support to the conclusion that AIP-based treatment planning is a clinically acceptable approach for estimating the actual dose for lung tumors, even when they are in close proximity to the diaphragm, with its relatively large motion.

For OARs with small respiratory motion (spinal cord, esophagus and heart), dose discrepancies between AIP and 4D plans were negligible, but for those with large respiratory motion, dose discrepancies were prominent. The planned dose to the lung tissue was significantly higher than the actual dose. Because the treatment plan for AIP was designed to deliver a sufficient dose to the PTV, which was generated from the ITV with an additional margin, the volume of the lung on the AIP plan scheduled for high-dose irradiation was larger than that on the 4D plan. However, the dose discrepancy was limited and appeared to be clinically insignificant. For the liver, bowel and stomach, the doses estimated with the AIP plan were less than those estimated with the 4D plan. These findings could be explained by the fact that OARs included in the irradiated volume at the exhale phase were greater in volume than those at the inhale phase. Due to the blurred image quality, the shape of the organs contoured on the AIP was more like that at the inhale phase than at the exhale phase. Because the liver is considered to be a parallel organ, the dose discrepancy may not be clinically significant. However, for organs with lower tolerance for irradiation, such as bowel and stomach, underestimation of the dose on the AIP plan could cause serious harm in large-dose hypofractionated treatment. Therefore, we consider 4D dose calculation to be essential for predicting the actual dose to such organs. Otherwise, treatment with larger fraction number, e.g. 60 Gy in 10 fractions, might be required to reduce the biological effect of radiation for OARs.

A new radiotherapy modality of respiratory-gated VMAT could offer a solution for predicting actual doses to the targets as well as to the OARs. Gating irradiates the tumor only when it is in a given location, that is when it is near the exhale phase with a duty cycle of 25–70% [18]. Therefore, treatment planning for a gated VMAT does not require the AIP generated from full-phase image sets of 4DCT, and the optimization process can be carried out without being affected by the lack of scatter contribution. Moreover, this method would diminish the interplay effect on a target dose. The resultant planned dose distribution would constitute an accurate representation of the actual dose to a target and OARs. However, gated VMAT is only available for a limited number of machines due to the complexity resulting from repeated interruptions by the gating signal during VMAT dose delivery. Real-time target tracking with CyberKnife would be another solution for a moving target. Chan *et al.* evaluated 4D dose distributions of CyberKnife and VMAT in lung SBRT and concluded that CyberKnife had some advantage over free-breathing VMAT in the treatment of tumors showing large motion range and/or which are surrounded by multiple critical organs [19].

Recently, another approach for lung VMAT–SBRT planning has been proposed by Wiant *et al.* [20]. In their phantom study, treatment plans based on free-breathing image sets with the ITV set at tumor density and the PTV minus ITV set to a density intermediate between lung and tumor resulted in a reduction in beam modulation and significantly higher gamma passing rates than the ones based on AIP. Moreover, in their clinical study of five patients, the tumor volume was covered by the prescription dose for all respiratory phases, and the normal lung irradiation was reduced. That method might thus be a more effective approach than AIP for predicting the actual dose.

In conclusion, the phantom and clinical study presented here demonstrated the feasibility of AIP-based VMAT–SBRT planning. The AIP approach was found to be practical, and the dose discrepancies between the AIP and 4D plans were clinically acceptable (<3%). AIP could therefore constitute an approach to be recommended for a moving target located in close proximity to a diaphragm. However, the AIP approach underestimated doses for OARs with large respiratory motion. We thus consider 4D dose calculation to be essential when such OARs are located near the irradiated target.

FUNDING

Funding to pay the Open Access publication charges for this article was provided by a grant from the Japan Society for the Promotion of Science (JSPS) Core-to-Core Program (Grant No. 23003).

REFERENCES

1. Timmerman R, Bastasch M, Saha D, et al. Optimizing dose and fractionation for stereotactic body radiation therapy. Normal tissue and tumor control effects with large dose per fraction. *Front Radiat Ther Oncol* 2007;40:352–65.
2. Suzuki O, Mitsuyoshi T, Miyazaki M, et al. Dose–volume–response analysis in stereotactic radiotherapy for early lung cancer. *Radiother Oncol* 2014;112:262–6.
3. Timmerman RD, Galvin J, Gore E, et al. *RTOG 0618. A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Operable Stage I/II Non-small cell Lung Cancer.* RTOG 2007.
4. Verbakel W, Senan S, Cuijpers J, et al. Rapid delivery of stereotactic radiotherapy for peripheral lung tumors using volumetric intensity-modulated arcs. *Radiother Oncol* 2009;93:122–4.
5. Merrow C, Wang I, Podgorsak M. A dosimetric evaluation of VMAT for the treatment of non-small cell lung cancer. *J Appl Clin Med Phys* 2013;14:228–38.
6. Jiang S, Pope C, Jarrah K, et al. An experimental investigation on intra-fractional organ motion effects in lung IMRT treatments. *Phys Med Biol* 2003;48:1773–84.
7. Ong C, Verbakel W, Cuijpers J, et al. Dosimetric impact of interplay effect on Rapidarc lung stereotactic treatment delivery. *Int J Radiat Oncol Biol Phys* 2011;79:305–11.
8. Stambaugh C, Nelms B, Dilling T, et al. Experimentally studied dynamic dose interplay does not meaningfully affect target dose in VMAT SBRT lung treatments. *Med Phys* 2013;40:091710.
9. Li X, Yang Y, Li T, et al. Dosimetric effect of respiratory motion on volumetric-modulated arc therapy–based lung SBRT treatment delivered by TrueBeam machine with flattening filter-free beam. *J Appl Clin Med Phys* 2013;14:195–204.
10. Chin E, Loewen S, Nichol A, et al. 4D VMAT, gated VMAT, and 3D VMAT for stereotactic body radiation therapy in lung. *Phys Med Biol* 2013;58:749–70.

11. Kang Y, Zhang X, Chang J, et al. 4D proton treatment planning strategy for mobile lung tumors. *Int J Radiat Oncol Biol Phys* 2007;67:906–14.
12. Ehlera E, Tomé W. Lung 4D-IMRT treatment planning: an evaluation of three methods applied to four-dimensional data sets. *Radiother Oncol* 2008;88:319–25.
13. Glide-Hurst C, Hugo G, Yan D. A simplified method of four-dimensional dose accumulation using the mean patient density representation. *Med Phys* 2008;35:5269–77.
14. Shirai K, Nishiyama K, Katsuda T, et al. Phantom and clinical study of differences in cone beam computed tomographic registration when aligned to maximum and average intensity projection. *Int J Radiat Oncol Biol Phys* 2014;88:189–94.
15. Kashani R, Hub M, Balter J, et al. Objective assessment of deformable image registration in radiotherapy: a multi-institution study. *Med Phys* 2008;35:5944–53.
16. Admiraal M, Schuring D, Hurkmans C. Dose calculations accounting for breathing motion in stereotactic lung radiotherapy based on 4D-CT and the internal target volume. *Radiother Oncol* 2008;86:55–60.
17. Tomé W, Fowler J. On cold spots in tumor subvolumes. *Med Phys* 2002;29:1590–8.
18. Qian J, Xing L, Liu W, et al. Dose verification for respiratory-gated volumetric modulated arc therapy. *Phys Med Biol* 2011;56: 4827–38.
19. Ding C, Chang CH, Haslam J, et al. A dosimetric comparison of stereotactic body radiation therapy techniques for lung cancer: robotic versus conventional linac-based systems. *J Appl Clin Med Phys* 2010;11:212–24.
20. Wiant D, Vanderstraeten C, Maurer J, et al. On the validity of density overrides for VMAT lung SBRT planning. *Med Phys* 2014;41:081707.

Journal of Radiation Research, 2015, 56, 346–353
doi: 10.1093/jrr/rru115 Advance Access Publication 22 January 2015

Definitive radiotherapy for primary vaginal cancer: correlation between treatment patterns and recurrence rate

Naoyuki KANAYAMA[1,2], Fumiaki ISOHASHI[1,*], Yasuo YOSHIOKA[1], Sungjae BAEK[1], Masashi CHATANI[3], Tadayuki KOTSUMA[4], Eiichi TANAKA[4], Ken YOSHIDA[5], Yuji SEO[1], Osamu SUZUKI[1], Seiji MABUCHI[6], Yasuhiko SHIKI[7], Keiji TATSUMI[8], Tadashi KIMURA[6], Teruki TESHIMA[2] and Kazuhiko OGAWA[1]

[1]Department of Radiation Oncology, Osaka University Graduate School of Medicine, 2-2 (D10) Yamadaoka, Suita, Osaka 565–0871, Japan
[2]Department of Radiation Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi, Higashinari, Osaka 537–8511, Japan
[3]Department of Radiation Oncology, Osaka Rosai Hospital, 1179-3 Nagasone-cyo, kita-ku, Sakai, Osaka 591–8025, Japan
[4]Department of Radiation Oncology, National Hospital Organization Osaka National Hospital, 2-1-14 Hoenzaka, Chuo-ku, Osaka 540–0006, Japan
[5]Department of Radiology, Osaka Medical College
[6]Department of Obstetrics and Gynecology, Osaka University Graduate School of Medicine
[7]Department of Obstetrics and Gynecology, Osaka Rosai Hospital
[8]Department of Obstetrics and Gynecology, National Hospital Organization Osaka National Hospital
*Corresponding author. Fumiaki Isohashi, Department of Radiation Oncology, Osaka University Graduate School of Medicine, 2-2 (D10) Yamadaoka, Suita, Osaka 565-0871, Japan. Tel: +81-6-6879-3482; Fax: +81-6-6879-3489; Email: isohashi@radonc.med.osaka-u.ac.jp

(Received 21 July 2014; revised 27 October 2014; accepted 10 November 2014)

The purpose of this study was to determine the outcomes and optimal practice patterns of definitive radiotherapy for primary vaginal cancer. Between 1993 and 2012, 49 patients were treated with definitive radiotherapy for primary vaginal cancer in three hospitals. Of these, 15 patients (31%) had clinically positive regional lymph node metastasis. A total of 34 patients (70%) received external beam radiotherapy with high-dose-rate brachytherapy (interstitial or intracavitary), and 8 (16%) (with small superficial Stage I tumors) were treated with local radiotherapy. The median follow-up was 33 months (range: 1–169 months). The 3-year overall survival (OS), disease-free survival (DFS), and loco-regional control (LRC) rates were 83%, 59% and 71%, respectively. In multivariate analysis, the histological type ($P = 0.044$) was significant risk factors for LRC. In Federation of Gynecology and Obstetrics (FIGO) Stage I cases, 3 of 8 patients (38%) who did not undergo prophylactic lymph node irradiation had lymph node recurrence, compared with 2 of 12 patients (17%) who underwent prophylactic pelvic irradiation. For Stage III–IV tumors, the local recurrence rate was 50% and the lymph node recurrence rate was 40%. Patients with FIGO Stage I/II or clinical Stage N1 had a higher recurrence rate with treatment using a single modality compared with the recurrence rate using combined modalities. In conclusion, our treatment outcomes for vaginal cancer were acceptable, but external beam radiotherapy with brachytherapy (interstitial or intracavitary) was needed regardless of FIGO stage. Improvement of treatment outcomes in cases of FIGO Stage III or IV remains a significant challenge.

Keywords: high-dose-rate brachytherapy; prophylactic pelvic irradiation; radiotherapy; vaginal cancer

INTRODUCTION

Vaginal cancer is rare, comprising only about 2% of all gynecologic malignancies. Radiotherapy plays a significant role in the management of primary vaginal cancer, but there have been no prospective randomized trials for this cancer [1]. Thus, analysis of institutional retrospective data is important for obtaining a better understanding of patterns of

failure and for determining optimal treatment regimes for radiotherapy. However, most retrospective studies have had a limited number of patients and have used a variety of modalities, schedules and total doses. Therefore, the optimal dose and combinations of modalities are still poorly understood.

Here, we present a retrospective analysis of definitive radiotherapy for primary vaginal cancer at our hospital (Osaka University Hospital) and related hospitals (Osaka Rosai Hospital and the National Hospital Organization Osaka National Hospital). The goal of this study was to determine the optimal treatment practice patterns for this disease by evaluating the outcomes, toxicities, prognostic factors, and correlations of recurrence rates with the extent of radiotherapy and total dose.

MATERIALS AND METHODS

Patient characteristics

Between May 1993 and July 2012, 49 patients were treated with definitive radiotherapy for primary vaginal cancer at Osaka University Hospital, Osaka Rosai Hospital and the National Hospital Organization Osaka National Hospital. Patient characteristics and outcomes were obtained from hospital records. For patients who were no longer being followed up, we contacted them or their family by telephone. Informed consent was obtained from all patients. The study was approved by the institutional review board of Osaka University Hospital.

Patient and disease characteristics are listed in Table 1. Of the 49 patients, 21 (43%) were treated at Osaka University Hospital, 16 (33%) at Osaka Rosai Hospital, and 12 (24%) at the National Hospital Organization Osaka National Hospital. Vaginal cancer occurring 5 or more years after complete response of uterine cervical cancer was defined as primary vaginal cancer, based on the definition of the International Union Against Cancer. Therefore, four patients with a history of uterine cervical cancer and five with a history of pelvic irradiation were included in the study. Pretreatment abdominal and pelvic computed tomography (CT) scans were obtained for all patients, and a positive diagnosis was made based on a lymph node short axis >10 mm. Of the 49 patients, 15 (31%) had clinically positive regional lymph node metastasis. One patient had distant lymph node metastasis (common iliac lymph node), but was treated with radical intent. Chemotherapy was used for six patients (12%), including concurrently with radiotherapy in two cases. The other four patients received pre- or post-radiotherapy. All cases treated with chemotherapy received platinum-based regimens, including two patients given weekly cisplatin concurrently with radiotherapy and four who received pre- or post-radiotherapy with: (i) carboplatin and peplomycin; (ii) pirarubicin, cisplatin and peplomycin; (iii) nedaplatin and peplomycin; and (v) carboplatin and paclitaxel, respectively.

Table 1. Patient and disease characteristics

Characteristics	*n*	%
Age, years		
<69	25	51
≥70	24	49
Histological type		
Squamous cell carcinoma	42	86
Adenocarcinoma	6	12
Carcinosarcoma	1	2
FIGO stage		
I	20	41
II	19	39
III	7	14
IV	3	6
Clinical N stage		
N0	34	69
N1	15	31
Size, cm		
<4	31	63
≥4	18	37
Location		
Upper 2/3	30	61
Lower 1/3	11	22
Whole vagina	8	16
Chemotherapy		
Yes	6	12
No	43	88
Radiotherapy		
EBRT alone	8	16
ICBT alone	4	8
ISBT alone	3	6
EBRT + ICBT	9	19

FIGO = International Federation of Gynecology and Obstetrics, EBRT = external beam radiotherapy, ICBT = intracavitary brachytherapy, ISBT = interstitial brachytherapy.

Radiotherapy

All three hospitals had facilities for high-dose-rate (HDR) brachytherapy with a ^{192}Iridium source. The treatment strategy was almost the same in the three hospitals. Generally, patients with small, superficial tumors (tumor thickness <5 mm) were treated with local radiotherapy [brachytherapy or external beam radiotherapy (EBRT)] alone. Other tumors were treated with EBRT with brachytherapy, except in two

cases with a poor performance status. The initial 20–40 Gy was delivered to the whole pelvis, and then pelvic irradiation with a central shield was performed. If the tumor remained large (tumor thickness >5 mm) at the time of brachytherapy, HDR interstitial brachytherapy (ISBT) was performed instead of HDR intracavitary brachytherapy (ICBT). The EBRT to brachytherapy ratio and the total dose were determined on an individual basis by each physician. EBRT was administered to 42 patients (86%), including 41 with a primary lesion and regional lymph node drainage defined by the primary lesion location.

For primary tumors confined to the proximal two-thirds of the vagina, the clinical target volume (CTV) for EBRT included the areas of the obturator lymph nodes, external and internal iliac lymph nodes, and common iliac nodes. For tumors that had invaded the distal one-third of the vagina, the area of the inguinal lymph nodes was included, in addition to that of the pelvic lymph nodes. The planning target volume (PTV) for EBRT was generated using a 10-mm uniform expansion of the CTV. The prescribed doses of EBRT were at the center of the PTV. The CTV for brachytherapy comprised the whole tumor (at the time of brachytherapy) plus 5 mm in all directions, except for the posterior (rectal) margin. The posterior margin varied from 2 to 5 mm, depending on the distance to the rectal wall. Prophylactic vaginal wall irradiation was not performed. Measurement of the tumor thickness was carried out by palpation and ultrasound.

HDR-ISBT was performed in 28 patients (57%) at a median dose of 30 Gy in 5 fractions (range: 10–50 Gy in 2–10 fractions). HDR-ICBT was performed in 13 patients (27%) at a median dose of 30 Gy in 5 fractions (range: 10–38 Gy in 2–6 fractions). The ICBT dose was defined at a depth of 5 mm from the vaginal surface. In HDR-ISBT, the planning system used was either PLATO or Oncentra (Elekta, Stockholm, Sweden) was used in combination with manual modification to ensure the 100% isodose line encompassed the CTV on every slice after computer optimization using the geometrical optimization algorithm.

Practice patterns of radiotherapy are shown in Table 1. Radiotherapy using EBRT alone, ICBT alone, ISBT alone, EBRT + ICRT and EBRT + ISBT was performed in 16%, 8%, 6%, 19% and 51% of cases, respectively. Collectively, radiotherapy using a single modality and combined modalities was performed in 30% and 70% of cases, respectively.

To compare the combined dose of brachytherapy (ICBT or ISBT) and EBRT with a single modality dose (brachytherapy or EBRT alone), the total dose was calculated as the biologically equivalent dose in 2-Gy fractions (EQD_2) using the linear quadratic model. The dose to the primary tumor was the prescription dose of EBRT (excluding the fractions with central shielding) plus the prescription dose of brachytherapy. The value used for assessing effects on the tumor was $\alpha/\beta = 10$ Gy. The equation used to calculate the EQD_2 was as follows:

$$EQD_2 = EQD_{2EBRT} + EQD_{2brachytherapy}$$
$$= Nd(d + \alpha/\beta)/(2 + \alpha/\beta) + N_B d_B(d_B + \alpha/\beta)/(2 + \alpha/\beta),$$

where N is the fraction number for EBRT, d is the dose fraction for EBRT, N_B is the fraction number for brachytherapy, and d_B is the dose fraction for brachytherapy.

We divided the radiation field into three regions: primary lesion, enlarged lymph nodes and prophylactic lymph nodes, and evaluated the correlation between total EQD_2 and recurrence rates in the respective regions. Recurrence was defined as a tumor that recurred or persisted in the same region (primary, obturator, external iliac, internal iliac, common iliac or inguinal) after radiotherapy.

Statistical analysis

Overall survival (OS), disease-free survival (DFS) and loco-regional control (LRC) rates were calculated from the start of initial treatment. In evaluating LRC, common iliac LN recurrence was defined as regional recurrence. Rates were estimated using the Kaplan–Meier method, and differences between factors were examined by log-rank test. A Cox proportional hazard model was used for multivariate analysis. $P < 0.05$ or a 95% confidence interval (CI) of the hazard ratio >1.0 was considered to indicate a significant difference. All statistical analysis was performed using Stat Mate IV (ATMS Co., Ltd, Tokyo, Japan).

RESULTS

Outcome analysis

At the time of analysis, the median follow-up time of the 49 patients was 33 months (range: 1–169 months). The 3-year OS, DFS and LRC rates were 83%, 59% and 71%, respectively (Fig. 1A). According to FIGO stage, the 3-year OS for Stages I, II and III–IV patients was 81%, 86% and 83%, respectively (Fig. 1B), and the corresponding 3-year DFS was 60%, 65% and 40%, respectively (Fig. 1C). Relationships among outcomes, tumor types, and treatment factors are summarized in Table 2. The histological type ($P = 0.037$) and FIGO stage ($P = 0.026$) were significantly associated with DFS; and histological type ($P = 0.028$), FIGO stage ($P = 0.019$), and clinical N stage ($P = 0.023$) were significantly associated with LRC. In patients treated with brachytherapy, LRC did not differ significantly between patients treated with ISBT and ICBT. Multivariate analysis was performed with histological type (SCC vs others), FIGO stage (I/II vs III/IV) and clinical N stage (N0 vs N1), which were judged to be potential risk factors in univariate analysis. In multivariate analysis, the histological type (HR = 3.82, 95% CI = 1.04–13.08, $P = 0.044$) was a significant risk factor for LRC. OS showed no significant differences between different tumor types and treatment factors.

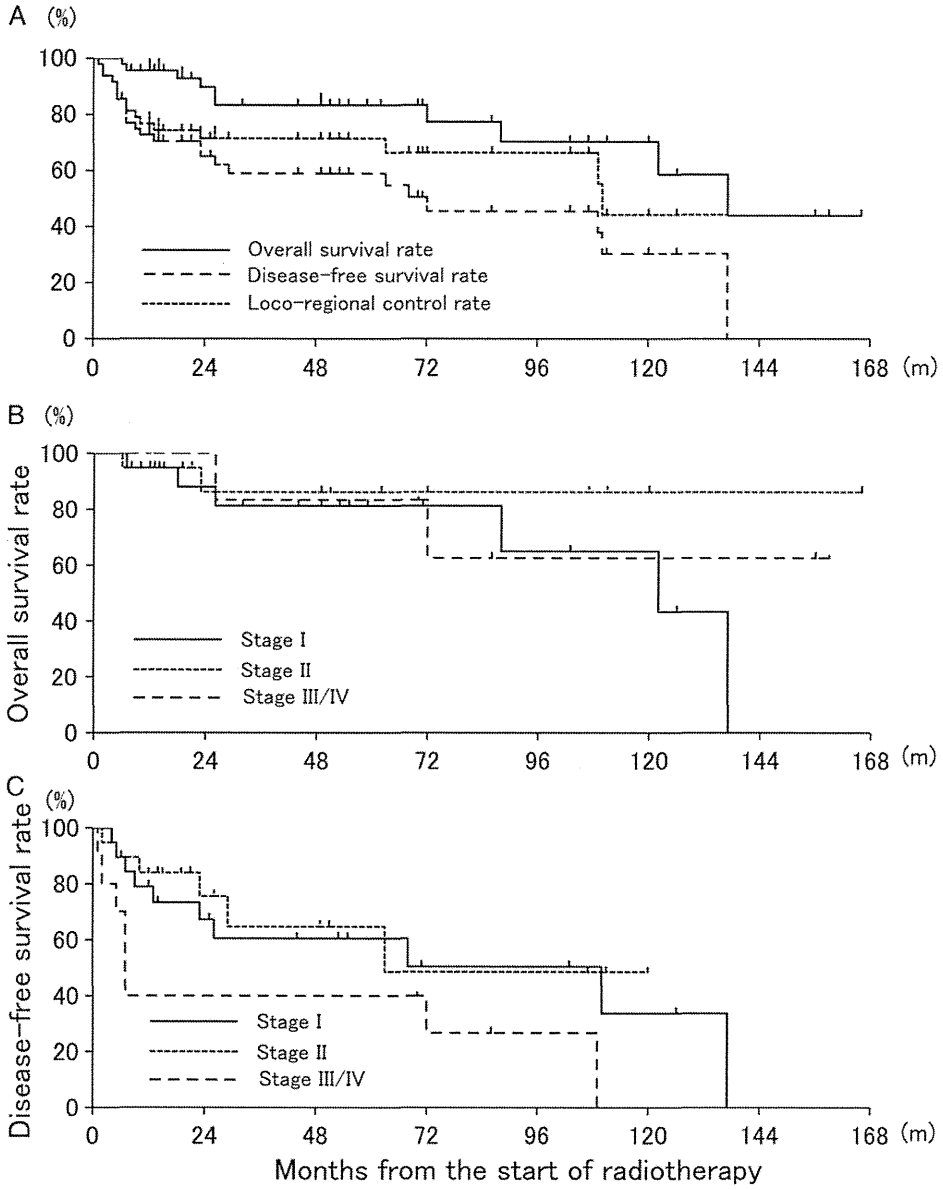

Fig. 1. (**A**) Overall survival, disease-free survival, and loco-regional control rates after definitive radiotherapy for vaginal cancer. (**B**, **C**) Overall survival and disease-free survival rates according to FIGO stage.

Correlation between total EQD_2 and recurrence rate

Correlations between total EQD_2 doses to primary lesions, enlarged lymph nodes and prophylactic lymph nodes with tumor recurrence rates for lesions of different FIGO stages are shown in Table 3. In primary lesions, recurrence clearly increased for a primary tumor with a diagnosis of Stage III or higher, despite use of a relatively high dose (median EQD_2 dose: 79 Gy). For enlarged lymph nodes, 11 cases (73%) with good control of the tumor received a total dose of >50 Gy (median EQD_2 dose: 60 Gy), whereas all four cases with recurrence received a total dose of ≤50 Gy. In FIGO Stage I cases, three of eight patients (38%) who did not undergo prophylactic lymph node irradiation had lymph node recurrence, compared with two of 12 patients (17%) who received prophylactic pelvic irradiation (median EQD_2 dose: 50 Gy), but the difference was not significant ($P = 0.29$). The rate of lymph node recurrence remained high (40%), even with prophylactic irradiation, in all Stage III or IV patients (median EQD_2 dose: 50 Gy).

Practice patterns and recurrence rate

Practice patterns (single modality vs combined therapy) were analyzed according to tumor or patient characteristics (Table 4). Patients with FIGO Stage I/II or clinical N1 stage had a higher recurrence rate in treatment with a single

Table 2. Univariate analysis of prognostic factors for OS, PFS and LRC in patients with carcinoma of the vagina treated with definitive radiotherapy.

Characteristics	*n*	3-year OS	*P*	3-year DFS	*P*	3-year LRC	*P*
		%		%		%	
Age, years			0.114		0.207		0.846
<70	25	90		66		70	
≥70	24	73		47		73	
Histological type			0.591		0.037		0.028
SCC	42	88		66		77	
Others	7	50		19		38	
FIGO stage			0.687		0.026		0.019
I/II	39	83		63		77	
III/IV	10	83		40		48	
Clinical N stage			0.395		0.100		0.023
N0	34	84		65		80	
N1	15	82		47		53	
size, cm			0.477		0.582		0.117
<4	31	82		59		77	
≥4	18	85		58		62	
Involvement of lower 1/3			0.976		0.831		0.280
NO	30	85		59		77	
YES	19	81		58		62	
Chemotherapy			0.268		0.657		0.764
NO	43	85		58		72	
Yes	6	67		63		63	
Brachytherapy			0.555		0.258		0.075
YES	41	84		61		76	
NO	8	67		50		50	

OS = overall survival rate, DFS = disease-free survival rate, LRC = loco-regional control rate, SCC = squamous cell carcinoma, FIGO = Federation of Gynecology and Obstetrics.

modality compared with that with combined modalities. However, all three patients with clinical N1 stage who had recurrence had received EBRT alone as a single modality. Additionally, these patients received ≤50 Gy to the enlarged lymph node and subsequently had recurrence in the same lesion. Age, histological type, tumor size and length of vaginal invasion did not influence the recurrence rate in either single or combined modalities.

Toxicities

Treatment-related late toxicity was evaluated using the Common Terminology Criteria for Adverse Events ver. 4.0. Six patients (12%) had Grade 3 late toxicities, including rectovaginal fistula ($n = 5$) and perforation of the sigmoid colon ($n = 1$). All of these patients were treated with ISBT, and two had a history of radiotherapy for pelvic lesions. Patients with previous pelvic irradiation had higher rates of Grade 3 complications compared with those without previous pelvic irradiation [2/5 (40%) vs 4/44 (9%), P = 0.04]. There were no vaginal complications of Grade 3 or higher and no Grade 4–5 late toxicities.

DISCUSSION

The outcomes in the current study are similar to or better than those in previous studies and showed 3-year and 5-year OS rates of 39–63% and 21–57%, respectively, for patients treated with HDR brachytherapy with or without EBRT [2, 3, 5], and rates of 0–15.8% for serious late complications [2–6]. However, the main reason for the better outcome may

Table 3. Correlation between total EQD_2 dose and tumor control according to FIGO stage

		FIGO	*n*	Mean EQD_2 ($Gy_{\alpha/\beta 10}$)	Median EQD_2 ($Gy_{\alpha/\beta 10}$)	Range	Percent recurrence (number)
Primary	Overall			65	70	38–96	18 (9/49)
		I	20	57	57	38–80	5 (1/20)
		II	19	70	70	53–96	16 (3/19)
		III–IV	10	73	79	44–90	50 (5/10)
Gross node	Overall		15	56	60	44–66	27 (4/15[a])
Prophylactic	Overall			39	50	0–60	22 (11/49)
		I[b]	8	0	0	0	38 (3/8)
		I	12	46	50	30–50	17 (2/12)
		II	19	47	50	30–60	11 (2/19)
		III–IV	10	49	50	40–60	40 (4/10)

[a]All four cases with recurrence received a total dose of 50 Gy or less. [b]Prophylactic lymph node irradiation was not performed. EQD_2 = equivalent dose in 2-Gy fractions, FIGO = Federation of Gynecology and Obstetrics.

be the shorter median follow-up period of 33 months in the current study.

The varying outcomes for the three hospitals and the lack of a pre-specified protocol were significant limitations in the analysis and interpretation of outcomes. To overcome these limitations and to compare the combined total dose in several different modalities and the extent of the radiation field, we calculated the total dose as an EQD_2 dose using the linear–quadratic model. We also divided the radiation field into three regions (primary lesion, enlarged lymph nodes, and prophylactic lymph nodes) and then evaluated the respective recurrence rates. Additionally, practice patterns (single modality vs combined therapy) were analyzed according to tumor or patient characteristics.

Patients with FIGO Stage I/II had a higher recurrence rate in a single modality. Additionally, among Stage I patients, 40% received radiotherapy for the primary lesion alone without prophylactic lymph node coverage. In cases without prophylactic lymph node irradiation, the recurrence rate in the prophylactic lesion tended to be higher, compared with cases with pelvic node irradiation (38% vs 17%) ($P = 0.29$). In a study of 21 FIGO Stage I patients treated with local radiation only (without regional node coverage), Frank *et al.* [10] found that three of nine patients (33%) treated with brachytherapy alone developed recurrent disease in the pelvis, whereas patients who had received EBRT with or without brachytherapy did not have pelvic recurrence. Collectively, these findings indicate that the optimal radiation practice is EBRT with brachytherapy (interstitial or intracavitary) regardless of FIGO stage. Patients with clinical N1 stage had a higher recurrence rate after treatment with a single modality, and all three patients with clinical N1 stage who had recurrence had received EBRT as a single modality. These patients received ≤50 Gy to the enlarged lymph node and had recurrence in the same lesion. These data indicate that recurrence in these patients was due mainly to a suboptimal EBRT dose to enlarged lymph nodes, and not to the practice pattern.

Improvement of treatment outcome in cases of FIGO Stage III or IV vaginal cancer remains a significant challenge. In previous studies, 5-year OS rates for patients with Stage III disease have ranged from 4% to 58% [2, 3, 15], with LRC rates of 57% to 69% [2,9,10]. The outcome for Stage IV disease is even worse, with survival rates of 0% to 35% [2, 3,15].

In this study, the local recurrence rate was very high (50%) with a median EQD_2 of 79 Gy, and the rate of prophylactic lymph node recurrence was also high (40%) with a median EQD_2 of 50 Gy for Stage III–IV tumors. The total dose for the primary lesion or prophylactic lymph node may be considered as the upper limit for normal tissue. However, 3D image-based HDR brachytherapy has recently been used in cervical cancer. Therefore, these results using EQD_2 of the prescribed dose require verification in studies using image-based brachytherapy.

For achievement of higher LRC, concurrent chemoradiation (CCRT) therapy has been attempted for locally advanced disease. In a study of 14 patients with vaginal cancer [including 11 (71%) with Stage II or III disease] who received CCRT with a 5-FU-based regimen, only one patient had local recurrence and died of the disease [16]. In a review of 12 patients with vaginal cancer in Stages II to IV who

Table 4. Practice pattern and recurrence rate according to tumor and patient characteristics

	Combined modalities recurrence rate		Single modality recurrence rate		
	%	Number	%	Number	*P*
Age, years					
<69	29	(6/21)	75	(3/4)	0.076
≥70	23	(3/13)	36	(4/11)	0.476
Histological type					
SCC	21	(6/30)	42	(5/12)	0.149
Others	75	(3/-4)	67	(2/3)	0.809
FIGO stage					
I/II	15	(4/26)	46	(6/13)	0.038
III/IV	50	(4/8)	100	(2/2)	0.197
Clinical N stage					
N0	18	(4/22)	42	(5/12)	0.137
N1	33	(4/12)	100	(3/3)	0.038
Size, cm					
<4	17	(4/23)	43	(3/8)	0.241
≥4	45	(5/11)	57	(4/7)	0.629
Involvement of lower 1/3					
No	19	(4/21)	44	(4/9)	0.149
Yes	38	(5/13)	50	(3/6)	0.636

SCC = squamous cell carcinonma, FIGO = International Federation of Gynecology and Obstetrics.

were treated with concurrent weekly cisplatin at a dose of 40 mg/m^2 for 5 weeks, Samant *et al.* found 5-year OS and PFS rates of 66% and 75%, respectively [17]. These findings led to the conclusion that CCRT is feasible and effective for management of primary vaginal cancer and should be considered as an option for patients being treated with curative intent [17].

Despite these promising outcomes in patients with vaginal cancer treated with CCRT, a randomized trial comparing radiation alone with radiation plus chemotherapy has not been performed in vaginal cancer. Additionally, many retrospective studies of CCRT for primary vaginal cancer are limited by the small number of patients or inclusion of other cancers, such as cervical and vulvar cancers. Therefore, further studies are needed to clarify the potential therapeutic benefits of CCRT. However, the design and execution of prospective randomized trials is challenging because of the rarity of this disease. In this study, the treatment and outcomes for vaginal cancer were acceptable, but EBRT with brachytherapy (interstitial or intracavitary) was needed regardless of FIGO stage. Thus, improvement of treatment outcome in cases of FIGO Stage III or IV remains a significant challenge.

FUNDING

This work was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number 25861097. Funding to pay the Open Access publication charges for this article was provided by the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number 25861097.

REFERENCES

1. Hacker NF, Eifel PJ, van der Velden J. Cancer of the vagina. *Int J Gynaecol Obstet* 2012;**119S2**:S97–9.
2. Nonaka T, Nakayama Y, Mizoguchi N *et al.* Definitive radiation therapy for invasive carcinoma of the vagina: impact of high-dose rate intracavitary brachytherapy. *Int J Clin Oncol* 2013;**18**:314–20.
3. Mock U, Kucera H, Fellner C *et al.* High-dose-rate (HDR) brachytherapy with or without external beam radiotherapy in the treatment of primary vaginal carcinoma: long-term results and side effects. *Int J Radiat Oncol Biol Phys* 2003;**56**:950–7.
4. Nanavati PJ, Fanning J, Hilgers RD *et al.* High-dose-rate brachytherapy in primary stage I and II vaginal cancer. *Gynecol Oncol* 1993;**51**:67–71.
5. Kushner DM, Fleming PA, Kennedy AW *et al.* High dose rate ^{192}Ir afterloading brachytherapy for cancer of the vagina. *Br J Radiol* 2003;**76**:719–725.
6. Murakami N, Kasamatsu T, Sumi M *et al.* Radiation therapy for primary vaginal carcinoma. *J Radiat Res* 2013;**54**: 931–7.
7. Chyle V, Zagars GK, Wheeler JA *et al.* Definitive radiotherapy for carcinoma of the vagina: outcome and prognostic factors. *Int J Radiat Oncol Biol Phys* 1996;**35**:891–905.
8. Jang WI, Wu HG, Ha SW *et al.* Definitive radiotherapy for treatment of primary vaginal cancer: effectiveness and prognostic factors. *Int J Gynecol Cancer* 2012;**22**:521–7.
9. Tran PT, Su Z, Lee P *et al.* Prognostic factors for outcomes and complications for primary squamous cell carcinoma of the vagina treated with radiation. *Gynecol Oncol* 2007; **105**:641–9.
10. Frank SJ, Jhingran A, Levenback C *et al.* Definitive radiation therapy for squamous cell carcinoma of the vagina. *Int J Radiat Oncol Biol Phys* 2005;**62**:138–47.
11. Shah CA, Goff BA, Lowe K *et al.* Factors affecting risk of mortality in women with vaginal cancer. *Obstet Gynecol* 2009;**113**:1038–45.
12. Creasman WT, Phillips JL, Menck HR. The National Cancer Data Base report on cancer of the vagina. *Cancer* 1998;**83**: 1033–40.
13. Perez CA, Camel HM, Galakatos AE *et al.* Definitive irradiation in carcinoma of the vagina: long-term evaluation of results. *Int J Radiat Oncol Biol Phys* 1988;**15**:1283–90.

14. Stock RG, Chen AS, Seski J. A 30-year experience in the management of primary carcinoma of the vagina: analysis of prognostic factors and treatment modalities. *Gynecol Oncol* 1995;**56**:45–52.
15. Fine BA, Piver MS, McAuley M *et al.* The curative potential of radiation therapy in the treatment of primary vaginal carcinoma. *Am J Clin Oncol* 1996;**19**:39–44.
16. Dalrymple JL, Russell AH, Lee SW *et al.* Chemoradiation for primary invasive squamous cell carcinoma of the vagina. *Int J Gynecol Cancer* 2004;**14**:110–7.
17. Samant R, Lau B, EC *et al.* Primary vaginal cancer treated with concurrent chemoradiation using Cis-platinum. *Int J Radiat Oncol Biol Phys* 2007;**69**:746–50.

Journal of Radiation Research, Vol. 56, No. 5, 2015, pp. 841–848
doi: 10.1093/jrr/rrv036
Advance Access Publication: 24 June 2015

Treatment outcomes of patients with FIGO Stage I/II uterine cervical cancer treated with definitive radiotherapy: a multi-institutional retrospective research study

Takuro Ariga[1], Takafumi Toita[1]*, Shingo Kato[2], Tomoko Kazumoto[3], Masaki Kubozono[4], Sunao Tokumaru[5], Hidehiro Eto[6], Tetsuo Nishimura[7], Yuzuru Niibe[8], Kensei Nakata[9], Yuko Kaneyasu[10,21], Takeshi Nonoshita[11], Takashi Uno[12], Tatsuya Ohno[13], Hiromitsu Iwata[14], Yoko Harima[15], Hitoshi Wada[16], Kenji Yoshida[17], Hiromichi Gomi[18], Hodaka Numasaki[22], Teruki Teshima[19], Shogo Yamada[4] and Takashi Nakano[20]

[1]Department of Radiology, Graduate School of Medical Science, University of the Ryukyus, 207 Uehara, Nishihara-cho, Okinawa, 903-0215, Japan
[2]Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan
[3]Department of Radiation Oncology, Saitama Cancer Center, Saitama, Japan
[4]Department of Radiation Oncology, Tohoku University School of Medicine, Sendai, Japan
[5]Department of Radiology, Saga University, Saga, Japan
[6]Department of Radiology, Kurume University Hospital, Fukuoka, Japan
[7]Division of Radiation Oncology, Shizuoka Cancer Center Hospital, Shizuoka, Japan
[8]Department of Radiology and Radiation Oncology, Kitasato University School of Medicine, Kanagawa, Japan
[9]Department of Radiology, Sapporo Medical University, Sapporo, Japan
[10]Department of Radiation Oncology, Hiroshima University Graduate School of Biomedical & Health Sciences, Hiroshima, Japan
[11]Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[12]Department of Diagnostic Radiology and Radiation Oncology, Chiba University Graduate School of Medicine, Chiba, Japan
[13]Gunma University Heavy Ion Medical Center, Gunma University, Gunma, Japan
[14]Department of Radiation Oncology, Nagoya Proton Therapy Center, Nagoya City West Medical Center, Aichi, Japan
[15]Department of Radiology, Takii Hospital, Kansai Medical University, Osaka, Japan
[16]Department of Radiation Oncology, Miyagi Cancer Center, Miyagi, Japan
[17]Division of Radiation Oncology, Kobe University Graduate School of Medicine, Hyogo, Japan
[18]Department of Radiation Oncology, St Marianna University, School of Medicine, Kanagawa, Japan
[19]Department of Radiation Oncology, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka, Japan
[20]Department of Radiation Oncology, Gunma University Graduate School of Medicine, Gunma, Japan
[21]Department of Radiation Oncology, National Hospital Organization, Fukuyama Medical Center, Hiroshima, Japan
[22]Department of Medical Physics and Engineering, Osaka University Graduate School of Medicine, Osaka, Japan
*Corresponding author. Department of Radiology, Graduate School of Medical Science, University of the Ryukyus, 207 Uehara, Nishihara-cho, Okinawa, 903-0215, Japan. Tel: +81-98-895-1162; Fax: +81-98- 895-1420; Email: b983255@med.u-ryukyu.ac.jp
Received February 20, 2015; Revised May 7, 2015; Accepted May 14, 2015

ABSTRACT

The purpose of this study was to analyze the patterns of care and outcomes of patients with FIGO Stage I/II cervical cancer who underwent definitive radiotherapy (RT) at multiple Japanese institutions. The Japanese Radiation Oncology Study Group (JROSG) performed a questionnaire-based survey of their cervical cancer patients who were treated with definitive RT between January 2000 and December 2005. A total of 667 patients were entered in this study. Although half of the patients were considered suitable for definitive RT based on the clinical features of the tumor, about one-third of the patients were prescribed RT instead of surgery because of poor medical status.

The RT schedule most frequently utilized was whole-pelvic field irradiation (WP) of 30 Gy/15 fractions followed by WP with midline block of 20 Gy/10 fractions, and high-dose-rate intracavitary brachytherapy (HDR-ICBT) of 24 Gy/4 fractions prescribed at point A. Chemotherapy was administered to 306 patients (46%). The most frequent regimen contained cisplatin (CDDP). The median follow-up time for all patients was 65 months (range, 2–135 months). The 5-year overall survival (OS), pelvic control (PC) and disease-free survival (DFS) rates for all patients were 78%, 90% and 69%, respectively. Tumor diameter and nodal status were significant prognostic indicators for OS, PC and DFS. Chemotherapy has potential for improving the OS and DFS of patients with bulky tumors, but not for non-bulky tumors. This study found that definitive RT for patients with Stage I/II cervical cancer achieved good survival outcomes.

KEYWORDS: cervical cancer, early stage, radiotherapy

INTRODUCTION

Several retrospective studies have reported favorable outcomes for patients with cervical cancer who were treated with definitive radiotherapy (RT), not only for early-stage, but also for advanced-stage cancer [1–9]. One randomized clinical trial (RCT) found that there was no significant difference in the overall survival (OS) of patients treated with surgery and those treated with definitive RT [10]. After the results of that RCT, the clinical practice guidelines of the National Comprehensive Cancer Network (NCCN) recommended both surgery and definitive RT as treatment modalities for patients with resectable early-stage uterine cervical cancer [11, 12]. The RCT also found significantly poorer outcomes for patients with bulky tumor (diameter >4 cm) who underwent either surgery or definitive RT [10]. Therefore, additional treatment is thought necessary for patients with bulky tumors. Although several RCTs of neoadjuvant chemotherapy (NAC) followed by surgery versus surgery alone have been performed, none demonstrated improved survival for the NAC arm [13, 14]. Intermediate or high-risk pathological findings in the surgical specimen are indications for adjuvant treatments such as postoperative RT or concurrent chemoradiotherapy (CCRT) [11, 12]. However, increased incidence and grades of complications were reported for patients treated with surgery followed by postoperative RT [10]. On the other hand, several RCTs have demonstrated that definitive CCRT improved survival compared with RT alone [15]. The effect was significant, especially for patients with FIGO Stage I or II uterine cervical cancer [15]. Based on these findings, it seems reasonable to choose definitive RT or CCRT as the first treatment, except for some surgical cases who would not need adjuvant RT/CCRT.

The Japan Society of Obstetrics and Gynecology (JSOG) have periodically conducted a nationwide clinical practice pattern survey of uterine cervical cancer. Although the Japan Society of Gynecologic Oncology (JSGO) guidelines have recommended either surgery or definitive RT as treatments for early-stage cervical cancer [14], the JSOG survey reported that only 7% of patients with Stage I cervical cancer and 33% of patients with Stage II disease were treated with RT or CCRT [16].

Most clinical data on RT for Stage I/II Japanese cervical cancer patients have been derived from the experience of single institutions with small numbers of patients. Additional evidence on the efficacy and safety of RT for patients with early-stage cervical cancer is needed before the use of RT for these patients will increase. In addition, there is no available information on the use of RT for patients with bulky disease, although treatment results from a prospective multicenter study of RT for non-bulky disease have recently been reported [17]. The objective of this retrospective study was to analyze the treatment outcomes of a large number of patients with early cervical cancer who were treated with RT at multiple Japanese institutions.

MATERIALS AND METHODS

The Japanese Radiation Oncology Study Group (JROSG) sent a questionnaire-based survey to 18 institutions that treated patients with FIGO Stage I/II uterine cervical cancer between January 2000 and December 2005 using definitive RT. Data were sent back to the data center at the Department of Medical Physics and Engineering, Osaka University.

The study was approved by the institutional ethical committee affiliated with the study chair (University of the Ryukyus). The questionnaire consisted of the following items: age, FIGO stage, indications for RT, pathology, maximum tumor diameter, lymph node status, modalities used for evaluation, start and end date of external beam radiotherapy (EBRT), total dose and dose per fraction of EBRT (with or without midline block), dose rate of intracavitary brachytherapy (ICBT), dose prescribing point of ICBT, total dose and dose/fraction (fr) of ICBT, chemotherapy regimen and timing of delivery (concurrent or not), starting date of chemotherapy, date of recurrence, recurrence site, and date and site of adverse effects (rectum, small intestine, bladder, other organs). The median follow-up time of all patients was 65 months (range, 2–135 months).

The Kaplan–Meier method was used to derive estimates of the OS, pelvic control (PC), and disease-free survival (DFS) rate. For all tests, P values < 0.05 were considered statistically significant. The tests for equivalence of the estimates of OS, PC and DFS consisted of the Breslow and log-rank tests. Multivariate analysis was performed using the Cox proportional hazards regression model. Adverse effects that occurred 90 days or more from the start of treatment were defined as late complications. Late complications were classified according to the Radiation Therapy Oncology Group (RTOG) late morbidity scoring criteria [18].

RESULTS

A total of 667 patients were entered in this study. Patients treated with ICBT alone were excluded. Table 1 shows the number of patients from each institution. Table 2 summarizes the characteristics of the patients, focusing on the tumor. Although half of the patients were considered suitable for definitive RT, based on the features of the

Table 1. Participating institutions

Institution	Number of patients
National Institute of Radiological Sciences	114
University of the Ryukyus	100
Saitama Cancer Center	72
Tohoku University	58
Saga University	52
Kurume University	45
Shizuoka Cancer Center Hospital	34
Kitasato University	31
Sapporo Medical University	27
Hiroshima University	25
Kyushu University	23
Chiba University	22
Gunma University	18
Nagoya City University	17
Kansai Medical University	10
Yamagata University	9
Kobe University	7
St Marianna University	3
Total:	667

Table 2. Patient and tumor characteristics (n = 667)

Characteristics	n	%
Median age (year): 63 (range: 24–95)		
FIGO stage		
IA	1	
IB	199	30
IB1	122	18
IB2	51	8
IB unknown	26	4
IIA	87	13
IIB	380	57
Pathology		
SqCC	612	92
Adeno + AS	46	7
other	9	1
Primary tumor diameter		
median (mm): 41 (range: 3–125)		
<4 cm	262	39
≥4 cm	352	53
unmeasurable	53	8
	667	
Lymph node metastasis[a]		
negative	512	78
positive	145	22
unknown	10	1
Indication for definitive radiotherapy:		
Characteristics of the cancer	334	50
Unsuitable for surgery (e.g. poor physical condition)	239	36
Patient's decision	47	7
Other	47	7

[a]Lymph nodes ≥10 mm in minimum diameter by computed tomography or magnetic resonance imaging. SqCC = squamous cell carcinoma, Adeno = adenocarcinoma, AS = ademosquamous carcinoma.

tumor, about one-third of the patients were prescribed RT instead of surgery because of age or poor physical condition.

Table 3 summarizes the details of RT and chemotherapy. The median total dose of EBRT without a midline block (MB) was 30 Gy/15 fr (range, 0–65 Gy), and the median total dose with MB was 20 Gy/10 fr (range, 0–50.4 Gy). The median total dose of ICBT at point A was 24 Gy/4 fr (range, 5–35 Gy for high-dose-rate [HDR] and 20–54 Gy for low-dose-rate [LDR]). The median overall treatment time for RT was 47 days (range, 14–160). The most frequent chemotherapy was concurrent delivery of cisplatin (CDDP).

The five-year OS, PC and DFS rates for all 667 patients were 78% (95% confidence interval [CI], 75%–81%), 90% (95% CI, 88%–93%) and 69% (95% CI, 66%–73%), respectively. Mortality included 113 patients who died of cervical cancer, and 45 patients who died of other causes. Figure 1 shows the OS curves according to FIGO stage. Table 4 shows the 5-year actuarial outcomes of various tumor-related factors. Patients with adenocarcinoma and adenosquamous carcinoma had significantly poorer OS and DFS than patients with squamous cell carcinoma, but there was no significant difference in PC. Patients with bulky tumor (≥4 cm) had significantly poorer OS, PC and DFS than those with non-bulky tumors. Patients with lymph node metastasis had significantly poorer OS, PC and DFS than those without nodal metastasis. Table 5 shows the 5-year actuarial outcomes according to maximum tumor size and lymph node status.

For all 667 patients, no significant differences were observed in the respective OS, PC or DFS of patients treated with RT alone or those treated with chemoradiotherapy (5-year OS: 81% vs 76%, $P = 0.14$; 5-year PC: 89% vs 92%, $P = 0.13$; 5-year DFS: 81% vs 76%, $P = 0.98$).

Chemotherapy was administered to 68% of patients with bulky tumors (240 of 352) and 79% of lymph node metastasis patients (114 of 145). Chemotherapy was most frequently administered to these high-risk patients concurrently with RT.

Table 3. Details of radiotherapy and chemotherapy

	n	%
Radiotherapy (*n* = 667)		
EBRT		
Whole pelvic field	622	94
Extended field	27	4
Small pelvic field[a]	10	1
Others or details not available	8	1
	667	
ICBT		
HDR-ICBT	637	95
LDR-ICBT	24	4
No ICBT	6	1
Chemotherapy (*n* = 306)		
Concurrent	268	88
Neoadjuvant	18	6
Adjuvant	2	
Intra-arterial injection	5	2
Details were not available	13	4

[a]Small pelvic field excluded the common iliac region. EBRT = external beam radiotherapy, ICBT = intracavitary brachytherapy, HDR = high-dose-rate, LDR = low-dose-rate.

Table 6 summarizes the 5-year actuarial outcomes as a function of tumor size/nodal status and treatment. Among the patients with bulky tumors, OS and DFS were significantly better for patients treated with chemotherapy than for those who did not undergo chemotherapy, and there was no significant difference in PC between the two treatment groups. For patients with non-bulky tumors, there were no significant differences in OS, PC or DFS between the patients who were treated with CCRT and those who received RT alone.

Among lymph-node–positive patients, OS was better for patients treated with chemotherapy than for those who did not undergo chemotherapy. There were no significant differences in the PC or DFS between the two treatment groups. For patients without lymph node metastasis, similar trends were observed. OS was better for patients treated with chemotherapy than for those who did not receive chemotherapy, and there were no significant differences in PC or DFS between the two treatment groups.

Table 7 summarizes the results of multivariate analysis of outcomes according to prognostic factors. Administration of chemotherapy had a significant impact on OS and DFS, but there was no significant impact on PC.

Recurrence developed in 159 of 667 patients as follows: 60 patients (9%) had pelvic recurrence alone, 86 patients (13%) had distant metastases only, and 13 patients (2%) developed both pelvic recurrence and distant metastases. The most frequent site of distant metastasis was the extrapelvic lymph nodes. The rate and site of metastases to lymph nodes were as follows: 52 patients (8%) had para-aortic metastatic lymph nodes, 18 patients (3%) had scalene nodes, 12 patients (2%) had mediastinal nodes, and 4 patients (1%) had other nodes. Other sites of metastases were as follows: 35 patients (5%) had lung metastases, 16 patients (2%) had bone metastases, 5 patients (1%) had liver metastases, and 4 patients (0.6%) had brain metastases.

Late complications developed in 178 patients (27%). There were 35 patients (5%) who developed severe (Grade 3 or higher) complications. The 5-year severe complication rate was 5.5% (95% CI: 3.6%–7.9%). The details are shown in Table 8. LDR-ICBT had a significant impact on the incidence of severe complications ($P = 0.036$).

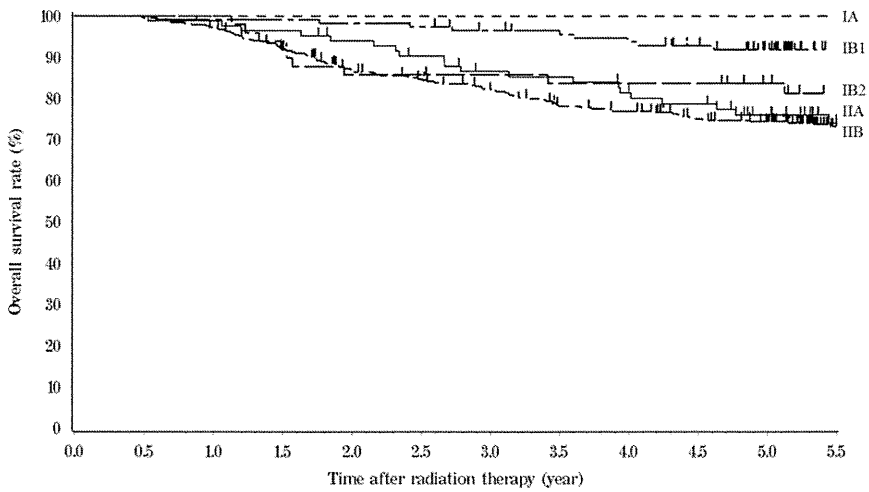

Fig. 1. Overall survival curves of cervical cancer patients treated with definitive radiotherapy according to FIGO stage.

Table 4. Five-year actuarial outcomes according to tumor-related factors ($n = 667$)

		(*n*)	OS (%)	PC (%)	DFS (%)
FIGO stage					
	IA	1	100	100	100
	IB	199			
	IB1	122	92	98	86
	IB2	51	84	96	77
	IB unknown	26	65	91	61
	IIA	87	76	89	68
	IIB	380	74	88	65
			$P < 0.001$	$P = 0.003$	$P = 0.001$
Pathology	SqCC	612	80	91	72
	Adeno + AS	46	61	89	50
			$P = 0.001$	NS	$P = 0.001$
Maximum tumor diameter					
	<4 cm	262	83	93	75
	≥4 cm	352	75	88	65
			$P = 0.02$	$P = 0.01$	$P = 0.004$
Lymph node metastasis					
	Negative	512	82	92	75
	Positive	145	65	83	50
			$P < 0.001$	$P < 0.001$	$P < 0.001$

OS = overall survival, PC = pelvic control, DFS = disease-free survival, SqCC = squamous cell carcinoma, Adeno = adenocarcinoma, AS = adenosquamous carcinoma.

Table 5. Five-year actuarial outcomes by tumor size/nodal status

		n	OS (%)	PC (%)	DFS (%)
Tumor size[a]	Nodal status				
Bulky	Positive[b]	119	64	82	49
Bulky	Negative	230	80	91	74
Non-bulky	Positive[b]	23	68	90	56
Non-bulky	Negative	237	84	94	77
			$P < 0.001$	$P = 0.003$	$P < 0.0001$

OS = overall survival, PC = pelvic control, DFS = disease-free survival, [a]Bulky = maximum tumor diameter ≥4 cm. [b]Lymph nodes with minimum diameter ≥10 mm as measured by computed tomography or magnetic resonance imaging.

Other factors (total dose of EBRT without MB, total dose and dose/fr HDR-ICBT, administration of chemotherapy) did not have a significant impact on the incidence of severe complications.

DISCUSSION

To the best of our knowledge, this is the largest study ($n = 667$) of patients with early cervical cancer who were treated with definitive

RT, mainly with HDR-ICBT. The standard Japanese RT schedule achieved favorable survival rates and acceptable rates of complications that were comparable with previous studies [1–9].

The JSOG survey reported that the 5-year OS rates of patients with Stage I cervical cancer who were treated with surgery or RT were 93% and 80%, respectively, and the rates of Stage II patients were 81% and 74%, respectively [16]. The 5-year OS rates of our Stage I/II patients treated with RT were similar to the results of the JSOG RT group, but poorer than the results of the JSOG surgery group. Landoni *et al.* reported the results of their RCT, showing that the 5-year OS of Stage IB–IIA patients undergoing surgery was 83%, which was equivalent to the survival of patients undergoing definitive RT [10]. Selection bias might partially account for why the results of our study were inferior to the JSOG surgery group. The JSOG survey reported that ≥90% of Stage I patients and 67% of Stage II patients were treated with surgery [16]. It may be that the JSOG RT patients were mainly those who were unsuitable for surgery (poor general physical condition, elderly, metastatic lymph nodes). Our study might have had a similar selection bias. About one-third of our patients were elderly and/or in poor physical condition; one-third of the patients eventually died of other diseases.

Table 6. Five-year actuarial outcomes as a function of tumor size/nodal status and treatment

		n	OS (%)	PC (%)	DFS (%)
Tumor size					
Bulky	RT	112	60	86	56
(≥4 cm)	CRT	240	81	88	70
			$P = 0.002$	NS	$P = 0.02$
Non-bulky	RT	206	83	94	76
(<4 cm)	CRT	56	81	90	72
			NS	NS	NS
Nodal status					
Positive[a]	RT	31	43	77	36
	CRT	114	71	85	54
			$P = 0.062$	NS	NS
Negative	RT	325	79	91	73
	CRT	187	87	93	80
			$P = 0.016$	NS	NS

OS = overall survival, PC = pelvic control, DFS = disease-free survival, RT = radiotherapy alone, CRT = chemoradiotherapy. [a]Lymph nodes with minimum diameter ≥10 mm as measured by computed tomography or magnetic resonance imaging.

A prospective study of definitive RT for patients with Stage I/II cervical cancer without bulky tumor or lymph node metastasis demonstrated an excellent 3-year PC of 96% and a 3-year OS of 95% [17]. In our study, the patients without bulky tumors and lymph node metastasis achieved good OS compared with the JSOG patients who underwent surgery. Even though they were treated with RT alone, non-bulky tumor and/or node-negative patients achieved good OS, PC and DFS. In contrast, our study patients with bulky tumors and/or lymph node metastasis had poor OS and PC. RTOG9001, a RCT of definitive CCRT, also included patients with Stage I/II cervical cancer with bulky tumors (>5 cm) and/or lymph node metastasis, as well as Stage III/IVA patients [19]. The outcomes of RTOG9001 were good for patients with Stage I/II disease treated with CCRT; the 5-year PC was 87% and the 5-year OS was 79%.

Our study patients treated with CCRT achieved PC and OS, similar to RTOG9001. We believe the fact that our outcomes were inferior to those of the JSOG patients undergoing surgery might have been accounted for by the low rate of chemotherapy administration to our patients. In our study, only 70% of patients were treated with chemotherapy, while the remaining patients did not receive chemotherapy even if they had bulky tumors and/or lymph node metastasis. This lower rate of chemotherapy treatment for high-risk patients might have adversely affected our outcomes, which were slightly worse than the JSOG surgery patients. In our study, patients with bulky tumors who were treated with chemotherapy achieved significantly better OS and DFS compared with patients who did not receive chemotherapy, and the same trend was observed for the patients with metastatic lymph nodes. Our results indicate that

Table 7. Multivariate analyses for outcomes according to prognostic factors

	OS (%)			PC (%)			DFS (%)		
	HR	95%CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age (<63 vs ≥63)			NS			NS			NS
FIGO Stage (IB1 vs IB2 vs IIA vs IIB)	1.4	1.2–1.7	0.0005	2.0	1.3–2.9	0.001	1.3	1.1–1.5	0.0003
Pathology (SCC vs Adeno/AS)	2.3	1.3–4.3	0.005			NS	2.3	1.4–3.9	0.0009
Tumor diameter (<4 cm vs ≥4 cm)			NS			NS			NS
Lymph node status (negative vs positive)	2.1	1.4–3.1	0.0003	1.9	1.0–3.4	0.05	2.6	1.9–3.7	<0.0001
Administration of chemotherapy (no vs yes)	0.4	0.3–0.6	<0.0001			NS	0.6	0.4–0.8	0.0006

HR = hazards ratio, CI = confidence interval, OS = overall survival, PC = pelvic control, DFS = disease-free survival, Adeno = adenocarcinoma, AS = adenosquamous carcinoma.

Table 8. Details of late complications* ($n = 667$)

	Grade 1		Grade 2		Grade 3		Grade 4		Total	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Proctitis	63	9	30	4	5	1	2	0.3	100	15
Cystitis	14	2	20	3	3	0.4	3	0.4	40	6
Enterocolitis	12	2	17	3	8	1	2	0.3	39	6
Others	11	2	17	3	7	1	8	1	43	6

*Some patients had complications in multiple organs. Toxicity was judged by the Radiation Therapy Oncology Group late morbidity scoring criteria.

chemotherapy did not provide additional improvement of local control for Stage I/II patients, although OS and DFS were improved by chemotherapy. Based on these findings, although chemotherapy acts as an RT sensitizer, we think that the predominant role of chemotherapy for Stage I/II patients is to prevent distant metastases. Patients with bulky tumors and/or lymph node metastasis have been regarded as being at some risk of distant micrometastasis; therefore, we believe that it is important to administer chemotherapy if applicable. Prospective clinical trials of CCRT for Stage I/II cervical cancer patients with bulky tumors and/or lymph node metastasis are warranted. Because it is believed that patients in poor physical condition or of advanced age may be poor candidates for chemotherapy, we should also conduct trials that investigate suitable regimens for elderly patients or those in poor physical condition. Mitsuhashi *et al.* reported acceptable toxicity for low-dose CDDP for elderly patients [20]. Several reports have shown that nedaplatin achieved good survival with acceptable toxicity [21, 22]. We think that conducting clinical trials using similar less toxic regimens or drugs is valuable.

However, our patients with non-bulky tumors achieved good OS, PC and DFS, even though they were treated with RT alone. These findings are consistent with the results of a prospective clinical trial previously performed in Japan [17]. Taken together with our results, the findings suggest that for patients with non-bulky tumors, RT alone may be an adequate treatment for achieving good PC, OS and DFS.

Our study had some limitations. Some patients in this study had inadequate follow-up periods. This could be a critical flaw. If an adequate follow-up had been achieved for all patients, the outcomes might have changed. The JSOG's annual survey for survival analysis only includes patients from institutions with follow-up rates of >80% for treated patients [16]. A national cancer registration system that can achieve an adequate follow-up should be developed. Another limitation was on the types of data collected in this study. Unfortunately, we minimized the numbers of survey items to reduce the workload of our collaborators.

In conclusion, this study demonstrated that definitive RT for patients with Stage I/II cervical cancer achieved excellent PC. The results indicate that definitive RT can be considered the treatment of choice for patients with early-stage cervical cancer. However, it was difficult to compare the survival outcomes of our series directly with the outcomes from surgical series because of the diversity of patient backgrounds in our series. Prospective studies of definitive CCRT for patients with bulky tumors and/or lymph node metastasis are warranted. Moreover, for appropriate outcome reports, we suggest that a national database of patients treated with RT in Japan should be developed.

ACKNOWLEDGEMENTS

The authors thank members of the Japan Radiation Therapy Oncology Group (JROSG) for their support.

FUNDING

Funding to pay the Open Access publication charge for this article was provided by a Grant-in-Aid for Scientific Research A (No. 21249066) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT); and the Japan Society for the Promotion of Sciences (No. 60158194); the National Cancer Center Research and Development Funds (23-A-21, 26-A-4 and 26-A-28) Japan.

REFERENCES

1. Nakano T, Kato S, Ohno T, et al. Long-term results of high-dose rate intracavitary brachytherapy for squamous cell carcinoma of the uterine cervix. *Cancer* 2005;103:92–101.
2. Wong FC, Tung SY, Leung TW, et al. Treatment results of high-dose-rate remote afterloading brachytherapy for cervical cancer and retrospective comparison of two regimens. *Int J Radiat Oncol Biol Phys* 2003;55:1254–64.
3. Wang CJ, Leung SW, Chen HC, et al. High-dose-rate intracavitary brachytherapy (HDR-IC) in treatment of cervical carcinoma: 5-year results and implication of increased low-grade rectal complication on initiation of an HDR-IC fractionation scheme. *Int J Radiat Oncol Biol Phys* 1997;38:391–8.
4. Souhami L, Corns R, Duclos M, et al. Long-term results of high-dose rate brachytherapy in cervix cancer using a small number of fractions. *Gynecol Oncol* 2005;97:508–13.
5. Petereit DG, Sarkaria JN, Potter DM, et al. High-dose-rate versus low-dose-rate brachytherapy in the treatment of cervical cancer: analysis of tumor recurrence—the University of Wisconsin experience. *Int J Radiat Oncol Biol Phys* 1999;45:1267–74.
6. Lee SW, Suh CO, Chung EJ, et al. Dose optimization of fractionated external radiation and high-dose-rate intracavitary brachytherapy for FIGO stage IB uterine cervical carcinoma. *Int J Radiat Oncol Biol Phys* 2002;52:1338–44.
7. Teshima T, Inoue T, Ikeda H, et al. High-dose rate and low-dose rate intracavitary therapy for carcinoma of the uterine cervix. Final results of Osaka University Hospital. *Cancer* 1993;72:2409–14.
8. Hareyama M, Sakata K, Oouchi A, et al. High-dose-rate versus low-dose-rate intracavitary therapy for carcinoma of the uterine cervix: a randomized trial. *Cancer* 2002;94:117–24.
9. Anker CJ, Cachoeira CV, Boucher KM, et al. Does the entire uterus need to be treated in cancer of the cervix? Role of adaptive brachytherapy. *Int J Radiat Oncol Biol Phys* 2010;76:704–12.
10. Landoni F, Maneo A, Colombo A, et al. Randomised study of radical surgery versus radiotherapy for stage Ib–IIa cervical cancer. *Lancet* 1997;350:535–40.
11. NCCN Clinical Practice Guidelines in Oncology – Cervical Cancer v.1.2015. National Comprehensive Cancer Network. http://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf (11 August 2014, date last accessed).

12. Saito T, Saito T, Suzuki N, et al. Chapter 3. Stage IB and II disease. In: Japan Society of Obstetrics and Gynecology (eds). *Treatment Guidelines for Uterine Cervical Cancer*, 2011 edition. Tokyo: Kanehara & Co. Ltd, 2011, 54–88 (in Japanese).
13. Tierney JF, Stewart LA, Parmar MK. Can the published data tell us about the effectiveness of neoadjuvant chemotherapy for locally advanced cancer of the uterine cervix? *Eur J Cancer* 1999;35:406–9.
14. Katsumata N, Yoshikawa H, Kobayashi H, et al. Phase III randomised controlled trial of neoadjuvant chemotherapy plus radical surgery vs radical surgery alone for stages IB2, IIA2, and IIB cervical cancer: a Japan Clinical Oncology Group trial (JCOG 0102). *Br J Cancer* 2013;108:1957–63.
15. Vale C, Tierney JF, Stewart LA, et al. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol* 2008;26:5802–12.
16. Aoki Y. The Treatment Annual Report in 2005. *Acta Obstet Gynaecol Jpn* 2013;65:1147–208.
17. Toita T, Kato S, Niibe Y, et al. Prospective multi-institutional study of definitive radiotherapy with high-dose-rate intracavitary brachytherapy in patients with nonbulky (<4-cm) stage I and II uterine cervical cancer (JAROG0401/JROSG04–2). *Int J Radiat Oncol Biol Phys* 2012;82:e49–56.
18. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;31:1341–6.
19. Eifel PJ, Winter K, Morris M, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. *J Clin Oncol* 2004;22: 872–80.
20. Mitsuhashi A, Uno T, Usui H, et al. Daily low-dose cisplatin-based concurrent chemoradiotherapy in patients with uterine cervical cancer with emphasis on elderly patients: a phase 2 trial. *Int J Gynecol Cancer* 2013;23:1453–8.
21. Niibe Y, Tsunoda S, Jobo T, et al. Phase II study of radiation therapy combined with weekly nedaplatin in locally advanced uterine cervical carcinoma (LAUCC): Kitasato Gynecologic Radiation Oncology Group (KGROG 0501)—initial analysis. *Eur J Gynaecol Oncol* 2008;29:222–4.
22. Mabuchi S, Ugaki H, Isohashi F, et al. Concurrent weekly nedaplatin, external beam radiotherapy and high-dose-rate brachytherapy in patients with FIGO stage IIIb cervical cancer: a comparison with a cohort treated by radiotherapy alone. *Gynecol Obstet Invest* 2010;69:224–32.

Esophagus
DOI 10.1007/s10388-015-0503-7

ORIGINAL ARTICLE

Efficacy of lymph node dissection for each station based on esophageal tumor location

Yuji Tachimori[1] · Soji Ozawa[2] · Hodaka Numasaki[3] · Hisahiro Matsubara[4] · Masayuki Shinoda[5] · Yasushi Toh[6] · Harushi Udagawa[7] · Mitsuhiro Fujishiro[8] · Tsuneo Oyama[9] · Takashi Uno[10] · The Registration Committee for Esophageal Cancer of the Japan Esophageal Society

Received: 24 February 2015 / Accepted: 8 July 2015

Abstract

Background The area of nodal dissection should be modified by the location of the primary tumor in an individual patient. The purpose of this study was to evaluate the efficacy of lymph node dissection based on station by the location of the primary tumor based on a multi-institutional nationwide registry of esophageal cancer.

Methods The study group comprised 1295 patients who underwent R0 resection and three-field esophagectomy. The Efficacy Index (EI) was calculated by multiplying the incidence of metastases to a station and the 5-year survival rate of patients with metastases to that station, by tumor location.

Results There were 550 patients without nodal metastases and 745 patients with them. In patients with upper tumors, the EIs of recurrent nerve nodes, cervical paraesophageal nodes and supraclavicular nodes were highest. In patients with middle tumors, the EIs of recurrent nerve nodes, cardiac nodes and lesser curvature nodes were highest, and the EIs of supraclavicular nodes and cervical paraesophageal nodes were not negligible. In patients with lower tumors, the EIs of cardiac nodes, lesser curvature nodes and left gastric artery nodes were highest, and the EIs of recurrent nerve nodes were also high.

Conclusion The EIs of certain node stations were different by location of the primary tumor. Node stations for dissection should be modified by the location of the primary tumor. For upper and middle esophageal tumors, the three-field approach is recommended. Dissection of the upper mediastinum is recommended for patients with lower esophageal tumors.

Keywords Esophageal cancer · Lymphadenectomy · Metastasis · Survival · Classification

✉ Yuji Tachimori
ytachimo@ncc.go.jp

1 Division of Esophageal Surgery, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

2 Department of Gastroenterological Surgery, Tokai University School of Medicine, Isehara, Japan

3 Department of Medical Physics and Engineering, Osaka University Graduate School of Medicine, Osaka, Japan

4 Department of Frontier Surgery, Chiba University Graduate School of Medicine, Chiba, Japan

5 Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya, Japan

6 Department of Gastroenterological Surgery, Kyushu Cancer Center, Fukuoka, Japan

7 Department of Gastroenterological Surgery, Toranomon Hospital, Tokyo, Japan

8 Department of Endoscopy and Endoscopic Surgery, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

9 Department of Gastroenterology, Saku General Hospital, Nagano, Japan

10 Department of Radiology, Graduate School of Medicine, Chiba University, Chiba, Japan

Introduction

The prognosis of esophageal carcinoma is determined by the extent of the primary tumor and the lymphatic spread of the disease. In addition to primary tumor resection, removal of all potentially involved lymph nodes is essential for achieving cure. In the present 7th UICC TNM classification [1] and the 7th AJCC Cancer Staging manual [2], the regional lymph nodes are those in the esophageal drainage area from the paraesophageal nodes in the neck to the

Published online: 30 July 2015

celiac axis nodes, irrespective of the site of the primary tumor. In classifying N, grades are designated by grouping the number of involved regional nodes. The extent of lymph node dissection in esophageal cancer surgery is estimated by the number of resected regional lymph nodes, irrespective of the area of dissection [2]. However, many surgeons accept that the area of nodal dissection should be modified according to the location of the primary tumor in an individual patient.

In the Japanese Classification of Esophageal Cancer, authorized by the Japan Esophageal Society, the lymph nodes are designated by stations, and each station is classified into four grades (N1, N2, N3, N4) by the location of the primary tumor [3]. N1–3 lymph nodes are defined as regional nodes, and N4 lymph nodes are defined as distant nodes. The extent of lymph node dissection is classified into three grades (D1, D2, or D3) by the location of the primary tumor. Dissection of N1 and N2 lymph nodes (D2) is recommended as the standard treatment for curable esophageal cancer. Dissection of N3 lymph nodes (D3) is considered for advanced situations but is not a required procedure. Dissection of N1 lymph nodes (D1) is considered a minimal procedure for early stage tumors and patients with morbidity.

The purpose of this retrospective study was to evaluate the efficacy of lymph node dissection by station based on the location of the primary tumor, calculating the frequency and patient survival of metastases to the station in patients with thoracic esophageal carcinoma who underwent esophagectomy with curative intent. This study was based on a large, multi-institutional, nationwide registry of esophageal cancer maintained by the Japan Esophageal Society. The appropriateness of the grading of lymph nodes according to the present Japanese classification was verified.

Methods

Patients

A comprehensive registry of esophageal cancer in Japan was established and has been maintained by the Registration Committee for Esophageal Cancer of the Japan Esophageal Society since 1976. Registration was not restricted to patients who underwent surgery, but included patients who underwent non-surgical therapy. All patient data, including demographic characteristics, symptoms, clinical stage, treatment features, and survival information, were collected. Surgical features, pathological stage, and detailed lymph node metastatic status were also collected for patients who underwent surgery.

A total of 12,880 patients with primary esophageal carcinoma treated in 2001, 2002, and 2003 were registered in 2008, 2009, and 2010, respectively, from 241 institutions in Japan [4–6]. Of the 12,880 patients, 10,896 had primary thoracic esophageal carcinoma, excluding cervical esophageal cancer and Siewert type II and type III junction cancers [7]. Of the 5734 patients who underwent esophagectomy, 5111 underwent R0 resection, and the 623 patients who underwent R1 and R2 resections were excluded due to limited node dissection. Of the 5111 patients who underwent R0 resection. 1768 patients underwent three-field esophagectomy [8, 9]. For the purpose of evaluating the incidence of metastasis to all regional node stations precisely, only the patients who underwent three-field esophagectomy were selected. The cervical, mediastinal, and abdominal lymph nodes were dissected. Since it was based on a multi-institutional, nationwide registry, the selection of patients and indications for three-field dissection depended on each institution and were not specified. Of the 1768 patients who underwent three-field esophagectomy for R0 resection, information about the locations of pathological metastatic lymph nodes was available for 1427 patients, and outcome evaluations were available in 1309 patients. Excluding 14 patients who received definitive chemoradiotherapy and underwent salvage esophagectomy, the total study group comprised 1295 patients who underwent R0 resection and three-field esophagectomy from 155 institutions (Fig. 1).

Tumor classification

Pathological stages for all patients were re-assessed according to the 10th edition of the Japanese Classification of Esophageal Cancer [3] edited by the Japan Esophageal Society. The clinical stage using the Japanese Classification was not available in this registration database for patients treated in 2001, 2002, and 2003. The Japanese

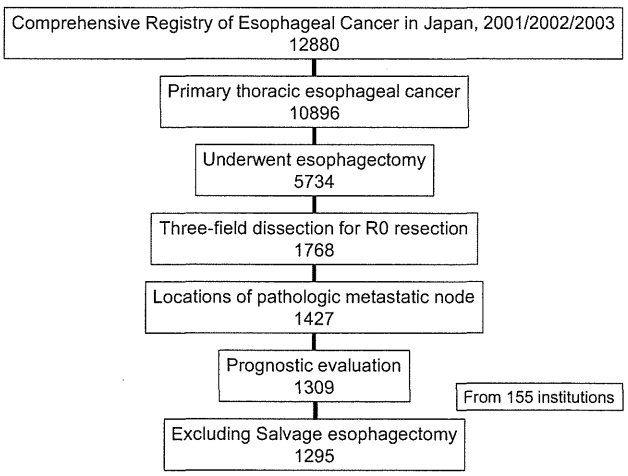

Fig. 1 Patient disposition chart