Supraclavicular lymph node metastases in cervical cancer

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Summary

Purpose of investigation: To evaluate the outcome and prognostic factors of patients with supraclavicular lymph node (SCLN) involvement at primary diagnosis.

Methods: We reviewed the medical records of cervical cancer patients primarily treated at Chang Gung Memorial Hospital between 1987 and 2005. Thirty-three patients with histologically confirmed SCLN metastasis at primary diagnosis were eligible for analysis. Clinical and pathological features were analyzed for association with outcome.

Results: The 3- and 5-year survival rates of patients with SCLN metastasis were 16.5% and 16.5%, respectively. Multivariate analysis showed the serum level of squamous cell carcinoma antigen (SCC-Ag) < 15 ng/ml at initial diagnosis ($p = 0.021$) and staging/restaging including [^{18}F] fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) ($p = 0.006$) to be associated with a better prognosis.

Conclusion: Primary SCLN metastasis in cervical cancer is not incurable. The benefit from PET findings might help in selecting appropriate patients for curative primary and/or salvage treatment.

Key words: Cervical cancer; Supraclavicular lymph node; FDG-PET; Prognostic factor.

Introduction

The overall frequency of supraclavicular lymph node (SCLN) metastasis in patients with invasive carcinoma of the uterine cervix is rare. The presence of grossly positive paraaortic LN (PALN) metastasis was predictive of a high likelihood of SCLN metastasis [1, 2]. The outcome of SCLN metastasis in cervical cancer is considered dismal. The 3-year or 5-year overall survival (OS) rates of several studies were virtually 0% [1-4]. Tran *et al.* recommended that cervical cancer patients with documented SCLN metastasis should have palliative radiotherapy (RT) for relief of symptoms and improved quality of life [3]. However, in our previous study on recurrent cervical cancer, patients with SCLN metastasis were not invariably fatal and the 3-year OS for patients with SCLN metastasis with/without concomitant PALN relapse was 28% [5]. We have not studied patients with involvement of the SCLN at primary diagnosis at our institution. Moreover we also wanted to determine the impact of [^{18}F] fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) for staging/restaging on the management and outcome of these poor prognostic patients. We retrospectively reviewed the data for cervical cancer patients with SCLN metastasis at primary diagnosis and analyzed the disease course, clinical-pathological variables and long-term outcome. We also aimed to investigate prognostic factors in order to select appropriate patients for curative-intent therapy.

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Materials and Methods

Patients

Through a search of the disease code database (International Classification of Diseases of Oncology [ICDO]) and Systematized Nomenclature of Medicine (SNOMED) code for cervical cancer and histologic diagnosis of SCLN metastasis seen in Chang Gung Memorial Hospital between January 1987 and June 2005, we retrospectively reviewed the hospital medical records and pathological reports. One hundred and thirty patients were identified initially. Thirty-three of these 130 patients were eligible for analysis. The remaining 97 cases were eliminated due to SCLN metastasis only at recurrence (n = 62), missing charts (n = 17), incorrect diagnosis (n = 10), positive imaging finding but no pathological proof (n = 4), previous other malignancy (n = 1), initial diagnosis at outside hospital and referral for recurrence (n = 2) or lost to follow-up (n = 1). Patient characteristics are given in Table 1.

Clinical work-ups

All patients underwent pelvic and abdominal magnetic resonance imaging (MRI) or computed tomography (CT) to evaluate the primary tumor extension and lymph node status. Since the introduction of FDG-PET at our hospital in March 2001, we have conducted several prospective studies to define the role of FDG-PET in primary staging of untreated advanced cervical cancer [6-8], including one ongoing trial which is aimed to evaluate the value of FDG-PET in previously untreated cervical cancer with MRI or CT defined PALN with or without SCLN metastasis (unpublished).

Patients did not undergo the FDG-PET scan if they (1) had disseminated abdominal, parenchymal metastasis or pleural lesions with positive fluid cytology; (2) were judged inappropriate to receive curative therapy, such as more than two regions of distal nodal metastases (pelvic LN [PLN] was not counted); (3) were medically or psychologically unfit to receive curative salvage therapy; (4) had a history of other malignancy, excluding basal cell carcinoma of the skin; or (5) were not considered

Table 1. — *Clinical features of cervical cancer patients with supraclavicular node metastasis (n = 33).*

	No. (%)
Age (mean ± SD), years	53.7 ± 13.1
range	36.6-81.5
Cell type	
Squamous carcinoma	29 (87.8)
Adenocarcinoma	2 (6.1)
Adenosquamous carcinoma	1 (3.0)
Small cell carcinoma	1 (3.0)
Grade	
Well differentiated	0
Moderate differentiated	15 (45.5)
Poorly-differentiated	15 (45.5)
unclassified	3 (9.1)
Using FDG-PET for staging/restaging	
Yes	10 (30.3)
No	23 (69.7)
Metastasis status	
Limited nodal sites (≦ 3)	23(69.7)
LN sites > 3 or other distant sites[a]	10 (30.3)
Primary treatment	
CCRT	24 (72.7)
RT alone[b]	9 (27.3)
Salvage treatment	
Surgery ± RT/CCRT/IORT	5 (15.2)
RT/CCRT	3 (9.1)
Palliation	23 (69.7)

LN: lymph node; CCRT: concurrent chemoradiation; IORT: intraoperative radiotherapy. [a]Inguinal LN (n = 5), mediastinal LN (n = 2), liver (n = 2), lung (n = 1), and bone (n = 1); [b]Medically unfit/palliative purpose for CCRT (n = 3) or before 1999 when CCRT had not been a standard (n = 6).

suitable to undergo a PET study (body weight over 106 kg, pregnancy or afraid of the test) [6-8].

Primary RT

Patients were usually treated with a combination of external RT and intracavitary brachytherapy. The treatment method was similar to that previously reported [5, 9]. In brief, patients received 40-45 Gy whole pelvic RT with 10-MV X-ray by either parallel-opposed anteroposterior or four-field box beams. Parametria were boosted up to 50~58 Gy by a parallel-opposed anteroposterior field with a 4-cm-wide midline block. The daily fraction was 1.8-2 Gy, five fractions per week. High-dose-rate brachytherapy was given as six fractions with two fractions per week; and dose to point A was 4.3 Gy per fraction. Concurrent chemotherapy was given as weekly cisplatin 40-50 mg/m^2 for six courses. RT to the SCLN was done synchronously with pelvic irradiation. The RT dose to the SCLN ranged from 30 to 60 Gy using 6MV-X-ray by parallel-opposed anteroposterior or single anterior beam with cord sparing. The daily fraction was 2-3 Gy, with five fractions weekly. The paraaortic region was included in the treatment field when positive. The upper margin of the field was at the T12-L1 intervertebral space and a total of 40~45 Gy was given. The individual treatment decision was based on the clinical situation, preference of the responsible attending physician and patient's choice.

Post-therapy surveillance

Our protocol of post-therapy surveillance consists of 3-monthly visits for two years, 4-monthly for the third year, 6-monthly between the third and fifth year, and yearly thereafter. Clinical history, physical and pelvic examination, Pap smear, and serum tumor markers (squamous cell carcinoma antigen [SCC-Ag] and carcinoembryonic antigen [CEA]) were checked on every visit. Yearly chest X-ray studies were advised in asymptomatic patients, while CT or MRI scans were performed yearly for the first three consecutive years for high-risk groups or when clinically indicated (suspicious symptoms/signs, or elevated tumor markers) [10]. Post-therapy FDG-PET scans were performed according to the protocol selection criteria [11-13].

PET protocol and image interpretation

The PET protocols have been described previously [5, 9-11]. Briefly, FDG was provided by the Institute of Nuclear Energy Research of Taiwan (Lungtan, Taiwan). The imaging instrument used was an ECAT EXACT HR PET camera (CTI, Knoxville, TN) using dual-phase PET (adding 3-hour delayed images to the 40-min scans). Fusion of CT or MRI and PET images using a commercially available software program (Hermes; Nuclear Diagnostics AB, Hagersten, Sweden) was performed for abnormally raised FDG uptake regions or in case of discrepant results. For the potential FDG-PET scan candidates in many prospective studies, the clinical information and imaging study findings, including MRI or CT, were presented and reviewed at a weekly conference that included gynecology-oncology, RT, pathology, radiology, and nuclear medicine physicians. Patients who fit the selection criteria underwent PET free of charge after providing informed consent.

Clinical and pathological variables studied

The data analyzed included birth date, date of initial diagnosis, histologic type, initial International Federation of Gynecology and Obstetrics (FIGO) stage, initial tumor grade, site metastases, primary treatment(s) (RT, regimens of chemotherapy, and/or surgery), dates and levels of serum tumor markers (SCC-Ag, CEA), site(s) and date(s) of confirmed recurrent or persistent disease, salvage therapy (type of RT, regimens and courses of chemotherapy, and/or surgery), treatment after subsequent recurrence if any, date and status (alive or dead, with disease or disease-free) at last follow-up.

Statistical analyses

Overall survival (OS) was defined as the length of time from the date of initial diagnosis of cervical cancer to either the date of death or of last follow-up for those presenting SCLN metastases primarily. Survival curves were calculated with the Kaplan-Meier method and the curves were compared using the log-rank test. Univariate and multivariate analyses were performed by Cox regression proportional hazards model to identify independent prognostic factors. Hazard ratios (HRs) were obtained and 95% confidence interval (CI) values were calculated. Data were also analyzed by using the SPSS PC software package (Version 11.0, SPSS Inc, Chicago, IL). The chi-square or Fisher exact tests were used for categorical data. A two-tailed value of $p < 0.05$ was considered significant. However, variables with p between 0.05 and 0.1 were included in the Cox's proportional hazard model as the sample size was small.

Results

Patients

Thirty-three patients were eligible for analysis. Thirty patients were FIGO Stage IVb for the presence of clinical palpable SCLN and histologically documented metastases at primary diagnosis. Three patients (two FIGO Stage IIIb and one Stage IIb) had abnormal FDG uptake in left SCLN without palpable disease. All three patients

underwent sonography-guided fine-needle aspiration of the left SCLN and confirmed the SCLN metastases. Only two of the 33 were isolated SCLN metastases, and the others were associated with positive PALN (n = 15) and/or PLN (n = 18) or involvement of other extranodal distant sites such as the lung (n = 1), bone (n = 1) and liver (n = 2). Five patients had incomplete imaging data, therefore their PALN and PLN status were unknown. The median age at the time of the initial diagnosis was 49.6 years (range 36.6-81.5). Twenty-nine (87.8%) patients had squamous carcinomas. A total of 16 PET scans were performed in ten patients. Six patients had a FDG-PET for both primary staging and restaging at documented or suspected recurrence/persistence, two for primary staging only, and two for restaging at recurrence.

Treatment and outcome

Primary and salvage therapy are shown in Table 1. Nine patients received RT alone due to medically unfit/palliative purposes for concurrent chemoradiation (CCRT) (n = 3) or before 1999 when CCRT had not been a standard (n = 6). Of the 33 study patients, two patients were disease-free without recurrence after primary CCRT for 84 and 23 months, respectively. Thirty-one of the 33 subjects developed recurrence or persistent disease, of which 23 patients (69.7%) received palliation treatment. The remaining eight patients underwent curative-intent salvage therapy. Of these eight patients, three were alive with no evidence of disease and another one was alive with disease. Up to May 1, 2006, 27 patients had died of disease and the other six were alive. The median follow-up of surviving patients after diagnosis of SCLN metastases to the date of analysis was 66 months (range 23-84 months). The median OS was 15.0 months for primary cervical cancer with a positive SCLN. Three and 5-year survival rates of patients with SCLN involvement at primary diagnosis were 16.5% and 16.5%, respectively (Figure 1).

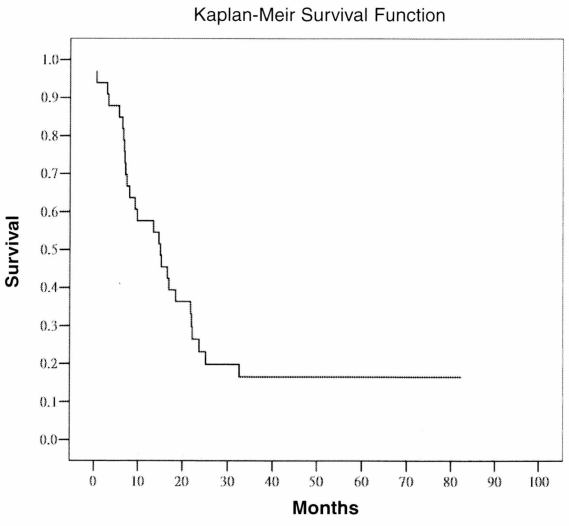

Figure 1. — Overall survival for cervical cancer patients with supraclavicular node metastases at primary diagnosis.

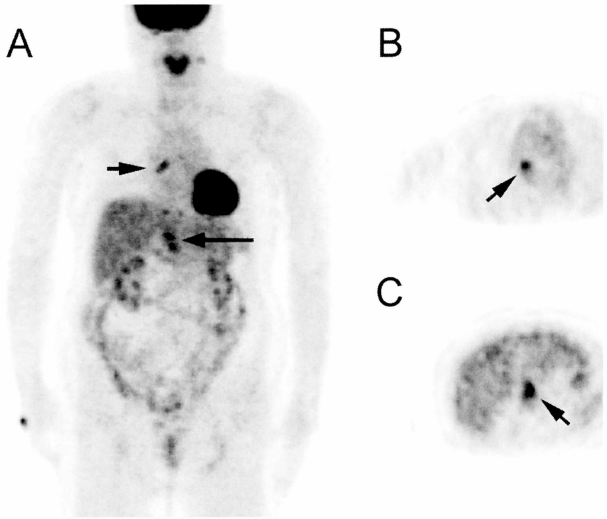

Figure 2. — Elevation of serum squamous cell carcinoma antigen was found 39.9 months after completion of initial chemoradiation when computed tomography was negative. FDG-PET showed recurrence at higher paraaortic and mediastinal lymph node (PALN and MLN) metastases (A, coronal section: long arrow, PALN and short arrow, MLN; B: axial section, MLN; C: axial section, PALN).

Detailed information of the six survivors is depicted in Table 2. All these six patients were Stage IVB with clinically palpable SCLN, while the three patients with SCLN (FIGO Stage IIB, IIIB, IIIB) found by PET died of disease. Of these six patients, one is alive with disease and five patients are alive and disease-free. Patients 3 and 4 had PLN, PALN and SCLN metastases at initial diagnosis. Since these three sites could be encompassed by RT, they underwent curative-intent CCRT. Both had a complete remission but later developed unexplained elevation of SCC-Ag found during post-therapy surveillance (patient 3 at 17 months and patient 4 at eight months from initial diagnosis). FDG-PET showed isolated contralateral SCLN and mediastinal LN (MLN) metastases, respectively. Since no other uncontrollable sites were present, a further attempt for salvage seemed feasible. Therefore, CCRT was given, and both have been alive and disease-free for 58 and 49 months up to the date of this analysis, respectively.

Patient 5 had a sole site of SCLN involvement, and abdominal MRI, chest CT and bone scan were all negative. She developed cervical recurrence 15 months after completion of initial CCRT. FDG-PET was not available at that time. She underwent a restaging workup including MRI and bone scan which was negative and underwent a type II radical hysterectomy, bilateral salpingo-oophorectomy and retroperitoneal lymph node dissection for salvage. Patient 6 is the only survivor alive with disease. She had an initial diagnosis of PLN, PALN and SCLN metastases in February 2000, and achieved complete remission after CCRT. Elevation of SCC-Ag was found 39.9 months after completion of initial CCRT when CT was negative. FDG-PET showed recurrence of higher

Table 2. — *Detailed information of the six survivors among cervical cancer patients with supraclavicular node metastases at primary diagnosis.*

Case No.	Age (yrs)	Histology	FIGO stage	Sites of metastases at initial	SCC-Ag (ng/ml) at initial	Initial treatment	PET staging/ restaging	Clinical impact of PET	Recurrent sites	Salvage treatment	Outcome
1	47	SCC	Stage IVb	SCLN, PALN	10.50	CCRT	No	NA	–	–	NED (84 M)
2	53	SCC	Stage IVb	SCLN, PALN PLN	54.40	CCRT	Yes/at primary and post-therapy F/U	Positive (a)* Positive (b)*	–	–	NED (23 M)
3	45	SCC	Stage IVb	SCLN (L), PALN, PLN	8.18	CCRT	Yes/at primary and recurrence	Positive (a)* Positive (a)*	SCLN (R)	CCRT	NED (58 M)
4	43	SCC	Stage IVb	SCLN, PALN, PLN	14.8	CCRT	Yes/at primary and post-therapy F/U	Positive (a)* Positive (c)*	MLN	CCRT	NED (49 M)
5	44	SCC	Stage IVb	SCLN	NA	CCRT	No	NA	Cervix	RH-PLND	NED (81 M)
6	60	SCC	Stage IVb	SCLN, PALN, PLN	105.0	CCRT	Yes/at recurrence	Positive (a)*	MLN PALN#	MLN dissection+ CCRT	AWD (74 M)

SCC-Ag: squamous cell carcinoma antigen; SCC: squamous cell carcinoma; CCRT: concurrent chemoradiation; L: left; R: right; MLN: mediastinal lymph node; SCLN: supraclavicular lymph node; PALN: para-aortic lymph node; PLN: pelvic lymph node; ILN: inguinal lymph node; MLN: mediastinal lymph node; RH-PLND: radical hysterectomy and pelvic lymphadenectomy; AWD: alive with disease; NED: no evidence of disease, NA: not applicable. * See text. #Failure at higher PALN not in-field.

PALN and MLN metastases. Thoracoscopic MLN biopsy was positive. MLN dissection was performed and CCRT with 5-FU to PALN and MLN was given. She had been alive for 74 months from initial diagnosis even though she had a subsequent recurrence at the left common iliac LN just before this analysis (Figure 2).

Clinical impact of FDG-PET for the survivors

Two survivors (patients 1 and 5) presented in the earlier study years without PET. The clinical impact from FDG-PET was determined on a scan basis (Table 2). They were defined as having a positive clinical impact if [a] curative-intent therapy was administered and sustained remission was achieved because of the endorsement of PET (first studies of patients 2, 3, and 4; second study of patient 3 and patient 6); or [b] persistent abnormality of the PALN or SCLN found by CT but not FDG-PET negative and remaining free of progression (second study of patient 2); or [c] histologically unproven concordant positive site(s) were treated due to PET backup and the follow-up imaging showed regression after salvage (second study of patient 4). Negative impact was designated if false-positive FDG-PET findings led to unnecessary, additional invasive procedures (none in this study population). No change if additional incurable lesions were found by FDG-PET (n = 5).

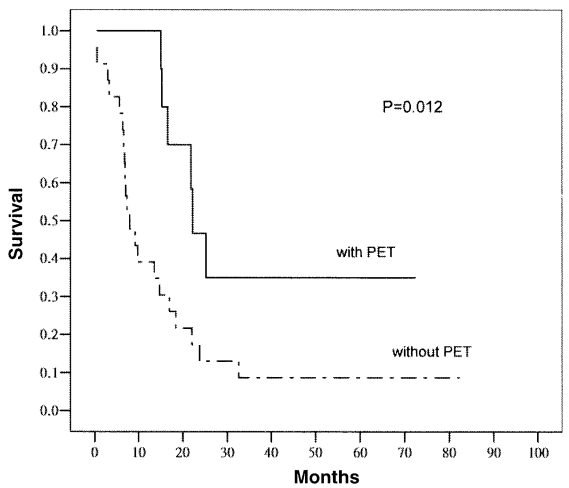

Figure 3. — Overall survival according to staging or restaging with positron emission tomography vs without.

Univariate and multivariate analyses of overall survival and prognostic factors

The cut-off of 15 ng/ml of serum SCC-Ag was determined according to the minimum p value analysis. Univariate analyses using Cox's proportional hazard ratio showed covariates such as SCC-Ag of ≥ 15 ng/ml at initial diagnosis (HR = 2.24, 95% CI = 0.87-5.79; p = 0.095) and metastasis status (LN > 3 sites or others; HR = 2.10, 95% CI = 0.92-4.79; p = 0.077) and log-rank test (p = 0.088 and p = 0.071, respectively) were marginally associated with survival. Although all the four patients with non-squamous carcinoma did not survive and six of the 29 with squamous carcinoma were alive, the difference was not significant because of the small number (Table 3). Only a covariate of staging/restaging including FDG-PET (p = 0.017) was a significant prognostic factor. The difference of OS curves by the log-rank test were also significant (p = 0.012) (Figure 3). Other covariates such as age, histopathology, grade of differentiation, or initial solid organ metastastic sites did not significantly influence OS.

A multivariate analysis showed SCC-Ag of ≥ 15 ng/ml at initial diagnosis (HR = 3.76, 95% CI = 1.23-11.51; p = 0.021) and staging/restaging including FDG-PET

Table 3. — *Univariate analyses of cervical cancer patients with supraclavicular lymph node metastasis at primary diagnosis (n = 33).*

	Alive	Expired	Total	p (log-rank)	p (cox regression)
Age (mean ± SD), years					
< 50	4	12	16	0.229	0.234
≧ 50	2	15	17		
Cell type					
Squamous carcinoma	6	23	29	0.255	0.262
Non-squamous carcinoma	0	4	4		
Grade					
Well or Moderate differentiated	3	12	15	0.940	0.940
Poorly	3	13	16		
Unclassified	0	2	2		
Use of PET for staging				0.012	0.017
Yes	4	6	10		HR = 1
No	2	21	23		HR = 3.06 (1.22~7.65)
Metastasis status				0.071	0.077
Limited nodal sites (≦ 3)	6	17	23		HR = 1
[a]LN sites > 3 or other distant sites	0	10	10		HR = 2.10 (0.92~4.79)
[b]SCC-Ag level when SCLN metastases				0.088	0.095
< 15 ng/ml	3	7	10		HR = 1
≧ 15 ng/ml	2	13	15		HR = 2.24 (0.87~5.79)

LN: lymph node; SCC-Ag: squamous cell carcinoma antigen; PET: positron emision tomography. [a]Inguinal LN (n = 5), mediastinal LN (n = 2), liver (n = 2), lung (n = 1), and bone (n = 1). [b]Only 25 patients had SCC-Ag data, and the cutoff was determined by the receiver operating curve method.

Table 4. — *Cox's proportional hazard model of overall survival.*

Variable	Overall survival	
	HR (95% CI)	p
SCC-Ag of at initial diagnosis		0.021
< 15 ng/ml	reference	
> = 15 ng/ml	3.76 (1.23-11.51)	
Staging/restaging including PET		0.006
Yes	reference	
No	5.04 (1.61-15.81)	

HR: hazard ratio; SCC-Ag: squamous cell carcinoma antigen; PET: positron emision tomography.

(without vs with FDG-PET: HR, 5.04 [95% CI 1.61-15.81], p = 0.006) to be significant prognostic factors (Table 4). Other cut-offs (4-14 ng/ml) of SCC-Ag were also significant in univariate analyses but only a cut-off at 15 ng/ml was selected in the multivariate model. As a matter of fact, among the ten patients with a SCC-Ag < 15 ng/ml, the three patients with non-squamous cancer and normal SCC-Ag levels all died of cancer. Of the remaining seven with squamous histology, three survived without evidence of disease.

Discussion

Historical results have shown that the overall frequency of SCLN metastases in invasive cervical cancer is less than 5% by physical examination alone [1, 2]. Brant *et al.* found 28% (n = 7) of SCLN metastases among those with positive PALN (n = 25) by routine scalene node biopsy [14]. Their whole series included 11 patients with SCLN metastases (the other four patients were either palpable SCLN or associated with other metastases). Of the 11 patients, ten died of disease (longest survival 17 months) and one was alive with disease at eight months.

Stehman *et al.* reported a Gynecologic Oncology Group study which investigated scalene node biopsy in those who had documented PALN (n = 47) or common iliac LN metastases (n = 8) excluding palpable scalene node cases. Only four of the 55 study patients had positive SCLN metastases. Although all of these four patients received treatment, three of whom had SCLN relapse either alone or with other new metastases and the remaining one had pelvic recurrence, all died of disease (15). Using FDG-PET, Grigsby *et al.* showed that the SLN detection rate was elevated to 8% (8 of 101) when PET was applied prior to primary RT (all eight patients died of disease), approximately 15% of SCLN was detected by FDG-PET for FIGO Stage IIIb and 40% of those with PALN metastases also had SCLN metastases [3, 4].

SCLN involvement at primary diagnosis of cervical cancer is usually associated with a dismal prognosis and often only palliative therapy is done, while few others would still try to control the disease by different therapeutic modalities [4, 14, 15]. With the improvement of diagnostic modalities and treatment regimens, we did observe a long-term survival in some recurrent cervical cancer patients with SCLN metastases [5, 11, 12], which led to this retrospective study. In this series, the 3- and 5-year survival rates of patients with SCLN metastases were 16.5% and 16.5%, respectively. In the current series, staging/restaging using FDG-PET and SCC-Ag < 15 ng/ml at initial diagnosis were associated with a better prognosis. Our previous studies identified 10 ng/ml as a significant cut-off of outcome predictor in patients treated with primary RT [16], while the optimal cutoffs in patients with documented recurrence was 4 ng/ml [11]. The fact that other cut-offs (4-14 ng/ml) of SCC-Ag at initial diagnosis were also significant in univariate analyses but only a cuf-off at 15 ng/ml was selected in the multivariate model might reflect the nature of squamous cervical cancer with SCLN involvement which tends to have high SCC-Ag. However, the prognosis of whose SCC-Ag was < 15 ng/ml could still have a better chance to be successfully treated. Because patients with obvious disseminated disease were excluded from the PET study might bias the results of patients receiving PET to better prognoses, the implication of the finding that staging/restaging using FDG-PET was associated with better outcome probably means that the benefit from PET findings might help in selecting appropriate patients for curative primary and salvage treatment.

Although standard guidelines or therapeutic clinical trials exist for different types and stages of cervical cancer (16, 17), diseases with extremely poor prognoses (such as SCLN metastases) need research efforts and individualized treatment in order to improve outcomes

for these patients. The use of FDG-PET scans helps clinicians more accurately detect the presence and location of cancer cells. Facing a situation of clinically palpable SCLN, both patients and physicians are reluctant to obtain histological proof by invasive procedures. One of the contributions of FDG-PET could provide a functional image (metabolic biopsy) to assist clinical decisions.

Given poor outcomes and a short life span after diagnosis of Stage IVb with multiple metastases, some patients would refuse to have a SCLNs biopsy for tissue proof. It is important to point out that these patients would eventually be missed in a retrospective study. As a result, the actual results may not be as good as that of this series. However, providing curative-intent treatment to well selected patients, such as SCC-Ag < 15 ng/ml at initial diagnosis and without other evidence of extranodal distant metastases (especially with FDG-PET back-up), is justified. Such treatment includes combined-modality therapy (CCRT with or without adjuvant surgery), and a deliberate restaging when a potentially curable recurrence is suspected [5, 9-13].

Conclusion

We have demonstrated in this retrospective study that primary cervical cancer patients with SCLN metastases are not incurable. The benefit from PET findings might help in selecting appropriate patients for curative primary and/or salvage treatment.

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