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Appendix 1. The items of the stress inventory

(1) Do you tend to give priority to what you want to do even when there are many demands from people around you?
(2) Do you tend to talk to someone when you experience something heartbreaking?
(3) Do you have any circumstances or conditions that you have been very frustrated with for a long period of time?
(4) Do you often have feelings that change to the extremes; such as first looking at a person with much attraction, then later with distaste?
(5) Do you under all circumstances try to control your reasoning and avoid, as much as possible, being emotional?
(6) In your whole life, have you experienced outrage about something?
(7) Do you find it difficult to altogether forget about things that have made you very angry?
(8) Do you have a certain person with whom you cannot seem to develop a good relationship and who has caused you sadness and loneliness?
(9) Is there a certain person who, although they are a thing of the past, still so frustrates or angers you that they repeatedly come to mind?
(10) Do you tend to give up your own needs so as to get along well with others?
(11) Do you tend to think of your happiness first?
(12) Have you frequently had the experience of coming across an annoying matter about which you thought you might feel fine if only you could talk about it to someone, but in reality you could not?
(13) Even towards those who behave very offensively, do you try not to confront them emotionally by trying to understand them?
(14) Do you often see your feelings changing to the extremes by getting very upset with a certain person who is at other times very important to you?
(15) Do you have a certain person who makes you feel that you cannot be happy unless they are happy?
(16) Do you tend to talk to someone when you experience something difficult?

(17) Have you frequently had the experience of being angry about something and thought that talking about it to someone would make you feel fine, but in reality you found that difficult?
(18) Do you find it difficult to forget about things that were extremely tough on you?
(19) Do you have a certain person with whom you know you may never establish a good relationship, but you cannot stop trying?
(20) Is there a certain person who understands your feelings so little that you always get frustrated?
(21) In your whole life, have you experienced jumping for joy about something?
(22) Do you tend to give up what you really want to do in consideration of others?
(23) Are you the kind of person who places priority on your happiness above the happiness of others?
(24) Do you tend to talk to someone when you have something you are worried about?
(25) Have you had many experiences in which you came suddenly to dislike a certain person, which resulted in you leaving them, even though you had previously gotten along very well with them?
(26) Do you have any circumstances or conditions that you find deeply unpleasant because they cannot be changed?
(27) Even if your heart is very badly hurt by someone, do you try to be calm in your thinking and try not to criticize them in an emotional manner?
(28) Have you frequently had the experience of feeling distressed and wanting someone to share your feelings with, but in reality you found that difficult?
(29) Do you find it rather difficult to emotionally recover after experiencing something very disappointing?
(30) Do you have a certain person who, among those you are separated from or who have passed away, you could not forget about?
(31) Do you time and again get upset over a certain person when you think about them?
(32) In your whole life, have you experienced deep sorrow about something?
(33) Do you tend to have troublesome matters on your hands often?
(34) Even if someone does a terrible thing to you, do you try not to become emotional and try to deal with the situation within the boundaries of commonsense?
(35) Do you try to stay away as much as possible from relationships from which you do not gain anything?
(36) Do you often change your attitude towards a certain person who is important to you, being kind to them and then being harsh?
(37) Do you have a certain person who makes you feel you cannot be happy without them?
(38) Do you tend to talk to someone when you are experiencing something unpleasant?
(39) When you are put into a position where you become very angry, do you often think that you cannot change the situation?
(40) Do you often feel heartbroken when remembering a certain person?
(41) Have you frequently had the experience of being distressed and thinking that talking to somebody would lighten your mind, but in reality you could not?
(42) In your whole life, have you experienced heart thumping happiness about something?
(43) Is there a certain person who always frustrates you because they seldom change their attitude?
(44) Do you often feel that you cannot be yourself and behave more freely, even though you want to?
(45) Even if someone does a terrible thing to you, are you the kind of person who cannot be emotional in front of people, even in front of family members?

Appendix 2. Brief description of the stress inventory (SI) scales and their hypothesized disease-proneness

The SI scales[1]	Brief descriptions	Disease proneness		Item No.[2]
		Cancer	CHD	
Group 1: Sense of control over stressful situations				
Low sense of control[4]	Decreased sense of control over stressful situations leading to hardship, despair, or anger.	•	•	7, 18, 29, 39
Group 2: Emotional well-being dependent on other persons and situations				
Object-dependence/loss[4]	Having an important person who causes persistent hopelessness and depression.	•		8, 19, 30, 40
Object-dependence/happiness[4]	Having a valued person on whom one's happiness is greatly dependent.	•		15, 37
Object-dependence/anger	Having a persecuting person who causes chronic irritation and anger.		•	9, 20, 31, 43
Annoying barrier	Having a persecuting situation that causes chronic irritation and anger.		•	3, 26
Object-dependence/ambivalence[5]	Repeatedly experiencing ambivalent interpersonal relationships.	○	○	4, 14, 25, 36
Group 3: Telling problems to others and unfulfilled needs for acceptance by others				
Disclosure of negative experiences	A tendency to disclose one's experiences with negative feelings to others.			2, 16, 24, 38
Unfulfilled needs for acceptance[3]	Chronically having unfulfilled needs for acceptance by others.	•		12, 17, 28, 41
Group 4: Self-defensiveness in conflicting interpersonal situations				
Altruism[3]	An altruistic tendency, accompanied by stress, in interpersonal and social relationships.	•		10, 22, 33, 44
Egoism[5]	A self-defensive, self-interest-oriented attitude in interpersonal and social relationships.	○	○	1, 11, 23, 35
Rationalizing conflicts/frustrations[3]	An extreme tendency to rationalize one's interpersonal situations accompanied by conflicts or frustrations.	•	•	5, 13, 27, 34, 45
Group 5: Lacking experiences with strong positive and negative emotions				
Lack of emotional experiences	Lack of experiences with strong emotions such as grief, rage or delight.			6, 21, 32, 42

CHD, coronary heart disease; •, increased risk; ○, decreased risk. [1]The SI items and relevant scales were grouped into five in the process of their development. [2]See Appendix 1. Scales related to [3]emotional suppression, [4]loss-hopelessness and [5]hysterical personality.

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FROM THE ASCO-JSCO JOINT SYMPOSIUM

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Current status of chemoradiotherapy for locally advanced pancreatic cancer in Japan

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Abstract Although the results of randomized controlled trials for locally advanced pancreatic cancer conducted between 1969 and 1988 demonstrated a survival advantage for concurrent radiotherapy and bolus 5-fluorouracil (FU) injection, the prognosis of patients with this disease remains very poor. In an attempt to improve patient outcome after chemoradiotherapy, various clinical trials for this disease have been conducted in Japan. These trials were designed to evaluate novel chemotherapy regimens combined with conventional radiotherapy, or intensive radiotherapy in combination with chemotherapy. After gemcitabine was shown to yield a better survival outcome than 5-FU in patients with advanced disease, this drug was investigated as a chemotherapeutic agent and/or radiosensitizer for locally advanced pancreatic cancer in a number of trials. S-1, a novel oral fluoropyrimidine derivative that appears promising for the treatment of metastatic disease, is also being intensively evaluated in Japan for the treatment of locally advanced pancreatic cancer. In this review, we summarize recent treatment strategies that are being used in Japan with the goal of establishing a new standard therapy for locally advanced pancreatic cancer.

Key words Pancreatic cancer · Chemoradiotherapy · Gemcitabine · S-1

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Introduction

Pancreatic cancer accounts for only 3% of all cancers but it is now the fifth leading cause of death from cancer in Japan.[1] These statistics indicate a rapid increase in the number of deaths and the death rate as a result of pancreatic cancer in Japan, but the precise reasons for these trends are not clear, with the exception of the contribution of smoking. The prognosis of patients with this disease is extremely poor, with fewer than 5% of patients alive 5 years after their diagnosis.[2] Of all the treatment modalities available for pancreatic cancer, only resection offers the opportunity for a cure. However, approximately half of all patients already have metastases at the time of their diagnosis, and approximately one-third of patients are diagnosed as having locally advanced disease, whereas only a small proportion of patients are eligible for surgery. Even in patients with resectable disease, the long-term outcome remains unsatisfactory because of early recurrence after resection. To improve the prognosis of these patients, the development of effective nonsurgical treatments is essential.

Concomitant chemoradiotherapy combines the modalities of radiation therapy with chemotherapy in an attempt to control local disease and counteract systemic tumor spreading. Chemoradiotherapy is the treatment of choice for locally advanced disease and as an adjuvant therapy for resectable disease. However, its use has been intensively investigated in Japan mainly for patients with locally advanced stages of pancreatic cancer, whereas chemother-

Table 1. Results of randomized controlled trials of treatment for locally advanced pancreatic cancer

Author Year	Regimen	Maintenance chemotherapy	Number of patients	Median survival time	*P* value
Moertel[3] 1969	Chemoradiotherapy (35–40 Gy + 5-FU)	–	32	10.4 Months	<0.05
	Radiotherapy alone (35–40 Gy)	–	32	6.3 Months	
GITSG[4] 1981	Chemoradiotherapy (40 Gy + 5-FU)	5-FU	28	42.2 Weeks	<0.01
	Chemoradiotherapy (60 Gy + 5-FU)	5-FU	31	40.3 Weeks	<0.01
	Radiotherapy alone (60 Gy)	5-FU	25	22.9 Weeks	
Klaassen (ECOG)[5] 1985	Chemoradiotherapy (40 Gy + 5-FU)	5-FU	47	8.3 Months	NS
	Chemotherapy alone (5-FU)	5-FU	44	8.2 Months	
GITSG[6] 1988	Chemoradiotherapy (54 Gy + 5-FU)	SMF	22	42 Weeks	0.02
	Chemotherapy alone (SMF)	SMF	21	32 Weeks	
Cohen (ECOG)[7] 2005	Chemoradiotherapy (59.4 Gy + 5-FU + MMC)	–	55	8.4 Months	0.16
	Radiotherapy alone (59.4 Gy)	–	49	7.1 Months	
Chauffert[8] 2006	Chemoradiotherapy (54 Gy + 5-FU + CDDP)	GEM	59	24%*	0.03
	Chemotherapy alone (GEM)	GEM	60	51.4%*	

ECOG, Eastern Cooperative Oncology Group
GITSG, Gastrointestinal Tumor Study Group
CDDP, cisplatin
GEM, gemcitabine
5-FU, 5-fluorouracil
MMC, mitomycin-C
SMF, streptozotocin, mitomicin-C, and 5-fluorouracil
NS, not significant
*1-Year survival rate

apy has been investigated mainly as an adjuvant therapy. In this review, we will discuss recent treatment strategies that are being used in Japan to improve the prognosis of patients with locally advanced pancreatic cancer.

Summary of randomized controlled trials conducted in Western countries (Table 1)

Randomized controlled trials reported before 1990

In 1969, Moertel et al.[3] reported the results of the first randomized controlled trial to evaluate the efficacy of chemoradiotherapy for the treatment of locally advanced pancreatic cancer. In that study, 64 patients were randomized to a group receiving radiation therapy (35–40 Gy) plus 5-fluorouracil (FU) or a radiation therapy-alone group. The overall survival in the chemoradiation group was significantly better than that in the radiation group ($P < 0.05$); the median survival times were 10.4 and 6.3 months, respectively. In a second randomized controlled trial, conducted by the Gastrointestinal Tumor Study Group (GITSG), both high-dose (60 Gy) radiation plus 5-FU and moderate-dose (40 Gy) radiation plus 5-FU produced a highly significant survival improvement when compared with radiation alone (60 Gy); the median survival times were 42.2, 40.3, and 22.9 weeks, respectively ($P < 0.01$).[4] The Eastern Cooperative Oncology Group (ECOG) conducted a study comparing radiation therapy (40 Gy) plus 5-FU to chemotherapy with 5-FU alone, but they did not obtain a significant survival difference.[5] The median survival times were 8.3 months in the chemoradiation group and 8.2 months in the chemotherapy group. GITSG reported the results of another randomized controlled study indicating a significant survival advantage for the combination of radiation with 5-FU (median survival time, 42 weeks) over multiagent chemotherapy alone with streptozocin, mitomycin C, and 5-FU (median survival time, 32 weeks, $P < 0.02$).[6] Based on these three positive results among the four randomized controlled studies, chemoradiotherapy with 5-FU has been regarded as a standard treatment for locally advanced pancreatic cancer. Since the 1990s, numerous clinical trials of chemoradiotherapy have been conducted in many countries, including Japan.

Recently reported randomized controlled trials

In 2005, ECOG reported the results of another randomized study comparing 59.4-Gy radiation therapy plus 5-FU and mitomycin C to radiation therapy alone.[7] This study demonstrated no difference in overall survival time between the combination and radiation therapy-alone arms, with median survival times of 8.4 vs 7.1 months, respectively ($P = 0.16$). At the American Society of Clinical Oncology Annual Meeting in 2006, a French group reported an inferior outcome with 60-Gy radiation therapy plus 5-FU and cisplatin to chemotherapy with gemcitabine alone.[8] Both of these recently reported randomized controlled trials failed to confirm a survival advantage of combined radiation and chemotherapy over either radiation or chemotherapy monotherapy.

Recent strategies in Japan for improving therapeutic results in patients with locally advanced pancreatic cancer

Since the 1990s, various clinical trials of treatments for locally advanced pancreatic cancer have been performed in

Japan. Most of them were phase II studies using chemoradiotherapy in an attempt to improve the results of radiation plus 5-FU that were demonstrated in the early Western studies. The main strategies for improving the efficacy of chemoradiotherapy have involved two approaches: improving the chemotherapy or improving the radiotherapy.

Trials of chemoradiotherapy with novel chemotherapy regimens

In the early Western randomized controlled studies that showed a survival advantage with chemoradiotherapy, 5-FU was commonly administered as a bolus injection. 5-FU is an antimetabolite with a very short plasma half-life, and its major cytotoxicity occurs during the S-phase. Therefore, protracted infusion increases the percentage of tumor cells exposed to 5-FU. To intensify systemic chemotherapy during the treatment of locally advanced pancreatic carcinoma, a phase II trial of protracted 5-FU infusion with concurrent radiation was conducted.[9] Unfortunately, the 10.3-month median survival time in this study was almost the same as those in the previous studies, although the toxicity seemed to be milder. A retrospective study of a protracted FU infusion regimen in the United States also resulted in less toxicity, compared with that for a bolus infusion regimen.[10]

Radiation with protracted 5-FU infusion was compared with best supportive care in a small randomized trial in which survival and quality of life were used as the outcome measures.[11] Both survival and the Karnofsky score were significantly better in the chemoradiation group; the median survival period for the therapy group was 13.2 months, compared with 6.4 months for the best supportive care group. After the promising results shown by these trials,[10,11] protracted 5-FU infusion with concurrent radiation became widely employed as a practical standard treatment regimen in Japan.

Cisplatin is a chemotherapeutic agent that is used to enhance radiation-induced damage to tumors. The administration of cisplatin immediately before or shortly after daily irradiation is considered to produce the most significant damage to tumor cells. However, a cooperative phase II study of radiotherapy with daily cisplatin, conducted in Japan, resulted in a disappointing median survival time of 7.7 months.[12]

Gemcitabine, which has demonstrated a significant clinical benefit and survival improvement compared with 5-FU in patients with advanced pancreatic cancer, has also been shown to be a potent radiosensitizer in human pancreatic tumor cell lines. A phase I trial determined the recommended dose of weekly gemcitabine for a phase II chemoradiotherapy trial to be 250 mg/m^2.[13] Radiotherapy combined with gemcitabine in a phase II study had moderate activity; the median survival time was 9.5 months, but the toxicity was relatively severe and one patient died as a result of duodenal bleeding and sepsis.[14,15] Furthermore, 97% of the patients exhibited distant metastasis as the cause of the initial disease progression. To further explore innovative approaches, we concluded that future investigations of treatments with more systemic effects and lower toxicity were needed.

On the other hand, another phase II trial of radiation with weekly (250 mg/m^2) gemcitabine showed very promising results, with a median survival time of 17 months and an acceptable toxicity profile.[16] A small phase III study conducted in Taiwan, comparing gemcitabine-based chemoradiation to 5-FU-based chemoradiation, indicated a significant superiority in survival for the gemcitabine-based regimen.[17] Further studies are needed to confirm these favorable results for radiotherapy plus gemcitabine, because the median survival of 6.7 months for the group receiving the 5-FU-based regimen in the Taiwan study was relatively poor compared with historical data.

S-1 is a novel orally administered drug (a combination of tegafur, 5-chloro-2, 4-dihydroxypyridine, and oteracil potassium), which potentiates the antitumor activity of 5-FU and reduces gastrointestinal toxicity. S-1 has promising antitumor activity against metastatic pancreatic cancer,[18,19] and because it is taken orally, it is much more convenient to administer than an intravenous 5-FU infusion. This agent has been extensively evaluated for the treatment of locally advanced disease, and several phase I studies of S-1 combined with radiotherapy have been conducted in Japan.[20–22] A multi-institutional phase II trial of this combination therapy is now underway.

Trials of intensive radiotherapy combined with chemotherapy

Several trials have attempted to improve chemoradiotherapy by enhancing the radiation dose, because an improvement in local control may translate into prolonged survival. Intraoperative radiation therapy (IORT) and conformal external-beam radiation therapy plus protracted 5-FU infusion were evaluated in a phase II study; IORT allows a high dose of irradiation to be delivered to the primary tumor without damaging the tissues surrounding the pancreas.[23] In one-third of the enrolled patients with locally advanced pancreatic cancer, metastatic spread was detected in the abdominal cavity during a laparotomy performed prior to IORT. Unfortunately, the combination of intraoperative and external-beam radiation with 5-FU resulted in a poor survival outcome: the median survival times were 7.8 months for all of the enrolled patients, 12.9 months for the patients without metastatic spread, and 5.8 months for those with metastatic spread.

Hyperfractionated radiation is another treatment option; one possible advantage of this approach is that it may permit an improvement in tumor control by increasing the total tumor dose without increasing the risk of late complications. In a phase II study, hyperfractionated radiation therapy with protracted 5-FU infusion enabled good local control, with a 40% response rate and a 13.2-month median survival time.[24] However, this combined regimen is unlikely to become an alternative to conventional chemoradiotherapy because it increased severe nonhematological toxicity,

including the development of treatment-resistant gastric ulcers in two patients, as late complications.

Carbon ion radiotherapy, which is the most effective modality for dose-localization, is currently being investigated in clinical trials for the treatment of a variety of malignancies, including pancreatic cancer. In a dose-escalation study of carbon ion radiotherapy alone, the dose was escalated from 38.4 Gy to 48.0 Gy in 5% increments. The 1-year survival rate was 44.4% for the 31 enrolled patients with locally advanced pancreatic cancer.[25] The results of this study suggested the potential activity of this treatment modality, and a subsequent trial of carbon ion radiotherapy with the concomitant use of gemcitabine is underway.

Trials of chemoradiotherapy with induction chemotherapy

A subset of patients with locally advanced pancreatic cancer develop metastases within a few weeks and die very quickly, regardless of the type of treatment that they undergo. Chemoradiotherapy is a time-consuming and constraining therapy with adverse effects.[26] To select patients who might benefit from chemoradiation, several groups are investigating the use of initial induction chemotherapy prior to chemoradiotherapy. An early phase II study was conducted to examine the efficacy of gemcitabine plus S-1 chemotherapy for 12 weeks prior to short-course radiation (30 Gy delivered over 2 weeks) with concurrent weekly doses (250 mg/m^2) of gemcitabine, followed by maintenance gemcitabine at a dose of 1000 mg/m^2.[27] This multimodal treatment produced encouraging results, with a median survival time of 14.4 months in the 20 enrolled patients. Another regimen containing induction chemotherapy is being explored. In this phase II study (The Japan-Multinational Trial Organization [JMTO] RO04-01), gemcitabine is administered weekly at a dose of 1000 mg/m^2 for 3 weeks, followed by weekly gemcitabine at a dose of 250 mg/m^2 combined with accelerated hyperfractionated radiotherapy (45 Gy) for 3 weeks. A prospective phase III study is warranted to confirm the advantages of including induction chemotherapy in treatment strategies.

New trials evaluating chemoradiotherapy versus chemotherapy alone

Gemcitabine has improved the outcome of patients with advanced pancreatic cancer, including those with both locally advanced and metastatic diseases, by improving survival with a significant clinical benefit.[28] Since the introduction of gemcitabine in Japan in 2001, many arguments have been made for and against radiotherapy as a partner to chemotherapy for the treatment of locally advanced pancreatic cancer. Clinical trials are being conducted in Japan to evaluate radiotherapy's therapeutic contribution when used in conjunction with chemotherapy. In a randomized phase II study, 72 patients were randomized to either a chemoradiotherapy with gemcitabine and conventional radiation arm or a gemcitabine-monotherapy arm. In the chemoradiotherapy group, limited-field irradiation, using three-dimensional radiotherapy planning, and concurrent gemcitabine (1000 mg/m^2) were delivered.[29] The results of this study are expected to be available in the near future. The Japan Cooperative Oncology Group (JCOG) is also conducting a phase II trial of gemcitabine monotherapy to clarify the outcomes for locally advanced disease, prior to an anticipated phase III study comparing chemotherapy with gemcitabine vs conventional chemoradiotherapy.

Conclusion

After the significant survival benefits of combination therapy consisting of external fractionated radiation and 5-FU infusion were demonstrated in Western phase III studies conducted between 1969 and 1988, this treatment modality became a standard treatment for locally advanced pancreatic cancer throughout the world, including Japan. Recent phase III trials, however, have failed to confirm a survival advantage for 5-FU-containing chemoradiotherapy, and a globally accepted standard therapy for locally advanced pancreatic cancer has not been identified. Gemcitabine, which is used in chemotherapy or in combination with radiation, may be a key agent in the creation of a novel treatment standard, and S-1 is being extensively evaluated with much anticipation in Japan. High-quality, multicenter randomized controlled trials are warranted, and we hope that such studies will result in the establishment of a global standard for the treatment of locally advanced pancreatic cancer.

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Ultrasound-guided percutaneous pancreatic tumor biopsy in pancreatic cancer: a comparison with metastatic liver tumor biopsy, including sensitivity, specificity, and complications

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Background. The aims of this study were to investigate the diagnostic value and safety of ultrasound-guided percutaneous pancreatic tumor biopsy (pancreatic biopsy) in patients with suspected unresectable pancreatic cancer, and to compare the data with those obtained by metastatic liver tumor biopsy (liver metastases biopsy). ***Methods.*** Data were collected retrospectively from 388 patients (398 procedures) for whom a final diagnosis was available and who underwent ultrasound-guided pancreatic or liver metastases biopsy with a 21-gauge needle (core biopsy) or a 22-gauge needle (fine-needle aspiration biopsy: FNAB). The sensitivity, specificity, and accuracy of pancreatic and liver metastases biopsies were evaluated. Biopsy-related complications were collected and analyzed. ***Results.*** Data from 271 pancreatic and 112 liver metastases biopsy procedures were available. For pancreatic core biopsy and FNAB, the sensitivity, specificity, and accuracy were 93%, 100%, and 93%, and 86%, 100%, and 86%, respectively, all of which were comparable to those of liver metastases biopsy. The complication rate in pancreatic biopsy was 21.4%, including a 4.4% incidence of post-biopsy ephemeral fever. The complication rate in liver metastases biopsy was 38.7%, including an 8.0% incidence of ephemeral fever. Fever and infection occurred more frequently among patients who underwent liver metastases biopsy (4.4% vs. 11%; $P = 0.038$). In pancreatic biopsy cases, a prebiopsy high serum total bilirubin level was a statistically significant predictor of ephemeral fever. ***Conclusions.*** Ultrasound-guided percutaneous pancreatic biopsy is an effective and safe modality for confirming the pathologic diagnosis in patients with unresectable pancreatic cancer.

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Key words: pancreatic cancer, biopsy, sensitivity, complications, fever

Introduction

The majority of patients with pancreatic cancers have metastatic or locally advanced disease at the time of diagnosis, and are not candidates for surgical resection. In such patients with unresectable disease based on imaging findings, it is important to verify the histopathologic diagnosis of cancer before starting nonsurgical treatment, so as to exclude patients with pseudotumors or benign diseases from inappropriate aggressive therapies such as chemotherapy and radiotherapy. It is also important to distinguish pancreatic cancer with predominantly exocrine differentiation from others, such as cancer with endocrine differentiation or lymphoma, because their treatment strategy and tumor biology are completely different.

Pancreatic biopsy is a common procedure for obtaining histological specimens for diagnosis of a pancreatic mass. It can be performed endoscopically, intraoperatively, or percutaneously with computed tomographic (CT) or ultrasound (US) guidance. In our department, US-guided percutaneous pancreatic tumor biopsy (pancreatic biopsy) is the preferred method in patients whose tumors are suggested to be unresectable from preoperative abdominal imaging, because it allows accurate placement of the biopsy needle tip during real-time imaging and is less invasive than an endoscopic procedure or diagnostic laparotomy.

However, the diagnostic value and safety of US-guided percutaneous pancreatic biopsy have not yet been fully evaluated in patients with unresectable pancreatic cancer. In the present study, we aimed to assess the sensitivity, accuracy, complication rate, and risk factors of this procedure in comparison with US-guided

metastatic liver tumor (liver metastases) biopsy, a common diagnostic procedure both in Japan and in other countries.

Patients and methods

Patients

We conducted a retrospective review of US-guided pancreatic or liver metastases biopsies performed during a 5-year period from January 1999 through December 2003. All patients were inpatients in whom preoperative abdominal imaging (dynamic CT or angiography) suggested that their pancreatic tumors were unresectable. Tumors encasing the celiac or superior mesenteric arteries or obstructing or bilaterally invading the portal vein were considered to be unresectable. Exclusion criteria were postoperative recurrence and pathological confirmation of cancer from biliary cytology, ascites cytology, or exploratory laparotomy.

For patients with both pancreatic tumor and liver metastases, the decision about which organ was to be targeted for biopsy was made by physicians on the basis of visualization of the lesion by transabdominal US, the patient's anatomy, and the physician's preference. The technique used for biopsy and the incidence of complications were reviewed from the clinical records. Coagulation measurements were performed before biopsy when the patient's history or presentation suggested an increased risk of bleeding, and we did not perform a biopsy if the results showed a bleeding tendency. We did not routinely use antibiotics prophylactically. A blood culture was routinely performed if patients had fever of ≥38.0°C after biopsy. All patients provided written informed consent for the biopsy procedures.

Biopsy techniques

In the case of both pancreatic biopsy and liver metastases biopsy, we used a convex probe or a linear-array probe, both of which were equipped with a guide attachment, and we performed biopsy with continuous real-time monitoring. The most appropriate approach was chosen after local sterilization with povidone–iodine, which was also used as the contact medium for the US probe. Local anesthesia was administered in all cases. The medial approach was always used for pancreatic biopsies. For liver metastases biopsies, in principle, the intercostal approach was used for tumors located in the right lobe and the medial approach for tumors in the left lobe. In pancreatic biopsies, the needle occasionally passed through the stomach. All patients who underwent pancreatic biopsy fasted from the night before the biopsy until after the biopsy itself to obtain good visualization of the pancreatic mass and to reduce the risk of peritonitis as a complication.

We used two types of needle, a 21-gauge needle (Sonopsy-C1; Hakko, Tokyo, Japan) for tissue core biopsy to obtain both pathologic and cytologic materials, and a 22-gauge needle (15cm PTCD needle; Top, Tokyo, Japan) for aspiration biopsy to obtain cytologic material. The physician who performed the biopsy selected the more appropriate needle on the basis of US imaging and tumor size. The number of passes varied, but one or two passes were common. Biopsy material obtained from one pass was always checked macroscopically for adequacy before making the next pass.

When we performed core biopsies with the 21-gauge needle, the needle was advanced gently and withdrawn within the tumor lesion several times to obtain enough tissue for histologic diagnosis. Tissue core specimens were immediately preserved in 10% formalin, then the residual mucus was expressed onto glass slides, thin smears were prepared, and these were immersed in 95% ethanol. The needle tip was also cleansed in heparin-containing saline, and the wash-through fluid was examined cytologically.

We performed fine-needle aspiration biopsy (FNAB) with the 22-gauge needle. Once the needle had been placed within the lesion, the stylet was removed and suction was applied to the needle with a 20-ml disposable syringe. During the application of suction, the needle was gently advanced and withdrawn in the lesion several times. The aspirates were expressed onto glass slides and the needle tip was cleansed, as in the case of core biopsies.

Each pathologic diagnosis was determined by two or three pathologists specialized in pancreatic cancer and other cancers. A core sample was defined as tissue with preserved histologic structure. The final diagnosis was determined on the basis of autopsy or the clinical course of the patient. A diagnosis of benign pancreatic tumor was made together with a follow-up of at least 1 year during which there was no evidence of malignancy. The clinical course of the patient was used to confirm the histologic and cytologic diagnoses of malignancy.

Complications

We examined the clinical records of all patients in this study, and identified all complications such as pain, fever, and some infections. We defined pain as the need for additional analgesics after biopsy. Fever was classified into two categories: ephemeral fever and persistent fever. Ephemeral fever meant that patients had fever of ≥38.0°C within 24h after the biopsy, but just once and never again (without antibiotics). Persistent fever meant that patients had fever of ≥38.0°C of unknown origin for more than 2 days after the biopsy, without any clini-

cally or microbiologically documented infection. Antibiotics were not used for ephemeral fever, but they were used for persistent fever.

Statistical analysis

The biopsy procedure for each organ was analyzed with regard to its ability to accurately diagnose malignancy or a benign tumor, and its safety in terms of the incidence of post-biopsy complications. The sensitivity, specificity, and accuracy of biopsies were calculated including specimens inadequate for diagnosis that were considered negative for malignancy. Biopsy specimens of both exocrine and endocrine carcinoma, including those diagnosed pathologically as neuroendocrine tumor, were considered positive for malignancy. For continuous variables, comparisons were made by t test. For categorical data, frequency comparisons were performed by χ-squared test. Logistic regression analysis was used to identify potential predictors of complications. Statistical significance was established at the $P < 0.050$ level.

The sensitivity of biopsies was calculated as the ratio of [true positives] / [true positives + false negatives]. The specificity of biopsies was calculated as the ratio of [true negatives] / [true negatives + false positives]. The accuracy of biopsies was defined as the ratio of [true positives] + [true negatives] divided by the total number of biopsy procedures.

Results

Patient characteristics

The study comprised 388 patients with suspected pancreatic cancer (Fig. 1); 170 had an unresectable pancreatic mass alone, 178 had liver metastases, and 40 had metastases to sites other than the liver. Among them, 274 patients underwent US-guided pancreatic biopsy, 110 underwent US-guided liver metastases biopsy, and four underwent both procedures on two separate occasions (Fig. 1). Six patients underwent biopsy of the same organ on two separate occasions (pancreas in five patients, liver in one); these were counted as two separate procedures. Among a total of 398 biopsy procedures, 15 (12 pancreas, 3 liver) that were performed with both types of needle during the same procedure were

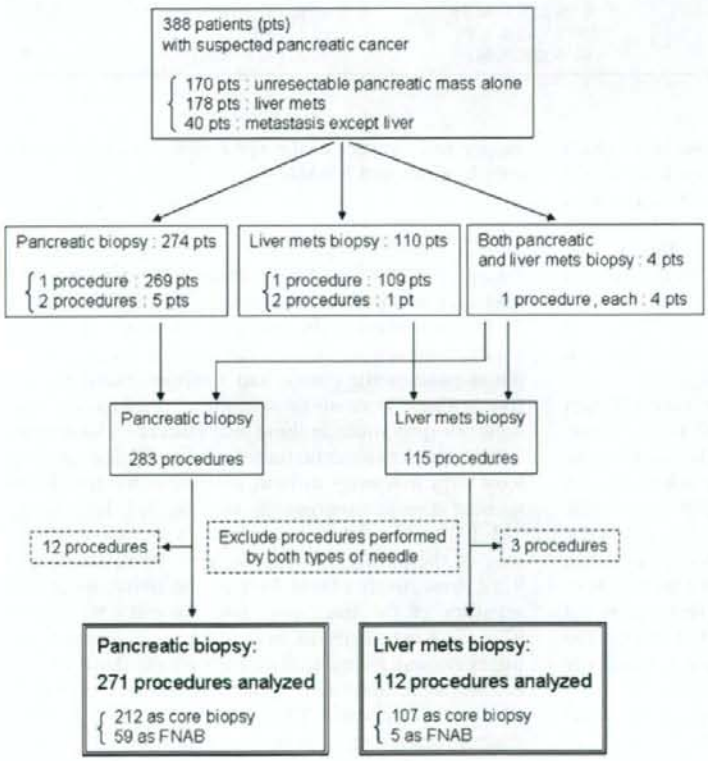

Fig. 1. A procedure-counting flow chart. "1 procedure" means that a patient underwent one organ biopsy on one occasion; "2 procedures" means that a patient underwent biopsy of the same organ on two separate occasions. We excluded procedures performed with both types of needle because it was impossible to determine which type provided the pathologic diagnostic material and produced the complications. Consequently, 271 (71%) pancreatic biopsy and 112 (29%) liver metastases (*mets*) biopsy procedures were performed. A total of 383 procedures were investigated and analyzed in this study. FNAB, fine-needle aspiration biopsy

Table 1. Patient demographics and clinical characteristics of targeted tumors

	Pancreatic biopsy			Liver metastases biopsy
	Total	Head	Body/tail	
No. of patients	266			111
Male	149			71
Female	117			40
Age, median years (range)	62 (32–86)			58 (37–79)
No. of biopsies, procedures	271			112
		106	165	
Mean tumor size, mm (SD)	42.2 (14.7)			26.2 (13.1)*
		37.0 (11.5)	45.6 (15.5)**	
Mean no. of passes	1.6			1.8
Core biopsy	1.6			1.8
FNAB	1.8			1.8

FNAB, fine-needle aspiration biopsy
* $P < 0.001$ vs. pancreatic biopsy
** $P < 0.001$ vs. pancreatic head biopsy

Table 2. Diagnostic value by site of biopsy in all 383 procedures

	Pancreatic biopsy	Liver metastases biopsy	*P* value
Final diagnosis			
Carcinoma, no. of procedures (patients)	266 (262)	112 (111)	
Benign disease, no. of procedures (patients)	5 (4)	0 (0)	
True positive, no. of procedures	244	109	
False positive, no. of procedures	0	0	
Sensitivity (95% CI)	92% (87.8–94.7)	97% (92.4–99.4)	0.713
Specificity (95% CI)	100% (47.8–100)	NE	
Accuracy (95% CI)	92% (88.0–94.8)	97% (92.4–99.4)	0.720

CI, confidence interval; NE, not evaluable

excluded because it was impossible to determine which type of needle had obtained the specimen from which pathologic diagnosis was made and which had caused any complications. Therefore, a final total of 383 biopsy procedures (271 pancreatic biopsy and 112 liver metastases biopsy procedures) were examined in the present study (Fig. 1).

At the time of analysis, 278 of the patients (73%) had died. The median follow-up time (from biopsy to death or the day to be censored) was 276 days.

In the pancreatic biopsy group, there were 149 men and 117 women with a median age of 62 years (range, 32–86 years) (Table 1). In the liver metastases biopsy group, there were 71 men and 40 women with a median age of 58 years (range, 35–79 years). In the pancreatic biopsy group, 106 targeted tumors were located in the pancreas head and 165 in the pancreas body and/or tail. The targeted tumors for pancreatic head biopsy were significantly smaller than those for pancreatic body/tail biopsy (37.0 mm vs. 45.6 mm; $P < 0.001$). The targeted tumors for liver metastases biopsy were significantly smaller than those for the pancreatic biopsies (26.2 mm vs. 42.2 mm; $P < 0.001$). There were no significant differences among the patient groups according to the site of biopsy with respect to the mean number of passes for core biopsies and FNABs.

Diagnostic value

Except for five procedures (four patients), the final diagnosis in all patients was pancreatic carcinoma (Table 2). The diagnoses of the four patients with benign pancreatic tumors were chronic pancreatitis (one), autoimmune pancreatitis (two), and retroperitoneal fibrosis (one). There were no false-positive histologic or cytologic interpretations in these four patients. The diagnosis of benign pancreatic tumor was confirmed again by long-term follow-up without anticancer treatment and without disease progression (median, 815 days; range, 322–1030). The sensitivity, specificity, and overall accuracy of the pancreatic biopsies were 92%, 100%, and 92%, respectively (Table 2). The sensitivity and overall accuracy of the liver metastases biopsies were both 97%. The specificity of liver metastases biopsies was not evaluated, because all patients who underwent liver metastases biopsy were finally diagnosed as having pancreatic carcinoma. There were no significant differences in sensitivity ($P = 0.713$) or accuracy ($P = 0.720$)

Table 3A. Diagnostic value of the core biopsy (21-gauge) by site and by type of specimen

Core biopsy (21-gauge) procedures	Pancreatic biopsy			Liver metastases biopsy (n = 107)
	Total (n = 212)	Head (n = 78)	Body/tail (n = 134)	
Tissue core specimen for histology				
Sensitivity (n)	77% (161/209)	68% (52/77)	83% (109/132)	84% (90/107)
Specificity (n)	100% (3/3)	100% (1/1)	100% (2/2)	NE (—)
Thin smears and needle-tip washing for cytology				
Sensitivity (n)	89% (187/209)	87% (67/77)	91% (120/132)	94% (101/107)
Specificity (n)	100% (3/3)	100% (1/1)	100% (2/2)	NE (—)

Table 3B. Diagnostic value by site and by type of biopsy needle

	Pancreatic biopsy			Liver metastases biopsy
	Total	Head	Body/tail	
Core biopsy (21-gauge) procedures[a]	n = 212	n = 78	n = 134	n = 107
Sensitivity (n)	93% (195/209)	90% (69/77)	96% (126/132)	97% (104/107)
Specificity (n)	100% (3/3)	100% (1/1)	100% (2/2)	NE (—)
Accuracy (n)	93% (198/212)	90% (70/78)	96% (128/134)	97% (104/107)
FNAB (22-gauge) procedures	n = 59	n = 28	n = 31	n = 5
Sensitivity (n)	86% (49/57)	85% (22/26)	87% (27/31)	100% (5/5)
Specificity (n)	100% (2/2)	100% (2/2)	NE (—)	NE (—)
Accuracy (n)	86% (51/59)	86% (24/28)	87% (27/31)	100% (5/5)

[a] Final diagnosis of core biopsy was defined as positive based on histological or cytological results

between pancreatic biopsy and liver metastases biopsy (Table 2).

Pancreatic biopsies yielded a sufficient amount of tissue to allow diagnosis in 93% of core biopsies, and an adequate yield of cells was obtained in 90% of FNABs. Liver metastases biopsies yielded a sufficient amount of material in 97% of core biopsies and in 100% of FNABs.

For procedures using the 21-gauge core biopsy needle, the sensitivity of the tissue core specimen for histology was 77% for pancreatic biopsy and 84% for liver metastases biopsy (Table 3A). The sensitivity of thin smears and needle-tip washing for cytology was 89% for pancreatic biopsy and 94% for liver metastases biopsy (Table 3A). When the result of the core biopsy procedure was defined as positive by histology or cytology, the total sensitivity, specificity, and accuracy were 93%, 100%, and 93%, respectively, for pancreatic biopsy and 97%, not evaluable, and 97%, respectively, for liver metastases biopsy (Table 3B).

For procedures using the 22-gauge aspiration biopsy needle (FNAB), the sensitivity, specificity, and accuracy were 86%, 100%, and 86%, respectively, and for pancreatic biopsy, and 100%, not evaluable, and 100%, respectively, for liver metastases biopsy (Table 3B).

There were no significant differences in sensitivity (core biopsy, $P = 0.810$; FNAB, $P = 0.819$) or accuracy (core biopsy, $P = 0.814$; FNAB, $P = 0.825$) between pancreatic biopsy and liver metastases biopsy according to the type of needle employed.

Complications

Regardless of the biopsy needle used, the proportion of patients with no complications was 79% for pancreatic biopsy and 75% for liver metastases biopsy (Table 4). There were no significant differences in the incidence of no complications ($P = 0.742$) or pain ($P = 0.999$). The total incidence of fever and infection, including ephemeral fever, cholangitis, and persistent fever, was significantly lower for pancreatic biopsy than for liver metastases biopsy ($P = 0.038$). None of the blood cultures collected from patients with fever and infection were positive.

For the core biopsy procedures, the incidence of pain was almost the same between pancreatic biopsy and liver metastases biopsy (Table 4). The incidence of ephemeral fever was lower for pancreatic biopsy (4.2%) than for liver metastases biopsy (7.5%), but not to a significant degree ($P = 0.252$). Cholangitis and persistent fever occurred only after liver metastases biopsy. For FNAB procedures, pain occurred only after pancreatic biopsy (15%). Cholangitis and persistent fever did not occur after either pancreatic or liver metastases FNAB.

There were no biopsy-related deaths, or life-threatening complications such as biopsy-related pan-

Table 4. Complications by site of biopsy

	Pancreatic biopsy	Liver metastases biopsy	*P* value
Core biopsy (21-gauge)	*n* = 212	*n* = 107	
No complication	168 (79%)	80 (75%)	
Pain[a]	38 (18%)	20 (19%)	
Ephemeral fever[b]	9 (4.2%)	8 (7.5%)	
Cholangitis	0	2 (1.9%)	
Persistent fever[c]	0	1 (0.9%)	
FNAB (22-gauge)	*n* = 59	*n* = 5	
No complication	47 (80%)	4 (80%)	
Pain[a]	9 (15%)	0 (0%)	
Ephemeral fever[b]	3 (5.1%)	1 (20%)	
Total	*n* = 271	*n* = 112	
No complication	215 (79%)	84 (75%)	0.742
Pain[a]	47 (17%)	20 (18%)	0.999
Fever and infection[d]	12 (4.4%)	12 (11%)	0.038*

*Statistically significant
[a] Patients needed additional analgesics after biopsy
[b] Patients had a single episode of fever of ≥38.0°C within 24 h after biopsy (without antibiotics).
[c] Patients had fever of ≥38.0°C of unknown origin for more than 2 days after biopsy, without clinically or microbiologically documented infection
[d] Includes ephemeral fever, cholangitis, and persistent fever

creatitis, macroscopic or symptomatic hematoma, or obvious needle-tract seeding.

Since ephemeral fever was the only clinically problematic complication of the pancreatic biopsy procedure that could reduce a patient's performance status, a logistic regression analysis was performed to examine the potential predictors of ephemeral fever in pancreatic biopsy cases. Potential predictors were the serum levels of total bilirubin (T-bil), aspartate aminotransferase, alanine aminotransferase (ALT), alkaline phosphatase, amylase, and C-reactive protein before biopsy, age, and size and location of the targeted pancreas tumor, which were considered to be related to retention of bile or pancreatic juice, or inflammation. Univariate analysis showed that T-bil ($P = 0.008$) and ALT ($P = 0.048$) before biopsy were significant predictors of ephemeral fever (Table 5). Multivariate analysis showed that only T-bil was a statistically significant predictor of ephemeral fever ($P = 0.006$, relative risk = 2.45; 95% confidence interval, 2.01–66.39).

Discussion

Because of dramatic developments in the technology of imaging diagnosis in the past decade, the resectability of pancreatic cancer can now be determined very accurately purely on the basis of diagnostic imaging techniques such as high-resolution spiral CT scan. However, histopathologic confirmation is necessary in patients deemed to have inoperable tumors or those who are medically unsuitable for surgery. In the National Comprehensive Cancer Network (NCCN) guidelines for pancreatic adenocarcinoma,[1] it is strongly recommended that all patients with unresectable pancreatic cancer should have cancer confirmation prior to nonsurgical treatment, and that a negative biopsy result should be confirmed by at least one repeat biopsy. Our present retrospective study demonstrated that US-guided percutaneous pancreatic biopsy is an effective modality for confirmation of the pathologic diagnosis in patients with unresectable pancreatic cancer. We also confirmed that it is as safe as liver metastases biopsy in these patients.

The reported sensitivity of US- or CT-guided percutaneous pancreatic biopsy procedures ranges from 80% to 97% with various types of needle.[2-6] The sensitivity observed in our study (92%, Table 2) is slightly higher than that reported in studies of US-guided biopsy studies.[5,6] This may be attributable to the design of our study, which yielded a high level of sensitivity for US-guided pancreatic biopsy. This was a retrospective study of all patients who underwent attempted biopsies of pancreatic masses by US, preselecting only those individuals in whom the mass could be seen, although in general US is often unable to visualize the pancreas completely.

Another selection bias was the fact that we usually selected FNAB from the viewpoint of safety when US visualization of the targeted pancreatic lesion was poor or unclear, and this may have lowered the sensitivity and accuracy of pancreatic biopsies in FNABs compared with core biopsies (86% vs. 93%, Table 3B), although not to a significant degree.

The complication rate associated with US- or CT-guided percutaneous pancreatic biopsy procedures is extremely low, ranging between 0% and 2%.[4,7-10] The

Table 5. Correlation of prebiopsy clinical data with ephemeral fever[a] after pancreatic biopsy

	Fever positive	
	No. of procedures (%)	*P* value*
Total bilirubin		**0.008**
≥2.0 mg/dl ($n = 15$)	3 (20%)	
<2.0 mg/dl ($n = 256$)	9 (3.5%)	
AST		0.995
≥40 IU/l ($n = 45$)	2 (4.4%)	
<40 IU/l ($n = 226$)	10 (4.4%)	
ALT		**0.048**
≥40 IU/l ($n = 67$)	6 (9.0%)	
<40 IU/l ($n = 204$)	6 (2.9%)	
Alkaline phosphatase		0.113
≥300 U/l ($n = 98$)	7 (7.1%)	
<300 U/l ($n = 173$)	5 (2.9%)	
Amylase		0.842
≥100 IU/l ($n = 79$)	4 (5.1%)	
<100 IU/l ($n = 178$)	8 (4.5%)	
CRP		0.095
≥0.5 mg/dl ($n = 76$)	6 (7.9%)	
<0.5 mg/dl ($n = 195$)	6 (3.1%)	
Age, years		0.571
≥65 ($n = 114$)	6 (5.3%)	
<65 ($n = 157$)	6 (3.8%)	
Size of targeted pancreas tumor		0.261
≥4.0 cm ($n = 160$)	9 (5.6%)	
<4.0 cm ($n = 111$)	3 (2.7%)	
Location of targeted pancreas tumor		0.853
Head ($n = 106$)	5 (4.7%)	
Body/tail ($n = 165$)	7 (4.2%)	

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein
* Univariate analysis with logistic regression; statistically significant *P* values are shown in bold
[a] Single episode of fever of ≥38.0°C within 24 h after biopsy (without antibiotics)

most serious complications are postbiopsy pancreatitis, hemorrhage, and peritoneal dissemination.[4,7] Although a review of the literature has reported six deaths resulting from pancreatic biopsy,[7] there were no deaths or cases of biopsy-related pancreatitis in our series. Although acute pancreatitis after pancreatic biopsy is rare, it can be serious and sometimes fatal when it occurs, and this may be the main reason why the procedure is not commonly performed. The reported rate of postbiopsy pancreatitis ranges from 0% to 1.7%.[4,5,8,11–13] In patients with unresectable pancreatic cancer, the tumors are large and usually located just under the surface of the pancreas, allowing percutaneous puncture of the tumor without penetrating the normal pancreatic tissue. This is probably why biopsy-related pancreatitis is unlikely to develop, as Smith[7] has suggested.

Although the exact frequency of pancreatic biopsy-related peritoneal dissemination is not known, it may not have any influence on the prognosis of patients with unresectable pancreatic cancer, which is invariably poor.[14] On the other hand, in patients with resectable pancreatic cancer, preoperative percutaneous pancreatic biopsy is regarded as controversial because some studies have suggested a high frequency of procedure-related peritoneal dissemination (16.3%–75%).[15,16] The NCCN guidelines state that biopsy proof of malignancy is not required before surgical resection and that a non-diagnostic biopsy should not delay surgical resection, which is the only curative therapy for pancreatic cancer.[1]

In the present study, no cases of clinically or microbiologically documented infection were associated with pancreatic biopsy. There were, however, 12 cases (4.4%) of postbiopsy ephemeral fever, a lower incidence rate than that following liver metastases biopsy. We are not aware of any other published data on this type of fever. We routinely checked the serum level of amylase, but not that of lipase. Among 12 patients with postbiopsy ephemeral fever, two had amylase levels higher than the upper normal limit after pancreatic biopsy. Since leakage of pancreatic juice can occur after pancreatic biopsy, ephemeral fever could be an initial sign of pancreatitis, which has the potential to become life-threatening.

Pancreatic tumor biopsy can be performed using CT guidance with a complication rate ranging from 3.8% to 7%,[4,17,18] and our data showed a very similar rate. It can also be performed under endoscopic ultrasound guidance with a complication rate similar to that observed in our study.[19–22] However, we consider that US-guided pancreatic biopsy may be most useful in patients with unresectable pancreatic cancer, because their tumors are usually large enough to warrant a safe US-guided biopsy (mean size in our study, 42.2mm, Table 1). Furthermore, although we did not perform a cost and patient satisfaction analysis, the procedure for US-guided pancreatic biopsy is obviously more time-saving and less stressful to patients than other biopsy modalities.

In conclusion, in patients with unresectable pancreatic cancer, US-guided percutaneous pancreatic biopsy is an effective and safe modality for confirmation of the pathologic diagnosis. If US visualization is obtained with enough care, pancreatic biopsy is as accurate and safe as liver metastases biopsy, which is well established and commonly perceived as safer. Another important conclusion is that even if a mass in the pancreas seems to be cancer and is large enough to warrant US-guided biopsy, 1.5% (4/266, Table 2) of such cases are not cancer. This indicates that all patients with unresectable pancreatic cancer should have cancer confirmation prior to nonsurgical treatment. Our study was a retrospective analysis, which precludes any firm conclusion. Therefore, a prospective study is needed for adequate evaluation of US-guided pancreatic biopsy as a diagnostic tool.

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CANCER STATISTICS

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Epidemiological study of malignant tumors in the oral and maxillofacial region: survey of member institutions of the Japanese Society of Oral and Maxillofacial Surgeons, 2002

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Abstract We studied 1809 patients with oral cancer who visited and were treated, in 2002, at the 148 institutions certified as training facilities by the Japanese Society of Oral and Maxillofacial Surgeons. Of these institutions, 39 are dental university hospitals, 44 are medical university hospitals, 64 are general hospitals, and for 1 institution, the classification was not known. The patients consisted of 1071 (59.2%) males and 738 (40.8%) females (male: female ratio, 1.45:1), who had a average age of 65.2 years. The tongue (40.2%) was the most common site affected, followed by the gingiva (32.7%), buccal mucosa (10.1%), and oral floor (9.0%). There were 6 cases of multiple intraoral cancers. On histopathological examinations, squamous cell carcinoma (88.7%) was the most common type found, followed by adenoid cystic carcinoma (2.1%), and mucoepidermoid carcinoma (1.7%). Cases classified as T2N0 were the most common (32.1%), followed by T1N0 (21.4%), T4N0 (8.0%), and T2N1 (7.6%). Distant metastasis occurred in 17 patients (1.0%). Nonepithelial tumors, among which malignant melanoma was the most common type, accounted for 1.8% of the tumors.The sizes of the nonepithelial malignant tumors ranged from 1.0 to 7.0 cm, with an average size of 3.7 cm.

Key words Oral cancer · Epidemiological study · Oral surgery

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Introduction

We carried out an epidemiological study of malignant tumors in the oral and maxillofacial region in patients who were treated at member institutions of the Japanese Society of Oral and Maxillofacial Surgeons to determine the status of patients treated by oral surgeons in Japan.

In 1986, a nationwide epidemiological study was conducted in regard to the status of patients with cancer in the oral and maxillofacial region who were treated at member institutions of the Japanese Society of Oral and Maxillofacial Surgeons, and findings from that investigation were first reported in 1988.[1] In 2005, as part of a project established by the Fiscal 2004 Survey Planning Committee (Masashi Shimahara, Chairman; along with members Etsuhide Yamamoto, Harumi Mizuki, Hiroshige Chiba, Yutaka Imai, Shigeyuki Fujita, and Masanori Shinohara) the Japanese Society of Oral and Maxillofacial Surgeons began an annual

survey of patients with cancer in the oral and maxillofacial region who were treated at member institutions of the Society. Prior to that survey, a preliminary investigation had been conducted on oral cancer found in new patients during their initial visit during the 1-year period from January to December 2002. The purpose of the present study was to assess the current situation by investigating results from that 1-year survey performed in 2002, and to analyze the data of those patients with cancer in the oral and maxillofacial region who consulted member institutions of the Society for treatment.

Subjects and methods

The subjects of the investigation were new patients with malignant tumors who visited the member institutions of the Society during the 1-year period from January 1 to December 31, 2002, and who fulfilled the following criteria: (1) histopathologically confirmed malignant tumor; (2) presence of a primary tumor either in the lip and oral cavity (ICD-O C00, C02-C06), maxillary sinus (ICD-O C31.0), salivary gland (ICD-O C07, C08), or other oral regions (ICD-O C41.1) classified according to the *General rules for clinical studies on head and neck cancer*, 3rd edition;[2] (3) previously untreated; and (4) records noting age, sex, tumor location, and tumor size. For the initial registration, a registration form for patients with malignant tumors of the head and neck, prepared by the Japanese Society for Head and Neck Cancer, was sent to the member institutions and used.

Returned registration forms were analyzed for five items. (1) Institutions that participated in the survey were classified into faculties of dentistry and departments of oral surgery of dental colleges (hereinafter, referred to as dental colleges), faculties of medicine and departments of oral surgery of medical colleges (medical colleges), and departments of other types of dentistry and oral surgery, of general hospitals (hospitals). The number of participating institutions and average number of patients treated at each institution were analyzed. (2) Age at the first consultation and sex were analyzed by tumor location. (3) Tumors were classified as malignant epithelial tumors and nonepithelial malignant tumors, such as sarcoma, malignant lymphoma, and malignant melanoma, and analyzed according to age, sex, primary tumor location, and histologic type. For histopathological diagnosis and primary tumor location, the ICD-10 code was used (Tables 1, 2). (4) Malignant epithelial tumors were analyzed according to the number of cases classified as T or N, number of cases by TN classification, number of cases by M classification, and number of tumors by T classification according to tumor location. (5) Nonepithelial tumors were analyzed according to tumor size, which was determined according to the description in the registration form with the maximum diameter expressed in centimeters (after rounding out fractions of centimeters). Tumor size was also analyzed by location, in the lip (C00.0, C00.1, C00.6), tongue (C02.0, C02.1, C02.2, C02.3), gingiva (C03.0, C03.1), oral floor (C04.0, C04.1, C04.9), palate (C05.0), buccal mucosa (C00.3, C00.4, C06.0, C06.1, C06.2), maxillary sinus (C31.0), jawbone (C41.1), and major salivary gland (C07, C08, C08.0, C08.1).

Table 1. Histopathological diagnosis (International Classification of Diseases; ICD-10)

Carcinoma
8000/3: Neoplasm, malignant
8010/3: Carcinoma, NOS
8020/3: Carcinoma, undifferentiated, NOS
8051/3: Verrucous carcinoma, NOS
8052/3: Papillary squamous cell carcinoma
8070/2: Squamous cell carcinoma in situ, NOS
8070/3: Squamous cell carcinoma, NOS
8071/3: Squamous cell carcinoma, keratinizing, NOS
8072/3: Squamous cell carcinoma, large cell, nonkeratinizing
8073/3: Squamous cell carcinoma, small cell, nonkeratinizing
8074/3: Squamous cell carcinoma, spindle cell
8076/2: Squamous cell carcinoma in situ with questionable stromal invasion
8076/3: Squamous cell carcinoma, microinvasive
8140/3: Adenocarcinoma, NOS
8200/3: Adenoid cystic carcinoma
8430/3: Mucoepidermoid carcinoma
8470/3: Mucinous cystadenocarcinoma, NOS
8550/3: Acinar cell carcinoma
8560/3: Adenosquamous carcinoma
8940/3: Mixed tumor, malignant, NOS
8980/3: Carcinosarcoma, NOS
8982/3: Myoepithelial carcinoma, NOS
9270/3: Odontogenic tumor, malignant
Sarcoma
8720/3: Malignant melanoma, NOS
8810/3: Fibrosarcoma, NOS
8830/3: Fibrous histiocytoma, NOS
8890/3: Leiomyosarcoma, NOS
9120/3: Hemangiosarcoma
9180/3: Osteosarcoma, NOS
9240/3: Mesenchymal chondrosarcoma
9590/3: Malignant lymphoma, NOS
9670/3: Malignant lymphoma, small lymphocytic, NOS
9680/3: Malignant lymphoma, large cell, diffuse, NOS
9731/3: Plasmacytoma, NOS
9732/3: Multiple myeloma

There were no cancers with a histopathological diagnosis not listed above

Cases of multiple cancers were analyzed as follows. In the present survey, each malignant tumor was registered in each registration form. Tumors registered under the same patient name, institution case number, date of birth, age at first consultation, sex, and date of first consultation were regarded as being from the same patient. Each patient was treated as a separate case when determining the number of cases, age, and sex. For histopathological diagnosis, T classification, N classification, and site of primary tumor, each registration form was treated as representing a single tumor.

The difference in average age between male and female patients was analyzed using an unpaired *t*-test, with the level of significance set at 5%. For building a database from the registration form data and significant difference tests, JMP version 5.1.2 (SAS Institute, Cary, NC, USA) was used.

Results

Participating institutions

We sent registration forms to 234 institutions – 54 dental colleges, 60 medical colleges, and 120 hospitals. Of the 234 institutions, 148 (63.2%) returned completed registration forms. Classified by kind of institution, hospitals had the highest return rate, as they comprised 43.2% of the institutions that returned the forms, while 39 (26.4%) dental colleges and 44 (29.7%) medical colleges returned the forms. One institution that returned forms was of unknown classification. The average number of patients per institution was 18.7 for dental colleges and 17.5 for medical colleges; these averages tended to be greater than that for hospitals (Table 3).

Table 2. Classification by location (ICD-O)

Lip	C00.9
Upper lip	C00.0
Lower lip	C00.1
Commissure of lip	C00.6
Oral cavity	C06.9
Tongue	
Anterior 2/3 of tongue	C02.3
Dorsal surface of anterior tongue	C02.0
Border of tongue	C02.1
Tip of tongue	C02.1
Ventral surface of tongue	C02.2
Floor of mouth	C04.9
Anterior floor of mouth	C04.0
Lateral floor of mouth	C04.1
Lower gum	C03.1
Upper gum	C03.3
Buccal mucosa	
Mucosa of upper lip	C00.3
Mucosa of lower lip	C00.4
Cheek mucosa	C06.0
Vestibule of mouth (upper)	C06.1
Vestibule of mouth (lower)	C06.1
Retromolar area	C06.2
Hard palate	C05.0
Maxillary sinus	C31.0
Major salivary gland	
Parotid gland	C07
Submandibular gland	C08.0
Sublingual gland	C08.1
Other	C08.9

No cancer was found in locations not listed above

Age, sex, primary tumor location, and age at first visit by tumor location

A total of 2128 registration forms were returned, in which 1809 patients (85.0%) fulfilled all the requirements for registration. Of these, 6 patients had multiple cancers (5 had tumors that developed at two sites, and 1 had tumors at three sites). Accordingly, 1816 tumors in 1809 patients were subjected to analysis.

Males accounted for 1071 (59.2%) patients and females for 738 (40.8%) (male: female ratio, 1.45:1; Table 4). The average age at the first visit was 65.2 ± 13.9 years. The ages ranged from 12 to 99 years, with a median of 67 years. The average age at the first visit was 63.6 ± 13.1 years for males and 67.6 ± 14.5 years for females; thus, age was significantly higher for female patients than for male patients($P < 0.05$). The average age at the first visit was 65.3 ± 13.8 years for patients with malignant epithelial tumors and 59.2 ± 16.5 years for patients with nonepithelial tumors; thus, age was slightly higher for those with epithelial tumors (for age distribution by sex and age group, see Tables 5 and 6).

As for location, 730 (40.2%) tumors developed in the tongue, demonstrating the highest incidence, followed by 594 (32.7%) in the gingiva (223 in the upper, 371 in the lower), 184 (10.1%) in the buccal mucosa, and 164 (9.0%) in the oral floor (Table 7). The ratio of males and females stratified by primary location varied widely. The ratio of male patients was higher for tumors located in the lip, tongue, oral floor, maxillary sinus, and jawbone, while that for female patients tended to be higher for tumors in the gingiva and palate (Table 7). Regarding age at the first visit stratified by primary tumor location, average age was higher in order of the lip, palate, and buccal mucosa, while it tended to be lower for tumors in the jawbone, major salivary gland, and tongue (Table 8). Of the six patients with multiple cancers three were women and three, men, and the age at the first visit was over 75 years for all but one of these patients.

Table 4. Sex distribution

	Epithelial tumors	Nonepithelial tumors	Total
Male	1051	20	1071
Female	726	12	738
Total	1777	32	1809

Table 3. Participating institutions

Institution	Registered institution/ Nominated institution	Average number of patients per institution (range)
Dental universities and faculties of dentistry	39/54	18.7 (2–59)
Medical universities and faculties of medicine	44/60	17.5 (3–41)
Other institutions (general hospitals)	64/120	9.7 (1–45)
Type not known	1/–	12

Registered institutions means those institutions that returned completed registration forms; nominated institutions means the member institutions of the Society