Pancreatic Frozen Section Guides Operative Management With Few Deferrals and Errors

Five Year Experience at a Large Academic Institution

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Context.—Pancreatic adenocarcinoma is the third leading cause of cancer death in the United States. Surgery remains the mainstay of treatment, and frozen section analysis is used to confirm diagnosis and determine resectability and margin status.

Objective.—To evaluate use and accuracy of frozen section and how diagnosis impacts surgical procedure.

Design.—We reviewed patients with planned pancreatic resections between January 2014 and March 2019 with at least 1 frozen section. Pathology reports including frozen sections, preoperative cytology, and operative notes were reviewed. Frozen sections were categorized by margin, primary pancreatic diagnosis, metastasis, or vascular resectability. The deferral and error rates and surgeons’ response were noted.

Results.—We identified 898 planned pancreatic resections and 221 frozen sections that were performed on 152 cases for 102 margins, 94 metastatic lesions, 20 primary diagnoses, and 5 to confirm vascular resectability. The diagnosis was deferred to permanent sections in 13 of 152 cases (8.6%) on 16 of 221 frozen sections (7.2%): 6 for metastasis, 8 for margins, and 2 for primary diagnosis. Discrepancies/errors were identified in 4 of 152 cases (2.6%) and 4 of 221 frozen sections (1.8%). Surgeon’s response was different than expected in 8 of 221 frozen sections (3.6%), but their actions were explained by other intraoperative findings in 6 of 8.

Conclusions.—Frozen section remains an important diagnostic tool used primarily for evaluation of margins and metastasis during pancreatectomy. In most cases, a definitive diagnosis is rendered, with occasional deferrals and few errors. Intraoperative findings explain most cases where surgeons act differently than expected based on frozen section diagnosis.

Pancreatic cancer is the third leading cause of cancer-related death in the United States, with poor survival (9% 5-year relative survival rate).1,2 Pancreatic ductal adenocarcinoma and its variants account for the vast majority (90%) of pancreatic malignancies.3 Survival is impacted by multiple factors, with late stage at diagnosis being the most important.4 Surgery is still regarded as the mainstay of treatment and the only curative option.3,4 Nevertheless, only up to 20% of cases are eligible for surgical resection at presentation2,5,6 and disease in most patients will eventually recur, even in those who underwent complete resection.7,8

The definition of resectability has been modified over time, and in general, it is determined based on the extent of vascular involvement and the possibility of reconstruction in conjunction with resection of the associated vascular structures.6 Tumor is typically classified as resectable, borderline resectable, or locally advanced and unresectable.4 Borderline resectable is defined by the absence of distant metastases and some level of involvement of the surrounding vascular structures, including the superior mesenteric vein or portal vein, celiac axis, and superior mesenteric artery.6,9

Frozen section (FS) analysis may be used not only to confirm diagnosis, but to help determine vascular resectability, margin positivity, and status of extraregional lymph nodes and other metastatic sites (eg, liver or peritoneal nodules). Accuracy varies and is somewhat associated with the purpose of the FS. We and others previously reported a high FS overall accuracy for primary pancreatic lesion diagnosis (>90%),10-14 whereas Nelson et al15 reported a lower accuracy for primary diagnosis (83%). Frozen section evaluation of margins has been reported to be very accurate (>97%),10,15 whereas FS to help determine resectability has been shown less accurate by Nelson et al16 (66%).

The FS evaluation of margins includes the pancreatic, bile duct, and uncinate. Five-year survival is impacted by microscopic margin status, and is approximately 11% when
positive and 21% when negative.\textsuperscript{16} A positive pancreatic neck margin has been associated with poor overall survival but not when other adverse pathologic factors are taken into consideration.\textsuperscript{17} Even with negative margins, a high recurrence rate has been observed (71%).\textsuperscript{16} Nevertheless, positive FS margins are reresected when possible.

Frozen sections are useful in diagnosing pancreatic adenocarcinoma, margins, and metastasis, but the true impact is unclear as surgeons’ responses do not always appear to be consistent with the intraoperative FS diagnosis. The purpose of this study was to evaluate the current status of FS for pancreatic surgery use at a major academic center and determine the accuracy and rate of deferrals and errors. In addition, we wanted to determine how often surgeons’ actions are in accordance with pathologists’ expectations based on the FS diagnosis.

**Materials and Methods**

With previous approval by the institutional review board, a computer-generated search was performed for patients who underwent pancreatic resection between January 2014 and March 2019. Any type of pancreatic resection was included, and the procedure types consisted of pancreaticoduodenectomy, total/distal pancreatectomy, proximal subtotal pancreatectomy/duodenum-preserving pancreatic head resection, and enucleation of pancreatic tumor, amongst others. In cases where the pancreatic resection was not performed after FS of possible metastatic sites or benign primary pancreas diagnosis were also included.

The total number of procedures was determined and compared with the departmental FS records in order to accurately determine the percentage of cases in which at least one FS was performed. Patient charts were reviewed on all cases with FS, including preoperative cytology, FS results, final diagnoses, and synoptic reports. Frozen sections were categorized according to the clinical indication: margin, primary diagnosis, metastasis, and vascular resectability, as defined by the surgeon. The FS results were compared with the final diagnoses to determine whether the pathologist’s diagnosis at the time of FS was accurate, and classified as definite diagnosis, defer, or error. Definite diagnosis was considered in any case for which a distinction between benign and malignant tissue was provided. A defer was any case with an inconclusive diagnosis, defined by a diagnostic line that included the words “atypical, defer to permanent sections,” “suspicious for adenocarcinoma/malignancy,” or “malignancy cannot be ruled out.” “Atypical” diagnoses were not counted as errors, whereas cases called suspicious for malignancy that were incorrect were counted as errors. Two pathologists reviewed all the slides of cases with a defer or error, including the FS, the permanent section (PS), and the resection specimen.

The surgeon’s response to the FS was evaluated in all cases. In cases where a definite diagnosis or suspicious for malignancy was rendered at the time of the FS, the surgeon’s response was categorized as expected or unexpected. Surgeons’ actions were considered expected if the pancreatic resection was aborted in cases of confirmed metastatic adenocarcinoma or the resection was performed as planned when the FS of a liver lesion or distant lymph node was benign. Additionally, resection was expected in patients who had liver metastasis from pancreatic tumors with more favorable prognosis, such as neuroendocrine tumor and solid pseudopapillary neoplasm. The surgeons’ response was considered expected if additional tissue was resected when the margin was called positive for high-grade dysplasia or adenocarcinoma, or if no additional tissue was resected with a negative margin. Furthermore, the surgeons’ action was considered expected if the planned resection was performed when the FS for primary diagnosis was called adenocarcinoma and aborted if called benign. Even with a benign FS diagnosis, surgery is warranted in some cases with high clinical suspicion or when the patient’s symptoms require the resection. In all cases in which the surgeon’s response appeared to be inconsistent with the FS diagnosis, the operative reports were reviewed to determine whether the surgeons had changed their management because of the FS diagnosis, and if there were other operative findings (such as gross tumor elsewhere in the abdomen or gross tumor at a margin) or clinical indications that modified their response to the FS. Operative reports were reviewed for errors and deferrals to determine how the diagnosis affected the management, but surgeons’ response could not be classified as expected or not for deferred cases that were not called suspicious.

In our institution, we have a specialized team of pathologists covering the FS service. In addition, second opinions from specialized gastrointestinal and pancreas pathologists can be sought if needed intraproactively. In many cases margins were sent separately by the surgeon for FS, whereas in others, the resected pancreatectomy specimen was sent intact and the FS pathologist sectioned the margin. When the FS pathologist sampled margins, the margins were taken en face except for the uncinate margin and other margins that appeared closer than 1 cm. These margins were perpendicularly sampled. Two serial FSs were initially cut for margins.

**Results**

**Study Cohort**

A total of 898 planned pancreatic resections were performed at our institution between January 2014 and March 2019. Frozen section was performed in 152 cases (16.9%), for a total of 221 FSs. The number of FSs varied from 1 to 5 per case, with an average of 1.4. Preoperative diagnoses included 99 pancreatic carcinoma, 22 cystic lesion/neoplasm, 20 cholangiocarcinoma, 4 ampullary/peripancreatic mass, 3 pancreatic neuroendocrine tumor, 3 pancreatitis, and 1 metastatic tumor versus primary pancreatic carcinoma. On final diagnosis, these 152 resection cases were 89 pancreatic ductal adenocarcinoma, 17 intraductal papillary mucinous neoplasm (3 with invasion), 16 cholangiocarcinoma, 11 chronic pancreatitis (including 1 type 1 and 1 type 2 autoimmune pancreatitis), 5 ampullary adenocarcinoma, 3 serous cystadenoma, 3 pseudocyst, 2 pancreatic neuroendocrine tumor, 2 duodenal adenocarcinoma, 1 metastatic clear cell renal cell carcinoma, 1 diffuse large B-cell lymphoma, 1 benign common bile duct with large calculus/fibrosis, and 1 benign biliary stricture.

Preoperative cytology was performed in 73 of the 152 cases (48%) and was diagnostic for neoplasm in 46 of 73 cases (63%). These 46 cases included adenocarcinoma (43); mucinous neoplasm (2); and tumor, favor neuroendocrine (1). Nine cases were called suspicious for adenocarcinoma. The diagnosis for the other 18 cases was negative/inconclusive and included the following: no malignant cells identified (15), favor reactive (1), rare clusters of endocrine cells (1), and atypical ductal cells in background of mucin (1). Those cases with preoperative cytology diagnostic of tumor had FSs done predominantly for evaluation of metastasis (31 FSs), margins (14 FSs), and resectability (1 FS). Frozen sections were not done for primary diagnosis in those cases definitively diagnosed by preoperative fine-needle aspiration (FNA) and cytology. Seven of the 9 cases with preoperative FNA suspicious for malignancy proved to be pancreatic adenocarcinoma on resection. The other 2 cases were chronic pancreatitis, 1 due to alcoholism and 1 with only low-grade pancreatic intraductal neoplasia on resection.

**Indications for FS During Pancreatic Resections**

Of the 221 FSs, most were performed for intraoperative margin assessment (102; 46.1%), including 60 pancreatic, 37 bile duct, and 5 uncinate (Table 1). These cases included...
Table 1. Number of Frozen Sections Performed According to Clinical Indication and Anatomic Location (N = 221)

<table>
<thead>
<tr>
<th>Anatomic Location</th>
<th>Margin Status</th>
<th>Metastatic Lesion Evaluation</th>
<th>Primary Diagnosis</th>
<th>Vascular Resectability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic neck</td>
<td>60</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Bile duct</td>
<td>37</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Uncinate</td>
<td>5</td>
<td>70</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Liver</td>
<td>...</td>
<td>70</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Lymph node</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Other</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Pancreas</td>
<td>...</td>
<td>20</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>SMV</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>SMA</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Hepatic artery</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Celiac trunk</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Porta hepatis</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Total</td>
<td>102</td>
<td>94</td>
<td>20</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviations: SMA, superior mesenteric artery; SMV, superior mesenteric vein.

preoperative diagnoses of pancreatic adenocarcinoma, 50% (51); cholangiocarcinoma, 23.5% (24); cystic lesion/neoplasm, 21.6% (22); ampullary/peripancreatic mass, 2% (2); duodenal mass, 2% (2); and neuroendocrine tumor, 1% (1).

The second most common indication for FS was evaluation of a possible metastatic lesion (94 of 221 FSs; 42.5%), including 70 liver lesions, 17 peritoneal lesions (peritoneal surface, mesenteric, gallbladder, omental), and 7 non-regional lymph nodes. Of the 70 FSs for liver metastasis, 60 were for presumed pancreatic adenocarcinoma, 5 for cholangiocarcinoma, 2 for cystic lesions/neoplasm, 2 for ampullary/peripancreatic mass, and 1 for pancreatic neuroendocrine tumor. Of the 27 cases aborted for liver metastasis, all were for adenocarcinoma (pancreatic or cholangiocarcinoma).

Primary diagnosis represented a minority of the requests for FS (20 of 221 FSs; 9.1%), and FSs were performed either to confirm clinical suspicion and imaging findings or to rule out other benign mimickers of pancreatic adenocarcinoma. A total of 17 cases (20 FSs) were done for primary diagnosis, with preoperative diagnoses including pancreatic carcinoma, cystic lesion/neoplasm, and pancreatitis. None of these cases were suspected to be neuroendocrine or other lower-grade tumors. Of the 17 cases, 2 (11.8%) had a preoperative FNA suspicious for adenocarcinoma/malignancy. The other 15 cases (88.2%) either did not have a preoperative FNA (8) or had a negative/inconclusive preoperative FNA (7). On final diagnosis, 5 of 17 cases (29.4%) were carcinoma, including 4 pancreatic adenocarcinoma and 1 metastatic renal cell carcinoma. The other 12 cases were pancreatitis (9) and pseudocyst (3).

In general, vascular resectability was either determined preoperatively or intraoperatively by visual inspection. However, surgeons used FS as a tool to help confirm vascular resectability in a few occasions where they found lesions possibly involving a vessel (5 of 221 FSs; 2.3%).

FS Deferral Cases

Although definitive diagnosis at the time of FS was provided the vast majority of the time (205 of 221; 92.8%), FS was deferred to PS in 13 of 152 cases (8.6%) on 16 FSs: 2 for primary pancreatic mass diagnosis, 6 for metastasis evaluation, and 8 for evaluation of margins (5 pancreatic, 3 bile duct) (Table 2). Resection was aborted in 1 of the 2 deferred cases for primary diagnosis (Figure 1, A through C), based on intraoperative finding of mesenteric metastasis confirmed on a separate FS. The FS from the deferred FS was diagnosed as poorly differentiated adenocarcinoma. In the other FS case for primary diagnosis, the Whipple procedure was performed, and adenocarcinoma was diagnosed on the PS of the FS (Figure 1, D through F). The surgeon aborted 3 of the 6 deferred cases for metastasis. In 2 of these cases, other intraoperative findings suggested unresectability, including 1 case (Figure 1, G through I) for which the PS was signed out as atypical ductular proliferation after p53, Ki67, deeper sections, and intradepartmental consultation remained inconclusive. Because the patient was unresectable intraoperatively, the surgeon did not require a definitive diagnosis. In the other 3 FS deferrals for metastatic liver lesions, Whipple procedures were completed. This included 1 case (Figure 1, J through L) that was definitely diagnosed as metastatic adenocarcinoma on PS.

The surgeon’s response on the 8 FSs (performed on 6 cases) for margins that were deferred varied. In 4 of the cases, 1 FS was performed on each for margin, and additional tissue was resected in only 1 case (pancreas margin, PS confirmed cancer). In the other 3 of these 4 cases, no additional resection was done and all PSs were benign (2 pancreas and 1 bile duct margin). In the other 2 margin cases, additional tissue was resected followed by a second FS. One of these cases included 2 bile duct margins that were benign on PS. The other case had 2 pancreatic FS margins (first FS called atypical, second FS diagnosed as suspicious for cancer) with a completion pancreatectomy, both diagnosed as benign on PS. This case is further discussed in the next section because the second FS was additionally counted as an error.

Discrepancy Between FS and PS

Discrepancies/errors between FS and PS were identified in 4 of 152 cases (2.6%) on 4 of 221 FSs (1.8%) (Table 2). There were 2 errors of 102 margin FSs (1.96%), including 1

Table 2. Definitive Diagnoses, Deferrals, Errors, and Surgeons’ Responses

<table>
<thead>
<tr>
<th>FS Category (N = 221)</th>
<th>Definitive Diagnosis</th>
<th>Deferral</th>
<th>FS Error</th>
<th>Surgeon’s Response Not Consistent With FS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary diagnosis</td>
<td>18</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Vascular resectability</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Metastasis</td>
<td>88</td>
<td>6</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Margin status</td>
<td>94</td>
<td>8</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total (%)</td>
<td>205 (92.8)</td>
<td>16 (7.2)</td>
<td>4 (1.8)</td>
<td>8 (3.6%)</td>
</tr>
</tbody>
</table>

Abbreviation: FS, frozen section.
pancreatic margin and 1 uncinate margin. There were 2 errors of 94 metastasis FSs (2.13%), both on liver metastasis evaluation. In the 20 FSs for primary diagnosis and 5 for resectability, no errors were made. All errors were found in cases that postoperatively were diagnosed as pancreatic adenocarcinomas. No errors were seen in other types of tumors (eg, ampullary carcinoma, neuroendocrine tumor, cholangiocarcinoma).

The first error occurred in a FS on a liver lesion to exclude metastasis. The FS was called suspicious for metastatic adenocarcinoma, and the surgeon aborted the pancreatic resection as expected. Permanent sections showed a bile duct hamartoma (von Meyenburg complex) (Figure 2, A through C). The patient was brought back to the operating room for the resection at a later date given the absence of metastasis. The patient died within weeks after the second metastasis evaluation. The final diagnosis was malignant (hematoxylin-eosin, original magnifications ×100 [A, D, G, and J], ×400 [B, C, H, I, and L], and ×200 [E, F, and K]).

Figure 1. Frozen section (FS) deferrals. A through C, Frozen section for primary diagnosis. A and B, FS deferred as atypical; Whipple aborted because of a separate FS with metastasis (not shown). C, Permanent section (PS) from atypical FS block, diagnosed as malignant. D through F, Another case of FS for primary diagnosis. D and E, Frozen section deferred as atypical; Whipple performed. F, Permanent section diagnosed as adenocarcinoma. G through I, Frozen section for liver lesion. G and H, Frozen section deferred with atypia; Whipple not performed because of vascular encasement seen intraoperatively. I, Permanent section with final diagnosis of atypical ductular proliferation that could not be further classified, despite additional workup (deeper sections, immunostains for Ki67, p53, and intradepartmental consultations). J through L, Another case of FS for liver lesion. J and K, Frozen section deferred as atypical. L, Permanent section diagnosed as malignant (hematoxylin-eosin, original magnifications ×100 [A, D, G, and J], ×400 [B, C, H, I, and L], and ×200 [E, F, and K]).
procedure. The autopsy showed that the liver contained multiple bile duct hamartomas and scar with bile ductular proliferation from several preoperative attempted biopsies, but no metastases. The cause of death was felt to be an operative complication. The second error was on a liver metastasis FS that was diagnosed as well-differentiated glandular proliferation suspicious for adenocarcinoma but cannot rule out bile duct adenoma. The PS was signed out as bile duct hamartoma. Although this FS was an error, there was another FS of a metastatic adenocarcinoma (confirmed on PS), so the Whipple procedure was stopped appropriately in spite of the error. The third error was an uncinate margin FS diagnosed as negative, but review of the FS and PS demonstrated clear-cut carcinoma on both (Figure 2, D through F). The final error was on a pancreatic margin FS (mentioned in the previous deferral section) that was called suspicious for carcinoma, but for which review of the FS and PS showed cautery artifact and no cancer. Completion pancreatectomy was performed. Of note, of these 4 errors, 1 had a definitive FS diagnosis, and the other 3 were called suspicious. Nevertheless, because the FS did not confirm the FS, they were still counted as errors.

Surgeons' Responses to FS Result

Surgeons' responses were different than expected in 8 FSs (3.6%), but their actions were explained by other intraoperative findings in 6 of these (Table 3). In 3 FSs for possible metastasis and 1 for vascular involvement, a pancreatic resection was not performed after a benign diagnosis. Review of the operative reports revealed that disease was unresectable because of gross vascular involvement noted by the surgeon. In 1 FS for primary diagnosis, the pancreatectomy was performed even with a negative preoperative FNA and benign FS of the mass because of strong clinical and intraoperative suspicion for malignancy. Final diagnosis was consistent with type 2 autoimmune pancreatitis. Three FSs showed adenocarcinoma at the margin; however, no additional tissue was taken in 1 case because of the uncinate margin location. Uncinate margins tend to be much less commonly sampled in pancreatic surgery because, in most cases, no additional tissue is present to be resected regardless of the diagnosis. There were 2 cases for which we could not find an explanation for the surgeon not taking additional margin despite a positive FS result on a pancreatic neck margin. In 1 case, the surgery was complicated by an unexpected vascular reconstruction. No discussion of the positive margin was found in the operative note. The second case appeared to contain a miscommunication between the FS pathologist and surgeon. In the operative note, the surgeon commented on significant treatment effect at the margin but no malignancy being present (the FS had been called malignant) and no additional tissue was taken.

DISCUSSION

Pancreatic resections are performed for malignant and sometimes benign disease, and the mortality is less than 2% in specialized centers.18 Intraoperative FSs are often performed during pancreatic resections for indications including primary pancreatic lesion diagnosis, metastasis and resectability evaluation, and margin assessments. However, data are limited regarding the impact and how surgeons respond to the FS diagnosis.

We reviewed the use of FS in pancreatic resections at a large academic institution to evaluate use, accuracy, ability to provide definite diagnosis, and the impact on patient care by assessing surgeons’ response. We found that the most common indication for FS during pancreatic resection was
Table 3. Unexpected Surgeon Responses Based on Frozen Section Diagnosis

<table>
<thead>
<tr>
<th>Location</th>
<th>FS Category</th>
<th>Diagnosis</th>
<th>Reason for Action From Operative Report</th>
<th>Sampled Site</th>
<th>Expected Response</th>
<th>Surgeon’s Action</th>
<th>Reason for Action From Operative Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>Primary diagnosis</td>
<td>Inflammation, no malignancy</td>
<td>Patient's young age and clinical suspicion</td>
<td>Pancreas</td>
<td>No resection performed</td>
<td>Distal pancreatectomy</td>
<td>Patient's young age and clinical suspicion for adenocarcinoma</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Primary diagnosis</td>
<td>Adenocarcinoma</td>
<td>No additional tissue taken</td>
<td>No additional tissue taken</td>
<td>No additional tissue taken</td>
<td>No additional tissue taken</td>
<td>No additional tissue taken</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Margin assessment</td>
<td>Adenocarcinoma</td>
<td>Major vessels grossly involved</td>
<td>Distal pancreatectomy</td>
<td>Whipple aborted</td>
<td>Whipple aborted</td>
<td>Whipple aborted</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Margin assessment</td>
<td>Fibrosis with scattered malignant cells</td>
<td>Unresectable with gross infiltration of hepaticoduodenal ligament and common hepatic artery</td>
<td>Distal pancreatectomy</td>
<td>Whipple aborted</td>
<td>Whipple aborted</td>
<td>Whipple aborted</td>
</tr>
<tr>
<td>Liver</td>
<td>Metastasis</td>
<td>Benign</td>
<td>Unable to separate pancreatic neck from superior mesenteric vein</td>
<td>Distal pancreatectomy</td>
<td>Whipple aborted</td>
<td>Whipple aborted</td>
<td>Whipple aborted</td>
</tr>
<tr>
<td>Liver</td>
<td>Metastasis</td>
<td>Benign, consistent with biliary microhamartoma</td>
<td>Unable to separate pancreatic neck from superior mesenteric vein</td>
<td>Distal pancreatectomy</td>
<td>Whipple aborted</td>
<td>Whipple aborted</td>
<td>Whipple aborted</td>
</tr>
<tr>
<td>Liver</td>
<td>Metastasis</td>
<td>Benign</td>
<td>Unable to separate pancreatic neck from superior mesenteric vein</td>
<td>Distal pancreatectomy</td>
<td>Whipple aborted</td>
<td>Whipple aborted</td>
<td>Whipple aborted</td>
</tr>
<tr>
<td>Liver</td>
<td>Vascular resectability</td>
<td>Normal</td>
<td>Unable to separate pancreatic neck from superior mesenteric vein</td>
<td>Distal pancreatectomy</td>
<td>Whipple aborted</td>
<td>Whipple aborted</td>
<td>Whipple aborted</td>
</tr>
</tbody>
</table>

Abbreviation: FS, frozen section.

The majority (12 of 17; 70.6%) of cases with FS performed had metastasis or malignancy. Two cases were called suspicious for malignancy, with the remainder benign or inconclusive. Interestingly, the majority (12 of 17; 70.6%) of cases with FS performed for metastasis evaluation was the second most common FS use after margin assessment. A total of 94 FSs (42.5%) were performed for this purpose, with liver being the most common location sampled. Most of the time, a definitive diagnosis was rendered (88 cases; 93.6%), with only 6 deferral cases. Other operative findings and patient’s clinical condition, including age, may have impacted decisions in these cases. There are inherent challenges in assessing liver metastasis, especially in liver lesions composed of atypical ducts with stromal changes. Half (2) of the errors in this study were on FS liver lesion evaluation. The primary differential diagnosis includes metastatic adenocarcinoma, bile duct adenoma, von Meyenburg complex, and reactive bile ductular proliferation. As we and others have reported, low-power evaluation for disorganized duct distribution with ill-defined borders is most helpful to suggest metastatic adenocarcinoma. Other features of malignancy include anisonucleosis (at least 4:1), perineural invasion, single infiltrating cells, infiltration of normal hepatic structures, desmoplastic stroma, necrosis, and mitosis. Comparison with interlobular bile ducts of the surrounding liver may be helpful if present.

Frozen section for primary diagnosis was used in only 17 of the 152 pancreatic resections (11.2%), with a total of 20 of the 221 FSs (9.0%) performed. Of the 17 cases, 9 (53%) had preoperative FNA, and none were diagnostic of adenocarcinoma. Two cases were called suspicious for malignancy, with the remainder benign or inconclusive. Interestingly, the majority (12 of 17; 70.6%) of cases with FS performed for

Preoperative FNA and cytology was performed in nearly half the study cases (73 of 152 cases; 48%) and was diagnostic for neoplasm in 46 of 73 (63%). As expected, in those cases diagnostic of malignancy, FSs were done mainly for metastasis and margin assessment and not for primary diagnosis. Frozen section for primary diagnosis were used in some cases that either did not have FNA or had nondiagnostic cytology. In many cases without preoperative FNA or with nondiagnostic FNA, and no FS for primary diagnosis, the surgeons appropriately performed the resections based upon clinical and radiologic findings. In some cases, resections were performed for chronic pancreatitis based upon severe symptoms or inability to exclude malignancy.

In our study, the most common use of FS was for margin assessment, especially the pancreatic neck margin, where accuracy and utility has been previously shown to be very high. Controversy remains around the utility of FS of margins and the impact on overall survival. Studies have described contradictory findings, with some suggesting the useful impact of achieving negative pancreatic neck margin at the time of surgery, whereas others indicate no significant improvement in overall survival. Positive margin status on FS has been shown to be a negative independent predictor of overall survival, but not when other factors are taken into consideration, such as large tumor size, lymphovascular invasion, and perineural invasion, among others.

We found that metastasis evaluation was the second most common FS use after margin assessment. A total of 94 FSs (42.5%) were performed for this purpose, with liver being the most common location sampled. Most of the time, a definite diagnosis was rendered (88 cases; 93.6%), with only 6 deferral cases. Other operative findings and patient’s clinical condition, including age, may have impacted decisions in these cases. There are inherent challenges in assessing liver metastasis, especially in liver lesions composed of atypical ducts with stromal changes. Half (2) of the errors in this study were on FS liver lesion evaluation. The primary differential diagnosis includes metastatic adenocarcinoma, bile duct adenoma, von Meyenburg complex, and reactive bile ductular proliferation. As we and others have reported, low-power evaluation for disorganized duct distribution with ill-defined borders is most helpful to suggest metastatic adenocarcinoma. Other features of malignancy include anisonucleosis (at least 4:1), perineural invasion, single infiltrating cells, infiltration of normal hepatic structures, desmoplastic stroma, necrosis, and mitosis. Comparison with interlobular bile ducts of the surrounding liver may be helpful if present.

Frozen section for primary diagnosis was used in only 17 of the 152 pancreatic resections (11.2%), with a total of 20 of the 221 FSs (9.0%) performed. Of the 17 cases, 9 (53%) had preoperative FNA, and none were diagnostic of adenocarcinoma. Two cases were called suspicious for malignancy, with the remainder benign or inconclusive. Interestingly, the majority (12 of 17; 70.6%) of cases with FS performed for
primary diagnosis were found to be benign (pancreatitis and pseudocyst) on final diagnosis. Therefore, FS for primary diagnosis was likely requested on cases where malignant diagnosis could not be definitely made on preoperative cytology, and clinical and intraoperative findings were inconclusive to the surgeons. The small number of FSs performed for primary diagnosis in part can be explained by the advancement of diagnostic imaging modalities. Computer tomography has been reported to have a sensitivity and specificity of up to 89% and 90%, respectively. Frozen section is only occasionally performed for primary diagnosis and is most useful when confirmation of malignancy was not possible preoperatively and is necessary to allow chemotherapy in unresectable cases or when there are unusual operative findings. Preoperative endoscopic ultrasound-guided fine needle aspiration is commonly used in this setting and has replaced the need for FS for primary diagnosis in many cases.

Reliability of FS’s diagnostic utility as a tool for primary diagnosis has been controversial. Some authors suggest more than one biopsy is needed to accurately diagnose adenocarcinoma in order to achieve a low false-negative rate, and others suggest a negative predictive value of only 50% when negative for malignancy. A negative FS does not exclude the possibility of sampling error, as chronic pancreatitis is commonly found adjacent to pancreatic adenocarcinoma. Pancreatic resections are felt warranted in suspicious cases, even when the diagnosis cannot definitively be made by preoperative cytology and intraoperative FS. In addition, pancreatic resections are also sometimes performed for complicated chronic pancreatitis.

Resectability is typically determined by the surgeon at the time of surgery by assessing for possible metastasis and vascular involvement, with advanced imaging less reliable. Frozen section has proven to be useful, especially when positive and when additional intraoperative findings, not previously documented with imaging studies, are observed. In our study, only 2.3% (5 of 221) of FSs were performed for the purpose of determining vascular resectability.

Diagnostic errors rarely occurred in our FSs (4 of 152 cases [2.6%] and 4 of 221 FSs [1.8%]). This is consistent with the low false-negative (1.2%) and false-positive (0.3%) rates that we previously reported, and similar to other studies. Our error rate is lower than that reported by Nelson et al (14%). However, it is unknown whether their deferrals were classified as errors or not. In our study, deferrals included atypical and suspicious for malignancy, whereas only suspicious cases that were incorrect were also counted as error. Of note, the accuracy of margin evaluation (97%) in the Nelson et al study is similar to ours, and margin evaluation represented the most common FS in our cohort. Other possible factors that could explain the difference in the error rate include the number of cases evaluated (68 in Nelson et al versus 152 in this study), different mix of cases and indications for FS, and specialized FS pathologists in our institution.

In almost all cases reviewed, the surgeons appeared to act as expected based upon our FS diagnoses. The surgeons in our institution treated all cases that were diagnosed as suspicious for malignancy as if they were malignant. For the atypical defer to FS diagnoses, the management was variable depending on other clinical and intraoperative findings. When surgeons acted differently than we expected based upon the FS, their actions were explained by other intraoperative findings in almost all cases. Of the 8 cases in which it initially appeared that the surgeon did not act as expected, 6 could be explained by other intraoperative findings as indicated in the operative reports. In the 2 positive pancreatic neck margins for which the surgeons did not resect more tissue as expected, we could not find a specific reason in the operative notes. In 1 of the cases, it appeared that the surgeon mistakenly thought the FS was negative, whereas in the other, no comment was made on the FS but there was an unexpected vascular complication during the surgery, possibly diverting the surgeon’s attention.

CONCLUSIONS

During pancreatectomy, FS remains an important diagnostic tool used primarily for evaluation of margin status and metastasis. In most cases, a definitive diagnosis is rendered, with only occasional deferrals and few errors. In difficult cases, deeper sections or obtaining a second opinion might help reduce the number of deferrals and mistakes. Surgeons act accordingly on pathologists’ diagnoses almost all the time, and other intraoperative or clinical findings explain most cases in which they act differently than expected based on FS diagnosis.

References


