in 8 fractions with a median follow-up of 24 months [49]. This has prompted the initial investigation of using SBRT in operable patients [15]. In a multicentric approach, it could be demonstrated that patients in good condition have an even higher benefit than patients with severe comorbidity.

Within the following years, SBRT became more popular in areas besides the northern European countries and Japan. In all those clinical trials, the major focus was on local control. The authors report values of about 90%: 87% (30/37) for 60 Gy in 3 fractions with a median follow-up of 15 months [42], 85% for 48–60 Gy in 8 fractions with a median follow-up of 17 months [52], 95% for 45–56.2 Gy in 3 fractions with a median follow-up of 10 months [53], 90% for 30–40 Gy in 4 fractions with a median follow-up of 21 months [65], and 97% (44/45) for 48 Gy in 4 fractions with a median follow-up of 22–30 months [39]. In the most recent trials, with even higher BED of more than 150 Gy (with an α/β-relation of 3), local control reaches up to 98% [66, 63] (table 3).

A few publications exist on single fraction SBRT (radiosurgery), with doses between 15 and 40 Gy. Only two trials from Germany document the feasibility of this approach, whereas the other trials [64, 67, 68] lack both a good quality and long-term follow-up. In the trials from Hof et al. [47] and Fritz et al. [58], local control is at a similar level as with hypofractionated SBRT at 2 years when at least 26 Gy have been applied, but decreasing to 67.9 and 81% at 3 years. A comparison of the BED of all available concepts explains the difference, and is demanding for further dose escalation trials especially in radiosurgery.

However, the definition of local control after radiotherapy is difficult independent of the fractionation schedule, because local tumor failure and radiation-induced lung damage (RILD) cannot be clearly delineated. A so-called mass-like shadow which cannot be delineated from residual tumor has been reported by several authors [69–71]. To optimize follow-up, FDG-PET-CT scan may be introduced, but conclusive data are still lacking (fig. 3).

Even though the definition of local control is different between each trial, a BED larger than 100 Gy may be effective for SBRT of solitary lung cancer with a local control rate of more than 85% [15]. We recommend calculations for the PTV-including isodose, especially for calculation models using a dose prescription to less than the 80%-surrounding isodose.

Survival Data

The survival rates of stage IA (T1N0M0) and stage IB (T2N0M0) lung cancer have not been reported separately by several authors. In a series of stage IA cancer, the 1- and 5-year local relapse-free survival rates were 100 and 95%. The disease-free survival rates after 1, 3 and 5 years were 80, 72 and 72%, respectively, and the

Table 4. Side effects from different recent trials of SBRT in early NSCLC

First author (year)	BED	2 Gy equivalent dose	Lung toxicity >II° %	Pneumonitis I–II° %	Other toxicity
Ng (2008) [59]	270–297	162–178.2	0	n.g.	3 rib fractures
Takeda (2009) [63]	216.7	130	5	3	
Onishi (2007) [15]	252–330	151.2–198	5.4	5.5	0.8% esophagitis, 1.6% rib fracture
Onimaru (2008) [60]	117–161.3	70.4–96.8	~10		1 pleural effusion
Guckenberger (2007) [30]	186.7–251.3	112–150.8	0.6	12; >50% in CT scan	2 pneumothorax, 16% pleural effusion, 1 esophageal ulceration
Timmerman (2007) [57]	460–550	276–330	n.g.	n.g.	In total toxicity >II: peripheral tumors:17; central tumors:46
Brown (2007) [64]	90–371.3	54–222.8	~2	~5	3 esophagitis, 5 pneumothorax by fiducial implantation
Fritz (2008) [58]	216	129.6	0	75 (only on CT scan)	25% pleural effusion, 3 rib fractures
Hof (2007) [47]	92.2–216	55.3–129.6	0	64 (mostly on CT scan only)	
Baumann (2006) [31]	270	162	~5	16	21% toxicity III° in total, 2 pain, 1 rib fracture, 13 pleural effusion
Uematsu (2001) [51]	327.8–460	196.7–276	0	only on CT scan in most patients	
Zimmermann (2006) [32]	72–193.7	43.2–116.2	6.4	39.1 with symptoms	3.4% pleural effusion, 5.0% rib fractures
Wulf (2005) [33]	270–407	162–244.2	0	6	13% mild pain, fever, chills
Hata (2007) [40]	13–180	79.8–108	0	only in CT scan in most patients	3 mild hematologic, 2 chest wall pain
Salazar (2008) [62]	150.8–173.3	90.5–104	0	6	2 esophagitis, 1 pleural effusion

mBED = minimal biological effective dose ($\alpha/\beta = 3$) in the PTV.

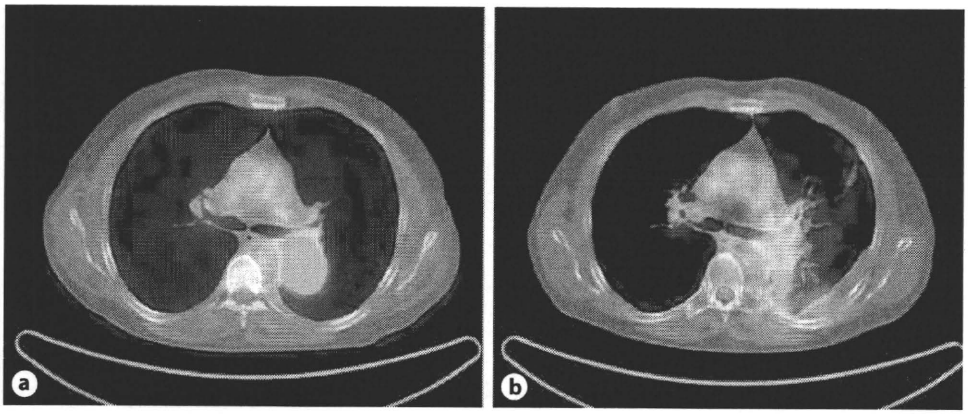

Fig. 3. NSCLC of the left lower lobe. T2/N1 tumor. FDG-PET-CT scan. **a** Before SBRT. **b** 12 months after SBRT with 5 × 7.0 Gy (calculated on the 60% isodose). Local lung fibrosis. Complete remission. SUV in PET scan <2. Courtesy of Institute of Nuclear Medicine, MRI, Munich.

overall survival rates were 93, 83 and 83%, respectively. In stage IB cancer, the local relapse-free survival rates were 100%. The disease-free survival after 1, 3 and 5 years were 92, 71 and 71%, respectively, and the overall survival rates were 82, 72 and 72%, respectively [39]. Onishi et al. [15] recently reported the results for 13 institutions in Japan, which summarized 245 patients: 155 with stage IA lung cancer and 90 with stage IB lung cancer. There were 87 operable and 158 inoperable patients, and their results showed that the intercurrent death rate was especially high in the inoperable patient group. Moreover, the 5-year survival rates of operable patients irradiated with more than BED = 100 Gy was 70.8% for the whole group, with 72.3% for stage IA and 65.9% for stage IB, and their clinical results were as good as those for surgery [15] (table 3).

These survival rates should be compared with the results of surgery; however, the results of SBRT may differ depending on how many patients of each groups are operable and inoperable, and how many of them have central and peripheral tumors. Additionally, the clinical staging is still less precise than the intraoperative one, mainly due to the detection of subclinical tumor spread around the primary and the higher detection rate of subclinical lymph node metastases by resection of N1 and N2 sites.

Side Effects

The great concern of pulmonary toxicity with this SBRT treatment was relieved by the very low rates of complications in early studies. Compared to conventional

radiotherapy, lung toxicity occurs relatively late after SBRT (e.g. 9–12 months or more). The most serious toxicity after SBRT for lung tumors is predominantly related to the bronchi and bronchioles located in the vicinity of the treated tumor. Frequently, dramatic imaging changes can be seen on CT scans consisting of in-field and downstream consolidation and fibrosis. Nevertheless, symptomatic radiation pneumonitis which consists of inflammation and fluid extravasation within the terminal bronchioles and alveoli is seen less frequently after SBRT than with conventional radiotherapy. Drop in oxygen exchange parameters, including diffusing capacity and arterial oxygen tension can be seen soon after treatment, but are scarce. Most pulmonary complications are less than NCI-CTC version 2.0 grade 2 (table 4).

The effects of a hypofractionated dose on the main bronchus, pulmonary artery, heart and esophagus have not been followed up for a sufficiently long time. However, a few serious complications have recently been reported by several institutions in Japan [72]. These complications include grade 5 pulmonary complications, radiation pneumonitis, hemoptysis and radiation esophagitis. Lethal pulmonary bleeding and esophageal ulcer have been previously reported by several authors. Timmerman [43] recently reported a series of complications with SBRT. Most cases of grade 5 radiation pneumonitis were accompanied by interstitial pneumonitis. Cases of interstitial pneumonitis should be carefully considered. Thoracocutaneous fistula was reported in a patient with previous tuberculosis history. Acute cholecystis was reported in a patient with gallstones who had been pressed with an abdominal press board at the time of SBRT. Finally, it is not uncommon for patients to experience chest wall pain months after SBRT, especially if treating tumors adjacent to the pleura, as a sign of intercostal neuralgia. Some, but not all, of these patients will have pleural effusions associated with chest wall pain. The problem seems to be mostly self-limited and conservative management with over-the-counter analgesics or anti-inflammatory medicines is typically effective. Some of those patients later develop rib fractures, which should be strongly separated from local tumor progression, either by FDG-PET scan or biopsy. When the esophagus, trachea or main bronchus are near the target, there is a higher risk of early dysphagia, severe cough, and late strictures [43, 73]. Therefore, central hilar tumors adjacent to mediastinal organs should be carefully considered for SBRT, or only treated with lower single fraction doses [32, 74] (table 4).

Comparison of SBRT with Surgical Data

Less than 25% of all patients diagnosed with lung cancer will present with early stage disease (less than 10% in stage I). These patients have the greatest hope for cure following standard procedure of resection. Survival varies, with reports on

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PET and/or spirometry can be performed. The first examination is usually 6 weeks after irradiation followed by further examinations every 3–6 months. The results and especially the acquired images should be sent to and co-evaluated by the treating physician, because assessment of changes such as distinguishing scar tissue and inflammation from tumor (recurrence) might be difficult and requires a certain amount of experience [57] (fig. 2). Even with positive FDG-PET scan for months and years after SBRT, false-positive interpretation should be excluded by biopsy. Pneumonitis and pneumonia can pretend tumor progression, with SUV up to 7.

Future

While anatomical surgical resection has long been the standard treatment for stage I patients, SBRT could offer a less toxic, less costly, and more convenient alternative. With the promising preliminary results from single institutions, the maturing evaluation of late radiation toxicity, and the conduct of multicenter prospective trials in both operable and medically inoperable patients, SBRT shows considerable promise to be one of the most important recent innovations for effectively treating patients with primary and secondary lung cancer. However, prospective testing is required to insure that cure rates are not compromised. Clinical prospective phase II trials testing SBRT in operable patients is ongoing or planned in Japan (Japan Clinical Oncology Group, JCOG, protocol 0403) and the United States (Radiation Therapy Oncology Group, RTOG, protocol 0618), and a comparison of SBRT with surgery in the US. In medically inoperable patient groups, a Nordick multi-institutional consortium is comparing 3 fraction SBRT to conventional radiotherapy in an ongoing randomized phase II study. The RTOG has finished a phase II study of 3 fraction SBRT for peripheral tumors and is planning a phase I study with 5 fractions in patients with central tumors (RTOG 0633), and the JCOG is finishing a phase II study using a 4-fraction treatment for peripheral tumors and is planning a phase II study using a higher dose specifically for T2 tumors. Further trials in planning stages at the RTOG include the addition of targeted systemic therapies to SBRT (RTOG 0624) [12].

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

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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.

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

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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

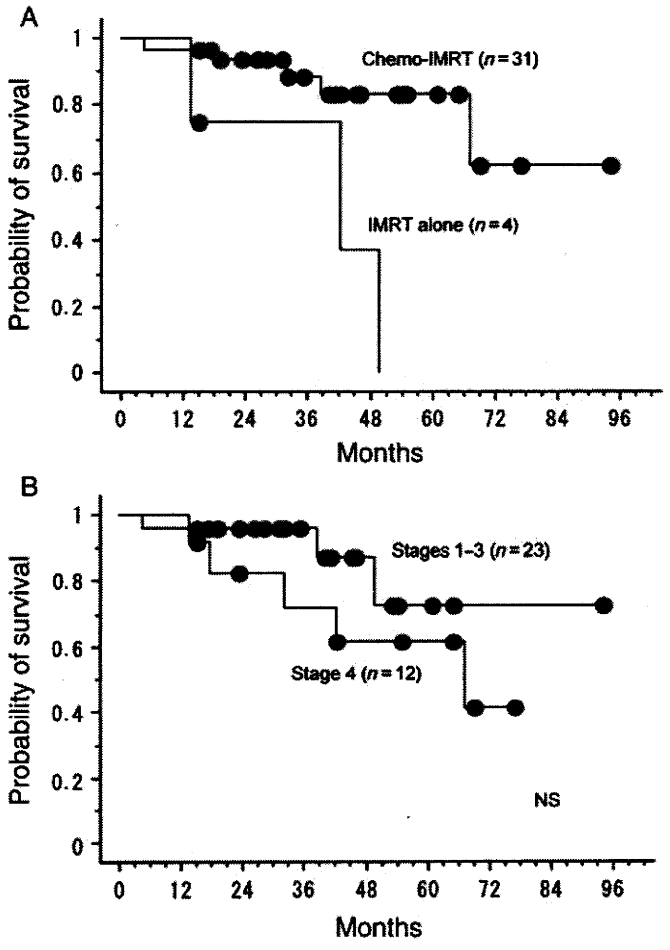

Figure 1. (A, B) Overall survival rates for 35 patients according to (A) concurrent chemotherapy or (B) clinical stage.

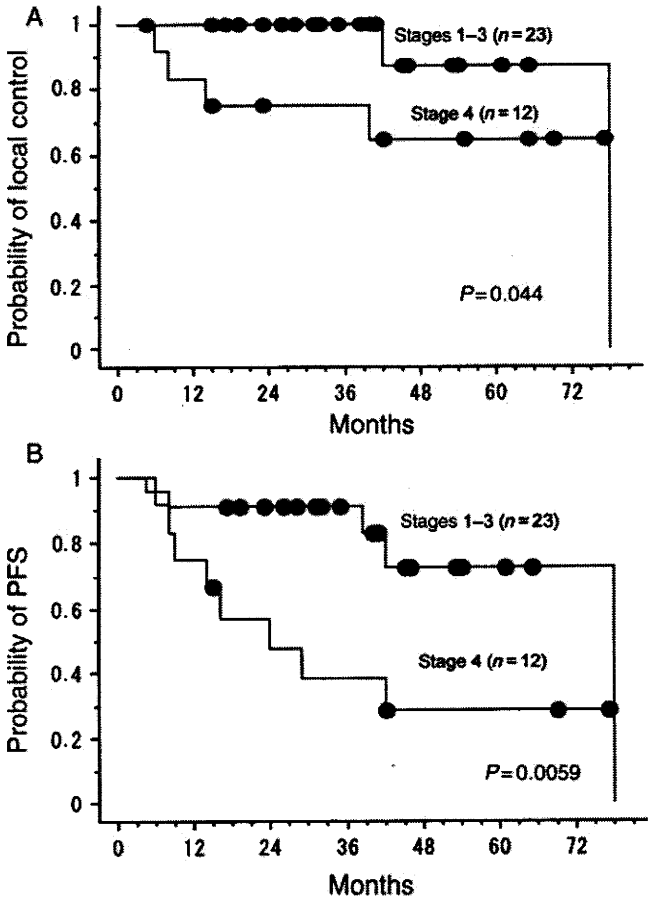

Figure 2. (A) Local control rates and (B) progression-free survival rates for 23 patients with Stage 1–3 disease and 12 patients with Stage 4 disease.

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.