図 1　耳鼻咽喉科病棟での嚥下リハビリテーションの実際

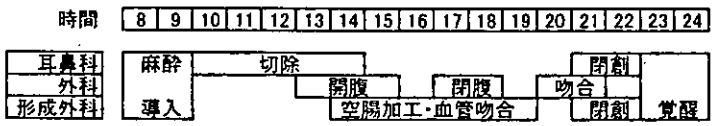

図 2　3科による咽喉食摘・遊離空腸再建手術の術中の推移

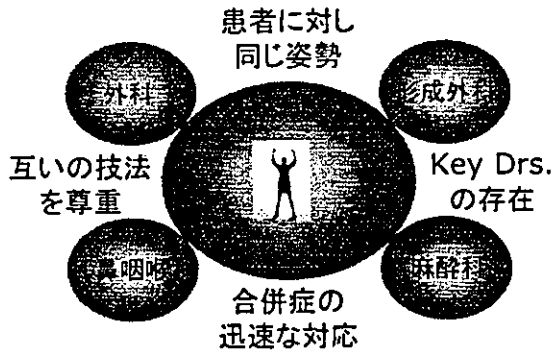

図 3　3科合同手術の要点

癌で亡くなる年間30万人の患者の90%が病院死といわれている。しかし実際にはその2人に1人が自宅で最後を迎えたいというニーズがあるとされている[5]。人生の継続性，自己決定権の維持を尊重した自立支援の視点が求められている[6]。

2000年に介護保険が施行されたのをきっかけに，当院では総合相談部の訪問保健師を中心に医師，外来・病棟看護師が協力して条件が整う末期患者については積極的に在宅緩和医療を支援してきた。

大学病院の限られた人員で在宅を可能にする要因は1）家族にリーダーシップを発揮できるkey personがいること，2）介護が多様かつ複雑化した時に攻めの姿勢でいること，3）主治医や受持医も在宅訪問し，採血や診察を行えること，である。家族の中で生活者の介護に中心的な役割を果たすkey personは必須で，家族全員をまとめ，地域の介護ケアのスタッフや病院の訪問保健師との密接な連携に不可欠である。生活者の病状が複雑になり様々なケア（吸引，在宅酸素，尿管カテ，胃管栄養，中心静脈栄養，など）が必要になった時に，医療者側や地域介護サポートが家族と一丸となって攻めの姿勢でいることが大切である[7]。主治医や受持医の在宅訪問では採血や簡単な診察を行っている（図4）。これは医療的側面のみではなく，患者と家族にとって精神的にも安心感が得られる要因となる。

大学病院が在宅緩和医療を行う意義は1）患者の疾患（disease）の高度なケアを追求するだけではなく，人の病気（illness）を診ることができる感性を養えること，2）生活者の多様性に対応することで，病院での医療のあり方を改めて見つめ直せること，3）在宅訪問を行った患者の死後しばらくしてから焼香に訪れ，ご遺族からの貴重なメッセージを聞くことができること，である。疾患だけではなく人の病気を診ることのできる在宅

図 4　大学病院の主治医，受持医による訪問診療

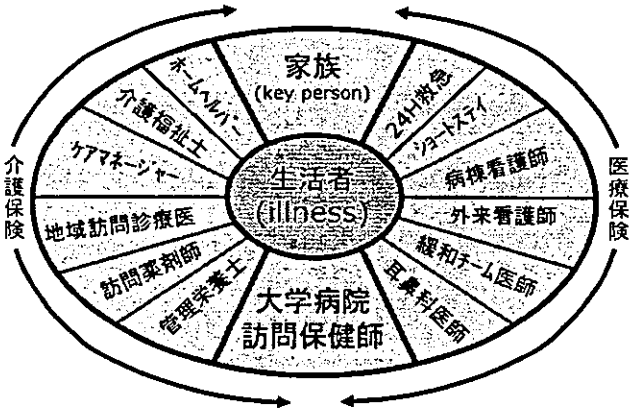

図 5　大学病院が行う在宅緩和医療の概念

医療は医師の卒後研修においても重要である。在宅では患者に医療者の標準化を当てはめる従来型の病院医療は通用しない。生活者の多様性に対応することで改めて病院での医療を客観的に見つめ直せると考えている。特に，患者の死を病院内のみで見取る医療者がご遺族から聞ける本音のメッセージは貴重である。当院での取り組みは昨年行われた厚生労働省の特定共同指導にて取り上げられ，評価を頂いた。

内部から全体の平衡状態を維持する生活世界のゲシュタルト論[8]を元に大学病院が行う在宅緩和医療のモデルを提示した（図5）。医療保険と介護保険の両者を適切に組み合わせ支援することが大切である。その際，大学病院には生活者の急な症状の悪化に対応できる24時間の受け入れ態勢，またショートステイとしての短期入院の支援を整えておくことが重要である。短期入院は患者のみでなく介護している家族の休養の目的でも有意義である。大学病院の訪問保健師を中心に関係各職種が十分な連携を取り，生活者の地域スタッフと協力することが大切である。

まとめ

理想的なチーム医療のために常に自問を続けたい3つの問いかけは：

1）真の peer review ができているか，すなわち医療者間に気軽に意見が言い合える雰囲気があるか。

2）各分野にリーダーシップを発揮できる key persons がいるか，すなわち vision を示し責任を取れる人がいるか。

3）Cutting edge（または State of the art）に身を置いているか，すなわち各職種がプロとして安易な妥協をせず，伝統を重んじつつも常に先を見据えているか。

早渕ら[9,10]が述べているように「当たり前のことをきちんと行えているか」を自問しながらこれからもチーム医療に当たって行きたい。

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Expression of Matrix Metalloproteinase 9 Is a Prognostic Factor in Patients with Non-Hodgkin Lymphoma

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BACKGROUND. Non-Hodgkin lymphoma (NHL) represents a heterogeneous group of tumors that vary with regard to their biologic aggressiveness and clinical course. In in vitro studies, matrix metalloproteinase 9 (MMP9) was reportedly expressed by human NHL cells and elevated levels of MMP9 have been observed in a subset of patients with high-grade NHL.

METHODS. The expression of MMP2 and MMP9 was evaluated in 158 patients with NHL and the relation between the expression of these proteins and clinicopathologic factors was analyzed. All but 1 patient had received radiation therapy and 92 patients also were treated with intensive combination chemotherapy.

RESULTS. Nearly all the patients with extranodal natural killer NK/T-cell lymphoma nasal type and anaplastic large cell lymphoma, T-cell/null cell type expressed MMP9. In contrast, only a small fraction of the patients with mucosa-associated lymphoid tissue (MALT) lymphomas and follicular lymphomas expressed MMP9. Approximately 50% of the diffuse large B-cell lymphoma (DLBCL) cases expressed MMP9. The expression of MMP2 was noted in some of the patients with DLBCL and nasal NK/T-cell lymphoma. The overall survival rates of patients who expressed MMP9 were significantly lower than that of those who did not. Such a correlation was not demonstrated in MMP2 expression. When MMP9 expression was analyzed in DLBLC patients, the overall survival rates of patients who expressed MMP9 were significantly lower than those who did not express MMP9. Chemotherapy was associated with better overall survival in DLBCL patients who expressed MMP9. Overall survival rates of T-cell/NK-cell lymphoma patients who expressed MMP9 appeared to be lower than that in those who did not express MMP9. However, chemotherapy was not found to improve overall survival in patients who expressed MMP9.

CONCLUSIONS. MMP9 expression was observed in patients with aggressive NHL and was characterized by poor overall survival. *Cancer* **2004;100:356–65.**
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KEYWORDS: Non-Hodgkin lymphoma (NHL), matrix metalloproteinase 9 (MMP9), matrix metalloproteinase 2 (MMP2), prognostic factor, Epstein–Barr encoded small RNA 1 (EBER1).

Non-Hodgkin lymphoma (NHL) represents a heterogeneous group of tumors that vary in their biologic aggressiveness and clinical course.[1]

A variety of lymphoma classifications have been advanced on the basis of both morphologic and molecular parameters. The most recent classification scheme, the Revised European–American Lymphoma classification, and the World Health Organization classification system were introduced to categorize distinct clinicopathologic

TABLE 1
Primary Tumor Sites and Pathologic Classification

Pathology	Brain	Orbit	NC	PS	NP	WR	Thyroid	SG	LN	Others	Stage I	Stage II	Stage III or IV
MALT L		29					3	2		1	30	3	2
DLBCL	7	3	4	4	6	31	1	1	15	3	35	29	11
Follicular L		3				2		3	5	1	8	4	2
Peripheral T cell L			4			1			2	1	6		2
Anaplastic large cell L	1		1			1				1	1	3	
Nasal NK/T-cell L			17								11	4	2
Stage I	7	29	17	4	3	8	4	4	12	3			
Stage II	1	4	6		2	23		1	4	2			
Stage III or IV		2	2		1	4		1	6	2			

NC: nasal cavity; PS: paranasal sinus; NP: nasopharynx; WR: Waldeyer ring excluding the nasopharynx; SG: salivary glands; LN: lymph nodes; MALT L: mucosa-associated lymphoid tissue lymphoma; DLBCL: diffuse large B-cell lymphoma; Follicular L: follicular lymphoma; Peripheral T-cell L: peripheral T-cell/ lymphoma; Nasal NK/T-cell L: nasal natural killer cell/T-cell lymphoma.

entities. However, within this classification system, various morphologic subtypes were unified into groups despite the suspicion that they included several disease entities.[2,3] Despite the variety of clinical, morphologic, and molecular parameters currently used to classify human malignancies, patients receiving the same diagnosis can have markedly different clinical courses and responses to treatment.[4] Therefore, developing an algorithm for selecting the treatment modality suitable for each patient with NHL is very important.

The matrix metalloproteinases (MMPs) are a family of zinc- and calcium-dependent proteolytic enzymes capable of degrading most extracellular matrix (ECM) components.[5] Depending on their substrate specificity, MMPs are broadly divided into collagenases, stromelysins, and gelatinases. The latter group, comprised of Gelatinase A (MMP2) and Gelatinase B (MMP9), degrade denatured collagens (gelatin), native Type IV and Type V collagens, and elastin.[6] Because Type IV collagen is one of the integral components of the basement membrane (BM), the uncontrolled expression of two Type IV collagenases, MMP2 and MMP9, is believed to play a critical role in the invasion of the BM by tumor cells.[7] MMPs have been implicated in tumor invasion and metastasis.[8,9]

In the current study, we performed an immunohistochemical study of the expression of MMP2 and MMP9 in patients with NHL to examine their value as prognostic factors.

MATERIALS AND METHODS

Patient Characteristics

Between 1983 and 2001, 158 patients with histologically confirmed NHL were treated at the Department of Radiology at Sapporo Medical University Hospital.

There were 35 patients with extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type (MALT lymphoma) (mean age, 61.9 years; range, 28–89 years); 75 patients with diffuse large B-cell lymphoma (DLBCL) (mean age, 60.8 years; range, 28–89 years); 14 patients with follicular lymphoma (mean age, 57.0 years; range, 19–86 years); 17 patients with extranodal natural killer (NK) cell/T-cell lymphoma, nasal type (nasal NK/T-cell lymphoma) (mean age, 51.1 years; range, 27–74 years); 8 patients with unclassified peripheral T-cell lymphoma (mean age, 56.0 years; range, 35–73 years); 4 patients with anaplastic large cell lymphoma, T-cell/ null cell type (mean age, 53.5 years; range, 40–69 years); and 5 others. The mean age for the total generation was 59.0 years and nasal NK/T-cell lymphoma appeared to be prevalent in the younger generation, compared with the other lymphomas. The gender distribution for the total generation was 81 male and 77 female patients. The gender distribution according to pathologic classification was as follows: 16 males and 19 females with MALT lymphoma, 41 males and 34 females with DLBCL, 7 males and 7 females with follicular lymphoma, 10 males and 7 females with nasal NK/T-cell lymphoma, 5 males and 3 females with peripheral T-cell lymphoma, and 4 females with anaplastic large cell lymphoma. The clinical stage was defined according to Ann Arbor classification. 94 had Stage I disease, 45 patients had Stage II disease, 10 patients had Stage III disease, and 9 patients had Stage IV disease.

Table1 shows the histopathologic distribution according to primary tumor sites. The majority of MALT lymphomas originated from the orbit (29 patients) or thyroid gland (3 patients). Of the eight peripheral T cell L cell lymphoma cases, four originated in the nasal cavity and two originated in the lymph nodes. Nasal

NK/T-cell lymphoma was noted in the nasal sinus only. DLBCL cases were all from primary tumor sites.

Treatment

All but one patient received radiation therapy. Sixty patients received radiation therapy alone. Radiation therapy usually was delivered to the involved field. The dose per fraction ranged from 1.8–2.0 grays (Gy). All treatment regimens included five daily fractions per week. A total dose of 50 Gy for intermediate or more aggressive diseases and 40 Gy for low-grade lymphomas was usually planned.

Ninety-two patients received the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen, a modified CHOP regimen, or more intensive chemotherapy and 9 patients were treated with other combination or single-agent chemotherapy.

Statistical Analysis

Disease-specific survival rates of the patients were measured using the Kaplan–Meier method. Statistical significance was compared using the log-rank test.

Immunohistochemical Examination

All the biopsies were obtained at the initial time of the diagnosis. Immunohistochemical staining was performed using the avidin–biotin–peroxidase complex method.[10]

Biopsy specimens from formalin-fixed and paraffin-embedded tumor and normal tissues were stained using antibodies to each protein. After deparaffinization, the tumor specimens were cut at 5-um thickness and stained using an immunohistochemical procedure. The streptoavidin–biotin–peroxidase complex technique (SAB) was used for staining sections. The SAB technique was performed as follows. After blocking with 1% hydrogen peroxide in methanol, Fc receptor was blocked with 30% bovine serum for 15 minutes. The sections were incubated overnight at room temperature with each specific primary antibody. The sections then were incubated with a second biotinylated antibody of rabbit antimouse specificity (Nichirei, Tokyo, Japan) for 10 minutes. The avidin–peroxidase reagent (Nichirei) then was applied for 10 minutes. All sections were counterstained with hematoxylin. Reactivity was visualized with 3,3'-diaminobenzidine tetrahydrochloride (DAB) as the substrate, yielding a brown reaction product.

Immunohistochemical detection was performed using the following monoclonal antibodies: antihuman MMP2 (Daiichi Fine Chemical Company., Ltd., Takaoka Japan) (1:200 dilution) and antihuman MMP9 (Daiichi Fine Chemical Company, Ltd.) (1:200 dilution). Normal mouse serum was substituted for primary antibodies as a negative control. For MMP2 and MMP9, tumors that contained at least focally moderate to strong immunoreactivity were considered positive.

In Situ Hybridization

RNA-DNA in situ hybridization was performed on formalin-fixed and paraffin-embedded tissue sections using the biotinylated synthetic DNA probe as previously described, with modifications.[11] Briefly, 5-um tissue sections were cut on sialinized slides, dewaxed in xylene, and rehydrated. The endogenous peroxidase activity was blocked with 0.5% hydrogen peroxide in phosphate-buffered saline (PBS) and the slides were dried after dehydration. The biotinylated probe was an oligonucleotide DNA complimentary to the EBER1 sequence that was chemically labeled with 6 biotin molecules (5'-CCCTAGCAAAACCTCTAGGGCAGC-(TAG)5-BBB-(TAG)2-BBB-3).[11] The probe was diluted to a concentration of 1 ug/mL in Brigati Probe Diluent (Research Genetics, Huntsville, AL). Depending on the size of the tissue section, 50–100 uL of the diluted probe solution was spotted on to the sections and a coverslip placed on top. After incubation in a humidified chamber at 45 °C for 2 hours, the slides were immersed in PBS 3 times at room temperature. The hybridization signal was detected by using the avidin-biotin-peroxidase technique with DAB as the chromogen (Nichirei). The sections then were counterstained with hematoxylin, dehydrated, mounted with permount, and investigated under a light microscope.

RESULTS

Expression of MMP2 and MMP9

Immunohistochemically, the MMP9 gene product was localized in lymphoma cells, macrophages, and neutrophils (Fig. 1A). All cells that were positive for MMP9 were intensely stained, indicating that they expressed high levels of MMP9. Cells that expressed MMP9 existed at the invasive edge of tumor cell nests and the peripheral regions of the necrotic zone. MMP2 gene product was detected only on stromal fibroblasts and macrophages surrounding the tumor cells (Fig. 1B).

The expression rates of MMP2 and MMP9 are shown in Table 2. MMP9 was expressed in T-cell lymphomas more frequently compared with B-cell lymphomas. Of particular note, nearly all the patients with nasal NK/T-cell lymphoma and anaplastic large cell lymphoma expressed MMP9. In contrast, only a small section of the patients with MALT lymphomas and follicular lymphomas expressed MMP9. Approximately 50% of the DLBCL patients expressed MMP9. The MMP9 expression rates in DLBCL according to

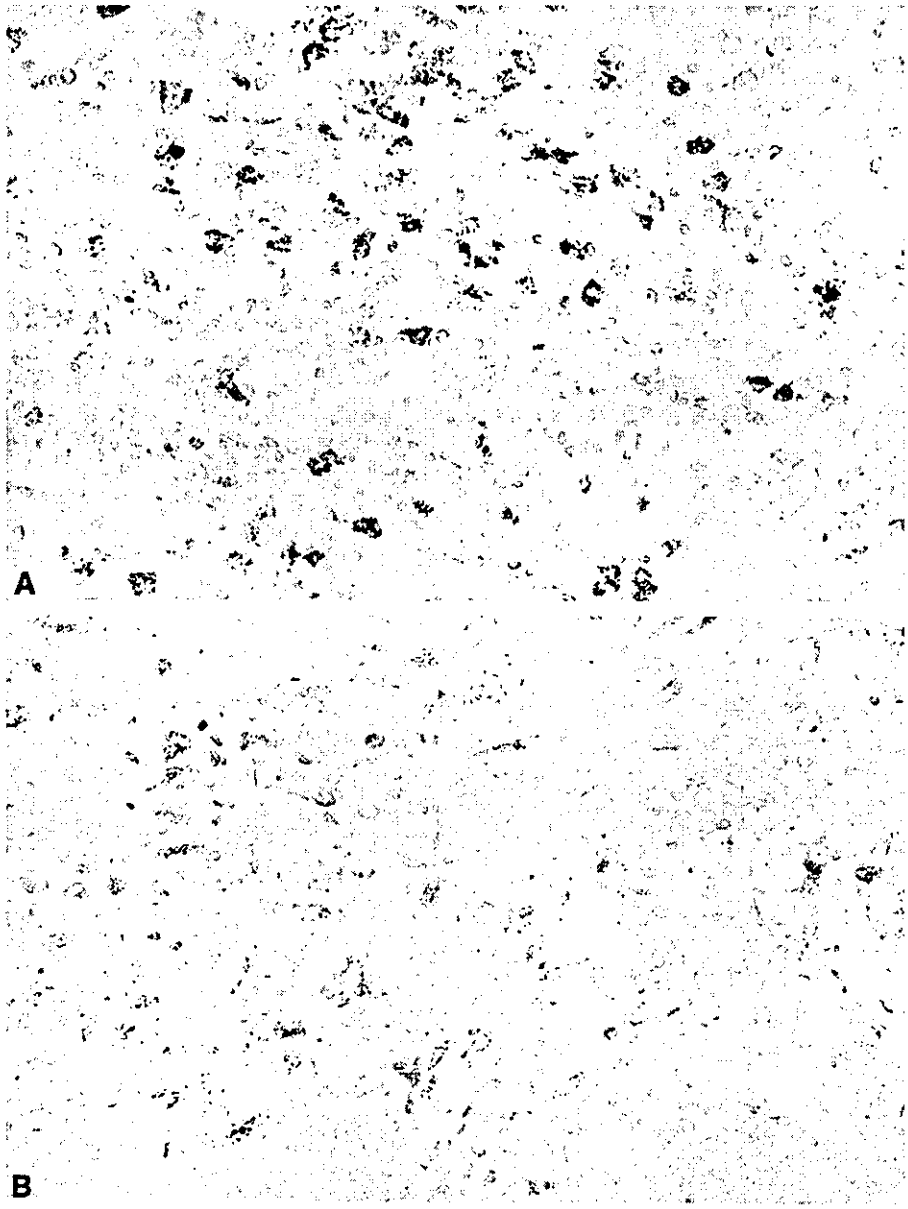

FIGURE 1. (A) Cells that expressed matrix metalloproteinase 9 (MMP9) existed at the invasive edge of tumor cell nests. (B) Only stromal fibroblasts and macrophages surrounding the tumor cells were found to express MMP2. (C) Expression of Epstein–Barr virus encoded small RNA 1 (EBER1) transcripts. In situ hybridization profiles demonstrated signals of the EBER1 RNA transcripts in the nuclei of the great majority of tumor cells (original magnification ×400, A–C).

stage of disease were 17 of 35 patients with Stage I disease, 16 of 29 patients with for Stage II disease, and 5 of 11 patients with Stage III or Stage IV disease. The MMP9 expression rates in peripheral NK/T-cell lymphoma according to stage of disease were three of six patients with Stage I disease and two of two patients with Stage IV disease.

Approximately 45% of the patients with DLBCL and 29% of those with nasal NK/T-cell lymphoma expressed MMP2. However, none or very few patients with the other types of lymphomas expressed MMP2. The MMP2 expression rates in DLBCL according to stage of disease were 12 of 35 patients with Stage I disease, 21 of 29 patients with Stage II disease, and 1 of 11 patients with Stage III or Stage IV disease. MMP2 expression rates in patients with nasal NK/T-cell lymphoma according to disease stage were 3 of 11 patients with Stage I disease, 1 of 4 patients with Stage II disease, and 1 of 2 patients with Stage IV disease.

Survival

Figure 2 shows overall survival rates in patients with Stage I and Stage II NHL according to histologic classification. The overall 5-year survival rate for patients

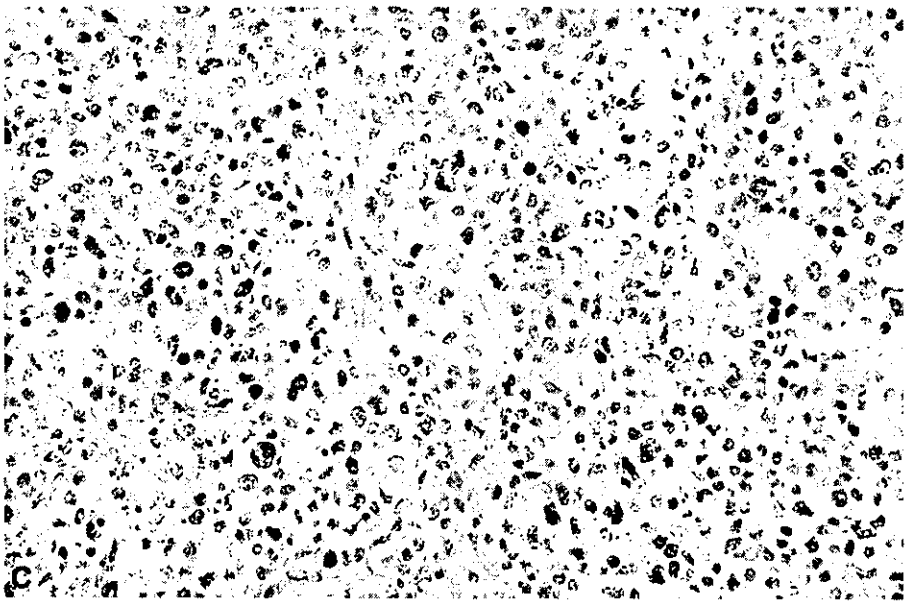

FIGURE 1. *(continued)*

TABLE 2
Expression of MMP2 and MMP9 According to Pathology

Pathology	MMP2	MMP9
Marginal zone B-cell lymphoma	1/35 (2.9%)	3/35 (8.6%)
Diffuse large B-cell lymphoma	34/75 (45%)	37/75 (49%)
Follicular lymphoma	0/14 (0%)	2/14 (14%)
Extranodal NK/T-cell lymphoma, nasal type	5/17 (29%)	15/17 (88%)
Peripheral T-cell lymphoma	0/8 (0%)	5/8 (63%)
Anaplastic large cell lymphoma	0/4 (0%)	4/4 (100%)

MMP2: matrix metalloproteinase 2; MMP9: matrix metalloproteinase 9; NK: natural killer cell.

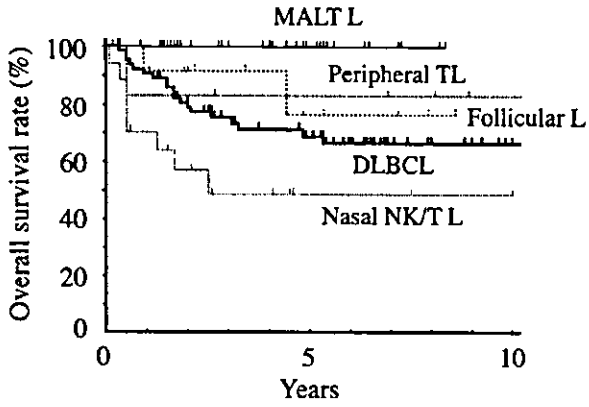

FIGURE 2. Overall survival curves for patients with Stage I and II non-Hodgkin lymphoma according to histologic examination. MALT L: mucosa-associated lymphoid tissue lymphoma; Peripheral TL: unclassified peripheral T-cell lymphoma; Follicular L: follicular lymphoma; DLBCL: diffuse large B-cell lymphoma; NK/T L: natural killer/T-cell lymphoma.

with MALT lymphoma was 100%. Patients with MALT lymphoma demonstrated higher survival rates than patients with follicular lymphoma ($P < 0.05$), DLBCL ($P < 0.01$), or peripheral T-cell lymphoma ($P < 0.05$). Patients with nasal NK/T-cell lymphoma were found to have significantly lower survival rates than patients with MALT lymphomas ($P < 0.01$), follicular lymphomas ($P < 0.05$), or DLBCL ($P < 0.05$).

Figure 3A shows the overall survival rates of all patients with Stage I or Stage II lymphoma according to MMP9 expression. The 5-year overall survival rate for those patients who expressed MMP9 was 50%. The 5-year overall survival rate for patients who did not express MMP9 was 88%. The difference was found to be statistically significant ($P < 0.01$).

Figure 3B shows the overall survival rates for all patients with Stage I or Stage II according to the expression of MMP2. The 5-year overall survival rate for patients who expressed MMP2 was 62%. The 5-year overall survival rate for patients who did not express MMP2 was 73%. There was no statistically significant difference.

DLBCL and MMP9 Expression

Figure 4A demonstrates the overall survival rates of DLBCL patients with Stage I or Stage II disease according to MMP9 expression. The 5-year and 10-year overall survival rates for patients who expressed MMP9 were 58% and 54%, respectively. The 5-year and 10-year overall survival rates for patients who did not express MMP9 were 83% and 83%, respectively. The difference was statistically significant ($P < 0.01$).

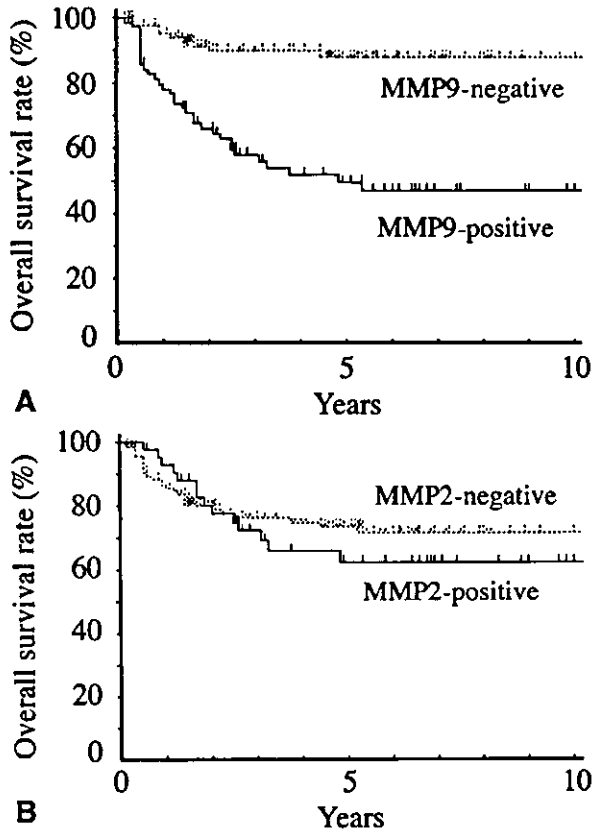

FIGURE 3. (A) Overall survival rates of patients with Stage I and II non-Hodgkin lymphoma according to matrix metalloproteinase 9 (MMP9) expression. (B) Overall survival rates of patients with Stage I and II non-Hodgkin lymphoma according to MMP2 expression.

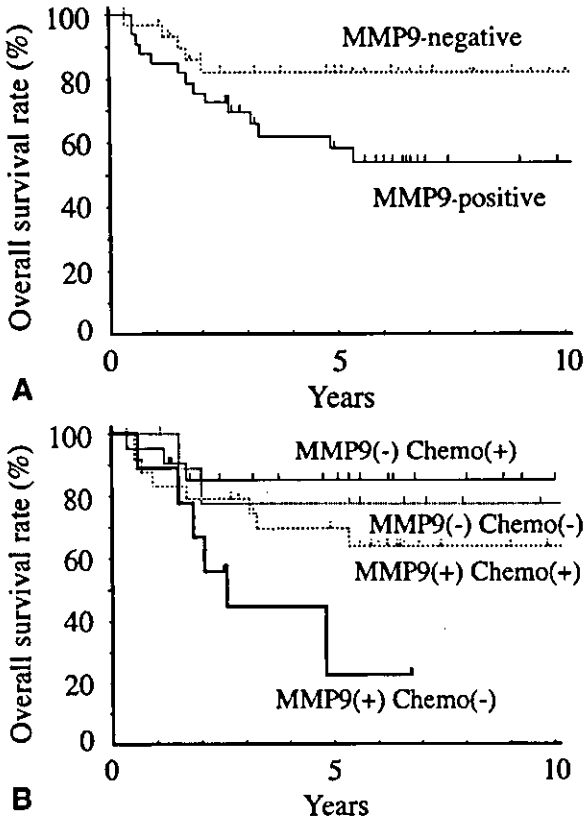

FIGURE 4. (A) Overall survival rates of patients with Stage I and II diffuse large B-cell lymphoma (DLBCL) according to matrix metalloproteinase-9 (MMP9) expression. (B) Overall survival rates of patients with Stage I and II DLBCL according to MMP9 expression and use of chemotherapy (Chemo). Patients treated with chemotherapy (Chemo [+]) included patients treated with the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen; a modified CHOP regimen; or more intensive chemotherapy. Patients treated with other combination or single-agent chemotherapy were not included in this group.

Figure 4B presents the effect of chemotherapy on overall survival rates in DLBCL patients with Stage I or Stage II disease.

Chemotherapy was associated with better survival in patients whose tumors expressed MMP9. However, the difference was not found to be statistically significant, most likely because of the inadequate sample size.

Chemotherapy did not appear to significantly improve the overall survival of patients whose tumors did not express MMP9.

T-cell/ NK Lymphoma and MMP9 Expression

Figure 5A demonstrates the overall survival rates of T-cell/ NK-cell (T/NK) lymphoma patients with Stage I or Stage II disease according to the expression of MMP9. The 5-year and 10-year overall survival rates for patients who expressed MMP9 were 43% and 43%, respectively. The 5-year overall survival rate for patients who did not express MMP9 was 80%. Although difference was not statistically significant, this most likely was because of the small sample size.

Figure 5B shows the effect of chemotherapy on overall survival rates of patients with T/NK lymphoma with Stage I or Stage II disease. Chemotherapy did not appear to improve the overall survival of those patients who expressed MMP9.

Epstein–Barr Virus Encoded Small RNA 1 Detection Rates

Epstein–Barr virus encoded small RNA 1 (EBER1) transcripts were detected in nearly all patients with nasal NK/T-cell lymphoma (Fig. 1C; Table 3). There were EBER1 transcripts in DLBCL patients and those with peripheral T-cell lymphoma. However, detec-

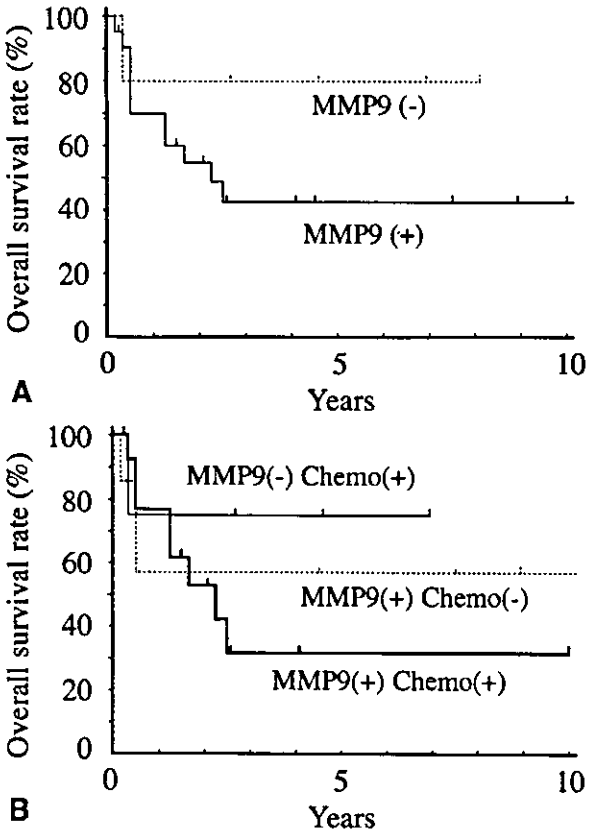

FIGURE 5. (A) Overall survival rates of patients with Stage I and II T-cell/natural killer cell (T/NK) lymphoma according to matrix metalloproteinase-9 (MMP9) expression. (B) Overall survival rates of patients with Stage I and II T/NK lymphoma according to MMP9 expression and use of chemotherapy. Patients treated with chemotherapy (Chemo [+]) included patients treated with the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen; a modified CHOP regimen; or more intensive chemotherapy. Patients treated with other combinations or single-agent chemotherapy were not included in this group.

tion rates of DLBCL and peripheral T-cell lymphoma were much lower than those of nasal NK/T-cell lymphoma. Detection rates of EBER1 transcripts in patients who expressed MMP9 were similar to detection rates in the total number of patients with DLBCL and peripheral T-cell lymphoma. Detection rates of EBER1 in patients with DLBCL according to stage of disease were 2 of 32 patients with Stage I disease, 4 of 22 patients with Stage II disease, and 1 of 11 patients with Stage III or Stage IV disease. The EBER1 detection rates for patients with peripheral T-cell lymphoma based on stage of disease were two of six patients with Stage I disease and neither of the two patients with Stage III or Stage IV disease.

TABLE 3
Detection Rates of EBER1 Transcripts According to Histologic Examination

Pathology	In overall cases	In MMP9-positive cases
DLBCL	7/65 (11%)	4/33 (12%)
Peripheral T-cell lymphoma	4/8 (50%)	2/5 (40%)
Anaplastic large cell lymphoma	0/4 (0%)	0/4 (0%)
Nasal NK/T-cell lymphoma	16/17 (94%)	14/15 (93%)

EBER1: Epstein–Barr virus encoded small RNA 1; MMP9: matrix metalloproteinase 9; DLBCL: diffuse large B-cell lymphoma; NK: natural killer cell.

DISCUSSION

In the current series, 157 of 158 patients received radiation therapy. Sixty patients received radiation therapy alone. This is an unusual distribution in terms of chemotherapy versus radiation therapy for NHL patients in the U.S. and Europe. One possibility for this difference is the referral bias to a radiology department because this study is based on patients treated at the Department of Radiology at Sapporo Medical University Hospital. Another possibility is the differing frequencies of NHL in Japan and in Western countries. Follicular lymphoma is the second most common lymphoma in the U.S. and western Europe, accounting for 20% of all NHL cases and up to 70% of low-grade lymphoma cases reported in American and European clinical trials.[12,13] Most patients with follicular lymphoma have widespread disease at the time of diagnosis, and are treated with chemotherapy. However, follicular lymphoma is relatively rare in Japan.[14]

Essential steps in the process of tumor invasion and metastasis include the degradation of the ECM and BM. The invasion of the BM by tumor cells is believed to be one of the critical steps in metastasis, which includes sequential multistep processes.[15] Many proteolytic enzymes degrade components of the ECM and BM.[16] Among these, the MMPs are attractive candidates for enzymes required for tumor metastasis. The MMPs can degrade native collagens and other ECM components.[17] The MMP family includes 4 types of collagenase (MMP1, MMP8, MMP13,and MMP18), 3 types of stromelysin (MMP3, MMP10, and MMP11), and the 72-kilodalton (kD) and 92-kD Type IV gelatinases or collagenases (MMP2 and MMP9). Because Type IV collagen is one of the integral components of the BM, the uncontrolled expression of two Type IV collagenases, MMP2 and MMP9, is believed to play a critical role in the invasion of the BM by tumor cells.[7] The release of MMP2 and/or MMP9 has been associated with metastasis in a variety of model systems.[18–20]

It was demonstrated in an in vitro study that MMP9 is expressed by human NHL cells and elevated levels of MMP9 were observed in a subset of high-grade NHL cases.[21,22] To our knowledge, the current study is the first study published to date in which the expression of MMP9 and MMP2 in lymphoma tissues were investigated immunohistochemically to examine their values as prognostic factors. The findings of the current study agreed with findings obtained with in vitro studies. NHL patients who expressed MMP9 appeared to have a significantly worse prognosis compared with patients who did not express MMP9 (Fig. 3A). MMP9 positivity was more prevalent in aggressive lymphomas compared with indolent lymphomas (Table 2). Nearly all patients with nasal NK/T-cell lymphoma and anaplastic large cell lymphoma expressed MMP9. In contrast, only a small section of patients with MALT lymphomas and follicular lymphomas expressed MMP9.

The current study results observed in DLBCL patients were compatible with previous results obtained with chemotherapy alone.[23] However, the study by Miller et al. included histologies other than DLBCL. Approximately 50% of the DLBCL patients expressed MMP9, indicating that DLBCL can be divided into different malignancy groups according to MMP9 expression. We also demonstrated that chemotherapy was associated with improved overall survival in patients who expressed MMP9 (Fig. 4B). However, chemotherapy did not appear to improve the overall survival significantly in patients who did not express MMP9. The overall survival rate of DLBCL patients who did not demonstrate MMP9 expression and were treated with radiation therapy alone was approximately 80%. Actually, only 2 of the 11 DLBCL patients without MMP9 expression who were treated with radiation therapy alone died. In such patients who have high survival rates, an improvement in the survival rate with the use of chemotherapy would translate into only a small change. Therefore, a considerable number of patients are required to detect the statistically significant benefit.

DLBLC is clinically heterogeneous.[12] The morphologic diagnosis of DLBCL was insufficiently precise to identify definitive diagnostic subgroups, even when supplemented with immunohistochemistry for a few markers. Using DNA microarray, Alizadeh et al.[4] demonstrated two molecularly distinct forms of DLBCL that had gene expression patterns indicative of different stages of B-cell differentiation. The two DLBCL subgroups are distinguished from each other through the differential expression of hundreds of different genes, and these genes relate each subgroup to a separate stage of B-cell differentiation and activation. Alizadeh et al. claimed that it is quite possible that more subgroups will emerge through the use of gene expression profiling.[4] The findings of the current study may help distinguish that subgroup of DLBCL patients who should be treated with a combination of chemotherapy and radiation therapy.

T/NK lymphoma patients who expressed MMP9 appeared to have worse overall survival rates than those who did not express MMP9. However, in marked contrast with the results of chemotherapy in patients with DLBCL, chemotherapy was not found to improve the overall survival of patients who expressed MMP9 (Fig. 5B). Combination chemotherapy and involved-field radiation therapy have been reported to improve the outcome of patients with intermediate-grade or high-grade NHL (aggressive lymphoma).[23] Nevertheless, many patients do not achieve a complete disease remission or ultimately develop a disease recurrence. To identify those patients who are not expected to be cured by the combined modality comprised of a short course of CHOP followed by radiation therapy, it is necessary to detect the adverse prognostic factors in patients with localized, aggressive NHL. If such patients could be identified at the time of diagnosis, they might benefit from strategies other than conventional chemotherapy. The results of the current study imply that T/NK lymphoma patients who express MMP9 may be candidates for treatment strategies other than conventional chemotherapy.

Nearly all patients with nasal NK/T-cell lymphoma expressed MMP9 (Table 2). Nasal NK/T-cell lymphoma is highly associated with Epstein–Barr virus (EBV).[24] In the current study, the majority of the nasal NK/T-cell lymphoma patients were found to be EBV positive by EBER1 in situ hybridization (Table 3). The expression of MMP9 has been shown to be enhanced by the EBV oncoprotein latent membrane protein 1 (LMP1).[25] LMP1 is considered the principal oncoprotein of EBV and is essential for lymphocyte immortalization.[26] An in vitro study demonstrated that transfection of an LMP1 expression plasmid increased MMP9 expression. However, LMP1 did not induce MMP2 expression.[27] LMP1 might be related to the strong expression of MMP9 observed in nasal NK/T-cell lymphoma.

The similar findings were demonstrated in nasopharyngeal carcinoma (NPC). NPC is a highly metastatic carcinoma whose consistent association with EBV has been established. Both LMP1 and MMP9 proteins were predominantly immunolocalized in NPC tumor nests. The expression of MMP9 demonstrated a significantly positive correlation with the expression of LMP1. In addition, MMP9 expression was found to be correlated with lymph node metastasis. The results

of the current study suggest that the induction of MMP9 by LMP1 contributes to the metastatic potential of NPC.[28]

EBER1 transcripts were detected in 11% of patients with DLBCL and 50% of patients with peripheral T-cell lymphoma in the current study. These detection rates were in agreement with those reported in the study by Hamilton-Dutoit and Pallesen.[29] In their study, EBER1 was detected in 8 of 115 Chinese patients with sporadic B-cell NHL (7%). In patients with peripheral T-cell lymphoma, EBER1 was reportedly detected in 18 of 67 patients in Denmark (27%)[29] and in 24 of 37 patients in China (65%) in China.[30] The detection rates of DLBL and peripheral T-cell lymphoma were found to be much lower than those of nasal NK/T-cell lymphoma. Detection rates of EBER1 transcripts in patients who expressed MMP9 were similar to those in the total number of patients with DLBCL and peripheral T-cell lymphoma (Table 3), indicating that the correlation between the expression of MMP9 and EBV infection might be weak.

Resistance to chemotherapy was common in patients with nasal NK/T-cell lymphoma. Cheung et al. reported that of the 61 patients who were treated with chemotherapy, 31 demonstrated disease progression while receiving chemotherapy, 17 of whom developed locoregional disease progression. They concluded that the addition of anthracycline-containing chemotherapy to radiation therapy does not appear to confer any survival benefit in patients with Stage I disease.[31] The reasons for the resistance to chemotherapy are not clear. The frequent expression of the multidrug resistant phenotype (P-glycoprotein positive) may account for a certain proportion,[32] but not all, of the failures with chemotherapy. The use of P-glycoprotein/multidrug resistance (MDR)1 unrelated drugs (such as carboplatin), P-glycoprotein/MDR1 modulators (such as cyclosporin A), and calcium channel blockers is one possible way to improve the results obtained with chemotherapy. It is reported that high-dose chemotherapy and autologous bone marrow rescue were effective for the treatment of nasal NK/T-cell lymphoma,[33,34] making it is another possibility for the treatment of nasal NK/T-cell lymphoma patients with a poor prognosis.

At the current time, the inhibition of the function of MMPs is being pursued most actively for anticancer therapy. Tissue inhibitors of metalloprotease were to our knowledge the first compounds to be considered for clinical development. However, the lack of effective methods of systemic gene delivery has limited the clinical utility of this approach, whereas the development of synthetic inhibitors of MMPs has been actively pursued and widely tested in clinical trials.[35] Inhibitors of MMPs fall into three pharmacologic categories: 1) collagen peptidomimetics and nonpeptidomimetics, 2) tetracycline derivatives, and 3) bisphosphonates. Some of these inhibitors currently are undergoing clinical trials to establish whether any of them are therapeutically useful.

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Erectile Function Following External Beam Radiotherapy for Clinically Organ-confined or Locally Advanced Prostate Cancer

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Background: External beam radiotherapy (XRT) has been a standard treatment for clinically localized prostate cancer. However, preservation of erectile function following XRT is controversial. In this study, the influence of XRT on erectile function of patients with clinically organ-confined or locally advanced prostate cancer was retrospectively evaluated.
Methods: The study included 34 of 84 patients with organ-confined or locally advanced prostate cancer who underwent XRT between 1995 and 2002. Erectile function following radiotherapy was assessed by a simple mailed questionnaire that was constructed for the study. To determine the predictive factors for erectile dysfunction following radiotherapy, data were analyzed by multivariate analysis with the Cox proportional hazards model.
Results: The modality of XRT was the only factor to independently predict erectile dysfunction following XRT. The maintenance rates of erectile function were 47.6% at 1 year and 19% at 3 years in patients who received the 3-dimensional conformal radiotherapy, which were significantly higher than in those who received conventional radiotherapy ($P = 0.026$).
Conclusions: XRT significantly reduced the maintenance rate of erectile function during the follow-up period, with the rate being 19% at 3 years in patients who received 3-dimensional conformal radiation. The XRT modality was involved in the reduction of erectile function. These results suggest that erectile dysfunction is a possible adverse event following XRT.

Key words: external beam radiotherapy – erectile dysfunction – prostate cancer

INTRODUCTION

Radical prostatectomy and external beam radiotherapy (XRT) are standard treatments for clinically localized prostate cancer and they help in achieving favorable cancer control. However, these treatments are not free of adverse events that may decrease the quality of life (QOL) in such cancer patients. Preservation of erectile function following XRT for prostate cancer is controversial (1–8). Especially in Japanese men, the influence of XRT on erectile function has not been investigated, partly because their attitude toward sexual function is somewhat different from that of American men (9) and partly because only a small proportion of patients receive XRT for prostate cancer.

The aim of this study is to clarify the impact of XRT on erectile function and to determine predictive factors of erectile dysfunction (ED) following the treatment.

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SUBJECTS AND METHODS

We evaluated 84 Japanese patients with clinically organ-confined or locally invasive prostate cancer who underwent XRT between August 1995 and June 2002. We assessed the erectile function following XRT by a simple mailed questionnaire that was especially developed for this study in July 2002 (see Appendix). Questions 2 and 3 of this questionnaire were designed to inquire about erectile function before XRT, and questions 4 and 5, the onset of ED. To evaluate these aspects, we modified the questions regarding frequency and rigidity in our Japanese questionnaire that was previously validated (10).

During the study period, two patients died of prostate cancer and three patients died of diseases other than prostate cancer. Of the remaining 79 patients, only 72 (91.1%) responded to the questionnaire. To assess the influence of XRT on erectile function, we excluded 38 patients from the study because of the reasons listed below; therefore, only 34 were evaluable in the study. Those excluded were five patients with neoadjuvant hormonal therapy, three with immediate adjuvant or concomitant hormonal therapy, and 30 with ED before the treatment. In this

study, ED was defined as the erection not being sufficiently firm to penetrate, or it swelled but was not at all firm.

XRT was delivered to the prostate using the conventional four-field box (anterior, posterior and right and left laterals) technique and the 3-dimensional conformal technique (3-D CRT). The total dose ranged from 65 to 66 Gy (median, 66.0 Gy) in 24 to 30 fractions within 6 to 7.5 weeks in the conventional technique, and 65 to 70 Gy (median, 70.0 Gy) in 33 to 35 fractions within 6.5 to 7 weeks in the conformal technique. Conventional XRT was used in one institution, and 3-D CRT in the other two institutions. At each institution, the treatment modality for all patients who underwent XRT depended on the institutions' setting; therefore, radiologists could not choose another modality.

To determine the predictive factors of ED following XRT, data were analyzed by multivariate analysis with the Cox proportional hazards model. The variables for this multivariate analysis were determined according to previous reports (11, 12). They included age (continuous), pretreatment prostate-specific antigen (PSA) (<10 ng/ml versus ≥10 ng/ml), clinical stage (T1 versus T2 and T3), XRT modality (conventional XRT versus 3-D CRT), the Brinkmann Index (continuous), alcohol intake (every day or frequently versus occasionally or never), hypertension (yes versus no), diabetes (yes versus no), and history of transurethral resection of the prostate (TURP) (yes versus no). In this analysis, we used 'T1 versus T2 and T3' as the clinical stage variables because pathological overlap between T2 and T3 clinical stages was more frequent than that between T1 and T2. To assess the history of smoking, we used the Brinkmann Index, which includes the number of cigarettes smoked per day and duration (years) of smoking history, although it does not distinguish between past smokers and current smokers.

Pretreatment serum PSA concentrations were measured by radioimmunoassay (Hybritech Inc., San Diego, CA). Clinical stages were classified on the basis of TNM classification of the American Joint Committee on Cancer (AJCC) (13).

We used Stat View 5.0 for Windows (SAS Institute, Cary, NC) for the statistical analyses. The maintenance rate of erectile function was determined by the Kaplan–Meier method, and the log-rank test was used for statistical analysis. Mann–Whitney *U* test was used for comparison of the questionnaire scores and characteristics between the two groups. A *P*-value of <0.05 was considered to be statistically significant.

RESULTS

The median age of the 34 patients in this study was 71 years (range, 57–81 years), and the median follow-up period was 24 months (range, 1–85 months). More than 60% of the patients had either a past history of TURP or current association of hypertension or diabetes (Table 1). The pretreatment median PSA level was widely distributed between the levels of 0.5 to 81.9 ng/ml, reflecting clinical stage distribution. Conventional radiotherapy was administered to six patients and 3-D CRT to 28 patients. There were no major complications that required specific surgical or medical management during or after treatment. Four patients (1; conventional, 3; 3-D CRT) experienced mild diarrhea and eight (2; conventional, 6; 3-D XRT) experienced a slight increase in urinary frequency as acute reactions. All these complications were transient and did not compromise the scheduled plan of radiotherapy. Seven patients had PSA recurrence as defined by the American Society of Therapeutic Radiology and Oncology (ASTRO) Consensus Panel (14). Although they received hormone therapy after the recurrence, their data on erectile function before the start of the therapy were included in the study.

Table 1. Clinical and pathological characteristics of the 34 patients

Patient characteristics	No. of patients	
Past history and associated diseases (%)		
TURP	3	(8.8)
Hypertension	14	(41.2)
Diabetes	5	(14.7)
Smoking – current and previous smoker (%)	18	(52.9)
Median serum PSA; ng/ml (range)	13.1	(0.5–81.9)
Clinical stage (%)		
T1b	2	(5.9)
T1c	10	(29.4)
T2a	11	(32.4)
T2b	5	(14.7)
T3a	6	(17.6)
Gleason sum; biopsy (%)		
≤6	15	(44.1)
7	10	(29.4)
8–10	3	(8.8)
Data not available	6	(17.6)
Patients with PSA failure during follow-up (%)	7	(20.6)
Radiation modality (%)		
3-dimensional conformal radiotherapy	28	(52.9)
Conventional	6	(17.6)
Median radiation dose; Gy (range)	70.0	(65–70)

Before initiation of XRT for the 34 patients, 16 had erectile function sufficiently firm to penetrate, while in 18 it was almost sufficiently firm to penetrate, as evaluated by question 3 of the current questionnaire. Of the 28 patients who received 3-D CRT, sufficient erectile function was observed in 13, and an almost sufficient function in 15. Of the six patients with conventional XRT, three had sufficient function and three did not. The median ages were 72 years (range, 61–81 years) in the conventional XRT group, and 71 years (range, 57–79 years) in the 3-D CRT group. No difference in age distribution was found between the two groups ($P = 0.541$; the Mann–Whitney *U* test). However, the median follow-up periods were significantly different: 39.6 months (range, 25.2–86.4 months) for conventional XRT and 18.1 months (range, 1.0–60.2 months)

Table 2. Factors involved in erectile dysfunction following radiotherapy

Variables	Odds ratio	95% CI	*P* value
Age	0.99	0.91–1.09	0.89
Pretreatment PSA	0.41	0.14–1.18	0.10
Clinical stage	1.44	0.39–5.26	0.58
Radiation modality	3.70	1.07–12.83	0.04
Brinkmann index	1.00	1.00–1.001	0.40
Alcohol intake	2.78	0.53–14.52	0.22
Hypertension	1.02	0.36–2.93	0.97
Diabetes	2.30	0.46–11.52	0.31
TURP	0.76	0.10–6.0	0.79

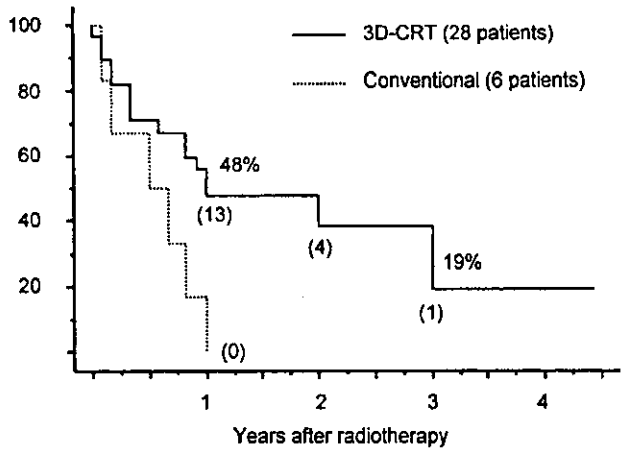

Figure 1. Maintenance of erectile function following radiotherapy. Log-rank test: $P = 0.026$; 3-D CRT: 3-dimensional conformal radiotherapy; Conventional: conventional radiotherapy; ( ): patients at risk.

for the 3-D CRT group ($P = 0.010$, Mann–Whitney U test). Although most patients with ED following XRT responded to questions 4 and 5, four patients did not respond. In this situation, we arbitrarily determined that ED started at the time of the current study to avoid a bias toward a worse maintenance rate.

Multivariate analysis with the Cox proportional hazards model revealed that the modality of radiation was the only predictive factor for ED after XRT, with a statistically significant odds ratio of 3.7 (Table 2). When patients were divided into two groups, conventional XRT and 3-D CRT, those who received 3-D CRT had a significantly higher maintenance rate of erectile function than those with conventional XRT (Fig. 1). The estimated maintenance rates of the function were 0% at 1 year in the conventional XRT group, and 47.6% at 1 year and 19.0% at 3 years in the 3-D CRT group.

DISCUSSION

The preservation rate of erectile function varies widely from 1 to 63% at 3 years following XRT (1–7). The wide range can be attributed to the differences in the definition of ED, pretreatment erectile function and modality of XRT across the studies. As for the definition of ED, the National Institutes of Health (NIH) consensus on ED defined impotence as the consistent inability to attain and maintain a penile erection sufficient to permit satisfactory sexual intercourse (15). In this study, we focused on patients who had normal erectile function sufficient to penetrate, as defined by the NIH, at the onset of XRT treatment, and assessed its function over time after the treatment. Thus, more than half of the cases were excluded in order to assess the direct impact of the radiotherapy on normal erectile function.

In the study by Goldstein et al. (16) that assessed the causes of ED following XRT, color-Doppler ultrasonography indicated abnormal vascularity in all patients with ED while hormone levels and neurological tests were normal. Moreover, selective pudendal arteriography performed on two patients revealed bilateral narrowing of the internal iliac arteries, and tortuosities and occlusions of the internal pudendal and penile arteries. Merlin et al. (17) have also reported that ED following XRT is arteriogenic because radiation damages the wall and endothelium of the blood vessels.

Another aspect of XRT, which supports the idea that ED following XRT is vasculogenic, is the efficacy of sildenafil. Sildenafil is effective for vasculogenic ED rather than neurogenic ED. Its efficacy in ED following XRT is reported to be as high as 71 to 77% (18–20).

Our study revealed that the modality of XRT was the only predictive factor of ED following XRT. Inevitable exposure of tissues surrounding the prostate to radiation may produce an unfavorable effect on erectile function. Indeed, the modality of XRT has been reported to affect preservation of erectile function. The preservation rate for conventional XRT was as low as that of radical prostatectomy (5). A 3-D CRT showed a favorable outcome of erectile function in 100% of patients at 1 year and 63% of the patients at 3 years following XRT (4). A comparative study between conventional XRT and 3-D CRT with the same questionnaire showed that preservation of erectile function was higher in 3-D CRT than in the conventional therapy (3), which is similar to the result of our study. These results also suggest that 3-D CRT possibly contributes to a better outcome of erectile function because critical structures receive low radiation exposure. However, even 3-D CRT may not guarantee complete preservation of the function because approximately 43% of the total dose for the prostate is delivered to the cavernosum (21).

The estimated maintenance rate of erectile function following XRT in the current study appeared to be lower than that of previous reports (1–7). This rate might have been affected by the patients' background such as the presence of hypertension, diabetes, history of TURP and higher age that may have possibly influenced the baseline erectile function. Hypertension and diabetes are well known as risk factors of ED. Furthermore, patients with previous TURP were more likely to become impotent after radiotherapy (22). The impact of aging might not be negligible in erectile function, which is suggested in the

Massachusetts Male Aging Study (23). However, the results of the present study suggest that the influence of aging led to approximately 1% increase in ED over 3 years. Thus, even though our study population was old, the impact of aging on erectile function was minimal during the 3-year follow-up period.

Japanese elderly men were found to differ with regard to QOL in a community-based study comparing Japan and United States (9). They might have less interest in their sexual life, and ED did not contribute to deterioration of the QOL (24). This can be possibly attributed to the difference in culture and customs between Japan and Western countries. Thus, elderly Japanese men might not seek ED treatment aggressively even if they have ED. Therefore, in this study group, very few ED patients following XRT sought highly effective oral medicine.

The current study has some limitations. The study is retrospective and used a mailed questionnaire that depended on the patient's memory concerning erectile function before and after treatment. The questionnaire used in this study has only been partially validated. We developed a new questionnaire for this study for the purpose of assessing the subjective quality of erectile function regardless of sexual activity, and the onset of ED. The different outcomes between 3-D CRT and conventional XRT might be influenced by confounding variables among institutions. However, in the two institutions where 3-D CRT was used for treatment, there was no statistically significant difference in the maintenance rates of erectile function following XRT.

Another limitation of this study is the small number of patients who received conventional XRT and the significantly different follow-up period compared to those with 3-D CRT. The difference in the follow-up period might have influenced the outcomes of patients. Recently, 3-D CRT has become a mainstream modality of administering XRT for localized prostate cancer. Thus, a large-scale prospective trial is crucial to draw a definitive conclusion for ED following well-designed 3-D CRT using a validated questionnaire.

CONCLUSION

The only predictive factor of ED following XRT was the modality of XRT. However, even patients who received 3-D CRT achieved only a 19% preservation rate for erectile function at 3 years following XRT. This study suggests that XRT does not always guarantee preservation of erectile function.

Appendix

QUESTIONS FOR ERECTILE FUNCTION

1. How often did you have sexual intercourse before initiating radiotherapy?

Never
Less than once a month
Once or twice a month
Once or twice a week
More than three times a week

2. How often did you notice your erection regardless of sexual activity before initiating radiotherapy?

Never
Less than once a month
Once or twice a month
Once or twice a week
More than three times a week

3. How firm was your erection? (except for the persons who answered never in question 2)

Swollen but not firm at all
Insufficient to penetrate
Sufficient to penetrate but not satisfactory
Sufficient to penetrate satisfactorily

4. When did you notice that your erection was not firm enough after initiating radiotherapy?

5. When was your erection insufficient to penetrate after initiating radiotherapy?

QUESTION FOR QOL

6. How do you feel about your current erectile function condition lasting for the rest of your life?

Very dissatisfied
Rather dissatisfied
Slightly dissatisfied
Satisfied
Rather satisfied
Very satisfied

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CLINICAL INVESTIGATION **Head and Neck**

A MULTI-INSTITUTIONAL RETROSPECTIVE ANALYSIS OF EXTERNAL RADIOTHERAPY FOR MUCOSAL MELANOMA OF THE HEAD AND NECK IN NORTHERN JAPAN

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Purpose: A multi-institutional retrospective study was performed in northern Japan to analyze the outcome of external radiotherapy as the definitive treatment modality for localized mucosal melanoma of the head and neck.
Patients and Methods: Thirty-one patients with localized mucosal melanoma of the head and neck treated by external radiotherapy at nine institutions of the Northern Japan Radiation Therapy Oncology Group between 1980 and 1999 were enrolled in this study. Radiotherapy alone was performed in 21 patients, and the remaining 10 patients received postoperative radiotherapy for gross residual tumors. The fraction size of radiotherapy varied from 1.5–13.8 Gy, with the total dose ranging from 32–64 Gy (median, 50 Gy). The follow-up periods ranged from 1–214 months (median, 16 months).
Results: Complete or partial responses were observed in 9 patients (29%) and 18 patients (58%), respectively. Local recurrence occurred in 13 patients (41.9%) and distant metastasis occurred in 11 patients (35.5%). Most incidences of local recurrence and distant metastasis developed within 2 years after the initial treatment. Overall cause-specific survival rates of patients at 1 and 3 years were 73% and 33%, respectively. Univariate analysis showed that high dose per fractionated radiotherapy doses (≥3 Gy) was associated with better prognosis for both local control ($p = 0.048$) and survival ($p = 0.045$). Multivariate analysis indicated that age (better prognosis in younger patients, $p = 0.046$) was the only significant factor. Radiotherapy for gross residual lesions after surgery did not seem to impact the significant gain of local control and survival. We observed two fatal late complications of mucosal ulcer and bleeding in the high dose per fractionated radiotherapy group.
Conclusion: Radiotherapy at a dose of 3 Gy or more per fraction was effective in gaining local control in patients with localized mucosal melanoma of the head and neck, and subsequently better survival was possible, especially in younger patients. © 2004 Elsevier Inc.

Mucosal melanoma, Head and neck, Radiotherapy, Fractionation, Age.

INTRODUCTION

Mucosal melanoma of the head and neck is a rare lesion worldwide, although it is relatively common in Japan (1). This disease is often fatal because of its high rate of local failure and frequent appearance of distant metastasis. Many clinicians have concluded that surgery offers the best chance for local control of localized mucosal melanoma of the head and neck (2–11), with radiotherapy playing a small role in managing these cases because the lesions are generally radioresistant (2, 4, 9–12). However, radiotherapy is a less invasive modality for patients for whom surgery would result in cosmetic or functional deformities. Some authors (13–15) reported good local control of localized mucosal melanoma of the head and neck with high-dose per fractionated radiotherapy (HF-RT), but the numbers of patients in these studies were small. Therefore, the significance of HF-RT as a primary treatment modality is still investigative.

This multi-institutional retrospective study was performed to analyze the outcome of external radiotherapy as a definitive treatment modality for localized mucosal melanoma of the head and neck.

PATIENTS AND METHODS

A total of 66 patients with localized mucosal melanoma of the head and neck from nine institutions belonging to the Northern Japan Radiation Therapy Oncology Group between 1980 and 1999 were included in the present study. Thirty-one patients treated by radiotherapy were grouped as

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Table 1. Patient and treatment characteristics

Characteristic	*n*
Sex (male/female)	12/19
Age (years) (median/range)	69/39–86
Primary site (NC/PS/others)	16/7/8
Stage (I/II/III)	27/4/0
Dose per fraction (1.2–2.5 Gy/3–13.8 Gy)	14/17
Operation (no/yes)	21/10
Chemotherapy (no/yes)	19/12
Immunotherapy (no/yes)	20/11

Abbreviations: NC = nasal cavity; PS = paranasal sinus.

follows: 21 patients with definitive radiotherapy alone, and 10 patients with postoperative radiotherapy for macroscopic residual tumors.

Table 1 lists patient and treatment characteristics. The major primary site was the nasal cavity, and the second most common site was the paranasal sinus. Other sites were as follows: the hard palate (3 cases), the nasopharynx (1 case), the mesopharynx (1 case), the middle ear (1 case), the upper gingiva (1 case), and the orbit (1 case). We adopted the most common staging scheme (7, 14–15): Stage I, primary localized lesion (27 patients, 87.1%); Stage II, cervical nodal metastasis (4 patients, 12.9%); Stage III, distant metastasis (no cases). Unfortunately, we could not estimate the tumor status, e.g., tumor size, precisely in some of the primary lesions. All patients had the World Health Organization performance status between 0 and 2.

Twenty-four patients received radiotherapy with 4–10 megavoltage linac X-rays, and 7 received radiotherapy with ^{60}Co. Primary tumor and gross cervical lymph node metastases were principally included in the treatment field. A clinical target volume plus 5-mm margin or more was mainly used in treating primary tumors and gross cervical lymph node metastases. The dose per fraction of radiotherapy varied from 1.5–13.8 Gy. In this analysis, we defined a dose of 3 Gy or more as high-dose per fractionated radiotherapy (HF-RT; 17 patients), and a dose of 1.5–2.5 Gy as low-dose per fractionated radiotherapy (LF-RT; 14 patients). Four patients treated with the accelerated hyperfractionation radiotherapy protocol (1.5–1.8 Gy per fraction, twice daily) were included in the LF-RT group. Total doses to each isocenter ranged from 32–64 Gy (median, 50 Gy). To facilitate comparison between different fractionation schedules, we referred to the biologically equivalent dose (BED) using a linear-quadratic model (16). The BED is defined as

$$nd\left(1 + \frac{d}{\alpha/\beta}\right)$$

in Gy, where n is the fractionation number and d is the daily dose. We used the α/β ratio of 2.5 Gy for malignant melanomas advocated by Overgaard *et al.* (17). The BED ranged from 72–358.6 Gy (median, 118.8 Gy). Radiotherapy was principally performed 5 times per week, but some patients in the HF-RT group received treatment 2–3 times per week. Of the 10 patients in the postoperative radiotherapy group, 9 (90%) received LF-RT. Twelve patients received chemotherapy; 75% of these patients received combination therapy with dacarbazine, nimustine hydrochloride, and vincristine sulfate. Eleven patients received immunotherapy.

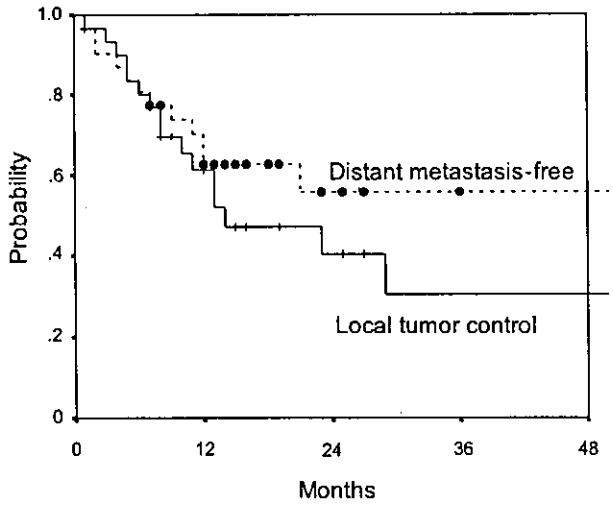

Fig. 1. Local tumor control and distant metastasis-free survival of all patients. The local 1-year and 3-year tumor control rates were 61% and 30%, respectively. The 1-year and 3-year distant metastasis-free survival rates were 70% and 56%, respectively. The circles and ticks indicate censored cases.

The period of follow-up after radiotherapy ranged from 1–214 months (median, 16 months). The last follow-up was in July 2000. We calculated survival periods from the start of radiotherapy or operation as the first treatment. The survival curve was calculated with the Kaplan-Meier algorithm, and the log-rank test was used to assess the statistical significance of differences. Univariate analysis of the factors correlating with local tumor control was performed, and cause-specific survival was estimated. Cox's regression analysis was used for multivariate analysis.

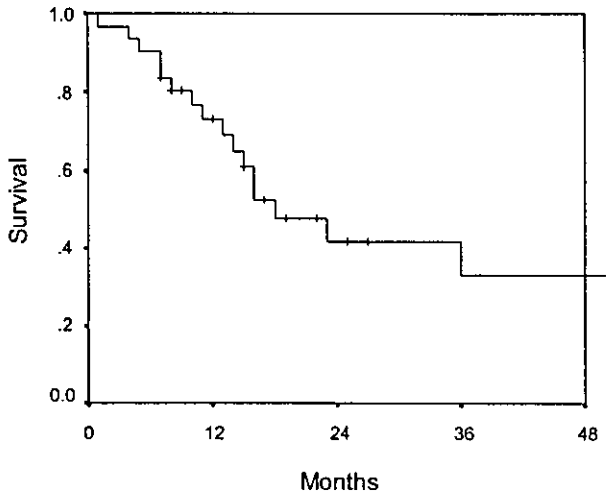

Fig. 2. Cause-specific survival of all patients.