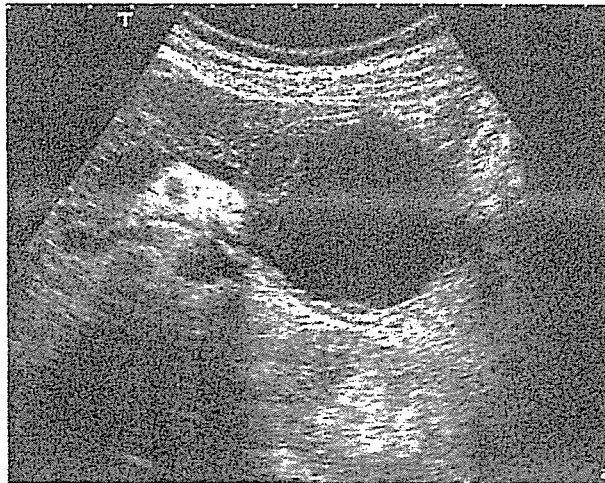


**Fig. 1.** Pancreatograms using a balloon catheter retained by ERCP showing a main duct IPMN (a) with mural nodules (arrow) and a branch duct IPMN in the head of the pancreas with clear communication with the pancreatic duct (b).



**Fig. 2.** Ultrasonogram (a) and computed tomogram (b) demonstrating an MCN.

neoplasms of the pancreas are being increasingly identified, often as incidental findings [2].

In 1996, the World Health Organization (WHO) classified cystic mucin-producing pancreatic neoplasms into two distinct entities [3], i.e., intraductal papillary mucinous tumor and mucinous cystic tumor. In the revised WHO classification in 2000 [4], the two neoplasms were renamed as intraductal papillary mucinous neoplasm (IPMN) (fig. 1) and mucinous cystic neoplasm (MCN)

(fig. 2), respectively. Since then much has been learnt about the clinical, radiographic, and histological characteristics of these neoplasms. For example, the presence of ovarian-type stroma has been proposed as a characteristic feature of MCN that distinguishes it from IPMN. While there have been rapid advances in our understanding of the prevalence of cancer at diagnosis and the risk of recurrence following resection, there are still considerable gaps in our knowledge of the natural history of these neo-

**Table 1.** List of clinical questions

**1. Definition and Classification**

- 1a. It has been suggested that IPMNs arising in the branch ducts are less aggressive than those arising in the main duct. Can we preoperatively distinguish main duct IPMN from branch duct IPMN?
- 1b. In most IPMNs there are papillary growths in both the main duct and branch duct by histology. Do we still need the mixed category or should the mixed type IPMNs be considered as advanced branch duct IPMNs?
- 1c. Should ovarian-type stroma be a histological requirement for diagnosing MCN?
- 1d. If all mucinous neoplasms need resection, is distinction between MCN and IPMN merely an academic exercise?

**2. Preoperative evaluation**

- 2a. Can we reliably distinguish branch duct IPMN from MCN preoperatively? If so, which imaging modality is best to distinguish between branch duct IPMN and MCN? Is there a preferred order to the tests that should be performed?
- 2b. Is it possible to diagnose minimally invasive carcinoma derived from IPMN and MCN preoperatively?

**3. Indication for resection**

- 3a. Should all main duct IPMNs be resected? If not, what criteria should be employed to separate those that should be resected from those that can be watched (size, mural nodules, etc.)?
- 3b. Should all branch duct IPMNs be resected? If not, what criteria should be employed to separate those that should be resected from those that can be watched (size, mural nodules, etc.)?
- 3c. Should all MCNs be resected? If not, what criteria should be employed to separate those that should be resected from those that can be watched (size, mural nodules, etc.)?

**4. Method of resection**

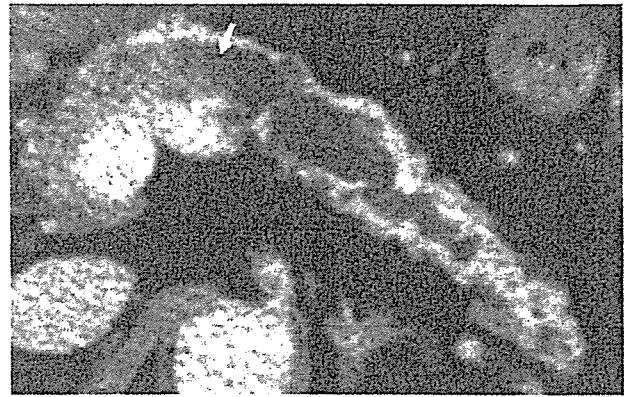
- 4a. Pancreatectomy with lymph node dissection is necessary when an invasive carcinoma is suspected. What is an appropriate surgical procedure for non-invasive MCNs and IPMNs? Is pancreatectomy limited to some extent without lymph node dissection appropriate?
- 4b. Does limited resection (e.g., middle segmental pancreatectomy) have a role in surgical management of MCNs or IPMNs?
- 4c. What should be the approach to multifocal branch duct IPMNs? In an older patient, is it reasonable to resect the portion of the gland with the largest cyst(s) alone and follow clinically to avoid total pancreatectomy?

**5. Histological questions**

- 5a. What is the role of intraoperative frozen section consultation in the surgical management of patients with IPMNs and MCNs? In particular, should pancreatic parenchymal margins be frozen and what should be done if mucinous epithelium is identified in the larger or in the smaller pancreatic ducts?
- 5b. Are there special instructions for specimen processing in MCNs and IPMNs?
- 5c. Are there special instructions for specimen processing to differentiate branch duct IPMNs from main duct IPMNs?

**6. Method of follow-up**

- 6a. How should patients with non-resected IPMNs and MCNs be followed? How often should they be followed and which techniques should be employed as baseline investigations?
- 6b. How should patients with surgically resected IPMNs and MCNs be followed? How often should they be followed and which techniques should be employed as baseline investigations?
- 6c. Should care be taken to the possible occurrence of other malignant neoplasms in patients with IPMNs on follow-up?



**Fig. 3.** Computed tomogram showing a markedly dilated main pancreatic duct in a patient with a main duct IPMN with a mural nodule in the body of the pancreas (arrow).

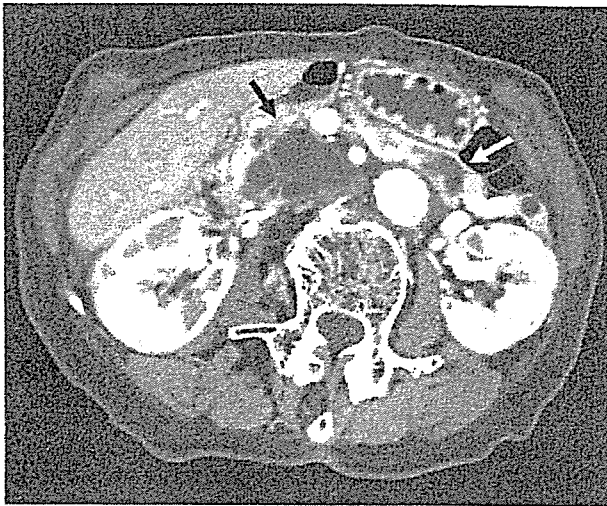
plasms. However, in view of the increasing frequency with which these neoplasms are being diagnosed worldwide, it would be helpful for physicians managing patients with cystic neoplasms of the pancreas to have guidelines for the diagnosis and treatment of IPMN and MCN. No doubt, as our understanding grows, these guidelines will need revision.

During the Eleventh Congress of the International Association of Pancreatology held in Sendai, Japan, from July 11 through 14, 2004, we had a consensus meeting on this topic. The working group set up 6 clinical questions with 18 subdivisions (table 1), and continued to work on the answers. The proposed guidelines represent a consensus of the working group of the International Association of Pancreatology at this moment.

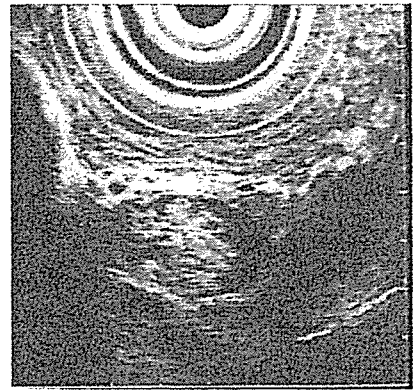
**1. Definition and Classification**

*1. It has been suggested that IPMN arising in the branch ducts are less aggressive than those arising in the main duct. Can we preoperatively distinguish main duct IPMN from branch duct IPMN?*

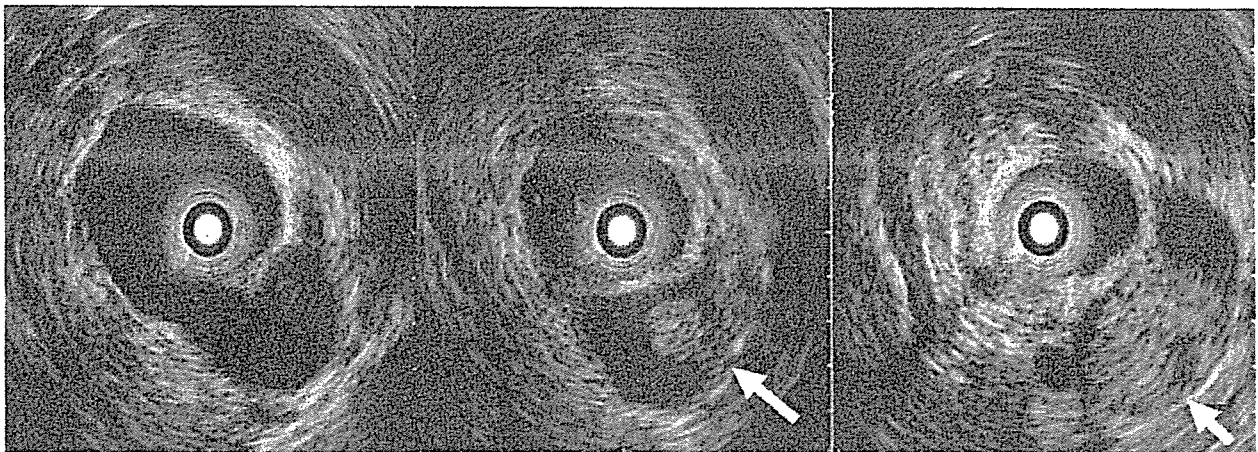
IPMN can be classified as main duct IPMN or branch duct IPMN based on imaging studies or by histology [5]. On conventional imaging (i.e., computed tomography (CT) or magnetic resonance cholangiopancreatography (MRCP)), dilation of the main duct  $\geq 1$  cm strongly suggests main duct IPMN (fig. 3), whereas a presence of a pancreatic mucinous cyst communicating with the pancreatic duct without main duct dilation suggests branch



**Fig. 4.** Computed tomogram demonstrating a multilocular cystic lesion in the head of the pancreas (black arrow) and a unilocular cyst in the tail (white arrow), representing multiple branch duct IPMNs.



**Fig. 5.** Endosonogram demonstrating a mural nodule in a branch duct IPMN in the head of the pancreas.



**Fig. 6.** Intraductal ultrasonogram visualizing a mural nodule in a branch duct IPMN in the head of the pancreas (arrows).

duct IPMN (fig. 4) [6–8]. The presence of the papillary growth in branch or main ducts can be ascertained with greater degree of certainty using more sophisticated and invasive imaging studies, such as endoscopic ultrasonography (EUS) (fig. 5) [9, 10], endoscopic retrograde cholangiopancreatography (ERCP) with or without the use of a balloon catheter (fig. 1a, b), intraductal ultrasonography

(fig. 6) [11, 12] and peroral pancreatoscopy (fig. 7) [13, 14], or by a combination of intraductal ultrasonography and peroral pancreatoscopy [15]. However, these techniques are not widely available. The most definitive classification of IPMN into main or branch duct type is made by histology, provided the resected specimen is properly sectioned.

**Table 2.** Malignancy in main duct IPMNs (including the mixed type IPMN)

Reference (first author)	Year published	Patients	Malignant including CIS, %	Invasive malignancy, %
Kobari [16]	1999	13	92	23
Terris [17]	2000	30	57	37
Doi [18]	2002	12	83	Not stated
Matsumoto [19]	2003	27	63	Not stated
Choi [20]	2003	34	85	Not stated
Kitagawa [21]	2003	37	65	54
Sugiyama [22]	2003	30	70	57
Sohn [23]	2004	69	Not stated	45
Salvia [24]	2004	140	60	42
Mean of all series			70	43

**Table 3.** Malignancy in branch duct IPMNs

Reference (first author)	Year published	Patients	Malignant including CIS, %	Invasive malignancy, %
Kobari [16]	1999	17	31	6
Terris [17]	2000	13	15	0
Doi [18]	2002	26	46	Not stated
Matsumoto [19]	2003	16	6	Not stated
Choi [20]	2003	12	25	Not stated
Kitagawa [21]	2003	26	35	31
Sugiyama [22]	2003	32	40	9
Sohn [23]	2004	60	Not stated	30
Mean of all series			25	15

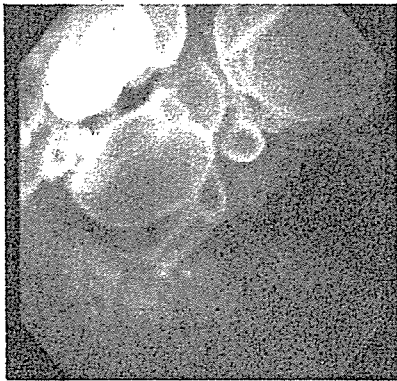
Main duct IPMN and branch duct IPMN have significant differences in prevalence of cancer ranging from 57 to 92% [16–24] and 6 to 46% [16–23], respectively (tables 2, 3) and therefore the classification has prognostic implications. In practice, patients classified as branch duct IPMN based on preoperative imaging studies sometimes show microscopic involvement of the main duct not detectable preoperatively. It is unclear if such subjects with ‘predominantly’ branch duct IPMN with microscopic main duct involvement have a higher prevalence of malignancy compared to those with dysplasia confined solely to the branch duct.

*1b. In most IPMNS there are papillary growths in both the main duct and branch duct by histology. Do we still need the mixed category or should the mixed type IPMNS be considered as advanced branch duct IPMNS?*

The categorization of IPMN according to the differential involvement of the branch vs. main duct is mostly

based on imaging findings, and as such this classification scheme appears to have substantial value in preoperative management algorithms for IPMN. The role of this classification, however, may be overridden once the neoplasm is resected, re-evaluated pathologically, and graded as adenoma, borderline, CIS or invasive. On the other hand, there are significant pathologic correlates of this classification: IPMNs categorized as ‘branch type’ by radiographic methods are typically found to be smaller, less complex (less papillary), and non-malignant (more commonly adenomas with gastric/foveolar type epithelium), which explains why many branch duct IPMNs have been successfully managed by conservative therapy, even ‘wait and watch’.

One pitfall in this classification scheme, however, is that many of the branch duct IPMNs prove, by microscopic examinations, to have some degree of involvement in the main duct as well. Therefore, predominantly main duct type and predominantly branch duct type may be a more accurate conceptualization of these categories, al-



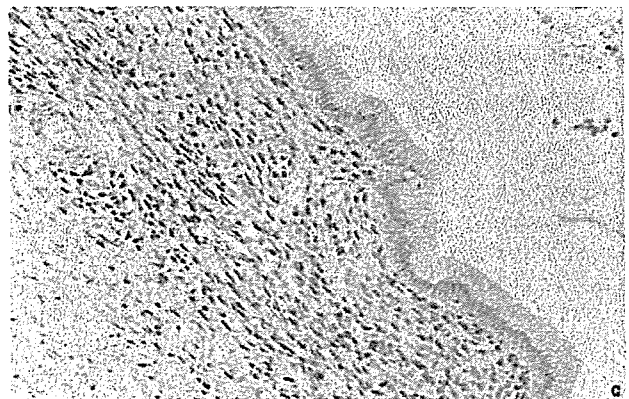
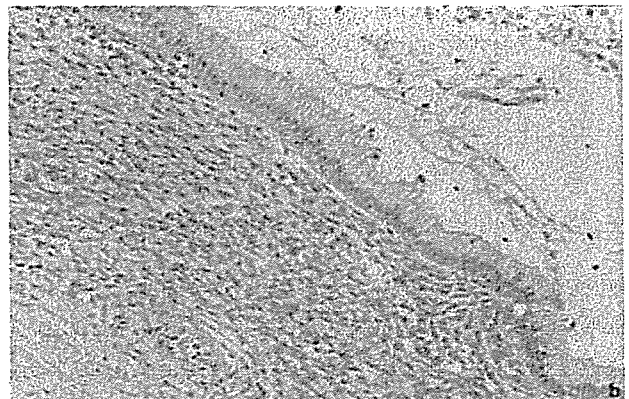
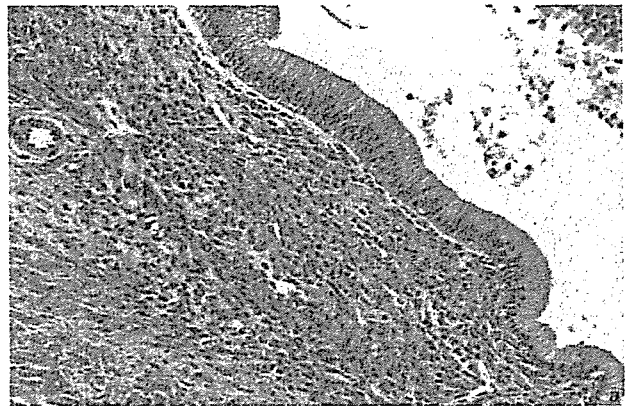
**Fig. 7.** Fish egg-like appearance of a main duct IPMN by peroral pancreatoscopy.

though the word predominantly is omitted for practical purposes. In fact, 'branch limited' vs. 'beyond the branch' may be even more accurate. On the other hand, there are more important and practical implications of this conceptual issue. First, it is difficult to determine how much of the main duct involvement is necessary to qualify the lesion as 'main duct IPMN'. In this regard, more clinical follow-up data need to accumulate before the criteria for this distinction can be established. In the meantime, however, the criteria advocated for the definition of IPMN in the recent international consensus manuscript [25] may be applicable for practical purposes. Even when these criteria are applied, however, many IPMNs would still fall into a mixed category. Therefore, it is necessary to retain this mixed category until future studies further clarify the criteria to distinguish these two groups.

Since clinicopathologic correlation is imperative in the management of IPMNs as well as in understanding the biologic behavior of the subsets of this type of neoplasm, it is recommended that surgical pathologists make every attempt to determine branch vs. main duct type, if nothing else, in order to provide verification to this clinical classification. For this purpose, the findings regarding the distribution of ductal involvement may be communicated in a note or comment following the main diagnosis in the surgical pathology report.

*1c. Should ovarian-type stroma be a histological requirement for diagnosing MCN?*

The most characteristic histological finding in MCN is the presence of a unique ovarian-type stroma (fig. 8) [26] not found in other pancreatic neoplasms. This ovarian-



**Fig. 8.** Ovarian-type stroma in a mucinous cystic neoplasm. Hematoxylin and eosin staining (a) and immunohistochemical staining of estrogen receptor (b) and progesterone receptor (c).  $\times 200$ .

type stroma forms a layer of variable thickness beneath the epithelial lining. The stromal cells have oval nuclei and spindled cytoplasm, and are arranged in long fascicles. The resemblance to ovarian stroma is further

strengthened by the presence of occasional 'lutenized' cells – epithelioid cells with abundant clear cytoplasm. A study of 34 pancreatic MCN and 10 ovarian MCN showed the ovarian stroma of MCN from the two organs shared the same immunohistochemical and histological characteristics [27].

Like its ovarian counterpart, the stroma of pancreatic MCN variably stains for estrogen and progesterone receptors (fig. 8b,c), with 61.8% of pancreatic MCN staining for human chorionic gonadotropin [27].

The most important question with regard to the accurate classification of MCN and its differentiation from branch duct form of IPMN is whether the presence of ovarian-type stroma is required to diagnose MCN. Three studies on MCN have used ovarian-type stroma as a requisite criterion for diagnosis of MCN [28–30]. When defined by the presence of ovarian-type stroma, MCN has a distinct demographic profile; it occurs almost exclusively in women and is almost always found in the pancreatic body/tail region [28, 29]. It has been argued that theoretically it may be possible that postmenopausal women and men with MCN may fail to demonstrate ovarian-type stroma. In a study of 56 MCN defined strictly by presence of ovarian stroma, 9 patients (16%) were >60 years of age [28]. Also, there are male patients with mucinous cystadenoma with ovarian-type stroma [28, 31].

In the absence of a definitive marker, other than ovarian-type stroma, to distinguish MCN from IPMN, it is currently impossible to say if neoplasms classified on the basis of any criterion other than presence of ovarian-type stroma (for example, non-communication with the duct) are indeed MCN. It has become clear over the past few years that making exceptions to the ovarian-type stroma rule frequently leads to misclassification of IPMN as MCN [28]. Therefore the term MCN should be restricted to neoplasms exhibiting ovarian-type stroma.

Clearly, typical MCN with ovarian-type stroma is rare in males and it is less common in postmenopausal women than in women of childbearing age. Occasionally, mucin-producing pancreatic cystic lesions are seen in men or postmenopausal women that neither have ovarian-type stroma nor have typical histological features seen in branch duct IPMNs such as a thin wall, grape-like appearance and a communication with the pancreatic duct. Rather than classify such lesions as MCNs, we propose the use of the term 'indeterminate mucin-producing cystic neoplasm of the pancreas'. In future, when specific markers of IPMN and MCN become available, these lesions may be more definitively classified.

*1d. If all mucinous neoplasms need resection, is distinction between MCN and IPMN merely an academic exercise?*

The general recommendation has been that all mucin-producing neoplasms undergo resection in view of their malignant potential, which questions the clinical utility of careful differentiation of MCN from IPMN [30, 32–34]. However, there are crucial differences between MCN and IPMN with regard to pathogenesis, multifocality, need for follow-up and prevalence of cancer that impact clinical management.

Due to its close histological and immunohistochemical resemblance to ovarian mucinous cystadenomas, MCN has been postulated to arise from ovarian rests in the pancreas [29]. IPMN appears to arise from the pancreatic duct.

MCN and IPMN also have important clinical differences. MCNs are generally solitary and do not recur after complete resection [35, 36]. On the other hand, branch duct IPMNs have been reported to be multifocal in distant regions of the pancreas in up to 30% of patients [37–39], and there is at least a 10% recurrent rate in those patients with non-invasive IPMN who undergo partial pancreatic resection with negative margins [40]. Thus, while no follow-up is needed after resection of non-invasive MCN, young patients with IPMN need follow-up, especially if they have unresected synchronous lesions.

The prevalence of invasive carcinoma reported in MCN has varied widely from 6 to 36% [28–30]. However, data on prevalence of invasive carcinoma in MCN are hard to interpret as few studies have used ovarian-type stroma as a necessary criterion for diagnosis of MCN. Even in studies restricted to neoplasms with ovarian-type stroma the prevalence of cancer has varied from 6 to 27% [28, 29]. In IPMN, prevalence of invasive carcinoma at diagnosis has been reported to be high in main duct IPMN (23–57%, table 2) and lower in branch duct IPMN (0–31%, table 3).

## 2. Preoperative Evaluation

*2a. Can we reliably distinguish branch duct IPMN from MCN preoperatively? If so, which imaging modality is best to distinguish between branch duct IPMN and MCN? Is there a preferred order to the tests that should be performed?*

There are some obvious differences in clinicopathological features between IPMN and MCN with ovarian-type stroma (table 4) [28–30, 41–47]. Understanding of

**Table 4.** Typical features of MCN and branch duct IPMN

Characteristic	MCN	Branch duct IPMN
Gender (% female)	>95%	~30%
Age (decade)	4th and 5th	6th and 7th
Location (% body/tail)	95%	~30%
Common capsule	Yes	No
Calcification	Rare, curvilinear, in the wall of cyst	No
Gross appearance	Orange-like	Grape-like
Internal structure	Cysts in cyst	Cyst by cyst
Pancreatic duct communication	Infrequent	Yes (though not always demonstrable)
Main pancreatic duct	Normal or deviated	Normal, or if dilated, suggests combined type

these distinctive features and characteristics of each imaging modality lead to differentiation of the two diseases in most patients. Cystic lesions in males and those in the head of the pancreas are unlikely to be MCN. Magnetic resonance imaging (MRI) with MRCP is the best to outline the gross appearance. Communication with the pancreatic duct demonstrated on imaging studies such as ERCP (most reliable), MRCP (helpful), and EUS (of some help) strongly suggests branch duct IPMN. However, even ERCP in branch duct IPMN may fail to fill the cystic side branch due to mucus plugging the communication. On the other hand, there has been a report of a histologically proven MCN showing communication with pancreatic ducts [47]. In some patients it may therefore be impossible to distinguish between the two entities with certainty preoperatively.

*2b. Is it possible to diagnose minimally invasive carcinoma derived from IPMN and MCN preoperatively?*

The Japan Pancreas Society (JPS) defined a non-invasive type of intraductal papillary mucinous carcinoma as limited to the pancreatic duct and a minimally invasive type as having invaded slightly beyond the ductal wall [48]. However, this definition is not so clear. If the minimally invasive intraductal papillary mucinous carcinoma is defined as microscopic cancer invasion to the pancreatic parenchyma, it is impossible to diagnose the minimal invasion preoperatively [49] at present as is the case in minimally invasive MCN.

### 3. Indication for Resection

*3a. Should all main duct IPMNs be resected? If not, what criteria should be employed to separate those that should be resected from those that can be watched (size, mural nodules, etc.)?*

The frequency of malignancy (in situ and invasive) in main duct IPMNs in 8 recent series from Japan, Europe, and the USA has ranged between 60 and 92%, with a mean of 70% [16–24], and approximately two-thirds of these malignant neoplasms have been invasive (table 2). In many studies there has been an attempt to identify radiologic or clinical characteristics that predict malignancy, although unfortunately many of these analyses have been made without separating main duct from branch duct variants. In a series reported by Sugiyama et al. [22], univariate analysis showed that presence of symptoms, a main pancreatic duct diameter >15 mm, and mural nodules were all significant predictors of malignancy in main duct or mixed type IPMNs, although there were patients without nodules or such marked pancreatic duct dilation that had in-situ or invasive carcinoma. The largest published series on main duct IPMNs combines the experiences of the Massachusetts General Hospital and the University of Verona [24]. This study comprised 140 patients, and found that patients with malignant neoplasms were significantly older (by 6.4 years), and had a higher likelihood of presenting with jaundice and/or worsening of diabetes; however, the study also showed that 29% of patients with malignant IPMNs involving the main duct were asymptomatic, and therefore reliance on symptoms could not exclude malignancy. Given the high prevalence of cancer and the data from the reviewed studies it is unlikely that any combination of clinical and radiological

parameters will accurately discriminate between malignant and non-malignant main duct IPMNs. Furthermore, evidence of 'clonal progression' in these neoplasms [50] and the age difference between patients with malignant and benign lesions (which was also shown in another large study) [30] are indicative that most if not all benign main duct IPMNs may progress into invasive cancer, and the long-term follow-up of resected patients shows excellent survival for benign and non-invasive neoplasms and 5-year survival between 36 and 60% for invasive carcinomas [21, 23, 24, 40]. Based on this, our current recommendation is to resect all main duct and mixed variant IPMNs as long as the patient is a good surgical candidate with a reasonable life expectancy. It is important that resections for IPMNs be carried out by surgeons familiar with this diagnosis and in centers where pancreatic surgery can be done safely.

### *3b. Should all branch duct IPMNs be resected?*

Review of 7 recent series describing branch duct IPMNs shows a frequency of malignancy between 6 and 46%, with a mean of 25%, and a frequency of invasive cancer ranging between 0 and 31%, with a mean of 15% (table 3) [16–23]. It is of note that the two studies with the highest frequency of invasive cancer (30 and 31%, respectively) do not describe asymptomatic patients within their series [21, 23], whereas other series with low prevalence of invasive cancer show a significant proportion of incidentally discovered IPMNs [17, 19, 22]. In the series of Sugiyama et al. [22], 53% of branch duct IPMNs were asymptomatic, and none of those patients had invasive cancer. Two studies from Japan have looked at morphologic features of branch duct IPMNs and risk of malignancy. Matsumoto et al. [19] found no malignancy (in situ or invasive) in neoplasms measuring <30 mm and without mural nodules, and described non-operative management in 12 patients with branch duct IPMNs who either refused operation or were at high surgical risk. The majority of these patients were asymptomatic, and had no radiologic progression of their neoplasms during an average follow-up of 33 months. In the second study, Sugiyama et al. [22] found with multivariate analysis that the size >30 mm and presence of mural nodules were the strongest predictors of malignancy in branch duct IPMNs. Only 1/15 patients with a neoplasm <30 mm had in-situ carcinoma (none had invasive cancer), and only 5/22 patients without mural nodules had malignancy. Thus, the overall lower prevalence of malignancy in branch duct IPMNs and the reassurance from the above studies that the likelihood of invasive cancer is very low in small cysts

raise the possibility of management with careful observation in asymptomatic patients. Patients with branch duct IPMNs who are symptomatic should be treated with resection not only to alleviate the symptoms, but also because of a higher likelihood of malignancy. It is important to emphasize that the decision to treat should be individualized and based on patient preferences and willingness or unwillingness to undergo follow-up studies, as well as on the availability of safe pancreatic resection. Moreover, more data based on pathological studies of branch duct IPMNs >30 mm and without main duct dilation or mural nodules are needed to determine if all branch duct IPMNs >30 mm in size should be resected immediately.

### *3c. Should all MCNs be resected? If not, what criteria should be employed to separate those that should be resected from those that can be watched (size, mural nodules, etc.)?*

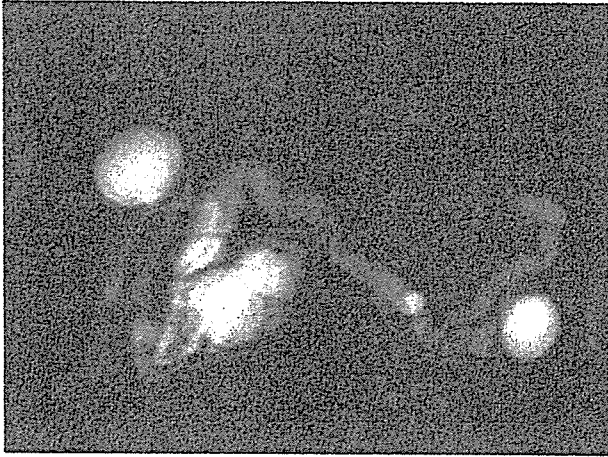
Unless there are contraindications for operation, all MCNs should be resected. Usually these neoplasms are localized in the body-tail of the gland and affect middle-aged women [29, 35, 36]. Current thinking is that all MCNs may progress to malignancy, and the life expectancy of most of these patients will allow development of mucinous cystadenocarcinoma, which has a very low resectability and a very poor prognosis [35, 36]. Furthermore, the operation, usually a left pancreatectomy, has a low morbidity and practically no mortality [51]. Predictors of malignancy such as large size, mural nodules, and eggshell calcification [32] mean only that spleen preserving techniques, either laparoscopically or open, must be avoided in order to obtain a correct oncological lymph node dissection [52–55].

## **4. Method of Resection**

### *4a. Pancreatectomy with lymph node dissection is necessary when an invasive carcinoma is suspected. What is an appropriate surgical procedure for non-invasive MCNs and IPMNs? Is pancreatectomy limited to some extent without lymph node dissection appropriate?*

It is not always easy to assess pre- and intraoperative-ly the grade of invasiveness [56]. Whenever any doubt exists, a typical resection (pancreatoduodenectomy, left pancreatectomy, total pancreatectomy according to the site and the extension of the disease) with lymph node dissection must be pursued [34, 57]. In very limited size lesions, without any laboratory, clinical or radiological





**Fig. 9.** MRCP outlining two branch duct IPMNs in the head and tail of the pancreas in the same patient as shown in figure 4.

suspicion of malignancy, limited resections can be planned, but should always be contingent on a careful intraoperative final assessment.

*4b. Does limited resection (e.g., middle segmental pancreatectomy) have a role in surgical management of MCNs or IPMNs?*

The aim of limited pancreatic resection is to preserve exocrine and endocrine pancreatic functions. Newer understanding of surgical anatomy of the pancreas has led to the proposal of various types of limited pancreatectomy [58, 59]. However, limited pancreatectomy has its problems, including technical difficulty (mostly related to a complicated surgical anatomy), a higher incidence of postoperative complications including pancreatic fistulae, and the risk of recurrence from potentially residual neoplasm. For pancreatic head lesions, duodenum-preserving pancreas head resection [60–62], pancreatic head resection with second portion duodenectomy [63], ventral pancreatectomy [64], resection of uncinate process [65], and ductal branch-oriented minimal pancreatectomy [66] have been proposed, for pancreatic body diseases, a dorsal pancreatectomy [67] and middle segmentectomy [68, 69], and for pancreatic tail neoplasms, spleen-preserving distal pancreatectomy [52–54]. Branch duct IPMNs with possible in-situ carcinoma and MCNs can be candidates for limited pancreatectomy as far as negative ductal margins can be obtained and safe pancreatectomy can be performed but no good follow-up data on recurrence are available.

*4c. What should be the approach to multifocal branch duct IPMNs? In an older patient, is it reasonable to resect the portion of the gland with the largest cyst(s) alone and follow clinically to avoid total pancreatectomy?*

Branch duct IPMNs can often be multifocal and located in distant segments of the pancreas (fig. 9). This is especially evident when EUS or MRCP is performed. It is unclear if multifocality confers a higher risk of invasive cancer than that predicted by the cyst size alone. If there is an indication for surgical resection (i.e., the patient is symptomatic, or the lesions are >3 cm and/or have mural nodules), a decision to proceed with a total pancreatectomy in order to remove all the lesions must be weighed carefully against the ability of the patient to manage the metabolic consequences of an apancreatic state. The age of the patient plays an important role in this decision, since the longer the life expectancy, the greater the risk of development of invasive cancer. While some studies have suggested a time lag of 5–7 years between adenomas and carcinomas (based on age differences of resected patients with benign and malignant IPMNs) [23, 24], in reality there is practically no information on the natural history of branch duct IPMNs, and it may be equally reasonable to resect the dominant lesion and observe the remainder until they become symptomatic or growth is documented.

## 5. Histological Questions

*5a. What is the role of intraoperative frozen section consultation in the surgical management of patients with IPMNs and MCNs? In particular, should pancreatic parenchymal margins be frozen and what should be done if mucinous epithelium is identified in the larger or in the smaller pancreatic ducts?*

The role of frozen section for MCNs is somewhat different from that for IPMNs:

*Frozen Section for IPMNs*

Frozen section of the surgical margins has an important role in the intraoperative management of IPMNs. Microscopic extension of the neoplastic cells beyond the grossly (radiologically and macroscopically) visible boundaries of the main lesion is a common occurrence in IPMNs, and this often needs to be investigated by performing a frozen section.

Caution should be exercised in interpreting the frozen section result, keeping in mind the following concerns:

(1) It should be remembered that even a negative margin does not assure the absence of neoplastic cells in the remaining pancreas. It has been well documented that IPMNs can be multifocal, and that there are sometimes 'skip' lesions in IPMNs, with non-neoplastic tissue intervening neoplastic foci. Along similar lines, there is also evidence that IPMNs may, in some instances, be a marker of invasive carcinoma [70]. This is exemplified by the cases that have an IPMN in the pancreatic head and a seemingly independent invasive ductal carcinoma in the tail of the organ. In other words, in some patients, IPMN may be a marker of a field defect and propensity for cancer formation in the pancreas, in some cases, away from the IPMN itself. Therefore, every effort should be made, preoperatively and intraoperatively, to rule out the presence of the neoplasm in the remaining pancreas. Furthermore, it has been well documented that a third of the IPMN patients have a separate malignancy in other organs [71, 72].

(2) It should also be remembered that grading of IPMNs can be subjective, and frozen tissue exhibit artifacts that accentuate the difficulty in interpretation of the histomorphologic findings. The decision to resect additional pancreatic parenchyma should be individualized and based on careful discussion between the surgeon and pathologist. A problem commonly encountered is denuded epithelium, where evaluation of the margin becomes impossible. To avoid this, gentle handling of the tissue (both in the operating room and the laboratory) is necessary. Stepwise sections of the tissue in the laboratory or even re-melting and re-embedding the reverse side of the tissue (i.e., if the fragment has not been oriented) may be considered.

#### *Management of Positive Margins in IPMNs*

The relative risk and biologic significance of various grades and subsets of IPMNs have not yet been fully established. However, the following assumptions can be made based on the current data in the literature:

*IPM Adenoma.* It is generally believed that IPM adenomas do not warrant further resection. This impression mostly stems from the fact that most branch duct IPMNs have been successfully followed up for decades, and only rarely developed invasive cancer. These branch duct IPMNs are typically adenomas (with no cytoarchitectural atypia) and have gastric/foveolar type epithelium, the type that used to be classified as 'IPMT (intraductal papillary-mucinous tumor) hyperplasia' in the JPS classification system [48, 73]. Whether these represent hyperplasia or adenoma is a discussion beyond the scope of this article. Regardless of the term, it is generally believed that

such lesions bear only minimal risk of progression to cancer, which warrants close follow-up of the patient but does not justify (further) operation. Along the same lines, if a coincidental low-grade PanIN (1 and 2) is encountered in a resection margin, it is believed that no further resection is necessary. This impression is based on the fact that PanIN-1 and -2 are common incidental findings in the general population [40, 74].

*IPMN with Borderline Atypia.* This category is difficult to characterize and hence its management decision is also difficult. Not surprisingly, some of these borderline lesions are closer to adenomas and hence assumed to be less clinically significant and may not require further resection. On the other hand, those that have florid papilla formation (with villous-intestinal or pancreatobiliary patterns) may warrant further attention [75]. Typically, if there are florid papillary nodules at the margin, there are a lot more papillary nodules in the remaining pancreas, some of which prove to have higher-grade dysplasia in further examination. Therefore, such lesions may require further resection, if clinically indicated.

*IPMN with CIS or Invasive Carcinoma.* The relative risk of 'progression' and fatal outcome in IPMNs is difficult to calculate. Even patients with tubular type invasive carcinoma arising in IPMNs sometimes experience a more protracted clinical course than those with conventional ductal adenocarcinoma of this organ. Nevertheless, there is general consensus that IPMNs with CIS or invasive carcinoma are potentially fatal diseases if left untreated, and ought to be completely resected whenever feasible. To a lesser degree, the same may also apply to PanIN-3, which may be coincidentally encountered in patients with IPMN [76]. It should be noted that in some patients with IPMNs, it is difficult to determine whether some of the neoplastic changes within the small ducts represent PanINs or IPMNs [40, 77, 78]. At this point, this question is more an academic exercise than a practical issue, because, if such a lesion is encountered at the margin, the management should be based on the degree of cytologic atypia, and if frank CIS is noted, further resection may be attempted, if clinically indicated.

#### *Frozen Section for MCNs*

For MCNs, the role of frozen section appears to be more limited. Typically, MCNs have thick-walled cysts and their boundaries are easily discernible. The vast majority forms a localized mass in the tail or body, and unlike in IPMNs, microscopic extension of the lesion into the seemingly uninvolved pancreas is very uncommon. However, frozen section is indicated to rule out invasive

carcinoma, in particular, if a dubious firmness is close to the resection margin. If invasive carcinoma is detected at the margin, it ought to be treated as any other invasive carcinoma of this organ. Rarely, an incidental PanIN may also be detected at the margin. As discussed previously, PanIN-1 and -2 are common incidental findings, including in pancreata with MCNs [74, 79]. These are generally regarded as clinically inconsequential. Coincidental PanIN-3, on the other hand, is exceedingly uncommon in the absence of ductal adenocarcinoma. If encountered at the margin, PanIN-3 may require further attention.

*5b. Are there special instructions for specimen processing in MCNs and IPMNs?*

In IPMNs and MCNs, in-situ and invasive carcinoma may be multifocal and macroscopically (grossly) invisible. Therefore, it is not possible to rule out the presence of carcinoma unless the neoplasm is examined thoroughly. This is probably the main reason for the discrepancy in the literature regarding the value of grade (classification as adenoma, borderline, CIS, etc.) in these neoplasms [26, 30, 36]. It appears that undergrading due to undersampling is possibly the main reason for the 'unexpectedly' aggressive clinical course of some lower-grade examples of IPMNs and MCNs. Accordingly, some authors advocate pathologic sampling of the entire neoplasm [36, 40].

*5c. Are there special instructions for specimen processing to differentiate branch duct from main duct IPMNs?*

Once the neoplasm is resected and examined pathologically, the significance of classifying an IPMN as branch duct vs. main duct type is largely overridden by the other pathologic parameters such as the presence, type and extent of invasive carcinoma or grading of the IPMN component. Nevertheless, there is some evidence that branch duct IPMN may be a distinct subset, and it is suggested that the pathologists make every attempt to classify the process as branch duct or main duct type by documenting the distribution of the lesion in the ductal system. There are no special instructions for specimen processing for this purpose. However, it should be kept in mind that there are no reliable histological features to distinguish main ducts from the branch ducts in the pancreas by microscopic examination alone, especially when the duct is dilated by IPMN. Therefore, careful dissection of the specimen and proper identification of the main duct in the sections guide (either in a text form or by a diagram) is imperative in documenting the findings in the main duct. There are different approaches to dissection

of these specimens, and the Japanese approach is well described in the textbook [80]. Taking a photo and a photocopy of the gross cut sections makes it easy to compare the relationships between the lesion and the main and/or branch duct.

## 6. Method of Follow-Up

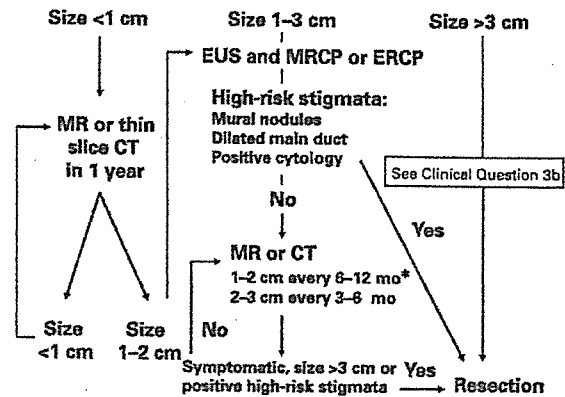
*6a. How should patients with non-resected IPMN and MCN be followed? How often should they be followed, and which techniques should be employed as baseline investigations?*

The decision to follow rather than resect a pancreatic cystic lesion is a matter of clinical judgment based on the age of the patient, comorbidities, and estimation of the cancer risk in the lesion. It is clear that the risk of prevalent cancer is high in main duct IPMN (table 2). Although this has not been formally studied, a review of studies on branch duct IPMN suggests that the prevalence of invasive cancer may be high (up to 30%) in symptomatic branch duct IPMN and low (0–5%) in those with asymptomatic branch duct IPMN. There are few reports in the English literature on identifying predictors of malignancy in asymptomatic mucinous lesions [22]. There have been four reports in the English literature describing the natural history of pancreatic IPMN evaluated by ERCP, CT or MRCP [81–84].

Based on limited available data from these studies it appears that asymptomatic cystic lesions without main duct dilation (>6 mm), those without mural nodules, and those <30 mm in size have a low risk of prevalent cancer and a low risk of progressing to invasive cancer in near-term (12- to 36-month) follow-up.

Ideally the imaging modality at baseline and follow-up should provide adequate information regarding the size of the lesion, size of the main pancreatic duct, and presence of intramural nodules. At least the first two criteria can be assessed satisfactorily by using non-invasive imaging studies such as multidetector high-resolution CT or MRCP, or by more invasive tests such as EUS. Assessment for intramural nodules requires EUS. Transabdominal ultrasonography is useful for follow-up in thin patients with clearly visualized cysts.

The interval between follow-up examinations remains to be determined. However, until definitive studies are performed to answer this question, it would appear reasonable to do yearly follow-up if lesion is <10 mm in size, 6–12 monthly follow-up for lesions between 10 and 20 mm, and 3–6 monthly follow-up for lesions >20 mm



**Fig. 10.** Algorithm for the management of branch duct IPMN.  
 \* The interval of follow-up can be lengthened after 2 years of no change.

(fig. 10). On follow-up studies, appearance of symptoms attributable to the cyst (e.g., pancreatitis), presence of intramural nodules, cyst size >30 mm, dilation of the main pancreatic duct (>6 mm) would be indications for resection. The interval of follow-up can be lengthened after 2 years of no change.

*6b. How should patients with surgically resected IPMNs and MCNs be followed? How often should they be followed and which techniques should be employed as baseline investigations?*

Patients with resected benign MCNs do not need follow-up, since several studies have shown that the risk of recurrence following resection is nil [29, 35]. Patients with resected malignant MCNs do have a significant risk of recurrence, and should be followed up every 6 months regarding local recurrence and distant metastasis (mainly hematogenous) using either CT or MRI. Patients with resected benign IPMNs do have a risk of recurrence in the remaining pancreas, and if it occurs can benefit from further resection. The frequency of this event and its relationship to surgical margins (i.e., positive, negative or indeterminate) is not clear, since most series thus far have had relatively short median follow-up, but seems to be at least 7% in non-invasive IPMN [23, 24, 40]. There is no evidence in the literature to define the frequency and type of surveillance that is required to detect these recurrences. One study suggests only clinical follow-up, and imaging if symptoms appear [40], but it is not clear if imaging in absence of symptoms could be beneficial by detecting earlier lesions. It may be reasonable to get yearly follow-

up with CT or MRI, and then space this interval if no changes have occurred over several years. Patients with invasive IPMNs do have a significant risk of recurrence, and probably should be evaluated every 6 months. Serum levels of CEA and CA19-9 have no proven value in the follow-up of these patients, and if obtained it should be done for the purposes of research.

*6c. Should care be taken to the possible occurrence of other malignant neoplasms in patients with IPMNs on follow-up?*

There have been several reports in the English literature describing the high prevalence of malignant neoplasms in patients with IPMNs but not in those with MCNs. Yamaguchi et al. [85] reported that 27% of 48 patients with IPMNs had synchronous or metachronous malignant neoplasms in the stomach, colon, rectum, lung, breast, liver, but only in 5% of 21 patients with MCNs. Sugiyama and Atomi [71] also documented that 32% of 42 patients with IPMNs developed extrapancreatic malignant neoplasms. Adsay et al. [72] found a history of another malignancy in 29% or 8 of 28 patients with IPMNs. Osanai et al. [86] gave a 24% prevalence of extrapancreatic malignancies in a large series of 148 patients with IPMNs. Furthermore, Yamaguchi et al. [70] reported synchronous or metachronous occurrence of pancreatic cancer of ordinary type in the pancreas harboring IPMNs. Although there is not yet definitive evidence, care should be taken to the possible occurrence of malignant neoplasms in the pancreas and other organs in patients with IPMNs on follow-up.

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● 症 例 ●

## 肝転移巣に S-1 単独療法が奏効し消失した進行膵癌患者の 1 例

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Resolution of Liver Metastases in Response to S-1 Monotherapy in Advanced Pancreatic Cancer—A Case Report: Nobumasa Mizuno, Akira Sawaki and Kenji Yamao (*Dept. of Gastroenterology, Aichi Cancer Center Hospital*)

## Summary

We report a case in a late phase II clinical study investigating the efficacy and safety of the oral fluoropyrimidine anticancer drug S-1. The drug proved effective in a patient with inoperable advanced pancreatic cancer in whom radiation therapy was not indicated. The antitumor effect after 4 courses was rated excellent, with a target site (liver) evaluation of CR and overall evaluation of PR. In particular, two liver metastases, measuring 18.7×15.4 mm and 16.2×14.6 mm, respectively, both resolved, and S-1 was found to exert a potent antitumor effect against metastases. Assessment of adverse events revealed no grade 3 or 4 adverse reactions, and other adverse events were all mild. Based on the above results, S-1 appeared to be effective against advanced pancreatic cancer and showed excellent tolerability. Key words: Advanced pancreatic cancer, S-1, Liver metastases (Received Aug. 15, 2006/Accepted Aug. 31, 2006)

要旨 切除不能で放射線療法の適応のない進行膵癌患者に、経口フッ化ピリミジン (FP) 系抗癌剤 S-1 を投与して、その有効性と安全性を検討した後期臨床第 II 相試験にて奏効した 1 症例を報告した。4 コースまでの抗腫瘍効果は、評価部位 (肝) CR、総合評価 PR と優れた判定を得た。特に治療前の、① 18.7×15.4 mm、② 16.2×14.6 mm の 2 か所の肝転移巣はともに消失し、S-1 の転移巣に対する強力な抗腫瘍効果を認めた。有害事象については、grade 3~4 の副作用を認めず、その他はいずれも軽微であった。以上の成績から、S-1 は進行膵癌に有効かつ忍容性に優れた薬剤であると考えられた。

## はじめに

膵癌は各種の画像診断が進歩した今日でも、ほとんどの症例が進行癌で発見され、しかも極めて難治な癌の一つである。膵癌に対する全身化学療法としては、従来 5-FU が汎用されてきたが奏効率は低く、さらに 5-FU の血中濃度の上昇による消化器毒性から重篤な下痢や口内炎などの有害事象の頻発が問題となっていた。1997 年に Burris らは、切除不能進行膵癌に対する gemcitabine (GEM) と 5-FU との比較試験において、GEM 群の生存期間が有意に優れていたと報告し<sup>1)</sup>、以降 GEM が切除不能進行膵癌の標準治療となっているが、その治療成績は未だ満足できるものではない。近年、強力な 5-FU の分解抑制作用を有するギメラシル (CDHP) および消化器毒性軽減のモジュレーターとして見いだされたオテラシルカリウム (Oxo) をテガフル (FT) に配合した経口

FP 系抗癌剤 S-1 が開発され、高い抗腫瘍効果と消化器毒性による副作用軽減効果が報告されている<sup>2)</sup>。今回、切除および放射線療法の適応がなく、測定可能な転移巣を有する膵癌患者を対象に実施した、S-1 単独療法の後期臨床第 II 相試験において奏効した 1 症例を報告する。

## I. 治療法

S-1 の初回投与量は、患者の体表面積 (m<sup>2</sup>) に合わせ 1 回量を 1.25 m<sup>2</sup>未満の場合は 40 mg/回、1.25 m<sup>2</sup>以上~1.50 m<sup>2</sup>未満の場合は 50 mg/回、1.50 m<sup>2</sup>以上の場合は 60 mg/回とし、朝夕食後の 1 日 2 回、28 日間連日経口投与し、その後 14 日間の休薬をもって 1 コースとする<sup>3)</sup>。本コースによる投与を繰り返し行うが、忍容し難い有害事象が生じた場合は、投与量を 1 段階下げて投与を再開する。初回基準量が 50 mg/回の場合は 40 mg/回、60 mg/回の場合は 50 mg/回とそれぞれ減量する。40 mg/



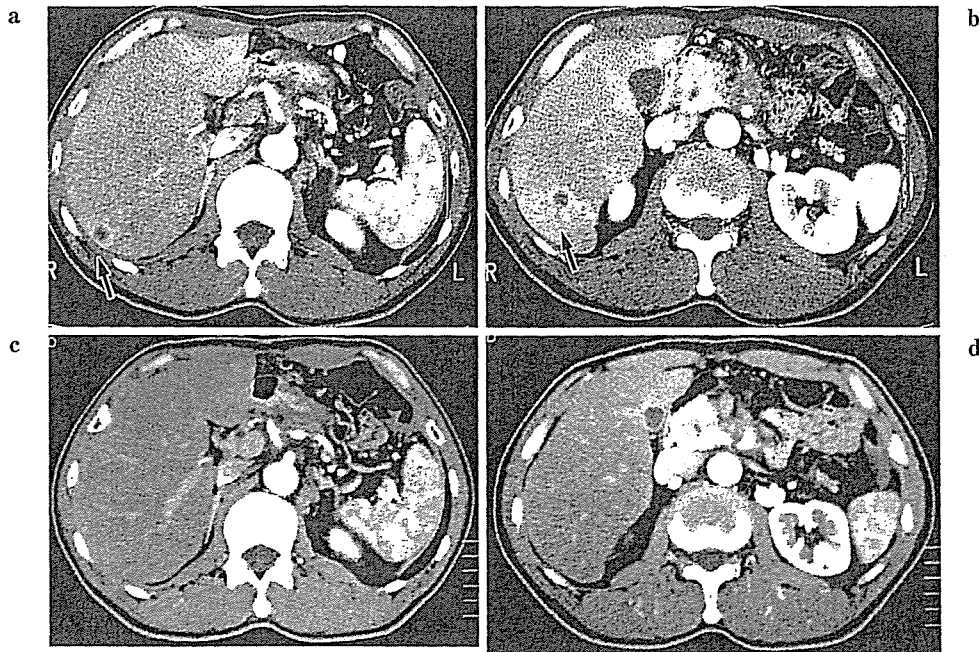


図1 肝転移巣のCT検査所見  
 a, b: 治療前 (① 18.7×15.4 mm, ② 16.2×14.6 mm)。  
 c, d: 4コース後CR (① 0.0×0.0 mm, ② 0.0×0.0 mm)。

回の場合は休薬とする。その後、さらに有害事象を示す症状が発現した場合は、当該コースにおける投与期間の短縮が考慮される。また、病態進行(PD, 臨床症状の悪化を含む)が認められない限り、最低2コース以上4コースまで投与を繰り返した。なお、抗腫瘍効果が不変(NC)以上と認められる場合は、5コース以降、患者からの中止の申し出(同意撤回)がなく、明らかな病態の進行あるいは投与継続が困難な有害事象が発現しない限り治験期間中は治療を続行することができることとした。

## II. 症 例

症例: 50歳代, 男性。身長 168.5 cm, 体重 58.0 kg, 体表面積 1.613 m<sup>2</sup>, Karnofsky performance status (KPS) 100%。

主訴: 腹痛。

既往歴: 十二指腸潰瘍で幽門側胃切除術。

家族歴: 特記すべきものなし。

現病歴: 腹痛を主訴に近医を受診, CTにて膵体部腫瘍を疑われ紹介受診となり, 精査加療目的で入院となった。

入院時現症: 胸部に異常なし。腹部正中に手術痕を認め, 上腹部に軽度圧痛を認めた。

血液検査所見: Hb 12.5 g/dl, WBC 4,050/ $\mu$ l (好中球 62.0%), Plt 14.4×10<sup>4</sup>/l, T-Bil 0.8 mg/dl, AST 16 IU/l, ALT 25 IU/l, ALP 151 IU/l, Alb 4.1 g/dl, Cr 0.71 mg/dl, CEA 1.4 ng/ml, CA19-9 221.8 U/ml。

CT検査所見: 膵体部に長径約5 cmの造影効果の乏しい腫瘍を認め, 肝に多発腫瘍を認め膵癌の肝転移と考え

られた。

病理検査: 確定診断目的に, 膵体部腫瘍に対して超音波内視鏡下穿刺吸引(EUS-FNA)を行い腺癌を認め, 膵癌・多発肝転移と診断した。

治療経過: 本人の同意を得て, 肝の2病変を標的病変としてS-1単独療法の後期臨床第II相試験に登録された。2003年12月24日よりS-1 60 mg/回×2/日で28日間継続投与し, 14日間を休薬とし, 3コースの投与を行った。4コース目には, 悪心を認め120 mg/日は9日間とし, 以降100 mg/日に投与量を減量して5日間投与し, さらに80 mg/日に減量して残り14日間の投与を行った。血液毒性ではgrade 3, 4の有害事象は認めず, その他についてはいずれも軽微であった。

抗腫瘍効果: 膵原発巣の判定はNCであったが, 肝転移巣(2病変)の治療前のCT所見(図1 a, b)に対し, 2コース投与1週後の判定では12.6%と著明に縮小し, 4コース後の判定では腫瘍の消失を認めた(図1 c, d)。これらの結果から, S-1の標的病変(肝転移巣)における高い抗腫瘍効果が注目され, 総合評価はPRであった。また腫瘍マーカーについては, CA19-9は登録前が221.8 U/ml, 1コース開始時が252.3 U/mlと高値を示したものの, 1コース終了時点では218.9 U/mlとほとんど低下せず, その後3コース目終了後に80.4 U/mlまで低下したが, 4コース終了後には103.4 U/mlとやや高値を示した(図2)。6コース終了時のCT所見で肝に新病変を認め, 2004年10月12日PDと判断し, S-1の内服を中止した。2004年10月19日より二次治療としてGEM

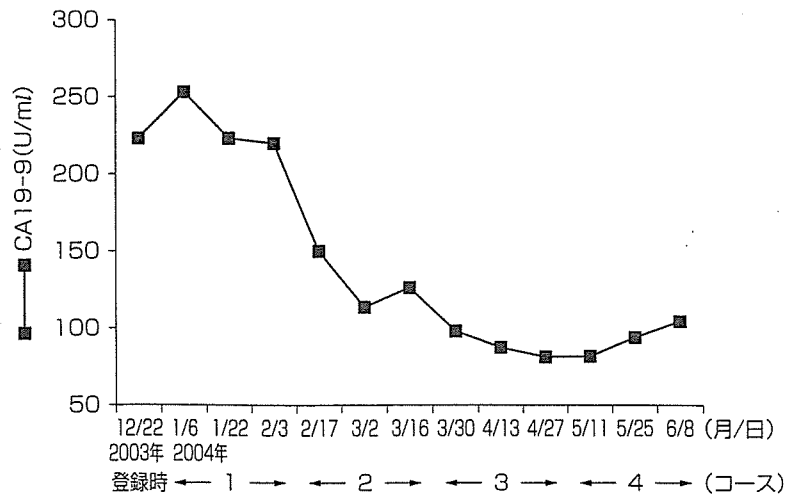


図2 CA19-9の推移

を投与したが、2005年2月1日に腫瘍死した。全治療期間は1年1か月であった。

### III. 考 察

今回報告した症例は、S-1単独投与により4コースまでの抗腫瘍効果については総合評価でPRを得た。膵原発巣の判定はNCであったが、肝転移巣の判定ではCRが得られた。

5-FUは、ジヒドロピリミジンデヒドロゲナーゼ(DPD)により分解され、不活性となる。従来、5-FUは肝でDPDによって分解されると理解されてきたが、近年、非小細胞肺癌、胃癌、乳癌などの癌組織にDPDの高発現を認め<sup>4)</sup>、腫瘍組織における5-FUの抗腫瘍効果の減弱化が問題視されるようになった。DPDを拮抗的に阻害するCDHPにより、腫瘍組織における強力な抗腫瘍効果の発現が見いだされ、OxoとともにFTと配合したS-1は、すでに基礎実験においては種々の癌に対して、静注5-FUや経口UFTと比較して高い抗腫瘍活性の発現が判明している<sup>5)</sup>。

毒性に関してはgrade3の副作用を認めず、好中球減少(grade2)を認めたが回復し、他はすべて軽微であった。S-1はCDHPとOxoをFTとモル比1:0.4:1で配合されているが、Oxoは消化器部位におけるリン酸化物の生成を抑制し、消化器障害を軽減する。同時に、FTから生成された5-FUのDPDによる分解に対し、CDHPが強力に抑制して高い抗腫瘍効果を発揮し、さらに5-FUからの分解産物を原因とする中枢神経毒性、神経毒性や手足症候群などの軽減作用を発現していることが推測される。今回の症例では、5-FUの活性化による代表的な消化器毒性の発現はいずれも軽微であったことから、CDHPとOxoの相加効果が判明したと考える。

また、2006年に発行された「膵癌診療ガイドライン」

の化学療法では、切除不能膵癌に対する一次化学療法として、投与継続が困難な有害事象が発現しなければ、病態の明らかな進行を認めるまでGEMの投与継続を推奨している<sup>6)</sup>。しかし、GEMの無効例や奏効後の再燃例に対する二次化学療法が模索され、さらに生存期間の延長によって患者のQOLへの配慮がより重要となることが指摘される現在、S-1はその抗腫瘍効果や有害事象発現が少ないこと、さらに経口投与であることから在宅投与が可能でQOLの向上が期待され、その高い有用性が注目される。

前期臨床第II相試験では、19人中4人にPRを認め(21.1%)、生存期間中央値は5.6か月であった。有害事象の多くは一過性で、外来治療が可能であった。

後期臨床第II相試験は、未治療の進行膵癌患者を対象に、7施設の40例を被験者とし、S-1単独投与の有効性と安全性を目的に実施された。40例中PR15例、NC11例、PD13例、評価不能1例で奏効率は37.5%(95%信頼区間:22.7~54.2%)、生存期間中央値8.8か月(7.5~10.8か月)と、前期臨床第II相試験を大幅に上回る成績が得られた<sup>7)</sup>。症状緩和効果は評価対象10例中4例で有効であった(40%)。grade3~4の有害事象は食欲不振(12.5%)、下痢(7.5%)、悪心(7.5%)、好中球減少(7.5%)であり、治療関連死は認められていない。

今回報告した症例では、容認し難い有害事象の発現を認めず、また膵癌では疼痛や全身状態の悪化などの症状が高率であることからその抑制が重要であるが、高い症状緩和効果を示すS-1は、進行性膵癌に有効かつ忍容性に優れた薬剤であると考えられる。

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# A randomized multicenter trial comparing resection and radiochemotherapy for resectable locally invasive pancreatic cancer

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**Background.** Though the outcome of resection for locally invasive pancreatic cancer is still poor, it has gradually improved in Japan, and the 5-year survival is now about 10%. However, the advantage of resection over radiochemotherapy has not yet been confirmed by a randomized trial. We conducted this study to compare surgical resection alone versus radiochemotherapy without resection for locally invasive pancreatic cancer using a multicenter randomized design.

**Methods.** Patients with pancreatic cancer who met our preoperative criteria for inclusion (pancreatic cancer invading the pancreatic capsule without involvement of the superior mesenteric artery or the common hepatic artery, or without distant metastasis) underwent laparotomy. Patients with operative findings consistent with our criteria were randomized into a radical resection group and a radiochemotherapy group (200 mg/m<sup>2</sup>/day of intravenous 5-fluorouracil and 5040 cGy of radiotherapy) without resection. The 2 groups were compared for mean survival, hazard ratio, 1-year survival, quality of life scores, and hematologic and blood chemical data.

**Results.** Twenty patients were assigned to the resection group and 22 to the radiochemotherapy group. There was 1 operative death. The surgical resection group had better results than the radiochemotherapy group as measured by 1-year survival (62% vs 32%,  $P = .05$ ), mean survival time (>17 vs 11 months,  $P < .03$ ), and hazard ratio (0.46,  $P = .04$ ). There were no differences in the quality of life score or laboratory data apart from increased diarrhea after surgical resection.

**Conclusions.** Locally invasive pancreatic cancer without distant metastases and major arterial invasion appears to be best treated by surgical resection. (*Surgery* 2004;136:1003-11.)

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PANCREATIC CANCER remains one of the most difficult diseases to cure by resection. The results of surgical treatments including super-radical resections are

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poor.<sup>1-3</sup> Pancreatic cancer currently kills more than 17,000 persons per year in Japan and is the fifth leading cause of cancer death.<sup>4,5</sup> The overall 5-year survival in patients undergoing margin-negative resection varies from 6.8% to 25%.<sup>6-10</sup> However, most surgeons maintain that resection is the only way to provide long-term survival to pancreatic cancer patients, especially since improvements in operative and perioperative management have reduced operative mortality and decreased hospital stay.<sup>9-11</sup>

Pancreatic cancer is one of the most chemoresistant human malignancies.<sup>12-14</sup> The results