Is It Necessary to Follow Patients after Resection of a Benign Pancreatic Intraductal Papillary Mucinous Neoplasm?

Jin He, MD, PhD, John L Cameron, MD, FACS, Nita Ahuja, MD, FACS, Martin A Makary, MD, FACS, Kenzo Hirose, MD, FACS, Michael A Choti, MD, FACS, Richard D Schulick, MD, FACS, Ralph H Hruban, MD, Timothy M Pawlik, MD, PhD, FACS, Christopher L Wolfgang, MD, PhD, FACS

BACKGROUND: Little is known about the risk of subsequently developing a new or progressive intraductal papillary mucinous neoplasm (IPMN) after partial pancreatic resection of a noninvasive IPMN.

STUDY DESIGN: One hundred thirty patients with more than 1 year of follow-up after resection were included in this analysis.

RESULTS: At a median follow-up of 38 months, 22 (17%) developed imaging evidence of a new or progressive IPMN. Eleven (8%) underwent completion resection. Three of the 11 patients had invasive adenocarcinoma. Two other patients developed metastatic pancreatic adenocarcinoma and did not undergo resection. All 5 patients (4%) with cancer had negative margins at initial operation. Sixteen of 100 patients (16%) with negative margins for IPMN at the initial operation developed a new IPMN vs 6 of 30 patients (20%) with margins positive for IPMN ($p = ns$). Five of 22 patients (23%) with a new IPMN had a family history of pancreatic cancer, while 8 of 108 patients (7%) without a new IPMN had a family history ($p < 0.05$).
Overall, the chances of developing a new IPMN at 1, 5, and 10 years after the initial surgery were 4%, 25%, and 62%, respectively, and of requiring surgery were 1.6%, 14%, and 18%, respectively. The estimated chances of developing invasive pancreatic cancer were 0%, 7%, and 38% at 1, 5, and 10 years, respectively.

CONCLUSIONS: Patients who have undergone resection for noninvasive IPMN require indefinite close surveillance because of the risks of developing a new IPMN, of requiring surgery, and of developing cancer. A family history of pancreatic cancer, but not margin status or degree of dysplasia, is associated with a risk of development of a new or progressive IPMN. (J Am Coll Surg 2013; 216:657–667. © 2013 by the American College of Surgeons)

Intraductal papillary mucinous neoplasms (IPMN) of the pancreas are cystic precursor lesions to invasive adenocarcinoma (ductal adenocarcinoma). There is a strong interest in the study of IPMNs because they represent an opportunity for early detection and cancer prevention in the subset of patients with this specific type of pancreatic neoplasm. These lesions were first described by Ohhashi and colleagues in 1982, and criteria for their diagnosis were established by the World Health Organization (WHO) in 1996.[1] Over the past decade there have been major advances in our understanding of the biology and natural history of IPMN as a result of extensive research effort in this field.[2-5]

Current evidence suggests that IPMNs progress to invasive carcinoma through a series of morphologic and genetic changes similar to their microscopic counterpart called pancreatic intraepithelial neoplasms (PanINs). At the light microscopic level, IPMNs are associated with a spectrum of dysplastic changes of the epithelium that range from low- to high-grade dysplasia. High-grade dysplasia, also known as carcinoma in situ, is similar in appearance to invasive carcinoma but does not breach the basement membrane. The entire spectrum of dysplastic changes, including carcinoma in situ, is considered to be noninvasive, and long-term survival after resection of these lesions is excellent in relation to invasive ductal adenocarcinoma.[6]

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From the Department of Surgery (He, Cameron, Ahuja, Makary, Hirose, Choti, Schulick, Pawlik, Wolfgang), and the Department of Pathology and the Sol Goldman Pancreatic Cancer Research Center (Hruban), Johns Hopkins Medical Institutions, Baltimore, MD.

Correspondence address: Christopher L Wolfgang, MD, PhD, FACS, Department of Surgery, Johns Hopkins Hospital, 600 N Wolfe St, Blalock 685, Baltimore, MD 21287. email: cwolfga2@jhmi.edu

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An interesting feature of IPMNs is their propensity toward multifocality. The rate of synchronous IPMN lesions has been reported in some studies to be as high as 83%.[7] In addition to the finding of synchronous disease, several studies report a significant risk for developing metachronous lesions over time.[8] The association of IPMN with nonpancreatic primary cancers such as colorectal cancer has also been documented.[9] Taken together, these studies suggest a "field-defect," which places the entire pancreas at risk for neoplasia. It would follow that patients undergoing partial pancreatic resection for noninvasive IPMN are at risk for developing subsequent disease within their pancreas. Indeed, previous work has demonstrated that this is the case in up to 8% of patients.[10-13] Because most of these studies include both malignant and benign IPMN, or are based on relatively few patients, numerous questions still remain about recurrence after partial pancreatectomy of a noninvasive IPMN.

The goal of this study was to evaluate the risk of developing a new or progressive IPMN and invasive pancreatic cancer after resection of a noninvasive IPMN. Because IPMNs are known precursors to invasive cancer and are multifocal in nature, we hypothesized that patients undergoing partial resection of a noninvasive IPMN are at risk of developing subsequent clinically significant IPMN disease. We specifically sought to quantify the risk of developing clinically significant disease and to identify factors associated with progression.

METHODS

Patient characteristics

A retrospective review of a prospectively collected pancreatic resection database was performed. We identified 260 patients who underwent a partial pancreatic resection for a noninvasive IPMN at the Johns Hopkins Hospital between January 1995 and October 2010. Patients who had a total pancreatectomy or a pancreatectomy for IPMN with an associated invasive carcinoma were excluded from this study. We further limited the study to patients with at least 1 year of follow-up and with at least 1 follow-up imaging study available for review. Based on this selection process, a cohort consisting of 130 patients was identified and analyzed for this project.

Clinicopathologic data such as patient age, sex, lesion size on the pathologic specimen, lesion location, pathologic type, margin status, and overall survival were collected. The association between various clinicopathologic parameters and clinical outcome was assessed. Positive family history was defined as pancreatic cancer diagnosis in a first-degree family member (parent, sibling, or child) or a second-degree relative (an aunt, uncle, niece, or nephew).

Description of follow-up

Various diagnostic modalities including CT, magnetic resonance cholangiopancreatography (MRCP), or endoscopic ultrasound (EUS) were used as follow-up imaging studies. Follow-up was performed with imaging every 6 months for 2 years and annually thereafter. Data were collected on date of last follow-up, imaging result, and survival.

New IPMN was defined as new radiographic evidence of disease in the pancreatic remnant after partial pancreatectomy. Progression was defined as growth or development of a solid component in a nonresected synchronous IPMN. A clinically significant lesion was defined based on the International Consensus Guidelines (Sendai criteria): main duct dilation believed to not be associated with the operation, symptoms related to the new lesion, new lesion size >30 mm, or solid component in the new lesion, growth of >5 mm in cross section in a 6-month period, or evidence of pancreatic malignancy. By definition, for the purposes of this study, a clinically significant lesion warranted a completion pancreatectomy.

Pathologic examination

All pathologic specimens were reviewed by pathologists at our institution. Tumor size was referred to as the maximal size measured on the final pathologic specimen. Neoplasms were classified into 3 subtypes based on the principal site of tumor involvement: the main duct type, in which the lesion was located in the dilated main pancreatic duct with or without involvement of dilated branch ducts; the branch duct type, in which the branch ducts were dilated without involvement of the main pancreatic duct; and the mixed type. Noninvasive IPMNs were classified according to standard nomenclature as IPMN with low-grade dysplasia, IPMN with intermediate-grade dysplasia, and IPMN with high-grade dysplasia.[14,15] The new classification correlates with previous terminology in which IPMN with low-grade dysplasia, intermediate-grade dysplasia, and high-grade dysplasia was called "adenoma," "borderline," or "carcinoma in situ" (CIS), respectively.[16]

An intraoperative frozen-section examination of the pancreatic transection margin was performed, and the pancreatectomy was extended based on the presence of intermediate- or high-grade dysplasia. In our analysis, results were based on the final margin, not the intraoperative frozen section.

Statistical analysis

Statistical Package for the Social Sciences software was used to analyze data. Survival curves and recurrence curve were estimated using the Kaplan-Meier method and

compared using the Breslow test. Continuous variables were expressed as median ± standard deviation and were compared using the Mann-Whitney test. Categorical variables were compared using a chi-squared test (or Fisher's exact test). Overall survival was computed from the time of operative resection to the date of last follow-up. The presence of a statistically significant difference was denoted by $p < 0.05$.

RESULTS

Patient characteristics, surgical treatment, and pathologic results

We identified a total of 130 patients who underwent resection of a noninvasive IPMN with curative intent between 1995 and 2010 and had at least 1 year of follow-up. The characteristics of this cohort are summarized in Table 1. This study included 64 men (49%) and 66 women (51%), with a mean age of 67.5 years (range 37 to 90 years). Ninety-one (70%) of 130 patients had their initially diagnosed disease localized within in the head of the pancreas and underwent pancreaticoduodenectomy. In 39 (30%) patients, their initial IPMN was located in the body or tail of the pancreas and they underwent distal pancreatectomy with splenectomy. No patients underwent an enucleation or spleen-preserving distal pancreatectomy. There were no 30-day operative or in-hospital deaths.

Table 1. Demographics and Clinical Characteristics of 130 Patients with Noninvasive Intraductal Papillary Mucinous Neoplasm

Variable	Data
Median tumor size, cm (range)	2 (0–8)
Mean age, y (range)	67.5 (37–90)
Sex, male, n (%)	64 (49)
Location in pancreas, n (%)	
Body or tail	39 (30)
Head	91 (70)
Duct type, n (%)	
Main duct	23 (18)
Branch duct	79 (61)
Mixed	28 (22)
Pathologic grades, n (%)	
IPMN with low-grade dysplasia	23 (18)
IPMN with intermediate grade dysplasia	57 (44)
IPMN with high-grade dysplasia	43 (33)
Noninvasive IPMN	7 (5)
Resection margin status, n (%)	
All negative	104 (80)
Atypia/dysplasia at surgical margin	26 (20)

IPMN, intraductal papillary mucinous neoplasm.

Pathologic features of the resected IPMN are listed in Table 1. The median tumor size of the entire cohort was 2.0 cm (range 0 to 8 cm). Twenty-three patients had an IPMN (18%) classified as a main duct type and 79 (61%) had a branch duct type IPMN. The remaining 28 patients had an IPMN that was classified as mixed duct type. The median tumor sizes of each group were: 2.0 cm for the main duct group, 2.0 cm for the branch duct group, and 2.4 cm for the mixed duct type. The distribution of histologic grade among the cohort was: low-grade dysplasia in 23 (18%), intermediate-grade dysplasia in 57 (44%), and high-grade dysplasia in 43 (33%). The tumor size was not statistically different among the various categories of dysplasia ($p = 0.4$). The distribution of dysplasia in different types of IPMN is summarized in Table 2. No significant difference in distribution of dysplasia was identified among different types of IPMN. Consistent with the noninvasive nature of IPMN with high-grade dysplasia, no patients had lymph node metastases.

The pancreatic resection margins were negative for IPMN of any grade in 104 patients (80%). Atypia or low-grade dysplasia was present in the resection margin of 26 (20%) patients.

Fate of remnant pancreas

The median follow-up for the entire cohort was 38 months (range 12 to 207 months). Of the 130 patients, 22 (17%) developed suspected evidence of a new IPMN in the remnant pancreas based on postoperative surveillance imaging. The median time to development of a new IPMN was 46 months (range 13 to 134 months) after the initial resection. Among these 22 patients, 13 developed a lesion that met the Sendai criteria[17] or had evidence of widespread pancreatic cancer. The new

Table 2. Distribution of Dysplasia among Different Types of Intraductal Papillary Mucinous Neoplasm

Pathologic grade	Main duct, n (%)	Branch duct, n (%)	Mixed type, n (%)	Total, n
IPMN with low-grade dysplasia	3 (13)	18 (23)	2 (7)	23
IPMN with intermediate-grade dysplasia	10 (43)	38 (48)	9 (32)	57
IPMN with high-grade dysplasia	9 (39)	18 (23)	16 (57)	43
Noninvasive IPMN	1 (4)	5 (6)	1 (4)	7
Total	23	79	28	130

IPMN, intraductal papillary mucinous neoplasm.

lesions in the remaining 9 patients failed to meet the criteria for resection and were stable on follow-up.

Of the other 108 patients who had no evidence of a new IPMN or progression of an IPMN after initial resection, 15 patients (12%) had at least 1 synchronous cystic lesion that was identified before operation but not resected because it did not meet the criteria for resection and was considered not clinically significant.

Completion pancreatectomy and outcomes

In the 22 patients who developed a new or progressive IPMN in the remnant pancreas, 11 patients (8%) underwent a completion pancreatectomy. The median interval between resections was 46 months (range 13 to 134 months). In the patients undergoing repeat pancreatectomy, 8 patients underwent a completion distal pancreatectomy and 3 patients underwent a completion pancreaticoduodenectomy (Table 3). Two patients presented with metastatic pancreatic cancer during follow-up and did not undergo an additional pancreatic resection. There were no operative or in-hospital deaths among the patients undergoing completion pancreatectomy. The pathologic findings of the completion pancreatectomy are summarized in Table 4. Three patients were found to have invasive ductal adenocarcinoma, 3 were found to have high-grade dysplasia, and the remainder had low- or intermediate-grade dysplasia.

During the entire study period, which began with the initial resection, 31 of 130 patients (24%) died. Five deaths were in the 22 patients who developed a new IPMN during follow-up. Three of the 5 deaths were related to metastatic pancreatic cancer that was identified after the initial resection. No deaths in this cohort were related to another malignancy. The other 26 deaths were in the cohort who had no evidence of a new IPMN or progression of an IPMN after initial resection. Interestingly, 6 deaths within the cohort who had no evidence of a new IPMN or progression of an IPMN after initial resection were related to another primary malignancy. These included 2 patients with metastatic prostate cancers, 1 with urothelial carcinoma, 1 with non-small cell lung cancer, 1 with metastatic oral adenocarcinoma, and 1 patient with metastatic melanoma.

The actuarial 5-year overall survival rate for all 130 patients undergoing resection of a noninvasive IPMN was 81%. No difference in survival was observed among those with different tumor types ($p = 0.23$). The actual 5-year and 10-year survival rates for all 130 patients were 55% and 7%, respectively. Survival differed among patients undergoing resection of IPMN with high-grade

Table 3. Characteristics and Prognosis of 11 Re-resection Cases

Initial operation	Second operation	Interval, y	Initial pathology	Margin	Indication of second operation	Second pathology	Outcomes
Whipple	Distal	11.2	High-grade 3 cm Mix duct		Symptom	High-grade 1 cm IPMN	Death (unrelated lower gastrointestinal bleed). 6 y later.
Whipple	Distal	3.3	High-grade 3.5 cm Branch		Solid component	Ductal adeno. T2N0Mx	Alive
Whipple	Distal	3.8	High-grade 2 cm Branch		Size Symptom	Ductal adeno. T3N1MX	Death (cancer carcinomatosis). 5 mo later.
Whipple	Distal	4.8	High-grade 1.5 cm Branch		Family history	Intermediate-grade IPMN 1 cm	Alive
Whipple	Distal	1.1	Intermediate grade 1.5 cm Branch	+	Size	Intermediate-grade IPMN 5.5 cm	Alive
Whipple	Distal	1.3	Low-grade 4.5 cm Branch		Size Symptom	Low-grade IPMN 1.5 cm	Alive
Whipple	Distal	4.0	Low-grade 1.5 cm x 2 Branch		Solid component	Low-grade IPMN 1.6 cm x 3	Alive
Whipple	Distal	5.8	Benign 3 cm Mix duct	+	Size	High-grade IPMN 5 cm	Death (unrelated gastrointestinal bleeding). 2 y later.
Distal	Whipple	1.9	High-grade 2.5 cm Branch		Family history	Intermediate-grade IPMN 1.5 cm	Alive
Distal	Whipple	4.4	High-grade 3 cm Mix duct		Size	Ductal adeno. T3N0Mx	Alive
Distal	Whipple	2.5	Low-grade multiple Branch	+	Size change	High-grade IPMN 2 cm	Alive

IPMN, intraductal papillary mucinous neoplasm.

Table 4. Univariate Analysis of Factors Associated with Recurrence

Variable	Patients without new lesions (n = 108)	Patients with new lesions (n = 22)	p Value
Mean age, y	67.9	67.5	ns
Sex, male/female	53/55	2.3	ns
Mean tumor size, cm	2.4	2.3	ns
Location in pancreas, n (%)			
Body or tail	30 (28)	9 (41)	ns
Head	78 (72)	13 (59)	ns
Duct type, n (%)			
Main duct	21 (19)	2 (9)	ns
Branch duct	63 (58)	16 (73)	ns
Mixed	23 (21)	4 (18)	ns
Pathologic grades, n (%)			
IPMN with low-grade dysplasia	18 (17)	5 (23)	ns
IPMN with intermediate-grade dysplasia	49 (45)	8 (36)	ns
IPMN with high-grade dysplasia	34 (31)	9 (41)	ns
Noninvasive IPMN	7 (6)	0 (0)	ns
Family history of pancreatic cancer, n (%)			
Positive	8 (7)	6 (27)	0.015
Negative	100 (93)	16 (73)	ns
Resection margin status, n (%)			
All negative	84 (78)	16 (73)	ns
Positive	24 (22)	6 (27)	ns

IPMN, intraductal papillary mucinous neoplasm.

dysplasia (estimated 5-year overall survival 72%) in comparison to low- or intermediate-grade dysplasia (estimated 5-year overall survival 85%; p = 0.02). However, the presence of noninvasive IPMN of any grade at the resection margin did not influence survival (p = 0.3).

The median length of follow-up in the 11 patients who underwent completion pancreatectomy was 60 months (range 4 to 110 months). In the 3 patients who were found to have invasive carcinoma in their completion pancreatectomy specimen, 2 remain alive with no evidence of recurrent disease at last follow-up. The remaining patient who underwent completion pancreatectomy for an IPMN without an associated invasive carcinoma also remains alive at last follow-up.

Identification of factors associated with recurrence of intraductal papillary mucinous neoplasm

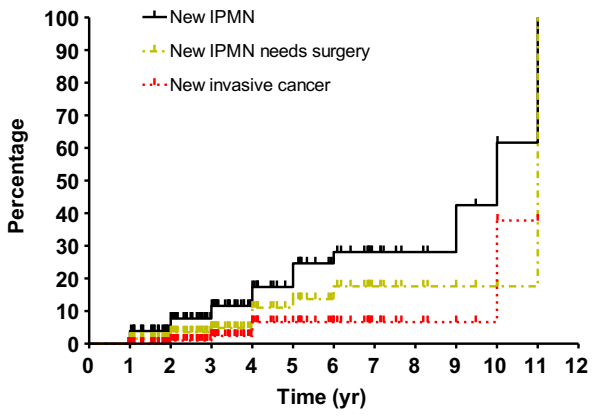
The association between clinical and pathologic features in patients undergoing resection of an IPMN without an associated invasive carcinoma and follow-up for both IPMN and invasive carcinoma was assessed. A total of 8 factors were included in a logistical regression model (Table 4). On univariate analysis, the only predictor of a new lesion after resection of noninvasive IPMN was a family history of pancreatic cancer (Table 4.) A multivariate analysis confirmed family history as the only predictive preoperative feature, with an odds ratio of 4.2, 95% CI, 1.3 to 14.1; p = 0.02.

The recurrence rates of patients with low-, intermediate-, and high-grade dysplasia were 5 of 23 (22%), 8 of 57 (14%), and 9 of 43 (21%), respectively. These values were not statistically different (p = 0.58). The rate of high-grade dysplasia (9 of 22, 41%) in patients who had a recurrence or progression, including 2 patients who had extrapancreatic recurrences of pancreatic cancer, was similar to that in patients without recurrence, who had a rate of high-grade dysplasia of 31% (p = 0.45; Table 4.) It should be noted, however, that all 3 patients who had pancreatic ductal adenocarcinoma found at completion pancreatectomy had high-grade dysplasia in their first pathologic specimen. The incidence of new IPMN in the remnant pancreas did not correlate with the presence of IPMN of any grade at the resection margin (p = 0.59). In patients who had IPMN at the margin, 20% (6 of 30) had a recurrence; 16% (16 of 100) without IPMN at the margin suffered recurrence. The classification of IPMN as main duct, branch duct, or mixed at the time of initial resection did not correlate with risk of recurrence or progression (p = 0.39).

Using Kaplan-Meier analysis, the chances of developing a new IPMN at 1, 5, and 10 years after the initial surgery were 4%, 25%, and 62%, respectively, and of requiring surgery were 1.6%, 14%, and 18%, respectively. The chances of developing pancreatic cancer were 0%, 7%, and 38% at 1, 5, and 10 years, respectively (Fig. 1).

DISCUSSION

The number of resections being performed for IPMN has dramatically increased over the past decade.[11,17] This is likely due to the increased awareness of this condition, the widespread use of cross-sectional imaging, and the general acceptance of the consensus guidelines for the management of cystic neoplasms.[17-19] In general, the long-term survival of patients undergoing resection of a noninvasive IPMN has been presumed to be excellent. This is particularly true when compared with survival of patients who undergo resection of invasive pancreatic cancer. However, in contrast to this notion, the results of this study demonstrated that patients who undergo resection of a noninvasive IPMN have a significant chance



	1yr	5yr	10yr
New IPMN	4%	25%	62%
New IPMN requiring completion pancreatectomy	2%	14%	18%
New invasive cancer	0%	7%	38%

Figure 1. Estimated recurrence curve after resection of noninvasive intraductal papillary mucinous neoplasm (IPMN).

of developing progressive disease and even succumbing to disease-specific mortality. We report here that 17% of patients developed a new IPMN, and 60% of these IPMNs were clinically significant, requiring a completion pancreatectomy or presenting with metastatic pancreatic cancer. Interestingly, despite the preinvasive nature of their initial pathology, some patients presented with malignant disease. A family history of pancreatic cancer, but not margin status or degree of dysplasia, was associated with a risk of development of a new or progressive IPMN.

The estimated 5-year overall survival for patients undergoing resection of a noninvasive IPMN was 81%. It should be noted that this reported survival is not disease-specific, and it is likely that the majority of deaths at the 5-year mark are not IPMN related. The cause of mortality was directly related to pancreatic malignancy in 3 (2%) of 130 patients and to a second malignancy in 6 (4%) patients. Despite this, the estimated risk of developing new or progressive IPMN disease is significant—approximately 25% at 5 years—and the estimated risk of developing pancreatic cancer is 7% at 5 years. Taken together, this analysis supports the notion that new or progressive IPMN disease after resection of IPMN is common and can be clinically significant or even fatal in some patients. These findings demonstrate that long-term follow-up is necessary in this patient population and is consistent with other recent published reports. A recent study demonstrated that 57% of patients initially undergoing surveillance of IPMN had progression and ultimately underwent resection. In this group, 18% were found to have invasive disease.[20]

Previous work that evaluates the natural history after resection of the benign IPMN has been published and is consistent with the findings of our study.[12,21,22] In one study, 191 patients who underwent resection of a noninvasive IPMN were evaluated. In this study, 20% of patients had known residual IPMN either at the margin or a separate lesion; the remainder had no apparent residual disease. The estimated overall survival and 5-year progression-free survival in these groups were not significantly different, at 88% and 83%, respectively. This is similar to the 81% overall survival reported in our study. Interestingly, 3 of the 153 patients in the group with no residual disease developed pancreatic cancer, while 1 of 38 with residual disease developed cancer. In this study, 11 patients (5.7%) underwent re-resection of IPMN, also similar to the 8.5% of patients in our study who underwent completion pancreatectomy. As with our work, the presence of high-grade dysplasia in the initial specimen appeared to correlate with subsequent development of cancer. Overall, 20% of patients in the Indiana study with no residual disease developed a new lesion, including the 3 who developed cancer.[12] Although this number cannot be compared directly with our study because we combined those with and without residual IPMN, the result is similar to our finding of 17% with new or progressive disease.

Finally, consistent with our findings, the presence of any grade of dysplasia at the margin did not correlate with recurrence. An earlier report of patients undergoing resection of noninvasive IPMN, from Memorial Sloan Kettering Cancer Center, also demonstrated the risk of developing subsequent disease.[22] In this study of 78 patients, 7.7% developed "recurrent" IPMN disease, including 3 patients who died of pancreatic cancer. Unlike our study and that of the Indiana group, the Memorial group found a correlation of recurrence with the presence of any grade atypia at the margin ($p = 0.02$). Another earlier manuscript from the Mayo Clinic, which included both invasive and noninvasive IPMN, reported an 8% "recurrence" rate, including 2 cancers, in the 60 patients undergoing an initial resection of a noninvasive IPMN.[21] These studies, in addition to several more peripherally related works regarding recurrence after resection of benign IPMN, are summarized in Table 5.

The findings of this study are consistent with the known multifocal nature of IPMN on imaging, grossly at resection, and genetically. Others have reported identification of synchronous IPMN in up to 83% of patients.[8] In addition, several longitudinal studies report that metachronous lesions develop at a significant rate, and known lesions can undergo progression to concerning lesions.[11,23] These observations suggest that IPMN may represent

Table 5. Recurrence after Resection of Noninvasive Intraductal Papillary Mucinous Neoplasm

First author	n	Median follow-up, mo	Recurrence, n (%)	Recurrence with invasive transformation, n (%)	Estimated 5-y OS, %
Chari[21]	60	37	5 (8.3)	2 (3.3)	85
Sohn[16]	84	–	7 (8.3)	5 (5.9)	77
Salvia[32]	80	31	1 (1)	0	100
Raut[31]	28	34	0	0	100
White[22]	78	40	6 (7.7)	4 (5.1)	87
Fujii[10]	103	–	10 (9.7)	8 (7.8)	–
Wada[33]	75	–	1 (1.3)	0	100
Miller[12]	191	–	31 (20)	4 (2)	83
This study	130	38	22 (17)	5 (4)	81

OS, overall survival.

a field defect of the pancreas, with the entire gland at risk for development of neoplastic disease. This conclusion would explain the findings of this study and is consistent with similar reports of other investigators. Recent genetic studies suggest that multifocal IPMNs are not the result of a single diffuse neoplasm producing multiple gross cysts. For example, using the unique genetic signature of individual clones, work from our group demonstrated that cells within an individual cluster of cysts were genetically related; those of physically separate cysts were not related.[8,24,25] So, the molecular basis for multifocal IPMN and the etiology of the field defect is unknown and may turn out to be epigenetic or environmental.

The determination of risk factors for recurrence would aid in a tailored approach or at the very least, aid in the management of postoperative patients with more intensive surveillance of the remnant. Before this study, no such risk factors for local recurrence of noninvasive IPMN were identified. We reported that family history is a risk factor for recurrence. Of 22 patients with a recurrence of IPMN, 6 patients (27%) had family history of pancreatic cancer. This recurrence rate was significantly higher than that for patients with no family history (8 of 108, 7%; $p = 0.015$). Multivariate analysis confirmed that family history of pancreatic cancer was an independent risk factor for recurrence of IPMN, with a hazard ratio of 4.2. No other clinical or pathologic factor was found to be a risk factor, including presence of IPMN at the resected margin.

The results of our work affect clinical decision making in the care of patients who are undergoing resection of a noninvasive IPMN. Due to the long-term mortality for metabolic complications after total pancreatectomy,[26] most surgeons prefer to perform a partial resection of the clinically most concerning portion of the pancreas. The reported rates of developing subsequent cancer in our series and others are low, ranging from 2% to 4%, and support this practice. There are limited data that document the long-term impact associated with the metabolic derangements caused by a total pancreatectomy, but the mortality is likely to be higher than the risk for developing cancer. Moreover, a total pancreatectomy presumably does not reduce the risk of developing second primary malignancies. Despite this, our observations rekindle the debate as to what the optimal extent of resection is in selected patients undergoing a resection of benign IPMN. From a strict oncologic point of view, our work, along with that of others,[27,28] supports a total pancreatectomy as the option with the lowest likelihood of development of pancreatic cancer. In our opinion, consideration for total pancreatectomy should be given in high risk patients based on the collective findings of the studies evaluating the natural history of partial pancreatectomy of noninvasive IPMN.

Furthermore, in light of recent genetic data that demonstrate that it takes approximately 10 to 12 years for pancreatic neoplasia to develop metastatic potential after the initial mutation,[29] one may want to consider a total pancreatectomy in a young individual who is expected to have numerous years of life remaining. This information should be tempered by clinical circumstances such as the patient's life expectancy, the patient's ability to manage apancreatic diabetic disease, and the likelihood that invasive malignancy is present or will develop in the pancreatic remnant. In light of these issues, we advocate a tailored approach in which certain patients may benefit from a total pancreatectomy. For example, these include young and/or healthy patients with a relatively long life expectancy who are already diabetic, have high-grade dysplasia in the main lesion on intraoperative frozen section, or have a family history of pancreatic cancer.

The status of the surgical margin did not appear to correlate with development of subsequent IPMN in our study, and the results in the literature are mixed on this topic. The lack of correlation calls into question surgical decision making based on the results of an intraoperative frozen section of the margin. In this study, 24 of 108 patients (22%) without a new IPMN had positive resection margin, while 6 of 22 patients (27%) with a new IPMN had a positive resection margin. This was not statistically significant and is consistent with other reports showing that margin status has no relationship with recurrence.[30] The number of patients included on our study is relatively small, making definitive recommendations difficult.[10,31] It should be noted that at least 1 other study does suggest that the presence of IPMN at the

margin may correlate with development of new or progressive IPMN disease. Therefore, despite the lack of correlation in our series, we believe that the intraoperative frozen section is informative and in some cases, may alter operative decision making. One may want to more strongly consider a total pancreatectomy in a young patient with high-grade dysplasia at the margin vs the same patient with low-grade dysplasia at the margin. This is based on the premise that recurrences are due to multifocal disease, with a synchronous IPMN present within the pancreatic remnant or the development of a second metachronous IPMN, rather than progression of margin-positive disease. In this regard, the margin is used as a marker of residual disease throughout the remnant. The International Consensus Guidelines for Management of Intraductal Papillary Mucinous Neoplasms and Mucinous Cystic Neoplasms of the Pancreas[17] are reasonable to guide surgical decisions based on this argument. These guidelines state that benign adenomas (low-grade dysplasia) at the resected margin do not warrant further resection because they are at minimal risk of progression to cancer. However, patients with an IPMN with an associated invasive carcinoma or an IPMN with high-grade dysplasia would benefit from total pancreatectomy.

The relatively high rate of developing a new and progressive IPMN and the potential to develop invasive cancer reported in this study demonstrate the need for continued surveillance in patients with resected noninvasive IPMN. Currently, there are no clear guidelines regarding the frequency, duration, or methods of postoperative surveillance in these patients. Based on our study, it seems prudent to manage these patients in a manner similar to that in patients not undergoing resection of IPMN. One should be cautioned, however, that the mere fact that patients were previously selected for resection suggests that they have a more aggressive natural history than patients with IPMN that never met criteria for surgical resection. We recommend cross-sectional imaging (CT or MR) every 6 to 12 months for the first 5 years, and annually thereafter. Endoscopic ultrasound can be used in selected cases. Meanwhile, because IPMN patients have been shown to have increased risk of developing extrapancreatic malignancies, general recommended cancer screening guidelines should be strongly encouraged.[6]

This study had several limitations. Because determination of the development of a new IPMN is made on radiographic imaging studies, it is likely that we underestimated the true extent of disease and recurrence. For example, it is possible that some patients progress to invasive carcinoma in the absence of a detectable cyst, as evidenced by our patients who presented with an invasive carcinoma. In this regard, patients with resected IPMN might harbor synchronous invasive carcinoma, but we are unable to identify their lesion as clinically significant based on imaging. In addition, 11 recurrence patients diagnosed by CT did not undergo resection, and we do not have pathologic confirmation that their clinical progression correlated with histologic progression. Moreover, this was a retrospective study, and given that our hospital is a tertiary referral center, there is likely selection bias and heterogeneity in management. Finally, the clinically significant recurrence does not allow strict determination of risk factors for recurrence.

CONCLUSIONS

In conclusion, we have demonstrated that patients undergoing resection of a noninvasive IPMN have a high risk of developing a new IPMN, additional malignancies, and are at risk for disease-specific mortality. It should be noted that their long-term survival is clearly favorable in comparison to pancreatic ductal adenocarcinoma. The high rate of recurrence and progression calls for close surveillance in the postoperative period and supports consideration of a total pancreatectomy in some patients. Although margin status can be helpful in the surgical decision making, it did not correlate with outcomes in our study. A family history of pancreatic cancer was the only risk factor for development of a new IPMN in our study.

Author Contributions

Study conception and design: He, Cameron, Wolfgang
Acquisition of data: He, Cameron, Ahuja, Makary, Hirose, Choti, Schulick, Hruban, Pawlik, Wolfgang
Analysis and interpretation of data: He, Cameron, Wolfgang
Drafting of manuscript: He, Cameron, Wolfgang
Critical revision: Cameron, Ahuja, Makary, Hirose, Choti, Schulick, Hruban, Pawlik, Wolfgang

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Discussion

DR KEITH D LILLEMOE (Boston, MA): The Hopkins group has made many key contributions to our understanding of this new entity of intraductal papillary mucinous neoplasm (IPMN) since it made one of its initial presentations of the very first large US series more than 10 years ago at this meeting. We have learned much from the Hopkins group and others about IPMN over this