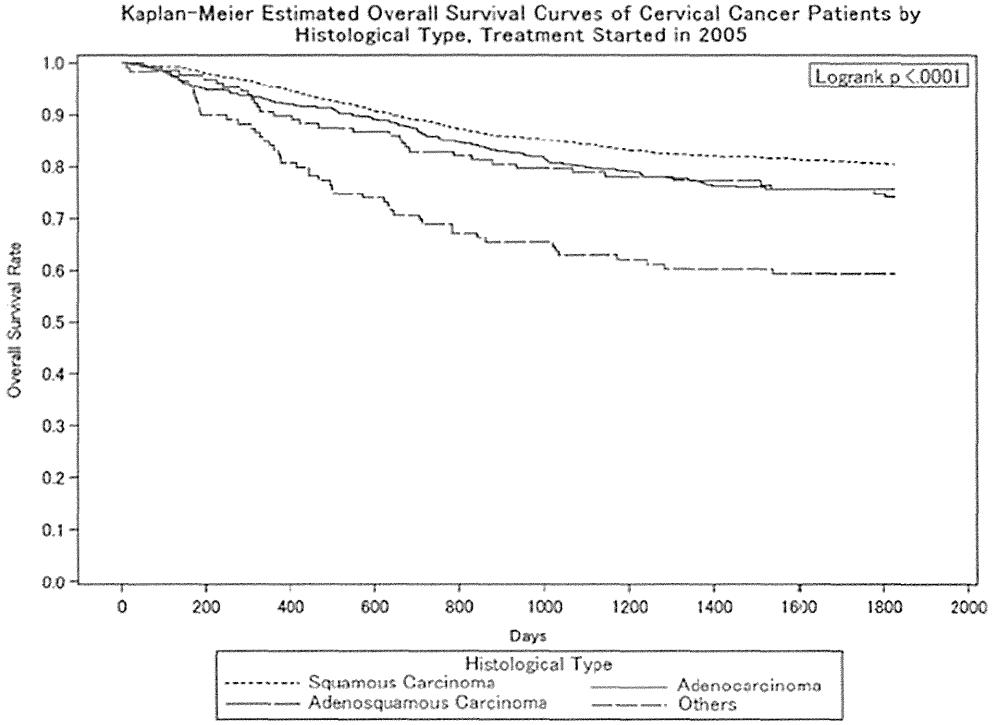

Fig. 1 Kaplan-Meyer survival curve of patients with stages I–IV cervical cancer of the uterus by histological type, treated in 2005 [14] (cited with permission)

Prognostic Factors

Pattern of dissemination has been reported to be different between AC and SCC. Some studies show that the sites of recurrence for SCC are lymphatic, whereas AC seems to disseminate more hematogenously [25]. There are also higher rates of ovarian metastases seen with AC than SCC (5.31 versus 0.79 %) in some series [25]. Thus, the frequency of distant metastasis appears higher in AC than in SCC [16, 26], with a higher tendency for intraabdominal carcinomatosis and hematogenous metastases compared with SCC [25]. For example, there is a report showing that peritoneal cytology was positive in 9 of 228 cervical cancer patients (3.9 %). Three of them were SCC (3/139; 2.2 %) and 6 of them (6/89; 6.7 %) were AC. Only 30 % of patients with SCC who had positive cytology recurred, while all patients with AC had recurrence. In this study, multivariate analysis revealed that peritoneal cytology (p=0.029) and histological type (p=0.004) were independent prognostic factors [27].

Tumor size also appears to be a significant prognostic factor with AC being more endophytic and "bulkier." Several studies have shown that tumors >4 cm have a worse prognosis for AC compared to SCC [16]. It has also been reported that AC is more likely to have lymph node involvement compared to SCC resulting in a worse prognosis [16, 28].

One possible explanation for the worse prognosis among women with AC might be a lower sensitivity to radiotherapy [29]. Eifel et al. reported worse prognosis of stage IB AC patients than SCC when the majority of patients were treated with radiotherapy [16]. Subset analyses of several studies also suggest a higher recurrence rates after radiation in AC compared to SCC [30].

Pathology

A better understanding of the histopathology may help explain the differences in the pathogenesis and outcomes of AC compared to SCC.

Pathologically, AC is more heterogeneous than SCC. Although SCC has several subtypes as shown in Table 1, most of them (more than 90 %) are non-keratinizing or keratinizing. In contrast, the distribution of subtypes of AC varies (Table 1). This may explain the clinical differences in the behavior of AC versus SCC.

To identify the distinguishing features between endocervical AC and endometrial subtypes of AC, immunohistochemistry is usually used. Carcinoembryonic antigen (CEA) and p16 expression (a surrogate of HPV) together with the absence of hormone receptors and vimentin favor a cervical origin.

Cervical ACs are subdivided into several histological subtypes as outlined below [1•].

Usual-type adenocarcinoma

Usual-type adenocarcinoma is the most common subtype, accounting for 80–90 % of all cervical AC [31]. In the past, this variant has been referred to as mucinous AC, but there is no or little mucin in the

Table 1 WHO Classification of carcinoma of the uterine cervix [1•]

Adenocarcinoma	Percentage	Squamous cell carcinoma
Endocervical adenocarcinoma, usual type	80	Keratinizing
Mucinous carcinoma, NOS		Non-keratinizing
Gastric type	1–2	Papillary
Intestinal type		Basaloid
Signet ring cell type		Warty
Villoglandular carcinoma		Verrucous
Endometrioid carcinoma	5–7	Squamotransitional
Clear-cell carcinoma	2–4	Lymphoepithelioma like
Serous carcinoma	3	
Mesonephric carcinoma		
Adenocarcinoma admixed with neuroendocrine carcinoma		
Adenosquamous carcinoma	4	
Glassy cell variant	1–2	

	majority of cells. The tumor is composed of glands of varying sizes and papillae lined by columnar cells with eosinophilic cytoplasm and brisk mitotic activity and frequent apoptotic bodies. There is a frequent association with adenocarcinoma in situ, which is the precursor of this type of carcinoma. In 12 % of cases, the depth of stromal invasion is less than 5 mm from base of the surface epithelium, corresponding to an *early invasive AC*. Usual type of cervical ACs are always associated with high-risk HPV.
Mucinous adenocarcinoma	Mucinous adenocarcinoma is characterized by the presence of abundant cytoplasmic mucin in the majority of tumor cells. They are subdivided into gastric and intestinal-type endocervical adenocarcinomas.
Mucinous carcinoma, gastric-type	Mucinous carcinoma, gastric-type [32, 33] is rare in Western countries but represents up to 20 % of cervical ACs in Japan. This tumor is composed of glands with a pyloric phenotype (voluminous, clear, pale eosinophilic cytoplasm, and distinct cell borders) and immunoprofile (HIK1083 and MUC6 expressions). There is no association with HPV. The patients with this type of mucinous carcinomas have a poor prognosis with a decreased 5-year survival rate of 30 versus 77 % for usual-type adenocarcinoma.
Minimal deviation adenocarcinoma (adenoma malignant)	Minimal deviation adenocarcinoma (adenoma malignant) is an uncommon variant of gastric-type mucinous carcinoma of the cervix (1.3 %), extremely well differentiated, seen in women at any age (20–78, mean 45 years) [34]. This tumor may arise in patients with Peutz-Jeghers syndrome, with germline inactivation of the *LKB1* (STK11) gene. Sporadic adenoma malignant displays also a loss of heterozygosity at *LKB1* (STK11) locus [35]. HPV DNA is not detected in these tumors which are usually not associated with an in situ AC component. Patients usually present with high-stage tumor because of the delay in the diagnosis and having a poor prognosis, with 30 % overall survival at 2 years.

Mucinous carcinoma, intestinal type	Mucinous carcinoma, intestinal type [33], is rare and is composed of glands with goblet cells and rarely Paneth cells. MUC-2, a goblet cell marker, is detected in 85 % of cases. The tumor may present with extensive extra glandular mucin and a colloid carcinoma appearance. An intestinal-type adenocarcinoma in situ may be seen in association with the invasive component. High-risk HPV has been detected in this variant.
Mucinous carcinoma, signet ring cell type	Mucinous carcinoma, signet ring cell type, is very rare and shows focal or diffuse signet ring cell morphology.
Villoglandular adenocarcinoma	Villoglandular adenocarcinoma shows a distinct exophytic, villous-papillary growth, and is characterized by a frond-like pattern resembling villoglandular adenoma of the colon. This tumor usually occurs in younger women and has an excellent prognosis in its pure form [36]. When superficially invasive, this variant has an excellent prognosis with very rare lymph node metastases. HPV 16, 18, or 45 have been identified.
Endometrioid adenocarcinoma	Endometrioid adenocarcinoma account for 5 % of cases and presents the same morphology than its endometrial counterpart, even though squamous metaplasia is less common. This histological type of AC may be developed from cervical endometriosis, but usually, adenocarcinoma in situ (sometimes of endometrioid type) is seen in close vicinity of the tumor.
Clear-cell adenocarcinoma	Clear-cell adenocarcinoma is composed of glands, cysts, and papillae lined by clear or hobnail cells. This type of cervical carcinoma is very rare (2 %) and has been associated with in utero exposition to diethylstilbestrol (DES).
Serous adenocarcinoma	Serous adenocarcinoma is also very rare in the cervix accounting for less than 2 % of cases. A diagnosis of primitive cervical serous AC should not be rendered until a primary serous carcinoma in the endometrium has not been excluded. Most are HPV related. The morphology and the immunoprofile of serous AC of the cervix are identical to its counterparts in the female genital tract and peritoneum except for a solid pattern which is rare [37].
Mesonephric adenocarcinoma	Mesonephric adenocarcinoma is a rare variant of cervical AC that is developed from cervical mesonephric remnants and is typically HPV unrelated, seen in reproductive and postmenopausal women [38]. The tumor may be incidentally found but a cervical mass is usually seen. Tubular, ductal, retiform (with slit-like spaces), and solid patterns have been described. The cells are columnar with atypia and mitoses. Typically, a colloid-like material is seen in the lumen of tumor glands, and mesonephric remnants are seen at the periphery of AC. The tumor expresses both keratin and vimentin, with androgen receptor and CD10 positivity. This variant is usually of stage I at the time of diagnosis and has a good prognosis except for those with a sarcomatoid component.
Adenocarcinoma admixed with neuroendocrine carcinoma	Adenocarcinoma admixed with neuroendocrine carcinoma is a tumor with a little component of AC either in situ or invasive. The bulk of the tumor is composed of neuroendocrine carcinoma,

Table 2 Comparison between squamous and various types of adenocarcinomas of the uterine cervix [2, 3, 5, 30, 47–53]

Cervical carcinomas	Squamous cell carcinoma	Endocervical adenocarcinoma, usual type	Mucinous carcinoma, gastric-type adenoma malignum	Mucinous carcinoma, intestinal type	Clear-cell carcinoma	Adenosquamous carcinoma
Incidence Mean age at diagnosis	75 % of cases 52 years old	20–25 % of cases 46 years old	Most frequent in Japan: 20 % of ADC Adenoma malignum: 1 % 42 years old	Rare pure signet ring cells and colloid ADC are rare	Rare DES exposure: 19 years old Sporadic: 47 years old	4 % of cervical cancers 28 % of ADC
Precursor	SIL	AIS	Atypical LEGH	AIS, intestinal type	None	SIL and AIS Possible: SMILE
Morphology	Polygonal, spindle cells Masses with central keratin and necrosis	Columnar cells Glands, papillae, and solid pattern Scant intracellular mucin Apoptotic bodies	Small and cystic glands Gastric and pyloric type mucin	Glands and papillae Goblet cells, argentaffin, and Paneth cells	Tubulo-cystic, papillary pattern Clear (glycogen rich), hobnail cells with high-grade nuclei	Malignant-appearing squamous and glandular elements
Immunoprofile	Pankeratin +++ CK7 −/+ CK14 + CK5/6 + Neuroendocrine markers usually − P16 +++ TTF1 − P63 +++ CEA − ER and PR usually +	Pankeratin +++ CK7 +++ Neuroendocrine markers usually − P16 +++ TTF1 − P63 usually − CEA cytoplasmic +++ ER and PR usually −	Pankeratin +++ CK7+++ CK 20 focally + HIK1083 + MUC6 + P16 usually − CEA + (apical borders) P53 may be +++ ER and PR −	Pankeratin +++ CK7 +++ CK20 focally + CDX2 focally + CEA + P16 +++	Pankeratin +++ CK7+++ ER and PR − P16 − (patchy +) CEA − HNF1 beta +++	Pankeratin +++ CK7 + and CEA + in ADC elements CK5/6 + in squamous P16 +++
Molecular biology	HPV 16 > HPV 18 (15 %) *TP53* mutation 5.9 % (codon 249) Deletion of 3p (85 %) Deletion 9p21 (11 %) Gain 20q (>50 %) 10 % *EGFR* amplification Rare *KRAS* mutations	HPV 18 (50 %) > HPV 16 *TP53* mutation 13.3 % (codon 282) Deletion 3p Deletion 2q (25 %) Deletion 5p (38 %) No *EGFR* amplification No *KRAS* mutation	No HPV-related association to Peutz-Jeghers syndrome Mutations in STK11 tumor suppressor gene on chromosome 19p in 50 % of cases	High-risk HPV related	In utero exposure to DES (unrelated to HPV) Sporadic: may be associated to high-risk HPV	HPV 18 > HPV 16 Loss of expression of ARID1A
Behavior	16.9 % stage IB1 at diagnosis	26.7 % stage IB1 at diagnosis	Higher stage at diagnosis due to lack of cytology/		85 % stage I or II Positive lymph nodes 18 %	Prognosis is worse with dead rates 1.8 times greater

Table 2 (continued)

Cervical carcinomas	Squamous cell carcinoma	Endocervical adenocarcinoma, usual type	Mucinous carcinoma, gastric-type adenoma malignum	Mucinous carcinoma, intestinal type	Clear-cell carcinoma	Adenosquamous carcinoma
	Positive lymph nodes (15–20 % stage IB, 50 % stage III) Pelvic recurrences Distant metastases rare (lung 6 %)	Positive lymph nodes 20 % Metastases ovary (5 %), intraabdominal, para-aortic lymph nodes, adrenal glands, lung, and pleura	molecular screening sensitivity 5-year survival 30 % (versus 77 % usual ADC) Early peritoneal and abdominal spread (ovarian metastases) Possible synchronous mucinous and neoplasia in female genital tract		of stage I and 50 % of stage II Distant metastases <3 years (lung, supraclavicular nodes)	than SCC and 2.8 times greater than ADC

LEGH lobular endocervical glandular hyperplasia, *AIS* adenocarcinoma in situ, *SMILE* stratified mucin-producing intraepithelial lesion, *SIL* squamous intraepithelial lesion

usually high grade with small cell morphology. The prognosis is that of small cell neuroendocrine carcinoma of the cervix.

Molecular

In contrast to squamous cell carcinomas, which are the most frequent tumors of the cervix, a few molecular alterations have been described for adenocarcinomas. Gene expression profiling showed upregulation of four genes (*CEACAM5*, *TACSTD1*, *S100P*, and *MSLN*) belonging to the tetraspanins family that might be associated with tumor progression [39]. More recently, oncogenic mutations have been identified in *PI3KCA* (25 %) and *KRAS* (17.5 %) genes [40].

Table 2 summarizes the difference of adenocarcinomas and squamous cell carcinomas of the uterine cervix.

Future Imprecations

As indicated in this review, uterine cervical AC is clearly different from SCC based on its molecular pathogenesis, histological appearance, and clinical behavior. Therefore, it will be necessary to make a different treatment strategy, particularly for patients with locally advanced and metastatic or recurrent disease. This needs to be integrated into international guidelines in order to change practice patterns. Those strategies might include neoadjuvant chemotherapy for stages IB2 to IIB disease. Since the prognosis is not optimal for this patient population when treated by current standard CCRT or radical hysterectomy [41], neoadjuvant chemotherapy followed by radical hysterectomy and postsurgical adjuvant chemotherapy [42, 43] using a less toxic regimen, such as docetaxel and carboplatin, should be investigated [44].

There is preliminary experience showing that CCRT with paclitaxel plus cisplatin is potentially more effective than single-agent cisplatin [45]. Therefore, a randomized phase III trial for stages IIB to IVA AC patients comparing CCRT with cisplatin versus with cisplatin plus paclitaxel, which will be soon launched by Japanese Gynecologic Oncology Group, is important. Another approach will be CCRT with neoadjuvant or adjuvant chemotherapy as indicated by Tang et al. [46]. They recently reported on a phase III study in which 880 patients with IIB–IVA AC were randomized to either CCRT alone versus neoadjuvant chemotherapy followed by CCRT followed by two further cycles of chemotherapy. The chemotherapy regimen was cisplatin plus paclitaxel, and both disease-free survival and OS

were improved ($P<0.05$) with among those receiving additional cycles of therapy ($P<0.05$) [46].

It is, however, most important to intensify our research into the molecular profile of AC, so that we can develop more appropriate targeted therapies.

Because of its rarity, international collaboration among clinical trials with translational components will be the key to increasing cure rates and improving survivorship.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Keiichi Fujiwara and Dr. Mojgan Devouassoux-Shisheboran have no conflict of interest.

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Gynecologic Cancer InterGroup (GCIG) Consensus Review for Cervical Adenocarcinoma

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Abstract: Cervical adenocarcinoma is known to be less common than squamous cell carcinoma of the cervix comprising approximately 25% of all cervical carcinomas. Differences in associated human papillomavirus types, patterns of spread, and prognosis call for treatments that are not always like those for squamous cancers. In this review, we report a consensus developed by the Gynecologic Cancer InterGroup surrounding cervical adenocarcinoma for epidemiology, pathology, treatment, and unanswered questions. Prospective clinical trials are needed to help develop treatment guidelines.

Key points: Differences between adenocarcinoma and squamous cell carcinoma, and Individualization of the therapy

Key Words: Cervical Cancer, Adenocarcinoma, Pathology, Staging, Clinical management

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Cervical cancer is the third most common cancer in women worldwide. Most cases are of squamous cell carcinoma (SCC) histology. Less common types include adenocarcinoma (AC), adenosquamous (AS) (generally considered together), and several rare histological subtypes. In the 1950s and 1960s, the proportion of cervical cancers that were either AC or AS was only 5% to 10%; but recent studies suggest that the proportion of cases with AC has increased, and currently, SCC represents approximately 75% of cases of invasive cervical carcinoma, whereas AC comprises approximately 20% to 25%. Reasons

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for the increase in AC compared to SCC is likely multifactorial. A relative increase is likely due to the success of the screening program with Papanicolaou test leading to a fall in invasive SCC. Papanicolaou testing is not as effective in detecting preinvasive and invasive AC, which is generally located in the endocervical canal rather than on the ectocervix. Furthermore, preinvasive adenocarcinoma in situ cytology is less consistently described and recognized. The increasing incidence may also relate to other risk factors including obesity and reduced parity.

Currently, AC and AS carcinoma of the cervix are treated similar to SCC. However, there is increasing evidence to suggest that these subtypes behave differently, with different epidemiology, prognostic factors, patterns of spread, and failure after treatment. Emerging evidence also suggests that AC may be more radio resistant. Owing to the relative rarity of this tumor subtype, randomized studies have been challenging. This review summarizes the current data and provides some direction where treatment may differ between histological subtypes. Given the paucity of data, no attempt is made to create consensus guidelines but rather to summarize our existing understanding of this uncommon cancer.

EPIDEMIOLOGY

Whereas AC and SCC share many similar risk factors, there are also some differences. Both SCC and AC are associated with human papillomavirus (HPV) infection; however, there are some differences in the pattern of this association. Adenocarcinoma is associated with a higher likelihood of HPV-16 and HPV-18, which is present in more than 80% of cases.[1] Human papillomavirus 18 accounts for approximately 50% of AC but only 15% of SCC.[2] Squamous cell carcinoma is also associated with a wider diversity of uncommon HPV subtypes.

The use of oral contraceptives has been associated with an increased relative risk of cervical cancer, but the risk is similar for both SCC and AC.[3] In contrast, smoking is strongly associated with SCC of the cervix but seems to be less associated with AC.[4] Adenocarcinoma has been linked to several other risk factors more commonly associated with endometrial cancer, including obesity[1] and nulliparity.[5]

PROGNOSTIC FACTORS

The prognostic significance of histological subtype remains controversial. However, most studies suggest a worse prognosis for AC compared to SCC, with a 10% to 20% difference in 5-year overall survival (OS) rates.[6,7]

Clinical stage remains the most important prognostic factor for all cervix cancer subtypes, including AC. One study[8] involving 305 patients with AC found 5-year OS reduced from 80% in International Federation of Gynecology and Obstetrics stage I to 37% in stage 2 and less than 11% in stage 3. The difference between SCC and AC prognosis in early-stage cervical cancer is controversial. Kasamatsu et al[9] showed no difference, but Hopkins et al[10] showed a worse prognosis in AC compared with SCC. Nevertheless, it becomes more apparent as the stage increases.[8,10] Hopkins et al reported that patients with stage II squamous cell disease had a 62% survival compared with patients with AC who had 47% survival ($P = 0.01$); patients with stage III squamous cell disease had a 36% survival, compared with patients with AC who had 8% survival ($P = 0.002$).[10]

An example of the difficulty in ascertaining the prognostic significance of cell type is seen among prospective clinical trials performed by the Gynecologic Oncology Group (GOG). The GOG has a long history of combing AC and SCC together in their studies. On behalf of the GOG, Monk et al[11] retrospectively reviewed data from 335 women with primary, previously untreated, histologically confirmed invasive (stages IIB to IVA) cervical carcinoma who received weekly cisplatin and pelvic radiation while participating in similar arms of 2 GOG studies (protocols 120 and 165). This ancillary data project was only able to demonstrate a trend in worse survival for AC compared to SCC (PFS: hazard ratio, 1.40; $P = 0.147$ and OS: hazard ratio, 1.32: $P = 0.261$). This nonstatistical difference may clearly be a result of small numbers as only 11.4% had AC.[11]

Tumor size is also a significant prognostic factor. Differences in prognosis are less evident with small tumors but increase with larger tumor size. Several studies have shown that tumors greater than 4 cm had a poorer prognosis in AC compared with SCC.[7] Adenocarcinoma has also been reported to have a higher likelihood of lymph node involvement, compared to SCC, and a worse prognosis.[12]

For stage I AC, survival was significantly related to tumor differentiation, lymph node status, and amount of residual disease present in the cervix after radical hysterectomy. Survival was not significantly influenced by histologic subtype, patient's age, number of positive lymph nodes, or tumor size greater than 3 cm.[13]

Adenosquamous carcinoma is generally included with AC in most studies.[14] However, there are some data suggesting that AS has a poorer prognosis compared with AC.[15,16]

Patterns of Dissemination and Recurrence

There are also differences in the pattern of dissemination of advanced or recurrent disease with a possible higher rate of ovarian metastases seen with AC than SCC (5.31% vs 0.79%) and also a higher tendency for intra-abdominal carcinomatosis and hematogenous metastases compared with SCC.[17] Outcome for patients with ovarian metastasis is generally believed to be very poor and not related to International Federation of Gynecology and Obstetrics stage and histological type. The presence of ovarian metastasis has no correlation with lymph node involvement or parametrial invasion. Kuji et al[18] found that peritoneal cytology was positive in 9 patients (3.9%), with 3 (2.2%) of 139 patients having SCC and 6 (6.7%) of 89 patients having AC. Thirty percent of patients with SCC who had positive cytology had a recurrence, whereas all patients with AC had recurrence. In this single study, multivariate analysis revealed that peritoneal cytology ($P = 0.029$) and histological type ($P = 0.004$) were independent prognostic factors.[18]

One possible reason for the poor prognosis associated with AC in some studies might be a lower sensitivity to radiotherapy[19] as well as a higher rate of lymph node metastasis.[7,12] Subset analyses of several studies suggest higher recurrence rates after radiation in AC compared to SCC.[20] However, one study also shows a higher local control rate for

AC with postoperative adjuvant radiotherapy than for SCC.[20] In a prospective GOG trial, Peters et al[21] reported a similar prognosis for patients with AC and SCC when adjuvant treatment involved chemoradiotherapy after radical hysterectomy.

Tang et al[22] recently reported a large phase 3 study in 880 patients with stages IIB to IVA AC comparing concurrent chemoradiation therapy (CCRT) to chemoradiation with one cycle of cisplatin and paclitaxel followed by radiation then 2 further cycles of cisplatin/paclitaxel. Results showed an improved disease-free ($P < 0.05$), survival ($P < 0.05$), and long-term tumor control ($P < 0.05$) in patients receiving neoadjuvant and consolidation chemotherapy in addition to radiotherapy.[22]

There have also been several small studies in AC and substudies of patients with cervical cancer with metastatic disease receiving platinum-based combination chemotherapy showing activity similar if not better than seen with SCC. The GOG protocol 240 demonstrated that chemotherapy plus bevacizumab significantly improved OS in advanced and recurrent cervical cancer.[23] In an unplanned hypothesis generating subgroup analysis, the benefit conferred by bevacizumab was not sustained among the 27% with AC histology, suggesting that AC is a different disease than SCC when treated with antiangiogenesis therapy. Three other phase 3 GOG studies of chemotherapy in this setting have also been reviewed (179, 204, and 240). Binary exchange analysis was performed using the Pearson test to evaluate response rate, the Kaplan-Meier method to estimate progression-free survival and OS, and the Cox proportional hazards model to estimate the effect of histology on progression-free survival and OS. Eligible patients (N = 994) were evaluated, of whom 25% (n = 246) had AC/AS and 75% (n = 748) had SCC. There were no significant differences in response rates and time to response between histologic subgroups. The hazards of progression and death for AC + AS vs SCC were 1.13 (95% confidence interval [CI], 0.97–1.33; $P = 0.119$) and 0.97 (95% CI, 0.82–1.15; $P = 0.747$), respectively. The hazards of progression and death for AC vs SCC + AS were 1.01 (95% CI, 0.84–1.23; $P = 0.893$) and 0.89 (95% CI, 0.73–1.10; $P = 0.277$), respectively. The GOG protocol 240 was underpowered for AC/AS to draw any conclusions regarding the efficacy of incorporation of antiangiogenesis therapy in these uncommon histologies. Given the relative infrequency of AC + AS, these pooled data support the hypothesis that these histologic subtypes are not significantly different in their biologic response to systemic therapy in the recurrent/metastatic setting.[24]

PATHOLOGY

Fifty percent of cervical ACs are exophytic or polypoid, but 15% of patients have no visible lesion especially for early invasive AC or adenocarcinoma in situ.[25] In cases of invasive AC, immunohistochemistry is usually used to separate a primary endocervical tumor from an endometrial tumor, for instance, carcinoembryonic antigen and p16 expression (a surrogate of HPV) together with the absence of hormone receptors and vimentin favor a cervical origin.

Cervical ACs are subdivided into several categories[25] including endocervical, mucinous, villoglandular, endometrioid, clear cell, serous, mesonephric ACs, and AS carcinomas.

Endocervical AC of usual type represents the most frequent subtype of cervical ACs (90% of cases).

Mucinous ACs are subdivided into gastric type including its variant adenoma malignum, intestinal type, and signet-ring cell type. The adenoma malignum variant of gastric-type AC is the most difficult diagnosis because their well-differentiated tumor glands are difficult to distinguish from normal endocervical glands. In this case, the key histological feature is the depth of invasion together with clinical data. Somatic mutations of the *STK11* gene responsible for the Peutz-Jeghers syndrome have been described in 55% of these tumors.[26] The gastric-type cervical AC[27,28] is composed of glands with a pyloric phenotype (voluminous, clear, pale eosinophilic cytoplasm and distinct cell borders) and immunoprofile (HIK1083 and MUC6 expression). There is no association with HPV. Patients with this type of mucinous carcinomas have a poor prognostic with a decreased 5-year survival rate of 30% versus 77% for usual-type AC.

Villoglandular AC of the cervix is rare, showing a distinct exophytic and villopapillary growth. When superficially invasive, this variant has an excellent prognosis with very rare lymph node metastases.

Endometrioid (5% of cervical ACs), serous, and clear cell ACs are less frequent and exhibit the same morphological and phenotypic features of their endometrial and/or ovarian counterparts. Diagnosis of cervical serous AC should be made only when an ovarian or endometrial tumor has been excluded. As it is the case with vaginal tumors, cervical clear cell AC is associated with in utero exposure to diethylstilbestrol.

Finally, mesonephric AC, which arises from mesonephric remnants, is a very rare tumor located in the lateral and posterior wall of the cervix. The main characteristics of these tumors are the presence of eosinophilic hyaline secretion within tubules and the coexpression of both CD10 and vimentin in the absence of hormone receptors.[29]

In contrast to SCCs, which are the most frequent tumors of the cervix, a few molecular alterations have been described for ACs. Gene expression profiling showed upregulation of 4 genes (*CEACAM5*, *TACSTD1*, *S100P*, and *MSLN*) belonging to the tetraspanins family that might be associated with tumor progression.[30] More recently, oncogenic mutations have been identified in *PI3KCA* (25%) and *KRAS* (17.5%) genes.[31]

PRIMARY TREATMENT

The currently recommended treatment for AC of the uterine cervix, according to each disease stage, is described later in the text based on the National Comprehensive Cancer Network guideline.[32] Clear treatment differences between AC and SCC are not evidence based.

Adenocarcinoma in situ

Simple total hysterectomy (the cone is considered for fertility preservation)

Stage IA Adenocarcinoma

Invasions of 3 to 5 mm: type-B radical hysterectomy with retroperitoneal lymph node dissection Invasions of less than 3 mm: simple total hysterectomy is recommended. In cases where fertility preservation is needed, conization or trachelectomy is considered.

Stage IB/II AC

Radical hysterectomy or CCRT for patients with small tumors, less than 2 cm, and negative lymphovascular space invasion, the survival difference between AC and SCC is negligible, so the treatment strategy for the patients with AC should be same as that for the patients with SCC.

Although literatures showed inferior survival of stage IB1 (<4 cm),[33] radical hysterectomy or CCRT is the standard care because of the lack of evidence that adjuvant chemotherapy is efficacious to improve the survival.

In patients with tumor sizes greater than 4 cm and progressively advanced disease, CCRT is the primary treatment.[34] A pretherapeutic aortic nodal staging by laparoscopy has been proposed.[35,36]

Some Asian studies suggested that the prognosis of AC is worse than SCC in patients with pathologically high-risk factors after radical hysterectomy.[14,37]

Neoadjuvant chemotherapy followed by radical hysterectomy has been controversial[38,39]; however, it is of great interest by using less toxic regimen, docetaxel and carboplatin.[40]

Stage IIIA/IVA AC

Concurrent chemoradiation therapy (CCRT) mainly uses weekly administration of cisplatin. Standard radiotherapy (RT) technique is as follows[41]: Patients generally receive 40- to 45-Gy whole pelvic RT with 10-MV x-rays using either parallel-opposed anteroposterior or 4-field box beams, with 1.8 to 2 Gy per fraction and 5 fractions weekly. An extended field to the para-aortic region is not routinely given for patients without imaging findings of para-aortic lymphadenopathy. The parametria receives a boost of 57.6 Gy or less to 58 Gy using a parallel-opposed anteroposterior field with a 4-cm-wide midline block in patients with stage IIB or greater disease. The intracavitary brachytherapy boost is usually given using an iridium 192 source. The typical dose to point A was 4.3 Gy per fraction for 6 fractions, with 2 fractions weekly. The median cumulative dose and biologically equivalent dose to point A was 70.8 and 90 Gy, respectively, with the a/b ratio for tumor effects assumed to be 10 Gy. For patients with lower vaginal tumor extension, bladder or rectal invasion, or persistent bulky tumor after 44 to 45 Gy of initial RT, the external beam doses to the low pelvis are increased to 50 to 54 Gy without a central block, followed by either intracavitary brachytherapy or an additional primary tumor boost of 70 or less to 72 Gy without brachytherapy.

There is a report showing that CCRT with paclitaxel plus cisplatin is potentially more effective than single-agent cisplatin.[42]

Stage IVB AC

Systemic chemotherapy with platinum and paclitaxel is reasonable in patients with good performance status and is similar to those with recurrent disease.

TREATMENT OF METASTATIC DISEASE AND RELAPSE

The frequency of ovarian metastasis is higher in AC than in SCC (5% vs 0.8%).[17] The differences in the sites of recurrence suggest that SCC predominantly disseminates lymphatically, whereas AC may do so hematogenously.[17] The frequency of distant metastasis is higher in AC than in SCC.[7,43]

Chemotherapy Regimen

At present, the same chemotherapy regimen might be recommended for both AC and SCC[44]: paclitaxel plus cisplatin as standard treatment[45] and paclitaxel and carboplatin as alternative treatment (JCOG 0505). The effectiveness of paclitaxel[46,47] or docetaxel plus carboplatin[48] have been reported for AC. Adding bevacizumab is an option.[23]

Should AC be studied separately from SCC?

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Gynecologic Cancer InterGroup (GCIG) Consensus Review for Clear Cell Carcinoma of the Uterine Corpus and Cervix

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Abstract: Clear cell carcinomas of the uterine corpus and cervix are rare gynecological cancers with limited information regarding the pathogenesis and biology. At present, the approach to management is the same as for patients with the more common histological subtypes of endometrioid endometrial cancer and adenocarcinoma of the cervix. Surgical resection is the standard treatment for patients with early-stage disease, but there is no evidence-based approach to direct the management of patients with more advanced-stage disease at presentation or with recurrent disease. We review the epidemiology, pathology, and what is known about both uterine corpus and cervical clear cell cancers and make management recommendations.

Key Words: Clear cell carcinoma, Uterine corpus, Uterine cervix, Histological feature, Immunohistochemical, Treatment

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CLEAR CELL CARCINOMA OF THE UTERINE CORPUS

Uterine clear cell carcinoma (UCCC) is a rare histological subtype of endometrial cancer. It is not associated with maternal exposure to diethylstilbestrol (DES), and the etiology and risk factors for UCCC are unknown. In patients with early-stage disease, a hysterectomy and a lymphadenectomy are indicated similar to the approach in the more common endometrioid endometrial cancers.[1] It has been suggested that UCCC may be more resistant to radiotherapy or chemotherapy, which underscores the importance of establishing a registry to collate treatment outcomes in patients with such rare tumors as it is unlikely that clinical trials would ever be feasible.

Background and Epidemiology

The UCCC accounts for only 1% to 6% of cases of all endometrial cancers.[2–4] The most common nonendometrioid histological subtype is serous (10%), followed by clear cell (1%–5%).[2,3] It typically occurs in postmenopausal nonobese women (mean age, 65years), is not associated with estrogen

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use, and has a higher incidence in African-American women.[5] They are considered as poorly differentiated. Unlike CCC of the cervix, clear cell carcinoma of the uterus is not associated with maternal DES exposure.[6] Venous thromboembolic events area recognized complication similar to CCC of the ovary.[7]

A subset may be associated with paraneoplastic hypercalcemia secondary to parathyroid hormone-related protein production.[8] There are limited data available regarding the biology of UCCC, but it seems that they are commonly associated with an aggressive clinical behavior with a high propensity toward extrauterine spread and have a relatively poor prognosis. Occult metastases are present in 40% of patients even with disease apparently clinically confined to the uterus.[9]

Patients with UCCC commonly relapse in the pelvis as well as para-aortic nodes and at distant sites, but they do not seem to have a high propensity for peritoneal dissemination.[10] According to the International Federation of Gynecology and Obstetrics annual report 2006, the 5-year overall survival was approximately 60% for UCCC, compared with 80% for endometrioid carcinoma. Five-year survival according to stage was as follows: I, 79%; II, 77%; III, 47%; and IV, 21% for UCCC. The 5-year disease-free survival is only 43% for UCCC as a group.[9]

There are no prospective trials specifically focusing on the women with UCCC. Available data are derived from subset analysis of large prospective studies, and there are small retrospective reviews.

Pathologic and Molecular Features

Pathologic Features

Although the histological features of UCCC are similar to those observed in clear cell cancer of the ovary, UCCC is far less common. Along with uterine serous adenocarcinoma, UCCC is categorized as a type II tumor, that is, nonestrogenic etiology.

The term *clear cell carcinoma* was first defined by Scully and Barlow[11] who described tumors that originated from the Mullerian epithelium. On microscopy, the tumors show tubulocystic, papillary, or solid patterns and have a clear appearance because of their high glycogen content (and not intracellular mucin). They sometimes include eosinophilic cells and typical hobnail cells. Most CCCs have a characteristic clear cytoplasm, which may vary in amount from minimal to abundant. On endometrial cytology, the recognition of light green–favored matrices enclosed by the tumor cells is a diagnostic feature.[12] Psammoma bodies are sometimes seen in UCCC but not as frequently as uterine serous adenocarcinomas. Rarely, UCCC may arise from adenomyosis or from an endometrial polyp.

Endometrial carcinomas of mixed histology are not unusual. Craighead and co-workers reported that 11% of their patients had tumors of mixed histology including a combination of endometrioid carcinoma, CCC, and serous carcinoma.[13] Many pathologists have used an approach similar to that used in ovarian cancers, in which the term *mixed-cell type* is used if each cell type constitutes at least 10% of the tumor volume. Cirisano and colleagues[14,15] reported that tumors with mixed histology (at least 25% of uterine serous carcinoma or CCC) had a clinical behavior comparable with that of uterine serous carcinoma. Some UCCCs have a minor counterpart of typical endometrioid adenocarcinoma (EMA). Therefore, it has been suggested that CCC is an aggressive form of EMA. The biological behavior of UCCC has been reported to be either similar to or worse than stage-matched grade 3 EMA[16] but more favorable than serous carcinoma in the uterine body.[14,15] Different putative precursor of serous and CCC lesions have been described, but the precise relationship between the 2 entities and their nomenclature remains to be elucidated.[17]

Immunohistochemical Features

According to the immunohistochemical expression profiles of ER, PR, Ki-67, and p53, UCCC is regarded as intermediate between EMA and serous adenocarcinoma,[18] but like uterine serous carcinoma, UCCC has low expression of ER and PR. P53 expression is intermediate between those reported in uterine serous carcinoma and those in endometrioid cancers.[19] Cyclin A is significantly overexpressed in clear cell compared with endometrioid carcinomas, whereas the opposite is seen for cyclin E, suggesting that the proliferative activity and cell cycle kinetics of these 2 carcinomas are quite different. E-cadherin is also significantly less expressed in CCCs than in endometrioid carcinomas. Ki-67 index expression is higher in UCCC (similar to that in serous carcinomas; median index of 50%) when compared with low-grade endometrioid carcinoma (median proliferative index of approximately 20%). A recent study has shown that HNF-1b is uniformly positive in most UCCCs.[20] This is in contrast to lack of expression in ovarian endometrioid carcinomas. This marker is probably related to glycogen metabolism and may prove to be specific for CCCs. Insulinlike growth factor II mRNA-binding protein 3, another new marker widely expressed in serous carcinomas of the endometrium and ovary, is also commonly positive in UCCC but not in endometrioid carcinomas of the endometrium.

Molecular Features

Unlike endometrioid type, ER and PR expression is usually absent or at most weak and focal.[12] HER2 overexpression seems to be more common in UCCC than in other endometrial carcinoma subtypes.[17,18] The UCCC shows high Ki67 index and p53 overexpression, although usually not as diffuse and strong as seen in the serous subtype.[12] Ap53 mutation was found in 14% of UCCC,[21] and a PTEN mutation was reported in 18% of UCCC.[21] Loss of MLH1, MSH2, or MSH6 in UCCC by immunohistochemistry correlates with the presence of mismatch repair gene mutations.[22] In contrast to serous carcinoma, microsatellite instability and PTEN inactivation seem to be rarely found in CCC. The loss of DNA mismatch repair genes in UCCC might disproportionately represent patients with Lynch syndrome. As in serous carcinoma, K-*ras* mutations have not been reported. The epidermal growth factor receptor was frequently overexpressed in a small number of CCCs.[23] Gene expression profiles of UCCC showed a remarkable similarity to those of clear cell ovarian and kidney cancers rather than other histotypes of endometrial cancers.[24] Integrated genomic analysis was performed by the Cancer Genome Atlas Research Network.

They reported the genomic features of endometrial carcinomas and suggested classification into 4 categories, but UCCC is not included in this study.[25]

Retrospective series have used differing definitions for UCCC making interpretation difficult because, as with ovarian cancers, mixed serous/CCC or endometrioid/CCC may have very different biology, etiology, and clinical behavior. It is therefore essential that an international consensus is agreed for the histological and molecular classification of these tumors to facilitate prospective trials and registries.

Initial Treatment

In general, clinical staging of women with endometrial cancer is associated with a large margin of error with respect to the true extent of disease, and surgical staging is recommended. It has been reported that 52% of patients with UCCC clinically confined to the uterus had extrauterine disease detected with comprehensive surgical staging.[9] Patients with clinical stage I and II UCCCs were upstaged to III or IV in 39% of patients compared with 12% with an endometrioid subtype.[26]

The importance of surgical staging and maximal cytoreductive surgery in UCCC was emphasized in a recent review by Thomas et al.[9] They recommended total hysterectomy and bilateral salpingo-oophorectomy with comprehensive surgical staging, including pelvic and para-aortic lymph node dissection and omentectomy if patients are medically fit.

Although no evidence for survival benefit with surgical staging was shown, not unexpectedly, there was a worse prognosis in patients with omental metastasis and lymph node metastasis. If extrauterine disease is present, cytoreductive surgery is also recommended. Women with advanced-stage disease who were completely cytoreduced had a superior progression-free and overall survival compared with patients with residual disease at the end of surgery.[9]

Because UCCC is more likely to present with extrauterine spread compared with lower-grade endometrioid cancers, there may be a role for adjuvant therapy after complete surgical staging.

Adjuvant Treatment

There is limited evidence for the efficacy of adjuvant treatment in patients with UCCC. Most reports have combined patients with clear cell and serous histologic subtypes with only a few studies published including UCCC alone. In general, management with aggressive adjuvant therapy has been recommended although there is no strong evidence base to support this. According to National Comprehensive Cancer Network guidelines,[27] observation, chemotherapy, or tumor-directed radiation therapy (RT) after primary surgery is recommended for stage IA UCCC without myometrial invasion. Chemotherapy ± tumor-directed RT are recommended for stage IA (with myometrial invasion), IB, II, II,I and IV uterine serous carcinomas, UCCC, and carcinosarcoma of the endometrium, which are all considered high-risk subtypes. However, Thomas et al[9] suggested that vaginal brachytherapy alone may be sufficient for patients with early-stage UCCC. Adjuvant chemotherapy does not seem to benefit these patients, but the data are quite limited. Two retrospective studies have evaluated radiotherapy for UCCC and both suggest that adjuvant radiotherapy may provide local disease control.[9,26] GOG122 favored chemotherapy compared with radiation.[28] In this trial, only 12 patients with UCCC were enrolled among 396 patients. Although serous histology was associated with a worse prognosis compared with other histological types, UCCC was not, but the numbers of patients with UCCC were small. The Nordic Society of Gynaecologic Oncology/European Organization of Research and Treatment of Cancer trial compared pelvic radiation with or without chemotherapy.[29] Improved survival was reported in patients treated with adjuvant chemotherapy. The combination of radiation plus chemotherapy seems a rational approach in selected patients, but it should be stressed that there are no randomized controlled trials in this specific subtype.[30]

The UCCCs have generally been included in endometrial cancer clinical trials. GOG177 showed that combination of paclitaxel, doxorubicin, and cisplatin (TAP) regimen was associated with an improvement in overall response rate, PFS, and overall survival when compared with doxorubicin and cisplatin (AP) regimen, but they did not specifically look at response in the rare subtypes.[31] GOG209 compared TAP regimen with a less toxic regimen TC (paclitaxel and carboplatin) and reported noninferiority for TC compared with the TAP regimen for endometrial cancer.[32] Thus, paclitaxel and carboplatin are a reasonable first-line therapy for UCCCs.

Metastatic Disease and Relapse

Patients with recurrent or metastatic disease not suitable for surgery or irradiation should receive chemotherapy. The most active chemotherapy combination has not been determined for patients with recurrent UCCC. Current options include cisplatin, taxol, and doxorubicin either administered in a doublet or triplet combination as they have demonstrated efficacy in UCCC.[2,33] In general, patients are treated with the same regimens that are used to treat patients with recurrent endometrioid carcinoma, and TC is therefore also a reasonable option.

McMeekin et al[34] analyzed the relationship between histological subtype and clinical outcome in patients with advanced and recurrent endometrial cancer who were enrolled in 4 GOG first-line chemotherapy trials. Although there was a trend for a lower response rate for UCCC, histological subtype, this was not an independent predictor of response.[33]

Phase II trials with temsirolimus or everolimus have reported a response rate of around 25% in patients with recurrent or metastatic endometrial cancer.[35] The PTEN plays an important role in preventing activation of AKT and downstream pathways including the mTOR pathway. It has been speculated that mutations/inactivation of PTEN or PIK3CA mutations may be predictive biomarkers for response to mTOR inhibitors, but this remains uncertain. Less than 20% of UCCCs have PTEN mutations/inactivation,[21,36] and the role of mTOR inhibitors in UCCC is unclear.[37] Bevacizumab as a single agent has also been reported to have efficacy in the treatment of recurrent endometrial cancer with a response rate of 13.5% and PFS at 6 months of 40.4%. Increased vascular endothelial growth factor expression was observed in nearly 60% endometrioid

endometrial carcinomas and was strongly correlated with a poor patient outcome.[38] It is possible that combining an angiogenesis inhibitor with a taxane and platinum-based backbone could improve outcomes, but to date, there is no evidence to suggest that this approach will be more active in UCCC.

CCC OF THE UTERINE CERVIX

Introduction

The CCC of the uterine cervix is very rare. An association between prenatal DES exposure and increased risk for vaginal and cervical clear cell adenocarcinoma (CCAC) has been proposed.[39] In the United States and the Netherlands, many women used DES during pregnancy in the 1950s and 1960s in an attempt to prevent adverse pregnancy outcomes. Recently, many non–DES-associated CCACs of the cervix have been reported.

Epidemiology

The CCAC accounts for 4% of all adenocarcinomas of the uterine cervix. Among DES-exposed women, the estimated incidence of CCAC from birth to age of 39 years is 1.6 per 1000 women.[40] There are clearly separated peaks of incidence in young and advanced age in DES-exposed women. In contrast, non–DES-exposed women have single a peak.[41,42]

Pathology

This tumor is histologically similar to CCAC of the ovary. It is mainly composed of clear or hobnail cells arranged in solid, tubulocystic, or papillary patterns or a combination of these features.[43]

Molecular Biology and Genetics

In contrast to squamous cell or other adenocarcinomas, CCAC does not seem to be associated with human papillomavirus infection.[44] Causal mutations in CCACs have not been identified. Genomic instability is suggested as a mechanism of DES-related carcinogenesis.[45,46]

Diagnosis

Vaginal bleeding is the most frequent initial symptom. The accuracy of cervical cytology in the diagnosis of CCAC is low.[41,42]

Initial Treatment

Approximately 75% of patients are diagnosed with stage I/II disease and are treated surgically.[41,42] A laparoscopic radical trachelectomy has been reported in carefully selected young patients.[12]

Patients without lymphatic dissemination have excellent prognosis irrespective of the use of adjuvant chemotherapy (3-year overall survival was reported to be approximately 90%).[9] Lymphatic involvement is associated with a worse survival.[41] Lymphadenectomy may be useful in predicting prognosis, but it is not known whether lymphadenectomy has a therapeutic benefit.

Ansari et al[47] and Chan et al[48] reported cases that showed a benefit from chemotherapy or radiotherapy in CCAC, but no prospective clinical trial exists to confirm or refute their data.

Metastatic Disease and Relapse

There are very limited data regarding the response to either chemotherapy or radiotherapy in patients with metastatic/recurrent CCAC.[41] A combination of RT and chemotherapy has been reported to be associated with patients with advanced CCAC after surgical resection[36]

CONCLUSIONS

The current approach to management for patients with UCCC and CCAC is based on the same principles and is similar to the management of patients with the more common endometrioid carcinoma of the uterus and adenocarcinoma of the cervix, respectively. As it is impossible to carry out clinical trials in patients with such rare subtypes, it would seem appropriate to include these patients into clinical trials of the more common subtypes and to analyze them separately or include them in other clear cell studies. In addition, we recommend establishing a consensus on pathological definition and a registry of these rare tumors and prospectively collecting information regarding management and patient outcomes as well as tissue samples for translational research.

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Gynecologic Cancer InterGroup (GCIG) Consensus Review for Small Cell Carcinoma of the Cervix

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Abstract: Small cell carcinoma of the cervix (SCCC) is a rare histological entity of uterine cervical cancer. Compared with other common histological types, squamous cell carcinoma or adenocarcinoma, the outcome of SCCC is poor because of the high incidence of nodal or distant metastasis even with early stage. In this review, current consensus of epidemiology, pathology, and initial treatment for SCCC will be discussed.

Key Words: Small cell carcinoma of the uterine cervix, Cervical cancer, Surgery, Chemotherapy

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First reported by Wentz and Reagan[1] in 1958, small cell carcinoma of the cervix (SCCC) is a rare histological entity of uterine cervical cancer and has a poor prognosis. The outcome of patients with SCCC is worse than those with squamous carcinoma (SC) and adenocarcinoma (AC), because of the high incidence of nodal involvement and distant metastasis even with early-stage disease.[2–4]

No clear treatment guidelines specific for SCCC have been published. The general approach taken is to offer surgery for early-stage disease, concurrent chemoradiotherapy (CCRT) for locally advanced-stage SCCC, and chemotherapy for metastatic and recurrent disease.

Interestingly, surgery and adjuvant chemotherapy have been performed for patients with extrapulmonary small cell cancer.[5] The chemotherapy regimen is based on the recommendation for patients with pulmonary small cell carcinoma,[6–9] without any specific evidence for these drugs in SCCC. However, it seems reasonable to use the same drugs that are used in pulmonary small cell carcinoma.

Differences between SCCC and squamous cell carcinoma or adenocarcinoma of the cervix are summarized in Table 1[4,10–13] and will be discussed in the following section.

EPIDEMIOLOGY

Small cell carcinoma of the cervix represents less than 5% of all cases of cervical cancer.[14] From 1977 to 2003, 290 women with SCCC were identified from the Surveillance, Epidemiology, and End Results (SEER) database. In the same period, the SEER database recorded 27,527 patients with SC of the cervix and 5231 patients with AC of the cervix.[3] In

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