CONCLUSION

The addition of chemotherapy to standard RT provides a small, but significant, survival benefit in patients with NPC. This benefit is essentially observed when chemotherapy is administered concomitantly with RT. The role of induction chemotherapy and adjuvant chemotherapy given alone or added to concomitant chemotherapy is more questionable.

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APPENDIX

A complete list of the MAC-NPC collaborative group follows.

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Cancer Chemother Pharmacol (2006)
DOI 10.1007/s00280-006-0193-x

ORIGINAL ARTICLE

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A phase I/II study of nedaplatin and 5-fluorouracil with concurrent radiotherapy in patients with esophageal cancer

Received: 11 July 2005 / Accepted: 11 January 2006

Abstract *Purpose*: To determine the recommended dose (RD) of cis-diammine-glycolatoplatinum (nedaplatin) when given concurrently with 5-FU and high dose radiation therapy in the treatment of esophageal cancer. The purpose of the phase II trial is to determine efficacy and further define the side effect profile. *Methods*: Twenty-six patients with clinical stage I to IVA squamous cell carcinoma of the esophagus were enrolled in a non-surgical treatment comprised of a fixed dose of fluorouracil (400 mg/m^2 administered as continuous intravenous infusion on days 1–5 and days 8–12) plus escalating doses of nedaplatin (40 mg/m^2 in level 1, 50 mg/m^2 in level 2, or 60 mg/m^2 in level 3 on days 1 and 8), repeated twice every 3 weeks with concurrent radiotherapy (60 Gy). *Results*: Between July 1998 and February 2004, a total of 26 patients entered this trial, all of whom were considered evaluable for toxicity assessment. In phase I of the study, 12 patients were treated in sequential cohorts of three to six patients per dose level. The maximum tolerated dose was reached at level 3 with two grade 4 neutropenia and one grade 4 thrombocytopenia. Thus, the recommended dosing schedule is level 2. Of the 20 patients treated at the RD level 2, including 6 patients of the RD phase I portion, 8 out of 20 patients (40%) had grade 3–4 neutropenia, 5 patients (25.0%) had grade 3–4 thrombocytopenia, 4 patients (20.0%) had grade 3 anemia and 4 patients (20.0%) had grade 3–4 esophagitis. Other toxicities were relatively mild and usually of grade 2 or less. Objective responses were noted in the 26 patients (overall response rate, 88.5%) including 11 (42.3%) complete remissions. The 1- and 3-year survival rates were 65.1 and 37.2%, respectively, with a median survival time of 21.2 months. *Conclusions*: The combination of nedaplatin and 5-FU with radiation is a feasible regimen that shows promising antitumor activity with an acceptable safety profile in patients with esophageal cancer.

Keywords Nedaplatin · Esophageal cancer · Chemoradiotherapy

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Introduction

Esophageal cancer is highly malignant. In the USA, 14,520 new cases of esophageal cancer were diagnosed in 2005, more than 90% (13,570) of which were fatal, comprising 2.4% of all cancer deaths [1]. In Japan, with at least 10,000 new cases being discovered every year, it now accounts for 3.4% of cancer deaths and is the sixth leading cause of cancer death among Japanese males. However, treatment for patients with esophageal cancer remains unsatisfactory. Although surgery is considered the standard treatment in locally advanced esophageal cancer, results of surgery remain poor, with the 5-year survival rate in the range of 5–30% [2]. Chemoradiotherapy (CRT) has revealed promising results in the treatment of esophageal cancer in the past decade. In the report of a intergroup randomized controlled trial (Radiation Therapy Oncology Group 85–01), which compared CRT with radiotherapy alone, the 5-year survival rate was 27% after CRT while after radiation therapy alone (64 Gy) was 0% [3]. Therefore, CRT became an important option in the treatment of esophageal cancer.

Cisplatin and 5-FU were the key drugs in these treatment protocols [3–8]. However, it has been reported that cisplatin-based chemotherapy often produces substantial toxicity, including nephrotoxicity and gastrointestinal toxicity, requiring frequent modifications of the treatment, and these toxicity levels increase when combined with radiotherapy [9]. Therefore, there is a need to identify a new combination with a drug that is less toxic than CDDP or a drug that can provide better therapeutic results with reduced adverse reactions. Several platinum complexes have been synthesized such as Cis-diammine-glycolatoplatinum (nedaplatin, CDGP). Nedaplatin combines with DNA, interfering with its duplication, similarly to the way CDDP does. It is now marketed in Japan as a drug with an antitumor activity comparable to that of cisplatin [10], with less renal toxicity due to its property of being approximately ten times as soluble in water as CDDP [11, 12]. A phase I study against various advanced cancers demonstrated the maximum tolerated dose (MTD) and the recommended dose (RD) for phase II studies of nedaplatin were 120 and 100 mg/m^2 every 4 weeks, respectively, and dose-limiting toxicity (DLT) was evidenced by thrombocytopenia; no severe renal or gastrointestinal toxicities were observed [13]. Nedaplatin produced promising response rates in phase II trials for treatment of squamous cell carcinoma (SCC) of the head and neck [14], lung [15], uterus cervix [16] and esophagus [17]. However, it is still inconclusive whether nedaplatin could replace cisplatin for the treatment of esophageal cancer since phase III trails have not been performed to allow direct comparison of nedaplatin to CDDP.

A combination of nedaplatin and 5-FU resulted in the synergistically enhanced inhibition of tumor growth seen in the combination of cisplatin and 5-FU in a preclinical murine tumor model [18]. In a clinical study, combination chemotherapy using nedaplatin and 5-FU has been reported to be a safe and effective regimen for treating advanced esophageal cancer with an overall response rate of 50% [19].

To date, there have been few reports of CRT using nedaplatin and 5-FU for both primary and preoperative therapy of esophageal cancer, each of which used a different dosing schedule [20–22]. In addition, none of these reports include a phase I dose escalation study. We therefore have conducted this phase I/II study to determine the MTD of nedaplatin and to evaluate its efficacy when administered in combination with 5-FU to patients with esophageal cancer as part of the CRT treatment.

Patients and methods

Eligibility

Patient were considered eligible for this study based on the following criteria: histologically proven esophageal cancer; clinical stage I to IVA (International Union Against Cancer tumor-node-metastasis system, 1997); no prior radiation therapy or chemotherapy; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; age 20–78 years; adequate baseline bone marrow function (hemoglobin level 9 g/dl, white blood cell count $>4{,}000/mm^3$ and $<10{,}000/mm^3$, neutrophil count $>2{,}000/mm^3$ and platelet count $>100{,}000/mm^3$); adequate hepatic function (total bilirubin level 1.5 mg/dl and aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase levels 2.0× the upper limit of normal); adequate renal function (serum creatinine level 1.5 mg/dl); adequate respiratory and cardiac function (PaO_2 60 mmHg, normal ECG); and a life expectancy of at least 2 months. Patients were excluded from the study for the presence of any of the following: active concomitant malignancy; tracheoesophageal fistula; serious complications (severe heart disease, pulmonary fibrosis, interstitial pneumonitis or a tendency to bleeding); history of drug hypersensitivity; pregnant or lactating females. Written informed consent was obtained from all patients. This study was approved by the review boards at our institution.

Pretreatment evaluation

The extent of disease evaluation included barium esophagography, esophagoscopy and cervical, chest and abdominal computed tomography (CT) scans. The T-factor in patients with less than T4 was determined by endoscopic ultrasound of the esophagus (if technically possible). Bronchoscopy was performed for cervical or mid-esophageal tumors. Positive lymph nodes were defined as being ≥1 cm on any of the images.

Treatment protocol

Treatment consisted of two cycles of nedaplatin (Shionogi Co Ltd, Osaka, Japan; nedaplatin doses were escalated to 40, 50, or 60 mg/m^2 in subsequent cohorts) on days 1 and 8 and continuous infusion of 5-FU 400 mg/m^2/day on days 1–5 and on days 8–12, repeated twice every 3 weeks, with concurrent radiotherapy (60 Gy) in 30 fractions over 6 weeks. Nedaplatin was diluted in 500 ml saline and infused over a period of 2 h. 5-FU was diluted in saline (250 mg/500 ml saline) and drip-infused continuously over a period of 120 h. Concomitant medications routinely administered before nedaplatin administration included 8 mg ondansetron plus 8 mg dexamethasone, both given intravenously. Radiation therapy was started on day 1 concomitantly with chemotherapy and was delivered with megavoltage equipment using anterior–posterior opposed fields up to 46 Gy to the primary tumor, the metastatic lymph nodes and the regional nodes. A boost dose of 14 Gy was given to the primary tumor and to the metastatic lymph nodes for a total dose of 60 Gy using bilateral oblique or multiple fields. The clinical target volume for the

primary tumor was defined as the gross tumor volume plus 3 cm craniocaudally. The planning target volumes for the primary tumor and the metastatic lymph nodes were determined with 1.0–1.5 cm margins to compensate for setup variations and internal organ motion. The radiation dose to the spinal cord was kept at a maximum of 50 Gy. During the treatment, a complete blood count, including differential and serum chemistry, and urinalysis were performed at least twice a week.

Study design

In phase I of the study, three patients were initially enrolled at each dose level. If none of the patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If one of the three patients experienced DLT, then three additional patients were enrolled at the same dose level. If two or more DLTs occurred at a given dose level, that level was considered to be the MTD and the dose escalation had to be stopped. The RD for phase II trials was defined as the dose preceding the MTD. DLT was defined as the occurrence of any one of the following during treatment: Grade 4 neutropenia lasting more than 7 days, any febrile neutropenia, grade 4 thrombocytopenia, grade 3 nonhematologic toxicity lasting more than 7 days or grade 4 nonhematologic toxicity. Any event resulting in treatment discontinuation for longer than 2 weeks was also considered to be a DLT. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI–CTC), version 2.0. CRT was interrupted in the face of grade 4 hematological toxicity or febrile grade 3 or 4 neutropenia, and resumed with 25% reduction in doses of 5FU and nedaplatin if symptoms resolved to grade 2 or less. If grade 4 esophagitis occurred, CRT or radiaton was interrupted until it resolved to grade 3. Prophylactic granulocyte colony-stimulating factor (G-CSF) was not given with the treatment. However, when grade 4 neutropenia more than 7 days or febrile neutropenia was noted, CRT was interrupted, and 50 mg/m^2/day of G-CSF was optionally given subcutaneously starting the following day and continued until symptoms recovered to grade 2. Any patient who required more than 4 weeks for recovery of adverse reactions was taken off the study.

Evaluation

The primary end-point of this trial was to evaluate the frequency of DLT, and the secondary end-point was to evaluate the potential antitumor activity. Within 4–8 weeks from the completion of CRT, upper endoscopy (with biopsy as clinically indicated), barium esophagraphy and chest and abdominal CT were performed. Response of the primary tumor was evaluated by modified criteria of the Japanese Society for Esophageal Diseases [23]. In brief, CR for the primary tumor was considered attained when endoscopy showed no visible tumors and biopsies proved negative for at least 4 weeks. PR was assigned if the primary tumor was observed on esophagography as being reduced in area by ≥50%. Progressive disease was considered to be an increase of ≥25% in the area of the tumor. Responses of the metastatic lymph nodes were assessed using the World Health Organization response criteria for measurable diseases. An independent review committee confirmed the observed responses by radiological and endoscopic examinations. Patients were evaluated every 2 months for the first 2 years after treatment and then twice a year. Upper endoscopy and chest and abdominal CT were performed every 4 months for 2 years and annually thereafter. Overall survival was defined as the time from the start of treatment until death from any cause. The distribution of time to death from date of study entry was estimated using the Kaplan–Meier product-limit method.

Results

Patient characteristics

Between July 1998 and February 2004, a total of 26 patients entered this trial, all of whom were considered evaluable for toxicity assessment. In phase I of the study, 12 patients were treated in sequential cohorts of 3–6 patients per dose level. After the MTD was defined, 14 additional patients were enrolled to confirm the suitability of this RD in phase II of the study. All patients were assessable for both toxicity and response. A summary of patient characteristics is given in Table 1. There were 6 female and 20 male patients, and their median age was 63 years. Only one patient had a WHO performance status of 2, and the remaining patients had good performance status. The majority of patients had tumors of the mid thoracic esophagus (14/26:53.8%). All patients had histologically proven SCC. Forty-six percent of the patients were diagnosed as being in stage IVA. The characteristics of both phases before treatment were similar.

DLTs and recommended dose level

Twelve patients were enrolled in phase I of the study and were administered three dose levels of nedaplatin combined with 5-FU 400 mg/m^2 and concurrent radiotherapy (60 Gy). The various dose levels, the number of patients and the DLTs which were observed during the CRT in determination of MTD are summarized in Table 2. At the starting dose (level 1) of nedaplatin (40 mg/m^2), no grade 3 or 4 toxicity was observed in the three patients treated. At level 2 of nedaplatin (50 mg/m^2), one of the first three patients developed grade 4 neutropenia which continued for more than 7 days during treatment, thus an additional three patients were recruited for the same dose level. No DLTs occurred among these last patients. Dose level 3 of nedaplatin

Table 1 Patients characteristics

Nedaplatin (mg/m^2)	Phase I portion			Phase II portion	Total
	40	50	60	50	
No. of patients	3	6	3	14	
Age years					
Median	64	67.3	57	62.3	63.0
(Range)	(54–76)	(60–72)	(53–61)	(51–68)	(51–76)
Male/female	3/0	5/1	1/2	11/3	20/6
Performance status					
PS 0	2	6	2	9	19
PS 1	1	0	1	4	6
PS 2	0	0	0	1	1
Tumor location					
Proximal	0	1	1	3	5
Middle	2	4	1	7	14
Distal	1	1	1	4	7
Tumor[a]					
1	1	0	0	3	4
2	0	1	0	2	3
3	1	4	2	3	10
4	1	1	1	6	9
Node[a]					
0	1	1	0	5	7
1	2	5	3	9	19
Metastasis [a]					
0	2	4	1	7	14
1a	1	2	2	7	12
Clinical stage					
I	1	0	0	3	4
II	0	1	0	2	3
III	1	3	1	2	7
IVA	1	2	2	7	12

[a]Numbers correspond to the tumor-node-metastasis system of classification. (UICC1997)

Table 2 Results of dose escalation

Dose level	Nedaplatin (mg/m^2)	No. of patients	Type of DLTs (no of patients)
1	40	3	None
2	50	6	Neutropenia (1)
3	60	3	Neutropenia (2) Thrombocytopenia (1)

DLT Dose-limiting toxicity

(60 mg/m^2) constituted the toxic dose, with 3 of 3 patients experiencing DLT. The first patient had grade 4 neutropenia for more than 7 days plus grade 3 thrombocytopenia. The second had grade 4 neutropenia for more than 7 days plus grade 3 anemia. The third patient, who had T4 disease, experienced grade 4 thrombocytopenia (concurrently with grade 3 neutropenia) plus grade 3 esophagitis for less than 1 week (the latter toxicity did not result in a DLT). Therefore, this dose level was identified as the MTD for this study. We concluded that dose level 2 should be considered as the RD for further study.

Safety profile

All 26 patients were assessable for toxicity. Table 3 lists the treatment-related clinical adverse events experienced by patients treated at each dose level throughout the treatment period. A separated analysis of the data from 20 patients treated at RD level 2 (6 patients accrued during phase I plus 14 additional patients from phase II) was also performed. Major treatment toxicities included myelosuppression and esophagitis. Grade 3–4 neutropenia was recorded in 11 of 26 patients (42.3%). Of the 20 patients treated at the RD, 8 (40.0%) patients experienced grade 3–4 neutropenia. Grade 3–4 thrombocytopenia was observed in 7 of 26 patients (26.9%), with 5 patients (25.0%) presenting with grade 3–4 toxicity at RD. Grade 3 anemia was detected in five patients (19.2%) with no patients experiencing grade 4. Of the 20 patients treated at the RD, 4 (20.0%) patients experienced grade 3 anemia. Non-hematological side effects were manageable. Esophagitis was observed in 14 of 26 patients (53.8%). However, at RD level 2, severe esophagitis (grade 3–4) was observed in only four patients (20.0%, three patients were grade 3, one patient was grade 4), who had T4 disease. One patient with grade 4 esophagitis required transient TPN support for 1 week but completed protocol radiotherapy. Nausea developed in 53.8% (14/26) of patients, but there were no cases of grade 3 nausea. Other treatment-associated symptoms were infrequent or negligible, and it is noteworthy that no patients experienced grade 3–4 renal dysfunction. There was no treatment-related death that occurred during CRT. All patients received the full planned RT dose (60 Gy). Treatment was interrupted

Table 3 Toxicity occurring in patients throughout the study period by dose level

Dose level (Nedaplatin)	Phase I									Phase II			All patients ($n=26$)		
	1 (40 mg/m^2, $n=3$)			2 (50 mg/m^2, $n=6$)			3 (60 mg/m^2, $n=3$)			2 (50 mg/m^2, $n=14$)					
Toxicity/grade	G1 or 2	G3	G4	G1 or 2	G3	G4	G1 or 2	G3	G4	G1 or 2	G3	G4	G1 or 2	G3	G4
Neutropenia	3	0	0	4	1	1	0	1	2	7	4	2	14	6	5
Anemia	2	0	0	2	1	0	2	1	0	3	3	0	9	5	0
Thrombocytopenia	2	0	0	2	1	0	1	1	1	3	4	0	8	6	1
Nausea	2	0	–	4	0	–	2	0	–	6	0	–	14	0	–
Diarrhea	0	0	0	0	0	0	2	0	0	2	0	0	4	0	0
Mucositis	0	0	0	1	0	0	1	0	0	3	0	0	5	0	0
Esophagitis	1	0	0	2	1	0	1	1	0	5	2	1	9	4	1
Renal	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
Fatigue	1	0	0	2	0	0	2	0	0	4	0	0	9	0	0
Hepatic	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0

during the CRT in 4 (20.0%) of the 20 patients, three for persistent neutropenia (within 10 days) and one for persistent grade 4 esophagitis (12 days). All of these events occurred during the second course of CRT.

Response to therapy

All patients were available for response assessment. As shown in Table 4, the overall response rate was 88.5%, including 11 complete remissions (CR; 42.3%) and 12 partial remissions (PR; 46.2%). Two (22.2%) of nine patients with T4 disease had a CR. Of the patients treated at RD, 18 of 20 patients (90%) responded to treatment, including 9 CR (45%). At the time of this report, the median survival time (MST) was 21.2 months, and the 1- and 3-year overall survival rates were 65.1 and 37.2%, respectively (Fig. 1).

Discussion

Nedaplatin, an analogue of cisplatin, is an attractive candidate for use in combination with 5-FU as it is lower in toxicity than cisplatin yet equally or more effective. Therefore, we aimed to determine the MTD of nedaplatin and assess its safety and efficacy in combination with 5-FU in patients with esophageal cancer in the CRT setting. Possibly the most widely used regimen for CRT therapy for localized esophageal cancer is that used in two landmark trials, RTOG 85-01 and INT 0123, which utilize a standard radiotherapeutic dose of 50.4 Gy or a standard course of chemotherapy which would involve two cycles of concurrent therapy followed by two cycles of adjuvant therapy [3, 5, 8]. However, our study consisted of four cycles of concurrent therapy along with a high dose of 60 Gy irradiation, the aim of which was to enhance the radiosensitization effect and conserve the antitumor effect in esophageal cancer with concurrent CRT, rather than sequential CRT [24]. In fact, a retrospective Japanese study [25] of definitive CRT consisting of 60 Gy irradiation along with four cycles of concurrent therapy of CDDP and 5-FU produced an overall radiologic CR rate of 56% and a 5-year survival rate of 29%, comparable with surgery. The dose levels of nedaplatin were set at 40, 50, and 60 mg/m^2 once per week based on the approved dosage for use in Japan being 100 mg/m^2 per course given as a 1-h intravenous infusion every 4 weeks [17].

Table 4 Response rate

	N	CR	PR	NC	PD	Response rate (%)
Total						
Stage I	4	4	0	0	0	100.0
Stage II	4	3	1	0	0	100.0
Stage III	6	2	4	0	0	100.0
Stage IVA	12	2	7	2	1	75.0
Overall	26	11	12	2	1	88.5
RD						
Stage I	3	3	0	0	0	100.0
Stage II	3	3	0	0	0	100.0
Stage III	5	2	2	1	0	100.0
Stage IVA	9	1	7	1	0	88.9
Overall	20	9	9	2	0	90.0

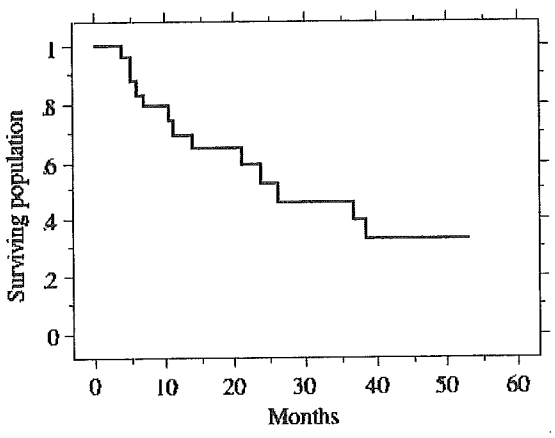

Fig. 1 Overall survival data for all patients

Phase I of this study has demonstrated the recommended dosing (RD) of nedaplatin to be 50 mg/m^2 on days 1 and 8 in combination with 5-FU at 400 mg/m^2/day on days 1–5 and days 8–12, repeated twice every 3 weeks with concurrent radiotherapy (60 Gy). The DLT associated with this regimen was hematological toxicity, consisting of neutropenia and thrombopenia. However, at RD, grade 4 leukopenia lasting for more than 7 days were observed only in three patients and improved rapidly (within 3 days) after the administration of G-CSF. Similarly, grade 4 thrombocytopenia was observed in only one patient at dose level 3, whereas no grade 4 thrombocytopenia was observed at the RD. With regard to the non-hematological toxicity, the present study generally presented with mild symptoms. Grade 4 esophagitis was only observed in one patient, who was dosed at RD, and was manageable. Four (44.4%) of nine patients who had T4 disease experienced grade 3–4 esophagitis, while non-T4 patients had no severe esophagitis. This is because the volume of tissue irradiated will vary greatly between stages I and IVA patients, leading to a much different risk of radiation induced toxicity.

In the RTOG85-01 trial, CRT was associated with 44 and 20% grade 3 and 4 acute toxicities, respectively, mostly neutropenia and esophagitis. Other 5-FU and cisplatin-based regimens have also been associated with significant toxicities [26]. In fact, with regard to hematological toxicity, Ishikura et al. [25] reported that grade 3 or higher leukopenia, anemia and thrombopenia were observed in 43, 23 and 18% of 139 patients, respectively, treated with cisplatin plus 5-FU and 60 Gy of radiotherapy. Toita et al. [27] reported grade 3–4 neutropenia in 30% of patients treated with CRT using cisplatin plus 5-FU. When comparing the hematological toxicity to our study at RD, the incidence was roughly the same but with manageable hematologic toxicity. In the RTOG 85-01 trial, grade 3 or 4 esophagitis occurred in 33% of patients receiving CRT, compared with 18% in those receiving radiotherapy alone [6]. However, the current treatment was associated with a 20% rate of esophagitis at RD, despite the higher RT dose delivered. This was consistent with the results of other Western trails [28, 29] and a Japanese phase 2 study (66.7% of T4 tumor) [30] which employed a total RT dose of ≥60 Gy. Because of the difference of study design and the relatively small number of enrolled patients, comparison of the toxicity data of this study to those of the RTOG 85-01 may be difficult. Nephrotoxicity was not specifically noted in the RTOG 85-01 trial, so it is difficult to compare the toxicity seen in this trial with that landmark trial, but given the lack of nephrotoxicity seen with nedaplatin, it certainly exhibits safety for that endpoint.

Among several different nedaplatin-based CRT regimens [20–22], grade 3–4 leukocytopenia or thrombocytopenia were found in 15.4–25.0 and 7.7–11.7% of patients, respectively. The regimens employed in these studies used lower doses of radiation or lower dosage drug regimens than our study. This is presumed to be the cause of the greater toxicity observed during our study. Although there was a high percentage (34.6%, 9/26) of patients with T4 disease, our study achieved encouraging results with a response rate of 88.5% (including 42.3% CR), a MST of 21.2 months and 1- and 3-year overall survival rates of 65.1 and 37.2%, respectively. Of note is that our results were comparable with the reported trials of CRT using the cisplatin and 5-FU protocol, including RTOG 85-01 [8] and an INT 0123/RTOG 94-05 [5], despite the limitation of a small number of patients. Previously reported nedaplatin-based CRT regimens showed relatively good response rates of 76.5% (CR rate 11.85%) [20] and 77% (CR rate 9%) [22]. Nemoto et al. [21] performed one or two cycles of treatment with nedaplatin (median dose 65 mg/m^2) and 5-FU (median dose 507 mg/m^2/24 h, 5-day continuous infusion) with radiation therapy (60–70 Gy) and reported a response rate of 94% (16/17; CR rate 41%) in spite of the low-dose regimen in which the total dose of the agents was half or less than that used in our study. However, their study involved fewer patients with T4 disease (2/17, 11.8%) than our study (34.6%).

In conclusion, this phase I/II study has demonstrated the feasibility of administering combined therapy with nedaplatin, 5-FU and radiation and has shown evidence of anti-tumor activity with an acceptable safety profile.

Conflict of interest statement

None declared.

Acknowledgments We thank Kevin S. Litton (Bachelor of English literature at University of Massachusetts, Amherst) for assistance in the preparation of this manuscript.

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Int. J. Radiation Oncology Biol. Phys., Vol. 63, No. 5, pp. 1290–1294, 2005

0360-3016/05/$–see front matter

doi:10.1016/j.ijrobp.2005.05.011

CLINICAL INVESTIGATION **Esophagus**

SALVAGE RADIATION THERAPY FOR RESIDUAL SUPERFICIAL ESOPHAGEAL CANCER AFTER ENDOSCOPIC MUCOSAL RESECTION

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Purpose: To analyze the outcomes of radiation therapy for patients with residual superficial esophageal cancer (rSEC) after endoscopic mucosal resection (EMR).

Methods and Materials: From May 1996 to October 2002, a total of 30 rSEC patients without lymph node metastasis received radiation therapy at Tohoku University Hospital and associated hospitals. The time interval from EMR to start of radiation therapy ranged from 9 to 73 days (median interval, 40 days). Radiation doses ranged from 60 Gy to 70 Gy (mean dose, 66 Gy). Chemotherapy was used in 9 of 30 patients (30%).

Results: The 2-year, 3-year, and 5-year overall survival rates and cause-specific survival rates were 91%, 82%, and 51%, respectively, and 95%, 85%, and 73%, respectively. The 2-year, 3-year, and 5-year local control rates for mucosal cancer were 91%, 91%, and 91%, respectively, and those for submucosal cancer were 89%, 89%, and 47%, respectively. These differences in survival rates for patients with two types of cancer were not statistically significant. Local recurrence and lymph node recurrence were more frequent in patients with submucosal cancer than in patients with mucosal cancer ($p = 0.38$ and $p = 0.08$, respectively). Esophageal stenosis that required balloon dilatation developed in 3 of the 30 patients, and radiation pneumonitis that required steroid therapy developed in 1 patient.

Conclusions: Radiation therapy is useful for preventing local recurrence after incomplete EMR.

Superficial esophageal cancer, Endoscopic mucosal resection, Radiation therapy.

INTRODUCTION

Superficial esophageal cancer (SEC) is defined as esophageal cancer limited to the submucosal layer and includes mucosal and submucosal cancer and is squamous cell carcinoma in most patients (1). The number of SEC cases has been increasing recently because of advances in endoscopic and dye-scattering techniques, and SEC cases now account for 20% of esophageal cancer cases in Japan (1). About 60% of patients diagnosed with SEC are between the ages of 60 and 79 years (1). SEC is asymptomatic in most patients and is frequently found incidentally during endoscopic examination of the upper gastrointestinal tract.

Surgery (2–7), endoscopic mucosal resection (EMR) (6–8), and radiation therapy (9–12) have been used to treat SEC. Lymph node metastasis is very rare in mucosal cancer but is frequently found in cases that have infiltrated the submucosa (2, 4, 7). Therefore, the standard management of small mucosal esophageal cancer is generally endoscopic mucosal resection (EMR). For large mucosal cancer and submucosal cancer, definitive radiation therapy or surgery has been the most popular choice of treatment.

Among these treatment methods, EMR is the least invasive therapy for small mucosal SEC lesions, and the number of patients treated by EMR is increasing. Usually, the aim of EMR is complete resection of tumor; however, in clinical practice, cancer cells are occasionally found in resection margins of EMR specimens examined histologically. EMR may be repeated for these patients, but it is difficult in cases with large tumor area, unclear tumor margins, or deeply invasive tumors. Radiation therapy, as well as surgery, is frequently indicated for such residual cancer. Although positive outcomes of definitive radiation therapy for SEC have been reported (9–12), outcomes of radiation therapy for patients with residual SEC after EMR (rSEC) have not been investigated.

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Received Mar 8, 2005, and in revised form April 30, 2005. Accepted for publication May 6, 2005.

METHODS AND MATERIALS

Patients

From May 1996 to October 2002, a total of 32 patients with rSEC received radiation therapy at Tohoku University Hospital and its three associated hospitals. Among these patients, 1 patient with supraclavicular lymph node metastasis and another patient with large mediastinal lymph node metastasis were excluded from analysis. Patients with local recurrence after EMR were not included among these patients. The interval from EMR to start of radiation therapy ranged from 9 to 73 days (median interval, 40 days). Patient demographics and tumor characteristics are listed in Table 1.

Radiation therapy

Radiation treatment characteristics are listed in Table 2. A linear accelerator (10 to 15 MV) was used as the X-ray source for radiation therapy.

In 23 cases, only the primary lesion was irradiated by use of anterior-posterior opposing initial fields (5 to 6 cm in width and 3-cm to 5-cm margin for both the oral and anal margins of the tumor) with conventional fractionation (2 Gy/day, 5 times/week). After irradiation of 40 Gy, the beam direction was changed to avoid the spinal cord. In 5 patients, the initial field included the bilateral supraclavicular fossa and whole esophagus (T-shaped field). In 2 patients with lower thoracic esophageal tumor, the initial field included the primary lesion and lymph nodes around the esophagocardial junction (L-shaped field).

Selection of initial radiation fields was determined by radiation oncologists. When the primary tumor site could not be identified by X-ray, a surgical clip was placed endoscopically on the tumor margin and was used to mark the tumor area. Chemotherapy with cisplatin (CDDP), 5-fluorouracil (5-FU), or both was used in 9 patients on the basis of the radiation oncologist's decision.

Staging and statistics

Tumors were staged according to the UICC TNM classification (2002). The depth of invasion was determined by histologic examination of EMR specimens and endoscopic ultrasonography. The cumulative survival rates and cause-specific survival rates were used as endpoints. Cause of death was determined by review of the clinical records. The last follow-up was performed in October 2004. The observation period ranged from 14 months to 87 months (mean, 33 months). Survival curves were generated by the Kaplan-Meier method. The log–rank test was used to test the difference between survival curves for patients with mucosal vs. submucosal tumors. Cox's regression analysis was used for multivariate analysis to examine the prognostic factors. Prognostic factors were compared by application of Fisher's exact probability test.

Table 1. Patient demographics and tumor characteristics

Gender	
No. males	26
No. females	4
Age range (y)	53–82 (median = 68)
No. clinical stage I*	30
Tumor location	
No. upper thoracic	3
No. middle thoracic	18
No. lower thoracic	9
Tumor depth	
No. mucosa	11
No. submucosa	19
Interval between EMR and radiation (days)	9–73 (median = 40)

Abbreviation: EMR = endoscopic mucosal resection.
* Internationl Union Against Cancer (UICC) 2002 classification.

Table 2. Treatment characteristics

Radiation dose (Gy)	60–70 (mean = 66)
Fractionation* (No. treated)	30
Radiation field	
No. local alone	5
No. T shaped	23
No. L shaped	2
Chemotherapy	
No. not receiving	21
No. receiving	9

* 2 Gy/fraction, 5 times a week.

RESULTS

Survival and cause of death

The overall survival and cause-specific survival are shown in Fig. 1. The 2-year, 3-year, and 5-year overall survival rates and cause-specific survival rates were 91%, 82%, and 51%, respectively, and 95%, 85%, and 73%, respectively. At the time of analysis, 6 patients had already died. Three of the 6 patients died of esophageal cancer recurrence and the other 3 died of intercurrent disease.

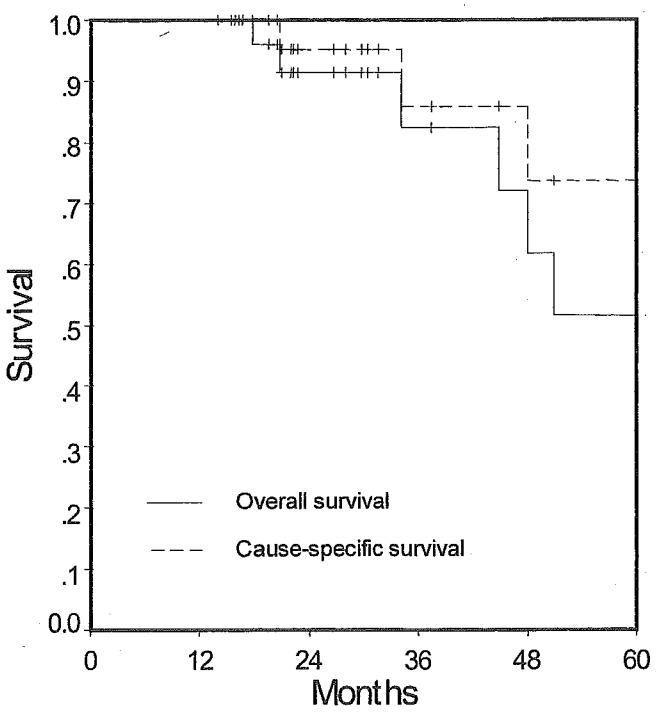

Fig. 1. Overall survival and cause-specific survival.

Local control rate

Local control rates by tumor depth are shown in Fig. 2. The 2-year, 3-year, and 5-year local control rates for mucosal and submucosal lesions were 91%, 91%, and 91%, respectively, and 89%, 89%, and 47%, respectively. For 1 patient with mucosal cancer, laser therapy was performed for local recurrence after radiation therapy. This patient was alive without recurrence 14 months after laser therapy.

Prognostic factors

Prognostic factors for cause-specific survival were evaluated by univariate analysis (Table 3) and multivariate analysis. Age, gender, tumor depth, interval from EMR to radiation, radiation field, radiation dose, and use of chemotherapy were evaluated. Survival of patients younger than 68 years was better than that of patients older than 69 years, but the difference was not statistically significant (p = 0.06). Survival of patients with mucosal cancer was numerically better than that of patients with submucosal cancer, but the difference was not statistically significant (p = 0.15). Multivariate analysis using Cox's regression model revealed no significant prognostic factors.

Pattern of recurrence and depth of invasion

Recurrence was observed in 6 patients. Distant metastasis was not observed in this series. Three patients experienced local recurrence, and 1 patient had lymph node recurrence. Combined local and lymph node recurrence was noted in 2 patients. All local recurrences developed within the radiation field, and all of the lymph node recurrences developed outside of the radiation field. Localized radiation was used to treat the 3 patients in whom lymph node recurrence developed. The relationship between depth of tumor invasion and pattern of recurrence is shown in Table 4. Although the difference was not statistically significant, local recurrences (p = 0.38) and lymph node recurrences (p = 0.08) were more common in patients with submucosal cancer than in patients with mucosal cancer.

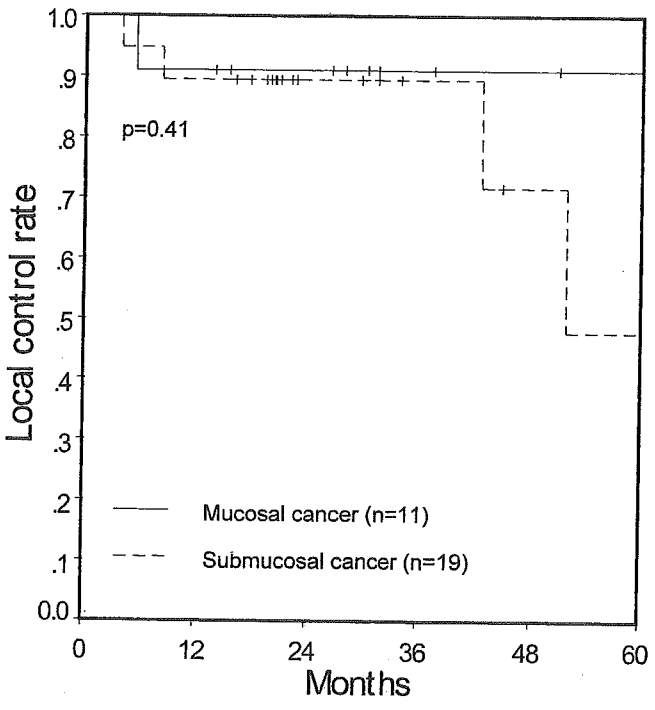

Fig. 2. Local control rate by tumor depth.

Table 3. Univariate analysis of prognostic factors

	5-year CSS (%)	p value
Age (y)		
≤68 (n = 17)	100	0.06
>68 (n = 13)	48	
Gender		
Male (n = 26)	74	0.28
Female (n = 4)	66	
Tumor depth		
Mucosa (n = 11)	100	0.15
Submucosa (n = 19)	58	
Interval from EMR to radiation		
≤40 days (n = 16)	76	0.64
>40 days (n = 14)	75	
Radiation field		
Local field (n = 23)	67	0.34
With lymph node area (n = 7)	100	
Radiation dose		
≤66 Gy (n = 19)	85	0.31
>66 Gy (n = 11)	59	
Chemotherapy		
Yes (n = 9)	0	0.23
No (n = 21)	81	

Abbreviations: CSS = cause-specific survival; EMR = endoscopic mucosal resection.

Complications

Esophageal stenosis that required balloon dilatation developed in 3 patients, and radiation pneumonitis that required steroid therapy developed in 1 patient. Severe, life-threatening complications such as esophageal perforation were not observed in this series.

DISCUSSION

Endoscopic mucosal resection alone is the least-invasive and most-effective treatment method for small mucosal SEC (2, 4, 6, 7), and additional treatment is not used if the resection is complete, because the control rate after complete resection by EMR is usually very high (close to 100%), and lymph node metastasis is very rare in mucosal

Table 4. Pattern of recurrence by tumor depth

	Mucosal cancer (n = 11)	Submucosal cancer (n = 19)	p value
Local recurrence (−)	10	15	0.38
Local recurrence (+)	1	4	
Lymph node metastasis (−)	11	14	0.08
Lymph node metastasis (+)	0	5	

cancer. On the other hand, EMR is occasionally found to have produced incomplete destruction of tumor tissue upon pathologic examination of a resected specimen. Surgery and radiation therapy are indicated for such cases if re-EMR is difficult. However, to our knowledge, outcomes of surgery or radiation therapy for rSEC have not been investigated in detail.

In cases of SEC not suitable for EMR, surgery has been the main treatment method, and 5-year survival rate ranges from 40% to 80% (2–6). However, good outcomes of radiation therapy for SEC comparable with those of surgery have been reported (9–12), and radiation therapy may become a standard therapy for SEC not suitable for EMR.

Okawa *et al.* (9) investigated outcomes of radiation therapy for 105 SEC patients. The overall 5-year survival rate was 39%, and the 5-year disease-specific survival rate was 71% in their series. Murakami *et al.* (10) treated SEC patients with combination therapy that consisted of external-beam radiation therapy, intracavitary radiation therapy, and chemotherapy with cisplatin and 5-FU and reported that overall 1-year and 3-year survival rates were 100% and 83%, respectively. Nemoto *et al.* (12) performed a retrospective analysis of 147 SEC patients treated with radiation therapy at nine institutions in Japan and reported that the 5-year cause-specific survival rates for mucosal and submucosal cancer patients were 81% and 64%, respectively. The 2-year, 3-year, and 5-year overall survival rates and cause-specific survival rates in this series were 91%, 82%, and 51%, respectively, and 95%, 85%, and 73%, respectively. These data suggest that the survival rate of rSEC patients treated with radiation therapy is almost the same as that of SEC patients treated with definitive radiation therapy alone.

The natural course of rSEC has not been reported; however, local recurrence will occur in most cases if additional therapy is not indicated, because the cancer cells remain in the esophageal wall. In this study, the 2-year, 3-year, and 5-year local control rates for patients with mucosal lesions and for patients with submucosal lesions were 91%, 91%, and 91%, respectively, and 89%, 89%, and 47%, respectively. Therefore, radiation therapy seems to be useful for preventing local recurrence of rSEC.

Esophageal stenosis that required balloon dilatation developed in 3 (10%) of the 30 patients. The frequency of esophageal stenosis after definitive radiation therapy for SEC has been reported to be 0% to 5% (9, 11, 12). Therefore, the rate of esophageal stenosis after radiation therapy for rSEC seems to be higher than that after definitive radiation therapy for SEC without EMR. On the other hand, esophageal stenosis is one of the most frequent complications after EMR for SEC and has been reported to occur in 2.9% to 9.1% of patients (1, 13, 14). In this series, both radiation therapy and EMR seem to have influenced the high rate of esophageal stenosis.

In SEC patients, depth of tumor invasion is an important prognostic factor, regardless of the treatment method (1–7, 12). Five of the 19 patients with submucosal cancer in our series experienced local recurrence, lymph node recurrence, or both. Recurrence was observed in only 1 of 11 patients with mucosal cancer. However, the difference in recurrence rates was not statistically significant, and the number of patients in this series is small.

Chemoradiation therapy is superior to radiation therapy alone in the treatment of advanced esophageal cancer (15–17). However, chemotherapy did not improve cause-specific survival of the rSEC patients in our series. Because the number of patients in this series is small, the usefulness of chemotherapy in the treatment of rSEC should be evaluated in a study with a larger patient population.

In this series, 3 patients experienced lymph node recurrence outside of the original radiation field. Therefore, expansion of the initial radiation field to include the supraclavicular area, the abdominal lymph node area (perigastric area), or both may help to prevent lymph node recurrence for patients with submucosal rSEC. However, lung and cardiac complications increase when a large radiation field is used, which must be considered as well (18).

In advanced esophageal cancer, EMR has been used as a salvage therapy with good outcomes in cases in which tumor recurrences are detected early (19). In the present series, additional EMR was considered difficult (because of the large tumor area, unclear tumor margins, or deeply invasive tumors) when patients were referred to the radiotherapy department. However, laser therapy was performed on 1 patient for tumor recurrence after radiation therapy, and this patient was alive without re-recurrence 14 months later. In our institution, regular endoscopic evaluations are performed every 3 months until 2 years, and every 6 months thereafter. Regular follow-up examinations for local recurrence may be important to obtain good final treatment outcomes.

Endoscopic mucosal resection alone is used as a treatment method for small mucosal cancer with good outcomes. However, a combination of EMR and radiation therapy for submucosal cancer seems to be a promising treatment method. Shimizu *et al.* (20) reported outcomes of EMR combined with chemoradiotherapy. EMR was performed for the purpose of complete local tumor control, and chemoradiotherapy was performed for regional and distant control. In their series, none of the 16 patients who underwent EMR combined with chemoradiation therapy had local recurrence or metastasis. Comparison of outcomes of definitive radiation therapy alone with EMR plus radiation therapy for submucosal cancer should be performed in the future.

CONCLUSION

Radiation therapy is useful for preventing local recurrence after incomplete EMR.

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Evaluation of Inter- and Intrafraction Organ Motion during Intensity Modulated Radiation Therapy (IMRT) for Localized Prostate Cancer Measured by a Newly Developed On-board Image-guided System

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Reprinted from Radiation Medicine Vol. 23 No. 1
February 2005

ORIGINAL ARTICLE

Radiation Medicine: Vol. 23 No. 1, 14–24 p.p., 2005

Evaluation of Inter- and Intrafraction Organ Motion during Intensity Modulated Radiation Therapy (IMRT) for Localized Prostate Cancer Measured by a Newly Developed On-board Image-guided System

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Purpose: To investigate prostatic organ motion at both setup and intrafraction using an on-board image-guided system. An intrafraction field-based repositioning method also was evaluated.

Materials and Methods: A dual fluoroscopy with amorphous-silicon flat panel (DFFP) system was used for the three-dimensional registration of implanted markers in the prostate of eight organ-confined cancer patients planned for treatment with intensity modulated radiation therapy (IMRT). Day-to-day motion errors were quantified and intrafraction displacements of more than ±1 mm were corrected.

Results: Among 214 fractions and 565 system views, day-to-day mean magnitude of marker discrepancy±standard deviation (SD) was 1.76±1.4 mm, 3.14±1.6 mm, and 3.78±2.4 mm in the right-left, cranial-caudal, and anterior-posterior directions, respectively. The intrafractional mean magnitude±SD of marker displacement was 0.45±0.7 mm, 1.08±1.38 mm and 1.45±1.70 mm in the right-left, cranial-caudal, and anterior-posterior directions, respectively. Intrafraction corrected sessions (84/214) showed a median (range) of motion of 0.1 mm (−1.2 to 0.7 mm), −0.2 mm (−2.1 to 1.1 mm), and −0.2 mm (−1.7 to 2.0 mm) in the right-left, cranial-caudal, and anterior-posterior directions, respectively.

Conclusion: Motion uncertainty can be considerably decreased with daily use of the DFFP system. Reduced intrafraction organ motion clearly endorsed the value of the repositioning approach, allowing a safer dose escalation protocol.

Key words: interfraction motion, intrafraction motion, image-guided radiation therapy, localized prostate cancer, intensity modulated radiation therapy (IMRT)

Introduction

The goal of all radiation therapy is to irradiate tumors with a lethal dose while limiting the radiation received by the normal tissue that surrounds the tumor. To date, increasing numbers of tumors have been treated with higher radiation doses while limiting high doses to critical structures. The development of three-dimensional conformal radiation therapy (3D-CRT) and intensity modulated radiation therapy (IMRT) has provided tools to account for geometrical uncertainties that affect optimization of the conformal plans. The treatment of prostate cancer patients however, presents a challenge to increasing the dose to best achieve tumor eradication.[1,2]

New technology has arisen for decreasing treatment errors arising from tumor delineation, organ motion, and daily patient positioning so that therapy can be delivered safely, accurately, and with fewer time-consuming steps. This includes sequential CT acquisitions,[3,4] portal image acquisitions,[5-8] MRI,[9] ultrasound (US)[10-14] and fluoroscopy-based fiducial marker-guided radiation therapy.[15,16]

Accounting for treatment errors including random error (variation of a landmark's position about its mean value), systematic error (average displacement of a landmark's position relative to its position at simulation), and volume changes (time trends) is an increasingly

Received April 14, 2004; revision accepted June 20, 2004.

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important part of the clinical radiation therapy process. Therefore, knowledge of treatment errors, their characteristics, and possible techniques for reducing them need to be prioritized when modeling the radiation therapy process. In the case of prostate IMRT, there has been a great deal of effort to better shape high dose distributions, with physicists and engineers making most of this effort. Interfraction and intrafraction organ motion measurements have direct implications for the size and design of planning target volume (PTV).

Techniques for decreasing treatment geometrical errors have been implemented widely for many years,[5,17,18] with experiences varying according to strategies used. These procedures include variables such as patient immobilization style, treatment position, rectum or bladder filling, and the use of "gold standard" images or newer imaging systems at the time of simulation or during treatment fractions.

At our institution, an advanced clinical and technological method has been put into use to overcome some of the past limitations of irradiation of organ-confined prostate cancer and, hence, to increase the probability of higher local tumor control.

Although it is impossible to abolish all treatment uncertainty, knowledge of the actual extent of target motion is of paramount importance for implementing high dose escalation protocols and decreasing the extension of larger margins around the clinical target volume (CTV).

Fractionated radiation therapy treatments require patient positioning of about 35 times at similar planned positions. To achieve this goal, several techniques and imaging tools have been used, with most of them aiming to account for the uncertainty by increasing treatment margins[19] or by monitoring and controlling organ shift.[18,20]

This study focused on the measurement of interfraction (setup) and intrafraction (during delivery) organ motion. Organ motion was analyzed on the basis of real-time registration of the tri-dimensional (3D) position of internal markers implanted in the prostate. For this, a newly developed image-guided system was implemented to register, online, fiducial marker location distributions at megavoltage (MV) and kilovoltage (KV) X-ray energies using paired amorphous silicon (a-Si) flat panels mounted on a medical linear accelerator, namely, a dual fluoroscopy and flat panel (DFFP) system. In addition, the study was extended to the description of an intra-treatment field-based correction method.

Materials and Methods

At the Department of Radiation Oncology of Tohoku University Hospital, high dose irradiation using IMRT has been offered since January 2001. This technique has been implemented for the treatment of clinical and pathologically diagnosed adenocarcinoma of the prostate as a definitive treatment.

Table 1. Patient characteristics

Characteristic	Patients	(%)
Pre TX PSA		
<10	6	75
10-20	1	12.5
>20	1	12.5
Biopsy Gleason score		
2-6	0	0
7	7	87.5
8-10	1	12.5
Clinical stage		
$T1_c$	3	37.5
$T2_a$	2	25
$T2_b$	0	0
$T3_a$	2	25
$T3_c$	1	12.5
*Neo-adj. hormone therapy	8	100
Prescribed dose		
72 Gy	5	62.5
76 Gy	3	37.5
Age		
Median	72.6	
Range	63-78	

PSA = Prostate-specific antigen. * Applied 3-6 months before radiation treatment.

Defining patients and preparation characteristics

Patient selection

The data of a group of eight organ-confined prostate cancer patients selected for IMRT as the entire treatment was used for organ motion analysis. The patients' characteristics are shown in Table 1. For all patients, neoadjuvant hormone therapy was prescribed for three to six months before the start of treatment, as done and reported by other authors.[21-23] As patient selection criteria, we included those with a confirmed histological diagnosis of adenocarcinoma, classified according to the Gleason grading system,[24] with clinical stages from T1c to T3 according to the International Union Against Cancer (UICC).[25] In addition, negative lymph node status (N0) or negative metastatic status (M0) was required. All patients presented intermediate to high prognostic risk factors. An absolute rule was acceptable performance status (Karnofsky scale). The consent of all patients was obtained before the study was carried out.

Fiducial markers

Patients underwent transrectal ultrasound-guided implantation of three gold markers (Hakko guiding marker system), under local anesthesia, each one sized 3×0.8 mm for maximal position, reproducibility, and accuracy throughout the treatment period. After the insertion procedure, a week is given to check for any post-procedure inflammation or foreign body reaction sign. In addition, prophylactic antibiotic coverage is routinely prescribed to all patients. Markers were intended to be inserted at the base of the gland and/or at mid-gland position.

Radiation therapy and planning methods

Patient indications

Our patients underwent radiation therapy with restrictions on some specific dietetic components (those producing much intestinal gas). They were asked to avoid such foods on the day of CT image acquisition and subsequent treatment days. Because of the difficulty of eliminating all forms of motion uncertainty, we instructed the patients carefully in using constant ventilation cycles. In addition, all patients were asked to defecate every morning and to void the bladder 30 to 60 minutes before CT imaging and fraction delivery, so that partial bladder filling is obtained and large variations can be avoided, as recommended and reported by other authors.[17,26]

Immobilization

To achieve accurate patient positioning and reproducibility, patients were immobilized in the supine position with an individually fashioned whole-body vacuum cast that molds to the patient's external contours; this is fitted within an external whole-body frame (Fig. 1). Moreover, two over-hip belts were placed to prevent potential body-induced motion, even while recognizing the subjectivity of the method.

CT acquisition

Images for IMRT planning were obtained from the contrast-enhanced axial CT scan data of the patients. To improve soft tissue visualization and periprostatic vasculature, 1.25- to 2.5-mm slice intervals were used in target volumes and organs at risk (OAR) areas; the rest of the scan was taken with a slice interval of 5 mm up to 8-10 cm above and under the prostate gland. The images were transferred to an IMRT planning workstation (CADPLAN, VMS, Palo Alto, CA), where contours for the prostate, seminal vesicles, rectum, bladder, and femoral heads were outlined on each axial image by one physician (K.B.).

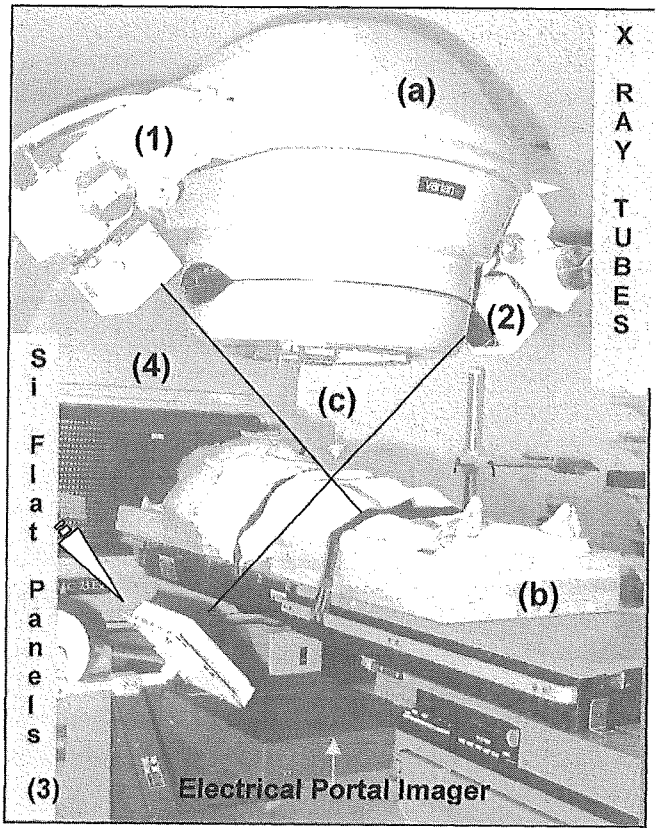

Fig. 1. Dual fluoroscopy and paired flat panel system (a). Typical (supine) patient setup positioning used for CT and image-guided IMRT with external body fixation frame and vacuum cast (b). Isocentered gold marker (GS-1-iso) is aligned at the intersection between kv ray beam axis and accelerator isocenter (c). Shown are X-ray tubes (1, 2), a-Si flat panels (3), and Linac (4). CT = computerized tomography, SI = silicon.

Planning methods

Inverse planning optimization software was used to create the intensity-modulated pattern with the CADPLAN (VMS, Palo Alto, CA) planning system. Target volume consisted of the prostate and entire seminal vesicles, referred to as the CTV. A margin of 5 mm in all directions was used to account for the PTV based on a preliminary approach where intrafractional motion was seen to be <5 mm in 100% of the right-left (R-L) axis and in 98% of the cranial-caudal (C-C) and anterior-posterior (A-P) axes.

The bladder was contoured as a whole structure; rectum outer wall, bilateral femoral heads, and gold markers were also outlined. Of the inserted gold seeds (GS), the nearest to the mid-gland or an intra-tumor seed was used as the target isocenter (GS-1-iso) and for positional verification purposes; markers were designated as GS-1-iso, GS-2, and GS-3. The beam arrangement consisted of five coplanar non-colinear fields in the transverse plane isocentered to GS-1-iso.

This arrangement consisted of a direct posterior field, with two oblique anterior (45 degrees apart from gantry 0 degrees) and two oblique posterior fields (75 degrees apart from gantry 180 degrees). Treatment delivery was made using a dynamic multileaf collimator (DMLC) and the sliding window technique. Radiation doses delivered for this study group (Table 1) were in the range of 72-76 Gy (depending on the pre-established phase I/II dose escalation protocol assigned) in 2 Gy per fraction to the ICRU 50 (International Commission on Radiation Units and Measurements)[27] point.

DFFP system

A new system installed in the gantry of a medical linear accelerator (Clinac 23 EX, VARIAN Medical Systems, Palo Alto, CA.) consisted of dual X-ray generators (RAD II simulator, Haynes Radiation, Ltd.) powered by high-frequency (32 kW) and paired a-Si flat panel imagers (PaxScan 2520, VARIAN, V.M.S., Palo Alto, CA) (Fig. 1). The active area of the detector comprises 1408×1888 pixels, resulting in an imaging area of 17.9×23.8 cm. The system was used for intrinsically recognizing the coordinates, in 3D, of the center of the implanted GS as the pixel positions in the a-Si flat panels by x-ray sensors, through computer-controlled steps. The flat panels operate at a frame time of 33 ms, with further imaging processing through digital video signals and video graphic array (VGA) monitors. Views are always taken from 0° (degrees) of the gantry. The values are quantified as the geographical coordinates of the markers and expressed as digital figures. The accuracy and stability of the system has been discussed in previous reports.[28-30]

Registration method

The localization and measurement of the implanted gold markers' 3D coordinates, day-to-day and from the beginning to the end of the fraction, confirmed the primordial base of the organ motion analysis, assuming stable, accurate reproducibility of the DFFP system images.

At the time of the start of each treatment fraction, the patient is aligned by the skin marks drawn with the laser localizer signal in the treatment room. An initial real-time fluoroscopic view of the GS-1-iso marker coordinates is taken in 3D and sent as digital figures to the DFFP system workstation. This measured target isocenter location is changed, if needed, to the prescribed position 0, 0, 0 (defined by the intersection between the system beam axis and the accelerator isocenter point). After this, electronic portal images (EPID, Portal vision aS 500, VMS, Palo Alto, CA) are taken in order to verify the first field's R-L, superior-inferior (C-C), and A-P axis margins as well as the GS-1-iso with an energy of 6 MV X-photons.

After the setup process, the gold marker coordinates are recorded either prior to every field delivery or every other field delivery for the on-line isocenter location and to maintain a predetermined shift range equal to or less than ±1 mm in any of the R-L, C-C, or A-P axes. Over the course of a fraction delivery, "off-range" (O-R) displacements were corrected by shifting the treatment couch to the initial coordinates as many times as necessary.

In this study, our interest was to measure the changes in target isocenter location and the daily accurate alignment between the radiation beam and the target isocenter at patient setup and throughout the treatment process.

The analysis of organ motion was carried out 1) by measuring each patient's corresponding isocenter shifts relative to the system isocenter position derived after the manual skin laser-guided setup. Shifts in the left, inferior, and posterior directions were counted as negative (−) direction axis and shifts to the right, superior, or anterior, as positive (+). Interfractional motion error was determined by the difference between the measured position (day-to-day isocenter position) and the system isocenter. For each patient, estimation of the average magnitude of displacement of the daily setup is the patient's systematic error (organ motion + setup error). These average values are represented along with their variations (1 SD). Reported data are given for each patient and also for the entire study group. The mean magnitude of displacement [average of the displacement error of each patient's treatment regardless of the direction sign (±) of shift], overall absolute magnitude (mean of all patients as a whole), SDs, overall SDs, and extreme (±) values of isocenter shifts were calculated for the whole study group. 2) In addition, successive calculations of target isocenter misalignments through the whole intrafraction period (total of 3-5 system views depending on case) were carried out for analysis of intrafractional (random) organ motion. This would enable repositioning when O-R isocenter shifts existed. Registered coordinates, until correction was seen as necessary, accounted for this analysis. Like the analysis done for day-to-day variations, the values for variations during treatment were expressed for each patient and for the entire group as the mean magnitude with variation (1 SD).

Furthermore, after the last fraction field was delivered, another registration of the isocentered gold marker was obtained by the system in order to assess the end-of-treatment location. Post-treatment organ motion is referred to as the markers position just after the end of treatment. At this point, motion ranges in the R-L, C-C,

Table 2. Prostate interfraction (organ + setup) discrepancy of target isocenter between daily measured position and DFFP system isocenter

	Right-left			Cranial-caudal			Anterior-posterior		
	Range	Mean magnitude (mm)	SD (mm)	Range	Mean magnitude (mm)	SD (mm)	Range	Mean magnitude (mm)	SD (mm)
1	{−0.3 to 5.7}	3.20	2.41	{−2.6 to 6.7}	4.00	2.19	{−2.1 to 2.8}	1.60	1.05
2	{−2.3 to 2.7}	1.40	0.70	{−2.5 to 3.2}	1.60	0.90	{−13.4 to −0.9}	9.00	3.50
3	{−10.5 to 6.0}	2.68	2.29	{−7.1 to −0.3}	3.87	1.99	{−5.3 to 4.6}	1.42	1.50
4	{−1.6 to 1.8}	0.83	0.61	{−8.6 to 0.0}	4.62	2.48	{−11.3 to 4.0}	3.36	3.20
5	{−1.9 to 5.7}	1.39	1.36	{−4.2 to 3.7}	1.77	1.25	{−4.2 to 12.1}	3.34	2.77
6	{−0.7 to 4.1}	1.77	1.16	{−6.3 to 0.3}	3.41	1.64	{−13.1 to 0.0}	6.59	2.97
7	{−2.3 to 4.6}	1.53	1.09	{0.0 to 9.3}	4.60	1.68	{−11.9 to 5.9}	3.48	3.02
8	{−1.0 to 9.0}	1.25	1.64	{−1.5 to 2.7}	1.23	0.78	{−3.5 to 5.7}	1.42	1.22
all	{−2.5 to 4.95}	1.76	1.41	{−4.6 to 3.2}	3.14	1.61	{−8.9 to 4.2}	3.78	2.40

Abbreviations: mm (millimeters); SD: standard deviation; range values represent extreme values of marker shift in each direction (±).

and A-P directions were evaluated by extreme (±) values and mean shifts.

The study of seed migration was not part of this analysis, nor were other sources of motion uncertainty, like possible leg or organ rotations or motion induced by pelvic components.

RESULTS

Interfraction organ motion

A total of 214 treatment fractions were analyzed. For patient's setup positioning and marker localization over the course of treatment, 565 DFFP system images of the implanted gold markers were acquired successfully, allowing for prospective positional verifications with a high degree of reliability. The DFFP system yielded high-resolution imaging of markers as well as referent anatomical structures.

Ranges, mean absolutes of shifts, and SDs of the isocenter positional distributions for all patients are displayed in Table 2. The mean magnitude of uncertainty in the R-L, C-C, and A-P directions were in the range of 0.83 mm to 3.20 mm, 1.23 mm to 4.62 mm, and 1.42 mm to 9.0 mm, respectively. The overall mean magnitude of isocenter displacement was 1.76 mm, 3.14 mm, and 3.78 mm in the R-L, C-C, and A-P directions, respectively. The overall SD of isocenter shifts were 1.4 mm, 1.6 mm, and 2.4 mm in the R-L, C-C, and A-P directions, respectively. As shown in Fig. 2, the absolute values of marker motion frequency were seen to be <5 mm in 96.3%, 78.6%, and 69.6% in the R-L, C-C, and A-P directions, respectively. On the other hand, misalignments higher than or equal to 8 mm were found in only 0.5%, 1%, and 12% in the R-L, C-C, and A-P directions, respectively.

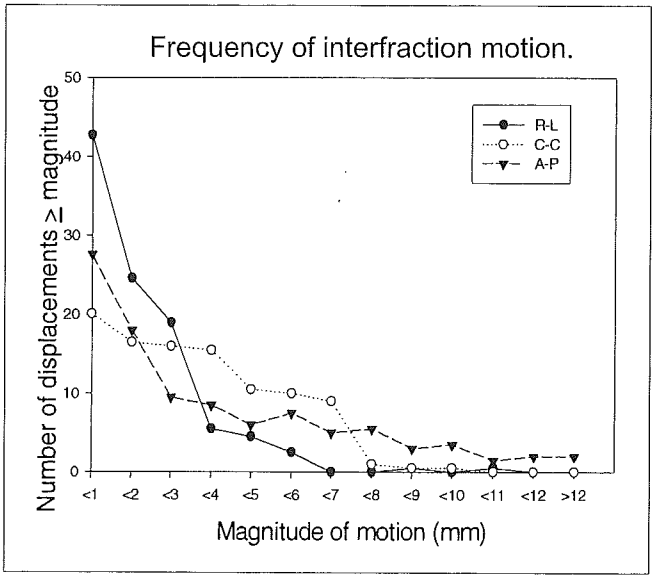

Fig. 2. Overall patients' interfractional target isocenter (GS-1-iso) frequency distributions relative to laser-skin marks, by axis. Right-left (R-L), cranial-caudal (C-C), and anterior-posterior (A-P).

Intrafraction organ motion/corrected fractions

The intrafraction marker positional distribution for all studied fractions is presented in Table 3. Marker positional corrections ("repositioning"), as described in registration methods, were necessary in 39.2% of the fractions studied (84/214). On the other hand, in the other 60.8% of fractions (130/214), repositioning was not required during the delivery process.

In this study, the overall median of organ intrafraction motion was 0.0 mm, 0.35 mm, and 0.65 mm in the R-L,