Gynecologic Oncology 129 (2013) 522–527

Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Diagnosis, clinicopathologic features, treatment, and prognosis of small cell carcinoma of the uterine cervix; Kansai Clinical Oncology Group/Intergroup study in Japan

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HIGHLIGHTS

- This is a multicenter, collaborative study to accumulate cases of small cell carcinoma of the uterine cervix.
- We know pathologic features of the resected uterus by radical hysterectomy in stages I and II.
- In early stage patients, by adding postoperative chemotherapy, the prognosis may improve.

ARTICLE INFO

Article history:
Received 26 November 2012
Accepted 19 February 2013
Available online 26 February 2013

Keywords:
Small cell carcinoma
Neuroendocrine carcinoma
Cervical cancer
Chemotherapy
Early stage
Systemic chemotherapy

ABSTRACT

Objectives. This is a multicenter, collaborative study to accumulate cases of small cell carcinoma of the uterine cervix (SmCC), to clarify its clinical and clinicopathologic features and prognosis, and to obtain findings to establish future individualized treatment.

Methods. At medical centers participating in the Kansai Clinical Oncology Group/Intergroup, patients diagnosed with SmCC between 1997 and 2007 were enrolled. Clinicopathologic features and prognosis were retrospectively evaluated in patients with SmCC diagnosed at a central pathologic review.

Results. A total of 71 patients were registered at 25 medical centers in Japan. Of these, 52 patients (73%) were diagnosed with SmCC based on a pathological review. These 52 patients diagnosed with SmCC were analyzed. The median follow-up period was 57 months. The 4-year progression-free survival (PFS) was: IB1, 59%; IB2, 68%; IIB, 13%; and IIIB, 17%. The 4-year overall survival (OS) was: IB1, 63%; IB2, 67%; IIB, 30%; IIIB, 29%; and IVB, 25%. For postoperative adjuvant therapy, postoperative chemotherapy (a platinum drug in all cases) was compared to non-chemotherapy. The 4-year PFS was 65% and 14%, and the 4-year OS was 65% and 29%. PFS was significantly better ($p = 0.002$), and the OS tended to be better ($p = 0.073$) in the group with postoperative chemotherapy.

Conclusion. Even in patients with early stage SmCC, the prognosis is poor. However, in early stage patients, by adding postoperative chemotherapy, the prognosis may improve. Currently, various treatment protocols are used at each medical center, but in the future, a standardized treatment protocol for SmCC will hopefully be established.

Introduction

Small cell carcinoma of the uterine cervix (SmCC) is a very rare disease representing only 1% to 3% of all uterine cervical cancers. In the currently used WHO histological classification of tumors of the uterine cervix (2003), SmCC is classified as a neuroendocrine

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http://dx.doi.org/10.1016/j.ygyno.2013.02.025

tumor [1]. SmCC progresses rapidly to hematogenous and lymphogenous metastases, and has a poor prognosis [2–10]. Reported 5-year survival rates are: stages IA2–IB1, 55% to 85%; stages IB2–II, 25% to 30%; and stages III–IV, 0% to 16% [3–7]. Even in stage I, compared to other histologic types, the prognosis is significantly worse [3,4]. On the other hand, SmCC is characterized by being highly sensitive to anticancer drugs and radiotherapy. Thus, SmCC requires a different management strategy than the more common squamous cell carcinomas and adenocarcinomas [2–7,11–15]. However, because of the low incidence of SmCC, prospective international studies have not been conducted, and appropriate guidelines have not been established.

The objectives of this study were to: collect cases of SmCC from multiple medical centers, clarify clinical and clinicopathologic features and prognosis, and obtain findings to establish future individualized treatment. In this study, by a central pathologic review, a more reliable analysis of cases of SmCC could be conducted.

Patients and methods

Study population and clinical evaluation

This study enrolled patients who were diagnosed with SmCC between January 1997 and December 2007 at medical centers participating in the Kansai Clinical Oncology Group/Intergroup. In total, 71 patients were registered from 25 medical centers throughout Japan. Information about patient characteristics, FIGO stage, pretreatment imaging assessment, treatment methods and results, site of recurrence, progression-free survival (PFS), overall survival (OS), and final outcome was obtained from patient medical records at each medical center. FIGO stage was classified according to the FIGO clinical staging system (1994). For auxiliary diagnosis, CT, MRI, and PET-CT were used. On CT, MRI, or PET-CT, if distant metastases or para-aortic lymph node metastases were found, the disease was classified as FIGO stage IVB. Para-aortic lymph node biopsy was not specified. In surgical cases, information about tumor size, lymph–vascular space invasion, stromal invasion, tumor margin (cut end), parametrial invasion, number of resected lymph nodes, and lymph node metastases was obtained from patient medical records and pathology reports from each medical center.

Pathologic diagnosis: Central review

Pretreatment biopsy specimens for initial diagnosis and their pathology reports were required. Surgically resected specimens were also collected. Immunohistochemically stained slides, such as CD56, chromogranin A and synaptophysin, were collected whenever possible. In all cases, a histopathologic review was conducted independently by two pathologists from different medical centers. Patients diagnosed with SmCC based on agreement of the two pathologists were analyzed. Regarding the pathologic criteria, because the WHO (2003) histopathologic diagnostic criteria for cervical small cell carcinoma are only vaguely described, the pathologic criteria of this study were defined in accordance with the WHO (2004) small cell lung cancer criteria [16].

The detailed WHO histological definition is as follows. Architectural patterns include nesting, trabeculae, peripheral palisading, and rosette formation as shared by other neuroendocrine tumors. Sheet-like growth without these neuroendocrine morphologic patterns is common. Tumor cells are usually less than the size of three small resting lymphocytes and have round, ovoid, or slightly spindle-shaped nuclei and scant cytoplasm. Nuclear chromatin is finely granular, and nucleoli are absent or inconspicuous. Cell borders are rarely seen, and nuclear molding is common. There is a high mitotic rate, averaging over 60 mitoses per 2 mm [2,16]. Mixed type cases included small cell carcinoma that accounted for at least 10% of the tumor area.

Statistical analysis

Fisher's exact test was used for categorical variables. OS was defined as the time from starting initial treatment to last follow-up or death. PFS was defined as the time from starting initial treatment to first recurrence or progression of disease and death. PFS and OS were calculated using the Kaplan–Meier method, and the survival curves were compared using the log-rank test. A p-value < 0.05 was considered significant. Factors significantly associated with survival in cervical cancer were identified by multivariate analysis based on the Cox proportional hazards model.

Results

Central pathologic review

At the central pathologic review, both of the pathologists agreed that 52 (73%) of 71 cases had SmCC. For the other 19 cases, there was disagreement between the original diagnosis and at least one of the reviewer's diagnoses. Among the reviewers' diagnoses, 5 were large cell neuroendocrine carcinoma (LCNEC), and the others included squamous cell carcinoma non-keratinizing type, basaloid squamous cell carcinoma, adenocarcinoma, mucinous adenocarcinoma, and poorly differentiated adenocarcinoma.

Patients' characteristic (Table 1)

The 52 patients diagnosed with SmCC were analyzed. The median follow-up period was 57 months (4–126 months). Stage was: FIGO IB1, 17 cases (33%); IB2, 10 (19%); IIB, 10 (19%); IIA, 0; IIIA, 1 (2%); IIIB, 7 (13%); IVA, 1 (2%); and IVB, 6 (12%). Subtype was pure type in 29 cases (56%) and mixed type in 21 (40%). In the other 2 cases, the diagnosis of the two pathologists differed. Tumor size was >4 cm (bulky tumor) in 54% of cases.

Table 2 shows the pretreatment blood test and tumor marker results as the frequency outside the normal range. Of the tumor

Table 1
Patients' characteristic.

		n	(%)
Follow-up period	Median: 57 m	(4~126 m)	
Age	Median: 40 year-old	(20~84 year-old)	
FIGO	IB1	17 case	(33)
	IB2	10	(19)
	IIB	10	(19)
	IIIA	1	(2)
	IIIB	7	(13)
	IVA	1	(2)
	IVB	6	(12)
Histological homology	Pure	29	(56)
	Mix	29	(40)
	Other	2	(4)
Tumor size	≦2 cm	11	(21)
	2<, ≦4	13	(25)
	4<	28	(54)
Initial treatment with all stage	Surgery alone	3	(6)
	Surgery, CT	12	(23)
	Surgery, CCRT	9	(17)
	Surgery, RT	6	(12)
	NAC, surgery alone	2	(4)
	NAC, surgery, CT	5	(10)
	NAC, surgery, CCRT	1	(2)
	CCRT	10	(19)
	CT alone	2	(4)
	Not any treatment	2	(4)

n = 52.
RT: radiotherapy.
CT: chemotherapy.
CCRT: concurrent chemoradiotherapy.
NAC: neoadjuvant chemotherapy.

markers, neuron specific enorase (NSE) was above the reference range in stage I in 44%, in stages II–IV in 92%, and overall, in 63% of cases. The other tests showed no characteristic abnormal values.

The frequency of pelvic lymph node metastases found on CT, MRI, or PET-CT was IB1, 18% (3/17); IB2, 70% (7/10); IIB, 50% (5/10); IIIA, 100% (1/1); IIIB, 57% (4/7); and IVB, 6/6 (100%). For stages IB1–IIB, the frequency of pelvic lymph node metastases is shown for patients who had a total hysterectomy and pelvic lymphadenectomy. At surgery, the median number of resected lymph nodes was 29 (13–86). The actual rate of lymph node metastases was similar to the positive rate on imaging: IB1, 20% (3/15); IB2, 88% (7/8); and IIB, 33% (2/6).

Initial treatment was surgery in all 27 cases of stages IB1 and IB2. In stage IIB, 8 of 10 patients had surgery, and 2 had concurrent chemoradiotherapy (CCRT). Of the 35 patients with stages I–II who had surgery, 5 (14%) had preoperative chemotherapy. In addition, postoperative adjuvant therapy was given in 31 of the 35 cases (89%). Postoperative adjuvant therapy was chemotherapy (CT) alone in 16, CCRT in 10, and radiotherapy (RT) alone in 5 cases. In 9 cases of stages IIIA–IVA, primary treatment was CCRT in 6, surgery + adjuvant therapy in 2, and CT alone in 1 case. For stage IVB, primary treatment was CCRT in 2, surgery + adjuvant therapy in 1, and best supportive care in 2 cases.

The chemotherapy regimen in 22 cases (including initial treatment, neoadjuvant chemotherapy (NAC), and postoperative adjuvant therapy) included a platinum drug. The most frequently used regimen was cisplatin + etoposide (PE) in 9 cases, followed by cisplatin + CPT-11 (PI) in 4 cases, carboplatin + paclitaxel (TC) in 2 cases, and others. For CCRT, the concurrent drug regimen was cisplatin alone in 6 cases, CAV (cyclophosphamide + adriamycin + vincristine)/PE alternate treatment in 6 cases, nedaplatin alone in 4 cases, PI in 3 cases, and TC in 1 case.

Outcomes

Fig. 1-1 shows PFS and OS. The 4-year PFS was: FIGO IB1, 59%; IB2, 68%; IIB, 13%; and IIIB, 17%. For stage IB1, even among 10 cases with tumor size ≤2 cm, 5 had recurrence in 3 to 23 months. The 4-year OS was: FIGO IB1, 63%; IB2, 67%; IIB, 30%; IIIB, 29%; and IVB, 25%.

Of the cases with a complete response (CR) with primary treatment (surgery and/or RT and/or CCRT), the recurrence site was evaluated in 21 patients who subsequently had recurrence. Initial recurrence was hematogenous in 14 cases (67%), lymphogenous in 7 (34%), and local in 2 (10%) (some overlap) (Table 3). The most frequent site of hematogenous metastases was the liver in 8 cases, followed by the lung in 4, bone in 3, and other. In addition, for all cases of relapse/recurrence, when the recurrence site during survival was examined, 6 of 27 patients (22%) had brain metastases. Of those with brain metastases, only 2 also had lung metastases.

Table 2
Blood examination of pre-treatment.

	All stages	(%)	FIGO IB1–IB2	(%)	FIGO IIB–IVA	(%)
LDH ↑	15/46	(33)	6/26	(23)	9/20	(45)
ALP↑	0/38	0	0/22	0	0/16	0
Na ↓	3/44	(7)	1/25	(4)	2/19	(11)
NSE ↑ *	19/30	(63)	8/18	(44)	11/12	(92)
CA19-9 ↑	3/36	(8)	3/20	(15)	0/16	0
CA125 ↑	5/40	(13)	2/23	(9)	3/17	(18)
CEA ↑	7/41	(17)	2/23	(9)	5/18	(28)

This shows the pretreatment blood test and tumor marker results as the frequency outside the normal range. The cases that exceed the reference range of NSE were high rate. The others showed no characteristic abnormal values.

Surgical cases

For FIGO stages IB1–IIB, 35 patients underwent surgery for radical treatment. Of these, 28 patients who had no preoperative treatment and underwent an initial treatment either a radical hysterectomy (based on Okabayashi method) or modified radical hysterectomy (semi-radical hysterectomy) with retroperitoneal lymphadenectomy were analyzed (FIGO IB1, 15; IB2, 7; IIB, 6). Of these 28 cases, the histopathologic findings of 15 FIGO IB1 cases are shown in Table 4. Median tumor size was 2 cm (0.7–3.5 cm). There were lymph node metastases in 3 cases (20%), parametrial invasion in 3 (20%), lymph–vascular space invasion in 8 (67%), ≥2/3 stromal invasion in 6 (50%), and a positive surgical margin in 2 (15%). In addition, even when limited to 10 patients with tumor size ≤2 cm on imaging, there were lymph node metastases in 3 cases (33%), parametrial invasion in 2 (20%), lymph–vascular space invasion in 4 (40%), and ≥2/3 stromal invasion in 1 (10%). Thus, there was a high frequency of risk factors for recurrence.

For postoperative adjuvant therapy, in the previously mentioned 28 patients with FIGO IB1–IIB who had initial surgery, postoperative chemotherapy (CT alone or CCRT) was compared to non-chemotherapy (RT alone or non-adjuvant therapy). The 4-year PFS was 65% and 14%, respectively, and the 4-year OS was 65% and 29%, respectively. PFS was significantly better ($p = 0.002$), and the OS tended to be better ($p = 0.073$) in the group with postoperative chemotherapy (Fig. 1-2). The postoperative chemotherapy or CCRT regimen was platinum alone in 7 cases (33%) and a multi-drug combination with platinum in 14 (67%). There were no differences in background factors (pT, operative procedure, the rate of residual tumor, tumor size, lymph vascular invasion, the depth of stromal invasion, parametrium invasion, the rate of lymph node metastasis) between the chemotherapy and non-chemotherapy groups (Supplementary Table S-1). On the other hand, in these 28 cases, post operative radiotherapy (RT or CCRT) was compared to non-radiotherapy (CT or non-adjuvant therapy). There were no differences in PFS and OS (Supplementary Fig S-1).

Discussion

For neuroendocrine tumors of the uterine cervix, there have been changes in the pathologic diagnostic criteria over time. In the 1994 WHO classification, these were classified into two categories, carcinoid and small cell carcinoma. In 1997, Albores-Saavedra et al. [16] proposed a classification of neuroendocrine tumors of the uterine cervix based on the classification of lung cancer. In the 2003 WHO classification, 4 categories were listed for neuroendocrine tumors of the uterine cervix: carcinoid, atypical carcinoid, small cell carcinoma, and LCNEC on the pattern of lung neuroendocrine carcinoma. However, the morphology of the categories was not detailed in the classification [2,17].

In addition, small cell carcinoma can be diagnosed by HE staining, and on light microscopy, neuroendocrine granules do not have to be demonstrated. As a result of such changes in classification and the difficulty in diagnosis, cases reported as small cell carcinoma to date, may have included LCNEC, other neuroendocrine tumors, or other histologic types. In the present study, at a central pathologic review, 52 of 71 cases (73%) were diagnosed as small cell carcinoma.

About 60% of SmCC is diagnosed in FIGO stages I and II. However, because of early lymph node metastases or hematogenous metastases, many patients are diagnosed with advanced cancer [11]. In the present report, the rate of lymph node metastases in stage IB1 was 20%, and in stage ≥IB2, at least half had lymph node metastases. Thus, the frequency of lymph node metastases was high. On the other hand, when initial recurrence site was analyzed among cases with a complete response to primary treatment, 67% had hematogenous metastases, and 34% had lymphogenous metastases. Thus, a very high rate of hematogenous metastases was observed. In a report by Lan-Fang et al. [15], which examined the site of recurrence in patients with a recurrence during a 2-year follow-up period, 90% had hematogenous metastases, and 33%

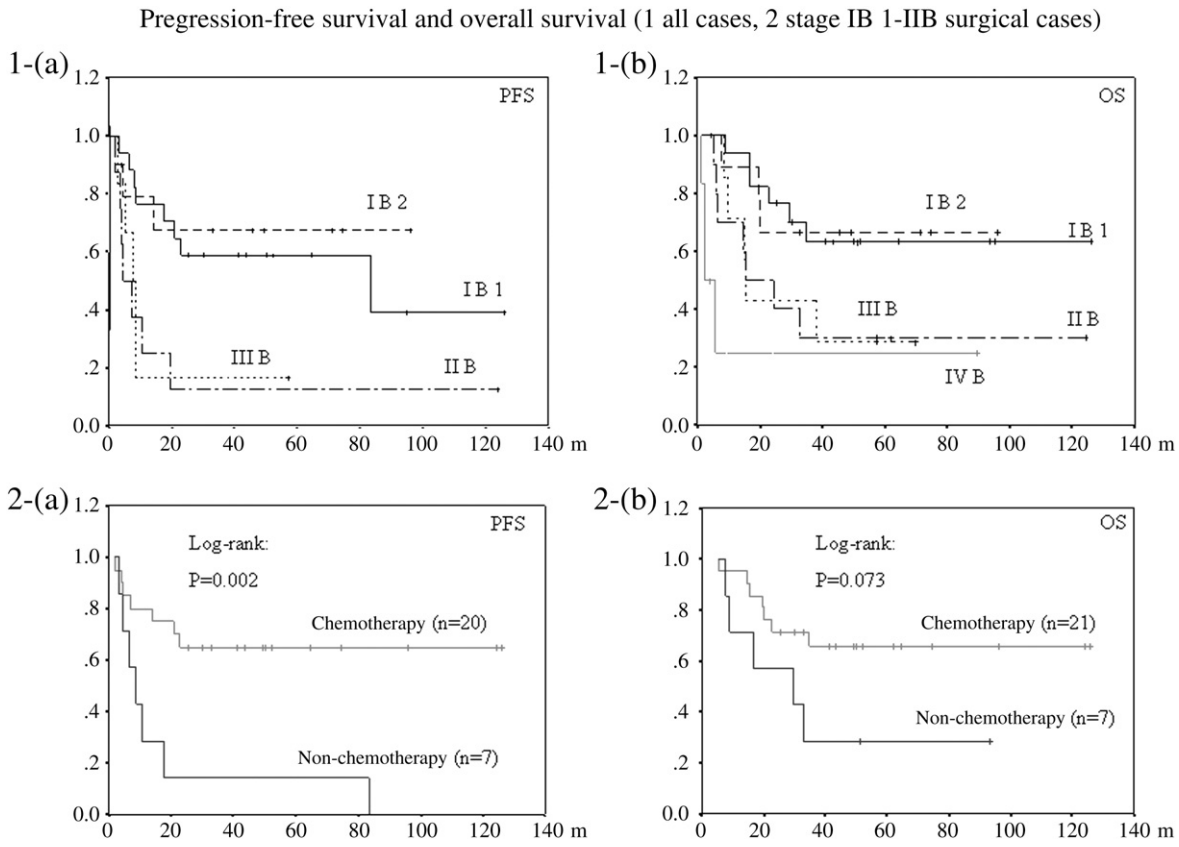

Fig. 1. Progression-free survival and overall survival. 1 PFS (1-(a)) and OS (1-(b)) for all cases. 2 Efficacy of adjuvant therapy on twenty-eight cases of stages IB1–IIB who were treated radical surgery. (2-(a,b)) Postoperative chemotherapy vs. non-chemotherapy.

had lymphogenous metastases. In other words, lymph node metastases are common from an early stage, but after treatment, there is a high likelihood of hematogenous metastases.

Brain metastases have been reported in 10% to 20% of SmCC cases [3,18]. In the present study, of 51 enrolled cases, 6 (12%) had brain metastases. Considering the 1.2% rate reported in more common cervical cancers, [19] this is a very high frequency.

In the early cases with radiotherapy or surgery that is aimed at local control, the addition of systemic chemotherapy may improve prognosis, as described in several reports [2,3,5,12,14,15]. In the present study as well, based on pathologic findings from surgical cases of stage IB1, there was a higher frequency of histologic risk factors for recurrence at an early stage (lymph node metastases, parametrial invasion, lymph–vascular space invasion, deep stromal invasion) than in cervical adenocarcinoma stage IB1 [20]. In other words, SmCC compared to other histological types of cervical cancer, invades and spreads more easily than other histological types of cervical cancer. From this standpoint as well, adding systemic therapy from an early stage may also be necessary.

Table 5 lists previously reported SmCC treatment regimens and prognosis. In patients with surgery and/or radiotherapy, so-called local therapy only, the prognosis was poor. On the other hand, in patients with CCRT or systemic CT added to local therapy, the prognosis was clearly better than with local therapy alone. Although all were retrospective studies, adding systemic chemotherapy to local therapy may improve the prognosis. As primary treatment for early stage cases, only one study using CCRT, by Hoskins et al., has been reported. The 3-year PFS was 80%, a very good prognosis, but because the staging method differed ('radiologic stage' instead of FIGO stage), a simple comparison with other reports is not possible. As for postoperative chemotherapy, there were no differences between chemotherapy alone and CCRT [5,15].

Regarding chemotherapy regimens, there have been some reports of therapy with a platinum drug and etoposide (ETOP). There have also been other reports of multi-drug regimens including platinum, but not limited to ETOP. In each of these reports, there were no large differences in prognosis (Table 5). However, Chang et al. [21], examining postoperative adjuvant therapy, compared a group using cyclophosphamide + doxorubicin + vincristine (CAV) (which has

Table 3
Initial recurrence site.

The site of metastasis	n = 21	(%)
Hematogenous	12	57
Hematogenous + lymphogenous	2	10
Lymphogenous	5	24
Local	2	10

Of the cases with a CR with primary treatment (surgery and/or RT and/or CCRT), the recurrence site was evaluated in 21 patients who subsequently had recurrence.

Table 4
Pathologic detail with FIGO IB1.

	Total (n = 15)	Tumor size 2 cm≧ (n = 10)
Tumor size	2 cm (0.7~3.5 cm)	
Lymph node metastasis	3/15 (20%)	3/10 (33%)
Parametrium invasion	3/15 (20%)	2/10 (20%)
Lymph–vascular space invasion	8/12 (67%)	4/10 (40%)
Deep stromal invasion(≧2/3)	6/12 (50%)	1/10 (10%)
Cut end positive	2/13 (15%)	–

This shows the histopathologic findings in 15 cases of FIGO IB1 who had no preoperative treatment and underwent radical surgery.

Table 5
Previous reports of early SmCC.

	Stage	n	Prognosis	Treatment	Regimen
Local therapy and systemic therapy					
Hoskins et al. [12]	Radiologic stage IA~IIB	16	3y PFS: 80%	CCRT ± CT	PE
Lee et al. [5]	FIGO IB~IIA	24	5y OS: 53%	Ope + CT	Multi-drug combination including Platinum
Lee et al. [5]	FIGO IB~IIA	24	5y OS: 46%	Ope + CCRT	Multi-drug combination including platinum
Zivanovic et al. [2]	FIGO IA2~IB2	6	3y PFS: 67% 3y OS: 83%	Ope → CCRT or CT CCRT	PE CBDCA + ETOP
Lan-Fang et al. [15]	FIGO IB~IIA	28	3y OS: 57(CT) 56(CCRT)	Ope → CCRT or CT	PE (26 cases) TP (2 cases)
Current study	FIGO IB–IIB	21	4y PFS: 65% 4y OS: 65%	Ope → CCRT or CT	Multi-drug combination including platinum or single agent of platinum
Only local therapy					
Sheets et al.[10)] [28]	FIGO IB~IIA	14	3y OS: 16% 5y PFS: 0%	Ope ± RT	
Sevin et al.[11)] [29]	FIGOIA~IIA (Exclude IB2 and bulky tumor)	12	5y PFS: 36%	Ope ± RT	
Zivanovic et al. [2]	FIGO IA2–IB2	5	3y PFS: 0% 3y OS: 20%	Ope or RT	
Current study	FIGO IB–IIB	7	4y PFS: 14% 4y OS: 29%	Ope ± RT	

Ope: operative therapy.
RT: radiotherapy.
CT: chemotherapy.
CCRT: concurrent chemoradiotherapy.
PE: cisplatin + etoposide.
CBDCA: carboplatin.
ETOP: etoposide.
The decimal point is described with rounded.

been used in lung small cell carcinoma) or PE therapy and a group using other chemotherapy; the first group had a significantly higher survival rate. In the present study, the prognosis was compared between a group with a platinum drug including ETOP or CPT-11and a group with platinum doublet other than ETOP or CPT-11. There were no differences for both PFS and OS.

Currently, PE therapy or PI therapy is recommended as standard primary chemotherapy for extensive small cell carcinoma of the lung [22]. In a randomized study that served as a basis for establishing current standard treatment for extensive small cell carcinoma of the lung, the response rates were 78% for PE therapy and 84% for PI therapy [23]. Thus, excellent results were reported. For treatment of poorly differentiated neuroendocrine tumors of the pancreas and gastrointestinal tract as well, PE or PI therapy has been used and relatively good response rates have been reported. However, when analyzed by organ system, the response rates vary widely, from 14% to 83%, depending on the primary site [24–27]. However, by selecting a platinum-based regimen that is used in lung small cell carcinoma, there may be hope for an improved prognosis.

Conclusion

Because SmCC has different biological characteristics than squamous cell carcinoma and adenocarcinoma, the treatment strategy must also be changed. However, because of its low incidence, standard treatment for this small cell carcinoma has not yet been established. Nevertheless, it is suggested that, local therapy + systemic chemotherapy may improve the prognosis of early stage cancer.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2013.02.025.

Conflict of interest
Finding sources, grants: none.
Financial Disclosure: none.

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