The median OS for their entire group was 20 months, which was better than previously published data.[6] Also, the Okayama Lung Cancer Study Group (OLCSG) 0007 trial showed a median OS of 24 months in the MVP arm.[19] The reason for this favorable survival is not clear, but it appears that recent Japanese trials are reporting better OS than previously published data.

Another possible reason for the better OS in our study was our adoption of modern radiotherapy planning, which decreased toxicities, whereas previous studies[18,19] did not adopt dosimetric parameters such as V20. In our study, only 1 patient developed severe pneumonitis; the remaining 58 patients had no grade 3/4 pulmonary toxicity. Also, grade 3 esophagitis did not occur, except in 1 patient. In addition, 58% of the patients in our study underwent PET staging, which may have introduced a selection bias and resulted in better OS, in that patients in whom distant metastases were detected by PET were no longer continued on chemoradiotherapy.

Although there was the limitation that our study was a retrospective analysis, the difference in survival between the two groups was likely to have been due to the chemotherapy regimen selected, because the baseline patient characteristics were well matched and the radiotherapy was homogeneous in terms of the total tumor dose, daily fraction size, and the beam arrangements. Theoretically, there are other possible explanations for the advantageous survival outcome in the group treated with the weekly regimens. First, the radiosensitizing effect[20] of weekly administrations may have played a more important role. However, there was no significant difference in either the LRC or DMFS between the weekly-regimen and full-dose-regimen groups; thus, the radiosensitizing effect of the weekly regimens could not be confirmed.

In our study, the prescribed dose was 60 Gy in 30 fractions for all patients. Although several trials have tested high-dose radiotherapy to improve the LRC, no randomized study of high-dose radiotherapy vs standard-dose radiotherapy has been published. Therefore, 60 Gy remains the standard radiation dose for stage III NSCLC.[21]

In patients with metastatic NSCLC (without radiotherapy), third-generation regimens have been proven to be more effective than second-generation regimens.[8–11] Thus, the lower survival outcome of patients treated with the full-dose regimen in our study may be attributable to the MVP regimen, in which second-generation agents are used. However, in both our regimen groups, including the patients with consolidation chemotherapy, distant visceral recurrences did not seem to be suppressed. On the other hand, one-quarter of patients with locally advanced NSCLC had no recurrence and were deemed curable.

In the present study, the toxicities of and compliance with the regimens were favorable and were comparable between the two groups. However, a 1-week split in the planned thoracic radiotherapy was needed for recovery from myelosuppression in the group of patients treated with the MVP regimen. Thus, the duration of radiotherapy was more prolonged in patients treated with the MVP regimen than in those treated with a weekly regimen. This shorter duration of radiotherapy is another advantage of a weekly regimen.

Although there is the limitation that our study was small and retrospective, the results suggested favorable survival of the patients with weekly regimens compared with that in the patients with the full-dose regimens. Confirmation of the results by randomized phase III trials is warranted.

Conflict of interest statement

No author has any conflict of interest.

References

1. Spira A, Ettinger DS (2004) Multidisciplinary management of lung cancer. N Engl J Med 350:379–392
2. Pfister DG, Johnson DH, Azzoli CG, et al. (2004) American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. J Clin Oncol 22:330–353
3. Dillman RO, Herndon J, Seagren SL, et al. (1996) Improved survival in stage III non-small-cell lung cancer: 7-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. J Natl Cancer Inst 88:1210–1215
4. Sause W, Kolesar P, Taylor S IV, et al. (2000) Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. Chest 117: 358–364
5. Jeremic B, Shibamoto Y, Acimovic L, et al. (1995) Randomized trial of hyperfractionated radiation therapy with or without concurrent chemotherapy for stage III non-small-cell lung cancer: J Clin Oncol 13:452–458
6. Furuse K, Fukuoka M, Kawahara M, et al. (1999) Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol 17:2692–2699
7. Curran W, Scott C, Langer R, et al. (2003) Phase III comparison of sequential vs concurrent chemoradiotherapy for pts with unresected stage III non-small cell lung cancer (NSCLC): report of Radiation Therapy Oncology Group (RTOG) 9410 (abstract). Proc Am Soc Clin Oncol 22:2499
8. Bunn PA Jr, Kelly K (1998) New chemotherapeutic agents prolong survival and improve quality of life in non-small cell lung cancer: a review of the literature and future directions. Clin Cancer Res 4:1087–1100
9. Hoffman PC, Mauer AM, Vokes EE (2000) Lung cancer. Lancet 355:479–485,
10. Kubota K, Watanabe K, Kunitoh H, et al. (2004) Phase III randomized trial of docetaxel plus cisplatin versus vindesine plus cisplatin in patients with stage IV non-small-cell lung cancer: The Japanese Taxotere Lung Cancer Study Group. J Clin Oncol 22:254–61
11. Le Chevalier T, Brisgand D, Douillard JY, et al. (1994) Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small cell lung cancer: results of a European multicenter trial including 621 patients. J Clin Oncol 12:360–367
12. Chen Y, Okunieff P (2004) Radiation and third-generation chemotherapy. Hematol Oncol Clin North Am 18:55–80
13. Belani CP, Choy H, Bonomi P, et al. (2005) Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. J Clin Oncol 23:5883–5891
14. Vokes EE, Herndon JE II, Kelley MJ, et al. (2007) Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III non-small-cell lung cancer: cancer and leukemia group B. J Clin Oncol 13:1698–1704

15. Hanna NH, Neubauer M, Ansari R, et al. (2007) Phase III trial of cisplatin (P) plus etoposide (E) plus concurrent chest radiation (XRT) with or without consolidation docetaxel (D) in patients (pts) with inoperable stage III non-small cell lung cancer (NSCLC): HOG LUN 01–24 / USO-023 (abstract) Proc Am Soc Clin Oncol 387s
16. Therasse P, Arbuck SG, Eisenhauer EA, et al. (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
17. Curran W, Scott C, Langer CJ, et al. (2000) Phase III comparison of sequential vs concurrent chemoradiation for patients with unresected stage III non-small cell lung cancer: initial report of RTOG 9410 (abstract). Proc Am Soc Clin Oncol 19:484a
18. Kimura T, Uejima H, Satouchi M, et al. (2007) Randomized, phase III study of mitomycin/vindesine/cisplatin (MVP) versus weekly irinotecan/carboplatin (IC) or weekly paclitaxel/carboplatin (PC) with concurrent thoracic radiotherapy (TRT) for unresectable stage III non-small cell lung cancer (NSCLC) (abstract). Proc Am Soc Clin Oncol 25:7530
19. Kiura K, Takigawa N, Segawa Y, et al. (2008) Randomized phase III trial of docetaxel and cisplatin combination chemotherapy versus mitomycin, vindesine, and cisplatin combination chemotherapy with concurrent thoracic radiation therapy for locally advanced non-small-cell lung cancer: OLCSG 0007 (abstract). Proc Am Soc Clin Oncol 26:7515
20. Geard CR, Jones JM (1994) Radiation and taxol effects on synchronized human cervical carcinoma cells. Int J Radiat Oncol Biol Phys 29:565–569
21. Perez CA, Stanley K, Rubin P, et al. (1980) A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat cell carcinoma of the lung: preliminary report by the Radiation Therapy Oncology Group. Cancer 45:2744–2753

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2010;40(2)130–138
doi:10.1093/jjco/hyp136
Advance Access Publication 19 October 2009

A Two-step Intensity-modulated Radiation Therapy Method for Nasopharyngeal Cancer: The Kinki University Experience

Yasumasa Nishimura[1], Toru Shibata[1], Kiyoshi Nakamatsu[1], Shuichi Kanamori[1], Ryuta Koike[1], Mitsuru Okubo[1], Tatsuyuki Nishikawa[1], Izumi Tachibana[1], Masaya Tamura[1] and Masahiko Okumura[2]

[1]Department of Radiation Oncology, Kinki University School of Medicine and [2]Department of Central Radiological Service, Kinki University School of Medicine, Osaka, Japan

For reprints and all correspondence: Yasumasa Nishimura, Department of Radiation Oncology, Kinki University School of Medicine, Ohno-Higashi, Osaka-Sayama, Osaka 589-8511, Japan. E-mail: ynishi@med.kindai.ac.jp

Received July 29, 2009; accepted September 14

Objective: The aim of this study was to analyze the clinical results of our adaptive radiation therapy scheme of a two-step intensity-modulated radiotherapy (IMRT) method for nasopharyngeal cancer (NPC) at Kinki University Hospital.
Methods: Between 2000 and 2007, 35 patients with Stage I–IVB NPC treated by IMRT were included. For all patients, treatment-planning computed tomography was done twice before and during IMRT to a total dose of 60–70 Gy/28–35 fractions (median 68 Gy). Chemotherapy (cisplatin 80 mg/m^2/3 weeks × 1–3 courses) was given concurrently with IMRT for 31 patients.
Results: The 3- and 5-year overall survival rates for the 31 patients treated with concurrent chemotherapy were 88% and 83%, respectively. The 3- and 5-year loco-regional control rates for the 31 patients were 93% and 87%, respectively. Planning target volume delineation for the primary site or involved nodes was insufficient for three early cases, resulting in marginal recurrence in the three patients (9%). Except for one patient with early death, xerostomia scores at 1–2 years were: Grade 0, 11; Grade 1, 17; Grade 2, 5; Grade 3, 1.
Conclusions: Excellent overall survival and loco-regional control rates were obtained by a two-step IMRT method with concurrent chemotherapy for NPC, although marginal recurrence was noted in some early cases.

Key words: intensity-modulated radiotherapy – nasopharyngeal cancer – radiation therapy

INTRODUCTION

For locally advanced nasopharyngeal carcinoma (NPC), concurrent chemo-radiotherapy (CRT) showed better overall survival rates compared with radiotherapy (RT) alone by several randomized clinical trials and a meta-analysis (1–5). In the meta-analysis, significant benefit for overall survival and event-free survival was observed when chemotherapy was administered concomitantly with RT (1). In the randomized clinical trials comparing RT alone and concurrent CRT for locally advanced NPC, the 3-year overall survival rates were 46–65% for RT alone and 76–85% for CRT (2–5). Thus, for locally advanced NPC, concurrent CRT is regarded as a standard treatment.

Another advance in the treatment of NPC is the successful clinical use of intensity-modulated RT (IMRT). IMRT is effective especially for head and neck cancers, since the clinical target volumes (CTVs) are in contiguity with organs at risk such as the salivary glands, brain stem and spinal cord. Two randomized clinical trials comparing IMRT and conventional RT for patients with early-stage NPC showed significant benefit of IMRT on the salivary function and quality of life of patients (6,7). Single institutional reports on IMRT for NPC showed excellent loco-regional control rates and overall survival rates (8–14).

Although it is really exciting to use this new technique to improve the therapeutic ratio, questions remain whether the conformation of target coverage and normal tissue sparing may cause marginal failure (15–17). As treatment planning and quality assurance (QA) of IMRT plans require a long time to prepare, most investigators use the initial plan of IMRT for the whole course of IMRT. However, significant

anatomic changes including shrinking of the primary tumor or nodal masses and body weight loss during fractionated RT have been reported for head and neck cancers (13,18). Our previous analysis revealed that the volume of the parotid glands decreased to 74% during the course of IMRT (19). These changes in body contour, target volumes and risk organs during IMRT can affect the dose distribution to the target volume and risk organs, which can be a cause of marginal recurrence or late toxicities. In fact, marginal recurrences after IMRT for head and neck cancer are reported by several investigators (20,21).

To avoid the risk of changes in the dose distribution during IMRT of 7–8 weeks, we adopted a two-step IMRT method for head and neck cancers. For all patients, treatment-planning computed tomography (CT) was done before IMRT (CT-1) and at the third or fourth week of IMRT for the treatment planning of boost IMRT after 46–50 Gy (CT-2) (19). In the present study, the clinical results of our adaptive RT scheme of a two-step IMRT method for patients with NPC were analyzed retrospectively.

PATIENTS AND METHODS

Between December 2000 and December 2007, 38 consecutive patients with NPC were treated at our institution. Excluding three patients with Stage IVc disease (UICC, sixth edition in 2002), 35 patients treated by IMRT were included. Patients and tumor characteristics are shown in Table 1. Staging work-up included clinical examination, laryngo-pharyngeal fiberscope with biopsy from the primary tumors, plain chest XP, head and neck magnetic resonance imaging (MRI) and thoraco-abdominal CT scan. CT scan was performed with contrast enhancement whenever possible. After October 2005, positron emission tomography (PET) was performed for all patients, and for 14 patients, an integrated PET-CT simulation was performed at CT-1 after April 2006 (22,23).

Informed written consent for IMRT as a new method of RT was obtained from all patients. All 35 patients were treated by a two-step IMRT method; 34 treated with whole-neck radiotherapy to 46–50 Gy/23–25 fractions by IMRT, followed by boost IMRT to the high-risk CTV to a total dose of 60–70 Gy/30–35 fractions (median 70 Gy), and one patient treated with whole-neck radiotherapy to 44 Gy/22 fractions by a conventional method, followed by IMRT to a total dose of 70 Gy/35 fractions. The median follow-up period of the patients was 39 months with a range of 5–94 months.

When we started IMRT in December 2000, the present institutional protocol for Stage I–IVB NPC was adopted, i.e. concurrent chemotherapy (cisplatin 80 mg/m^2/3 weeks × 3 courses) was given with a two-step IMRT method (70 Gy/35 fractions/7 weeks), followed by two courses of adjuvant chemotherapy (cisplatin 70 mg/m^2, 5-fluorouracil 700 mg/m^2 × 4 days). The dose of chemotherapy was reduced compared with the Intergroup Study 0099 because the dose used in the USA was too toxic for Japanese patients (2,24). For two elderly patients (>76 years old) and two patients with poor renal function, concurrent chemotherapy was not given, and they were treated with IMRT alone (Table 2). The remaining 31 patients were treated with concurrent chemotherapy, but the third course of concurrent chemotherapy was not administered for most patients because of acute toxicities. Although we recommended adjuvant chemotherapy for the patients, eight patients refused to receive adjuvant chemotherapy because of the toxicities associated with chemotherapy. Thus, adjuvant chemotherapy was given for 23 patients (Table 2).

Table 1. Patient and tumor characteristics

Age	Median: 56 y.o.	Range: 14–81 y.o.			
Gender	Male: 26	Female: 9			
PS	PS 0: 27	PS 1: 7	PS 2: 1		
Histology	WHO type I;	6			
	WHO type II;	26			
	WHO type III;	3			
Double cancer: 3 patients					
Nasal NK/T cell lymphoma; 3 years after NPC					
Colon cancer (mucosal cancer); 1 year after NPC					
Carcinoma *in situ* of the tongue; 4 years after NPC					
TNM stage (UICC, 2002)					
T1: 10	T2a: 3	T2b: 6	T3: 7	T4: 9	
N0: 12	N1: 9	N2: 10	N3a: 2	N3b: 2	
I: 5	IIa: 1	IIb: 6	III: 11	IVa: 8	IVb: 4

PS, performance status; NK/T cell, natural killer T cell; NPC, nasopharyngeal cancer.

Table 2. Summary of treatment parameters

Radiation therapy
Full IMRT: 34 patients, conv. RT + IMRT: 1 patient
Total dose: 60–70 Gy/2 Gy (median: 68 Gy)
Overall treatment time: 44–66 days (median: 51 days)
Concurrent chemotherapy: cisplatin 80 mg/m^2/3 weeks
O course: 4 patients, 1 course: 1 patient, 2 courses: 21 patients, 3 courses: 9 patients
Adjuvant chemotherapy: cisplatin 70 mg/m^2, 5-FU 700 mg/m^2 × 4 days
O course: 12 patients, 1 course: 5 patients, 2 courses: 17 patients, 4 courses: 1 patient

IMRT, intensity-modulated radiotherapy; 5-FU, 5-fluorouracil.

Simulation and Treatment Planning

All patients were immobilized with a thermoplastic mask covering the head, neck and shoulders (Type-S thermoplastic-based system, MED-TEC, Orange City, IA, USA) Treatment-planning CT scans were obtained with contrast medium at 2 or 5 mm slice intervals from the head through the aortic arch. For all patients, treatment-planning CT was done before IMRT (CT-1) and at the third or fourth week of IMRT for boost IMRT (CT-2). For most patients, a new thermoplastic mask was made for CT-2.

Treatment planning for IMRT was done by inverse planning with commercial treatment-planning systems (TPSs) (Cadplan Helios, Varian Associates, Palo Alto, CA, USA; Eclipse, Varian Medical Systems International Inc., Baden, Switzerland). The IMRT beam arrangements consisted of seven coplanar beams. Typically, seven beam angles of 60–75°, 105–115°, 135–150°, 180°, 210–225°, 245–255° and 285–300° were used.

Target Definition and Dose Specification

Following the recommendations of the International Commission on Radiation Units reports 50 and 62, the gross tumor volume (GTV) including the primary tumor and involved lymph nodes and CTV were determined. The definition of involved lymph nodes (GTV) was as followed. Cervical lymph nodes with the shortest axial diameter of $\geq$10 mm and retropharyngeal lymph nodes with the shortest axial diameter of $\geq$5 mm on CT or MRI were defined as malignant. Lymph nodes of borderline size with abnormal enhancement were also indications of malignancy (25,26). The nasopharyngeal area, bilateral Level II–V nodes and the retropharyngeal nodes were included in the initial CTV (27). Submandibular lymph nodes (Level Ib) were only included in the CTV when involved lymph nodes were suspected in the area.

Margins of 3–5 mm for treatment set-up and internal organ motion error were added to the CTV to determine the planning target volume (PTV) (28). For planning organ at risk volume, a margin of 3 mm was added to the spinal cord. For the parotid glands, no margin was added in treatment planning.

After whole-neck irradiation of 44–50 Gy in 22–25 fractions, boost IMRT was given to the PTV2 including the GTV with appropriate margin on the basis of CT-2. The daily prescribed dose to the PTV was 2.0 Gy. The prescribed dose was normalized to the dose to 95% volume (D95) of the PTV, and the dose to 10% volume (D10) of the PTV was $<$110% of the prescribed dose to the PTV (27).

Our goals on dose–volume histogram (DVH) were PTV-max $<$120% of the prescribed dose, PTV-mean $<$105% (usually 103–104%), D10 of PTV $<$110%, maximum dose of the spinal cord $<$48 Gy, maximum dose of the brain $<$64 Gy, median dose $<$19 Gy or mean dose $<$25 Gy for at least one parotid gland.

Treatment Delivery and QA

IMRT was delivered using dynamic multileaf collimation with one of two linear accelerators equipped with a 40-leaf dynamic multileaf collimator (Clinac-600C, Clinac-21EX; Varian Associates). Beam energy of 4 or 6 MV X-rays was used. The daily treatment time was 15–20 min. To verify the leaf motion of each beam, various QA performance tests were conducted. Details of QA procedures at our hospital have been described elsewhere (28,29).

Follow-up, Survival and Toxicities

After the end of IMRT with or without adjuvant chemotherapy, loco-regional control and distant progression was evaluated every 3–4 months for $>$5 years by clinical examination and laryngo-pharyngeal fiberscope, and every 6 months by head and neck MRI or CT scan and thoraco-abdominal CT scan. When tumor recurrence or distant metastasis was noted, salvage treatment was mandatory for attending physicians.

The probability of survival was estimated using the Kaplan–Meier method with statistical significance assessed by the log-rank test. Survival was calculated from the first date of RT. Overall survival considered deaths due to any cause. Progression-free survival (PFS) considered any loco-regional or distant tumor progression and any cause of deaths as events. Loco-regional control rate considered any recurrence in the primary site or regional lymph nodes as an event.

Acute and late toxicities were graded according to the Common Toxicity Criteria for Adverse Events (CTCAE), version 3.0. Although this is a retrospective analysis, grade of acute hematologic and non-hematologic toxicities were scored prospectively once a week during RT by one of two attending physicians (Y.N. and T.S.) after the start of IMRT and recorded in the clinical chart. Late toxicities on xerostomia, hearing and dysphagia were also scored prospectively and recorded in the clinical chart every 3–4 months. In terms of xerostomia, the attending physicians asked patients on dietary alteration and necessity of a water bottle every 3–4 months, and the best grade at 12–24 months after the start of IMRT was recorded.

RESULTS

Figure 1A shows overall survival rates according to concurrent chemotherapy for all the 35 patients included. The survival rate for patients treated without chemotherapy was apparently worse than that for the 31 patients treated with concurrent chemotherapy. The 3- and 5-year overall survival rates for the 31 patients treated with concurrent chemotherapy were 88% and 83%, respectively. The 5-year overall survival rates for 23 patients with Stage 1–3 disease and 12 patients with Stage 4 disease were 73% and 62%, respectively (Fig. 1B). As of March 2009, five patients died of

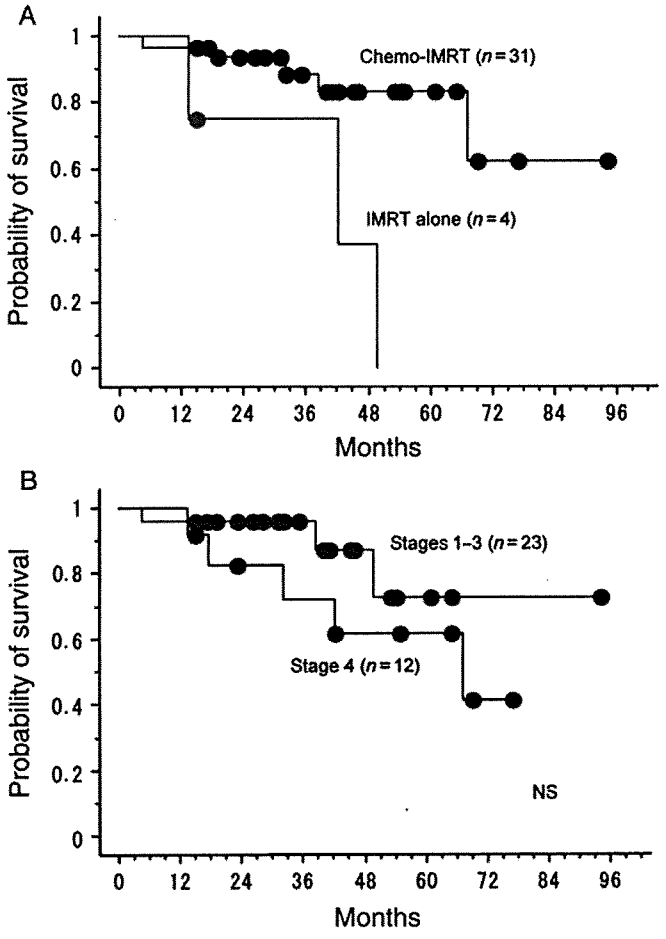

Figure 1. (A, B) Overall survival rates for 35 patients according to (A) concurrent chemotherapy or (B) clinical stage.

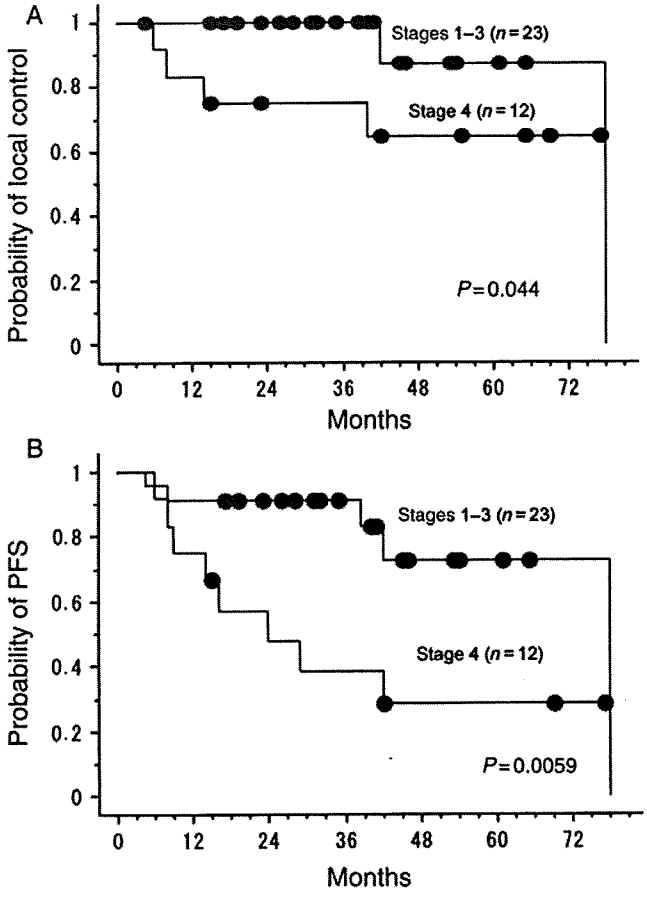

Figure 2. (A) Local control rates and (B) progression-free survival rates for 23 patients with Stage 1–3 disease and 12 patients with Stage 4 disease.

NPC, three patients died of intercurrent disease (pneumonia, nasal natural killer T cell lymphoma and suffocation by food) without evidence of recurrence of NPC and two patients are alive with the disease. The remaining 25 patients are alive without evidence of the disease.

Figure 2A shows loco-regional control rates according to clinical stages (Stages 1–3 vs. Stage 4). The 5-year loco-regional control rates for patients with Stage 1–3 disease and those with Stage 4 disease were 88% and 64%, respectively, with significant difference ($P = 0.044$). The 3- and 5-year loco-regional control rates for the 31 patients treated with concurrent chemotherapy were 93% and 87%, respectively. Figure 2B shows PFS rates according to clinical stages (Stages 1–3 vs. Stage 4). The 5-year PFS rates for patients with Stage 1–3 disease and those with Stage 4 disease were 73% and 29%, respectively, with significant difference ($P = 0.0059$).

Recurrence or persistent tumors in the primary site were noted in six patients (17%). Recurrence or a persistent tumor was noted at the area of PTV receiving 60–68 Gy in four of the six patients, whereas recurrence from the PTV margin was noted in two patients at the pterygopalatine fossa or at the posterior edge of the clivus (Fig. 3A–D). One late recurrence at the nasopharynx was noted 66 months after chemo-IMRT (65.4 Gy/35 fractions). For this patient, second chemo-IMRT (66 Gy/30 fractions) was done and there was no evidence of the disease at 94 months after the initial IMRT without significant late toxicities.

Residual or recurrence of neck lymph nodes was noted in four patients (11%). In two patients, PTV delineation for the neck nodes was insufficient, and recurrences were noted at posterior chain lymph nodes and at a periparotid lymph node (Figs 3E–F and 4A–D). As both the primary site and neck node recurrence were noted in one patient (Fig. 3), the PTV marginal recurrence was noted in three patients (9%). In two of the three patients with marginal recurrences, keen review of the pretreatment MRI or CT scan of the patients showed the involved nodes or the extension of the primary tumor at the edge of the PTV. In the remaining one patient, marginal recurrence was noted at the pterygopalatine fossa 3 years after chemo-IMRT. For this patient, pre-treatment MRI and CT scan did not show the tumor invasion to the pterygopalatine fossa. After February 2003, no marginal recurrence was noted at our institution.

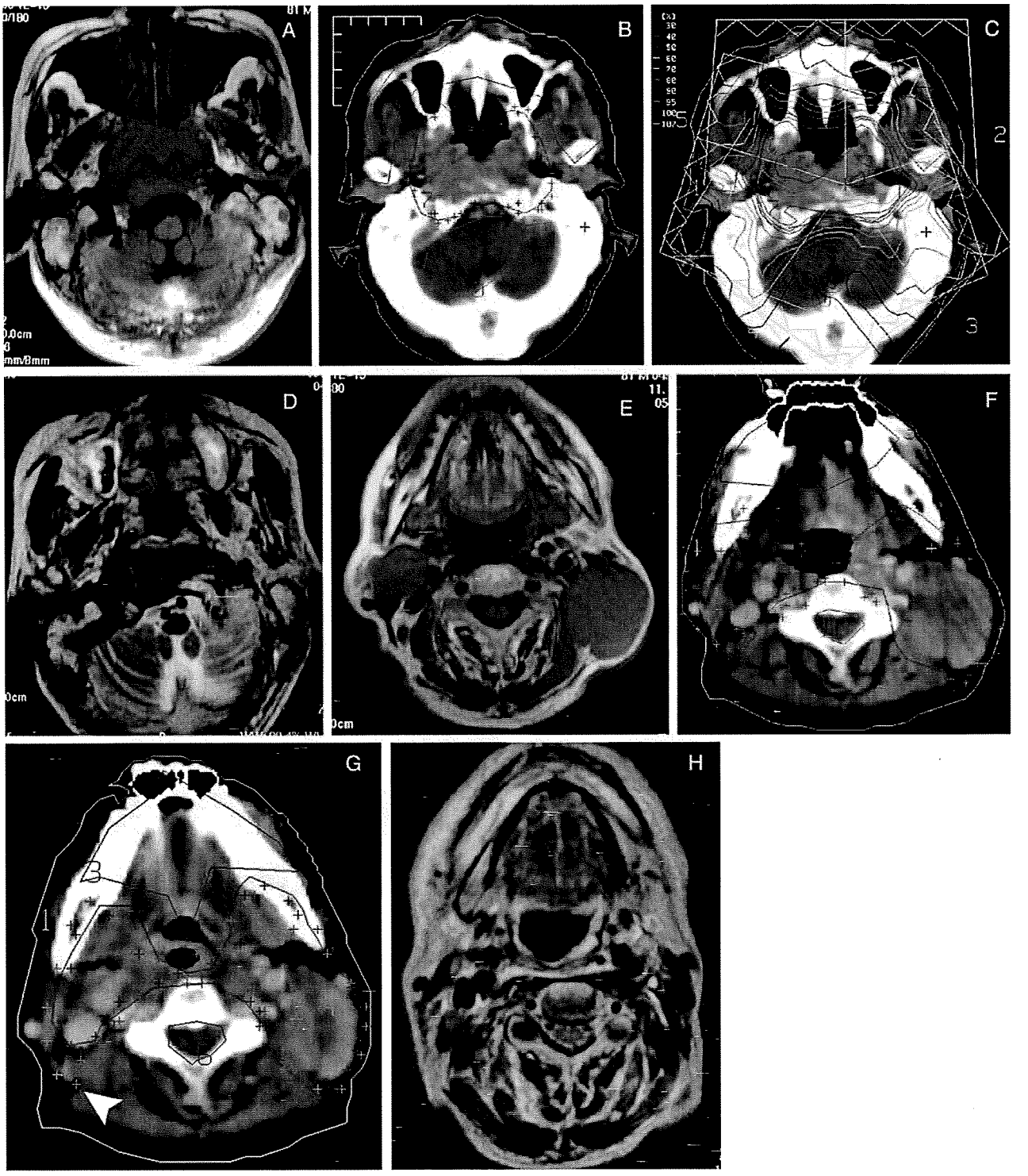

Figure 3. An 81-year-old man with NPC (T4N3aM0). This patient was treated with 66 Gy/35 fractions without concurrent chemotherapy. (A) MRI before IMRT showing primary tumor invading to the clivus. (B) Red line indicates PTV, which misses the right posterior edge of the clivus. (C) Isodose curves. The right posterior edge of the clivus was covered only by the 80% dose line (outer pink line). (D) Ten months after the start of IMRT, MRI showed recurrence from the right posterior edge of the clivus. No recurrence was noted on the mucosal surface of the nasopharynx. (E) MRI before IMRT showing bilateral three upper jugular neck lymph nodes (Level IIa,b). (F) Red line indicates PTV for the initial plan. (G) Red line indicates PTV for the boost plan after 47 Gy. The right posterior lymph node (Level IIb) was not included in the PTV. (H) Ten months after the start of IMRT, MRI showed recurrence from the smallest right posterior lymph node, although the other two lymph node metastases were controlled by IMRT. NPC, nasopharyngeal cancer; MRI, magnetic resonance imaging; IMRT, intensity-modulated radiotherapy; PTV, planning target volume.

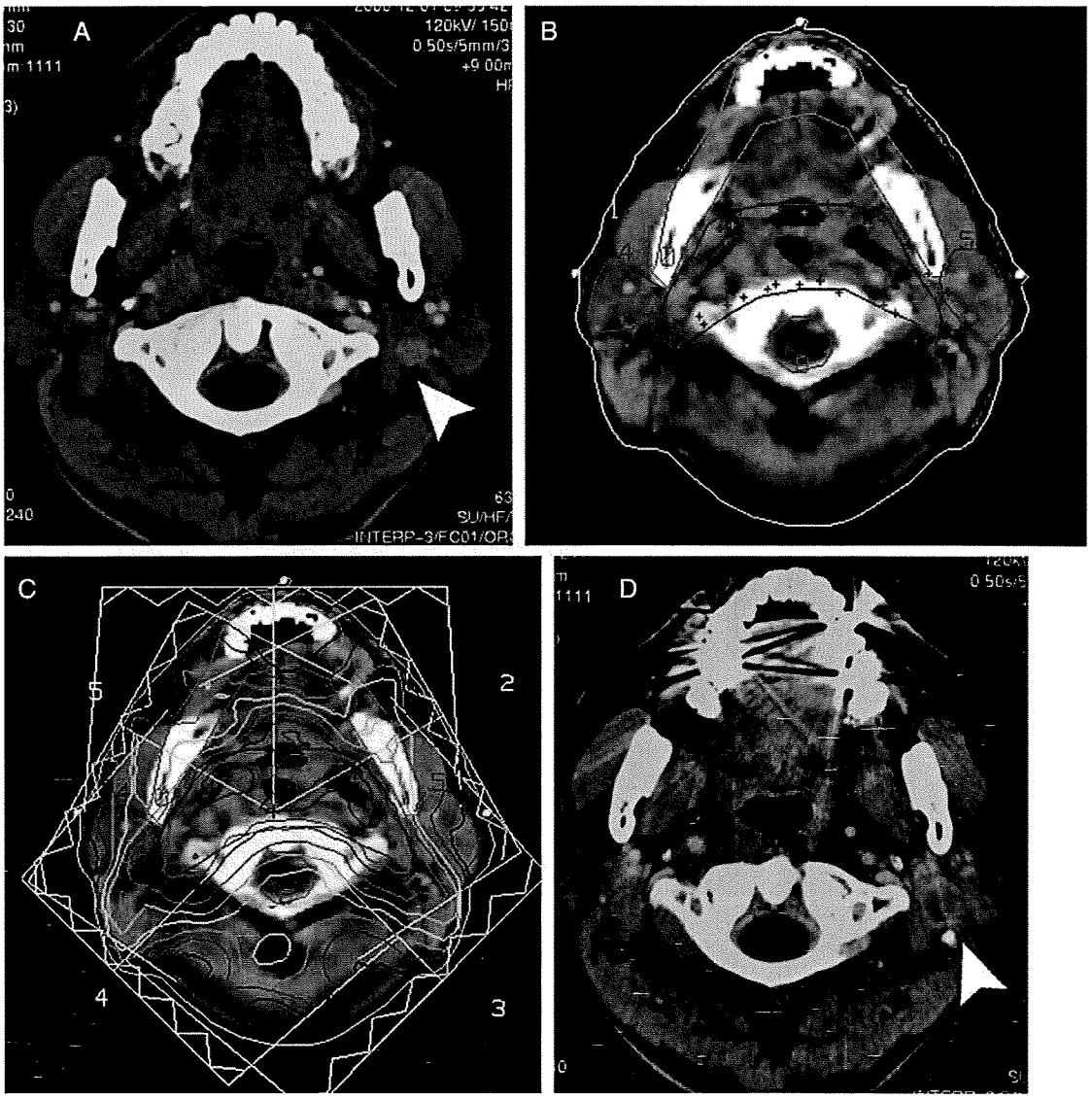

Figure 4. A 63-year-old man with NPC (T4N2M0). This patient was treated with 66 Gy/35 fractions and concurrent cisplatin of 370 mg in three courses. (A) Computed tomography before IMRT showing lt periparotid lymph node of 7 mm in diameter. (B) Red line indicates PTV, which misses the periparotid lymph node. (C) Isodose curves. The lt periparotid lymph node was located at the dose gradient region between PTV and the lt parotid grand. (D) Fourteen months after the start of IMRT, computed tomography showed recurrence of the lt periparotid lymph node. Re-irradiation was done for the recurrent lymph node.

Table 3 shows the acute toxicities associated with IMRT with or without concurrent chemotherapy. Hematological toxicities were mild, and no Grade 4 hematological toxicity was noted. Two patients showed Grade 4 mucositis. One patient with Grade 4 mucositis refused CRT after 60 Gy with two doses of concurrent cisplatin, and this patient required interruption of RT for 22 days. Sepsis with high fever of Grade 4 toxicity was noted immediately after the first chemotherapy in one patient. RT was interrupted for 10 days for this patient. Except for the two patients, no treatment interruption due to acute toxicities was necessary, and the median overall treatment time was 51 days (Table 2).

Late toxicities associated with IMRT with or without concurrent chemotherapy are shown in Table 4. Hearing difficulty, tinnitus and otitis were common late toxicities. However, most patients with auditory toxicities had the same symptom at presentation. Although several patients complained of dysphagia after treatment, no patient needed percutaneous endoscopic gastrostomy. One patient died of suffocation by food 3 months after the end of IMRT without evidence of disease. Except for the patient with early death, xerostomia scores at 1–2 years were: Grade 0, 11; Grade 1, 17; Grade 2, 5; Grade 3, 1. The patent with Grade 3 xerostomia was treated by conventional RT followed by boost IMRT.

Table 3. Acute toxicities (CTCAE, version 3.0)

Toxicities	G2	G3	G4
WBC	16	10	0
Hb	11	0	0
Plt	0	1	0
Mucositis	16	13	2
Dysphagia	19	14	0
Dermatitis	8	2	0
Nausea	22	9	0
Vomiting	16	1	0
Infection	0	1	1
Fever	3	0	1
Fatigue	0	1	0
Creatinine	1	0	0
Liver	2	0	0

CTCAE, Common Toxicity Criteria for Adverse Events; WBC, white blood cells; Hb, hemoglobin; Plt, platelets.

Table 4. Late toxicities (CTCAE, version 3.0)

Toxicities	G1	G2	G3	G4	G5
Hearing	0	5	1	1	0
Tinnitus	0	6	0	0	0
Otitis, middle ear	1	5	0	0	0
Xerostomia at 12–24 months	17	5	1	0	0
Dysphagia	4	3	0	0	1?
Pharyngeal wall	5	0	1	0	0
Larynx	11	0	0	0	0
Hypothyroidism	0	2	0	0	0
Skin	1	0	0	0	0
Creatinine	1	0	0	0	0

DISCUSSION

Clinical results of our adaptive RT scheme of a two-step IMRT method for NPC were analyzed in the present study, and excellent overall survival and loco-regional control rates were obtained when concurrent chemotherapy was combined with IMRT. When introducing IMRT for head and neck cancers at our hospital, we chose a most conservative method, although it is a time-consuming strategy. Inverse planning for IMRT was performed twice. This two-step IMRT method obviously took a longer time for the treatment planning and QA than a single-step simultaneous integrated boost (SIB) method which gives several dose levels for CTVs and GTV simultaneously (8,10,11,14). It took 5 working days at our institution for the inverse planning and its verification, and the IMRT plan was started 7–10 days after CT simulation. Because CT-2 for boost IMRT plan was performed at an RT dose of 36–40 Gy, no treatment interruption due to treatment planning was inserted for all patients. A two-step IMRT method has an advantage, in that it can adapt the treatment to changes in body contour, target volumes and risk organs during IMRT. As patients with locally advanced NPC frequently appeared with large neck lymph nodes swelling and as both primary tumors and neck lymph nodes regress rapidly by RT, a two-step IMRT method is especially desirable for locally advanced NPC. In the only other report of a two-step IMRT method, Lee et al. (13) described a Phase I/II study of a two-step SIB method for 20 patients with NPC.

No direct comparison in terms of clinical or DVH results between a single-step and a two-step IMRT was shown in the present study, because all patients with NPC were treated with a two-step IMRT method at our institution. We do not argue a two-step IMRT method is a new standard method of IMRT. A two-step method has been used in the conventional RT for head and neck cancer. Thus, a two-step IMRT method is a conventional and conservative method of IMRT compared with a single-step SIB IMRT method with larger fraction sizes for GTV. For early-stage NPC with T1,2N0M0 disease, effects of tumor regression during IMRT may be small, and a single-step method may be applicable. In fact, a single-step SIB IMRT method is applied for early oropharyngeal cancer (T1,2N0,1M0) at our institution. However, even for patients with early NPC, body weight and contour can be changed when concurrent CRT is used. Therefore, we consider that a two-step IMRT method is one of the safe methods of IMRT for patients with NPC treated by concurrent CRT.

In our early cases, PTV marginal recurrence was noted in three patients (9%). There may be several reasons for the early marginal recurrence. In our first TPS (Cadplan Helios), the function of adding a margin to CTV or GTV was lacking, i.e. PTV was contoured directly at that time (Figs 3 and 4). In two of the three patients with marginal recurrences, pre-treatment MRI or CT scan of the patients could depict the involved nodes or the extension of the primary tumor. Precise contouring of CTV and PTV based on various imaging modalities including MRI and FDG-PET is most important for the success of IMRT. TPS was changed to the second generation type (Eclipse) in 2004 and PTV margins of 3–5 mm were added to CTV (28). In addition, an integrated PET-CT simulation was started in 2006 (22,23). PET-CT simulation was especially effective to depict GTV invading the skull base. Along with improvements in equipment and knowledge of contouring, PTV marginal recurrence has never occurred since 2003.

Only six patients (18%) complained of Grade 2 or 3 xerostomia 1–2 years after IMRT. Thus, a two-step IMRT is also effective for preventing xerostomia. One notable late toxicity is dysphagia. Recently, several investigators have noted the importance of the RT dose to the pharyngeal constructors (30–32). Seven patients complained of Grade 1 or 2 dysphagia, and one patient died of suffocation by food

3 months after the end of IMRT without evidence of the disease. As this patient had complained of dysphagia, this accident may have been a treatment-related death (Grade 5 toxicity).

In conclusion, excellent overall survival and local-PFS rates were obtained by a two-step IMRT method with concurrent chemotherapy for NPC. This two-step IMRT method as an adaptive RT scheme could correspond to changes in body contour, target volumes and risk organs during IMRT. A prospective multi-institutional clinical trial of a two-step IMRT method for NPC is warranted.

Funding

This study was partially supported by a Grant-in-Aid for Scientific Research (17591300) from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and a Grant-in-Aid for Cancer Research (20S-5) from the Ministry of Health, Labor and Welfare, Japan.

Conflict of interest statement

None declared.

References

1. Baujat B, Audry H, Bourhis J, Chan AT, Onat H, Chua DT, et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. *Int J Radiat Oncol Biol Phys* 2006;64:47–56.
2. Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup Study 0099. *J Clin Oncol* 1998;16:1310–7.
3. Chen Y, Liu MZ, Liang SB, Zong JF, Mao YP, Tang LL, et al. Preliminary results of a prospective randomized trial comparing concurrent chemoradiotherapy plus adjuvant chemotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma in endemic regions of China. *Int J Radiat Oncol Biol Phys* 2008;71:1356–64.
4. Wee J, Tan EH, Tai BC, Wong HB, Leong SS, Tan T, et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. *J Clin Oncol* 2005;23:6730–8.
5. Lin JC, Jan JS, Hsu CY, Liang WM, Jiang RS, Wang WY. Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival. *J Clin Oncol* 2003;21:631–7.
6. Pow EH, Kwong DL, McMillan AS, Wong MC, Sham JS, Leung LH, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. *Int J Radiat Oncol Biol Phys* 2006;66:981–91.
7. Kam MK, Leung SF, Zee B, Chau RM, Suen JJ, Mo F, et al. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. *J Clin Oncol* 2007;25:4873–9.
8. Lee N, Xia P, Quivey JM, Sultanem K, Poon I, Akazawa C, et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. *Int J Radiat Oncol Biol Phys* 2002;53:12–22.
9. Fang FM, Chien CY, Tsai WL, Chen HC, Hsu HC, Lui CC, et al. Quality of life and survival outcome for patients with nasopharyngeal carcinoma receiving three-dimensional conformal radiotherapy vs. intensity-modulated radiotherapy—a longitudinal study. *Int J Radiat Oncol Biol Phys* 2008;72:356–64.
10. Wolden SL, Chen WC, Pfister DG, Kraus DH, Berry SL, Zelefsky MJ. Intensity-modulated radiation therapy (IMRT) for nasopharynx cancer: update of the Memorial Sloan-Kettering experience. *Int J Radiat Oncol Biol Phys* 2006;64:57–62.
11. Kwong DL, Sham JS, Leung LH, Cheng AC, Ng WM, Kwong PW, et al. Preliminary results of radiation dose escalation for locally advanced nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2006;64:374–81.
12. Lee AW, Lau KY, Hung WM, Ng WT, Lee MC, Choi CW, et al. Potential improvement of tumor control probability by induction chemotherapy for advanced nasopharyngeal carcinoma. *Radiother Oncol* 2008;87:204–10.
13. Lee SW, Back GM, Yi BY, Choi EK, Ahn SD, Shin SS, et al. Preliminary results of a phase I/II study of simultaneous modulated accelerated radiotherapy for nondisseminated nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2006;65:152–60.
14. Kam MK, Teo PM, Chau RM, Cheung KY, Choi PH, Kwan WH, et al. Treatment of nasopharyngeal carcinoma with intensity-modulated radiotherapy: the Hong Kong experience. *Int J Radiat Oncol Biol Phys* 2004;60:1440–50.
15. Mendenhall WM, Mancuso AA. Radiotherapy for head and neck cancer; is the 'next level' down? *Int J Radiat Oncol Biol Phys* 2009;73:645–6.
16. Mendenhall WM, Amdur RJ, Palta JR. Intensity-modulated radiotherapy in the standard management of head and neck cancer: promises and pitfalls. *J Clin Oncol* 2006;24:2618–23.
17. Harari PM. Beware the swing and a miss: baseball precautions for conformal radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;70:657–9.
18. Barker JL Jr, Garden AS, Ang KK, O'Daniel JC, Wang H, Court LE, et al. Quantification of volumetric and geometric changes occurring during fractionated radiotherapy for head-and-neck cancer using an integrated CT/linear accelerator system. *Int J Radiat Oncol Biol Phys* 2004;59:960–70.
19. Nishimura Y, Nakamatsu K, Shibata T, Kanamori S, Koike R, Okumura M, et al. Importance of the initial volume of parotid glands in xerostomia for patients with head and neck cancers treated with IMRT. *Jpn J Clin Oncol* 2005;35:375–79.
20. Cannon DM, Lee NY. Recurrence in region of spared parotid gland after definitive intensity-modulated radiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys* 2008;70:660–5.
21. Schoenfeld GO, Amdur RJ, Morris CG, Li JG, Hinerman RW, Mendenhall WM. Patterns of failure and toxicity after intensity-modulated radiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys* 2008;71:377–85.
22. Okubo M, Nishimura Y, Nakamatsu K, Okumura M, Shibata T, Kanamori S, et al. Static and moving phantom studies for radiation treatment planning in a positron emission tomography and computed tomography (PET/CT) system. *Ann Nucl Med* 2008;22:579–86.
23. Okubo M, Nishimura Y, Nakamatsu K, Okumura M, Shibata T, Kanamori S, et al. Radiation treatment planning using positron emission and computed tomography (PET/CT) for lung and pharyngeal cancers: a multiple thresholds method for FDG activity. *Int J Radiat Oncol Biol Phys*; in press.
24. Isobe K, Kawakami H, Uno T, Yasuda S, Aruga T, Ueno N, et al. Concurrent chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma: is Intergroup Study 0099 feasible in Japanese patients? *Jpn J Clin Oncol* 2003;33:497–500.
25. Tang L, Li L, Mao Y, Liu L, Liang S, Chen Y, et al. Retropharyngeal lymph node metastasis in nasopharyngeal carcinoma detected by magnetic resonance imaging. *Cancer* 2008;113:347–54.
26. Zheng XK, Chen LH, Wang QS, Wu HB, Wang HM, Chen YQ, et al. Influence of FDG-PET on computed tomography-based radiotherapy planning for locally recurrent nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2007;69:1381–8.
27. Eisbruch A, Foote RL, O'Sullivan B, Beitler JJ, Vikram B. Intensity-modulated radiation therapy for head and neck cancer: emphasis on the selection and delineation of the targets. *Semin Radiat Oncol* 2002;12:238–49.

28. Suzuki M, Nishimura Y, Nakamatsu K, Okumura M, Hashiba H, Koike R, et al. Analysis of interfractional set-up errors and intrafractional organ motions during IMRT for head and neck tumors to define an appropriate planning target volume (PTV)- and planning organs at risk volume (PRV)-margins. *Radiother Oncol* 2006;78:283–90.
29. Suzuki M, Nakamatsu K, Kanamori S, Okumura M, Uchiyama T, Akai F, et al. Feasibility study of the simultaneous integrated boost (SIB) method for malignant gliomas using intensity modulated radiotherapy (IMRT). *Jpn J Clin Oncol* 2003;33:271–7.
30. Teguh DN, Levendag PC, Noever I, van Rooij P, Voet P, van der Est H, et al. Treatment techniques and site considerations regarding dysphagia-related quality of life in cancer of the oropharynx and nasopharynx. *Int J Radiat Oncol Biol Phys* 2008;72:1119–27.
31. Eisbruch A, Schwartz M, Rasch C, Vineberg K, Damen E, Van As CJ, et al. Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: which anatomic structures are affected and can they be spared by IMRT? *Int J Radiat Oncol Biol Phys* 2004;60:1425–39.
32. Caglar HB, Tishler RB, Othus M, Burke E, Li Y, Goguen L, et al. Dose to larynx predicts for swallowing complications after intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;72:1110–8.

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2010;40(1)54–59
doi:10.1093/jjco/hyp137
Advance Access Publication 16 October 2009

Cisplatin and Etoposide Chemotherapy Combined with Early Concurrent Twice-daily Thoracic Radiotherapy for Limited-disease Small Cell Lung Cancer in Elderly Patients

Kunio Okamoto[1], Isamu Okamoto[1], Ken Takezawa[1], Izumi Tachibana[2], Masahiro Fukuoka[3], Yasumasa Nishimura[2] and Kazuhiko Nakagawa[1]

[1]Department of Medical Oncology, Kinki University School of Medicine, [2]Department of Radiation Oncology, Kinki University School of Medicine and [3]Department of Medical Oncology, Kinki University School of Medicine, Sakai Hospital, Osaka, Japan

For reprints and all correspondence: Isamu Okamoto, Department of Medical Oncology, Kinki University School of Medicine, 377-2 Ohno-higashi, Osaka-Sayama, Osaka 589-8511, Japan. E-mail: chi-okamoto@dotd.med.kindai.ac.jp

Received August 7, 2009; accepted September 13, 2009

Objective: The optimal management of elderly patients with limited-disease small cell lung cancer (LD-SCLC) has not been established.
Methods: The records of elderly (≥70 years of age) patients with LD-SCLC who had been treated with etoposide and cisplatin chemotherapy with early concurrent twice-daily thoracic radiotherapy (TRT) were reviewed retrospectively.
Results: Of the 25 elderly patients with LD-SCLC identified, 12 (48%) individuals received etoposide–cisplatin chemotherapy with early concurrent twice-daily TRT. The main toxicities of this treatment regimen were hematologic, with neutropenia of Grade 4 being observed in all patients and febrile neutropenia of Grade 3 in eight patients during the first cycle of chemoradiotherapy. The toxicity of TRT was acceptable, with all patients completing the planned radiotherapy within a median of 29 days (range, 19–33). No treatment-related deaths were observed. The median progression-free survival and overall survival times were 14.2 months (95% confidence interval, 4.3–18.2) and 24.1 months (95% confidence interval, 11.3–27.2), respectively.
Conclusions: Etoposide–cisplatin chemotherapy with early concurrent twice-daily TRT was highly myelotoxic in elderly patients with LD-SCLC, although no treatment-related deaths were observed in our cohort. Prospective studies are required to establish the optimal schedule and dose of chemotherapy and TRT in such patients.

Key words: elderly – small cell lung cancer – chemoradiotherapy – cisplatin – etoposide – concurrent thoracic radiotherapy

INTRODUCTION

Small cell lung cancer (SCLC) accounts for 10–15% of all lung cancer cases, with individuals aged 70 years or older constituting up to 25–40% of the SCLC patients (1,2). Limited-disease (LD) SCLC is a disease that is confined to one hemithorax and its regional lymph nodes and which can be encompassed by a single radiation therapy port. About 30–40% of all SCLC patients present with LD-SCLC (1,2). The proportion of elderly SCLC patients continues to increase with the growing geriatric population (1,3).

The combination of radiotherapy and chemotherapy, specifically etoposide and cisplatin chemotherapy with early concurrent twice-daily thoracic radiotherapy (TRT), is now regarded as the standard treatment for LD-SCLC (4). However, many clinical trials of potential new treatments for LD-SCLC have excluded elderly patients for various reasons, such as the presence of concomitant chronic illness, a decline in organ function that may interfere with drug clearance and possible decreased bone marrow tolerance to myelosuppressive agents (5). The optimal management of elderly patients with LD-SCLC has therefore not been defined to date.

We have now performed a retrospective analysis to evaluate patient characteristics as well as treatment delivery, toxicity and antitumor efficacy for elderly individuals (70 years or

older) with LD-SCLC who were treated with etoposide and cisplatin chemotherapy and early concurrent twice-daily TRT.

PATIENTS AND METHODS

We retrospectively evaluated the records of elderly (≥70 years) patients with LD-SCLC who were treated at Kinki University School of Medicine from January 2003 to December 2008. All patients had a pathological diagnosis of SCLC. LD-SCLC was defined as cancer that is confined to one hemithorax including contralateral mediastinal and hilar lymph nodes as well as ipsilateral or bilateral supraclavicular lymph nodes, but excluding malignant pleural effusion. Response evaluation was assessed after completion of treatment on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST). Laboratory testing and toxicities were graded weekly during the whole treatment according to the National Cancer Institute—Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 3). Progression-free survival time was measured from the date of initiation of treatment to the date of disease progression. Overall survival time was measured from the date of initiation of treatment to death or to the time that the patient was last known to be alive. After completion of all treatment, patients were followed up at 1- to 2-month intervals until the time of progression or death. Median progression-free survival time and overall survival time were estimated by the Kaplan–Meier method.

RESULTS

Patient Characteristics

Of the 170 SCLC patients treated between 2003 and 2008, 48 individuals were diagnosed with LD-SCLC and 25 of these individuals were 70 years of age or older. Among these 25 patients, 12 (48%) elderly patients with LD-SCLC received etoposide and cisplatin chemotherapy with early concurrent twice-daily TRT. The characteristics of these 12 patients are shown in Table 1. They included eight men and four women as well as seven individuals aged between 70 and 74 years and five aged 75 years or older. All the patients were in good general condition, although they had some complications. The remaining 13 patients' characteristics are shown in Table 2. Two of the 13 elderly patients with LD-SCLC were treated with chemotherapy and sequential TRT, and 1 patient was treated with etoposide–carboplatin and concurrent TRT. Chemotherapy alone was administered in 4 of the 13 patients. Two patients were subjected to surgery followed by chemotherapy. Four patients did not receive intensive therapy.

Treatment Delivery

The treatment plan consisted of an initial cycle of concurrent chemoradiotherapy followed by three cycles of consolidation chemotherapy (Table 3). All patients received the same chemotherapy regimen of cisplatin at 40–80 mg/m^2 on day 1 combined with etoposide at 80–100 mg/m^2 on days 1–3. Twice-daily TRT was performed with X-rays at 6–10 MV and with an interval of at least 6 h and a total dose of 45 Gy (1.5 Gy bid) over 3 weeks. TRT was initiated on day 1 of the first cycle of chemotherapy. All patients completed the TRT protocol, with the days of irradiation ranging from 19 to 33 (median of 29). Reasons for a delay in TRT included febrile neutropenia of Grade 3 in eight patients and leukopenia of Grade 4 in three patients. All patients proceeded to consolidation chemotherapy. However, five patients (42%) did not complete the planned three cycles of consolidation

Table 1. Characteristics of the study cohort

Patient	Age/sex	TNM stage	PS	Complications	Smoking history
1	70/M	T2N1M0	1	HT	20/day × 50 years
2	70/M	T3N1M0	0	Berger disease, old TB	40/day × 50 years
3	71/M	T3N2M0	0	DM, bladder cancer	20/day × 50 years
4	71/M	T1N2M0	1	Harada disease	20/day × 50 years
5	72/F	T2N2M0	1	HT, old TB, asthma, one kidney	20/day × 35 years
6	72/M	T1N2M0	0	HT, hyperlithuria	10/day × 50 years
7	73/M	T1N2M0	1	HT	25/day × 60 years
8	76/M	T2N1M0	0	None	20/day × 50 years
9	77/F	T3N0M0	1	Deafness	15/day × 57 years
10	78/M	T3N0M0	0	DM, ASO, old TB	20/day × 58 years
11	79/F	T2N2M0	1	None	None
12	79/F	T1N2M0	0	HT	5/day × 50 years

PS, Eastern Cooperative Oncology Group performance status; HT, hypertension; TB, tuberculosis; DM, type 2 diabetes mellitus; ASO, arteriosclerosis obliterans.

Table 2. Characteristics of patients who did not received EP with concurrent TRT

Patient	Age/sex	TNM stage	PS	Complications	Treatment	Reason[a]
1	70/M	T4N2M0	1	HT, renal dysfunction	CE and sequential TRT	Complication
2	70/M	T1N0M0	1	HT, DM	Surgery	Physician's decision
3	71/M	T3N2M0	1	HT	Best supportive care	Patient's refusal
4	72/M	T2N1M0	1	DM, renal dysfunction	CE and concurrent TRT	Complication
5	74/M	T3N2M0	1	HT, renal dysfunction	CE and sequential TRT	Complication
6	74/M	T2N1M0	2	DM, IP, chronic renal failure, dialysis, old TB	Chemotherapy	Complication
7	75/M	T3N2M0	3	HCC, chronic HCV	Best supportive care	Complication
8	77/M	T2N1M0	2	renal dysfunction, dementia	Chemotherapy	Complication
9	78/M	T1N1M0	1	SSS, HT, DM	Chemotherapy	Physician's decision
10	81/M	T2N2M0	1	renal dysfunction	Chemotherapy	Patient's refusal
11	82/M	T1N2M0	1	HT	Surgery	Physician's decision
12	84/M	T2N0M0	2	HT	Best supportive care	Patient's refusal
13	84/M	T2N0M0	2	HT, asthma, heart failure, cerebral infarction	Best supportive care	Complication

EP, etoposide and cisplatin; TRT, thoracic radiotherapy; CE, carboplatin and etoposide; IP, interstitial pneumonia; HCC, hepatic cancer; HCV, hepatitis C virus; SSS, sick sinus syndrome.
[a]The reason for not to select the combination therapy of etoposide and cisplatin with early concurrent TRT.

chemotherapy because of the development of pneumonitis of Grade 3 in one patient, a decline in renal function in one patient, suspected invasive aspergillosis in one patient and refusal by two patients. A dose reduction was necessary in seven patients because of the development of febrile neutropenia of Grade 3 in three patients, leukopenia of Grade 4 in two patients and nausea–vomiting of Grade 3 in two patients. The actual dose intensities of cisplatin and etoposide were 13.7 mg/m^2/week (68.7% of the planned dose intensity) and 52.4 mg/m^2/week (69.9% of the planned dose intensity), respectively.

Toxicities

Reported toxicities during the concurrent chemoradiotherapy are listed in Table 4. Leukopenia and neutropenia of Grade 3 or 4 were observed in all patients (100%), and eight patients (67%) had febrile neutropenia of Grade 3. Thrombocytopenia of Grade 3 or 4 was apparent in three patients (25%), with one patient requiring platelet transfusion. Reported toxicities during the consolidation chemotherapy are listed in Table 5. Leukopenia and neutropenia of Grade 3 or 4 were observed in 8 (67%) and 11 (92%) patients, respectively, and 4 patients (33%) developed febrile neutropenia of Grade 3. Anemia and thrombocytopenia of Grade 3 or 4 were each observed in four patients (33%). The major non-hematologic toxicity observed during the entire treatment period was nausea–vomiting. None of the patients developed esophagitis of Grade 3 or 4, but one patient manifested radiation pneumonitis of Grade 3 during consolidation chemotherapy. There were no treatment-related deaths.

Response and Survival

All 12 patients were evaluated for progression-free survival and overall survival. With a median follow-up time of 23.1 months (ranged, 7.2–45.0 months), six patients were still alive. An objective tumor response was observed in all patients: a complete response (CR) in five patients and a partial response in seven patients (Table 3). Prophylactic cranial irradiation was not routinely administered and delivered to three patients who achieved CR after completion of the planned treatment. The median progression-free survival time was 14.2 months, and the median overall survival time was 24.1 months.

Pattern of Relapse

Seven of the 12 patients relapsed, 3 with local regional failure inside the radiation field and 4 with distant failure. Among the latter four patients, three individuals manifested metastases in the brain as the sole site and the remaining individual had both local and distant failure including the liver.

DISCUSSION

Two meta-analyses have shown that the combined modality of chemotherapy and TRT improves the survival of individuals with LD-SCLC in comparison with chemotherapy alone (6,7). The schedule, dose and fractionation of TRT have been extensively investigated in patients with LD-SCLC in several randomized controlled trials (8,9). On the basis of two pivotal Phase III trials (10,11), etoposide and cisplatin

Table 3. Treatment details and outcome for the study cohort

Patient	Regimen (mg/m^2)	Total no. of cycles	Dose reduction in consolidation chemotherapy	DI of P (mg/m^2/week)	RDI of P (%)	DI of E (mg/m^2/week)	RDI of E (%)	Duration of TRT (days)	V20 (%)	Response	PFS (months)	Survival time (months)
1	E(100) + P(40)[a] + TRT	2	No	5.0	25.0	37.5	50.0	23	21	CR	14.0+	14.0+
2	E(100) + P(80) + TRT	4	Yes	17.2	86.0	73.7	98.2	19	25	CR	7.3+	7.3+
3	E(100) + P(80) + TRT	4	Yes	17.8	89.1	68.7	91.6	27	35	CR	10.7+	10.7+
4	E(100) + P(80) + TRT	4	Yes	15.7	78.4	61.6	82.1	30	13	PR	9.3	22.2
5	E(100) + P(80) + TRT	2	No	9.5	47.5	35.6	47.5	29	20	PR	4.3	11.4
6	E(100) + P(80) + TRT	4	No	19.6	98.2	73.7	98.2	29	30	PR	18.2	48.1+
7	E(100) + P(80) + TRT	4	No	17.2	86.2	64.6	86.2	26	27	PR	13.1	26.1+
8	E(80)[b] + P(80) + TRT	3	Yes	11.4	56.9	39.4	52.5	30	21	PR	8.3	17.1
9	E(100) + P(60)[a] + TRT	4	Yes	14.4	71.8	61.0	81.4	30	25	CR	20.6+	20.6+
10	E(100) + P(80) + TRT	4	Yes	13.1	65.5	49.1	65.5	28	NA	PR	14.4	16.5
11	E(100) + P(80) + TRT	2	Yes	7.9	39.5	30.5	40.6	33	26	PR	3.9	14.8
12	E(100) + P(80) + TRT	2	No	9.9	49.6	37.2	49.6	29	22	CR	14.1	27.2

DI, dose intensity; P, cisplatin; RDI, relative dose intensity; E, etoposide; V20, the percentage of lung volume receiving >20 Gy; PFS, progression-free survival; CR, complete response; +, without event; PR, partial response; NA, not available.
[a]Dose reduction because of a decline in renal function.
[b]Dose reduction because of physician's decision.

Table 4. Toxicities during concurrent chemoradiotherapy

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3 or 4 (%)
Leukopenia	0	0	2	10	100
Neutropenia	0	0	0	12	100
Anemia	2	1	0	0	0
Thrombocytopenia	0	2	2	1	25
Febrile neutropenia	—	—	8	0	67
Nausea–vomiting	2	2	2	0	17
Esophagitis	1	3	0	0	0
Appetite loss	5	2	2	0	17

Table 5. Toxicities during consolidation chemotherapy

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3 or 4 (%)
Leukopenia	0	2	4	4	67
Neutropenia	0	0	2	9	92
Anemia	2	4	3	1	33
Thrombocytopenia	2	2	2	2	33
Febrile neutropenia	—	—	4	0	33
Nausea–vomiting	2	5	2	0	17
Appetite loss	4	1	1	0	8
Radiation pneumonitis	3	0	1	0	8

chemotherapy with early concurrent twice-daily TRT is currently considered the standard treatment for patients with LD-SCLC. An age-specific subset analysis of one of these Phase III trials (11), in which patients received etoposide–cisplatin with early concurrent TRT, showed that the survival outcomes for individuals aged 70 years or older were similar to those of their younger counterparts, although the elderly patients experienced greater toxicity, in particular hematologic toxicity (12). However, given that the patients in this subgroup analysis were assigned either once- or twice-daily TRT, the significance of early concurrent twice-daily TRT in the management of elderly patients with LD-SCLC has remained undefined. No specific Phase III trial of elderly patients with LD-SCLC has been reported. We therefore retrospectively analyzed the feasibility and antitumor efficacy of etoposide–cisplatin chemotherapy with early concurrent twice-daily TRT for treatment of LD-SCLC in patients aged 70 years or older.

The median overall survival time of 24.1 months in our cohort is similar to that described for non-elderly patients with LD-SCLC in previous studies (10,11). This favorable survival outcome may be attributable to the strict selection of elderly patients in good general condition; all 12 patients in the present study had normal organ function, an Eastern

Cooperative Oncology Group performance status of 0 or 1 and no severe co-morbidity. Given that the elderly are more likely to have reduced organ function as well as concomitant morbidities or medications, the general condition of elderly SCLC patients is worse than that of younger patients (1). Among LD-SCLC patients, increasing age was found to be significantly associated with a lower likelihood of receiving combined chemoradiotherapy (7). Indeed, in the present study, only 12 (48%) of the 25 identified elderly patients with LD-SCLC were treated with etoposide–cisplatin and early concurrent twice-daily TRT.

Despite the strict selection of patients, highly treatment-related toxicity was observed in our cohort. The major adverse events were hematologic toxicities, with neutropenia of Grade 4 being apparent in all patients (100%) and febrile neutropenia of Grade 3 in eight patients (67%) during the first cycle of concurrent chemoradiotherapy. The previous analysis of the outcome of elderly patients in the Phase III study in which individuals received etoposide–cisplatin chemotherapy with early concurrent once- or twice-daily TRT found statistically significant differences not only in the incidence of hematologic toxicity (Grade 4 or 5: 61% in younger patients vs. 84% in patients aged 70 years or older, $P < 0.01$) but also in that of treatment-related deaths (1% vs. 10%, respectively, $P = 0.01$) (12). Although no treatment-related deaths were observed in the present study, severe hematologic toxicity was consistent with that in this foregoing analysis (12). In addition, maintenance of the optimal dose intensity of chemotherapy was difficult in our cohort because of frequent dose reductions or treatment delays due to hematologic or infection-related toxicities. Indeed, the actual dose intensity was <70% of the planned dose intensity for both etoposide and cisplatin in the present study, a value much smaller than that for non-elderly patients in a previous Phase III study (>90% for both agents) (10). On the other hand, the toxicity of radiotherapy was acceptable in our study, with all patients completing TRT within a median of 29 days (range, 19–33). None of our patients developed radiation esophagitis of Grade 3 or higher. With regard to pulmonary complications, one patient developed radiation pneumonitis of Grade 3. A recent meta-analysis of randomized trials in which patients with LD-SCLC were treated with chemoradiotherapy reported that the time between the first day of chemotherapy and the last day of radiotherapy was an important prognostic factor for LD-SCLC, with the survival advantage being more pronounced if the TRT was completed in <30 days (13). In the present study, a shorter time to completion of TRT may also be associated with our favorable survival outcome. However, elderly patients with LD-SCLC must be carefully selected and monitored during treatment because of the increased potential for the development of treatment-related morbidity and mortality.

The optimal therapeutic strategy for elderly patients with LD-SCLC remains a matter of debate. Despite the highly treatment-related toxicity, patients in our cohort derived a survival benefit with no treatment-related deaths, suggesting that the full-dose chemoradiotherapy may represent a valid option for 'fit' elderly patients with adequate organ function. Since the general condition of elderly patients varies widely from patients to patients, prospective evaluation and definition of 'fit' elderly patients who are candidates for full-dose chemoradiotherapy are important. Research is also needed to develop modified chemoradiotherapy regimens that are less toxic for the elderly. A modified chemotherapy schedule designed to reduce toxicity for elderly patients with LD-SCLC was evaluated in a Phase II trial, with two cycles of a chemotherapy regimen (oral etoposide and carboplatin) combined with early concurrent twice-daily TRT being found to have acceptable toxicity and to produce promising results, with a 5-year survival rate of 13% (14). A recent Phase III trial specifically designed for elderly or poor-risk patients with extensive-disease SCLC found that split doses of cisplatin plus etoposide (cisplatin at 25 mg/m^2 and etoposide at 80 mg/m^2 on days 1–3) could be safely administered and were effective (15). Such split-dose chemotherapy might also be suitable for the treatment of patients with LD-SCLC. We are currently conducting a clinical trial to evaluate the feasibility of etoposide at 80 mg/m^2 and cisplatin at 25 mg/m^2 on days 1–3 with early concurrent twice-daily TRT for elderly patients with LD-SCLC.

The overall findings of the present study suggest that administration of full-dose chemotherapy and early concurrent twice-daily TRT is highly myelotoxic for elderly patients with LD-SCLC. Development and assessment of modified treatment regimens with reduced toxicity are thus warranted for such patients.

Conflict of interest statement

None declared.

References

1. Sekine I, Yamamoto N, Kunitoh H, Ohe Y, Tamura T, Kodama T, et al. Treatment of small cell lung cancer in the elderly based on a critical literature review of clinical trials. *Cancer Treat Rev* 2004;30:359–68.
2. Gridelli C, Langer C, Maione P, Rossi A, Schild SE. Lung cancer in the elderly. *J Clin Oncol* 2007;25:1898–907.
3. Morita T. A statistical study of lung cancer in the annual of pathological autopsy cases in Japan, from 1958 to 1997, with reference to time trends of lung cancer in the world. *Jpn J Cancer Res* 2002;93:15–23.
4. Socinski MA, Bogart JA. Limited-stage small-cell lung cancer: the current status of combined-modality therapy. *J Clin Oncol* 2007;25:4137–45.
5. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. *J Clin Oncol* 2004;22:4626–31.
6. Pignon JP, Arriagada R, Ihde DC, Johnson DH, Perry MC, Souhami RL, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med* 1992;327:1618–24.
7. Ludbrook JJ, Truong PT, MacNeil MV, Lesperance M, Webber A, Joe H, et al. Do age and comorbidity impact treatment allocation and outcomes in limited stage small-cell lung cancer? A community-based population analysis. *Int J Radiat Oncol Biol Phys* 2003;55:1321–30.

8. Bonner JA, Sloan JA, Shanahan TG, Brooks BJ, Marks RS, Krook JE, et al. Phase III comparison of twice-daily split-course irradiation versus once-daily irradiation for patients with limited stage small-cell lung carcinoma. *J Clin Oncol* 1999;17:2681–91.
9. Schild SE, Bonner JA, Shanahan TG, Brooks BJ, Marks RS, Geyer SM, et al. Long-term results of a phase III trial comparing once-daily radiotherapy with twice-daily radiotherapy in limited-stage small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2004;59:943–51.
10. Turrisi AT, 3rd, Kim K, Blum R, Sause WT, Livingston RB, Komaki R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 1999;340:265–71.
11. Takada M, Fukuoka M, Kawahara M, Sugiura T, Yokoyama A, Yokota S, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. *J Clin Oncol* 2002;20:3054–60.
12. Yuen AR, Zou G, Turrisi AT, Sause W, Komaki R, Wagner H, et al. Similar outcome of elderly patients in intergroup trial 0096: cisplatin, etoposide, and thoracic radiotherapy administered once or twice daily in limited stage small cell lung carcinoma. *Cancer* 2000;89:1953–60.
13. De Ruysscher D, Pijls-Johannesma M, Bentzen SM, Minken A, Wanders R, Lutgens L, et al. Time between the first day of chemotherapy and the last day of chest radiation is the most important predictor of survival in limited-disease small-cell lung cancer. *J Clin Oncol* 2006;24:1057–63.
14. Jeremic B, Shibamoto Y, Acimovic L, Milisavljevic S. Carboplatin, etoposide, and accelerated hyperfractionated radiotherapy for elderly patients with limited small cell lung carcinoma: a phase II study. *Cancer* 1998;82:836–41.
15. Okamoto H, Watanabe K, Kunikane H, Yokoyama A, Kudoh S, Asakawa T, et al. Randomised phase III trial of carboplatin plus etoposide vs split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer: JCOG 9702. *Br J Cancer* 2007;97:162–9.

Radiotherapy and Oncology 92 (2009) 260–265

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Phase II randomised trial

A randomized phase II study of cisplatin/5-FU concurrent chemoradiotherapy for esophageal cancer: Short-term infusion versus protracted infusion chemotherapy (KROSG0101/JROSG021)

Yasumasa Nishimura [a,*], Michihide Mitsumori [b], Masahiro Hiraoka [b], Ryuta Koike [a], Kiyoshi Nakamatsu [a], Masashi Kawamura [c], Yoshiharu Negoro [d], Kazuhisa Fujiwara [e], Hideyuki Sakurai [f], Norio Mitsuhashi [g]

[a] Department of Radiation Oncology, Kinki University School of Medicine, Osaka, Japan
[b] Department Radiation Oncology & Image-applied Therapy, Kyoto University Graduate School of Medicine, Japan
[c] Department of Radiology, Nara Social Insurance Hospital, Japan
[d] Department of Radiology, Fukui Red Cross Hospital, Japan
[e] Department of Radiology, National Hospital Organization Kyoto Medical Center, Japan
[f] Department of Radiation Oncology, Gunma University Graduate School of Medicine, Japan
[g] Department of Radiology, Tokyo Women's Medical University School of Medicine, Japan

ARTICLE INFO

Article history:
Received 7 November 2008
Received in revised form 29 December 2008
Accepted 29 December 2008
Available online 21 January 2009

Keywords:
Esophageal cancer
A randomized phase II study
Chemoradiotherapy

ABSTRACT

Purpose: A randomized phase II study was conducted to compare the toxicity and efficacy of combining short-term chemotherapy (CT) or protracted CT with radiotherapy (RT) for esophageal cancer.
Materials and methods: Eligible patients were <75 years and with performance status (PS) of 0–2, and had stages II–IVA esophageal cancer. Two cycles of cisplatin 70 mg/m^2 for 1 day and 5FU 700 mg/m^2 for 5 days (arm A) or cisplatin 7 mg/m^2 for 10 days and 5FU 250 mg/m^2 for 14 days (arm B) were given with RT of 60 Gy/30 fractions/7 weeks (1-week split).
Results: Of 91 patients enrolled, 46 were randomized to arm A and 45 to arm B. Two cycles of CT were given concurrently with RT for 89% in arm A and for 71% in arm B with significant difference ($P = .031$). The 2- and 5-year overall survival rates for arm A were 46% and 35%, while those for arm B were 44% and 24%, respectively, without significant difference. The 2- and 5-year progression-free survival rates for arm A were 30% and 30%, while those for arm B were 29% and 12%, respectively.
Conclusions: Protracted infusion CT with RT provides no advantage over standard short-term infusion CT with RT for esophageal cancer.
 Radiotherapy and Oncology 92 (2009) 260–265

For locally advanced esophageal cancer, a significant improvement in local control and overall survival was achieved with concurrent chemoradiotherapy (CRT) as compared with radiotherapy (RT) alone [1–3]. In the phase III randomized trial (RTOG-8501), four cycles of full-dose 5-FU/cisplatin were concurrently combined with 50 Gy of RT [1,2]. However, the incidence of local failure was still as high as 44–54%. To improve these results, a phase III trial comparing standard dose RT (50.4 Gy) and high-dose RT (64.8 Gy) concurrently combined with 5-FU/cisplatin was conducted [4]. In the INT0123 trial, the high-dose RT arm did not offer a survival benefit compared with the standard RT dose arm [4]. Thus, at present, four cycles of full-dose 5-FU/cisplatin combined with 50 Gy of RT are a standard CRT regimen for advanced esophageal cancer in the USA.

In Japan, surgical resection is preferably performed for esophageal cancer with the T1-3N0, 1M0 disease, staged according to the 1997 International Union Against Cancer TNM classification (UICC 1997). Thus, many patients to be treated with CRT in Japan have T4 squamous cell carcinomas. Our previous study of concurrent CRT with the protracted infusion of cisplatin and 5-FU for T4 esophageal cancer with or without a fistula showed a 2-year survival rate of 27% for patients with stage III disease [5]. Several investigators also showed promising clinical results of low-dose protracted infusion CT combined with full-dose RT of 60–66 Gy for locally advanced esophageal squamous cell carcinomas [5–10]. Low-dose protracted infusion of 5-FU or 5-FU plus cisplatin was proposed to decrease the acute toxicities of concurrent CRT [8,10]. In addition, to obtain maximum radiosensitization by CT, daily administration of low-dose protracted CT combined with RT may be better than full-dose short-term CT plus RT.

To test the hypothesis, a randomized phase II study was conducted to compare the relative toxicity and efficacy of combining

* Corresponding author. Address: Department of Radiation Oncology, Kinki University School of Medicine, 377-2, Ohno-Higashi, Osaka-Sayama, Osaka, Japan.
E-mail address: ynishi@med.kindai.ac.jp (Y. Nishimura).

0167-8140/$ - see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.radonc.2008.12.012

full-dose short-term CT or low-dose protracted CT with RT for esophageal cancer.

Patients and methods

Investigational design

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

Eligibility criteria

Inclusion criterion was histologically confirmed esophageal squamous cell carcinoma or adenocarcinoma with stages II–IVA (UICC 1997). Only patients with no prior therapy, age <75 years, performance status (PS) of 0–2, and adequate bone marrow, hepatic and renal functions were eligible. Patients with a serum creatinine level <1.5 mg/dl, creatinine clearance value ≧60 ml/min, white blood cell count (WBC) ≧4000/mm^3, hemoglobin (Hb) ≧10 g/dl, and platelet count ≧100,000/mm^3 were eligible. Patients treated with thoracotomy alone for unresectable tumors were eligible, but patients after complete or incomplete resection of tumors were ineligible. Multiple esophageal tumors were also eligible, but tumors with fistula were excluded. Exclusion criteria were patients with serious infection, uncontrolled heart disease, uncontrolled diabetes mellitus, suffering from other cancers within 3 years, and esophageal stent.

Staging work-up included clinical examination, plain chest XP, upper gastrointestinal fiberscope with biopsies, an upper gastrointestinal series, and thoraco-abdominal computed tomography scan. Computed tomography was performed with contrast enhancement whenever possible. Endoscopic ultrasonography (EUS), bronchoscopy, brain MRI or computed tomography, or bone scintigraphy was performed optionally when available. Although EUS was performed to determine the depth of tumors for most T1 or T2 tumors, EUS was not done for more advanced tumors due to stenosis of the esophageal lumen. Positron emission tomography (PET) was not performed for most patients because availability of PET was limited in most participating institutions during the study period.

Design and random assignment

All eligible patients were registered at the office of the primary investigator. The patients were randomly assigned either to arm A (full-dose short-term CT) or to arm B (low-dose protracted CT) by customized randomization software; patients were stratified according to tumor length (≤6 cm vs. >6 cm), clinical stage (stages IIA, IIB vs. stages III, IVA), and institution. Because the Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 was not available in 2001, acute toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) (version 2.0), and late toxicity was graded according to the RTOG/EORTC Late Radiation Morbidity Scoring Scheme.

Treatment: radiation and chemotherapy

Two courses of concurrent CT were combined with RT of 60 Gy/30 fractions/7 weeks (1-week split at the 4th week) (Fig. 1). A 6–15 MV X-ray was used. The daily fractional dose of RT was 2 Gy administered 5 days a week. The primary tumor and the involved

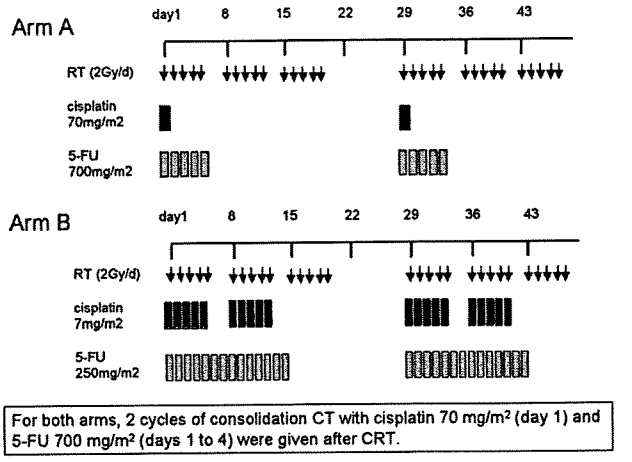

Fig. 1. Treatment design of the KROSG-0101/JROSG-021. CT, chemotherapy; RT, radiation therapy. Arm A full-dose short-term CT with RT. Arm B low-dose protracted CT with RT.

lymph nodes of ≧0.5 cm in the shortest diameter on computed tomography were gross tumor volume (GTV). The initial 40 Gy was delivered to clinical target volume 1 (CTV1), and the final 20 Gy was delivered to a reduced volume defined as clinical target volume 2 (CTV2), including the GTV with a margin (lateral and anterior/posterior directions 0.5 cm; cranio-caudal direction 1 cm). CTV1 for cervical, upper, and middle thoracic esophageal cancers included the GTV with a margin plus the supraclavicular and mediastinal lymph nodal areas (T-shaped field). For cervical esophageal cancer, lower mediastinal lymph nodal areas were excluded from CTV1. For tumors originating in the lower thoracic esophagus, CTV1 included the GTV with a margin plus the mediastinal and perigastric/celiac lymph nodal areas (I-shaped field).

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

At 40 Gy, the RT field was reduced to the PTV2. The total RT dose delivered to the spinal cord was limited to 40 Gy, usually by using oblique opposed fields. RT was stopped if grade-4 leukocytopenia, thrombocytopenia of <20,000/mm^3, grade-4 esophagitis, or a fever of >38 °C was observed.

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

For both arms, the second to fourth cycles of CT were started when WBC count of ≧3000/mm^3, a platelet count of ≧75,000/mm^3, and a creatinine level of <1.5 mg/dl were confirmed. CT was postponed if grade-3 leukocytopenia or thrombocytopenia was noted. When grade-4 hematological toxicities or grade-3 non-hematological toxicities excluding nausea, vomiting, and esophagitis were observed in the first course of CT, 80% dose for both 5-FU and cisplatin was used in the second course of CT.

Follow-up

The local response was evaluated 2–4 weeks after the CRT by barium swallow, esophageal endoscopy with biopsy, and thoracoabdominal computed tomography scan with contrast enhancement. Esophagography or endoscopy was performed every 2–4 months for asymptomatic patients, and any clinically suspected tumor recurrence required biopsy and histopathological confirmation. Computed tomography scans were obtained at 3- to 6-month intervals, and used to evaluate the recurrence of primary tumors and regional lymph nodes. When tumor progression or recurrence was noted, salvage treatment was mandatory for the attending physicians.

Endpoints

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

Statistical analysis

In the RTOG-8501 trial, in which T4 tumors were not included, the 2-year survival rate of patients treated with 50 Gy CRT was 36% [1,2]. In one Japanese phase II trial for advanced esophageal cancer with T4 or distant lymph node metastasis, the 2-year survival rate of patients treated with 60 Gy CRT was 31.5% [11]. As our protocol included T4 tumors, the baseline 2-year survival rate was expected to be 35%. In this protocol, two arms were studied. The sample size for a randomized phase II trial was calculated as 35 patients per arm, with a probability of 0.80 of selecting the treatment schedule that had a 2-year survival rate of 35% + 10% = 45% [12]. In the protocol, the sample size was estimated as 45 patients per arm supposing several ineligible or dropped cases.

The probability of survival was estimated using the Kaplan–Meier method with statistical significance assessed by the log-rank test. Data were analyzed according to the intent-to-treat principle. Survival was calculated from the date of randomization. For overall survival, deaths due to any cause were considered. For progression-free survival, any local or distant tumor progression and deaths due to any causes were considered as an event. The difference in compliance rates was assessed by the chi-squared test.

Results

From December 2001 to June 2006, 91 patients were registered. Forty-six patients were randomly assigned to arm A, and 45 were assigned to arm B (Fig. 2). Although all the 91 patients were eligible at registration, bone metastasis was detected 13 days after registration by bone scintigraphy in one patient in arm A. This patient was also included according to the intent-to-treat analysis. Table 1 shows the characteristics of the 91 patients and treatment parameters according to treatment arm. There were no significant differences in patient characteristics and treatment parameters between the two arms.

Table 2 shows the compliance rates according to treatment arm. The planned dose of 60 Gy was delivered to 88 patients (97%), while RT was terminated at 30 Gy for three patients. Two patients

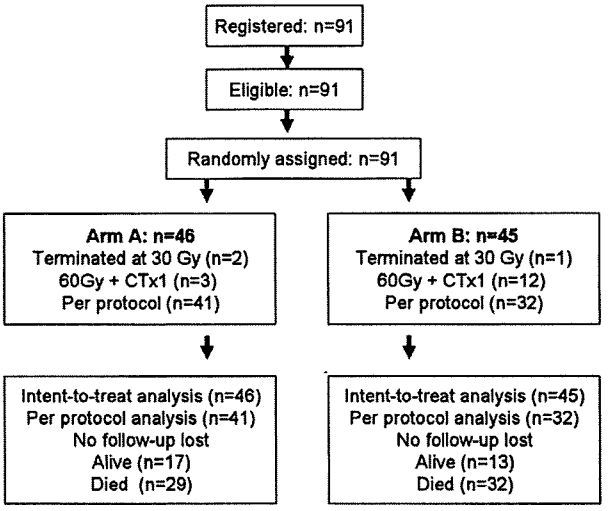

Fig. 2. The flow diagram of the patients registered.

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

Arm	A (n = 46)	B (n = 45)
Age (median)	45–74 (63)	48–74 (63)
Male/female	41/5	41/4
PS: 0/1/2	23/20/3	22/21/2
Body surface of patients		
Range (median)	1.20–1.97 m^2 (1.59)	1.15–1.90 m^2 (1.52)
Comorbidity	11	11
Double cancer	2 (1)[a]	5 (3)[a]
Histology		
Sq/Ade	45/1	45/0
Primary site		
Ce/Ut/Mt/Lt	6/13/15/12	4/15/19/7
Length of the tumor		
≤6 cm/>6 cm	23/23 (2–12 cm)	21/24 (1–19 cm)
TNM stage (UICC 1997)		
T1/2/3/4	4/7/14/21	4/9/13/19
N0/1	8/38	9/36
St 2/3/4a	11/30/5	11/27/7
Shape of initial RT field		
T-field	38	38
I-field	8	7
Length of initial RT field		
Range (median)	18–35 cm (26)	19–33 cm (26)

Note: There was no significant difference between arms for any of the characteristics. Sq, squamous cell carcinoma; Ade, adenocarcinoma; Ce, cervical esophagus; Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus.

[a] Detected other cancers in the follow-up period of CRT for esophageal cancer.

in each arm underwent surgery due to poor tumor regression by 30 Gy of CRT. The remaining one patient in arm A refused further treatment due to grade-3 acute toxicities and worsening of depression, and committed suicide at the 67th day of the protocol treatment.

Although the full compliance rate was higher in arm A (54%) than in arm B (36%), there was no significant difference. When patients with full and partial compliance were combined as per the protocol set, the rate of per protocol in arm A (89%) was significantly higher than that in arm B (71%) (P = 0.031). Because of prolonged leukopenia (<3000/mm^3), second CT could not be started during RT as a protocol for eight patients in arm B, while there was only one such patient in arm A (Table 2). As the patients in