

Original Papers

**Surgical experiences of intraductal papillary mucinous neoplasms of the pancreas
at a single Japanese institute: Characteristics of malignant histology**

*Atsushi Nanashima, MD, Yoriyisa Sumida, MD, Takafumi Abo, MD,
Masahiro Oikawa, MD, Hiroaki Takeshita, MD, Shigekazu Hidaka, MD,
Terumitsu Sawai, MD, Toru Yasutake, MD, Naoe Kinoshita, MD,*
Tomayoshi Hayashi, MD,* Takeshi Nagayasu, MD*

Division of Surgical Oncology and *Department of Pathology, Nagasaki University
Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan

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Corresponding and reprint requests to: Atsushi Nanashima, M.D.

Division of Surgical Oncology, Department of Translational Medical Sciences,
Nagasaki University Graduate School of Biomedical Sciences,
1-7-1 Sakamoto, Nagasaki 852-8501, JAPAN

Tel.: +81-95-819-7304 , Fax: +81-95-819-7306

E-mail: a-nanasm@alpha.med.nagasaki-u.ac.jp

ABSTRACT

Background/Aims: Characteristics of intraductal papillary mucinous neoplasms of pancreas (IPMN) have been clarified by a worldwide survey and meeting. However, the malignant behavior or prognosis of the disease is not always uniform.

Methodology: We examined the clinicopathologic demographics, surgical records and outcome according to degree of histologic malignancy in 18 IPMN patients between 1994 and 2006.

Results: Main duct type was observed in 3 patients, branch duct type in 6, and mixed type in 9. Eight of 18 patients (44.4%) had other malignancies, and other synchronous tumors were observed in the adenoma group. CA 19-9 was increased in invasive carcinomas. The size of the main pancreatic duct and cysts were not correlated with degree of malignancy. Mural nodules were more frequently observed in minimally invasive and invasive carcinomas. Segmental resection or observation was selected in the adenoma group; however, combined resection of main vessels was performed in invasive carcinoma groups. Although 3 of 5 patients with invasive carcinomas had a recurrence and poor patient prognosis, recurrence was not observed in other groups.

Conclusions: Surgical results for IPMN were satisfactory; however, it is necessary to determine the operative indication before the carcinoma becomes invasive as such lesions have a poor prognosis.

KEYWORDS: intraductal papillary mucinous neoplasms, pancreas, invasiveness

ABBREVIATIONS: intraductal papillary mucinous neoplasms (IPMN), intraductal papillary mucinous carcinomas (IPMC)

INTRODUCTION

Intraductal papillary mucinous neoplasms (IPMN) include the pancreatic diseases such as precancerous lesions, carcinoma in situ, and non-invasive or invasive advanced carcinomas, which are classified into three types: branch, main and mixed duct type (1, 2). This disease has been fully understood worldwide, and recently, the International consensus guidelines for management of IPMN of the pancreas were published (3). However, the malignant behavior or prognosis of the disease is not always uniform in each case. Some reports emphasize the importance of examination of histologic type difference (4-5) and the malignant characteristics of IPMN have not been fully clarified. Therefore, it is still necessary to examine the characteristics associated with the degree of histological malignancy or patient outcomes at this stage. In the present report, to clarify characteristics, we examined the clinical demographics, pathological data and outcome in 18 IPMN patients at a single Japanese institute.

METHODOLOGY

Definition and Pathological Diagnosis of IPMN

In the present study, IPMN was classified as main duct IPMN or branch duct IPMN, based on the histological diagnosis (3). The definition of main duct type was when the size of the main pancreatic duct was more than 5 mm. However, lesions in patients who did not undergo resection were diagnosed by image diagnosis. All patients underwent enhanced computed tomography, magnetic resonance image, endoscopic ultrasonography or endoscopic retrograde pancreatography for preoperative diagnosis.

We analyzed 18 patients with IPMN who did or did not undergo surgical resection in the Division of Surgical Oncology, Nagasaki University Graduate School of Biomedical

Sciences (NUGSBS), and its related hospitals between 1996 and 2006. The study design was approved by the Human Ethics Review Board of our institution. Informed consent for data collection was obtained from each patient during this period. Anesthetic and patient data were retrieved in the NUGSBS database. Tumor stage and curability were determined according to the second English edition of *Classification of Pancreatic Carcinoma* (6). Definition and criteria were followed by *the International Consensus Guidelines for Management of Intraductal Papillary Mucinous Neoplasms and Mucinous Cystic Neoplasms of the Pancreas* (3). Subjects were divided into four groups by histologic classification: 1) *Adenoma* including borderline atypia in 6 patients, 2) *non-invasive* in 3, 3) *minimally invasive* carcinomas in 4 and 4) *invasive* carcinomas in 5.

Statistical Analysis

Data from different groups were compared using one-way analysis of variance (ANOVA) and examined by Student's *t*-test and categorical data were analyzed by the Fisher's exact test. A two-tailed *P* value of < 0.05 was considered significant. Statistical analyses were performed using SAS software (Statistical Analysis System Inc., Cary, NC).

RESULTS

Patients included 12 men and 6 women aged 49-81 years old (mean 69.9±11.1) (**Table 1**). IPMN lesions were in the pancreas head in 13 patients, body in 2, and tail in 4. One patient had 2 IPMN, 1 in the head and 1 in the tail. IPMN lesions were not significantly different between the 4 histologic groups. Carcinoma of IPMN (IPMC) was main duct type in 2 patients, branch duct type in 1, and mixed type in 9. Most cases of

IPMC were main duct type or mixed type, and therefore, branch type was dominant in adenoma of IPMN. Diabetes and hypertension were frequently associated with IPMN patients. Eight of 18 patients (44.4%) had other malignant neoplasms, which were observed in each histologic group. Synchronously accompanying malignant tumors were observed only in the group of adenoma. Preoperative tumor markers such as CEA and CA 19-9 were increased in minimally invasive and invasive carcinomas. One patient in the adenoma group showed increased levels of CA 19-9; however, this increase might have been influenced by associated gallbladder carcinoma.

The size of the main pancreatic duct or cyst size was not correlated with degree of malignancy (**Table 2**). Mural nodule was more frequently observed in minimally invasive and invasive carcinomas, but not in adenomas. Operative procedures were not significantly different between groups; however, segmental resection or observation was selected in the adenoma group. On the other hand, combined resection of surrounding main vessels was performed in the invasive carcinoma group because of direct vascular involvement. In groups of adenoma, non-invasive and invasive carcinomas, recurrence of IPMN was not observed. Hence, 3 of 5 (60%) patients with invasive carcinomas had a severe tumor recurrence, which led to a poor patient prognosis. Two other patients with invasive carcinoma showed long-term survival without tumor recurrence. Regardless of being tumor recurrence-free, 3 patients died and 2 died from other malignant diseases at an early period after operation for IPMN in adenoma, non-invasive and minimally invasive carcinoma groups.

DISCUSSION

IPMN is an established concept and therefore diagnostic and treatment criteria are similar worldwide (3). Surgical removal of this disease is the only curable treatment (7). In the present study, we compared clinical parameters in each degree of histological malignancy according to the international consensus guidelines (3). Based on the report by Tanaka et al., most cases of branch type IPMN showed benign neoplasm (8); however, in our series 1 of 12 IPMC cases were branch type, which was located in the pancreatic uncus. Previous reports reported the relationship of IPMN and other concomitant malignant neoplasm (9). In the present study, concomitant neoplasm was frequent as well, particularly in adenoma patients. Genetic instability may be associated with this multiple carcinogenesis (10). CA19-9 is a useful predictive marker of pancreatic or biliary carcinomas (11); however, the usefulness of CA19-9 as a predictor of malignant behavior in IPMN has not been clarified to our knowledge. In our series, an increase of CA19-9 was rarely observed, even in minimally invasive IPMC. An increase in CA19-9 value was thought to predict invasiveness of IPMC preoperatively.

The surgical indication of IPMN is based on the size of the main pancreatic duct, presence of a cyst in branch type, or presence of mural module in the duct (3, 12). Our criteria of surgical resection for IPMN has been main pancreatic duct >5 mm, peripheral cysts >30 mm or presence of mural nodule. Some reports have indicated the necessity of resection in smaller cysts <30 mm because of the malignant potential (13, 14). Schmidt et al. reported that predictors of malignant and invasive pathology of IPMN were mainly pancreatic duct diameter (more than or equal to 6 mm), multiple side branch lesions and the presence of mural nodules; however, branch size, location and distribution of lesion were not related to invasiveness (14). At this stage, however, it is still difficult to judge

the malignancy of small lesions of branch type IPMN using the available diagnostic tools. Careful follow-up seems to be better in branch type IPMN with small cysts <30 mm without mural nodules to avoid unnecessary resection, because the possibility of operative risk with limited resection of the pancreas is not low (15). In the present series, the size of the main pancreatic duct or cyst size was not significantly associated with the malignant histologic degree; however, the presence of mural nodule was correlated with degree of histological malignancy. This factor is the most reliable predictor for the diagnosis of invasive IPMC. Most cases underwent major pancreatic resection such as pancreaticojejunostomy or distal pancreatectomy because of the tumor location, size and difficulty of preoperative determination of malignancy or invasiveness of IPMN, as in other reports (16, 17). IPMN often spreads along the epithelium of the pancreatic duct (18), which is a serious problem in the decision of whether to resect the stump of the pancreas. Total pancreatectomy is often performed based on other reports (19).

Postoperative outcomes in adenoma, non-invasive carcinoma and minimally invasive carcinoma of IPMN were satisfied in our results. Unfortunately, 3 patients died of other diseases. Previous reports also indicated good long-term IPMN outcomes without invasiveness after complete resections (14, 20). Based on these degrees of histological malignancy, surgical resection is strongly recommended at this stage. Occurrence or simultaneous presence of other malignant lesions should be followed, as these sometimes influence prognoses (21). On the other hand, in invasive IPMC, combined resection of the surrounding main vessel was necessary in two cases; however, the prognosis was extremely poor in 3 of 5 patients. Adjuvant chemotherapy or brachiotherapy is necessary to improve the prognosis (22). Our results indicate that the treatment strategies for invasive IPMC should be considered the same as those for

advanced tubular adenocarcinomas of the pancreas (23). Recent reports showed better patient prognoses in invasive IPMN in comparison with those in tubular adenocarcinomas of the pancreas (14, 24, 25). Our result also showed a good long-term prognosis in 2 patients with invasive IPMN. The surgical benefits for invasive IPMN still require further examination, and future work in a larger number of cases is necessary.

In conclusion, we examined 18 patients with IPMN including 17 who underwent surgical treatment. Surgical removal of the disease provided a good prognosis in adenoma, non-invasive carcinoma and minimally invasive carcinoma cases of IPMN. However, careful management of combined malignant neoplasms is necessary. Aggressive surgical resection for invasive IPMN improves the long-term prognosis, and, furthermore, adjuvant anti-cancer treatment is expected to improve patient survival.

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Table 1. Preoperative patient demographics according to degree of malignancy

	Age (years), Gender	Lesions	Duct type	Accompanied disease	History of other cancer	CEA (ng/mL; N<3.0)	CA19-9 (U/mL; N<37)
<i>Adenoma</i>							
1	77y male	tail	branch	—	—	2.2	<1.0
2	60y male	body	branch	—	—	1.0	13.1
3	78y female	body	main	DM,HT	Uterine ca.	2.5	3.2
4	69y male	head	branch	—	Bile duct ca.*	1.3	35.2
5	75y female	head	mixed	HT	Renal cell ca.*	2.1	2
6	79y female	head	branch	Arrhythmia	Gallbladder ca.*	3.4	137
<i>Non-invasive carcinomas</i>							
7	79y female	head	mixed	HT	—	1.7	18
8	72y male	head	main	—	—	2.7	14.2
9	49y male	tail	mixed	—	Esophageal ca.	1.5	19.9
<i>Minimally invasive carcinomas</i>							
10	70y male	head	mixed	—	Gastric ca.	2.1	9.8
11	64y male	head & tail	mixed	HT	—	2.2	77.2
12	59y male	head	mixed	DM, HT	Colon ca.	1.5	52
13	77y male	head	main	HT, Tuberculosis	—	1.7	12
<i>Invasive carcinoma</i>							
14	59y male	head	branch	—	—	6.3	809.5
15	79y male	head	mixed	DM	—	2.9	131.9
16	71y female	head	mixed	—	—	1.2	30.6
17	61y male	head	mixed	HT	—	165	182.6
18	81y female	tail	mixed	HT	Colon ca.	1.5	15.2

DM; diabetes mellitus, HT; hypertension, *, synchronous diseases, Ca.; carcinomas, N; normal

Table 2. Surgical and pathological data, and patient outcomes

	Size of main duct (mm)	Size of cyst (mm)	Mural nodule	Operation	Tumor recurrence	Prognosis (months)
1	3	25	No	DP	No	Survival (21)
2	3	10	No	SR	No	Survival (78)
3	12	0	No	DP	No	Died from uterine ca. (10)
4	5	20	No	PPPD	No	Survival (50)
5	8	52	No	PPPD	No	Survival (22)
6	3	35	No	observation	—	Died from gallbladder ca.(14)
7	10	60	No	PPPD	No	Survival (79)
8	20	0	Yes	PD	No	Survival (51)
9	8	35	No	DP	No	Survival (8)
10	9	60	No	PD	No	Survival (44)
11	7	55	No	PPPD+DP	No	Died from pneumonia (84)
12	10	36	Yes	PPPD	No	Survival (40)
13	5	0	Yes	PPPD	No	Survival (8)
14	4	34	Yes	PPPD+SMV resection	Liver metastasis (8M)	Cancer death (12)
15	12	35	Yes	PD	No	Survival (61)
16	17	48	No	PPPD	Peritonitis carcinomatosa (41M)	Cancer death (43)
17	8	70	Yes	PD+PV resection	Liver metastasis (1M)	Cancer death (4)
18	9	20	Yes	DP	No	Survival (24)

(SR; segmental resection, DP; distal pancreatectomy, PPPD; pylorus preserving pancreatoduodenectomy, PD; pancreatoduodenectomy, SMV; superior mesenteric vein, PV; portal vein, ca.; carcinomas)