Examining the accuracy and clinical usefulness of intraoperative frozen section analysis in the management of pancreatic lesions

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Abstract
BACKGROUND: Intraoperative frozen section analysis is often performed in the surgical management of pancreatic lesions. This test is used to obtain histologic diagnosis, to assess resectability because of unanticipated locoregional spread, and to ensure negative margins after resection. We sought to define the accuracy and clinical usefulness of intraoperative frozen section analysis in patients with pancreatic lesions and to determine the impact on long-term outcomes.

METHODS: A retrospective database review was performed for all patients who underwent pancreatic resection at our institution from 2002 to 2011. Patient demographics, indications for frozen section analysis, final pathology, and long-term outcomes were analyzed. Five-year survival was compared using the Kaplan-Meier method.

RESULTS: Sixty-eight patients were identified (mean age 65 ± 14 years, 52% female). Malignancy was identified on final pathology in 38 (56%) patients. Intraoperative frozen section analysis was performed in 59 (87%) patients. Frozen section analysis was performed for histologic diagnosis in 6 (10%) cases, to determine resectability in 15 (25%) cases, and to evaluate margin status in 58 (98%) cases. Frozen section analysis for histologic diagnosis was associated with a sensitivity of 80%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 50% with an overall accuracy of 83%. Frozen section analysis for the determination of resectability was associated with a sensitivity of 38%, specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 50% with an overall accuracy of 66%. Intraoperative frozen section analysis for the determination of the final margin status was associated with a sensitivity of 33%, specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 97% with an overall accuracy of 97%. There were no false-positive results on frozen section analysis. Errors on frozen section analysis interpretation did not negatively impact survival outcomes (mean survival = 2.2 years in those with concordant frozen section analysis vs 1.7 years in those with discordant frozen section analysis, P = .69).

CONCLUSIONS: Although intraoperative frozen section analysis is helpful for ensuring negative final margins, its usefulness for obtaining histologic diagnosis and determining resectability is limited...
Intraoperative frozen section analysis has traditionally played an important role in the surgical management of pancreatic lesions. Before advanced imaging modalities such as computed tomographic scanning, intraoperative frozen section biopsy was commonly used to obtain a confirmatory histologic diagnosis before proceeding with radical resection.

Although less commonly used today for the purpose of obtaining a tissue diagnosis, intraoperative frozen section analysis is still frequently used to determine resectability caused by unanticipated locoregional spread and to ensure negative final margin status after resection.

Currently, limited data exist in the surgical literature regarding the accuracy of frozen section analysis for the purpose of determining resectability and assessing final margin status. Therefore, we sought to further define the accuracy and clinical usefulness of intraoperative frozen section analysis for pancreatic malignancy and to determine the correlation between frozen section results and survival outcomes.

Methods

This study was performed at a military tertiary-care referral center and was approved by the local institutional review board. A retrospective database review was performed using our local cancer registry and pathology database to identify all patients who had undergone pancreatic resection at our institution from 2002 to 2011. Pancreatic resections included pancreaticoduodenectomy and distal pancreatectomy.

Data collected included patient demographics, indications for frozen section analysis, pathologic interpretation, and the duration of survival after resection. Patients with incomplete records were excluded.

Indications for frozen section analysis

Common indications for intraoperative pathology consultation include the establishment of a tissue diagnosis, determining the potential for resection of a pancreatic neoplasm, and evaluating final margin status. Distinguishing chronic pancreatitis from a neoplasm can be challenging via frozen analysis, but the criteria established by Hyland et al can be helpful in distinguishing between the 2 processes. Major criteria include nuclear size variation of 4:1 or greater in ductal epithelial cells, incomplete ductal lumens, and disorganized ductal distribution. When evaluating tissue margin status, the proximity of adenocarcinomas or any other abnormalities to the resection margin is reported to the surgeon.

Histopathologic analysis

After pancreaticoduodenectomy, resection margins were routinely evaluated by frozen section analysis at the pancreatic duct, the hepatic duct, and uncinate margins. After distal pancreatectomy, frozen section analysis was performed on the pancreatic duct margin. Pancreatic tissue requiring frozen section analysis was evaluated using a specified protocol as defined by our institution. Specimens were received by the pathologist fresh from the operating room placed on a Telfa pad (Covidien, Mansfield, MA), within a specimen cup, or on an alternative material that lacks significant moisture wicking properties. After the gross characteristics were recorded, the tissue was placed within an optimum temperature cutting medium and cooled to at least \(-15^\circ\text{C}\) in a Leica CM1850 Cryostat device (Leica Biosystems, Wetzlar, Germany). After the tissue was frozen and firmly embedded within the optimum temperature cutting medium, it was sectioned into slices measuring 5 to 7 \(\mu\text{m}\) in thickness depending on the properties of the tissue. The sections were then stained with hematoxylin-eosin before they were examined microscopically. Frozen sections were commonly reviewed by a team of 2 to 3 pathologists at our institution.

Statistical methods

Categoric variables were compared using the chi-square or Fisher exact test for nonparametric data and the Student \(t\) test for parametric data where appropriate. In addition, the Kaplan-Meier method was used to compare 5-year survival outcomes between those patients with discordant frozen section and final pathology results with those with concordant findings. The significance for all analyses was set at \(P < .05\). All data analysis was performed using SPSS version 11.1 (SPSS Inc, Chicago, IL).

Results

Between 2002 and 2011, a total of 68 patients underwent pancreatic resection at our institution. The mean age was 65 ± 14 years, and 52% (35) were women. Operative resections included 72% (49) pancreaticoduodenectomies, 27% (18) distal pancreatectomies, and 1 distal gastrectomy for primary gastric adenocarcinoma in which invasion into the head of the pancreas was suspected intraoperatively. Malignancy was confirmed on final histology in 56% (38) of cases. Only 3% (2) of patients underwent pancreatic resection with the eventual diagnosis of chronic pancreatitis. Table 1 depicts a complete breakdown of all final pathologic diagnoses.
Intraoperative frozen section consultation was obtained in 87% (59) cases. Indications for intraoperative frozen section analysis included 10% (6) to obtain histologic diagnosis, 25% (15) to determine resectability because of unanticipated locoregional spread, and 98% (58) to evaluate final resection margins. Some patients had multiple indications for intraoperative frozen section analysis.

In our study group of patients, intraoperative frozen section analysis for histologic diagnosis was associated with a sensitivity of 80%, a specificity of 100%, a positive predictive value (PPV) of 100%, and a negative predictive value (NPV) of 50% with an overall accuracy of 83%. The false-negative rate was 16%, and there were no false-positive results.

In cases in which unanticipated locoregional spread was identified intraoperatively, tissue samples were sent from around the superior mesenteric artery in 40% (6), the portal vein in 33% (5), the superior mesenteric vein in 13% (2), the hepatic artery in 7% (1), and the periaortic nodes in 7% (1). Frozen section analysis to determine resectability was associated with a sensitivity of 38%, a specificity of 100%, a PPV of 100%, and an NPV of 58% with an overall accuracy of 66%. The false-negative rate was 33%, and there were no false-positive results. Of the false-negative results, 60% were from samples taken from around the superior mesenteric artery.

Frozen section analysis for the evaluation of final resection margins was associated with a sensitivity of 33%, a specificity of 100%, a PPV of 100%, and an NPV of 97% with an overall accuracy of 97%. There were 2 cases in which frozen section analysis was misinterpreted as negative, and final pathology identified positive margins giving a false-negative rate of 3%. There were no false-positive results.

Overall, errors on intraoperative frozen section analysis were identified in 14% (8) of cases. In order to determine if error on frozen section analysis had any negative impact on survival outcomes, Kaplan-Meier analysis was performed comparing 5-year survival between patients with concordant frozen section analysis and final pathology results and those patients in whom frozen section analysis and final pathology results were discordant. As shown in Fig. 1, there was no significant difference in survival outcomes between the 2 groups, with both achieving survival rates of 20%. Mean survival was 2.2 years for patients with concordant frozen section analysis and final pathology results and 1.7 years for patients with discordant frozen section analysis and final pathology results ($P = .69$).

Table 1  Final pathology results for all patients undergoing pancreatic resection

<table>
<thead>
<tr>
<th>Malignant</th>
<th>Premalignant and benign</th>
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<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>IPMN</td>
</tr>
<tr>
<td>Islet cell tumor</td>
<td>Cystic neoplasms</td>
</tr>
<tr>
<td>Mucinous cystadenocarcinoma</td>
<td>Chronic pancreatitis</td>
</tr>
<tr>
<td>Metastatic (colon)</td>
<td>Other</td>
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<tbody>
<tr>
<td>56% (n = 38)</td>
<td>48.5 (33)</td>
<td>8.8 (6)</td>
<td></td>
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<tr>
<td>4.4 (3)</td>
<td>14.7 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5 (1)</td>
<td>2.9 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5 (1)</td>
<td>17.6 (12)</td>
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IPMN = Intraductal papillary mucinous neoplasm.

Comments

The usefulness of intraoperative frozen section biopsy for pancreatic lesions has long been a matter of debate. Nearly 20 years ago, Harris et al noted that with historic perioperative mortality rates of up to 20%,\(^1\) many surgeons would not perform radical resection without confirmatory tissue diagnosis.\(^2\) Conversely, Cohen et al\(^4\) reported low perioperative mortality rates and argued that even for benign lesions it would be considered sound surgical judgment to proceed with resection because unrecognized early resectable cancer may exist.

In an attempt to define the accuracy of frozen section biopsy, multiple studies have been performed over the last 4 decades.\(^2,5-12\) Most of these studies have focused on the diagnostic accuracy of needle and wedge biopsy for the purpose of obtaining a histologic tissue diagnosis in order to guide intraoperative surgical decision making. All of these studies have shown a low incidence of false-positive results on frozen section analysis. However, the incidence of false-negative results has ranged widely in the literature from 1.2% to 75%.\(^2,10-13\) Nonetheless, advancements in
diagnostic imaging modalities such as computed tomography scanning, which has been shown to diagnose pancreatic malignancy with up to 97% accuracy, and improvements in the safety of pancreatic resection have essentially obviated the need for confirmatory tissue diagnosis before surgical resection.

Similar to previous reports, our study showed frozen section analysis for the purpose of obtaining a histologic diagnosis to be fairly accurate (83%) in the setting of a positive test result (PPV = 100%). However, in the setting of a negative frozen section, this test is of more limited value with an NPV of only 50%, suggesting that if the biopsy result was negative for malignancy, there remains a 50% chance that cancer was missed.

Despite a growing trend to forego frozen section analysis for tissue diagnosis and rely more on preoperative diagnostic imaging and surgical judgment, frozen section analysis still plays an important role in the surgical management of pancreatic lesions. Advanced imaging has been shown to be less reliable with regards to preoperative determination of resectability with sensitivities and specificities ranging from 78% to 96% and 33% to 76%, respectively. With this in mind, it is clear that intraoperative frozen section biopsy may often be necessary to assist with the determination of resectability because of an intraoperative discovery of unanticipated locoregional spread.

In cases of locoregional spread, few studies have assessed the accuracy of frozen section analysis. One report documented a 97.3% accuracy associated with frozen section analysis for this purpose. However, this differs from the results obtained in the current study in which frozen section analysis to determine resectability was associated with an accuracy of only 66%. Similar to biopsy for histologic diagnosis, biopsy to determine resectability was associated with a low NPV (58%), again suggesting that if the biopsy result was negative for malignancy, there remained a nearly 50% likelihood that cancer had been missed.

Finally, intraoperative frozen section analysis is also commonly used to ensure negative final margins after resection. Complete tumor removal has been shown to be associated with improved long-term outcomes, and, therefore, positive resection margins discovered on intraoperative frozen section analysis are commonly addressed by extending resection margins, which inevitably results in more frequent margin negative resection. In this case, we found that frozen section analysis of resection margins was highly reliable with an overall accuracy of 97% and a PPV and NPV of 100% and 97%, respectively.

Taken together, these results suggest that frozen section analysis for the purpose of obtaining a histologic diagnosis and determining resectability is useful in the setting of a positive result. However, these tests are less reliable in the setting of a negative result, and, therefore, surgical judgment based on preoperative imaging and intraoperative clinical impression should be relied on in these cases. On the other hand, frozen section analysis is more accurate when used for assessing final resection margin status and can be relied on to guide the need for further resection. Fortunately, error on frozen section interpretation does not appear to negatively impact survival outcomes because both patients with discordant and concordant findings achieved 5-year survival rates of approximately 20%.

We acknowledge certain limitations to the present study. This study was retrospective, and, therefore, is limited by the inherent biases that accompany such a study design. In addition, because all types of pancreatic lesions encountered were included in analysis and patients may have had multiple indications for frozen section analysis, there may reside a significant degree of heterogeneity among the population studied. Finally, because our study group included only 59 patients over a 10-year period, it is not sufficiently powered to truly define the accuracy of intraoperative frozen section analysis. Despite these limitations, we believe these results provide evidence to suggest that frozen section analysis must be interpreted cautiously by the surgeon. Further investigation by institutions with access to greater numbers of patients undergoing pancreatic resection in order to further define the accuracy and clinical usefulness of frozen section analysis are warranted.

References

Discussion

Anders Merg, M.D. (Whitehorse, Yukon, Canada): The introduction clearly states the goal of the article is to define the accuracy and clinical usefulness of intraoperative frozen section analysis for pancreatic malignancy and to determine the correlation between frozen section results and survival outcomes. These data can determine the accuracy of frozen sections, but they do not address clinical usefulness and do not reliably determine the correlation between frozen section results and survival outcomes. In the Methods section, the authors do not state how many patients were excluded for incomplete medical records. It would also be helpful to describe which margins were assessed on each patient in the Methods section; this was mentioned in the Results section. A brief description of the protocol for assessing the frozen and final margins is needed. Also, if available, it would be relevant how the specimen was oriented, the manner in which the serial sectioning was performed, and what defined a positive margin for the permanent margins. This series of 67 (1 patient underwent a distal gastrectomy as defined in the Results section) patients all had either a pancreaticoduodenectomy or distal pancreatectomy, and the intraoperative decision making regarding the frozen section was not reported. Therefore, the clinical usefulness of intraoperative frozen section cannot be assessed.

1 patient undergoing a distal gastrectomy for gastric adenocarcinoma needs to be removed from the series; it does not appear that that patient underwent pancreatic surgery, and the primary was gastric cancer. The authors do a nice job of defining the sensitivity, specificity, positive predictive value, and negative predictive value for frozen sections obtained for diagnosis, defining locoregional spread, and margin status. However, segregating these patients undergoing frozen section into 2 groups depending on the concordance of frozen and permanent pathology results in significant heterogeneity and likely contamination. The heterogeneity arises not only from different malignant diagnoses with different prognosis but also the fact that 44% of the patients who had a benign pancreatic pathology were included in the prognostic outcomes. An example of contamination is the 1 patient having a false-negative diagnostic frozen section was classified into the group of patients without concordance. This patient may have a great prognosis based on the pathologic diagnosis. Similarly, 3 of the 15 patients having a true-positive result on the frozen section performed to determine locoregional spread still underwent major pancreatic surgery and would likely be placed into the group of patients with concordant results, but this would be a presumably poor prognostic group of patients. This erodes any meaningful analysis of the survival curves. Therefore, the statistical measures (ie, sensitivity, specificity, positive and negative predictive values, and accuracy) are the strengths of this series. However, even here the power is quite limited when evaluating frozen sections for diagnostic purposes because there were only 6 patients. The margin analysis statistical measurements are contaminated because 44% of the patients had a benign or premalignant histology. The discussion is correct in that “imaging modalities...have essentially obviated the need for confirmatory tissue diagnosis before surgical resection.” The data regarding the frozen section for margins or resectability support the notion that if the results are positive they are meaningful, but if they are negative they are questionable and require clinical judgment.