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Original Article

Risk Stratification for Failure in Patients with Advanced Cervical Cancer after Concurrent Chemoradiotherapy: Another Way to Optimise Treatment Results

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ABSTRACT:
Aims: **To identify risk factors for disease-free survival (DFS) and para-aortic lymph node (PALN) metastasis in advanced cervical cancer patients after concurrent chemoradiotherapy (CCRT) using risk stratification.**
Materials and methods: **In total, 148 patients with stage IB2–IVA cervical cancer without PALN metastasis treated with a full course of CCRT were included for analysis. Radiotherapy consisted of external beam irradiation followed by four courses of high-dose rate intracavitary brachytherapy using 6.0 Gy to point A. Chemotherapy consisted of weekly cisplatin at a dose of 40 mg/m^2 for a planned six cycles. Cox's proportional hazards model was used for risk stratification for DFS and PALN relapse-free survival.**
Results: **Patients were divided into low- and high-risk groups. The low-risk group was composed of patients with stage IB–IIB disease without enlarged pelvic nodes, whereas the high-risk group was comprised of patients with stage IB2–IIB tumours with enlarged nodes or those with stage III–IVA disease. The 4-year DFS for the low- and high-risk groups was 83 and 52%, respectively ($P = 0.0001$, relative risk 4.51, 95% confidence interval 1.3–10.7), whereas the 4-year PALN metastasis-free survival for the low- and high-risk groups was 92 and 61%, respectively ($P = 0.0003$, relative risk 4.93, 95% confidence interval 1.2–12.5).**
Conclusion: **The risk of failure in advanced cervical cancer patients treated in the CCRT era can be predicted. For patients with high risk of PALN relapse, this study can provide patient selection criteria when considering prophylactic PALN irradiation. Liang, Ji-An. *et al*. (2008). *Clinical Oncology* 20, 683–690**

Key words: Cervical cancer, concurrent chemoradiotherapy, para-aortic lymph node metastasis, predictive model, risk stratification

Introduction

The superiority of cisplatin-based concurrent chemotherapy and radiotherapy (CCRT) over radiotherapy alone for treating advanced cervical cancer has been shown in several randomised trials [1–4]. The outcomes of both arms were compared, and 10–20% differences in survival or disease-free survival (DFS) curves were shown. The gynaecological oncology 85 and 120 trials showed reduced lung metastasis in patients receiving either cisplatin alone or cisplatin plus 5-fluorouracil, but no decrease in metastasis at other sites [2,4]. In contrast, a phase III trial from Canada showed that concurrent single-agent cisplatin (40 mg/m^2 weekly) did not improve local control or metastasis [5]. Despite sufficient evidence that concurrent use of cisplatin-based chemotherapy plus pelvic irradiation should be used in patients with advanced cervical cancer, the details of failure patterns stratified by stage or other pre-treatment parameters were not always well addressed in these trials [1–5]. On the other hand, Hong *et al*. [6] reported a precise risk stratification for patients with squamous cell carcinoma of the cervix treated by radiotherapy alone. In the era of CCRT for advanced cervical cancer, questions remain unanswered whether the treatment outcome in certain subgroups of patients might be further optimised through either analysis of failure patterns or risk stratification. For example, the para-aortic lymph nodes (PALN) are often the first site of extrapelvic disease. PALN metastasis was the most important prognostic factor in previous Gynecologic Oncology Group trials [7]. If a subgroup of patients is found to have a substantial chance of developing PALN metastasis after CCRT, they might benefit from prophylactic extended-field irradiation (EFRT) of the PALN.

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Computed tomography is a useful tool for the detection of enlarged pelvic nodes or PALN, and it should remain the first-line imaging modality for staging [8]. For patients with enlarged pelvic nodes but no obvious PALN metastasis, pre-treatment 18-fluorodeoxyglucose positron emission tomography (FDG-PET) can supplement the conventional imaging study in adjusting the irradiation field [9]. However, the use of pre-treatment FDG-PET cannot preclude the existence of micrometastasis in the PALN due to the limited resolution of the γ-camera [9,10]. A subsequent PALN relapse might be observed after CCRT with pelvic irradiation if occult tumour foci cannot be effectively eradicated by drug therapy. A Radiation Therapy Oncology Group (RTOG 79-02) trial showed an 11% difference in overall survival in the extended field arm when compared with the pelvic irradiation arm for patients with bulky stage IB—IIB disease [11]. However, the cumulative incidence of grade 4 and 5 toxicity was 8% for the EFRT arm, compared with 4% for the pelvic irradiation arm ($P = 0.06$). The RTOG 90-01 trial showed that the survival rate for patients treated with concurrent chemotherapy and pelvic irradiation was better than for patients treated with EFRT [12]. However, chemotherapy did not eliminate the risk of PALN disease recurrence. The reported rate of PALN failure in the CCRT arm of this trial was 9% at 8 years. To avoid unacceptable toxicity in concurrent chemotherapy and EFRT, the selection criteria for EFRT should be meticulous. It is essential to conduct a randomised trial to examine whether this improvement with CCRT plus EFRT can be achieved in certain subgroups of patients. Before the initiation of this clinical trial, more detailed stratification of failure patterns could be helpful in analysing who will have a greater likelihood of benefiting from concurrent chemotherapy and EFRT.

This study was designed to carry out risk stratification and to develop a prediction model for local and distant failures, and PALN metastasis after concurrent chemotherapy with pelvic irradiation by using available clinical data. In this study, we retrospectively reviewed 148 patients with International Federation of Gynecology and Obstetrics (FIGO) stage IB2—IVA carcinoma of the cervix, who were treated with pelvic irradiation and concurrent weekly cisplatin. After combining the different independent risk factors from the multivariate analysis, the patients were stratified into low- and high-risk groups for both DFS and the PALN failure rate.

Materials and Methods

Patient Characteristics

Between January 2001 and June 2006, 163 consecutive patients with previously untreated stage IB2—IVA cervical cancer completed curative-intent CCRT at China Medical University Hospital. Fifteen patients were excluded because of evidence of enlarged PALN on pre-treatment imaging. Nodal involvement was defined as the presence of at least one enlarged lymph node with a maximal dimension of more than 1 cm on computed tomography of the abdomen. In total, 148 patients were included in this retrospective study. Patient characteristics of the enrolled patients are summarised in Table 1.

Radiotherapy

Irradiation treatment consisted of external beam radiotherapy followed by high-dose rate intracavitary brachytherapy (HDRICB) (Table 2). Initially, the whole pelvis was treated with 10 MV X-rays via anterior and posterior parallel fields or box variants where the AP diameter was over 18 cm. The standard prescribed dose was 45 Gy, consisting of 25 fractions given over 5 weeks. The radiation dose for patients diagnosed with FIGO stage IIB—IVA bilateral parametrial disease was boosted to 54—57.6 Gy, with 4 cm wide midline shielding. For patients with positive pelvic nodes, the irradiated doses to involved nodes were escalated to 61.2—64.8 Gy with a small boost field.

After adequate tumour regression, HDRICB was carried out using an Ir-192 remote afterloading technique at 1 week intervals. One hundred and twenty-six patients (85.1%) received four insertions and 22 patients (14.9%) received five insertions.

Table 1 — Patient characteristics ($n = 148$)

Characteristic	Value
Age (years)	31—76 (median 54)
<45	16 (10.8%)
45—65	95 (64.2%)
>65	37 (25.0%)
Stage	
IB2	18 (12.2%)
IIA (bulky)	10 (6.8%)
IIB	83 (56.1%)
III	34 (23.0%)
IVA	3 (2.0%)
Tumour size	
<4 cm	11 (6.7%)
4—6 cm	92 (62.2%)
>6 cm	45 (30.4%)
Pelvic lymph node	
Negative CT <1 cm	126 (85.1%)
Positive CT 1—2 cm	14 (9.5%)
CT 2—3 cm	6 (4.1%)
CT >3 cm	2 (1.4%)
Pathology	
Squamous cell carcinoma	135 (91.2%)
Adenocarcinoma	13 (8.8%)
Radiation therapy duration (days)	45—77 (median 55)
Follow-up (months)	19—89 (median 49)
Delivered cisplatin cycles	Median 6 cycles
3	7 (4.7%)
4	13 (8.8%)
5	21 (14.2%)
6	81 (54.7%)
7	20 (13.5%)
8	6 (4.1%)

Bulky tumours are defined as lateral dimension of cervical tumour >4 cm. CT, computed tomography.

Table 2 — Radiotherapy technique

External radiotherapy	
Equipment: Elekta SL18 linear accelerator	
Portal: AP/PA, Box (AP diameter >18 cm)	
Energy: 10 MV X-ray	
Daily dose: 1.8 Gy	
Whole pelvis dose: 45.0 Gy (median 45 Gy)	
True pelvis dose: 45.0—50.4 Gy (median 45 Gy)	
Parametrium dose: 45.0—59.4 Gy (median 57.6 Gy)	
Boost dose to enlarged pelvic nodes: 61.2—64.8 Gy (median 63 Gy)	
Brachytherapy	
Equipment: Ir-192 high-dose rate afterloading (GammaMed)	
No. of insertion:	
4 course	126
5 course	22
Point A dose: 6.0 Gy	127
Modification of point A dose to 5 Gy:	21
(1) Age >70 years	19
(2) High rectal ICRU reference dose (>6 Gy)	2
Fractions: once/week	

The rationale for five insertions was based on histopathologically proven residual tumour through biopsy before the fourth brachytherapy. The standard prescribed dose for each HDRICB was 6.0 Gy to point A. This was decreased to 5 Gy for 19 patients who were over 70 years of age. Also, two patients were treated with an initial calculated International Commission of Radiation Unit (ICRU) rectal dose of over 6.0 Gy [13].

Orthogonal radiographic films were produced to define the ICRU rectal-point and cervical-orifice doses. HDRICB was carried out using Henschke applicators and colpostats with diameters of 1.0—2.0 cm, selected based on the individual's anatomy. The detailed method for the calculation of rectal and bladder reference doses is described in our previous study [14]. Total prescribed point A doses (external beam irradiation without central block + total cumulative HDRICB) ranged from 65.0 to 75.0 Gy (median 69.0 Gy). The biologically equivalent dose to point A ranged from 83.1 to 101.1 Gy_{10} (median 91.5 Gy_{10}). The biologically equivalent dose was calculated using the linear-quadratic model, and the α/β ratio for the tumour was assumed to be 10 Gy.

During the radiotherapy course, weekly monitoring of haemoglobin levels was required. Blood transfusion was mandatory if the haemoglobin level was less than 10 g/dl.

Chemotherapy

For CCRT, chemotherapy consisted of cisplatin delivered weekly at a dose of 40 mg/m^2 intravenously, with a total dose of up to 60 mg. The first cycle of cisplatin was initiated at the first treatment of radiotherapy. In accordance with the duration of radiotherapy, the treatment plan included a total of five to six cycles of cisplatin.

Adequate bone marrow function and serum creatinine, and a creatinine clearance of at least 50 ml/min before cisplatin administration were required. Renal function and blood counts were assayed before each cycle. Chemotherapy was delayed week by week until the granulocyte count was more than 2.0×10^9/l, the platelet count was more than 100×10^9/l, or if the serum creatinine level did not return to 1.4 mg/dl. Cisplatin administration was also suspended if the patient could not tolerate the acute gastrointestinal toxicity during the CCRT course.

Tumour Response at First Brachytherapy

HDRICB was usually initiated after external beam radiotherapy of 40 Gy was given. A pelvic examination was carried out for all patients under general anaesthesia, with insertion of the applicator before the first brachytherapy session. The tumour response to external beam radiotherapy was recorded on a subjective basis as follows:

(1) NRT response (no gross residual tumour): complete or nearly complete regression of the pelvic tumour, nonspecific fibrosis or granulation over the cervix.

(2) GRT response (gross residual tumour): gross tumour or palpable nodularity on the cervix, and/or palpable induration of the parametrium.

Follow-up and Complication Analysis

We assessed the treatment response 4 weeks after the completion of treatment. If residual disease was suspected, a biopsy was carried out. Patients underwent regular follow-up examinations every 1—2 months for the first year and then every 3 months thereafter. A pelvic examination was carried out during each follow-up visit. Tumour markers (squamous cell carcinoma antigen and carcinoembryonic antigen) were checked every 3—6 months and radiographic examinations (chest radiograph, abdominopelvic computed tomography) were conducted yearly. Pelvic recurrence was confirmed if the disease was detected within the irradiated field either by pathological proof of cancer or imaging findings showed regrowth of the tumour or any enlarged pelvic lymph node. Distant metastases were confirmed if tumours occurred in the PALN or elsewhere outside the pelvis on imaging. Once local recurrence or distant metastasis was suspected, FDG-PET was carried out to detect the sites of recurrence to facilitate the evaluation of salvage treatment. In this study, the definition of local or distant failure was based on the locations of lesions detected at the first relapse after a comprehensive workup. Patients were considered to have both pelvic and distant failure when two lesions were detected within a 1 month interval. Any new lesions detected >1 month after the first relapse were not considered in this analysis.

Statistical Analysis

Patient survival was measured from the date of the initiation of therapy to the date of the last follow-up examination. DFS,

Table 3 — Univariate analysis of different parameters on pelvic relapse, distant failure and para-aortic lymph node failure

Variables	4-year PRFS	*P* value	4-year DMFS	*P* value	4-year PNRFS	*P* value
Stage						
IB2—IIB (111)	94	0.01	82	0.01	85	0.01
III—IVA (37)	80		63		68	
Age (years)						
≤65 (112)	90	0.78	76	0.57	80	0.58
>65 (36)	93		79		84	
Pelvic lymph node						
Negative (126)	91	0.53	84	0.002	90	0.0002
Positive (22)	84		32		31	
Histology						
Squamous cell carcinoma (135)	93	0.002	79	0.57	83	0.37
Adenocarcinoma (13)	62		75		75	
EUA						
NRT (37)	94	0.61	78	0.78	85	0.53
GRT (111)	89		76		80	
Initial haemoglobin level						
<10 mg/dl (26)	79	0.23	65	0.12	68	0.11
>10 mg/dl (122)	92		79		82	
Pre-treatment squamous cell carcinoma antigen						
<10 ng/dl (106)	92	0.88	78	0.56	82	0.79
>10 ng/dl (42)	90		75		79	

PRFS, pelvic relapse-free survival; DMFS, distant metastasis-free survival; PNRFS, para-aortic lymph node relapse-free survival; EUA, examination under anaesthesia on first brachytherapy; NRT, no gross residual tumour; GRT, gross residual tumour. The values in parentheses represent the patient number.

pelvic relapse-free survival and distant metastasis-free survival were calculated using the Kaplan—Meier method. Significance levels between the curves were calculated using the Log-rank test. Multivariate analyses were carried out using Cox's proportional hazards model to assess both DFS and PALN relapse-free survival. All patients were stratified by pelvic node involvement, stage, tumour size, histology, age, examination under anaesthesia findings and initial haemoglobin level. Statistical significance was considered for $P < 0.05$.

Results

Treatment Outcome

The median duration of follow-up was 49 months (range 19—89 months). One hundred and twenty-two patients were alive (112 without evidence of disease, four with pelvic failure and six with distant metastasis); 26 patients died of the disease (three with pelvic recurrence, 18 with distant metastasis and six with both). The 4-year DFS was 92% for stage IB2—IIA, 78% for stage IIB and 51% for stage III—IVA. The 4-year pelvic relapse-free survival was 100% for stage IB2—IIA, 92% for stage IIB and 81% for stage III—IVA. The 4-year distant metastasis-free survival was 91% for stage IB2—IIA, 79% for stage IIB and 59% for stage III—IVA. Among the 13 patients with pelvic failure, 12 had recurrent tumours in the central pelvis; only one patient was categorised as having pelvic lymph node recurrence.

Risk Factors Associated with Local and Distant Failure

The results of the univariate analysis for failure patterns with different clinical parameters are listed in Table 3. The risk factors associated with disease relapse and PALN metastases were examined by multivariate analyses, as listed in Table 4. The independent risk factors for disease relapse were positive pelvic lymph node ($P = 0.001$, hazard ratio 6.6, 95% confidence interval 2.5—22.8) and stage III—IVA disease ($P = 0.01$, hazard ratio 3.7, 95% confidence interval 1.2—11.7). The 4-year DFS was 81% for patients without pelvic lymph node metastasis and 27% for patients with pelvic lymph node metastasis, whereas the 4-year DFS was 81% for patients with stage IB—IIB disease and 51% for patients with stage III—IVA disease.

Risk Stratification for Para-aortic Lymph Node Failure

Of the 30 patients with distant failures, 25 patients (83.3%) had concurrent PALN metastases. Ten patients developed isolated PALN recurrence and 15 patients had a combination of metastasis in the PALN and distant metastasis in other sites. Five patients developed systemic tumours outside the pelvis without evidence of PALN failure through FDG-PET (lung in three, bone in one and combined lung and bone in one). The 4-year actuarial survival was 92% for patients without PALN metastasis and 21% for patients with PALN

Table 4 — Multivariate analysis of prognostic factors on disease-free survival, cause-specific survival

Prognostic factors	Disease-free survival			PNRFS		
	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Pelvic lymph node status						
Negative	1			1		
Positive	6.6	2.5—22.8	0.001	11.8	2.6—35.7	0.0001
Stage						
IB2—IIB	1				1	
IIIA—IVA	3.5	1.2—11.7	0.01	3.3	1.1—10.7	0.03
Age						
>65 years	1			1		
≤ 65 years	1.2		0.72	1.1		0.71
Histology						
Squamous cell carcinoma	1			1		
Adenocarcinoma	2.1		0.83	1.7		0.50
EUA						
NRT	1			1		
GRT	1.0		0.90	1.1		0.48
Initial haemoglobin level						
>10 mg/dl	1			1		
<10 mg/dl	1.2		0.39	1.1		0.62
Pre-treatment squamous cell carcinoma antigen						
<10 ng/dl	1			1		
>10 ng/dl	1.1		0.66	1.4		0.28

Abbreviations as in Table 3. CI, confidence interval.

metastasis ($P = 0.0001$). The independent risk factors for PALN metastasis were positive pelvic lymph node ($P = 0.0001$, hazard ratio 11.8, 95% confidence interval 2.6—35.7) and stage III—IVA disease ($P = 0.03$, hazard ratio 3.3, 95% confidence interval 1.1—10.7).

Classification of Low- and High-risk Groups

On the basis of the results of risk stratification, patients could be divided into two groups. The low-risk group had stage IB—IIB disease without enlarged pelvic nodes, and the high-risk group had stage IB2—IIB tumours with enlarged nodes or stage III—IVA disease. This stratification could be used not only for DFS, but also in terms of PALN recurrence, as illustrated in Figs. 1 and 2. The low-risk group comprised 98 patients, of whom 14 developed disease recurrence, and seven had PALN metastasis. The high-risk group comprised 50 patients, of whom 22 developed disease recurrence, and 18 patients had PALN metastasis. The 4-year DFS for the low- and high-risk groups was 83 and 52%, respectively ($P = 0.0001$, relative risk 4.51, 95% confidence interval 1.3—10.7), whereas the 4-year PALN metastasis-free survival was 92 and 61%, respectively ($P = 0.0003$, relative risk 4.93, 95% confidence interval 1.2—12.5).

Discussion

In CCRT for treating invasive cervical cancer, the drugs used in previous studies included cisplatin, cisplatin plus 5-fluorouracil, or hydroxurea. Although the optimal chemotherapy schedule in combination with radiotherapy is still debatable, the addition of weekly cisplatin at a dose of 40 mg/m^2 has become a well-tolerated drug therapy used in the CCRT era. On the other hand, its routine use in HDRICB has been questioned because of a narrow therapeutic window and a lack of consensus on fractionation [15]. Despite some scepticism, HDRICB has been widely used in

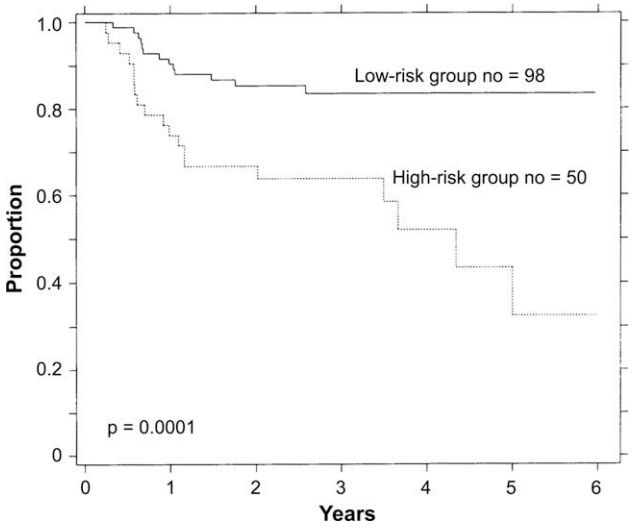

Fig. 1 — Disease-free survival curves according to risk groups.

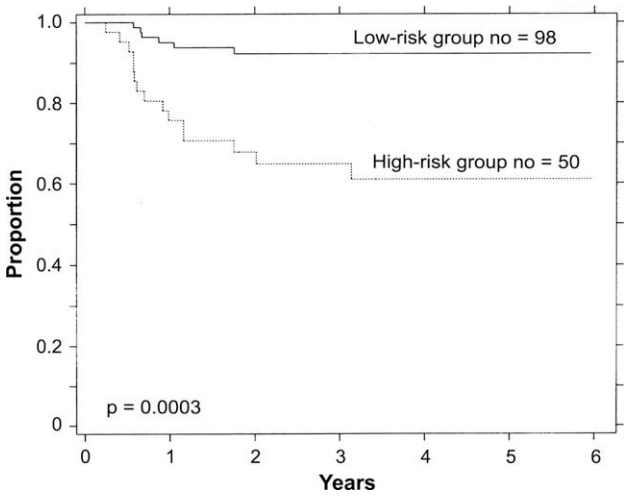

Fig. 2 — Para-aortic lymph node relapse-free survival curves according to risk groups.

the management of cervical cancer for many decades in Asia and Europe, and a long-term report has proved its efficacy and safety [16]. This study showed that the addition of concurrent weekly cisplatin to treatment with external beam radiotherapy and four courses of HDRICB with a prescribed dose of 6 Gy to point A seems to be a very effective regimen for patients with advanced cervical cancer in terms of pelvic control, as also reported in our previous study [17]. Nonetheless, some effort should be made to eradicate systemic disease outside the current irradiated field for further optimisation of treatment results.

Although a combination of drugs with radiotherapy theoretically seems to be the treatment of choice to reduce distant metastasis, its effects in reducing distant failures are still uncertain. Three phase III trials showed trends of reduction in lung metastases, but this was not observed in other sites [2,4]. The RTOG 90-01 trial showed that distant metastasis, excluding PALN failure, was reduced from 31 to 18% ($P = 0.001$) for patients treated with concurrent chemotherapy and pelvic irradiation compared with patients treated with EFRT [12]. However, chemotherapy did not eliminate the risk of PALN recurrence. The reported rate of PALN failure in the CCRT arm in this trial was 9% (95% confidence interval 4—13%). Radiotherapists feel that in addition to exhaustive efforts to improve local control within the irradiated field, modification of the irradiated field might be another feasible approach to achieve a better treatment outcome if drugs cannot effectively eradicate micrometastasis outside the pelvis. However, two important issues remain to be investigated further.

First, it would be interesting to know whether certain subgroups of patients would gain more benefit from the use of EFRT. The role of prophylactic EFRT has been investigated for more than 10 years in a RTOG trial [11]. Significant increases in survival, locoregional disease control, and time to distant metastasis in patients with stage IB2—IIB disease were noted. However, the cumulative incidence of grade 4 and 5 toxicity was 8% for the EFRT arm and 4% for the pelvic irradiation arm ($P = 0.06$). In another study by Grigsby *et al.* [18] in the RTOG 92-10 trial, an unacceptably high rate of grade 4 late toxicity (17%) was reported with a combination of cisplatin plus 5-fluorouracil and twice-day radiation with a total dose 54—58 Gy to the PALN. These studies imply that it is necessary to be more meticulous when a combination of concurrent chemotherapy plus prophylactic EFRT has to be used.

Because of the rarity of pelvic recurrence in our series, subsequent sites of relapse outside the irradiated field could be well documented. Our study showed that patients could be divided into low- and high-risk groups according to pelvic node status and clinical stage. In 2008, the National Comprehensive Cancer Network guidelines for cervical cancer reported that EFRT might be a treatment of choice for patients with positive pelvic nodes without definitive histological proof of PALN micrometastasis. However, many physicians might be concerned about the risks of treatment-related morbidity. Our study can provide sound patient selection criteria when considering prophylactic EFRT in the CCRT era. On the basis of our data, more than half of high-risk patients might be over-treated. However, it is essential to conduct a clinical trial to justify the use of EFRT in this group.

A major criticism of this study is the sensitivity and specificity of positive lymph nodes. Undoubtedly, FDG-PET might be a powerful tool for the assessment of metastatic nodes, but it is still an expensive diagnostic tool in many developing countries. Thus, its routine use for all patients with cervical cancer might not be feasible financially. Our data showed a good correlation with treatment outcome when positive nodes were defined as the presence of at least one enlarged lymph node of more than 1 cm in maximal dimension on computed tomography. In an irradiation series, O'Hara *et al.* [8] reported lymph node size measured by computed tomography in 84 patients with stage IIB—IVA cervical cancer. Lymph node status was described as negative (<5 mm), possibly positive (5—10 mm) and probably positive (>10 mm). All patients were treated with definitive irradiation and none underwent surgical staging. They reported that patients with nodes >10 mm were more likely to develop distant metastases than patients with lymph nodes <10 mm. Lymph node failure was not detailed in that study. In our study, only 4.5% (1/22) of patients with positive pelvic lymph nodes developed solitary recurrence after a small boost field with irradiated doses of 61.2—64.8 Gy. Thus, the presence of positive pelvic nodes might imply a risk for developing disease failure outside the irradiated field. In another study by Grigsby *et al.* [19], pre-treatment FDG-PET and computed tomography were carried out for all patients, and the existence of pelvic nodes was also not a major concern for local control if an adequate irradiation dose was used. If their patients were stratified into group A (PET negative or PET positive/node <1 cm on computed tomography) and group B (PET positive/node >1 cm on computed tomography), the respective distant metastasis rate was 14.5% for group A and 27.9% for group B ($P = 0.05$).

Thus, the use of the enlarged pelvic nodes >1 cm on pretreatment computed tomography might be a useful predictor for developing distant failure in the CCRT era.

The second question that should be further clarified concerns whether the elimination of PALN micrometastasis by EFRT might subsequently reduce the risk of metastasis in other sites. Theoretically, the micrometastic foci in PALN might increase the risk of tumour spreading to other sites. It seems interesting because our data showed an extremely high association between PALN failure and distant metastasis in other sites. However, it was difficult to discern the sequence of two events by our current follow-up protocol. In the RTOG 79-20 trial [11], more patients failed distally when treated with pelvic radiotherapy when the first disease failure patterns were examined. The estimated cumulative distal failure rate at 10 years in the EFRT arm was 16%, compared with 23% in the pelvic arm ($P = 0.05$). Survival after the first failure proved to be longer in the EFRT arm ($P < 0.01$). In contrast, the reduction in PALN recurrence by EFRT did not decrease metastasis in other sites in the RTOG 90-01 trial. This might be attributed to the higher pelvic failure rate in the EFRT arm compared with the CCRT arm (34% vs 18%).

Of course, a major limitation of this study was that the total patient numbers and the observed numbers of failures were relatively small. Thus, our analysis can only suggest a crude classification using two combinations of the predictive factors. Due to the possibility of statistical inaccuracy, our data could only show the differences between the high- and low-risk groups, but do not show the evidence of a clearly defined distinction. Thus, it is essential to conduct a large randomised trial to examine whether this improvement by CCRT plus EFRT can be achievable for high-risk patients.

In summary, we have developed a prognostic model based on easily obtainable information in patients with advanced cervical cancer treated in the CCRT era. Patients can be simply divided into low- and high-risk groups for DFS and PALN recurrence according to currently available pretreatment parameters. To reduce the risk of systemic metastasis, satisfactory pelvic control is fundamentally required. Otherwise, selection of a high-risk group when considering EFRT might be another approach. With the advent of novel radiation techniques, the high complication rates shown in RTOG 79-20 trials need to be re-evaluated. However, more clinical trials are essential to investigate the toxicity profile of EFRT plus concurrent chemotherapy, and also to answer whether this approach will reduce the risk of metastasis to other sites.

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