A Selective Approach to Resection of Cystic Lesions of the Pancreas: Results From 539 Consecutive Patients

To the Editor:

I would like to congratulate Dr. Allen and colleagues for this very fine paper on what is probably the largest series to date addressing cystic lesions of the pancreas (CLP).[1] The authors concluded that adopting a selective approach was appropriate in the management of CLP based on the results of their study, and this could be done by using preoperative characteristics such as cyst size, presence of solid components, presence of symptoms, and age of patients. They came to this conclusion as their data demonstrated that these characteristics were significantly different in patients who underwent immediate surgery compared with those who were initially managed conservatively and that the proportion of malignant cysts in those managed conservatively was only 3% compared with those who underwent immediate surgery (18%). However, I do not agree entirely with their conclusion.

In my opinion, the conclusion that the proportion of malignant cysts in patients managed conservatively was only 3% may be an underestimate. The authors came up with this calculation by dividing the entire cohort of 369 patients who were selected for observation with the number of patients (n = 11) who had a malignant cyst. By doing this, they were working on the assumption that the majority of patients without a definite pathologic diagnosis (n = 340) did not have a malignant CLP. In fact, of the 29 patients selected for observation whom eventually underwent resection, 11 (38%) were found to have a malignant cyst. Hence, I would challenge the assumption that all the patients without a pathologic diagnosis did not have a malignant cyst. I would argue that it is possible that a significant proportion of the patients observed may harbor a malignant cyst, which has yet to manifest as the median follow-up of these patients was only 24 months. This hypothesis is further supported by the fact that the authors reported that 3 of the 11 patients only had the malignancy identified after more that 48 months from initial detection. It is also interesting to note that, despite this study spanning a period of 10 years, the median follow-up was only 24 months. Was this because many patients were lost to follow-up or that the surgeons tended to adopt a more conservative approach only recently?

Curiously although it is widely known that pancreatic pseudocysts are the most common CLP,[2] the proportion of pseudocysts in this series is potentially relatively low as only 38 patients (7%) had a history of pancreatitis. Could this be due to the referral pattern at MSKCC, which is a tertiary level cancer institution, or were some of these patients for some reason or another not included in the study? How many of the CLP managed conservatively were clinically diagnosed as pseudocysts based on a history or biochemical or radiologic evidence of pancreatitis? In my opinion, these patients should be excluded and only patients with "suspected cystic neoplasms" or "indeterminate CLP" be included in the analysis as it gives a "false impression" that many CLP can be managed safely with follow-up. Furthermore, was a clinical picture suggestive of pancreatitis a criterion used in favor of conservative management? It would be important to know how many of the patients with pancreatitis eventually were found to have pseudocysts or other pancreatic neoplasms.

I think it would also be useful if the authors can provide us with some data from the 199 patients with a pathologic diagnosis on the predictive effect of each of the above-mentioned characteristics on the premalignant and/or malignant potential of CLP. The utility of the selection criteria would be further supported if these characteristics did indeed predict a premalignant or malignant CLP with a high positive predictive value. We and several others have also previously demonstrated that the presence of symptoms and cyst size are useful predictors of malignancy.[3,4] Additionally, did the authors use other criteria, such as serum tumor markers and presence of a dilated pancreatic duct, which have been shown to be useful in predicting malignancy in CLP?[5]

Finally, I would like to add that the finding in this study where none of the 40 small (<3 cm) mucinous neoplasms was found to have an invasive carcinoma is important as it confirms the strong association of cyst size with malignancy for mucinous neoplasms. This finding is also reflective of the results from our recent review of 344 mucinous cystic neoplasms where we found that none of the malignant mucinous cystic neoplasms was less than 3 cm.[6]

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Reply:

We appreciate Dr. Goh's thoughtful comments regarding our recent paper on the management of pancreatic cysts, and we would like to respond to several points discussed in his letter. We agree that 3% may be an underestimate with respect to the percentage of patients followed radiographically who are later identified with a malignant cyst. The median follow-up in our study was 24 months, and the percentage of pa-

tients with malignancy can only increase as follow-up continues. We would like to highlight, however, that the 11 patients with malignancy who were initially followed radiographically (11 of 349, 3%) consisted of 8 patients with adenocarcinoma and 3 patients with neuroendocrine tumors. We would anticipate that any cystic lesion truly associated with pancreatic adenocarcinoma would demonstrate some progression within 24 months. We would also highlight that no patient with a malignant mucinous tumor underwent delayed resection. With longer follow-up, additional lesions may develop changes that prompt resection; however, many of these may also be resected prior to the development of malignancy.

There were very few patients (n = 38, 7%) in this study with a history of pancreatitis, and this certainly reflects the referral bias of our institution. We did not exclude these patients because they comprised a significant minority of the overall group, and the level of certainty as to whether the lesion represented a pseudocyst or cystic neoplasm was variable. In addition, several of these patients presented with an episode of pancreatitis, were resected, and were discovered to have a malignant process. Certainly, our approach toward patients with presumed pseudocyst is different from the approach toward patients with cystic neoplasms. However, since such a small percentage of patients in this study group had pancreatitis, we did not find this to be associated with management.

We do not have enough data to comment on the value of serum markers. Patients with dilation of the main pancreatic duct are typically considered to have main-duct intraductal papillary mucinous neoplasm (IPMN), which has a high rate of invasive malignancy, or pancreatic adenocarcinoma not in association with IPMN. Both of these groups of patients are not typically labeled as "cystic lesions of the pancreas" and are treated with resection. The primary characteristics listed in the decision tree analysis included the presence of a solid component and cyst size. Resection was performed in 80 of the 105 patients with solid component, and malignancy was identified in 22 of these patients (28%). The radiographic diameter of the lesions without a solid component was <2.5 cm in 309 patients; and in 272 of these patients, radiographic follow-up was performed. Within this group of 272 patients, subsequent malignancy has been identified in 8 patients (3%).

We agree with Dr. Goh's recommendations for the management of small (<3 cm) mucinous lesions. Similar to Dr Goh's group, we have not encountered invasive malignancy in any mucinous cyst <3 cm, and this is similar to other reported series.[1,2] Our goal in initiating this project was to help identify a group of patients with cystic lesions who have a risk of malignancy that is less than the risk of mortality from pancreatectomy, and this group of patients appears to fit into this category. It must be emphasized, however, that these lesions do have malignant potential and must be followed radiographically. We are encouraged by the fact that no patient with a malignant mucinous tumor underwent delayed resection, and we think that, with careful follow-up, we may be able to selectively resect those mucinous lesions progressing toward malignancy.

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A Selective Approach to the Resection of Cystic Lesions of the Pancreas: Results From 539 Consecutive Patients

To the Editor:

We read with interest the recent article by Allen et al on pancreatic cysts, which discusses the role of nonoperative management for the majority of these lesions. We fully agree with them that a selective approach is needed when evaluating a patient with a pancreatic cyst, particularly if it is an incidental finding, to avoid operations on benign neoplasms that may be associated with early and late complications.

However, we have some reservations about this study:

1. The term "cystic lesions of the pancreas" is too heterogeneous, and any decision regarding treatment needs to go several steps further by selective use of dedicated pancreatic imaging (computed tomography and/or magnetic resonance imaging resonance with cholangiopancreatography) and endoscopic ultrasound. Even assuming that a distinction between inflammatory and neoplastic cyst has been made (hopefully on the basis of a clinical correlate), merely dichotomizing neoplastic cysts into serous and mucinous may result in dangerous oversimplification, since not all mucinous cysts are equal.[1–7] It is important that both the radiologist and the clinician who is responsible for the patient make the effort to differentiate between a mucinous cystic neoplasm, a branch-duct intraductal papillary mucinous neoplasm (IPMN), or a main-duct IPMN. Dr. Allen and coworkers wrongly assume that main-duct IPMNs are unlikely to present as a cystic lesion in the pancreas. Several papers have highlighted that the radiologic presentation of main-duct IPMN can be that of an isolated cyst[8–10]; and with a frequency of malignancy in main-duct IPMN of 70% and a rate of invasive carcinoma of 40%,[1,11] this is not a lesion that should be observed. Likewise, if the lesion is suspected to be a mucinous cystic neoplasm (because there is no connection to the ductal system of the pancreas, the patient is female, and the cyst is in the distal pancreas), the current recommendation is to proceed with resection and not to observe.[11] The radiologist and the clinician also need to keep in mind that there are other neoplastic cysts that are nonserous and nonmucinous. These include solid pseudopapillary neoplasm and cystic neuroendocrine tumors, both of which should be resected. Finally, other factors, such as a family history

of pancreatic cancer or an elevated serum CA 19.9, should be considered in the decision-making.

2. An adenocarcinoma was found in 8 patients initially followed radiographically and, unfortunately, 5 of them had unresectable or metastatic disease when surgical intervention was finally taken. In 3 of them, the time between initial diagnosis and identification of a malignancy was more than 4 years. In these patients, the definitive histologic diagnosis is not known since their neoplasms were not resected (a biopsy showing adenocarcinoma cannot distinguish between ductal adenocarcinoma and adenocarcinoma arising in IPMN). The authors make the statement that "no patient with a malignant mucinous tumor underwent a delayed resection." We challenge that assertion and propose that some or all of those 5 patients *could* have had a malignant mucinous neoplasm at the onset because it is extremely unlikely that ductal adenocarcinoma of the pancreas would progress so slowly (range, 57–84 months). In these cases, it is more likely that an adenocarcinoma arose in the background of an IPMN.
3. Among mucinous neoplasms, a nonoperative management should be proposed only for branch-duct IPMNs, as suggested by the International Association of Pancreatology guidelines.[11] These guidelines state that asymptomatic patients affected by branch-duct IPMN with a diameter less than 3 cm, with a nondilated (<5 mm) main pancreatic duct and without any malignancy-related parameters (presence of nodules and/or thick wall) can be considered for careful nonoperative follow-up with computed tomography or magnetic resonance imaging resonance with cholangiopancreatography every 6 months, at least initially.
4. The 3% malignancy risk in cysts <3 cm and without solid component may not be accurate because the denominator of 369 that the authors used included patients who had solid component, symptoms, or lesions >2.5 cm, but still were managed nonoperatively. It would be very useful to the reader to know what happened to the 25% of patients with solid components and the 37% who had symptoms but were not resected. Furthermore, the 3% may be falsely reassuring because the median follow-up was only 24 months, which is very short for malignant neoplasms with a less aggressive biology, such as IPMNs and neuroendocrine neoplasms.

We would like also to highlight that knowledge of the natural history of these neoplasms is incomplete; therefore, data from large series with longer follow-up are needed to confirm the proper application and safety of a surveillance approach. For this reason, follow-up should preferably be performed in referral centers by surgeons, radiologists, and gastroenterologists with expertise and interest in pancreatic diseases.

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Reply:

We appreciate the interest that Dr. Crippa and Dr. Fernandez-del Castillo had in our article, and we appreciate the opportunity to respond to their comments and criticisms. We would like to begin with where we agree. We agree that not all cystic lesions of the pancreas should be resected. We agree that selected patients with branch-duct IPMN <3 cm in diameter and without concerning radiographic features can be monitored safely. We agree that the natural history of these lesions (serous cystadenoma, mucinous cystic neoplasm, IPMN) is unknown and that only through careful assessment and surveillance by dedicated surgeons, gastroenterologists, and radiologists will the optimal treatment approach be realized.

These statements alone are a dramatic departure from what was typically published just a decade ago, when most reports recommended resection for all patients with cystic lesions of the pancreas.[1–3] Recent improvements in cross-sectional imaging, the resultant increase in identification of small asymptomatic cysts (often between 4 mm and 2 cm in diameter), and the improving ability to determine histologic subtype without resection make the former approach impractical and potentially harmful to the patient. After a thorough diagnostic evaluation, treatment recommendations should be made that are based on the balance between the risk of malignancy within the given lesion and the risk of pancreatectomy to the individual patient.

For patients with presumed mucinous tumors, this balance must also include the possible risk of developing malignancy in the future.

We agree with some of Dr. Crippa's concern regarding the terminology used to describe these lesions; and with improvements in diagnosis we hope to approach these lesions with histopathologic terminology (serous, mucinous, malignant IPMNs) rather than radiologic terminology (cystic lesion). We do approach main-duct IPMNs differently than branch-duct IPMNs, and Dr Crippa's statement that we "assume that main-duct IPMNs are unlikely to present as a cystic lesion of the pancreas" is a misunderstanding of statements within the discussion of the paper and should be clarified. This is a denominator issue and one that was touched upon in the discussion by Dr Lillemoe. Patients were included in this study (as noted in METHODS) if they were coded for the ICD-9 diagnosis of pancreatic cyst (577.2), had a cystic lesion of the pancreas on imaging, and were evaluated by a surgeon or gastroenterologist. We thought that these criteria best defined the group of patients with the radiographic finding of a "cystic lesion of the pancreas." Most patients with main-duct IPMNs will have malignancy, and these patients were typically coded with the ICD-9 code 157.9 (pancreatic adenocarcinoma). This would be similar in a patient with an obvious pancreatic adenocarcinoma that had cystic degeneration: they would not typically be coded as a pancreatic cyst but rather as an adenocarcinoma. Patients with a cystic tumor that was biopsy-proven as an adenocarcinoma were also not included. Including these patients would have changed the overall denominator but would not have changed the number of patients initially followed radiographically. Yes, main-duct IPMNs are "cystic" but these lesions have a high-rate of malignancy and should be approached in that fashion.

Where do we disagree? We disagree with Dr. Crippa's conclusion in point 2. The 8 patients with adenocarcinoma who were initially followed radiographically *could* have had a malignant mucinous tumor that slowly progressed, but most likely did not. In only 3 of the 8 patients was the period between the identification of the cyst and the diagnosis of carcinoma >48 months, and in these patients it is unclear whether there was an association between the cyst and the subsequent malignancy. In addition, pathology reports from the 3 resected patients (including the patient presented in Fig. 5) demonstrated retention cysts in the same location as the cysts that were identified radiographically. No IPMN was noted in the specimen. We think that these cysts most likely represented retention cysts that developed adjacent to a radiographically occult carcinoma. We emphasize the need to thoroughly assess both the cyst and the surrounding parenchyma during the evaluation of these lesions. With the increase in awareness of this phenomenon, we hope to decrease even further the possibility of overlooking small carcinomas.

We disagree that all mucinous cystic neoplasms (MCNs) should be resected. Current diagnostic limitations make it very difficult to differentiate between a small branch-duct IPMN and a small MCN in the tail of the pancreas.[4] Because of this, Dr Crippa's recommendation to resect all MCNs cannot practically be followed. Our data, as well as data from other series, have yet to identify malignancy within small (<3 cm) MCN.[5,6] The time period during which MCNs progress to malignancy is unknown; therefore, our approach to the small presumed MCN is similar to that of the small branch-duct IPMN.

We appreciate the ongoing dialogue regarding the management of these lesions. Future efforts must be directed at improvements in nonresectional diagnosis and improvements in the understanding of progression to malignancy in mucinous lesions. Until these improvements are realized, treatment recommendations must balance the risk of pancreatectomy with the risk of malignancy (or future malignancy) within the specific lesion.

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Authors' Response to a Letter to the Editor Re: Sentinel Node Biopsy for Early-Stage Melanoma

Reply:

We thank Dr. Twomey for his recent letter endorsing the design of the first Multicenter Selective Lymphadenectomy Trial (MSLT-I).[1] Although he challenges our statement that sentinel node biopsy is now a standard of care for patients with primary melanoma, his concerns relate primarily to outcome measures of clinical efficacy. As stated in our paper,[2] these measures were not considered in that report on the accuracy and morbidity of the procedure. However, outcome measures based on the third interim analysis of MSLT-I have since been reported in the *New England Journal of Medicine*.[3,4]

We caution Dr. Twomey not to conflate elective lymph node dissection and sentinel node biopsy, a common error. Elective lymph node dissection blindly excises clinically normal regional nodes as a prophylactic measure; sentinel node biopsy selectively removes only the most likely nodal tar-

get(s) of metastasis. Elective dissection thus carries considerable potential morbidity; sentinel node biopsy does not. Only if careful histopathologic examination of the sentinel node specimen reveals tumor will the patient undergo complete lymphadenectomy. Remember that only about 20% of patients with intermediate-thickness melanoma will have nodal metastases; in clinical trials, the benefit of elective lymph node dissection in this minority was inevitably diluted by its lack of benefit in the remaining ≥80% without nodal metastases.

Interim comparison of the 2 treatment arms of MSLT-I shows that nodal management based on sentinel node status confers a survival benefit: disease-free survival (an endpoint used as a basis for regulatory approval of new cancer drugs[5]) was significantly higher in patients assigned to wide excision plus sentinel node biopsy than in those assigned to wide excision plus watch-and-wait nodal observation ($P = 0.009$).[3] Moreover, among patients with nodal metastases, the 5-year survival rate was higher for those who underwent immediate lymphadenectomy than for those in whom lymphadenectomy was delayed (72.3% vs. 52.4%, hazard ratio for death 0.51, $P = 0.004$). MSLT-I data also show the prognostic importance of the sentinel node's tumor status: 5-year survival rate was 90.2% for patients with tumor-negative sentinel nodes compared with 72.3% for patients with tumor-positive sentinel nodes ($P \leq 0.001$).[3]

Dr. Twomey notes a higher incidence of nodal metastases in the sentinel node biopsy group than in the observation group at the time of interim analysis, and he criticizes the "excess rate of node dissection" in the biopsy group. However, it is not accurate to compare the incidence of early (subclinical) metastases and delayed (clinically palpable) metastases because the latter will steadily increase with time. In fact, our recent data indicate that by 10 years the mean projected incidence of nodal metastases in patients with intermediate-thickness melanomas will be 20.5% ± 2.6% (standard error) in the observation group and 20.8% ± 1.7% in the biopsy group.[4]

Data from interim analysis of MSLT-I provide evidence that occult micrometastases in the sentinel node usually progress to aggressive regional or distant disease. Were this not the case, we would not have seen an overall improvement in disease-free survival among patients assigned to sentinel node biopsy, nor would there have been a significant difference in the rate of nodal relapse between patients with tumor-negative sentinel nodes and those assigned to nodal observation (4% vs. 15.6%, $P < 0.001$).[3] For all patients with nodal metastases identified either by sentinel node biopsy or during observation, the mean number of tumor-involved nodes was only 1.4 in the biopsy group, as compared with 3.3 in the observation group, indicating disease progression in the regional nodal basin during nodal observation. The impact of the sentinel node's tumor status on disease-free and melanoma-specific survival also indicates the aggressive potential of micrometastases in this node ($P \leq 0.001$ for both comparisons).

We firmly believe that sentinel node biopsy is the standard of care for staging primary melanomas of intermediate thickness and for treatment planning. Although the standard of care designation is applied to many clinical procedures that do not directly lead to survival benefit,[6] our findings indicate that immediate complete lymphadenectomy after identification of a tumor-positive sentinel node improves survival. In patients with primary melanomas that are intermediate in thickness, sentinel node biopsy is preferred to nodal observation.

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