($n = 17$). 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-, 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.

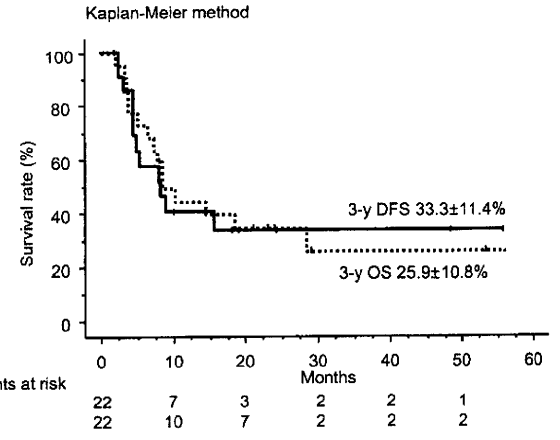

Fig. 1 Survival curves showing overall survival (OS; solid line) and disease-free survival (DFS; dashed line).

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

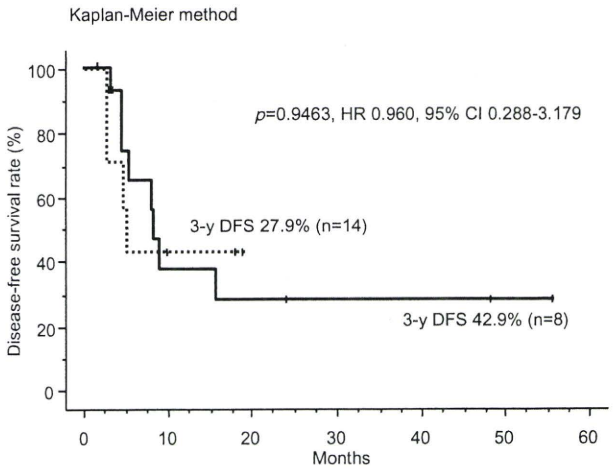

Fig. 2 Survival curves showing disease-free survival (DFS) for number of total cycles of chemotherapy of 1–2 (dashed line) and 3–4 (solid line).

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 diseases 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

			Univariate analysis			Multivariate analysis		
Factor	No.	3-year DFS (%)	*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 overestimated, 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.

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当院における声門癌の臨床的検討

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要　旨

1998年～2004年の間に当科にて治療を施行した声門癌一次根治症例179例について検討した。当科において施行した治療法は，T1症例は放射線単独療法，T2症例は放射線単独療法或いは少量cisplatin（CDDP）併用放射線療法，T3，T4症例は喉頭全摘術であった。

5年死因特異的累積生存率は95.1％，病期別では，Stage Ⅰ：96.5％，Stage Ⅱ：96.6％，Stage Ⅲ：92.9％，Stage Ⅳ：68.6％であった。早期声門癌放射線治療群におけるT分類別局所制御率は，T1a：83.1％，T1b：60.7％，T2：62.5％であり，T2症例群の照射単独群と少量CDDP併用群においてはそれぞれ49.2％，83.6％であった。T2症例において少量CDDPの併用が，局所制御率の向上に影響すると考えられた。

キーワード：声門癌，放射線治療，少量CDDP併用，局所制御，喉頭温存

A clinical study of glottic carcinoma:

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Summary

A clinical study was made of 179 patients with previously untreated glottic carcinoma registered in our department between 1998 and 2004. In our facility, T1 glottic cancer was treated by radiotherapy, T2 glottic cancer by radiotherapy or chemoradiotherapy using low-dose CDDP, and T3 and T4 glottic cancer by laryngectomy.

The five-year cause-specific survival rate for glottic carcinoma was 95.1%, 96.5% for stage I, 96.6% for stage II, 92.9% for stage III, and 68.6% for stage IV. The five-year local control rate for early glottic carcinoma treated by radiotherapy was 83.1% for T1a, 60.7% for T1b, and 62.5% for T2. In T2 cases, the local control rate was 49.2% for treatment by radiotherapy, and 83.6% for low-dose CDDP with radiotherapy. Low-dose CDDP with radiotherapy contributes to high local control rate in T2 cases.

Key words：Glottic carcinoma, Radiotherapy, Low dose CDDP, Local control, Larynx preservation

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はじめに

本邦における喉頭癌罹患率は，人口10万人あたり約3人であり，他臓器の悪性新生物と比較すると頻度の低い癌である。しかし頭頸部領域において最も頻度の高い癌であり，死亡率は人口10万人あたり約1人，年間総死亡者数は約1000人と僅かながら年々増加傾向にある[1,2]。その中でも声門部喉頭癌は，病変が局所に限局した比較的早期の段階で発見される事が多く，根治性と機能温存の観点から治療が施行されている。今回我々は，当科にて初回治療を行った声門癌症例の治療成績を統計学的に分析し，今後の治療上の問題点についてretrospectiveに検討したので，

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若干の文献的考察を加えて報告する。

対象および方法

1998年1月から2004年12月の7年間に東京大学医学部附属病院耳鼻咽喉科を受診し，一次治療として根治治療を行った声門癌患者179例に対して検討を行った。累積粗生存率，死因特異的累積生存率，局所制御率および喉頭温存率をKaplan-Meier法によって算出し，各群の有意差をログランク検定により検定した。$p < 0.05$を有意差ありとした。

結　果

1. 性別および年齢

対象となった179例の内訳は，男性が171例，女性が8例であった。男女比は21：1と圧倒的に男性症例が多かった。罹患年齢は50歳以上が96.1%を占め，平均年齢65.2歳（44～91歳）であった。男性平均年齢65.1歳，女性平均年齢65.2歳と性別間に年齢差は認められなかった。

2. 臨床病期別分類

2002年UICC臨床病期別分類を用い，TNM分類を行った。初診時の内訳としては，Tis：3例（1.6%），T1a：54例（30.2%），T1b：28例（15.6%），T2：71例（39.7%），T3：15例（8.4%），T4：8例（4.5%）であり，T1とT2症例で全体の85%を占めていた。初診時に頸部リンパ節転移を認めた症例は，T3症例2例とT4症例1例の計3例（1.7%）であった（表1）。

3. 病理組織型分類

病理組織型は扁平上皮癌175例，上皮内癌3例，疣状癌1例で，ほとんどが扁平上皮癌であった。

4. 当科における治療方針と治療方法

当科における治療方針を以下に述べる。T1症例に対しては根治照射（総線量：60～70Gy）を施行し，T2症例に対しては，根治照射（総線量：70Gy）或いは少量cisplatin（CDDP）併用根治照射（総線量：70Gy）のいずれかを施行した。原則として，合併症，腎機能障害が無くインフォームドコンセントが得られたT2症例に対しては，少量CDDP併用根治照射を施行した。少量CDDPの施行方法としては，照射30Gy終了時点より（残放射線照射2Gy×20回），照射日に一致してCDDP 5mg/日×20回を点滴静注した。T3，T4症例に対しては，喉頭全摘術を施行した。

実際の治療法の内訳としては，T1症例82例のうち69例（84.1%）に根治照射，2例（2.4%）に部分切除，11例（13.4%）にCO_2レーザー蒸散術を施行した。T2症例では，71例のうち43例（60.1%）に根治照射，25例（35.2%）に少量CDDP併用根治照射を施行し，喉頭全摘を要した症例が3例（4.2%）であった。T3・T4症例に対しては，ほぼ全例喉頭全摘術を施行した（表2）。T3症例において，初診時に頸部リンパ節転移を認めた2例中，喉頭全摘術を施行した1例は（1例は放射線療法），両側の頸部郭清術を施行した。T3N0症例において，喉頭全摘術を施行した12例中，両側5例，患側5例の予防的頸部郭清術を施行し，頸部郭清術を施行しなかった症例は2例であった。T4症例において，初診時に頸部リンパ節転移を認めた1例は，喉頭全摘術，患側の頸部郭清術を施行した。またT4N0症例において，喉頭全摘術を施行した6例中，両側4例，患側1例の予防的頸部郭清術を施行し，頸部郭清術を施行しなかった症例は1例であった。

表1　TNM分類（UICC TNM分類第6版 2002）

	N0	N1	N2	N3	計
Tis	3	0	0	0	3（ 2%）
T1a	54	0	0	0	54（30%）
T1b	28	0	0	0	28（15%）
T2	71	0	0	0	71（40%）
T3	13	2	0	0	15（ 9%）
T4	7	0	0	1	8（ 4%）
計	176(98%)	2(1%)	0(0%)	1(1%)	179(100%)

表2　T分類と主体となる治療法

	Laser	RT	CCRT	ope	計
Tis	3	0	0	0	3
T1	11	69	0	2	82
T2	0	43	25	3	71
T3	0	1	1	13	15
T4	0	1	0	7	8
計	14(8%)	114(63%)	26(15%)	25(14%)	179

※RT：放射線療法，CCRT：化学放射線療法（T2症例は全例少量CDDP併用）

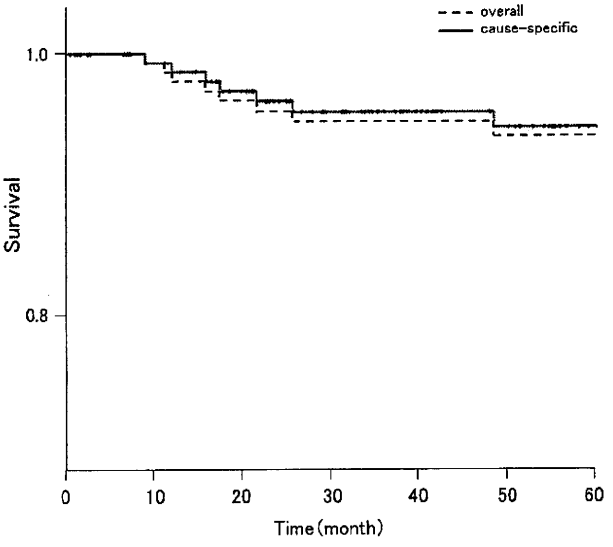

図1　5年累積粗生存率と5年死因特異的累積生存率

5. 治療成績

1）生存率

声門癌179例の5年累積粗生存率は94.6%，5年死因特異的累積生存率は95.1%であった（図1）。病期別5年

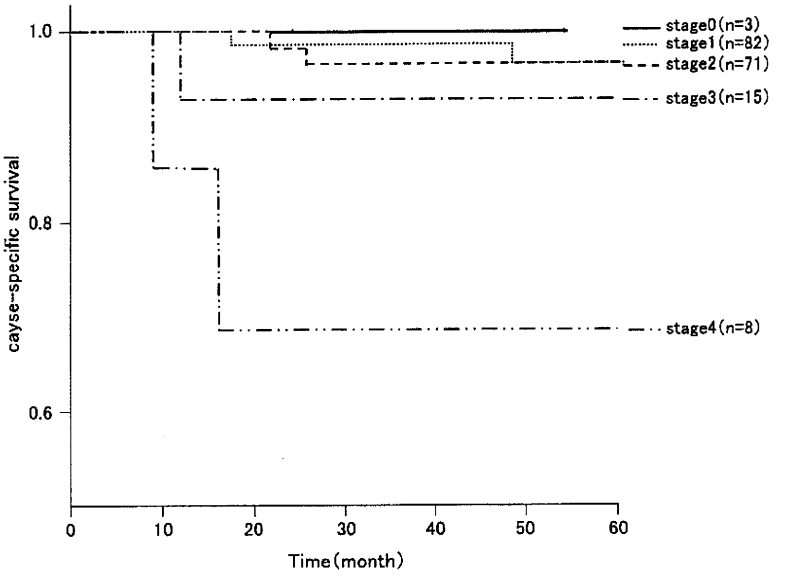

図 2 病期別5年死因特異的累積生存率

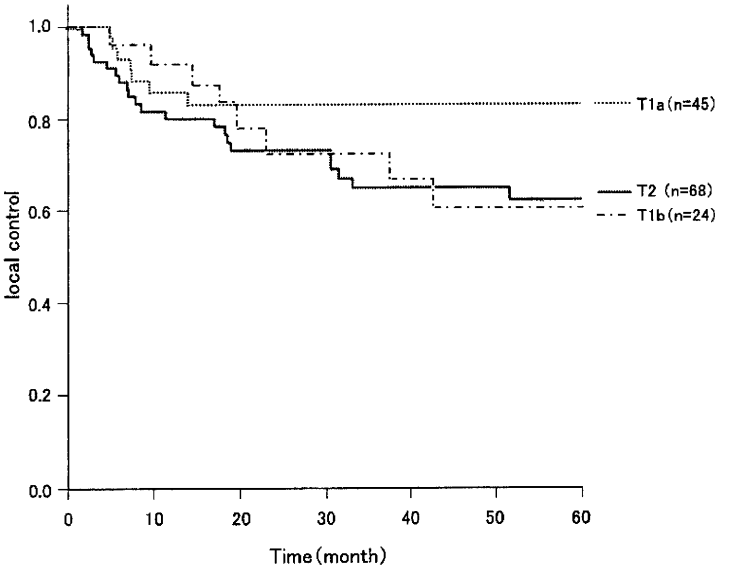

図 3 早期声門癌局所制御率

死因特異的累積生存率は，Stage Ⅰ：96.5％，Stage Ⅱ：96.6％，Stage Ⅲ：92.9％，Stage Ⅳ：68.6％であった(図2)。

2) 早期声門癌における局所制御率

早期声門癌（T1・T2症例）153例におけるT分類別局所制御率はT1a：83.1％，T1b：60.7％，T2：62.5％という結果となった（図3)。

3) 早期声門癌における喉頭温存率

早期声門癌（T1・T2症例）153例における喉頭温存率は87.9％であり，T分類別ではT1a：95.9％，T1b：96.2％，T2：78.3％であり，T1とT2の間に統計学的有意差が認められた（図4)($p = 0.032$)。

4) T2症例における治療法別局所制御率

T2症例71例中，根治照射単独群43例と少量CDDP併用根治照射群25例の局所制御率は，それぞれ49.2％，83.6％であり，2群間に明らかな有意差（$p = 0.010$）が認められた（図5)。

5) 再発症例の検討

声門癌179例中41例（22.9％）に再発を認めた。再発時期の中央値は511日（137～2477日）であった。再発部位としては，原発巣再発34例，頸部再発5例，遠隔転移1例，重複（頸部再発＋遠隔転移）1例であった。

6) 照射後再発症例に対する治療と予後

T1症例は，根治照射施行82例中14例（17.1％）に再発を認め，いずれも原発巣再発であった。初回CO_2レーザー治療群に再発は認められなかった。治療として，8例に喉頭部分切除，4例に喉頭全摘，1例にCO_2レーザー蒸

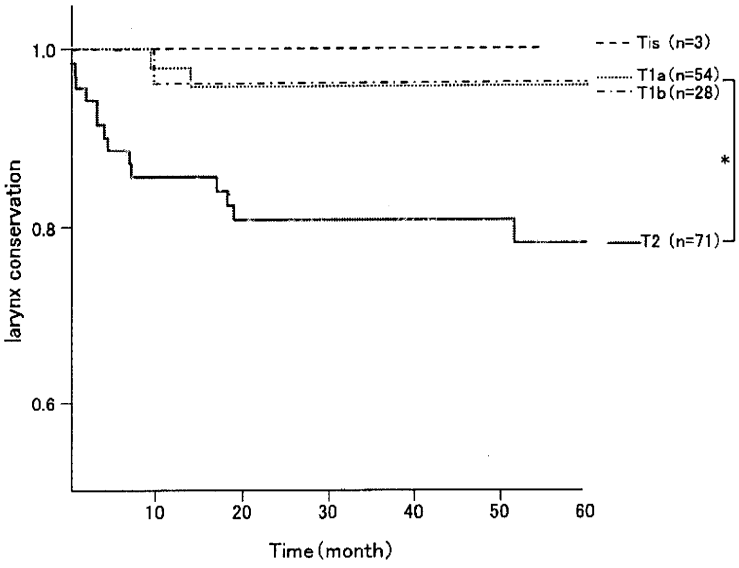

図 4　T 分類別喉頭温存率（*p = 0.032）

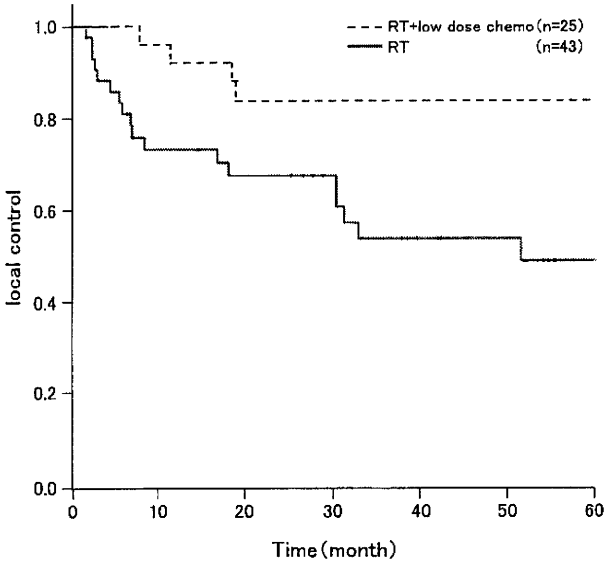

図 5　T2 治療法別局所制御率（p = 0.010）

散術が施行された（1 例は他院にて手術施行）。転帰としては，原病死 2 例（喉頭部切後遠隔転移 1 例，喉頭全摘後遠隔転移 1 例），他癌死 1 例（喉頭部切後食道癌）であった。

T2 症例は，根治照射施行 68 例中 19 例（27.9％）に再発を認めた。少量 CDDP 併用例は 5 例（26.3％）であった。根治照射後再発 19 例中，原発巣再発 17 例，頸部再発 1 例，重複 1 例であった。救済治療として，8 例に喉頭全摘，6 例に喉頭部分切除，3 例に CO_2 レーザー蒸散術，1 例に頸部郭清術を施行した（1 例は再発後来院無し）。転帰としては，原病死 2 例（喉頭全摘後頸部再発 1 例，遠隔転移 1 例），他癌死 1 例（喉頭全摘後原発性肺癌）であった。

7）手術後再発症例に対する治療と予後

初回治療として，喉頭全摘を施行された T3 症例 13 例中 2 例（15.4％）に再発を認めた。気管孔断端に再発した症例に対し，手術，放射線化学療法を施行するも制御不能であり原病死となった。非郭清側の頸部再発を来たした症例に対しては，転移リンパ節が総頸動脈を全周性に取り囲んでいたため，放射線療法を施行したが制御不能であった。

T4 症例においては，初回治療として喉頭全摘を施行した 7 例中 3 例（42.9％）に再発を認めた。遠隔転移（肺）症例 2 例中，1 例はビデオ補助胸腔鏡手術（VATS）を施行し健存となったが，1 例は放射線治療（50Gy）施行するも原病死となった。非郭清側の頸部再発の 1 例に対し，放射線治療（54Gy）を施行するも原病死となった。

考　察

当院における声門癌の病期別検討では，5 年死因特異的累積生存率は Stage Ⅰ：96.5％，Stage Ⅱ：96.6％，Stage Ⅲ：92.9％，Stage Ⅳ：68.6％であり，諸家の報告と比較し若干よい結果であった[3-6]。

一方，局所制御率では T1a：83.1％，T1b：60.7％，T2：62.5％であり，T1b，T2 においては諸家の報告よりも悪い結果であった[3,7,8]。これまでの報告では，T1b，T2 症例局所制御不良因子と考えられる，大きい腫瘍体積[9,10]，前交連浸潤例[9,11]に対し，放射線療法に加え CO_2 レーザーによる腫瘍体積減量術[7]，或いは化学療法併用療法[12]が有用であり，放射線単独療法（一部 T2 症例において少量 CDDP 併用）のみを施行した当科の局所制御率が劣っていた可能性があると考えた。

T2 症例において，放射線単独療法と少量 CDDP 併用療法を施行したため，局所制御率の比較を行った結果，それぞれ 49.2％，83.6％であり，2 群間に統計学的有意差（p = 0.010）が認められた。少量 CDDP 併用療法が臓器温存率を向上させるという報告もあり[12,13]，Akimoto らは，

CDDP 或いはドセタキセルを併用した T2 症例の 5 年局所制御率は 89％と良好な結果であったと報告している[14]。今回の我々の検討においても少量 CDDP 併用群において 83.6％と良好な 5 年局所制御率を得られており，CDDP の併用が局所制御に大きく関与している事が明らかとなった。また，経口抗癌剤を併用し良好な局所制御率を得られたとの報告もある[15]。さらに Niibe らは，経口抗癌剤（テガフール合剤）を併用した T2 症例で，高い 3 年局所制御率が得られたと報告している[16]。経口抗癌剤は，外来治療継続の観点において CDDP よりも有利であることから，データの蓄積と共に T2 症例の治療に有用な薬剤の一つになり得ると考えられた。

T2 症例の中には，局所制御不良因子と考えられている腫瘍体積の大きいものや，前交連浸潤例が含まれている可能性が高く，放射線療法に加え少量 CDDP などの化学療法の併用は，局所制御率の向上に有用であると考えられた。

喉頭温存率については，T1a：95.9％，T1b：96.2％，T2：78.3％であり，諸家の報告とほぼ同様の結果であった。T1a と T2（$p = 0.022$），T1b と T2（$p = 0.047$）の間に統計学的有意差が認められた。

当科早期声門癌症例において，局所制御率こそ悪かったものの，5 年死因特異的累積生存率は他施設よりも良好な結果であった。密な外来 follow で再発癌を早期発見し，適切な救済手術を施行できた結果と考えられた。

これまで当科では，T3・T4 症例に対して喉頭全摘術を中心とした治療を施行してきた。現在当科では T3 症例において，docetaxel（DOC），CDDP，5-FU の 3 剤を併用した導入化学療法を 2 コース施行し，Partial responce（以下 PR）以上のレスポンスが得られた症例に関しては，照射を中心とした治療，PR 未満の症例に関しては喉頭全摘術を施行する方針としている。T4 症例において，T4a 症例は化学放射線療法でも腫瘍のコントロールは困難と考え喉頭全摘術を第一選択とし，T4b 症例は切除不能のため化学放射線療法を第一選択としている。近年海外では頭頸部進行癌に対する化学放射線療法の有用性が示されており，臓器および機能温存と根治の両方を目指す上で，化学放射線療法は重要な役割を担う事は言うまでもない。しかしながら，化学放射線療法後の不根治例に対する救済手術は困難を極め，術後合併症発生の risk も高い。頭頸部進行癌において根治を大前提とし，臓器および機能温存を目指す為には，病期或いは T 分類毎に化学放射線療法，手術療法をうまく組み合わせた集学的治療が不可欠と考えられる。今後の症例の蓄積により，根治及び機能温存の観点から，病期或いは T 分類毎に最も適した療法が確立される事を期待したい。

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ガンマナイフ（Gamma Knife）

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はじめに

スウェーデンの脳神経外科医であったレクセルは、1951年に、定位的手法（stereotactic technique）を用いて1回に高線量の放射線を正確に頭蓋内の標的に照射することにより、開頭術を行うことなく標的部のみの破壊を行う方法を"Radiosurgery"と定義した[1]。その実現のために考案されたのがガンマナイフである。

1968年に、その最初のユニットがSophia-hemmet病院（ストックホルム）に設置された[2]。当初は、三叉神経痛や癌性疼痛などといった通常の脳外科的治療ではコントロールできない機能的障害を治療する目的で用いられた。この治療によって破壊された部位の辺縁が非常にきれいであり、あたかもナイフでカットしたようであったため、この装置はガンマ「ナイフ」とよばれるようになった。

脳動静脈奇形（AVM：arterio-venous malformation）や聴神経腫瘍、下垂体腫瘍といった、血管造影や断層撮影でその部位が捉えられる疾患がおもな対象となっていたが、その後、CT、MRIに代表される3次元画像診断の開発およびその後の普及によって、頭蓋内病変の存在位置、範囲をより正確に3次元的に捉えることが可能になり、その臨床応用範囲が拡がっていった。

日本においては、1990年に東京大学医学部附属病院に最初のガンマナイフが導入され、今年で20年となる。導入当初はAVMおよび聴神経腫瘍、髄膜腫といった良性腫瘍の治療におもに用いられていたが、高度先進医療から保険適応となった頃から、転移性脳腫瘍の治療に広く用いられるようになり、導入施設も急速に増加した。2010年8月の時点で55施設に設置されている。

ガンマナイフの構造

現時点で日本で最も多く使用されているモデルBあるいはCのガンマナイフの外観は、図1に示すとおり、照射ユニット、コリメータヘルメット、治療テーブルよりなっている。

照射ユニット内には201個のコバルト線源が円周状に5列配置され、コリメータにより照射ユニットの中心を焦点としてガンマ線が一点に集中するようになっている（図2）。最終的なビームのコリメーションはコリメータヘルメットによって行われ、コリメータの大きさにより4、8、14、18mmの4種類があり、またそれぞれのコリメータは開口のないプラグに取り替えて遮蔽することも可能となっている。

ガンマナイフの治療手順

高い照射位置精度を確保するために、患者の頭部に定位フレーム（レクセル座標フレーム）を、4本のピンを用いて頭蓋骨にしっかりと固定されるようにとりつける。その後、定位的位置情報取得用のインジケータを装着した上で、治療計画用の定位的画像（MRI、CT、血管造影など）を撮影し、その画像をガンマプランという専用のシステムに転送して治療計画を行う。頭部外表面のフレーム中心からの距離を24点において測定した値を入力することにより、シミュレーションされた頭部

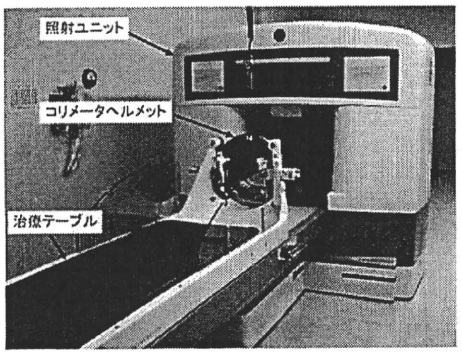

図1　ガンマナイフの外観（4Cモデル）

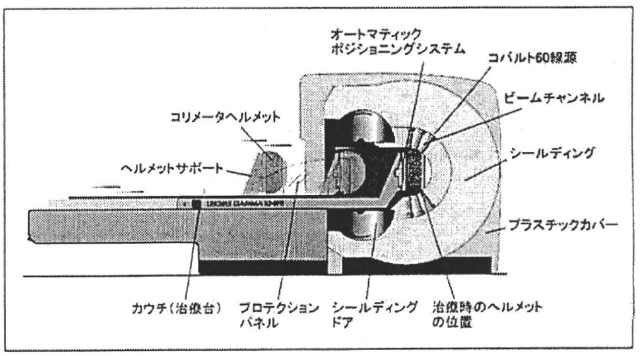

図2　ガンマナイフの内部構造（エレクタ株式会社提供）

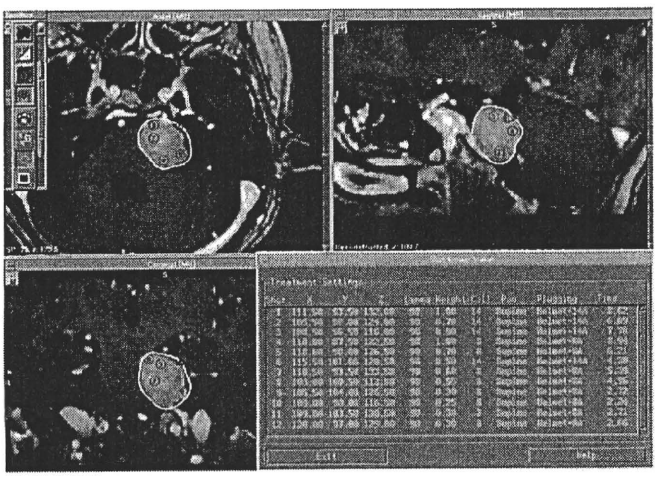

図3　ガンマプランによる治療計画
12ショットを用い、50%の等線量曲線によって、腫瘍を過不足なく囲んでいる（左小脳橋角部髄膜腫症例）。

形状をもとに線量分布計算が行われ、電子密度補正は用いられていない。

1つの焦点に対する照射（ショット）によって、頭尾方向にややつぶれた球形の高線量領域の照射が可能である。ターゲットの大きさや形状に合わせて、必要に応じて複数のショットを組み合わせ、ショットの位置、使用するコリメータの大きさ、ショット数、それぞれのショット間の重みなどを調整して最適な線量分布が得られるようにする。線量勾配は最大線量の30%から70%付近において急峻となっているため、この部分（通常は40～50%）でターゲットを可及的に過不足なく囲むように治療計画を行う（図3）。

最後に、ガンマプランによって作成された治療計画データをもとに計画されたショットを順に照射していく。モデルBにおいては、マニュアルで3軸方向の座標スケールの目盛りを合わせる必要があったが、モデルCにおいては、自動位置合わせ装置（APS：automatic positioning system）を利用して各ショットの位置合わせを自動的に行うことが可能となっている。照射開始のボタンを押すと、シールドドアが開き、治療テーブルが照射ユニットの中に入っていく。ヘルメットのコリメータが照射ユニット内のコリメータと一致した時点で照射が開始される（図2）。照射時間は計10分から2時間程度である。

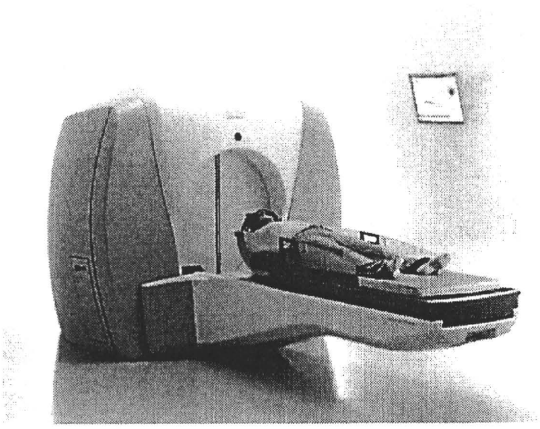

図4　ガンマナイフ『パーフェクション』の外観
（エレクタ株式会社提供）

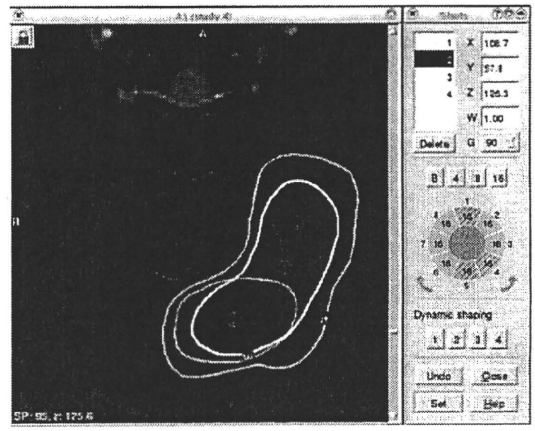

図5　ガンマナイフ『パーフェクション』の治療計画
（エレクタ株式会社提供）

新型のガンマナイフ『パーフェクション』

最新型のガンマナイフであるパーフェクション（図4）が2008年5月に薬事承認され、日本への導入が開始された。2010年8月現在、国内に5台導入されている。これまでのガンマナイフと異なり、コバルト線源は192個であり、3種類のサイズ（4、8、16mm）のコリメータを内蔵しており、線源の位置をずらすことによって、ビームに対するコリメータサイズを治療計画に従って自動的に変えることが可能となっている[3~5]。そのため、コリメータヘルメットを交換する手間がなく、また内部のクリアランスが拡がることで、定位フレームあるいは頭部がぶつかるリスクも低減し、治療可能範囲が拡がっている。

位置合わせについても、定位フレームだけを移動させるAPSとは異なり、寝台ごと移動する機構であり、すべて自動で行うことが可能となったことで、治療時間が短縮されている。治療計画システムも更新され、内蔵コリメータは8つのセクターごとに独立して設定できるため、異なるサイズあるいはオフのセクターを混在したショットが可能となっており、ターゲットの形状に合わせた高線量域を作成し、リスク臓器を避けることがさらに容易となっている（図5）。

さらに、日本ではまだ薬事未承認であるが、エクステンド（extend）という分割照射にも対応する非侵襲的固定方法が選択可能となっており、2010年8月現在、世界で5ヵ所の施設において実際に稼働している[6]。これはフレームに固定されたマウスピースのようなバイトブロックを用いた固定法であるが、中央に空いた穴から空気を抜くことにより、陰圧で上顎に固定するため、患者がしっかりと噛む必要はなく、真空枕（vacuum pillow）と合わせて用いることによって、高い位置精度を確保できるとされている（図6）。

おわりに

ガンマナイフは、わが国へ導入されてから20年が経過し、治療症例および臨床データの累積に伴い、その放射線治療における役割についても一定の評価が得られ、確立した治療方法として認められている[7~11]。日本では、ガンマナイフによる2008年までの累計治療患者数約13万4千人のうち、約6割を転移性脳腫瘍が占めている。この点については一部で批判もあるが、ガンマナイフは多発性の転移病変にも対応可能であり、多くの脳転移患者のQOLの維持や脳転移死の予防に貢献していることも事実である[12~14]。

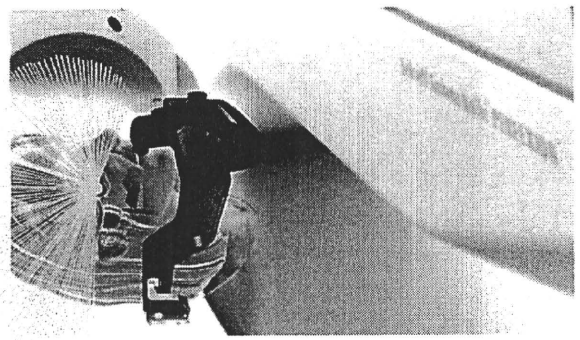

図6　エクステンド（エレクタ株式会社提供）

これまで、臨床データや知見の蓄積に伴い、処方線量の変更や照射法の修正が行われてきた[15, 16]。また、さらなる治療方法の改良や三叉神経痛などの機能的疾患を中心とした適応拡大の試みも続けられている[17]。さらに、パーフェクションの導入による照射可能領域の拡大、および将来的にはエクステンドの使用によって、頭部のみならず上頸部領域の病変に対する分割照射を用いた定位放射線治療（SRT）も可能となるものと思われ、ますます適応範囲が拡大することが期待されている。

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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

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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.

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Historical analysis of cisplatin and docetaxel chemotherapy with concurrent thoracic radiotherapy for locally advanced stage III non-small cell lung cancer in an institute - weekly *versus* conventional schedule of docetaxel -

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Summary

In our institute, the cisplatin (CDDP) + docetaxel chemotherapy regimen is used for treatment of patients with stage III non-small cell lung cancer (NSCLC), who are scheduled for concurrent thoracic radiation therapy. CDDP (80 mg/m^2, day 1) combined with two different administration schedules of weekly divided (20 mg/m^2, day 1, 8, 15 every 4 weeks) or conventional (60 mg/m^2, day 1) docetaxel was performed. Here, we present a summary and comparison of the efficacy and toxicity of concurrent chemoradiotherapy with these chemotherapeutic regimens.

Forty-nine patients under 75 years old with locally advanced stage III NSCLC were enrolled in this study. Initially, 34

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patients received intravenous infusions of docetaxel weekly. Subsequently, 15 patients received the conventional docetaxel regimen. Standard concurrent thoracic radiotherapy was given for 6 weeks (2 Gy per fraction; total dose, 60 Gy) in both chemotherapy regimens.

The frequency of neutropenia over grade 3 in the conventional group (80.0%) was significantly higher than that in the weekly group (23.5%). However, severe esophagitis and pulmonary toxicity were observed in 17.6% and 11.8% of patients in the weekly group, respectively, which were significantly higher than those in the conventional group (0 % and 0% respectively). The objective response rate was 61.2%, with a median survival time (MST) of 26.0 months and 1- and 3- year survival rates of 76.5% and 41.2%, respectively. There were no significant differences in response rate or survival between the groups.

CDDP + docetaxel with concurrent radiotherapy is a feasible and effective regimen for locally advanced NSCLC, but the toxicity profiles are different.

Introduction

Locally advanced unresectable non-small cell lung cancer (NSCLC), *i.e.*, stage IIIA and stage IIIB disease without pleural effusion, is a major target of clinical research in the field of medical oncology. Thoracic radiotherapy (TRT) combined with chemotherapy is currently the standard medical treatment for locally advanced unresectable NSCLC (1 – 5). In addition, recent clinical trials and a meta-analysis suggested the superior efficacy of concurrent over sequential TRT with chemotherapy in patients with locally advanced NSCLC, although there are still insufficient amounts of available clinical data (4,5). Furuse *et al.* (4) reported that concurrent TRT with cisplatin (CDDP), vindesine, and mitomycin chemotherapy yielded a superior response rate and median survival time as compared to sequential radiotherapy with the same chemotherapeutic regimen. The median survival time was 16.5 months and the 2- and 3-year survival rates were 34.6% and 22.3%, respectively, in the concurrent chemoradiotherapy group.

Several novel agents have been introduced since the 1990s and their feasibility and efficacy when combined with concurrent thoracic radiotherapy for stage III NSCLC have been examined. Among these agents, the semisynthetic taxoid docetaxel has been shown to exhibit significant activity against NSCLC. Docetaxel has a radiosensitizing effect *via* induction of cell cycle arrest in the most radiosensitive G2/M phase of the cell cycle (6,7). Based on these advantages, alternative

therapeutic schedules, especially weekly administration of docetaxel with concurrent TRT, have been studied in breast cancer (8) and NSCLC patients (9,10), and encouraging high response rates have been obtained.

We evaluated the feasibility and efficacy of weekly docetaxel (20 mg/m^2, days 1, 8, and 15) plus cisplatin (80 mg/m^2, day 1) with concurrent thoracic irradiation (60 Gy) against stage III NSCLC, and reported that this combination was a potentially feasible combined-modality treatment with moderate toxicity (11).

After that, we conducted a standard chemotherapy regimen of docetaxel (60 mg/m^2, day 1) and CDDP (80 mg/m^2, day 1) with concurrent thoracic irradiation (60 Gy) for patients with stage III NSCLC. Here, we present a summary of our experiences and a comparison of the differences in toxicity and feasibility between weekly and conventional administration of docetaxel.

Materials and methods

Patient eligibility

The summarized data of 34 patients treated with weekly docetaxel + CDDP + TRT have been published previously (11). The eligibility criteria for the conventional docetaxel protocol were similar to those in our previous study (11). Briefly, (1) histologically or cytologically proven unresectable locally advanced NSCLC (clinical stage III), with no history of prior therapy, (2) age 20 to 75 years old, (3) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1, (4) measurable disease and estimated life expectancy of over 3 months, (5) adequate bone marrow function (neutrophil count > 2000/μL, hemoglobin > 10 g/dL, platelet count > 100000/μL), normal renal function (creatinine < 1.5 mg/dL, creatinine clearance > 60 mL/min), normal hepatic function (total bilirubin < 1.5 mg/dL, serum aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase levels < 2× upper limit of the normal range), and normal pulmonary function (partial arterial oxygen tension > 70 Torr, forced expiratory volume in 1 s > 70%). Patients were excluded from the therapy if they had (1) malignant pleural effusion or supraclavicular nodes, or the primary tumor size exceeded half of one lung in stage III, (2) active infection, (3) severe heart disease, (4) past history of hypersensitivity to drugs, (5) pericardial effusion requiring drainage, (6) pregnancy, (7) active double malignancy, (8) interstitial pneumonia as detected on a chest radiography, or (9) an initial radiation field exceeding 50% of one lung. No other concomitant anticancer therapy or experimental drug administration of any type was permitted. Written informed consent was obtained from each of the patients prior