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Enhanced efficacy of adjuvant chemotherapy and radiotherapy in selected cases of surgically resected neuroendocrine carcinoma of the uterine cervix

A retrospective cohort study

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Abstract

The aim of the present study is to identify the prognostic factors of overall survival and examine the effects of adjuvant chemotherapy and radiotherapy on the overall survival in neuroendocrine carcinoma of the uterine cervix (NECUC) patients.

Forty-eight surgically treated patients were retrospectively recruited and clinicopathologic characteristics and treatments were reviewed. Kaplan–Meier product-limit method and Cox proportional-hazards regression were utilized for univariate and multivariate analyses.

The median follow-up time was 20.6 months and the median overall survival was 30.7 months. The estimated 2-year and 5-year overall survival rates were 57.5% and 31.3%, respectively. Forty patients had $\leq$ stage IIA disease and 8 had >IIA disease. Univariate analysis identified the clinical stage $\leq$ IIA ($P=0.042$), tumor size $\leq$ 4 cm ($P=0.005$), negative lymph nodes metastasis ($P<0.001$), depth of stromal invasion $\leq$ 1/2 ($P=0.001$), negative parametrial involvement ($P=0.004$), and weak staining of synaptophysin ($P=0.037$), and chromogranin ($P=0.011$) as the prognostic factors for an improved overall survival, while chemotherapy and radiotherapy were not prognostic factors in the whole cohort. However, surgery combined with chemotherapy and radiotherapy produced a survival advantage over surgery alone in patients with large tumors ($P=0.006$). The combination of surgery and chemotherapy (with or without radiotherapy) did not show any significant difference in overall survival for small tumors ($P=0.816$), compared with no chemotherapy (with or without radiotherapy). In addition, radiotherapy for tumors with squamous cell carcinoma or adenocarcinoma components achieved a better survival ($P=0.01$), and there was a tendency of an unfavorable survival for radiotherapy in homogeneous carcinoma ($P=0.099$). Tumor size was an independent prognostic factor in the multivariate analysis (HR: 12.724, 95% CI: 1.697–95.423, $P=0.013$).

In conclusion, clinicopathologic features significantly influence a NECUC patient's outcome. Tumor size and tumor histology can influence the effect of adjuvant chemotherapy and radiotherapy on overall survival. We recommend that platinum-based adjuvant chemotherapy should be used in all cases, while radiotherapy should be reserved for the selected NECUC patients whose tumors have mixed histology.

Abbreviations: B = bleomycin, CD56 = neural cell adhesion molecule, CgA = chromogranin, DOI = depth of stromal invasion, E = etoposide, FIGO = International Federation of Gynecology and Obstetrics, HPV = human papilloma virus, LNM = lymph nodes metastasis, LVSI = lymph-vascular space invasion, NACT = neoadjuvant chemotherapy, NECUC = neuroendocrine carcinoma of the uterine cervix, NSE = neuron-specific enolase, P = platinum-derivatives, PACT = postoperative adjuvant chemotherapy, PMI = parametrial involvement, SCCC = small cell neuroendocrine carcinoma of the uterine cervix, SCLC = small cell lung cancer, Syn = synaptophysin, T = paclitaxel.

Keywords: cervix, multimodality therapy, neuroendocrine carcinoma, prognostic factors

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1. Introduction

Neuroendocrine carcinoma of the uterine cervix (NECUC) is a rare, but aggressive subset of uterine solid tumors, accounting for less than 3% of the malignancies of the uterine cervix.[1] Owing to its rarity, it was quite often for pathologists and clinicians to mistake NECUC for other carcinomas before an explicit classification system of NECUC was introduced by the College of American Pathologists and National Cancer Institute in 1997.[2] NECUC comprises small cell neuroendocrine carcinoma, large cell neuroendocrine carcinoma, typical carcinoid tumor, and atypical carcinoid tumor histologic subtypes.[2–4] The first 2 subtypes represent the majority of NECUCs and are poorly differentiated with a poor prognosis. In contrast, the latter 2 subtypes are extremely rare with a well differentiation and an uncertain or unfavorable prognosis.[4,5]

Previous studies of NECUC were mainly some isolated case reports and retrospective studies of relatively small series, lacking large sample volume, and prospective design. Therefore, standard management of the patients has not been well established yet. Although a comprehensive strategy that combines surgical resection with chemotherapy and/or radiotherapy is generally employed to improve the pelvic control and prevent the systematic metastasis in NECUC patients even including the early-stage patients,[1] few patients achieve a long-term survival, with an estimated median survival of about 24 months[6,7] and 5-year overall survival between 10% and 35.7%.[8,9] However, emerging evidence suggests that the clinical outcome of a patient is strongly associated with the intrinsic nature of her disease and individual long-term survival may have little to do with any clinical intervention.[10] Besides, the conclusions drawn in the previous studies may have been influenced by sampling bias, due to the fact that no universal pathological inclusion criteria were established among the previous studies in the literature.[11–13] Due to these concerns, in this study, we retrospectively included a cohort of 48 NECUC patients who underwent hysterectomy, but excluded NECUC patients with only focal neuroendocrine differentiation, and then analyzed the clinicopathologic characteristics and primary treatments to identify the prognostic factors and evaluate the impact of adjuvant therapy on overall survival for this patient group.

2. Methods

All pathologically confirmed NECUC patients who underwent hysterectomy from the January, 2005 to the December, 2014 were retrieved from the database of the Department of Pathology of West China Second University Hospital and recruited into the cohort in an effort to incorporate all the histologic subtypes of NECUC, except those with little neuroendocrine differentiation. All surgically resected specimens were subjected to pathological examination. Tissue sections were undergone antigen retrieval in sodium citrate solution in a high-pressure cooker, and neuroendocrine markers including neuron-specific enolase (NSE), chromogranin (CgA), synaptophysin (Syn), neural cell adhesion molecule (CD56) were selectively immunohistochemically stained using rabbit antihuman NSE polyclonal antibody (RAB-0131, MXB Biotechnologies, Fuzhou, China), mouse antihuman CgA monoclonal antibody (MAB-0202, MXB Biotechnologies, China), rabbit antihuman Syn monoclonal antibody (Kit-0022, MXB Biotechnologies, China), and mouse antihuman CD56 monoclonal antibody (Kit-0028, MXB Biotechnologies, China) with an EnVision 2-step kit (GTVision GK500705, Dako, Glostrup, Denmark), by an Autostainer Link48 (Dako, Denmark). All patients included were positive for at least one of the neuroendocrine markers. No obvious sign of positive staining was defined as −, percentage of positive cells less than 25% was defined as +, between 25% and 50% was defined as ++, and above 50% was defined as +++. Those patients with focal neuroendocrine differentiation were excluded.[14] Clinical stage upon initial diagnosis was defined according to the International Federation of Gynecology and Obstetrics (FIGO) staging system. Relevant clinicopathologic characteristics and treatment modalities were acquired from any clinical documents available, while survival profiles were either secured from clinic visits or telephone interviews. Overall survival was calculated from the date of initial diagnosis to the date of death from the disease, or censored by the interval from the initial diagnosis to the last follow-up. The last date of follow-up was March 11, 2016. Individual cases were excluded from univariate analysis if the data for needed parameters were not available. The Kaplan–Meier product-limit method with log-rank test and Cox proportional-hazards regression were adopted for statistical analysis using PASW statistics 18.0.0 (IBM SPSS). $P < 0.05$ was considered statistically significant.

This study was approved by the ethics committee of West China Second University Hospital. Informed consent was waived because the study design involves only data analysis of existing medical report and follow-up data, patients' privacy was not breached and clinical decision was not interfered by any part of the research.

3. Results

A total of 62 patients were retrieved. Among them, 48 patients who met the inclusion criteria were included as the sample population; 3 patients without the survival data and 11 patients whose tumors had little neuroendocrine differentiation were excluded.

3.1. Clinicopathologic characteristics

The median age of disease onset was 41 years old, ranging from 25 to 67 years old. The distribution of the FIGO clinical stage among these patients was IA (1 patient), IB (28 patients), IIA (11 patients), IIB (7 patients), and IIIA (1 patient).

Among the 10 patients whose human papilloma virus (HPV) tests were performed, only 1 patient was negative for high-risk HPV subtypes, such as 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. Two patients were positive for HPV-16, 7 patients were positive for HPV-18, and 1 patient was positive for HPV-58. In addition, there were 2 patients positive for high-risk HPV with unspecified subtypes. These findings supported Stoler finding that small cell neuroendocrine carcinoma of the uterine cervix (SCCC) is associated with high-risk HPV-18 infection.[15]

As for tumor size, the largest diameter of the tumor >4 cm or ≤ 4 cm was observed in 13 and 32 patients, respectively (Table 1). Pathologic parametrial involvement (PMI) was seen in 7 patients (Table 1), while lymphovascular space invasion (LVSI) occurred in almost all cases (43/48) (Table 1), which was apparently higher than the LVSI reported in the literature.[1] Lymph nodes metastasis (LNM) were spotted in 9 of 40 early-stage patients ($\leq$IIA) and 3 of 8 advanced-stage patients ($\geq$IIB) (Table 1). Paraaortic nodes were negative in all 16 patients who had taken the sampling test, among whom 14 had the FIGO stage I–IIA diseases.

Table 1

Univariate analysis of each clinicopathologic parameter and multivariate analysis.

		Univariate analysis			Multivariate analysis	
Parameters	**Group**	**Median overall survival, mo**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
FIGO stage	≤IIA (n=40)	30.8	2.394 (1.002–5.716)	**0.042**	1.209 (0.241–6.058)	0.818
	≥IIB (n=8)	17.5				
Size*	≤4 cm (n=32)	40.8	3.031 (1.353–6.791)	**0.005**	**12.724 (1.697–95.423)**	**0.013**
	>4 cm (n=13)	15.1				
Histology	Homogeneous (n=38)	30.6	1.020 (0.413–2.519)	0.996		
	Mixed (n=10)	23.7				
LNM	Yes (n=12)	10.4	6.075 (2.638–13.989)	**<0.001**	2.023 (0.436–9.376)	0.368
	No (n=36)	53.1				
DOI*	≤1/2 (n=19)	>33.0	4.786 (1.764–12.987)	**0.001**	1.519 (0.317–7.270)	0.601
	>1/2 (n=24)	17.0				
PMI	Yes (n=7)	12.4	3.681 (1.419–9.552)	**0.004**	1.372 (0.111–16.884)	0.805
	No (n=41)	34.4				
LVSI	Yes (n=43)	25.9	4.275 (0.576–31.722)	0.122		
	No (n=5)	>30.3				
Syn*	−/+ (n=14)	>30.3	2.944 (1.012–8.566)	**0.037**	0.239 (0.017–3.372)	0.289
	++/+++ (n=31)	25.1				
NSE*	−/+ (n=16)	37.6	2.153 (0.815–5.689)	0.113		
	++/+++ (n=13)	17.8				
CgA*	−/+ (n=23)	>33.0	2.748 (1.216–6.210)	**0.011**	15.481 (0.931–257.443)	0.056
	++/+++ (n=22)	21.4				
CD56*	−/+ (n=7)	21.2	1.136 (0.252–5.108)	0.867		
	++/+++ (n=11)	21.2				
NACT	Yes (n=15)	16.4	1.781 (0.827–3.836)	0.135		
	No (n=33)	38.4				
Chemotherapy*	Yes (n=30)	30.3	0.872 (0.360–2.109)	0.760	0.284 (0.034–2.379)	0.246
	No (n=10)	28.1				
Radiotherapy*	Yes (n=30)	29.2	1.470 (0.541–3.995)	0.447	3.256 (0.296–35.867)	0.335
	No (n=10)	47.2				

Numerals in bold represent statistical significance.

CD56 = neural cell adhesion molecule, CgA = chromogranin, DOI = depth of invasion, LNM = lymph nodes metastasis, LVSI = lymphovascular space invasion, NACT = neoadjuvant chemotherapy, NSE = neuron-specific enolase, PMI = parametrial involvement, Syn = synaptophysin.

* Pathologic parameters are analyzed only when the tests have been performed, and the 8 patients with unknown postoperative adjuvant therapy were not analyzed for adjuvant therapies.

As for tumor histology, homogeneous NECUC were found in 38 patients and mixed histology, that is neuroendocrine carcinoma accompanied by squamous cell carcinoma or adenocarcinoma, were observed in 10 patients, among 48 patients. In terms of histological subtypes, 31 patients had small cell NECUC, 1 patient had large cell NECUC, and the remaining 16 patients had unspecified subtypes. This further confirms that small cell NUCUC is the most common histological subtype as reported in the literature. The immunohistochemical results for each neuroendocrine marker, if performed, are listed in Table 2.

3.2. Treatment and survival profiles

Neoadjuvant chemotherapy (NACT) was administered in 11 stage I–IIA patients and 4 stage IIB–IIIA patients. All patients underwent total hysterectomy except 1 stage IB1 patient, who had subtotal hysterectomy plus radiotherapy and chemotherapy and died 60.3 months after the initial diagnosis. Thirty-three patients (68.8%) adopted postoperative adjuvant chemotherapy (PACT) or radiotherapy, while 5 early-stage patients and 2 advanced-stage patients had surgery only. Chemotherapeutic agents included paclitaxel (T), cisplatin, carboplatin, nedaplatin, bleomycin (B), etoposide (E), adriamycin, 5-fluorouracil, and vincristine. Regimens based on paclitaxel and platinum-derivatives (P), with or without Adriamycin, 5-fluorouracil, and vincristine, formed the main body of the combination of NACT and PACT [10 of 15 patients (66.7%) and 25 of 30 patients (83.3%), respectively]. Other combinations for NACT included EP (with or without bleomycin) in 2 patients and BP in 3 patients. Among the 5 patients who did not adopt TP regimen in PACT, 4 used EP (with or without bleomycin) and 1 used BP. Radiotherapy was given either separately from PACT or concurrently with chemotherapy. The combinations of adjuvant therapy and the corresponding survival data are listed in Table 3.

Twenty-eight patients died at the end point of this study, 16 patients survived, and 4 patients were lost to follow-up. Eleven patients survived more than 48 months, among whom 8 patients are still free of disease. The median follow-up time was 20.6 months, and the median overall survival for all patients

Table 2

Neuroendocrine markers selectively stained for pathological diagnosis.

	Cases stained		
Markers	**Positive**	**Negative**	**Cases unstained**
Syn	45	0	3
NSE	25	4	19
CgA	37	8	3
CD56	17	1	30

Every patient is positive for at least 1 marker.

CD56 = neural cell adhesion molecule, CgA = chromogranin, NSE = neuron-specific enolase, Syn = synaptophysin.

Table 3

The combinations of adjuvant therapy and the patients' survival data.

	Stage ≤IIa		Stage ≥IIb		
Adjuvant therapy	**Death**	**Survival**	**Death**	**Survival**	**Total**
CHT+RT	7.3, 8.7, 9.8, 14.9,15.7, 15.7, 16.4, 18.5, 20.5, 24.4, 25.7, 46.7, 60.3	17.2, 17.3, 18.1, 20.7, 35.7, 40.9, 58.5, 99.3, 103.6	5.5, 15.9, 36.4, 56.3	22.6	27
CHT	/	17.7, 103.3, 107.9	/	/	3
RT	30.3, 33.0	105.0	/	/	3
NULL	7.7, 16.1, 77.3	23.7,64.3	2.3, 17.0	/	7
NK	8.0, 15.2, 30.7	3.7*, 15.6*, 41.5*, 59.6*	17.9	/	8
Total	21	19	7	1	48

The numerals represent the time of survival (unit: months).

/ – no data for this combination, CHT = platinum-based chemotherapy, NK = not known, NULL = no adjuvant therapy, RT = radiotherapy.

* These 4 patients were lost to follow-up after the last visit.

was 30.7 months, with the estimated 2-year and 5-year overall survival rates being 57.5% and 31.3%, respectively (Fig. 1).

3.3. Outcome and prognostic factors

We analyzed the multiple clinicopathologic features for their potential survival-prognostic values (Table 1). Univariate analysis showed that the median overall survival of patients with the FIGO stage ≤ IIA ($P=0.042$), tumor size ≤ 4 cm ($P=0.005$), negative LNM ($P<0.001$), or negative PMI ($P=0.004$) was significantly prolonged (Fig. 2, stage, size, LNM, PMI). The median survival of patients whose depth of stromal invasion (DOI) >1/2 was 17.0 months, compared with a median survival longer than 33.0 months for patients whose DOI ≤1/2 ($P=0.001$) (Fig. 2, DOI). In addition, the weak immunohistochemistry staining (− or +) for Syn ($P=0.037$) and CgA ($P=0.011$) also correlated with the improved median overall survival, compared with the strongly positive staining (++ and +++) (Fig. 2, Syn, CgA). Although not statistically significant, there was a tendency of prolonged survival for patients with negative LVSI ($P=0.122$) or weak NSE staining ($P=0.113$) (Fig. 2, LVSI, NSE). In contrast, tumor histological homogeneity ($P>0.996$) and CD56 staining ($P=0.867$) were not prognostic factors for survival (Table 1).

We also assessed the influence of treatment modalities on survival. Survival data were univariately analyzed with respect to treatment modality. Surprisingly, the univariate analysis did not identify chemotherapy ($P=0.76$) or radiotherapy ($P=0.447$) as prognostic factors for the overall survival in the whole cohort of patients. When patients with small primary tumor (bump diameter ≤ 4 cm) were excluded from this univariate analysis, we found that surgery combined with chemotherapy and radiotherapy improved 5-year survival rate, compared with surgery alone (9 patients vs 2 patients, $P=0.006$). However, for the 26 patients with bump diameter ≤ 4 cm whose treatment modalities could be gained from medical record, the adjuvant chemotherapy (with or without radiotherapy) did not show any survival benefit or disadvantage (19 patients vs 7 patients, $P=0.816$), compared with no adjuvant chemotherapy (with or without radiotherapy). Interestingly, radiotherapy (with or without chemotherapy) yielded a better overall survival in patients with mixed histology (8 patients vs 2 patients, $P=0.01$), but showed a tendency toward decreased overall survival in patients with homogeneous neuroendocrine histology (22 patients vs 8 patients, $P=0.099$) (Fig. 3).

To identify independent prognostic factors, we performed a multivariate analysis using COX proportional-hazards regression model. Variables with $P<0.10$ in univariate analysis were incorporated into this model. Considering that adjuvant chemotherapy and radiotherapy were frequently reported as prognostic factors in several large cohorts,[1,16,17] we also added these 2 parameters to the regression equation for exclusion of any confounding factors that may have compromised the effect of adjuvant therapy. As a result, primary tumor size remained as an independent prognostic factor for overall survival (HR 12.724, 95% CI 1.697–95.423, $P=0.013$) (Table 1).

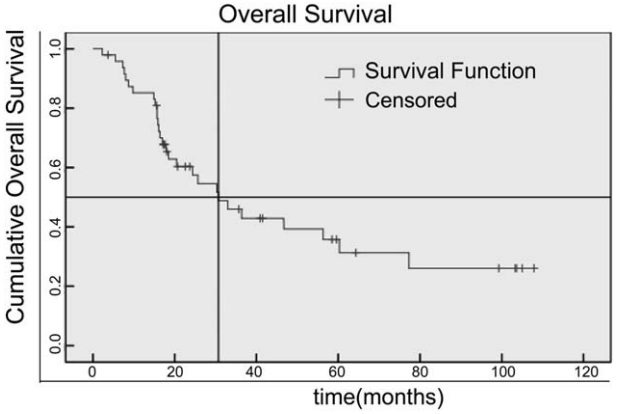

Figure 1. Survival curve for all patients. The vertical line indicates a median overall survival of 30.7 months.

4. Discussion

An agreement has not been reached among pathologists in terms of the diagnostic standard of NECUC. On one hand, Sheridan et al[11] posited that the diagnosis of small cell NECUC (SCCC) should be based on a combination of morphology and its aggressive clinical course, but the absence of immunohistological neuroendocrine differentiation should not exclude the existence of NECUC. On the other hand, some researchers regard neuroendocrine differentiation as a common sign in cervical neoplasms,[12] and the appearance of focal neuroendocrine differentiation had little impact on outcome.[13] Therefore, we excluded 11 cases with controversial diagnostic pathology.

The prognosis of NECUC is much worse, compared with squamous carcinoma and adenocarcinoma of the cervix.[18,19] Even the early-stage NECUC patients also face a dismal clinical outcome.[18,20] The current treatment options benefit only a small

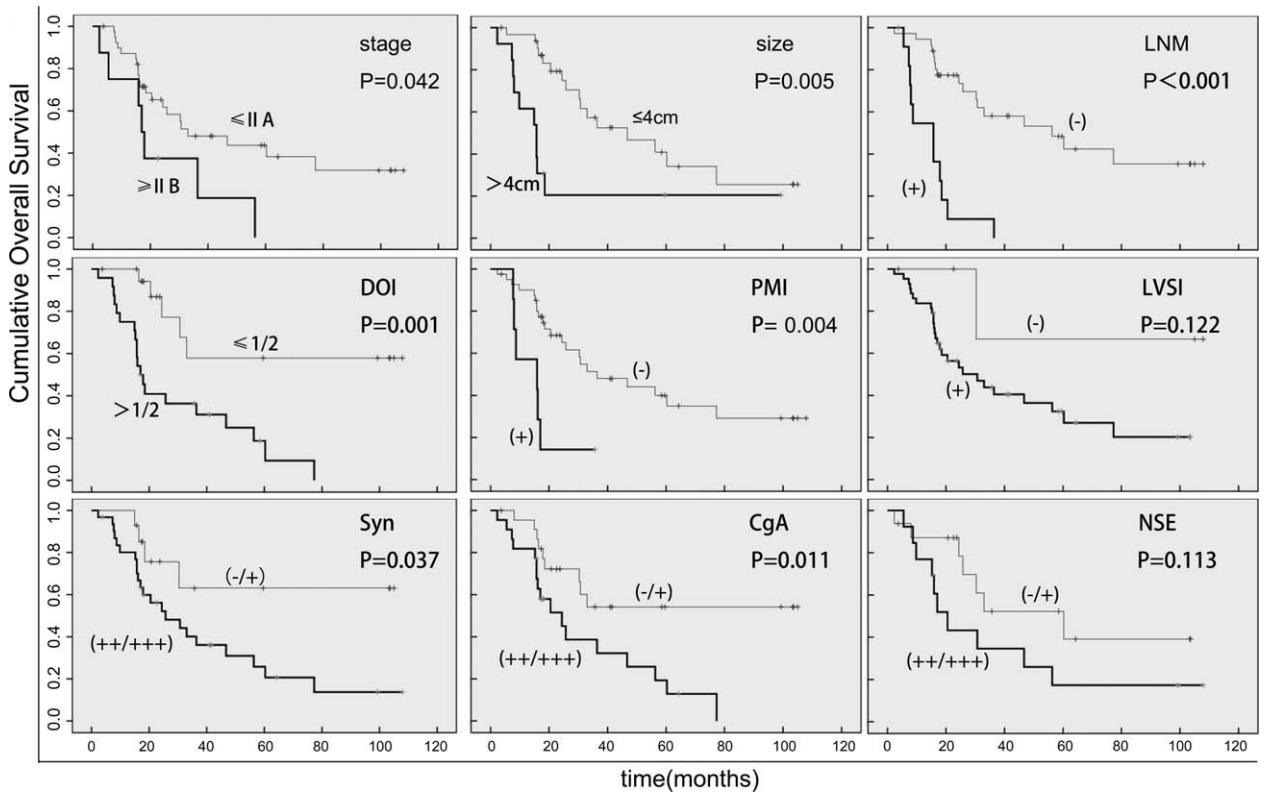

Figure 2. Typical survival curves for different groups of some of the parameters in univariate analysis. CgA = chromogranin, DOI = depth of invasion, LNM = lymph nodes metastasis, LVSI = lymphovascular space invasion, NSE = neuron specific enolase, PMI = parametrial involvement, Syn = synaptophysin.

portion of patients.[1,6] Due to these facts, it is imperative to identify potential prognostic factors to select these NECUC patients who might benefit the most from the current therapeutic regimens. In agreement with the previous studies,[6,7,10,20–22] we observed a prolonged median overall survival for patients with FIGO stage $\leq$ IIA, tumor size $\leq$ 4 cm, DOI $\leq$ 1/2, negative LNM, and negative PMI. In addition, low expression of Syn and CgA also predicted a better survival. Among all these parameters, tumor size was identified as a strong independent prognostic factor. There were 2 stage IB patients who had radical surgery alone without any adjuvant therapy, but the outcome of them was surprisingly opposite, with one still free of disease for more than 57 months and another died of disease 8 months after the initial treatment. The only apparent difference between them, to our knowledge, was the tumor size and the presence of LNM, somehow suggesting the potent prognostic value of tumor size and LNM. Of Course, there could be other biological or social factors that might have contributed to the strikingly different prognoses of these 2 patients, such as gene mutations and economic status, which we did not examine in this study.

Unlike squamous cell carcinoma of the cervix, NECUC is especially sensitive to chemotherapy. Given its efficacy, it is believed that platinum-based chemotherapy has the capacity to improve overall survival or progression-free survival and should be used to treat NECUC patients including patients even with an early-stage disease.[23,24] Complying with this viewpoint, Zivanovic et al[25] demonstrated that platinum-based chemotherapy significantly increased 3-year distant recurrence-free survival rate for the stage IA1-IB2 patients of SCCC. Regimens containing cisplatin and etoposide have been considered to have a survival advantage over other therapeutic combinations in either small cell lung cancer (SCLC)[26,27] or SCCC.[6,17] The most prevailing combination chemotherapy in our series was paclitaxel combined with platinum-derived agents, and we found that this combination chemotherapy achieved a favorable overall survival in NECUC patients with a large tumor size, but failed to further improve the prognosis of patients with small tumors, probably because that the inherent better prognosis with small tumors had masked the effect of chemotherapy. The conventional use of paclitaxel combined with cisplatin instead of the reported cisplatin and etoposide might also have participated in this phenomenon. A multicenter randomized controlled trial may be necessary to establish a standard regimen.

It is generally believed that surgery or radiotherapy is indispensable for local control of NECUC. NECUC is considered a systemic disease with an inclination to metastasize to local lymph nodes or distant sites at an early stage, so systemic control is also required. Chemotherapy is generally used to achieve local and systemic controls. However, the efficacy of surgery and combined adjuvant therapy (chemotherapy, radiotherapy, or chemoradiation therapy) for local and systemic controls may be different in NECUC patients with the different stages and different tumor histology. In fact, radical surgery is identified as an important method for local control in limited disease SCLC[27] and in SCCC.[1,28] Hoskins achieved a 3-year overall survival of 60% using concurrent chemoradiation in SCCC patients.[29] In contrast, a Korean research group found that adjuvant chemoradiation seemed to yield outcome no better than adjuvant chemotherapy alone.[16] More recently, Nakajima et al[30] discovered that the patients-derived SCCC cells were sensitive

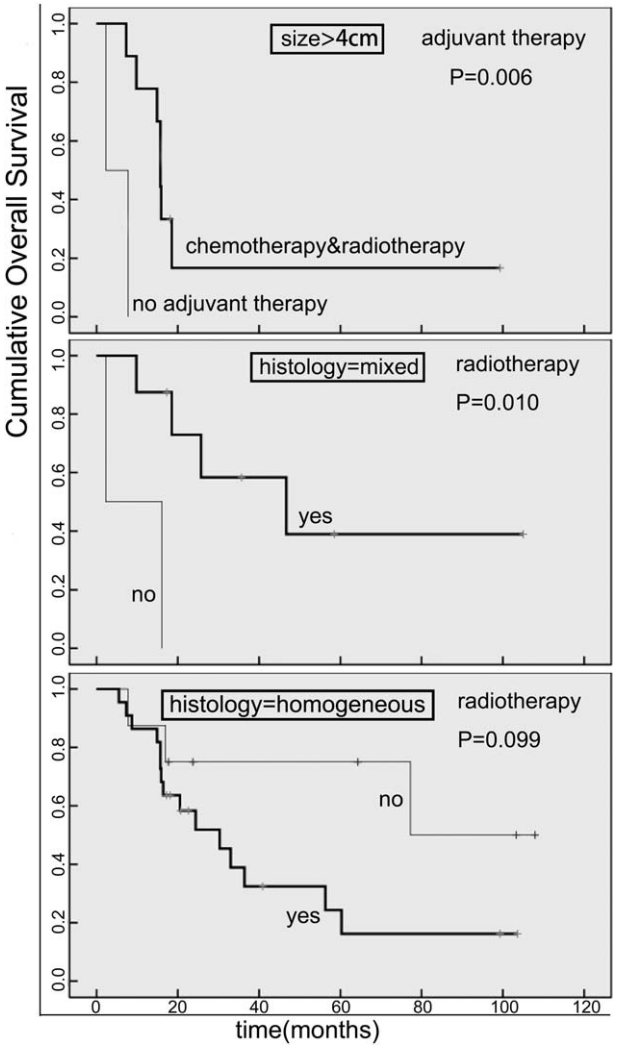

Figure 3. Effects of chemotherapy and radiotherapy on overall survival. Patients with large tumors or with mixed histology exhibited better outcome toward chemotherapy and/or radiotherapy to a statistically significant extent.

to radiation in vitro. However, other studies found that SCCC patients who had radiotherapy achieved unfavorable outcomes.[17,28] Indeed, radiotherapy achieved a better overall survival for NECUC with mixed histology (10 of 48 cases) in our series, while it only achieved a contradictory, althouth not statistically significant, result in the patients with a homogeneous histology (38 of 48 cases), which warrants a follow-up research with a larger sample size or longer observation. Together with above studies, it suggests that radiotherapy may not be suitable for disease control at least for some NECUC patients. In addition, although previous studies did not correlate the effect of radiotherapy on the overall survial based on the tumor histology of NECUC,[17,28] our data suggest that the histology of the NECUC tumors may affect the efficacy of radiotherapy.

Some of our data are not in agreement with the previous studies. Our study was about prognostic factors of overall survival based on a southwestern Chinese female population, among whom the positive rate of LVSI was extremely high. In contrast with the study of Wang et al[6] we did not find a survival predicting role for LVSI. Different from our analysis on histological components, a latest Korean study found that patients with homogeneous NECUC had a favorable prognosis.[31] Such discrepancies also existed in LNM[1,17] and radiotherapy.[17,32] The population differences might contribute to these discrepancies observed. A meta-analysis may be needed.

In conclusion, NECUC is a highly malignant disease whose clinicopathologic features may significantly influence patient's outcome, and platinum-based chemotherapy should be used to treat all patients, while radiotherapy should be carefully used in selected patients with mixed histology.

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