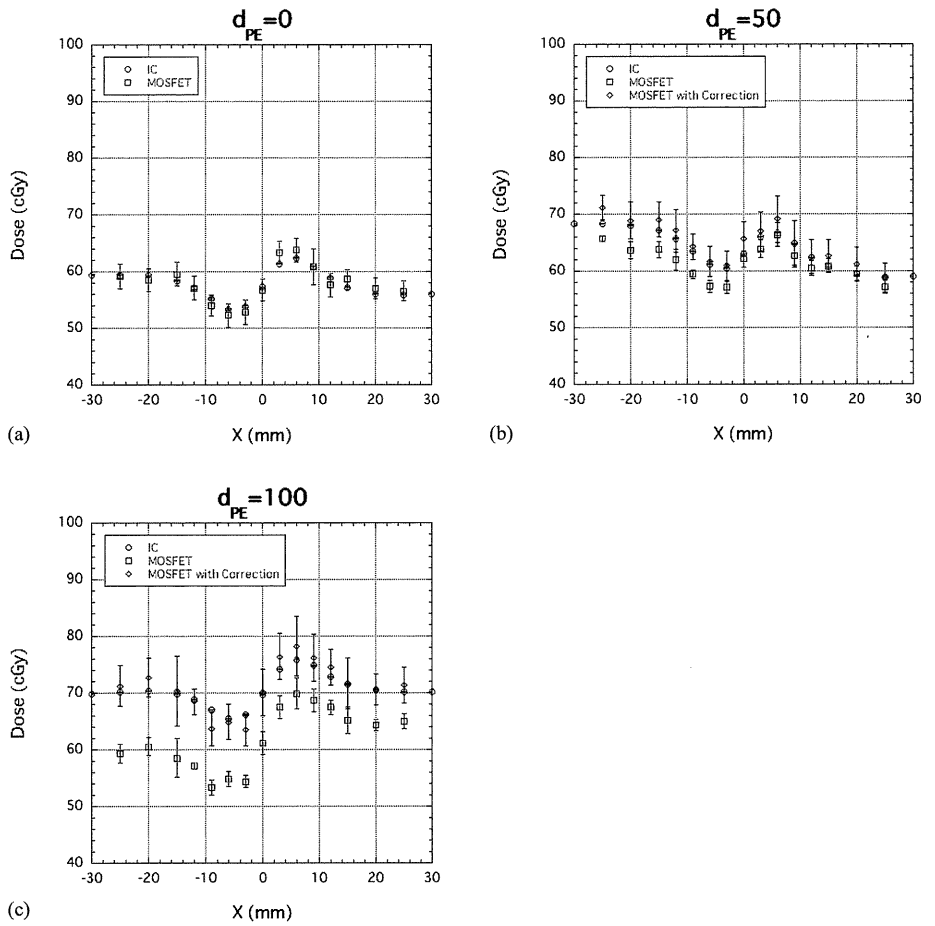

FIG. 7. Comparison of lateral-dose distribution measurements obtained using IC, uncorrected MOSFET (MOSFET) and corrected MOSFET detectors (MOSFET with Correction) at PE thicknesses of 0 (a), 50 (b) and 100 (c) mm for a SOBP proton beam.

IV. CONCLUSIONS

We experimentally evaluated the proton beam dose reproducibility, angular dependence and depth-dose relationships for a new TN-252RD MOSFET detector at high-bias voltages. The reproducibility of the MOSFET detector was within 2%, and the angular dependence was less than 9%. For depth-dose distribution measurements, the relative response of the MOSFET detector at the Bragg peak region was 26% lower than measurements obtained using an ionization chamber. A thinner oxide layer thickness improved the LET dependence in proton dosimetry, although LET dependence was still the limiting factor in accurate depth-dose estimation.

In order to measure dose distributions using a MOSFET detector, we developed a practical method for correcting the MOSFET response to proton beams. For dose distributions resulting from protons passing through an L-shaped bolus, the corrected MOSFET dose agreed well with the IC results. Absolute proton dosimetry was performed using MOSFET detectors with a precision of approximately 3% (1 sigma), and from this we conclude that it is possible to measure proton doses using MOSFET detectors.

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DISEASES OF THE ESOPHAGUS

Original article

Submucosal tumor appearance is a useful endoscopic predictor of early primary-site recurrence after definitive chemoradiotherapy for esophageal squamous cell carcinoma

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SUMMARY. **Chemoradiotherapy (CRT) for esophageal cancer is disadvantageous because of a high locoregional failure rate. Detecting early small recurrent cancers at the primary site is necessary for potential salvage treatment. However, most endoscopists are inexperienced and therefore, a role for surveillance endoscopy after complete remission (CR) has not been established. We retrospectively evaluated serial surveillance endoscopic images from patients eventually proved to have primary-site recurrence in order to identify useful endoscopic features for early diagnosis. From January 2000 to December 2004, 303 patients with esophageal squamous cell carcinoma underwent definitive CRT, and 133 of them achieved CR. The surveillance endoscopic images stored at intervals of 1–3 months for the 16 patients with recurrence only at the primary tumor site and the 61 patients with no recurrence were collected for reexamination. Among 133 patients who achieved CR, 16 (12%) developed only local recurrence at the primary site. Thirteen of the 16 primary-site recurrent tumors (81%) appeared as submucosal tumors (SMT), with the remaining appearing as erosions or mild strictures. Of biopsy-proven recurrences, 81% were preceded by newly developed lesions such as SMT, erosions, or mild strictures detected by earlier surveillance endoscopies. For all 77 patients achieving CR with no metastasis, 86% of the evolving SMT with negative biopsies were eventually confirmed as cancer at later endoscopies. Thirteen of the 21 evolving lesions were subsequently confirmed as recurrent cancer. Early primary-site recurrence of esophageal cancer after a complete response to CRT is detectable with frequent endoscopic surveillance. SMT appearance is a useful endoscopic sign of early recurrence, as well as a predictor of subsequent diagnosis of recurrence.**

KEY WORDS: **chemoradiotherapy, esophageal cancer, recurrence, surveillance.**

INTRODUCTION

Definitive chemoradiotherapy (CRT) is widely accepted as a standard treatment option in the management of locally advanced esophageal cancer because of its high response rate and significant survival benefit.[1,2] A major drawback to this nonsurgical approach is locoregional treatment failure. At least 40% of patients undergoing CRT experienced local failure, some of whom did not develop distant metastases.[1,3–5]

These primary-site recurrence patients are traditionally managed with salvage esophagectomy for a chance of long-term survival, particularly in those with an earlier pathological stage (T1N0 and T2N0).[6,7] However, high perisurgical mortality and morbidity rates are major concerns.[7,8] Recently developed nonsurgical techniques, such as salvage endoscopic mucosal resection and photodynamic therapy,

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have the advantages of greater safety and fewer treatment-related sequelae, while conferring promising survival benefits for local failures after definitive CRT.[9,10] Technically, endoscopic mucosal resection and photodynamic therapy are feasible only when the volume of the locally recurrent tumor is small enough to be amenable to these endoscopy-based procedures. Therefore, the application of these newer treatments depends crucially on the ability to identify early recurrent tumors by endoscopy.

A strategy of frequent surveillance endoscopy initiated early after remission of the cancer should theoretically improve the chances of detecting primary-site recurrent tumors in their early stages. This requires the prompt recognition of minute tumors arising from the former neoplastic bed, instead of from the uninvolved normal esophageal mucosa. However, the complete regression of cancer cells results in residual fibrosis, radiation-induced tissue injury, and the distortion of normal microstructures,[11,12] which may render relapsing neoplastic growth morphologically different from typical primary tumors. Apparently, most endoscopists are inexperienced in hunting for these difficult lesions. To our knowledge, no study of the skills in endoscopic detection of such lesions has been published. Not surprisingly, a follow-up endoscopy after the completion of CRT is considered 'optional' in the National Comprehensive Cancer Network clinical practice guidelines for esophageal cancer.[13] We believe that a reliable endoscopic diagnostic technique is necessary to support a strategy of intense endoscopic follow-ups.

As a cancer referral and research hospital, our institute is unique in its implementation of a vigorous endoscopic follow-up program after primary treatment for all patients with esophageal cancer. Therefore, it is possible to analyze the filed imaging data of endoscopic monitoring on the post-CRT mucosa. In the present study, we aimed to identify useful endoscopic findings through reviewing the image data pool to predict recurrent esophageal cancers limited to the primary site after complete remission (CR) is achieved by CRT.

MATERIALS AND METHODS

Patient population

Between January 2000 and December 2004, 303 patients with esophageal squamous cell carcinoma underwent definitive CRT at the National Cancer Center Hospital East, Kashiwa, Japan. The CRT consisted of 50.4–60 Gy irradiation, together with two cycles of continuous infusion with 5-fluorouracil (5FU) and cisplatin. Up to four courses of CRT were added for those patients who showed a good initial response to treatment.[9]

Table 1 Clinical data of 133 patients achieving complete remission with definitive chemoradiotherapy

Characteristic		Number of patients	%
Sex			
Male		110	82.7
Female		23	17.3
Age (years)			
Mean	62		
Range	39–76		
T stage			
T1		30	22.6
T2		21	15.8
T3		70	52.6
T4		12	9.0
N stage			
N0		46	34.6
N1		87	65.4
M stage			
M0		123	92.5
M1		10	7.5
Clinical stage			
I		16	12.0
II		45	33.8
III		62	46.6
IV		10	7.5
Macroscopic classification			
Type 0		30	22.6
Type 1		19	14.3
Type 2		60	45.1
Type 3		24	18.0

Response to treatment was assessed at the completion of CRT. CR was defined when all the following criteria were met: (i) the disappearance of the tumor lesion or ulcer at the primary site, with negative biopsies; (ii) no esophageal stricture or any condition that prevented a thorough endoscopic examination of the whole esophagus; (iii) no remaining measurable disease or distant metastasis on computer tomography and chest roentgenography; and (5) these criteria were met for at least 4 weeks.

Of the 303 patients, 133 (43.9%) were defined as being in CR at the completion of CRT. Of these 133 patients, 110 were men, with a median age of 62 years. Pretreatment staging of their esophageal cancers was determined with the tumor-node-metastasis classification of the International Union Against Cancer.[14] Seventy (52.6%) patients had T3 tumors; most patients had N1 (65.4%) or M0 (92.5%) disease. Forty-five (33.8%) and 62 (46.6%) patients were classified as clinical stages II and III, respectively (Table 1).

Study design

After achieving CR, initial follow-up endoscopy to confirm CR was scheduled within at most 1–2 months for each patient, accompanied with other necessary studies for the assessment of metastases. After the confirmation of CR, follow-up endoscopy was scheduled every 2–3 months for the first year and every 4–6

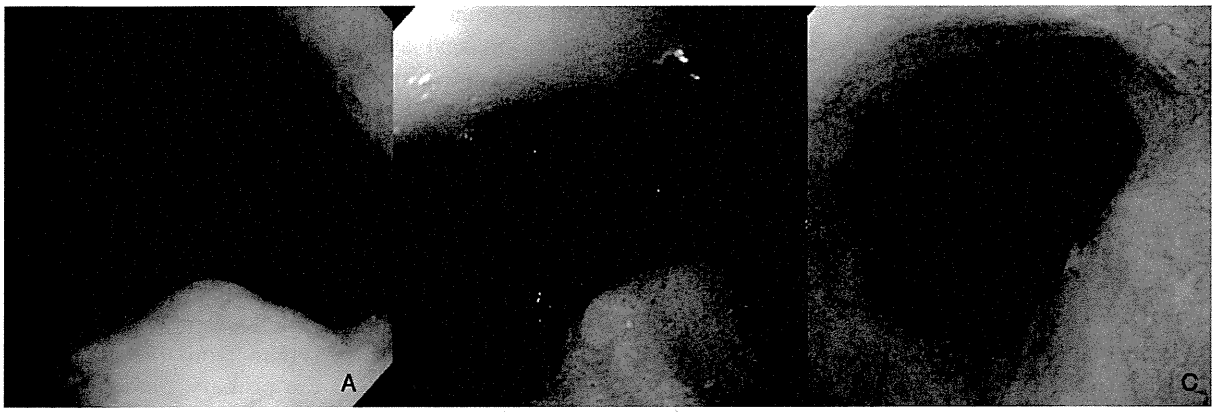

Fig. 1 Initially growing recurrent esophageal cancer at the primary tumor site after complete remission was achieved with chemoradiotherapy may be detected by endoscopy, with features of a submucosal tumor (A), a submucosal tumor with superficial ulcer (B), or a flat erosion (C).

months for 2 years thereafter. Lugol staining and multiple biopsies at the primary site were routinely required.[15] The diagnosis of local recurrence was determined by a positive biopsy.

Of the 133 CR patients, 61 had no recurrence, 56 developed lymph node or distant metastases, and the remaining 16 developed local recurrence at the primary tumor site with no evidence of metastasis. We excluded the 56 patients with lymph node or distant metastases from this study because for them, evaluation of the primary site was not important and only those patients eligible for salvage treatment on local tumors were of interest. Therefore, the endoscopic images of the remaining 77 patients were retrospectively enrolled. This population comprised patients with esophageal squamous cell carcinoma who achieved CR after the initial CRT and developed no metastasis during follow-up, regardless of local recurrence. All of the filed endoscopic images stored after achieving CR, both conventional endoscopy and Lugol-stained chromoendoscopy, were retrospectively collected for reexamination. The stored endoscopic images were evaluated by consensus among three endoscopists experienced in upper gastrointestinal cancer diagnosis (K. T., M. M., K. M.).

RESULTS

Upon the diagnosis of primary-site recurrence for the 16 patients, 13 (81%) had endoscopic findings resembling submucosal tumors (SMT), typically a focal bulge mostly covered by normal-appearing mucosa (Fig. 1A).[16] Eleven of the 13 tumors contained central eroded areas recognized as ulcers or erosions (Fig. 1B and 1C). The remaining three tumors were detected as flat erosions without features of SMT (Table 2).

Images of surveillance endoscopies performed at intervals between CR and the diagnosis of recurrence in the 16 patients were sequentially examined. Newly developed gross lesions at the primary site with negative biopsies were interpreted as recurrent lesions. Evolving lesions were discovered in 13 (81%) patients, including six (38% of the 16 patients) SMT, five (31%) erosions, and two (12%) mild luminal strictures (Table 3).

For all 77 patients achieving CR and free of metastasis, lesions newly developed between CR and the most recent endoscopic surveillance were considered evolving lesions. Therefore, an evolving lesion may be eventually proven to be a recurrence or remain biopsy-negative at the most recent endoscopy. Six of the seven (86%) evolving SMT were subsequently confirmed as recurrent cancer by follow-up

Table 2 Endoscopic findings at primary-site with biopsy-proven recurrence

Endoscopic finding	Number of patients	%
SMT	13	81
SMT with erosion or ulceration	11	
SMT without erosion or ulceration	2	
Erosion	3	19
Total	16	100

SMT, submucosal tumor.

Table 3 Endoscopic findings of newly developed lesion for primary-site recurrent tumors

Preceding newly developed lesions with negative biopsies	Findings at diagnosis of recurrence	Number of patients
SMT	SMT	6
Erosion	SMT	4
Erosion	Erosion	1
Mild stricture	SMT	2
No newly developed lesion	SMT	1
No newly developed lesion	Erosion	2
Total		16

SMT, submucosal tumor.

Table 4 Primary-site biopsy results of the latest surveillance endoscopy for patients who achieved complete remission and remained free of metastasis

Evolving lesion found at preceding endoscopies	Numer of patients (%)	Biopsy result of the latest endoscopy	Number of patients (%)
SMT	7 (9)	Recurrence	6 (86)
		Negative	1 (14)
Erosion	8 (10)	Recurrence	5 (63)
		Negative	3 (37)
Mild stricture	6 (8)	Recurrence	2 (33)
		Negative	4 (67)
No evolving lesion	56 (73)	Recurrence	3 (5)
		Negative	53 (95)
Total	77 (100)		

SMT, submucosal tumor.

endoscopic biopsies. Similarly, five of eight (63%) evolving erosions and two of six (33%) evolving mild strictures were finally confirmed as recurrence. Fifty-six patients were never found to have evolving lesions throughout the follow-up, including three (5%) who were confirmed as recurrence upon the first appearance of an endoscopic lesion. In total, eight of the 21 (38%) patients who developed evolving lesions remained biopsy-negative at their most recent endoscopic follow-up (Table 4).

DISCUSSION

We discovered that the most frequent (81%) endoscopic indicator of primary-site recurrence at its earliest possible stage for a histological diagnosis is SMT. Eighty-one percent of biopsy-proved recurrences were preceded by newly developed lesions such as SMT, erosions, or mild strictures detectable with surveillance endoscopies. Most (86%) evolving SMT with negative biopsies were eventually confirmed as cancer at later endoscopies, but the proportions were lower for other evolving lesions such as erosions (63%) and strictures (33%). This is the first study to describe the morphological changes of early recurring tumors by serial endoscopic observations at short intervals. Our findings will be helpful for improving the skills to detect potentially treatable primary-site recurrence after definitive CRT for esophageal squamous cell carcinoma.

For the endoscopic diagnosis of primary esophageal cancer, several features have been previously described to detect early stage squamous cell carcinoma: localized mucosal erosions in contrast to normal surrounding mucosa; circumscribed mucosal protuberances with irregular configurations; focal areas of mucosal coarsening and congestion; and, rarely, white mucosal plaques.[16] However, these features are not reliable when applied to early recurrent tumors arising from the mucosal bed of a former primary cancer that regressed after CRT. The original esophageal layering and vascular structures have been disrupted by the primary tumor. Furthermore, the expansion and arrangement of recurring neoplastic cells are disrupted by tissue reactions to previous chemotherapy and radiotherapy, as well as by subsequent repair processes. Tumor necrosis, foam cell formation, vascular granulation, inflammatory exudation, and fibrosis are frequent histological sequelae of CRT.[17,18] The minute foci of the initial neoplastic growth may arise from scattered residual cancer cells in deeper tissues, rather than from the superficial mucosal layer, as does the primary cancer.[11] These factors have largely precluded endoscopic ultrasound as a feasible tool in the assessment of residual or recurrent esophageal cancers.[19,20] For the same reason, the endoscopic diagnostic features for recurrent tumors are likely to be different from those for primary tumors.

We speculate that most of the SMT lesions discovered in our study were formed by expanding tumor cells in the submucosal layers, but barely reached the luminal surface because of their depth and constraining fibrosis. Although the overlying mucosa appeared normal, they manifest their first sign by bulging outward. Malignant cells can be captured by biopsy forceps only when they reach the surface in sufficient numbers, or more efficiently, destroy the surface to make an erosion. This might explain why all of the six newly developed SMT yielded negative results at their first biopsies but eventually proved to be recurrences (Table 3).

Several previous studies have aimed to improve the detection of local recurrence by measures other than endoscopy. In addition to pretreatment staging, F-18-fluorodeoxyglucose–positron emission tomography (FDG–PET) is highly sensitive (up to 96%) in detecting recurrent esophageal cancer, but with somewhat lower specificity (68–82%).[21–23] However, its utility in detecting locoregional recurrence is limited by its low specificity (57–75%) for postesophagectomy patients. Postsurgical inflammation and anatomical changes are largely responsible for the false positivity. Detecting small residual or early recurrent cancers is even more challenging because low tumor volume could greatly reduce the sensitivity of FDG–PET. Moreover, such lesions are not distinguishable from post-CRT inflammation or regional lymph-node metastasis.[24,25]

The results of our study disagree with the conventional belief that endoscopy is of limited utility in the management of esophageal cancer after CRT.[13,26] We believe that routine endoscopy, particularly focused on the primary tumor site, is advisable for all patients with esophageal squamous cell carcinoma after the completion of CRT. We also suggest regular endoscopic surveillance at least every three months for those who have achieved CR. The occurrence of

SMT-like lesions after CR is an alarming sign that deserves intensive investigation and follow-up if a modality of salvage treatment is available. Any evolving lesion at the primary site with negative biopsy should be followed closely.

Our retrospective study design has introduced a knowledge bias because the evaluating endoscopists were not totally blinded to the outcomes. Therefore, a randomized controlled trial comparing the clinical outcomes is necessary to establish the role of surveillance endoscopy after definitive CRT for esophageal squamous cell carcinoma.

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CLINICAL INVESTIGATION **Prostate**

MULTI-INSTITUTIONAL PHASE II STUDY OF PROTON BEAM THERAPY FOR ORGAN-CONFINED PROSTATE CANCER FOCUSING ON THE INCIDENCE OF LATE RECTAL TOXICITIES

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Purpose: Proton beam therapy (PBT) is theoretically an excellent modality for external beam radiotherapy, providing an ideal dose distribution. However, it is not clear whether PBT for prostate cancer can clinically control toxicities. The purpose of the present study was to estimate prospectively the incidence of late rectal toxicities after PBT for organ-confined prostate cancer.

Methods and Materials: The major eligibility criteria included clinical Stage T1-T2N0M0; initial prostate-specific antigen level of ≤20 ng/mL and Gleason score ≤7; no hormonal therapy or hormonal therapy within 12 months before registration; and written informed consent. The primary endpoint was the incidence of late Grade 2 or greater rectal toxicity at 2 years. Three institutions in Japan participated in the present study after institutional review board approval from each. PBT was delivered to a total dose of 74 GyE in 37 fractions. The patients were prospectively followed up to collect the data on toxicities using the National Cancer Institute-Common Toxicity Criteria, version 2.0.

Results: Between 2004 and 2007, 151 patients were enrolled in the present study. Of the 151 patients, 75, 49, 9, 17, and 1 had Stage T1c, T2a, T2b, T2c, and T3a, respectively. The Gleason score was 4, 5, 6, and 7 in 5, 15, 80 and 51 patients, respectively. The initial prostate-specific antigen level was <10 or 10–20 ng/mL in 102 and 49 patients, respectively, and 42 patients had received hormonal therapy and 109 had not. The median follow-up period was 43.4 months. Acute Grade 2 rectal and bladder toxicity temporarily developed in 0.7% and 12%, respectively. Of the 147 patients who had been followed up for >2 years, the incidence of late Grade 2 or greater rectal and bladder toxicity was 2.0% (95% confidence interval, 0–4.3%) and 4.1% (95% confidence interval, 0.9–7.3%) at 2 years, respectively.

Conclusion: The results of the present prospective study have revealed a valuable piece of evidence that PBT for localized prostate cancer can achieve a low incidence of late Grade 2 or greater rectal toxicities. © 2011 Elsevier Inc.

Proton beam therapy, Prostate cancer, Radiotherapy, Clinical trial, Rectal toxicity.

INTRODUCTION

The number of patients with organ-confined prostate cancer has been increasing annually because of the widespread screening using prostate-specific antigen (PSA) measurement and aging society. However, organ-confined prostate cancer can now be cured by radical local treatment, including prostatectomy, external beam radiotherapy (EBRT), or brachytherapy, with or without systemic hormonal therapy.

A total dose of >70 Gy using a standard fractionation schedule is considered to be necessary for EBRT to control the disease (1–3); however, the frequency of normal tissue complications increases when the total dose is >70 Gy for conventional EBRT (4, 5). To deliver higher doses to the prostate without increasing the dose to normal tissues, high-technology EBRT, such as three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), and particle therapy have been developed and

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used for more than one decade. Although high-technology techniques of EBRT using X-rays such as 3D-CRT and IMRT have been prospectively evaluated (6–9), the amount of prospective information on the use of proton beam therapy (PBT) alone is limited.

The proton beams used in the modality of particle therapy have distinct physical advantages over conventional photon beams. Proton beams have a low entrance dose, a maximal dose at any prescribed depth called the "Bragg peak," and no exit dose. The "Bragg peak" can be spread out and shaped to conform to the depth and volume of an irregular target. PBT can thus create an inherently three-dimensional conformal dose distribution without exposure of the surrounding normal tissues to excessive doses as compared with the case in conformal photon treatment.

PBT for prostate cancer allows a good dose distribution to be obtained using simple bilateral opposed fields, without exposure of the rectum and bladder to excessive doses. Thus, PBT is theoretically an excellent therapeutic modality owing to its efficacy with reduced toxicity to normal tissues. However, because of the lack of prospective data, it is not yet clear whether PBT can control the incidence of toxicity in the clinical setting. With this background, we started a multi-institutional Phase II trial for patients with organ-confined prostate cancer, focusing on the incidence of late Grade 2 or greater rectal toxicity.

METHODS AND MATERIALS

Patients

The eligibility criteria for inclusion of patients in the present study were (*1*) histologically proven prostate adenocarcinoma, (*2*) clinical Stage II disease (2002 TNM classification, 6th edition, cT1-T2N0M0), (*3*) an initial PSA level of ≤20 ng/mL and Gleason score (GS) of ≤7, (*4*) no history of hormonal therapy or hormonal therapy within 12 months before registration, (*5*) performance status (Eastern Cooperative Oncology Group) 0–2, (*6*) preserved organ function, (*7*) no other active malignancy, and (*8*) written informed consent. Patients with a GS of <7 and PSA level of <10 ng/mL and those with a GS of 7 and/or a PSA level of >10 ng/mL were defined as the low- and intermediate-risk groups, respectively. Patients with Stage cT3-T4, GS 8–10, and/or PSA >20 were not eligible for the present study.

Study endpoints

The primary endpoint was the incidence of late Grade 2 or greater rectal toxicity at 2 years. The secondary endpoints included other toxicities (both acute and late), biochemical relapse-free survival, overall survival, and disease-specific survival. Biochemical failure in the present study was defined as a PSA value of nadir plus 2.0 ng/mL (10, 11), the initiation of any hormonal therapy, or death from any cause.

Study design and statistical analysis

A multi-institutional Phase II study was planned for prospective collection of the toxicity data. The sample size was calculated by the interval estimation method to maintain the accuracy of estimation, using 95% confidence intervals (CIs) of the primary endpoint. The expectation value of the primary endpoint has been defined as <10% according to previous reports of EBRT (12–16). The study sample size was calculated as 150 patients, such that the upper limit of the 95% CI of the primary endpoint was <16% when the actual incidence was <10%. The planned accrual period was 2 years.

Participating institutions

Five institutions were equipped to provide PBT at the beginning of the present study in Japan; three of them participated in the present study, and the institutional review board at each of the three institutions approved the present study (National Cancer Center Hospital East, Kashiwa; Shizuoka Cancer Center, Shizuoka; and Hyogo Ion Beam Medical Center, Hyogo).

Treatment planning

The patients were placed in the supine position and fixed with a vacuum cushion or a thermoplastic cast. The patients were instructed to maintain regular bowel movement; patients with constipation were prescribed laxatives such as magnesium oxide, sennoside, and/or picosulfate sodium to control bowel movement. The bladder filling was controlled by water drinking after urination, and all PBT sessions were performed with a full bladder.

The clinical target volume was defined as the prostate alone for low-risk patients and as the prostate plus the proximal seminal vesicles for intermediate-risk patients, at least encompassing all-known diseases identified by the planning computed tomography scan and other clinical information. The planning target volume consisted of the clinical target volume with optimal margins to account for the uncertainties from the patient setup or internal organ motion, which were estimated at each institution (Table 1). The rectum, from the sigmoid flexure to the anal verge, and the entire bladder as solid organs were delineated as the critical normal structures.

Proton beam therapy

The PBT was delivered at a total dose of 74 GyE in 37 fractions (2 GyE/d). In the low-risk patients, the prostate alone received 74 GyE; in the intermediate-risk patients, a booster dose of 24 GyE was added to the prostate alone after the initial 50 GyE was delivered to the prostate and proximal seminal vesicles. As listed in Table 1, the dose prescription was determined by each institutional method. The dose constraints for the normal tissues were as follows, on the basis of the results from our previous analysis (17) (V_X indicates the percentage of volume receiving more than x GyE): rectum, V_{50} <35%, V_{60} <25%, and V_{70} <15% in the low-risk patients; V_{50} <40%, V_{60} <30%, and V_{70} <20% in the intermediate-risk patients; bladder, V_{65} <50%, V_{70} <35%; femoral head, maximal dose <50 GyE.

Table 1. Details of treatment planning in each institution

Institution	PTV margin (mm)	Dose prescription	Bolus/collimator
NCCHE	7	90% dose to PTV	Individual bolus/ collimator
SCC	5	95% dose to PTV	Individual bolus/ collimator
HIBMC	8–10	To isocenter	No bolus/multileaf collimator

Abbreviations: NCCHE = national cancer center hospital east; SCC = shizuoka cancer center; HIBMC = hyogo ion beam medical center; PTV = planning target volume.

Bilateral opposed fields were used for proton dose delivery. The range modulation by bar-ridge filters was used to generate a spread-out Bragg peak. Proton beams with optimal energy in the range of 190–235 MeV were selected, and individual boluses and collimators were manipulated to conform to the target volume. Daily verification of patient positioning was performed in all patients using orthogonal radiography according to the bony structures. The relative biologic effectiveness of the proton beam was estimated to be 1.1 compared with that of the photon X-rays (GyE = proton Gy × 1.1), in animal experiment conducted at each institution.

Assessments

The registered patients were prospectively followed up to collect data on the toxicities and PSA values at 1 month and once every 3 months after PBT completion for the first 2 years and once every 6 months thereafter.

Late toxicities were defined as those observed >90 days after the start of PBT, but the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme was not used in the present study to assess the late toxicities. Instead, so that the observed symptoms could be individually assessed and scored objectively, the National Cancer Institute Common Toxicity Criteria, version 2.0, was used to assess the acute and late toxicities. The symptoms of rectal and/or bladder toxicities assessed in the present study included proctitis, rectal bleeding, rectal pain, hematuria, urinary frequency/urgency, urinary retention, and dysuria (painful urination). Toxicity grading was determined using the severity of each symptom assessed objectively. The Common Terminology Criteria for Adverse Events, version 3.0, was not available when preparing the present study and was not used.

The cumulative incidence of the toxicities and the survival rates were analyzed using the Kaplan-Meier method.

RESULTS

Patients

Between March 2004 and March 2007, 151 patients were enrolled at the 3 institutions for the present study. The patient characteristics are listed in Table 2. Of the 151 patients, 77 and 74 were low- and intermediate-risk, respectively. All the patients enrolled in the present study received the planned PBT up to a dose of 74 GyE in 37 fractions. The median follow-up period was 43.4 months (range, 3–62). Of the 151 patients, 3 were lost to follow-up within the first 2 years, and 1 patient died of other causes on Day 165, without biochemical failure. These 4 patients were excluded from the analysis of late toxicity. All the patients enrolled in the present study were included in the assessment of the acute toxicities and efficacy.

Acute toxicities

The acute rectal and bladder toxicities observed within 90 days of the initiation of PBT are listed in Table 3. All the acute toxicities observed were transient and resolved spontaneously after completion of PBT. No Grade 3 or greater acute toxicities were observed. The rectal toxicities observed included anal pain at defecation, soft stool, anal discomfort, and rectal bleeding. The bladder toxicities were urinary frequency, dysuria, narrow stream, and urinary retention.

Table 2. Patient and tumor characteristics

Characteristic	Value
All patients (*n*)	151
Age (y)	
Median	67
Range	51–82
cT Stage (*n*)	
T1c	75
T2a	49
T2b	9
T2c	17
T3a	1
Gleason score (*n*)	
4	5
5	15
6	80
7	51
iPSA (ng/mL)	
10	102
10–20	49
Hormonal therapy (*n*)	
Yes	42
No	109
Risk group (*n*)	
Low risk	77
Intermediate risk	74

Abbreviation: iPSA = initial prostate-specific antigen.

Late toxicities

The late toxicities at the final follow-up of the 147 patients who had been followed up for >2 years are listed in Table 4. No Grade 3 or greater late rectal toxicities were observed. The late rectal toxicities observed included rectal bleeding, urgency of defecation, and anal pain. The bladder toxicities were transient gross hematuria and urinary retention.

The Kaplan-Meier curves of late rectal and bladder toxicities are shown in Fig. 1. The incidence of late Grade 2 or greater rectal toxicity was 2.0% (95% CI, 0–4.3%) at 2 years (primary endpoint of the present study) and 4.1% (95% CI, 0.4–7.7%) at the final follow-up. The corresponding data for bladder toxicity were 4.1% (95% CI, 0.9–7.3%) at 2 years and 7.8% (95% CI, 2.9–12.8%) at the final follow-up.

Efficacy

The median follow-up period was 43.4 months in the present study. We evaluated the biochemical relapse-free survival

Table 3. Acute toxicities

Toxicity	Patients (*n*)
Total	151 (100)
Rectum	
Grade 0	135 (89)
Grade 1	15 (10)
Grade 2	1 (0.7)
Bladder	
Grade 0	46 (30)
Grade 1	87 (58)
Grade 2	18 (12)

Data in parentheses are percentages.

Table 4. Late toxicities

Toxicity	Patients (*n*)
Total	147* (100)
Rectum	
Grade 0	115 (78)
Grade 1	27 (18)
Grade 2	5 (3)
Bladder	
Grade 0	128 (87)
Grade 1	9 (6)
Grade 2	8 (5)
Grade 3	2 (1)

Data in parentheses are percentages.
* Number of patients followed up for >2 years.

using the failure definition of nadir plus 2.0 ng/mL; the Kaplan-Meier curve is shown in Fig. 2. Two patients died of other causes on Day 165 and Day 1,202, respectively, without biochemical failure. No patients died of prostate cancer. The biochemical relapse-free survival rate was 94% at 3 years (95% CI, 90–98%).

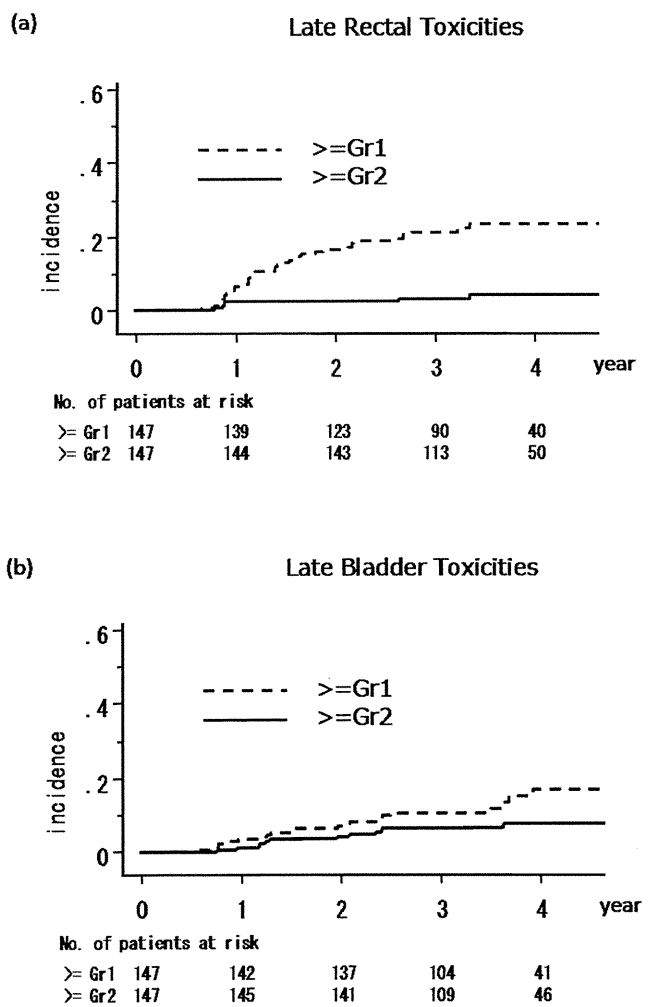

Fig. 1. Kaplan-Meier curves of late (a) rectal and (b) bladder toxicity. Gr = grade.

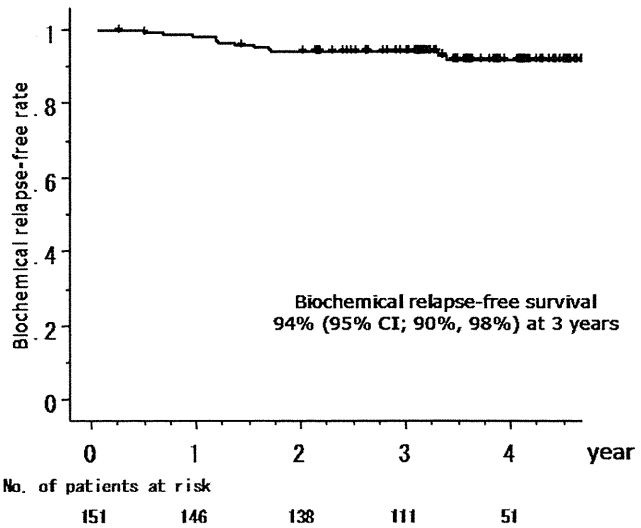

Fig. 2. Biochemical relapse-free survival using definition of nadir plus 2.0 ng/mL. CI = confidence interval.

DISCUSSION

The results of the present prospective study have provided valuable evidence to show a low incidence of late Grade 2 or greater rectal toxicities after PBT for organ-confined prostate cancer. Although PBT is theoretically an excellent modality for EBRT, providing an ideal dose distribution, few well-designed prospective clinical trials are available to corroborate its superiority. The present prospective study was conducted with the aim of scientifically clarifying whether PBT can control the incidence of late rectal toxicity.

The RTOG conducted a Phase I-II dose-escalation study to determine the maximal tolerated dose of 3D-CRT for prostate cancer (RTOG 94-06). The toxicity results of RTOG 94-06 showed a significantly lower incidence of Grade 3 or greater late toxicity but a significantly greater incidence of Grade 2 or less late toxicity than expected from the results of previous RTOG trials (13–15, 18). Although Grade 2 toxicity is generally defined as moderate in severity and is often underestimated, the patients' quality of life can suffer even from such moderate toxicity. Therefore, it is becoming increasingly important to devise sophisticated techniques for high-dose EBRT, such that even the frequency of moderate Grade 2 or less toxicity can be reduced in patients with prostate cancer.

Of the late toxicities that characteristically occur in patients receiving high-dose EBRT for prostate cancer are rectal toxicities, which in most cases, are represented by rectal bleeding, occurring within 2 years of treatment completion. For this reason, the primary endpoint of the present study was defined as the incidence of late Grade 2 or greater rectal toxicity at 2 years after treatment completion.

Since the 1990s, when the existence of a dose–response relationship was suggested in prostate cancer patients undergoing EBRT, dose escalation has been eagerly pursued using high-technology EBRT. In a randomized Phase III trial of 3D-CRT at the M.D. Anderson Cancer Center, the toxicity results revealed an incidence of late Grade 2 or greater

gastrointestinal (GI) toxicity in a high-dose arm (78 Gy in 39 fractions) and standard-dose arm (70 Gy in 35 fractions) of 26% and 12%, respectively (16). Michalski *et al.* conducted a multi-institutional dose-escalation Phase I-II study of 3D-CRT (RTOG 9406; Level 1, 2, and 3, 68.4, 73.8, and 79.2 Gy at 1.8 Gy/fraction; Level 4 and 5, 74 and 78 Gy in 2 Gy/fraction, respectively) and reported the late toxicity profiles at each dose level. Late Grade 2 or greater GI toxicity occurred in 9–13%, 7–9%, 11–14%, 10–16%, and 25–26%, respectively, at dose levels 1–5 (6).

Intensity-modulated RT (IMRT) is a modality of high-technology EBRT. The Memorial Sloan-Kettering Cancer Center has been conducting a single-institutional dose-escalation trial of 3D-CRT and IMRT. Zelefsky *et al.* (7–9) reported that Grade 2 or greater late GI toxicity occurred at an incidence of 16% in patients who had undergone 3D-CRT to a total dose of 75.6–81 Gy (1.8 Gy/fraction). The corresponding incidence was only 2%, even in patients who had undergone IMRT to a total dose of 81–86.4 Gy (7–9). According to a retrospective analysis from the Fox Chase Cancer Center, Grade 2 or greater late GI toxicity occurred at an incidence of 2.4% in patients who had undergone IMRT to a total dose of 74–78 Gy (2 Gy/fraction) (19). However, in some reports, no reduction in the incidence of late toxicity could be achieved despite using IMRT. De Meerleer *et al.* (20) reported that 18% of patients experienced Grade 2 or greater late GI toxicity after receiving a total dose of 74–76 Gy (2 Gy/fractions). Vora *et al.* (21) also reported an incidence of late Grade 2 or greater toxicity of 24% in patients who had undergone IMRT to a total dose of 75.6 Gy.

The PBT facility was installed at Loma Linda University Medical Center in 1990, and the morbidity results for the prostate cancer patients treated to a total dose of 74–75 GyE (1.8–2.0 GyE/fraction) were reported. Late Grade 2 GI toxicity had developed in 21% of the patients at 3 years after treatment completion (22).

The toxicity results in previous reports are summarized in Table 5. The incidence of late Grade 2 or greater rectal toxicity in patients who had undergone 3D-CRT was 9–16% (6, 8). The Memorial Sloan-Kettering Cancer Center and Fox Chase Cancer Center reported a very low incidence of late Grade 2 or greater rectal toxicity (2–2.4%) in patients who had undergone IMRT (7, 9, 19). In contrast, some other centers have reported a high incidence of late rectal toxicity (>15%) even in patients who had undergone IMRT (20, 21). Our results have shown that the incidence of late Grade 2 or greater rectal toxicity was 2.0% at 2 years and 4.1% at the final follow-up; the upper limit of the 95% CIs of these values was 4.3% and 7.7%, respectively. Our results cannot be directly compared with the toxicity data from previous reports, because these studies used different grading scales and also included retrospective and/or single institution-specific data. However, the incidence of late rectal toxicity associated with PBT in the present study was lower than those from the 3D-CRT series and, at least, was not greater than the historical data on the incidence of late Grade 2 or greater GI toxicity after 3D-CRT and IMRT (12–16). The result for the primary endpoint in the present study was 2.0% (95% CI, 0–4.3%) at 2 years, providing at least one piece of scientific evidence of PBT in patients with prostate cancer.

Table 5. Overview of late gastrointestinal toxicity in EBRT for localized prostate cancer

Institution/study	Patients (*n*)	Dose (Gy)	Technique	Grading scale	Grade 1	Grade 2	Grade 3	Follow-up (y)
MDACC (16)	150	70	3D-CRT	RTOG/LENT	36%	11%	1%	6
	151	78			28%	19%	7%	6
					23%, Grade 2/3			2
RTOG 9406 (6)	112	68.4	3D-CRT	RTOG	9-13%, Grade 2/3			9–12
	300	73.8			7-9%, Grade 2/3			7–10
	167	79.2			11-14%, Grade 2/3			9
	256	74			10-16%, Grade 2/3			7–8
	220	78			25-26%, Grade 2/3			6
MSKCC (7–9)	695	75.6–81	3D-CRT	Modified RTOG/CTCAE,	16%, Grade 2/3			5
	561	81–86.4	IMRT	version 3.0	2%, Grade 2/3			7
FCCC (19)	216	74–78	IMRT	Modified RTOG/LENT	2.4%, Grade 2/3			3.5
Ghent University (20)	133	74–76	IMRT	Modified RTOG	47%	17%	1%	3
Mayo Clinic Arizona (21)	145	75.6	IMRT	Modified RTOG	20%	23%	1%	4
LLUMC (22)	643	74	PBT alone	RTOG	—	21%	—	3
		75	X+PBT					
Present study	151	74	PBT alone	NCI-CTC, version 2.0	14%	2.0%, Grade 2/3		2

Abbreviations: EBRT = external beam radiotherapy; MDACC = M.D. Anderson Cancer Center; 3D-CRT, three-dimensional conformal radiotherapy; RTOG = radiation therapy oncology group; LENT = late effects normal tissue task force; MSKCC = memorial sloan-kettering cancer center; IMRT = intensity-modulated radiotherapy; CTCAE = common terminology criteria for adverse events; FCCC = fox chase cancer center; LLUMC = loma linda university medical center; X = photon radiotherapy; PBT = proton beam therapy; NCI-CTC = national cancer institute common toxicity criteria.

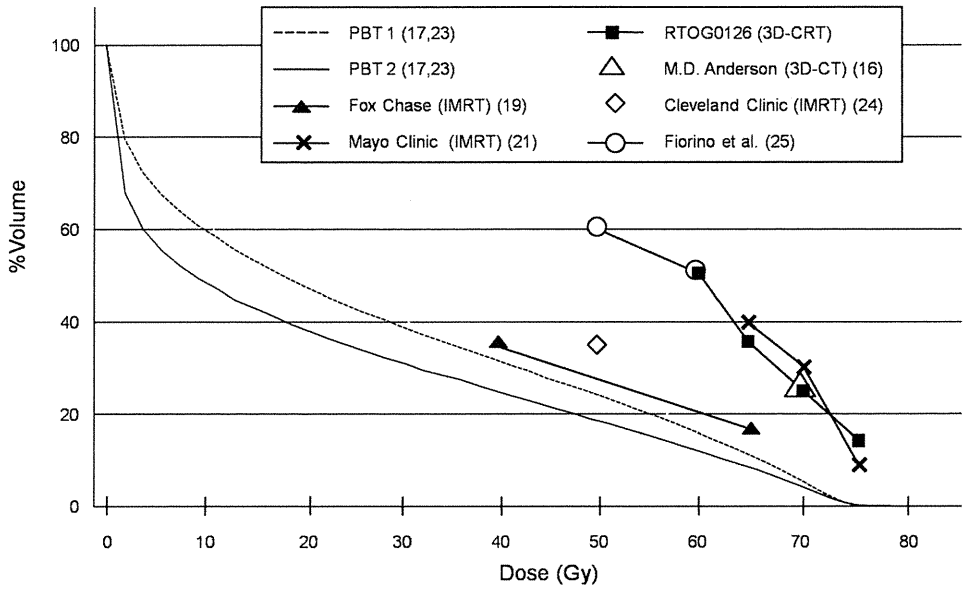

Fig. 3. Average dose–volume histograms (DVHs) for rectum in photon beam therapy (PBT) compared with other dose constraints used in three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT). PBT1 = PBT for intermediate-risk patients; PBT2 = PBT for low-risk patients; RTOG = Radiation Therapy Oncology Group. Data in parentheses indicate reference report.

The previously reported average dose–volume histograms for the rectum in PBT performed at National Cancer Center Hospital East are shown in Fig. 3 (17, 23) and were compared with the other dose constraints used in 3D-CRT or IMRT (16, 19, 21, 24, 25). PBT with simple bilateral opposed fields can thus reduce the dose to the rectum through high to intermediate dose levels, thereby achieving the ideal dose–volume histogram for the rectum. Although bilateral opposed fields can present another issue regarding the dose to the femoral head, the maximal dose to the femoral head in PBT with simple bilateral opposed fields is <35 GyE (45% of the prescribed dose), and V_{30} of the femoral head is <40%.

The total dose of PBT used in the present study was 74 GyE, administered using a conventional fractionation schema (2 GyE/fractions); however, the possible benefit of additional dose escalation and hypofractionation of EBRT for prostate cancer has been suggested, and the efficacy of such a strategy is now under investigation in some randomized trials (16, 26–28). As shown in Fig. 3, the excellent dose–volume histograms for the rectum in PBT might allow the implementation of these strategies; however, additional prospective data are required to ascertain whether PBT administered using these investigational approaches can yield a low frequency of late rectal toxicity.

A more objective grading scale might be necessary to allow comparison of the morbidity data, because different grading scales have been used in previous reports. Thus, the health-related quality of life might be a more rigid and comparable indicator for assessing the toxicities.

Late genitourinary toxicity often occurs after a longer follow-up period (29, 30) and is another issue that needs to be addressed with the use of high-dose EBRT for prostate cancer. As shown in Fig. 1, the incidence curve of late bladder toxicity seems to have been increasing over the years, and that of late rectal toxicity reached a plateau after a few years. Longer follow-up is needed for a more precise assessment of both late genitourinary and GI toxicity.

Quality assurance procedures for clinical assessments have an important role in enhancing confidence in the results of multi-institutional clinical trials. At the beginning of the present study, the specifications for PBT facilities differed among the participating institutions, and the method of delivery of the proton beams to the target organs was defined at the discretion of each institution (Table 1). Although such institutional differences in the method of dose delivery can affect the incidence of toxicity, no significant difference was found in the incidence of toxicity among the three institutions in the present study. Owing to the increasing number of PBT facilities, implementation of quality assurance procedures for PBT in multi-institutional trials, from both the clinical and the physics aspect, is gaining importance.

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Original Article

Efficacy of Concurrent Chemoradiotherapy as a Palliative Treatment in Stage IVB Esophageal Cancer Patients with Dysphagia

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Objective: To retrospectively assess the efficacy and safety of palliative chemoradiotherapy in Stage IVB esophageal cancer patients with dysphagia due to the primary lesion.
Methods: Forty patients with dysphagia caused by metastatic esophageal cancer, which had been treated between January 2004 and June 2009, were retrospectively investigated. The treatment consisted of two courses of chemotherapy (5-fluorouracil and cisplatin) and concurrent irradiation of 40 Gy in 20 fractions to the esophageal primary tumor. The grade of dysphagia was evaluated; nutrition-support-free survival was evaluated using the status of nutritional support of patients. Response to treatment, overall survival, progression-free survival and toxicities were also evaluated.
Results: Dysphagia score improved in 75% of the patients. Seventeen of the 20 patients (85%) who had required nutritional support at baseline improved their oral intake to no longer need the support, in a median time of 43 days. The median nutrition-support-free survival was 301 days in the 20 patients who had had adequate oral intake before the treatment. Disease control rate of the primary lesion was 95%, including 12 patients (30%) who achieved a complete response. The overall response rate was 55%. The median survival was 308 days, and the 1-year-survival rate was 45.0%. The median progression-free survival was 139 days. Toxicities were generally well tolerated. Major toxicities (Grade 3 or 4) involved hemoglobin (23%), leukocytes (15%), neutrophils (20%), anorexia (10%), nausea (3%), esophageal perforation (5%) and febrile neutropenia (3%). Two patients (5%) died within 30 days of terminating radiotherapy.
Conclusions: Palliative chemoradiotherapy using 5-fluorouracil plus cisplatin combined with concurrent 40 Gy irradiation effectively improved the symptom of dysphagia in Stage IVB esophageal cancer with acceptable toxicity and favorable survival.

Key words: esophageal cancer – squamous cell carcinoma – Stage IVB – dysphagia – palliative chemoradiotherapy

INTRODUCTION

Esophageal cancer is the sixth most common form of cancer in male and the sixth most common cause of all cancer death. In 2008, estimated 482 600 new cases are diagnosed, and the estimated deaths were 406 800 worldwide (1). In Japan, 11 669 patients died of esophageal cancer in 2007 (2). For 8.6% of the patients, the disease has already spread to other organs of the body at the time of diagnosis (3), and a cure is not expected. Most of these metastatic patients experience dysphagia due to the progression of the primary lesion.

Dysphagia is the most common and serious symptom of esophageal cancer. It severely affects the patient's quality of

life and necessitates nutritional support, such as intravenous infusion or feeding through percutaneous gastrostomy or nasogastric tube, when inadequate oral intake persists. For patients with unresectable, metastatic esophageal cancer, long-term relief of dysphagia is one of the most important issues in their daily life (4).

Of the multiple treatment options for dysphagia, radiotherapy and metallic stent placement have been considered to be the standard of care. When rapid relief of dysphagia is required, stent placement is the preferred treatment; however, its efficacy is short term due to the fact that the tumor masses are only pressed mechanically. Stent deployment in inoperable patients has been reportedly associated with a median survival time of only 13–20 weeks (5–7). For patients in better health, radiotherapy could offer a more prolonged effect (8).

According to the National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology™ v.1.2010, palliative chemotherapy is proposed as the standard treatment in metastatic patients, with the aims of controlling tumor growth, improving quality of life and prolonging survival. Response rates to chemotherapy alone ranged from 16 to 43% for metastatic disease (9–14). However, there is little evidence to suggest that chemotherapy alone improves survival and/or quality of life including dysphagia in patients with metastatic disease (9,15,16).

With respect to palliative chemoradiotherapy in patients with further advanced esophageal cancer, including metastatic cases, previous studies have shown considerable effects in the improvement of dysphagia (17–23). However, there have been only a few studies covering exclusively Stage IVB esophageal cancer.

The aim of this retrospective study was to provide basic data on the efficacy and toxicity of palliative chemoradiotherapy in Stage IVB esophageal cancer. We especially focused on the improvement of dysphagia, and survival time without nutritional support, because these parameters reflect clinically relevant symptomatic indices in patients suffering from dysphagia due to incurable, metastatic esophageal cancer.

PATIENTS AND METHODS

Patients

The subjects were recruited from our database of patients who were treated at National Cancer Center Hospital East (Kashiwa, Chiba, Japan) between January 2004 and June 2009, according to the following criteria: (i) histologically confirmed squamous cell carcinoma of the esophagus; (ii) metastatic disease classified as Stage IVB, according to the TNM classification of malignant tumor of UICC, sixth edition; (iii) radiation therapy consisted of 2 Gy fractions (Fr) daily for 20 days (total 40 Gy); (iv) chemotherapy consisted of 5-fluorouracil (5-FU) and cisplatin (CDDP); (v) primary lesion present in thoracic esophagus; (vi) age 20–75 years; (vii) performance status (PS) $\leq$2 on the Eastern Cooperative Oncology Group scale; (viii) no previous history of chemotherapy or radiotherapy; (ix) white blood cell count between 4000 and 20 000/μl; (x) platelet count 100 000/μl or more; (xi) adequate liver function, as indicated by serum concentrations of total bilirubin $\leq$2.0 mg/dl, aspartate aminotransferase $\leq$200 IU/l and alanine aminotransferase (ALT) $\leq$200 IU/l; (xii) serum creatinine concentration $\leq$1.5 mg/dl. The metastatic lesions were confirmed with computed tomography scans. The presence of a measurable metastatic lesion was not mandatory. Patients with other active synchronous carcinomas or concurrent uncontrolled medical illness were excluded. The study was performed in accordance with the Declaration of Helsinki and Japanese ethical guidelines for epidemiological research. We obtained an institutional review board (IRB) waiver to conduct this study from the chairperson of the IRB.

Treatment Schedule

Chemotherapy comprised protracted infusion of 5-FU combined with a 2 h infusion of CDDP with adequate hydration and antiemetic coverage. In general, patients were treated with 5-FU 700 mg/m^2 on days 1–4 and 29–32, and CDDP 70 mg/m^2 on days 1 and 29 (Fig. 1). Doses were modified according to the judgment of the attending physician: the doses of 5-FU and CDDP were generally reduced to 50–80% when Grade 4 hematological or Grade 3 or 4 non-hematological toxicity occurred. Once serious toxicity was observed, treatment was suspended until recovery.

Radiation treatment (10 MV) was administered for 4 weeks (5 days/week) at 2 Gy/day with a total radiation dose of 40 Gy/20 Fr, concomitantly with chemotherapy (Fig. 1). The chemotherapy and radiotherapy were started within 7 days of each other. The targeted area for irradiation included only the primary tumor with a 3 cm superior and inferior margin and a 2 cm lateral margin. Metastatic lesions were not included in the targeted area. Irradiation was applied in anterior and posterior opposed fields.

When there was a need, nutritional support was provided by fluid administration including intravenous hyperalimentation or feeding through a percutaneous gastrostomy tube.

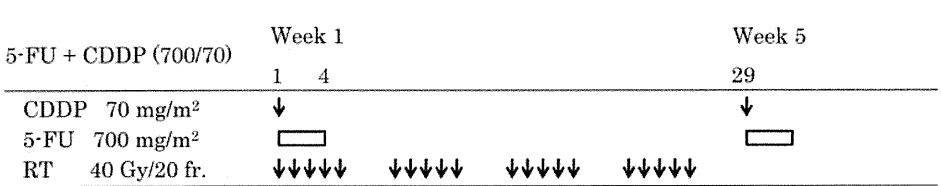

Figure 1. Treatment schedule. 5-FU, 5-fluorouracil; CDDP, cisplatin; RT, radiotherapy.

For patients who showed an objective response to treatment, additional courses of chemotherapy alone were administered, which consisted of the same regimen or protracted infusional 5-FU 800 mg/m^2/day on days 1–5 and a 2 h infusion of CDDP 80 mg/m^2/day on day 1. These treatments were repeated every 4 weeks until disease progression, development of unacceptable toxicity or the patient's refusal to continue. Further additional courses of chemotherapy were optional. When disease progression or unacceptable toxicities were observed, second-line chemotherapy was initiated.

Response and Toxicity Evaluation

The grade of dysphagia was determined by the dysphagia score as described previously and shown in Table 1 (24,25). Improvement of dysphagia was defined as a decrease of at least 1 point in dysphagia score.

Objective responses of measurable metastatic lesions were evaluated according to the response evaluation criteria in solid tumors (RECIST v 1.0) guideline. Tumor response was evaluated using computed tomography scan every 8 weeks after the initiation of treatment. Response of the primary tumor was evaluated by the criteria of the Japan Esophageal Society (26,27). Complete response (CR) of the primary lesion is judged, using endoscopy, with the fulfillment of all of the following conditions: (i) disappearance of all endoscopic findings that suggest the presence of tumor, such as irregular erosive lesions, ulcerative lesions or obvious elevated lesions; (ii) no histologic findings of malignant cells by endoscopic biopsy from the area where the primary tumor had been; (iii) the entire esophagus can be observed by endoscopy; and (iv) no findings of active esophagitis by endoscopy. Progressive disease (PD) of the primary lesion means distinct tumor growth or progression in esophageal stenosis during treatment. Incomplete response/stable disease (IR/SD) means that the response of the primary lesion does not meet the conditions for CR or PD.

Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0). Toxicity was assessed on a weekly basis during chemoradiotherapy and then biweekly during the subsequent chemotherapy.

Table 1. Dysphagia score

Score	Swallowing status
0	Asymptomatic
1	Eat solid diet with some dysphagia
2	Eat semi-solid diet
3	Drink liquid diet
4	Complete dysphagia

Statistical Analysis

Overall survival was calculated from the initiation of treatment to the date of death or the last follow-up day in survivors. Progression-free survival was calculated from the initiation of treatment to the detection of disease progression or death from any cause. In patients who had not required

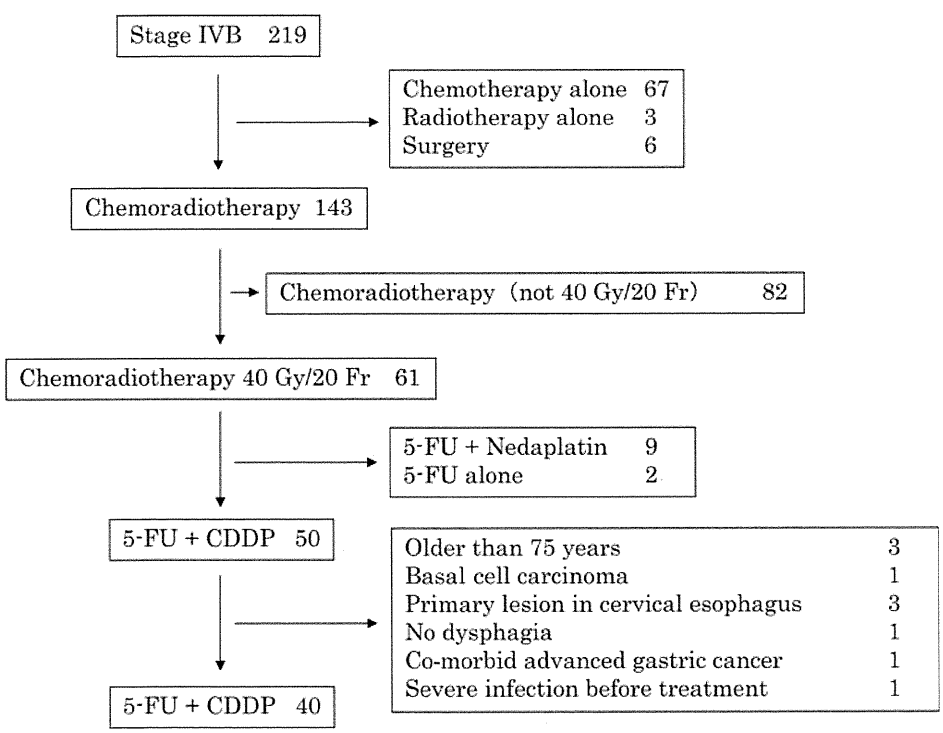

Figure 2. Between January 2004 and June 2009, 219 patients with Stage IVB esophageal cancer were treated at National Cancer Center Hospital East.

nutritional support before chemoradiotherapy, nutrition-support-free survival was calculated from the initiation of treatment to the date when nutritional support was first started. The oral intake of patients who had initially required nutritional support was considered to have improved when nutritional support could be stopped. Overall survival, progression-free survival and nutrition-support-free survival were calculated using the Kaplan–Meier method and the SPSS software program.

RESULTS

Patients' Characteristics and Treatment

From January 2004 to June 2009, 219 patients with Stage IVB esophageal cancer were treated in our hospital. Of these 219 patients, 143 patients were treated with chemoradiotherapy, 67 with chemotherapy alone, 3 with radiotherapy alone and 6 received palliative surgery as initial management (Fig. 2).

Of the 143 patients treated with chemoradiotherapy, 50 were treated with the palliative regimen of chemotherapy with 5-FU and CDDP and 40 Gy/20 Fr of irradiation to exclusively the primary lesion. Of these 50 patients, 10 were excluded from our study: 3 were older than 75 years; 1 had basal cell carcinoma; 3 had a primary lesion located in the cervical esophagus; 1 did not experience dysphagia; 1 had advanced gastric cancer; and 1 developed a severe infection immediately before treatment started. The remaining 93 patients had been treated with other regimens, such as 5-FU and CDDP combined with 50.4 or 60 Gy irradiation, or 5-FU plus nedaplatin with radiation.

The characteristics of the 40 eligible patients are shown in Table 2. Most of the patients (95%) had good PS of 0 or 1.

Table 2. Patients' characteristics ($n = 40$)

Characteristic	
Age (years), median (range)	64 (43–74)
Sex	
Male	36
Female	4
PS	
0	24
1	14
2	2
Primary tumor site[a]	
Ut	8
Mt	20
Lt	12
Macroscopic type	
1	3
2	18
3	18
4	1
T stage	
T1	0
T2	0
T3	24
T4	16
Tumor length (cm), median (range)	8 (3–17)
Tumor circumference	
<1/3 of circumference	1
≥1/3 and <2/3 of circumference	7
≥2/3 of circumference, but not entire circumferential	9
Entire circumferential	23
Metastatic organs	
Lymph nodes	24
Distant organs	16
Liver	10
Lung	8
Others	4

PS, performance status; Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus.
[a]Anatomical subsites of esophagus are defined according to the TNM classification of malignant tumors, seventh edition.

Compliance and Efficacy

All patients completed the planned radiotherapy. Radiation schedule was interrupted for 1 day or more in seven cases (18%) because of infection or high fever (Grade 1 or 2), but all completed the program after an intermission.

The median number of courses in the initial regimen of chemotherapy was four, ranging from one to seven courses. Treatment discontinuation within two courses was observed in two patients. The regimen was changed to 5-FU and nedaplatin in one patient at the physician's discretion. Chemotherapy was terminated in the other patient because of disease progression after the first course of chemotherapy. In seven patients, the dose was reduced (to 50–80%) for the second course because of toxicities observed in the first course.

The responses of the primary lesions are shown in Table 3: 12 patients (30%) achieved a CR in their primary lesion and 26 (65%) were categorized as having IR/SD. Of these patients, 24 demonstrated apparent regression of the primary lesion, which means that 90% of the patients showed volume reduction in the primary lesion after chemoradiotherapy. As for the overall response including metastatic lesions, objective improvement was seen in 22 patients, a 55% response rate (Table 4).

Evaluation of Dysphagia and Survival

All patients were assessable for degree of dysphagia, history of oral intake, toxicity, overall survival and progression-free

Table 3. Response of the primary lesion ($n = 40$)

Response of primary lesion	No. of patients
CR	12 (30%)
IR/SD	26 (65%)
PD	0 (0%)
NE	2 (5%)
Disease control rate	95%

CR, complete response; IR/SD, incomplete response/stable disease; PD, progressive disease; NE, not evaluated.

Table 4. Overall response to treatment ($n = 40$)

Overall response	No. of patients
CR	2 (5%)
PR	20 (50%)
SD	10 (25%)
PD	6 (15%)
NE	2 (5%)
Response rate	55%

PR, partial response.

Table 5. Change in dysphagia score after treatment ($n = 40$)

Improved	Unchanged	Worsened	Improvement rate
30	7	3	75%

survival. Nutrition-support-free survival could also be assessed in all patients. Twenty patients who had received nutritional support of total parenteral nutrition or percutaneous gastrostomy at the onset of treatment were assessable for improvement in oral intake.

The overall improvement rate of dysphagia score was 75% (30/40) (Table 5). The nutrition-support-free survival of the 20 patients with initially adequate oral intake is shown in Fig. 3. The median nutrition-support-free survival was 301 days (10.0 months). The median overall survival in this group of patients was 410 days (13.7 months). Of the other 20 patients who had initially required nutritional support, 85% (17/20) were relieved from nutritional support: median overall survival was 249 days (8.3 months). Of the 17 patients who were relieved from nutritional support, the median time until relief of nutritional support was 43 days (1.4 months) and the median nutrition-support-free duration was 137 days (4.6 months).

The median follow-up period was 617 days in survivors at the time of analysis. The overall survival time is shown in Fig. 4. The median survival time was 308 days

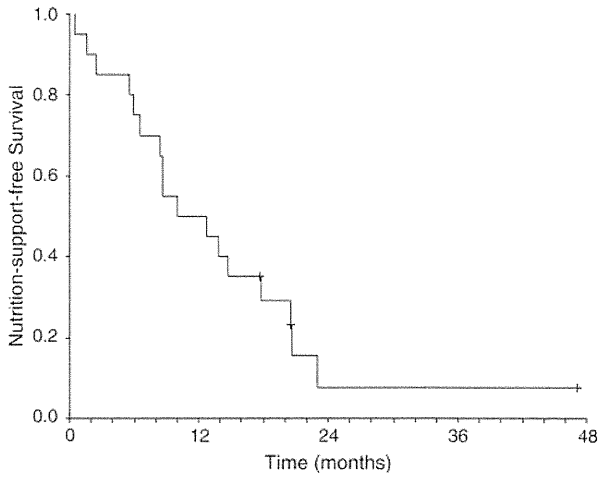

Figure 3. Nutrition-support-free survival ($n = 20$).

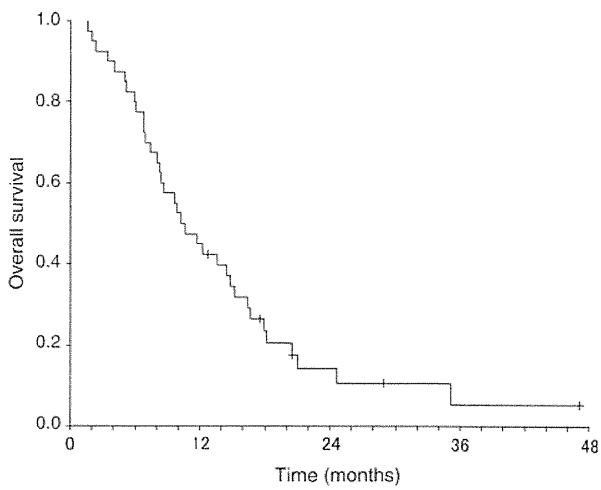

Figure 4. Overall survival ($n = 40$).

(10.3 months), and the 1-year-survival rate was 45.0%. The median progression-free survival was 139 days (4.6 months) (Fig. 5).

Toxicity

The grades of toxicity during the treatment course (radiotherapy and first and second course of chemotherapy) are summarized in Table 6. Toxicity profiles with Grade 3 and 4 are shown except for platelet. Hematological toxicities were generally mild. Anemia was the most common hematological toxicity, but only 23% of the patients experienced Grade 3 or 4 anemia. Grade 3 or 4 neutropenia and leukopenia occurred in 15 and 20% of the patients, respectively. Grade 3 or 4 non-hematological toxicities were hyponatremia (18%), anorexia (10%), nausea (3%), esophageal perforation (5%), ALT (5%), creatinine (3%), febrile neutropenia (3%), rash (3%) and constipation (3%).

No patient died during radiotherapy. However, early death, within 30 days of terminating radiotherapy, occurred

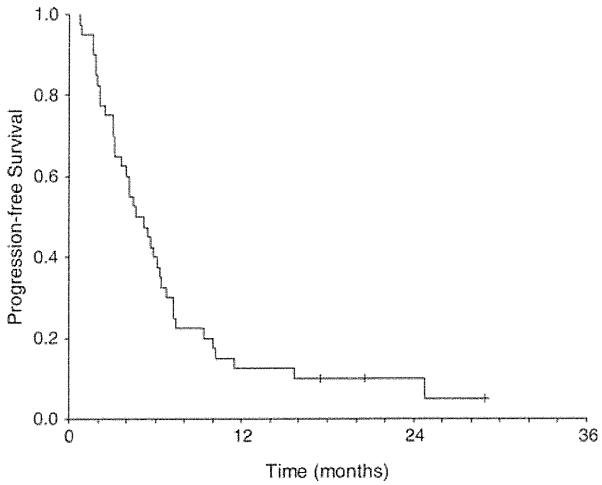

Figure 5. Progression-free survival ($n = 40$).

Table 6. Adverse events ($n = 40$)

CTCAE VER3.0	Gr. 1	Gr. 2	Gr. 3	Gr. 4	≥Gr. 3
Hemoglobin	10	17	8	1	9 (23%)
Leukocytes	13	10	5	1	6 (15%)
Neutrophils	19	13	8	0	8 (20%)
Platelet	9	5	0	0	0 (0%)
Rash	1	0	1	0	1 (3%)
Anorexia	11	8	4	0	4 (10%)
Constipation	3	2	1	0	1 (3%)
Mucositis/stomatitis	4	3	0	0	0 (0%)
Nausea	16	7	1	0	1 (3%)
Esophageal perforation	0	0	2	0	2 (5%)
Alanine aminotransferase	16	2	2	0	2 (5%)
Creatinine	8	2	1	0	1 (3%)
Hyperkalemia	21	3	1	0	1 (3%)
Hyponatremia	28	—	7	0	7 (18%)
Febrile neutropenia	0	0	1	0	1 (3%)

Two patients (5%) died within 30 days of completion of radiotherapy.
CTCAE, Common Terminology Criteria for Adverse Events.

in two patients: one was a 64-year-old man who had supraclavicular lymph node metastases. The primary tumor had not invaded adjacent organs (T3), but one metastatic lymph node had invaded the wall of the aorta. On the 13th day after terminating radiotherapy, the patient was admitted to the hospital as an emergency due to severe right pneumonia; he died the next day. Chest X-ray indicated pneumonia due to aspiration or perforation, so the probability of radiation pneumonitis was low. The other patient was a 71-year-old man who had deep cervical and supraclavicular lymph node metastases and pericardial dissemination. The primary tumor invaded the wall of the aorta, bronchus and pericardium (T4). On the 26th day after terminating radiotherapy, the patient complained of severe back pain. After a few hours, he was found in cardiac arrest. The causes of death in these two cases are not clear, but they could be related to treatment.

DISCUSSION

Palliative chemoradiotherapy using 5-FU plus CDDP combined with concurrent 40 Gy irradiation effectively improved the symptom of dysphagia in Stage IVB esophageal cancer with acceptable toxicity and favorable survival in our study.

To date, the best palliative method for dysphagia due to advanced esophageal cancer has not been established. Of the multiple treatment options, chemoradiotherapy had been reported to be effective for the palliation of dysphagia through tumor regression in advanced, incurable esophageal cancer (17–23). However, these previous studies included patients who were not uniform in terms of TNM clinical classification. In palliative chemoradiotherapy for patients with Stage IVB esophageal cancer accompanied by dysphagia, it is most important to balance management of primary and metastatic sites with tolerance of toxicity. Therefore, to prolong survival without nutritional support, it is important to establish the appropriate dose of individual agents and irradiation dose and field. Our study is one of only a few to investigate the palliative effects of chemoradiotherapy exclusively in patients with Stage IVB esophageal cancer.

In our study, the palliative chemoradiotherapy was satisfactory, with an overall improvement rate in dysphagia score as high as 75%. Of the patients who had required nutritional support at the onset of treatment, 85% no longer needed the support after the treatment. The toxicity was tolerable, and the median overall survival was 10.3 months in patients with Stage IVB esophageal cancer accompanied by dysphagia. We suggest that concurrent chemoradiotherapy of 5-FU plus CDDP combined with 40 Gy irradiation is effective in improving dysphagia.

Published reports of palliative chemoradiotherapy are summarized in Table 7 (17,18,20–23). The chemotherapy regimens in these studies are basically a combination of 5-FU and another agent, and the radiation dose ranges between 30 and 54 Gy, which is generally lower than the dose used in definitive chemoradiotherapy. Our regimen, chemotherapy with 5-FU and CDDP, and concurrent radiation of 40 Gy, can be properly categorized in the spectrum of palliative therapy. Hayter et al. (18) showed in detail the palliative efficacy of 30 Gy radiation in 10 Fr with concurrent chemotherapy consisting of 5-FU and mitomycin C in 22 patients with advanced incurable esophageal cancer. In that study, complete relief of dysphagia was observed in 68% of the patients. The median time to normalization of swallowing was 5 weeks, and the median dysphagia-free interval from the onset of improvement was 11 weeks. In the other reports, the improvement rate of dysphagia ranged