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G. 知的財産権の出願・登録状況（予定を含む）

１．特許取得

なし

２．実用新案登録

なし

３．その他

なし

研究成果の刊行に関する一覧表

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CLINICAL INVESTIGATION **Cervix**

NONOPERATIVE ASSESSMENT OF NODAL STATUS FOR LOCALLY ADVANCED CERVICAL SQUAMOUS CELL CARCINOMA TREATED BY RADIOTHERAPY WITH REGARD TO PATTERNS OF TREATMENT FAILURE

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Purpose: Lymph node metastasis is a major prognostic factor in the treatment of cervical cancer, but its nonsurgical assessment is not necessarily accurate, particularly in small nodes. We evaluated whether node-negative status could be accurately assessed using a low cutoff measure.

Methods and Materials: The subjects were 84 patients with Stage IIB–IVA cervical squamous cell carcinoma treated by definitive radiotherapy. Nodal status was assessed by CT as negative (<5 mm), possibly positive (5–10 mm), or probably positive (>10 mm). Cause-specific survival and the disease-free rate, including the pelvic recurrence-free and distant metastasis-free rates, were estimated.

Results: The cause-specific survival, disease-free rate, and pelvic recurrence-free rate at 5 years were significantly higher for the 32 patients with node-negative disease (83.5%, 86.1%, and 86.1%) and the 17 patients with possibly node-positive disease (59.2%, 93.8%, and 93.8%) than for the 35 patients with probably node-positive disease (32.6%, 22.0%, and 46.8%), respectively. No significant difference was found between negative and possibly node-positive status. In contrast, the distant metastasis-free rate differed significantly among node-negative (96.4%), possibly node-positive (59.3%), and probably node-positive (35.1%) status.

Conclusion: Node-negative status assessed using a strict cutoff measure may be useful as a strong predictor of cervical cancer being confined to the pelvis. © 2003 Elsevier Science Inc.

Chemoradiotherapy, Standard treatment, Para-aortic lymph node, Tumor bulk.

INTRODUCTION

Lymph node metastasis and tumor bulk are major prognostic factors, independent of clinical stage, in the treatment of cervical cancer (1–8). The U.S. National Cancer Institute currently recommends using radiotherapy (RT) plus chemotherapy as the sole standard treatment instead of traditional RT alone to improve survival of patients with locally advanced stage disease (9). This recommendation is based on large-scale randomized clinical studies that showed concurrent use of RT with cisplatin-containing chemotherapy agents improves survival as a whole by reducing local recurrence and distant metastasis (10–12). Locally advanced disease, however, cannot necessarily be judged by these prognostic factors. A favorable subset of diseases for which these factors do not apply is included among so-called advanced disease. In fact, a substantial proportion of patients with locally advanced disease have been cured by RT alone.

Tumor bulk is now readily assessed nonoperatively by MRI even more accurately than by manual pelvic examination, but no imaging modality provides accurate assessment of nodal status because no imaging modality is able to depict small metastatic foci directly (13). Lymph nodes <10 mm (conventional cutoff measure) on images are generally regarded as nonmetastatic (14). These small nodes, however, can harbor micrometastasis (15), resulting in a false-negative assessment. Therefore, surgical nodal staging may be justified (15, 17), and the new functional positron emission tomography (PET) with fluoro-deoxy-glucose (FDG) may be promising for directly depicting metastatic foci (18, 19). We incorporated two cutoff measures, 5 and 10 mm, to attempt to differentiate nonmetastatic nodes from metastatic nodes accurately. We evaluated this method of nodal status determination against patterns of treatment failure in definitive RT for patients with locally advanced cervical squamous cell carcinoma.

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METHODS AND MATERIALS

Patients

The study subjects were 84 individuals, selected from among 117 consecutive patients with histologically proven cervical squamous cell carcinoma treated primarily by RT with or without chemotherapy between June 1991 and December 1999. The inclusion criteria were International Federation of Gynecology and Obstetrics clinical Stage IIB-IVA disease (20), definitive RT consisting of external and intracavitary RT, and pretreatment contrast-enhanced CT study of the pelvis and abdomen. CT, rather than MRI, was used for nodal assessment, because the CT studies routinely covered both pelvic nodes and para-aortic nodes (PANs). The exclusion criteria were discontinuation of RT and follow-up of <1 year. Patient age ranged from 32 to 91 years (median 67); 31 patients (39.6%) were ≥70 years. The clinical stage was IIB in 20, IIIA in 5, IIIB in 40, and IVA in 19.

Treatment

External beam RT was performed by 10-MV X-rays through AP opposed whole pelvic portals, with a fraction size of 1.8 or 2.0 Gy at 5 fractions weekly to a total dose of 50.4 or 50.0 Gy. A midline block was placed after 19.8–50.0 Gy in accordance with the start of intracavitary RT. Boost RT was given at total doses ≤64.0 Gy to 28 patients with persistent parametrial induration or pretreatment lymphadenopathy (>10 mm). Para-aortic RT was feasible for 13 patients with positive PANs and was given through AP opposed portals at doses ranging from 40.0 to 50.4 Gy concurrent with, or after, pelvic RT. Intracavitary RT was performed with a high-dose-rate remote afterloading system with ^{60}Co sources before September 1993 and with an ^{192}Ir source thereafter. The prescribed dose to reference point A was 6.0 Gy per insertion, and 1–6 weekly insertions were performed according to tumor size and central dose delivered by external beam RT.

Twenty patients (23.8%) underwent neoadjuvant chemotherapy before RT. Chemotherapy was indicated for patients with a bulky tumor (approximately ≥6 cm) or positive PANs. Chemotherapy was given electively by intra-arterial administration of cisplatin-containing agents (n = 3) before 1996. After 1996, chemotherapy was given when considered feasible using a consistent regimen of i.v. platinum analog Nedaplatin (80 mg/m^2, Day 1), ifosfamide (1000 mg/m^2, Days 1–5), and peplomycin (5 mg, Days 1–6), administered every 4 weeks for two to four cycles (n = 11). The remaining 6 patients, treated after 1997, underwent two to three cycles of Nedaplatin-based intra-arterial chemotherapy at a referring hospital.

Nodal status determination

Pretreatment CT was performed with oral contrast material and i.v. contrast enhancement at a slice thickness of 3 mm and interval of 7 mm. Nodal status was assessed before treatment by diagnostic radiologists and was not reassessed for this study. Lymph nodes <5 mm were considered negative, nodes 5–10 mm were considered possibly positive, and those >10 mm were considered probably positive. Positive nodal status was also subclassified by location: pelvis-only positive and PAN positive.

Statistical analysis

Survival and patterns of treatment failure were determined in relation to clinical stage and nodal status. Both overall survival (OS) and cause-specific survival (CSS) were estimated. In the estimation of OS, death was counted as an event, and survival was censored at the time of the last follow-up visit. In the estimation of CSS, death caused specifically by the disease was counted as an event, and death from other causes and survival were censored. Recurrent disease that appeared initially in the pelvis or vagina was defined as pelvic recurrence; disease that developed outside the pelvis was defined as distant metastasis. Persistent local disease was regarded as pelvic recurrence and counted from the day when the decision for additional treatment was made. The patterns of failure were analyzed in terms of the disease-free interval, and expressed as the disease-free rate (DFR). The DFR was further computed as the pelvic recurrence-free rate (PFR) and the distant metastasis-free rate (MFR). In the estimation of these rates, the occurrence of pelvic recurrence or distant metastasis was counted as an event, and death from other causes and survival without evidence of disease were censored. In the estimation of the PFR and MFR, however, pelvic recurrence or distant metastasis that occurred after the initial failure was not counted as an event. Survival and these rates were estimated by the Kaplan-Meier method and analyzed statistically by the log–rank test. The time to events was measured from the start of RT or chemotherapy. StatView, version 5.0 (SAS Institute, Cary, NC) was used for all statistical analyses. p <0.05 was considered statistically significant.

RESULTS

Nodal status

Pelvic nodal status was negative for 32 patients (39.1%), possibly positive for 18 patients (21.4%), and probably positive for 34 patients (40.5%). The relations among clinical stage, nodal status, and use of chemotherapy are shown in Table 1. Of the 52 patients given a node-positive status (possibly positive plus probably positive), 37 (71.2%) were pelvis-only positive, and 15 (28.8%) were PAN positive. The node-positive status was found significantly less frequently in cases of Stage IIB disease (40.0%) than in cases of Stage III disease (68.9%). The frequency of chemotherapy treatment did not differ significantly between stage (p = 0.5701, chi-square test) or nodal status (p = 0.8942).

Survival

At the time of the last follow-up in December 2001, 30 patients (35.7%) had died of the disease, 10 (11.9%) had

Table 1. Nodal status according to clinical stage and use of chemotherapy

		Pelvic nodal status				
		Positive (PAN)				
	Use of chemotherapy	Probably	Possibly	Subtotal	Negative	p*
Total (n = 84)	20 (23.8%)	35 (14)	17 (1)	52 (15)	32	
FIGO stage						
IIB (n = 20)	3 (15.0%)	6 (1)	2 (1)	8 (2)	12	0.0751 vs. IVA
III (n = 45)†	12 (26.7%)	20 (9)	11 (0)	31 (9)	14	0.0282 vs. IIB
IVA (n = 19)	5 (26.3%)	9 (4)	4 (0)	13 (4)	6	0.9706 vs. III
Use of chemotherapy	—	9 (25.7%)	4 (23.5%)	13 (25.0%)	7 (21.9%)	

Abbreviations: PAN = para-aortic node; Negative = node negative (node size <5 mm); Probably = probably node-positive (node size >10 mm); Possibly = possibly node positive (node size 5–10 mm); FIGO = International Federation of Gynecology and Obstetrics.
Numbers indicate the patient number.
Numbers in parentheses indicate the number of patients presenting positive PAN status.
Percentages indicate the proportion of patients undergoing chemotherapy in each group.
* Calculated by the chi-square test; P value between positive and negative groups.
† Stage III disease included 5 stage IIIA and 40 Stage IIIB cases.

died of intercurrent disease or natural causes (old age), 5 (6.0%) were alive with the disease, and the remaining 39 (46.4%) were alive with no evidence of the disease. The follow-up period for the 44 surviving patients ranged from 12.3 to 107.9 months (median 47.3); 18 of these 44 patients were lost to follow-up after 12.3–92.8 months (median 52.5). The 5-year OS rate for all patients was 50.0%, and the 5-year CSS rate was 58.2%. OS and CSS are shown according to clinical stage and nodal status in Table 2. Both OS and CSS (Fig. 1) decreased with increases in clinical stage, but the differences were not statistically significant. In contrast, both OS and CSS were significantly higher for those with node-negative disease than for those with node-positive disease. Moreover, the differences in OS and CSS (Fig. 2) between those with node-negative and probably positive disease and between those with possibly positive and probably positive disease were statistically significant. The differences in CSS were also significant among those with node-negative, pelvis-only positive, and PAN-positive disease.

Patterns of initial failure

Treatment failure was identified in 39 patients by cytology, diagnostic imaging, or elevation of serum tumor marker levels in addition to physical and pelvic examinations. The site of initial failure was the pelvis in 11 patients (28.2%), distant in 23 patients (60.0%), and a combination in 5 patients (12.8%). Thus, pelvic failure occurred in 16 patients (19.0%) and distant failure in 28 (33.3%). The sites of initial failure are shown according to clinical stage and nodal status in Table 3.

The DFR, PFR, and MFR are shown according to clinical stage and nodal status in Table 4. The DFR and PFR were significantly higher for those with Stage IIB disease than for

Table 2. Overall survival and cause-specific survival according to clinical stage and nodal status

	Overall survival		Cause-specific survival	
	5-yr rate (%)	p*	5-yr rate (%)	p*
FIGO stage				
IIB (n = 20)	60.3	0.6119 vs. III	69.3	0.4579 vs. III
III (n = 45)	54.3	0.1874 vs. IVA	61.6	0.4222 vs. IVA
IVA (n = 19)	21.3	0.1668 vs. IIB	25.7	0.2068 vs. IIB
Nodal status				
Positive (n = 52)	37.1	0.0090 vs. negative	41.8	0.0012 vs. negative
Probably (n = 35)	27.4	0.0005 vs. negative	32.6	<0.0001 vs. negative
Possibly (n = 17)	55.7	0.0264 vs. probably	59.2	0.0292 vs. probably
PAN (n = 15)	17.6	0.0001 vs. negative	19.6	<0.0001 vs. negative
Pelvis only (n = 37)	42.6	0.0306 vs. PAN	48.0	0.0001 vs. PAN
Negative (n = 32)	70.0	0.6686 vs. possibly 0.0677 vs. pelvis only	83.5	0.2400 vs. possibly 0.0120 vs. pelvis only
Total (n = 84)	50.0		58.2	

Abbreviations as in Table 1.
* Calculated by log-rank test.

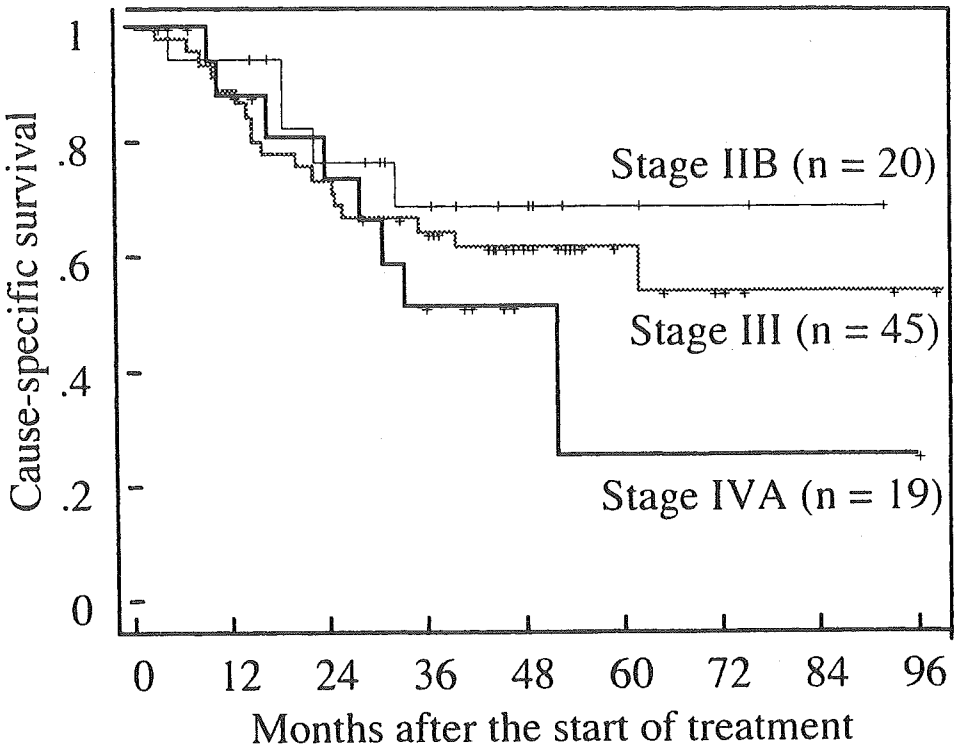

Fig. 1. CSS based on initial treatment failure according to clinical stage.

those with either Stage III or Stage IVA disease, but the MFR did not differ among the three stages (Fig. 3). In contrast, the DFR and MFR were significantly higher for those with node-negative disease compared with those with node-positive disease; the PFR did not differ significantly between node-negative and node-positive disease. The DFR

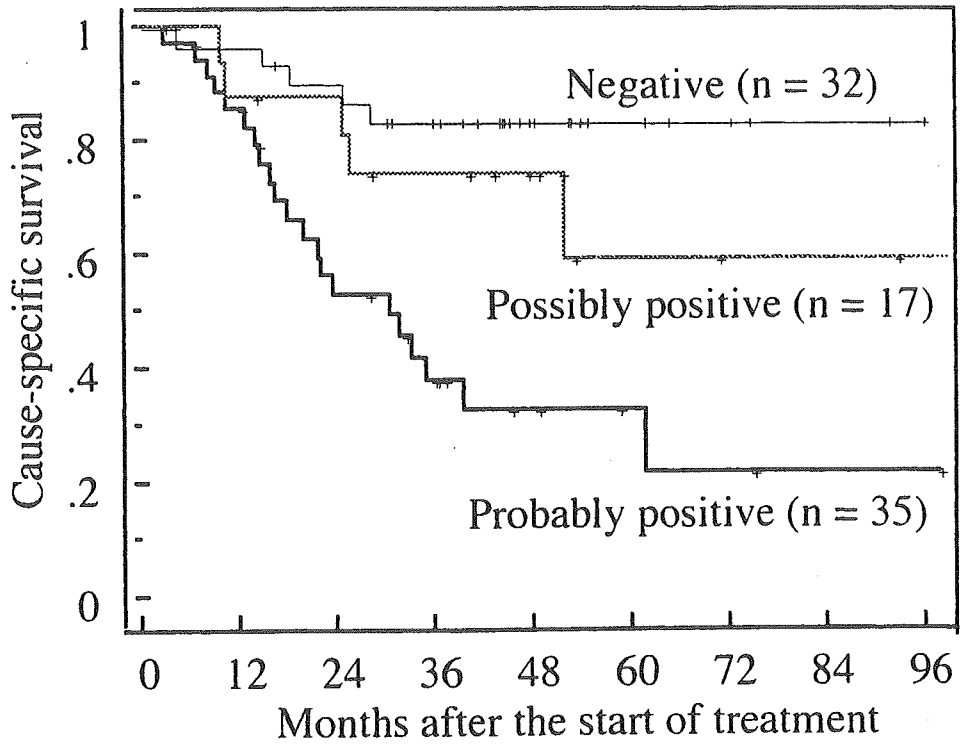

Fig. 2. CSS based on initial treatment failure according to nodal status.

Table 3. Sites of initial treatment failure according to clinical stage and nodal status

	Pelvis (*n*)	Pelvis and distant (*n*)	Distant (*n*)	Total (*n*)
FIGO stage				
IIB (*n* = 20)	0	0	4	4
III (*n* = 45)	6	5	13	24
IVA (*n* = 19)	5	0	6	11
Nodal status				
Positive (*n* = 52)	7	5	22	34
Probably (*n* = 35)	6	5	16	27
Possibly (*n* = 17)	1	0	6	7
PAN (*n* = 15)	1	2	10	13
Pelvis only (*n* = 37)	6	3	12	21
Negative (*n* = 32)	4	0	1	5
Total (*n* = 84)	11	5	23	39

Abbreviations as in Table 1.

and MFR (Fig. 4) differed significantly between node-negative and possibly node-positive disease and also between possibly node-positive and probably node-positive disease. The rates decreased with increases in nodal status. The PFR was significantly low for those with probably node-positive disease. The DFR and MFR (but not PFR) differed significantly among those with node-negative, pelvis only-positive, and PAN-positive status and decreased with increases in status (Fig. 5).

DISCUSSION

Clinical staging of cervical cancer is based on the local extent of the disease; tumors are not measured directly except in Stage I disease, and nodal status is not incorporated. Nevertheless, treatment outcomes in terms of CSS and DFR clearly differ between clinical stages. Discrimination occurs because the extent of disease approximates the tumor size and the tumor size has a close correlation with the frequency of lymph node metastasis (2, 6). However, large tumors are not necessarily associated with lymph node metastasis. Moreover, tumor size and lymph node metastasis as prognostic factors differ in their implications; that is, bulky tumors tend to recur locally, and lymph node metastasis is often associated with distant metastasis. Therefore, the independent determination of each of these factors will contribute to improving survival if the factors are addressed separately. This individual approach is realized in cases of surgical treatment when histopathologic determinations are made (7, 21, 22). Adjunctive treatment is considered in light of each factor identified, and no further treatment is considered for patients without risk factors. When node-negative status is determined nonoperatively, RT alone can be administered, and adjunctive chemotherapy can then be given only to patients with node-positive status, as far as the risk factor of nodal status is concerned.

Nodal status was shown in our study to be a much more powerful prognostic factor than clinical stage. The DFR differed quite distinctively between node-negative and probably positive disease and was marginally different between possibly positive and probably positive disease. However, the DFR differed significantly only between Stage IIB and the other clinical stages. Moreover, the high 5-year DFR of 83.1% for node-negative status was comparable to the reported disease-free survival for Stage IB disease treated by RT alone (2, 4, 5), even though node-negative status included 12 Stage IIB tumors, 14 Stage III tumors, and 4 Stage IVA tumors. Conversely, probably positive disease, particularly PAN-positive disease, was shown to be a powerful indicator of a poor prognosis.

The DFR or disease-free survival based on nodal status will differ by the cutoff measures used. In our study, the 5-year DFR was 83.1% for node-negative status (<5 mm)

Table 4. Disease-free rate, pelvic recurrence-free rate, and distant metastasis-free rate according to clinical stage and nodal status

	Disease-free rate		Pelvic recurrence-free rate		Distant metastasis-free rate	
	5-y (%)	*p**	5-y (%)	*p**	5-y (%)	*p**
FIGO stage						
IIB (*n* = 20)	78.5	0.0300 vs. IVA	100.0		78.5	0.4018 vs. IVA
III (*n* = 45)	46.7	0.0392 vs. IIB	71.1	0.7381 vs. IVA	56.4	0.1483 vs. IIB
IVA (*n* = 19)	37.3	0.5940 vs. III	60.8		61.4	0.8113 vs. III
Nodal status						
Positive (*n* = 52)	32.7	<0.0001 vs. negative	67.2	0.0670 vs. negative	41.7	<0.0001 vs. negative
Probably (*n* = 35)	22.0	<0.0001 vs. negative	46.8	0.0024 vs. negative	35.1	<0.0001 vs. negative
Possibly (*n* = 17)	55.6	0.0040 vs. probably	93.8	0.0082 vs. probably	59.3	0.0195 vs. probably
PAN† (*n* = 15)	13.3	<0.0001 vs. negative	57.1	0.0540 vs. negative	17.8	<0.0001 vs. negative
Pelvis only (*n* = 37)	41.1	0.0065 vs. PAN	69.5	0.6268 vs. PAN	56.3	0.0012 vs. PAN
Negative (*n* = 32)	83.1	0.0601 vs. possibly 0.0005 vs. pelvis only	86.1	0.5293 vs. possibly 0.1080 vs. pelvis only	96.4	0.0027 vs. possibly 0.0002 vs. pelvis only
Total (*n* = 84)	51.5		75.7		62.7	

Abbreviations as in Table 1.
* Calculated by log–rank test.
† Rates shown as of 2 years.

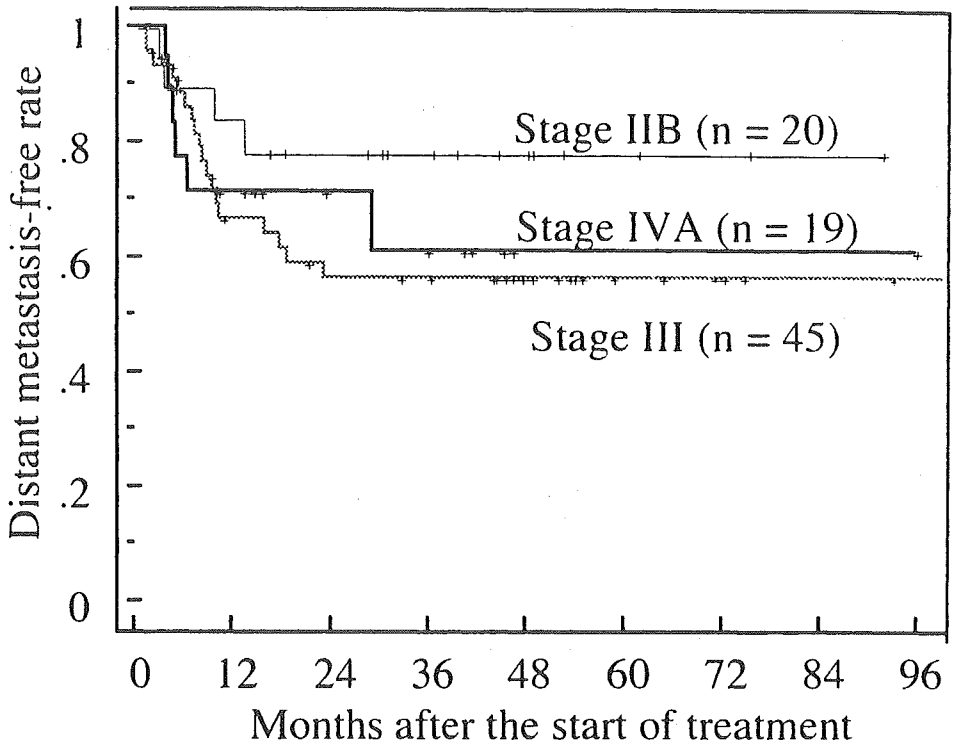

Fig. 3. MFR based on initial treatment failure according to clinical stage.

and 22.0% for probably positive status (>10 mm). Toita and colleagues (23) had a disease-free survival rate at 2 years of 78% for node-negative status (≤10 mm, n = 34) and 10% for node-positive status (>10 mm, n = 10) in a cohort of patients with Stage IB-IVA squamous cell carcinoma treated by RT. Kodaira and colleagues (24) found a

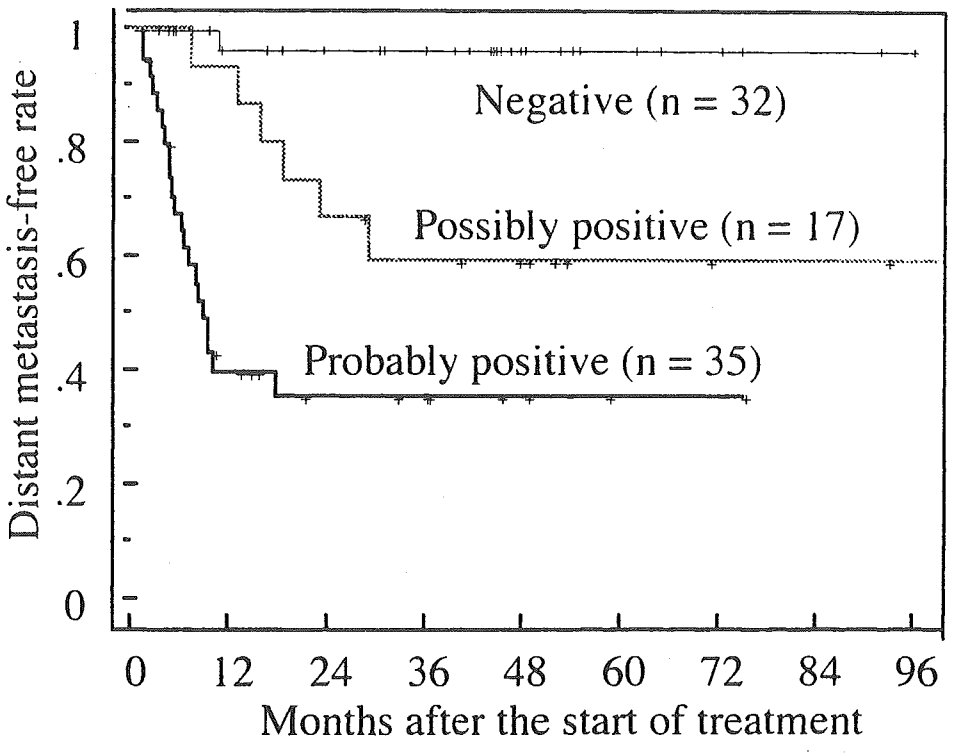

Fig. 4. MFR based on initial treatment failure according to nodal status.

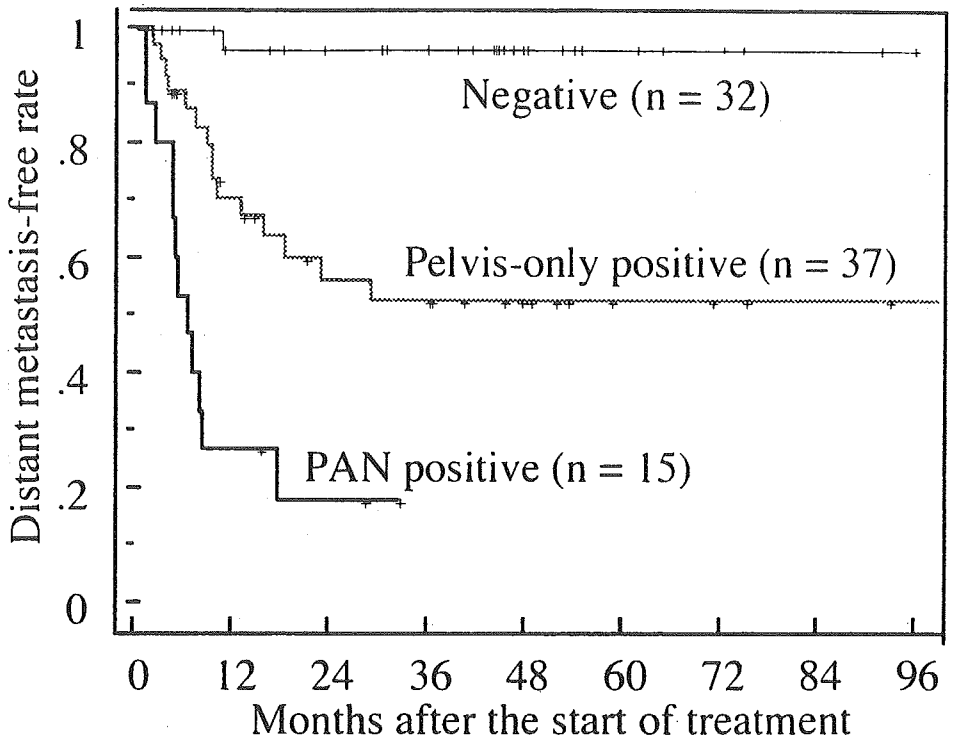

Fig. 5. MFR based on initial treatment failure according to nodal status per node location.

5-year disease-free survival rate after definitive RT of Stage II squamous cell carcinoma of 80.9% for node-negative status (≤10 mm, n = 69) and 38.9% for node-positive status (>10 mm, n = 15). Ogino and colleagues (25) reported a 5-year disease-free survival rate of 61.4% for node-negative status (≤15 mm, n = 199) and 19.9% for node-positive status (>15 mm, n = 34) in patients with Stage IIB-IVA squamous cell carcinoma treated by RT. They focused on the accurate identification of metastatic nodes using a high cutoff measure (25), and we focused on the accurate identification of nonmetastatic nodes using a low cutoff measure.

CT was shown to be the most specific modality for detecting metastatic lymph nodes >10 mm compared with MRI and FDG-PET in gynecologic malignancy (19). In particular, FDG-PET was inferior to the other two modalities in both specificity and sensitivity, because urinary FDG in the ureters or bladder masked or imitated metastatic nodes. High specificity is important in detecting small nodes (<10 mm), and therefore CT is considered the most appropriate imaging modality in identifying patients with node-negative disease.

Prognostic stratification of disease by nodal status became much more distinctive by analysis of the patterns of failure. Nodal status showed a close relation to the MFR. The difference in MFR was significant between possibly node-positive status and node-negative status; both are usually assessed as negative. Moreover, the MFR for node-negative status was as high as 96.4%, suggesting that node-negative status determined under a low cutoff measure is reliable for identifying disease truly confined to the pelvis. Although lymph nodes <5 mm may harbor micrometastasis, such slight metastasis is only rarely associated with distant metastasis. The size and number of metastatic nodes have been shown to have a close correlation with survival (2, 15, 17, 21).

Use of neoadjuvant chemotherapy might have influenced our treatment outcomes but will not have significantly influenced the results of our analysis because the percentage of patients undergoing chemotherapy was similar among the groups. Moreover, if chemotherapy influenced the treatment outcome positively, the difference in survival or DFR would have lessened, because chemotherapy was used preferentially for patients showing risk factors for treatment failure. Therefore, if all our patients had been treated by RT alone, the statistical difference in the treatment outcome would have strengthened our results rather than weakened them.

CONCLUSION

Node-negative status determined by a low cutoff measure predicts disease actually confined to the pelvis well and therefore may be useful for identifying patients who do not need adjunctive chemotherapy against occult systemic metastasis.

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COMPARISON OF PROGNOSTIC VALUE OF MRI AND FIGO STAGE AMONG PATIENTS WITH CERVICAL CARCINOMA TREATED WITH RADIOTHERAPY

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Purpose: To compare the efficacy of MRI and FIGO stage, we performed retrospective multicenter analysis of patients with Stage II–III disease treated with radiation alone.

Methods and Materials: From three institutions, 164 patients diagnosed with cervical carcinoma were entered into the study. The majority of this cohort received intracavitary brachytherapy combined with external beam radiotherapy ($n = 161$). Uni- and multivariate analyses were performed to identify the prognostic factors for overall survival (OAS), disease-free survival (DFS), pelvic control (PC), and distant metastasis-free survival (DMFS).

Results: The 5-year OAS, DFS, PC, and DMFS rates were 68.8%, 60.4%, 77.4%, and 71.7%, respectively. Using uni- and multivariate analyses, both large tumor size/volume and positive lymph node enlargement (LN) showed a significantly unfavorable influence on survival and local and/or distant failure ($p < 0.05$). Using these two prognostic factors, patients were divided into three subgroups; the 5-year DFS rates of patients with risk 0 (volume ≤50 cc and negative LN), 1 (volume >50 cc or positive LN), and 2 (volume >50 cc and positive LN) were 72.9%, 53.3%, and 26.1%, respectively ($p < 0.0001$). Among patients with volume ≤50 cc, disease stage proved to be a significantly prognostic factor of OAS, DFS, and PC ($p < 0.05$). However, these correlations were not observed in the large volume group ($p > 0.05$).

Conclusion: MRI will provide more useful and practical information than will FIGO stage classification for patients with bulky disease, although this will remain a prognostic factor for patients with nonbulky disease (volume ≤50 cc). With the aid of MRI, accurate and practical evaluation of clinical outcome could be achieved.

Cervical cancer, Magnetic resonance imaging, Tumor volume, Lymph node enlargement, Stage II–III.

INTRODUCTION

The classification of the International Federation of Gynecology and Obstetrics (FIGO stage) has been a widely used staging system for gynecologic cancer. This staging system requires clinical examinations for the most part, except for Stage IA disease. The stage is defined by the extent of disease beyond the cervix to surrounding tissues including parametria, pelvic sidewall, vagina, bladder, or rectum. Only chest X-ray to assess lung metastasis and an intravenous pyelogram to assess hydronephrosis are permitted. Lymph node status is not included in the staging system (1). In addition, tumor size is not evaluated for Stage II–IV patients. However, these have been reported as meaningful prognostic factors by several investigators (2–4).

Locally advanced disease is usually treated with definitive radiotherapy. Survival estimates of patients with Stage II and III disease, who were treated with radiotherapy, were reported to be 70% and 30%–50%, respectively (5). Patients with Stage III disease are thought to have an unfavorable outcome compared with those with Stage II disease; however, the difference between these criteria is only decided by physical examination. This nonreproducible technique leads to both intra- and interobserver variations in patient staging.

Magnetic resonance imaging (MRI) is believed to have benefits for the management of cervical carcinoma (6–9). MRI has great advantages in terms of excellent soft-tissue contrast resolution, capability of three-dimensional measurement, accurate judgment of invasion surrounding normal tissue and lymph node metastasis, and probability for evaluation of tissue characteristics. Several reports have

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Table 1. Patient characteristics

Factors	Total	Aichi Cancer Center	University of the Ryukyus	University of Mie
Patient number	164	66	67	31
Patient age				
Median	68	68	67	71.0
Range	30–87	47–86	30–87	48–84
FIGO stage				
IIA	14	10	2	2
IIB	70	26	26	18
IIIA	6	5	1	0
IIIB	74	25	38	11
SCC				
Median	5.5	6.3	4.7	6.9
Range	0.3–169	0.3–169	0.9–153	0.5–47.7
CEA				
Median	3.2	3.2	1.6	4.65
Range	0.3–96.2	0.3–96.2	1.1–2.1	1–14.6
Subtype				
Keratinizing	39	28	4	7
Large cell nonkeratinizing	100	20	58	22
Small cell type	5	5	0	0
Others	3	3	0	0
Not assessed	17	10	5	2

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; SCC = squamous cell carcinoma antigen; CEA = carcinoembryonic antigen.

noted that surgical confirmation proved to correlate well with the findings obtained by MRI in cervical cancer (10, 11). In this retrospective analysis, we try to compare the FIGO stage and MRI findings as clinical predictors.

METHODS AND MATERIALS

Patient selection

This analysis included previously untreated patients with cervical carcinoma who were treated with radiation alone for definitive intent from three institutes between 1990 and 1999: the Aichi Cancer Center, the University of the Ryukyus School of Medicine, and the University of Mie School of Medicine. At the Aichi Cancer Center, chemoradiotherapy has been adopted since 1997, and radiation alone has been the standard treatment policy before 1997. Forty-four patients with Stage III disease at the University of Mie School of Medicine and 111 patients at the University of the Ryukyus School of Medicine were registered during the investigation period. Almost half of patients from both institutes received chemoradiotherapy, so they were excluded from this analysis. The histopathologic diagnosis of all patients was squamous cell carcinoma. The subtypes of histopathologic diagnosis are recorded in Table 1. Patients with other histopathologic diagnoses were excluded from the present analysis.

Patient age (t test; $p > 0.05$) and stage (chi-square test; $p > 0.05$) distribution were not significantly different among the three institutes. The pretreatment work up included history, gynecologic pelvic examination, chest X-ray study, abdominopelvic computed tomography, peripheral blood count, and blood chemistry profiles. The staging workup using the FIGO staging system was determined with the agreement of both a gynecologist and radiation oncologist at each institute. MRI was performed for all patients before the start of radiotherapy. The patient characteristics of each institute are summarized in Table 1.

MRI imaging protocol

Immediately before the start of radiotherapy, MRI was performed on all patients. At two institutes (the Aichi Cancer Center and the University of Mie School of Medicine), MRI examinations were obtained on a 1.5 T superconductive scanner (Signa, General Electric Medical Systems, Milwaukee, WI). At the University of the Ryukyu School of Medicine, 34 patients were imaged with a 0.5 T, and 33 patients with a 1.5T superconductive scanner. The details of the imaging protocol in these institutes were published in another report (6, 8).

Acquired images were judged by at least two radiologists in each institute without knowledge of the clinical findings or treatment outcomes. The images were evaluated according to tumor size/volume and lymph node enlargement. Maximal tumor diameter was measured three-dimensionally based on T2-weighted images; anteroposterior (D_{ap}), lateral (D_l), and craniocaudal (D_{cc}). Tumor size was also calculated as the maximal diameter (D_{max}) among three computed diameters. The MRI-derived tumor volume was calculated by the equation ($V = D_{ap} \times D_l \times D_{cc} \times \pi/6$) as an ellipsoid approximation. Lymph nodes greater than 10 mm in minimum diameter were interpreted as positive nodes (12).

Table 2. Radiotherapy treatment

Factors	Aichi Cancer Center	University of the Ryukyus	University of Mie
External beam radiotherapy			
Beam energy	6 MV	18 MV	10 MV
Whole pelvis + boost dose (Gy)			
Median	55.3	50	50.4
Range	15–69.6	38–60	50.4–70.2
Whole pelvis (Gy)			
Median	45.6	40	30.6
Range	45.3–51.3	19.8–40	30.6
Radiation boost (number)			
Parametrium	26	8	2
Pelvic node	4	9	0
Local	6	0	0
Intracavitary brachytherapy source	LDR	HDR	MDR
Fraction			
Median	2	3	4
Range	1–11	2–4	4–5
Total dose at point A (Gy)			
Median	25.0	18.0	32
Range	15–50.9	12–24	20–40

Abbreviations: LDR = low-dose rate; MDR = medium-dose rate; HDR = high-dose rate.

Radiotherapy

All except 3 patients received both external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT), whereas the 2 remaining patients with Stage IIIB received EBRT alone, and only 1 patient with Stage IIA disease received ICBT alone. The treatment details of both EBRT and ICBT in each institute are summarized in Table 2. EBRT was given using 6–18 MV photon beams with a daily dose of 1.8–2.0 Gy, five times a week. A total dose of 45.6–50.4 Gy was delivered to the whole pelvic region. At the Aichi Cancer Center, EBRT was prescribed with a unique technique; namely, "two axial arc therapy using a multileaf collimator" (13). In this manner, the radiation doses to the bladder and rectum were reduced. In other hospitals, EBRT was delivered through anteroposterior parallel opposite portals, after which a center shield was inserted at the initiation of ICBT.

Fifty-four patients received a radiation boost to the parametrium (n = 36), the pelvic lymph node (n = 13), and central tumor (n = 6). Only 1 patient received a radiation boost to both the lymph node and parametrium. The median radiation boost dose was 11.1 Gy, ranging from 2 to 24 Gy. Seven patients also received paraaortic nodal irradiation of 46 Gy with prophylactic intent.

One hundred and sixty-two patients were treated with ICBT during the treatment sessions. Forty-nine patients at the Aichi Cancer Center received two insertions of a radium (226) source. Twelve patients in the Aichi Cancer Center and 25 patients at the University of Mie School of Medicine received medium-dose rate (1–1.5 Gy/h) ICBT using a cesium (137) source via a remote afterloading system (RALS). Three patients from the Aichi Cancer Center were treated with a combination of both radium (226) and cesium (137). Six patients at the University of Mie School of Medicine and all at the University of the Ryukyus School of Medicine were treated by high-dose-rate RALS-ICBT using an iridium (192) source.

Follow-up

Patients were followed by radiation oncologists and gynecologic oncologists at 1–2 month intervals for the first 2 years, and 3–4 month intervals thereafter. Local failure was defined as tumor recurrence after complete remission by clinical or cytologic examination or persistence/progression after initial treatment. Follow-up examinations included physical and pelvic examinations, abdominopelvic computed tomography, Pap smears, blood counts, and chemistry profiles. Chest X-rays were obtained every year in principle. The schedule for follow-up MRI on the pelvis varied slightly at each institute.

The last follow-up was performed in March 2002. At that time, 100 patients were alive without disease and 16 patients were alive with disease. One patient was alive without accurate information on tumor recurrence 21.4 months after the initial treatment. Forty patients died from disease 5.2–59.2 months after the initial treatment (median 22.5 months). Seven patients died from intercurrent disease without any evidence of recurrent disease. The follow-up period for the 117 survivors ranged from 6.5 to 116.1 months (median 60.4 months).

Statistical analysis

Overall survival (OAS), disease-free survival (DFS), pelvic control (PC), and distant metastasis free survival (DMFS) rates were calculated from the beginning of radiotherapy according to the Kaplan-Meier method (14). DFS was defined for all deaths and recurrences as the event. PC was defined, with only local or pelvic failure, as the event.

Table 3. Clinical findings assessed by magnetic resonance imaging

Factors	Median	Range
Tumor diameter (cm)		
Anteroposterior (D_{ap})	3.4	1.0–10.5
Lateral (D_l)	4.0	1.2–8.6
Craniocaudal (D_{cc})	4.3	1.0–10.0
Maximum diameter (D_{max})	4.9	2.1–10.5
Volume (cc)	33.5	1.87–472.6
Pelvic note status		**Number**
Negative		121
Positive		43
Solitary		22
Multiple		16
Unknown		5
Unilateral		26
Bilateral		16
Unknown		1

Volume was calculated with the following formula = $D_{ap} \times D_l \times D_{cc} \times \pi/6$.

Vaginal recurrence was defined as local failure. Death or recurrence without pelvic failure was not counted as event in this category. DMFS accounted for all distant metastases as event. Extrapelvic lymph node metastasis was defined as distant metastasis. No deaths or pelvic recurrences without distant metastases were estimated as event.

For uni- and multivariate analysis, patient age, overall treatment time (OTT), serum concentration of SCC antigen and CEA, tumor size, and volume were divided into two groups at several points. Histopathologic subtype was also used in the present analysis. Proportions and means were compared by the chi-square test and the Student *t*-test,

Table 4. The correlation of tumor size/volume and lymph node status

Factor	Lymph node positivity (percentage)	*p* value
Tumor diameter (mm)		
Anteroposterior (D_{ap})		
≤50 mm	34/145 (23.4)	0.0258
>50 mm	9/19 (47.4)	
Lateral (D_l)		
≤50 mm	27/124 (21.8)	0.0227
>50 mm	16/40 (40)	
Craniocaudal (D_{cc})		
≤50 mm	20/115 (17.4)	<0.0001
>50 mm	23/49 (46.9)	
Maximum diameter (D_{max})		
≤50 mm	16/95 (16.8)	0.0014
>50 mm	27/69 (39.1)	
Volume (cc)		
≤50 cc	20/112 (17.9)	0.0004
>50 cc	23/52 (44.2)	

Table 5. The correlation of clinical findings by magnetic resonance imaging with FIGO stage

FIGO stage	Stage II	Stage III
Tumor diameter (mm)		
Anteroposterior (D_{ap})	30.7	40.6*
Lateral (D_l)	36.7	46.9*
Craniocaudal (D_{cc})	38.0	50.6*
Maximum diameter (D_{max})	42.1	54.2*
Volume (cc)	36.4	62.6†
Lymph node positivity (percentage)	15/84 (17.9)	28/80‡ (35.0)

* $p < 0.0001$ (*t*-test).
† $p = 0.0006$ (*t*-test).
‡ $p = 0.0126$ (chi-squared test).

respectively. The log–rank test (15) was used to compare survival curves. Cox's proportional-hazards model (16) was used to estimate the relative risk after adjusting for prognostic factors. The final model considered only those variables that were statistically significant at the 5% level in step-wise regression.

RESULTS

Assessment by MRI examination

Tumor size was recorded on MRI findings (Table 3). The D_l of the Aichi Cancer Center was significantly larger than those of the University of the Ryukyus (*t* test; $p = 0.049$). Linear regression analysis showed a statistically significant correlation within each pair of diameters and the calculated volume ($p < 0.0001$). Therefore, we did not use the two parameters of size and volume in the subsequent multivariate analysis.

The status of lymph node enlargement is shown on Table 3. The frequency of lymph node enlargement was significantly higher in patients with larger size/volume compared with those with smaller size/volume (chi-square test; $p < 0.05$). The correlation of tumor size/volume and lymph node status is shown in Table 4. The size/volume did not significantly differ within the groups divided by patient age, tumor marker, or OTT ($p > 0.05$). The size/volume of patients with Stage III disease was significantly larger compared to that of patients with Stage II disease (*t* test; $p < 0.001$). The correlation of MRI findings with FIGO stage is shown in Table 5.

Treatment outcomes and failure patterns

For all 164 patients, the 5-year OAS, DFS, PC, and DMFS rates were 68.8% (95% confidence interval [CI] 61.2–76.4%), 60.4% (95% CI 52.6–68.2%), 77.4% (95% CI % 70.5–84.3%), and 71.7% (95% CI 64.4–79.0%), respectively. There were considerable differences regarding the radiation treatment contents among the three institutes. However, the results acquired from the three institutes were not significantly different ($p > 0.05$). Thus we concluded that the radiation treatments at each institute were equally