MY APPROACH

Intraoperative assessment of the Whipple resection specimen

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Intraoperative consultation for the Whipple resection procedure has evolved due to the increasing influence of imaging techniques in surgical planning and decision-making. The indications and utilisation of this service vary, at least to some degree, from one institution to the other. The following discussion is a single institutional approach, which is hoped to provide assistance to the practising pathologists in this field. Special emphasis is given to the relevant anatomical considerations and the most common indications for an intraoperative consultation.

The Whipple procedure is a radical operation performed for the resection of a variety of tumours involving the head of pancreas, ampulla of Vater, common bile duct (CBD) or duodenum. The last decade has witnessed an increasing influence of improved modern imaging techniques, such as CT and MRI, on the management approach of pancreato-biliary and duodenal tumours. These techniques not only help to make a preoperative diagnosis with reasonable accuracy but also help in planning of the type and extent of surgery. Concurrently, the safety of pancreatic resection has been consistently improving, making the procedure less morbid.^{1–3} In many complicated cases of chronic pancreatitis presenting as a periampullary mass, the Whipple procedure is now considered justifiable.⁴ For all these reasons, we and others⁵ have witnessed a shift in practice, with the Whipple resection becoming more confidently planned based on the clinical and imaging findings, with diminishing need for a confirmed preoperative tissue diagnosis. In a recent audit of the last 15 years of our practice at Sunnybrook Health Sciences Center, only 8.5% of all patients who received pancreatic surgery had a preoperative tissue or cytological diagnosis.

In no other organ system does the surgeon plan such a radical resection surgery without obtaining a tissue diagnosis. This has impacted the role of pathologists as intraoperative consultants and made it challenging, since they were typically not involved in the preoperative workup of the case. A classic example of this challenge is when the Whipple resection specimen arrives in the frozen section suite for an intraoperative assessment of its margins when the pathologist has no record of the type of its primary tumour. In fact, neither the surgeon nor the pathologist may be absolutely confident of the presence of a tumour. The difficult anatomy of the pancreas and the potential unfamiliarity of some pathologists with its subtleties, including the possible “normal” anatomical

variants of the structures involved, all add more challenge to the already difficult intraoperative consultation process.

There is increasing literature emphasising the impact of proper specimen handling on improving patient survival and our ability to predict prognosis of hepato-pancreato-biliary malignancies.^{6–9} Handling of the Whipple specimen for comprehensive and informative final reporting is becoming increasingly critical for oncologists as they categorise their respective patients for postoperative adjuvant therapy and follow-up. The final pathology report is expected to conform to the established checklists ensuring its completeness,^{10,11} use the terminology of well-recognised diagnostic entities,^{12,13} and embrace the modern concepts of precancerous lesions.^{14–16} Yet it needs to be constructed in the context of the given clinical scenario and should attempt to reconcile such relevant issues as whether the patient was jaundiced, the biliary tree was stented, and preoperative images were accurate in predicting respectability, and also the possibility of coexistent neoplasia(s). Intraoperative consultation offers the pathologist a first hand opportunity to examine the specimen and to ensure its adequate processing in the best manner to address these issues. The relative rarity of this specimen, especially outside large tertiary referral medical centres, makes all of these tasks particularly challenging.

This article aims to help pathologists adopt safer practice strategies as they handle Whipple resection specimens. It sheds light on some of the relevant anatomical subtleties, increases awareness of the common pitfalls, addresses issues that are mutually significant to the surgeons, and hopefully will alleviate the stress of performing the intraoperative consultation.

ANATOMICAL CONSIDERATIONS

The right hepatic duct collects bile from the right lobe of the liver. The left hepatic duct collects from the left, quadrate and caudate lobes. The two ducts meet to form the common hepatic duct, which unites with the cystic duct at the level of the superior border of the first part of the duodenum. This union creates the CBD, which passes behind the first part of the duodenum to enter the pancreas where it joins the main pancreatic duct; these open in the ampulla of Vater in the second part of the duodenum.¹⁷ Many anatomical variants along this theme exist; for instance, the cystic duct may meet the common hepatic duct above or below the level of the superior border of the first part of the duodenum or may even open in the right hepatic duct. The CBD is adherent to the posterior wall of the duodenum, therefore no

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Figure 1 (A) Low-magnification of a previously stented common bile duct with significant inflammation changes. Mucosal glands feature reactive changes but are benign. Deep-seated adenocarcinoma is apparent (arrows) surrounded by desmoplasia. (B) High-power view of the malignant focus.

surgical plane can be achieved between the two structures. Depending on the local circumstances and the indications for any given surgery, the surgeon performing a Whipple resection may cut the biliary tree slightly above the level of the superior border of the duodenum before the common hepatic and cystic ducts united. In other instances, the cut may be positioned below that level, going through the CBD.

As the CBD is adherent to the posterior wall of the duodenum, distal extra-hepatic cholangiocarcinomas are usually resected by a Whipple procedure. On the other hand, proximal extra-hepatic cholangiocarcinomas that occur above the level of the superior border of the duodenum can be managed by segmental resection of the biliary tree with or without hepatic lobectomy.

The head of the pancreas is defined as the part of pancreas present to the right of the left border of the superior mesenteric vein (SMV)/portal vein (PV). The uncinate process is the portion of the pancreatic head that curves posteriorly, creating a groove. The SMV meets the splenic vein and continues in that groove behind the pancreas as the PV. The superior mesenteric artery (SMA) originates from the aorta and passes down slightly posteriorly and to the left of the SMV.¹⁸ The tip of the uncinate process is separated from the SMA by only a narrow rim of connective tissue rich in lymphatics and nerve plexus structures.⁸ The surgeon's dissection to free the uncinate process from the SMA creates what is known as "the uncinate surgical margin" which is sometimes critical to assess intraoperatively. It is also known as "the retroperitoneal margin". The remainder of the "radial margin" consisting of the posterior surface of the pancreatic head, including its groove, which is in direct contact with the SMV/PV, is assessed on permanent sections.

INDICATIONS AND SCOPE OF THE WHIPPLE RESECTION

Similar to many of the greatest discoveries in medicine, the Whipple procedure, also known as the pancreaticoduodenectomy resection, was an accident. In 1935, Dr Allen O Whipple (1881–1963) of New York City was giving a surgical demonstration to distinguished American and foreign visiting surgeons on a patient who was believed to have gastric cancer. Halfway through the surgery, he discovered that the lesion was

actually carcinoma of the pancreatic head, so he had to spontaneously devise and execute on the spot this elaborate operation which is still being used.¹⁹ Today, the Whipple procedure is the standard curative procedure for carcinoma of the head of pancreas, carcinoma (or large/carpet adenoma) of the ampulla of Vater, distal cholangiocarcinoma of the CBD, or carcinoma of the duodenum. In Sunnybrook Health Sciences Center, the Whipple resection may be performed only in patients who: (i) have no distant metastases; (ii) have no vascular invasion of the SMA or SMV-PV as shown by preoperative imaging; (iii) are medically fit; and (iv) are <82 years old. The resected specimen typically includes: (i) the distal stomach (pylorus might be spared); (ii) all four parts of the duodenum; (iii) a small portion of the proximal jejunum; (iv) the gallbladder (sometimes submitted separately or not submitted at all if previously resected); (v) the CBD; (vi) the head of the pancreas (including the uncinate process); and (vii) in rare cases, a portion of the PV or even the SMA. It is important to recognise Whipple specimens that include portions of the adjacent great vessels removed en bloc either as part of the extended²⁰ or the augmented²¹ pancreaticoduodenectomy procedures. The presence of great vessel segments in the resected specimen results in additional surgical margins (proximal and distal vascular margins), which may need to be assessed intraoperatively.

INTRAOPERATIVE CONSULTATION

The pathologist may be called on to render an intraoperative consultation (IOC) for a variety of reasons, depending on the circumstances pertaining to the individual case and the indication for the Whipple resection. In most cases, the intraoperative interpretation is "definitive". However, due to a variety of reasons, the pathologist's interpretation could be less than definitive and is offered with the disclaimer of "suspicious for" or "suggestive of". It is our experience that due to the constraints of this complex operative procedure, when circumspect terminology is used in reporting the IOC, surgeons are likely to proceed based on the rendered diagnosis, disregarding its disclaimer. In 13 of the 17 cases where a non-definitive IOC was given in our hospital over the past 15 years, the surgeon disregarded the disclaimer and acted based on the perceived given diagnosis. Deferring the diagnosis could

Figure 2 A pancreatic margin with significant cautery artefact, precluding accurate assessment.

be a safer approach to dealing with IOC uncertainty. In one series, a deferral rate of 6.6% was considered acceptable.³ When the IOC is deferred, the impression of an experienced surgeon, empowered by accurate and reliable preoperative imaging studies is satisfactorily safe.³ This is one of the privileges our modern practice offers; older reports, when imaging techniques were less reliable, found it dangerous for surgeons to proceed when the frozen section diagnosis was deferred.²²

In most cases, the IOC is requested to answer more than one question. In our experience, the status of the surgical margins is the most common intraoperative question, while making a diagnosis of benign versus malignant neoplasia is the least common. We find that experienced surgeons plan their surgeries with the aid of extremely accurate preoperative imaging and minimal need for an intraoperative “benign versus malignant” diagnosis. This is especially true in cases of duodenal/ampullary tumours where a preoperative tissue diagnosis is easier to obtain by means of endoscopy.

Assessment of the surgical margins

The first and probably the most difficult step in assessing the Whipple specimen is orienting it and identifying its anatomical landmarks. In our institution, the submitting surgeon plays an active role during this step, particularly if any aspect of the specimen or surgery is unusual. We ink the entire posterior surface (radial margin), including the uncinate process (retroperitoneal margin), superior and inferior surfaces with one colour. The pancreatic margin (see below) is inked with a different colour. Once sections are taken for intraoperative

analysis, the specimen becomes even more difficult to orient at the time of final grossing. Therefore, standardising the protocol and establishing effective lines of communication are critical in large institutions where the final prosectors of the specimen may be different from those who conducted the IOC. In some institutions, margins that were taken for IOC are re-inked with a special colour so that these areas become readily identifiable later as “not” true margins. When these steps are routinely documented in the surgical pathology suite, the Whipple specimen is usually grossed smoothly and becomes less problematic.

Few surgical margins are routinely assessed intraoperatively in the Whipple resection specimen. The status of the biliary tree and pancreatic margins is almost always assessed intraoperatively. The intraoperative assessment of the uncinate margin is critical in cases where a pancreatic head tumour involves the uncinate process. In the rare cases where segments of the SMV or SMA are included in the specimen, assessment of the luminal proximal and distal surgical margins of these great vessels may be requested intraoperatively.^{20, 21} Other surgical margins such as the luminal gastric, duodenal/jejunal, peri-pancreatic soft tissue, and posterior (radial) pancreatic margins are usually assessed on permanent sections.

The biliary tree margin

This margin results from the surgeon’s cut through the biliary tree. In cases where the cholecystectomy is performed en bloc, the gallbladder is included in the specimen, and the biliary tree margin will consist of the common hepatic duct. Alternatively, the cholecystectomy could be performed early as a separate step of surgery; in this case the gallbladder will not be part of the Whipple resection specimen. The received resection specimen will have two openings of ductal structures in its superior aspect; one is the cystic duct, and the other, which is a true surgical margin, is the common hepatic duct. As indicated above, the surgeon’s cut may be positioned below the union of the common hepatic and cystic ducts; in this case the resected specimen will only have one duct opening, which is that of the CBD. In some cases, the surgeon may submit the margin separately at an early stage of the surgery as a “donut”. The biliary tree margin is submitted for frozen section en face with the true margin (most proximal end) facing the knife.

The most common pitfall leading to a false negative IOC of this margin arises from the fact that malignant cells of extrahepatic cholangiocarcinomas or pancreatic ductal adenocarcinoma involving the CBD tend to be present in the deep layers of the wall of the extrahepatic biliary tree. A pathologist who focuses mainly on examining the mucosa may overlook the few malignant cells that dissected their way through the deeper connective tissue from a more distal location (fig 1). It is also important to make the effort to identify all the nerves in the tissue in order to detect any possible perineural invasion at

Figure 3 Pancreatic ductal adenocarcinoma. Note: (A) nuclear size variation; (B) disorganised duct distribution with pointed ends and angulation; (C) neural invasion.

the margin. In cases where the CBD has been stented prior to surgery, the wall tends to be inflamed and oedematous, which may mask subtle malignant cells present at the margin. It has been shown that a false negative IOC of the CBD margin has a significant negative impact on patient survival.²³ A false positive IOC, although a less common error, may result from the unfamiliarity with the reactive changes which may involve the normally present mucosal glands. Non-neoplastic mucosal glands tend to maintain their lobular arrangement, which is readily appreciated on low power magnification even in the presence of severe chronic inflammation which typically accompanies preoperative stenting. A high-power examination could complicate matters by demonstrating large, atypical nuclei with prominent nucleoli in the otherwise benign reactive lining mucosal cells. Again, the maintained lobular architecture and the strict adherence to the diagnostic criteria of malignancy discussed later should help avoid an overcall in these situations.

The pancreatic margin

In the standard Whipple procedure, the surgeon transects the pancreatic neck to separate the tumour-harboring tissue from the body and tail of the pancreas, which are left in situ. This transaction creates a surgical margin, commonly referred to as "the pancreatic margin". A thin tissue slice is shaved off the margin and is submitted for frozen section with the true margin (away from the tumour) facing the knife. As expected, this margin is particularly critical in Whipple resections performed for a ductal carcinoma located at the pancreatic head. In cases of distal CBD cholangiocarcinomas or duodenal/ampullary tumours, assessment of the pancreatic margin may seem to be less critical. It is of note that since most Whipple resections are currently planned on the basis of preoperative images, we have encountered rare incidents where the resected specimen arrived at the frozen section suite with the preoperative diagnosis of "distal CBD carcinoma", only to find out a positive pancreatic margin. In these cases, further examination of the specimen by obtaining a frozen section from the head of pancreas proves that the tumour was rather an intrapancreatic ductal adenocarcinoma which was misinterpreted radiologically as a CBD cholangiocarcinoma.

Assessment of the pancreatic margin is one of the most challenging IOCs, where misdiagnosis, both in the false-positive and false-negative directions, can occur due to a host of technical factors. Usually, there are the inevitable cautery and freezing artefacts (fig 2). In some instances, the cautery artefact is so handicapping that it may warrant shaving a 1 mm slice to allow for examining a non-artifactual tissue section rather than the absolute true margin. A positive result in this case would indicate at the very least, an undesirable nearness of the malignancy to the true margin and may justify its revision. A negative result, on the other hand, would be reassuring.²⁴ We also find it extremely helpful in these situations to simultaneously obtain a benchmark frozen section from the tumour at the head of pancreas where the tissue is distinctly firm. Assessment of a difficult margin is significantly improved by establishing the morphological characteristics of the actual tumour for comparison. Assessment of the pancreatic margin is further complicated by the presence of chronic pancreatitis in almost every case of pancreatic ductal carcinoma which results in fibrosis, atrophy and glandular distortion of the ductal system mimicking adenocarcinoma. Furthermore, mucinous metaplasia and ductal epithelial hyperplasia are common in chronic pancreatitis and may be misinterpreted as malignant features.

Overcalling the pancreatic margin (a false positive IOC) will result in its unnecessary revision. Usually, this is not technically challenging for the surgeon since excising few extra millimetres from the pancreatic body is a relatively easy procedure.

However, even excising few extra millimetres could still be unnecessarily morbid to a patient whose pancreatic function is already compromised by Whipple resection and a concomitant chronic pancreatitis. On the other hand, undercalling this margin (a false negative IOC) may result in subsequent tumour recurrence and death in only few months.²⁵⁻²⁹ It is, therefore, critical for the consulted pathologist to spend adequate time examining this section at high power magnification. Consulting with another pathologist with more experience in this area might be helpful in difficult cases.

Malignancy is identified by the haphazard proliferation of ducts of different sizes and shapes without lobular orientation, which is often most easily recognised on low power magnification. At higher power, haphazard orientation of cells, hyperchromasia and pleomorphism are helpful. Necrosis within glands, atypical mitoses, and perineural or vascular invasion are among the most reliable features. High grade pancreatic intraepithelial neoplasia (PIN), including carcinoma in situ (PIN-3) detected in pancreatic ducts at the margin should be reported.³⁰⁻³¹ It is our experience that surgeons typically choose to revise the pancreatic margin when a high grade PIN is detected at the margin intraoperatively. To date, the most reliable criteria for making a malignant diagnosis on frozen sections of pancreatic tissue are those proposed by Hyland *et al.*³² These authors proposed three major criteria (nuclear size variation of 4:1 or greater, incomplete duct lumens (fig 1B), and disorganised duct distribution (seen on low power)), and five minor criteria (large irregular nucleoli, necrotic glandular debris, glandular mitoses, glands in muscle without connective tissue stroma, and vascular and perineural invasion (fig 3)). Another finding that could help confirm malignancy on frozen section is the presence of ductal structures adjacent to medium-sized arteries.³³⁻³⁴ We find the careful application of these criteria extremely helpful; especially to avoid undercalling a pancreatic margin.

The uncinate margin

The final step in removing the Whipple specimen from the patient is transecting the uncinate process. In order to deliver the specimen, the uncinate process needs to be divided as close to the SMA as possible, yet without damaging the SMA or the autonomic nerve plexus surrounding it. This is a technically challenging step of the Whipple procedure. There is a natural tendency on the part of the surgeon to leave behind, in the patient, the section of the uncinate tissue closest to the SMA. This can sometimes lead to a positive uncinate margin when a pancreatic head adenocarcinoma involves the uncinate process. As indicated earlier, our local protocol for the intraoperative assessment of the Whipple resection specimen with carcinoma in the head or the uncinate process of the pancreas requires inking of the posterior surface of the pancreas, including the uncinate process. The tip of the uncinate process, including its distal 1 cm, is then cut off the rest of the specimen and is serially sectioned at 3 mm intervals perpendicularly. This produces 6-8 pieces of tissue that are submitted for frozen section examination.³⁵ This protocol allows for an accurate assessment of the entire uncinate margin and produces clear sections that are relatively easy to interpret (fig 4). In cases where malignant cells are close to, but not at the surgical margin, these sections even allow for measuring the distance between the closest malignant cell and the true margin.

The great vessels margin

As indicated earlier, some Whipple specimens may include portions of the great vessels (SMV, PV and/or SMA). It is critical to be able to recognise these structures when they are attached to the vascular groove. It is helpful to prospectively establish a line of communication with the submitting surgeon

Figure 4 A negative uncinate margin perpendicular section showing the inked margin, a thin rim of adipose tissue and the inflamed fibrotic pancreatic parenchyma.

so that the pathologist is appropriately alerted in these situations. Often, a short segment of the vessel is removed with the specimen and is identified as a tubular structure. In this case, the proximal and distal vessel margins should be shaved off and assessed intraoperatively. The remainder of the vascular structure could later be processed and examined in permanent sections. However, surgeons may also remove just a smaller portion of the vessel wall, which looks like a round or oval “patch”, rather than a complete tubular structure, attached to the vascular groove. In this case, the entire edge of this “patch” is technically a margin. Therefore, it is inked, serially sectioned, and submitted in its entirety for the intraoperative assessment. If the “patch” is too big, its perimeter may be examined through multiple cuts intraoperatively, while the remainder is processed for permanent sectioning.

Assessment of extrapancreatic spread

One of the early steps of the Whipple procedure calls for the surgeon to assess resectability by ruling out extrapancreatic tumour spread. The liver, peritoneal surfaces, lymph nodes and major blood vessels in the vicinity are explored. Suspicious and unexpected lesions, including large lymph nodes, could be sampled and submitted for frozen section examination to rule out metastases. Most surgeons would terminate surgery with the intraoperative diagnosis of extrapancreatic spread and may only provide the patient with a palliative biliary bypass procedure. In our institutional 15-year experience, Whipple resection was terminated in 24.8% of planned cases due to either intraoperative technical non-resectability or a positive intraoperative diagnosis of metastases. It is of note that the same criteria discussed earlier for the frozen section diagnosis of malignancy are applied in this setting.³²

Metastases in tissue samples submitted from anatomical locations where glandular structures are normally absent (for example, the vicinity of great vessels or peritoneal surface) are relatively easy to diagnose by the confident demonstration of ductules and/or epithelial nests. The most common pitfall leading to a false positive IOC for extrapancreatic spread is overcalling benign bile duct proliferation or hamartoma when a “suspicious hepatic nodule” is submitted for frozen section examination. On low power, a bile duct hamartoma (von Meyenburg complex) is characterised by a sharp outline and irregularly shaped ductal structures which lack pointed ends or angulation. On high magnification, ductal cells lack nuclear

Take-home messages

- The author’s approach to the intraoperative consultation of the Whipple procedure, is described, highlighting some of the essential anatomical considerations.
- Evolution of the surgical practice in the era of increased dependence on preoperative imaging, and how it influenced the current shape of intraoperative consultation service is discussed.
- The common intraoperative pitfalls are discussed and special strategies are proposed to alleviate stress and increase patient safety.

atypia. Similarly, subcapsular and post-inflammatory bile duct proliferations feature bland nuclei with extremely sparse mitoses.

Obtaining a diagnosis

Due to the relative high accuracy of current imaging techniques, the Whipple procedure is usually planned based on the clinical and imaging findings with great precision. Modern techniques such as CT scans and MRI are now the mainstay of preoperative assessment for pancreatic surgery as they reliably determine diagnosis and respectability.^{5, 36} It is interesting to witness the evolution of this concept over the years. Earlier reports on the subject saw obtaining an accurate frozen section diagnosis as a critical step in pancreatic surgery.^{22, 37} In our institution, trying to establish a malignant diagnosis intraoperatively is currently the least likely indication for an IOC. This request is more likely to be made when the Whipple procedure is being performed for cases of pancreatic tumours than for duodenal/ampullary tumours, but nevertheless, it is still a rare occurrence. The surgeon may perform a needle core biopsy or a small wedge biopsy and submit it for frozen section examination. Distinguishing between chronic pancreatitis and adenocarcinoma in these situations could be very challenging, and the pathologist needs to strictly adhere to the reproducible criteria discussed above to avoid a false positive result.³² At the same time, the pathologist needs to appreciate the limitations posed on the surgeon when he/she asks for additional tissue. With every biopsy performed, there is an increased risk for pancreatic enzyme leakage; therefore, the surgeon will try to limit as much as possible the number of attempts to obtain diagnostic tissue.

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