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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TABLE 1. Comparison between small cell carcinomas, squamous carcinomas, and adenocarcinomas of the uterine cervix (McCusker et al,[4,10–13] Wistuba et al,[4,10–13] Hirai et al,[4,10–13] Scotto et al,[4,10–13] Tornesello et al[4,10–13])

Cervical Carcinomas	Small Cell Carcinoma	Squamous Cell Carcinoma	Endocervical Adenocarcinoma, Usual Type
Incidence, % of cases	2–5	75	20–25
Mean age at diagnosis, yrs	49	52	46
Morphology	Small or spindle cells	Polygonal or spindle cells	Columnar cells
	Scant cytoplasm	+/− Abundant eosinophilic cytoplasm	Abundant cytoplasm
	Hyperchromatic and smudged nuclei	Atypical, large nuclei	Scant intracellular mucin
	Nuclear molding	Coarse, granular chromatin	Large nuclei
	No nucleoli	Mitoses	Nucleoli
	Many mitosis+++	Masses with central keratin formation and necrosis	Mitoses
	Necrosis		Apoptotic bodies
	No gland		Gland formation, papillary and solid pattern
	Rosettes and ribbons		
	Lymphovascular invasion 60%–90%	Lymphovascular invasion 25%	Lymphovascular invasion
Immunoprofile	Pankeratin +	Pankeratin +++	Pankeratin +++
	CK7 −/+	CK7 −/+, CK14 +, CK5/6 +	CK7 +++
	Neuroendocrine markers 30 − 50% + for at least one	Neuroendocrine markers Usually −	Neuroendocrine markers Usually −
	P16 +++	P16 +++	P16 +++
	TTF1 may be +	TTF1 −	TTF1 −
	P 63 − (+/−30%)	P63 +++	P63 usually −
	CEA −	CEA −	CEA cytoplasmic +++
	ER and PR usually −	ER and PR usually +	ER and PR usually −
Molecular biology	HPV-18 (53%) >> HPV-16	HPV-16 > HPV-18 (15%)	HPV-18 (50%) > HPV-16
	TP53 mutation, 47%	*TP53* mutation, 5.9% (codon 249)	*TP53* mutation, 13.3% (codon 282)
	Deletion of 3p (47%)	Deletion of 3p (85%)	Deletion 3p
	Deletion 9p21 (43%)	Deletion 9p21 (11%)	Deletion 2q (25%)
	No *KRAS* mutation	Gain 20q (>50%)	Deletion 5p (38%)
		EGFR amplification (10%)	No *EGFR* amplification
		KRAS mutations rares	No *KRAS* mutation

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TABLE 1. *(Continued)*

Cervical Carcinomas	Small Cell Carcinoma	Squamous Cell Carcinoma	Endocervical Adenocarcinoma, Usual Type
Behavior	Very aggressive	16.9% stage IB1 at diagnosis	26.7% stage IB1 at diagnosis
	Positive lymph nodes > 50%	Positive lymph nodes (15%–20% stage IB, 50% stage III)	Positive lymph nodes, 20%
	Distant metastases lung, liver, bone, brain	Pelvic recurrences	Metastases ovary (5%), intra-abdominal, para-aortic lymph nodes, adrenal glands, lung, pleura
		Distant metastases rares (lung, 6%)	

CEA, Carcinoembryonic antigen; CK, cytokeratin; ER, estrogen receptors; HPV, human papillomavirus; PR, progesterone receptors; TTF-1, thyroid transcription factor −1.

addition, the Japanese Society of Obstetrics and Gynecology has reported that the incidence of SCCC was approximately 1%, and 0.6% in Korea[15] from 1993 to 2002. The incidence of SCCC in extrapulmonary small cell cancer was reported as 9.9%,[16] 18.0%,[17] and 4.7%[18] in each article. The median age at diagnosis for patients with SCCC was approximately 45 years,[19–21] similar to SC or AC. The stage distribution of SCCC is similar to SC and AC, mostly early stage at diagnosis, although in one study, lymph node involvement is more common in SCCC: 50% compared to 18% in SC.[1]

PATHOLOGY

From a diagnostic point of view, there may be problems distinguishing SCCC from other neoplasms, and in confirming a cervical origin. This is important, as management is critically dependent on the correct histologic diagnosis. Cervical neuroendocrine carcinomas (NECs) are subdivided into small cell NEC and large cell NEC and are usually characterized by immunohistochemical expression of pancytokeratin (AE1/AE3) and neuroendocrine markers (chromogranin, synaptophysin, and CD56). They are usually negative for P63, although some positive cases have been described,[22] whereas squamous cell carcinomas are P63 positive and chromogranin negative.[23] However, a significant proportion of cervical NECs may be negative for broad-spectrum cytokeratins and some of the commonly used neuroendocrine markers. Thyroid transcription factor 1 positivity is extremely common and may be a useful marker of an NEC, but this positivity is of no value in exclusion of a pulmonary primary.[22] p16 is almost always positive in cervical NECs, possibly owing to an association with oncogenic human papillomavirus, although other mechanisms of expression are also possible.[22] CK20 and neurofilament positivity in some cervical NECs is in keeping with a Merkel cell immunophenotype, similar to that described in small cell NECs in other organs[22].

MOLECULAR PATTERN

Several studies have described a spectrum of molecular changes involved in the pathogenesis of squamous cell carcinoma, the most frequent histologic type of cervical cancer. However, other than human papillomavirus (HPV) sequences, no data about genetic changes present in endocrine tumors of the uterine cervix have been reported. The morphologic and clinical features of the endocrine tumors of the uterine cervix are similar to those occurring in the lung, and a similar histologic classification has been adopted. In 1999, Wistuba et al[10] described the distinct molecular changes that are present in neuroendocrine tumors of the uterine cervix. They demonstrated a high incidence of oncogenic HPV sequences (especially HPV type 18) and TP53 gene abnormalities, relatively small deletions of chromosome 3p regions, and occasional 9p21 deletions. Thus, these tumors share some changes present in the neuroendocrine tumors of the lung (TP53 gene abnormalities and 9p21 allelic loss) as well those in squamous carcinomas of the cervix (oncogenic HPV

TABLE 2. Comparison of survival by stage in patients with small cell carcinoma of the cervix

Author	Stage							
	IB1	IB2	IIA	IIB	IIIA	IIIB	IVA	IVB
Cohen et al[20]	36.8% (35)				8.9% (53)			
Lee et al[25]		46%–53% (48)						
Wang et al[23]	51.1% (104)			50.4% (42)		13.0% (9)	6.1% (24)	
Kuji et al[31]	63% (17)	67% (10)		30% (10)		29% (7)		25% (6)

Five-year survival rate (number of patients).
For Kuji et al, 4-year survival rate (number of patients).

sequences and localized 3p deletions). However, their overall genetic profile is distinct and different from that of the other 2 tumor types.[10]

INITIAL TREATMENT

Management algorithm for NEC of the cervix has been published as a Society of Gynecologic Oncology clinical document.[24] As shown in Figure 1, radical surgery is recommended for early-stage disease either primarily or after neoadjuvant chemotherapy. For patients with advanced-stage disease, chemoradiation or systemic chemotherapy is suggested.

A retrospective study in 68 patients with stage IB1 to stage IIA disease reported by Lee et al[25] suggested that radical hysterectomy followed by adjuvant chemotherapy might be sufficient, as the patients who received CCRT did not seem to have a better outcome.[25] However, in a report from Tian et al[26] of 96 women with stage IB1-IIA SCCC adjuvant chemotherapy after radical hysterectomy did not appear to improve the prognosis. Similar findings were reported by Cohen et al; postoperative adjuvant chemotherapy on 135 patients with stage I to stage IIA disease in an analysis of 188 cases of stage I to stage IV disease did not seem to influence outcome.[20] However, Kuji et al demonstrated significantly better progression-free and overall survival for the patients with stage IB1 to IIB disease who received chemotherapy after radical surgery compared with the patients who did not receive chemotherapy. Therefore, the benefit of adding chemotherapy after radical hysterectomy is controversial at present. It is possible that the findings of no benefit by chemotherapy are due to poor activity of the regimens used. It has recently been reported that CCRT using a regimen consisting of vincristine, doxorubicin, and cyclophosphamide alternating with etoposide and cisplatin (EP) was a useful postoperative chemotherapy regimen in early-stage disease, although the number of cases reported was small.[27]

In advanced disease, stages IIB to IVA, Cohen et al[20] reported an improvement in prognosis in patients who were treated with chemotherapy. A combined modality approach, adding CCRT to chemotherapy, was reported by Wang et al.[28] The addition of at least 5 cycles of EP significantly improved the prognosis of 56 patients with stage IIB to IVB disease in an analysis of 179 cases of stage I to stage IV disease.[28] At present, it seems that chemotherapy may be effective in advanced stages of SCCC.

The EP regimen was used in approximately half of the cases reported by Lee et al, including the neoadjuvant setting. Other regimens used were paclitaxel and cisplatin, paclitaxel and carboplatin, and vincristine, cisplatin, and bleomycin.[25] Cohen et al used EP in 51.9% of their cases, and other regimens including cisplatin combination or cisplatin alone were used in 33.3%.[20] Wang et al reported that EP was used in 49%, and other regimens including cisplatin were used in 38%.[28] Etoposide and cisplatin (EP) is the most frequently used regimen, as used in the treatment of small cell lung cancer (SCLC),[29] but prospective trials in SCCC are lacking.

The typical EP regimen was proposed for advanced small cell carcinoma of the lung. Usually, cisplatin at 60 to

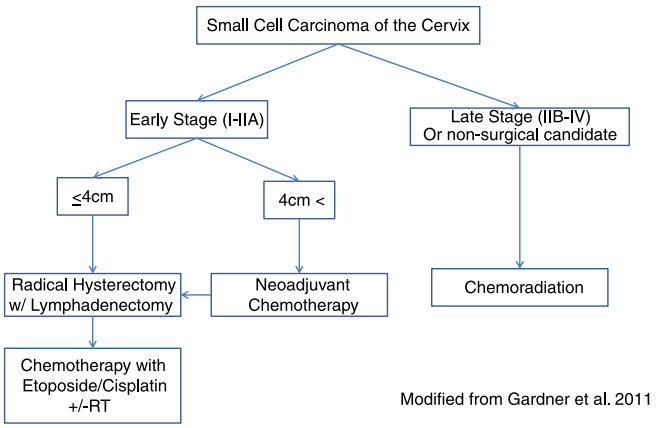

FIGURE 1. Management algorithm of SCCC (modified from Gardner et al.[24]).

80 mg/m^2 is given intravenously on day 1 and etoposide at 80 to 120 mg/m^2 IV on days 1 to 3 every 21 to 28 days.[6,8,9]

Prognostic Factors

The greatest differences in survival between SCCC and SC or AC were seen in patients with early-stage and node-negative disease (Table 2).[3] The 5-year disease-specific survival rates of patients with stage I to stage IIA SCCC (n = 135), IIB to IVA (n = 45), and IVB (n = 8) disease were 36.8%, 9.8%, and 0%, respectively.[20] The median overall survival for patients with early-stage disease (IA1-IB2 [n = 11]) was 31.2 months, and the median overall survival for patients with advanced-stage disease (IIB-IV [n = 6]) was 6.4 months.[19] The most recently reported 5-year cancer-specific survival rates for patients with stage I (n = 104), stage II (n = 42), stage III (n = 9), and stage IV (n = 24) disease were 51.5%, 50.4%, 13.0%, and 6.1%, respectively.[28]

Regarding the 5-year overall survival rate, Lee et al reported that the rate was 55% in patients with IB1 disease (n = 43) and 32% in patients with stage IB2 to IIA disease (n= 25).[25] Cohen et al[20] reported 36.8% in patients with stage I to stage IIA (n = 135), 9.8% in patients with stage IIB to IVA disease (n = 45), and 0% in patients with stage IVB disease (n = 8). Wang et al[28] reported 50% in patients with stage IA disease (n = 3), 54% in those with stage IB1 disease (n = 69), 46% in patients with stage IB2 disease (n = 32), 53% in patients with stage IIA (n = 19), 49% in patients with stage IIB disease (n = 23), 13% in patients with stage III disease (n = 9), 33% in patients with stage IVA disease (n = 3), and 0% in patients with stage IVB disease (n = 21).

The only independent prognostic factor Lee JM et al found was stage (IB1 vs IB2-IIA).[25] Stage (IA-IIA vs IIB-IVA vs IVB), radical hysterectomy, and the use chemotherapy (including CCRT), were the 3 independent prognostic factors Cohen et al[20] found. Wang et al[28] reported that 2 factors, stage (IA-IIA vs IIB-IV) and lymph node metastasis, were prognostic. In an analysis of 290 cases in the SEER database, Chen et al[3] identified 3 independent prognostic factors: age, stage, and race. Stage is the only prognostic factor common to all these studies. Liao et al[30] reported a large retrospective study with 293 patients, and the prognostic factors were International Federation of Gynecology and Obstetrics stage, tumor mass size, lymph node metastasis, depth of stromal invasion, and chromogranin A positivity by univariate analysis, and International Federation of Gynecology and Obstetrics stage, tumor size, and chromogranin A positivity were the prognostic factors by multivariate analysis. Kuji et al[31] showed significantly better of progression-free survival by addition of chemotherapy after radical surgery.

In addition, it is unclear if patients with SCCC benefit from the use of prophylactic cranial radiation after primary treatment in the same way as those with pulmonary small cell carcinomas. Several studies suggest that the rate of brain metastases with extrapulmonary small cell is much lower than seen in pulmonary small cell. Hence, several authors suggest that prophylactic cranial radiation could be omitted for these patients.[21,32,33]

METASTATIC DISEASE AND RELAPSE

The prognosis of patients with stage IVB disease with distant metastasis is very poor. None of the 29 patients with stage IVB disease survived 5 years.[20,28] There is no information on the results of treatment of recurrent disease. It is important that information on these women is collected. There is an urgent need to develop new and better treatments for SCCC. Kuji et al reported that 21 patients among 52 patients with SCCC had recurrence, and 67% of the initial recurrent sites were hematogenous or hematogenous and lymphogenous. Only 10% was local recurrence, suggesting the importance of chemotherapy in this patient population.

CURRENT STATUS AND FUTURE RESEARCH DIRECTIONS

As discussed in this review article, no standard treatment guideline has been established for SCCC because there has been no prospective randomized study. Therefore, the most important thing is to conduct a randomized phase 2/3 trial under the GCIG platform. The questions to be asked in the trial would include the optimal treatment strategy for early-stage SCCC and optimal chemotherapy regimen, more potent or less toxic regimen compared with EP. Target agents also should be investigated.

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