($n = 17$). Eleven patients received CTx with a reduction in dose from the first cycle, seven patients to 80%, three patients to 70%, and one patient to 66%, because of advanced age and/or comorbidities. Because unified method was not established, how to reduce in CTx dose was at the discretion of the mainly treating oncologist, considering of individuals.

Compliance of treatment

Twenty patients (91%) completed the planned RT. The median total irradiated dose was 50.4 Gy (range: 45.4–71.4 Gy), and the median radiation duration time was 41 days (range: 36–66 days). Two patients did not complete RT for the following reasons. One patient receiving involved-field RT discontinued treatment at 45.4 Gy because of Candida septicemia; this patient subsequently died. The other receiving extended-field RT had treatment interrupted for 23 days because of severe febrile neutropenia; an extra 10 Gy of RT was added on, resulting in a total treatment duration of 66 days. This patient developed a local recurrence 4.7 months later.

However, only two patients (9%) were able to complete four cycles of CTx without an additional dose reduction. Additional dose reductions or alterations were required for 6 of 10 patients with a total of two cycles, for 2 of 5 patients with a total of three cycles, and for 1 of 3 patients with a total of four cycles. Some alterations were made because of mild renal dysfunction: administration of only 5-FU alone ($n = 1$), dividing of CDDP dose into 5 days ($n = 1$), reduction in NDP dose ($n = 1$), and switch to NDP from CDDP ($n = 1$). The main reasons for inability to complete planned CTx were adverse events of grade 3 or higher, such as leukocytopenia or thrombocytopenia.

Treatment outcome and survival

It was possible to evaluate treatment effects in 20 of the 22 patients, and all patients achieved a response. To evaluate the response, almost all of the patients underwent endoscopy, biopsy, CT of chest and abdomen, and [18F] fluoro-2-deoxy-D-glucose positron emission tomography approximately a month after completing of RT, where possible.

Complete response (CR) was achieved in 13 patients (59%), and 11 of them (50%) gained pathological CR by endoscopic biopsy. The response rate was 91% (in 21 patients). For the remaining two patients, a response could not be determined because of treatment-related death (TRD).

The 3-year DFS rate was 33.3 ± 11.4%, with a median DFS period of 8.5 ± 0.9 months. The overall survival (OS) rate at 1, 2, and 3 years was 44.3 ± 10.8%, 34.5 ± 10.4%, and 25.9 ± 10.8%, respectively, with a median OS period of 8.6 ± 2.0 months. The 1-,
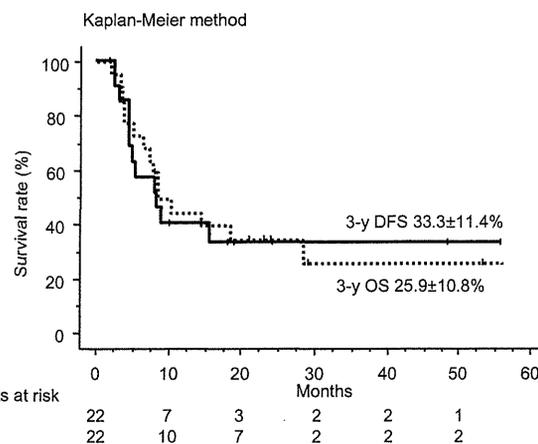

Fig. 1   Survival curves showing overall survival (OS; solid line) and disease-free survival (DFS; dashed line).

2-, and 3-year cause-specific survival rates were 60.4 ± 11.7%, 47.0 ± 12.4%, and 35.2 ± 13.8%, respectively, with a median cause-specific survival period of 18.6 ± 9.3 months. The Kaplan–Meier survival curves of OS and DFS are presented in Figure 1.

Univariate analyses of the DFS rate were done according to age; tumor location; T, N, M, and TNM stage; pretreatment KPS; tumor length; number of total cycles of CTx; and radiation dose. Among these factors, T stage, N stage, and TNM stage were statistically significant for DFS. The 3-year DFS rates of T1/2 versus T3/4 were 80.0% versus 16.0% ($P = 0.04$, hazard ratio [HR] 0.155, 95% confidence interval [CI] 0.020–1.210), N0 versus N1 were 80.0% versus 15.7% ($P = 0.02$, HR 0.133, 95% CI 0.017–1.035), and stage I/II versus III/IV were 80.0% versus 15.7% ($P = 0.02$, HR 0.133, 95% CI 0.017–1.035). However, tumor location ($P = 0.09$, HR 2.716, 95% CI 0.819–9.006) was marginally significant for DFS. Similarly, neither total radiation dose ($P = 0.54$, HR 0.664, 95% CI 0.178–2.485) nor number of total cycles of CTx ($P = 0.95$, HR 0.960, 95% CI 0.288–3.197; Fig. 2) was significant. We performed further multivariate analysis for DFS according to age, tumor location, and TNM stage. It showed that tumor location (Ce/Ut, $P = 0.012$, HR 9.529, 95% CI 1.645–55.210) and TNM stage (I/II, $P = 0.013$, HR 0.052, 95% CI 0.005–0.539) were identified as independent prognostic factors of DFS. While age (<80, $P = 0.059$, HR 0.200, 95% CI 0.038–1.063) was a marginal significant factor of DFS. Because this is a small sample size study, these results were underpowered (Table 2).

Recurrences occurred in 11 (55%) out of 20 patients with response rate. The first recurrent sites were predominantly more frequent in the intra-RT field (in nine patients [82%]) than outside the RT field (in two patients [18%]). Almost all (seven of nine) loco-regional recurrences included the primary site. Six of the nine patients who developed loco-regional
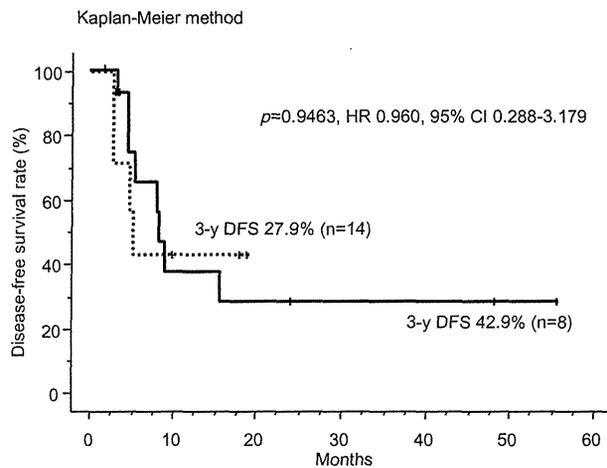
Kaplan-Meier method

Fig. 2 Survival curves showing disease-free survival (DFS) for number of total cycles of chemotherapy of 1–2 (dashed line) and 3–4 (solid line).

recurrences received extended-field RT; the remaining patients received involved-field RT.

Causes of death

At the time of analysis, 16 patients (73%) have died of the following causes: primary disease in 10 (63%), treatment-related toxicity in 4 (25%), and other dis-

eases in 2 (13%) patients. The other diseases included hepatocellular carcinoma (at 10.2 months) in one patient and pancreas cancer (at 56.0 months) in another patient, respectively. TRDs were suspected for up to four patients (18%); one patient (85 years, T2N0M0) developed Candida septicemia, and the treatment was discontinued; this patient died at 3.4 months. One patient (81 years, T1N0M0) died from hemorrhagic shock by gastrointestinal bleeding at 2.1 months. One patient (77 years, T3N0M0) died from sepsis at 3.8 months. The remaining one patient (80 years, T3N1M0) died unexpectedly at 3.5 months. For this patient, indeed, relation between treatment and death was not obvious. Seven days before death, the condition of this patient was normal, and endoscopy was undergone at outpatient visit, which showed CR.

Toxicity

Grade 3 and higher toxicities at acute phase are shown in Table 3. Grade 4 leukocytopenia and thrombocytopenia occurred in three and four patients, respectively. Meanwhile, seven patients (32%) had grade 3 or higher non-hematotoxicities, mainly comprising esophagitis (in five patients), esophageal bleeding (in one patient), diarrhea (in

Table 2 Univariate and multivariate analysis for DFS

Factor	No.	3-year DFS (%)	Univariate analysis			Multivariate analysis		
			P-value	HR	95% CI	P-value	HR	95% CI
Age								
≥80 years old	9	17.5	0.4419	0.638	0.200–2.039	0.0590	1.000	0.038–1.063
<80 years old	13	40.6					0.200	
Location								
Ce/Ut	6	16.7	0.0869	2.716	0.819–9.006	0.0120	9.529	1.645–55.210
Mt/Lt	16	42.4					1.000	
Tumor stage								
T1/T2	7	80.0	0.0405	0.155	0.020–1.210	–	–	–
T3/T4	15	16.0					–	–
Nodal stage								
N0	8	80.0	0.0228	0.133	0.017–1.035	–	–	–
N1	14	15.7					–	–
Metastatic stage								
M0	21	35.4	0.2632	0.318	0.037–2.734	–	–	–
M1	1	0.0					–	–
TNM stage								
I/II	8	80.0	0.0228	0.133	0.017–1.035	0.0130	0.052	0.005–0.539
III/IV	14	15.7					1.000	
KPS								
≥90%	12	39.0	0.3280	1.761	0.554–5.592	–	–	–
<90%	10	30.0					–	–
Tumor length								
<5 cm	5	100.0	<0.1052	0.216	0.028–1.673	–	–	–
≥5 cm	17	20.3					–	–
No. of total cycles of CTx								
1/2	14	27.9	0.9463	0.960	0.288–3.197	–	–	–
3/4	8	42.9					–	–
Radiation dose								
50–50.4 Gy	17	35.0	0.5387	0.6640	0.178–2.485	–	–	–
The others	5	26.7					–	–

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; KPS, Karnofsky Performance Status; –, not analyzed.

Table 3 Grade 3/4 toxicity at acute phase

Factor	Grade 3	Grade 4	Grade 5
	n (%)		
Leukopenia	13 (59.0)	3 (13.6)	–
Anemia	5 (22.7)	0 (0)	–
Thrombocytopenia	7 (31.8)	4 (18.2)	–
Esophagitis	5 (22.7)	0 (0)	–
Esophageal bleeding	1 (4.5)	0 (0)	–
Diarrhea	1 (4.5)	0 (0)	–
Neutropenic fever	1 (4.5)	0 (0)	–
Treatment-related death	–	–	4 (18.2)

–, Treatment-related death is as same as Grade 5. As for details, see the text.

one patient), and neutropenic fever (in one patient). Grade 3 or higher toxicity was not observed at late phase.

DISCUSSION

This is a retrospective study including a small population for elderly patients with esophageal cancer treated with CRT combined with several chemotherapeutic regimens using CDDP and NDP. Patients were allowed to treat with reduced dose and field regimens. Thus, basically, advanced age itself is not enough reason to be excluded for CRT, and there was no careful selection of patients in this institution.

At present, based on the Radiation Therapy Oncology Group (RTOG) 85-01[15] and Intergroup Trial (INT) 0123 (RTOG 94-05) studies,[16] the standard nonsurgical treatment for locally advanced esophageal cancer is concurrent CRT, consisting of CDDP/5-FU CTx and 50.4 Gy of RT. In the combined therapy group of RTOG 85-01, the treatment completion rate was 54%, TRD occurred in 1 out of 61 patients, and adverse events occurred severely (grade 3) in 44% and fatally (grade 4) in 20%. In this group, the proportion of patients aged 70 and over was only 26%, which calls into question the suitability of CRT treatment for elderly patients.

A prospective randomized trial from China showed that there was no difference in DFS between CRT (n = 36) and surgery (n = 44).[17] Both treatment modalities offered similar early clinical outcomes and survival for patients with SqCC of the esophagus. Another study from the University of Tokyo Hospital demonstrated retrospectively that there was no statistically significant difference between CRT (n = 33) and surgery (n = 49) in 3-year OS (48% vs 44%, P = 0.22) and 3-year DFS (65% vs 59%, P = 0.16) despite a selection bias.[18] CRT for locally advanced esophageal cancer has been widespread and popular; for example, it was delivered to approximately 60% of patients at this institution in 2007.[18] Thus, it is hoped

that future studies will further the development of CRT for locally advanced esophageal cancer, including for elderly patients.

In this study, 75 years was selected for the cutoff point of elderly patients, which may be older than other investigations and remains controversial. Some studies have shown that definitive CRT could be considered as an effective and safe treatment in elderly patients aged ≥65 or 70,[8,9] and as a result, a lot of elderly patients undergo such a treatment throughout the world. Meanwhile, according to the 20th Life Tables in 2005 in Japan, the life expectancy was 78.56 and 85.52 for men and women, respectively, the longest in the world, and now keeps increasing.[1] Although 75-year-old men and women may be able to live for another 11.07 years and 14.83 years, respectively, analyses by cause of death present mortality from malignant neoplasm in people aged 75 years remains to be 26.00% for men and 16.49% for women.[1] These backgrounds have caused frequent encounters with elderly patients and a tendency to use an older cutoff point for defining elderly patients in Japan.[4-7] It therefore seemed reasonable to elevate the cutoff point to 75 years for defining elderly patients.

In this study, whereas OS seemed to be poor as compared with previous studies on CRT for elderly patients with locally advanced esophageal cancer,[4-9] the 3-year DFS of 33.3 ± 11.4% was equivalent and not gloomy.

The fight against adverse events may be one of the most important issues for elderly patients. Although adverse events should be minimized as much as possible, these events were frequent despite reductions in CTx dose and RT field in this study.

Even though a half of the patients received dose-reduced CTx from the first cycle, additional reductions were required. Appropriate reduction in dose or alternation of drug is required, and how to do it differed depending on individual condition.

However, surprisingly, univariate analysis showed that the total number of cycles of CTx had a minor effect on DFS in this study. Although a longer term follow-up may offer a significant difference, additional CTx (the third and the fourth cycle of CTx in this regimen) after concurrent CRT phase is controversial, and it suggests that elderly patients do not have to receive this type of CTx. Many patients (18 of 22) completed at least concurrent CRT phase in this study, and this seemed to be the most important factor for effect and survival.

Furthermore, NDP may be considered to be helpful to reduce toxicity from a previous study. NDP instead of CDDP contribute to decrease toxicities, especially renal and heart toxicities, because there is no need for a lot of hydration fluid.

RT field reduction must also contribute to acceptable toxicities. Uno et al.[6] reported that local field irradiation of only the involved area provided good

compliance with less toxic events. It might also be favorable because no recurrence of lymph node metastases occurred. In this study, an extended field was irradiated for patients aged less than 80 years. The pattern of relapse revealed the dominance of intra-RT field over distant area, and indeed, almost all recurrences included the primary site. This finding suggests that an involved-field RT might also be favorable for patients younger than 80. Extended-field RT may be an overprescription for elderly patients in some cases. Furthermore, additional improvements in RT field, RT technique, and RT dose are needed.

As regards grade 4 or under toxicities, it was possible to minimize and make tolerable such adverse events with methods previously described and careful close monitoring. Hematotoxicity levels were acceptable: 14% of patients had grade 4 leukocytopenia and 18% had grade 4 thrombocytopenia; these levels suggest that the CRT treatment in this study posed no higher risk than in previous reports.[4–9] However, TRD and intercurrent death still cause some problems. In the present study, four TRDs (18%) at a maximum include obscure cases, which can not be denied in relation to CRT. Although it may be over-estimated, these outcomes account for a significant minority in elderly patients. Once toxicity occurs, it may be fatal because of decreased physiological reserve. This can also be said about surgical therapy. Takagawa et al. showed that although postoperative morbidity rate was the same between elderly and non-elderly patients, hospital deaths were more frequent in elderly patients.[7] There seemed to be no trend in their occurrence, and they were difficult to predict. The issues of how patients at high risk should be identified and when oncologists should discontinue treatment still remain. Esophageal cancer is considered to be one of the most aggressive and rapidly progressive cancers, resulting in a high rate of death from primary disease. In this regard, it tends to be given priority over almost all other diseases, even malignant neoplasm. Not only the primary disease but also any comorbidity should be evaluated and managed carefully for elderly patients, and oncologists must know the risk of disease progression and whether there is an uncontrollable state of comorbidities or complications in relation to treatment for esophageal cancer.

This is just a small retrospective study, which included a heterogenic patient population, so comparison between elderly and non-elderly patients could not be done. CRT was reaffirmed to be tolerable for elderly patients. By univariate and multivariate analyses, the effect of age itself showed no significant difference between patients younger than 80 and patients aged 80 or over. This finding suggests that we should not be negative, in spite of previous studies in which CRT was not delivered to patients over 80 years.[4,7] Tougeron et al. also reported that age criteria alone was not sufficient for guidance of therapy and that better characterization of patients with Charlson score, for example, might be helpful for decision making.[8] Takagawa et al.[7] reported no significant difference between elderly ($n = 44$) and non-elderly ($n = 136$) patients with stages I to III disease, whose mean survival time of 18 months and 15 months, respectively, and toxicities and mortality were similar. By contrast, Takeuchi et al.[4] revealed inferior survival for elderly patients. The 3-year OS was statistically different (29.3% in the elderly group vs 49.4% in the non-elderly group; $P = 0.010$), and the recurrence rate was higher in the elderly group (47.6% vs 33.7%, $P = 0.32$), a finding that might be because of the insufficient compliance of CTx. The differences among the three studies might be because of the CRT regimen. Another study by Uno et al.[6] reported that toxicities were tolerable; therefore, CRT was enough to select for elderly patients with adequate PS.

There remain some unanswered questions as to whether adjuvant CTx is needed or extended-field RT is required for elderly patients, and TRD should not be disregarded. However, the most important point to be emphasized is that physicians should not be unduly concerned about adverse events or be negative about selecting aggressive treatment for elderly patients, as long as comorbidities and complications are managed carefully. Novel aspects within treatment including reduction of CTx dose and RT field, and the appropriate two cycles of CTx may help to give elderly patients a lot of benefits from CRT, and this challenge may be of considerable value.

References

1 Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare. Vital statistics. [Cited Mar 20 2010.] Available from URL: http://www.mhlw.go.jp/
2 Tsukuma H, Ajiki W, Ioka A, Oshima A and Research Group of Population-Based Cancer Registry of Japan. Survival of cancer patients diagnosed in 1993–96: collaborative study of population-based cancer registries in Japan, Japanese Journal of Clinical Oncology 2006; 36: 602–7.
3 Matsuda T, Marugame T, Kamo K, Katanoda K, Ajiki W, Sobue T and The Japan Cancer Surveillance Research Group. Cancer incidence and incidence rates in Japan in 2003: based on data from 13 population-based cancer registries in the Monitoring of Cancer Incidence in Japan (MCIJ) project. Japanese Journal of Clinical Oncology 2009; 39: 850–8.
4 Takeuchi S, Ohtsu A, Doi T et al. A retrospective study of definitive chemoradiotherapy for elderly patients with esophageal cancer. Am J Clin Oncol 2007; 30: 607–11.
5 Uno T, Kawakami H, Funami Y et al. Chemoradiation for patients with esophageal cancer aged 80 and older. Anticancer Res 2001; 21: 4095–7.
6 Uno T, Isobe K, Kawakami H et al. Efficacy and toxicities of concurrent chemoradiation for elderly patients with esophageal cancer. Anticancer Res 2004; 24: 2483–6.
7 Takagawa R, Kunisaki C, Makino H et al. Therapeutic management of elderly patients with esophageal cancer. Esophagus 2008; 5: 133–9.
8 Tougeron D, Di Fiore F, Thureau S et al. Safety and outcome of definitive chemoradiotherapy in elderly patients with oesophageal cancer. Br J Cancer 2008; 99: 1586–92.

9 Anderson S E, Minsky B D, Bains M et al. Combined modality chemoradiation in elderly oesophageal cancer patients. Br J Cancer 2007; 96: 1823–7.

10 Yamashita H, Nakagawa K, Tago M et al. Radiation therapy combined with cis-diammine-glycolatoplatinum (nedaplatin) and 5-fluorouracil for Japanese stage II-IV esophageal cancer compared with cisplatin plus 5-fluorouracil regimen: a retrospective study. Dis Esophagus 2006; 19: 15–9.

11 Nemoto K, Matsushita H, Ogawa Y et al. Radiation therapy combined with cis-diammine-glycolatoplatinum (nedaplatin) and 5-fluorouracil for untreated and recurrent esophageal cancer. Am J Clin Oncol 2003; 26: 46–9.

12 Kato H, Fukuchi M, Manda R et al. Efficacy and toxicity of nedaplatin and 5-FU with radiation treatment for advanced esophageal carcinomas. Anticancer Res 2003; 23: 3493–8.

13 Zhang P, Feng F Y, Wu L Y et al. Phase II multicenter clinical trial of nedaplatin in the treatment of malignant tumors. [Chinese]. Zhonghua Zhong Liu Za Zhi 2006; 28: 230–4.

14 Miller A B, Hoogstraten B, Staquet M et al. Reporting results of cancer treatment. Cancer 1981; 47: 207–14.

15 Herskovic A, Martz K, al-Sarraf M et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 1992; 11: 1593–8.

16 Minsky B D, Pajak T F, Ginsberg R J et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002; 20: 1167–74.

17 Chiu P W Y, Chan A C W, Leung S F et al. Multicenter prospective randomized trial comparing standard esophagectomy with chemoradiotherapy for treatment of squamous esophageal cancer: early results from the Chinese University Research Group for Esophageal Cancer (CURE). J Gastrointest Surg 2005; 9: 794–802.

18 Yamashita H, Nakagawa K, Yamada K et al. A single institutional non-randomized retrospective comparison between definitive chemoradiotherapy and radical surgery in 82 Japanese patients with resectable esophageal squamous cell carcinoma. Dis Esophagus 2008; 21: 430–6.

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LETTER TO THE EDITOR

Late relapse of extranodal natural killer/T cell lymphoma, nasal type, after more than ten years

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Extranodal NK/T cell lymphoma, nasal type (ENKL) is a malignant lymphoproliferative disorder of NK cells characterized by an invasive nature with vascular damage and necrosis [1–3]. The upper aerodigestive tracts, especially nasal cavities, are commonly involved (the nasal type), and in minor populations, other sites such as the skin, intestines, or soft tissues other than the aerodigestive tracts are the main invasive sites (extranasal type). ENKL is more prevalent in Asians and Central Americans, and a lower incidence among Caucasians is recognized. ENKL is also characterized by a strong association with Epstein-Barr virus (EBV).

The clinical outcome of ENKL varies depending on the involved site and clinical stage, and the prognosis is considerably worse than that of other lymphomas, although the recent therapeutic progress including in concurrent chemo- and radiotherapy against limited-stage nasal type ENKL and the introduction of hematopoietic cell transplantation (HCT) might improve the outcome [4–6].

Some cases of ENKL have been known to relapse after a long duration of complete response [7,8]; however, the biological mechanisms of ENKL including those of such cases are still unknown.

Here, we report three Japanese cases of ENKL who relapsed after a period of longer than 10 years of complete response after the initial treatment.

Case one was a 44-year-old male who had suffered from intermittent nasal discharge and was diagnosed with non-Hodgkin lymphoma, diffuse pleomorphic

type, with clinical stage IIE in 1991. He had received combination chemotherapy of methotrexate (MTX), doxorubicin (ADR), cyclophosphamide (CY), vincristine (VCR), and bleomycin (MACOP-B) and local irradiation. He achieved complete response (CR) and had been well until 2007, when he noticed hoarseness and was found to have a paralaryngeal tumor. The tumor was diagnosed as ENKL with positivity for cytoplasmic CD3, CD56, TIA1, granzyme B, and EBV by immunohistochemical studies and *in situ* hybridization, respectively. He needed trachostomy for bronchial obstruction, and multiple skin lesions also developed. He was administered carboplatin, etopside, ifosdamide (IFO), and dexamethasone, with no improvement, so he was also given cytosine arabinoside, IFO, MTX, and L-asparaginase. He reached CR after three courses of chemotherapy. Months later, he died of exacerbation of his ENKL.

Re-examination of the histological specimen of the primary lesion taken in 1991 revealed identical morphological features and the same immunophenotypes and EBV positivity as the relapsed lesions. He was clarified as having had a relapse of ENKL after 16 years.

The second case was a 36-year-old female who was diagnosed with, diffuse, medium sized, NHL, which was positive for CD45RO and negative for CD20, in a right nasal tumor in 1989. She received four courses of MACOP-B and 50 Gy involved field irradiation (IFR). She had maintained a CR until

Table I. Clinical chracteristics of the three cases.

No.	Primary lesion	Initial stage	NK-PI*	Initial therapy	Duration until relapse (years)	Relapsed lesion	Outcome after relapse
1	Nasal	IIE	2	chemo/RT†	19	systemic	DOD‡
2	Nasal	IIE	2	chemo/RT	13	nasal	alive
3	Nasal	IE	2	RT	16	nasal	alive

*NK/T-cell prognostic factor (ref. 9).
†chemotherapy and irradiation.
‡died of disease.

2003, when a new lesion was noticed in her right nasal cavity. Her serum LDH level was elevated.

The lesion was diagnosed as ENKL with an angioinvasive nature, and positivity was found for cytoplasmic CD3, CD56, TIA1, granzyme B, and EBV. ADR, CY, VCR, and prednisolone (CHOP) were administered three times with consecutive 30Gy IFR. She has been well for 6 years with CR.

The available H&E stained specimen obtained at the initial presentation was confirmed to have the same morphological features as the relapsed lesion.

The third case was a 48-year-old male and was admitted to our hospital for the treatment of, diffuse type, poorly differentiated lymphocytic, left-sided nasal NHL in 1980 and received 60Gy IFR limited to left nasal and paranasal cavity. His disease relapsed in his right nasal cavity in 1996. Three courses of MACOP-B were performed with 30 Gy additional irradiation to the right nasal cavity. He has been well for 13 years without exacerbation. The specimen obtained at first presentation showed the infiltration of medium-sized lymphoid cells with rather abundant cytoplasm, and the relapsed lesion was confirmed as ENKL with positivity for cytoplasmic CD3, CD56, TIA1, granzyme B, and EBV.

The clinical characteristics of the three cases that demonstrated a late relapse are summarized in Table I. All patients had a limited stage nasal type disease and reached CR after chemotherapy and irradiation or only irradiation. After long periods of CR ranging from 13 to 19 years, two cases relapsed near to the original sites, and one relapsed at multiple sites. At the time of relapse, the clinical stage and NK/T cell prognostic index [9] of the two (cases 2 and 3) were IE and group 1, respectively in both cases, while case 1 showed clinical stage IV and group 4. The patients that showed limited stage relapse responded well to chemo/radio therapy and maintained a second CR for 6 years and 13 years, respectively, while the remaining case (case 1) died soon after the second relapse despite achieving a transient CR with intensive chemotherapy. No patient received HCT.

ENKL was defined as a new clinical entity in the 1990s and appeared officially in the WHO classification in 2001. Before this time, the pathological diagnosis varied. Its long term outcome remains unclear. Chim et al. suggested that the survival curve of ENKL cases showed a biphasic pattern and did not reach a plateau even after 5 years [10]. In our cases, relapse occurred after 10 years. Local relapse after durable CR is manageable, although systemic manifestation seems to require a novel approach. Although changes in the initial approach to ENKL of limited and advanced stages would have influenced the outcome, a therapeutic strategy focusing on late relapse should also be considered.

After a long period of CR, it is difficult to determine the identity of lymphoma cells at the initial presentation and at relapse, especially in the case of NK cell lymphoma because of the lack of useful clonal markers such as the T cell receptor gene or immunoglobulin gene in T and B cell lymphoma. However, in the relapsed lesions, morphological features in addition to immunophenotypes including the presence of the EBV genome strongly suggested that the lesions in the patients were the same NK cell-derived lymphoma.

Another concern is the potential relationship of ENKL with EBV-associated lymphoproliferative disorders (EBV-LPD) especially in childhood [11]. EBV-LPD occasionally leads to ENKL, a clonal expansion of EBV-containing NK cells. Genetic predispositions to ENKL including EBV-LPD might contribute to the late relapse. In our cases, the ages of the patients were rather high for patients with EBV-LPD, and no EBV-LPD related symptoms had been observed during the intermission; however, one case among the three showed a significantly high level of EBV viral load in their whole blood 8 years after the second response (unpublished data).

In summary, we presented the clinical features of cases of late relapsed ENKL. These patients might represent a unique subpopulation of ENKL.

References

1. Suzuki R, Takeuchi K, Ohshima K, Nakamura S. Extranodal NK/T-cell lymphoma: diagnosis and treatment cues. Hematol Oncol 2008;26:66–72.

2. Oshimi K. Progress in understanding and managing natural killer-cell malignancies. Br J Haematol 2007;139:532–544.

3. Swerdlow SH, Campo E, Harris NL, et al., editors. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.* Lyon: IARC; 2008.

4. Au WY, Weisenburger DD, Intragumtornchai T, et al. Clinical differences between nasal and extranasal NK/T-cell lymphoma: a study of 136 cases from the International Peripheral T-cell Lymphoma Project. Blood 2009;113:3931–3937.

5. Lee J, Au WY, Park MJ, et al. Autologous hematopoietic stem cell transplantation in extranodal natural killer/T cell lymphoma: a multinational, multicenter, matched controlled study. Biol Blood Marrow Transplant 2008;14:1356–1364.

6. Yamaguchi M, Suzuki R, Kwong YL, et al. Phase I study of dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) chemotherapy for advanced-stage, relapsed or refractory extranodal natural killer (NK)/T-cell lymphoma and leukemia. Cancer Sci 2008;99:1016–1020.

7. Chim CS, Ooi GC, Shek TW, et al. Lethal midline granuloma revisited: nasal T/natural-killer cell lymphoma. J Clin Oncol 1999;17:1322–1325.

8. Schrader C, Janssen D, Kneba M, Lennert K. A 38-year history of natural-killer-cell lymphoma. N Engl J Med 2004; 350:418–419.

9. Lee J, Suh C, Park YH, et al. Extranodal natural killer T-cell lymphoma, nasal-type: a prognostic model from a retrospective multicenter study. J Clin Oncol 2006;24:612–618.

10. Chim CS, Ma SY, Au WY, et al. Primary nasal natural killer cell lymphoma: long-term treatment outcome and relationship with the International Prognostic Index. Blood 2004;103: 216–221.

11. Cohen JI, Kimura H, Nakamura S, Ko YH, Jaffe ES. Epstein-Barr virus-associated lymphoproliferative disease in non-immunocompromised hosts: a status report and summary of an international meeting, 8–9 September 2008. Ann Oncol 2009;20:1472–1482.
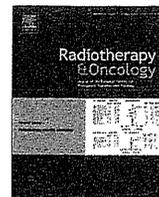
Recording of morbidity

Validation of the Total Dysphagia Risk Score (TDRS) as a predictive measure for acute swallowing dysfunction induced by chemoradiotherapy for head and neck cancers

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ABSTRACT

Background and purpose: Methods for predicting acute swallowing dysfunction in patients with head and neck cancers undergoing definitive chemoradiotherapy have not been established. We investigated the validity of the Total Dysphagia Risk Score (TDRS) as a predictive measure for this morbidity.
Materials and methods: Forty-seven patients with head and neck cancers who underwent definitive chemoradiotherapy between December 1998 and March 2006 were reviewed retrospectively. Median age was 63 years (range, 16–81). Almost all patients underwent platinum-based concomitant chemoradiotherapy. Factors of the TDRS were as follows: T-classification, neck irradiation, weight loss, primary tumour site and treatment modality. Patients were classified into three risk groups according to the TDRS.
Results: Swallowing dysfunction was observed in 27 patients (57%) as RTOG grade 2 or higher acute morbidity. This classification was significantly associated with grade 2 or higher acute swallowing dysfunction ($P < 0.001$). In ROC (receiver operator characteristic) analysis, the cut-off value of TDRS was set at 18 (sensitivity = 0.81; specificity = 0.85). Prediction of severe (grade $\geqslant$ 3) acute swallowing dysfunction was similarly obtained.
Conclusion: The TDRS is a useful tool to predict acute swallowing dysfunction induced by chemoradiotherapy for head and neck cancers.
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Definitive chemoradiotherapy is now a widely accepted treatment option for patients with head and neck cancers. In recent years, it has been revealed that addition of concomitant chemotherapy to radiotherapy not only improves the outcome but also increases toxicity of the treatment. Rosenthal et al. reported that 40–70% of patients undergoing concomitant chemoradiotherapy for head and neck cancers experienced severe mucositis and 50–80% required feeding tube placement during the course of therapy [1]. Severe swallowing dysfunction arising during the course of therapy reduces the patient's quality of life and adversely affects their physical condition. Prediction of this morbidity may facilitate prophylactic intervention and prevention of these adverse effects [2], but accurate predictive methods have not been established.

Recently, Langendijk et al. advocated a simple measure designated as the Total Dysphagia Risk Score (TDRS) to predict swallowing dysfunction after curative radiotherapy for head and neck cancers [3]. They also reported that this predictive model could also be adapted for acute morbidity. Here, a retrospective review of patients with head and neck cancers who underwent definitive

chemoradiotherapy in our facility was performed to investigate the validity of the TDRS as a predictive measure for acute swallowing dysfunction in these patients.

Materials and methods

Between December 1998 and March 2006, 47 patients with head and neck cancers underwent definitive chemoradiotherapy at our facility. The patients' characteristics are shown in Table 1. In our facility, definitive chemoradiotherapy is usually performed in patients with good performance status, with no distant metastasis and 75 years old or less.

All except two patients underwent platinum-based concomitant chemoradiotherapy; the two exceptions were treated by radiotherapy and docetaxel-alone chemotherapy, respectively. Various chemotherapy regimens were adopted (Table 2). As we had been searching for the optimal chemotherapy regimen for several years and the method of therapy had consequently changed over that time, the chemotherapeutic agents used in the cases included in the present study were heterogeneous. The cumulative dose of cis-diamminedichloroplatinum (cisplatin) ranged from 80 mg/m² to 300 mg/m² (median, 100 mg/m²). 5-Fluorouracil (5-FU) was administered to 43 patients. The cumulative dose of

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Table 1
Patient characteristics.

Characteristics		Number of patients
Gender	Male	41
	Female	6
Age		16–81 (median: 63)
Performance status	0	44
	≥1	3
T-classification	T2	24
	T3–T4	23
Stage	II	20
	III	6
	IV	21
Primary site	Larynx	18
	Oropharynx	11
	Nasopharynx	7
	Hypopharynx	7
	Nasal cavity	2
	Oral cavity	2
Histology	Squamous cell carcinoma	47
Chemotherapy	Platinum-based	45
	Docetaxel alone	2
Radiation schedule	Conventional fractionation	41
	Hyperfractionation	6
Neck irradiation	Local or unilateral	20
	Bilateral	27
Weight loss (baseline)	No weight loss	36
	1–10%	10
	>10%	1

Table 2
Chemotherapy regimens.

Chemotherapy agents	Number of patients
Cisplatin (10 mg/m² on days 36–40, 43–47) + 5-FU (400 mg/m² on days 36–40, 43–47)	26
Cisplatin (50 mg/m² on days 6–7, 41–42, 71–72) + 5-FU (800 mg/m² on days 1–5, 36–40, 43–47)	9
Cisplatin (80 mg/m² on day 29) + 5-FU (400 mg/m² on days 29–33)	5
Others	7

5-FU ranged from 2000 mg/m² to 12,000 mg/m² (median 4000 mg/m²).

In radiation therapy, casts for immobilisation and a photon beam of 4 MV were used in all patients. The fraction size was 1.5–2.0 Gy. The total dose of radiation therapy ranged from 50–70 Gy, and the median dose was 70 Gy. As various treatment protocols with different fraction sizes and total doses had been used in our facility, we also calculated the biologically effective dose (BED) in a linear-quadratic model [4]. BED was defined as $nd(1 + d/\alpha/\beta)$, with units of Gy, where n is the fractionation number, d is the daily dose and α/β was assumed to be 10 for tumours and acute toxicity. The BED ranged from 60 to 84 Gy (median 84 Gy). Forty-one patients received a once-daily fractionation schedule and six patients were treated with a partially accelerated hyperfractionation schedule. In this schedule, patients initially received 40 Gy in once-daily fractionation with a fraction size of 2 Gy. Subsequently, radiation field size was reduced to avoid the spinal cord and 30 Gy was added in twice-daily fractionation with a fraction size of 1.5 Gy. Lateral opposing portals alone or lateral opposing and anterior portals (3-field approach) were used according to the individual tumour spread. Stage II disease was usually treated by locally confined portals. The whole (bilateral) neck was usually included in the treatment of stage III–IV disease initially. The spinal cord was usually avoided by cone-down field reduction after administration of 40 Gy. CT images for radiation dose distribution were attained in 14 patients. None of the patients underwent intensity-modulated radiation therapy. Overall treatment time ranged from 31 to 109 days (median, 50 days).

Morbidity was retrospectively assessed using medical records, and scored by the Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring Criteria [5]. In these criteria, grade 2 swallowing dysfunction is defined as moderate dysphagia and/or odynophagia, which may require narcotic analgesics and/or pureed or liquid diet. Grade 3 is defined as severe dysphagia or odynophagia with dehydration or weight loss requiring naso-gastric feeding tube, intravenous fluids or hyperalimentation. The TDRS is a summation of the following risk points: T-classification (T3 = 4 points; T4 = 4 points), neck irradiation (bilateral neck irradiation = 9 points), weight loss (1–10% = 5 points; >10% = 7 points), primary tumour site (oropharynx = 7 points; nasopharynx = 9 points) and treatment modality (accelerated radiotherapy = 6 points; concomitant chemotherapy = 5 points). The definition used in this study was identical to that of Langendijk et al. [3]. In the present study, patients who underwent partially accelerated radiation therapy were not allocated to 6 points. Accordingly, the risk points of treatment modality were set at 5 in all patients. The patients were divided into a low risk group (TDRS = 0–9), intermediate risk group (TDRS = 10–18) and high risk group (TDRS > 18).

Statistical analyses were performed using the χ^2 test, and $P < 0.05$ was taken to indicate statistical significance. ROC (receiver operator characteristic) curves were also plotted to evaluate the predictive capability of TDRS for grade 2 or higher acute swallowing dysfunction.

These analyses were performed using the statistical software JMP version 5.1.1 (SAS Institute Inc., Cary, NC, USA).

Results

Grade 2 or higher swallowing dysfunction was observed in 27 patients (57%) as an acute morbidity. Of those, severe (grade ≥ 3) dysfunction occurred in 22 patients (81%). The results of classification into three risk groups according to TDRS and the relationship between the risk groups and RTOG grade are shown in Table 3. This classification was significantly associated with both grade ≥ 2 and grade ≥ 3 acute swallowing function. The ROC curve was plotted to evaluate the prediction capability of TDRS for grade ≥ 2 acute swallowing dysfunction (Fig. 1). The cut-off value was set at 18 (sensitivity = 0.81; specificity = 0.85), which was consistent with the borderline between the intermediate and high risk groups. Accuracy for prediction was moderate (area under the curve = 0.80). Almost the same accuracy was obtained when grade ≥ 3 acute swallowing dysfunction was defined as positive (area under the curve = 0.83). The cut-off value was also set at 18 (sensitivity = 0.86; specificity = 0.76).

The median duration of severe (grade ≥ 3) swallowing dysfunction was 53 days (range, 21–142 days). To manage the severe swallowing dysfunction, total parenteral nutrition was usually adopted at our facility. Enteral feeding was not usually adopted. Seventeen

Table 3
Relationships between the three risk groups and grading of swallowing dysfunction in RTOG Acute Radiation Morbidity Scoring Criteria.

Risk groups	Total	RTOG grade		
		0–1	≥2	≥3
Low	16	13 (81%)	3 (19%)	1 (6%)
Intermediate	9	4 (44%)	5 (56%)	4 (44%)
High	22	3 (14%)	19 (86%)	17 (77%)
Total	47	20 (43%)	27 (57%)	22 (47%)

The differences were statistically significant ($P < 0.001$; degrees of freedom = 2) in both grade ≥ 2 and grade ≥ 3 acute swallowing dysfunction.
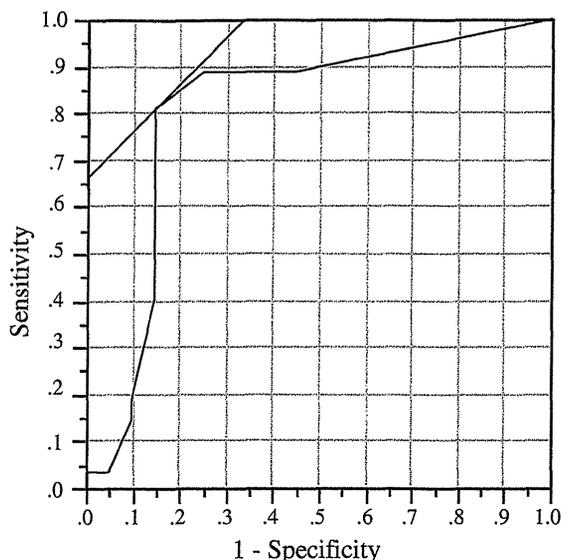
Fig. 1. ROC (receiver operator characteristic) curve to evaluate the prediction capability of the TDRS for grade 2 or higher acute swallowing dysfunction.

patients required total parenteral nutrition. No patients in the low risk group and three patients (33%) in the intermediate risk group required this procedure. In contrast, 14 patients (64%) in the high risk group required this procedure. Median duration of hospitalization after termination of treatment in the low, intermediate, and high risk group was 15 days (range, 1–31), 26 days (range, 7–117) and 41 days (range, 17–77), respectively.

Discussion

Cisplatin-based chemoradiotherapy for locally advanced head and neck cancers is now widely recognised as a standard form of therapy for patients with locally advanced disease, although considerable clinical problems remain to be resolved. This can be a rather toxic form of therapy despite using non-surgical modalities [6]. Swallowing dysfunction caused by the therapy sometimes becomes severe, and this is one of the largest obstacles in conducting concomitant chemoradiotherapy for head and neck cancers. Few previous studies have addressed this issue [7], but some reports mentioned that more than half of the cases required enteral feeding temporarily [8], and about 20% required long-term enteral feeding [1]. Nguyen et al. reported that aspiration was frequently observed during the course of therapy, sometimes leading to fatal aspiration pneumonia [9,10]. Swallowing dysfunction leads to malnutrition, which causes body weight loss during the course of therapy. This results in not only physical damage for the patients, but also worsening of the clinical outcome [11]. Body weight loss also causes dosimetric problems. The risk of delivering an inadequate radiation dose to the target volume and critical structures may arise if coordinated replanning is not performed during the course of the therapy, especially when using highly conformal methods [12].

As mentioned above, care must be taken regarding swallowing dysfunction during concomitant chemoradiotherapy for head and neck cancers and appropriate measures should be taken to alleviate secondary averse effects, such as aspiration or body weight loss. Nutritional support is a high priority issue in the management of these patients. Enteral feeding is generally the preferred method [13]. However, total parenteral nutrition was usually adopted in our facility. This might be due to preference of the attending physicians who were also in charge of the management of chemora-

diotherapy for oesophageal cancers. Another part of the reason might be that healthcare system in our district has not strictly regulated this procedure.

As a measure for enteral feeding, percutaneous endoscopic gastrostomy (PEG) tube placement is one of the most effective interventions. Prophylactic PEG tube placement has been recognised as a beneficial approach for ameliorating the nutritional status of these patients [2]. Although a relatively safe procedure, PEG placement is invasive and this may leads to critical complications [14]. Therefore, it is not reasonable to place a PEG tube in all patients, and a selection index to identify patients requiring prophylactic PEG tube placement is urgently needed [2]. Several studies have addressed risk factors for severe swallowing dysfunction in radiotherapy for head and neck cancers. Manger et al. argued that clinical stage, general condition and history of smoking may be risk factors for severe dysphagia in chemoradiotherapy for head and neck cancers [8]. Poulsen et al. suggested that irradiated volume of the pharyngeal mucosa and musculature are strongly related to the swallowing toxicity in radiotherapy alone for head and neck cancers [15]. Other factors such as primary site or combined modality were also described as risk factors [2], but there is no comprehensive index in the literature. The Total Dysphagia Risk Score (TDRS) proposed by Langendijk et al. is a predictive model for swallowing dysfunction after curative treatment for head and neck cancers [3]. As this model was derived from data regarding late radiation morbidity, it is intended for prediction of late swallowing dysfunction. However, this simple model may also be useful for predicting acute morbidity, as suggested by Langendijk et al. The results of the present study indicated that TDRS is a valid measure for predicting acute swallowing dysfunction in patients with head and neck cancers undergoing definitive chemoradiotherapy. The TDRS was applicable despite the differences in patient characters and method of therapy. Thus, the TDRS may become an international index to predict swallowing dysfunction. Initially, validity of the TDRS for predicting grade 2 or higher acute swallowing dysfunction was set as the endpoint of the present study. This was due to the fact that the TDRS was defined as a measure to predict RTOG grade 2 or higher swallowing dysfunction. However, more than 80% of the morbidity in patients with experienced grade 2 or higher swallowing dysfunction was severe (grade ≥ 3) in the present study. Then, we set validity of the TDRS for predicting severe acute swallowing dysfunction as another endpoint of this study. ROC analysis in our study suggested that severe acute swallowing dysfunction may be similarly predictive. These observations suggest that the TDRS could be a predictive tool for severe swallowing dysfunction. Thus, the TDRS would allow selection of the patients most likely to benefit from prophylactic PEG placement. Our previous study indicated that radiation portal size is a risk factor for severe swallowing dysfunction in chemoradiotherapy for head and neck cancers [16]. Of the five factors included in the TDRS, T-classification, neck irradiation and primary tumour site are related to radiation portal size.

The annual number of the patients included in this study was relatively low (5–6 patients per year). This was the actual number of patients which we treated during this period. In our facility, definitive chemoradiotherapy has been strictly confined to patients with quite good condition. This might lead to scarcity of the number of patients.

It is obvious that radiotherapy plays a major role in the occurrence of swallowing dysfunction. Broader mucous membranes and more anatomical parts important for swallowing would be affected to a greater degree by larger radiation portals, and these would be amplified by chemotherapy. Therefore, improving radiotherapy may allow reduction of this complication. Intensity-modulated radiotherapy (IMRT) has been widely used for head and neck cancers [17]. Using this advanced technique, complications

can now be reduced without compromising therapeutic outcome [18].

Determining whether a patient actually requires concomitant chemotherapy also must be considered [19]. Recently, use of biologically targeted therapy has been shown to improve the outcome without increasing the common toxic effects of radiotherapy plus chemotherapy [20]. These promising approaches combined with robust nutritional support may yield further improvement in the management of non-surgical therapy for head and neck cancers.

Conclusions

The TDRS has the potential to become a useful measure for predicting acute swallowing dysfunction induced by chemoradiotherapy for head and neck cancers. This measure may serve as an index to enable selection of appropriate candidates for prophylactic PEG placement.

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Conflict of interest statement

The authors report no actual or potential conflicts of interest.

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References

[1] Rosenthal DI, Lewin JS, Eisbruch A. Prevention and treatment of dysphagia and aspiration after chemoradiation for head and neck cancer. J Clin Oncol 2006;24:2636–43.

[2] Cady J. Nutritional support during radiotherapy for head and neck cancer: the role of prophylactic feeding tube placement. Clin J Oncol Nurs 2007;11:875–80.

[3] Langendijk JA, Doornaert P, Rietveld DH, Verdonck-de Leeuw IM, Rene Leemans C, Slotman BJ. A predictive model for swallowing dysfunction after curative radiotherapy in head and neck cancer. Radiother Oncol 2009;90:189–95.

[4] Yaes RJ, Patel P, Maruyama Y. On using the linear-quadratic model in daily clinical practice. Int J Radiat Oncol Biol Phys 1991;20:1353–62.

[5] Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341–6.

[6] Shikama N, Sasaki S, Nishikawa A, Koiwai K, Kadoya M. Chemoradiation for locally advanced squamous cell carcinoma of the head and neck. Curr Top Radiol 2001;3:27–38.

[7] Lewin JS. Dysphagia after chemoradiation: prevention and treatment. Int J Radiat Oncol Biol Phys 2007;69:S86–7.

[8] Mangar S, Slevin N, Mais K, Sykes A. Evaluating predictive factors for determining enteral nutrition in patients receiving radical radiotherapy for head and neck cancer: a retrospective review. Radiother Oncol 2006;78:152–8.

[9] Nguyen NP, Frank C, Moltz CC, et al. Aspiration rate following chemoradiation for head and neck cancer: an underreported occurrence. Radiother Oncol 2006;80:302–6.

[10] Nguyen NP, Moltz CC, Frank C, et al. Dysphagia following chemoradiation for locally advanced head and neck cancer. Ann Oncol 2004;15:383–8.

[11] Capuano G, Grosso A, Gentile PC, et al. Influence of weight loss on outcomes in patients with head and neck cancer undergoing concomitant chemoradiotherapy. Head Neck 2008;30:503–8.

[12] Hansen EK, Bucci MK, Quivey JM, Weinberg V, Xia P, Repeat CT. Imaging and replanning during the course of IMRT for head-and-neck cancer. Int J Radiat Oncol Biol Phys 2006;64:355–62.

[13] Colasanto JM, Prasad P, Nash MA, Decker RH, Wilson LD. Nutritional support of patients undergoing radiation therapy for head and neck cancer. Oncology (Williston Park) 2005;19:371–9. discussion 380–372, 387.

[14] Riera L, Sandiumenge A, Calvo C, et al. Percutaneous endoscopic gastrostomy in head and neck cancer patients. ORL J Otorhinolaryngol Relat Spec 2002;64:32–4.

[15] Poulsen MG, Riddle B, Keller J, Porceddu SV, Tripcony L. Predictors of acute grade 4 swallowing toxicity in patients with stages III and IV squamous carcinoma of the head and neck treated with radiotherapy alone. Radiother Oncol 2008;87:253–9.

[16] Koiwai K, Shikama N, Sasaki S, Shinoda A, Kadoya M. Risk factors for severe Dysphagia after concurrent chemoradiotherapy for head and neck cancers. Jpn J Clin Oncol 2009;39:413–7.

[17] Lee N, Puri DR, Blanco AI, Chao KS. Intensity-modulated radiation therapy in head and neck cancers: an update. Head Neck 2007;29:387–400.

[18] Vergeer MR, Doornaert PA, Rietveld DH, Leemans CR, Slotman BJ, Langendijk JA. Intensity-modulated radiotherapy reduces radiation-induced morbidity and improves health-related quality of life: results of a nonrandomized prospective study using a standardized follow-up program. Int J Radiat Oncol Biol Phys 2009;74:1–8.

[19] Garden AS, Asper JA, Morrison WH, et al. Is concurrent chemoradiation the treatment of choice for all patients with stage III or IV head and neck carcinoma? Cancer 2004;100:1171–8.

[20] Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006;354:567–78.