



*Invited Review for the 100<sup>th</sup> Anniversary of the TJEM*

## Impact of Histopathological Risk Factors on the Treatment of Stage IB-IIB Uterine Cervical Cancer

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In the past decade, the incidence of adenocarcinoma of the uterine cervix gradually increased. Recent literature revealed that the molecular pathogenesis differs by histological subtype, and the histological subtype should be considered in deciding treatments for patients with uterine cervical cancer. However, no treatment based on histological type or genomic signature has been recommended in various treatment guidelines. The Japanese treatment guidelines recommend either radical hysterectomy or definitive radiotherapy as primary treatment for patients with stage IB-IIB squamous cell carcinoma and a radical hysterectomy-based approach for those with non-squamous cell carcinoma because of its lower radiosensitivity. The impact of histological type on survival outcome of uterine cervical cancer is controversial. Our retrospective studies suggested that the difference in survival outcome by histological subtype might be remarkable with disease progression. Recent literature suggested that usual-type endocervical adenocarcinoma, which is the most common histological type of cervical adenocarcinoma, showed a similar survival outcome to squamous cell carcinoma. In contrast, gastric-type mucinous carcinoma of the uterine cervix, which has aggressive clinical behavior and is not associated with high-risk human papillomavirus infection, showed resistance to chemotherapy and radiotherapy. Importantly, gastric-type mucinous carcinoma is rather common in Japan, compared with Western countries. It is therefore conceivable that the survival outcome of non-squamous cell carcinoma may be affected by regional difference in the frequency of gastric-type mucinous carcinoma. A molecular target to refractory uterine cervical cancer, such as gastric-type mucinous carcinoma of uterine cervix, still remains to be identified.

**Keywords:** chemotherapy; concurrent chemoradiotherapy; radical hysterectomy; radiotherapy; uterine cervical cancer  
Tohoku J. Exp. Med., 2020 December, 252 (4), 339-351.

### Introduction

Uterine cervical cancer (UCC) was the fourth common female malignancy, which accounted for approximately 570,000 new cases and 311,000 deaths worldwide in 2018 (Arbyn et al. 2020). In Japan, UCC is also one of the most common female malignancies with 7,304 newly diagnosed women in 2018, and 1,591 women (21.8%) were diagnosed with non-squamous cell carcinoma (nSCC) (Yaegashi 2020). In the past decade, the incidence of adenocarcinoma of the uterine cervix increased from approximately 5% to 20% of cervical cancers (Smith et al. 2000).

World Health Organization (WHO) Classification of

Tumor of Female Reproductive Organs 2014 (Wibur et al. 2014) classified 11 histological subtypes by descriptive morphologic characteristics and primarily cytoplasmic features as following: i) Endocervical adenocarcinoma, usual type (UEA); ii) Mucinous carcinoma, not otherwise specified (NOS); iii) Mucinous carcinoma, gastric type (GAS); iv) Mucinous carcinoma, intestinal type; v) Mucinous carcinoma, signet ring cell type; vi) Villoglandular carcinoma; vii) Mesonephric carcinoma; viii) Serous carcinoma; ix) Clear cell carcinoma; x) Endometrioid carcinoma; and xi) Adenocarcinoma, NOS. In addition, the international endocervical adenocarcinoma criteria and classification (IECC) proposed to categorize endocervical adenocarci-

Received July 15, 2020; revised and accepted November 17, 2020. Published online December 11, 2020; doi: 10.1620/tjem.252.339.

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noma by Human papilloma virus (HPV) infectious status as following: HPV-associated (HPVA) and non-HPV-associated (NHPVA). UEA is the most common subtype (more than 75% of endocervical adenocarcinoma) and is categorized as HPVA by IECC. GAS has been newly categorized in WHO Classification of Tumor of Female Reproductive Organs 2014 (Wibur et al. 2014), and was reported to be the second most common subtype of endocervical adenocarcinoma (Stolnicu et al. 2018). Minimal deviation adenocarcinoma is categorized as extremely well differentiated subtype of GAS. GAS has been also associated with Peutz-Jeghers syndrome (Kuragaki et al. 2003).

Although several authors reported that the 5-year overall survival (OS) rate in nSCC is lower by 10-20% compared to that in squamous cell carcinoma (SCC) (Irie et al. 2000; Quinn et al. 2006; Galic et al. 2012), the impact of histological type on survival outcome of UCC is controversial (Katanyoo et al. 2012; Kasamatsu et al. 2009; Seamon et al. 2018) (Table 1). The largest retrospective studies using the Surveillance, Epidemiology, and End Results database, which is a premier source for cancer statistics in the United States, suggested that adenocarcinoma histology negatively affected survival for both early- and advanced-stage disease compared with SCC (Galic et al. 2012). In contrast, Kasamatsu et al. (2009) reviewed the medical records of 578 patients (endocervical/endometrioid adenocarcinoma, 123; SCC, 455) with stage I to IIB cervical cancer who underwent radical hysterectomy (RH); there was no significant difference in survival outcome between the patient groups separated by histological type (Kasamatsu et al. 2009). Irie et al. (2000) reported that the survival in

patients with stage IB UCC did not differ between SCC and nSCC, but in patients with stage II UCC, patients with nSCC showed significantly worse outcome than those with SCC. Shimada et al. (2013b) also demonstrated that histological subtype did not affect the 5-year OS in patients without pelvic lymph node involvement (adenocarcinoma, 91.2% vs. SCC, 93.9%,  $p = 0.4464$ ), but in patients with pelvic lymph node involvement, patients with adenocarcinoma had significantly worse outcome than those with SCC (adenocarcinoma, 46.4% vs. SCC, 72.3%,  $p = 0.0005$ ) in the retrospective studies that included 820 patients with UCC (SCC, 540; adenocarcinoma, 280). Patients who did not receive adjuvant treatment after RH also showed similar 5-year OS between SCC and adenocarcinoma (adenocarcinoma, 93.1% vs. SCC, 94.0%;  $p = 0.9497$ ). In contrast, in patients with adjuvant treatment, patients with adenocarcinoma showed significantly worse 5-year OS compared to those with SCC (adenocarcinoma, 73.7% vs. SCC, 83.1%,  $p = 0.0368$ ), suggesting that the difference in survival outcome by histological subtype may be remarkable with disease progression.

Recent literature suggested that adenocarcinoma is clearly different from SCC based on its molecular pathogenesis (Wright et al. 2013; Ojesina et al. 2014) and that the histological subtype should be considered in deciding treatments for patients with UCC. However, no treatment based on histological type or genomic signature has been established for patients with UCC. Consequently, National Comprehensive Cancer Network (NCCN) guidelines recommended that patients with adenocarcinoma should be treated in a similar manner as those with SCC (NCCN

Table 1. Treatment for stage IB-IIB patients with UCC by clinical stage in Japan.

Authors (year)	Numbers of patients		5-year OS	
	Stage	SCC/nSCC	SCC/nSCC	p value
Irie et al. (2000)	stage IB	99/29	94.4%/95.8%	NS
	stage II	99/28	89.5%/60.7%	0.0007
Katanyoo et al. (2012)	stage IIB	170/85	70.8%/71.9%	0.568
	stage IIIB/IVA	112/56	47.4%/41.1%	0.139
Kasamatsu et al. (2009)	stage IB	275/96	89%/89%	0.640
	stage IIA	51/5	89%/92%	0.317
	stage IIB	129/22	62%/38%	0.074
Shimada et al. (2013b)	stage IB-II <sup>*1</sup>	377/229	93.9%/91.2%	0.4464
	stage IB-II <sup>*2</sup>	163/51	72.3%/46.4%	0.0005
	stage IB-II <sup>*3</sup>	213/141	94.0%/93.1%	0.9497
	stage IB-II <sup>*4</sup>	327/139	83.1%/73.7%	0.0368
Galic et al. (2012)	stage I-II	10,381/2,998	HR: 1.16	95% CI: 1.05-1.27
	stage III/IV	8,598/1,105	HR: 1.22	95% CI: 1.13-1.33

SCC, squamous cell carcinoma; nSCC, non-Squamous cell carcinoma; NS, not significant; HR, hazard ratio; 95% CI, 95% confidence Interval.

<sup>\*1</sup>Patients without lymphnode metastasis.

<sup>\*2</sup>Patients with lymphnode metastasis.

<sup>\*3</sup>Patients without adjuvant treatment after surgery.

<sup>\*4</sup>Patients with adjuvant treatment after surgery.

## 1. Stage IB-IIIB

### **Patients with squamous cell carcinoma**

Stage IB1, IIA1	RH +/- adjuvant treatment or RT/ CCRT
Stage IB2, IIA2	RH +/- adjuvant treatment or CCRT
Stage IIB	RH +/- adjuvant treatment or CCRT

### **Patients with non-squamous cell carcinoma**

Stage IB-IIIB	RH +/- adjuvant treatment > CCRT
2. Stage III, IVA	CCRT
3. Stage IVB	Chemotherapy, palliative RT, or Best supportive care

Fig. 1. Recommended treatment for patients with uterine cervical cancer by JSGO guidelines 2017.

The Japan Society of Gynecologic Oncology (JSGO) guidelines recommended either RH-based approach or definitive radiotherapy, including concurrent chemoradiotherapy (CCRT), as primary treatment for patients with not only stage IB1, and IIA1 (FIGO 2008) but also stage IB2, IIA2, and IIB (FIGO 2008), especially for non-squamous cell carcinoma. The JSGO guidelines recommended CCRT for patients with stage III-IVA disease, and chemotherapy, palliative radiotherapy, and/or best supportive care for those with stage IVB disease.

Table 2. Treatment for stage IB-IIIB patients with UCC by clinical stage in Japan.

Stage	Surgical treatment <sup>*1</sup>	Radiotherapy <sup>*2</sup>	Others <sup>*3</sup>	Total
IB1	1,952 (89.6%)	222 (10.2%)	5 (0.2%)	2,179
IB2	504 (78.8%)	130 (20.3%)	6 (0.9%)	640
IIA1	156 (65.0%)	84 (35.0%)	0	240
IIA2	126 (59.2%)	86 (40.4%)	1 (0.5%)	213
IIB	452 (34.7%)	838 (64.4%)	12 (0.9%)	1,302

\*1Radical hysterectomy +/- adjuvant treatment including radiotherapy, concurrent chemoradiotherapy, or chemotherapy.

\*2Radiotherapy or Concurrent chemoradiotherapy.

\*3Others included chemotherapy +/- molecular targeting therapy.

2020).

Of 7,304 newly diagnosed women in 2018, 4,607 women (63.1%) were diagnosed with stage IB/II in Japan (Yaegashi 2020). The NCCN guideline suggested that radical hysterectomy (RH) is performed only in patients with stage IB1, IB2, and IIA1 (International Federation of Gynecology and Obstetrics [FIGO] 2018) UCC (NCCN 2020). In contrast, the Japan Society of Gynecologic Oncology (JSGO) guidelines recommended either RH-based approach or definitive radiotherapy, including concurrent chemoradiotherapy (CCRT), as primary treatment for patients with not only stage IB1, and IIA1 (FIGO 2008) but also stage IB2, IIA2, and IIB (FIGO 2008) (Ebina et al. 2019) (Fig. 1).

Table 2 shows the treatment for patients with stage IB-II UCC in Japan (Yaegashi 2020). A survey of the Japanese Gynecologic Oncology Group (JGOG) reported

that CCRT was performed at 53 (31.9%) of 166 institutions for women with stage IIB SCC but only 28 (17.0%) of 166 institutions for patients with stage IIB nSCC disease (Mikami et al. 2014), suggesting that histological subtype affected the selection of the management modality for patients with UCC in Japan.

This review presents the impact of histological subtype on the treatment and survival outcome of patients with stage IB-IIIB UCC.

### **RH as Primary Treatment for Patients with Stage IB-IIIB UCC**

The most important issue of primary treatment for patients with stage IB-IIIB UCC was selecting the local control strategy in the pelvic cavity. The difference in surgical methods between Japan and Western countries affects the recommended primary treatment for stage IB-IIIB UCC in

each country. Based on “the Okabayashi’s RH method,” Japanese gynecologic oncologists established RH with higher curability. The Okabayashi’s RH method makes it possible to remove the parametrial tissue widely with separation of the anterior/posterior leaf of the vesico-uterine ligament (Ebina et al. 2019). The JSGO guidelines therefore recommended the RH-based approach as primary local-control strategy for patients with IB-IIB UCC.

Importantly, the JGOG retrospective study, which examined clinical data of 5,964 patients with stage IB-IIB UCC who underwent RH, suggested that the hospital volume for RH might deeply affect the survival outcome of patients with stage IB1-IIB UCC, and surgery at high-volume centers was associated with decreased local recurrence risk and improved survival (Matsuo et al. 2019b). Mikami et al. (2018) also suggested that patients with UCC treated in JSGO accredited institutions showed significantly better survival outcome than those in JSGO non-accredited institutions in Japan. Since the curability of RH profoundly affects the outcome in patients with stage IB-IIB UCC, gynecologic oncologists have to strictly examine the patient before treatment and determine which is the better treatment, the RH-based approach or radiotherapy, for patients with stage IB-IIB UCC.

### Neoadjuvant Chemotherapy (NAC) Followed by RH

The aim of the strategy of NAC followed by RH is the goal of downstaging of the tumor to improve the surgical curability and safety of RH and inhibition of micrometastasis and distant metastasis (Ebina et al. 2019). Some authors evaluated the efficacy and safety of NAC followed by RH in patients with stage IB-IIB UCC in prospective studies (Table 3) (Angioli et al. 2012; Yamaguchi et al. 2012; Shimada et al. 2016; Tanioka et al. 2017). However, if patients did not respond to NAC and were not eligible for RH, NAC induced negative impacts of definitive radiotherapy, including CCRT, and decreased the survival of these patients. It remains uncertain whether NAC followed by RH is beneficial for patients with stage IB3, IIA2, and IIB UCC. As a result, JGOG survey showed that 44 institutions (45.5%) in Japan positively performed NAC followed by RH (Mikami et al. 2014).

A Gynecologic Oncology Group (GOG) randomized phase III study (GOG141) revealed that there was no evidence that NAC followed by RH offered any additional benefit to patients with stage IB3 UCC (Eddy et al. 2007). An international collaborative meta-analysis of NAC reported that NAC reduced the need of adjuvant radiother-

Table 3. Perioperative chemotherapy for patients with cervical cancer.

Author (year)	Stage	Histology	Numbers	Regimen	Response rate
Neoadjuvant chemotherapy					
Yamaguchi et al. (2012)	IB2-IIB	SCC	68	CPT-11/NDP <sup>*1</sup>	75.8%
Angioli et al. (2012)	IB2-IIB	SCC/nSCC	115	PTX/CDDP <sup>*2</sup>	87%
Shimada et al. (2016)	IB2-IIB	nSCC	61	DTX/CBDCA <sup>*3</sup>	69%
Tanioka et al. (2017)	IB2-IIB	SCC/nSCC	51	PTX/CDDP <sup>*4</sup>	94%
Mori et al. (2019)	IB2-IIB	SCC	32	CPT-11/NDP <sup>*1</sup>	81.2%
Author (year)	Histology	Numbers	Risk	Regimen	5-year survival rate
Adjuvant chemotherapy after radical hysterectomy					
Takeshima et al. (2006)	SCC/nSCC	65	IR/HR	BLM/VCR/MMC/CDDP <sup>*5</sup>	IR: 93.3% <sup>※1</sup> HR: 85.7% <sup>※1</sup>
Hosaka et al. (2012)	SCC/nSCC	32	IR/HR	PTX/CDDP <sup>*6</sup>	93.8%
Sato et al. (2016)	nSCC	37	HR	PTX or DTX/CBDCA <sup>*7</sup>	64.7%
Matoda et al. (2018)	SCC	62	HR	CPT-11/NDP <sup>*1</sup>	86.5%
Takekuma et al. (2018)	SCC	62	HR	PTX/NDP <sup>*8</sup>	93.5% (2-yr OS)

SCC, Squamous cell carcinoma; nSCC, non-squamous cell carcinoma; IR, intermediate risk; HR, high risk; OS, overall survival; CPT-11, irinotecan; NDP, nedaplatin; PTX, paclitaxel; CDDP, cisplatin; DTX, docetaxel; CBDCA, carboplatin; BLM, bleomycin; VCR, vincristine; MMC, mitomycin

<sup>\*1</sup>CPT-11, 60 mg/m<sup>2</sup>; NDP, 80 mg/m<sup>2</sup>; every 3 weeks.

<sup>\*2</sup>PTX, 175 mg/m<sup>2</sup>; CDDP, 100 mg/m<sup>2</sup>; every 3 weeks.

<sup>\*3</sup>DTX, 60 mg/m<sup>2</sup>; CBDCA, AUC = 6; every 3 weeks.

<sup>\*4</sup>PTX, 80 mg/m<sup>2</sup>, days 1, 8, and 15; CDDP, 75 mg/m<sup>2</sup>, day 1; every 3 weeks.

<sup>\*5</sup>BLM: 5 mg/body for 7 consecutive days; VCR, 0.7 mg/m<sup>2</sup>, day 7; MMC, 7 mg/m<sup>2</sup>, day 7; CDDP, 10 mg/m<sup>2</sup>, days 1-7; every 4 weeks.

<sup>\*6</sup>PTX, 135 mg/m<sup>2</sup> for 24 h, day 1; CDDP, 50 mg/m<sup>2</sup>, day 2; every 4 weeks.

<sup>\*7</sup>PTX, 175 mg/m<sup>2</sup> (or DTX, 60 mg/m<sup>2</sup>); CBDCA, AUC = 6; every 3 weeks.

<sup>\*8</sup>PTX, 175 mg/m<sup>2</sup>; NDP, 80 mg/m<sup>2</sup>; every 4 weeks.

※15-year disease-free survival.

apy by decreasing pathological risk factors and distant metastasis but concluded that NAC followed by RH failed to improve survival compared to RH without NAC in patients with stage IB1-IIA UCC (Kim et al. 2013). Recently, at the American Society of Clinical Oncology annual meeting, the randomized phase III study (EORTC55994) compared NAC followed by RH (NACT) and cisplatin (CDDP)-based CCRT (C-CCRT) in 626 patients with stage IB2-IIB UCC between May 2002 and June 2014 (NACT, 314 patients; C-CCRT, 312 patients) (Kenter et al. 2019). With a median follow-up duration of 8 years, the 5-year OS was not significantly different between the NACT group and C-CCRT group (5-year OS rate, NACT vs. C-CCRT, 71.7% vs. 75.5%,  $p = 0.297$ ). The 5-year progression-free survival (PFS) was significantly longer in the CCRT group compared to that in the NACT group (5-year PFS rate, NACT vs. C-CCRT, 56.9% vs. 65.6%;  $p = 0.021$ ), but in patients who underwent protocol-scheduled treatment, the difference was not significant (5-year PFS rate, NACT vs. C-CCRT, 61.8% vs. 67.7%;  $p = 0.154$ ).

Consequently, the strategy for NAC followed by RH needs a high response rate (RR) of NAC and high curability of RH. Since the JGOG study suggested that surgery at high-volume centers might be associated with decreased local recurrence risk and improved survival (Matsuo et al. 2019b), NAC followed by RH is the optional strategy for patients with stage IB3, IIA2, and IIB UCC at the appropriate institutions, such as high-volume centers. As a promising chemotherapeutic regimen of NAC, Tanioka et al. (2017) reported that dose-dense paclitaxel (PTX)/cisplatin (CDDP) (PTX, 80 mg/m<sup>2</sup>, day1, 8, 15; every 21 days, CDDP, 75 mg/m<sup>2</sup>, day1) before and after RH in 51 patients with stage IB2, IIA2, and IIB UCC (FIGO 2014) showed a high pathological complete response (pCR) rate (RR, 94%; pCR, 28%), and 5-year OS was 88.2% in the phase II study.

A meta-analysis of 11 studies analyzed the impact of NAC followed by RH on clinical outcomes in patients with various histological subtypes of UCC (He et al. 2014). The 5-year OS of patients with SCC was significantly better than of those with nSCC (HR, 1.47; 95% CI, 1.06-2.06), suggesting that nSCC is less chemosensitive than SCC. Some previous retrospective studies reported that the RR of patients with nSCC to NAC was relatively lower, ranging from 50% to 67% (Lissoni et al. 1997; Iwasaka et al. 1998; Saito et al. 2004). Since nSCC is a relatively rare histological subtype, few prospective or randomized studies focusing on this rare disease revealed the most appropriate chemotherapeutic regimen for patients with nSCC of the uterine cervix. Shimada and coworkers (2016) conducted a phase II study to evaluate the efficacy of NAC with docetaxel (DTX) and carboplatin (CBDCA) followed by RH in 51 eligible patients with stage IB3, IIA2, and IIB nSCC. In this phase II study, DTX/CBDCA combination chemotherapy showed an RR of 69% (complete response, 5; partial response, 31; stable disease, 15; progressive dis-

ease, 1) in the NAC setting. Recently, a JGOG nationwide retrospective cohort study evaluated the efficacy of the NAC regimen for various histological subtypes of stage IB-IIB UCC (Matsuo et al. 2019a). A JGOG study also reported that, among women who underwent NAC followed by RH, the disease-free survival tended to be worse in patients with nSCC than those with SCC. In addition, the use of taxane/platinum combination chemotherapy regimens for NAC significantly increased between 2004 and 2008, but taxane/platinum regimens showed a similar effect on survival compared to non-taxane/platinum regimens.

### **Definitive Radiotherapy as Primary Treatment for Patients with Stage IB-IIB UCC**

The mainstay treatment for locally advanced UCC is CCRT. Based on the results of landmark randomized trials, the NCCN guidelines mainly recommend CDDP-based CCRT as the most appropriate treatment for patients with stage IB3, IIA2, and IIB-IVA UCC, regardless of histological subtype (Keys et al. 1999; Rose et al. 1999; Whitney et al. 1999) (NCCN Guidelines® Cervical Cancer version 2.2020). Similar to the NCCN guideline, most guidelines do not subclassify treatment recommendation by histological subtype. As a result, a Cochrane systematic review revealed that CCRT reduced the mortality risk compared to conventional radiotherapy alone (HR, 0.81; 95% CI, 0.71-0.91) and improved the 5-year OS rate by 6% in patients with locally advanced UCC (from 60% to 66%) (CCCMAC, Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration 2010).

It is still unknown whether the efficacy of CDDP-based CCRT for locally advanced patients with nSCC of the uterine cervix is similar to those with SCC. A GOG retrospective study including 1,489 patients with SCC and 182 patients with nSCC evaluated the efficacy of radiotherapy alone and CCRT by histological subtypes with clinical database of some GOG trials (Rose et al. 2014). Although patients with nSCC had significantly slightly worse OS than those with SCC in patients who underwent radiotherapy alone, CDDP-based CCRT improved OS of patients with nSCC and showed a similar outcome to that of patients with SCC. However, these GOG studies did not include the sufficient subjects of nSCC, and chemotherapeutic regimen was not unified. Some authors suggested that radiosensitivity was poor in patients with nSCC (Niibe et al. 2010; Huang et al. 2011; Lee et al. 2015; Yokoi et al. 2017). The retrospective analysis by the national database in Korea reported that adenocarcinoma was still associated with worse OS compared to SCC in the era of CCRT (HR, 1.40; 95% CI, 1.30-1.50), although the survival of adenocarcinoma was improved after the introduction of CCRT (Lee et al. 2015). Thus, half of all Japanese gynecologic oncologists (53.7%: 88/164) selected RH for patients with stage IIB nSCC, while one third (35.5%: 59/164) selected RH for those with SCC (Mikami et al. 2014).

To further improve the efficacy of CDDP-based CCRT,

which is basically used with CDDP at a dose of 40 mg/m<sup>2</sup>/week, several authors investigated new CDDP-based CCRT by several combination chemotherapy regimens, along with changes in dose and timing (Dueñas-González et al. 2011; Umayahara et al. 2016; Chen et al. 2017). The randomized trial involving 515 patients with stage IIB-IVA UCC showed that CCRT with CDDP/gemcitabine (GEM) improved OS compared to conventional CDDP-based CCRT (HR, 0.68; 95% CI, 0.49-0.95, *p* = 0.022) (Dueñas-González et al. 2011). However, CCRT with CDDP/GEM also significantly increased severe hematologic toxicity and diarrhea. In addition, the optimal timing of CDDP/GEM during CCRT has been unclear, and CCRT with CDDP/GEM is not currently recommended. Umayahara et al. (2016) conducted the phase study of CCRT with weekly CDDP at 30 mg/m<sup>2</sup> and PTX at 50 mg/m<sup>2</sup> in patients with stage III-IVA UCC (JACCRO GY-01). In 60 eligible patients, the complete RR was 76.5% (95% CI, 66.4-86.6%), and the 2-year cumulative PFS and OS rates were 83.8% (95% CI, 75.1-92.6%) and 92.7% (95% CI, 86.4-98.9%), respectively (Umayahara et al. 2016). The 2-year cumulative late complication rate was 25% for all grades with 2.9% for grade 3 and 2.9% for grade 4, suggesting that CCRT with weekly CDDP and PTX might be one of the alternative strategies for locally advanced patients with UCC. Evaluation of these new CDDP-based CCRT in the phase III trial is warranted to assess the efficacy of patients with nSCC of the uterine cervix.

### Adjuvant Treatment after RH

Based on the histopathological findings of surgical specimens, patients were divided into three recurrent-risk groups: low-risk group, intermediate-risk group, and high-risk group in JSGO guidelines (Ebina et al. 2019). Patients in the low-risk group met all of the following criteria: small cervical tumor ( $\leq 4$  cm), negative pelvic node involvement, negative parametrial invasion, shallow cervical stromal invasion, and absence of lymphovascular space invasion. Patients in the intermediate-risk group had negative pelvic node involvement and negative parametrial invasion but who met one of the following criteria: large cervical tumor ( $> 4$  cm), deep cervical stromal invasion, and positive lymphovascular space invasion. Patients in the high-risk group met one of the following criteria: positive pelvic node involvement and positive parametrial invasion. The JSGO treatment guideline recommended adjuvant radiotherapy, such as radiotherapy alone or CCRT, for patients in the intermediate-risk group and adjuvant CCRT with weekly CDDP at a dose of 40 mg/m<sup>2</sup> for those in the high-risk group (Ebina et al. 2019).

Yessaian et al. (2004) reported that approximately 50% of patients had intermediate-risk factors, approximately 40% of them had high-risk factors, and only 10% of them had no pathological recurrent risk factors among patients with stage IB2 UCC (FIGO 2008). Then, only approximately 10% of patients with stage IB2 (FIGO 2008) can be

adequately treated with RH as an upfront single modality. The multimodality strategy consisting of RH followed by adjuvant radiotherapy is associated with not only impaired quality of life but also high cost. In addition, if patients have pelvic recurrence, they lose a useful treatment “radiotherapy” for recurrent disease in pelvis.

The significance of multimodality strategy consisting of chemotherapy before and after RH is evaluated (Angioli et al. 2012; Tanioka et al. 2017; Mori et al. 2019). These studies suggested a good outcome of multimodality strategy, which combined chemotherapy and RH, in patients with stage IB2-IIB UCC. However, these studies were not randomized studies but just phase II studies that included relatively small numbers of patients with stage IB2-IIB disease.

### Adjuvant Radiotherapy after RH

The JSGO guidelines recommend whole-pelvis irradiation, with a dose of 40-50 Gy (in fractions of 1.8-2.0 Gy/day), as adjuvant treatment for intermediate/high-risk patients after RH (Ebina et al. 2019). The clinical target volume of whole pelvic radiotherapy includes the pelvic lymph node region, supravaginal region (from the vaginal stump to approximately 3 cm of the lower part), parametrial tissue, and paravaginal tissue. In patients with intermediate risk, radiation therapy or CCRT was recommended depending on the number of recurrent-risk factor.

The GOG092 study was a pivotal study that investigated the significance of radiotherapy alone for patients with intermediate-risk cervical cancer after RH (Sedlis et al. 1999). Adjuvant radiotherapy showed a 47% reduction in the risk of recurrence compared to the absence of further adjuvant treatment. However, the improvement in OS with adjuvant radiotherapy did not reach statistical significance, while patients allocated to the adjuvant radiotherapy group had an increased incidence of severe toxicities compared with the no further adjuvant treatment group. Recently, Tsuchida et al. (2019) reported that intensity-modulated radiation therapy (IMRT) can reduce the radiation dose for normal tissues, including the small intestine, rectum, and bladder, used adjuvant irradiation. The Japan Clinical Oncology Group (JCOG) evaluated the efficacy and safety of IMRT as adjuvant treatment for high-risk patients in a nonrandomized confirmatory trial (JCOG 1402; jRCTs031180194).

In high-risk patients, CCRT with weekly CDDP at a dose of 40 mg/m<sup>2</sup> was basically recommended as adjuvant treatment after RH. The landmark clinical trial of adjuvant irradiation for high-risk patients with UCC is the randomized phase III trial to determine whether the addition of CDDP/5-fluorouracil (FU) chemotherapy to pelvic irradiation can improve the survival of high-risk patients (Peters et al. 2000). In this phase III study, CCRT with CDDP/5-FU chemotherapy showed a significant improvement in PFS and OS of high-risk patients with UCC compared to pelvic irradiation alone.

PTX and CDDP combination chemotherapy was reported to be more effective than CDDP alone for advanced/recurrent UCC (Moore et al. 2004). The JCOG also showed that PTX and CBDCA combination chemotherapy was non-inferior to PTX/CDDP chemotherapy for stage IVB and recurrent cervical cancer in the randomized phase III study (JCOG0505) (Kitagawa et al. 2015). Expecting to further improve the curative effect of CCRT for UCC, some authors evaluated the efficacy and safety of CCRT with PTX/CDDP or carboplatin (CBDCA) combination chemotherapy regimen. The phase II trial of IMRT with concurrent PTX/CDDP chemotherapy as adjuvant treatment for 67 patients with high-risk UCC demonstrated that the 4-year relapse-free survival, locoregional control, and distant failure rates were 92.9%, 98.0%, and 5.2%, respectively (Wang et al. 2015). After the evaluation of surgical specimens, patients underwent the first cycle of PTX/CDDP chemotherapy (PTX, 135 mg/m<sup>2</sup>; CDDP, 70 mg/m<sup>2</sup>) before radiotherapy. With 3 weeks interval from the first systemic chemotherapy cycle, patients received the second and third cycles of PTX/CDDP chemotherapy (PTX, 90 mg/m<sup>2</sup>; CDDP, 50 mg/m<sup>2</sup>) every 3 weeks during IMRT. After 3-4 weeks from the end of IMRT, the fourth cycle of PTX/CDDP chemotherapy was administered. CCRT with PTX/CDDP chemotherapy may be one of the most effective adjuvant radiotherapy for patients with high-risk UCC.

The Japanese retrospective study reported that, among patients receiving adjuvant radiotherapy after RH, patients with nSCC more frequently had recurrence compared to those with SCC, particularly in the pelvic cavity (Shimada et al. 2013a). In addition, a multi-institutional retrospective analysis of JCOG reported that gastric-type mucinous carcinoma (GAS) of the uterine cervix showed significantly higher resistance to postoperative radiotherapy compared to those with usual-type endocervical adenocarcinoma (UEA) (50%, 6/12 vs. 81.8%, 9/11;  $p < 0.0001$ ) (Nishio et al. 2019). Accordingly, a new adjuvant strategy, including molecular targeting therapy, is necessary for high-risk patients with non-SCC to reduce local recurrence and hematogenous distant metastasis as low as possible.

### Adjuvant Chemotherapy after RH

Based on the evaluation of surgical-pathological information obtained from the surgical specimen, patients with pathological risk of recurrence were recommended to receive radiotherapy or CDDP-based CCRT as adjuvant treatment. In patients with stage IB<sub>3</sub>, IIA<sub>2</sub>, and IIB UCC (FIGO 2018), the NCCN guidelines mainly recommended CDDP-based CCRT as the most appropriate treatment based on the results of previous randomized phase III trials.

Eifel et al. (1995) suggested that adenocarcinoma had statistically significantly increased distant relapse rates compared with SCC regardless of tumor size in patients with stage IB disease receiving radiotherapy. Our previous study, which included 3,471 surgically treated patients with stage IB-IIB UCC, also suggested that non-SCC predomi-

nantly recurred hematogenously, whereas SCC recurred lymphatically (Shimada et al. 2006). Adjuvant radiotherapy sometimes caused late adverse complications because of the anatomic locations, such as gastrointestinal complication, lower-limb lymphedema (Hosaka et al. 2008; Deura et al. 2015; Machida et al. 2019). Machida et al. (2019) reported that postoperative adjuvant chemotherapy increased the frequencies of bladder dysfunction after RH in patients with UCC by JGOG retrospective study. Thereby, many gynecologic oncologists in Japan also evaluated the superiority of adjuvant chemotherapy according to the complication rate (Ikeda et al. 2016). Several authors reported the efficacy of adjuvant chemotherapy in patients with intermediate/high risk of UCC after RH in Japan (Table 1) (Takeshima et al. 2006; Hosaka et al. 2012; Sato et al. 2016; Matoda et al. 2018; Takekuma et al. 2018). Sato et al. (2016) investigated the efficacy of adjuvant chemotherapy using taxane and CBDCA for patients with high-risk stage IB- IIB UCC after RH in their feasibility study. Of 37 eligible patients, 22 patients received PTX/CBDCA chemotherapy, and the remaining 15 patients received docetaxel (DTX)/CBDCA chemotherapy. With a median follow-up duration of 42.3 months, the 2-year PFS rate was 62.1% (95% CI, 44.6-75.5%). Patients receiving DTX/CBDCA chemotherapy showed better 2-year PFS than those receiving PTX/CBDCA chemotherapy, but the difference was not statistically significant (80.0% vs. 50.0%,  $p = 0.14$ ). Since the subjects of this feasibility study showed the worst outcome in patients who underwent RH, taxane/CBDCA combination chemotherapy, especially DTX/CBDCA chemotherapy, was one of the alternative chemotherapeutic regimens as postoperative adjuvant chemotherapy in pathological-risk patients with nSCC (Sato et al. 2016).

The JGOG retrospective cohort study examined survival of 555 women with stage IB disease in the intermediate-risk group (large tumor size > 4 cm, deep stromal invasion > 50%, lymphovascular space invasion) by adjuvant treatment patterns: chemotherapy alone ( $n = 223$ , 40.2%), CCRT ( $n = 172$ , 31.0%), and radiotherapy alone ( $n = 160$ , 28.8%) (Matsuo et al. 2017b). The most preferred chemotherapy regimen was taxane/platinum combination chemotherapy (52.2%). Women with nSCC were more likely to receive chemotherapy compared to those with SCC. Women who received adjuvant chemotherapy showed similar disease-free survival, cause-specific survival, cumulative local recurrence, and distant recurrence compared to those who received other adjuvant treatments, such as CCRT and radiotherapy alone. In another JGOG retrospective cohort study examining 1,074 women with pelvic node-positive stage IB-IIB cervical cancer who underwent RH, women who received adjuvant chemotherapy had similar survival outcomes compared to those who received CCRT (Matsuo et al. 2017a). However, systematic chemotherapy and irradiation had distinct recurrence patterns. While systematic chemotherapy was associated with increased risk of local

recurrence compared to CCRT, systematic chemotherapy was associated with decreased risk of distant recurrence compared to CCRT. Consequently, the higher curability with RH, such as the Okabayashi's RH, is indispensable for adjuvant chemotherapy in high-risk patients with UCC.

Since there is no prospective randomized study to compare chemotherapy and CCRT as adjuvant treatment for intermediate/high-risk patients who underwent RH, validity of postoperative chemotherapy is not yet confirmed. Consequently, the JSGO guidelines 2017 did not describe the recommendation of adjuvant chemotherapy for intermediate/high-risk patients with cervical cancer (Ebina et al. 2019). The JGOG conducted the randomized phase III study to investigate the efficacy and safety of adjuvant chemotherapy for patients with high-risk cervical cancer compared to those of CDDP-based CCRT (JGOG1082; JRCTs041190042).

### GAS of the Uterine Cervix

GAS of the uterine cervix is a relatively newly recognized variant of endocervical adenocarcinoma initially described by Japanese groups (Ishii et al. 1998; Mikami et al. 2004; Kojima et al. 2007) and was included as a subtype of endocervical mucinous adenocarcinoma in the World Health Organization (WHO) classification updated in 2014 (Kurman et al. 2014). It is defined as a mucinous carcinoma showing gastric-type differentiation, including minimal deviation adenocarcinoma (so-called adenoma malignum) in its morphologic spectrum. In contrast to UEA, GAS is frequently located in the upper endocervix and shows a bulky cervix without well-demarcated mass due to its highly infiltrating pattern of growth. While most UEAs are mostly related to human papillomavirus (HPV), GAS is reported to be unrelated to HPV (Mikami 2020) and importantly is associated with aggressive clinical behavior, and its outcome is worse than UEA (Kojima et al. 2007; Kusanagi et al. 2010; Houghton et al. 2010; Park et al. 2011; Karamurzin et al. 2015; Nishio et al. 2019). Of 328 eligible patients with endocervical adenocarcinoma in the JCOG retrospective study, 95 cases were reclassified as GAS by a central pathological review (Nishio et al. 2019). Compared to UEA, GAS was more significantly associated with bulky mass, deep stromal invasion, lymphovascular space invasion, parametrial invasion, ovarian metastasis, positive peritoneal cytology, pelvic lymph node involvement, and pathological T stage. Disease-free survival and OS were also poorer in patients with GAS than in those with UEA.

Kojima et al. (2018) evaluated the chemosensitivity of GAS compared with UEA in a subgroup of patients who had enrolled in their previous phase II study (Shimada et al. 2016) to investigate the efficacy of DTX/CBDCA combination chemotherapy in patients with stage IB3, IIA2, and IIB nSCC of the uterine cervix. Of 47 patients with nSCC who could be reevaluated by central pathological review, 20 (42.6%) were diagnosed with UEA, 13 (27.7%) with GAS,

and the remaining 14 were diagnosed with other histological subtypes (12, adenosquamous carcinoma; 1, small-cell carcinoma; and 1, serous carcinoma). The RR of GAS was significantly lower than that of UEA (46.2% vs. 85.0%,  $p = 0.048$ ). Of 16 patients with stage II UEA, 11 (68.8%) were down-staged on microscopic examination of postsurgical specimens, but none of the 8 patients with stage II GAS showed any response ( $p < 0.01$ ), and two inoperative tumors were diagnosed as GAS in the previous phase II study (Kojima et al. 2018).

In addition, the subset analysis of a JCOG study suggested that patients with GAS showed significantly higher resistance to radiotherapy compared with those with UEA (Nishio et al. 2019). Taken together, GAS may be resistant to both chemotherapy and radiotherapy compared to UEA. To achieve better oncologic outcome for patients with locally advanced aggressive UCC, such as GAS, various multidisciplinary therapeutic strategies incorporating cisplatin-based CCRT and molecular targeting therapy have been investigated. However, profiles of genomic signature of unusual UCC, represented by GAS, clear cell carcinoma, and serous carcinoma, are still limited, and definite treatment guideline for such cancers remains to be established.

### Survival by Histological Subtype in Patients with UCC

Some retrospective studies assessed the impact of histological type on survival outcome of UCC (Irie et al. 2000; Kasamatsu et al. 2009; Katanyoo et al. 2012; Galic et al. 2012; Shimada et al. 2013b; Seamon et al. 2018), but these studies have limitations, including lack of critical central pathology review, stratification by pathological prognostic factors, or information on management and low incidence of GAS in the series. In contrast, by focusing on histologic subtype, Kojima et al. (2018) demonstrated that patients with stage IB2-IIB UEA showed a high RR of 85% to DTX/CBDCA combination chemotherapy in the phase II study. All patients with UEA underwent RH after NAC and showed a favorable outcome in a similar degree to that in patients with SCC with the matched stage, while GAS showed clearly poorer prognosis. UEA is the most common form of endocervical adenocarcinoma, accounting for 80-90% of all adenocarcinomas of the cervix in many countries. Before the concept and diagnostic criteria of GAS were proposed, most GASs had been categorized into endocervical-type mucinous adenocarcinoma according the WHO 2003 classification (Mikami et al. 2004; Kusanagi et al. 2010). Although GAS is considered rare in Western countries (Holl et al. 2015), it is rather common in Japan, accounting for up to 20-25% of all endocervical adenocarcinomas (Kojima et al. 2007; Kusanagi et al. 2010). Under such a condition, it might affect the prognosis interpretation of the whole adenocarcinoma that there was a regional difference in the GAS frequency (Kojima et al. 2007; Kusanagi et al. 2010; Holl et al. 2015). Machida et al. (2020) also evaluated survival outcome in patients with cer-



vical adenocarcinoma subtype by two grouping as following: type 1 (endocervical usual type and endometrioid) and type 2 (serous, clear, mucinous, and not otherwise specified), using JSGO tumor registry database. They reported that patients with type 2 adenocarcinoma showed significantly worse survival compared with those with SCC (adjusted hazard ratio 2.00, 95% CI 1.84-2.15,  $p < 0.001$ ). Consequently, after controlling for prognostic pathological factors and clinical management, the survival outcome of the majority of patients with adenocarcinoma largely depends on relative incidence of UEA and GAS. In our hypothesis, prognosis of adenocarcinoma may be equivalent to that of patients with matched SCC among a series in which UEA is common, whereas it is not in areas where GAS is relatively common. The latest annual report of JSOG revealed that there were 142 patients with GAS (8.9%) in 2018 among 1,591 patients with endocervical adenocarcinoma (Yaegashi 2020). In contrast, Holl et al. (2015) reported that of 461 cases of cervical adenocarcinoma, there were only 7 patients with GAS (1.5%) in 17 European countries between November 2006 and August 2008.

### Biological Variables by Histological Subtypes in Patients with UCC

IECC proposed to categorize endocervical adenocarcinoma two groups (HPVA and NHPVA) by HPV infection status. Patients with HPVA, including UEA, showed less lymphovascular invasion and lymph node metastasis, better response to conventional treatment, and better survival outcome compared to those with NHPVA, such as GAS (Kojima et al. 2018; Stolnicu et al. 2018, 2019), suggesting that HPV infection status might be a useful clinical biomarker for patients with UCC.

Low expression of p16, p21, and p27 was reported as biomarkers of adenocarcinoma of the uterine cervix (Lu et al. 1998; Alfsen et al. 2003). Low p27 expression and high p16 expression were strongly associated with poor prognosis of adenocarcinoma (Alfsen et al. 2003), and p21 expression was also an independent predictor of good clinical outcome (Lu et al. 1998). Tornesello et al. (2013) reported that patients with adenocarcinoma showed significantly higher p53 mutation than those with SCC in a systematic review of 27 studies, but it is still unclear whether the p53 mutational status is associated with clinical outcome of patients with UCC (Tsuda et al. 1995; Lu et al. 1998; Tornesello et al. 2014).

Ueda et al. (2017) examined the expression profile of epidermal growth factor receptor (EGFR), human EGFR-related 2 (HER2), and c-Met in 43 specimens from patients with adenocarcinoma. Double positive expression of EGFR and HER2 correlated with lymph node metastasis, advanced stage, and worse disease-free survival (Ueda et al. 2017). Nakamura et al. (2019) reported that HER2 expression status was equivocal in 6 of 13 patients with GAS by immunohistochemistry, and HER2 amplification was identified in 1

patient with GAS.

Maspin is a member of the serpin family of protease inhibitors, and its cytoplasmic expression is associated with poorer clinical outcome in several malignancies (Umekita et al. 2002; Takagi et al. 2015). Nosaka et al. (2015) reported that positive immunostaining for maspin in 69.2% of 46 patients with adenocarcinoma of the uterine cervix and demonstrated that maspin-positive cases showed significantly worse 5-year PFS and OS than maspin-negative cases.

### Conclusion

The impact of histological type on survival outcome of UCC is controversial. However, in our hypothesis, the difference in survival outcome by histological subtype might be remarkable with disease progression, and the survival outcome of nSCC might be deeply affected by regional difference in the frequency of GAS of the uterine cervix.

The HPV vaccination program and cytological examination combined with screening testing for HPV were expected to prevent UCC. However, it is still uncertain whether HPV vaccination prevents UCC as trials were not designed to detect this outcome (Rees et al. 2020). In addition, under the circumstance, there are no useful strategies for refractory and uncommon UCC, such as GAS, which is not associated with HPV infection. To achieve better oncologic outcome for patients with locally advanced aggressive, refractory UCC, such as GAS, various multidisciplinary therapeutic strategies incorporating high-quality RH, CDDP-based CCRT, and molecular targeting therapy should be investigated. Unfortunately, profiles of genomic signature of unusual UCC, represented by GAS, clear cell carcinoma, and serous carcinoma, are still unknown. The integrated analysis including genomic profiles for these unusual, refractory UCC should be performed by an international joint research network, such as the Gynecologic Cancer InterGroup.

### Conflict of Interest

The authors declare no conflict of interest.

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