystic changes, and an ill-defined margin.[9] However, in a previous report of patients with findings of coagulative tumor cell necrosis, the incidence of LMS was limited to 68%, and in the 5% of the patients without findings of coagulative tumor cell necrosis, LMS was noted.[4] There are many case reports that had few of these typical imaging characteristics. On the other hand, there is also 1 report claiming that malignant tumors were rare in cases that were operated on solely because they seemed to be rapidly growing.[10]

Recently, by using diffusion-weighted MRI, it became possible to perform diagnoses that are more detailed.[11] We performed our very first uterine DWI in September 2008. From January 2010 onward, we performed DWI for all such cases. Namimoto et al[12] reported that ADC combined with T2-weigted imaging is significantly better than ADC or T2-weighted imaging alone at differentiating between sarcomas and leiomyomas. However, there are limitations to their study; the number of sarcomas was relatively small, and some leiomyomas were not proven diagnostically.[12]

In 2002, Kawamura et al reported obtaining good diagnostic results using a transcervical needle biopsy for the differential diagnosis between uterine sarcoma and leiomyoma.[7] They reported that a transcervical needle biopsy, using a histopathological scoring system that was established based on the criteria proposed by Bell et al,[8] is highly precise, with an especially high negative predictive value.

By performing a needle biopsy, we can diagnose whether the uterine mass is a benign or malignant tumor. As a result, we can avoid unneeded surgery in cases with a poor general status or distant metastasis, or do only limited procedures, such as fertility-sparing surgery, laparoscopic surgery, or transvaginal surgery.

In addition to it, DWI reduced the cases that needed needle biopsy. So we have performed needle biopsy with limited cases in recent years.

In our report, although the exact number of uterine tumors with high or undetermined T2-weighed MRI signal between January 2005 and August 2012 is unclear, we could recruit 63 cases for needle biopsy. Of those 63 cases, 13 cases turned out to be sarcomas. On the other hand, a total of 41 uterine sarcomas were treated in our hospital during that period.

TABLE 2. Characteristics of patients with a malignant tumor

Case Number	Age, y	FIGO Stage	Metastatic	T2WI	DWI	ADC	Hemorrhagic Necrosis	Irregular MRI Margin	Size, cm	Needle Biopsy Diagnosis	Internal Between Biopsy to Surgery, d	Surgical Diagnosis	Other Notes
1	48	IB		High	NE	NE	−	−	10	LMS suspected	45	LMS	Well-defined cystic area
2	70	IB		High	High	Low	−	−	9	LMS suspected	15	LMS	A nodule in leiomyoma
3	21	IA		High	NE	NE	−	+	4	LMS	45	LMS	
4	49	IA		High	NE	NE	+	−	4.5	ESS	16	ESS	
5	53	IA		High	NE	NE	+	−	2	LMS	25	LMS	
6	66	IB		High	NE	NE	+	−	10	LMS	14	LMS	
7	49	IB		High	NE	NE	+	+	10	LMS	48	LMS	
8	50	IB		High	High	NE	+	+	7	LMS	34	LMS	A nodule in leiomyoma
9	58	IVB	Lung	High	High	Low	+	−	11	LMS	Surgery not performed	Surgery not performed	Chemotherapy
10	50	IVB	Lung, bone, tumor, thrombosis	High	High	Low	+	−	5	LMS	113	LMS	Chemotherapy before surgery
11	57	IVB	Lung	High	NE	NE	+	+	8	LMS suspected	105	LMS	Chemotherapy before surgery
12	43	IVB	Lung	High	NE	NE	+	+	6	LMS suspected	41	LMS	
13	47	IVA	Adnexa, appendix, rectum	Undetermined	NE	NE	+	+	7	Leiomyoma	10	Low-grade ESS	

NE, not examined; T2WI, T2-weighted image.

Therefore 13 (31%) of 41 uterine sarcomas were biopsied as a consequence. Because conducting the needle biopsy provided a correct differential diagnosis, 24 of the 63 cases were able to avoid an unneeded operation altogether, 7 had laparoscopic surgery, and 4 had transvaginal surgery.

We only targeted tumors with high intensity T2 signal on MRI. On the other hand, there were no malignant cases among 51 patients with a low intensity T2 signal. We had suspected that these were malignant tumors because of their rapid growth or because they had hemorrhagic necrosis. Among the 46 patients who were not strongly suspected of having a malignant tumor (because they were only high signal intensity on T2-weighted images), there were 2 atypical cases of malignant tumor that were then diagnosed as malignant tumor by needle biopsy.

We evaluated 18 patients with DWI; in the group of 11 patients who had increases in DWI and decreases in ADC, there were 4 malignant tumors; in the 7 patients who had an increase DWI but no decrease in ADC, there were no malignant tumors. There is now the strong possibility that we can perform a needle biopsy more efficiently by restricting its use to patients with tumors that have a high signal with T2-weighted DWI imaging and a low signal with ADC.

One of the possible critical drawbacks of doing a needle biopsy is the possibility of spreading cancer cells. In the 12 tumor cases where we performed surgery after the needle biopsy, the median number of days from biopsy to surgery was 37.5 days (range, 10–113 days); in this cohort, there was no evidence that conducting the biopsy had spread the cancer. In cases where we strongly suspected a malignancy by MRI, we first evaluated with computed tomography whether there were distant metastases before conducting the needle biopsy. In 5 advanced cases, the computed tomography pointed out the presence of metastatic sites before the needle biopsy.

When performing a needle biopsy, there can be problems with accurate sampling, such as difficulties with the specimens, the diagnostic accuracy of any microsample, and the frequency of postbiopsy complications. In our report, 3 of the 68 specimens (4.8%) were difficult to diagnose; 1 was too small, and 2 consisted of only necrotic material. One patient underwent repeated ultrasound-guided needle biopsies and was with diagnosis of a malignant tumor. In another patient, repeating the biopsy was difficult because of an infection, and her condition was diagnosed after surgery with an LMS. Two other patients who underwent repeated biopsies did not undergo surgery because a malignant tumor was not strongly suspected.

In our research, the negative predictive value of the biopsy was 96.2%. There was 1 case in which the postsurgical diagnosis of a low-grade endometrioid stromal sarcoma (ESS) was different than by needle biopsy, which had suggested it was a leiomyoma. The existence of invasion is important for the distinction of an ESS from a benign tumor, and such invasion may be difficult to determine in a biopsy specimen.

There are numerous reports of cases simultaneously having leiomyoma and LMS. Mittal and Joutovsky reported that a spectrum of morphologic and immunohistochemical changes, from benign to malignant, is seen in 50% of LMSs, indicative of the progression of some leiomyoma to LMS.[13] Thus, when an unambiguous nodule is present within a myoma, we should bear in mind the possibility of the presence of a malignancy.

In our report, there were 2 cases of infection associated with an LMS with widespread necrosis. When we performed the needle biopsy on these cases, we had to consider carefully which area to perform the biopsy on and which type of patient management to conduct afterward.

Except in cases of low-grade malignancy, a presurgical guided needle biopsy for difficult cases may generally be as useful as a postsurgical histological examination of the tumor. Thus, we have found that in cases where a uterine malignancy is suspected by MRI, a preoperative needle biopsy is a highly effective tool for determining that most such cases are benign, a result which greatly expands our ability to use more conservative and appropriate treatment options.

On the other hand, there are complications, such as infection, that can occur from conducting a needle biopsy. It is also important to take into consideration that there will be rare cases that are just too difficult to diagnose by needle biopsy, that there may be the possibility of cancer spread after biopsy, and that malignancy can never be 100% ruled out by this means. We are thus ethically required to be selective of the cases we chose to diagnose in this manner.

There are now several other presurgical treatment options that can greatly benefit the patient. Examples are administering chemotherapy or molecular-targeted drugs, conducting radiotherapy, or induction of arterial embolism in the tumor. Going forward, a guided needle biopsy will help us choose which of these nonsurgical treatment plans is most appropriate for our patients.

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Gynecologic Cancer InterGroup (GCIG) Consensus Review for Clear Cell Carcinoma of the Ovary

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Abstract: Clear cell carcinoma of the ovary (CCC) is a histologic subtype of epithelial ovarian cancer with a distinct clinical behavior. There are marked geographic differences in the prevalence of CCC. The CCC is more likely to be detected at an early stage than high-grade serous cancers, and when confined within the ovary, the prognosis is good. However, advanced disease is associated with a very poor prognosis and resistance to standard treatment. Cytoreductive surgery should be performed for patients with stage II, III, or IV disease. An international phase III study to compare irinotecan/cisplatin and paclitaxel/carboplatin as adjuvant chemotherapy for stage IIV CCC has completed enrollment (GCIG/JGOG3017). Considering the frequent *PIK3CA* mutation in CCC, dual inhibitors targeting PI3K, AKT in the mTOR pathway, are promising. Performing these trials and generating the evidence will require considerable international collaboration.

Key Words: Clear cell carcinoma of the ovary (CCC), Deep venous thrombosis, Glycogen, Hepatocyte nuclear factor-1ß, *WT1*, Pulmonary embolism, Ethnics, *ARID1A*, *PIK3CA*, *PPM1D*, *PPP2R1A*, *KRAS*, Cytoreductive surgery, Paclitaxel, Platinum, Irinotecan hydrochloride, Cisplatin, PI3K/AKT/mTOR

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Ovarian cancer is made up of several different histological subtypes, and it is clear that these represent different diseases with distinct biology, pathogenesis, and clinical behavior. However, to date, they have all been treated in the same way. As understanding of the differences increases, this is no longer a rational approach. Most women included in clinical trials have high-grade serous (HGS) ovarian cancer, and it cannot be assumed that the results of these trials are applicable to women with other histotypes. Clear cell carcinoma of the ovary (CCC) is more likely to be detected at an early stage than HGS cancers, and when confined within the ovary, the prognosis is good. However advanced disease is associated with a very poor prognosis and resistance to standard treatment.[1] Histotype-specific trials and treatment protocols are required. Performing these trials and generating the evidence will require considerable international collaboration.

EPIDEMIOLOGY

The CCC is a histologic subtype of epithelial ovarian cancer with a distinct clinical behavior. There are marked geographic differences in the prevalence of CCC. In North America and Europe, CCC is the third most common histologic subtype of epithelial ovarian cancer, with an estimated prevalence of 1% to 12%.[2] Recent Surveillance, Epidemiology, and End Results data revealed that the incidences of CCC in women living in United States were 4.8% in whites, 3.1% in blacks, and 11.1% in Asians.[3] In Japan, the prevalence of CCC is higher than in western countries, although the reason for this remains unknown.[1] The annual report of the Japanese Gynecologic Cancer Committee showed an increasing incidence of CCC as a proportion of all epithelial ovarian cancers (Fig. 1),[4] now making up more than 25% of epithelial ovarian cancers in Japan.

The incidence of thromboembolic complications in CCC, such as deep venous thrombosis and pulmonary embolism, is reported to be higher than other epithelial ovarian cancers (16.9%–27.3% vs 0%–6.8%) and is considered as an independent prognostic factor.[5,6]

PATHOLOGY

Gross

Most CCCs are unilateral. Typically, the sectioned surface of the tumor reveals a unilocular cyst with 1 or more solid, yellow nodules protruding into the cyst. Cysts may contain watery, mucinous fluid or brownish "chocolate-colored" fluid. Multilocular cysts are less common, and occasional tumors are predominantly solid. The mean size of CCC is 15 cm.

Microscopic

The CCC is composed of glycogen-containing cells with abundant clear cytoplasm and hobnail cells. Many tumors also contain cells with granular eosinophilic cytoplasm. Nuclei are often eccentrically placed, with rounded-to-angulated contours. Hobnail cells have scant cytoplasm and enlarged, bulbous, hyperchromatic nuclei that protrude into tubule and cyst lumens. Bland and flattened cuboidal cells may line cysts or glands. It may arise within an endometriotic cyst, and benign endometriotic lesions or atypical endometriosis may be seen adjacent to CCC. Occasionally, CCCs also present in association with adenofibromatous, clear cell borderline tumors.

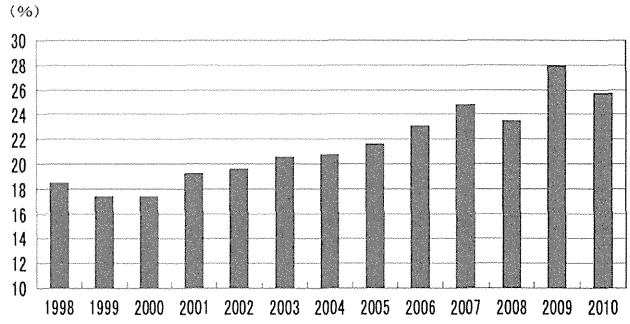

FIGURE 1. The rate of CCC among all epithelial ovarian cancers in Japan (annual reports on Japanese Gynecologic Cancer Committee).

The CCC exhibits high-grade nuclear features, although a spectrum of nuclear atypia may be present. The CCCs have traditionally been considered to be of high grade, but mitotic figures are relatively uncommon compared with other ovarian carcinomas.

Architectural patterns include tubulocystic, papillary, solid, and mixtures of them. Tubulocystic areas include tubules and cysts that are lined by flat-to-cuboidal cells with variable atypia and scattered hobnail cells (Fig. 2A). Papillary areas contain papillae that are small and round in comparison with those in serous carcinoma (Fig. 2B). The fibrovascular cores may be filled with either fibromatous, myxoid, spherulelike mucoid, or hyalinized basement membrane-type material. Solid areas are composed of sheets of polyhedral cells with clear cytoplasm (Fig. 2C).

Mixed subtypes of epithelial carcinomas are found. However, these should be considered as HGS tumors.[7]

Immunohistochemistry

The differential keratin profile is CK7+/CK20−, although CK7 may be focal in approximately 10% of cases.[8] In general, CCCs are negative for estrogen receptor, progesterone receptor, and *WT1*. Hepatocyte nuclear factor-1ß is a relatively new marker that is positive in CCC.[9] WT1 is useful in distinguishing CCC from mixed serous/clear cell tumors as it is typically positive in the latter.

Molecular Biology and Genetics

Unlike HGS tumors, CCCs are generally p53 wild type and have a lower frequency of *BRCA1* and *BRCA2* mutations.[10] The most frequent alterations are *ARID1A* and *PIK3CA* mutations.[11,12] *ARID1A* encodes the protein *BAF250a*, which is integral in the SWI-SNF chromatin remodeling complex. *ARID1A* mutations are seen in 40% to 60% of CCCs, but not in HGS carcinomas. In general, loss of *BAF250a* expression correlates with mutational status. *PIK3CA* mutations are seen in approximately 40% of clear cell tumors. Amplification and overexpression of the antiapoptotic protein, *PPM1D*, is seen in 10% of CCCs,[13] and mutation of *PPP2R1A* has been reported

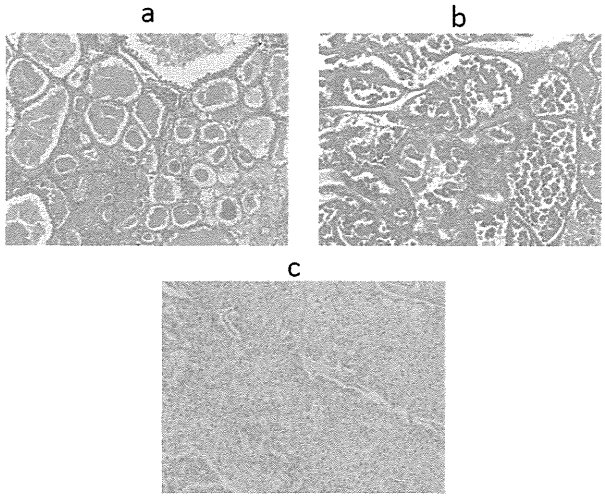

FIGURE 2. Microscopic findings of CCC. Tubulocystic areas include tubules and cysts that are lined by flat-to-cuboidal cells with variable atypia and scattered hobnail cells (A). Papillary areas contain papillae that are small and round in comparison with those in serous carcinoma (B). The fibrovascular cores may be filled with either fibromatous, myxoid, spherulelike mucoid, or hyalinized basement membrane-type material. Solid areas are composed of sheets of polyhedral cells with clear cytoplasm (C).

in 7%, whereas KRAS has been reported in 5%.[14] The CCCs are not a uniform group. Tan et al demonstrated groups with distinct patterns of copy number aberration in a comparative genomic hybridization analysis,[15] which seems to have prognostic significance.

Gene Expression Analysis

Yamaguchi et al[16] identified the gene signature that distinguishes CCC from other types of ovarian cancer using a microarray data set of ovarian cancers. The signature consisted of 437 genes and was designated as the CCC signature, which is specific for CCC. A categorical analysis demonstrated that genes belonging to 3 categories—stress response, sugar metabolism, and coagulation—are frequently involved in this signature.

INITIAL TREATMENT

Appropriate surgical treatment, followed by systemic chemotherapy, is recommended as an initial treatment for patients with CCC. The standard surgical treatment for patients with CCC is the same as for other epithelial ovarian cancers and includes hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic and para-aortic lymphadenectomy, and cytoreductive surgery. The recommended regimen of postoperative chemotherapy is paclitaxel (175 mg/m^2) combined with carboplatin (AUC 5–7.5), given every 3 weeks for 6 cycles.

Surgery

Lymphadenectomy is important to detect whether lymph nodes are involved in CCC because the presence of lymph node metastasis is an independent prognostic factor[17,18] and may guide the need for adjuvant therapy in early disease. Several authors have examined the therapeutic role of lymphadenectomy in therapy for this disease. In the Multicenter Italian Trials in Ovarian Cancer (MITO 9) retrospective study, disease-free survival in patients who underwent lymphadenectomy was longer than in other patients ($P = 0.0001$), in both early (I/II) ($P = 0.0258$) and advanced (III/IV) ($P = 0.037$) stages.[18] Lymphadenectomy also prolonged overall survival (OS) in patients with advanced stage ($P = 0.0039$). However, previous other reports have failed to show a therapeutic benefit from lymphadenectomy.[17,19] Further study will be required to identify the impact of lymphadenectomy on a patient's outcome from CCC.

Cytoreductive surgery should be performed for patients with stage II, III, or IV disease. Takano et al[20] reported no significant prognostic difference between the patients who underwent optimal cytoreduction (<1 cm) and those who had residual disease of greater than 1 cm. Complete surgery with no residual macroscopic disease was the only independent prognostic factor (median progression-free survival, 7 vs 5 vs 39 months, respectively). In a study by the Gynecologic Oncology Group, the markedly poor prognosis of CCC was observed even when patients have small-volume disease.[21] These findings suggest that a maximal effort should be made to remove all gross disease in patients with CCC.

Unilateral salpingo-oophorectomy preserving contralateral normal ovary and uterus should be considered for patients desiring to remain fertile. Several studies have examined outcomes of fertility-sparing surgery in patients with stage I CCC.[22,23] A total of 23 IA patients underwent fertility-sparing surgery, and all patients, excluding one (4%), were alive without recurrence. In contrast, 6 (25%) of the 24 patients at stage IC relapsed after surgery. Therefore, fertility-sparing surgery should only be offered for patients with stage IA disease.

Adjuvant Therapy

All patients with CCC have traditionally received postoperative systemic chemotherapy. However, observation may be considered for patients with surgical stage IA disease, because survival for these women is greater than 95%.[20,22,23]

It is generally accepted that CCC is resistant to conventional platinum-based chemotherapy compared with HGS ovarian cancer. The variation in reported response rates may reflect heterogeneity in patients included with some older studies including those with mixed tumors that would now be considered to be HGS tumors. Combination chemotherapy with paclitaxel plus platinum (TC) is thought to yield a higher response rate than conventional platinum-based chemotherapy (22%–56% vs 11%–27%) and improved survival in patients with advanced CCC, especially for those with optimal cytoreduction,[24,25] although the addition of a taxane was not an independent prognostic factor in the MITO 9 study. Nevertheless, responses remain much lower than with HGS, and there is an urgent need for more effective therapies.

In a randomized phase II study, the Japanese Gynecologic Oncology Group compared irinotecan hydrochloride plus cisplatin (CPT-P) with TC.[26] Both regimens were tolerated well, and progression-free survival between the 2 groups was

similar. An international phase III study to compare CPT-P and TC as adjuvant chemotherapy for stage I-to-IV CCC has completed enrollment (GCIG/JGOG3017). The results will be reported in 2014.

Adjuvant radiotherapy may have a role in the adjuvant treatment of early stage CCC. A retrospective series, which included 375 women with CCC, endometrioid and mucinous, found a benefit in survival for women treated with adjuvant chemotherapy plus whole abdominopelvic radiotherapy compared with chemotherapy alone.[27] The benefit seems to be mainly in high-risk stage 1C (positive peritoneal cytology and ovarian surface disease) and stage II disease.[28] These findings require confirmation in a prospective randomized trial.

METASTATIC DISEASE AND RELAPSE

Pattern of Relapse

The prognosis of recurrent CCC is very poor, even compared with that of recurrent serous adenocarcinoma with 5-year OS rates of 22.5% and 32.4%, respectively (P = 0.0007) and median OS of 25.3 versus 42.0 months. The 5-year postrecurrence survival rate is only 13.2% for CCC compared with 18.2% for HGS ($P < 0.0001$), with a median postrecurrent survival of 10.0 versus 18.9 months.[29] Recurrence rates of CCC were 29%, 30%, 62%, and 73% for stages I, II, III, and IV, respectively, with a median time to recurrence for the stages I and II of 12.2 months.[1] The prognosis is particularly poor relative to HGS tumors, where there is residual tumor after initial surgery.[1,29]

The pattern of recurrence also differs from HGS with higher rates of relapse in the lymph nodes (pelvic, para-aortic, and other lymph nodes) (40% vs 7%, $P < 0.001$) and parenchymal organs (liver, lung, bone, spleen, brain and others) (40% vs 13%, $P < 0.01$).[30]

Treatment

Treatment of recurrent CCC has, to date, followed the same protocols as are used for other recurrent ovarian epithelial carcinomas.[31] However, recurrent CCC is very resistant to chemotherapy with response rates of less than 10%.[32] Unlike in ovarian cancer in general, platinum-free interval does not seem to predict for further chemotherapy sensitivity. Despite evidence that recurrent CCC is resistant to subsequent chemotherapies,[32] no correlation between an efficacy of the second-line chemotherapy and histopathological types has been yet revealed.[33] However, this may be due to the small numbers of clear cell cancers included in trials of recurrent disease. For example, in a phase III study of paclitaxel plus carboplatin versus liposomal doxorubicin plus carboplatin in platinum-sensitive recurrence, the proportion of serous adenocarcinoma was 72%, whereas that of clear cell adenocarcinoma was only 2.8%.[34] In a phase III trial, liposomal doxorubicin was compared with gemcitabine in platinum-resistant recurrent cases; the proportion of serous adenocarcinoma was 80%, whereas that of clear cell adenocarcinoma was only 6.5%.[35]

Given the limited benefit from cytotoxic drugs, there is now great interest in the development of molecular targeted therapy for the treatment of CCC.

FUTURE DIRECTIONS

Table 1 lists the potential therapeutic targets in CCC. The continued development of targeted agents in the treatment of CCC requires investigation of a number of areas in the laboratory. The mechanisms of resistance to targeted agents are largely unknown, but an understanding of these will be essential for clinical development and application.

The lack of a mouse model of CCC is another important issue. For the deeper understanding of the pathogenesis of CCC as well as the more accurate evaluation of the antitumor activity of particular agents against CCC, a mouse model of CCC needs to be developed in the future.

Intelligently designed clinical trials are essential for the clinical development of novel therapies. There are a number of promising agents, but the optimal way to sequence and/or combine them needs to be established. Tumors require a vascular blood supply to grow beyond 2 to 3 mm; thus, subclinical ovarian tumors that develop after complete clinical response to

TABLE 1. Potential therapeutic targets in CCC

Targets	Roles in Tumor Development	Comments
Phospho-AKT	Proliferation/survival	Frequently in CCC and SAC
Phospho-mTOR	Proliferation/angiogenesis/metabolism	Frequently expressed in CCC
HIF-1α	Angiogenesis, adaptive response to hypoxia	Frequently expressed in CCC and SAC
VEGF	Angiogenesis	Frequently expressed in CCC and SAC
HNF-1β	Detoxification, chemoresistance, and survival	Frequently expressed in CCC
Annexin A4	Detoxification, chemoresistance	Frequently expressed in CCC
Osteopontin	Survival/migration/invasion	Frequently expressed in CCC and SAC
UGT1A1	Detoxification, irrinotecan resistance	Frequently expressed in CCC
IGFBP-1	Proliferation/survival	Frequently expressed in CCC
IGF2BP3	Translation, migration	Frequently expressed in CCC and SAC
IL-6/STAT-3	Proliferation/antiapoptosis/angiogenesis	Frequently expressed in CCC

SAC, serous adenocarcinoma.

first-line chemotherapy require angiogenesis for continued proliferation. Considering the significant antiproliferative and antiangiogenic activities of targeted agents, the activity of these agents as a maintenance therapy for preventing or delaying the development of recurrent disease needs to be investigated.

As the PI3K/AKT/mTOR signaling pathway is hyperactivated in CCC, strategies aimed to inhibit this pathway may have therapeutic activity for CCC.[36] Not only using them as a monotherapy, combination treatments may also be an attractive strategy to investigate in trials. For example, patients might start on mTOR-targeting therapy and then switch to VEGF-targeting therapy on progression. Other avenues of research include sequencing mTORC1 inhibitor initially and then switching to an mTORC1/2 inhibitor. Considering the frequent *PIK3CA* mutation in CCC,[12] dual inhibitors targeting PI3K, AKT in the mTOR pathway, are also promising. The efficacy and toxicities of simultaneous inhibition of different signaling pathways should be investigated. Another potential avenue is the combination of targeted agents with effective cytotoxic agents, as targeting agents are generally cytostatic. Intriguing preclinical results suggest that trabectedin is the most effective of the existing cytotoxic agents against CCC,[37] and this may be enhanced by the addition of an mTOR inhibitor. This combination warrants further investigation in future clinical studies.

Translating preclinical findings into successful treatment for patients is challenged by issues that are common to studying targeted agents in any tumor and studying any therapy in rare tumors. First, the method of efficacy evaluation of targeted agents needs to be reassessed. As many of the targeted agents have cytostatic rather than cytotoxic effects, the traditional criteria applied to cytotoxic agents, such as RECIST, might be less applicable when determining the clinical benefit of targeted agents. Second, identifying biomarkers that can be used to predict a patient's sensitivity to the targeted agents is a critical issue. The identification of surrogate markers to monitor the activity of targeted agents is also necessary. For this purpose, future clinical studies of targeted agents must incorporate translational research.

Finally, given the rarity of and the geographical difference in the prevalence of CCC, international collaboration, mediated by the Gynecologic Cancer InterGroup, may be essential to obtain adequate patient numbers. These efforts will allow selection of the best treatment for investigation in larger-scale clinical trials. Moreover, these challenges will aid in the development of optimal, personalized targeted therapies for CCC.

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Impact of Surgical Staging in Stage I Clear Cell Adenocarcinoma of the Ovary

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Aim: The aim of this study was to evaluate the impact of surgical staging in stage I clear cell adenocarcinoma of the ovary (CCC).

Methods: We performed a retrospective review of 165 patients with stage I CCC treated with optimal or nonoptimal staging surgery.

Results: The median follow-up period in this study was 67 months. No significant difference was detected in recurrence-free survival (RFS) or overall survival (OS) between patients optimally and nonoptimally staged (RFS: $P = 0.434$; OS: $P = 0.759$). The estimated 5-year RFS and OS rates were 92.1% and 95.3% in patients with stages IA/IC1 and 81.0% and 83.7% in stages IC2/IC3, respectively. The multivariate analysis indicated that stages IC2/IC3 predicted worse RFS and OS than stages IA/IC1 in stage I CCC patients (RFS: $P = 0.011$; OS: $P = 0.011$). Subsequently, we investigated the impact of surgical staging, respectively, in stages IA/IC1 and stages IC2/IC3. Significant differences were observed in PFS and OS between patients optimally and nonoptimally staged with stages IA/IC1 (RFS: $P = 0.021$; OS: $P = 0.024$), but no significant difference was found in those with stages IC2/IC3. The multivariate analysis indicated that nonoptimal staging surgery predicted worse RFS than the optimal staging surgery in stages IA/IC1 CCC patients ($P = 0.033$). In addition, we investigated the impact of surgical staging for stages IA/IC1 in the adjuvant chemotherapy group. The 5-year RFS and OS rates in patients optimally and nonoptimally staged with stages IA/IC1 in the adjuvant chemotherapy group were 97.8% and 100%, and 85.2% and 89.4%, respectively. The multivariate analysis indicated that nonoptimal staging surgery predicted worse RFS than the optimal staging surgery for stages IA/IC1 patients in the adjuvant chemotherapy group ($P = 0.019$).

Conclusions: The prognosis for women with stage 1A/IC1 is very good. Surgical staging category was the only independent prognostic factor for RFS in stages IA/IC1 CCC.

Key Words: Ovarian cancer, Clear cell carcinoma, Surgical staging, Lymphadenectomy, Adjuvant chemotherapy

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