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TOPIC HIGHLIGHT

Jose Manuel Ramia, MD, PhD, FACS, *Series Editor*

Pathology handling of pancreatoduodenectomy specimens: Approaches and controversies

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Abstract

Pancreatic cancer, with a 5% 5-year survival rate, is the fourth leading cause of cancer death in Western countries. Unfortunately, only 20% of all patients benefit from surgical treatment. The need to prolong survival has prompted pathologists to develop improved protocols to evaluate pancreatic specimens and their surgical margins. Hopefully, the new protocols will provide clinicians with more powerful prognostic indicators and accurate information to guide their therapeutic decisions. Despite the availability of several guidelines for the handling and pathology reporting of duodenopancreatectomy specimens and their continual updating by expert pathologists, there is no consensus on basic issues such as surgical margins or the definition of incomplete excision (R1) of pancreatic ductal adenocarcinoma. This article reviews the problems and controversies that dealing with duodenopancreatectomy specimens pose to pathologists, the various terms used to define resection margins or infiltration, and reports. After reviewing the literature, including previous guidelines and based on our own experience, we present our protocol for the pathology handling of duodenopancreatectomy specimens.

Key words: Pancreatic ductal adenocarcinoma; Duodenopancreatectomy specimens; Resection margins; Pathology protocols

Core tip: Pancreatic cancer, one of the most lethal tumor types, is the fourth leading cause of cancer death in developed countries. The need to prolong patient survival has prompted the development of improved protocols to evaluate duodenopancreatectomy specimens and their surgical margins by pathologists. Despite the availability of several guidelines and their continual updating, there is no consensus on basic issues such as surgical margins or the definition of incomplete excision. We herein review the controversies and approaches in the literature and present our own protocol for the handling and reporting of pancreatoduodenectomy specimens by pathologists.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the most common cancer affecting the exocrine pancreas and the fourth leading cause of cancer death in both sexes in

the United States[1]. In that country, pancreatic cancer accounts for 3% of all new malignancies. It is estimated that 45220 new cases will be diagnosed there during 2013 and it will be the cause of death for 38460 patients[1]. Death rates for pancreatic cancer between 2005 and 2009 were 12.5 and 9.5 per 100000 inhabitants (males and females, respectively)[1]. In Europe, pancreatic cancer accounted for 6.2% of deaths in 2012 (78000 patients)[2]. The overall 5 year survival rate remains dismal, at around 5%[1].

Unfortunately, only 8% of pancreatic cancer patients are diagnosed in the early stages and of those, only 20% are susceptible to surgical treatment[3].

The clinical management of oncological patients relies on robust pathological data for the assessment of the extent of the disease. Despite general guidelines for the handling and pathology reporting of pancreatic specimens which are constantly updated by expert pancreatic pathologists, there is no consensus in basic terms as to what margins of surgically resected PDAC must be reported or what exactly defines an incomplete excision (R1)[4]. In this report, we review these differences in the current literature and present the protocol that is used in our institutions, based on a European trend.

PATHOLOGY MANAGEMENT OF RESECTED PANCREATIC TUMORS

One of the most important steps in pathology reporting is the dissection procedure. There is a lack of consensus, however, in the development of a standardized guide for the macroscopic management of PDAC specimens. This is perhaps due to the fact that pancreatic surgery is not performed in all hospitals so not all pathologists have access to these pathologies. In addition, the precise evaluation of resection margins has been considered less critical due to the poor prognosis of this neoplasm and its lack of response to standard chemotherapy[5].

Despite the fact that resection margin status is a key prognostic factor, the rates of microscopic margin involvement (R1) vary enormously from study to study[6-10]. The disparities may be a result of differences as to what constitutes a resection margin, the controversy over the definition of R1 status and the lack of a standardized dissection protocol of PDAC specimens[5]. In recent studies[5,11,12], an important increase in R1 resections has been reported after the use of a standardized protocol of pathological reporting of PDAC specimens. An example is given in the study by Esposito *et al*[11] in which they show a change from 14% R1 resections to 76% when a standardized protocol was applied. Other series, including our preliminary report of 2007[13], have similar changes[5,11,14].

CONTROVERSIES IN THE HANDLING OF PDAC SPECIMENS

Nomenclature of relevant margins

Four relevant margins should be studied in PDAC: (1) luminal margins (proximal gastric or duodenal and distal jejunal); (2) bile duct margin (BDM), common bile duct or common hepatic duct margin; (3) pancreatic transection margin (PTM); and (4) pancreatic circumferential or radial margin (CRM).

The first three margins are universally accepted and easily recognizable in the specimen. In addition, the BDM and PTM can be examined intraoperatively.

According to Verbeke's reports, the CRM can be divided anatomically into an anterior surface or pancreatic anterior margin (PAM) and a posterior surface or pancreatic posterior margin (PPM). They are separated by a pancreatic medial margin (PMM), the part of the surface of the pancreatic head that faces the superior mesenteric (SM) vessels[5,15].

The PAM cannot be considered a true margin since there is no transection by the surgeon at this level. Although the PPM and PMM are truly the most important margins since they are frequently affected[5,12,13,16], we cannot ignore the fact that the presence of tumor cells on the anterior surface is likely to increase the risk of local tumor recurrence[5,17].

The PMM refers to the area that faces the superior mesenteric vessels, totally or partially surrounding the superior mesenteric vein. It has a shallow groove-like shape and a slightly glistening surface flanked by ties. Segments of vessels can be found when involved in the cancer[5]. The PMM is the margin most frequently involved and therefore requires careful assessment[15,18-20]. The PMM has many names, such as "vascular bed", "uncinated process margin", "mesenteric margin" or even "retroperitoneal margin". The last denomination may cause confusion[5,13,16] given that the entire head of the pancreas and not just this surface is located in the retroperitoneum.

The PPM is the area adjacent to the superior mesenteric artery the surgeon transects so it is a true margin[5].

In a recent publication by Khalifa *et al*[16], the nomenclature commonly used for pancreatic margins is reviewed. It makes evident the great variability, especially that in relationship to the circumferential margin, and the need for consensus. The terms "posterior" and "medial" margins are commonly used by European pathologists[11,16,21], while "deep retroperitoneal posterior surface" or "uncinated process" margins are the terms chosen by the College of American Pathologists (CAP) and the American Joint Committee on Cancer (AJCC)[22-24] (Figure 1).

Differences in dissection protocols

A wide range of different dissection techniques are used given the lack of consensus. Many of them are based on tradition rather than on an evidence-based rationale[5].

For many years, the longitudinal opening of the main pancreatic and biliary duct has been the standard technique used by European and American pathologists[15,18-21,25-27]. This method, however, interferes with the CRM assessment and is uninformative since the majority of PDAC do not arise in the main duct, with the exception of the intraductal papillary mucinous neoplasm[5].

In some classic American protocols, there is no speci-

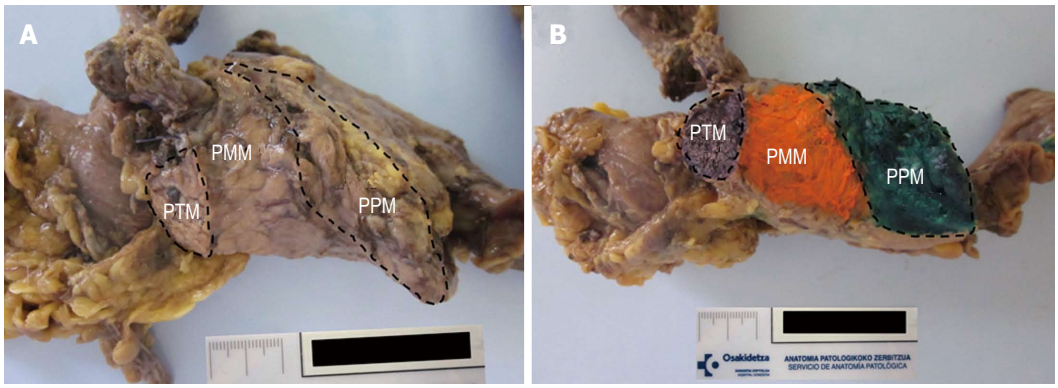

Figure 1 Pancreatoduodenectomy specimen images. A: Pancreatoduodenectomy specimen after fixation (posterior view); B: The circumferential soft tissue margins were inked (PTM: Violet, PMM: Orange, PPM: Green). PTM: Pancreatic transection margin; PMM: Pancreatic medial margin; PPM: Pancreatic posterior margin.

fied procedure for the specimen dissection[28] and the need to ink some of the margins and submit them is only superficially addressed[19,22,23,29].

Methods based on sections parallel to the pancreatic major axis, including a longitudinal section of the duodenal wall, have been used in Europe for many years[25]. The resulting sections are too thick and comprise different planes, something which makes it difficult for the pathologist to reconstruct the specimen or assess tumor size and margin status[5].

Both the *Armed Forces Institute of Pathology* (AFIP) in its 3rd edition[27] and Allen and Cameron in 2004[30] suggested a way of handling specimens based on the opening of biliary and pancreatic ducts with sections perpendicular to the ducts. Recently, in their 4th edition, the AFIP[31] recommended performing perpendicular sections to the main duct. That notwithstanding, these sections would be tangential to the duodenal wall, thus making the analysis of the ampulla, distal pancreatic and bile duct difficult[5].

The Japan Pancreas Society[32] has suggested slicing perpendicular to an axis that follows the curvature of the pancreatic head, even although the constant change of planes is an inconvenience[5].

The procedure performed by Westgaard *et al*[12] consists of inking the retroperitoneal margin, performing a 5-10 mm thick section parallel to this margin and serially slicing perpendicular to the ink.

In the last few years, a new standardized dissection technique[5,11,15,33] has been developed in Europe, especially in the United Kingdom. It is characterized by a serial slicing of the entire pancreatic head in a plane perpendicular to the longitudinal axis of the duodenum which avoids opening the biliary or pancreatic duct (Figure 2). The advantage of this method is its simplicity. There is no dependency of location or nature of the disease and a great number of sections are produced. This permits an extensive study of the lesion and its relationship with anatomical structures and surgical margins[5,15].

Differences in international protocols

The AJCC and CAP protocols recommend inking and cutting sections through the tumor at its closest approach to the retroperitoneal margin of the uncinate process (uncinate margin) and retroperitoneal posterior surface[22,23].

Only Allen and Cameron[30] recommend the need for analyzing the following margins in their book: superior, inferior, capsular anterior, posterior retroperitoneal and medial (superior mesenteric vein).

The Royal College of Pathologists[21] includes the transection margins (gastric, duodenum, pancreatic and common bile) and the dissected margins (superior mesenteric vessels and medial and posterior margins) in their histopathological report.

The anterior surface of the pancreas is not a true surgical margin but invasion of this surface has been associated with local relapse and decreased survival times[17,34]. For this reason, some authors and guides suggest reporting this margin[5,11,21,31], although it is not reported by the CAP[22] or by the 7th edition of the AJCC[23].

Margin involvement: R1 status

The lack of consensus on margins not only affects their nomenclature and inclusion in the pathological report, but also the definition of R1.

The role of margin involvement and its prognostic relevance has been well characterized in other cancer types, such as rectal cancer. Verbeke, though, states that *"margin status in pancreatic cancer has been neglected"*[5].

Resection margin involvement (R1) seems to be an important prognostic factor in pancreatic cancer but R1 rates reported in the literature vary enormously. Rates as disparate as 16% and > 75% have been reported in different studies and consequently clinical outcome correlation has been observed in some but not all[5,6,15,35].

For the majority of American pathologists, there is a positive margin (R1) only when the tumor is directly in contact with the inked margin (0 mm clearance)[13,16,22,31,35]. For European pathologists, R1 margin involvement is established when the distance between the tumor and the resection margin is 1 mm or less[5,11,12,15,21]. This is called the "1 mm rule" and was taken from the R1 definition of rectal cancer assessment[21].

Another confusing circumstance is when there is no

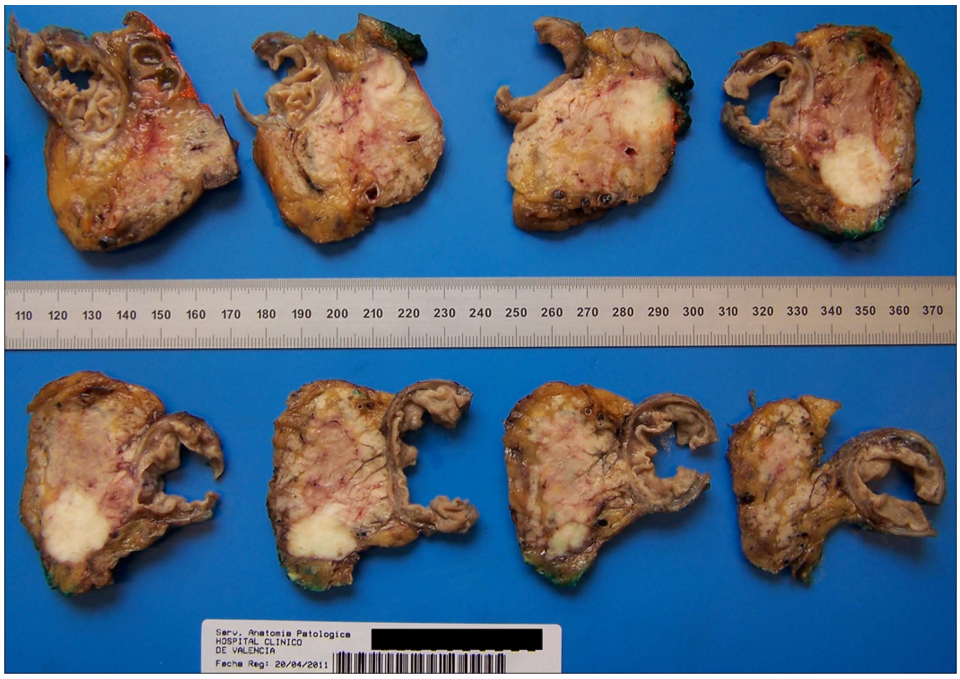

Figure 2 Consecutive parallel sections of 0.5 cm thickness following an axial plane perpendicular to the duodenal axis. Tumor seems to be in contact with the inked margin.

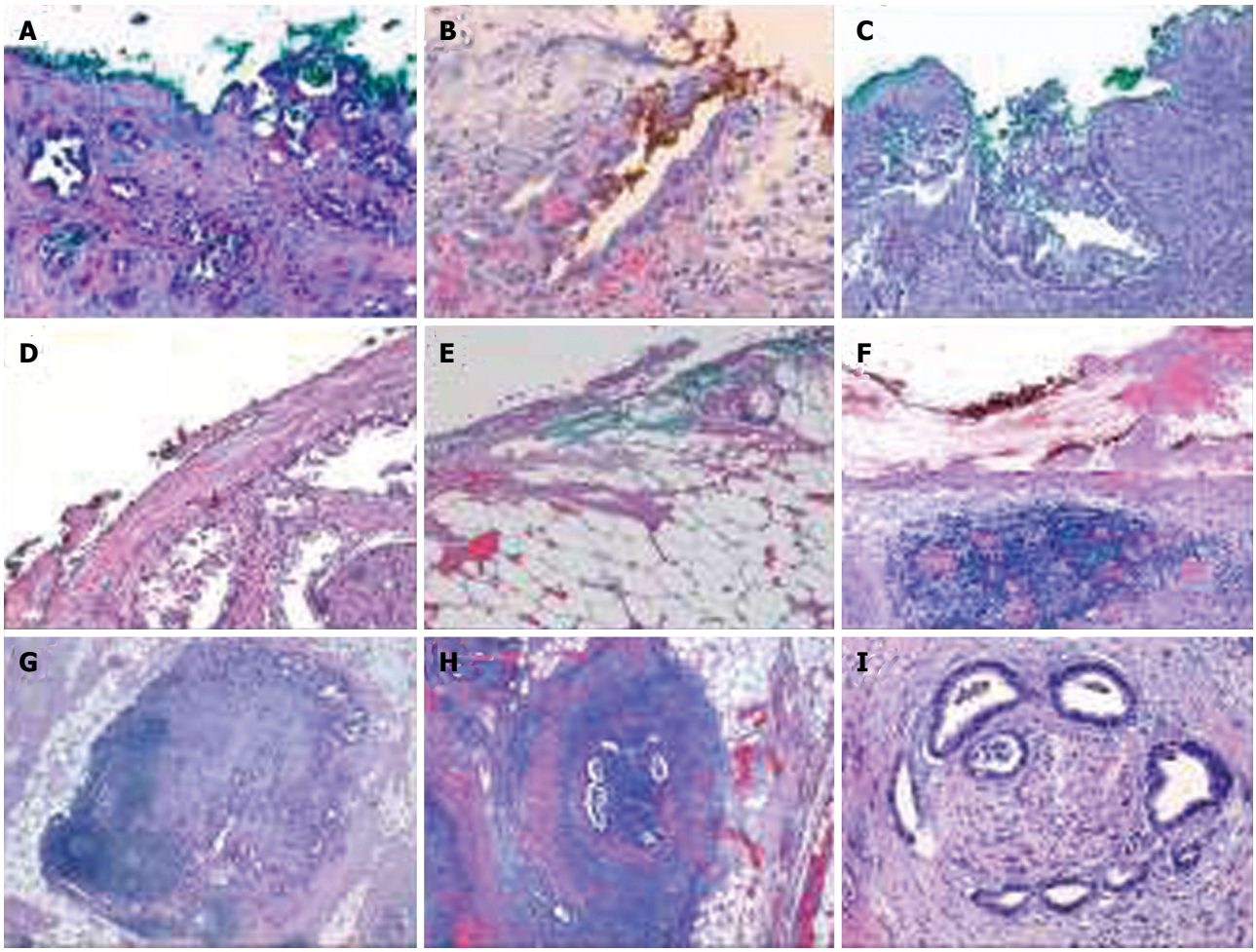

Figure 3 Microscopic picture. A-C: Microscopic picture of tumor glands in direct contact with an inked margin (R1 resection) (HE × 200, × 400 and × 200, respectively); D: Neoplastic cells within 1 mm of the resection margin colored in black (HE × 200); E, F: Examples of free medial or posterior margin (HE × 200); G: Ganglionar metastases (HE × 200); H: Vascular invasion (HE × 200); I: Perineural invasion (HE × 400).

PATHOLOGIC REPORT OF PANCREATIC CARCINOMA AT H.C.U.VALENCIA[1]

Name: _____ Age: _____
Case number: _____ Date: _____

Specimen type:
- ☐ Cephalic duodenopancreatectomy
- ☐ Cephalic duodenopancreatectomy with pyloric preservation
- ☐ Total pancreatectomy
- ☐ Distal pancreatectomy
- ☐ Central pancreatectomy

Tumor size: ____ x ____ x ____ cm

Macroscopic characteristic:
- ☐ Solid
- ☐ Cystic
- ☐ Polypoid
- ☐ Other: _____

Histologic type:[2]
- ☐ Ductal adenocarcinoma
- ☐ Adenosquamous carcinoma
- ☐ Other: _____

Histologic grade:[3]
- ☐ Well differentiated (G1)
- ☐ Moderately differentiated (G2)
- ☐ Poorly differentiated (G3)
- ☐ Undifferentiated (G4)
- ☐ Others: _____

Invasion:
- ☐ Vascular
- ☐ Lymphatic
- ☐ Perineural

Tumor site:
- ☐ Pancreatic head
- ☐ Pancreatic body
- ☐ Pancreatic tail
- ☐ Uncinate process
- ☐ Duodenal ampulla
- ☐ Other:_____

Tumor extension:[4]
- ☐ Carcinoma in situ (pTis)
- ☐ Limited to the pancreas ⩽ 2 cm (pT1)
- ☐ Limited to the pancreas >2 cm (pT2)
- ☐ Extends beyond the pancreas (pT3)
- ☐ Celiac axis or SMA involvement (pT4)

Precursor lesions:
- ☐ PanIN
- ☐ IPMN
- ☐ Others: _____

Non neoplastic lesions:
- ☐ Bile duct obstruction
- ☐ Pancreatic duct obstruction
- ☐ Pancreatic calculi
- ☐ Chronic pancreatitis
- ☐ Others: _____

Treatment effect (neoadjuvant therapy):[5]
- ☐ Complete response (grade 0)
- ☐ Moderate response (grade 1)
- ☐ Minimal response (grade 2)
- ☐ Poor response (grade 3)

Posterior circumferential margin (retroperitoneal)
- ☐ Uninvolved (> 1 mm)
- ☐ Involved
  - ☐ Direct: tumor in contact with inked margin
  - ☐ Direct: tumor ⩽ 1 mm (specify distance:_____)
  - ☐ Indirect (vascular, lymphatic or perineural) ⩽ 1 mm
  - ☐ Indirect lymph node metastasis ⩽ 1 mm

Medial circumferential margin (vascular)
- ☐ Uninvolved (> 1 mm)
- ☐ Involved
  - ☐ Direct: tumor in contact with inked margin
  - ☐ Direct: tumor ⩽ 1 mm (specify distance:_____)
  - ☐ Indirect (vascular, lymphatic or perineural) ⩽ 1 mm
  - ☐ Indirect lymph node metastasis ⩽ 1 mm

Bile duct margin: ☐ Uninvolved ☐ Involved

Pancreatic transection margin: ☐ Uninvolved ☐ Involved

Status Margins: ☐ R0 ☐ R1

Lymph node metastases: ☐ Nx ☐ N0 ☐ N1 Distance metastases: ☐ Mx ☐ M1

Lymph nodes	+	Total	Lymph nodes	+	Total
Peripancreatic (station 13, 17, 18)			Celiac (station 9)		
Suprapyloric (station 5)			Hepatoduodenal ligament (station 12)		
Infrapyloric (station 6)			Others:____		
Left gastric artery (station 7)			TOTAL		

Comments:

Explanatory notes:

1. This protocol is used for exocrine pancreatic and periampullary tumors.
2. Histologic types according to the WHO classification[51]
3. Differentiation grades (applicable only to ductal adenocarcinoma)[23]

Grade 1	Well differentiated	> 95% of tumor composed of glands
Grade 2	Moderately differentiated	50%-95% of tumor composed of glands
Grade 3[1]	Poor differentiated	5%-49% of tumor composed of glands
Grade 4[2]	Undifferentiated	< 5% of tumor composed of glands

- [1]Signet-ring cell carcinoma is considered grade 3
- [2]Undifferentiated (anaplastic) carcinoma is considered grade 4
- Other types are not graded.

4. Primary tumor (TNM classification)[23]

Tis	Carcinoma *in situ*
Pancreas	
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension
T2	Tumor limited to the pancreas, more than 2cm in greatest dimension
T3	Tumor extends beyond the pancreas, but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
Ampulla of Vater	
T1	Tumor limited to ampulla of Vater or sphincter of Oddi
T2	Tumor invades duodenal wall
T3	Tumor invades pancreas
T4	Tumor invades peripancreatic soft tissues, or other adjacent organs or structures
Distal extrahepatic bile duct	
T1	Tumor confined to the bile duct
T2	Tumor invades beyond the wall of the bile duct
T3	Tumor invades the gall bladder, liver, pancreas, duodenum or other adjacent organs
T4	Tumor involves the celiac axis or the superior mesenteric artery

5. Treatment effect (applicable to carcinomas treated with neoadjuvant therapy)[52]

No viable tumoral cells	Complete response (grade 0)
Single cells or small groups of tumoral cells	Moderate response (grade 1)
Residual tumor with fibrosis	Minimal response (grade 2)
Extensive residual tumor	Poor (grade 3)

Figure 4 Elaborated checklist for the pathological reporting of pancreatic ductal adenocarcinoma.

direct margin involvement by the tumor. Despite the absence of clear evidence, The Royal College of Pathologists suggests considering the incomplete excision to be an R1 resection if lymph node metastases or perineural/lymphovascular invasion is within the 1 mm limit (indirect invasion of R1)[5,11,21]. Conversely, according to the tumor-node-metastasis staging system of the AJCC, the resection margin is considered R1 indirectly only when tumor cells are attached to or invade the vessel wall[36] (Figure 3).

Lymph node metastases

Lymph node metastases (N1) have been shown to be an independent negative prognostic factor in multivariate analysis[10,37-41]. Nevertheless, the lymph node ratio, defined as the ratio of the number of positive lymph nodes to the total number of lymph nodes evaluated, is now considered a more powerful prognostic marker than the overall nodal status in resected pancreatic cancer[10,13,42-48].

In the 5th edition of the AJCC[49], N1 was subdivided into 2 categories, N1a and N1b, depending on the number of lymph nodes affected (3 or less for N1a and more than 3 for N1b). In the subsequent versions (6th and 7th), this subdivision was changed. They considered N1 to be lymphatic metastases no matter how many lymph nodes were involved[23,29,49]. The following lymph nodes were considered to be regional: hepatic artery nodes, superior mesenteric artery nodes, retroperitoneal and lateral aortic nodes, infrapyloric and subpyloric nodes for tumors in the head; and celiac, pancreaticolieno and splenic nodes for tumors arising in the body and tail[22]. Tumor involvement of other nodal groups is considered distant metastasis[50]. In the Japan Pancreas Society, lymph node stations are classified into groups designated by numbers[32].

According to the CAP, the optimal histological examination should include a minimum of 15 lymph nodes[22,40]. This number is an indicator of the quality of the surgical procedure and pathological handling.

Direct extension of the primary tumor into lymph nodes is classified as lymph node metastasis[22,51].

HANDLING AND REPORTING PROTOCOL OF PDAC AT HOSPITAL CLÍNICO UNIVERSITARIO, VALENCIA, SPAIN

Following the published reports and guidelines, we have elaborated on a checklist for the pathological reporting of PDAC at our institution[53] based on the Verbeke reports (Figure 4).

We propose the following steps for the dissection protocol: (1) leave the specimen for 24-48 h in formaldehyde for the correct fixation after opening through the antimesenteric border of the duodenum; (2) explore the pancreatic anatomy in order to identify the different parts (head, body and tail) and give it the correct orientation in readiness for dissection. Identify the margins (circumferential resection margin composed of the PAM, PPM and PMM and the pancreatic transection margin, or PTM); (3) ink the margins indicated in step 2 in different colors; (4) slice the luminal margins (proximal gastric or duodenal and distal jejunal), BDM, common bile duct or common hepatic duct margin and PTM; (5) analyze the gastro-intestinal lumen to identify any ampullary or other lesions; (6) following the European guidelines, slice the entire pancreatic head in a plane perpendicular to the longitudinal axis of the duodenum through the center of the ampulla. Identify the tumor, its size and relationships to structures and its distance to the margins; (7) continue slicing in parallel sections with a thickness of 5 mm in order to have samples of the tumor that show its relationship with the different anatomical structures (duodenum wall, ampulla) and inked resection margins; (8) separate a sample of non-neoplastic pancreas; and (9) identify lymph nodes from the different stations for individual analysis.

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