JMAJ
Japan Medical Association Journal
Vol.48, No.11 November 2005

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In an Aged Society the Effective Treatment of Osteoporosis Is Essential

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With the advancement of the aged society in Japan, the fragility of the human back bone, namely osteoporosis, has an impact on the deterioration of physical function and the quality of life of senior citizens. Compared to the occurrence of femoral neck fracture in Japan in 1987, the number of fractures in 2002 was estimated to be 2.2 times higher, amounting to 117,900 fractures in one year.[1] The increasing rate of femoral neck fracture over 15 years is greater than the rate of aged population over the same term. According to a 2004 publication by the National Research Group related to Geriatric Rehabilitation, approximately one third of elderly patients who could walk outside independently could no longer do so a year after suffering a femoral neck fracture. Further, the rate of bed-ridden elders was 1.5 times higher among patients who experienced a femoral neck fracture compared to those who had not suffered from such an injury.

To reduce the complications of osteoporosis, increase of bone mineral by change of life style or administration of anti-osteoporotic drugs, prevention of falls and application of a hip-protector are recommended for elder persons. Of these three approaches to preventing femoral neck fracture, therapy with anti-osteoporotic drugs has over a quarter century history and is the most effective strategy aside from its very slow prediction of efficacy. Compared to lipid and glucose metabolisms in human body, bone metabolism is extremely slow, so the effective response of medicament therapy can only be confirmed by measuring bone mineral density six months or a year after the administration of a drug, and at least three or six months after the treatment when using measurement of bone metabolic markers including urinary cross-linked N-telopeptides of type I collagen (NTX). Sebba AI et al. (2004) observed that 15–10% of patients treated with alendronate for one year continued to experience bone loss (N = 520).[2] Patients treated with an expensive osteoporosis drug over the long term, for whom no efficacy can be observed, will often be discouraged from continuing the therapy on the basis of cost, so practical doctors are anxious for a means to predict bone mineral change in as short a term as possible after the start of treatment of osteoporosis, as described by Takada J et al. Ten years ago, bone metabolic markers including bone resorption markers and bone formation markers had been noticed to optimize the procedures to assess the rate of bone loss or formation as like as the number of differential calculus of bone metabolism. As a result, bone metabolic markers have been continued to play a role both in the choice of anti-osteoporotic drugs and also in the evaluation of effectiveness of drugs. Bone resorption markers have also recently been noted to indicate the characteristics of bone fragility itself and, further, they have been acknowledged, same as bone mineral density, to play a role for the future risk of fracture.[3] If importance of bone resorption marker as a tool is taken into consideration, study using it for early prediction of changes at six months during the treatment of alendronate, will take courage on the part of many medical practitioners related to osteoporosis. Yet further study in order to realize the effective treatment of osteoporosis is essential in the aged society.

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Original Article

Changes in Bone Resorption Marker at One Month Predict Changes at Six Months in Patients Treated with Alendronate

JMAJ 48(11): 528–531, 2005

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Abstract

Ninety-nine postmenopausal Japanese women were evaluated to assess whether changes at one month in urinary NTX bone resorption marker as a result of alendronate treatment enable prediction of changes at 6 months. The percentage change at one month significantly correlated with that at 6 months ($R^2 = 0.290$, $P < 0.0001$) and predicted the changes at 6 months with sensitivity 72.2%, specificity 60.0%, positive predictive value 87.7%, and negative predictive value 35.5%, respectively. This study demonstrated that changes in bone resorption marker at one month could be used as a reliable method to monitor the effects of alendronate treatment, and to predict the response at six months.

Key words Osteoporosis, Alendronate, Bone resorption marker, Urinary NTX, Bisphosphonate

Introduction

Recent studies have indicated that oral administration of alendronate, a bisphosphonate, can prevent fracture in patients with osteoporosis.[1–5] Although bone mineral density (BMD) is an essential tool for estimating fracture risk in untreated populations, changes in BMD may explain only a small part of fracture risk reduction.[6] Accelerated bone resorption marker also independently contributes to fracture risk. Urinary cross-linked N-telopeptides of type I collagen (NTX), one of bone resorption marker, has been shown to reduce substantially after 6 months of treatment,[7–10] representing a decrease in fracture risk as a result of bisphosphonate treatment.[11] However, one of the most critical problems in the treatment of osteoporosis is that because there is no reliable method for early monitoring of the response to treatment, patients do not continue to adhere to motivation.

The aim of the present study was to determine whether changes in urinary NTX from baseline at one month after the start of alendronate treatment enable prediction of changes from baseline at 6 months.

Materials and Methods

Ninety-nine postmenopausal Japanese women aged 67.1 ± 8.8 years of age (mean ± SD, range; 46–84) were recruited. No clinical or laboratory evidence of confounding by systemic manifestation of any disease was observed for these patients. All patients satisfied the following preconditions: (1) at least 5 years since menopause, (2) lumbar spine BMD of more than 2.5 SD below the young adult mean of normal Japanese women, (3) no illness and receiving no medication that might affect bone mineral metabolism, (4) no clinical fracture within 6 months, and (5) receiving medication with alendronate (5 mg/day) and having taken all of

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the tablets prescribed for the first month and at least 90% of the tablets prescribed for each of the following 6 months. Medication was taken with 180 ml of water in the morning 30 minutes before breakfast or a beverage.

To ascertain a baseline, urinary NTX, corrected for creatinine, was measured using second morning void urine samples at one month and at six months after the start of alendronate treatment. According to the guidelines of the Japan Osteoporosis Society, the cut point (minimum significant change, MSC) for urinary NTX is determined as a decrease from baseline of 35%.[12]

The relationships between changes from baseline at one month and changes from baseline at 6 months were examined using simple regression. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were used to assess whether the change from baseline at one month could be used to predict the change from baseline at 6 months in individual patients. PPV and NPV were calculated according to the probability of a positive response in urinary NTX at 6 months in patients with a decrease to below the cut point at one month, and the probability of a negative response in urinary NTX at 6 months in the patients without a decrease to below the cut point at one month, respectively.

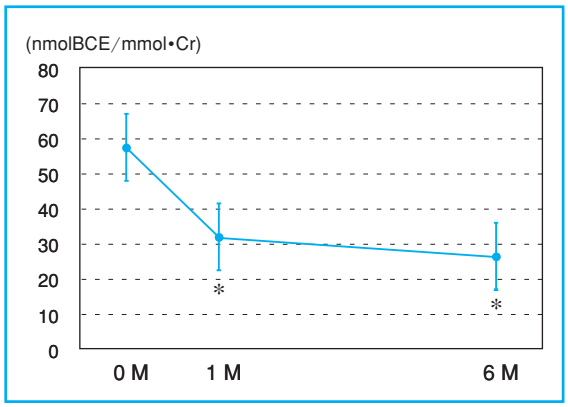

Fig. 1 Changes in urinary NTX

Absolute value (nmol bone collagen equivalent/mmol•creatinine; nmol BCE/nmol•Cr). * P<0.001 from baseline

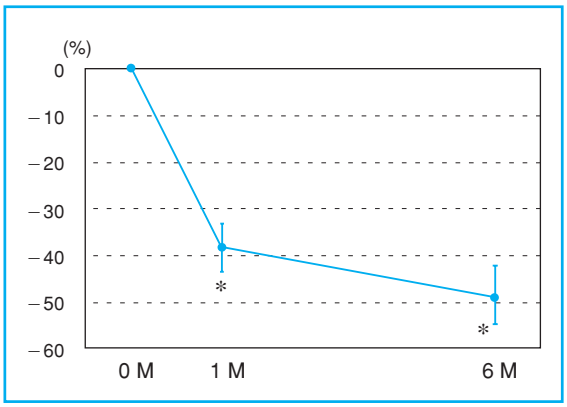

Fig. 2 Changes in urinary NTX

Changing ratios from baseline level (%). * P<0.001 from baseline

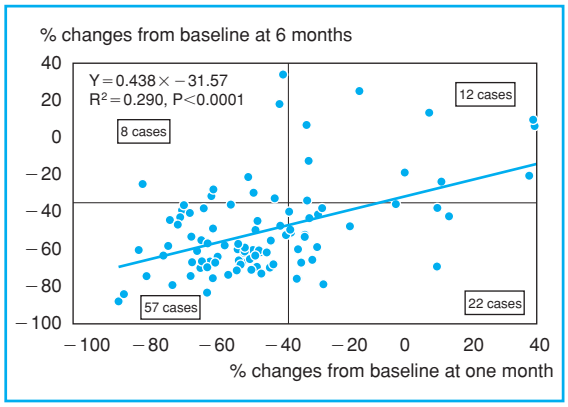

Fig. 3 The correlation between the percent changes in NTX from baseline at one month and at 6 months

The horizontal and vertical continuous lines are minimum significant change in urinary NTX (−35%).

Table 1 Number of cases that showed MSC or not at one and 6 months

		1 month		Total
		MSC	no MSC	
6 months	MSC	57 cases	22 cases	79 cases
	no MSC	8 cases	12 cases	20 cases
Total		65 cases	34 cases	99 cases

(MSC: minimum significant change)

Sensitivity: 57/79 = 72.2% Positive Predictive Value: 57/65 = 87.7%
Specificity: 12/20 = 60.0% Negative Predictive Value: 12/34 = 35.3%

Results

Urinary NTX values were 57.2 ± 27.7 nmolBCE/mmol•Cr (mean ± SD) at baseline, 31.8 ± 16.0 at one month, and 26.2 ± 17.1 at 6 months (Fig. 1). The percentage change in NTX from baseline at one and six months was −38.6% ± 31.9 and −48.5% ± 25.9 (mean ± SD), respectively (Fig. 2). The percentage change from baseline at one month significantly correlated with the percent change from baseline at 6 months ($R^2 = 0.290$, $P < 0.0001$; Fig. 3). Of 99 patients, 65 (65.7%) and 79 (79.8%) patients showed MSC at one month and 6 months, respectively. A change from baseline at one month predicted the change from baseline at 6 months with sensitivity 72.2% and specificity 60.0%. PPV indicated the probability of 87.7% that urinary NTX would remain below the cut point at 6 months if this had been the case at one month. Conversely, NPV indicated a 35.3% probability that urinary NTX would not decreased below the cut point at 6 months if uninary NTX had not decreased below the cut point at one month (Table 1).

Discussion

Although urinary NTX is known to be a reliable monitor in the treatment of osteoporosis, there is no previous report on whether change in urinary NTX at one month can predict the change in urinary NTX at six months. In this study, we observed that urinary NTX decreased significantly at one month, and that the magnitude of the decrease at one month was similar to that at six months. Moreover, the change from baseline in urinary NTX at one month significantly correlated with that at six months. The PPV was also high indicating a strong probability that urinary NTX would continue to be below the cut point at six months if it had been so at one month. However, compared to the PPV, the NPV at six months was a lower percentage, suggesting that a late response to alendronate treatment may occur in some cases.

This study clearly demonstrated that changes at one month in the biochemical marker of bone turnover NTX could be used as a reliable method to monitor the effects of alendronate treatment and to predict the response to treatment at six months.

These results suggest that patients with a decrease in urinary NTX at one month below the cut point should be encouraged to continue the alendronate treatment. If no decrease in urinary NTX below the cut point is observed at one month, it is advisable to ascertain whether or not the patient had been taking the medication correctly (with 180 ml of water in the morning, 30 minutes before breakfast or a beverage). Even if medication had been taken correctly, the patient should be advised to continue the treatment to the 6-month point because 64.7% (22/34) of patients without a decrease in urinary NTX below the cut point at one month showed a positive result at six months (Table 1).

Since the aim of treatment for osteoporosis is the prevention of osteoporotic fracture, the endpoint of treatment should be the prevention of fracture. In this study, fracture was not the endpoint due to the low incidence of fractures in one month; however, recent studies have suggested that the reduction of fracture risk is more dependent on the decrease of bone resorption marker than the increase of BMD.[12,13] Results of longer-term studies involving large populations are needed to determine whether early changes in biochemical markers can also be used as predictors of fracture risk.

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Is CT Necessary in the Diagnosis of Soft Tissue Masses?

JMAJ 48(11): 532–538, 2005

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Abstract

Background Computed tomography (CT) is still widely used in the diagnosis of soft tissue masses. However, overuse of CT brings increased radiation exposure and increased medical expenditure. The purpose of this study was to evaluate the necessity for CT in comparison with magnetic resonance (MR) imaging in the diagnosis of soft tissue masses.

Methods Forty-seven patients with soft tissue masses who underwent both CT and MR imaging were enrolled in this study. Contrast enhancement was performed in 27 cases out of the total 47 CT studies. Images were analyzed for 1) location; 2) extension; 3) internal structure; 4) benign and malignant differentiation of soft tissue masses. Two musculoskeletal radiologists scored each factor independently.

Results MR imaging scores of all four factors were significantly better than plain CT scores. Administration of contrast material in CT, improved agreement and kappa between CT and MR imaging scores to some extent. Diagnosis of benign and malignant differentiation was equivalent in enhanced CT and MR imaging, whereas CT scores were still inferior to MR imaging in terms of location, extension and internal structure. Compared to MR imaging as the gold standard, the sensitivity and specificity of CT diagnosis in terms of location, extension and internal structure were relatively low, but were high in the diagnosis of benign and malignant differentiation.

Conclusion These results suggest that MR imaging is superior to CT in the diagnosis of soft tissue masses. Use of CT is considered to be redundant when MR imaging is available.

Key words Computed tomography, Magnetic resonance imaging, Soft tissue mass, Diagnosis

Introduction

Before the introduction of magnetic resonance (MR) imaging, computed tomography (CT) was considered to be the most important imaging modality for the evaluation of soft tissue masses because its contrast resolution was better than that of conventional radiography. MR imaging is known to have even better contrast resolution than CT and the signal intensities are occasionally specific. As a result, the role of CT in the diagnosis of soft tissue masses has been diminishing.[1–3] Despite this fact, CT is still widely used in the current clinical practice of some institutions depending on the referring physicians. This is probably due at least in part to the introduction of high speed multislice CT, which has improved accessibility. However, overuse or improper use of CT brings increased

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This study was supported by the Grant for Guideline Development, Japanese College of Radiology.

radiation exposure, medical expenditure, and risk of allergic reaction to the iodine contrast. The purpose of this study was to evaluate the indications of CT in the diagnosis of soft tissue masses when MR imaging is available.

Methods

Fifty-one cases with soft tissue masses were collected from nine institutions between January and June 2002. They were consecutive cases for which both CT and MR imaging for the diagnosis of soft tissue mass were employed during the study period. In order to avoid bias to malignant tumors, both pathologically unproven materials and those that had been clinically confirmed were included. For example, one case of ganglion, which disappeared during the course of follow-up, was included in this series.

Four cases of those collected were excluded from this study. Two were the joint disorder, pigmented villonodular synovitis, rather than a soft tissue mass. The other two cases were excluded because of the lack of both pathological and clinical diagnoses. A total of 47 cases of soft tissue masses were used in this study. Sixteen were benign masses: schwannoma: 3; lipoma: 2; lymphangioma: 2; elastofibroma dorsi: 2; hematoma: 1; ganglion: 1; atheroma: 1; neurofibroma: 1; hibernoma: 1; fibroma: 1; giant cell tumor of tendon sheath: 1. Of these 16 benign masses, pathological confirmation was not obtained in six cases: lipoma: 2; elastofibroma dorsi: 2; ganglion: 1; lymphangioma: 1. We included these cases because we thought specific diagnosis was obtained based on both imaging findings and clinical course. In the remaining ten cases, pathological diagnosis was obtained. Thirty-one were malignant tumors: liposarcoma: 12; malignant fibrous histiocytoma: 7; synovial sarcoma: 2; leiomyosarcoma: 2; malignant lymphoma: 1; osteosarcoma: 1; malignant hemangiopericytoma: 1; angiosarcoma: 1; rhabdomyosarcoma: 1; alveolar soft part sarcoma: 1; malignant peripheral nerve sheath tumor: 1; dermatofibrosarcoma protuberans: 1. Pathological proof was obtained in all cases with malignant tumors.

The average age of patients was 52.7 (4–83 years old). There were 20 male and 27 female patients. With regards to the location of the masses, 18 cases were in the thigh, 7 in the shoulder, 7 in the inguinal and hip region, 5 in the lower leg, 4 in the abdominal wall, 2 in the scalp, 2 in the upper extremity, and 2 in the foot. CT without contrast medium was performed in 20 cases and post-contrast CT was performed in 27 cases, while MR imaging without Gd-contrast was performed in 19 cases, and MR imaging after intravenous Gd-contrast in 28 cases.

Since this is a multi-institutional study, images were obtained from different CT and MR units. CT was performed with either multislice CT or single helical CT. However, CT analysis was performed only on transverse images without 3-dimensional reconstruction. MR imaging was performed with either 1.0-Tesla or 1.5-Tesla field strength MR system. MR imaging was analyzed using both T1-weighted fast spin-echo image and T2-weighted fast spin-echo image. Fat suppressed image was also included if available. No dynamic CT or dynamic MR imaging was performed after contrast injection.

Image interpretation

Images were analyzed for: 1) anatomic location; 2) local extension; 3) internal structure; 4) benign and malignant differentiation. Each factor was scored on a four-point scale. For anatomic location, local extension, and internal structure, a score 4 lesion was characterized by clear delineation; a score 3 lesion was partly obscured but possible to determine; a score 2 lesion was partly obscured and difficult to determine; and for a score 1 lesion no determination was possible. As for benign and malignant differentiation, a score 4 meant definite differentiation; a score 3 was probable; a score 2 was difficult to determine; and for a score 1 no determination was possible. Two musculoskeletal radiologists, K.F. and S.E., evaluated the images independently without knowledge of the final diagnosis. K.F. viewed CT first and MR imaging later, and S.E. viewed the same images in the reverse order. If their scores were different, consensus between them was obtained through discussion.

Statistical analysis

Mean and standard deviation (SD) of each score derived from MR imaging and CT were calculated and analyzed as to whether there was significant difference between them using Wilcoxon rank sum test. In addition, scores of MR imaging and CT were also analyzed in the cases where contrast enhanced CT was

Table 1 Evaluation scores of CT and MRI (N=47)

	CT		MRI		
	mean	SD	mean	SD	P-value*
Anatomic location	3.60	0.65	3.91	0.28	0.0005
Local extension	3.34	0.76	3.87	0.34	<0.0001
Internal structure	3.38	0.77	3.87	0.34	0.0001
Benign/malignant	3.53	0.65	3.68	0.56	0.014

*: P-value was calculated based on Wilcoxon rank sum test.

Table 2 Evaluation scores of contrast enhanced CT and MRI (N=27)

	Contrast enhanced CT		MRI		
	mean	SD	mean	SD	P-value*
Anatomic location	3.74	0.53	3.93	0.27	0.045
Local extension	3.44	0.64	3.89	0.32	0.0016
Internal structure	3.59	0.64	3.93	0.27	0.008
Benign/malignant	3.63	0.56	3.78	0.42	ns

*: P-value was calculated based on Wilcoxon rank sum test.

performed to evaluate the usefulness of contrast enhancement in CT.

Results

Scores of MR imaging and CT were compared for anatomic location, local extension, internal structure, and benign and malignant differentiation with Wilcoxon rank sum test (Table 1). MR imaging scores were significantly superior to CT in all four categories. Contrast enhancement was performed in 27 cases out of 47 CT studies, and similarly scores of MR imaging and CT were compared (Table 2). For benign and malignant differentiation, the CT scores improved and became equivalent to the MR imaging scores. However, the CT scores for anatomic location, local extension, and internal structure of the masses remained significantly inferior to the MR imaging scores.

Discussion

Although MR imaging is an excellent diagnostic modality for soft tissue masses, there are some limitations in its clinical usage when compared with CT. The number of CT units in Japan was 12,868 in 2003[4] and that of MR imaging units was 4,350 in 2004.[5] Consequentially, patient access to CT is much better than MR imaging, and CT is almost always available in most institutions in Japan. Furthermore, the patient through-put of CT is faster than MR imaging per unit. While it is ideal to make an accurate diagnosis with the most informative examination available, it is not uncommon to perform CT after plain radiography and before MR imaging. In addition, the CT examination fee is 5,700 Japanese yen (approximately US$ 50) in Japan, which is cheaper than MR imaging by 5,900 Japanese yen (US$ 52). In addition, there are a number of contraindications for MR imaging examinations, including cardiac pacemaker implantation, artificial cochlea implant, and ocular prosthesis. Metallic artifacts cause severe degradation of image quality in MR imaging but have a limited influence in CT, especially in reconstruction images from thin slice CT data-set. Furthermore, longer scan time occasionally causes motion artifacts in MR imaging, which does not occur in CT.

In this study, scores of location, local extension, and internal structure of soft tissue masses were significantly higher in MR imaging

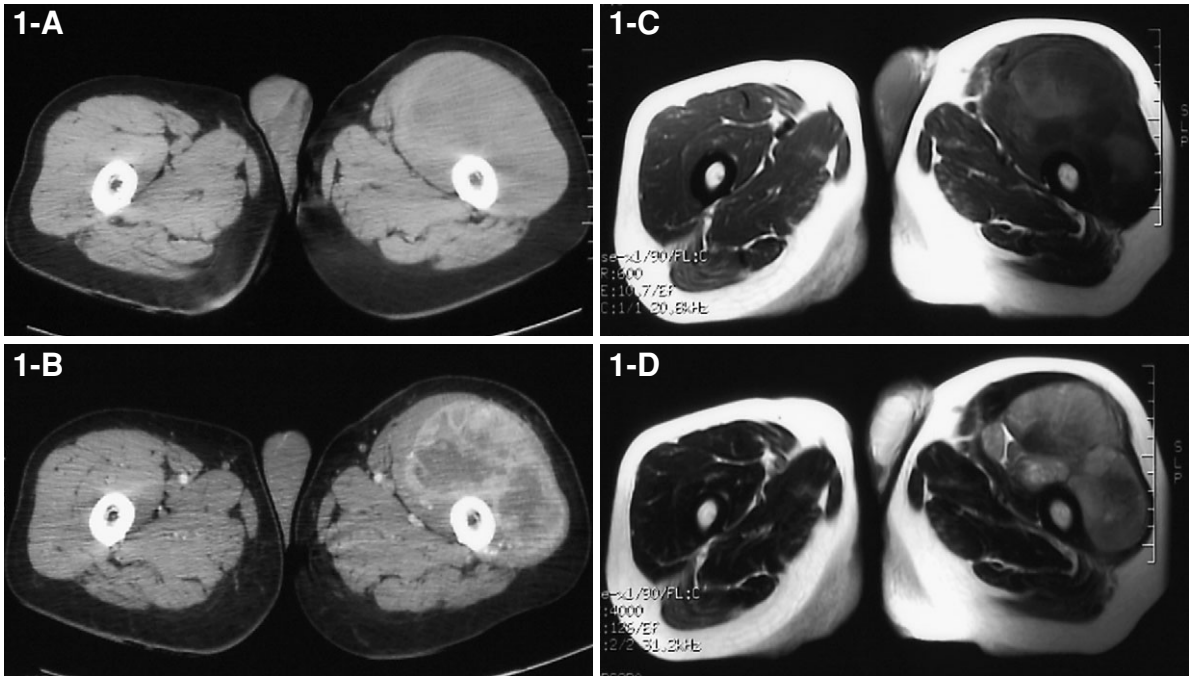


Fig. 1 A 76-year-old male with malignant fibrous histiocytoma of the left thigh

Post-contrast CT shows more precise tumor location and internal structure than plain CT, but is equivalent to MRI. This is an apparent malignant soft tissue tumor as it is a large deep-seated soft tissue mass.

1-A: Plain CT. A large soft tissue mass involving the left quadriceps femoris muscles.
1-B: Enhanced CT. Margin of the tumor is well demarcated by contrast enhancement with irregular central areas of unenhancement.
1-C: T1-weighted MR image. A large, low intensity mass in the thigh.
1-D: T2-weighted MR image. A well-defined large soft tissue mass with mixed intermediate and low intensities in the quadriceps femoris muscles.

(Courtesy of Dr H Nishimura MD, Kurume University, School of Medicine)

than CT. Moreover, there was no case where the CT score was higher than MR imaging score, even after contrast administration. Moderate improvement was noted in scores for location and mild improvement was present in scores for local extension and internal structure after contrast administration. However, if increased risk such as allergic reaction[6] and nephrotoxicity,[7] increased medical expenditure, increased workload for radiologists including obtaining informed consent, needle placement, and contrast injection in cases with contrast enhancement is taken into account, there is little advantage of post-contrast CT over MR imaging (Fig. 1).

It has been reported that CT is superior to MR imaging in delineating subtle calcification and ossification.[8] Zone pattern with peripheral calcification is a characteristic feature of myositis ossificans. This calcification can be shown by CT at an earlier stage than by plain radiography.[9] Previous trauma episodes are present in about 40–60% of cases with myositis ossificans. Marginal mineralization is rapid and progressive, and can even be seen on plain radiography within 4–6 weeks. T2-weighted MR image shows mixed moderate and high intensity mass lesion with extensive perifocal edema. In most cases, the characteristic low intensity ring-like area, corresponding to marginal mineralization, is seen along the margin of the mass lesion at an early stage.[10,11] In this way, diagnosis of myositis ossificans is correctly achieved through the combination of clinical course, plain radiography, and MR imaging in most cases.

Other soft tissue tumors with potential mineralization include synovial sarcoma and epithelioid sarcoma. Incidence of mineralization on radiography is reported as 30%[12] and

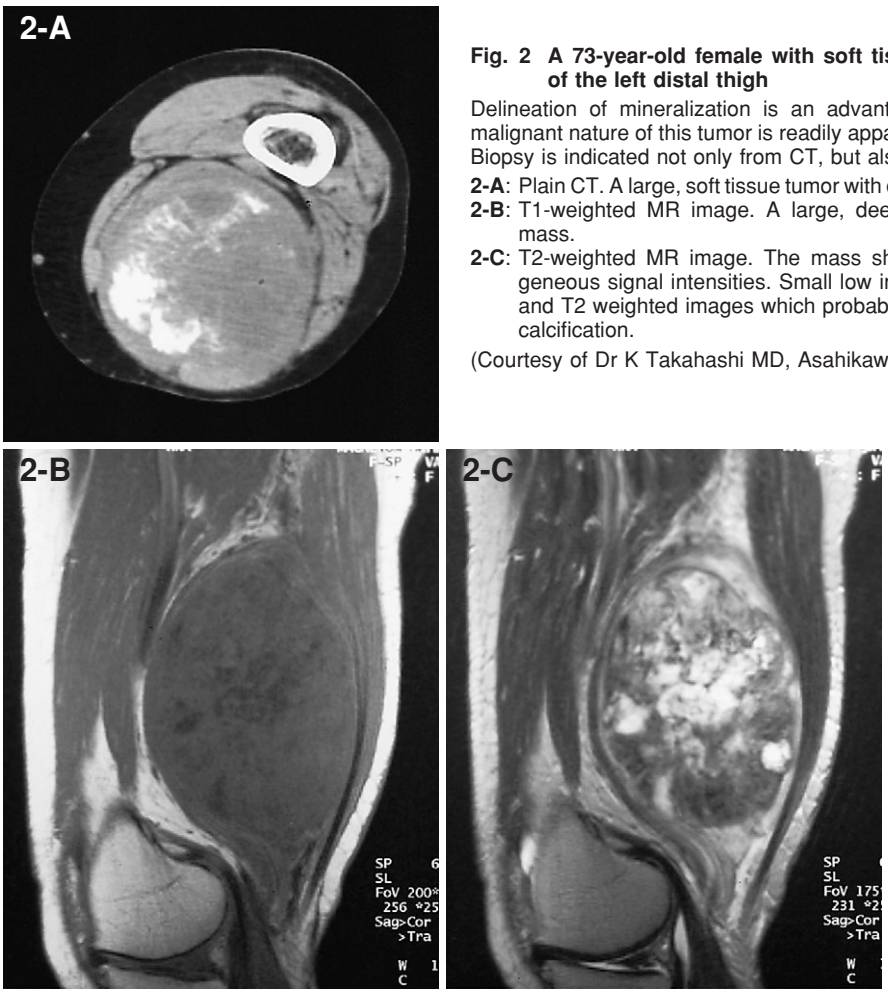


Fig. 2 A 73-year-old female with soft tissue osteosarcoma of the left distal thigh

Delineation of mineralization is an advantage of CT, but the malignant nature of this tumor is readily apparent on MR imaging. Biopsy is indicated not only from CT, but also from MR imaging.

2-A: Plain CT. A large, soft tissue tumor with dense mineralization.

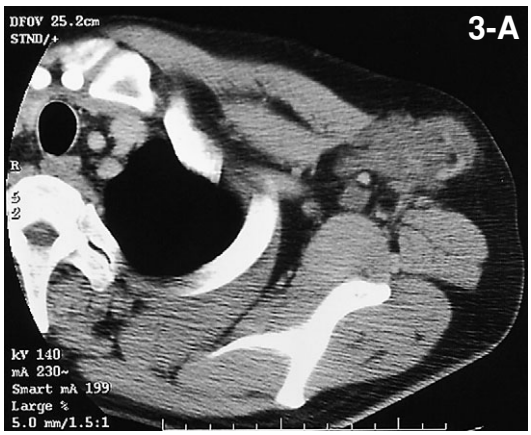
2-B: T1-weighted MR image. A large, deep-seated soft tissue mass.

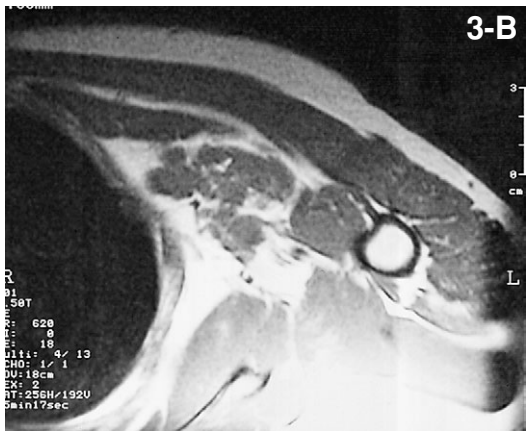
2-C: T2-weighted MR image. The mass shows mixed inhomogeneous signal intensities. Small low intensities on both T1 and T2 weighted images which probably represent areas of calcification.

(Courtesy of Dr K Takahashi MD, Asahikawa Medial College)

10–20%[13] respectively. The important point is that mineralization is a characteristic feature if present, but is not specific enough for diagnosis. Soft tissue osteosarcomas and chondrosarcomas may also contain mineralization, but the incidence of those tumors is low.[14,15] Also, further examination is required for patients in such cases as when MR imaging shows features of either an active or aggressive nature, regardless of the presence of mineralization or ossification on plain radiography (Fig. 2).

Differentiation between benign and malignant based on shape and internal structure is difficult. Many attempts to differentiate those entities have been made and reported through dynamic MR imaging, MR spectroscopy, and Tl-scintigraphy. However, there has been no satisfactory imaging method to accomplish this purpose. On the other hand, it is generally accepted that soft tissue tumors situated deeper than the fascia and larger than 5 cm in diameter are more likely to be malignant. It is also known that some superficial tumors, such as dermatofibrosarcoma protuberans, are malignant and some deep-seated tumors, such as lipoma and lymphangioma/hemangioma, are benign. However, lipoma and lymphangioma/hemangioma are characteristic findings on both CT and MR imaging (Fig. 3). Furthermore, there are a number of soft tissue masses in which specific diagnosis can be obtained because their location and appearance are typical on both CT and MR imaging. Morton neuroma is a reactive neuroma located in the sole of 2nd and 3rd interdigital area of the foot. Baker cyst is a synovial cyst located in the medial aspect of the popliteus fossa, projecting between hamstring





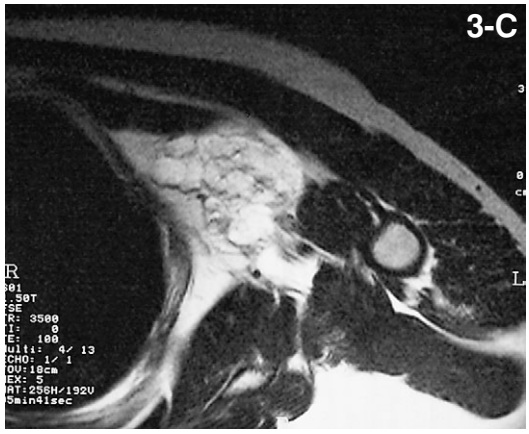


Fig. 3 A 51-year-old man with lymphangioma of the left axilla

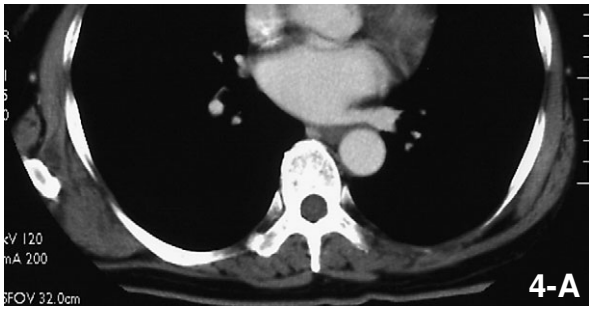
Although this tumor is deep-seated, its appearance in both CT and MR imaging is that of either lymphangioma or cavernous hemangioma.

3-A: Enhanced CT. A lobulated soft tissue mass with low attenuation. There is no apparent contrast enhancement within the mass lesion.

3-B: T1-weighted MR image. A low signal intensity mass with intervening fat tissue gives the appearance similar to that of a bunch of grapes.

3-C: T2-weighted MR image. The mass has very high signal intensity with low signal septa.

(Courtesy of Dr J Aoki MD, Gunma University)



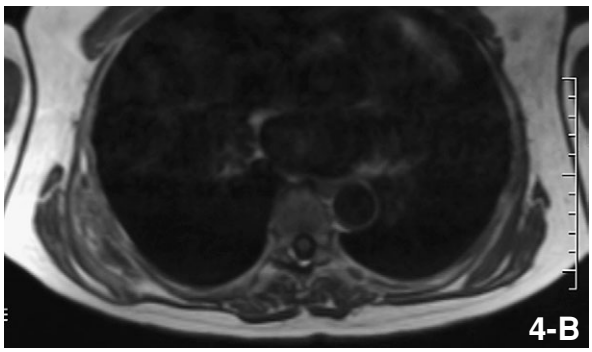


Fig. 4 A 54-year-old woman with elastofibroma dorsi of the right dorsal chest wall

Both CT and MR imaging show typical location and characteristic appearance of elastofibroma dorsi.

4-A: Enhanced CT. A soft tissue mass is located deep to the right rhomboid muscle. Fine linear areas of translucency are seen within the mass lesion.

4-B: T1-weighted MR image. Characteristic linear areas of mixed high and intermediate signals in the mass are also present.

(Courtesy of Dr T Aoki MD, University of Occupational and Environmental Health)

and medial head of the gastrocnemius muscle. Elastofibroma dorsi is a soft tissue mass located in the subscapular region between thoracic wall and the serratus muscle with characteristic strand-like fat infiltration within the soft tissue mass on both CT and MR imaging[16] (Fig. 4).

Therefore, the basic concept for the differential diagnosis between benign and malignant soft tissue tumors depends on the location, whether deep or superficial to the fascia, and on size of the tumor, larger or smaller than 5 cm, rather than on internal structure, except for certain tumors where specific appearances are known. This is probably the reason why the agreement rate in score concerning benign and malignant differentiation between CT and MR imaging was high in this study.

There were some limitations in this study. First, the subjects constituting this study were collected from nine different institutions and there was no uniform imaging protocol such as scan parameters, indication of contrast injection, and filming process. All examinations were performed as a part of each institution's routine work. However, all contributing institutions were university hospitals where musculoskeletal radiologists were present at the examinations. Therefore, image quality and indication of contrast injection were thought to have been reasonably well controlled. Second, since the introduction of multislice CT, fine images in any direction can be obtained using multiplanar reconstruction on CT. Therefore, evaluation of tumor location and local extension by CT may now actually be more accurate than is indicated by this particular study.

Conclusion

This study shows no superiority of CT in the diagnosis of soft tissue mass lesions over MR imaging, especially in the evaluation of anatomical location, local extension, and internal structure. Some improvement can be expected by use of contrast enhancement in CT diagnosis, but even contrast enhanced CT remains inferior to MR imaging. Therefore, the use of CT is impractical rather than complementary, when MR imaging is available for the diagnosis of soft tissue masses.

Acknowledgements

The authors thank the following individuals for their contributions to this study: Takatoshi Aoki MD, from University of Occupational and Environmental Health; Masahiko Fujii MD, from Kobe University; Hiroshi Nishimura MD, from Kurume University, School of Medicine; Kouji Takahashi MD, from Asahikawa Medial College; Kaoru Sasashita MD, from St. Marianna University School of Medicine. Also we would like to give special thanks to Ms Mamiko Yamaguchi for her support in the English transcription.

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Review Article

Behavior Therapy for Obesity

JMAJ 48(11): 539–544, 2005

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Abstract

Behavior therapy for obesity aims to make lifestyle modification necessary for weight loss in areas such as diet and exercise. It had been found that behavior therapy promotes weight loss and its maintenance by increasing treatment compliance. Lifestyle modification is regarded as essential for any treatment of obesity such as medication, dieting, surgery etc.

Physicians often tend to be unwilling to use behavior therapy in clinical practice considering it time-consuming and skill-intensive. However, behavior therapy for obesity can be standardized and used more readily. Furthermore non-face-to-face therapy and computer-assisted therapy have also been developed. We can use these materials conveniently.

To achieve the goals of behavior therapy, that is, to change habits and to maintain these changes, it is necessary to promote patient's self-care and to maximize the patient's own ability to undertake this. Above all behavioral techniques, the theory and the principle of operant conditioning that voluntary behavior is reinforced by the contingency of the behavior is the most fundamental and therefore also an indispensable principle in general clinical practice.

It is also necessary to ascertain the patient's readiness to lose weight and to adjust guidance targets accordingly. Patients who demonstrated sufficient readiness were able to achieve an average weight loss of about BMI $-0.9\,kg/m^2$ by correspondence intervention with target setting and one month's self-monitoring followed by six-months of regular observations only. Therefore if health professionals utilize these readymade educational materials and programs, they could save their limited time in creating an effective environment in which to motivate patients and manage their progress.

Key words Behavior therapy, Obesity, Lifestyle modification, Self-care, Computer-assisted program

Introduction

The maintenance of a reasonable body weight is a base of the treatment of diabetes, hypertension and hyperlipidemia. Even slight weight loss of about 5% of initial body weight could bring significant clinical improvement. In order to reduce excess body fat, the energy balance has to be kept negative by reducing food intake and increasing physical activities. As simple as this might seem in theory, in practice it can be extremely difficult to accomplish. Even if weight loss can be achieved in the short-term, it is even more difficult to maintain in the long-term. Since the 1960s, when obesity treatment first began to be taken seriously, the core challenges have been, and still remain that of motivating patients and of maintaining weight loss. By nature, many human beings prefer to eat as much as they want and like an easy life by avoiding exertion. Modern society has responded to these desires with the ready availability of convenience foods and the ever-increasing reliance on automated and motorized transportation. As a result, simple, healthy practices such as eating moderately and walking for an extra 20 minutes each day require even greater amounts of self-control and effort. Behavior therapy is psychotherapy that considers such human traits and tries to modify

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habitual behaviors. Its application to obesity started in the 1960s and its impact on motivation and the maintenance of effects became well established in the 1980s.[1]

Due to practical time constraints medical professionals tend to be reluctant to use psychotherapy, and behavioral change with their patients. They have also tended to underestimate the educational effects. However, in the author's experience weight reduction has been achieved by setting targets and self monitoring in a group treatment[2] and also our original non face-to-face program which provides computer-tailored advice.[3] Use of this program has shown that it is possible to standardize behavior therapy and facilitate implementation.

This paper gives an overview of behavior therapy for obesity, offers key pointers, and also describes specific ways in which medical professionals can promote and encourage self-care of patients.

Aim of Behavior Therapy and Its Problem-Solving Methods

The aim of behavior therapy is to increase the patient's capacity for self-control. Existing habits are considered learned behaviors to be changed gradually through a logical and methodical problem-solving approach. Initially, the problem is identified and described in terms of specific behaviors. These behaviors are then analyzed for stimulus-response relationships (Fig. 1). During this process, minute observations are made about the kinds of behaviors that happen at specific times and the consequences of those behaviors. To take the example of excessive drinking, the patient returns home in the evening and is bored on his own, he drinks too much beer, which he subsequently regrets, and as a result of the negative emotion wants to drink more. The environment and associated conditions are assumed to play a part in generating and sustaining the problem behavior. Once these have been identified, the patient can be encouraged to make changes in the environment so that the likelihood of desirable behavior is increased. Decision-making about subsequent courses of action is then dependent upon patients' actual behavior and ability to invoke change, in relation to the first analysis. Thus behavior therapy is evidence based, and the patient's efforts are essential.

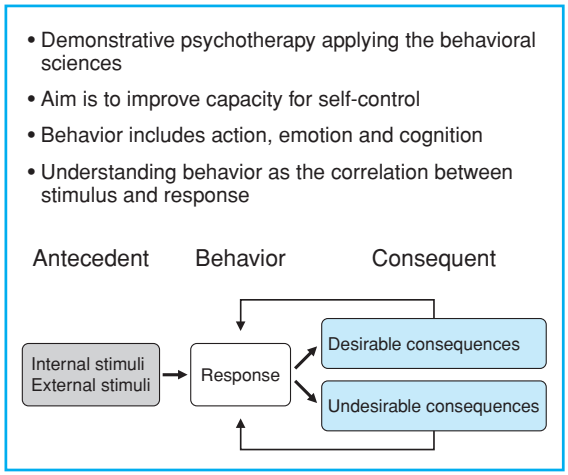


Fig. 1 Behavior therapy

Behavior therapy is the clinical application of behavioral sciences and is a general term for behavior correction and cognitive behavior therapy.[4] From the 1950s it came to be used mainly for problem behavior that is difficult to deal with in the psychiatric field. "Behavior" in this context includes both emotion, such as anxiety and depression, and cognition, including individual perception and mindset. Therefore, its application to a broad range of problem behaviors is possible. It has also been applied to psychosomatic medicine, general medicine[5] and preventive medicine.[6] Although understanding the theory requires familiarity with specialist terminology, the methods apply principles that appeal to common sense and in practice patients tend to be receptive to them.

Behavior Therapy for Obesity

Behavior therapy has long been applied to obesity and its usefulness was established ahead of other medical themes. Today, obesity is regarded as a chronic metabolic disorder caused by biological, behavioral, and socio-cultural factors. However, in the 1960s obesity was simply regarded as the result of "overeating." Based on clinical observations, two hypotheses were put forward to explain overeating (Table 1). The externality theory suggests that the obese tend to respond to external, physical stimuli such as the presence of favorite foods, certain

Table 1 Hypotheses of overeating and techniques

Externality theory, Schacter 1971
Conditioned to many external food cues (favorite food, time, place, etc.) besides internal stimuli (hunger)
↓
Stimulus control
Obese eating style
Eating quickly by taking large mouthfuls of food and fewer bites
↓
Modification of act of eating (Way of eating slowly)

Table 2 Behavior techniques for obesity

- Stimulus control (restriction of stimuli that precede eating)
- Make patient eat slowly (chew each mouthful 20 times and eat hard foods)
- Target setting (specific behavior and weight-loss goals)
- Self-monitoring (recording weight, meals and target behavior)
- Operant reinforcement (scoring practice of behavior, rewards)
- Response prevention/habit replacement (suppressing impulsive eating by competitive behavior)
- Stress management
- Problem-solving methods
- Cognitive restructuring (changing maladaptive stereotyped thoughts)
- Social support (family, friends, club, and public health workers)

smells, or a time of day, in addition to, or aside from internal factors such as hunger. The second theory posits the existence of an 'obese eating style' characterized by eating quickly, taking large mouthfuls of food and few bites.

Since food sustains life and is an essential part of daily living, it is susceptible to become linked with a wide variety of stimuli, for example, the end of a meal signals the expectation of a desert or watching TV becomes associated with snacking. As eating behavior can be triggered by the presence of such commonly occurring stimuli it easily becomes habitual, and so stimulus control was proposed with the aim of restricting the stimuli associated with eating. In specific terms this might mean, "only putting the amount you're going to eat on your plate," "not eating while watching TV or reading the newspaper," "putting sweets out of sight" and "eating at a set time in a set place and eating with set cutlery."

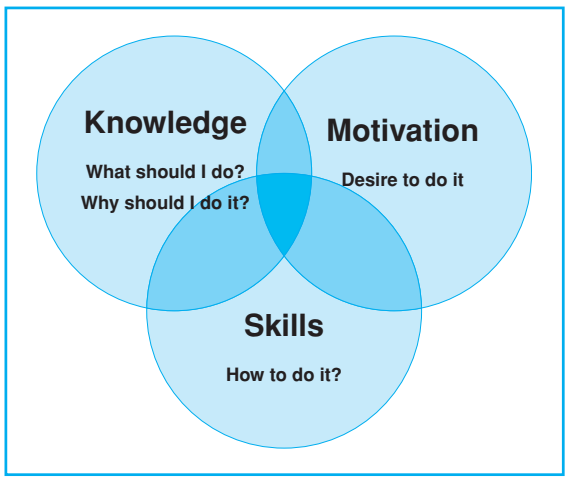
Faced with a patient who eats quickly, eating style modification to reduce the eating pace is applied such as "put your knife and fork down after each mouthful and chew 20 times," "avoid soft food and choose food that is hard and crunchy." Additional strategies include "target setting," i.e. establishing specific behavioral and weight-loss goals, "self-monitoring" i.e. recording weight, meals, exercise and behavior, "operant reinforcement," i.e. rewarding the attainment of desirable behavior, and "response prevention and habit replacement" i.e. the suppression of impulsive eating behavior, are behavioral techniques for obesity that have long been used (Table 2).

In 1967 Stuart provided individual treatment for one year using these methods and achieved a mean weight loss of 17 kg with eight patients.[7] This is an epoch making therapeutic outcome and has prompted much subsequent research. Recently, NIH reviewed 36 randomized control trials of behavior therapy in its clinical guidelines for the treatment of obesity,[8] concluding that 1) behavior therapy is effective in making diet and exercise habitual, 2) used together with dietary therapy and exercise therapy it definitely promotes therapeutic benefits and the subsequent maintenance of weight loss for up to one year, yet 3) such benefits do not, however, last for over three years if patients are left to their own devices. Besides the problem-solving behavioral techniques described above, various methods to keep efforts going in the long-term are being applied comprehensively where necessary, for example, "stress management," "cognitive restructuring" to correct maladaptive thought and cognition, "social skills training" (assertiveness training) to improve interpersonal communication, "relapse prevention" aimed at managing impulsive hunger and "social support" that makes use of the cooperation of family and friends.

The average therapeutic outcome of behavior therapy in the West today is about 9 kg weight loss in four months, while adding exercise or family therapy enables weight loss of up to about 11 kg. Because more drastic weight loss has adverse effects and abrupt weight loss is liable to

Table 3 Guidelines for weight control

1. At a slow pace (1–2 kg/month)
2. Set attainable goals (5–10% loss of body weight in six months)
3. By changing habits (lifestyle improvement)
4. For people who can be expected to have health benefits from weight loss
5. For people ready to lose weight
6. With both diet and exercise together



Source: Adachi Y ed. Lifestyle Therapy. Ishiyaku Publishers inc. 1998.

Fig. 2 Conditions for changing habits

rebound, the therapeutic guidelines set out in Table 3 have come to be considered as standard. For people who could expect health benefits from weight loss of about 5–10% of body mass, weight is reduced over a six-month period at a slow pace of about 1–2 kg a month through lifestyle improvements. To achieve lifestyle modification, the individuals in question must be properly informed (knowledge) and mentally prepared to commit themselves to losing weight (motivation), and acquire modification skills (Fig. 2). The necessity of exercise in weight loss has recently taken greater emphasis, since exercise prevents a reduction in energy consumption and a reduction in lean body mass as a result of cutting-back on food. Therefore increasing physical activities is essential for losing weight efficiently and maintaining the reduced weight.

Empowerment According to Readiness to Change Habits

The aim of behavior therapy is to change habits and to maintain changed habits. Maximizing an individual's own ability to effect that change is thus central. In order to achieve this, physicians, nurses, and nutritionists should guide the patients to make efforts to change their habits for themselves and support them by promoting self-care. Since the changing of long-established life habits such as diet and exercise involves sacrifice and pain, resolution and willpower are required. If individuals are ready for this, they can be coached in the techniques of behavior change. If they are not really ready, however enthusiastically they are encouraged, they are likely to resist, and the therapy may be counterproductive. The concept of "readiness" for habit change now has currency in the practice domain. Prochaska's "stage of change model" for smoking advocates five stages of readiness.[9] In this paper three of these stages are used: Not ready, Unsure and Ready, as detailed in the sections below:

Dealing with people who are not ready

Faced with patients who show no interest in losing weight whatsoever, briefly explain the need to lose weight by objectively feeding back the patients' physical risk and encourage them to be careful not put on any more weight. Their interest may be aroused by, for example, providing teaching materials, recommending weekly weigh-ins and checking weight changes at every clinical visit. In many cases, even if patients appear uninterested at first glance, it may be the case that they have given up on the possibility of ever losing weight as a result of previous failed attempts. Alternatively, apparent disinterest may stem from feelings of guilt about being obese. The best course of action is to make patients think about what they could do now, without forcing them to do anything that looks impossible.

Dealing with people who are unsure

In some cases, even if patients are aware they need to lose weight, they have yet to reach the stage where they are resolved to do so. Again, in cases such as these, make patients understand what benefits losing weight would bring them

Table 4 Selection of dietary targets

	Doing already	Could do	Couldn't do
Eat till you're 80% full		○	
Eat no more than one bowl of rice or one slice of bread	○		
Eat no more than three fried foods (tempura, etc.) a week	○		
Choose low-fat milk and yoghurt		○	
Choose low-fat or non-oil mayonnaise and dressings		○	
Avoid eating *rahmen* or *ocha-zuke* after drinking	○		
Choose a Japanese set meal when eating out			○
Leave some rice when eating *donburi*			○
Restrict sweet soft drinks	○		
Restrict sweets and snacks		○	
Limit alcohol to no more than a glass per day	○		
Choose low-calorie snacks with drinks (vegetable sticks, etc.)	○		
More than two no-drinking days per week		○	
Finish evening meals no later than two hours before going to bed	○		
Avoid eating after evening meals		○	
Eat vegetables at least twice a day		○	
Eat fish at least four times a week		○	

Select targets from those you could do

and explore with them what could improve. For some people, visualizing specific behaviors for losing weight can give them the motivation to carry it through. Using questionnaires to help patients observe their habits and situation can prompt patients to notice their own tasks for themselves. Using simple educational materials that present many specific examples of target behaviors in areas that could be improved can also be helpful in enabling patients to learn efficiently by themselves. Encouraging individuals to think for themselves about which behaviors they might be able to change can also increase their inclination to lose weight of their own accord.

Dealing with people who are ready

For patients who are ready, decide on specific target behaviors and have the patients practice these daily on self-monitoring. To make this habitual, it is necessary to repeat the same behavior for a certain period and to do this the following two strategies are fundamental:

(1) Setting of target behaviors

Specify four or five target behaviors including both diet and exercise that could be expected to be beneficial if achieved, and that patients have a 70–80% chance of achieving so long as they make a reasonable effort. If undertaken in an interview setting this will take a minimum of 30–40 minutes and also requires technique. However, such interviews often result in similar targets, such as for diet: "eating till you're 80% full," "no more than one sweet" and "no more than one bowl of rice or one slice of bread," and for exercise "brisk walking for more than 30 minutes," "walking for more than 40 minutes to and from work or on errands," "10,000 steps a day" and "15 minutes stretching."

As an alternative to time- and technique-intensive interviews, the author's program mentioned earlier[3] provides examples of commonly chosen behavior targets. Patients follow a series of preset steps that guide them through the process of selecting and setting themselves target behaviors[10] (Table 4). First, patients look at the list of specific examples of desirable behaviors and then classify each item under the headings: "Doing already," "Couldn't do" or "Could do with some effort." Second, patients choose about five target behaviors for diet and exercise from the items they considered they "could do with a some effort." This raises patients' awareness about their current habits, encourages them to be judge of what they are and are not capable of achieving, and lets them decide for

themselves what they are going to try to do. Given this process, target behaviors can be set comparatively easily even with limited time.

(2) Self-monitoring of weight and target behaviors

Patients subsequently carry out daily self-monitoring of their weight on a graph and of the achievement of their target behaviors using symbols. Self-monitoring is a useful means of self-control and consists of self-observation, self-evaluation, and self-reinforcement. When patients practiced such self-monitoring for at least one month, based on the author's experience, mean weight loss of about BMI $-0.9\,kg/m^2$ over a six-month period has been obtained. At around two or three weeks, it is acceptable for patients to change the targets if they are too easy or too difficult. Self-monitoring tends to become monotonous, and it is necessary for physicians themselves to have a good understanding of the significance of this technique and to check patients records and remark on patients' efforts during each consultation.

Operant Reinforcement

Physicians should always pay attention to the patients' practical efforts. That is the principle of operant reinforcement that physicians should be most conscious of in routine consultations. The responses of a reliable doctor are important reinforcing stimuli for the patient. When physicians take notice of patients' efforts and highlight their achievements, this serves to increase the patients' desired behavior as a positive social reinforcer. Without making a conscious effort, however, it is easy for physicians to overlook this fact. In addition to attending to test results, the author would like physicians to notice patients' behaviors and to acknowledge desirable effort and specific changes at the right time. This will increase the patients' self-esteem and satisfaction and encourage the continued practice of this behavior. In many cases, people are encouraged if they can lose as little as 1–2 kg by improving their habits and they are then able to keep up their efforts just through regular observations. Particularly at the introductory phase, it is effective to consciously focus on actual behavior rather than weight change.

Based on the above, behavior therapy for obesity can be summed up as follows: A gradual progression involving the use of various techniques, the provision of encouragement in an effort to improve the self-management ability of the individuals in question, having them embark on the dietary and exercise changes necessary to lose weight, and having them continue to practice this.

Some clinics have applied the aforementioned non-face-to-face program[3,10]: patients answered questionnaires in the outpatients waiting room and physicians provided guidance with reference to tailor-made advice automatically provided based on the patient's data. Overall, patients were highly satisfied with this service.

The role required of physicians and health professionals in busy clinical practices would be to guide habit changes by making good use of readymade educational materials and programs, creating an environment that will motivate patients, and supporting their progress in the future. Behavior therapy offers a clear course of action for both patients and medical staff.

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Short Communication

Increase of 'Health and Human Rights' Research Articles in Japan

JMAJ 48(11): 545–549, 2005

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Rika Fujiya,[*1] Susumu Wakai[*1]

Abstract

Research on health and human rights is increasing in Japan, but this trend has never been studied. We thus reviewed health and human rights articles in the Japanese biomedical journal database to reveal the research trend between 1983 and 2002. We found that the number of health and human rights articles in Japan increased substantially from 1994. The range of keywords associated with human rights issues also increased as the number of articles increased. During the period 1983 to 1987, articles on mental health related issues were most common. Concern shifted to *privacy* between 1988 and 1992, and then to *right to die* between 1993 and 1997. In the last 5-year period studied (1998–2002), *patient advocacy* became the most frequently associated keyword followed by *privacy*, *informed consent*, *freedom*, *confidentiality*, and *medical ethics*. This trend is different from that of the MEDLINE database in the global setting. In conclusion, this study suggests that a literature survey on health and human rights articles drawn from a national database reflects the culture of the country's medical community.

Key words Human rights, Japan

Introduction

Research on health and human rights is receiving increasing attention in biomedical journals. In 2000, Flanagin reported an increase of human rights articles cited in MEDLINE between 1966 and 1999 and noted that the top 5 coterms associated with human rights articles in MEDLINE were *medical ethics*, *torture*, *world health*, *public health*, and *refugees*.[1]

In Japan, the number of human rights articles has also been on the increase. However, this research trend has never been studied. Thus, we tried to determine the nature of these changes by conducting a survey of the literature to analyze the keywords that have been associated with human rights related articles published in Japan.

Methods

We conducted a review of citations in the *Igaku-chuo-zasshi* (Japana Centra Revuo Medicina) database, which was established in Japan in 1903, 24 years after the Index Medicus was introduced in the United States in 1879.[2] The *Igaku-chuo-zasshi* database cites over 300,000 articles annually from approximately 2,400 Japanese biomedical journals. Its online archives contain 5 million articles dating back to 1983.[2]

The term "human rights" (*jinken* in Japanese) was formally introduced in 1987, when the second edition of the Japanese database lexicon was published. In this database, *human rights* is supported by 9 medical subject heading (MeSH) categories and coterms called non-descriptors. As the MeSHs of this database are based on

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Table 1 Top 5 keywords in Japanese human rights articles from 1992 to 1997

Rank	1992 Keyword	1992 Frequency	1993 Keyword	1993 Frequency	1994 Keyword	1994 Frequency	1995 Keyword	1995 Frequency	1996 Keyword	1996 Frequency	1997 Keyword	1997 Frequency
1	Right to die	9	Privacy	9	Privacy	8	Right to die	22	Patient advocacy	26	Right to die	31
2	Patient	8	Dementia	9	Right to die	8	Patient	21	Right to die	25	Privacy	21
3	Mental health	6	Short-term visitor	8	Terminal care	5	Privacy	17	Patient	24	Patient advocacy	20
4	Privacy	5	Patient	7	Informed consent	4	Patient advocacy	12	Informed consent	15	Freedom	20
5	Drugs	4	Right to die	5	Attitude survey	3	Informed consent	10	Privacy	15	Nursing	18

Attitude survey (*ishiki-chosa*), Dementia (*chiho*), Drugs (*yakubutsu*), Freedom (*jiyu*), Informed consent (*infomudo-konsento*), Mental health (*seishin-hoken*), Nursing (*kango*), Patient (*kanja*), Patient advocacy (*kanja-no-kenri-yogo*), Privacy (*puraibashi*), Right to die (*shinu-kenri*), Short-term visitor (*tanki-taizaisha*), Terminal care (*taminaru-kea*)

Table 2 Human rights articles published in Japanese medical journals, 1983–2002 (N = 2,321)

1983–1987 (N = 128) Keyword	Frequency (%)	1988–1992 (N = 143) Keyword	Frequency (%)	1993–1997 (N = 397) Keyword	Frequency (%)	1998–2002 (N = 1,653) Keyword	Frequency (%)
Mental disorder	29 (22.7)	Privacy	37 (25.9)	Right to die	91 (22.9)	Patient advocacy	641 (38.9)
Mental health	23 (18.0)	Mental health	21 (14.7)	Privacy	70 (17.6)	Privacy	328 (19.9)
Patient management	18 (14.1)	Right to die	16 (11.2)	Patient	62 (15.6)	Informed consent	309 (18.8)
Mental hospital	11 (8.6)	Patient	15 (10.5)	Patient advocacy	59 (14.9)	Freedom	257 (15.6)
Privacy	8 (6.3)	Mental disorder	14 (9.8)	Informed consent	46 (11.6)	Confidentiality	107 (6.5)
Mental retardation	6 (4.7)	Medical ethics	8 (5.6)	Nursing	28 (7.1)	Medical ethics	102 (6.2)
Patient	6 (4.7)	Patient management	8 (5.6)	Terminal care	28 (7.1)	Mental disorder	95 (5.8)
Medical service	5 (3.9)	Schizophrenia	6 (4.2)	Freedom	27 (6.8)	Nurse	86 (5.2)
Nurse	4 (3.1)	Terminal care	5 (3.5)	Child	21 (5.3)	Terminal care	84 (5.1)
Child psychiatry	3 (2.3)	Cerebral death	4 (2.8)	Death	19 (4.8)	Right to die	82 (5.0)
Freedom	3 (2.3)	Drugs	4 (2.8)	Dementia	19 (4.8)		
Hospital administration	3 (2.3)	In patient	4 (2.8)	Euthanasia	19 (4.8)		
Life ethics	3 (2.3)	Nursing	4 (2.8)				
Medical certificate	3 (2.3)	Patient advocacy	4 (2.8)				
Nursing care	3 (2.3)						
Rehabilitation	3 (2.3)						

Cerebral death (*noshi*), Child (*shoni*), Child psychiatry (*jido-seishin-igaku*), Confidentiality (*shuhi*), Death (*shibo*), Dementia (*chiho*), Drugs (*yakubutsu*), Euthanasia (*anraku-shi*), Freedom (*jiyu*), Hospital administration (*byoin-kanri*), In patient (*nyuin-kanja*), Informed consent (*infomudo-consento*), Life ethics (*seimei-rinri*), Medical certificate (*shindansho*), Medical ethics (*i-no-rinri*), Medical service (*hoken-iryo-sabisu*), Mental disorder (*seishin-shogai*), Mental health (*seishin-hoken*), Mental hospital (*seishin-byoin*), Mental retardation (*seishin-hattatsu-chitai*), Nurse (*kango-shi*), Nursing (*kango*), Nursing care (*kango-kea*), Patient (*kanja*), Patient advocacy (*kanja-no-kenri-yogo*), Patient management (*kanja-kanri*), Privacy (*puraibashi*), Rehabilitation (*rihabiriteshon*), Right to die (*shinu-kenri*), Schizophrenia (*togo-shiccho-sho*), Terminal care (*taminaru-kea*)

those of MEDLINE, the MeSH categories listed under *human rights* mirror those of MEDLINE. Keywords in each article are determined by the indexers of the Japanese database. Japanese equivalents for the English keywords are given in result Tables 1 and 2.

We accessed the database on 18 August 2004 and identified articles associated with the

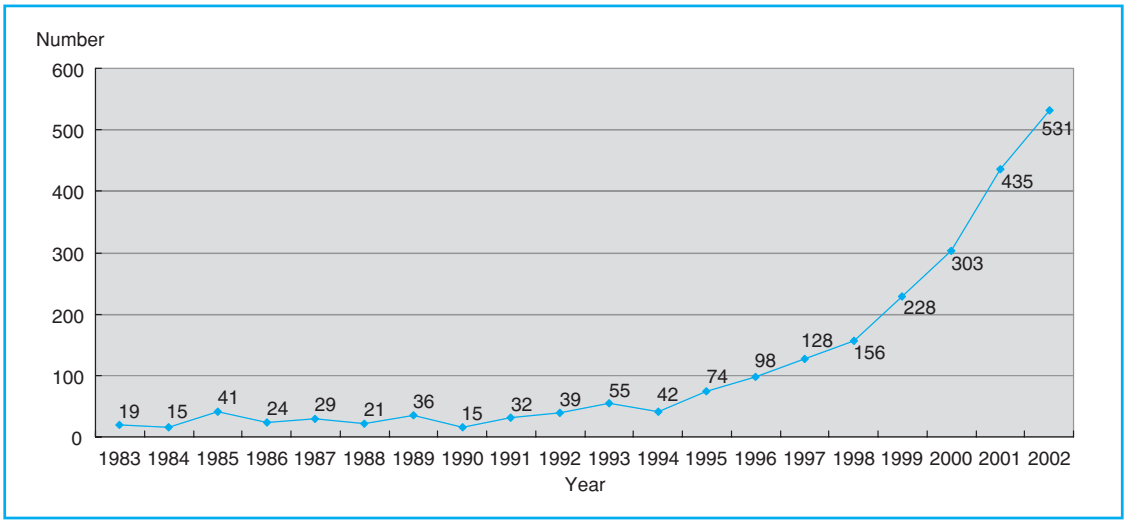

Fig. 1 Number of human rights articles in Japanese medical journals by year

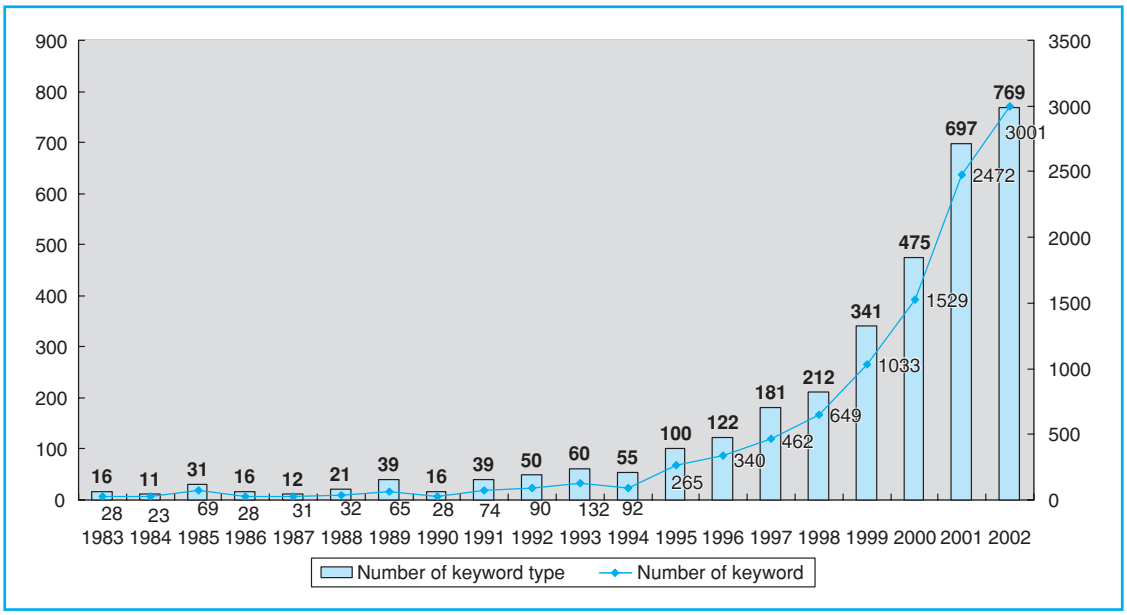

Fig. 2 Number of keywords and keyword types in Japanese human rights articles by year

keyword *human rights* as human rights articles. We first determined the number of the human rights articles cited in the database for each year from 1983 to 2002. We downloaded all the keywords associated with these articles into an Excel file by year to ascertain the total number of related terms and to reveal any trend. We then grouped the keywords into 5-year categories, sorted them in order of descending frequency, and identified the top 10 keywords. Finally, we searched the human rights articles in the Japanese database for the top 5 coterms associated with human rights articles in MEDLINE as identified by Flanagin.[1]

Results

The *Igaku-chuo-zasshi* database included 4,654,895

articles from 1983 to 2002. Of these, 2,321 articles dealt with human rights. Figure 1 shows that the number of human rights articles has risen consistently since 1995. Correspondingly, the number of keywords used for these articles almost tripled from 92 in 1994 to 265 in 1995 and the number of different keyword types used in human rights articles grew from 55 to 100 during the same period (Figure 2).

Table 1 shows changes that occurred in 1995 not only in terms of the range of keywords, but also the frequency with which each keyword was cited. Before 1994, even the five most frequently used keywords were cited less than ten times per year. After 1995, the frequency ranged from 10 to 31 citations. For example, the term *right to die* consistently ranks in the top five most frequently used keywords between 1992 and 1997; however, its citation frequency can be seen to increase quite substantially when the periods 1992–1994 and 1995–1997 are compared.

Table 2 shows the trend in topics of human rights articles as shown by keywords associated with these articles in each of the 5-year periods from 1983. During the years between 1983 and 1987, articles on mental health issues were most common. During the next 5 years, *privacy* emerged as the keyword most frequently associated with articles on human rights. *Right to die* became the most common subject among these articles between 1993 and 1997 while *privacy* ranked second. During the last 5-year period (1998–2002), *patient advocacy* became the most frequently associated keyword followed by *privacy*, *informed consent*, *freedom*, *confidentiality*, and *medical ethics*.

During the two decades under study, articles on medical ethics and human rights numbered 117, while MEDLINE's other top coterms received less attention: 13 articles on public health and human rights; 1 article on world health and human rights; and no articles either on refugees and human rights or on torture and human rights.

Discussion

Our review revealed the unique characteristics of biomedical literature on human rights in the Japanese database. In MEDLINE, the increase in human rights articles started in 1975.[1] In the Japanese database, the number of human rights articles began to grow from 1994, although the term *human rights* and related terms were formalized in the Japanese database lexicon in 1987.

In addition to a difference in the timing of the increases in human rights articles, the topics found in the Japanese database also differed from those of MEDLINE. According to Flanagin, biomedical literature on human rights reflects an evolving interest among the biomedical community to raise awareness of human rights problems and to improve practice and research of human rights.[1] In this article, we showed that mental health issues were the first concern, but this gradually shifted to death- and patient-related concerns in Japan. Although medical ethics were one of the top concerns, we found that the other concerns related to health and human rights that came out top in MEDLINE have not received the same attention in the Japanese database. This situation seems to reflect that of MEDLINE in the 1970s. In MEDLINE, only 2 articles were indexed on refugees and human rights for the years 1970–1979, then the number gradually increased up to 80 for 1990–1999.[1]

This study has a limitation in that we did not explain why these changes occurred when they did and what the implications might be. This is because we used only keywords from each article and did not look at full papers. However, we were successful in showing increases in keyword variety and in citation frequency per keyword after 1994 as can be seen in Table 2. This indicates the start of a broad and profound interest in human rights topics in Japan. Further study is necessary to explain the changes and their implications. This study is a valuable reflection of the macro picture of health and human rights research in Japan over two decades. In addition, it is the first of its kind as there has been no similar study of Japanese medical literature undertaken previously.

Articles that report on medical publications should not only comment on clinical or scientific problems. Each publication aims to prompt a broader debate on social, political, and economic factors that affect health by discussing issues and concerns at the forefront of their field.[3,4] As such, we believe that a country's local medical database is not simply a collection of journals, but also a reflection of the socio-political

and economic climate within the profession during particular periods of time. This study, in conclusion, suggests that a literature survey on health and human rights articles drawn specifically from a national database can reflect the culture of the medical community of the time in that country.

Acknowledgements

We thank the Mitsubishi Foundation for its financial support to the study.

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Percutaneous Radiofrequency Ablation and Endoscopic Esophageal Stenting for Undifferentiated Thyroid Cancer

JMAJ 48(11): 550–556, 2005

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Abstract

We report a 69-year-old woman who received chemotherapy and radiation for thyroid tumor (undifferentiated cancer) after surgery in 1998. Chemotherapy was regularly repeated in order to avoid relapse. However, the tumor increased gradually, eventually causing dysphagia. Although we offered nutritional management through intravenous hyperalimentation or gastrostomy, she strongly preferred the oral intake of nutrition. Therefore, after obtaining her consent, we performed percutaneous radiofrequency ablation (RFA) for the tumor using a Cool-Tip needle, on April 2, 2003. The algorithm of RFA was 9 min: 30→120 W, 12 min: 50→110 W, 9 min: 50→100 W. After 2 days, a covered stent was implanted to the esophagus, and oral intake was started. Although the operation for poorly differentiated thyroid cancer is controversial, we performed RFA and esophageal stenting to improve the patient's QOL. We believe this is the first such case in the world.

Key words Radiofrequency ablation (RFA), Thyroid cancer, Esophageal stent

Introduction

Radiofrequency ablation (RFA) is used for the treatment not only of primary hepatocellular carcinoma but also of other tumors including metastatic liver cancer,[1] lung cancer,[2,3] renal cancer,[4,5] adrenal tumor,[6] bone tumor,[7,8] and metastatic bone tumor.[9] In addition, extension of its application to pancreatic cancer is now under consideration.[10] Although the invasive treatment of undifferentiated thyroid cancer is controversial, we carried out RFA and esophageal stenting in a patient with this type of tumor for the first time in the world. Improvement in quality of life (QOL) was achieved in this patient. Although RFA was markedly effective, a tracheo-cutaneous fistula formed as a postoperative complication. This case is reported herein.

Case Report

[Patient] A 69-year-old woman.
[Chief complaint] Dysphagia.
[Family history] Thyroid disease (−).
[Past history]
Age 26: Resection of right goiter (details unknown).
Age 29: A mass occurred in the right cervical area. Right lobectomy and radiotherapy for thyroid cancer (histopathology: papillary carcinoma).
Age 40: Postoperative hypothyroidism (thyroid hormone replacement therapy initiated).

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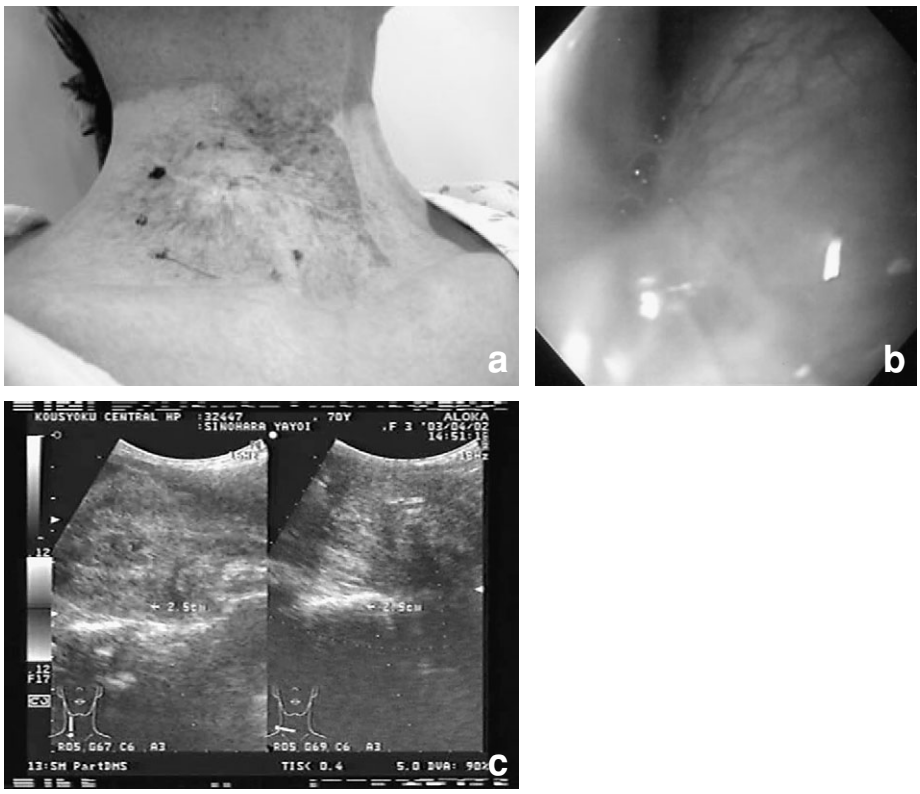

Fig. 1 Physical findings and imaging data on admission

a: Physical findings: De-pigment area and operation scar in the neck. Thyroid cancer was elastic hard (marked in black dots) and had no mobility.
b: Endoscopic findings: The endoscope was not able to pass by oppression of thyroid cancer in the esophageal orfice.
c: Ultrasound findings: The thyroid cancer with capsules was heterogenous in pattern and 5×5 cm in size.

Age 64: Undifferentiated thyroid cancer occurred. Treated by tumor resection (non-curative operation: histopathology: undifferentiated carcinoma) and 4 cycles of EP therapy (etoposide and cisplatin).

[Present illness] The patient was admitted to Shinshu University Hospital in 2001, at the age of 67, because of recurrence of undifferentiated thyroid cancer and its metastasis to the lung. There was no surgical indication because of involvement of the trachea and artery. Four cycles of chemotherapy (EP therapy) achieved a marked decrease in the tumor growth rate. Despite periodic implementation of the same chemotherapy regimen after discharge, the tumor increased gradually to cause dysphagia in December 2002. The patient was admitted to the hospital for close examination in March 2003.

[Physical findings on admission] The patient had hoarseness. There were depigmented macules throughout the cervical area, and a surgical scar 7 cm long was noted in the anterior cervical region. There was a palpable mass measuring 5 cm in diameter (no mobility, elastic hard, no tenderness) in the right cervical region (Fig. 1a). No abnormality was found in the thoracoabdominal region. There was no pretibial edema.

[Laboratory data on admission (Table 1)] No abnormality was found in blood count or biochemistry. Among the parameters of thyroid function, free T3 and free T4 were normal, TSH was suppressed to 0 μIU/ml, and thyroglobulin was less than 5.0 ng/ml.

[Imaging data on admission]

Chest radiography: The cardiothoracic ratio (CTR) was 45%. The trachea was slightly deviated to the left. There was no pleural effusion or tumor shadow.

Upper gastrointestinal endoscopy (Fig. 1b): Occlusion of the esophageal orifice was noted.

Table 1 Laboratory data on admission (March 2, 2003)

Peripheral Blood				**Urinalysis**	
WBC	4,400 /μl	γ-GTP	20 U/L	O.B.	(−)
RBC	486×10^4 /μl	ChE	406 U/L	Protein	(−)
Hb	13.2 g/dl	BUN	17.9 mg/dl	Glucose	(−)
Ht	43.0 %	Cre	0.8 mg/dl	Urobilinogen	(±)
Plt	15.9×10^4 /μl	UA	5.5 mg/dl		
		ZTT	3.9 U	**Thyroid Function**	
Blood Chemistry		Na	146 mEq/l	Free T3	2.75 pg/ml
TP	7.0 g/dl	K	4.6 mEq/l	Free T4	1.71 ng/dl
Alb	4.4 g/dl	Cl	108 mEq/l	TSH	0.00 μIU/ml
ALP	238 U/L	CPK	72 U/L	Thyloglobulin	<5.0 ng/ml
T-Bil	0.43 mg/dl	TC	190 U/L		
AST	21 U/L	TG	46 mg/dl		
ALT	15 U/L	CRP	0.13 mg/dl		
LDH	202 U/L				

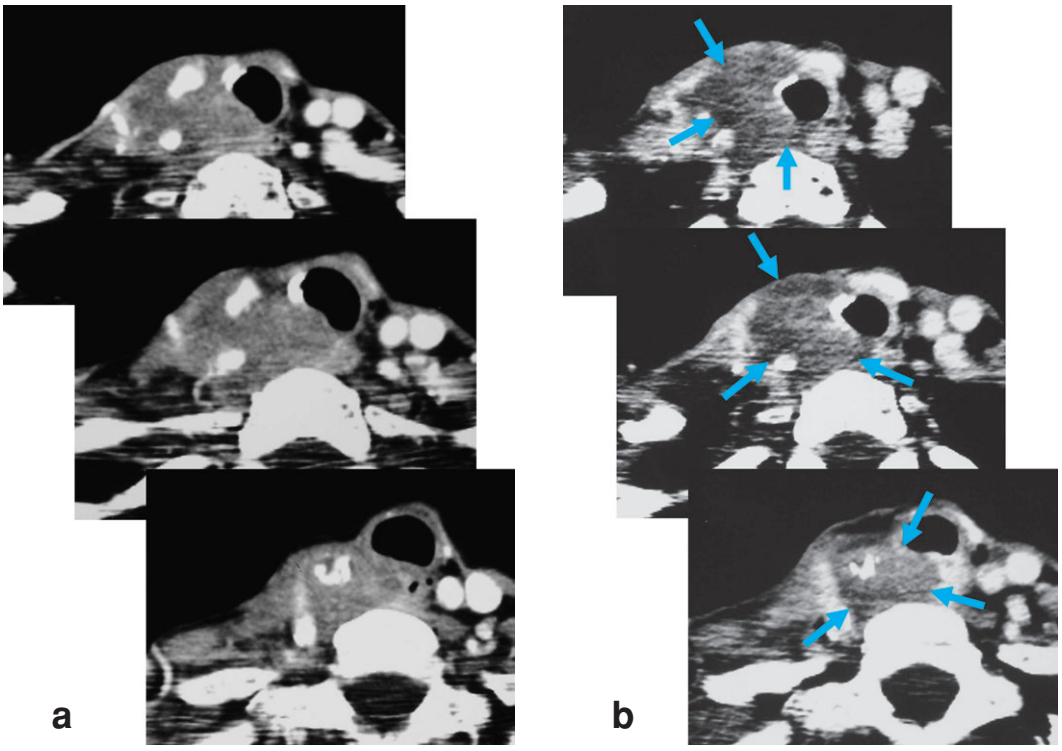

Fig. 2 CT findings

a: CT on admission. The thyroid cancer was not hypervascular tumor.
b: Two days after RFA. The majority of the tumor was not enhanced after RFA. The necrotic lesion was $30\times33\times38$ mm in size (arrows).

Ultrasound findings (Fig. 1c): The thyroid tumor with capsules was heterogenous in pattern and 5×5 cm in size.

CT (Fig. 2a): The thyroid tumor, which measured $32\times42\times48$ mm, pressed the trachea from the right posterior side, and the esophagus from the right anterior side, with distinct infiltration into the artery.

Table 2 Percutaneous radiofrequency ablation under ultrasonography (April 2, 2003)

Apparatus and Materials		
	Apparatus:	ALOKA SSD-5000
	Probe:	Convex probe for operation (10 MHz)
	Needle bracket:	CIV-614
	Needle:	17 G Cool-Tip (Radionics Co.: Diameter: 20 mm, Length: 20 cm)
RFA algorithm		
	Coagulation 1 (9 min):	30 W start→10 W/min up→max 120 W
		Final Intra-tumor Temperature 90°C
	Coagulation 2 (12 min):	50 W start→10 W/min up→max 110 W
		Final Intra-tumor Temperature 89°C
	Coagulation 3 (9 min):	Draw the needle 5 mm backward
		50 W start→10 W/min up→max 100 W
		Final Intra-tumor Temperature 94°C
		Break (impedance out) at 8 min: 1 time

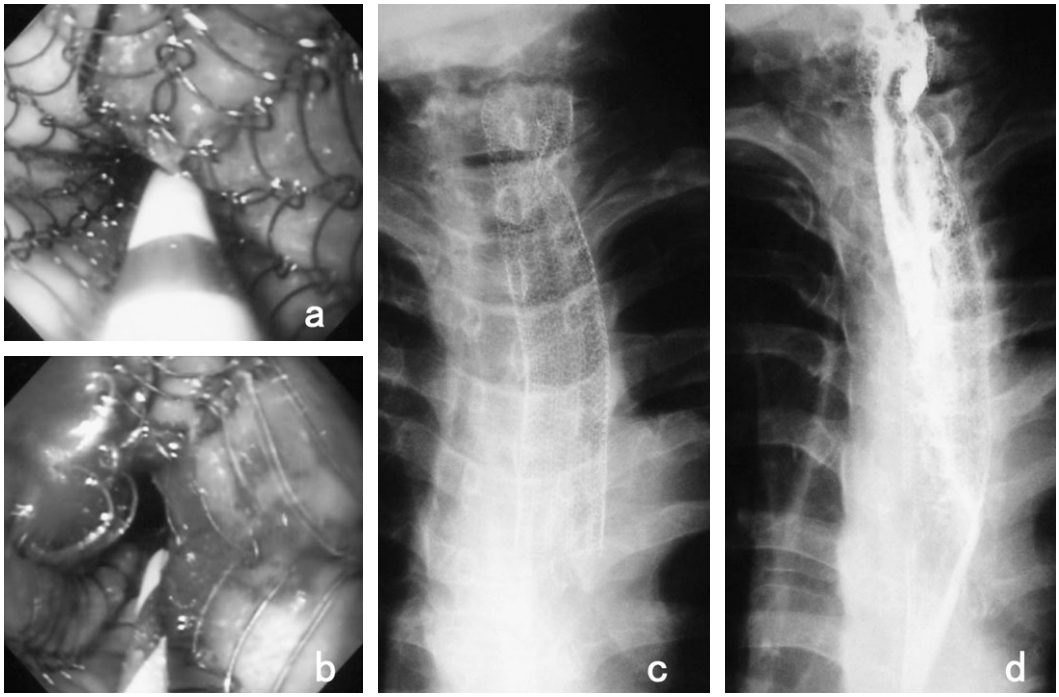

Fig. 3 Endoscopic stenting in esophagus (2 days after RFA)

a,**b**: Endoscopic stenting. Covered stent (Boston Scientific Co.: Ultraflex: length of whole stent 12 cm, outer diameter in covered portion 22 mm, length of covered portion 9 cm) was implanted.
c: X-ray findings after stenting.
d: Esophageal fluoroscopy 7 days after stenting. The favorable passage of contrast medium was confirmed.

[Course after admission] Although the patient was given an explanation of the need for nutritional management by intravenous hyperalimentation or gastrostomy, she persistently refused such procedures and strongly requested oral feeding. After sufficient information had been provided, the patient consented to RFA for treatment of the tumor.

[RFA] RFA was performed on April 2, 2003. The apparatus used was an ALOKA SSD-5000,

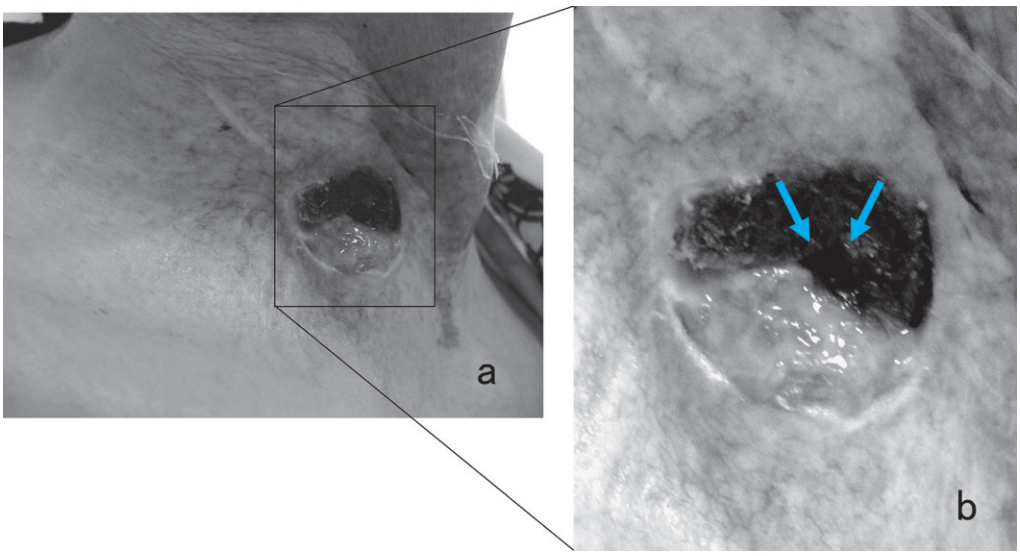

Fig. 4 Skin burn and fistula formation (24 days after RFA)
a: The circumference of a needle hole was split at 17 days after RFA, and a tracheo-cutaneous fistula was formed (arrows).
b: Magnification of a.

with the use of a convex intraoperative probe (10 MHz). Under ultrasonography, a 17 G Cool-Tip needle (Radionics: 20 mm in diameter, 20 cm in length) was punctured to provide ablation (9 min: 30→120 W, 12 min: 50→110 W, 9 min: 50→100 W) (Table 2). Two days later, CT evaluation revealed a necrotic area measuring 30×33×38 mm, although there was no change in tumor size (Fig. 2b).

[Endoscopic esophageal stenting (Fig. 3)] A covered stent (Ultraflex, Boston Scientific: outside diameter of the covered part, 22 mm; stent length, 12 cm; cover length, 9 cm) was implanted endoscopically 2 days after RFA (Fig. 3a,b,c). Oral feeding was resumed after favorable passage of contrast medium was confirmed by postoperative esophageal fluoroscopy (Fig. 3d).

[Postoperative course] RFA was carried out on April 2. The patient had a feeling of esophageal narrowing without pain on the following day, and she was able to eat an entire serving of 50% rice gruel diet. The perceived esophageal narrowing seemed to be attributable to temporary inflammation caused by tumor ablation. The day after RFA, palpation of the skin just above the tumor revealed obvious softening of the tumor, although there was no change in its size. On April 4, endoscopic esophageal stenting was performed. The patient complained of pharyngeal pain on April 6, but there was no sense of discomfort attributable to stent implantation. On April 9, esophageal fluoroscopy was performed. Since favorable passage of contrast medium was confirmed, oral feeding was resumed with fluid diet. Although the patient complained of severe sore throat, she was able to take food while controlling the pain with antipyretic analgesics (loxoprofen sodium; trade name: Loxonin®) and diclofenac sodium suppository (trade name: Voltaren suppository®). On April 19 (17 days after RFA), a tracheo-cutaneous fistula was formed, creating a whistling sound as air leaked out when the patient had a fit of coughing, and oral feeding was suspended (Fig. 4a,b). The tracheo-cutaneous fistula likely was formed by the following mechanism. First, a laceration of the skin occurred in the area burned by RFA. Then, the leading edge of the tumor that invaded the tracheal wall developed necrosis as a result of RFA and exfoliated, creating a hole in the tracheal wall. Owing to the increased intra-tracheal pressure created by coughing, the hole in the tracheal wall formed a connection to the laceration of the skin, resulting in the development of a tracheo-cutaneous fistula.

After the patient was intubated for respiratory management, a tracheal stent was placed, and extubation was performed. Although the patient's

spontaneous respiration was restored once, she showed worsening of her general condition, and she eventually died of subarachnoidal hemorrhage 56 days postoperatively.

The patient's preoperative performance status (PS) was rated as 2. Before performing RFA, oral feeding was not possible, but the patient refused hyperalimentation and was on nutritional management only through a peripheral vessel. Although the improvement unfortunately did not last long, the patient and her husband were delighted with her postoperative ability to ingest food and water without mis-swallowing. Because of the unexpected complication of tracheo-cutaneous fistula, oral feeding lasted only for about 2 weeks, but it improved the patient's QOL.

Discussion

According to Ain KB,[11] undifferentiated thyroid cancer is characterized by rapid growth of a cervical mass, which causes tracheal stenosis, leading to dyspnea, hoarseness, and dysphagia. The prognosis is extremely poor, with the 5-year survival rate just 13.6%. Most patients are reported to die within a year of diagnosis because of suffocation, infiltration into the superior mediastinum, or distant metastasis. Surgical treatment for undifferentiated thyroid cancer is controversial. In general, partial resection, radiotherapy following tracheostomy, and chemotherapy are repeated depending on the case.[11] RFA may create change in the treatment strategy for this disease.

The undifferentiated thyroid cancer in the present case was harder than primary hepatocellular carcinoma, and therefore required substantial force for puncture. The tumor was considered to be rich in connective tissue and to have poor thermal conductivity, judging from its hardness. However, taking into account that it was an encapsulated tumor that bordered on the trachea and carotid artery, partially infiltrated these organs, and was expected to have an oven effect, ablation was performed for a 9-min period (beginning with 30 W and increasing in steps to 120 W), a 10-min period (beginning with 50 W and increasing in steps to 110 W), and another 9-min period with the puncture needle drawn 5 mm backward (beginning with 50 W and increasing in steps up to 100 W).

In regard to the use of RFA in treating thyroid tumor, its use for well-differentiated carcinoma[12] has been reported in the literature. However, to our knowledge, there have been no reports on RFA employed for undifferentiated thyroid cancer. Although the optimal conditions were unclear, we adopted the above conditions based on our experience with RFA in cases of primary hepatocellular carcinoma. These conditions are considered to be adequate in view of the CT findings for evaluation of efficacy. To enhance safety, it seems better to apply a lower power for a shorter period of time, and to use an additional application, if necessary, based on the evaluation of efficacy.

We placed an interval of 2 days between the RFA session and esophageal stent implantation, expecting that the thyroid cancer would become softer after RFA. The tumor was obviously softened upon palpation of the skin just above the tumor the day after the RFA session. The esophageal orifice, which did not allow endoscopic entry preoperatively, allowed the endoscope to pass through 2 days after RFA. Thus, the 2-day interval seemed to be adequate for esophageal stenting.

Shiina et al.[13] reported that RFA caused burn injury in about 1% of patients with hepatocellular carcinoma treated by this procedure. In our patient, the skin at the site of puncture already had a surgical scar and radiodermatitis as a result of previous radiotherapy, and the subcutaneous connective tissue layer was thin because of the presence of the thyroid (carcinoma) just under the skin. Therefore, it is presumed that these poor skin conditions interfered with healing of the skin burn, resulting in rupture of the skin. On the other hand, it is thought that the leading part of the tumor, having infiltrated into the tracheal wall, developed coagulative necrosis and reduction after RFA, and the resultant hole in the tracheal wall was connected with the necrotic tumor and the crack in the skin, resulting in the formation of a tracheo-cutaneous fistula. Tracheal burn or injury caused by the tip of the Cool-Tip needle was considered a possibility, but was excluded because it was apparent that the Cool-Tip needle was oriented in a different direction. Due consideration must be given to the conditions of the skin at the site of puncture. This is thought to be a lesson from the present case.

Current controversy surrounds invasive treatment for undifferentiated thyroid cancer. However, RFA and esophageal stenting were used for this tumor for the first time in the world, and improvement of the patient's QOL was achieved.

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A Case of Obstructive Jaundice as the Initial Manifestation of Non-Hodgkin's Lymphoma

JMAJ 48(11): 557–563, 2005

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Abstract

We report a case of obstructive jaundice as the initial manifestation of malignant lymphoma. The patient was a 39-year-old woman, who visited our hospital because of epigastralgia and jaundice noted since February 2003. Diagnostic imaging revealed a 40 mm stenosis in the lower bile duct, but biliary biopsy showed no malignancy. FDG-PET revealed accumulation in the left breast, left axillary lymph nodes, stomach, lower bile duct, etc., and a diagnosis of malignant lymphoma was made based on cytodiagnosis of the breast mass and biopsy of axillary lymph nodes. CHOP therapy resulted in improvement of biliary stenosis and remission of lymphoma.

Key words Non-Hodgkin's lymphoma, Biliary stenosis

Introduction

Jaundice in patients with malignant lymphoma is usually attributed to tumor infiltration into the liver, and obstructive jaundice is a rare manifestation of malignant lymphoma. Only a few past reports of lymphoma presented with obstructive jaundice evaluated the time course of treatment effects involving biliary lesions. We report a case of non-Hodgkin's lymphoma (NHL) presenting with obstructive jaundice, providing literature-based discussion.

Case

Patient: A 39-year-old woman.
Chief complaints: Epigastralgia, right hypochondrial pain, yellow eyes.
Past history: Not remarkable.
Family history: Not remarkable.
Smoking: 15 to 20 cigarettes per day.
Alcohol use: None.
History of present illness: The patient is a Brazilian of Japanese descent who has lived in Japan since she was 20 years old. Epigastralgia and right hypochondrial pain began on February 25, 2003. As these symptoms persisted, the patient visited a local physician on February 27. Abdominal ultrasound revealed enlarged gallbladder, and blood tests showed increases in bilirubin and hepatobiliary enzymes. She was referred and admitted to our hospital on February 28, 2003 for detailed examination and treatment.
Clinical condition at admission: Blood pressure 122/65 mmHg, heart rate 76/min, regular pulse, temperature 36.8°C. No sign of anemia in palpebral conjunctiva and yellow staining of bulbar conjunctiva. Left axillary lymph nodes were palpable without tenderness. Chest auscultation was

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Table 1 Laboratory findings at admission

Urinalysis		**Blood chemistry**		**Tumor marker**	
Pro	(±)	TP	7.2 g/dl	CEA	1.5 ng/ml
Sugar	(−)	γ-gl	1.12 g/dl	CA19-9	12 U/ml
Blood	(3+)	Alb	4.4 g/dl		
		T. bil	3.46 mg/dl	**Serology**	
Hematology		D. bil	2.47 mg/dl	ANA	(−)
WBC	7,300 /μl	AST	564 IU/l	AMA	(−)
RBC	4.96×10^{6} /μl	ALT	1,257 IU/l	CRP	0.46 mg/dl
Hb	14.5 g/dl	ALP	971 IU/l	IgG	1,005 mg/dl
Ht	43.2 %	LDH	467 IU/l	IgM	80 mg/dl
Plt	31.8×10^{4} /μl	γ-GTP	922 IU/l	ACE	7.6 U/ml
neutro	63.0 %	BUN	8.9 mg/dl	MPO-ANCA	(−)
lymph	28.0 %	UA	3.9 mg/dl	sIL2R	1,120 U/ml
mono	7.0 %	Cre	0.40 mg/dl		
eosino	1.0 %	Na	138.6 mEq/l	**Virus marker**	
baso	0.0 %	K	4.3 mEq/l	HBs Ag	(−)
at-ly	1.0 %	Cl	101.5 mEq/l	HCV Ab	(−)
		Ca	10.4 mg/dl	HA-IgM	(−)
Coagulation		BS	117 mg/dl	HIV Ab	(−)
PT	63.7 %	Amy	54 IU/l		
APTT	74.9 %				
Fbg	372 mg/dl				

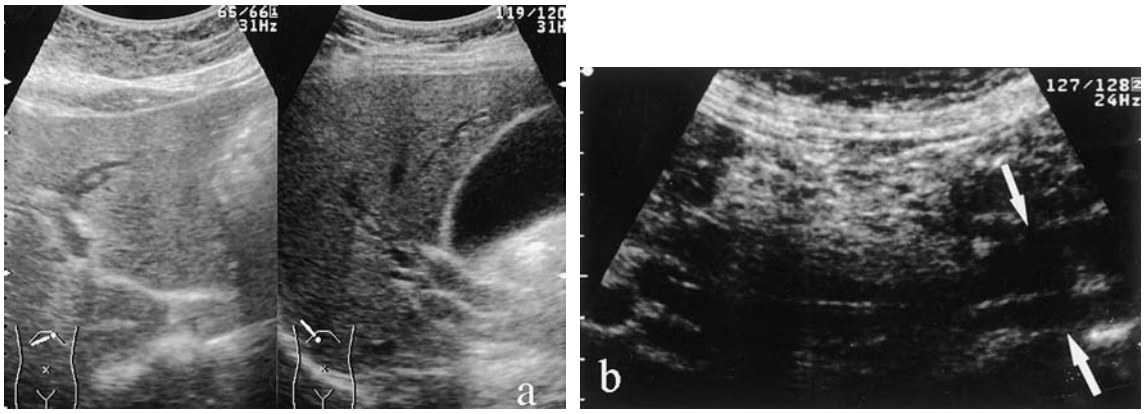

Fig. 1 Abdominal ultrasound
a: No remarkable dilation of intrahepatic bile ducts was seen. The common bile duct had been dilated to 13 mm.
b: When re-examined after insertion of NBD, the lower bile duct showed a hypo-echoic lesion consistent with 40-mm long wall thickening in the bile duct wall around the tube.

not remarkable. The abdomen was flat and soft. Mild tenderness was noted in the epigastric region.

Laboratory findings at admission (Table 1): An increase in predominantly direct bilirubin and increases in hepatobiliary enzymes were noted. A slight increase in soluble IL-2 receptors was noted.

Abdominal ultrasound (Fig. 1): Although there was no remarkable dilation of intrahepatic bile ducts, the common bile duct had been dilated to 13 mm. In the lower bile duct, re-examination after insertion of an NBD tube revealed changes consistent with wall thickening around the tube over a length of about 40 mm.

Abdominal CT (Fig. 2): The common bile duct had been slightly dilated and the intrapancreatic bile duct showed wall thickening.

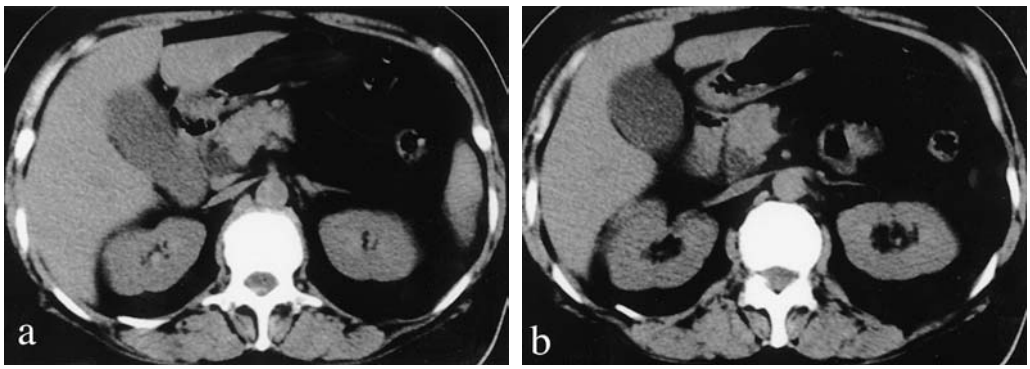

Fig. 2 Abdominal CT

a: The lower bile duct had been slightly dilated.
b: The pancreas showed no tumorous lesions, but wall thickening of the intrapancreatic bile duct was noted.

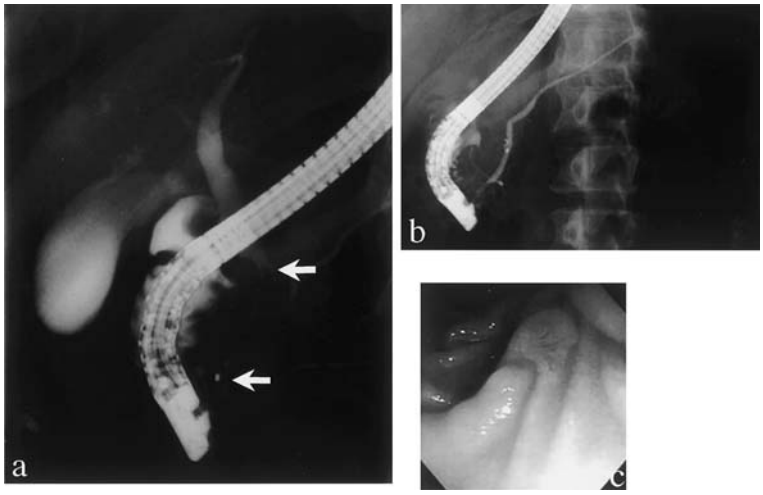

Fig. 3 ERCP

a: Cholangiography revealed an encircling stenosis measuring about 40 mm in the lower bile duct (←).
b: Pancreatography showed no abnormal changes in the main pancreatic duct, branching pancreatic ducts, and accessory pancreatic ducts.
c: No abnormality was found in the duodenal papilla.

Upper gastrointestinal endoscopy: Submucosal tumors with smooth surfaces were noted at 4 sites in the greater curvature of the gastric corpus. Biopsy demonstrated infiltration of atypical lymphocytes.

Endoscopic retrograde cholangiopancreatography (ERCP) (Fig. 3): No remarkable changes were found in the duodenal papilla. Cholangiography revealed an encircling smooth image of stenosis measuring about 40 mm in the lower bile duct. Intrahepatic bile ducts had been slightly dilated, and the cystic duct was normal. Pancreatography showed no abnormal changes.

Abdominal MRI (Fig. 4): MRI revealed a lesion that appeared as a low-signal area on T1-weighted image and a high-signal area on T2-weighted image in the wall of the lower bile duct in the pancreas. This lesion was considered to be thickening of the bile duct wall around the ENBD tube. Coronal section revealed multiple swelling

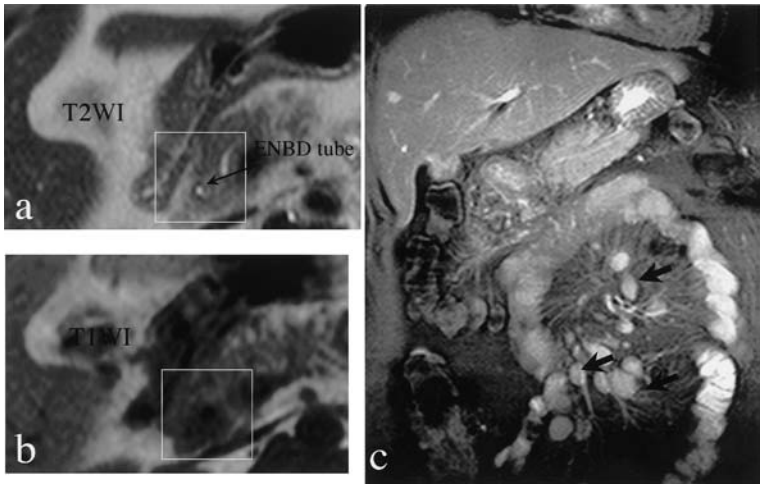

Fig. 4 Abdominal MRI

T2WI (a) and T1WI (b) MRI revealed a lesion that appeared as a low-signal area on T1-weighted image and a high-signal area on T2-weighted image in the wall of the lower bile duct in the pancreas. This lesion was considered to be thickening of the bile duct wall around the ENBD tube (←).
c: Coronal section revealed multiple swelling of mesentery lymph nodes (←).

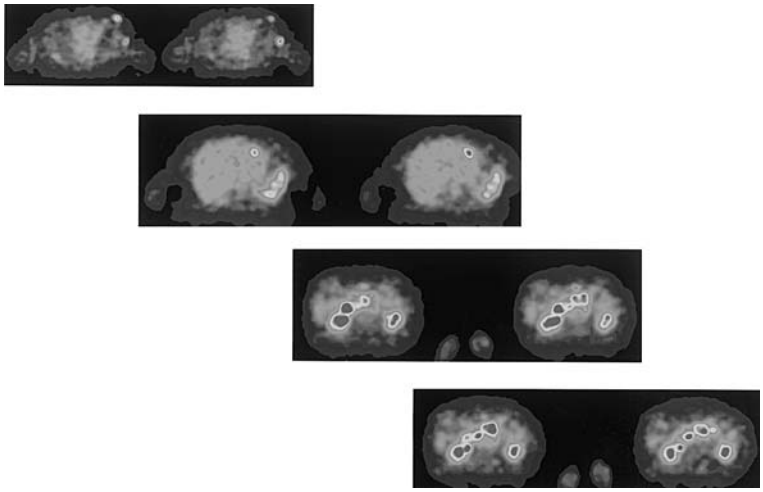

Fig. 5 ^{18}F-FDG-PET (before treatment)

Accumulation of FDG (SUV 14.77) was noted in the area around the bile duct, spleen (SUV 4.02), left breast (SUV 4.07), left axillary lymph nodes (SUV 5.57), and mesenteric lymph nodes.

of mesentery lymph nodes.

^{18}F-FDG-PET (Fig. 5): Accumulation of FDG (SUV 14.77) was noted corresponding to the area around the lower bile duct, spleen (SUV 4.02), left breast (SUV 4.07), left axillary lymph nodes (SUV 5.57), and mesenteric lymph nodes.

Clinical course

ERC revealed stenosis of the bile duct extending over the length of 40 mm, and bile duct biopsy at that time proved normal bile duct epithelium. As abdominal MRI showed swelling of numerous

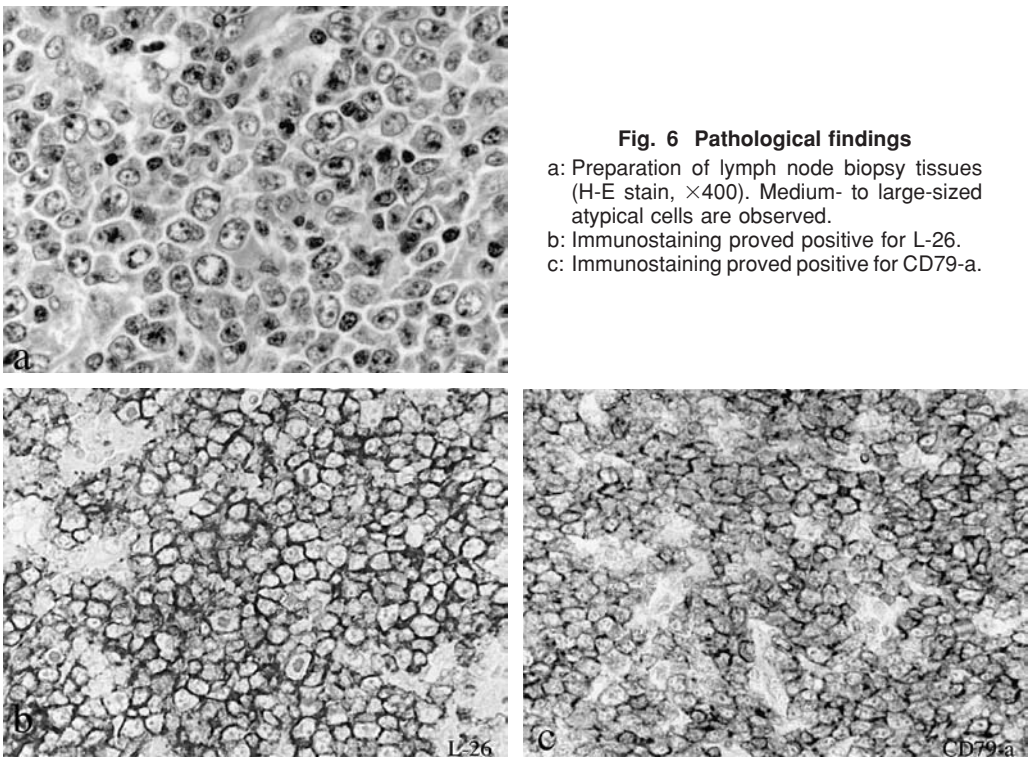

Fig. 6 Pathological findings
a: Preparation of lymph node biopsy tissues (H-E stain, ×400). Medium- to large-sized atypical cells are observed.
b: Immunostaining proved positive for L-26.
c: Immunostaining proved positive for CD79-a.

lymph nodes in the mesentery, we suspected a bile duct lesion due to cancer of unknown primary origin or malignant lymphoma. ^{18}F-FDG-PET was performed for detailed examination of the whole body, and accumulation was demonstrated in mesenteric lymph nodes, the area around the bile duct, the spleen, the left breast, and left axillary lymph nodes. Aspiration cytology of the mass in the left breast was performed, and the observation of scattered exfoliated juvenile lymphocyte suggested malignant lymphoma. In addition, biopsy tissues from left axillary lymph nodes contained medium- to large-sized atypical cells, and immunostaining proved positive for L-26 and CD79 (Fig. 6) and negative for CD3, CD5, CD10, and BCL2. Based on these findings, a diagnosis of malignant lymphoma, diffuse large B-cell, was made (stage IVA, international prognostic index (IPI) = low-int (LI):2). The lesion in the bile duct was considered to be diffuse infiltration of lymphoma cells into the bile duct wall, as diagnostic imaging revealed no swelling of lymph nodes around the bile duct. In addition, liver biopsy confirmed the lack of infiltration of lymphoma cells. For treatment, the ENBD tube

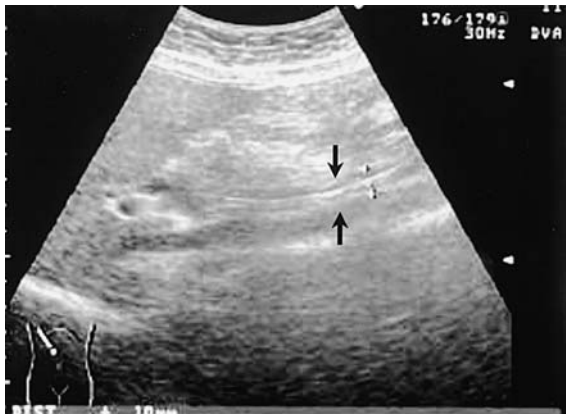

Fig. 7 Abdominal ultrasound (after treatment)
Hypo-echoic lesion had disappeared in the lower biliary duct (after insertion of plastic stent)

installed initially was removed and replaced with a plastic stent (7Fr, length 70 mm). Because the IPI was 2 and the patient was relatively young, CHOP therapy (CPA 1,200 mg × 1 day, DXR 80 mg × 1 day, VCR 2 mg × 1 day, PSL 100 mg × 7 days) was selected. Starting on May 13, 8 cycles of this treatment resulted in remission. The

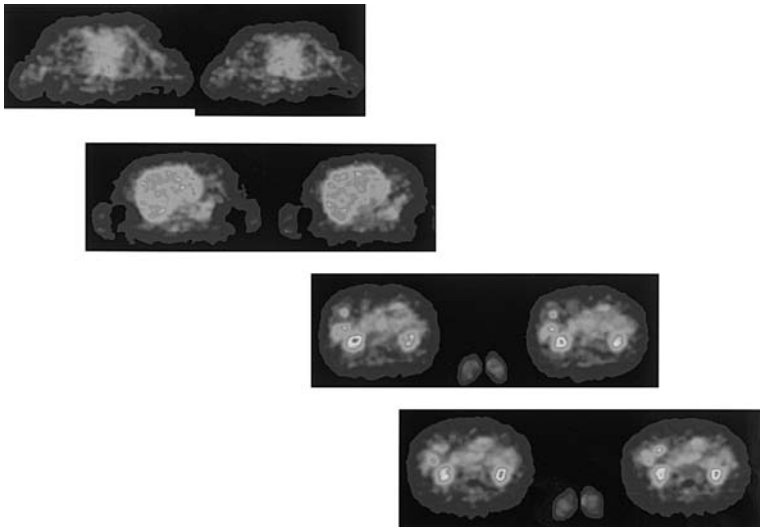

Fig. 8 ^{18}F-FDG-PET (after treatment)
The accumulation of FDG in abdominal lymph nodes, around the bile duct, and in the spleen had disappeared after treatment.

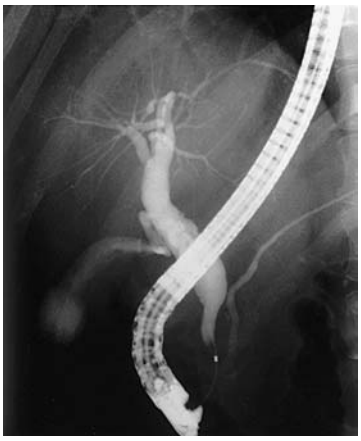

Fig. 9 ERCP (after treatment)
The previously observed encircling stenosis of the lower bile duct had improved, although slight dilation of the bile duct remained.

abdominal ultrasound examination after treatment showed nearly complete disappearance of the previously observed hypo-echoic lesion in the wall of the lower bile duct (Fig. 7). ^{18}F-FDG-PET showed disappearance of the previously observed accumulation in abdominal lymph nodes, around the bile duct, and in the spleen (Fig. 8). As ERC showed improvement of the previously observed elongated stenosis in the lower bile duct, although dilation of the bile duct remained, the tube stent was removed (Fig. 9). At present, malignant lymphoma is in a state of complete remission, and the patient is maintained in a stent-free condition.

Discussion

NHL rarely presents with occlusive jaundice as the initial manifestation. The occurrence of such cases has been reported to be 0.2 to 2.0%.[1–5] On the other hand, NHL is reported to represent 1 to 2% of biliary stenosis accompanying all types of malignant disease.[5] The leading cause of jaundice in NHL is diffuse infiltration into the liver,[6–7] while other causes include complication with hemolysis and compression of the biliary tract by lymph nodes. Occlusive jaundice in NHL usually results from the compression of the biliary tract by swollen lymph nodes.[8–9] In the present case, infiltration of lymphoma into the bile duct wall was suggested by the facts that diagnostic imaging showed wall thickening over the length of 40 mm accompanying no swelling of lymph nodes and that it was improved by treatment. So far as we could confirm by literature search, there have been no reports evaluating the time course of treatment for occlusive jaundice caused by the infiltration of lymphoma into the

bile duct wall. NHL is a disease for which various systemic chemotherapies capable of inducing remission have been established, and prognosis is relatively good in many cases, provided that treatment is given under accurate diagnosis.[10] In the cases complicated with occlusive jaundice, studies reported no difference in prognosis whether or not primary chemotherapy contained doxorubicin, an agent secreted into bile, and it was discussed that jaundice reduction should be attempted only in cases with abdominal symptoms and those with biliary tract infection.[3,5] In the present case, we removed the tube stent after chemotherapy. Stent removal is considered important for effective follow-up observation, because it facilitates early detection of possible relapse of primary disease and occlusive jaundice. Although endoscopic metallic stents (EMS) are used widely for malignant biliary stenosis, these stents are not removable and may mask the symptoms of later relapse of biliary tract lesions. This point needs serious attention in view of the recent widespread use of biliary stenting.

Conclusion

We experienced a case of NHL presenting with occlusive jaundice. The report of this case provides valuable input, because no such cases have been examined in detail using a wide range of methods such as abdominal ultrasound, ERC, and ^{18}F-FDG-PET before and after treatment.

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The Significance of the Scientific Session of WMA General Assembly, Tokyo 2004

JMAJ 48(11): 564–567, 2005

Nobuya Hashimoto*1

The Scientific Session of the WMA General Assembly Tokyo held from October 6 to 9, 2004 gave direction to resolving a variety of issues that directly confront global health care today. As a person involved in planning this session from the JMA side and as an executive board member from the host NMA responsible for this event, I would like to take this opportunity to review the significance of the Scientific Session (and WMA General Assembly), and make a few suggestions.

The Scientific Session provided a forum through which the overall state of medical and health care in the 21st century was reviewed through two themes—"Advanced Medical Technology and Medical Ethics" (Theme I) and "Progress in Information Technology and Health Care" (Theme II). Progress made in science and technology has greatly changed the environment around us today and has also affected medical and health care. Subsequently, it has also produced a variety of unforeseen problems that inevitably accompany the progress made by humanity and which are unavoidable. Thus, I believe a consensus was reached on how the issues that were discussed at the Scientific Session should be addressed. In summary, we, physicians, should secure the patient's safety based on a relationship of physician-patient trust and do our utmost best to provide high quality medical care. The themes that were addressed at the Scientific Session dealt with problems that health care related personnel have never had to face in the past. Therefore, there are no exemplar models that may provide the answers. However, the outcome of the day and a half of active discussions, was a shared recognition of the need for a code of behaviour for our profession by the participants from 42 countries. Thus, I hope that what was discussed at the Scientific Session will contribute to more effective discussions at the WMA.

The essential points of the Scientific Session were summarised as follows. The achievements of advanced medical technology and information technology (IT) based on the knowledge of past generations are indeed wonderful, and no one will deny this fact. But these achievements are not shared at large within the global community. As pointed out by Dr. Takaku, we must not forget the view that the benefits that are derived from this new technology should be shared equally and globally. In the advanced countries, concern regarding advanced medical technology and progress in IT has been increasing. As emphasized by JMA president, Dr. Uematsu, society as a whole must recognise that advanced medical technology should guarantee the safety and happiness of humanity, and that a system which enables only a handful of people to benefit from costly advanced medical technology should be reformed. As Dr. Sakurai has explained, in Japan, the JMA has lobbied the Japanese government to enable medical insurance to cover advanced medical technology under the guidance of the JMA. This is, of course, related to national financial issues, but it is the duty of medical associations to protect the public health by lobbying the government to prevent fiscal initiatives from dominating medical and health care issues. To achieve this, physicians must have the ability to foresee future developments in medical technology.

As Dr. Haddad has pointed out, we should constantly bear in mind that future developments

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in science and technology should supplement the knowledge and experience that physicians have accumulated through traditional methods and they should not replace them. If we lose sight of this basic concept, then physicians become merely the subcontractors of electronic engineers.

The need for common ethical guidelines for advanced medical technology was pointed out; and at the 2002 WMA General Assembly in Washington the JMA's draft proposal on Medical Ethics and Advanced Medical Technology was adopted as a WMA Declaration. This declaration is a general statement on advanced medical technology and medical ethics, and there is a continued need to review this issue from many different perspectives. For example, Japan has achieved the world's highest life expectancy with low health costs. But to sustain this feat, it has become essential to secure financial resources. In advanced countries, improving the financial foundations needed to secure the health level of its population has become a major problem, and there is wide scope for discussion.

In the area of medical technology and advanced IT, Dr. Kim pointed out the inevitable transformation of health care due to IT and genomics. But, as Dr. Uematsu has advocated, the goals that we physicians should aim for are to practice holistic medicine and to provide safe and high quality medical care. It is to be expected that medical costs will rise when quality medical care is provided. But, its quality should not be lowered as a means of containing health costs. However, financial resources for medical and health care are limited. Therefore, how these resources are allocated is a major issue which should be reviewed by the WMA.

Certainly, as Dr. Groth has pointed out, more than 90 percent of advanced technology is currently developed by less than 10 percent of the countries in the world (advanced countries). Of course, it is a fact that the social and financial foundations of advanced and developing countries differ greatly. However, it is also a fact that physicians in developing countries should do their ultimate best within the respective environment of the country.

Progress in IT technology will continue to influence developments in medical care. As noted by Dr. Kaihara, obtaining correct information will promote physician-patient relations and will help realize better medical care. Thus, balancing IT and medical care is one of the goals before us to attain. But, again, as stated by attorney, Dr. Higuchi, medical information must ultimately function under the principle that it will be used to provide the best treatment for patients and allow society at large to benefit from it. As pointed out by Dr. Takaku, that is the difficulty of resolving specific issues such as the need to protect individual gene related data. By whom, and how such issues will be resolved should be carefully addressed with the cooperation of physicians on a global scale through the WMA General Assembly meetings, rather than under the leadership of individual country governments and their financial concerns. Therefore, the WMA should be willing to provide a forum to discuss these issues as needed. As Dr. Haddad has indicated, WMA is also duty bound to alert each country about the responsibility not to leave our future generations with the burden of dealing with the destruction of the natural environment and environmental pollution caused by national greed.

These are my personal views on the important issues of CME and professional autonomy that are being debated in Japan today, based on the discussions that took place at the Scientific Session. Against a background of extensive mass media coverage about medical errors and publicity about distrust of medical care, CME for physicians is a vital issue that must be addressed to enable physicians to provide high quality medical care. Moreover, physicians voluntarily undertake CME, and this is where professional autonomy becomes important. Therefore, I would like to emphasise the need for voluntary discipline by physicians through reaffirmation of the WMA Declaration of Madrid on Professional Autonomy and Self-Regulation.

The following observations and proposals are made in the light of the opportunities which were presented at the Tokyo General Assembly.

In the past, many prominent declarations and statements have been drafted and adopted by the WMA Council and General Assembly, which have been used as guidelines by NMAs in resolving different issues, and I pay sincere homage to the efforts of the WMA to produce these invaluable statements.

In particular, the Declaration of Geneva, Declaration of Helsinki, Declaration of Madrid

World Medical Association General Assembly Tokyo 2004
Scientific Session, Oct. 7–8, 2004

Theme I "Advanced Medical Technology and Medical Ethics"

1. "Advanced Medical Technology and Medical Ethics"
   Fumimaro Takaku (President, Japanese Association of Medical Sciences)
2. "Advanced Medical Technology and Helth Insurance"
   Hideya Sakurai (Vice President, JMA)
3. "The Future of Medical Technology—Implications for Medical Education and Practice"
   Henry Haddad (Past President of the Canadian Medical Association)
4. "Advanced Technology and Medical Ethics—A WHO Perspective"
   Steffen Groth (Director, Department of Essential Health Tecnologies, WHO)

Address of the JMA President: "Modern Demands in Health Care"
Haruo Uematsu (President, JMA)

Theme II "Progress in Information Technology and Health Care"

1. "Coordination of Progress in Information Technology with Health Care in the 21st Century"
   Shigekoto Kaihara (Vice President, International University of Health and Walfare)
2. "Transforming Health Care through Integrated Biomedical Informatics and Applied Genomics"
   Ju Han Kim (Assistant Professor, Biomedical Informatics, College of Medicine, Seoul National University)
3. "Medical Information and Privacy in the Information Society"
   Norio Higuchi (Professor, Faculty of Law, University of Tokyo)

Special Address: "Continuing Medical Education for Physicians and Professional Autonomy"
Nobuya Hashimoto (Executive Board Member, JMA)

Panel Discussion: "Advanced Medical Technology and Medical Ethics in the Information Society"
Chair: Sir David Carter (British Medical Association)
Panelists: Henry Haddad, Steffen Groth, Shigekoto Kaihara, Ju Han Kim, and Norio Higuchi

on Professional Autonomy and Self-Regulation are some of the many very distinguished statements that have been produced so far. They have served as the golden rule for physicians throughout the world during both under and postgraduate education. Their principles remain immutable in both the East and the West.

Despite this fact, the WMA has repeatedly revised these historical declarations beginning with the Declaration of Helsinki. The Physician's Oath in the Declaration of Geneva embodied the Hippocratic Oath, the Declaration of Helsinki incidentally also had the effect of applying some of the principles of the Nuremberg Code, and the Declaration of Madrid provided the principles governing the complex physician-patient relationship and defined the attitude of the physician about professional autonomy and self-regulation.

The basic principles that are inherent in these declarations are important and they represent WMA's recognition of their significance in adopting them at that time. Therefore, they are also invaluable historical assets. To revise them unnecessarily may be to ignore the intent of those who originally drafted them. Moreover, it may also obliterate their significance as historical assets of the time. There is also concern that the original text will eventually disappear with repeated revisions.

The revisions of WMA declarations have hitherto been limited to unavoidable circumstances. But I would like to propose that in future, when there is a need for a declaration to reflect present-day medical and health care issues, a new and separate declaration be proposed, discussed, and adopted.

I would like to see the WMA Council spend its valuable time discussing current and important issues rather than revising past documents. There is a backlog of many significant issues that

we must discuss. Disclosure of medical information and protection of personal information, the spread of advanced medicine and soaring medical expenses, policies to control medical costs and improve quality of medical care, and the specialist and the general practitioner are just some of the many issues at hand that the WMA should address.

As a global professional organisation for physicians, the WMA must contribute to providing high quality medical care based on professional medical ethics against a background of changing social conditions and public awareness. Therefore, it must be vigilant in its efforts to resolve the many issues at hand.

In conclusion, I look forward to WMA's further growth and development.

Critical Pathway: Practical applications and its development in Japan

JMAJ 48(11): 568–571, 2005

Hisayoshi Miyazaki,[*1,3] Teruhiko Matsushima[*2,3]

Key words Critical pathway, Evidence-based medicine, Critical pathway library, Introduction rate, Medical quality, Medical cooperation

Critical Pathway, a medical management system consisting of a planning chart for standard medical processes and expected outcomes, has been introduced into many hospitals in Japan and its use is now spreading rapidly across the country's entire medical field. This paper reviews and discusses the popularization of Critical Pathway in Japan up to the present day, and identifies factors currently hindering its further adoption.

The Introduction and Popularization of Critical Pathway in Japan

Critical Pathway, a management methodology that was adapted from industry to the field of medicine by Ms. Karen Zander in the United States, was first introduced to Japan in the mid 1990s. In 1998, the Critical Pathway Research Association, the first of its kind in Japan, was established in Tokyo. Although only a few dozen medical professionals attended the early meetings, they traveled from all over Japan and were active in promoting the adoption of Critical Pathway throughout the country. In 1999, the first nationwide academic meeting for Critical Pathway, "the Japan Critical Pathway Forum for Research and Communications", was sponsored by the Association. The meeting, held in Tsukuba City, was attended by more than 1,200. Such momentum gave rise to a new organization, the Japan Society of Health Care Management (JHM), in place of the former Association. Since then, a series of Critical Pathway Seminars was held at venues across Japan, to commemorate the Society's establishment. The JHM deals with Critical Pathway as its central subject, in conjunction with infection control, medical safety management, clinical cooperation and other problems encountered at the site of medicine and health care.

In 2002, in order to further promote the use of Critical Pathway, JHM developed a Critical Pathway Design Software package and offered training workshops on its use throughout Japan. Over 2,000 health care professionals have since taken part in the workshops.

JHM is also actively publishing work related to Critical Pathway. In addition to its official journal, the Society has published progress reports on the use of Critical Pathway in 2003 and 2004, a training manual to support the Critical Pathway workshops, and a document titled "Critical Pathway for Medical Residents". Worthy of note is that the 2003 report has been translated into Korean, serving to publicize the method internationally as well as nationally.

From the second year of its establishment, JHM conferences have been held annually, starting with the Kumamoto conference, and subsequently at Yokohama, Kyoto, Sendai and Takamatsu. This year's 2005 conference marks the seventh annual conference. It was held

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Table 1 JHM annual Critical Pathway survey: results summary

Year	No. questionnaires sent	No. questionnaires returned	Critical Pathway already introduced	Planning to introducing Critical Pathway
2002	1,200	420	80%	18%
2003	2,187	559	82%	8%
2004	2,154	418	86%	3%

at Fukuoka and hosted by JHM conference president, Dr. Saku of the Kyushu Medical Center. Almost 4,000 participated, with over 500 presenting papers and 250 displaying Critical Pathway posters.

JHM's information resources include an internet-based Critical Pathway Library (URL = http://epath.medis.or.jp) hosted by the Medical Information System Development Center's (MEDIS-DC) website. The Library publishes Critical Pathways designed and developed to a high standard by hospitals around Japan. This work, to develop and share best practice in the design and implementation of Critical Pathways, forms part of a wider initiative supported by the Ministry of Health, Labour and Welfare, dating from November 29th, 2001, to promote use of information systems in the field of the healthcare and medical provision. Access to the site is free, and the Critical Pathways can also be downloaded free of charge by healthcare professionals, patients and the general public. The Library currently contains 157 Critical Pathways, drawn from 17 hospital facilities including sets designed specifically for medical staff and others for patients. The Critical Pathway Design Software mentioned above can also be downloaded free of charge from this site.

The Merits of Critical Pathway

Critical Pathway was introduced to the National Hospital Organization Kumamoto Medical Center in 1998. Its introduction not only set clear standards of best practice that were easy for staff to follow and adhere to, but also served as a standardized management tool, facilitating communication between different departments. Use of Critical Pathway, has facilitated the sharing the patient information, and has been used together with an Evidence-Based Medicine approach to further improve medical planning and as a consequence the quality and safety of medical practice at the hospital has shown significant improvement.

Another notable benefit of Critical Pathway is enhanced mutual understanding and collaboration between patients and medical professionals in terms of communicating medical practice and thus achieving an improvement in patients' quality of life.

Many reports on the use of Critical Pathway have also mentioned cost reduction benefits in terms of lowering overall medical costs and patient charges, and the increment of daily sales per bed.

The Current Status of Popularization of Critical Pathway in Japan

Since its inception, JHM has carried out an annual, Spring survey of hospitals around Japan to assess the extent to which use of Critical Pathway is spreading. In March 2002, a questionnaire was circulated to 1,200 hospitals with 300+ beds. Of the 420 questionnaires that were returned, 80% responded that they had already introduced Critical Pathway and 18% were planning its introduction. In March 2003, the questionnaire was sent out to 2,187 hospitals with 200+ beds, and responses were recovered from 559 hospitals indicating that 82% had introduced Critical Pathway and 8% were planning its introduction. In March 2004, 2,154 hospitals with 200+ beds received the questionnaire, and answers were recovered from 481. 86% of these had introduced Critical Pathway—an increase of 4% from the previous year. The number of hospitals planning to introduce Critical Pathway, at 3%, was lower than the previous year (Table 1).

The introduction rates at hospitals grouped according to establishing body are shown in

Table 2 Critical Pathway introduction rate according to hospital establishing body

Establishing body	Introduction rate	
	Already introduced	Planning to introduce
Ministry of Education, Culture, Sports, Science & Technology	78%	11%
Ministry of Health, Labour and Welfare	92%	4%
Japanese Red Cross	93%	7%
Social Welfare Organization Imperial Gift Foundation Saiseikai	87%	13%
Local government	90%	0%
Private	75%	5%

Table 3 Critical Pathway introduction rate by hospital bed capacity

No. of beds	Introduction rate
200–299	74.3%
300–399	94.9%
400–499	95.8%
500–999	94.6%
≧1,000	100.0%

Table 4 Stated purposes for introducing Critical Pathway

Purpose for introducing Critical Pathway	%
Standardization of medical processes	17.9%
Improvement of medical quality	16.0%
Service to patients	13.1%
Informed consent	13.3%
Promotion of teamwork	12.4%
Improvement of business	7.0%

Table 2. Although the rate differs from group to group, it is generally higher in so called public hospitals than in private hospitals. The introduction rate according to hospitals' bed capacity is shown in Table 3. The results appear to indicate that larger hospitals have a tendency to introduce Critical Pathway more readily. In the last two years, there has been a 15% increase in the use of Critical Pathway among the hospitals with the beds above 300.

The number of different Critical Pathways used within hospitals was less than 100 in 90% of the hospitals, however the number has increased during 2003 and 2004. Fewer than 50% of hospitals have less than 50 different kinds of Critical Pathways. Although introduction rates were generally slightly lower in private hospitals, it appeared that those that had already introduced it were using it quite extensively, as the number of private hospitals using more than 100 Critical Pathways was much higher than in public hospitals, with some private hospitals using in excess of 200 different Critical Pathways.

Hospitals' stated purposes for introducing Critical Pathway are as follows (Table 4): (1) standardization of medical processes 17.9%, (2) improvement of medical quality 16.0%, (3) service to patients 13.1%, (4) informed consent 13.3% and (5) promotion of teamwork 12.4%. The aim of (6) improvement of business, at 7.0%, was unexpectedly low, indicating that the salient characteristic of the expected merits of introducing Critical Pathway in Japan was centered around improving the quality of medicine rather than making cost savings (Table 4).

In terms of regional introduction of Critical Pathway, Hokuriku had the highest uptake with 96% of hospitals using Critical Pathway, Kanto ranked second with 91%, followed by Kinki 88%, and Kyushu 86%. Introduction in other areas was around 80% with Chugoku having the lowest rate at 61%.

As a questionnaire recovery rate of around 25% is quite low, it is possible that responses

were mainly received from hospitals with a greater than average interest in Critical Pathway. It is therefore likely that our figures are somewhat inflated and any attempt at interpretation should be treated with caution. In spite of this possible response bias, there does appear to be a trend of increasing interest in Critical Pathway. We plan to continue to administer this questionnaire on an annual basis, and to publicize results at JHM conferences in order to confirm these trends and interpretations.

Factors Hindering the Uptake of Critical Pathway

The most significant factor hindering the uptake of Critical Pathway is that it remains poorly understood by many in the field. As this relates, largely to our responsibilities for educating the medical profession and general public, it is crucial that we continue our efforts to publicize the benefits and methods of Critical Pathway, targeting also clinical residents under the new resident system in which the understanding and use of Critical Pathway is clearly mentioned as one of the major achievement targets by the Ministry of Health, Labour and Welfare.

Another factor inhibiting the spread of Critical Pathway relates to the shortening of patients' length of stay (LOS). Increased efficiency can of course have a positive effect on the quality of the medical process, and so should be desirable for both patients and medical professionals. However, the possible decrement of bed occupancy rates, caused by the shortening of LOS in some hospitals which do not have enough patients on the waiting list, worsens their business conditions and has also been responsible for the not insignificant number of people who oppose the introduction of Critical Pathway. It is our hope that an increased understanding of the trend for medical supply chain management and the potential benefits of medical cooperation and function sharing that can be promoted through use of this management tool at both local and regional level will outweigh any remaining negative perceptions.

Conclusion

The fundamental principle upon which recent trends in medical supply systems rely is that of medical cooperation and function sharing between facilities. We have shown that Critical Pathway can be utilized to enhance medical cooperation, and further, that Medical Cooperation Critical Pathways are currently attracting significant attention and are increasingly likely to play a central role in the allocation of resources and system development.

Finally, the recent popularization of electronic medical records system that has been implemented according to Critical Pathway provides further evidence of the pivotal role it is playing, and will play, in every aspect of medicine and health care. It is up to medical doctors to take an active role in producing and implementing Critical Pathways, and thus assume a leadership position within the health profession in relation to the introduction of Critical Pathway.