Dose Prescription and Treatment Techniques

The step-and-shoot technique with a 10 mm-wide multi-leaf collimator using a fixed nine beam arrangement of 6 million volt X-rays was used during this study period. PTV encompassed CTV with a 5 mm margin. Total RT doses to the PTV of high, intermediate and low risks were 70, 60 and 54 Gy, respectively. A simultaneous integrated boost using 33 fractions over 6.5 weeks was used, and the entire PTV was treated with extended-field IMRT. On treatment planning CT, dose distribution in each slice was meticulously evaluated, and the plans were optimized to eliminate hot spots receiving a total RT dose of $\geq$77 Gy. In principle, the IMRT plan was approved when >95% volume (D95) of the PTV received >95% of the prescribed dose. A part of the PTV within 3 mm beneath the skin surface was eliminated in this evaluation. The total RT dose to the chiasma and at least the unilateral optic nerve was always restricted to <60 Gy because none of the patients had clinical and radiographic signs of optic nerve invasion of the tumor at presentation. Otherwise, the dose constraint to the planning organs at risk volume was determined according to the Radiation Therapy Oncology Group 0225 Study protocol (5).

According to the previous trials (13,14), concomitant followed by adjuvant platinum-based chemotherapy was done in clinically fit patients with Stage III/IV disease. Those who had Stage I/II keratinizing squamous cell carcinoma also received concomitant chemotherapy because of poor expectation of local control in patients with this histology (16). For competent patients with N2/3 disease and/or T4 disease attaching to the optic chiasma, three courses of induction chemotherapy with docetaxel, cisplatin and S-1 were done (17). Dental examinations and placement of a percutaneous gastrostomy tube (PEG) were routinely done before the start of IMRT. Changes in the body contours were monitored at least weekly during the IMRT with megavoltage CT generated by the linac in all patients, with the intention of revising plans according to the estimated changes of dose distribution in the target volume and critical organs. In fact, revisions were made in four patients. IMRT plans were made using Xio version 4.5.0 (Elekta, Stockholm, Sweden) for the first five patients, and Pinnacle 3 (Philips, Amsterdam, the Netherlands) for the rest.

Outcome Measures and Statistical Considerations

Patients were monitored at least twice a week during IMRT. Follow-up visits were requested monthly within 2 years after completion of RT, at least once per 3 months during the third year, and once per 6 months thereafter. Radiological examinations including CT and/or MRI of the head and neck were performed at least twice within 6 months immediately after treatment, and at regular intervals of 6–12 months thereafter. Time-to-event analyses from the start of RT were made using the Kaplan–Meier estimates according to the data fixed on 1 November 2012. Biopsy-proven recurrence of the primary tumor or radiographic evidence of regrowth of neck adenopathy was considered as events for calculating the local and nodal control rates, respectively. Radiographic evidence of development of distant failure was determined as an event for calculating distant failure rates. Patterns of recurrences were classified according to the definition by Chao et al. (18). Patients who died without these events were censored at the time of last follow-up examination. Death from any cause was defined as an event in calculating overall survival. Also, recurrence at any site or death from any cause was used in estimating progression-free survival. Statistical significance was evaluated using the log-rank test. Adverse events were estimated according to the National Cancer Institute Common Terminology Criteria of Adverse Events version 4.0. All patients provided written informed consent. This retrospective analysis was approved by our institutional ethics committee.

RESULTS

Patients

One patient was lost to follow-up at 23 months with radiological evidence of nodal recurrence. The median follow-up period for other surviving patients was 45 months (25–62 months). The characteristics of patients are listed in Table 1. High-risk CTV within the mucosal space was confined within posterior one-third of the nasal cavity in all but one patient, while it was within the pharyngeal mucosal space above the level of inferior border of the second cervical vertebra (C2) in all but two patients. In patients with T4 disease, the entire ipsilateral medial and lateral pterygoid muscles were included in high-risk CTV in three patients, and otherwise, it was confined to the sphenoid and temporal bones, basiocciput, Meckel's cave, perivertebral, retropharyngeal and sinonasal/pharyngeal mucosal spaces. Concomitant chemotherapy was performed in 38 (95%) patients, and 20 (53%) of these 38 patients also received induction chemotherapy. The overall treatment time of RT ranged from 46 to 57 days (median, 50 days).

Tumor Control and Survival Outcomes

There were seven locoregional tumor persistence or recurrences as listed in Table 2. The local and nodal control rates at 3 years were 91% (95% confidence interval, 82–100%) and 89% (79–99%), respectively. The locoregional control rate at 3 years was 83% (71–96%). A review of IMRT dose distributions revealed that six of the seven locoregional failures were 'in-field', and one local recurrence at the Meckel's cave was 'marginal' according to the definition by Chao et al. This marginal recurrence occurred in patients who had T3 disease deeply invading the ipsilateral foramen lacerum. Although the site of recurrence was defined as high-risk CTV, the administered total dose was <63 Gy aiming at dose reduction to the adjacent temporal lobe of the brain. Local control rates in patients with T1/2 and T3/4 disease were 95% (95% CI 85–100%) and 90% (77–100%), respectively, at 3 years ($P = 0.744$). The distant failure rate at 3 years was 24% (8–40%). The Kaplan–Meier estimates of locoregional and

Table 1. Characteristics of patients

Characteristics	Number of patients	%
Gender		
Male	30	75
Female	10	25
Age, median (range), years	48 (17–74)	
Histology		
Keratinizing SCC	3	8
SCC, NOS	1	3
Non-keratinizing carcinoma		
Differentiated	13	33
Undifferentiated	23	58
T classification		
T1	12	30
T2	7	18
T3	7	18
T4	14	35
N classification		
N0	2	5
N1	14	35
N2	19	48
N3a	1	3
N3b	4	10
Stage		
I	1	3
II	6	15
III	14	35
IVA	14	35
IVB	5	13
Zubrod performance status		
0	1	3
1	35	88
2	4	10
Tumor location		
Lateral wall	19	48
Posterosuperior wall	10	25
Superior wall	7	18
Posterior wall	4	10

SCC NOS, squamous cell carcinoma, not otherwise specified.

distant failure rates are shown in Figure 2. Progression-free and overall survival rates at 3 years were 61% (45–76%) and 87% (76–98%), respectively (Fig. 3). Locoregional control, distant failure and overall survival rates at 3 years for patients with Stage I–III disease ($n = 21$) were 81% (95% CI, 64–98%), 17% (0–34%) and 90% (77–100%), respectively, whereas these rates were 89% (74–100%), 27% (8–46%) and 83% (65–100%), respectively, for 19 patients with Stage IV disease. Overall and progression-free survival rates at 3 years for 20 patients who received induction chemotherapy were 89 and 63%, and it was 85 and 59% for the rest, respectively ($P > 0.500$).

Adverse Events

Grade 3 dermatitis and symptomatic mucositis due to IMRT were observed in 5 (12%) and 25 (63%) patients, respectively. All surviving patients maintained their normalcy of diet and were not PEG dependent at 1 year after completion of IMRT. The median value of mean IMRT doses to the parotid gland on the side receiving lower dose was 33 Gy (19–49 Gy). The mean total IMRT dose to the spared cochlea was <55 Gy in all patients. The type and frequency of late adverse events for 37 patients who were alive at 2 years are listed in Table 3. One patient experienced Grade 3 neck induration at 4 years after IMRT (1 year after completion of salvage chemotherapy for bone metastasis). He died subsequently with radiological evidence of lung metastasis. Of 31 patients who were alive and disease-free at 24 months, hearing loss of Grade 3 was observed in 4 (13%) patients. Twenty-five (81%) of these 31 patients experienced sense of recovery of their mouth dryness and were able to intake a normal solid diet (xerostomia of ≤Grade 1) at 2 years (Fig. 4). One patient whose T4 disease collapsed at 4 months after completion of IMRT developed a deep ulcer at the parapahryngeal and masticator spaces (Grade 3 pharyngeal necrosis). Osteonecrosis of the ipsilateral mandible and temporal lobe necrosis were observed subsequently. She died of pneumonia without evidence of tumor recurrence at 35 months. Otherwise, no Grade 2 or worse adverse events were observed at the time of last follow-up.

DISCUSSION

Although excellent locoregional control after IMRT had been reported from certain centers that had abundant experience of two-to-three-dimensional RT for NPC, wide prevalence of these results in the medical community is indispensable. Assuming that inter-observer variation of the target definition is categorized as a systematic error, larger margins would be required to determine the planning target volume than accountable by random errors (19). Therefore, meticulous target definition based on the detailed estimation of extent of tumor and precise knowledge of patterns of tumor spread is indispensable. Pharyngeal and sinonasal mucosal spaces within GTVp +2 cm margins were determined as high-risk CTV during this study period because of our belief of the aggressive nature of NPC with regard to lymphovascular invasion. However, this should be done with extreme caution. It should be noted that GTVp at the mucosal space was determined by direct fiberscopy findings because GTVp definition based on imaging alone was likely

Table 2. Patterns of locoregional failure

Patient age/gender	TN classification	Histology	Site of recurrence	Time to event (months)	Salvage treatment	Final status (months)
49M	T2N2	SCC NOS	Local, in-field	0	None	11 DOD
54M	T3N1	Non-kerat. differentiated	Local, in-field	21	Re-RT	45 AWD
49M	T3N1	Non-kerat. differentiated	Local, marginal	36	Re-RT	43 AWD
53F	T2N3a	Non-kerat. undifferentiated	Nodal, in-field	0	None	12 DOD
34M	T1N2	Non-kerat. undifferentiated	Nodal, in-field	10	Re-RT	23 AWD
47F	T2N1	Non-kerat. differentiated	Nodal, in-field	28	Re-RT	54 NED
45M	T4N1	Keratinizing	Nodal, in-field	34	Chemotherapy	38 AWD

M, male; F, female; Non-kerat, non-keratinizing; Re-RT, reirradiation; DOD, died of index cancer; AWD, alive with disease; NED, no evidence of disease; in-field, within irradiated volume receiving 70 Gy/33 fractions; marginal, at the margin of irradiated volume receiving 70 Gy/33fractions according to the definition by Chao et al. (18).

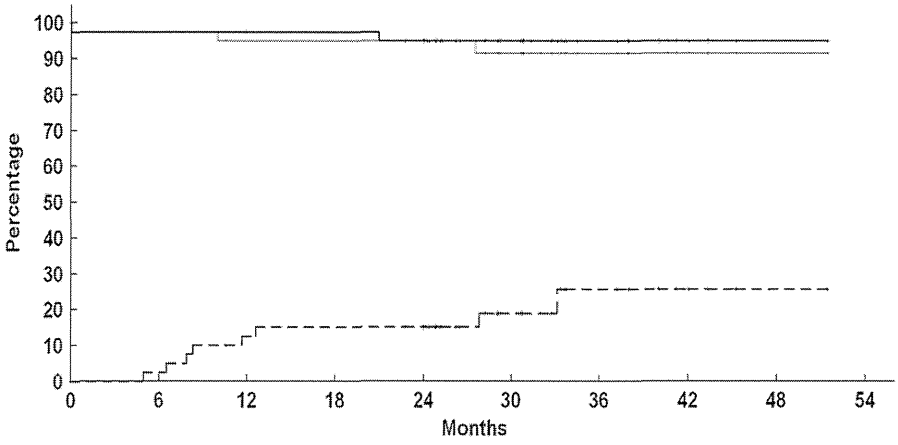

Figure 2. Kaplan–Meier estimates of local control (thick solid), nodal control (thin solid) and distant failure rates (dotted line).

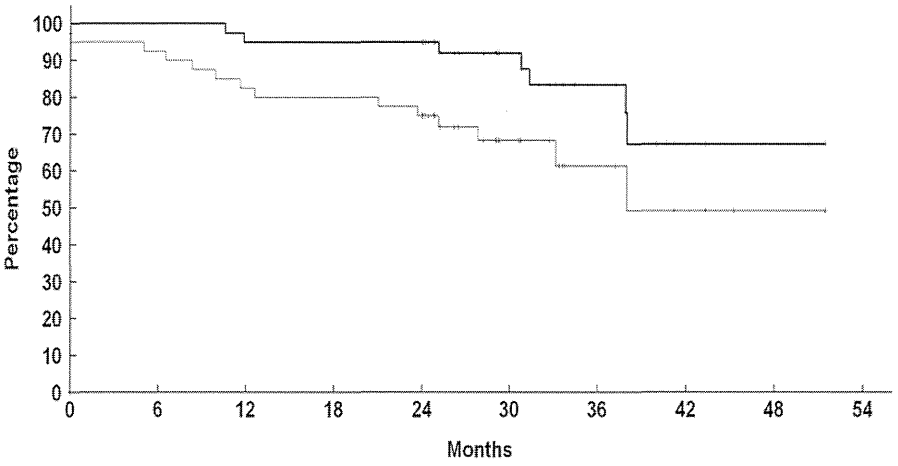

Figure 3. Kaplan–Meier estimates of overall (thick) and progression-free (thin line) survival rates.

to overestimate the real GTVp (6,20). Correct depiction of this mucosal GTVp for the planning CT is an extremely important process, because any regulation defining a GTV–CTV margin is meaningless without this effort. In our experience, high-risk CTV was confined within posterior one-third of the nasal cavity, and oropharyngeal mucosal space above the level of lower border of C2 with few exceptions. Therefore, the reason must be clearly recorded when high-risk CTV larger than these limits is defined. In other words, adding 2 cm margin to the GTV that was determined with imaging alone should not be done to avoid an unacceptably huge high-risk CTV.

Table 3. Type and frequency of late adverse events for 37 patients who were alive at 2 years

Adverse effect	Grade			
	0/1	2	3	NA[a]
Skin/soft tissue	35	1	1	0
Pharyngeal mucositis/necrosis	36	0	1	0
Salivary gland	27	7	0	3
Esophagus	34	0	0	3
Larynx	34	2	0	1
Central nervous system	33	0	1	3
Bone	36	0	1	0
Joint	36	0	1	0
Hearing impaired (at least unilateral)	23	10	4	0
Other	37	0	0	0
Worst overall				
Number of patients	20	10	5	2[b]
Percentage of total patients	54	27	14	5

[a]NA, not assessable because of aggravation of general conditions due to disease recurrence.
[b]Number of patients who did not experience ≥Grade 2 late adverse events other than NA items.

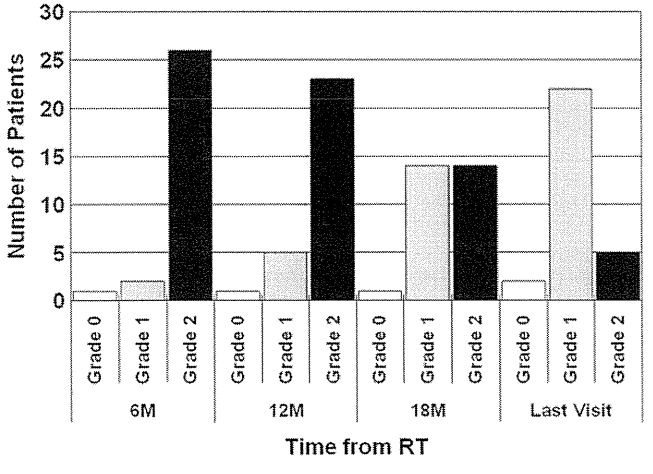

Figure 4. Frequency of Grade 0–2 xerostomia at 6, 12 and 18 months (M) after completion of RT and last follow-up visit.

NPC has a high propensity of parapharyngeal space invasion (8). The parapharyngeal space that was judged as free from tumor invasion was not encompassed within the CTV in this study period. However, no marginal recurrence was observed within the parapharyngeal space in this series of patients. If possibility of tumor invasion could not be completely denied, definition of the high-risk CTV within the parapharyngeal space by expansion of GTVp +1 cm as shown in Figure 1 was thought to be an appropriate option based on the results of previous reports (1,2,4,5,9). In general, most of the patients with NPC had nodal metastasis with radiological signs of extracapsular spread, which required extensive coverage of the ipsilateral parapharyngeal space. Therefore, to determine the entire ipsilateral parapharyngeal space as the high-risk CTV was considered justifiable when the patient had gross tumor invasion to this space on MRI. As noted by Grégoire et al., muscular fascias are strong barriers against muscle infiltration. When the fascia has been disrupted, the whole muscle is at risk (21). Based on this concept, the high-risk CTV encompassed the entire pterygoid muscles in three patients with T4 disease.

Adverse influence of variation in treatment planning was suggested in one patient who experienced marginal recurrence at Meckel's cave. Consequently, our method should be continuously fine-tuned according to the accumulation of clinical experiences. Otherwise, all locoregional failures were 'in-field', which could not be ascribable to inadequacy of our target definition. This single institutional study with a limited number of patients could not demonstrate the appropriateness of our target definition for all patterns of spread. Lin et al. (22) addressed a possibility to reduce IMRT target volume compared with that as defined in two- to three-dimensional radiotherapy era without deterioration of tumor control. Local and nodal control rates exceeded 95% at 3 years and no isolated recurrence was observed at reduced CTV in the posterior maxillary sinus, posterior clivus and/or posterior nasal cavity in 323 NPC patients (75% had T2/3 disease). In our study, three of the seven locoregional recurrences occurred at >2 years post IMRT. Therefore, longer follow-up is required to compare matured results among various definitions of the CTV and chemoradiotherapy procedures.

Lee et al. (5) reported that 46 of 68 (68%) patients experienced Grade 3 or worse acute gastrointestinal toxicities. Wolden et al. (2) showed that, in 74 patients (46% had N2/3 disease), the average mean dose to the parotid was 35.2 Gy and the mean dose was limited to ≤26 Gy in 30 of 84 parotid glands (35.7%). Grade 2 xerostomia was observed in 32% at 12 months, and the incidence of Grade 3 hearing loss was 15%. Ng et al. (9) showed that an average mean parotid dose was ~40 Gy in 193 NPC patients, 90% of them had N2/3 disease. All of these data were comparable that observed in this study. Nevertheless, our resources to conduct IMRT during this preliminary period were considered as one of the reasons for adverse events, which should be improved along with the advancement of technologies to spare normal tissues more efficiently. No firm conclusion could be made regarding the effect of chemotherapy because of heterogeneous background of patients. Needless to say, it is impossible to evaluate the risks and benefits of additional chemotherapy without adequate CTV definition.

Possibility of this method to reduce inter-observer variation was not supported by any evidence in this report. Nevertheless, a clear definition must be established before wide prevalence of IMRT for NPC. Although there were difference in the background of patients, local control rates for patients who had T3/4 disease were relatively poor in previous reports (2,4,9). In our

study, similar local control rates exceeding 90% at 3 years, which compared favorably with other series, were observed in patients with T1/2 and T3/4 tumors. Therefore, it is conceivable that the significance of our anatomical boundary-based target definition is worth testing further for patients with advanced disease, especially in the new departments intending to implement nasopharynx IMRT into their practice.

CONCLUSION

An anatomical boundary-based definition of the CTV instead of simple three-dimensional expansion of the GTV was feasible without compromising locoregional tumor control and adverse events on the premise that meticulous estimation of extent of the tumor was done with fiberscopic and modern radiographic examinations. This method has a possibility to standardize the target definition as experienced in surgical oncology, and to facilitate reduction of inter-observer variation in multicenter studies. Further study of this procedure is needed in accordance with accumulating experiences and advancing resources in IMRT.

Conflict of interest statement

None declared.

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International Journal of
Radiation Oncology
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Clinical Investigation: Head and Neck Cancer

[^{18}F]fluoromisonidazole and a New PET System With Semiconductor Detectors and a Depth of Interaction System for Intensity Modulated Radiation Therapy for Nasopharyngeal Cancer

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Received Aug 11, 2011, and in revised form Feb 4, 2012. Accepted for publication Mar 10, 2012

Summary

The impact of a New PET system using an ^{18}F-labeled fluoromisonidazole (FMISO)-guided intensity modulated radiation therapy plan was investigated by comparing the plan with a state-of-the-art PET/CT system in nasopharyngeal cancer (NPC) patients. New PET was found to be useful for accurate dose escalation in FMISO-guided IMRT for patients with NPC.

Purpose: The impact of a new type of positron emission tomography (New PET) with semiconductor detectors using ^{18}F-labeled fluoromisonidazole (FMISO)-guided intensity modulated radiation therapy (IMRT) was compared with a state-of-the-art PET/computed tomography (PET/CT) system in nasopharyngeal cancer (NPC) patients.

Methods and Materials: Twenty-four patients with non-NPC malignant tumors (control group) and 16 patients with NPC were subjected to FMISO-PET. The threshold of the tumor-to-muscle (T/M) ratio in each PET scan was calculated. The hypoxic volume within the gross tumor volume (GTVh) was determined using each PET ($_{NewPET}$GTVh and $_{PET/CT}$GTVh, respectively). Dose escalation IMRT plans prescribing 84 Gy to each GTVh were carried out.

Results: The threshold of the T/M ratio was 1.35 for New PET and 1.23 for PET/CT. The mean volume of $_{NewPET}$GTVh was significantly smaller than that of $_{PET/CT}$GTVh (1.5 ± 1.6 cc vs 4.7 ± 4.6 cc, respectively; $P = .0020$). The dose escalation IMRT plans using New PET were superior in dose distribution to those using PET/CT. Dose escalation was possible in all 10 New PET-guided plans but not in 1 PET/CT-guided plan, because the threshold dose to the brainstem was exceeded.

Conclusions: New PET was found to be useful for accurate dose escalation in FMISO-guided IMRT for patients with NPC.

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A part of this study was presented at the 53rd Annual Meeting of the American Society of Radiation Oncology (ASTRO), Miami Beach, FL, October 2-6, 2011.

This project received a grant-in-aid entitled "Formation of Innovation Center for Fusion of Advanced Technologies" from the Japanese Ministry of Education, Culture, Sport, Science and Technology.

Conflict of interest: This study is from the "Future Drug Discovery and Medical Care Innovation Program," which is a collaborative research project between Hokkaido University and Hitachi Co, Ltd.

Supplementary material for this article can be found at www.redjournal.org.

Acknowledgment—We appreciate advice from Dr Koji Oba regarding statistical analysis, help from Dr Kenji Hirata in providing patient data, and support from staff members at Hokkaido University.

Int J Radiation Oncol Biol Phys, Vol. 85, No. 1, pp. 142–147, 2013
0360-3016/$ - see front matter
doi:10.1016/j.ijrobp.2012.03.029

Introduction

Hypoxia is well known as an important factor relating to radioresistance (1). In head-and-neck cancer, hypoxia has been shown to be associated with poor outcome (2). A recent simulation study showed that dose escalation to the hypoxic region would contribute to the tumor control probability (3). The development of a dose escalation technique using intensity modulated radiation therapy (IMRT) or proton beam therapy is expected for use in treating patients with head-and-neck cancers, including nasopharyngeal cancer (NPC) (4, 5). Direct measurements using the Eppendorf electrode have been suggested as the gold standard for hypoxic measurement, but it is an invasive examination that is restricted to accessible tumors (6). A noninvasive approach to measuring the hypoxic region using positron emission tomography (PET) imaging has been developed and examined in previous studies (7).

[^{18}F]fluoromisonidazole (FMISO) is one of the hypoxia tracers. Its binding to the molecules in viable hypoxic cells is known to be proportional to the level of hypoxia (8). PET using FMISO (FMISO-PET) has been expected to be usable for mapping of the hypoxic region in head and neck cancers (9). There have been several studies of the usefulness of FMISO-PET in treatment planning for dose escalation in IMRT of head-and-neck cancers (10-12).

The hypoxic region is likely to be small, and thus, high spatial resolution is necessary for planning. We have shown that a prototype of a PET system with semiconductor detectors (New PET) has a spatial resolution of 2.3 mm, which is better than that of the conventional high-resolution whole-body PET system with bismuth germanium oxide scintillation detectors (13). New PET was shown to be useful for delineating the uptake of NPC because of its sharper edge at the tumor boundary in [^{18}F]fluoro-deoxyglucose (FDG)-PET images (14).

In this study, we established the threshold of FMISO normal uptake by using New PET and a state-of-the-art whole-body PET-computed tomography (PET-CT) system with lutetium oxyorthosilicate scintillation detectors and extended field of view (TruePoint Biograph 64 with True V and high-resolution option; Asahi-Siemens, Tokyo, Japan) (PET/CT) and compared the hypoxic volumes visualized by New PET and PET/CT. We performed IMRT simulation planning for the dose escalation to the hypoxic region in NPC and compared the differences in dose-volume histogram (DVH) between the plan using New PET and the plan using PET/CT. We also evaluated the predictive value of FMISO uptake before chemoradiation therapy for local control in patients with NPC.

Methods and Materials

Patient characteristics

Our institutional review board approved the protocol for this study in 2007. Between April 2008 and March 2011, 40 patients with newly diagnosed head-and-neck cancer and brain tumors were subjected to FMISO-PET. The process used to select study patients is shown in a flowchart in Appendix 1. Sixteen patients among them had NPC (NPC group) and received FMISO-PET before any treatment. These patients received standard treatment and were followed by radiation oncologists and otolaryngologists in our hospital, periodically. The status of local control and survival were investigated in this study. All patients in the NPC group received New PET, and 12 patients among them received both New PET and PET/CT.

Twenty-four patients with other tumors (10 brain tumors, 9 oral cancers, 4 thyroid cancers, and 1 laryngeal cancer) were defined as the control group in this study. The patients in the control group were examined with CT and magnetic resonance imaging to prove that there was no abnormality in the nasopharynx or the posterior cervical muscle. In the control group, 14 patients were examined with New PET, and 14 patients were examined with PET/CT, and thus, 4 were examined with both New PET and PET/CT. The median age was 64 years (range, 40-78 years) in patients examined with New PET and 67.5 years (range, 56-83 years) in patients examined with PET/CT. The number of males and females was 7 and 7, respectively, in patients examined with New PET, and 8 and 6, respectively, in patients examined with PET/CT.

Written informed consent for study participation was obtained from all patients before the FMISO-PET examination.

FMISO-PET scans

Details of the New PET system were described previously (13-15). Briefly, the New PET system is equipped with small semiconductor detectors and a depth of interaction system to obtain sufficient sensitivity and a higher spatial resolution.

FMISO-PET was performed with the New PET and with PET/CT. About 400 MBq of FMISO was injected intravenously 4 h before scanning. Details of the performances of these 2 scanners are listed in Appendix 2. In the patients who were subjected to both types of PET scan, the scan order was randomly determined, and the scans were performed sequentially. We used dedicated fixation during PET scanning.

Thresholds of the nasopharynx-to-muscle ratio and the tumor-to-muscle ratios

FMISO-PET images were registered to image analysis software (Vox-Base, J-MAC System, Sapporo, Japan). In the control group, the maximum standardized uptake value (SUVmax) in normal nasopharyngeal soft tissue was calculated using each PET scan image. Laterally displayed or fused CT images were used as the reference for localization. The region of interest (ROI) with a radius of 1 cm was placed in the left lateral, left medial, right medial, and right lateral positions of the posterior cervical muscle, and the average SUVmax of these ROIs was calculated. The nasopharyngeal SUVmax divided by the average of the SUVmax of the posterior cervical muscle ROI was calculated and defined as the nasopharynx-to-muscle (N/M) ratio. The N/M ratio was calculated for both New PET and PET/CT. After we confirmed the normal distribution, we calculated the upper threshold of the normal N/M ratio as the average + 1.96 × standard deviation (SD), which indicated the upper value of 95% confidence interval. Each upper threshold of the normal N/M ratio in New PET and PET/CT, respectively, was used as a threshold of the tumor-to-muscle (T/M) ratio in the patients with NPC.

Definition of the hypoxic region in NPC and comparison of hypoxic volumes by the 2 systems

In the NPC group, all patients underwent CT (Somatom Sensation; Siemens) with individualized head, neck, and

shoulder immobilization masks. Images from the CT scans with 2-mm slices were obtained for each patient. CT images and FMISO-PET images obtained by each PET scan were coregistered to make fusion images, using 3-dimensional radiation therapy planning software (Pinnacle3 version 80m; Philips Radiation Oncology Systems, Fitchburg, WI). The gross tumor volume (GTV) was determined on the CT image, and other available images (ie, magnetic resonance imaging or FDG-PET) were referenced. The hypoxic volume in GTV (GTVh) was determined as the volume that had a T/M ratio higher than the upper threshold using FMISO-PET. The hypoxic volumes in the GTV were named $_{NewPET}$GTVh and $_{PET/CT}$GTVh, respectively.

Dose escalation IMRT simulation planning targeting the hypoxic volume

Ten NPC patients received both types of FMISO-PET examination and had abnormally high FMISO uptake. The dose escalation IMRT simulation plans targeting the hypoxic volume were generated for these 10 patients. Pinnacle3 was used to make IMRT simulation plans.

Clinical target volume 1 (CTV1) was defined as the volume containing the GTV and any microscopic disease at risk. CTV2 and CTV3 were at high-risk and low-risk volumes, respectively. A margin of 3 mm was added to each CTV and defined as planning target volumes (PTV1, PTV2, and PTV3). The prescription dose to the PTVs and the dose constraints to the organ at risk (OAR) are shown in Table 1. Eighty-four Gy was prescribed to the D95 of each GTVh in this simulation study. Hypoxia-based IMRT dose escalation plans were generated for 10 NPC patients who underwent standard-dose IMRT for their disease. We did not add the margin to expand the GTVh to the PTVh, in agreement with the procedures followed by Chao et al (7) and Lee et al (10).

Statistics

We used statistics software (JMP9; SAS Institute Inc Cary, NC) to analyze the data. The *W* test of Shapiro-Wilk was used to approve the normal distribution of the FMISO activity in the nasopharyngeal region in the control group. A 2-sided Wilcoxon signed-rank test was used to compare DVH parameters between plans. A significance *P* value of .05 was used.

Results

Thresholds of the N/M ratios of New PET and PET/CT

The averages ± SD of the N/M ratios in the control group examined with New PET and PET/CT were 1.151 ± 0.103 and 1.054 ± 0.086, respectively. The distribution was approved to be normal by the *W* test ($P = .3902$ and $P = .9993$, respectively). The upper thresholds of the N/M ratio were calculated to be 1.35 with New PET and 1.23 with PET/CT. We also analyzed the 4 control cases on whom both types of PET were performed. The average of the N/M ratio and the upper threshold were 1.118 ± 0.042 and 1.20 with New PET and 1.099 ± 0.044 and 1.18 with PET/CT, respectively.

Table 1 Prescriptions to the target volumes and constraints of OARs in FMISO-guided IMRT simulation plan

Condition	Target	Dose
Prescription to the target volumes	GTVh	$D_{95} > 84$ Gy
	PTV1	$D_{95} > 70$ Gy; $V_{77Gy} < 20\%$; $V_{80.5Gy} < 5\%$
	PTV2	$D_{95} > 63$ Gy
	PTV3	$D_{95} > 56$ Gy
Constraints of OARs	Brainstem	Dmax < 54 Gy
	Spinal cord	Dmax < 45 Gy
	Optic nerve	Dmax < 54 Gy
	Parotid grand	$V_{30Gy} \leq 50\%$; Dmean ≤ 26 Gy
	Oral cavity	Dmean ≤ 50 Gy
	Oropharynx and hypopharynx	Dmean ≤ 45 Gy

Abbreviations: D_{95} = minimal dose to 95% of the volume; Dmax = maximal point dose of the volume; Dmean = mean dose of the volume; FMISO = [$_{18}$F]fluoromisonidazole; GTVh = hypoxic volume in the gross tumor volume; IMRT = intensity modulated radiation therapy; OAR = organ at risk; PTV = planning target volume; V_{77Gy} = percentage of the volume receiving ≥77 Gy.

Clinical relevance in the NPC group

Thirteen of the 16 patients in the NPC group experienced abnormally high uptake of FMISO (Table 2).

Twelve patients in the NPC group received both types of PET examination, and the judgments regarding whether they had abnormally high uptake were fully consistent. Ten of the twelve patients receiving both types of PET examination had abnormally high uptake. The data for these 10 patients were the materials used

Table 2 Characteristics of patients in the NPC group

Patient	Age (y)	Sex	T stage	N stage	M stage	FMISO uptake
1	61	Male	2a	2	0	+
2	48	Male	1	1	0	+
3	59	Female	4	1	0	+
4	53	Male	2b	1	0	+
5	45	Female	2b	2	0	+
6	66	Female	2a	0	0	+
7	40	Male	3	1	0	+
8	77	Male	2	2	0	−
9	50	Female	2b	2	0	+
10	61	Male	2b	2	0	−
11	73	Male	4	1	1	+
12	62	Female	4	3b	1	+
13	52	Male	3	2	0	+
14	53	Male	1	3b	1	−
15	57	Male	3	2	0	+
16	66	Male	3	0	0	+

Abbreviations: FMISO = [$_{18}$F]fluoromisonidazole; NPC = nasopharyngeal cancer

Table 3 Treatment, local relapse, and deaths of 10 NPC patients who received radical treatment and were followed for more than 1 y

Patient	FMISO uptake	Treatment	RT dose (Gy/fr)	Follow-up period (mo)	Local relapse	Death
1	+	CRT	70/35	30.8	+	+
2	+	CRT	70/35	27.7	+	–
3	+	CRT	66/33	27.0	–	–
4	+	CRT	70/35	24.2	–	–
5	+	CRT	70/35	23.6	+	–
6	+	CRT	70/35	22.5	–	–
7	+	CRT	70/35	19.7	–	–
8	–	RT	70/35	18.5	–	–
9	+	CRT	70/35	15.0	–	–
10	–	CRT	70/35	14.8	–	–

Abbreviations: CRT = chemoradiation therapy; FMISO = [$_{18}$F] fluoromisonidazole; fr = fraction; NPC = nasopharyngeal cancer; RT = radiation therapy.

for the comparison of New PET and PET/CT for simulation planning using FMISO-PET. All NPC patients received standard treatment with standard-dose radiation therapy (66-70 Gy).

Ten patients in the NPC group received radical treatment and were followed for more than 1 year with a median follow-up period of 23.1 months, ranging from 14.8-30.8 months (Table 3). Three patients experienced local relapse at 9, 11, and 12 months after the first examination in our department. One patient died as a result of NPC at 30.8 months. All patients who experienced local failure had high uptake in FMISO before treatment. No patients who showed normal uptake of FMISO-PET experienced local relapse.

SUVmax and the volume of $_{NewPET}$GTVh and $_{PET/CT}$GTVh

In the 10 NPC patients receiving both types of PET examination and having abnormal uptake, the mean SUVmax in $_{NewPET}$GTVh was 2.55 ± 0.71 and the mean SUVmax in $_{PET/CT}$GTVh was 2.38 ± 0.62 (P=.1934; Wilcoxon signed-rank test). Four patients received New PET first, and 6 patients received PET/CT first. The mean SUVmax in the first PET scanning was 2.38 ± 0.81, and the mean SUVmax in the later PET scanning was 2.41 ± 0.71 (P=.4316).

The mean volumes of $_{NewPET}$GTVh and $_{PET/CT}$GTVh were 1.5 ± 1.6 cc and 4.7 ± 4.6 cc, respectively (P=.0020) (Fig. 1). The GTVh was smaller with New PET for all 10 patients, irrespective of the order of the examinations. Figure 2 shows an example of both FMISO-PET images for 1 NPC patient. The mean fraction of $_{NewPET}$GTVh was 0.04 ± 0.04 of total GTV and that of $_{PET/CT}$GTVh was 0.14 ± 0.12 (P=.0020).

Dose escalation IMRT simulation planning

DVHs of the GTVh, PTV, and OARs are shown in Table 4. Dose escalation was possible in all 10 patients receiving both types of PET examination, using $_{NewPET}$GTVh in IMRT plans, maintaining dose constraints for OAR. However, it was not possible in 1 patient by using $_{PET/CT}$GTVh in the IMRT plan, because the threshold dose to the brainstem exceeded the dose constraint. The percentage of the volume receiving ≥80.5 Gy ($V_{80.5Gy}$) of the PTV (P=.0391), the V_{84Gy} of PTV (P=.0137), the mean dose to the right parotid gland (P=.0488), V_{30Gy} to the right parotid gland (P=.0156), V_{30Gy} of the left parotid gland (P=.0159), and the maximum dose to the brainstem (P=.0273) were significantly lower using $_{NewPET}$GTVh than $_{PET/CT}$GTVh in the IMRT plan.

Discussion

Hypoxic imaging has been recently developed, and FMISO, Cu(II)-diacetyl-bis(N^4-methylthiosemicarbazone) (Cu-ATSM), and [^{18}F]fluoroazomycin arabinoside (FAZA) have been investigated as hypoxic tracers (9). Among them, FMISO has been studied with the most extensive clinical experience. However, mainly because of the limited contrast between tumor and normal tissue, there has been skepticism about the use of FMISO as the standard in pretreatment examination as well as for image guidance in radiation therapy planning (7). If the resolution of PET scanners can be improved, the advantage of FMISO-PET, which has extensive preclinical and clinical experience, would be reappraised.

We scanned images at 4 h after FMISO injection. Thorwarth et al (16) reported that blood pooling remained at 2 h after FMISO injection, and good contrast was obtained at 4 h after injection. Our FMISO study adopted 4 h of delay before scanning and also showed good contrast (17).

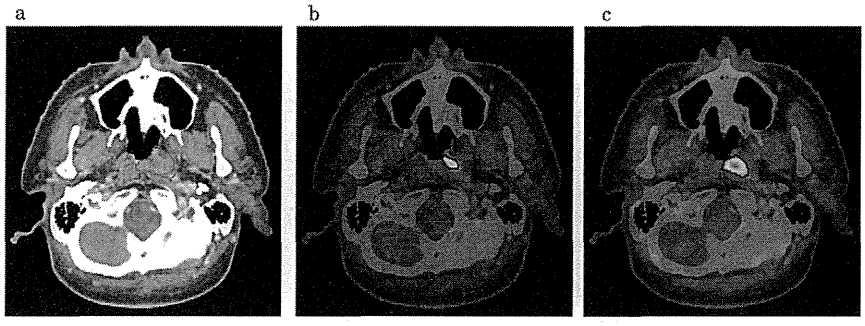
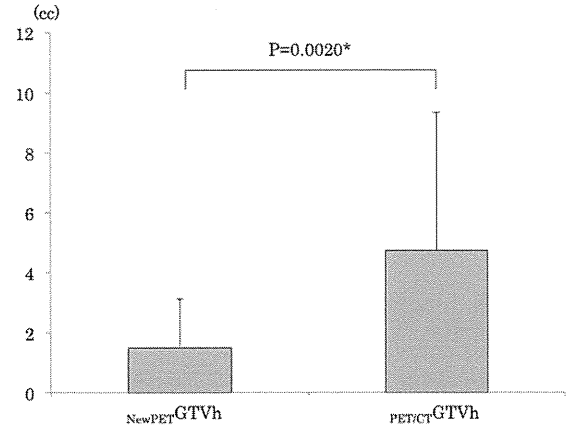


Fig. 1. Example of delineation in a NPC patient. (a) CT image: pink line indicates the GTV. (b) Semiconductor PET image fused to CT image; black line indicates hypoxic volume in the GTV ($_{NewPET}$GTVh). (c) Scintillator PET image fused to a CT image; brown line indicates hypoxic volume in the GTV ($_{PET/CT}$GTVh).



Abbreviations: $_{NewPET}$GTVh=GTVh defined by New PET, $_{PET/CT}$GTVh=GTVh defined by PET/CT

Fig. 2. Comparison of average volume of GTVh for each PET scan. Error bars indicate SDs.

We used the T/M ratio to evaluate FMISO uptake, because the T/M ratio was shown to correlate with the degree of hypoxia directly measured using an Eppendorf electrode (6). The threshold value of 1.24 was reported by Yeh et al (18) in 1996, using scintillator PET (PC4096-15WB; Scanditronix). In the present study, the threshold of the T/M ratio of FMISO-PET were calculated to be 1.23, using PET/CT, which is very close to the ratio reported previously by Yeh et al (18). However, it was 1.35 using New PET in the present study, suggesting that the threshold of the T/M ratio in FMISO-PET differs between New PET and PET/CT.

The present study showed that local relapse was observed only in NPC patients with a high uptake of FMISO. This may imply that higher uptake of FMISO before radiation therapy is related to radioresistance in patients with NPC, although the number of patients in the present study was too small to allow for such a conclusion. On the other hand, Lee et al (19) reported that the effects of pretreatment FMISO uptake in patients with oropharyngeal cancers could not be assessed because the population they examined was too sensitive to chemoradiation therapy and only 1 relapse was observed in their series. Their findings do not contradict our findings and suggest the importance of selecting the disease to be examined in future studies. Reducing the entire dose of PTV while maintaining the dose gradient with a high dose to the hypoxic volume could be one strategy for dose optimization focused on hypoxia.

The hypoxic volume defined by New PET was smaller than that defined by PET/CT. The spatial resolution after reconstruction and energy resolution of New PET was higher than that of PET/CT. On the other hand, the sensitivity per unit of time, defined as the detecting counts per second, of PET/CT was 1.8 times higher than that of New PET. Sensitivity is an important factor in the study of low-uptake radiopharmaceuticals such as FMISO. To compensate for the relatively low sensitivity per unit of time of New PET, we extended the emission scan time to 30 min, which was 3 times longer than that of PET/CT. As a result, the total counts in the New PET were comparable to those in PET/CT, and they were sufficient for analysis. The differences in GTVh may have been due to the difference of the scatter fraction and spatial resolution.

For head-and-neck cancers containing intratumoral hypoxia, the usefulness of dose escalation using hypoxic imaging has been investigated. Popple et al (3) reported that a modest boost dose (120%-150% of the primary dose) to the hypoxic subvolume increases tumor control probability, using a Monte Carlo model. In the present study, we performed FMISO-PET-guided IMRT simulations in 10 NPC patients. This is the first study that demonstrated the effect of the difference in PET scanners on dose escalation IMRT plans. The dose to OARs was significantly lower in the IMRT plan using New PET than in PET/CT. The reason is

Table 4 DVH comparison between new PET-guided and PET/CT-guided IMRT

Structure	Evaluation	New PET-guided IMRT average ± SD	PET/CT-guided IMRT average ± SD	*P* (Wilcoxon signed-rank test. *P<.05)
GTVh	V_{84Gy} (%)	96.1 ± 1.4	96.1 ± 1.2	.3223
PTV1	Dmin (Gy)	44.5 ± 10.7	44.4 ± 10.8	.6250
	$V_{65.1Gy}$ (%)	98.9 ± 0.4	99.0 ± 0.5	.2891
	Dmax (Gy)	87.4 ± 1.5	87.9 ± 1.4	.2754
	Dmean (Gy)	74.8 ± 0.7	75.0 ± 0.7	.0645
	V_{70Gy} (%)	95.6 ± 0.7	95.9 ± 0.9	.0957
	V_{77Gy} (%)	10.4 ± 4.5	11.9 ± 5.1	.3223
	$V_{80.5Gy}$ (%)	3.0 ± 1.6	4.2 ± 2.8	.0391*
	V_{84Gy} (%)	1.1 ± 0.9	2.0 ± 2.0	.0137*
Right parotid	Dmean (Gy)	36.9 ± 8.0	37.7 ± 7.5	.0488*
	V_{30Gy} (%)	50.1 ± 17.8	54.4 ± 17.4	.0156*
Left parotid	Dmean (Gy)	39.6 ± 5.1	39.9 ± 5.0	.1934
	V_{30Gy} (%)	57.3 ± 11.7	59.0 ± 12.6	.0195*
Brainstem	Dmax (Gy)	50.6 ± 4.2	53.2 ± 7.3	.0273*
Spine	Dmax (Gy)	44.3 ± 2.7	44.2 ± 2.4	.6953
Oral cavity	Dmean (Gy)	45.3 ± 5.1	45.6 ± 5.1	.2754
Carotid artery	Dmax (Gy)	80.6 ± 3.2	82.4 ± 4.6	.0840

Abbreviations: CT = computed tomography; Dmax = maximal point dose of the volume; Dmean = mean dose of the volume; Dmin = minimal point dose of the volume; DVH= dose-volume histogram; GTVh = hypoxic volume in gross tumor volume; IMRT = intensity modulated radiation therapy; PET = positron emission tomography; PTV= planning target volume; SD = standard deviation; V_{84Gy} = percentage of the volume receiving ≥84 Gy.

simply that $_{NewPET}$GTVh was smaller than $_{PET/CT}$GTVh. Because a lower dose can be delivered to OAR and better quality of life can result, the effort to develop an accurate PET scanner is important for the innovation of radiation therapy.

The shortcomings of this study are the small number of patients included and the absence of laboratory investigation or phantom study data. Although the local failure rate in this study seems relatively high, we could not draw any definite conclusion about the reason for this rate because of the small number of patients in this study. However, our results indicated the potential usefulness of FMISO-PET in radiation therapy and the need for caution when operating different PET scanners, such as in a multicenter clinical trial.

Conclusions

In conclusion, the difference in PET scanner used for examination affected the definition of hypoxic volume significantly. Using the threshold of abnormal uptake of FMISO, which was determined from data from normal nasopharyngeal tissue, the dose for the hypoxic region was escalated sufficiently with a lower dose to OAR by using New PET compared to using PET/CT, due to the smaller size of GTVh with New PET in an IMRT simulation plan. Development of a more precise and accurate PET scanner could be a breakthrough for accurate dose escalation in FMISO-guided IMRT for patients with NPC. Further investigations are required to confirm our findings.

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JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2012;42(9)807–812
doi:10.1093/jjco/hys112
Advance Access Publication 17 July 2012

Long-term Follow-up of a Randomized Phase II Study of Cisplatin/5-FU Concurrent Chemoradiotherapy for Esophageal Cancer (KROSG0101/JROSG021)

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Received May 20, 2012; accepted June 16, 2012

Objective: Long-term survival and late toxicities of a randomized Phase II study of chemoradiotherapy for esophageal cancer were analyzed.
Methods: Eligible patients were <75 years old and performance status 0–2, and had Stages II–IVA esophageal cancer. For arm A (short-term infusion), cisplatin 70 mg/m^2 Days 1 and 29 and 5-fluorouracil 700 mg/m^2 Days 1–5 and 29–33 were given concurrently with radiotherapy of 60 Gy/30 fr/7 weeks (1 week split). For arm B (protracted infusion), cisplatin 7 mg/m^2 Days 1–5, 8–12, 29–33 and 36–40, and 5-fluorouracil 250 mg/m^2 Days 1–14 and 29–42 were given with the same radiotherapy. Two cycles of consolidation cisplatin/5-fluorouracil chemotherapy were given to both arms.
Results: Between 2001 and 2006, 91 patients were enrolled; 46 were randomized to arm A, and 45 to arm B. The 2- and 5-year overall survival rates for arm A were 46 and 35% (95% confidence interval: 22–48%), while those for arm B were 44 and 22% (11–35%), respectively. Excluding four patients with early death, seven (17%) patients in arm A and eight (18%) in arm B showed late toxicities of Grade 3 or more. Most of the toxicities were cardiac or pleural toxicities. Patients with severe late toxicities often had coexistent hypothyroidism. There were three patients with a secondary malignancy possibly related to treatment.
Conclusions: Low-dose protracted infusion chemotherapy with radiotherapy is not superior to full-dose short-term infusion chemotherapy with radiotherapy for esophageal cancer. Late toxicities, including cardiac and pleural toxicities, hypothyroidism and secondary malignancy, should be carefully monitored.

Key words: esophageal cancer – chemoradiotherapy – late toxicities – hypothyroidism – secondary malignancy

INTRODUCTION

For esophageal cancer, a significant improvement in local control and overall survival was achieved with concurrent chemoradiotherapy (CRT) as compared with radiotherapy (RT) alone (1–3). To improve these results, a Phase III trial comparing standard dose RT (50.4 Gy) and high-dose RT (64.8 Gy) concurrently combined with 5-fluorouracil (5-FU)/cisplatin was conducted (4). In the INT0123 trial, the high-dose arm did not offer a survival benefit compared with the standard dose arm (4). Thus, at present, four cycles of full dose 5-FU/cisplatin combined with 50 Gy of RT is the standard CRT regimen for esophageal cancer in the USA.

Several investigators including ourselves also showed promising clinical results using low-dose protracted infusion chemotherapy (CT) combined with full dose RT of 60–66 Gy for locally advanced esophageal squamous cell carcinomas (5–10). A low-dose protracted infusion of 5-FU or 5-FU plus cisplatin was proposed to reduce the acute toxicities due to concurrent CRT (8,10). In addition, to obtain maximum radiosensitization by CT, daily administration of low-dose protracted CT combined with RT may be better than full dose short-term CT plus RT. When this protocol was started, low-dose protracted infusion CT combined with full dose RT of 60–66 Gy was popular for locally advanced esophageal squamous cell carcinomas in Japan (11).

To test the above hypothesis, this randomized Phase II study was conducted to compare the relative toxicity and efficacy of combining full dose short-term CT (arm A) or low-dose protracted CT (arm B) with RT for esophageal cancer (12). The primary endpoint of the study was the 2-year overall survival rate. In the initial report, the 2-year overall survival rates for arms A and B were 46 and 44%, respectively, without significant difference (12). However, the survival curve of arm A was slightly higher than that of arm B after 2 years, with 5-year survival rates of 35 and 24%, respectively. As all patients could be followed up for more than 5 years after randomization, the long-term survival rate and late toxicities of the trial were re-analyzed in this report.

PATIENTS AND METHODS

Investigational Design

This randomized Phase II multicenter study was started by the Kyoto Radiation Oncology Study Group (KROSG), and joined subsequently by the Japanese Radiation Oncology Study Group (JROSG). The protocol (KROSG0101/JROSG021) was approved by the institutional review boards or ethics committees of all participating institutions, and written informed consent was obtained before entry into the study. The details of the protocol have been published elsewhere (12).

Eligibility Criteria and Treatment Protocol

Inclusion criteria were histologically confirmed esophageal squamous cell carcinoma or adenocarcinoma of Stage II–IVA (UICC 1997). Only patients with no prior therapy, age <75 years, performance status of 0–2, and adequate bone marrow, hepatic and renal function were eligible. Multiple esophageal tumors were also eligible, but tumors with fistula were excluded.

All eligible patients were randomly assigned either to arm A (full dose short-term CT) or arm B (low-dose protracted CT) by customized randomization software; patients were stratified according to tumor length (≤6 vs. >6 cm), clinical stage (Stage IIA, IIB vs. Stage III, IVA) and institution.

Two courses of concurrent CT were combined with RT of 60 Gy/30 fractions/7 weeks (1 week split at the fourth week). A 6–15 MV X-ray was used. The daily fractional dose of RT was 2 Gy administered 5 days a week. The primary tumor and involved lymph nodes of ≥0.5 cm in the shortest diameter on computed tomography represented the gross tumor volume (GTV). The initial 40 Gy was delivered to clinical target volume 1 (CTV1), and the final 20 Gy was delivered to a reduced volume defined as clinical target volume 2 (CTV2) including the GTV with a margin (lateral and anterior/posterior directions 0.5 cm; cranio-caudal direction 1 cm). CTV1 for cervical, upper, and middle thoracic esophageal cancer included the GTV with a margin plus the supraclavicular and mediastinal lymph nodal areas (T-shaped field). For cervical esophageal cancer, lower mediastinal lymph nodal areas were excluded from CTV1. For tumors originating in the lower thoracic esophagus, CTV1 included the GTV with a margin plus the mediastinal and perigastric/celiac lymph nodal areas (I-shaped field).

For both CTV1 and CTV2, a margin (lateral and anterior/posterior directions 0.5 cm; cranio-caudal direction 1 cm) was added to make planning target volume 1 and 2 (PTV1,2). In addition, leaf margins for PTV1,2 of 0.5–0.8 mm were added. RT doses were specified in the center of the target volume and calculated with lung inhomogenous correction.

Two cycles of CT were delivered concurrently with RT for both arms. For arm A, cisplatin 70 mg/m^2 (Day 1) was delivered via 2 h intravenous infusion (IV), and 5-FU 700 mg/m^2/day was administered as a continuous IV (Days 1–5). For arm B, cisplatin 7 mg/m^2 (Days 1–5 and Days 8–12) was delivered 1 h IV, and 5-FU 250 mg/m^2/day was administered as continuous IV (Days 1–14). For arm B, RT was administered within 1 h after the administration of cisplatin. The total dose of CT was the same for the two arms. This schedule was repeated twice every 4 weeks concurrently with RT. For both arms, two cycles of consolidation CT with cisplatin 70 mg/m^2 (Day 1) and 5-FU 700 mg/m^2/day (Days 1–4) were given after CRT as the protocol.

Follow-up

Locoregional recurrence and distant metastasis were evaluated by barium swallow, upper gastrointestinal endoscopy, and thoraco-abdominal computed tomography scan at

3–6 month intervals after initial evaluation of tumor response. When tumor progression or recurrence was noted, salvage treatment was mandatory for the attending physicians.

Late toxicities observed after 4 months of the start of treatment was graded once a year according to the RTOG/EORTC Late Radiation Morbidity Scoring Scheme and the National Cancer Institute Common Toxicity Criteria (NCI-CTC) (version 2.0), because the CTC for Adverse Events version 3.0 was not available in 2001. Maximum grade scored in the follow-up period was recorded for each patient. Although hypothyroidism was scored once a year, periodical thyroid function tests were not mandatory in the protocol. In terms of secondary malignancy, only malignancies that appeared more than 3 years after the randomization in or near the RT field were recorded.

Endpoints

The primary endpoint of the study was the 2-year overall survival rate. Secondary endpoints were overall survival curves, local control curves, acute and late toxicities and the compliance rate of the protocol. When four cycles of CT and 60 Gy of RT could be given as the protocol, the patient was regarded as being in full compliance with the protocol. When two cycles of CT and 60 Gy of RT could be given concurrently, the patient was regarded as being in partial compliance with the protocol. As the concurrent phase of CRT is a major part of the protocol, when at least two cycles of CT and 60 Gy of RT could be given concurrently (full compliance and partial compliance), patients were regarded as per protocol set.

Statistical Analysis

The probability of survival was estimated using the Kaplan–Meier method with statistical significance assessed by the log-rank test. Data were analyzed according to the intent-to-treat principle. Survival was calculated from the date of randomization. Overall survival considered deaths due to any cause. Local control considered any local or regional tumor progression within CTV1 which received 40 Gy or more. When patients died of distant metastasis or other disease without loco-regional progression, local control was censored. Relationships between hypothyroidism and RT fields or other late toxicities were examined by the χ^2 test with Yates' correction.

RESULTS

From December 2001 to June 2006, 91 patients were registered. Forty-six patients were randomly assigned to arm A, and 45 to arm B (Fig. 1). As of June 2011, 71 patients had died, and 20 patients were alive. The follow-up period for the living patients ranged from 59 to 114 months with a median of 83 months. Table 1 shows the characteristics of the 91 patients and treatment parameters according to each treatment arm. There were no significant differences in patient characteristics or treatment parameters between the two arms. The planned dose of 60 Gy was delivered to 88 patients (97%), while RT was terminated at 30 Gy for three patients. When patients with full and partial compliance were combined as per the protocol set, the rate per protocol in arm A (41/46; 89%) was significantly higher than that in arm B (32/45; 71%) ($P = 0.031$).

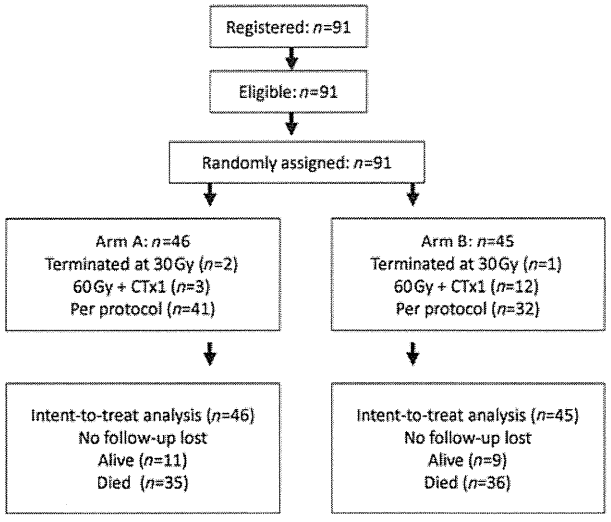

Figure 1. Flow diagram of the patients registered.

Table 1. Characteristics of patients and treatment parameters according to treatment arm (intention-to-treat analysis)

Arm	A ($n = 46$)	B ($n = 45$)
Age (median)	45–74 (63)	48–74 (63)
Male/female	41/5	41/4
PS: 0/1/2	23/20/3	22/21/2
Histology; Sq/Ade	45/1	45/0
Primary site		
Ce/Ut/Mt/Lt	6/13/15/12	4/15/19/7
Length of the tumor		
≤6 cm/>6 cm	23/23 (2–12 cm)	21/24 (1–19 cm)
TNM stage (UICC 1997)		
T1/2/3/4	4/7/14/21	4/9/13/19
N0/1	8/38	9/36
St 2/3/4a	11/30/5	11/27/7
Initial RT field		
T-field	38	38
I-field	8	7

PS, performance status; Sq, squamous cell carcinoma; Ade, adenocarcinoma; Ce, cervical esophagus; Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus; RT, radiotherapy; TNM, tumor node metastasis; UICC, International Union Against Cancer.

All 91 patients were evaluated in terms of survival based on the intent-to-treat principle. Figure 2 shows the overall survival curves for the two arms. The 2- and 5-year survival rates for arm A were 46% [95% confidence interval (CI): 31–59%] and 35% (95% CI: 22–48%), respectively. Those for arm B were 44% (95% CI: 30–58%) and 22% (95% CI: 11–35%), respectively. There was no significant difference between the overall survival curves.

Figure 3 shows the local control curves for both arms. The 2- and 5-year local control rates for arm A were 38% (95% CI: 24–52%) and 30% (95% CI: 17– 44%), while those for arm B were 34% (95% CI: 21–48%) and 21% (95% CI: 11–35%), respectively. There were no significant differences between the two curves. When residual or recurrent tumors were detected after 60 Gy of CRT, appropriate treatment was chosen by the attending physicians, and salvage surgery was performed for 16 patients. For 12 patients (6 patients in arm A and 6 in arm B), potentially curative resection was achieved, while non-curative resection was achieved in 4 patients (2 patients in arm A and 2 in arm B).

Late toxicities associated with CRT were scored for 87 patients excluding 4 patients who died within 4 months (Table 2). The follow-up period ranged from 4.5 to 114 months (median; 19.5 months). There were no significant differences in late toxicities between the two arms. Seven (17%) patients in arm A and eight (18%) in arm B showed late toxicities of Grade 3 or more. Most of the toxicities were cardiac or pleural toxicities. Five patients showed Grade 4 toxicities including pericardial effusion, pleural effusion and cardiac infarction. Notably, most patients with severe late toxicities had coexistent hypothyroidism. Table 3 shows the relationship between hypothyroidism and RT fields or other late toxicities in 41 patients who survived

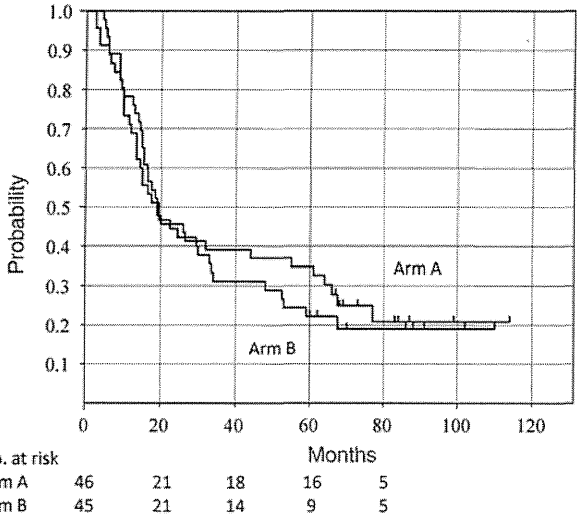

Figure 2. Intent-to-treat analysis of overall survival curves for arm A and arm B.

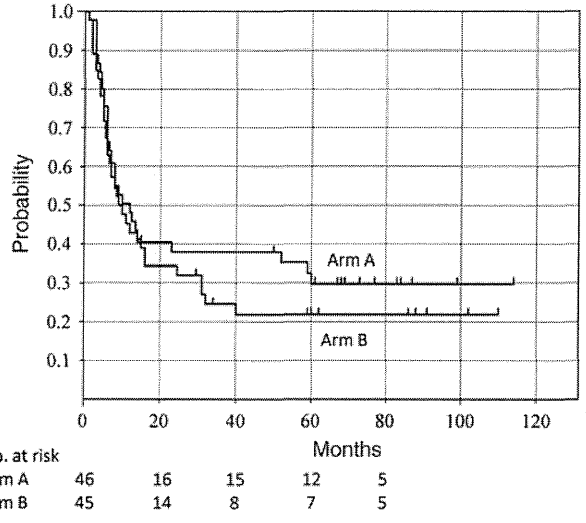

Figure 3. Intent-to-treat analysis of local control curves for arm A and arm B.

Table 2. Late toxicities according to treatment arm [National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0, RTOG/EORTC late radiation morbidity scoring scheme]

Arm	A ($n = 42$)	B ($n = 45$)
Esophagus G2/3/4	1/1/0	2/1/0
Heart G2/3/4	0/3/2	2/1/2
Lung G2/3/4	2/0/0	0/1/0
Pleura G2/3/4[a]	1/3/1	4/2/0
Pneumothorax G2/3/4[a]	1/0/0	0/0/0
Hypothyroid G2/3/4[a]	6/0/0	7/1/0
Kidney G2/3/4[a]	0/0/0	0/1/0
Second cancer G2/3/4/5[a]	0/0/1/1	0/0/1/0
Patient max G2/3/4/5	5/2/4/1	9/5/3/0
Patient max ≥G3	7 (17%)	8 (18%)

Four patients who died within 4 months were excluded from the analysis of late toxicities.
[a]Late toxicities graded according to NCI-CTC version 2.0.

Table 3. Relationship between hypothyroidism and RT fields or other late toxicities in patients who survived more than 24 months

Hypothyroidsm	T-field	I-field	
Grade 0	14	7	
Grade 1	7	0	G0 vs. G1–3; $\chi^2 = 5.86$, $P < 0.05$
Grade 2–3	13	0	G0–1 vs. G2–3; NS
	Other late toxicities		
	Grade 0–1	Grade 2–5	
Grade 0–1	18	10	
Grade 2–3	0	13	$\chi^2 = 12.40$, $P < 0.001$

NS, not significant.

more than 24 months. Hypothyroidism of Grade 1–3 was noted in 20 (49%) of the 41 patients. All of the patients with hypothyroidism (Grade 1–3) were treated with a T-shaped field (neck + mediastinum), and no patient treated with an I-shaped field (mediasinum + perigastric/celiac region) showed hypothyroidism ($P < 005$). All 13 patients with Grade 2–3 hypothyroidism had coexistent other late toxicities of Grade 2 or more, while only 10 of 28 patients with Grade 0–1 hypothyroidism had other late toxicities of Grade 2 or more ($P < 0.001$).

There were three patients with a secondary malignancy possibly related to cancer treatment. One patient in arm A died of acute myelogenous leukemia 77 months after CRT without recurrence of esophageal cancer (Grade 5). In another patient, follicular lymphoma of the duodenum was detected 53 months after CRT. This tumor occurred out of the perigastric RT field, and was treated successfully with CT. In one other patient, early gastric adenocarcinoma was detected out of the RT field 32 months after CRT. This tumor was resected endoscopically. For this patient, lung squamous cell carcinoma (T1N0M0) was detected 96 months after CRT in the irradiated volume of 20 Gy. Curative surgery was performed for this early lung cancer, and this patient showed no evidence of disease up to 110 months after the CRT. In this patient, gastric cancer was not regarded as a secondary malignancy because of the short interval, but the lung cancer that occurred in the RT field 96 months after CRT was regarded as a secondary malignancy.

DISCUSSION

The 5-year minimum follow-up of patients in this analysis is critical for evaluation of long-term survival rates and late toxicities associated with CRT for locally advanced esophageal cancer. Only a few prospective trials on CRT for esophageal cancer reported real long-term survival rates. In the RTOG-8501 trial, the 5-year survival rate of patients treated with 50 Gy CRT was 27% (1,2). In the trial, T4 tumors were not included. In the INT-0123 trial, only overall survival rates within 3 years were reported (4). In the Japan Clinical Oncology Group (JCOG) Phase II study of CRT for resectable esophageal cancer excluding T4 tumors, the 5-year overall survival rate was 37% (13). In arm A, the 5-year overall survival rate was 35% (95% CI: 22–48%), even though 46% of the tumors were T4 disease. Thus, the survival rate in this trial especially for arm A (full dose short-term infusion CT) seems excellent.

In the initial analysis, the survival curve of arm A was slightly higher than that of arm B after 2 years, with 5-year survival rates of 35 and 24%, respectively (12). In the present analysis, the 5-year survival rates were 35 and 22% for arm A and arm B, respectively (Fig. 2). Although the 5-year survival rate was still higher for arm A than for arm B, the difference was not statistically significant. In terms of long-term local control rates, arm A showed a better local control rate than arm B, although this was not significant (Fig. 3). Thus, our initial hypothesis that daily administration of low-dose protracted CT is better than full-dose short-term CT in enhancing radio-sensitization effects was not proved.

Grade 3–5 late toxicities were noted in 17–18% of the patients in this analysis. This rate is much lower than 37% in the 50.4 Gy arm of the INT-0123 or 29% in the CRT arm of RTOG-8501 (2,4). The two trials used the same RTOG morbidity scoring criteria for late toxicities as the present study. Most of the serious late toxicities were cardiac or pleural toxicities, and five patients showed Grade 4 pericardiac and/or pleural effusion. Notably, most patients with severe late toxicities had coexistent hypothyroidism. In the present analysis, a significant correlation was noted between Grade 2–3 hypothyroidism and Grade 2 or more other late toxicities (Table 3). Although pericardiac and pleural effusion are well-known late toxicities associated with CRT for esophageal cancer (9,13–15), no investigators have described the relationship between hypothyroidism and pericardiac and/or pleural effusion. Hypothyroidism was only noted for patients treated with a T-shaped field (neck + mediastinum) after several years of RT, and 14 patients needed thyroid hormone therapy. Hypothyroidism is a well-known late toxicity for head and neck cancer, including cervical esophageal cancer (16–18). However, pericardiac and/or pleural effusion are very rare for head and neck cancer. In the treatment of thoracic esophageal cancer, in addition to thyroid glands, the heart and pleura were also irradiated. Thus, the degree of pericardial or pleural effusion may be enhanced by coexistent hypothyroidism.

As a serious late toxicity, secondary malignancies possibly related to cancer treatment were noted in three patients. Although there are several case reports on therapy-related leukemia following definitive CRT for esophageal cancer (19,20), therapy-related solid tumors following CRT for esophageal cancer have not been reported. Acute myelogenous leukemia was noted 77 months after CRT, follicular lymphoma of the duodenum 53 months after CRT and lung squamous cell carcinoma 96 months after CRT. Because a lung tumor was detected 96 months after CRT in the irradiated volume of 20 Gy, the tumor was considered to be a therapy-related tumor. In the present study, two of the three secondary malignancies could be treated curatively. Careful follow-up examinations after 5 years of CRT may be necessary to detect multiple primaries, including CRT-induced secondary malignancies.

In conclusion, our results suggest that low-dose protracted infusion CT with RT is not superior to full-dose short-term infusion CT with RT for esophageal cancer. For long-term survivors after CRT for esophageal cancer, late toxicities including cardiac and pleural toxicities, hypothyroidism and secondary malignancies should be carefully monitored.

Funding

This study was supported in part by a Grant-in-Aid from the Japanese Radiation Oncology Study Group, by a

Grand-in-Aid for Cancer Research (H23-009) from the Ministry of Health, Labour and Welfare of Japan, and by the National Cancer Center Research and Development Fund (23-A-21).

Conflict of interest statement

None declared.

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Int J Clin Oncol (2012) 17:48–54
DOI 10.1007/s10147-011-0254-y

ORIGINAL ARTICLE

Clinical practice and outcome of radiotherapy for esophageal cancer between 1999 and 2003: the Japanese Radiation Oncology Study Group (JROSG) Survey

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Received: 31 January 2011 / Accepted: 2 May 2011 / Published online: 25 May 2011

Abstract
Background To determine the clinical results of radiotherapy (RT) for esophageal cancer in Japan.
Materials and methods A questionnaire-based survey was conducted for esophageal cancer treated by definitive RT between 1999 and 2003. Clinical results of definitive RT for patients were collected from 9 major institutions. Only patients with good performance status (PS 0–2) who received a total dose of 50 Gy or more were included. Patients were classified into three groups: (A) stage I, (B) resectable stages II–III, (C) unresectable stages III–IVA. For group A, all patients treated by RT alone or chemo-radiotherapy (CRT) were included. For groups B and C, only those treated by CRT were included.
Results In total, 167 patients were included in group A, 239 in group B, and 244 in group C. Approximately half of the patients in group A were treated by CRT. The median total RT dose ranged from 60 to 66 Gy. The median and range of the 5-year overall survival rates were 56% (48–83%) for group A, 29% (12–52%) for group B, and 19% (0–31%) for group C, respectively. A wide disparity in overall survival rates was noted among the institutions. A significant correlation between the number of patients treated per year and the 5-year overall survival rate was noted for groups B and C (both $p < 0.05$).
Conclusion Although the overall survival rates for stage I esophageal cancer were excellent, a significant disparity in survival rates was noted among the institutions for stage II–IVA tumors treated by CRT.

Keywords Esophageal cancer · Chemo-radiation therapy · Brachytherapy · National survey

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Introduction

In the treatment of esophageal cancer, significant improvements in local control and overall survival have been achieved with concurrent chemo-radiotherapy (CRT) compared with radiotherapy (RT) alone [1–3]. In a phase III randomized trial (RTOG-8501), four cycles of full-dose 5-FU/cisplatin (FP) combined with 50 Gy of RT was compared with RT alone (64 Gy), and the CRT arm showed a significant improvement in the overall survival rate [1, 2]. To improve these results, a phase III trial (INT-0123) comparing standard dose RT (50.4 Gy) and high-dose RT (64.8 Gy) concurrently combined with FP was conducted [4]. In the INT-0123 trial, however, the high-dose RT arm did not show a survival benefit compared with the standard-dose RT arm [4]. Therefore, four cycles of full-dose FP combined with 50.4 Gy of RT is the standard CRT regimen for esophageal cancer in the USA.

In Japan, surgical resection has been preferred for resectable esophageal cancer for T1–3N0,1M0 disease (International Union Against Cancer TNM classification; UICC 2002). Until the mid-1990s, many patients treated by CRT had unresectable T4 disease or metastatic cervical lymph nodes (M1-lymph). Even for these locally advanced T4 or M1-lymph esophageal cancers, 2-year overall survival rates of 20–30% have been reported by Japanese investigators using concurrent CRT of 60 Gy [5–7]. Because of the success of concurrent CRT for unresectable esophageal cancer, definitive CRT has been applied for resectable esophageal cancer (T1-3N0,1M0) since the late 1990s in Japan. Although no randomized clinical trials comparing definitive CRT and surgery for resectable esophageal cancer have been reported, clinical results of concurrent CRT for resectable esophageal cancer are very promising [8–10].

For superficial esophageal cancer (T1N0M0), RT alone with or without intraluminal brachytherapy (IBT) is also as effective as concurrent CRT [11–14]. Recently, a phase II clinical trial of concurrent CRT for superficial esophageal cancer with submucosal invasion has been reported by the Japan Clinical Oncology Group (JCOG) [15]. In the trial, 60 Gy of RT was combined with two courses of FP for 72 patients with stage I (T1N0M0) esophageal cancer, and the 4-year overall survival and major relapse-free survival rates were 81 and 68%, respectively. This survival rate is very similar to that of surgery.

In the early 2000s, concurrent CRT became one of the standard treatments for both resectable and unresectable esophageal cancers in Japan [10, 16, 17]. A questionnaire-based national survey on CRT or RT for esophageal cancer was conducted to evaluate the clinical results for esophageal cancer in major Japanese institutions.

Patients and methods

A questionnaire-based survey of RT for esophageal cancer treated definitively between January 1999 and December 2003 was conducted by the Japanese Radiation Oncology Study Group (JROSG). In May 2008, questionnaires on the results of definitive RT for patients with esophageal cancer were collected from 9 major institutions of the JROSG. Only patients with good performance status (PS 0–2) who received a total dose of 50 Gy or more were included. Patients treated by preoperative or postoperative RT (or CRT) were excluded.

Patients were classified into three groups: group A, those with superficial tumors (T1N0M0; stage I); group B, those with resectable tumors (T1N1M0, T2,3N0,1M0; stages II–III); group C, those with unresectable tumors (T4 or M1-lymph; stages III–IVA). For group A, all patients treated definitely by RT or CRT with or without IBT were included. For groups B and C, only those treated by concurrent CRT were included.

Results

Table 1 shows the numbers of patients in the institutions and groups. In total, 650 patients with esophageal cancer treated by definitive RT were included from nine institutions. All but 10 tumors (98.5%) were squamous cell carcinomas. The age of the patients ranged from 35 to 87 years, and the median ages at each institution ranged from 63 to 71 years. The clinical practice of each institution between 1999 and 2003 is also shown in Table 1. Periodic cancer board meetings consisting of radiation oncologists and surgical oncologists were performed at six institutions, and salvage surgery for locally recurrent or persistent esophageal tumors were performed at seven institutions. The median follow-up periods of surviving and censored patients ranged from 42 to 70 months with a median of 56 months.

Table 2 shows the treatment methods in the institutions between 1999 and 2003. For stage I disease (group A), 60 patients (36%) were treated by IBT following external RT. In terms of chemotherapy for stage I disease, 74 patients (44%) were treated by CRT with or without IBT, and 93 patients (56%) were treated by RT with or without IBT. For all institutions, the median total RT dose for CRT ranged from 60 to 66 Gy.

The type of chemotherapy given concurrently with RT differed significantly among the institutions. Full-dose FP was used most frequently, followed by low-dose FP. Various chemotherapy regimens of full-dose FP were included: (1) two cycles of cisplatin 70–80 mg/m^2 (day 1) and 5-FU 700–800 mg/m^2/day administered as continuous

Table 1 Numbers of patients and clinical practice in each institution

Institution	No. of patients				Cancer board	Salvage surgery	Median follow-up period of surviving patients (months)
	Group A	Group B	Group C	Total			
Nagoya Univ.	10	10	17	37 (1)	No	No	57
Niigata Univ.	16	12	17	45 (0)	No	No	56
Univ. Ryukyus	16	11	20	47 (1)	Yes	Yes	43
Kyoto Univ.	9	29	19	57 (2)	No	Yes	52
Kinki Univ.	7	17	42	66 (0)	Yes	Yes	69
Nara Med. Univ.	10	36	28	74 (1)	Yes	Yes	46
Hiroshima Univ.	38	15	26	79 (0)	Yes	Yes	70
Tenri Hospital	27	49	26	102 (2)	Yes	Yes	42
Tohoku Univ.	34	60	49	143 (3)	Yes	Yes	56
Total	167	239	244	650 (10)			

Values in parentheses indicate number of patients with non-squamous cell carcinoma histology

Group A, T1N0M0; Group B, T1N1M0,T2–3N0,1M0; Group C, T4,M1-lymph

Table 2 Treatment methods according to each institution between 1999 and 2003

Institution	Total no. of patients	Treatment for stage I			RT dose	Type of chemotherapy			
		CRT	RT	+IBT	Range (median)	Full FP	Low FP	Others	Consolidation
Nagoya Univ.	37	2	3	5	50–70 Gy (60 Gy)	1	19	11	No
Niigata Univ.	45	5	11	0	50–70.2 Gy (66 Gy)	1	22	11	No
Univ. Ryukyus	47	2	2	5	50–66.6 Gy (60 Gy)	28	4	0	No
Kyoto Univ.	57	2	2	5	60 Gy (60 Gy)	19	13	19	Some
Kinki Univ.	66	3	4	0	60 Gy (60 Gy)	11	51	0	Yes
Nara Med. Univ.	74	3	1	6	60–70 Gy (60.8 Gy)	10	58	0	No
Hiroshima Univ.	79	7	6	25	52–71 Gy (62 Gy)	16	15	19	No
Tenri Hospital	102	9	0	18	66 Gy (66 Gy)[a]	94	0	6	No
Tohoku Univ.	143	20	14	0	56–76 Gy (64 Gy)	57	23	49	Yes
Total	650	53	54	60 (21[b])		237	205	115	

[a] Hyperfractionation of 66/1.1 Gy b.i.d. was used

[b] Number of patients treated with CRT and IBT

intravenous infusion (IV) (days 1–4 or 1–5) [18–20], (2) two cycles of cisplatin 40 mg/m^2 (days 1 and 8) and 5-FU 400 mg/m^2/day as continuous IV (days 1–5 and 8–12) [6, 10], and (3) two or three cycles of cisplatin 60 mg/m^2 (day 1) and 5-FU 400 mg/m^2/day as continuous IV (days 1–4) [9, 21]. Low-dose FP included the following regimens: (1) two cycles of cisplatin 7 mg/m^2 (days 1–5 and 8–12) and 5-FU 250 mg/m^2/day as continuous IV (days 1–14) [5, 18, 19], and (2) six weekly cycles of cisplatin 3–5 mg/m^2 (days 1–5) and 5-FU 180–250 mg/m^2 as continuous IV (days 1–5 or 1–7) [19, 20, 22]. The other regimens included: (1) two cycles of *cis*-diammine-glycolatoplatinum (Nedaplatin) 55–80 mg/m^2 and 5-FU 300–700 mg/m^2 as continuous IV (days 1–5) [23], and (2) daily administration of 5-FU 300 mg/m^2/day as continuous IV for 6 weeks [7].

Two cycles of consolidation chemotherapy with cisplatin 70–80 mg/m^2 (day 1) and 5-FU 700–800 mg/m^2/day (days 1–4 or 1–5) were given after CRT at three institutions [10, 18]. No consolidation chemotherapy was given at the remaining six institutions.

Figure 1 shows the 3- and 5-year overall survival rates in the institutions for groups A, B, and C. The median and range of the 5-year overall survival rates of the nine institutions were 56% (48–83%) for group A, 29% (12–52%) for group B, and 19% (0–31%) for group C, respectively (Table 3). The 5-year overall survival rates for group A were good for all 9 institutions, although 56% of patients were treated by RT alone with or without IBT. A wide disparity in the 5-year overall survival rate was noted especially for group B.

The relationship between the number of patients treated per year and the 5-year overall survival rates of each