J Gynecol Oncol. 2023 Jan;34(1):e4
https://doi.org/10.3802/jgo.2023.34.e4
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

Impact of adjuvant chemotherapy on the overall survival of patients with resectable bulky small cell neuroendocrine cervical cancer: a JSGO-JSOG joint study

Received: Mar 12, 2022
Revised: Jul 19, 2022
Accepted: Aug 25, 2022
Published online: Sep 29, 2022

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ABSTRACT

Objective: The aim of this study was to review the clinicopathological characteristics of small cell neuroendocrine cervical cancer (SCNEC) and to identify the optimal treatment.
Methods: The Japanese Society of Gynecologic Oncology conducted a retrospective cohort study of SCNECs enrolled in the Gynecological Tumor Registry of the Japan Society of Obstetrics and Gynecology between 2004 and 2015. All cases were modified and unified by International Federation of Gynecology and Obstetrics 2008 (Union for International Cancer Control 7th edition).
Results: There were 822 registered patients diagnosed with SCNEC from 2004 to 2015 which comprised 1.1% (822/73,698) of all uterine cervical cancer cases. Rates of lymph-node and distant metastasis were significantly higher in T1b2 (38.9% and 13.7%, respectively) than T1b1 (14.2% and 4.4%, respectively) ($p<0.01$). In IB2 and T1bN1M0 SCNEC, the 5-year survival rate with surgery followed by chemotherapy was significantly higher than that with surgery followed by radiation therapy/concurrent chemoradiation therapy ($p<0.01$).
Conclusion: SNCEC tumors >4 cm in size had greater rates of lymph-node and distant metastasis when compared with tumors ≤4 cm. Adjuvant chemotherapy, rather than radiotherapy, may improve prognosis after surgery in T1bN1M0 SCNEC.

Keywords: Uterine Cervical Neoplasms; Small Cell Neuroendocrine Tumor; Pelvic Lymph-Node Metastasis; Adjuvant Therapy

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Conflict of Interest
The authors indicated no potential conflicts of interest.

Author Contributions
Conceptualization: S.M., N.S., M.M.; Data curation: S.M., N.S., O.T.; Formal analysis: S.M., N.S.; Investigation: S.M.; Methodology: S.M.; Supervision: N.S., Y.W., E.Y., K.Y., T.T., K.M., E.T., M.M.; Visualization: S.M.; Writing - original draft: S.M.; Writing - review & editing: N.S., O.T.

Synopsis
Small cell neuroendocrine cervical cancer (SNCEC) tumors >4 cm in size had greater rates of lymph-node and distant metastasis when compared with tumors ≤4 cm. In IB2 and T1bN1M0 SCNEC, the overall survival with adjuvant chemotherapy was significantly higher than that with adjuvant radiotherapy. Adjuvant chemotherapy, rather than radiotherapy, may improve prognosis after surgery in T1bN1M0 SCNEC.

INTRODUCTION

Cervical cancer affects 13,170 women annually in the United States, with a declining incidence [1]. However, the number of patients has not decreased in Hispanic and Asian countries, including Japan, with 10,978 women diagnosed with cervical cancer in 2018 [2]. The most common histological type is squamous cell carcinoma (SCC), and less than 5% of cases are small cell neuroendocrine cervical cancer (SCNEC) [3]. Primary gynecologic neuroendocrine tumors represent only 2% of all gynecological malignancies [4]. SCNEC and large cell neuroendocrine carcinoma are aggressive, high-grade tumors. SCNEC has a very poor prognosis because of frequent early nodal and distant metastasis, for which the 5-year overall survival (OS) has been reported to be 0%–63.5% [5-10]. SCNEC frequently have lymphovascular involvement, strong association with HPV18, and an increased risk of pelvic nodal metastasis at the time of diagnosis [11].

Some studies have reported the prognosticators and treatment options for SCNEC, however, the optimal treatment has not been well established due to the rarity of the disease [4,9]. Surgery, radiotherapy, and chemotherapy are used to treat SNCEC, but primary surgery is often chosen if the disease is confined to the cervix. If surgery is performed, higher risk factor, such as those >4 cm in size, and tumors associated with deep stromal invasion, lymph-node metastasis, or parametrium invasion are eligible for adjuvant therapy. Adjuvant therapies for common cervical cancers include radiotherapy with concurrent chemoradiotherapy, however, there is little evidence for adjuvant therapy for SCNEC. It has been reported that adjuvant chemotherapy may improve prognosis in SCNEC, but the available evidence is insufficient for standardization of treatment algorithms. Although recommendations from the SGO and NCCN guidelines have been issued, the standard therapeutic protocol is not available; however, certain opinions are controversial [12-14].

In this study, we compare the lymph-node status by cancer stage, treatment options such as adjuvant chemotherapy in stage IB SCNEC, and prognosis of women with SCNEC in Japan, using the gynecologic tumor registry database of the Japan Society of Obstetrics and Gynecology (JSOG).

MATERIALS AND METHODS

1. Study design and eligibility criteria

This is a retrospective nationwide observational study using the JSOG tumor registry database. This project was conducted by the Japan Society of Gynecologic Oncology, and patient data were provided by the Gynecologic Tumor Committee of JSOG [15]. This study was approved by the Ethics Committee of the JSOG. The JSOG tumor registration system is

an organ-based cancer registry for gynecologic cancer [15-17]. All patients with small cell carcinoma were identified, and those with missing data were excluded. The database records patient information, including the International Federation of Gynecology and Obstetrics (FIGO) stage, histologic type, treatment, and survival outcome [16]. The following clinical variables were collected using the database from patients who had SNCEC between 2004–2015: age, FIGO stage, treatment course, and survival outcome. Cases from 2004 to 2011 were classified by the 1994 FIGO staging system. These cases were modified staging using the 2008 FIGO system. Those with lymphadenopathy on pretreatment imaging radiologically were treated as node-positive (N1).

As the JSOG tumor registration system did not distinguish concurrent chemoradiation therapy (CCRT) from radiation therapy (RT) followed by chemotherapy, the primary treatment was classified into surgery, RT/CCRT, neoadjuvant therapy, and "others," which included chemotherapy or hormonal therapy. In this study, neoadjuvant chemotherapy (NAC) was defined as when chemotherapy and surgery were listed as the first and second therapeutic methods, respectively. External beam RT and brachytherapy were considered RT in this study.

SCNEC data were collected from the JSOG database from patients who were registered as having "small cell carcinoma" or "small cell neuroendocrine carcinoma." The histological type of small cell carcinoma was defined based on the World Health Organization (WHO) histological classification of tumors of the uterine cervix (1994), and SCNEC was defined based on the WHO Histological Typing of Female Genital Tract Tumours, 2nd edition (2004). In our study, small cell carcinoma and SCNEC were expressed uniformly in SCNEC.

2. Statistical analysis

The χ^2 test was used to compare qualitative data. OS was calculated using the Kaplan-Meier method and compared using the log-rank test. We used the statistical software, GraphPad Prism ver.6.00 (GraphPad Software, Inc., San Diego, CA, USA), for all analyses. The p-values <0.05 were considered to be statistically significant.

RESULTS

1. Patients characteristics and treatments

A total of 73,698 cervical cancer cases were registered in the JSOG tumor registration system from 2004 to 2015, and 822 (1.1%) of the 73,698 cases were small cell carcinomas or small cell neuroendocrine carcinomas. At the time of our analysis, the JSOG tumor registry database did not report recurrence or survival in patients diagnosed with SCNEC during 2012–2015. Data from 409 patients diagnosed with SCNEC from 2004 to 2011 was used to analyze prognosis. The median patient age was 46 years (range 20–96 years). The age distribution is shown in **Fig. S1** with 30–39 (n=212, 25.8%) and 40–49 (n=221, 26.9%) having higher proportions (**Fig. S1**). From these results, it is evident that SCNEC is most common among women aged 30–49. Among patients with SCNEC, 50.5% had stage I tumors (stage IA: 0.4%, IA2: 0.2%, IB1:34.7%, IB2: 14.1%, unknown subclass: 1.1%), 16.8% had stage II tumors (stage IIA1: 0.5%, IIA2: 1.5%, IIB: 12.5%, unknown subclass: 2.3%), 9.4% had stage III tumors (stage IIIA: 1.0%, IIIB: 8.4%), 23.4% had stage IV tumors (stage IVA: 0.7%, IVB: 22.3%, unknown subclass: 0.4%) (**Table 1**). Radiologically, pelvic and para-aortic lymph-node metastasis was noted in 314 (38.2%) and 30 (3.6%) patients, respectively, for all SCNEC

https://doi.org/10.3802/jgo.2023.34.e4

Table 1. Patient characteristics (2004–2015)

Characteristics (n=822)	Small cell carcinoma
FIGO 2008	
I	415 (50.5)
II	138 (16.8)
III	77 (9.4)
IV	192 (23.4)
Age (yr)	46 (22–96)
Lymph node metastasis	
Pelvic	314 (38.2)
Para-aortic*	30 (NA)
Treatment	
Surgery alone	77
Surgery + Chemotherapy	279
Surgery + RT/CCRT	88
RT/CCRT	167
Chemotherapy	79
NAC	75
Others	57

Values are presented as number (%) or median (interquartile range).
CCRT, concurrent chemoradiation therapy; FIGO, International Federation of Gynecology and Obstetrics; NA, not assessment; NAC, neoadjuvant chemotherapy; RT, radiation therapy.
*Because it could not assessment distant metastasis lesion in stage IVB, stage IVB data is not included.

stages. The rate of pelvic lymph-node metastasis was as follows: 11.6%, 31.0%, 25.0%, 16.7%, and 44.7% in patients with stage IB1, IB2, IIA1, IIA2, and IIB tumors, respectively. The rate of positive lymph-node metastasis in IB2 was significantly higher compared to the rate of that in IB1 ($p<0.01$).

Regarding the initial treatments in the 553 cases of stages I and II tumors, 267 (48.3%) patients had the surgery + chemotherapy, 74 (13.4%) had surgery alone, 85 (15.4%) had surgery + RT or CCRT, 42 (7.6%) had RT/CCRT, 52 (9.4%) had NAC, and 4 (0.7%) had chemotherapy alone (9.6%) (**Table S1**). In the 269 cases of stages III and IV, the most common treatment was RT/CCRT (46.5% of the patients), followed by chemotherapy (27.9%), and NAC. Approximately 15% patients with stages III and IV disease were administered treatment in addition to chemoradiotherapy or chemotherapy to surgery (**Fig. S2**). The detailed data on treatments is shown in **Table S1**.

2. Outcomes

The median follow-up period was 35.9 months (range 0.3–81.0 months). OS based on clinical stage is shown in **Fig. 1**. The 5-year OS was 56.7% for patients with stage I SCNEC, 41.0% for stage II, 27.6% for stage III, 5.3% for stage IV. The majority of our patients had stage IB disease, so we focused on the OS in stage IB. Overall, the 5-year OS was 70.7% for IB1 and 56.0% for IB2 (**Fig. 2A**), and this difference was statistically significant ($p=0.006$). Looking at the survival by treatment modality, the 5-year OS was 65.8% for patients treated with surgery + chemotherapy, and 60.0% for surgery + RT/CCRT in stage IB1 (**Fig. 2B**). There was no significant difference between the rates of OS between the 2 groups. Conversely, in stage IB2, the 5-year OS was 64.7% for surgery + chemotherapy and 32.0% for surgery + RT/CCRT (**Fig. 2C**), and this was statistically significant ($p<0.01$).

Lymph-node metastasis is a well-known negative prognosticator for cervical cancer, so we analyzed survival based on lymph-node status in stage IB SCNEC. The rate of 5-year OS in the negative pelvic lymph-node group (N0) was 63.7%, and 53.2% in the positive pelvic lymph-node group (N1) (**Fig. 3A**). Adjusting for the status of lymph-node metastasis and treatment,

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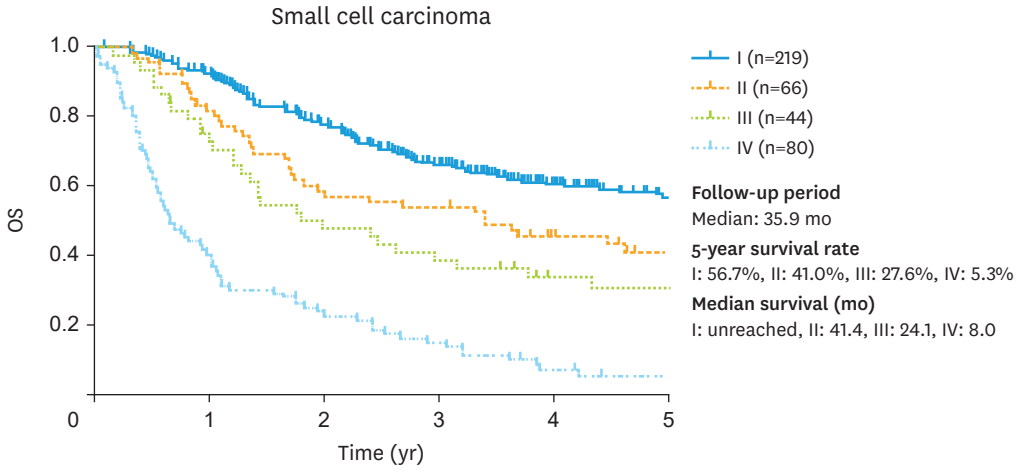

Fig. 1. Kaplan-Meier curves of OS and log-rank tests for different treatment strategies in International Federation of Gynecology and Obstetrics stage I–IV small cell carcinoma between 2004 to 2011 in Japan.
OS, overall survival.

the 5-year survival in N1 disease with surgery + chemotherapy (n=22) was 72.3%, and 25.0% in N1 with surgery + RT/CCRT (n=15) (**Fig. 3C**), and this was statistically significant (p=0.003). Conversely, there was no statistically significant difference in the 5-year survival in N0 disease treated with surgery + chemotherapy (63.0%) (n=93) versus N0 disease treated with surgery + RT/CCRT (63.7%) (n=32) (**Fig. 3B**).

We also examined the impact of local tumor progression on pelvic lymph-node or distant metastasis (**Tables 2** and **3**). T1b1 and T1b2 tumors had incidences of lymph-node metastasis at 14.2% and 38.9%, respectively (p<0.001). Similarly, the rates of distant metastasis in T1b1 and T1b2 disease were 4.4% and 13.7%, respectively (p<0.001).

DISCUSSION

In this study, we retrospectively examined the treatment for SCNEC in Japan. Neuroendocrine carcinoma of the cervix is an aggressive histological variant of cervical cancer, accounting for about 1%–1.5% of all cervical cancers [18]. In our cohort, SCNEC accounts for 1.1% of all cervical cancers, which is consistent with previous reports.

SCNEC is aggressive, even at an early stage. In the report of 71 Japanese SCNEC cases, the 4-year OS was as follows: IB1, 63%; IB2, 63%; IIB, 30%; IIIB, 29%; and IVB, 25% [12]. Other studies have reported the 5-year OS of SCNEC to be between 0%–63.5% [5-9]. In our study, the 5-year survival rate of stage I patients with SCNEC was 12.4%, which is similar to that of stage III patients with non-SCNEC cervical cancer from our registry [17]. Non-small cell cervical cancers had a 12.4% rate of being detected in stage IA, but this was far less for SCNEC (0.4%), which suggests that SCNEC is more aggressive and has a tendency to present with advanced stage disease. The presence of extrauterine disease also differs greatly with common cervical cancer. Analysis of the SSER database demonstrates that cervical neuroendocrine tumors presented with extrauterine disease in 66.9% of cases [4]. Similarly, our results demonstrate a high rate of lymph-node metastasis (38.2%), and the proportion of stage IV tumors (22.3% for SCNEC vs. 8.2% for all other histologies). This data supports the aggressive nature of SCNEC.

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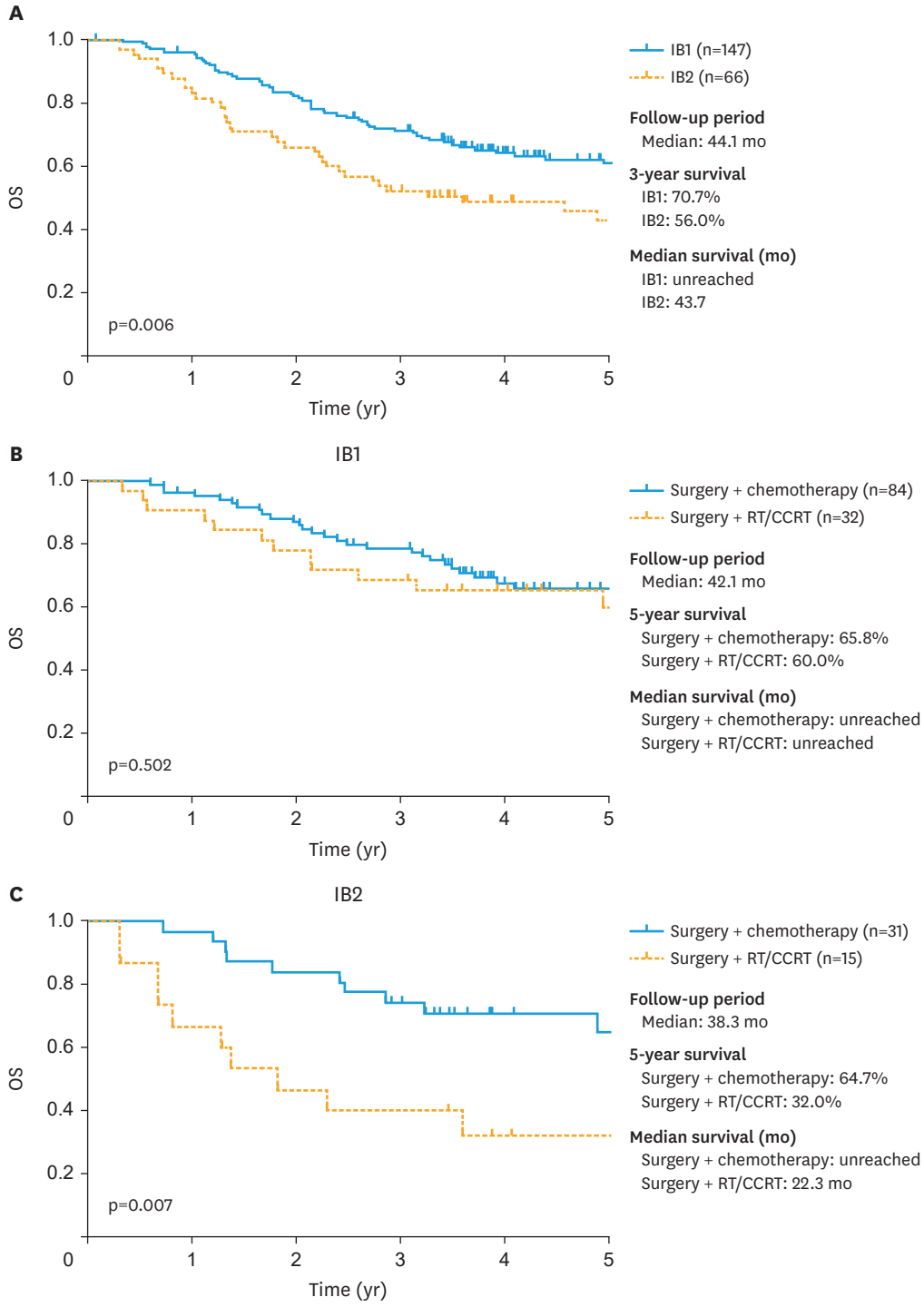

Fig. 2. Kaplan-Meier curves of OS and log-rank tests for different treatment strategies in International Federation of Gynecology and Obstetrics 2008 stage IB1 and IB2 small cell carcinoma between 2004 to 2011 in Japan. Log-rank tests performed: (A) IB1 vs. IB2, p=0.006; (B) surgery followed by chemotherapy vs. surgery followed by radiotherapy or concurrent chemoradiotherapy, p=0.502 in IB1. (C) Surgery followed by chemotherapy vs. surgery followed by radiotherapy or concurrent chemoradiotherapy, p<0.01 in IB2.
CCRT, concurrent chemoradiation therapy; OS, overall survival; RT, radiation therapy.

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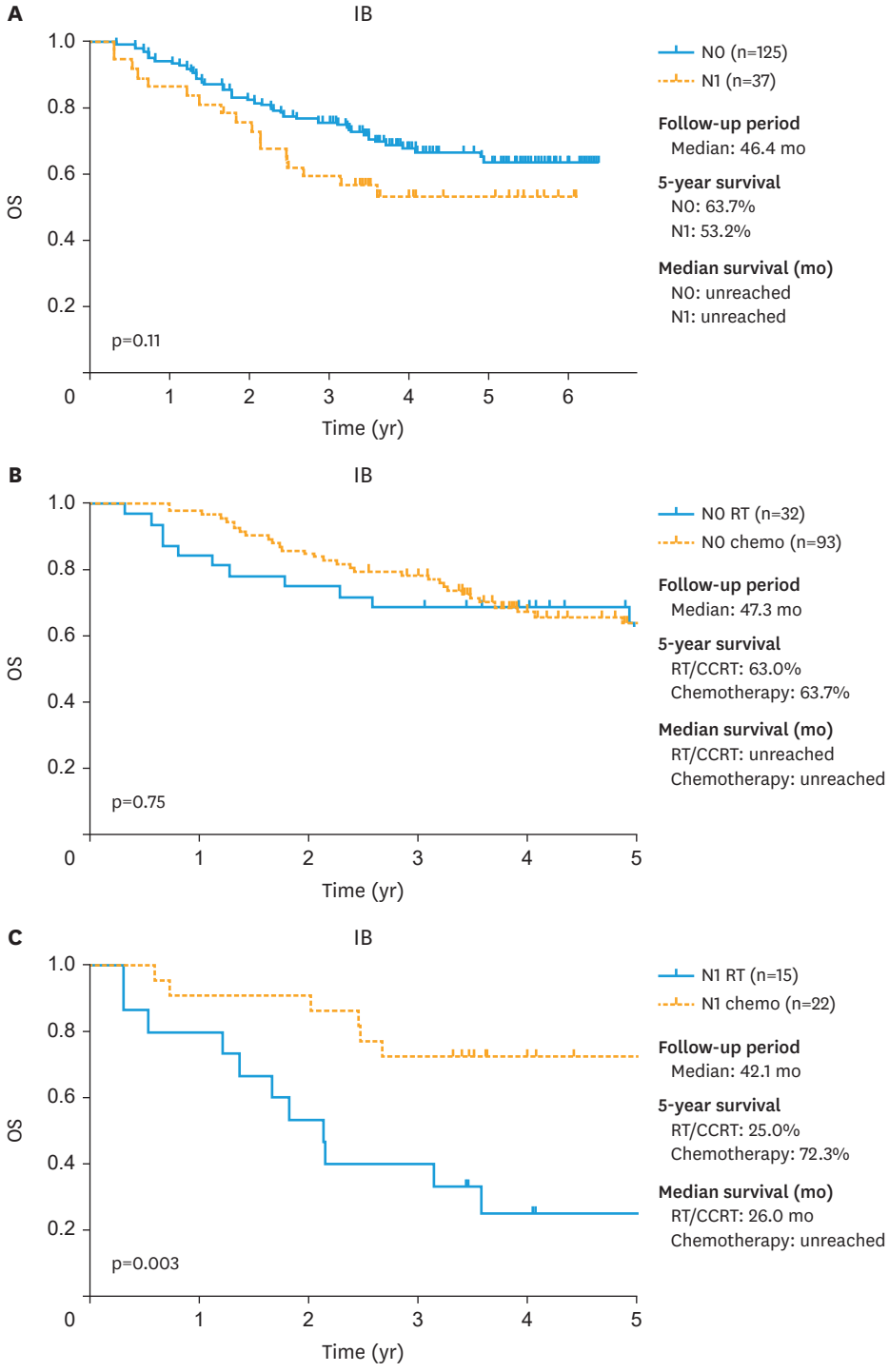

Fig. 3. Kaplan-Meier curves of OS and log-rank tests for pelvic lymph-node metastases in International Federation of Gynecology and Obstetrics 2008 stage IB small cell carcinoma between 2004 to 2011 in Japan. Log-rank tests performed: (A) patients without lymph-node metastasis (N0) vs. patients with lymph-node metastasis (N1) in IB, p=0.11; (B) surgery followed by chemotherapy vs. surgery followed by radiotherapy or concurrent chemoradiotherapy in N0 patients, p=0.75; (C) surgery followed by chemotherapy vs. surgery followed by radiotherapy or concurrent chemoradiotherapy in N1 patients, p=0.003.
CCRT, concurrent chemoradiation therapy; Chemo, chemotherapy; OS, overall survival; RT, radiation therapy.

https://doi.org/10.3802/jgo.2023.34.e4

Table 2. The percentage of pelvic-lymph node metastasis for small cell carcinoma of cervix between 2004 to 2015 in Japan

UICC TNM classification 7th edition (n=427)	Pelvic lymph-node metastasis	p-value
T1b1	42/296 (14.2)	<0.001
T1b2	51/131 (38.9)	

Values are presented as number (%).
TNM, tumor-node-metastasis; UICC, Union for International Cancer Control.

Table 3. The percentage of distant metastasis for small cell carcinoma of cervix between 2004 to 2015 in Japan

UICC TNM classification 7th edition (n=427)	Distant metastasis	p-value
T1b1	13/296 (4.4)	<0.001
T1b2	18/131 (13.7)	

Values are presented as number (%).
TNM, tumor-node-metastasis; UICC, Union for International Cancer Control.

The negative prognosticators of SCNEC have been reported to be an advanced stage, tumor size >2 cm, positive margins, age of the patient, treatment by primary radiotherapy, positive smoking status, and presence of lymph-node metastasis [6,10,19]. Our data did not show that lymph-node metastasis predicted OS rate in patients with IB SCNEC, but pelvic lymph-node metastasis was correlated with a poorer prognosis in stage IB1 disease (**Fig. 3**). Previous reports studying the association between lymph-node metastasis and prognosis have demonstrated that positive nodal disease is a negative prognosticator for DFS in stage I and II SCNEC, with no impact on OS [20]. Although pelvic lymph-node metastasis was not associated with decreased OS in stage IB disease in our study, the presence of distant metastasis was substantially higher in T1b2 than T1b1 tumors (**Table 3**). It is suggested that the distant micrometastasis, could not be detected in our study, exists with high probability in SCNEC tumors >4 cm in size. This may explain why OS is not improved with radiotherapy, which is utilized to control local disease.

Our study showed that surgery combined with adjuvant chemotherapy may improve outcomes in stage IB2 patients. However, the group of IB2 patients includes patients with lymph-node metastasis and tumor size >4 cm because this study was conducted using FIGO 2008 staging criteria. The incidence of pelvic lymph-node metastasis in stage IB, IIA, and IIB SCC and adenocarcinoma were 11.5%, 26.7% and 39.2%, respectively while the stage-for-stage incidences in SCNEC were 43%, 25%, and 45% (**Table 1**). Although the incidence of pelvic lymph-node metastasis between SCC and SCNEC was almost equal in stage IIA and IIB, stage IB tumors in SCNEC had higher rates of metastasis. In the FIGO 2018 classification, cases with lymph-node metastasis are categorized as stage IIIC, and NCCN guidelines recommend CCRT for patients with stage IIIC disease (FIGO 2018) [21]. However, this recommendation is for common cervical cancer, and may not be applied SCNEC. As shown in **Fig. 3C**, the 5-year OS with surgery followed by adjuvant chemotherapy for T1b patients with lymph-node metastasis (stage IIIC1; FIGO 2018) was relatively good at 72.3%. Considering that patients with tumors larger than 4 cm and N0 disease had better outcomes with adjuvant chemotherapy when compared with RT/CCRT (**Fig. S3**), surgery with adjuvant chemotherapy should be considered as a primary treatment for stage IIIC1 disease.

This study has several limitations. One limitation is that the chemotherapeutic regimen is undetermined. Previous studies of SCNEC utilized etoposide with a platinum-based agent, such as carboplatin, or paclitaxel [12,22]. The SGO and The Gynecologic Cancer InterGroup recommend etoposide/platinum (EP)-based chemotherapies for SCNEC NETs [10,23]. Another Japanese study reviewed the different adjuvant chemotherapy regimens utilized and found

that EP was used in 41/62 patients (66%), CPT-P in 17/62 (27.4%) and TC in 4/62 (6.5%) [11]. Molecular agents have been introduced into the treatment algorithms for pulmonary small cell carcinoma, and further investigation for extrapolation of this data to the treatment of uterine SCNEC will be necessary in the future. Furthermore, this is a retrospective study without centralized pathological evaluation. We did not have data on cancer recurrence. However, this study demonstrated that surgery with adjuvant chemotherapy is associated with better prognosis for T1B2 SCNEC patients, irrespective of lymph-node positivity. This information may help physicians devise treatment plans for SCNEC given the rarity of the disease.

In conclusion, rates of lymph-node and distant metastasis in SCNEC were significantly higher in tumors sized >4 cm. We suggest that surgery should be followed by adjuvant chemotherapy, and not radiotherapy or chemoradiotherapy, as this may improve prognosis in T1bN1M0 SCNEC.

SUPPLEMENTARY MATERIALS

Table S1

The kinds of therapy for small cell carcinoma of cervix between 2004 to 2015 in Japan

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Fig. S1

Age group distribution for small cell cervical carcinoma in Japan between 2004 and 2015. The patient number is displayed on the bar. Age distribution of the patients with small cell neuroendocrine cervical cancer was as follows: 20–29 (n=50, 6.1%), 30–39 (n=212, 25.8%), 40–49 (n=221, 26.9%), 50–59 (n=158, 19.2%), 60–69 (n=105, 12.8%), 70–79 (n=52, 6.3%), and 80 years or higher (n=24, 6.3%).

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Fig. S2

Distribution of treatment types by International Federation of Gynecology and Obstetrics 2008 stages for patients with small cell cervical carcinoma in 2004–2015.

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Fig. S3

Kaplan-Meier curves of overall survival and log-rank tests for different treatment strategies in FIGO stage IB2 without lymph-node metastasis as FIGO 2018 stage IB3 between 2004 to 2011 in Japan. Log-rank tests performed surgery followed by chemotherapy vs. surgery followed by radiotherapy or concurrent chemoradiotherapy, p=0.082.

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