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A multi-center retrospective study of neuroendocrine tumors of the uterine cervix: Prognosis according to the new 2018 staging system, comparing outcomes for different chemotherapeutic regimens and histopathological subtypes

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HIGHLIGHTS

- A multicenter, retrospective study of neuroendocrine tumors of the uterine cervix was undertaken.
- Locally-advanced and extra-pelvic disease were independent prognostic factors for NET of the cervix.
- HGNEC showed good responses to EP or CPT-P regimens but not to TC.
- ACT was less responsive to chemotherapy and had a prognosis identical to HGNEC.

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ABSTRACT

Objective: To analyze the clinical behavior of neuroendocrine tumors (NETs) of the uterine cervix, we conducted a multicenter, retrospective study of 193 patients.

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Methods: We evaluated the prognosis of NETs according to the new International Federation of Gynecology and Obstetrics (FIGO) staging system, compared the clinical response to different chemotherapy regimens, and compared different histological subtypes of NETS.
Results: Diagnoses of the subjects were atypical carcinoid tumor (ACT, n = 37), small cell neuroendocrine carcinoma (SCNEC, n = 126), large cell neuroendocrine carcinoma (LCNEC, n = 22), and NET, not elsewhere classified (n = 8), according to central pathological review. According to FIGO 2018, 69, 17, 74, and 33 patients were at stage I, II, III, or IV, respectively. Five-year survival was 64.5%, 50.1%, 30.2%, and 3.4% for patients at stage I, II, III and IV. About 40% of patients with stage IIIC1 survived >5 years. On multivariate analyses, locally-advanced disease, para-aortic node metastasis, distant metastasis, and <4 cycles of chemotherapy were associated with poor survival. Histological subtype and pelvic node metastasis had no prognostic significance. Response rates to etoposide-platinum (EP) or irinotecan-platinum (CPT-P) regimens were 43.8% (28/64), but only 12.9% to a taxane-platinum (TC) regimen (4/31). The response rate for ACT was 8.7% (2/23), significantly less than the 36.6% for high-grade neuroendocrine carcinomas (HGNEC: both SCNEC and LCNEC, 41/111).
Conclusions: Locally-advanced, extra-pelvic disease and insufficient chemotherapy were independent prognostic factors for cervical NET. HGNEC showed good responses to EP or CPT-P but not TC. Chemotherapy was less effective for ACT, which had a prognosis identical to HGNEC.

1. Introduction

Of the several different cancers of the uterine cervix, neuroendocrine tumors (NETs) are considered an aggressive histological type [1–7]. A NET of the uterine cervix is classified as being either a carcinoid tumor, an atypical carcinoid tumor (ACT), a small cell neuroendocrine carcinoma (SCNEC), or a large cell neuroendocrine carcinoma (LCNEC) [8]. The former two types are categorized as low-grade neuroendocrine tumors (LGNET) and the latter two as high-grade neuroendocrine carcinomas (HGNEC). HGNECs are considered much more aggressive diseases [2,3,5]. On the other hand, LGNETs are less well-known because they are much rarer.

To analyze clinical behavior of and prognostic factors for NETs of the uterine cervix, we conducted a multicenter, retrospective study. This involved constructing a database comprising 193 Japanese patients treated in 26 hospitals that are members of the Gynecologic Cancer Study Group of the Japan Clinical Oncology Group (JCOG–GCSG). We previously reported on prognostic factors and optimal therapy for early stage HGNECs [9]. The International Federation of Gynecology and Obstetrics (FIGO) staging system was recently revised from FIGO 2008 to FIGO 2018. In the present study, we evaluated the prognosis of NETs according to this new FIGO system. We also evaluated the efficacy of chemotherapy for NETs comparing response rates to different regimens. Finally, we also compared LGNETs with HGNECs in these respects.

2. Materials and methods

2.1. Patients

A total of 26 hospitals that were members of the Gynecologic Cancer Study Group of the Japan Clinical Oncology Group (JCOG–GCSG) participated in this retrospective study, which was approved by the institutional review board at each hospital and conducted in accordance with the Declaration of Helsinki. We constructed a database comprising patients with neuroendocrine tumors (NETs) of the uterine cervix [9]. Eligibility criteria for inclusion were (1) diagnosed with a NET of the uterine cervix – either carcinoid tumor, ACT, SCNEC or LCNEC, at a member hospital; (2) received initial treatment between 1989 and 2008; and (3) disease confirmed histologically as a NET by central pathological review (CPR). The following patients were excluded: (1) those for whom insufficient data on the clinical course were available; (2) untreated patients; or (3) those without a NET diagnosis after CPR.

2.2. Central pathological review

All patients included in this study were assessed by central pathological review (CPR). For patients who underwent surgery, representative slides of surgical specimens of the cervix were submitted, and for those who did not undergo surgery, biopsy specimens before the start of treatment were submitted. CPR was performed according to World Health Organization classifications [10] by four pathologists specialized in gynecological cancers. Carcinoid tumor was characterized by abundant cytoplasm, characteristic granular chromatin and visible to prominent nucleoli with organoid, spindled, nested, islands, or trabecular pattern. ACT was distinguished from the carcinoid tumor by its greater degree of nuclear atypia and mitotic activity as well as rare areas of necrosis. SCNEC was characterized by the presence of monotonous small cells with ovoid hyperchromatic nuclei, often showing nuclear moulding, and scanty cytoplasm. There was usually abundant mitotic and apoptotic activity with extensive necrosis, and lymphovascular and perineural invasion. LCNEC had a diffuse, organoid, trabecular, or cord-like pattern and was composed of neoplastic cells with abundant cytoplasm, large nuclei, prominent nucleoli, and a high mitotic rate. Immunohistochemical analyses were performed to confirm neuroendocrine features using several markers, including chromogranin A, synaptophysin, and CD56. Before starting CPR, these criteria were explained in detail and shared among the pathologists who then examined all specimens at the same time using a discussion microscope, conducted discussion, and agreed on the following histological diagnosis: carcinoid tumor, ACT, SCNEC, LCNEC, or others with specific diagnosis. The histological heterogeneity of each case was also evaluated. Cases with coexisting areas of squamous or glandular differentiation in the tumor (with a requirement that these were more than 5% of the tumor) were diagnosed as mixed tumors.

2.3. Patients, tumors and treatment variables

Clinical information was obtained from medical records. All patients were restaged according to the FIGO 2018 staging system [11] using clinical and pathological findings. For patients receiving surgery, restaging was done mainly using pathological findings. For patients who did not undergone surgery or who started treatment with neoadjuvant chemotherapy (NACT), restaging was done mainly using clinical findings by physical examination and imaging. Patients were further classified according to the 8th edition of the

Union for International Cancer Control TNM Classification of Malignant Tumors [12]. Information about treatment was collected. Chemotherapies were divided into NACT, adjuvant chemotherapy, chemosensitization of concurrent chemoradiation therapy (CCRT), chemotherapy for metastatic lesions (for unresected or not irradiated metastatic lesions at the initial treatment), or chemotherapy for recurrent disease.

2.4. Methods

The outcomes for each FIGO stage were evaluated. All end points were calculated from the date of the start of initial treatment to death, progression, recurrence, or patients censored at last follow-up. In this study, relapse, recurrence, and progression were all classified as disease progression. Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan–Meier method. The Cox proportional hazards model was used to identify prognostic factors. To evaluate the efficacy of chemotherapy, we collected information about the clinical response to NACT, or treatment of metastatic lesions or recurrent disease based on Response Evaluation Criteria in Solid Tumors [13]. We then calculated the response rate for each regimen. LGNETs and HGNECs were compared regarding clinical and pathological factors using Chi-square tests or Fisher's exact test. All statistical analysis was performed using JMP 9 (SAS Institute, North Carolina, USA). P values < 0.05 were considered statistically significant.

3. Results

3.1. Patients

A total of 238 patients with cervical NET was enrolled in our project. Forty-five of these were ineligible for the study. The reasons for exclusion were that pathological specimens of 32 patients were not submitted for CPR, 8 were diagnosed as non-NET by CPR, 4 patients were not treated, and one did not have cervical cancer but vaginal cancer. Histological diagnoses by CPR of the 8 patients who were diagnosed as non-NET was 4 squamous cell carcinoma, 2 adenocarcinoma, and 2 adenosquamous carcinoma. Eventually, 193 patients were enrolled into a database of NET cases of the uterine cervix. Age of the patients, histological tumor type, FIGO stage, T classification of primary disease, size of primary tumor, node and distant metastasis status are summarized in Table 1. In this series, no patients were diagnosed with carcinoid tumor. A diagnosis of ACT, SCNEC and LCNEC accounted for 37, 126, and 22 patients, respectively. Eight patients were classified as "NET, not elsewhere classified", because both HGNEC and LGNET components were present in these cases.

On staging using the FIGO 2008 system, 100 patients were at FIGO stage I, 42 stage II, 18 stage III, and 33 were at stage IV. Patients were then restaged using the FIGO 2018 system, which placed 69 at stage I, 17 stage II, 74 stage III, and 33 at stage IV. This comparison of staging according to FIGO 2008-vs-FIGO 2018 is shown in Supplemental Table 1. Of 100 patients at stage I according to FIGO 2008, 26 and 4 patients were upstaged to stage IIIC1 and IIIC2, respectively. Of 42 patients with stage II by FIGO 2008, 19 and 7 patients were upstaged to stage IIIC1 and IIIC2, respectively. Moreover, stage III patients numbered only 18 according to FIGO 2008 but this increased to 74 by FIGO 2018. There were 53 patients with IIIC1. Of these, 42 had IIIC1p and 11 had IIIC1r. Of the 17 patients with IIIC2, 10 had IIIC2p and 7 had IIIC2r. There were 32 patients with para-aortic node (PAN) metastasis, all of whom also had pelvic node (PLN) metastasis.

Initial treatment for each stage is summarized in Supplemental Table 2. Of the total of 193 cases, 148 received surgery, 70 received radiotherapy (RT, of which 40 received post-operative RT), and 134 received chemotherapy. Of the 86 cases with stage I and stage II, almost all received surgery as their primary treatment, and only 4 cases received definitive RT. Of 53 cases with stage IIIC1, 43 and 9 were treated surgically or with definitive RT for their first-line treatment, respectively. Finally, of 31 patients with stage IVB, 16 received local therapy at the pelvis (surgery and/or RT) plus chemotherapy, 11 received only chemotherapy, and 4 only local treatment without chemotherapy.

Table 1
Patient characteristics.

	n	(%)
Hystological type		
LGNET	37	19.2
Carcinoid	0	0
ACT	37	19.2
HGNEC	148	76.7
SCNEC	126	65.3
LCNEC	22	11.4
NET, not elsewhere classified	8	4.1
Age		
≤49	120	62.2
50 - 69	61	31.6
70 ≤	12	6.2
FIGO stage		
I	69	35.8
IA	1	0.5
IB1	22	11.4
IB2	36	18.7
IB3	10	5.2
II	17	8.8
IIA1	2	1.0
IIA2	2	1.0
IIAx	1	0.5
IIB	12	6.2
III	74	38.3
IIIA	0	0
IIIB	4	2.1
IIIC1	53	27.5
IIIC2	17	8.8
IV	33	17.1
IVA	2	1.0
IVB	31	16.1
T classification		
T1	94	48.7
T2	58	30.1
T3, T4	40	20.7
Unknown	1	0.5
Tumor size		
<2 cm	29	15.0
2–4 cm	62	32.1
4 cm ≤	98	50.8
Unknown	4	2.1
PLN metastasis		
No	99	51.3
Present	93	48.2
Unknown	1	0.5
PAN metastasis		
No	160	82.9
Present	32	16.6
Unknown	1	0.5
Distant metastasis		
No	162	83.9
Present	31	16.1

Note. LGNET: low grade neuroendocrine tumor; ACT: atypucal carcinoid tumor; HGNEC: high grade neuroendocrine carcinoma; SCNEC: small cell neuroendocrine carcinoma; LCNEC: large cell neuroendocrine carcinoma; NET: neuroendocrine tumor; FIGO: International Federation of Gynecology and Obstetrics; T classification: classification of primary tumor according to the 8th edition of the Union for International Cancer Control TNM Classification of Malignant Tumors; PLN: pelvic lymphnode; PAN para-aortic lymphnode.

3.2. Survival curves

Fig. 1 shows OS and PFS curves for patients at each stage. Five-year survival of stage I, II, III, and IV patients was 64.5%, 50.1%,

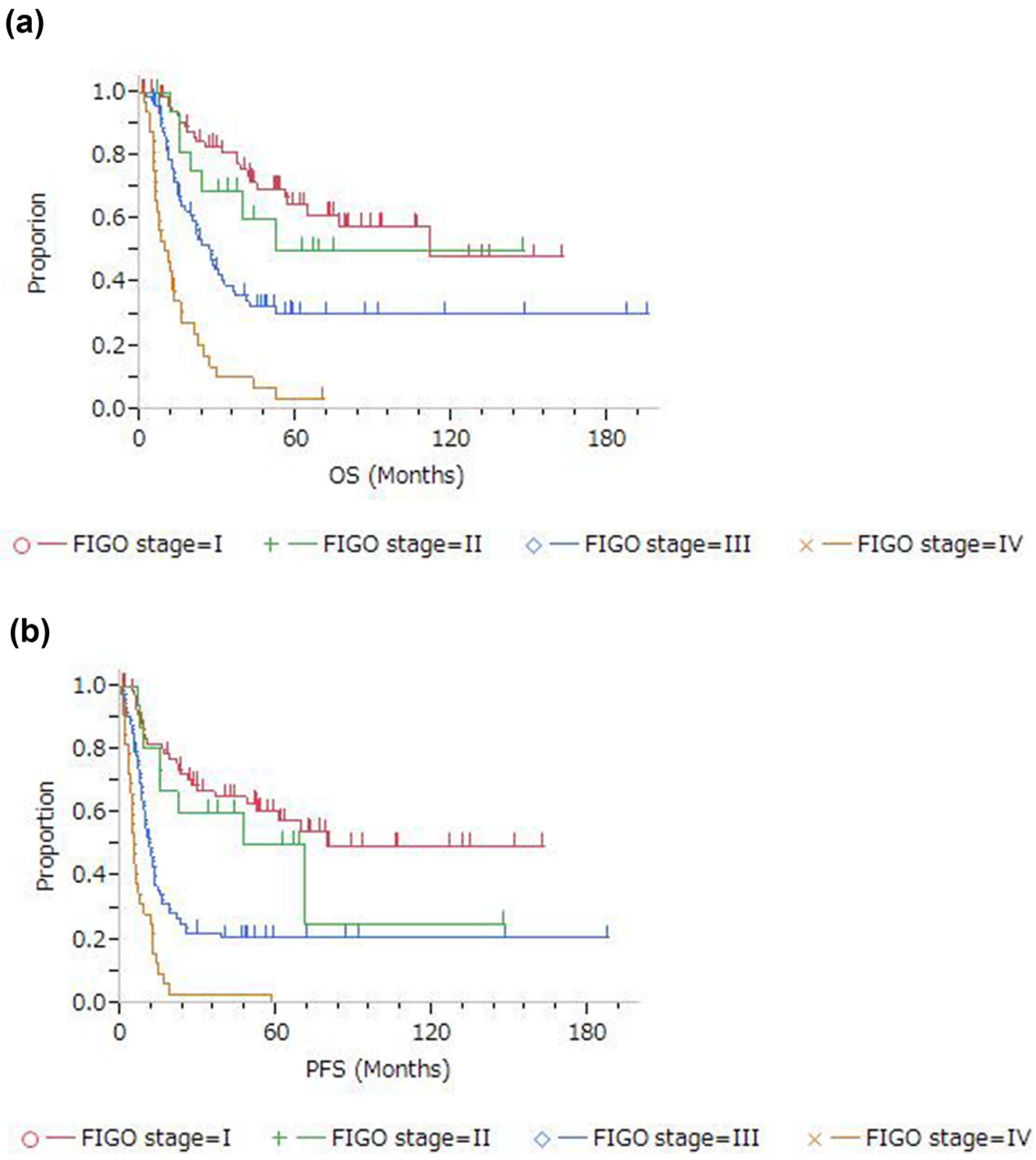

Fig. 1. Survival curves of patients at each stage: (1a) Overall survival (OS); (1b) Progression-free survival (PFS).
The x-axis denotes survival period (months) after the initial treatment, and the y-axis denotes survival rate (1.0 stands for 100%).

30.2% and 3.4%, respectively. Hazard ratios (HR) for death at stage II, III, and IV relative to stage I were 1.38 (95% confidence interval [CI]: 0.55–3.06), 2.79 (95%CI: 1.71–4.70), and 8.48 (95%CI: 4.87–14.97), respectively. Five-year progression-free survival rates of stage I, II, III, and IV patients were 60.6%, 50.2%, 20.8%, and 0%, respectively. HR for progression or death at stage II, III, and IV relative to stage I were 1.36 (95% CI: 0.58–2.87), 3.34 (95%CI: 2.11–5.40), and 8.98 (95%CI: 5.25–14.49), respectively. Survival curves for patients at different sub-stages are shown in Supplemental Fig. 1. There were too few patients at stage IA, IIA, IIIA, or IVA to construct survival curves. However, about 40% of patients with stage IIIC1 survived >5 years, but patients at stage IIIA, IIIC2 or IVB had a poor prognosis.

A comparison of survival curves between FIGO 2008 and FIGO 2018 is shown in Supplemental Fig. 2. Because all patients with stage IV by FIGO 2008 were also stage IV by FIGO 2018, the survival curves of stage IV by FIGO 2008 are completely consistent with those for FIGO 2018. Comparing the survival curves of each stage (stage I, II, and III), the prognosis based on FIGO 2018 (bold lines) tended to be better than FIGO 2008 (thin lines), and reached statistical significance for PFS of stage III patients (log-rank $p = 0.0151$).

3.3. Prognostic factors

To identify prognostic factors in these patients with NET of the cervix, histological type (LGNET vs HGNEC), patient age, T classification, tumor size, node status, distant metastasis, and number of chemotherapy cycles at initial treatment (0–4 vs 5 or more) were analyzed as variables (Table 2). Multivariate analyses revealed that T3/T4, PAN metastasis, distant metastasis, and fewer chemotherapy cycles (0–4) were associated with poor OS and PFS. Histological type, tumor size, and PLN metastasis were not prognostic.

Table 2
Prognostic factors for NET of the uterine cervix.

	n	Overall survival						Progression free survival					
		Univariate			Multivariate			Univariate			Multivariate		
		HR	95%CI	p value	HR	95%CI	p value	HR	95%CI	p value	HR	95%CI	p value
Hystological type													
LGNET	37	1			1			1			1		
HGNEC	148	1.66	0.999–2.93	0.0505	1.31	0.76–2.42	0.3448	1.30	0.83–2.12	0.2552	0.92	0.61–1.66	0.9446
Age													
≤49	120	1			1.18	0.75–1.89	0.4670	1.05	0.72–1.57	0.7890	1.33	0.88–2.05	0.1769
50 - 69	61	1.04	0.68–1.57	0.8478	1			1			1		
70 ≤	12	1.67	0.74–3.29	0.1997	2.36	0.98–5.11	0.0554	1.43	0.58–3.01	0.4085	1.80	0.72–3.94	0.1946
T classification													
T1	94	1			1			1			1		
T2	58	1.88	1.17–3.00	0.0093	1.64	0.92–2.94	0.0954	1.89	1.22–2.90	0.0045	1.55	0.91–2.65	0.1060
T3, T4	40	4.52	2.80–7.27	<.0001	2.13	1.05–4.43	0.0372	4.87	3.09–7.66	<.0001	2.08	1.04–4.27	0.0379
Tumor size													
<2 cm	29	1			1			1			1		
2–4 cm	62	2.22	1.07–5.22	0.0324	1.74	0.81–4.18	0.1591	1.82	0.97–3.66	0.0613	1.49	0.77–3.08	0.2426
>4 cm	98	4.22	2.15–9.55	<.0001	1.51	0.65–3.87	0.3500	3.41	1.92–6.63	<.0001	1.34	0.64–2.95	0.4449
PLN metastasis													
No	99	1			1			1			1		
Present	93	2.35	1.59–3.51	<.0001	1.12	0.65–1.91	0.6850	2.76	1.91–4.04	<.0001	1.49	0.91–2.46	0.1149
PAN metastasis													
No	160	1			1			1			1		
Present	32	4.45	2.81–6.85	<.0001	2.58	1.44–4.60	0.0016	4.62	2.95–7.10	<.0001	2.26	1.28–3.94	0.0054
Distant metastasis													
No	162	1			1			1			1		
Present	31	4.45	2.81–6.85	<.0001	2.43	1.25–4.70	0.0085	4.62	2.95–7.10	<.0001	1.96	1.04–3.72	0.0379
Cycle of chemotherapy													
0 - 4	118	1.35	0.91–2.03	0.1402	1.63	1.05–2.57	0.0307	1.32	0.92–1.91	0.1399	1.64	1.10–2.48	0.0159
>5	74	1			1			1			1		

Note. LGNET: low grade neuroendocrine tumor; HGNEC: high grade neuroendocrine carcinoma; T classification: classification of primary tumor according to the 8th edition of the Union for International Cancer Control TNM Classification of Malignant Tumors; PLN: pelvic lymphnode; PAN para-aortic lymphnode; HR: hazard ratio; CI: confidence interval.

Table 3
Chemotherapy regimens.

Regimen	Initial treatment				For recurrent disease	
	CCRT	NACT	Adjuvant CT	For metastatic lesion	1st recurrence	2nd or later
Platinum monotherapy	21	3	0	1	0	5
EP regimen	9	20	62	8	18	5
CPT-P regimen	1	4	26	4	23	3
TC regimen	0	3	9	9	18	5
Other platinum regimens	5	6	3	6	6	2
Non-platinum regimens	0	0	4	1	10	15
No. of patients	36	35	102	25	75	29

Note. EP regimen: etoposide + platinum; CPT-P regimen: irinotecan + platinum; TC regimen: taxane + platinum; CCRT: concurrent chemoradiation therapy; NACT: neo-adjuvant chemotherapy; Adjuvant CT: adjuvant chemotherapy. In some case, plural regimens were used.

3.4. Efficacy of chemotherapy

Chemotherapy was given to 36 patients (with CCRT), to 35 (as NACT), 102 (as adjuvant treatment), 25 (for metastatic lesions), and to 75 (for recurrent disease). Because this was a multi-center retrospective study, chemotherapy was used in various different combinations in a wide range of regimens. We classified these into six groups according to similarities as follows: 1) Platinum monotherapy: single-agent platinum, 2) EP regimen: etoposide + platinum, 3) CPT–P regimen: irinotecan + platinum, 4) TC regimen: taxane + platinum, 5) Other platinum regimens, and 6) Non-platinum regimens. The use of each regimen according to its purpose in the initial treatment or for recurrent disease are summarized in Table 3. For CCRT, platinum monotherapy was the most common regimen. For NACT, adjuvant treatment and treatment of metastatic lesions, the most common regimen was EP, followed by CPT–P. The TC regimen was sometimes used. For recurrent disease, CPT-P, EP, and TC were commonly used at the first recurrence. After the second recurrence, use of non-platinum regimens was increased.

To evaluate the efficacy of chemotherapy, we collected information about the clinical response for NACT and for treating metastatic or recurrence disease (Table 4). The response rate to 1st line therapy was 53.1% (34/64), but it decreased to 12.9% (9/70) for 2nd line or later. Taking each chemotherapy regimen separately, the 1st line response rate to EP or CPT-P regimens was 56.8% (21/37) but 25.9% (7/27) at the 2nd or more. In contrast, the response rate to the TC regimen was only 23.1% (3/13) for 1st line and 5.6% (1/18) for 2nd. Thus, the TC regimen was less effective than EP or CPT-P regimens.

3.5. Comparison between histological subtypes

LGNET (n = 37) and HGNEC (n = 148) were compared regarding patient age, stage, heterogeneity, immunostaining for chromogranin A, synaptophysin, and CD56, and response to chemotherapy (Table 5). LGNET disease was less advanced and had more mixed type disease. Age distribution and the rate of positive immunostaining were not significantly different between LGNET and

Table 4
Response rates to chemotherapy.

Regimen	Overall	1st line	2nd or more line
	RR % (CR + PR/n)	RR % (CR + PR/n)	RR % (CR + PR/n)
Platinum monotherapy	33.3 (2/6)	66.7 (2/3)	0 (0/3)
EP regimen	46.3 (19/41)	53.1 (17/32)	22.2 (2/9)
CPT-P regimen	39.1 (9/23)	80.0 (4/5)	27.8 (5/18)
TC regimen	12.9 (4/31)	23.1 (3/13)	5.6 (1/18)
Other platinum regimens	50.0 (8/16)	80.0 (8/10)	0 (0/6)
Non-platinum regimens	5.9 (1/17)	0 (0/1)	6.3 (1/16)
Total	32.1 (43/134)	53.1 (34/64)	12.9 (9/70)

Note. EP regimen: etoposide + platinum; CPT-P regimen: irinotecan + platinum; TC regimen: taxane + platinum; RR: response rate; CR: complete response; PR: partial response.

HGNEC. LGNET responses to chemotherapy were seen in only 6.7% (overall) and in 16.7% (on the EP or CPT-P regimen). This is significantly worse than in than HGNEC.

4. Discussion

We conducted a multi-center retrospective study of 193 patients with NET of the uterine cervix treated at 26 cancer institutes in Japan. We investigated variables affecting the prognosis at each stage of disease according to the new FIGO 2018 staging system. On multivariate analysis, T3/T4, PAN metastasis, distant metastasis, and number of chemotherapy cycles were independent prognostic factors for survival. The efficacy of chemotherapy was evaluated by response rate. Although CPT-P and EP regimens were effective for HGNEC, the TC regimen was less so. LGNET was less sensitive to chemotherapy than HGNEC, and did not have a better prognosis than HGNEC.

We previously reported that radical surgery followed by adjuvant chemotherapy with an EP or CPT−P regimen was the optimal treatment for patients with HGNEC of the uterine cervix at stages I and II [9]. That report was based on the FIGO 2008 system. Recently, FIGO staging was updated to the 2018 system and patients with lymph node metastasis are upgraded to stage IIIC1 or IIIC2. We therefore restaged the patients enrolled in our NET database using the new FIGO 2018 staging system, and conducted a retrospective analysis of prognosis for each stage.

Table 5
Comparison between LGNET and HGNEC.

	LGNET n = 37	HGNEC n = 148	p value
Age distribution			
≤49	28 (75.7)	87 (58.7)	0.1302
50-69	7 (18.9)	52 (35.1)	
70 ≤	2 (5.4)	9 (6.1)	
FIGO stage			
I	21 (56.8)	42 (28.4)	0.0023
II	5 (13.5)	11 (7.4)	
III	8 (21.6)	66 (44.6)	
IV	3 (8.1)	29 (19.6)	
Histological heterogeneity			
pure	22 (59.5)	113 (76.4)	0.0446
mix	15 (40.5)	35 (23.6)	
Immunostain positive rate			
Chromogranin	24/29 (82.8)	106/127 (83.5)	0.9269
Synaptophysin	26/28 (92.9)	99/118 (83.9)	0.1928
CD56	14/22 (63.6)	77/102 (75.5)	0.2658
Response rate for chemotherapy CR + PR/n (%)			
Overall	2/23 (8.7)	41/111 (36.9)	0.0038
EP or CPT-P regimen	2/12 (16.7)	26/51 (51.0)	0.0245

Note. FIGO: International Federation of Gynecology and Obstetrics; CR: complete response; PR: partial response; EP regimen: etoposide + platinum; CPT-P regimen: irinotecan + platinum; LGNET: low grade neuroendocrine tumor; HGNEC: high grade neuroendocrine carcinoma.

The number of patients at stage III was increased from 18 according to FIGO 2008 to 74 by FIGO 2018 staging. Patients with FIGO IIIC1 had a relatively good prognosis; about 40% of them survived more than five years. Comparing the survival curves of stage I, II, and III patients between FIGO 2008 and FIGO 2018, the prognosis according to FIGO2018 tended to be better than FIGO 2008. However, locally-advanced disease (T3/T4) and extra-pelvic disease (PAN and/or distant metastasis) was associated with an extremely poor prognosis. Local treatment and systemic chemotherapy are standard treatments for NET [6,9,14–23]. Drug treatment plays a very important role especially for advanced disease. To improve the prognosis of advanced cases with NET of the cervix, development of new drug treatments such as molecular targeting is desirable [24].

We evaluated the efficacy of chemotherapy given as NACT or as treatment for metastatic or recurrent disease by assessing response rates. EP or CPT-P regimens are considered effective regimens for small cell carcinoma of lung [25], and in our study HGNEC of the cervix showed a good response at 1st line use. We evaluated the efficacy at 2nd line or more. Although the response rates were decreased relative to 1st line use, EP and CPT-P regimens still showed relatively better efficacy than other regimens. Thus, as in earlier studies [14–17,26], our results support the notion that EP and CPT-P regimens are currently optimal for NET of the cervix. However, response rates decreased after first use, and new drug treatments must be developed for recurrent disease of NET. However, the TC regimen, which is the standard regimen for the usual type of cervical cancer at the moment, had poorer efficacy than EP and CPT-P regimens. In the present series, cisplatin, carboplatin, and nedaplatin were used as the platinum-containing agents. To compare these, we calculated the response rates for cisplatin-containing regimens, carboplatin-containing regimens, and nedaplatin-containing regimens. The response rate to carboplatin-containing regimens was lower (21.4%, 9/42) than cisplatin (46.0%, 29/63) and nedaplatin (33.3%, 4/12). Carboplatin was mainly used in the TC regimen. That may be the reason why carboplatin-containing regimens showed poorer efficacy. Of the patients used EP regimen, six patients used carboplatin for EP. Four of them showed response to EP. Thus we could not conclude that carboplatin had less effective than cisplatin.

We compared the characteristics of patients with cancer of different histological subtypes, LGNET-vs-HGNEC. Because no patients with typical carcinoid were included, all LGNET cases were patients with ACT. This was characterized by less advanced disease and less response to chemotherapy than HGNEC. ACT of the cervix was considered to have a relatively better prognosis than HGNEC. However, because ACT is an extremely rare disease, its biological behavior is almost unknown at present [27]. Our analysis revealed that response rates of ACT to chemotherapy are significantly worse than HGNEC, and ACT did not have better prognosis than HGNEC.

In conclusion, locally-advanced and extra-pelvic disease were independent prognostic factors for patients with NET of the cervix.

Also the number cycles of chemotherapy was associated with prognosis. HGNEC responded well to EP or CPT-P regimens, but TC showed poor efficacy. ACT was less responsive to chemotherapy and had a prognosis identical to HGNEC. Development of new drug treatments for NET of the cervix are urgently needed.

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Author contributions

M.I., H.T., and T.K. (Bokutoh Hospital) contributed to study concepts, study design, quality control of data, data analysis, interpretation, and manuscript preparation. Four authors (H.T., M.F., A.S., and T.K. (Fukuoka Sanno Hospital)) contributed to CPR (central pathological review). All of the authors contributed to data acquisition, manuscript editing, and manuscript review.

Declaration of competing interest

None of the authors reports that they have any conflict of interest to disclose.

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Appendix A. Supplementary data

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