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Frequency and risk factors of thoracic metastases and optimisation of the use of cross-sectional chest imaging in follow-up patients with cervical cancer

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AIM: To optimise cross-sectional chest imaging usage by identifying frequency and risk factors associated with thoracic metastases in cervical cancer patients after initial definitive treatment.

MATERIALS AND METHODS: This study, conducted during 2004–2015, examined 361 consecutive patients with histopathologically proven cervical carcinoma with at least 1 year of follow-up. Electronic medical records and all available imaging modes were used to record and assess patient and tumour characteristics and timing of thoracic metastases. Associations with these characteristics and thoracic metastases were assessed using univariate and multivariable Cox proportional hazards modelling.

RESULTS: Of the 361 patients, 31 developed thoracic metastases. Multivariate regression results showed that adeno/adenosquamous carcinomas (hazard ratio [HR], 2.46; 95% confidence interval [CI], 1.06 to 5.72), other histology (HR, 5.61; 95% CI, 1.81 to 17.42), high International Federation of Gynaecology and Obstetrics (FIGO) stage (HR, 2.84; 95% CI, 1.09 to 7.37), and presence of initial intra-abdominal lymph node metastases (HR, 2.46; 95% CI, 1.02 to 5.90) were associated significantly and independently with thoracic metastases. The second analysis among the subgroup of surgical treatment identified intermediate–high risk classification of recurrence (HR, 5.12; 95% CI, 1.14 to 22.94), high FIGO stage (HR, 2.73; 95% CI, 1.05 to 7.13), and other histology (HR, 11.51; 95% CI, 3.66 to 36.19) as independent predictors of thoracic metastases. Two of the 361 and 2/313 patients with thoracic metastases who did not correspond to the conditions above were in the respective evaluation groups.

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CONCLUSION: Assessment of negative prognostic factors for thoracic metastases might contribute to reduced need for chest cross-sectional chest computed tomography examinations.

Introduction

Uterine cervical cancer, the third most commonly diagnosed cancer and the fourth leading cause of cancer death in women worldwide, especially affects young women.[1] Most women present with early-stage disease. They are cured with definitive treatments, such as surgery and concurrent chemoradiation therapy (CCRT), irrespective of high-risk recurrent factors.[2] Approximately 8–26% of patients develop recurrent disease after primary treatment. The most common site of recurrence is the pelvis.[3,4]

The lung is the most common site involved in distant metastases from cervical cancer, followed by the hilar lymph nodes and pleura, which are commonly detected using chest radiography or computed tomography (CT).[5,6] The prevalence of pulmonary metastasis was reported as 2.1–6.1% in earlier studies.[5,7–11] Some studies have demonstrated that lung metastases occur in 0.6% of patients with early-stage and in 2–2.7% of patients with advanced diseases[8,9]; however, several studies have demonstrated that pulmonary metastases occur in as much as 10% of cervical cancer patients and that they show poor prognosis affected by haematogenous spread.[7,12,13] Detecting recurrent disease and administering treatment as early as possible improves quality of life (QOL).[14] Although an appropriate follow-up strategy after treatment will be necessary for better prognosis and longer survival,[15,16] little high-quality evidence exists to support the appropriate use of cross-sectional chest imaging in follow-up patients other than for ovarian cancer.[17,18] Hoogendam *et al.* reported that routine chest radiography was of no value for detecting lung metastasis in cervical cancer patients with early-stage[5]; however, the radiation dosage associated with chest CT might also be important because of the radiation dose to breast tissues, especially in young patients.[19,20] Currently, cross-sectional chest imaging is widely performed in patients with cervical cancer. It has become necessary to optimise the follow-up imaging strategy of these patients to use the available resources effectively, considering clinical needs and related costs.

This study was conducted to identify the frequency of and risk factors associated with thoracic metastases in cervical cancer patients after initial definitive treatment to support optimisation of the use of cross-sectional chest imaging.

Materials and methods

The institutional review board approved this single-centre retrospective study. The requirement for written informed consent was waived.

Patients

The institutional electronic radiology database was searched to identify all patients with cervical cancer who underwent initial definitive treatment during November 2004 through December 2015 with at least 1 year of follow-up. The search revealed a total of 484 patients with cervical cancer. Of 484 patients, 29 patients were excluded because of follow-up <1 year. Patients without histopathological evidence of cervical cancer (n=1), without initial definitive treatment (n=36), with coexistent malignancy (n=32), and with initial thoracic metastases (n=25) were all excluded. In total, 361 patients were identified. Thirty-one patients (8.6%) with thoracic metastases from cervical cancer were included in the study (Fig 1).

The medical records were reviewed. Clinical data at the time of initial presentation were collected, which included age, smoking history, International Federation of Gynaecology and Obstetrics (FIGO) stage, primary tumour size, the presence of abdominal lymph-node (LN) metastasis, histological subtype, and treatment. The pathology reports of patients with surgical treatment were also reviewed manually and pathological findings, such as lymphovascular space invasion (LVSI), parametrial involvement, cervical stromal invasion, uterine endometrial invasion, vaginal invasion, ovarian metastases, status of resection margin, and risk classification of relapse were recorded. Risk classification, which was the survival of patients with early-stage cervical cancer after radical hysterectomy (RH) and pelvic lymphadenectomy, are associated with several

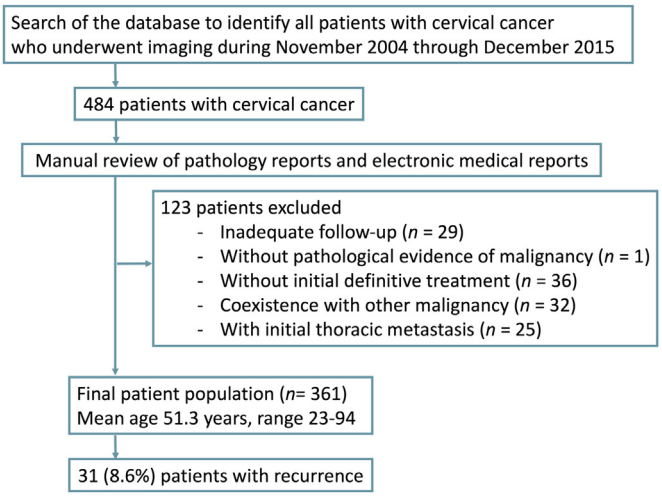

Figure 1 Flowchart of the selection process for the final cohort of 361 patients with cervical cancer.

Table 1
Physical, tumour, and treatment characteristics of 361 patients with cervical cancer.

Characteristic	All patients (n=361)	Thoracic metastasis development	
	(%)	No (n=330)	Yes (n=31)
Age (year)			
Mean±SD	51.3±14.5	50.7±14.5	56.1±14.4
Range 23–94			
Age			
≥60 year	108 (29.9)	94	14
<60 year	253 (70.1)	236	17
Size of the primary tumour (cm)			
Mean±SD	2.7±2.2	2.5±2.1	4.9±2.2
Range 0–15			
No. patients with unknown primary tumour size	22 (6.9)	20	2
Size			
≥4 cm	94 (26)	75	19
<4 cm	267 (74)	255	12
FIGO stage			
Stage IA	53 (14.7)	53	0
Stage IB	193 (53.5)	183	10
Stage IIA	15 (4.2)	14	1
Stage IIB	69 (19.1)	57	12
Stage IIIA	7 (1.9)	6	1
Stage IIIB	18 (5.3)	13	5
Stage IVA	3 (0.8)	3	0
Stage IVB	3 (0.8)	1	2
FIGO high stage			
≥Stage IIB	100 (27.7)	80	20
≤Stage IIA	261 (72.3)	250	11
Initial intra-abdominal LN metastasis			
Positive	91 (25.2)	73	18
Negative	270 (74.8)	257	13
PEN			
Positive	86 (23.8)	67	19
Negative	275 (76.2)	263	12
PAN			
Positive	15 (4.2)	9	6
Negative	346 (95.8)	321	25
Initial therapy			
Surgical treatment	313 (86.7)	290	23
CCRT	32 (8.9)	24	8
RT	16 (4.4)	16	0
Neoadjuvant chemotherapy (NAC)			
Done	77 (21.3)	63	14
None	284 (78.7)	267	17
Adjuvant chemotherapy			
Done	167 (46.2)	146	21
None	194 (53.8)	184	10
Histology			
Squamous cell carcinoma (SCC)	254 (70.4)	236	18
Adeno/adenosquamous carcinoma (ACA)	95 (26.3)	86	9
Others	12 (3.3)	8	4
Smoking			
Smoker	115 (31.9)	103	12
Never-smoker	246 (68.1)	227	19
Overall survival (months)			
Median	61.3	63.9	32.1
IQR	32.1–91.7	33.9–92.8	22.5–58.1
Range	14.2–152.5	14.2–152.5	14.8–140.7
Survival			
Alive	331 (91.7)	317	14
Dead	30 (8.3)	13	17
Thoracic metastasis-free interval (months)			
Median	59.4	63.2	19.6
IQR	30.2–89.6	34–93.7	9.6–32
Range	1.3–152.5	14.2–152.5	1.3–71.5
Thoracic metastasis			
Present	31 (8.6)		
Absent	330 (91.4)		
Disease-free survival (mo) (any site)			
Median	50.4	58.5	13.0
IQR	24–81.9	28.5–88.1	8.1–24.1
Range	1–150.7	1–150.7	1.3–71.5
Metastatic disease (any site)			
Present	67 (18.6)	36	31
Absent	294 (81.4)	294	0
Risk classification of relapse in surgical treatment group (n=313)			
Low	130 (41.5)	128	2
Intermediate	99 (31.6)	95	4
High	84 (26.9)	67	17

SD, standard deviation; FIGO, International Federation of Gynaecology and Obstetrics; LN, lymph node; CCRT, concurrent chemoradiotherapy; RT, radiotherapy; PEN, pelvic lymph node; PAN, para-aortic lymph node.

intermediate-risk and high-risk pathological factors. These factors are defined as risk classification[21] (Electronic Supplementary Material Table S1).

The routine surveillance protocol is a whole-body CT examination in every 6 months in first 2 years and once a year after 4 years. Whole-body CT, including chest CT imaging, is examined in all patients with definitive treatment, even though they are asymptomatic.

Terminology

Metastases in anatomical structures between the clavicles and the diaphragm, including pulmonary, nodal, pleural, thoracic spinal metastases, and thoracic soft-tissue are considered “thoracic” metastases. Metastases involving the structures from the dome of the diaphragm inferiorly, including metastases within the abdominopelvic structures, abdominal wall, and lumbar spine, are designated as “abdominal” metastases.

The thoracic metastasis-free interval (TMFI) was defined as the time from initial definitive treatment (RH, definitive conisation, CCRT, or radiotherapy [RT]) to the diagnosis of thoracic metastases from cervical cancer. Follow-up duration was calculated from the initial staging date to the last visit day. In addition, data at the time of thoracic metastases diagnosis were collected: the spread pattern, the presence of extra-thoracic metastases, visibility on abdominal images, onset time, and treatment. “Visibility on abdominal images” indicates the metastases covered by routine abdominal CT or magnetic resonance imaging (MRI), from the dome of the diaphragm inferiorly.[18,22] Finally, data related to clinical outcome were obtained.

Image analysis

One board-certified radiologist (K.N.) with 9 years of experience in gynaecological radiology reviewed all available

Table 2
Spread and characteristics of thoracic metastases of 31 patients.

Characteristic	No. (%)
Thoracic metastatic sites	
Lung	24 (77.4)
Inferior lobe	15 (48.4)
Non-inferior lobe	9 (29)
Lymph node (LN)	12 (38.7)
Mediastinal LN	5 (16.1)
Axillary LN	5 (16.1)
SCLN	6 (19.4)
Bone/soft tissue	0 (0)
Prior abdominal recurrence	
Present	11 (35.5)
Absent	20 (64.5)
Histology	
SCC	18 (56.3)
ACA	9 (31.3)
Small cell carcinoma	3 (9.4)
Carcinosarcoma	1 (3.1)
Disease identifiable on abdominal images	
Yes	10 (32.3)
No	21 (67.7)
Initial definitive treatment ≤2 year	18 (58.1)
Initial definitive treatment ≤3 year	25 (80.6)

SCLN, supraclavicular lymph node; SCC, squamous cell carcinoma; ACA, adeno/adenosquamous carcinoma.

images (CT, MRI, and combined 2-[^{18}F]-fluoro-2-deoxy-D-glucose [FDG] positron-emission tomography (PET)/computed tomography (CT) examinations performed for any indication following the initial diagnosis) and the associated radiology reports, along with pathology reports and clinical records to document metastatic spread.

For initial imaging evaluation, the primary tumour size was determined by reviewing histopathological reports in surgical treatment groups without neoadjuvant chemotherapy (NAC). In other patients who underwent NAC or CCRT/RT, we measured the maximum longitudinal length on MRI. Regarding the follow-up of patients after definitive treatment, local recurrence was detected by gynaecological examination and was determined by biopsy. For detecting regional and distant metastatic lesions, most patients undergo CT of the chest, abdomen, and pelvis. Some of them undergo MRI or FDG-PET/CT. Pulmonary metastases or pleural metastases were determined by biopsy or imaging such as CT or FDG-PET/CT (e.g., emergence of new lesions, unequivocal progression at follow-up). Pleural effusion was regarded as metastatic only if accompanied by positive cytological findings. Lymph nodes were considered involved if they measured >1 cm in the short axis, showed further changes in size in follow-up images, or were confirmed histopathologically. Imaging-related decisions were made on a case-by-case basis.

Statistical analysis

The proportion of patients with thoracic metastases was recorded. Effects of the following patient and primary tumour characteristics were examined in all 361 patients and surgical treatment group (n=313) using univariate analysis and a multivariable Cox proportional hazards models. The primary outcome measure was the presence of thoracic metastases. In the first Cox analysis of 361 patients, six variables were used for TMFI. Every variable other than histological variant had a binary classification: (a) age (≥60 versus <60 year); (b) initial high stage FIGO score (≥IIB versus <IIB); (c) presence of initial intra-abdominal LN metastases, such as pelvic lymph node (PEN) or para-aortic lymph node (PAN) (no versus yes); (d) type of treatment (surgical treatment versus CCRT/RT); (e) large initial primary tumour size (≥4 versus <4 cm); and (f) histology (squamous cell carcinoma [SCC], adeno/adenosquamous carcinomas [ACA], others). All variables were included in the multivariate analyses. The Kaplan–Meier curves were depicted to confirm the effects on TMFI of the factors selected from the first analysis. Secondly, among 313 patients with surgical treatments, clinical parameters at the initial definitive operation were evaluated as a predictor of thoracic metastases using Cox's proportional hazards model. In addition to prior variables as described for the first analysis, eight variables with binary classifications were included in this analysis: (a) parametrial involvement (present versus absent), (b) LVSI (present versus absent), (c) intermediate or deep cervical stromal invasion (present versus absent), (d) ovarian metastases (present versus absent), (e) uterine endometrial involvement (present versus absent), (f) vaginal involvement (present versus absent), (g) status of resection margin (positive versus negative), and (h) risk classification of relapse (intermediate or above versus low). To make the model parsimonious, only the

Table 3
Results of univariate and multivariate Cox proportional hazard regression analyses for the risk of thoracic metastasis with various clinicopathological factors in all 361 patients.

	p-Value with the univariate model	Hazard ratio	p-Value with the multivariate model	Hazard ratio
Age (≥60 years)	0.0470[a]	2.05 (1.01–4.14)	0.5773	1.26 (0.57–2.79)
FIGO high stage (≥IIB)	<0.0001[a]	5.43 (2.61–11.31)	0.0330[a]	2.84 (1.09–7.37)
Initial PEN/PAN metastases present	<0.0001[a]	5.32 (2.59–10.92)	0.0450[a]	2.46 (1.02–5.90)
Histology (ACA)	0.3590	1.46 (0.66–3.23)	0.0372[a]	2.46 (1.06–5.72)
Histology (Others)	0.0022[a]	5.42 (1.84–15.95)	0.0030[a]	5.61 (1.81–17.42)
Surgical treatment	0.0018[a]	0.38 (0.17–0.84)	0.9347	1.04 (0.41–2.65)
Primary tumour size (≥4 cm)	<0.0001[a]	5.07 (2.47–10.41)	0.0707	2.24 (0.94–5.33)

[a] p<0.05.
Numbers in parentheses are 95% confidence intervals.
PEN/PAN, pelvic lymph node or para-aortic lymph node; ACA, adeno/adenosquamous carcinoma.

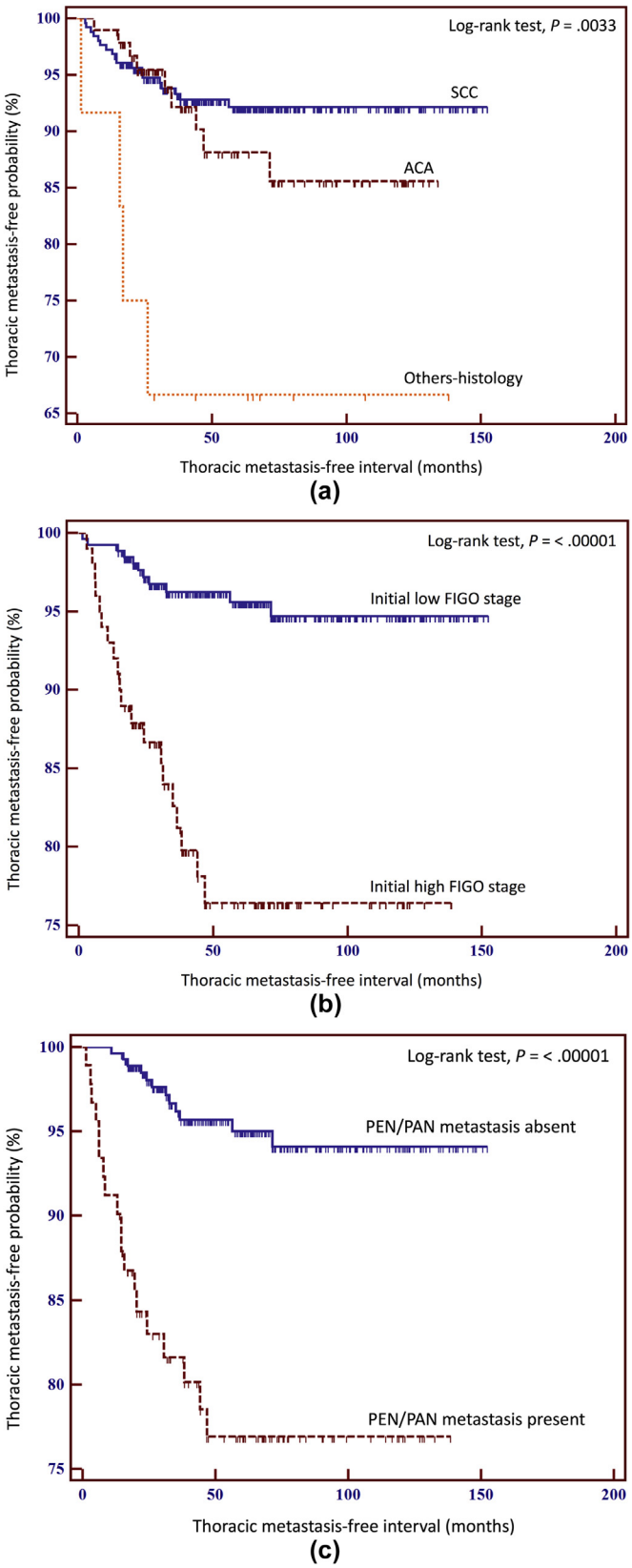

Figure 2 (a) Kaplan–Meier curves show differences in the thoracic metastatic free survival of SCC, ACA and other histology patients who developed thoracic metastases and those who did not (median, 62 months [IQR, 36–90] versus 41 months [IQR, 25 to 91] versus 54 months [IQR, 24–71], respectively; log-rank test, p=0.00033). (b) Kaplan–Meier curves show differences in the thoracic metastatic free survival of initial low FIGO stage (≤IIA) and initial high FIGO stage (≥IIB) which developed thoracic metastases and those which did not (median, 62 months [IQR, 33–96] versus 42 months [IQR, 23 to 74], respectively; log-rank test, p<0.00001). (c) Kaplan–Meier curves show the differences in the thoracic metastatic-free survival of patients with PEN/PAN metastasis and patients without PEN/PAN metastasis who developed thoracic metastases and those who did not (median, 60 months [IQR, 33–91] versus 47 months [IQR, 21 to 77], respectively; log-rank test, p<0.00001).

statistically significant variables in the univariate analyses were included in the multivariate analysis. Finally, the number of patients with thoracic metastases who had no accompanying negative prognostic factors were evaluated to optimise the use of cross-sectional chest imaging in each analytical group.

All p-values <0.05 were inferred as significant. Statistical analyses were conducted using software (Medcalc ver. 12.7.8.0; MedCalc Software, Ostend, Belgium).

Results

Patient characteristics and outcome

Clinicopathological characteristics of the 361 patients are shown in Table 1. The mean age was 51.3±14.5. The median follow-up period was 61 months (IQR, 32–90 months). In all, 246 patients (68.1%) had FIGO (2011) stage I disease, 84 (23.2%) had stage II disease, 25 (6.9%) had stage III disease, and six (1.7%) had stage IV disease. In addition, 254 patients (70.4%) had SCC, 95 patients (26.3%) had ACA, and 12 patients (3.3%) were other histology (carcinosarcoma, small cell carcinoma, etc.). Surgical treatments of primary cervical tumours were administered for 313 patients (86.7%). CCRT was administered to 32 (8.9%); 16 (4.4%) were given only RT.

According to the risk classification of relapse among 313 patients with surgical treatments, 130 patients (41.5%) were classified as low risk, 99 (31.6%) as intermediate risk, and 84 (26.9%) as high risk.

Metastatic diseases

Clinical characteristics of the thoracic metastases are presented in Table 2. Thirty-one patients (8.6%) developed thoracic metastases. Lung metastases occurred in 24 (77.4%) patients; 15 (48.4%) metastases were distributed in the inferior lobe of the lung. Results show that LN metastases occurred in 12 (38.7%). No bone metastasis, soft-tissue metastasis, pleural metastasis, or pleural effusion was identified. Ten (32.3%) cases were visible on abdominal images. Eighteen (58.1%) cases were detected within 2 years after initial treatment. Only one (3.2%) case developed thoracic metastasis >5 years after initial treatment. Eleven (35.5%) cases were followed by previous abdominal recurrence. Of the 23 thoracic recurrences among the surgical treatment group, 17 (73.9%) were high risk; two (8.7%) were of the low risk group. One hundred and fifteen patients (31.9%) were smokers and 12/115 patients had thoracic

Table 4
Results of univariate and multivariate Cox proportional hazard regression analyses for the risk of thoracic metastasis in 313 patients with surgical treatment.

	Hazard ratio	*p*-Value with the univariate model	Hazard ratio	*p*-Value with the multivariate model
Age (≥60 yr)	2.66 (1.17–6.04)	0.0202[a]	1.91 (0.81–4.51)	0.1403
fFIGO high stage (≥IIB)	4.73 (2.10–10.69)	0.0002[a]	2.73 (1.05–7.13)	0.0409[a]
Initial PEN/PAN metastases present	3.54 (1.57–8.00)	0.0024[a]		
Histology (ACA)	1.55 (0.61–3.94)	0.3547		
Histology (Others)	8.05 (2.55–24.33)	0.0004[a]	11.51 (3.66–36.19)	<0.0001[a]
Size (≥4.0 cm)	3.60 (1.59–8.12)	0.0022[a]		
Parametrial involvement	6.23 (2.74–14.14)	< 0.0001[a]		
Lymphovascular space invasion (LVSI)	5.82 (1.99–17.01)	0.0014[a]		
Cervical stromal invasion	6.61 (2.26–19.33)	0.0006[a]		
Ovarian metastasis	2.08 (0.28–15.38)	0.4762		
Uterine endometrial invasion	4.18 (1.66–10.57)	0.0026[a]	1.79 (0.62–5.18)	0.2837
Vaginal involvement present	1.34 (0.46–3.93)	0.5914		
Positive margins	3.71 (1.37–10.01)	0.0100[a]		
Risk classification (≥intermediate)	7.66 (1.81–32.41)	0.0060[a]	5.12 (1.14–22.94)	0.0336[a]

[a] $p<0.05$.
Numbers in parentheses are 95% confidence intervals.
PEN/PAN, pelvic lymph node or para-aortic lymph node; ACA, adeno/adenosquamous carcinoma.

metastasis that was 38.7% of thoracic metastasis patients. All of the 31 patients with thoracic metastasis were asymptomatic.

The treatments for thoracic metastasis were as follows: surgical resection (n=5), stereotactic body radiation therapy (SBRT; n=1), chemotherapy (n=11), and CCRT (n=7). All the cases with surgical excisions resulted in complete remission. Two patients with chemotherapy and two patients with CCRT were also considered to be in complete remission.

Associations of thoracic metastases

The first Cox analysis revealed six variables other than ACA histology significantly associated with increased risk of thoracic metastases in the univariate analysis (Table 3). Multivariate analysis revealed that ACA histology (hazard ratio [HR], 2.46; 95% confidence interval [CI], 1.06 to 5.72), other histology (HR, 5.61; 95% CI, 1.81 to 17.42), high FIGO stage (HR, 2.84; 95% CI, 1.09 to 7.37), and presence of initial PEN/PAN metastases (HR, 2.46; 95% CI, 1.02 to 5.90) were associated independently with shorter TMFI. Kaplan–Meier curves of these factors are presented in Fig 2.

Secondly, in surgical treatment patients, univariate analysis showed that age, high FIGO stage, initial primary tumour size, presence of initial intra-abdominal LN metastases, parametrial involvement, LVSI, cervical stromal invasion, uterine endometrial involvement, and risk classification of relapse were related to shorter TMFI (Table 4). Multivariate analysis, size, presence of initial intra-abdominal LN metastases, parametrial involvement, LVSI, cervical stromal invasion, and status of the resection margin were eliminated to avoid multicollinearity with risk classification of relapse. Although intermediate–high risk classification of recurrence (HR, 5.12; 95% CI, 1.14 to 22.94), high FIGO stage (HR, 2.73; 95% CI, 1.05 to 7.13) and other histology (HR, 11.51; 95% CI, 3.66 to 36.19) were independent prognostic factors drawn from the multivariate analysis.

Of all 361 patients, although 148 patients (41%) patients had no risk factors according to the first Cox analysis, two cases among them developed thoracic metastases. Both cases underwent surgical treatment. Their risk classification of recurrence was more than intermediate (Fig 3). Details show that one case had intermediate-risk classification disease and SCC histology with a small cell neuroendocrine component. The other case had high-risk classification disease because of parametrial involvement. Both had prior intra-abdominal recurrence and >2 cm sized primary tumour. No CCRT patient without some negative risk factor was found to have thoracic metastasis. The second analysis among 313 patients with surgical treatments revealed that 120 patients (38.3%) had no risk factor, of whom two

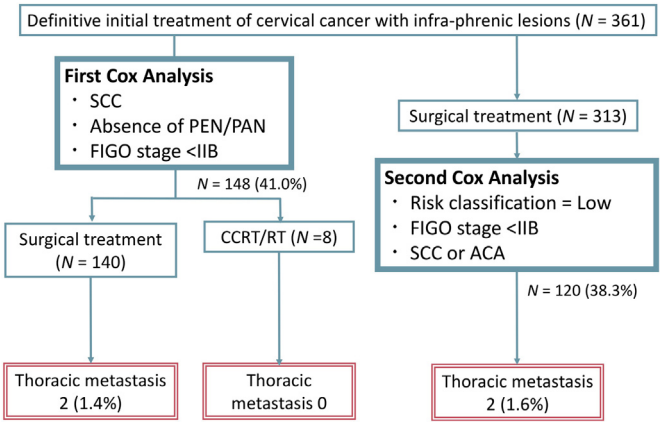

Figure 3 Summary of the first and the second Cox analysis of 361 patients with cervical cancer. Of all 361 patients, although 148 patients (41%) patients had no risk factors according to the first Cox analysis, two patients developed thoracic metastases. Both patients underwent surgical treatment and their risk classification of recurrence was more than intermediate. The second analysis among 313 patients with surgical treatments revealed that 120 patients (38.3%) had no risk factors, of whom two patients developed thoracic metastases. Both of them had ACA histology. One of them had prior intra-abdominal recurrence. In other cases, the thoracic lesion was identifiable on abdominal CT images.

patients developed thoracic metastases. Both of them had ACA histology. One had prior intra-abdominal recurrence. In other cases, the thoracic lesion was identifiable on abdominal CT images (Fig 3).

Discussion

This study revealed that most thoracic metastases develop within a few years after initial definitive treatment. The risk factors were ACA and other histology, high FIGO stage shown in pre-treatment images, and presence of initial intra-abdominal LN metastasis (PEN or PAN). In the second analysis of the surgical treatment group, intermediate-risk or high-risk classification disease and high FIGO stage were the negative prognostic factors of thoracic metastasis. In this study, not all cases with thoracic metastases were identified by the risk factors suggested by the analyses for TMFI, but most of them were, except for 2/31 of all the included patients and 2/23 patients with surgical treatment.

This report is the first to describe a study examining the frequency of "thoracic" metastases including pulmonary, nodal, pleural, thoracic spinal metastases, and thoracic soft tissue, although the risk factors identified are already well-known parameters for recurrence in general. To help optimise the necessity of cross-sectional chest imaging, the present study was undertaken to investigate the frequency and negative prognostic factors of "thoracic" metastases. Several studies have already been conducted to evaluate the risk factors of "pulmonary" metastases, but the relation of pulmonary metastases with initial tumour condition remains under discussion.[6,7] Imachi *et al.*[7] reported that the incidence of pulmonary metastases is closely associated with the initial stage and the size of primary cancer; however, Barter *et al.*[10] demonstrated that they are not associated with the initial stage. At present, no agreement exists on the follow-up protocols for cross-sectional chest imaging for cervical cancer patients,[17] even for the necessity or frequency of chest CT. The present results (Fig 3) also showed that the patients satisfying some conditions, such as the patients with histology of SCC, low-risk classification, and FIGO stage of <IIB, may omit the chest CT for follow-up in patients with surgical treatment; however, they were not statistically verified. Although the reported incidence of pulmonary metastases from cervical cancer is low, cross-sectional chest imaging is frequently used clinically. One reason for its frequent use is that thoracic metastases sometimes develop without prior intra-abdominal recurrent lesion, as shown in the present results that 20/31 (64.5%) patients with thoracic metastases did not accompany abdominal metastases (Table 2) and that those sudden metastases to cervicothoracic lesion make frequent screening for thoracic lesion by CT. Cervical cancer patients are younger than patients with other common cancers and likely to undergo longer follow-up examinations, including CT with radiation exposure. Therefore, the frequent use of cross-sectional chest imaging in the follow-up patients is not always effective for a certain group of people, although it is difficult to justify elimination of CT examinations entirely.

Results revealed a close relation of initial tumour condition, including non-SCC histology, high FIGO stage, and presence of abdominal lymph-node swelling, with shorter thoracic metastasis-free survival. Several reports have described a poorer prognosis for ACA because of frequent lymph node involvement, distant organ metastasis, or lower sensitivity to RT compared to SCC. Martínez-Jiménez *et al.* reported that pulmonary metastases occur more commonly and at an earlier stage in patients with ACA than in those with cervical SCC. The present study also proved that non-SCC pathology such as ACA and other histology was a negative prognostic factor only in the first Cox analysis, although no significant difference was found between SCC and ACA groups among surgical treatment patients. Therefore, the recommendation for patients with non-SCC might be to receive more intensive follow-up than SCC patients. In the present series, three small cell carcinomas and one carcinosarcoma developed thoracic metastases. Many reports have described a decrease in survival of small cell carcinoma compared with SCC and ACA, even with no node-negative or early-stage patients because of frequent LVSI or widespread haematogenous metastasis.[23,24] The results of the present study accord well with those of earlier reports. The present study did not evaluate the association NAC or adjuvant chemotherapy with thoracic metastases. For cervical cancer patients, especially with locally advanced disease, NAC followed by surgery is reportedly effective.[25] The use of NAC is determined depending on the tumour size or pelvic LN metastasis. The use of adjuvant therapy also has a strong association with risk classification of relapse. Therefore, to avoid multicollinearity with FIGO stage and risk classification of relapse, the presence of NAC and adjuvant therapy was not evaluated.

The present study has several limitations. The most important limitation derives from its retrospective design and observational study conducted at a single institution. Second, the number of patients with thoracic metastases included in the study was too small to support statistically conclusive results. Third, in Japan, some patients with stage IIB or more undergo surgical treatment such as radical hysterectomy with NAC or pelvic exenteration, but such patients in most other countries undergo CCRT. Fourth, this study divided patients into ≥4 cm and <4 cm tumour size groups, which divides FIGO IB1 and IB2. Recently, a <2 cm size criterion has been used widely as the standard for fertility-preserving procedures. Therefore, another mode of analysis might use the 2 cm size criterion. Finally, as described previously, the significance of NAC on thoracic metastases was unknown because some cases with thoracic metastases were not subjected to histopathological examination. Future studies should evaluate the prognostic factors more precisely through analyses of more data or through the use of prospective methods.

This study revealed that thoracic metastases develop early in the course of cervical cancer. Results clarified the negative prognostic factors of thoracic metastases for both all cervical cancer patients and the surgical treatment subgroup. According to these results, the assessment of negative prognostic factors for thoracic metastases might contribute to the suggestion of less frequent chest cross-sectional chest CT examinations.

Conflict of Interest

The authors declare that they have no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crad.2018.11.014.

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