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ORIGINAL ARTICLE

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Effects of anti-parathyroid hormone-related protein monoclonal antibody and osteoprotegerin on PTHrP-producing tumor-induced cachexia in nude mice

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Abstract We have previously demonstrated that parathyroid hormone-related protein (PTHrP) is a cachexia inducer, but it is still not known what PTHrP effects on target tissues induce the cachexia. Therefore, we examined the effects of anti-PTHrP antibody and osteoprotegerin (OPG) on PTHrP-producing tumor-induced cachexia. Nude mice bearing PTHrP-producing human lung cancer cells (HARA-B) exhibited cachexia with hypercalcemia 3–4 weeks after inoculation, accompanied by losses in body, adipose tissue, and muscle weight. OPG ameliorated hypercalcemia, as did neutralization of PTHrP with antibody; and it increased both body and adipose tissue weights. These increases in body and adipose tissue weight, however, were significantly less than those in mice treated with anti-PTHrP antibody. Simultaneous administration of OPG and anti-PTHrP antibody caused significant increases in body, adipose tissue, and muscle weight, along with an immediate decrease in blood ionized calcium levels. The increase in body weight was similar to that observed in mice treated with anti-PTHrP antibody alone, and the decrease in the blood ionized calcium levels was significantly greater than that in mice treated with OPG or anti-PTHrP antibody alone. These results suggest that an effect of PTHrP on target tissues other than hypercalcemia is involved in the development of cachexia. Expression of cachexia-inducing proinflammatory cytokines (interleukin-6 and leukemia inhibitory factor) is stimulated by PTHrP. This might be a mechanism by which PTHrP produces tumor-induced cachexia. It is also suggested that OPG and anti-PTHrP antibody synergistically act to ameliorate hypercalcemia, although the mechanism responsible for this is unclear.

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Key words PTHrP · cachexia · hypercalcemia · osteoprotegerin · anti-PTHrP antibody

Introduction

Cachexia is a debilitating condition of involuntary weight loss characterized by anorexia, depletion of fat and muscle tissues, hypoglycemia, and anemia [1]. It often accompanies various cancers in advanced stages and reduces the quality of life and the patient's response to chemotherapy [2]. For cachexic patients, the normal balance between energy intake and caloric expenditure is disrupted owing to increased catabolism. However, the molecular mechanism responsible for cachexia is poorly understood. Several cytokines, including tumor necrosis factor-α (TNFα [3]) interleukin-6 (IL-6) [4]) interferon-γ [5], and leukemia inhibitory factor ((LIF) [6]) have been implicated in the development of cancer cachexia; and recently we showed that parathyroid hormone-related protein (PTHrP) induces cachexia in experimental animals using cultured human lung cancer cells [7]. In this cachexia model, however, it remains unclear what PTHrP effects on target tissues induce cachexia.

Osteoprotegerin (OPG) is a member of the tumor necrosis factor receptor family and antagonizes the ability of receptor activator of nuclear factor κ-B ligand (RANKL) to bind to its receptor, the receptor activator of nuclear factor κ-B (RANK) [8,9]. OPG prevents and reverses hypercalcemia in an animal model of humoral hypercalcemia of malignancy (HHM) [10], and the effect of OPG on hypercalcemia occurs via the competitive inhibition of RANKL–RANK interaction regardless of the action of PTHrP. Thus, to determine the role of PTHrP in cachexia, we examined the effects of OPG on cachexia in an experimental cachexia model induced by a PTHrP-producing tumor and compared its effects to those of anti-PTHrP monoclonal antibody (mAb).

Materials and methods

HARA-B cachexia model

HARA-B cells were isolated from a bone metastasis of human lung cancer-derived cells (HARA), which induces cachexia with hypercalcemia [7]. The cells were cultured in RPMI-1640 plus 10% fetal bovine serum (FBS) and penicillin-streptomycin, harvested by trypsinization, and resuspended in phosphate-buffered saline (PBS). A single suspension of HARA-B cells (5×10^6 cells/0.2ml) were inoculated subcutaneously (s.c.) in the right flank of nude mice (5-week-old male mice).

Administration of anti-PTHrP antibody and OPG

Anti-human PTHrP mAb was provided by Chugai Pharmaceutical Japan; the characteristics of this mAb were previously described [11]. The recombinant OPG used was provided by Amgen and comprised the ligand-binding domain of human OPG fused to the Fc domain of human immunoglobulin G (IgG) [8].

HARA-B-bearing mice began losing body weight 3–4 weeks after inoculation. Tumor weight was estimated by the formula ($ab^2/2$), and the carcass weight was calculated as the difference between the whole-body weight and the estimated tumor weight. The followings were administered when the carcass weight fell to below 20g: anti-human PTHrP mAb (100μg IgG/mouse, intraperitoneal (i.p.) infusion on day 0); OPG (2.5mg/kg s.c. infusion on days 0–5); anti-human PTHrP mAb (100μg IgG/mouse i.p. infusion on day 0) + OPG (2.5mg/kg s.c. infusion on days 0–5); and PBS (0.1ml/mouse i.p. on day 0).

Body weight and tumor size were measured daily. Blood ionized calcium levels in retroorbital samples were measured on days 0, 2, 4, and 6 by the electrode method using an autoanalyzer (M-634; Chiba Corning Diagnostics, Toyko, Japan). Mice were killed on day 6 after administration of these agents. At this time blood was collected from the heart; and the epididymal adipose tissue, gastrocnemius muscle, and subcutaneous tumor were weighed. Serum samples obtained after centrifugation were stored at –30°C until serum PTHrP levels were determined. Serum PTHrP levels were measured using a radioimmunoassay (RIA) kit specific for the C-terminal portion of PTHrP (Daiichi, Toyko, Japan).

Statistics

Statistical analysis was performed using Welch's unpaired *t*-test. $P < 0.05$ indicated statistical significance.

Results

HARA-B-bearing mice exhibited a reduction in body weight 3–4 weeks after inoculation. The effects of anti-PTHrP mAb, OPG, and anti-PTHrP mAb plus OPG were examined in mice whose body weight dropped below 20g. The changes in body weight and blood ionized calcium levels are shown in Fig. 1. Administration of anti-PTHrP mAb or OPG caused weight gain, and the body weights of mice treated with anti-PTHrP mAb or OPG were significantly higher than those of the control mice over the observation period. However, the increase in body weight of mice treated with anti-PTHrP mAb was greater than that of mice treated with OPG, and the differences between them were significant from days 2 to 6 after administration. The blood ionized calcium levels of mice treated with anti-PTHrP mAb immediately decreased and remained at levels similar to those of mice treated with OPG. Blood ionized calcium levels in these groups were

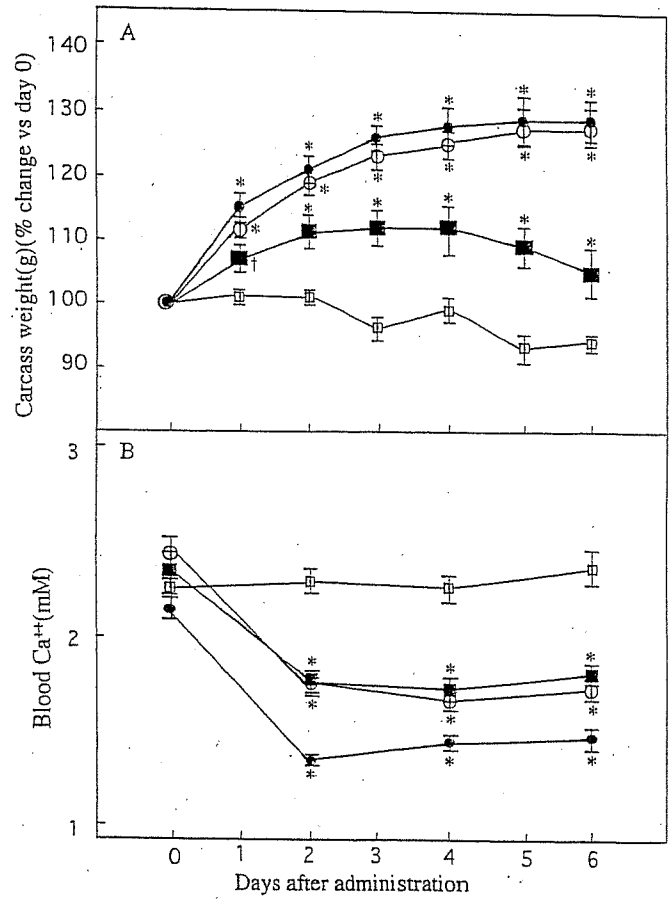

Fig. 1. Changes in body (carcass) weight (**A**) and blood ionized calcium levels (**B**) in HARA-B-bearing mice after administration of phosphate-buffered saline (control) (*open square*), osteoprotegerin (OPG) (*filled squares*), anti-parathyroid hormone-related protein (anti-PTHrP) monoclonal antibody (mAb) (*open circles*) and OPG plus anti-PTHrP mAb (*filled circles*). When the carcass weight fell below 20g, PBS and anti-PTHrP mAb (100μg immunoglobulin G) were administered to the peritoneal cavity on day 0, and OPG (2.5mg/kg) was administered subcutaneously from days 0 to 5. The body weight and tumor size were measured daily, and blood ionized calcium was measured on days 0, 2, 4, and 6. The mice were sacrificed on day 6 after administration. The carcass weight was calculated as the difference between the whole-body weight and the estimated tumor weight. The values represent means for groups of eight mice. *Vertical bars* are the SE. $^*P < 0.001$. $^\dagger P < 0.05$

Table 1. Cachexia parameters of HARA-B-bearing mice and age-matched non-tumor-bearing mice (normal) after various treatments

Parameter	HARA-B-bearing mice				Normal mice
	Controls	Antibody	OPG	Antibody + OPG	
Carcass weight (g)	17.0 ± 0.4	23.4 ± 0.5*	20.4 ± 0.6*	24.0 ± 0.6*	27.0 ± 0.7
Adipose tissue weight (mg)	18 ± 4.1	108 ± 9.2*	58 ± 11*	120 ± 9.2*	81 ± 9.4
Muscle weight (mg)	89 ± 2.4	108 ± 4.2*	94 ± 3.7	108 ± 2.2*	125 ± 2.8
Tumor weight (g)	2.9 ± 0.3	2.5 ± 0.3	2.3 ± 0.2	2.7 ± 0.3	
Blood Ca^{2+} (mM)	2.36 ± 0.09	1.72 ± 0.05*	1.80 ± 0.05*	1.46 ± 0.06*	1.34 ± 0.01
Serum PTHrP (pmol/l)	1102 ± 119	905 ± 82	1192 ± 159	1130 ± 198	59 ± 10

* $P < 0.001$ vs control

Data are expressed as the mean ± SE from eight mice treated with PBS (controls), anti-PTHrP mAb (Antibody), OPG, and anti-PTHrP mAb plus OPG (Antibody + OPG) and six non-tumor-bearing mice (Normal)

PBS, phosphate-buffered saline; PTHrP, parathyroid hormone-related protein; mAb, monoclonal antibody; OPG, osteoprotegerin

significantly lower than those of the controls on days 2, 4, and 6 after administration.

We also examined the combined effects of anti-PTHrP mAb plus OPG on HARA-B-bearing mice. Simultaneous administration of anti-PTHrP mAb plus OPG caused weight gain, and the change in body weight was similar to that of mice treated with anti-PTHrP mAb. Blood ionized calcium levels decreased to a greater extent than those of mice treated with anti-PTHrP mAb or OPG, and significant differences in the blood ionized calcium levels were found on days 2, 4, and 6 after administration.

Losses in adipose tissue weight and muscle weight usually develop in cachexic mice. HARA-B-bearing mice showed marked depletion of adipose tissue weight and mild depletion of muscle weight [7]. Several cachexia parameters measured on day 6 after administration are shown in Table 1. Treatment with anti-PTHrP mAb caused a significant increase in adipose tissue weight and muscle weight. Treatment with OPG also increased adipose tissue weight, but it was significantly less than that of mice treated with anti-PTHrP mAb. Simultaneous treatment with anti-PTHrP mAb plus OPG resulted in a significant increase in adipose tissue and muscle weights compared to the controls, which was similar to that of mice treated with anti-PTHrP mAb. There were no significant differences between the tumor weights or serum PTHrP levels among groups.

Discussion

We previously reported that PTHrP induces cancer cachexia in an experimental model using human lung cancer-derived cells [7]. However, it remains to be determined what PTHrP effects on target tissues induce cachexia. We therefore examined the effects of OPG, which inhibits hypercalcemia, on PTHrP-producing tumor-induced cachexia to elucidate the mechanism responsible for this condition. OPG inhibited hypercalcemia to the same extent as that caused by neutralization of PTHrP with antibody. OPG also increased the body and adipose tissue weights compared with the controls, although these effects were less when compared to those in mice treated with the neutralization of PTHrP with antibody. In addition, OPG failed to cause an increase in the muscle weight.

These results suggest that hypercalcemia is involved in the development of PTHrP-producing tumor-induced cachexia, but that its contribution is limited. The conditions responsible for cachexia cannot be explained by anorexia and energy expenditure, as nutritional support is unable to alleviate this syndrome [12]. Mechanisms other than anorexia could be involved in the induction of cachexia. The direct effects of cytokines may be involved in the loss of adipose tissue and muscle weights. IL-6 suppresses the expression of lipoprotein lipase, a key enzyme that regulates lipid metabolism in adipocytes during cachexia [13]. In the present study, the loss in adipose tissue and muscle weights were fully recovered, not by correcting the hypercalcemia but by neutralizing PTHrP with antibody. This raises the possibility that PTHrP causes the catabolism of adipose tissue and muscle through a mechanism other than hypercalcemia. PTHrP plays another role as a proinflammatory cytokine and stimulates the expression of IL-6 and LIF, which are both known as cachexia inducers, through the cytokine cascade [14]. In our previous study, however, serum levels of mouse IL-6 in HARA-B-bearing mice with cachexia were similar to those in the non-tumor-bearing mice [7]. We cannot exclude the possibility that PTHrP may act through the endogenous release of these cachexia-inducing proinflammatory cytokines (IL-6 and LIF) only at the target sites in a paracrine fashion, which would not influence the serum levels of these cytokines.

PTHrP is expressed in discrete regions of the brain [15]. We therefore cannot exclude the possibility that PTHrP induces anorexia by altering central neurohormonal signals that govern appetite. However, food intake was only minimally decreased due to HARA-B-induced cachexia in a previous study [7], suggesting that anorexia is not involved in this cachexia.

OPG was identified as an osteoclastogenesis inhibitory factor (OCIF) that inhibits osteoclast formation and activity [8,9]; and several studies have found that OPG inhibits bone resorption caused by several cytokines including PTHrP [16]. Furthermore, Capparelli et al. [10] showed that OPG prevents and reverses hypercalcemia in an HHM model mouse. In the present study, the hypercalcemia in HARA-

B-bearing mice was ameliorated by OPG, anti-PTHrP mAb, or both. The blood ionized calcium levels were decreased to a greater extent after simultaneous administration of OPG and anti-PTHrP mAb compared to those after OPG or anti-PTHrP mAb alone. OPG together with anti-PTHrP mAb almost completely normalized the hypercalcemia. Although the mechanism responsible for the synergistic effects of OPG and anti-PTHrP mAb on hypercalcemia is not clear, hypercalcemia in the HARA-B-bearing mice may be induced not only by PTHrP but also by other factors, and further studies are required to elucidate the mechanism for the development of hypercalcemia in HARA-B-bearing mice.

In conclusion, PTHrP is a known mediator of cachexia. Hypercalcemia, which is induced by PTHrP, as well as other effects of PTHrP (partly through the induction of cachexia-inducing proinflammatory cytokines at the target sites) cooperate to develop cachexia. In addition, OPG and anti-PTHrP antibody additively inhibit hypercalcemia.

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Characteristic features of disseminated carcinomatosis of the bone marrow due to gastric cancer: The pathogenesis of bone destruction

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Abstract. Disseminated carcinimatosis of the bone marrow is accompanied by solid tumors, and gastric cancer accounts for the majority. The prognosis of this condition is poor, however, the pathogenesis for wide-spread bone lesions has yet to be elucidated. In 9 patients with gastric cancer demonstrating disseminated carcinomatosis of the bone marrow, the characteristic clinicopathological features were examined. Immunohistochemistry for receptor activator of NF-κB ligand (RANKL) and parathyroid hormone-related protein was also performed on gastric cancer tissue and bone marrow specimens to identify the factors responsible for the occurrence of bone lesions in patients presenting with this condition. The characteristic features of disseminated carcinomatosis of the bone marrow due to gastric cancer include a yonger patient age, an elevation of serum alkaline phosphatase and/or lactate dehydrogenase levels, wide-spread bone metastases with osteolytic bone destruction, a low incidence of hypercalcemia and a histological gastric cancer type of either signet ring cell carcinoma or poorly diffentiated adenocarcinoma. The expression of RANKL, which is one of the master regulators of osteoclastic bone resorption in bone metastasis, was also found in gastric cancer cells obtained from such patients. The RANKL expressed in gastric cancer may therefore play a critical role in the promotion of osteoclast formation, which has been suggested to be involved in the pathogenesis of bone lesions.

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Key words: gastric cancer, bone marrow invasion, bone destruction, receptor activator of NF-κB ligand

Introduction

Bone metastases diffusely invading the bone marrow with hematological disorders [i.e., disseminated intravascular coagulation (DIC), microangiopathic hemolytic anemia, etc.] tend to be accompanied by solid tumors (1), and this condition is called disseminated carcinomatosis of the bone marrow. This condition is often caused by gastric cancer among solid tumors, although its overall incidence is rare (2,3). The prognosis for this condition is extremely poor, however, the pathogenesis of this condition, namely the cause for the development of such diffuse bone metastases, has yet to be elucidated. In the present study, we examined the characteristic clinicopathological features of disseminated carcinomatosis of the bone marrow accompanied by gastric cancer based on the clinical findings of 9 cases who presented with this condition at our cancer center from 1991 to 2002. We also examined the expression of receptor activator of NF-κB ligand (RANKL) and parathyroid hormone-related protein (PTHrP), which are known to be master regulators of osteoclastic bone resorption in bone metastasis (4,5), in gastric cancer tissue and bone marrow specimens obtained from these 9 patients to identify any factors related to the pathogenesis of such diffuse bone metastases observed in this condition.

Patients and methods

Patients. Nine patients with disseminated carcinomatosis of the bone marrow associated with gastric cancer, who were treated in our cancer center between 1991-2002, were examined.

The diagnosis of disseminated carcinomatosis of the bone marrow was made in patients with gastric cancer, who also demonstrated: i) an elevation of the serum alkaline phosphatase (ALP) and/or lactate dehydrogenase (LDH) levels, ii) DIC and/or anemia (macro- to normocytic and hyper- to normochromic anemia), and iii) diffuse bone metastases on the bone scintigraphy findings. A bone marrow puncture was performed on 2 patients (cases 5 and 9 in Table I), and metastatic infiltration of atypical epithelial cells (cancer cells) was found in a bone marrow aspiration smear (Fig. 1). Eight

Table I. Clinicopathological features of nine patients with disseminated carcinomatosis of the bone marrow associated with gastric cancer.

Case	Age (years)	Sex	ALP[a] (IU/l)	LDH[a] (IU/l)	Hematological disorders[b]		Hyper-calcemia[c]	Histological type[d]	Therapy[e]	Survival period (days)[f]	Immunohisto-chemistry		Type of bone metastasis
					DIC	Anemia					RANKL	PTHrP	
1	52	F	475	584	+	+	-	Sig	CDDP/5-FU	100	-	-	Osteolytic
2	40	F	395	1179	+	+	-	Mo	BSC	58	+	-	Osteolytic
3	49	F	1188	310	+	+	-	Sig	CDDP/5-FU	240	+	+	Osteolytic
4	45	M	892	4820	+	+	+	Po	BSC	43	+	-	Osteolytic
5	65	M	234	1915	-	+	-	Sig	BSC	10	+	-	NE
6	63	M	1336	1380	+	+	-	Sig	MTX/5-FU	190	-	+	NE
7	50	M	168	432	-	+	-	Mo	BSC	110	+	-	NE
8	63	M	668	465	-	+	+	Po	MTX/5-FU	220	-	+	Osteolytic
9	40	F	2404	1720	+	-	-	Mo	MTX/5-FU BP	330	+	-	Osteolytic

[a]Serum levels of alkaline phosphatase (ALP) (normal 45-130 IU/l) and lactate dehydrogenase (LDH) (normal 200-370 IU/l) at diagnosis. [b]Associated hematological disorders at diagnosis. [c]Incidence of hypercalcemia during the course of the disease. [d]Histological types of primary gastric cancer. Sig, signet ring cell carcinoma; Po, poorly differentiated adenocarcinoma; Mo, moderately differentiated adenocarcinoma. [e]CDDP, cisplatinum; 5-FU, 5-fluorouracil; MTX, methotrexate; BP, bisphosphonates; BSC, best supportive care. [f]Survival period since the diagnosis of disseminated carcinomatosis of the bone marrow. NE, not examined.

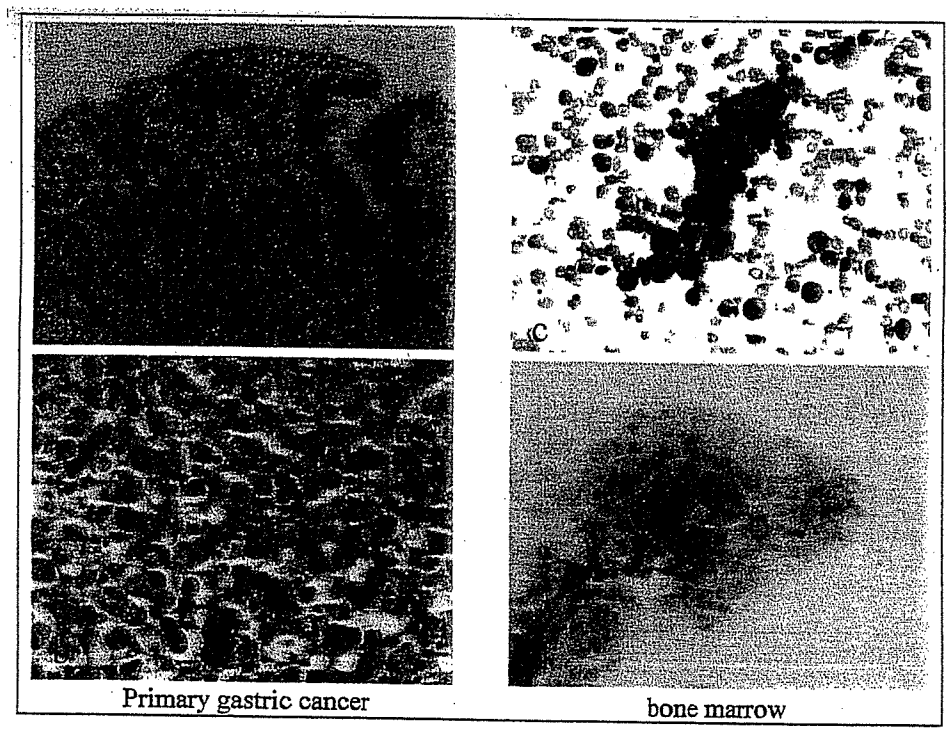

Figure 1. Photomicrographs of a primary gastric cancer specimen (a and b) and bone marrow aspiration smear (c and d) in disseminated carcinomatosis of the bone marrow (case 5). A gastric cancer specimen showed mucosal involvement by signet ring cell carcinoma cells (a, x20; b, x40; hematoxylin and eosin). A bone marrow aspiration smear showed metastatic infiltration by signet ring carcinoma cells (c, x40, Giemsa; d, x40, PAS).

patients had undergone prior surgery for gastric cancer before this condition was identified (cases 1-8 in Table I), and as a result, the diagnosis of gastric cancer was histologically proven in all 8 cases. In one patient (case 9 in Table I), on the other hand, the discovery of this condition preceded the diagnosis of gastric cancer, and the diagnosis was thus made based on the histological findings of the specimens obtained during a gastroendoscopic biopsy.

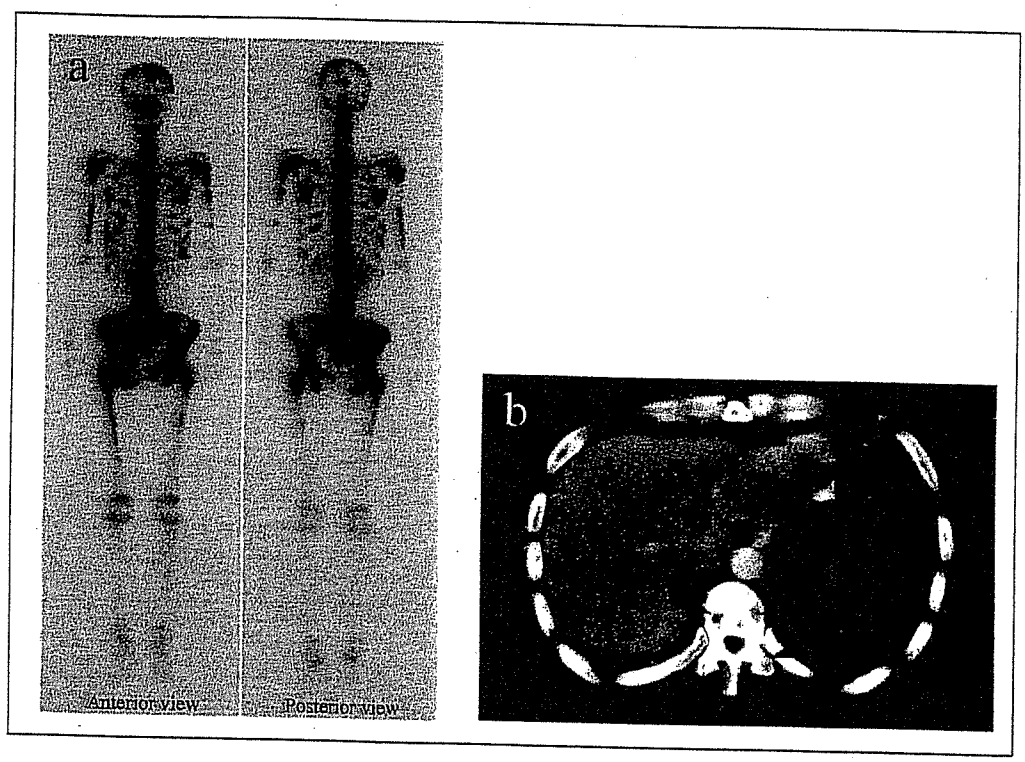

Figure 2. Typical radiological findings of bone lesions in disseminated carcinomatosis of the bone marrow associated with gastric cancer (case 9). The bone scintigraphy showed multiple hot spots throughout the entire skeleton (a). These bone lesions were composed predominantly of osteolytic bone destruction, which was disclosed by CT (b, arrow head).

We determined the clinicopathological features of the 9 patients as follows; age, sex, serum levels of ALP and LDH, presence of hematological disorders (DIC, anemia) at the time this condition was diagnosed, type of bone metastasis, incidence of hypercalcemia during the course of the disease, histological type of gastric cancer, therapy for this condition, and survival period since this condition was diagnosed. These factors are all listed in Table I.

Immunohistochemistry. Immunohistochemical staining for RANKL and PTHrP was performed on gastric cancer specimens obtained at surgery (cases 1-8, Table I) and/or biopsy under gastroendoscopy (case 9, Table I) and bone marrow specimens obtained by bone marrow puncture (cases 5 and 9, Table I) according to the previously described method (6). We also examined the expression of RANKL and PTHrP immunohistochemically in gastric cancer specimens obtained from 11 patients, in whom no metastasis was found 5 years after operation as a control. The histological types of these patients included 1 signet ring cell carcinoma, 7 poorly differentiated adenocarcinoma and 3 moderately differentiated adenocarcinoma. This composition of the histological types of the patients were similar to those of the gastric cancer patients who presented disseminated carcinomatosis of the bone marrow.

Briefly, the sections (4 μm) were de-waxed with xylene and rehydrated through a graded series of ethanol. After inhibition of endogenous peroxidase, the sections were incubated with primary antibodies at 4°C overnight, followed by incubation with biotinylated link antibody and peroxidase-labeled streptavidin (Nichirei, Tokyo, Japan) at room temperature for 20 min. The sections were then reacted in 3,3'-diaminobenzidine tetrahydrochloride (DAB), and then were counterstained with hematoxylin. We used goat polyclonal antibodies against RANKL (sc-7627, 1:50, Santa Cruz Biotechnology, Santa Cruz, CA) and PTHrP (sc-9680, 1:50, Santa Cruz Biotechnology) as a primary antibody. Tissue samples from giant cell tumors of the bone and PTHrP-producing lung cancer were used as positive controls for RANKL and PTHrP, respectively, while sections incubated with PBS instead of the primary antibodies were used as negative controls for both.

Statistics. The statistical analysis was performed using Welch's unpaired t-test, where a value of $p<0.05$ was considered to be statistically significant.

Results

The characteristic clinicopathological features of disseminated carcinomatosis of the bone marrow associated with gastric cancer. The clinicopathological features of the 9 patients with gastric cancer demonstrating disseminated carcinomatosis of the bone marrow are listed in Table I.

The nine patients with this condition included 5 males and 4 females with a median age of 52 years, which was younger than that for the majority of gastric cancer patients. An elevation in the serum ALP and LDH levels was a characteristic clinical finding, which is important for making the diagnosis, and the elevated ALP level was mainly related to bone origin. Wide-spread bone metastases to almost the entire skeleton were detected by bone scintigraphy (Fig. 2a), and the types of bone metastasis included osteolytic bone destruction in all 6 patients whose bone lesions were evaluated

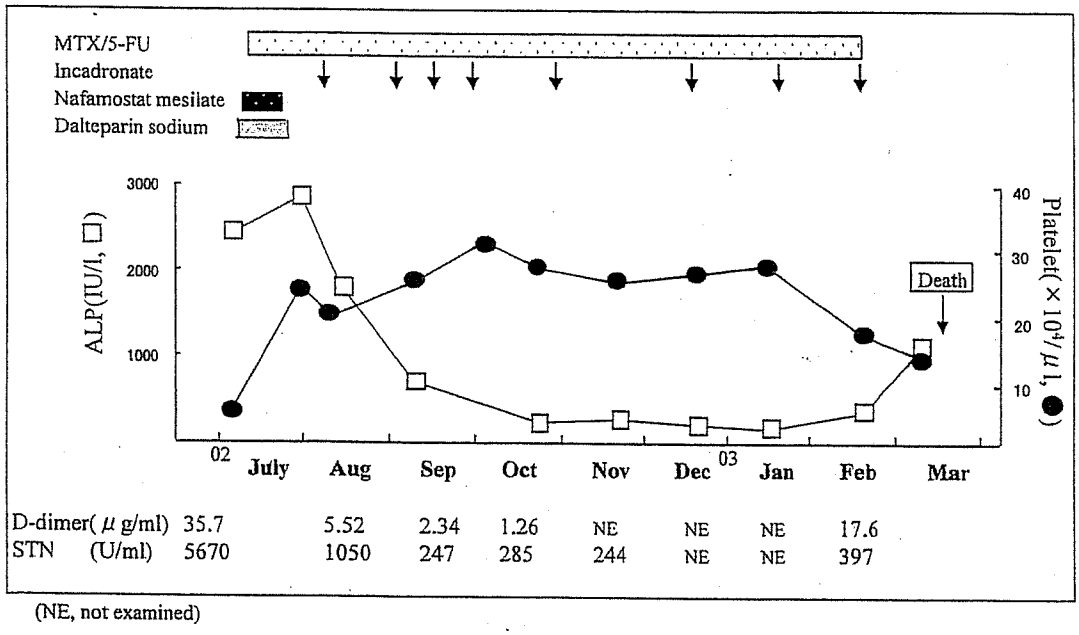

Figure 3. The treatment for disseminated carcinomatosis of the bone marrow associated with gastric cancer in case 9. The platelet count increased to the normal level (normal 12-32x10⁴/μl) along with marked reduction of the serum D-dimer level (normal <1 μg/ml) after three courses of chemotherapy (MTX/5-FU) and the treatment for DIC (Nafamostat mesilate, Dalteparin sodium). However, the serum levels of ALP, which represented the extent of bone lesions, and a tumor marker, STN, still remained extremely high. Then, a bone-targeted therapy using bisphosphonates (incadronate) was started in addition to chemotherapy, which resulted in a rapid reduction of serum ALP (normal 45-130 IU/l) and STN (normal <45 U/ml) levels.

by plain radiography, CT and/or magnetic resonance imaging (MRI) (Fig. 2b). DIC, the most common hematological complication associated with disseminated carcinomatosis of the bone marrow, was found in 6 of 9 patients. In the remaining 3 patients without DIC, macro- to normo-cytic and hyper- to normo-chromic anemia was noted as a hematological complication. This type of anemia together with an elevation of the serum LDH level suggest the possibility that the anemia had been caused by a diffuse infiltration of cancer cells into the bone marrow. Hypercalcemia is sometimes associated with multiple bone metastases in cancer patients. In the present study, however, only two of the 9 patients developed hypercalcemia during the course of the disease in spite of a widespread expansion of bone metastases.

The histological types of gastric cancer included 4 signet ring cell carcinomas, 2 poorly differentiated adenocarcinomas and 3 moderately differentiated adenocarcinomas. In the 3 gastric cancers with moderately differentiated adenocarcinoma, however, a poorly differentiated component was found in some parts of the gastric cancer in one patient. Chemotherapy [cisplatinum (CDDP)/5-fluorouracil (5-FU) or methotrexate (MTX)/5-FU] was performed in 4 patients (cases 1, 3, 6, 8; Table I), and the mean (±SD) survival period of these patients was 187±62 days. In the 4 patients without chemotherapy (cases 2, 4, 5, 7; Table I), on the other hand, the mean (±SD) survival period was 55±42 days, which was significantly shorter than that of the patients with chemotherapy ($p<0.02$). In the remaining one patient (case 9, Table I) who was treated most recently in our cancer center, a bone-targeted therapy using bisphosphonates (incadronate) was performed in addition to chemotherapy (MTX/5-FU). The clinical course of this patient is shown in Fig. 3. Chemotherapy for gastric cancer and treatment for DIC were started first, and DIC was no longer seen when the three courses of these treatments had finished. However, serum ALP levels, which represented the extent of bone metastases, still remained at a high level, thus, a bone-targeted therapy using bisphosphonates (incadronate) was started in addition to chemotherapy. As a result, serum ALP levels began to reduce along with the serum levels of a tumor marker, sialyl Tn-antigen (STN), and the reduced levels of serum ALP and STN were maintained for 6 months. However, the patient then died because of progression of DIC.

Expression of RANKL and PTHrP in gastric cancer. We performed immunohistochemistry for RANKL and PTHrP to identify any factors related to pathogenesis regarding the development of bone lesions in disseminated carcinomatosis of the bone marrow. RANKL showed positive staining in the gastric cancer tissue specimens from 6 of 9 patients (Fig. 4a and b), while PTHrP was positively stained in the same specimens in 3 of 9 patients (data not shown). In the bone marrow specimens, on the other hand, positive staining for RANKL was found in the gastric cancer cells invading the bone marrow in 2 patients examined (Fig. 4c and d), whereas PTHrP was not positively stained in these cells (data not shown).

We also examined the expression of these proteins immunohistochemically in the gastric cancer specimens without any metastasis as a control. RANKL was positively stained in only one of 11 patients, while PTHrP was positively stained in 3 of 11 patients (data not shown).

Discussion

Disseminated carcinomatosis of the bone marrow is accompanied by solid tumors and gastric cancer accounts for the majority of such cases (1-3), although the incidence of this

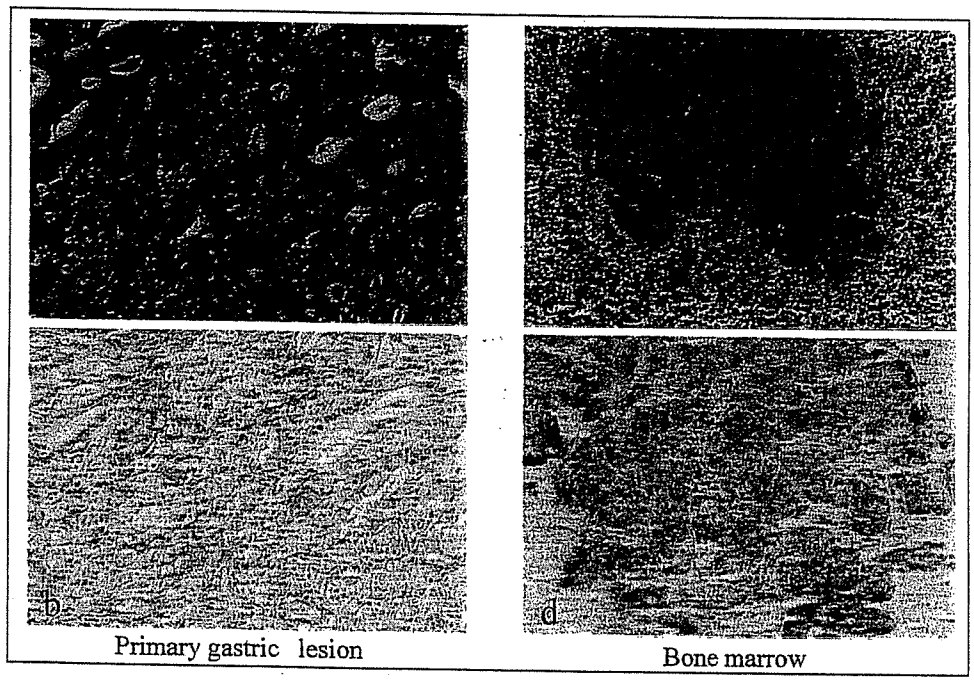

Figure 4. Representatives of immunohistochemistry for RANKL in gastric cancer demonstrating disseminated carcinomatosis of the bone marrow (case 9). (a) The findings for hematoxylin and eosin staining of gastric cancer show moderately differentiated adenocarcinoma (x20). (b) Immunohistochemistry for RANKL in a serial section of the same specimen in (a). RANKL shows positive staining predominantly in the cytoplasm and plasma membrane of moderately differentiated adenocarcinoma cells (x20). (c) The findings for hematoxylin and eosin staining of a bone marrow aspiration smear show infiltration of atypical epithelial cells indicating metastasis from known gastric cancer (x20). (d) Immunohistochemistry for RANKL in a serial section of the same specimen in (c). RANKL shows positive staining predominantly in the cytoplasm and plasma membrane of metastatic gastric cancer cells as is seen in the primary lesion (b) (x20).

condition is rare. In this condition, cancer cells diffusely infiltrate the bone marrow followed by explosive proliferation, which causes bone destruction and hematological complications. However, the pathogenesis for the development of bone lesions is still poorly understood. In the present study, we examined the characteristic clinicopathological features of disseminated carcinomatosis of the bone marrow from gastric cancer based on the clinical findings of our patients. The typical features included a younger patient age, an elevation in the serum ALP and/or LDH, extensive bone metastases with osteolytic bone destruction, a low incidence of hypercalcemia and histological types of gastric cancer with signet ring cell carcinoma or poorly differentiated adenocarcinoma. Only a few cases in a case report are available regarding disseminated carcinomatosis of the bone marrow. Morimatsu *et al* (7) examined 11 autopsy cases of gastric cancer patients with diffuse bone marrow metastasis, and found the patients to be relatively young (mean 47 years) while 9 of 11 cases had a signet ring cell component. These results are consistent with the findings in the present study.

The prognosis of these patients was poor regardless of the treatment. However, the survival period of the patients treated with chemotherapy was significantly longer than that for those without chemotherapy. Furthermore, the survival period of the patient treated with bisphosphonates in addition to chemotherapy was longer than that of the patients with chemotherapy alone although only one case was treated with bisphosphonates. Chemotherapy has been reported to improve the prognosis of metastatic gastric cancer (8). In addition, a new approach for the treatment for bone metastasis using bisphosphonates has been established (9). Bisphosphonates have an anti-proliferative effect on cancer cells by decreasing the supply of growth factors from the bone through the inhibition of bone resorption (10,11). Currently, nitrogen-containing bisphosphonates have been shown to inhibit cancer cell proliferation directly through the inhibition of the mevalonate signaling pathway (12-14). Bisphosphonates seem to be included in the treatment arm in combination with chemotherapy against disseminated carcinomatosis of the bone marrow.

To elucidate the pathogenesis of the development of bone lesions in disseminated carcinomatosis of the bone marrow, we immunohistochemically examined the expression of RANKL and PTHrP, which are master regulators of osteoclast differentiation and activation, in gastric cancer tissue and bone marrow specimens of these patients. Among various cancers, the expression of RANKL was found in myeloma (15,16) and/or ATL cells (17), whereas such expression was rare in solid tumors (18). In the present study, we demonstrated the high incicence of the expression of RANKL in gastric cancer cells, which extensively invaded the bone compared to that in gastric cancer without any metastasis. To our knowledge, this is the first study demonstrating the expression of RANKL in gastric cancer cells. This finding raises the possibility that gastric cancer cells act directly on osteoclast precursor cells via RANKL to promote osteoclast formation. This finding seems to imply the mechanism responsible for developing bone lesions in disseminated carcinomatosis of the bone marrow. We also found the expression of PTHrP in the gastric cancer tissue specimens obtained from patients with disseminated carcinomatosis of the bone marrow. However, its incidence was lower than that of RANKL, and similar to that of PTHrP in the control patients without any metastasis. PTHrP expression has been identified within tumor cells in 71 of 92

patients with gastric cancer (19). PTHrP expression might not be a specific event for the gastric cancer associated with disseminated carcinomatosis of the bone marrow.

In summary, RANKL, which is expressed in gastric cancer cells, is considered to play an important role in the development of bone lesions in disseminated carcinomatosis of the bone marrow by gastric cancer. Bone-targeted therapy using bisphosphonates, in addition to chemotherapy, is recommended as the treatment of choice for patients with this condition.

Acknowledgements

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Predictive Factors of Lymph Node Metastasis in Patients With Undifferentiated Early Gastric Cancers

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Background: For intramucosal differentiated early gastric cancer that has little risk of lymph node metastasis, local treatment such as endoscopic mucosal resection has been generally accepted as an adequate treatment. We studied clinicopathological characteristics of undifferentiated early gastric cancer at our institution to identify the predictive factors for lymph node metastasis and qualify lesions that should be referred for gastrectomy and not endoscopic mucosal resection.

Methods: We retrospectively analyzed the clinicopathological features (patient age and gender, tumor size, location, macroscopic type and histological type, presence of ulceration, depth of tumor invasion, and lymphatic-vascular involvement) in 332 patients with undifferentiated early gastric cancer who underwent gastrectomy with regional lymph node dissection.

Results: Lymph node metastasis was observed in 45 patients (14%). Univariate analysis revealed that depth of tumor invasion (submucosa), tumor size (> 30 mm), and lymphatic-vascular involvement (positive) were associated with lymph node metastasis. Only lymphatic-vascular involvement (positive) was found to have a significant association (odds ratio, 7.4; 95% confidence interval, 2.9–19.0) by multivariate analysis.

Conclusions: Lymphatic-vascular involvement was the only independent predictive risk factor for lymph node metastasis. This pathologic factor was not useful for identifying patients at high risk of lymph node metastasis who should be offered gastrectomy rather than endoscopic mucosal resection.

Key Words: early gastric cancer, lymph node metastasis, undifferentiated carcinoma, predictive factor, endoscopic mucosal resection

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Early gastric cancer (EGC) is defined as cancer localized to the mucosa or submucosa, regardless of lymph node metastasis. Radical gastrectomy with regional lymphadenectomy is the "gold standard" treatment for patients with EGC.[1] The incidence of EGC has been increasing because of advances in diagnostic procedures.[2] However, because the incidence of lymph node metastasis in intramucosal EGC is approximately 3% and that in submucosal EGC is around 20%,[3] gastrectomy with regional lymphadenectomy may be overtreatment for many patients with EGC.

Several studies have identified risk factors that are predictive of lymph node metastasis in EGC.[2–7] It is known that histologically undifferentiated intramucosal EGC tends to have lymph node metastasis more often than differentiated intramucosal EGC.[5–7] The survival rate for those with lymph node metastasis is significantly lower than for those without lymph node metastasis.[3,6,8] Some groups report a better prognosis for early signet ring cell carcinoma than for other types of cancer,[9] but this is controversial.[10] For intramucosal EGC that has little risk of lymph node metastasis, local treatment such as endoscopic mucosal resection (EMR) has been generally accepted as an adequate treatment. EMR is employed when an intramucosal cancer is diagnosed as differentiated adenocarcinoma, is < 2 cm in diameter, and has no central ulceration.[4,5]

Recently, a new method of EMR, so-called endoscopic submucosal dissection (ESD), has been developed.[11] Compared with classic methods such as strip biopsy, ESD can remove a larger size of gastric mucosa as a single fragment with an adequate, safe negative margin.[12] Complete removal of the lesion in a single fragment is essential for an accurate histological diagnosis to determine whether EMR alone will be curative. Several institutions have suggested that use of EMR should be extended to larger, differentiated intramucosal EGCs because lesions < 30 mm in diameter without lymphatic-vascular invasion or ulceration have little risk of lymph node metastasis. However, there have been few reports about lymph node metastasis from undifferentiated EGC,[13] and the applicability of local treatment for it is unknown.

One of the critical factors that needs to be considered in choosing local treatment for EGC is the accurate prediction of whether lymph node metastasis is present. In this study, we retrospectively analyzed the

clinicopathological characteristics of undifferentiated EGC by reviewing cases that had been treated previously at our institution in order to identify predictive factors of lymph node metastasis and qualify lesions that should be referred for gastrectomy and not EMR.

PATIENTS AND METHODS

Between January 1989 and April 2005, 1,004 patients with EGC underwent gastrectomy as an initial treatment at the National Hospital Organization Shikoku Cancer Center. Among these, 398 patients had undifferentiated EGC. Cases of multiple lesions and cases without regional lymph node dissection were excluded from this study, giving a final total of 332 patients whose clinicopathological features were retrospectively analyzed. They comprised 160 men and 172 women whose mean age was 58.0 years (range, 20 to 87 years), with a mean tumor size of 36.5 mm (range, 1 to 130 mm). Cancer description and histological evaluation of resected specimens were performed in accordance with the Japanese Classification of Gastric Carcinoma.[14]

A set of sections of the stomach parallel to the lesser curvature were made, and the histological classification was based on the predominant pattern of the tumor. Poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma were regarded as undifferentiated. Lymph nodes were cut into two pieces, and the cut surfaces were examined to define the status of the nodes. Lymph node metastasis was identified with use of hematoxylin and eosin staining, and ulceration was defined histologically if fibrosis or deformity in the submucosal layer or deeper was observed.

Tumors were classified macroscopically into two groups: protruded (types 0 I and 0 IIa) or depressed (types 0 IIb, 0 IIc, and 0 III). Lesions showing a combination of these types were classified into a mixed group. The association between each of the nine clinicopathological factors and the presence or absence of lymph node metastasis was examined to identify risk factors predictive of lymph node metastasis.

Univariate analysis was performed with use of the chi-square test. Subsequently, significant factors identified by univariate analysis were included in the multivariate stepwise logistic regression analysis to evaluate the independent risk factors for lymph node metastasis. The odds ratio in the multivariate analysis was defined as the ratio of the probability that an event would occur to the probability that it would not occur. Statistical analyses were performed with use of the Statistical Package for Social Science (SPSS 11.5 for Windows, SPSS, Chicago, IL). Differences of $P < 0.05$ were considered significant.

RESULTS

Univariate Analysis of Risk Factors Predictive of Lymph Node Metastasis

Of the 332 patients with undifferentiated EGC, 45 (14%) had lymph node metastasis. Lymph node metastasis was observed in eight (5%) of the 177 patients with intramucosal cancers and in 37 (24%) of the 155 with submucosal cancers. Nine clinicopathological factors were examined: patient age and gender, tumor size, location, macroscopic type and histological type, presence of ulceration, depth of tumor invasion, and lymphatic-vascular involvement. Univariate analysis revealed that the depth of tumor invasion (submucosa), tumor size (> 30 mm), and lymphatic-vascular involvement (positive) were associated with lymph node metastasis (Table 1).

Multivariate Analysis of Risk Factors Predictive of Lymph Node Metastasis

Only lymphatic-vascular involvement (positive) was shown to have a significant association (odds ratio, 7.4; 95% confidence interval, 2.9–19.0) by multivariate analysis (Table 2).

Survival

Median period of follow-up was 50.5 months (range, 0 to 199 months). Survival curves for patients with and without lymph node metastasis are shown in

TABLE 1. Univariate Analysis of Risk Factors for Lymph Node Metastasis in Patients With Undifferentiated Early Gastric Cancer (EGC)

Factor	Lymph Node Metastasis		P Value
	Positive (%) n = 45	Negative n = 287	
Age, years			
< 59	19 (11%)	151	
≥ 59	26 (16%)	136	0.256
Gender			
Male	21 (13%)	139	
Female	24 (14%)	148	0.952
Location			
Upper third	6 (17%)	29	
Middle third	30 (13%)	195	
Lower third	9 (13%)	63	0.794
Macroscopic type			
Protruded	3 (33%)	6	
Depressed	40 (13%)	275	
Mixed	2 (25%)	6	0.129
Ulceration			
Negative	23 (15%)	131	
Positive	22 (12%)	156	0.601
Depth of invasion			
Mucosa	8 (5%)	169	
Submucosa	37 (24%)	118	< 0.001
Histological type			
Poorly differentiated adenocarcinoma	28 (17%)	137	
Signet ring cell carcinoma	15 (9%)	144	
Mucinous adenocarcinoma	2 (25%)	6	0.089
Size of tumor			
< 30 mm	12 (8%)	140	
≥ 30 mm	33 (18%)	147	0.009
Lymphatic-vascular involvement			
Negative	13 (5%)	236	
Positive	32 (39%)	51	< 0.001

Values are number of cases.

TABLE 2. Multivariate Analysis of Risk Factors for Lymph Node Metastasis in Patients With Undifferentiated EGC

Factor	Odds Ratio (95% CI)	P Value
Lymphatic-vascular involvement (positive)	7.42 (2.89–19.03)	< 0.001
Size of tumor (≥ 30 mm)	1.98 (0.92–4.22)	0.079
Depth of invasion (submucosa)	1.75 (0.60–5.13)	0.310

CI, confidence interval.

Figure 1. The 5-year survival rate was 96.7% for those without lymph node metastasis and 91.4% for those with lymph node metastasis. There was no statistical difference in overall survival rate between patients with or without lymph node metastasis. Of the patients with lymph node metastasis, three died of recurrence of gastric cancer (one with bone metastasis, one with bone and lymph node metastasis, and one with lymph node metastasis). Of the patients without lymph node metastasis, one died of liver metastasis.

DISCUSSION

EGC has been reported to have a favorable prognosis after gastrectomy.[15] Lymph node metastasis is one of the most important prognostic factors for patients with EGC; the survival rate for patients with lymph node metastasis is significantly lower than for those without it.[3,16] However, the incidence of lymph node metastasis in intramucosal EGC is approximately 3%, whereas that in submucosal EGC is 20%. Excessive gastrectomy and lymphadenectomy may affect perioperative morbidity and mortality.[17] Therefore, minimally invasive treatments such as EMR and laparoscopic wedge resection are considered to be appropriate options for EGC patients without lymph node metastasis.

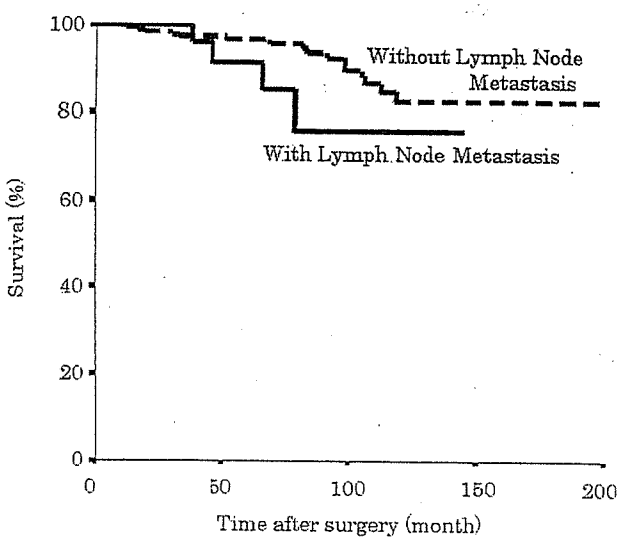

FIGURE 1. Survival curves for patients with and without lymph node metastasis. There was no statistical difference between them.

A new EMR technique that allows complete removal of a large lesion as a single fragment with an insulation-tipped diathermic knife[11] is promising for accurate histological examination of a specimen and subsequent determination of whether local treatment alone will be curative. Although undifferentiated EGC is reported to have more lymph node metastasis than differentiated EGC,[6,7] histological type has no association with survival.[18] Our survival data showed no statistical difference in overall survival rate between patients with or without lymph node metastasis. This may be due to the short follow-up period.

Current application of EMR is limited to differentiated EGC; thus, we sought to expand the use of EMR to undifferentiated EGC by retrospectively examining undifferentiated EGC to determine predictive factors of lymph node metastasis. Univariate analysis revealed three clinicopathological risk factors: depth of invasion, tumor size, and lymphatic-vascular involvement. These factors correlate with those reported previously for both differentiated and undifferentiated EGC by multivariate analysis.[3,4,6–8] Because lymphatic-vascular vessels are less likely to appear in the mucosal layer than in the submucosal layer, it would be reasonable to expect that submucosal tumors would have a more frequent association with lymph node metastasis than intramucosal tumors.

In the present study, multivariate analysis demonstrated that the presence of lymphatic-vascular involvement was the only independent predictive factor for lymph node metastasis, in agreement with previous studies of undifferentiated EGC.[13] Although lymphatic-vascular involvement seems to identify a high-risk population that perhaps should not be offered EMR, this can be determined only after a gastrectomy or EMR. Thus, this pathologic feature is not useful in EMR. There was no proper predictive factor to identify patients with undifferentiated EGC at high risk for lymph node metastasis who should be offered gastrectomy rather than EMR.

In our study, small, undifferentiated EGCs < 10 mm in size without lymphatic-vascular involvement had no lymph node metastasis, but with the narrow range of cases (seven in the mucosa and six in the submucosa), the statistical significance is too limited to make any conclusions. However, our trend is consistent with that described by Gotoda et al,[5] in which zero of 141 patients with undifferentiated intramucosal EGCs < 20 mm in size without ulceration had lymph node metastasis. In our study, one undifferentiated intramucosal EGC < 20 mm (13 mm) in size without ulceration and without lymphatic-vascular involvement had lymph node metastasis. Contrarily, Abe et al reported that lymph node metastasis was found in small, undifferentiated intramucosal EGC (10 mm and 12 mm) without ulceration.[13]

The prognosis for patients with differentiated EGC who undergo EMR is favorable.[19] Still, there is

some concern about how micrometastasis affects the survival rate; Lee et al[20] reported that patients with micrometastasis had a lower 5-year survival rate than patients without micrometastasis, especially in Stage IA. It is suggested that micrometastasis is missed on conventional histological examination and that immunohistochemical examination is needed. Although there has been no report on the prognosis for patients with undifferentiated EGC treated by EMR, Ishida et al[21] reported that micrometastasis was more frequent in the undifferentiated type than in the differentiated type, and it is feared that cases of small, undifferentiated EGC treated with EMR could potentially recur with lymph node metastasis.

Currently the treatment procedure is decided on the basis of clinical findings, and despite recent improvements in diagnostic techniques, it is sometimes difficult to define the tumor margin and tumor depth by endoscopic examination.[22] The accuracy of determining tumor depth is reported to be significantly lower for undifferentiated tumors than for differentiated tumors and lower for a depressed tumor than for an elevated one.[23] Miyata et al[24] reported that the complete resection rate of EMR for EGC in poorly differentiated adenocarcinoma was lower than in differentiated types.

According to our results, lymphatic-vascular involvement was the only independent predictive risk factor for lymph node metastasis. However, this cannot be confirmed before surgery or EMR. This pathologic factor was not useful to identify patients at high risk for lymph node metastasis who should be offered gastrectomy rather than EMR. Clinical characteristics such as tumor size and depth were not so strong predictors for lymph node metastasis in our study. Therefore, it is prudent to choose EMR as a therapeutic procedure for patients with undifferentiated intramucosal EGCs.

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●特 集● チーム医療で進める癌治療

がんセンターと医療連携（地域連携）

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Team Approach for Treatment of Patients with Cancer, How to Cooperate with Staffs of Other Medical Institutions—A Recent Trend in Japan: Masahito Tanimizu, Yuki Kikuuchi, Chiaki Funada, Kikuko Kameshima, Akira Kurita and Shigemitsu Takashima (*National Hospital Organization, Shikoku Cancer Center*)

Summary

For the team approach to patients with cancer, both of consistency of medical services and patient's satisfaction are important. Japanese health care reform planning prescribes an establishment of a section which accepts patient's consultation and provides proper advice or information. Technology of the internet is also promising for team approaches with staffs of other medical institutions as well as the patient support section in the cancer centers. Key words: Patient support, Consistency of medical services, Patient's satisfaction, the Internet, Corresponding author: Masahito Tanimizu, National Hospital Organization, Shikoku Cancer Center, 160 Minamiumenomotomachi-Kou, Matsuyama, Ehime 791-0288, Japan

要旨 医療制度改革の方向性に示された医療連携の要は，患者視点の重視と医療の一貫性・継続性の確保である。がん診療連携拠点病院の指定要件に記された「相談支援機能を有する部門」は医療連携のあり方を明確に方向付けている。中核病院における医療連携・患者支援部門の拡充とインターネット技術の導入に期待したい。

はじめに

がん医療は再編が進行中であり，都道府県がん診療連携拠点病院，地域がん診療連携拠点病院の整備が進められている。拠点病院に限らず多くの中核病院にはすでに医療連携室が設置されており，地域医療連携の要として働いているが，本稿では医療制度改革案，がん対策基本法などに示されたがん医療の視点から今後の医療連携のあり方を考察した。

Ⅰ．第5次医療制度改革案，がん対策基本法にみる医療連携の方向性

平成17年7月に「平成18年の医療制度改革を念頭においた医療計画制度の見直しの方向性」が公表された[1]。平成18年1月には第5次医療制度改革が閣議決定されており，その方向性が明らかになっている。新しい医療計画では患者中心の視点から医療連携体制の再構築をめざしている。従来の医療計画は1次，2次，3次医療と階層型構造で医療提供側からみた医療ニーズが重視されていたが，新しい医療計画では患者中心の視点が重視され，患者とかかりつけ医の協調関係を軸に患者の納得と医療の継続性を重視した医療連携像となっている。特記すべきは「連携，情報提供，研修などに関わり，患者と医療提供者を調整する組織の役割」が新たに提案されている点である[1]。

医療制度改革に向けての一連の動きから導かれるがん医療における医療連携の問題と新しい連携像を示す（図1）。

1．従来の医療提供体制，医療計画

患者は1次，2次，3次医療の間を移動しながら，医療ニーズの点から適切な医療を選択することが求められていた。医療提供側からみれば担当範囲の医療を提供し，守備範囲を外れる医療については他に対応を任せることになる。そこで問題となるのは医療提供体制と患者の受

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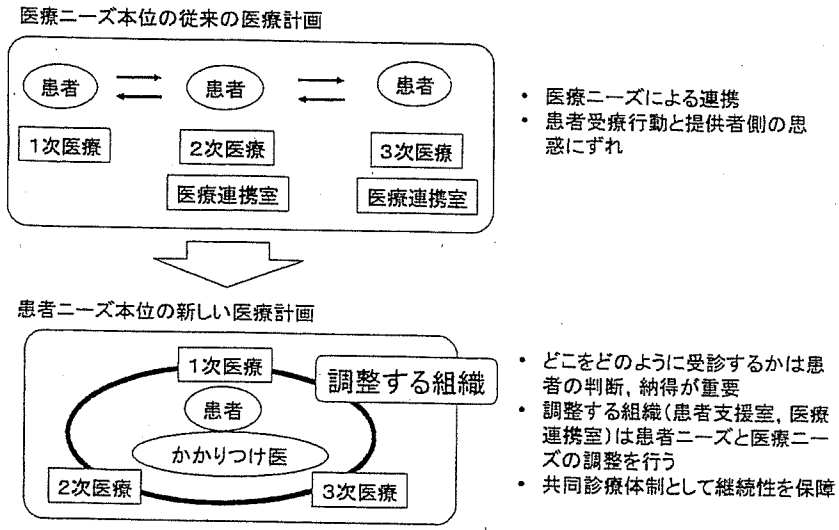

図 1　医療ニーズ本位から患者ニーズ本位へ

療行動とのずれである。医療機能の充実という点からは大病院が重視され，患者の受療行動は医療の情報不足から本来の医療ニーズとは乖離して大病院志向となる。本来，大病院を受診する必要のない患者までが大病院に集中するため，大病院では外来の混雑と待ち時間の延長，短時間診療と説明不足という患者の不満，不信感を生んでいた。同時に病院勤務医師の負担増，疲弊にもつながり，患者，医療者双方にストレスが増幅されていた。

2．今回の改革案，新しい医療計画

患者の視点から患者を適切に導く調整機関を創設し，医療の継続性と一貫性を確保することを提案している。中立公正な調整機関が患者からの相談に応じ，患者の納得と安心を確保し必要に応じた適切な医療に導く。疾患ごとにかかりつけ医の役割と医療ニーズ，患者ニーズ（受療行動）を調整する機関の役割と連携の具体的なあり方が例示されている[1]。がん医療の場合は他疾患に先行し具体的な施策が公表された。がん診療連携拠点病院の整備に関する指針[2]，がん対策基本法[3,4]が決定されるに至り，「患者と医療提供者を調整する組織の役割」が「相談支援機能を有する部門（相談支援センター等）を設置」として連携体制のなかに位置付けられた。すなわち患者自身が客観的な医療情報の提供を受けて個別の問題にも身近に相談に応じてもらえる「相談支援機能を有する部門（相談支援センター等）」の設置が拠点病院の要件に加えられた。

「相談支援機能を有する部門（相談支援センター等）」の業務は以下の 8 項目である[5]。

ア　各がんの病態，標準的治療法などがん診療に係る一般的な医療情報の提供

イ　地域の医療機関や医療従事者に関する情報の収集，紹介

ウ　セカンドオピニオンの提示が可能な医師の紹介

エ　患者の療養上の相談

オ　患者，地域の医療機関，かかりつけ医（特に紹介元・紹介先の医師）などを対象とした意識調査

カ　各地域における，かかりつけ医など各医療機関との連携事例に関する情報の収集，紹介

キ　アスベストによる肺がん及び中皮腫に関する医療相談

ク　その他，相談支援に関すること

II．四国がんセンターにおける「がん相談支援・情報センター」の立ち上げと活動

四国がんセンターは平成 14 年 3 月に旧地域がん診療拠点病院の指定を受けていたが，平成 18 年 4 月の新築移転を契機に，「相談支援機能を有する部門」に相当する「がん相談支援・情報センター」を立ち上げた。それまでに個々に異なる経緯で設けていた医療連携室，よろず相談室，患者相談室，退院調整部門を統合し，「相談支援機能を有する部門」として組織改編したものである。当院の規模は入院 405 床（緩和ケア 25 床，ICU 4 床），平均在院日数 21 日，病床稼働率 92%，入院患者のがん占有率 95%，外来患者数 500 人/日，医師数 70 名（レジデント 20 名を含む），看護師数 266 名（非常勤を含む，専門看護師 1 名，認定看護師 9 名），往診・訪問診療・訪問看護体制なし，であるが，今回立ち上げたがん相談支援・情報センターの構成と機能を示して患者視点を重視した医療連携，患者サポートのあり方を例示する。

1．四国がんセンターがん相談支援・情報センターの構成

がん看護専門看護師 1 名，看護師 2 名（以上常勤職員），メディカルソーシャルワーカー 1 名，事務職員 2 名（以上

表 1 がん相談支援・情報センター活動状況

		H 18/4月	5月	6月	7月
医療相談	電話/対面	156/39	136/53	322/52	377/58
よろず相談	電話/対面	44/50	11/31	8/60	10/56
退院調整	新規/継続	22/71	25/68	27/110	22/101
	他施設合同カンファ		0	12	3
在宅療養支援	新規/継続	18/18	8/39	3/47	11/49
	電話サポート	62	38	18	25
	入院調整	3	4	0	1
情報発信提供		0	0	0	0
医療連携	セカンドオピニオン	18	36	29	31
	FAX 紹介/直接紹介	248/108	277/95	309/115	312/94
	転入調整		8	7	8
	逆紹介		20	29	38
	他施設から問合わせ	183	178	116	111

非常勤職員），臨床心理士1名（週1日，6時間）の陣容である。統括診療部長がセンター長(併任)，外来部長が室長（併任）として運営に加わり，現場のリーダーはがん看護専門看護師(専任)である。2名の看護師(副師長)は病棟からの出向で確保した（専任1名，医療情報管理室との併任1名）である。

2．業　務

1）医療相談，よろず相談: 対面相談および電話相談。当院通院中の患者だけでなく，一般からの相談も対応。

2）退院調整: 退院困難例に対して病棟と協同し入院早期より介入。

3）在宅療養支援: 外来通院中，在宅療養中の患者に対する療養支援，電話サポート。

4）医療連携: セカンドオピニオン，地域の医療機関からのFAX紹介受け入れ，外来診察予約・画像検査予約，訪問看護ステーションなどとの調整。なお，相談を伴わない単純な外来予約は別部門の「予約コーナー」で対応。

5）情報発信・情報提供: がん患者数，治療症例数についての情報公開。またパンフレットやクリニカルパスなどの情報提供。ただしこの活動はまだ開始できていない。

3．活動（表1)。

400件/月を超える医療相談に対応している。セカンドオピニオン対応は，5月からの有料化(1件1万円，30〜60分）に関係なく件数は増加している。外部医療機関からの患者受診紹介は，FAX受信後20分以内に紹介元へ連絡する。なお，外部との相談や連携については必要に応じて院内各部門との間でも連携し調整している。

III. 情報ネットワーク化への期待と地域医師会を軸にした医療連携推進

患者は情報を欲している[6-8]。患者の知りたい客観的情報の一つとして医療機関などの医療機能に関する情報がある。自分に必要な医療がどこで受けられるかの情報である。がん対策基本法では「国及び地方公共団体は，がん医療に関する情報の収集及び提供を行う体制を整備するために必要な施策を講ずる」ことが定められ，附帯決議に「各がん専門医療機関の専門分野，専門的な知識及び技能を有する医師その他の医療従事者の数や設備の状況などの医療機能情報が，患者の視点に立って適切に提供される体制を整える」と掲げられている。今後，医療機関の機能について調査が行われ，患者が受診医療機関を選択する際の選択基準として公表されることになるが，都道府県の責務として実施されるという以外実施に至る道筋は示されていない。他方，平成13年からのIT基盤整備[9]で，IT化による構造改革と具体的成果を期待される分野には常に医療があげられている。レセプト請求オンライン化や電子カルテ化とともに地域の医療機能の共有は情報化に期待される大きな目標である。しかし，現実には医療の情報化は遅れている[10,11]。

われわれは平成7年から愛媛県医師会，松山市医師会でインターネットの活用を進めてきた。その一端を紹介する。愛媛県医師では医師会館にサーバー室を設け，ブロードバンドインターネット環境下にVPN技術（ルータ間VPN，ソフトウエアVPN）でセキュリティを確保して，医師会イントラネットへのアクセスが可能な仕組みを構築している。すべての郡市医師会と救急医療基幹施設，診療所の300施設が常時接続，ダイアルアップ利用を加え500施設が参加，アカウント登録は1,100名以上（病院勤務医師は病院独自のアカウントでの利用も可能）の規模である[12-14]。現在は理事会運営をはじめ多くの事業がメール，メーリングリスト中心に動いている。ホームページ情報提供，郡市医師会向けハウジングサービス，web mail患者紹介状システム，医師と医療機関のデータベースなどが活用されている。医療機関データ

ベースの一部は公開されている。地域の医療機能を共有するツールとして威力を発揮しつつある。しかし，全国的にみればこのような医師会ネットワークは例外的な存在である。全国的に医療機能などの情報共有の点でインターネットが効果を発揮できるようになるのはまだ先の話である。厚生労働省，日本医師会のリーダーシップを期待したい。

同時に医療機能情報の共有には日常の地道な医療連携推進活動が必要である。松山市医師会では平成10年から病診連携委員会，12年から在宅医療検討委員会を立ち上げ，各医療機関の医療連携室と共同歩調をとってきた。平成10年からは域内医療機関の機能，在宅医療対応の情報がイントラネットから検索閲覧可能である（冊子としても配布している）。在宅医療懇話会（コメディカルも参加，3回/年，参加者は毎回100～200名），在宅医の会（在宅医療に関心のある医師のみ，3回/年，参加者は毎回30～50名）などの定期的な講習会・勉強会も開催し，その後の意見交換会，懇親会なども顔のみえるつながりとして重視している。

IV. 考　察

今後の医療は医療連携体制を軸に進められていく。医療連携は病院の地域における医療機能を再編していくだけでなく，病院内の部門間連携も再編していく。能力を結集して医療連携部門の拡充を図るべきである。

世界的にみれば日本の医療は高い客観的評価を受けながら（WHO 2000年報告書），患者満足度が低いという不名誉なレッテルを貼られている（OECDの2003年調査，国民が自国の医療をどう評価しているか，18か国中17位）[15]。今回の医療法改正の方向性，がん対策基本法などは正にその反省に基づいている。「風邪なんかで来ないで近くにかかりなさい」とか「もうすることがなくなったから近くの医療機関に行きなさい」などという言葉は，病院医師からしばしば発せられてきた言葉ではないだろうか。しかし患者の立場からみれば「風邪でもがんかもしれない」と心配で受診したのであり，「もう治療できないといわれても誰に頼ればいいのか」など不安を抱えて路頭に迷わせられている。確かに医療ニーズの観点からは医師の言い分は間違っていないが，患者にしてみればいかにも無責任である。新しい医療計画で患者視点が重視されたのはそういう経緯によっている。患者の立場と医療者の立場のギャップを埋める役割を担う機関として新たに「調整する組織」が提案された。患者が納得の下に必要な医療が継続的に受けられることを目指している。かかりつけ医機能を補完する役割を大いに期待したい。医療制度改革では相談対応が公的な中立の別組織として想定されている[16]が，これは介護保険における地域包括支援センターからの連想である。創設されたばかりの介護保険制度と異なり，医療は個々の医療機関との密接な関係が必要である。相談支援組織（部門）は医療機関に付属する部門としての枠組みで整理，構築されていくであろう。

われわれのがん相談支援・情報センターの立ち上げと活動を踏まえて，問題点と今後解決すべき課題についてふれる。現在は当センターに寄せられる相談件数が急増し，マンパワーの不足が懸念されている。相談対応は潜在需要の掘り起こしであり，どの程度の人材を充てればよいかの判断は時期尚早であるが，拠点病院の指定条件にある「専任1名以上」というのは明らかに不足である。地域規模に合わせて必要数を算出することが重要である。また，このような部署は病院にとっては不採算部門とみなされがちであるが，部門単独で不採算という判断は意味がない。拠点病院としての病床回転率の改善，外来の活性化，患者満足度の向上，地域住民・患者への安心の提供などの効果は図りしれない。また，現在われわれの組織は院内各部門からの出向員で構成されているが，院内外への発言権を増して調整力を発揮するためには，部門としての独立が必要である。担当する現場には不測の事態にも対応できる高い問題解決能力が要求されており，それに見合う評価を与えるべきである。われわれは当面は眼前の相談対応に対応しつつ，相談内容の分析も踏まえて本来あるべき相談支援センターのモデルケースを示していきたい。

医療機能情報の収集・公開についてであるが，信頼性を確保した情報の収集，公表，管理には大きな労力と継続性が要求される。医師会は地域医療の中核として準公的な組織であり，立場上医療機関情報を収集しやすく，公平性も保ちやすい。調査機関，情報提供母体としては最も適している。ただし医師会の組織率からみて全国一律な対応は期待できず，地域特性に合わせて都道府県行政との共同作業が必要とされるであろう。また，調査による医療機能情報にまして重要なのは，実際の個別の医療連携体験に基づく生の情報である。調査で収集される情報は表向きの情報であり，実力としての医療機能は評価されていない。実例を通じて得た訪問看護師や在宅担当医の実力，患者の声は最も頼りになる情報である。患者に接し続ける相談支援・情報センターは公的な情報とは別に生の実力も把握し得る組織である。

インターネットによる情報化は重要である。われわれの地域医師会では巨大な医師会ネットワークの構築という幸運を得た。しかし，勤務医の平均年齢は42歳，開業医の平均年齢は58歳であり，デジタルディバイドは深刻

である[17]。また，情報化技術の難解さ，安くない情報化コストを考えると，医師会のように緩やかな結合で成り立っている団体で強制はできない。情報化においても個々の医療機関の自主性は尊重されるべきである。当面は「医療者向け情報，一般向け情報の発信に努めること」，「病診連携の中核（連携支援ツール）を提供すること」，「個々の医療機関IT化を支援すること」が重要であり，安全で容易なネットワークを用意し，情報化の利点を実感できるサービスを提供し続けることが重要である。慌てなくても遠くない将来，医療の情報化は必ず達成される。全国の各地域医師会で情報化へのひたむきな努力を続けている同志には励ましを送りたい。

まとめ

医療法改正の動き，がん対策基本法の制定から今後の医療連携のあり方を概括した。医療連携の核として「患者と医療提供者を調整する組織の役割」(相談支援機能を有する部門（相談支援センターなど）)のもつ意義と，医療機能情報の共有化の必要性，実現への方策を論じた。医療連携部門の拡充こそが地域医療，病院機能の効率化と活性化の要である。

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