

A PROSPECTIVE RANDOMIZED TRIAL TO STUDY THE IMPACT OF PRETREATMENT FDG-PET FOR CERVICAL CANCER PATIENTS WITH MRI-DETECTED POSITIVE PELVIC BUT NEGATIVE PARA-AORTIC LYMPHADENOPATHY

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Purpose: This prospective randomized study was undertaken to determine the possible impact of 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) on extrapelvic metastasis detection, radiation field design, and survival outcome for cervical cancer patients with enlarged pelvic nodes on MRI image.

Methods and Materials: Inclusion criteria were patients with newly diagnosed Stage I–IVA cervical cancer and with positive pelvic but negative para-aortic lymph nodes (PALN) as detected by magnetic resonance image and good performance status for concurrent chemoradiotherapy. Eligible patients were randomized to receive either pretreatment FDG-PET (study group) or not (control group). Whole pelvis was the standard irradiation field for the control group and those with no extrapelvic findings on PET. The radiation fields for the rest of the study group were extended to include the PALN region or were modified according to the extrapelvic PET finding.

Results: From January 2002 to April 2006, 129 patients were included, and 66 of them were randomized to receive FDG-PET. PET detected seven extrapelvic metastases (11%, 6 PALN and 1 omental node), and four of them remained disease-free after treatment modification. For patients who underwent PET compared with those who did not, there were no differences in the 4-year rates of overall survival (79% vs. 85%, $p = 0.65$), disease-free survival (75% vs. 77%, $p = 0.64$), and distant metastasis-free survival (82% vs. 78%, $p = 0.83$).

Conclusions: Pretreatment FDG-PET in conjunction with magnetic resonance imaging can improve the detection of extrapelvic metastasis, mainly PALN, and help select patients for extended-field radiotherapy. However, the addition of FDG-PET may not translate into survival benefit, even though PALN relapses are reduced. © 2010 Elsevier Inc.

Cervical cancer, Positive pelvic node, 18F-fluorodeoxyglucose positron emission tomography, Extended-field radiotherapy, Extrapelvic metastasis.

INTRODUCTION

Pelvic lymph node metastasis has a strong impact on the prognosis and management of patients with cervical cancer. Our studies and other studies have shown that positive pelvic nodes identified by computed tomography (CT) or magnetic resonance imaging (MRI) constitute an independent prognostic factor for survival in cervical cancer primarily treated with radiotherapy (1–4). Similar conclusions have also been obtained in a French cooperative study using lymphangiogram to evaluate the nodal status (5). All these studies demonstrated a strong association between pelvic node metastasis and distant failure after successful control of primary tumors, suggesting that patients with positive pelvic nodes have a higher risk of carrying distant metastasis undetected by conventional imaging studies.

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pelvic node metastasis than those who did not (6). Several prospective randomized trials have assessed the effect of routine prophylactic PALN irradiation for advanced-stage patients (7–9). Although some succeeded in reducing the incidences of distant failure, all were accompanied with a significant increase of enteric complications. The increased toxicities became more serious when extended-field irradiation was combined with concurrent chemotherapy, as illustrated in the Radiation Therapy Oncology Group (RTOG) 9210 and RTOG 0116 trials (10, 11). On the basis of these findings, clinicians are faced with a dilemma of whether extended-field irradiation with concurrent chemotherapy should be routinely applied to patients with positive pelvic nodes but negative PALN metastasis as shown on CT/MRI.

The 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) has a better detection rate in pelvic lymph node and PALN metastases than do conventional CT/MRI studies for cervical cancer (12–15). One study also demonstrated that a finding of abnormal lymph node status on FDG-PET is a better predictor for patients' survival than what CT scan can detect (16). Although accumulating evidence has shown FDG-PET to be complementary to CT/MRI in the staging of cancer, it is a relatively expensive modality. Routine use of FDG-PET for all cervical cancer patients may be financially unjustified. Therefore, the identification of a patient subset with a greater risk of extrapelvic metastasis should be reasonable to maximize the cost effectiveness of FDG-PET screening.

The present study was based on our previous observation that 5 out of 19 (26%) cervical cancer patients who had enlarged pelvic nodes but no enlarged PALN on MRI image were found to have para-aortic metastases by FDG-PET (17). Therefore, we conducted this Phase III trial in an attempt to validate such observations and to examine the possible benefit of pretreatment FDG-PET in the management of MRI-detected pelvic lymphadenopathy.

METHODS AND MATERIALS

Study design

This prospective study was a randomized, open-labeled clinical trial. Our hypothesis was that, for those with enlarged pelvic nodes but no PALN on conventional MRI imaging, FDG-PET could detect extrapelvic lesions in 20% of patients in this group. Eligible patients were randomized to receive either pretreatment FDG-PET (study group) or not (control group). The accrual goal was set at 100 eligible patients for either arm.

The cost of FDG-PET for cervical cancer was not covered by Taiwan national health insurance during the study period; thus, the FDG-PET study for each patient randomized to the study group was provided free of charge. The primary aim of this trial was to verify the hypothesis that early detection of extrapelvic metastasis by pretreatment FDG-PET and the resulting treatment modification would improve therapeutic outcomes.

Patient selection

The selection criteria for recruiting patients into this trial were as follows: (1) patients with previously untreated stage IB–IVA epithelial cervical carcinoma, as staged by physical examinations and

conventional imaging studies, (2) patients having Karnofsky performance scale ≥ 70 and no contradiction to cis-platinum-based concurrent chemoradiotherapy, (3) patients with positive pelvic node(s) but no PALN metastasis as shown on MRI. Positive lymphadenopathy was defined as a nodal size of ≥ 1 cm at its maximal dimension, or an aggregate group of small pelvic nodes (each < 1 cm). Exclusion criteria were as follows: known extrapelvic metastasis at presentation, nonepithelial carcinoma, chronic debilitating disease that might interfere with radiotherapy or chemotherapy, history of malignancy (except for nonmelanoma skin cancer), and unsuitability to receive MRI or PET for either technical (*e.g.*, history of metal hip prosthesis or cardiac pacemaker insertion) or psychologic reasons.

Image study and interpretation

MRI imaging. Pretreatment MRI studies were performed by a GE LX 1.5 Tesla closed scanner (General Electric Medical Systems, Milwaukee, WI). The scanning protocol included gadolinium enhancement and different sequences and axes of view for screening the abdomen and pelvis. The maximum field of view was confined to 32 cm because of the limitation of the surface coil. All MRI studies were interpreted prospectively by a radiologist (K.K.N.) who specialized in gynecologic cancer imaging. Each eligible case was presented at a weekly combined conference, and MRI images were carefully reviewed before randomization.

FDG-PET imaging. The FDG-PET protocol was the same as that described in previous studies (17–19). In brief, PET was performed using a PET scanner (ECAT HR Plus, Siemens, Knoxville, TN). The raw PET results were analyzed on attenuation-corrected emission images and reconstructed into coronal, sagittal, and transverse sections. The FDG accumulation was interpreted visually using a 5-point grading system (0 = negative findings; 1 = insignificant yet visible lesion; 2 = equivocal, needs additional follow-up and evaluation; 3 = probable metastasis; and 4 = significant metastasis). A score of ≥ 3 was considered positive and required the consensus of at least two of three nuclear medicine physicians. Standardized uptake values (SUVs) were used to measure FDG uptake for each visible lesion as adjuvant data for interpretation. For semiquantitative analysis, the SUVs were obtained for regions of interest that had previously been identified as suggestive after visual analysis. To minimize partial volume effects, the maximal SUV within a region of interest was used. The PET results were compared with MRI imaging, with discrepancies confirmed by tissue proof whenever accessible.

Radiotherapy and chemotherapy

The treatment fields for external beam irradiation were designed using CT-assisted virtual simulation with 5-mm contiguous slice intervals, and dosimetric calculation after image reconstruction was done using a commercial treatment planning software (Eclipse; Varian Medical Systems, U.S.A.). Each treatment field was tailored according to the perceived anatomic extent of the primary tumor and possible lymphatic involvement. Findings from MRI and PET studies were used to determine the need of standard vs. extended coverage designed respectively for either randomized group.

Pelvic irradiation with concurrent weekly cisplatin was the standard baseline treatment for both groups. Patients received 45 Gy in 25 fractions of whole pelvic irradiation with 10-mV x-ray beams delivered via a four-field box technique. The para-aortic region was included if the PET scan showed positive findings. Inasmuch as all patients had enlarged pelvic node(s) on MRI, they received a boost dose (5.4–12.6 Gy) to the parametria and iliac nodes by

parallel-opposed anterior-posterior fields with a 4-cm-wide midline block. A lower boost dose was usually given to those with negative PET findings in the pelvic nodes or clinical Stage IB–IIA disease. For tumors with lower vaginal extension, bladder or rectal invasion, or persistent bulky tumor after 45 Gy, external beam doses to the lower pelvis were either increased to 50–54 Gy without central block followed by brachytherapy, or to 70.2–72 Gy without brachytherapy. For intracavitary brachytherapy, a high-dose-rate technique using an ¹⁹²Ir source was given for six fractions, with two fractions per week. The dosage to point A was 4.3 Gy per fraction. The total radiotherapy course was expected to be completed within 8 weeks.

The treatment protocol for chemotherapy included six cycles of weekly intravenous infusions of cisplatin (50 mg/m² body surface) during the radiotherapy course. However, chemotherapy would be withheld when the granulocyte count was <1,500/mL or the platelet count was <100,000/mL, and restarted after recovery from such low cell counts. Completion of all six courses of cisplatin was not compulsory if radiotherapy had been completed earlier.

Follow-up and statistical consideration

The follow-up protocol was the same as that in our pilot study (17): MRI or CT imaging was performed every 6 months for the first year or whenever relapse was suspected. Serum tumor markers of squamous cell carcinoma antigen and carcinoembryonic antigen were checked regularly. The time to failure was calculated from the date of registration into the study to the date of failure confirmation; a similar principle was also applied to calculating the time to death.

Baseline characteristics were expressed as percentages or means ± standard deviation for continuous variables. The chi-square test was used to compare categorical variables. Overall and disease-free survival curves were determined using the Kaplan-Meier method and compared with the log-rank test (20), whereas the rates of locoregional failure and distant metastases were calculated as cumulative incidence. All analyses were performed using the software Statistical Product and Service Solutions (SPSS Inc., Chicago, IL).

Ethics

This study was approved by the Committee for Medical Research Ethic of the Chang Gung Memorial Hospital (N0.92-135) and registered on ClinicalTrials.gov (NCT00146458). Written informed consent was obtained for each patient before randomization.

Early closure of this study

The accrual of this study was closed early after 129 patients were enrolled, 65% of the expected sample size. There were two reasons for this early closure. First, from January 2002 to the end of April 2006, 36 cases accrued in the 1st and 2nd years, 28 in the 3rd year, and 26 in the 4th year, but only 3 in the last 4 months. More eligible patients preferred to undergo FDG-PET at their own expense and declined randomization. Besides, our interim analysis (21) showed that the detection rate of extrapelvic metastasis by FDG-PET was only 11% (half of the value assumed in our case calculation); thus, it was difficult to recruit enough patients within a reasonable period to complete this study.

Second, after May 2006, FDG-PET study in our institute was performed on a new PET/CT machine (Discovery ST16 PET/CT scanner, GE Healthcare), and a new 3 Tesla MR scanner (Tim Trio, Siemens, Erlangen, Germany) was used for cervical cancer patients. Both machines had the potential to provide better imaging quality for diagnosis and to create inconsistencies in interpretation between images taken by new and old machines.

Table 1. Baseline characteristics of all randomized patients

Characteristic	FDG-PET (n = 66)		Control (n = 63)	
	n	%	n	%
Age (y)				
31–39	7	11	8	13
40–49	21	32	24	38
50–59	14	21	16	25
≥60	24	36	15	24
FIGO stage				
IB1	5	8	3	5
IB2	16	24	8	13
II	29	44	39	62
III	15	23	11	17
IVA	1	1.5	2	3
Initial serum tumor marker				
SCC <1.5 (normal)	16	24	15	24
SCC 1.5–9.9	27	41	25	40
SCC 10–19.9	14	21	8	13
SCC >20	9	14	15	24
CEA <5.0 (normal)	39	59	42	67
CEA 5–9.9	18	27	8	13
CEA >20	9	14	11	17
Histology				
Squamous cell carcinoma	64	97	62	98
Adeno/adeno-squamous carcinoma	2	3	1	2
Concurrent chemotherapy weekly CDDP 50 mg/m ² (standard 6 courses)				
0–3 courses	7	11	6	10
4–5 courses	21	32	19	30
6 courses	38	58	38	60
Radiotherapy				
Incomplete (external beam <54 Gy)	4	6	2	3
Complete irradiation				
Whole pelvis + brachytherapy	54	82	57	90
External beam alone (70.2–72 Gy)	2	3	4	6
Extended field + brachytherapy	6	9		

Abbreviations: FDG-PET = 18F-fluorodeoxyglucose positron emission tomography; FIGO = International Federation of Gynecology and Obstetrics; SCC = squamous cell carcinoma; CEA = carcinoembryonic antigen; CDDP = cisplatin.

RESULTS

Patient characteristics and trial profile

From January 2002 to April 2006, there were 139 eligible candidates after MRI images were reviewed at a combined conference, but 10 of them refused to enter this study. A total of 129 patients were randomized into the study group (66 patients with MRI and PET scans) or the control group (63 patients with MRI only). These two groups were well balanced regarding their basic characteristics, as described in Table 1. The mean age of patients was 53.4 ± 11.9 years, and squamous cell carcinoma was the dominant histology type. Ninety-four percent of patients were at Stage IB2 or above as defined by the International Federation of

Gynecology and Obstetrics, in agreement with the fact that lymph node metastasis was more common in patients with advanced stage disease.

The execution of radiation treatment is given in Table 1, and the trial profile is shown in Fig. 1. Radiotherapy was not completed in 6 patients: 4 refused further treatment after 41.4–45 Gy of radiation, 1 died of deep vein thrombosis and sepsis after 54 Gy of radiation and one course of chemotherapy, and another refused further chemoradiotherapy and received a hysterectomy after one course of chemotherapy and 3.6 Gy of radiation. Two patients who should have received pelvic irradiation after randomization were treated with extended-field radiation therapy at another hospital because transportation was more convenient and were classified as a protocol violation. These 8 patients were included in our intent-to-treat analyses.

FDG-PET finding and treatment modification of study group

Avid FDG uptakes were found in all primary cervical tumors, with SUVs ranging from 5.1 to 44.1 (median, 13.7). However, only 48 out of 66 (73%) patients had positive PET findings for pelvic nodes; the rest had no pelvic node involvement, inasmuch as only a background level was detected or the SUV was <2.

Pretreatment FDG-PET detected extrapelvic lesions in 7 out of 66 (11%) patients. As shown in Table 2, PALN was the dominant site for extrapelvic metastasis, except for a 2-cm omentum node in one patient. All PALNs detected by FDG-PET could be identified on the CT images taken for virtual simulation and their transverse diameters were reordered. As expected, the transverse diameter of these nodes fell between 0.5 and 0.8 cm. Limited by the small size, deep-seated location, or high risk of injuring the major vessels, CT-guided biopsy of the PALN was done in only 1 patient, but the tissue obtained was insufficient for diagnosis. The metastatic

omental mass was confirmed by CT-guided biopsy and excised by laparoscopic surgery. Radiation fields were modified according to the PET findings, either extended to the para-aortic region or broadened to cover the omental tumor bed. The treatment fields were modified in 11% (7/66) of patients receiving FDG-PET.

Treatment outcome and failure pattern

The observation of this analysis ended on September 30, 2008, and the follow-up period ranged from 29 to 81 months (median, 53 months). Twenty-three (17.8%) patients died of cervical cancer, and another 2 died of second malignancies (cholangiocarcinoma and gastric cancer) with no evidence of cervical cancer recurrence. Thirty-three patients (18 in the PET study group and 15 in the control group) experienced disease recurrence. A summary of the failure pattern and outcome is shown in Table 3.

The local-regional failure rate inside the pelvis was 11% vs. 14% ($p = 0.60$), respectively, for the PET group vs. the control arm, and the corresponding figure for extrapelvic metastasis after treatment was 20% vs. 22% ($p = 0.83$). Although the difference for incidence of distant metastasis between these two groups did not reach statistical significance, the major relapse sites were disparate. The PET study group had less para-aortic and supraclavicular nodal relapse than did the control group. Because the supraclavicular node was the draining site for PALN, it was counted into extrapelvic lymph node relapse. The difference approached statistical significance for PALN only (4/66 vs. 10/63, $p = 0.09$) but reached statistical significance when the events of PALN and supraclavicular lymph nodes were counted together (5 events/66 patients vs. 15 events/63 patients, $p = 0.01$). On the other hand, incidences of extranodal metastasis did not differ significantly between the two groups (14 events/66 patients vs. 8 events/63 patients, $p = 0.25$).

As shown in Figs. 2, 3, and 4, the 4-year overall survival rates were 79% and 85% ($p = 0.65$) for the PET and the

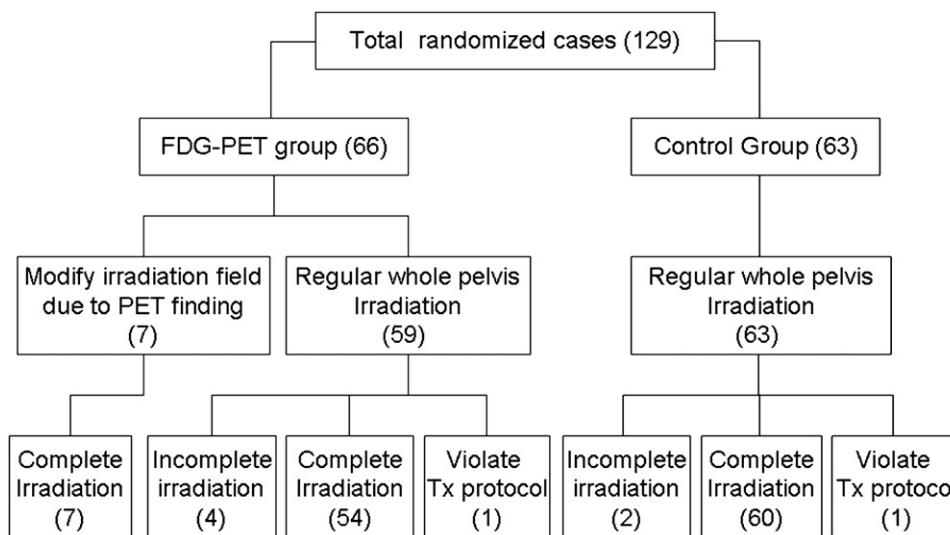


Fig. 1. Trial profile of all randomized patients ($n =$ case number).

Table 2. Summary of patients with extrapelvic FDG-PET findings, their modified radiation fields, and treatment outcomes

Patient	PET finding	Treatment	Last status/survival (month)
4	Omentum node 2 cm	Laparoscope excision and modified RT field	Alive/ NED (79)
17	PALN, L3, 0.7 cm	Extended-field RT	Dead (27)/ lung meta
35	PALN, L3, 0.5 cm	Extended-field RT	Alive/NED (70)
38	PALN, L4, 0.5 cm	Extended-field RT	Dead (16)/ liver meta
41	PALN, L3, 0.6 cm	Extended-field RT	Alive/ NED (67)
57	PALN, L3, 0.6 cm	Extended-field RT	Alive (62)/ axillary node meta
120	PALN, L4, 0.8 cm	Extended-field RT	Alive/ NED (36)

Abbreviations: FDG-PET = 18F-fluorodeoxyglucose positron emission tomography; L3 = para-aortic lymph node at level of 3rd lumbar spine; L4 = para-aortic lymph node at level of 4th lumbar spine; RT = radiotherapy; NED = no evidence of disease; meta = metastasis.

control groups, respectively. The corresponding figures for disease-free survival were 75% and 77% ($p = 0.64$), and for distant metastasis-free survival they were 82% and 78% ($p = 0.83$), respectively. If the 7 patients with extrapelvic metastasis were excluded, there was still no significant difference in overall survival between patients with negative extrapelvic metastasis on PET (59 patients) and the those in the control group (Fig. 5, $p = 0.74$).

DISCUSSION

The roles of FDG-PET for cervical cancer patients primarily treated with radiotherapy have become rather diverse in recent years. It can be used for pretreatment measurement of tumor volume (22), detection of lymph node status (16, 23), reference for three-dimensional brachytherapy treatment planning (24), evaluation of response during and after treatment (25, 26), and prediction of patients' survival after treatment (27). For patients with newly diagnosed cervical cancer, FDG-PET is covered by Medicare and Medicaid in the United States as a supplemental diagnostic tool after conventional imaging results that are negative for extrapelvic metastasis (28). However, the incidence of cervical cancer is higher in underdeveloped or developing countries (29, 30), where PET is expected to be relatively expensive and is not covered by medical insurance. We have thus conducted a series of studies to identify patients who may have a greater risk of extrapelvic metastasis and potentially can benefit from confirmation by a PET study in determining the optimal radiation target volume coverage.

In our pilot study, which enrolled 19 patients with the same inclusion criteria as in this trial, 5 (26%) had positive PALN on FDG-PET, and 1 also had supraclavicular nodal metastasis

Table 3. Treatment outcome and failure patterns

Outcome	FDG-PET ($n = 66$)		Control ($n = 63$)		
	<i>n</i>	%	<i>n</i>	%	
Cause of death					
Cervical cancer	12	18	11	17	
2 nd primary cancer	2	3	0	0	
Noncancer disease	0	0	1	1.6	
Case number	14		12		
1st metastatic site after treatment					
PALN	4	6	10	16	
Neck node	1	1.5	5	8	
Lung/mediastinum	9	14	4	6	
Liver	3	5	1	1.6	
Bone/spine	0	0	2	3	
Other	2	3	1	1.6	
Case number*	13		14		$p = 0.83$
Local-regional (persistent or recurrence)					
Cervix/uterus	6 [†]	9	6 [‡]	10	
Pelvic node	1	1.5	3	5	
Case number	7		9	14	$p = 0.60$

Abbreviations: FDG-PET = 18F-fluorodeoxyglucose positron emission tomography; PALN = para-aortic lymph node.

* A patient may have one or more distant metastatic lesions.

[†] Includes 3 patients who received incomplete irradiation dose (41.4–54 Gy).

[‡] Includes 2 patients who received incomplete irradiation dose.

(17). In the current randomized study, FDG-PET detected only 11% extrapelvic metastases, which included six PALNs and one omental node. The difference is possibly caused by the experience we gained from the pilot study and the modification of our MRI protocol. In the pilot study, two PALNs detected by PET were 1.1 cm and 1.3 cm, respectively, as measured on CT simulation scans, which should have been positive on MRI but were missed because of the relatively

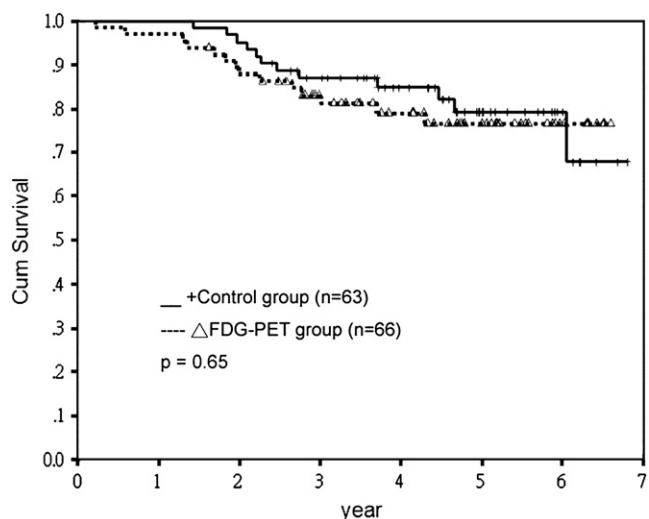


Fig. 2. Overall survival curves for 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) group ($n = 66$) vs. control group ($n = 63$).

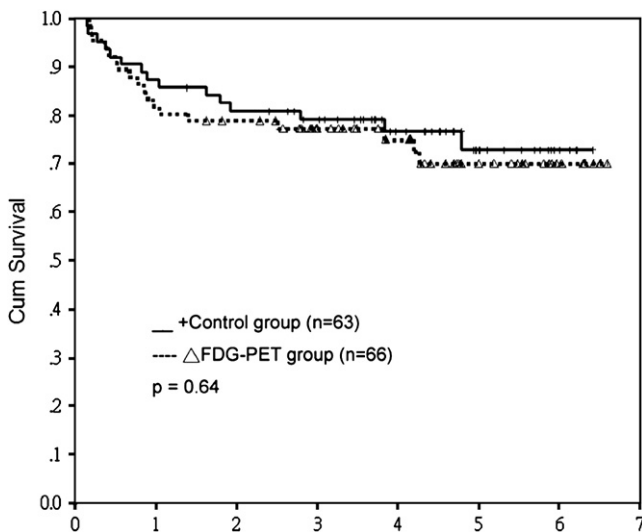


Fig. 3. Disease-free survival curves for 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) group ($n = 66$) vs. control group ($n = 63$).

large slice thickness. Therefore, in the present study, the slice interval of MRI was reduced to 5 mm for axial views of the para-aortic region. In addition, special care was taken to identify any questionable lymph nodes at this region. These changes improved the detection of PALN >1 cm in size, and 5 patients during this study period were excluded from the initial list after their MRI review at our combined conference. The improvement in MRI interpretation is further illustrated by the fact that sizes of PALNs identified in the current study were between 0.5 and 0.8 cm.

Several important findings were obtained in this study even after early termination. Four of the 7 patients with PET-detected extrapelvic metastasis remain alive and disease-free for more than 3 years (Table 2). This is in agreement with one other report that a relatively good outcome can be achieved by early detection of PALN metastasis with pre-

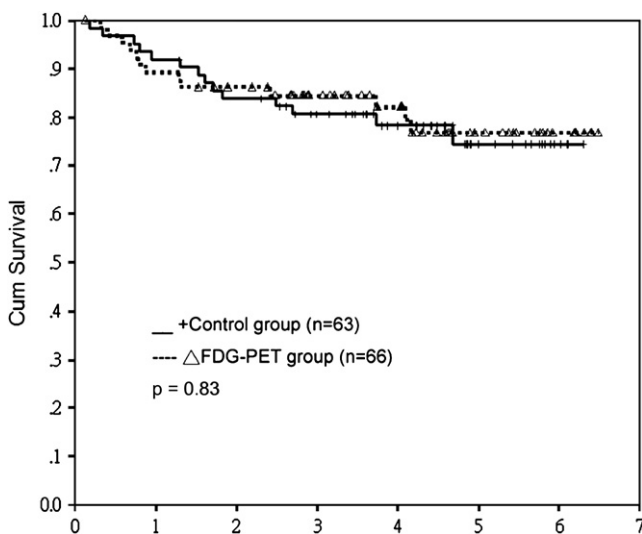


Fig. 4. Curves for interval of freedom from distant metastasis for 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) group ($n = 66$) vs. control group ($n = 63$).

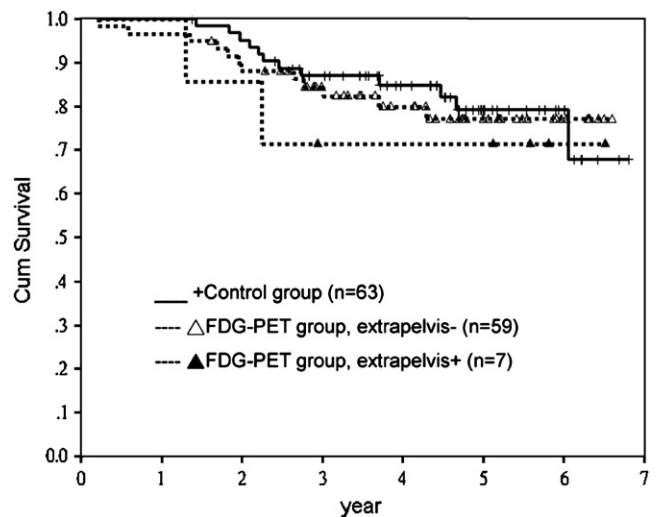


Fig. 5. Overall survival curves for three subgroups: control group ($n = 63$), 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) group without extrapelvic metastases ($n = 59$), and FDG-PET group with extrapelvic metastases ($n = 7$).

planning FDG-PET (31). For patients who received whole pelvic irradiation, only 7% (4/59) in the PET arm had a relapse at the para-aortic region, in contrast to 16% (10/63) in the control arm. If we counted the events of PALN involvement, either detected by PET before treatment or discovered as the initial relapse after treatment, there was an interesting similarity in the incidences: 15.2% (10/66) in the PET study group and 15.9% (10/63) in the control group. We also found that 18 patients with enlarged pelvic nodes on MRI but negative findings on FDG-PET all remained alive and disease-free. This is in agreement with the suggestion by 1Grisby *et al.* (32) that such patients have favorable outcomes and may be treated with radiotherapy alone to spare them from the toxicities of concurrent chemoradiotherapy.

One of the limitations in this study is the absence of pathologic validation of PET-detected PALNs. A surgical approach was avoided because our previous study had shown the detrimental effects of staging lymphadenectomy for advanced cervical cancer patients (33). Besides, most of the PET-detected PALNs could not be accessed safely by CT-guided biopsy. However, several studies with pathologic confirmation have already demonstrated that FDG-PET is superior to MRI in recognizing of metastatic lymph nodes (13, 34) and has a high specificity and positive predictive value in detecting PALN metastasis in cervical cancer (14, 35, 36). These earlier results have paved the way for FDG-PET to serve as a useful substitute to biopsy (or “metabolic biopsy”) and hence may help offset the shortcomings of this study.

Although FDG-PET has benefit in detecting and staging for cervical cancer, we are unaware of any prospective randomized study to validate its potentially positive effect on survival. Our study showed that some patients with PET-detected extrapelvic metastasis may achieve long-term disease-free survival with appropriate treatment. By contrast, patients without extrapelvic disease on PET image did not

have a better survival outcome than did those in the control group, and treatment in most of them failed because of distant metastasis. This result suggests that FDG-PET has a serious limitation in detecting small metastases.

In conclusion, pretreatment FDG-PET can improve the detection of extrapelvic metastasis, mainly PALN, and help

select patients for extended-field concurrent chemoradiation therapy. The addition of FDG-PET did not translate into a survival benefit, as we had expected, although the relatively low detection rate of extrapelvic lesions in this trial (11% vs. 26% in our pilot study) and the insufficient number of cases might be the culprits.

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