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分担研究報告書

がんの診療科データベースと Japanese National Cancer Database (JNDCB)の構築と運用
分担研究：地域施設での医療連携とがん登録データベースについての考察

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【目的と方法】米国のがん医療の地域連携の実態とがん登録との関連をみるため、米国ミネソタ州ロチェスターMayo Clinic の Radiation Oncology 部門を見学し、地域連携のあり方、データ交換と登録などについて見学した。【結論】①医療連携には強固な医療情報系の確立が前提と考えられる。Mayo Clinic においても米国 NCI のがん医療方針が提唱するネットワークが Mayo Regional Cancer Program の形で形成されており、有機性をもって維持運営されていた。②このシステムはがん登録とも一体化したシステムと考えられる。

【目的】がん医療の地域連携の体制を考察するため、米国のがん医療の地域連携の実態とがん登録との関連をみる。

【方法】2007 年 11 月 2 日、米国ミネソタ州ロチェスターMayo Clinic の Radiation Oncology 部門を見学し、地域連携のあり方、データ交換と登録などについて見学した。

【結果】①Mayo Health System と呼ぶシステムを持っている。放射線治療部門では Mayo Clinic Radiation Oncology Regional Practice Network がそれに当る。Mayo Clinic にはその 100 km 圏内に 4 つの Regional Cancer Center があり、そこでは腫瘍内科医による外来化学療法とともに外部照射放射線治療が外来基盤で行われている。システムについては周囲 100km 以内の病院と契約を結ぶ。Mayo は人と品質を、施設は設備を提供する、という契約であるが、いずれは人も機械も提供する体制である。

② Mayo Clinic の放射線治療部門は Methodist Hospital 内にある。リニアック 6 台、CT-Simulator は 3 台。他に IORT 用が 1 台(St. Marys 病院にある)、ドクターは 7 名、レジデント数名がつく。年間 2200 名の新患者を治療している。医学物理士は 20 名で、彼らは Mayo Health System で契約した周辺施設のも合わせ計 14 台を管理している。契約病院には人材（腫瘍医師、物理士、技師、Dosimetrist など）をセットとして派遣する。契約病院として 4 つの Regional Cancer Center があり、そことも連携している。連携病院ではリニアックは 2 台が通常規模である。Regional Cancer Center は更にその地区のホームドクターと連携し、治療可能な患者を放射線治療している。Mayo Clinic から Regional Cancer Center へは、地域 TV ネットワークを通じて会議が可能で、それらからの放射線治療計画あるいは検証の要請もある。

③患者記録が IT 化されている。病院放射線治療の電子システムは IMPAC が開発導入した（＝現在 ELEKTA 社）が、極めてよく動くようである。周辺地域とも連携はこれによっている。即ちこのシステムは現在では IT に依

存している。

Regional Cancer Centerは外来化学療法の部屋ももっていて、いわば「外来医療センター」である（但し、必ずしも内科腫瘍医と一緒でもない施設もある模様)。現在、ミネアポリス方向に延ばそうとしている。

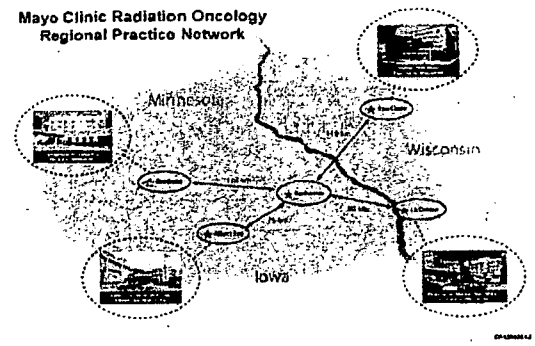
【考察】①米国はNCIの理念に基づいて地域連携が成立していると考えられる。これにも近隣施設間での競合がある模様だが、Mayoは力があるので（いわば力による連携として）動いている。このように医療連携は確立しているが、問題の患者に関してはフォローアップは通常主治医＝地域家庭医に任すだけでなく、自分でも診るという方針である。カナダの場合は英国に倣っているはずで、もっと連携は強いはずであるが、今回は見学考察の機会はなかった。

②Mayo の患者記録はその保存状況（過去の病歴がみられ、経験として活かされる）からも有名であるが、今では全システムが電子化されている。IMPAC社が関与していると考えられるが、IT化されて使いやすい印象を受けた。がん登録とも一体化したシステムと考えられ、がん登録が地域にも還元されるべき基盤となっているはずである。

【結論】①医療連携には強固な医療情報系の確立が前提と考えられる。Mayo Clinicにおいても米国NCIのがん医療方針が提唱するネットワークがMayo Regional Cancer Programの形で形成されており、有機性をもって維持運営されていた。

②このシステムはがん登録とも一体化したシステムと考えられる。

【参考文献】Miller, RC, et al.: Use of telemedicine to improve quality of care in a regional radiation oncology treatment network. (unpublished)



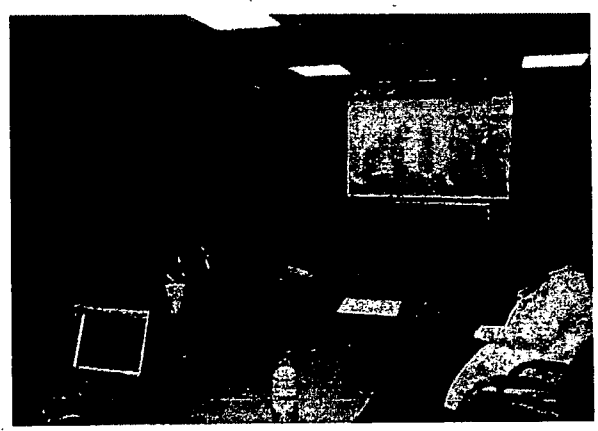


図1．Mayo Clinic の Regional Network

図2. Mayo Clinic System 各施設の放射線物理の会合（Courtesy: R. Miller, RO, Mayo Clinic)

別添５

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第３次対がん総合戦略研究事業

がんの診療科データベースとJapanese National Cancer Database(JNCDB)の構築と運用

Ⅳ　研究成果の刊行物・別冊　　(別冊)

主任研究者　手島　昭樹

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Initial Experience with the Quality Assurance Program of Radiation Therapy on behalf of Japan Radiation Oncology Group (JAROG)

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Background: We evaluated the efficacy of our quality assurance (QA) program of radiation therapy (RT) in a prospective phase II study. This is the first description of the experience of the Japan Radiation Oncology Group (JAROG) with this program.
Methods: Clinical records, all diagnostic radiological films or color photos that depicted the extent of disease of 37 patients with stage IEA extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) were collected for review. Radiation therapy charts, simulation films or digitally reconstructed radiographs, portal films and isodose distributions at the central axis plan were also reviewed. All documents were digitally processed, mounted on Microsoft PowerPoint, and for security returned from researchers by mail in CD-ROM format. The QA committee members reviewed all documents centrally, utilizing the slide show functionality.
Results: All patients were prescribed their specified dose to the dose specification point in accordance with the protocol. Three patients were regarded as deviations, because of a smaller margin than that specified in the protocol ($n = 2$) or a prolonged overall treatment time ($n = 1$). No violations were observed in this study.
Conclusions: This is the first report with regard to the QA program in MALT lymphoma. We demonstrated that our QA program was simple and inexpensive. We also confirmed that the radiation oncologists in Japan adhered closely to the protocol guidelines.

Key words: MALT lymphoma – quality assurance – QA program – radiation therapy

INTRODUCTION

It has been estimated that about 170 thousand cancer patients will be treated with radiation therapy (RT) either as part of their primary treatment or in connection with recurrences or palliation in 2005 in Japan (1). It is anticipated that RT will play an increasingly important role because of the improvements of early detection of and screening for cancer. Furthermore, other factors will also prompt the use of RT: the trend toward less drastic organ-conserving surgery combined with adjuvant RT; the improvement in identification of patients with high risk of developing loco-regional recurrences following surgery; and the aging population of Japan. It is undeniable that the deleterious consequences of poor quality treatment contribute not only to the rise of complications but also to deterioration of outcomes. They also lead to both an increase in health care costs and a decrease in the

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quality of life. Thus, it has long been recognized that quality assurance (QA) in RT is vital to guarantee provision of safe and effective treatments (2–12).

The Radiation Therapy Oncology Group (RTOG) and European Organisation for Research and Treatment of Cancer (EORTC) are the two largest working organizations presenting the models for the application of valid QA procedures in radiation oncology trials. Both organizations have funding for centralized data collection, inter-institutional dosimetry programs and regular site visits, utilizing medical, dosimetric and physics staff. For the data to be useful with regard to RT, a rigorous review process must be implemented to document the radiation used, volume irradiated, fraction size and dose delivered to comply with the designated therapeutic protocol. This is the most accurate way to confirm the uniformity of the treatment and usefulness of the outcome data.

The Japan Radiation Oncology Group (JAROG) conducted a QA program to guarantee the treatment quality of RT in a phase II study. This study evaluated the efficacy and toxicity of moderate dose RT for patients with extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). In pursuing the project, the JAROG were faced with a difficult situation in order to ensure that the clinical and technical compliance to the specified protocol was satisfactory, without having the financial, structural or personnel resources to conduct a comprehensive clinical QA program. Thus, we developed a simple and less expensive computer based method to easily execute our QA program.

Our QA program was based on a central radiation oncological review of all patients' diagnostic imaging, color photographs and clinical findings. Additionally, an individual RT prescription for every patient was provided. All of these documents were digitally processed, and were mailed to researchers in CD-ROM format. The purpose of the present study was to assess the feasibility of such a procedure in multicenter trials and its impact on the definition of the extent of disease and patients' treatment among Japanese radiation oncologists. This is the first report describing the QA program in MALT lymphoma.

METHODS

Study Design

From April 2002 to November 2004, 37 eligible patients with stage IEA MALT lymphoma received RT. The protocol specified three different total doses of RT, which were dependent on the tumor location and its maximum diameter. Patients with orbital disease or those who had minimal residual disease after surgical removal received 30.6 Gy. Patients with tumors that were less than 6 cm received RT with 36 Gy, and those with $\geq$ 6 cm of disease were treated with 39.6 Gy. A fraction size was 1.8 Gy in every setting. The clinical target volume (CTV) was defined as an entire involved organ (orbit, thyroid, salivary gland, breast) or gross tumor volume (GTV) with a margin of at least 20 mm. We did not intend to treat the adjacent first echelon lymph node region. A lens shield was placed to prevent this except where the block compromised tumor coverage. Radiation doses were specified according to the report of ICRU 50. In electron beam therapy, doses were specified at the peak dose on the beam axis reached.

Procedure of Quality Assurance Program

Clinical records, all diagnostic radiological films or color photos that depicted the extent of disease of all patients were collected for review. Radiation therapy charts, simulation films or digitally reconstructed radiographs, and portal films were reviewed. In cases of patients who received electron beam RT, color photos demonstrating the treatment position in the treatment room were assessed. The isodose distributions at the central axis were also submitted for review. In addition to the evaluation of adherence of the protocol, an evaluation of the response assessment was examined by reviewing the clinical records, diagnostic radiological films and color photos. All documents were digitally processed, and mounted using Microsoft PowerPoint. Each researcher de-identified all materials before submission. Afterwards, each researcher returned the data via a CD-ROM, and the QA committee member reviewed it using the slide show functionality. The patient data was not delivered via the internet for reasons of security. Figure 1 shows an example of the PowerPoint template.

Our QA programs included evaluation of the fraction size, the elapsed days, the prescribed dose to the reference point, the relationship between GTV, CTV and radiation field, and the difference between simulation film and portal film. The isodose distributions were also examined as reference data.

Definition of Protocol Violations and Protocol Deviations

Protocol violations were defined as a fractional dose less than 1.5 Gy, a total dose to the reference point either $<$90% or $>$110% of the dose prescribed in the protocol, the incomplete coverage of GTV, and more than 1 cm of difference between simulation film and portal film. In addition, protocol deviations were defined as an overall treatment time either $<$three weeks or $\geq$six weeks, the difference between simulation film and portal film $>$5 mm, the field border $<$20 mm away from CTV, and a dose to the reference point either $<$95% or $>$105% of the dose prescribed in the protocol.

RESULTS

We held the QA committee meeting on 19 March 2005. There were no missing data for any patients, and all documents were of adequate quality for review. Table 1 shows the relationship between the RT technique and primary site.

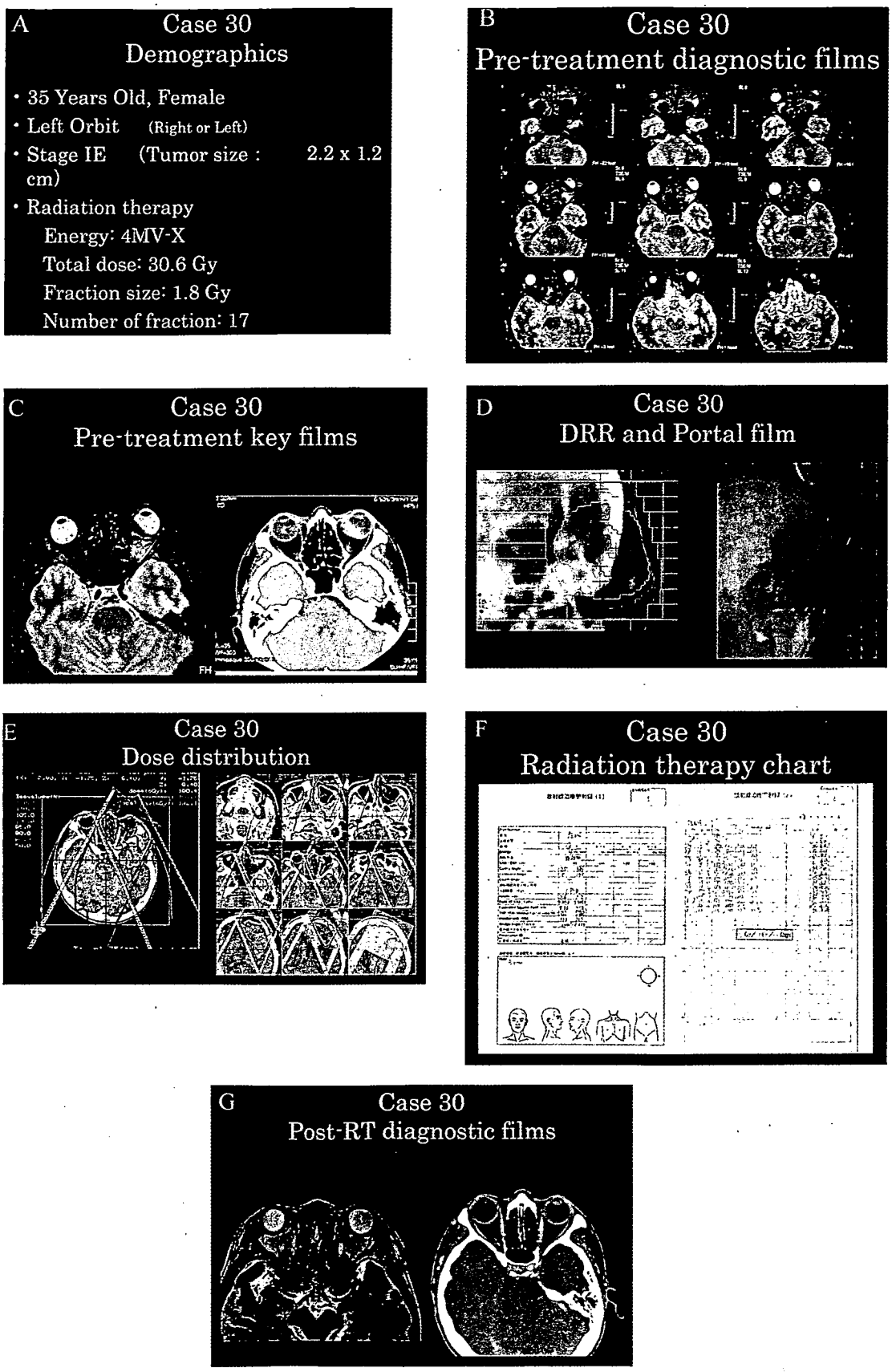

Figure 1. Examples are shown of the types of data that were used in this template. (A) a patient demographics, (B) pretreatment diagnostic films, (C) pretreatment key films, (D) digitally reconstructed radiograph (DRR) and portal film, (E) dose object, (F) radiation therapy chart, and (G) post treatment diagnostic films. The original documentation was written in Japanese. (Please note that a colour version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org)

The most common field arrangement was a single anterior–posterior field (41% of patients), and two oblique fields follow (30%). Two anterior–posterior or lateral opposing field techniques were employed in nine patients (24%). No patient received RT with a 3D conformal technique or intensity modulated radiation therapy (IMRT). All patients were prescribed their specified dose to the dose specification point in accordance with the protocol. No patients received RT with a fraction size other than 1.8 Gy. Only one patient required an overall treatment time more than 6 weeks, which was defined as deviation. The cause of this prolonged treatment time was merely personal. Adequate tumor coverage was achieved in 95% of the patients. Although CTV was covered enough in the treatment volume, the field border was placed with smaller margin (<20 mm) than that specified in the protocol in the remaining two patients. These two cases were defined as deviations. The isodose distributions at the central axis plan were acceptable in all patients. Overall, deviations were observed in three patients and the QA committee concluded that 92% of patients received RT as specified by the protocol. No protocol violations were observed in this study.

Because all documents were digitally processed in this study, the cost per patient, including CD-ROM and postage, was about ¥150 (i.e. about US$1.30). It took about an hour to prepare each patient data for review.

DISCUSSION

This report described our initial experience with a QA program in a multi-institutional prospective study. Our program is very simple and inexpensive. Ishikura et al. (13) investigated the quality of RT in a Japanese clinical trial and found that 60% of patients received less satisfactory RT in 2001. They extended their research to 2005 and demonstrated that protocol violation decreased dramatically to less than 5%. The early RTOG study also showed that the frequency of major and minor deviation was as high as between 60 and 70%. They reported that the appropriateness rate rose over time, because the participating radiation oncologists became familiar with the protocol (2). The Trans-Tasman Radiation Oncology Group (TROG) also demonstrated an improvement in QA over time (14). Our observation that 92% of patients received RT per protocol specification was very promising for the initial QA experience. In addition to the decrease of protocol violation over time, Halperin et al. (15) reported that institutional experiences affected the incidence of major deviations. RTOG also found that the QA performance was significantly better at principal centers compared with satellites. We were not able to assess institutional difference, because only three patients were judged as being a violation of protocol guidelines.

It has long been realized that the quality of treatment seriously affects the outcome of clinical trials. Several groups have evaluated the relationship between violation and staging, treatment strategies, and outcome. The German Hodgkin's Study Group (GHSG) evaluated the quality of RT for early stage HL (Hodgkin's lymphoma) and found that freedom from treatment failure (FFTF) was significantly influenced by the quality of RT. Those who received RT as per protocol obtained 82% of FFTF, and those with violation demonstrated only 70% of FFTF after five years (16). Furthermore, they observed that the disease extent recorded on the case report forms was significantly different from that shown on diagnostic CT, which resulted in a change of disease stage, treatment group allocations, and treatment volume (17,18). As these misinterpretations lead to protocol violations, they recommended an early central prospective review. Dieckmann and colleagues (19) also concluded that an up-front centralized review of patient data and consecutive set-up and delivery of individualized treatment proposals for every patient are feasible within a large multicenter trial involving pediatric HL.

However, two groups have concluded that violation did not lead to a detrimental treatment outcome. The EORTC 20884 trial evaluating the efficacy of involved field RT in patients with advanced HL demonstrated that 47% of patients received RT with major violation (20). However, their conclusion was that the outcome was not influenced by violation of the radiotherapy protocol. In another multicenter trial involving pediatric medulloblastoma, 57% of the fully evaluable patients had one or more major deviations in their treatment schedule (21). Major deviations regarding the treatment site were also found in more than 40% of patients. Despite these high major deviation rates, underdosage or geographical misses were not associated with a worse outcome. Although these two groups did not demonstrate a relationship between violation and treatment outcome, it is assumed that these high violation rates make it difficult to correctly understand the true message of clinical trials. With respect to violation rates, our present trial was satisfactory and the outcome data are robust.

Table 1. Primary site and RT technique

Primary site	RT technique			
	AP	Oblique	Opposing field	Others
Orbit	15	6	3	0
Thyroid	0	3	1	0
Salivary gland	0	2	2	0
Waldeyer's ring	0	0	2	0
Prostate	0	0	0	1
Lung	0	0	0	1
Cecum	0	0	1	0
Total	15	11	9	2

RT, radiation therapy; AP, single anterior-posterior field; Opposing field, two anterior-posterior or lateral opposing field techniques.

Advances in imaging and other technology have enhanced our ability to create complete anatomic and functional 3D data for each patient that facilitates the use of advanced technology RT delivery tools, including 3D conformal RT, intensity modulated RT, stereotactic RT and radiosurgery, and image-guided RT. Implementing these advanced technologies safely in clinical practice will require innovative and efficient methodologies for clinical QA. For example, Palta et al. (22) introduced the new web-based QA program to allow the rapid peer review of radiotherapy data through a simple personal computer-based web browser. RTOG has already developed a web-based QA program, and EORTC will also adopt a similar system to facilitate their QA program.

This is the first report that evaluates the QA program in MALT lymphoma. The technical deviation rate, technical data quality and completeness of this phase II trial were acceptable, and in addition our QA procedures were inexpensive and not time consuming. Furthermore, in multi-institutional studies, this analysis continues to lend credence to efforts related to QA for RT.

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Conflict of interest statement

None declared.

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Case Reports

Induction of Peptide-Specific Immune Response in Patients with Primary Malignant Melanoma of the Esophagus after Immunotherapy Using Dendritic Cells Pulsed with MAGE Peptides

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Primary malignant melanoma of the esophagus (PMME) is a very rare disease with an extremely poor prognosis. Surgery is currently considered its best treatment, while any other measures are ineffective. We studied the effect of active specific immunotherapy using monocyte-derived dendritic cells (DCs) pulsed with the epitope peptides of melanoma-associated antigens (MAGE-1, MAGE-3) in patients with PMME after surgery, for the first time. The patient received passive immunotherapy with lymphokine-activated killer cells concomitantly. Two HLA-A24-positive patients with PMME were treated. Both patients initially received radical esophagectomy with regional lymphadenectomy, followed by adjuvant chemotherapy with dacarbazine, nimustine, vincristine and interferon-α. In the case 1 patient, active specific immunotherapy was used to treat a large abdominal lymph node metastasis that became obvious 21 months after surgery. The disease remained stable for 5 months, and the patient survived for 12 months after the initiation of immunotherapy. In the case 2 patient, immunotherapy was tried as post-operative adjuvant treatment after adjuvant chemotherapy. There was no tumor recurrence for 16 months after the immunotherapy. As of 49 months after esophagectomy, the patient is still alive. In both patients, the ability of peripheral lymphocytes to produce IFN-γ *in vitro* in response to peptide stimulation was significantly enhanced and delayed-type hypersensitivity skin test response to MAGE-3 peptide was turned positive after immunotherapy. In conclusion, active specific immunotherapy for PMME with the use of DCs and MAGE peptides was safe and capable of inducing peptide-specific immune responses. This case report warrants further clinical evaluation of this immunotherapy for PMME.

Key words: esophageal malignant melanoma – cellular immunotherapy – dendritic cell – lymphokine-activated killer cell – MAGE peptide

INTRODUCTION

Primary malignant melanoma of the esophagus (PMME) is an uncommon tumor comprising only 0.1–0.2% of all esophageal malignancies (1,2). Only about 250 cases have been reported in the English-language literature to date (3,4). The prognosis of PMME is extremely poor, with a reported median overall survival of 10–14 months (1,2). Radical esophagectomy with regional lymphadenectomy is the mainstay of therapy for patients with resectable PMME; however, the 5-year survival rate after surgery is less than 5% (1). Various regimens have been tried as post-operative adjuvant treatment to prolong survival, including chemotherapy, radiotherapy, and immunotherapy using recombinant cytokines. However, because very few studies on PMME are available, potential benefits of these treatments remain uncertain.

Since the latter half of the 1990s, dendritic cell (DC)-based immunotherapy has been used to treat cancer,

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