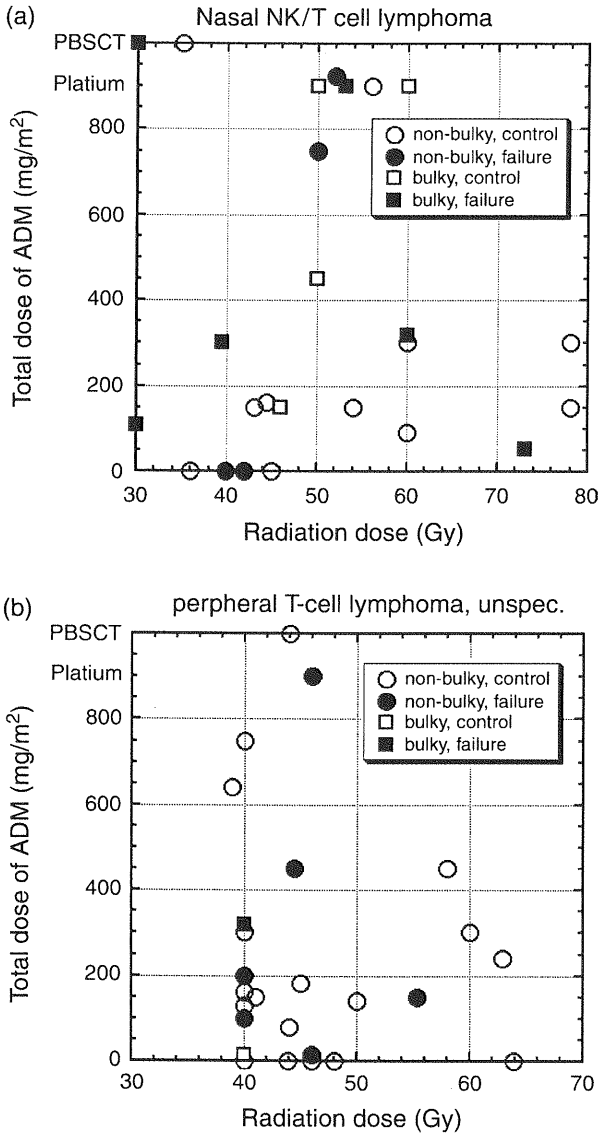


Fig. 1. Relationship among in-field control, dose of ADM, and radiation dose: (a) nasal NK/T-cell lymphoma and (b) peripheral T-cell lymphomas, unspecified. In this analysis, 26 tumors of 23 patients with peripheral T-cell lymphomas, unspecified were included. The patients treated with regime including platium-based drugs or high dose chemotherapy+PBSCT are separately demonstrated in the vertical axis.

eight courses of CHOP after radiotherapy. A patient with enteropathy-type T-cell lymphoma treated with 45 Gy of radiotherapy and eight courses of CHOP after radiotherapy had in-field control.

There were no apparent differences in radiosensitivity between nasal NK/T-cell lymphoma and peripheral T lymphoma, unspec. when the radiation dose versus in-field control curves were compared. Since the chemotherapy had no apparent influence on local control of mature T/NK-cell lymphomas and there were no significant differences in radiosensitivity among subtypes of mature T/NK-cell lymphomas, we have hereafter combined all patients with mature T/NK-cell lymphomas evaluable for in-field control for analytic purposes.

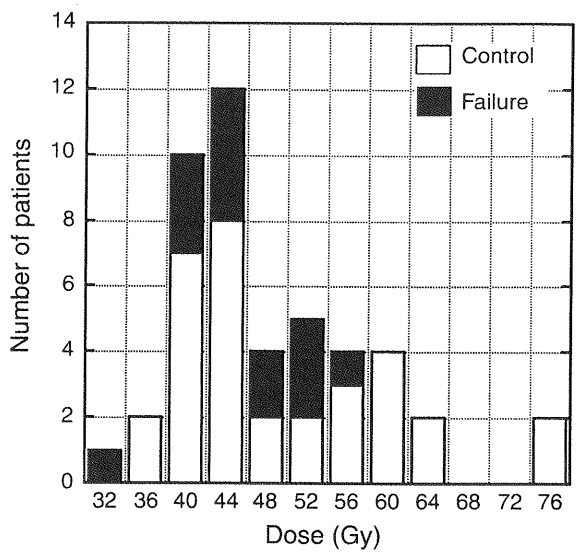


Fig. 2. The distribution of in-field control and failure of non-bulky mature T/NK-cell lymphomas with respect to the radiation dose as a function of patient numbers. The white column represents in-field control and the closed column represents in-filed failure.

Fig. 2 demonstrates the distribution of in-field control and failure of non-bulky mature T/NK-cell lymphomas with respect to the radiation dose as a function of patient numbers. The radiation doses for in-field control for non-bulky mature T/NK-cell lymphomas, shown as a histogram in Fig. 2, ranged from 31.1 to 78 Gy with median values of 45 Gy for all patients, 45 Gy for the patients who obtained in-field control and 45 Gy for the patients who suffered in-field failure. Although the numbers were small, the data showed a dose-response relationship. To obtain the sufficient in-field control rate, radiation doses of more than 52 Gy were required. However, there was no apparent relationship between radiation dose and in-field control in bulky mature T/NK-cell lymphomas. All two patients treated with 40 Gy or less had in-field failure. Three of four patients treated with 46-53 Gy had in-field control, but only one of three patients with 60 Gy or more had in-field control.

Discussion

Studies of mature T/NK-cell lymphomas have been limited by the uncommon nature of these disease. Optimal therapy for mature T/NK-cell lymphomas has yet to be defined and the patients on mature T/NK-cell lymphomas, has mainly been administered the same therapeutic regimen as patients with DLBCL [13]. Prospective randomized trials are required to elucidate the optimal therapy. However, prospective randomized trials are difficult to be performed in mature T/NK-cell lymphomas due to the rarity of this disease. Therefore, the accumulated experiences of various institutions should be utilized to obtain a more effective treatment for this tumor. In this retrospective multi-institutional study, we tried to elucidate the radiosensitivity of mature T/NK-cell lymphomas and the effect of chemotherapy on mature T/NK-cell lymphomas, especially

focusing on in-field control. However, retrospective studies using non-randomized data have bias in patient characteristics and treatment. Such bias may influence results. We should take such possibilities of bias into consideration when we interpret data.

In this study, the overall five-year survival rate for stage I or II patients with peripheral T lymphoma, unspec. was 84% and that with NK/T-cell lymphoma was 62%. We reported the overall five-year survival rate for stage I or II patients with DLBCL was 70% [14], indicating there was no significant differences in overall survival between mature T/NK-cell lymphomas and DLBCL. There are an increasing number of papers reporting that mature T/NK-cell lymphomas patients have poorer prognoses than patients with B-cell lymphoma [2,5]. However, these reports cannot be compared with our results, since they included all stages (stages I-IV) patients. Compared with B-cell NHL, T-cell NHL presented more often with disseminated disease and extranodal presentation [5]. Such bias can influence the treatment results of mature T/NK-cell lymphomas when all stages (stages I-IV) are included in analysis. Therefore, more information about the treatment results of mature T/NK-cell lymphomas according to stage are required in order to select appropriate treatments in the clinical setting.

We reported that 58 of 61 patients with DLBCL obtained in-field control [14]. In contrast, the in-field control for mature T/NK-cell lymphomas is poor even when treated by radiation combined with multi-agent combination chemotherapy. Actually, the dose level of ADM had no influence on local control of T-cell lymphoma (Fig. 1a and b). Nasal NK/T-cell lymphoma in particular expressed *p*-glycoprotein [15], and it is therefore highly resistant to chemotherapy. Kim et al. [16] recently reported that a combination of chemotherapy and involved-field radiotherapy demonstrated no therapeutic advantage over radiotherapy alone for stages I and II angiocentric lymphomas of the head and neck. According to these findings, radiation therapy is the key treatment method for this type of lymphoma to date. However, our results demonstrated that mature T/NK-cell lymphomas were more radioresistant than DLBCL. Even in the absence of bulky tumor, the in-field control rate for mature T/NK-cell lymphomas was much poorer than for DLBCL.

We have found that a relationship existed between radiation dose and in-field control in non-bulky mature T/NK-cell lymphomas (Fig. 2). Our study indicated that radiation doses of more than 52 Gy were required to obtain in-field control of non-bulky mature T/NK-cell lymphomas (Fig. 2). However, it is very difficult to obtain local control of bully T-cell lymphomas and we could not find a relationship between radiation dose and in-field control. In such cases, concomitant chemoradiotherapy may be considered to improve the radiation effect.

Recently, Koom et al. reported a retrospective study about patients with stages I and II angiocentric T-cell or NK/T-cell lymphoma who were treated with radiotherapy alone [11]. The dose-response curve was sigmoid in shape within the range of 20-54 Gy. In contrast to our results, dose escalation up to >54 Gy could not improve the local control. However, they did not include the size of tumor in their analysis, indicating that treatment results of bulky tumor influenced heavily their conclusion. Besides, their study included patients treated before 1980 and the diagnosis was made by only microscopic findings without immunohistochemical analysis in most cases.

There was no significant difference in radiosensitivity between nasal NK/T-cell lymphoma and peripheral T lymphoma, unspec. when the radiation dose versus in-field control curves were compared. It is unclear whether there is a difference in responses to radiotherapy among subtypes of mature T/NK-cell lymphomas other than nasal NK/T-cell lymphoma and peripheral T lymphoma, unspec. due to the small numbers of these lymphomas.

In summary, mature T/NK-cell lymphomas were more radioresistant than DLBCL. Chemotherapy such as CHOP did not improve the in-field control of mature T/NK-cell lymphomas. Our study indicated that radiation doses of more than 52 Gy might be required to obtain in-field control of non-bulky mature T/NK-cell lymphomas. Besides, it was difficult to obtain local control of bully T-cell lymphomas. These results were obtained by using non-randomized data and the interpretation of these results should be careful due to bias in data. However, our results indicate that the standard treatment strategy for DLBCL, that is, a combined modality consisting of three cycles of CHOP and radiotherapy [17,18], may not be sufficiently effective for mature T/NK-cell lymphomas.

* **Corresponding author. Koh-ichi Sakata**, Department of Radiology, Sapporo Medical University School of Medicine, S1W16, Chuo-Ku, Sapporo 060-0061, Japan. *E-mail address:* sakatako@sapmed.ac.jp

Received 28 April 2005; received in revised form 13 March 2006; accepted 23 March 2006; Available online 27 April 2006

References

[1] A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The non-hodgkin's lymphoma classification project. Blood 1997;89:3909-18.

[2] Melnyk A, Rodriguez A, Pugh WC, et al. Evaluation of the Revised European-American Lymphoma classification confirms the clinical relevance of immunophenotype in 560 cases of aggressive non-Hodgkin's lymphoma. Blood 1997;89:4514-20.

[3] Cheng AL, Chen YC, Wang CH, et al. Direct comparisons of peripheral T-cell lymphoma with diffuse B-cell lymphoma of comparable histological grades—should peripheral T-cell lymphoma be considered separately? J Clin Oncol 1989;7:725-31.

[4] Sakata K, Hareyama M, Ohuchi A, et al. Treatment of lethal midline granuloma type nasal T-cell lymphoma. Acta Oncol 1997;36:307-11.

[5] Gisselbrecht C, Gaulard P, Lepage E, et al. Prognostic significance of T-cell phenotype in aggressive non-Hodgkin's lymphomas. Groupe d'Etudes des Lymphomes de l'Adulte (GELA). Blood 1998;92:76-82.

[6] Chen HH, Fong L, Su IJ, et al. Experience of radiotherapy in lethal midline granuloma with special emphasis on centrofacial T-cell lymphoma: a retrospective analysis covering a 34-year period. Radiother Oncol 1996;38:1-6.

[7] Tsutsui K, Shibamoto Y, Yamabe H, et al. A radiotherapeutic experience for localized extranodal non-Hodgkin's lymphoma: prognostic factors and re-evaluation of treatment modality. Radiother Oncol 1991;21:83-90.
[8] Weidmann E, Boehrer S, Chow KU, et al. Treatment of aggressive, or progressing indolent peripheral T- and NK-cell neoplasias by combination of fludarabine, cyclophosphamide and doxorubicine. Onkologie 2001;24:162-4.
[9] Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994;84:1361-92.
[10] Harris NL, Jaffe ES, Diebold J, et al. World health organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the clinical advisory committee meeting-airlie house, Virginia, November 1997. J Clin Oncol 1999;17:3835-49.
[11] Koom WS, Chung EJ, Yang WI, et al. Angiocentric T-cell and NK/T-cell lymphomas: radiotherapeutic viewpoints. Int J Radiat Oncol Biol Phys 2004;59:1127-37.
[12] Ferreri AJ, Reni M, Villa E. Therapeutic management of primary central nervous system lymphoma: lessons from prospective trials. Ann Oncol 2000;11:927-37.
[13] Pellatt J, Sweetenham J, Pickering RM, et al. A single-centre study of treatment outcomes and survival in 120 patients with peripheral T-cell non-Hodgkin's lymphoma. Ann Hematol 2002; 81:267-72.
[14] Sakata K, Satoh M, Someya M, et al. Analysis of local control in patients with non-Hodgkin's lymphoma according to the WHO classification. Strahlenther Onkol 2005;181:385-91.
[15] Yamaguchi M, Kita K, Miwa H, et al. Frequent expression of *p*-glycoprotein/MDR1 by nasal T-cell lymphoma cells. Cancer 1995;76:2351-6.
[16] Kim GE, Lee SW, Chang SK, et al. Combined chemotherapy and radiation versus radiation alone in the management of localized angiocentric lymphoma of the head and neck. Radiother Oncol 2001;61:261-9.
[17] Horning SJ, Glick JH, Kim K, et al. Final report of E1484: CHOP vs. CHOP+Radiotherapy (RT) for limited stage diffuse aggressive lymphoma. Proceedings of ASH 2001; 98:724a.
[18] Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med 1998;339:21-6.

Cancer Chemother Pharmacol (2006) 58: 570–576
DOI 10.1007/s00280-006-0193-x

ORIGINAL ARTICLE

Yasushi Sato · Tetsuji Takayama · Tamotsu Sagawa
Tetsuro Okamoto · Koji Miyanishi · Tsutomu Sato
Hironobu Araki · Satoshi Iyama · Seiichiro Abe
Kazuyuki Murase · Rishu Takimoto
Hisayasu Nagakura · Masato Hareyama
Junji Kato · Yoshiro Niitsu

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 / Published online: 4 February 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

Y. Sato · T. Takayama (✉) · T. Sagawa · T. Okamoto
K. Miyanishi · T. Sato · H. Araki · S. Iyama · S. Abe
K. Murase · R. Takimoto · J. Kato · Y. Niitsu
Fourth Department of Internal Medicine,
Sapporo Medical University, South 1 West 16,
Chuo-ku, 060-8543 Sapporo, Japan
E-mail: ttakayam@sapmed.ac.jp
Tel.: +81-11-6112111
Fax: +81-11-6127987

H. Nagakura · M. Hareyama
Department of Radiology,
Sapporo Medical University,
School of Medicine, Sapporo, Japan

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) Thrombocytcpcnia (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

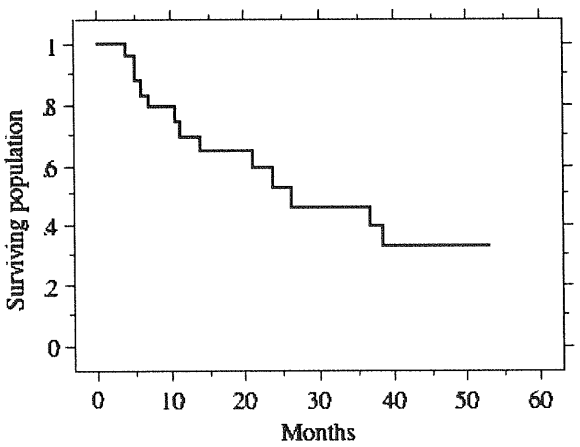


Fig. 1 Overall survival data for all patients

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.

References

1. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, Feuer FJ, Thun ML (2005) Cancer statistics. CA Cancer J Clin 55:10–30
2. National Cancer Institute. Esophageal cancer treatment (PDQ®): treatment information for health professionals. http://www.cancer.gov/cancerinfo/pdq/treatment/esophageal/healthprofessional/
3. Al-Sarraf M, Martz K, Herskovic A, Leichman L, Brindle JS, Vaitkevicius VK, Cooper J, Byhardt R, Davis L, Emami B (1997) Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. J Clin Oncol 15:277–284
4. Smith TJ, Ryan LM, Douglass HO Jr, Haller DG, Dayal Y, Kirkwood J, Tormey DC, Schutt AJ, Hinson J, Sischy B (1998) Combined chemoradiotherapy vs radiotherapy alone for early stage squamous cell carcinoma of the esophagus: a study of the Eastern Cooperative Oncology Group. Int J Radiat Oncol Biol Phys 42:269–276
5. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, Okawara G, Rosenthal SA, Kelsen DP (2002) INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 20:1167–1174

6. Herskovic A, Martz K, al-Sarraf M, Leichman L, Brindle J, Vaitkevicius V, Cooper J, Byhardt R, Davis L, Emami B (1992) Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 326:1593–1598
7. Araujo CM, Souhami L, Gil RA, Carvalho R, Garcia JA, Froimtchuk MJ, Pinto LH, Canary PC (1991) A randomized trial comparing radiation therapy versus concomitant radiation therapy and chemotherapy in carcinoma of the thoracic esophagus. Cancer 67:2258–2261
8. Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA Jr, Al-Sarraf M, Byhardt R, Russell AH, Beitler JJ, Spencer S, Asbell SO, Graham MV, Leichman LL (1999) Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA 281:1623–1627
9. Enzinger PC, Ilson DH, Kelsen DP (1999) Chemotherapy in esophageal cancer. Semin Oncol 26:12–20
10. Kobayashi H, Takemura Y, Miyachi H, Ogawa T (1991) Antitumor activities of new platinum compounds, DWA2114R, NK121 and 254-S, against human leukemia cells sensitive or resistant to cisplatin. Invest New Drugs 9:313–319
11. Kameyama Y, Okazaki N, Nakagawa M, Koshida H, Nakamura M, Gemba M (1990) Nephrotoxicity of a new platinum compound, evaluated with rat kidney cortical slices. Toxicol Lett 52:15–24
12. Sasaki Y, Amano T, Morita M, Shinkai T, Eguchi K, Tamura T, Ohe Y, Kojima A, Saijo N (1991) Phase I study and pharmacological analysis of cis-diammine(glycolato)platinum (254-S; NSC 375101D) administered by 5-day continuous intravenous infusion. Cancer Res 51:1472–1477
13. Ota K, Wakui A, Majima H, Niitani H, Inuyama Y, Ogawa M, Ariyoshi Y, Yoshida O, Taguchi T, Kimura I (1992) Phase I study of a new platinum complex 254-S, *cis*-diammine (glycolato)-platinum (II). Gan To Kagaku Ryoho 19:855–886
14. Inuyama Y, Miyake H, Horiuchi M, Hayasaki K, Komiyama S, Ota K (1992) A late phase II clinical study of *cis*-diammine glycolato platinum, 254-S, for head and neck cancers. Gan To Kagaku Ryoho 19:871–877
15. Fukuda M, Shinkai T, Eguchi K, Sasaki Y, Tamura T, Ohe Y, Kojima A, Oshita F, Hara K, Saijo N (1990) Phase II study of (glycolate-*O*,*O'*) diammineplatinum(II), a novel platinum complex, in the treatment of non-small-cell lung cancer. Cancer Chemother Pharmacol 26:393–396
16. Noda K, Ikeda M, Yakushiji M, Nishimura H, Terashima Y, Sasaki H, Hata T, Kuramoto H, Tanaka K, Takahashi T (1992) A phase II clinical study of *cis*-diammine glycolato platinum, 254-S, for cervical cancer of the uterus. Gan To Kagaku Ryoho 19:885–892
17. Taguchi T, Wakui A, Nabeya K, Kurihara M, Isono K, Kakegawa T, Ota K (1992) A phase II clinical study of *cis*-diammine glycolato platinum, 254-S, for gastrointestinal cancers. 254-S Gastrointestinal Cancer Study Group. Gan To Kagaku Ryoho 19:483–488
18. Uchida N, Takeda Y, Hojo K, Maekawa R, Sugita K, Yoshioka T (1998) Sequence-dependent antitumour efficacy of combination chemotherapy of nedaplatin, a novel platinum complex, with 5-fluorouracil in an in vivo murine tumour model. Eur J Cancer 34:1796–1801
19. Yoshioka T, Gamoh M, Shineha R, Ishibashi S, Shibata H, Suzuki T, Murakawa Y, Kato S, Shimodaira H, Ishioka C, Kanamaru R (1999) A new combination chemotherapy with *cis*-diammine-glycolatoplatinum (Nedaplatin) and 5-fluorouracil for advanced esophageal cancers. Intern Med 38:844–848
20. Yamanaka H, Motohiro T, Michiura T, Asai A, Mori T, Hioki K (1998) Nedaplatin and 5-FU combined with radiation in the treatment for esophageal cancer. Jpn J Thorac Cardiovasc Surg 46:943–948
21. Nemoto K, Matsushita H, Ogawa Y, Takeda K, Takahashi C, Britton KR, Takai Y, Miyazaki S, Miyata T, Yamada S (2003) Radiation therapy combined with *cis*-diammine-glycolatoplatinum (Nedaplatin) and 5-fluorouracil for untreated and recurrent esophageal cancer. Am J Clin Oncol 26:46–49
22. Kato H, Fukuchi M, Manda R, Nakajima M, Miyazaki T, Sohda M, Masuda N, Fukai Y, Tsukada K, Kuwano H (2003) Efficacy and toxicity of nedaplatin and 5-FU with radiation treatment for advanced esophageal carcinomas. Anticancer Res 23:3493–3498
23. Japanese Society for Esophageal Disease (1992) Guidelines for the clinical and pathologic studies on carcinoma of the esophagus, 8th edn. Kanehara & Co. Ltd.
24. Coia LR (1994) Chemoradiation as primary management of esophageal cancer. Semin Oncol 21:483–492
25. Ishikura S, Nihei K, Ohtsu A, Boku N, Hironaka S, Mera K, Muto M, Ogino T, Yoshida S (2003) Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol 21:2697–2702
26. Rich TA, Shepard RC, Mosley ST (2004) Four decades of continuing innovation with fluorouracil: current and future approaches to fluorouracil chemoradiation therapy. J Clin Oncol 22:2214–2232
27. Toita T, Ogawa K, Adachi G, Kakinohana Y, Nishikuramori Y, Iraha S, Utsunomiya T, Murayam S (2001) Concurrent chemoradiotherapy for squamous cell carcinoma of thoracic esophagus: feasibility and outcome of large regional field and high-dose external beam boost irradiation. Jpn J Clin Oncol 31:375–381
28. Coia LR, Engstrom PF, Paul AR, Stafford PM, Hanks GE (1991) Long-term results of infusional 5-FU, mitomycin-C, and radiation as primary management of esophageal carcinoma. Int J Radiat Oncol Biol Phys 20:29–36
29. Minsky BD, Neuberg D, Kelsen DP, Pisansky TM, Ginsberg RJ, Pajak T, Salter M, Benson AB III (1999) Final report of Intergroup Trial 0122 (ECOG PE-289, RTOG 90–12): phase II trial of neoadjuvant chemotherapy plus concurrent chemotherapy and high-dose radiation for squamous cell carcinoma of the esophagus. Int J Radiat Oncol Biol Phys 43:517–523
30. Ohtsu A, Boku N, Muro K, Chin K, Muto M, Yoshida S, Satake M, Ishikura S, Ogino T, Miyata Y, Seki S, Kaneko K, Nakamura A (1999) Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. J Clin Oncol 17:2915–2921

Int. J. Radiation Oncology Biol. Phys., Vol. 65, No. 4, pp. 1045–1050, 2006

0360-3016/06/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2006.02.001

CLINICAL INVESTIGATION **Head and Neck**

MULTI-INSTITUTIONAL ANALYSIS OF EARLY SQUAMOUS CELL CARCINOMA OF THE HYPOPHARYNX TREATED WITH RADICAL RADIOTHERAPY

KATSUMASA NAKAMURA, M.D.,* YOSHIYUKI SHIOYAMA, M.D.,* MITSUHIKO KAWASHIMA, M.D.,† YOSHIHIRO SAITO, M.D.,‡ NAOKI NAKAMURA, M.D.,§ KENSEI NAKATA, M.D.,¶ MASATO HAREYAMA, M.D.,¶ TAKAHIRO TAKADA, M.D.,‖ KUMIKO KARASAWA, M.D.,‖ TOSHIICHI WATANABE, M.D.,# ATSUNORI YOROZU, M.D.,** HIROYUKI TACHIBANA, M.D.,†† GEN SUZUKI, M.D.,‡‡ NAOFUMI HAYABUCHI, M.D.,‡‡ TAKASHI TOBA, M.D.,* AND SHOGO YAMADA, M.D.§§

*Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka; †Division of Radiation Oncology, National Cancer Center Hospital East, Chiba; ‡Department of Therapeutic Radiology, Saitama Cancer Center, Saitama; §Department of Radiology, University of Tokyo Graduate School of Medicine and Faculty of Medicine, Tokyo; ¶Department of Radiology, Sapporo Medical University School of Medicine, Sapporo; ‖Department of Radiology, Jyuntendo University School of Medicine, Tokyo; #Department of Radiology, Saku Central Hospital, Saku; **Department of Radiology, Tokyo Medical Center, National Hospital Organization, Tokyo; ††Department of Radiation Oncology, Aichi Cancer Center Hospital, Nagoya; ‡‡Department of Radiology, Kurume University School of Medicine, Kurume; §§Department of Radiation Oncology, Tohoku University Graduate School of Medicine, Sendai, Japan

Purpose: To analyze the outcomes of patients with early hypopharyngeal cancer treated with radical radiotherapy (RT).

Methods and Materials: Ten institutions combined the data from 115 patients with Stage I–II hypopharyngeal squamous cell carcinoma treated with definitive RT between 1990 and 2001. The median patient age was 67 years; 99 patients were men and 16 were women. Of the 115 patients, 39 had Stage I and 76 had Stage II disease. Conventional fractionation was used in 98 patients and twice-daily RT in 17 patients; chemotherapy was combined with RT in 57 patients. The median follow-up period was 47 months.

Results: The overall and disease-specific 5-year survival rate for 95 patients without synchronous malignancies was 66.0% and 77.4%, respectively. The 5-year disease-specific survival rate by T stage was 95.8% for patients with T1 disease and 70.1% for patients with T2 disease ($p = 0.02$). Of the 115 patients, local control with laryngeal voice preservation was achieved in 34 of 39 patients with T1 lesions, including 7 patients successfully salvaged, and in 56 of 76 patients with T2 lesions. Sixty-five patients (56.5%) had synchronous or metachronous cancers. Of the 115 patients, 19 died of hypopharyngeal cancer, 10 died of second primary cancers, and 14 died of other causes during the study and follow-up periods.

Conclusions: Patients with early hypopharyngeal cancer tended to have a good prognosis after RT. However, second malignancies had an adverse effect on the overall outcomes of patients with early hypopharyngeal cancer.

Radiotherapy, Hypopharyngeal cancer, Early stage, Chemoradiotherapy, Second primary cancer.

INTRODUCTION

The optimal treatment for early hypopharyngeal cancer has been debated for years (1, 2). Treatment options have included surgery and radiotherapy (RT) with or without chemotherapy. More recently, endoscopic laser resection has been used at a limited number of institutions (3). Although some authors have advocated for the effectiveness of conservation surgery or endoscopic laser resection in patients in the early stages of hypopharyngeal cancer, the functional results in terms of voice preservation have seemed unsatisfactory (3–5). RT may be the treatment of choice in terms of functional preservation. However, because early-stage hypopharyngeal cancer is relatively rare, few reports have been published on the efficacy of RT for this type of cancer (2, 6, 7).

Reprint requests to: Katsumasa Nakamura, M.D., Department of Clinical Radiology, Kyushu University Graduate School of Medical Sciences, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan. Tel: (+81) 92-642-5695; Fax: (+81) 92-642-5708; E-mail: nakam@radiol.med.kyushu-u.ac.jp

Supported in part by a Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Sciences.

Received Nov 20, 2005, and in revised form Jan 22, 2006. Accepted for publication Feb 3, 2006.

Table 1. Patient characteristics

Characteristic	Stage I (n = 39)	Stage II (n = 76)
Gender (n)		
Male	33	66
Female	6	10
Age (y)		
Median	63	68
Range	48–84	43–88
Performance status (n)		
0	31	33
1	1	27
2	1	6
3	0	1
4	0	0
Unknown	6	9
Tumor differentiation (n)		
Well	8	15
Moderate	17	34
Poor	3	7
Unknown	11	20
Subsite		
Pyriform fossa	27	53
Posterior wall	8	13
Postcricoid region	0	6
Unknown	4	4

In the present multi-institutional retrospective study, we reviewed the clinical records of patients with early squamous cell carcinoma of the hypopharynx treated with radical RT or chemoradiotherapy at 10 institutions to analyze the outcomes of RT for early hypopharyngeal cancer.

METHODS AND MATERIALS

Ten institutions with significant experience in RT for head-and-neck cancer collaborated in the present study. We collected the clinical records of 115 patients with early-stage squamous cell carcinoma of the hypopharynx who underwent RT with radical intent between 1990 and 2001. Early-stage cancer was defined as Stage I (T1N0M0, tumor limited to one subsite of the hypopharynx and to ≤2 cm in the greatest dimension) or II (T2N0M0, tumor that had invaded more than one subsite of the hypopharynx or an adjacent site or measured >2 cm but not >4 cm in the greatest dimension, without fixation of the hemilarynx), according to the International Union Against Cancer 2002 classification (8).

The patient characteristics are presented in Table 1. The age range of the 99 men and 16 women in the study group was 43–88 years (median 67). The performance status (PS) according to the Eastern Cooperative Oncology Group was 0 for 64 patients, 1 for 28 patients, 2 for 7 patients, and 3 for 1 patient. PS data were not obtained for 15 patients. The patients with Stage II disease tended to have a poorer PS than the patients with Stage I. All tumors were diagnosed as squamous cell carcinoma by histopathologic examination of the biopsy specimens. Of the 115 patients, 23 had well-differentiated tumors, 51 had moderately differentiated tumors, 10 had poorly differentiated tumors, and 31 had squamous cell carcinoma of unknown differentiation. The primary sites were the pyriform fossa in 80 (69.6%), posterior pharyngeal wall in 21 (18.3%), and postcricoid region in 6 (5.2%); 8 patients (6.9%) had an unknown primary site. Most patients underwent CT as a part of their staging workup. At the initial workup, 39 patients were diagnosed with Stage I cancer and 76 with Stage II disease.

All patients underwent RT with radical intent, primarily using supervoltage X-rays (Table 2). The techniques and doses varied by institution. Because the clinical data from the multiple institutions were retrospectively analyzed for this study, it was not possible to standardize these data completely. A conventional fractionation schedule of 1.5–2.0 Gy/d was used in 98 patients, and twice-daily RT with doses of 1.2–1.6 Gy/fraction was used in 17 patients. Local irradiation of the primary site was performed using parallel-opposed lateral fields or three-dimensional conformal techniques. Elective bilateral neck irradiation was also performed using parallel-opposed lateral fields with or without a matched anterior lower neck field or anterior and lateral wedged fields. In the case of elective nodal irradiation, the primary lesion was boosted with reduced fields after 36–50 Gy.

Of the 39 patients with T1 tumors, 17 (43.6%) were treated with local irradiation only and 22 (56.4%) with elective neck irradiation. Of the 76 patients with T2 tumors, 8 (10.5%) were treated with local irradiation only and 68 (89.5%) were treated with fields encompassing the primary lesion and nodal areas. Of the 90 patients treated with elective nodal irradiation, the radiation fields included the retropharyngeal region and supraclavicular nodes, in addition to the entire neck in 12 patients with T1 tumors and 44 patients with T2 tumors. Smaller fields were used in the remaining patients. The median total dose for T1 or T2 lesions was 63.0 Gy or 66.0 Gy with once-daily fractionation and 63.5 Gy or 70.0 Gy with twice-daily fractionation, respectively.

Chemotherapy, which was chosen according to the policy of the patient's physician or on the basis of the patient's condition, was given in 57 patients (49.6%), of whom 17 had T1 tumors and 40 had T2 tumors. Neoadjuvant chemotherapy was performed in 8 patients, concurrent chemoradiotherapy in 46 patients, and alternative chemoradiotherapy in 3 patients. Chemotherapy was administered daily to 34 patients, weekly to 5 patients, and monthly to 18 patients. In 40 patients, 5-fluorouracil was used with (n = 24) or without (n = 16) cisplatin, carboplatin, or Nedaplatin. Single-agent chemotherapy using cisplatin was given to 7 patients; the other agents used in the present study included docetaxel, peplomycin, tegafur-uracil, and oral fluoropyrimidine anticancer drug TS-1.

The median follow-up period was 47 months (range, 2–156 months). The overall and disease-specific survival rates were evaluated in 95 patients without synchronous malignancies, using the Kaplan-Meier method. The statistical significance of the differences between the survival curves was assessed using the log–rank

Table 2. Dose and radiation field by stage

	Stage I (n = 39)	Stage II (n = 76)
Radiation dose (Gy)		
Once daily	35	63
Median	63.0	66.0
Range	50.0–70.5	50.0–80.0
Twice daily	4	13
Median	63.5	70.0
Range	55.5–69.0	59.5–72.0
Radiation field		
Local	17	8
Locoregional	22	68

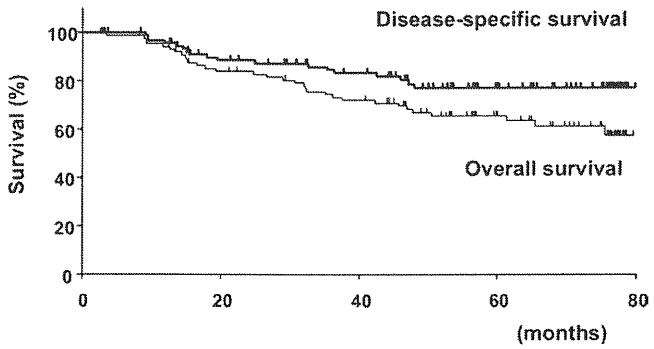


Fig. 1. Overall and disease-specific survival rates for 95 patients without synchronous malignancies.

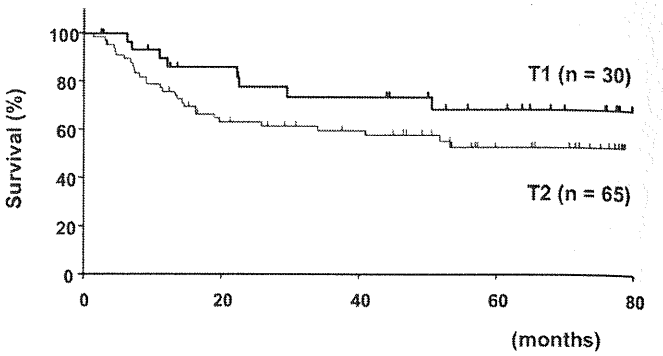


Fig. 3. Progression-free survival rates for 95 patients without synchronous malignancies as a function of tumor stage.

test. The local control rate was calculated for all 115 patients. Cox's proportional hazards model was used in the multivariate analysis. A p value of <0.05 was considered to indicate a statistically significant difference. The Radiotherapy Oncology Group late toxicity scales were used to assess late morbidity.

RESULTS

Survival

The 5-year overall and disease-specific survival rate for 95 patients without synchronous malignancies was 66.0% and 77.4%, respectively (Fig. 1). The 5-year disease-specific survival rate according to T stage was 95.8% for patients with T1 disease and 70.1% for patients with T2 disease (p = 0.02; Fig. 2). The 5-year progression-free survival rate according to T stage was 67.6% for patients with Stage T1 disease and 51.5% for patients with Stage T2 disease (p = 0.13; Fig. 3).

Failure patterns

Table 3 shows the patterns of failure we encountered in the present study. Of the 115 patients, 42 (36.5%), 10 with T1 tumors and 32 with T2 tumors, developed disease recurrence; 30 patients (26.1%) had a local recurrence. Although local control was good for patients with Stage T1 tumors, local recurrence was more frequent with T2 tumors. Fourteen patients developed a relapse in the neck. Of these, 3 patients with T1 tumors underwent local irradiation only, and 8 of the remaining 11 patients, who had Stage T2 disease, underwent elective neck irradiation. Three patients developed distant metastases. Of 76 patients with locoregional control, 3 (3.9%) had failure at distant sites.

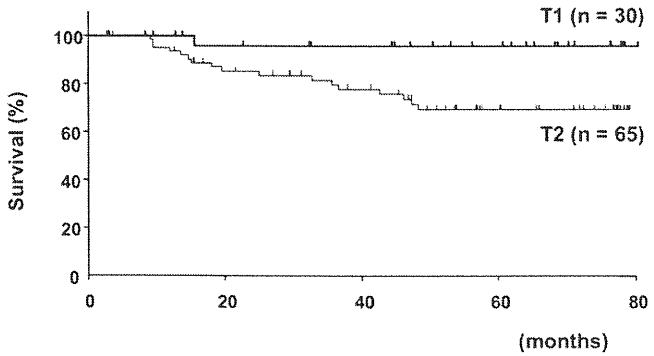


Fig. 2. Disease-specific survival rates for 95 patients without synchronous malignancies as a function of tumor stage.

Treatment factors and T stage were analyzed in all 115 patients as potential prognostic factors for local control using the univariate log–rank and the multivariate Cox regression method (Table 4). PS, T stage, and concurrent chemoradiotherapy showed statistical significance for local control in multivariate analysis.

Salvage treatment

Of the 30 patients with local recurrence, 26 (86.7%) underwent attempted radical salvage of their primary recurrence. Total laryngopharyngectomy with or without neck resection was performed in 20 patients, partial pharyngectomy was performed in 3, endoscopic mucosal resection in 1, laser surgical excision in 1, and RT in 1. As a result, 17 patients remained disease free, and 9 patients died of subsequent recurrences. Other salvage treatments for nodal recurrence or distant metastasis included RT in 4 patients and neck dissection in 3 patients. The remaining 9 patients were treated with best supportive care.

Local control with laryngeal voice preservation was achieved in 34 (87.2%) of 39 patients with T1 lesions, including 7 patients successfully salvaged after local recurrence, and in 56 (73.6%) of 76 patients with T2 lesions.

Adverse effects

Three patients had Grade 2 laryngeal edema, 1 had Grade 2 laryngeal stenosis, and 1 had Grade 3 dysphagia. One patient

Table 3. Distribution of initial failures

Failure	Stage I (n = 39)	Stage II (n = 76)	Total (n = 115)
Local	6	19	25
Nodal	3	6	9
Local + nodal	0	5	5
Distant	1	2	3
Total (%)	10 (25.6)	32 (42.1)	42 (36.5)

Table 4. Results of multivariate analysis of prognostic factors for local control

Prognostic factor	*n*	5-y local control rate (%)	Univariate *p*	Multivariate *p*	Multivariate Risk ratio
Age (<70 vs. ≥70 y)	76/37*	58.6/82.6	0.064	0.052	0.39
Performance status (0 vs. 1–3)	64/36*	67.4/71.2	0.37	0.0242	0.33
T stage (T1 vs. T2)	39/76	76.5/62.6	0.077	0.0021	5.25
Total dose (<60 vs. ≥60 Gy)	28/87	75.4/63.6	0.57	0.79	1.15
Once-daily (yes vs. no)	99/16	64.4/87.5	0.24	0.143	0.38
Chemotherapy (yes vs. no)	57/58	69.5/64.7	0.72	0.24	0.53
Concurrent CRT (yes vs. no)	46/69	79.3/60.8	0.108	0.0031	6.76

Abbreviation: CRT = chemoradiotherapy.
* Because some data were missing, the total numbers of patients were less than actual number.

had Grade 4 laryngeal necrosis, and total laryngectomy was performed. The remaining 109 patients had no severe complications other than Grade 2–3 acute radiation mucositis.

Synchronous and metachronous cancers

Of our 115 patients, 65 (56.5%) had 83 synchronous or metachronous malignancies. Of these malignancies, 34, 22, and 27 tumors occurred before, during, and after treatment for hypopharyngeal cancer, respectively. The anatomic sites of synchronous or metachronous malignancies included the esophagus in 41 patients, stomach in 12, lung in 6, colon in 5, rectum in 4, tongue in 3, oral floor in 3, urinary bladder in 2, thyroid in 2, oropharynx in 1, breast in 1, uterine cervix in 1, liver in 1, and bone marrow (myelodysplastic syndrome) in 1. Seven patients had triple synchronous or metachronous malignancies, and 5 patients had quadruple malignancies. All metachronous malignancies before hypopharyngeal cancer were completely controlled.

The simultaneous occurrence of hypopharyngeal cancer and other primary cancers was noted in 20 patients (17.4%), 15 of whom had esophageal cancer. Both hypopharyngeal and esophageal cancers were treated simultaneously with chemoradiotherapy ($n = 8$) or RT ($n = 1$) in 9 patients. Subsequently, esophagectomy was performed in 3 patients, and endoscopic mucosal resection was used in 1 patient. Esophagectomy ($n = 4$) or endoscopic mucosal resection ($n = 1$) was performed before chemoradiotherapy for hypopharyngeal cancer in 5 patients. Esophagectomy was performed after RT for hypopharyngeal cancer in 1 patient. However, 6 patients died of esophageal cancer recurrence. Other synchronous malignancies included gastric cancer in 2 patients, tongue cancer in 1, colon cancer in 1, and thyroid cancer in 1, all of which were successfully treated.

Overall, a total of 19 patients died of hypopharyngeal cancer, 6 died of esophageal cancer, 2 of lung cancer, 1 of myelodysplastic syndrome, 1 of hepatocellular carcinoma, and 14 of other intercurrent diseases or unknown causes.

DISCUSSION

Extensive data have been published on patient outcomes after RT for hypopharyngeal cancer; however, the previously published series have typically focused on the outcomes of RT for all stages of this cancer. Because most patients with hypopharyngeal cancer have either large primary tumors or lymph node metastases, patients with early hypopharyngeal cancer were relatively small cohorts in these works. Mendenhall *et al.* (7) described the outcome of 73 patients with T1–T2 carcinoma of the pyriform sinus after RT, yet only 14 patients (19%) had Stage I or II disease. In the study reported by Okamoto *et al.* (9) on 134 patients with hypopharyngeal cancer, only 11 (8%) had Stage I disease and 13 (10%) had Stage II disease. Only a few reports have focused on the efficacy of RT for early-stage hypopharyngeal cancer, and the optimal treatment approach remains highly controversial.

RT has long been recognized as an effective therapy for hypopharyngeal cancer. Mendenhall *et al.* (7) achieved excellent local control in 80% of patients with T1–T2 pyriform sinus carcinoma treated with RT alone, and Garden *et al.* (6) reported that the 2-year actuarial local control rate for T1 and T2 tumors after RT alone was 89% and 77%, respectively. They concluded that patients with early hypopharyngeal cancer were highly radiocurable. The present results compare favorably with these reports.

Local recurrence after definitive RT is the most common form of disease failure, despite the relatively high overall control rate (6). Because nodal or distant failure is infrequent, local control is still an important factor in controlling early-stage hypopharyngeal cancer. Although concurrent chemoradiotherapy was a strong prognostic factor for local control on multivariate analysis, our study was not able to definitively show that other possible prognostic factors such as radiation dose or hyperfractionation regimen were associated with an improved local control rate. However, improvement of the local control rate with a hyperfractionation regimen or with a combination of RT and chemotherapy has been documented in published reports. Even in patients with advanced pyriform sinus carcinoma, Samant *et al.* (10) demonstrated an organ preservation rate of 88% using concomitant RT and cisplatin chemotherapy. Additionally, Okamoto *et al.* (9) showed that of 88 patients with hypopharyngeal cancer treated with chemoradiotherapy, the larynx was preserved in 74% of patients, a far better preservation rate than that in the

surgery group. Although evidence has now clearly shown that chemoradiotherapy provides a substantial improvement compared with RT alone in both survival and locoregional control (1, 11), the efficacy of the combination of chemotherapy with RT in early hypopharyngeal cancer remains unclear. However, the combination of RT with chemotherapy has generated great interest because of its improved outcomes, considering that a considerable number of patients (26% in the present study) developed local recurrence. In Japan, a national survey on the current status of treatment of early hypopharyngeal cancer revealed that chemotherapy was combined with RT for Stage I disease in 60% of institutions and for Stage II disease in 80% of institutions (12). However, large, well-designed clinical trials, which will allow any estimates of the risk for severe late side effects, as well as improved local control rates, are necessary.

Some authors have advocated for the effectiveness of hyperfractionation for head-and-neck cancers, including hypopharyngeal cancer. A Radiation Therapy Oncology Group randomized study demonstrated that locoregional control significantly increased in patients with locally advanced head-and-neck cancer who received treatment with hyperfractionation rather than standard fractionation (13). Although hyperfractionation has also been shown to improve the outcome of RT for head-and-neck cancer in other randomized trials, very little evidence has shown an increased local control rate of early-stage cancer as a result of hyperfractionation.

Because of the high propensity for metastasis to the lymph nodes at multiple levels, one researcher has recommended that the retropharyngeal and supraclavicular areas, in addition to the entire neck, should be part of the treatment volume, even in patients with early T stage tumors and negative neck lymph nodes (14). In contrast, another researcher has shown that treatment should focus on smaller fields that include the primary tumor and upper cervical lymph nodes for T1–T2N0M0 pyriform sinus carcinoma (15). Because of limited material available in published studies and in our series, the optimal radiation field for early hypopharyngeal cancer remains controversial.

The crude incidence of synchronous and metachronous primary malignancies was extremely high in our series and had a major impact on overall survival. Specifically, second primary tumors of the aerodigestive tract are known to occur in approximately 26% of patients with hypopharyngeal cancers (16). In the present study, 56.5% of our patients had synchronous or metachronous cancers, and esophageal cancer in particular had a major impact on overall survival. Because patients with early head-and-neck cancers generally have a good prognosis, careful follow-up and the early detection of second primary tumors are critical.

To the best of our knowledge, this is the largest reported series of patients with early hypopharyngeal cancer treated with RT. The present study was a nonrandomized retrospective study, and we could not exclude the possibility of bias and limitations to the results. Although 24 (31.6%) of 76 T2 tumors recurred locally in our study, patients with Stage II disease had a poorer PS than patients with Stage I. Also, a considerable number of the patients in this study might not have been candidates for surgery because of old age or medical problems. However, in the absence of other large series, multi-institutional analyses of this type provide important information on therapeutic efficacy. Patients with early hypopharyngeal cancer seem to have a good prognosis after RT; however, the exact benefits of RT can be elucidated only by prospective randomized studies.

REFERENCES

1. Garden AS. Organ preservation for carcinoma of the larynx and hypopharynx. *Hematol Oncol Clin North Am* 2001;15: 243–260.
2. Nakamura K, Shioyama Y, Sasaki T, *et al.* Chemoradiation therapy with or without salvage surgery for early squamous cell carcinoma of the hypopharynx. *Int J Radiat Oncol Biol Phys* 2005;62:680–683.
3. Bernal-Sprekelsen M, Vilaseca-Gonzalez I, Blanch-Alejandro JL. Predictive values for aspiration after endoscopic laser resections of malignant tumors of the hypopharynx and larynx. *Head Neck* 2004;26:103–110.
4. Godballe C, Jorgensen K, Hansen O, *et al.* Hypopharyngeal cancer: Results of treatment based on radiation therapy and salvage surgery. *Laryngoscope* 2002;112:834–838.
5. Czaja JM, Gluckman JL. Surgical management of early-stage hypopharyngeal carcinoma. *Ann Otol Rhinol Laryngol* 1997; 106:909–913.
6. Garden AS, Morrison WH, Clayman GL, *et al.* Early squamous cell carcinoma of the hypopharynx: Outcomes of treatment with radiation alone to the primary disease. *Head Neck* 1996;18:317–322.
7. Mendenhall WM, Parsons JT, Stringer SP, *et al.* Radiotherapy alone or combined with neck dissection for T1-T2 carcinoma of the pyriform sinus: An alternative to conservation surgery. *Int J Radiat Oncol Biol Phys* 1993;27:1017–1027.
8. Sobin LH, Wittekind C. TNM classification of malignant tumours. 5th ed. New York: Wiley Liss; 1997.
9. Okamoto M, Takahashi H, Yao K, *et al.* Clinical impact of using chemoradiotherapy as a primary treatment for hypopharyngeal cancer. *Acta Otolaryngol* 2002;547(Suppl.):11–14.
10. Samant S, Kumar P, Wan J, *et al.* Concomitant radiation therapy and targeted cisplatin chemotherapy for the treatment of advanced pyriform sinus carcinoma: Disease control and preservation of organ function. *Head Neck* 1999; 21:595–601.
11. Zackrisson B, Mercke C, Strander H, *et al.* A systematic overview of radiation therapy effects in head and neck cancer. *Acta Oncol* 2003;42:443–461.
12. Nakamura K, Hareyama M, Shioyama Y, *et al.* Radiotherapeutic management of early hypopharyngeal cancer: A questionnaire survey. *J Jpn Soc Ther Radiol Oncol* 2005;17:41–45 [in Japanese].
13. Fu KK, Pajak TF, Trotti A, *et al.* A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and

neck squamous cell carcinomas: First report of RTOG 9003. *Int J Radiat Oncol Biol Phys* 2000;48:7–16.
14. Fu KK. The endolarynx and hypopharynx. In: Cox JD, editor. Moss' radiation oncology. 7th ed. St. Louis: Mosby-Year Book; 1994. p. 214–245.
15. Dobbs J. Hypopharynx. In: Dobbs M, Barrett A, Ash D, editors. Practical radiotherapy planning. 3rd ed. London: Arnold; 1999. p. 86–93.
16. Emami B, Shmidt-Ullrich RK. Hypopharynx. In: Perez CA, Brady LW, editors. Principles and practice of radiation oncology. 4th ed. Philadelphia: JB Lippincott; 2003. p. 1071–1093.

BMC Cancer

BioMed Central

Research article

Open Access

Results of radiation therapy combined with nedaplatin (cis-diammine-glycoplatinum) and 5-Fluorouracil for postoperative locoregional recurrent esophageal cancer

Keiichi Jingu*†, Kenji Nemoto†, Haruo Matsushita, Chiaki Takahashi, Yoshihiro Ogawa, Toshiyuki Sugawara, Eiko Nakata, Yoshihiro Takai and Shogo Yamada

Address: Department of Therapeutic Radiology, Tohoku University School of Medicine, Seiryo-machi 1-1, Aoba-ku, Sendai 980-8574, Japan

Email: Keiichi Jingu* - kjingu-jr@rad.med.tohoku.ac.jp; Kenji Nemoto - knemoto@rad.med.tohoku.ac.jp; Haruo Matsushita - h-matsushita@rad.med.tohoku.ac.jp; Chiaki Takahashi - chiakitakahashi@rad.med.tohoku.ac.jp; Yoshihiro Ogawa - ogaway@rad.med.tohoku.ac.jp; Toshiyuki Sugawara - sugatoshi@rad.med.tohoku.ac.jp; Eiko Nakata - e-nakata@rad.med.tohoku.ac.jp; Yoshihiro Takai - y-takai@rad.med.tohoku.ac.jp; Shogo Yamada - shogo-y@rad.med.tohoku.ac.jp

* Corresponding author †Equal contributors

Published: 04 March 2006

*BMC Cancer*2006, **6**:50 doi:10.1186/1471-2407-6-50

Received: 01 November 2005

Accepted: 04 March 2006

This article is available from: http://www.biomedcentral.com/1471-2407/6/50

Abstract

Background: Although the effectiveness of radiotherapy with concurrent administration of several anti-tumor drugs for postoperative recurrent esophageal cancer has been demonstrated, the results are not satisfactory. The purpose of the present study was to evaluate the effectiveness and safety of radiotherapy combined with nedaplatin and 5-FU for postoperative locoregional (excluding hematogenous metastasis) recurrent esophageal cancer.

Methods: In June 2000, we started a phase II study on treatment of postoperative locoregional recurrent esophageal cancer with radiotherapy (60 Gy/30 fr/6 weeks) combined with chemotherapy consisting of two cycles of nedaplatin (70 mg/m^2/2 h) and 5-FU (500 mg/m^2/24 h for 5 days).

The primary endpoint of the present study was overall survival rate, and the second endpoints were irradiated-field control rate, tumor response and toxicity.

Results: A total of 30 patients were included in this study. The 1-year and 3-year overall survival rates were 60.6% and 56.3%, respectively, with a median survival period of 39.0 months, and the 1-year and 3-year irradiated-field control rates were 86.4% and 72%, respectively. Complete response and partial response were observed in 13.3% and 60.0% of the patients, respectively. Grade 3 or higher leukocytopenia and thrombocytopenia were observed in 30% and 3.3% of the patients, respectively, but renal toxicity of grade 3 or higher was not observed. The regimen was completed in 76.7% of the patients.

In univariate analysis, the difference between survival rate in preradiotherapy performance status, recurrent pattern (worse for patients with anastomotic recurrence) and age (worse for younger patients) were statistically significant.

Conclusion: Radiotherapy combined with nedaplatin and 5-FU is a safe and effective salvage treatment for postoperative locoregional recurrent esophageal cancer.

Background

Since the mid-1980's, extended radical esophagectomy with three-field (neck, mediastinum, and abdomen) lymph node dissection has been performed, and it seems to have improved survival of patients with esophageal cancer [1-3]. However, there is recurrence in 27~52% of operated patients and locoregional recurrence in 41.5~55% of patients with postoperative recurrence [3-9]. Although the effectiveness of radiotherapy and concurrent chemoradiotherapy using cisplatin (CDDP) + 5-fluorouracil (5-FU) or a combination of several anti-tumor drugs for postoperative recurrent esophageal cancer has been demonstrated, median survival periods have been only 7.0~11.0 months [9-19]. These results are not satisfactory.

Nedaplatin (Cis-Diammine-Glycoplatinum:CDGP), a derivate of CDDP that shows anti-tumor activity similar to that of CDDP and has less renal and gastrointestinal toxicity [20-23], is now being used clinically to treat cancer patients in Japan. The chemical structures of CDGP and CDDP are shown in Fig. 1. The rate of response to CDGP alone for treatment of esophageal cancer was reported to be 51.7% (15 partial responses obtained in 29 patients) [21]. CDGP + 5-FU seemed to have a superior effect to that of CDDP + 5-FU in a preclinical study [22] and has been shown to be safe and effective for treatment of esophageal cancer in some clinical studies [16,17,24,25].

Based on these facts, we started a phase study II on the effectiveness of radiotherapy combined with CDGP and 5-FU for postoperative locoregional recurrence of esophageal cancer.

Methods

In June 2000, we started the present study in three institutes, Tohoku University Hospital and two affiliated hospitals, according to the following protocol.

All patients had histologically proven squamous cell carcinoma of the esophagus. Patient selection criteria included 1) 30 to 80 years of age, 2) Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 3, 3) no other active cancer, 4) no serious cardiac, liver, or pulmonary disease, 5) creatinine clearance of more than 50 ml/min, 6) adequate bone marrow function (leukocyte count of 4000/μl, platelet count of 100,000/μl, 7) locoregional recurrence (including para-aortic lymph node metastasis) without distant metastasis after no residual tumor (R0) resection; extended radical esophagectomy with three-field (neck, mediastinum, and abdomen) lymph node dissection, and 8) no previous therapy other than R0 resection.

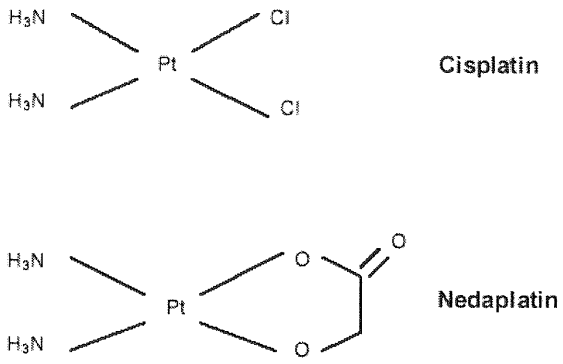
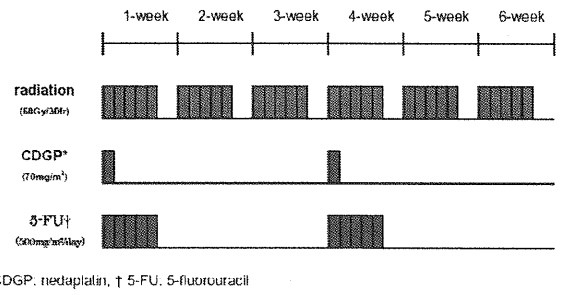


Figure 1
Chemical structures of cisplatin and nedaplatin.

Recurrence was diagnosed comprehensively by upper gastrointestinal endoscopy, ultrasonography, computed tomography (CT), physical findings and/or cytology.

A linear accelerator (4 MV or 10 MV) was used as the X-ray source. The target volume was localized for radiotherapy in all patients by CT planning. The daily fractional dose of radiotherapy was 2.0 Gy, administered 5 days a week, and the total dose was 60.0 Gy. For 11 patients who had metastasis of lymph nodes in some regions or metastasis of many lymph nodes in one region, a T-shaped field (including the bilateral supraclavicular, mediastinal and abdominal regions) was used. For the remaining 19 patients, local fields with a margin of 1 to 2 cm from the macroscopic tumor were used. After a total dose of 40 Gy, the field was changed for all patients to avoid the spinal cord, and only macroscopic lesions were irradiated with a margin of 1 to 1.5 cm. To decrease the incidence of radiation pneumonitis, we avoided as much as possible irradi-



*CDGP, nedaplatin, † 5-FU, 5-fluorouracil

Figure 2
Schedule of the protocol of chemoradiotherapy.

Table 1: Patient characteristics

Patients	
Age	**years old**
median	64
range	50–72
Gender	**Number of patients**
male	29
female	1
Preoperative Stage (UICC* 1997)	**Number of patients**
I	4
II A	2
II B	3
III	17
IV	2
unknown	2
Site of recurence	**Number of patients**
supraclavicular lymph node	9
mediastinal lymph node	14
abdominal lymph node	7
local	9
Performance Status (ECOG†)	**Number of patients**
0	10
1	15
2	3
3	2
4	0
State at last observation date (August 31, 2005)	**Number of patients**
alive	15
dead	13
unknown	2

* UICC: Union Internationale Contre le Cancer, † ECOG: Eastern Cooperative Oncology Group

ating more than 30% of V_{20}, which is the percentage of the total lung volume that received > 20 Gy.

Each cycle of chemotherapy consisted of 120-minute infusion of CDGP at 70 mg/m^2 and a 5-day period of 5-FU at 500 mg/m^2/day. The median doses per body of CDGP and 5-FU were 100 mg/day (range, 80 to 125 mg/day) and 750 mg/day (range, 500 to 900 mg/day), respectively. This cycle of chemotherapy was repeated with an interval of 3 or 4 weeks, for a total radiotherapy dose of 60 Gy (Fig. 2). However, if toxicity of grade 3 or higher was noted and prolonged, we suspended or discontinued chemotherapy or reduced the dose of CDGP alone or the dose of both CDGP and 5-FU by 25~30% in the subsequent cycle.

Completion of the regimen in this study was defined as completion of two cycles of full-dose CDGP + 5-FU for a total radiotherapy dose of 60 Gy without suspension of treatment.

The overall survival, relapse-free survival and irradiated-field control rates were calculated from the first date of radiotherapy.

The primary endpoint of the current study was overall survival rate, and the second endpoints were tumor response, relapse-free survival rate, irradiated-field control rate and toxicity.

RECIST (Response Evaluation Criteria in Solid Tumors) was used to determine the tumor response. Tumor response was evaluated by CT 1~2 months after chemoradiotherapy. The number of mean measurable lesions was 1.8 per patient, and the response was evaluated according to agreement of more than two radiation-oncologists. In the present study, metastasis of para-aortic lymph nodes was defined as regional recurrence.

Follow-up evaluations were performed every 3~6 months for the first 2 years and every 12 months thereafter by endoscopy and CT.

We defined what only progression disease (PD) according was the failure of the present regimen (relapse again).

Survival estimates were calculated using the Kaplan-Meier method, and differences were evaluated by the log-rank

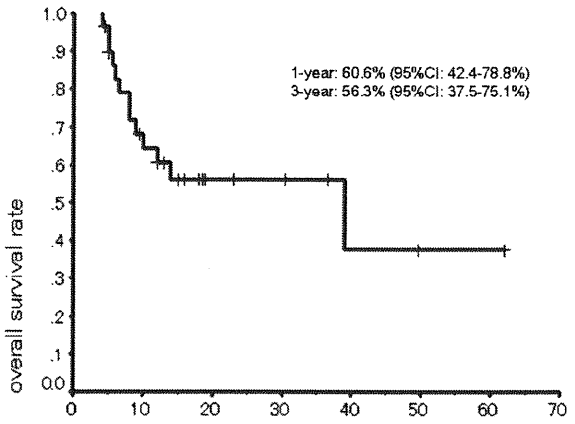


Figure 3
Overall survival of patients with postoperative locoregional recurrent esophageal cancer/(Kaplan-Meier method).

test. Cox's proportional hazards regression model was used for univariate survival analysis. Age, preoperative stage (I – II vs. III – IV: Union International Contre le Cancer 1997 (UICC1997)), time interval between surgery and recurrence, pre-radiotherapy performance status (0–1 vs. 2–3), radiation field (local alone vs. T-shaped), acute tumor response (complete regression (CR) ~ partial regression (PR) vs. stable disease (SD) ~ PD), relapse again inside the irradiated field (yes vs. not), number of cycles of chemotherapy (one vs. two), recurrent pattern (anastomotic vs. non-anastomotic) and number of recurrent regions (one region vs. multiple regions) were entered into univariate analysis. In univariate analysis, age and time interval between surgery and recurrence were not classified in categories. A p value of less than 0.05 was considered significant. All analyses were performed using SPSS 11.0.

Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE v3.0).

The present study protocol was reviewed and approved by the Tohoku University Hospital Institutional review board, and informed consent was obtained from each patient before conducting the treatment.

Results

From June 2000 to December 2004, a total of 30 patients (29 males, 1 female; median age, 64 years; age range, 50 to 72 years) were enrolled in this phase II study. Patient characteristics are shown in Table 1. The sites of recurrence were supraclavicular lymph nodes (9 patients), mediastinal lymph nodes (14 patients), abdominal (including para-aortic) lymph nodes (7 patients) and anastomotic recurrence (9 patients). Five patients had recurrence or metastatsis in two regions and 2 patients had recurrence in three regions. The median time interval from surgery to recurrence was 12.5 months (range, 4 to 102 months). The median period of the regimen in the present study was 42 days (range, 37 to 106 days). Although all of the patients except for one patient who had a 59-day idle period because of acute cholecystitis completed the regimen of radiotherapy without suspension of treatment, 7 patients did not complete the regimen of chemotherapy because of adverse events in the acute phase (The second cycle of chemotherapy was cancelled in 5 patients, and the dose of CDGP alone or the dose of both CDGP and 5-FU were reduced in 2 patients.). The rate of completion of this regimen was 76.7%.

Table 2: Treatment response (RECIST: Response Evaluation Criteria in Solid Tumors)

Treatment response	No.
CR*	4
PR§	18
SD†	7
PD#	1

CR: complete response, §PR: partial response, † SD: stable disease, #PD: progression disease

The last observation date was August 31, 2005. The median follow-up period was 12.5 months (range, 4.0 to 62.0 months) for all patients and 18.0 months (range, 4.5 to 62.0 months) for patients still alive. Sixteen of the 30 patients had relapse again. Thirteen patients out of a total of 30 died; 10 patients due to progression disease, 2 patients due to intercurrent diseases and one patient due to iatrogenic cause. At the last observation date, 15 patients remained alive, and 2 patients were lost to follow up.

The 1-year and 3-year overall survival rates were 60.6% (95%CI = 42.4–78.8) and 56.3% (95%CI = 37.5–75.1), respectively, with a median survival period of 39.0 months (95% CI = 0.0–82.3) (Fig. 3). Overall response rate, including complete responses in 4 patients and partial responses in 18 patients, was 73.3% (Table 2). There was not correlation between tumor response and site of recurrence or between overall survival rate and site of recurrence.

The 1-year and 3-year relapse-free survival rates were 53.4% and 35.6%, respectively, and the 1-year and 3-year irradiated-field control rates were 86.4% and 72%, respectively (Fig. 4).

As the major toxicity in the acute phase, grade 3 leukocytopenia was observed in 9 (30%) of the patients. However, grade 4 leukocytopenia was not observed in any of