



Guideline



Evidence-based Guidelines for Standardized Pathologic Sampling and Diagnostic Reporting of Pancreatic Cancer in China

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Abstract

Standardized pathologic sampling and reporting are essential for pancreatic cancer staging, prognosis assessment, and comparable clinical data. This guideline aimed to develop evidence-based recommendations for standardized pathologic sampling and diagnostic reporting of pancreatic cancer in China. Literature searches were conducted in English and Chinese databases, guideline websites, Google, and reference lists for records published before December 31, 2023. Two investigators screened and extracted the evidence; methodological quality and certainty were assessed using AMSTAR/AGREE II and GRADE, respectively; and recommendations were formulated through two rounds of modified Delphi consultations, with an agreement threshold of $\geq 75\%$ for consensus. The final guideline includes 11 recommendations, including six strong and five weak recommendations, addressing margin and surface assessment, sampling methods, histologic classification and grading, lymphovascular and perineural invasion, TNM staging, tumor regression grading after neoadjuvant therapy, background lesions, and structured reporting. These recommendations provide a standardized framework for pathologic assessment and reporting of pancreatic cancer resection specimens and may support more consistent prognostic evaluation and clinical decision-making.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) and its variants and subtypes account for approximately 90% of adult pancreatic tumors.^{1,2} Surgical resection remains the only potentially curative treatment modality.³ The evaluation of pathologic features—such as extent of tumor invasion and margin status—is critical for prognostic assessment. Accurate evaluation depends on systematic and standardized sampling and reporting of pancreatic resection specimens. Such standardization not only facilitates individualized and high-quality patient management but also provides reliable and comparable pathologic data for clinical research. The increas-

ing adoption of neoadjuvant therapy in pancreatic cancer may induce tumor regression, improve resectability and R0 resection rates, and thereby potentially improve disease-free survival and overall survival.⁴⁻¹⁰ However, there is currently a lack of standardized guidelines for pathologic examination and reporting of pancreatic cancer specimens after neoadjuvant therapy worldwide. This lack of standardization leads to significant variability in the assessment of key pathologic parameters—such as the extent of tumor regression and margin status—across different institutions.^{11,12} Such inconsistency not only hampers accurate evaluation of treatment response but also limits the comparability of clinical studies and the accumulation of comparable evidence.

Beyond its role in diagnosis and treatment, standardized pathologic evaluation is also important for screening-related research and practice. The current lack of uniform criteria for diagnosing precursor lesions—such as pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN)—hampers systematic surveillance, risk stratification, and the clinical validation of early-detection biomarkers in high-risk populations (e.g., individuals with familial pancreatic cancer or chronic pancreatitis). Consistent pathologic standards would

Keywords: Pancreatic cancer; Pathologic specimen sampling; Surgical margin; Pathology report; Structured reporting; Clinical practice guideline.

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enable uniform diagnosis of these lesions and provide a pathologic basis for risk stratification in screening cohorts. Furthermore, a standardized tumor regression grading system could support objective evaluation of the response to neoadjuvant therapy, inform subsequent clinical management, and promote personalized treatment. Therefore, developing and implementing standardized guidelines for pathologic processing and reporting of pancreatic cancer specimens may improve clinicopathologic diagnostic quality and support consistent early screening, high-risk population surveillance, and treatment response evaluation in pancreatic cancer.

To standardize pathologic diagnosis of pancreatic cancer in China, the National Clinical Research Center for Digestive Diseases (Shanghai), the Pancreatic Disease Committee of the Chinese Medical Doctor Association, and the Chinese Journal of Pancreatology led the development of this evidence-based guideline. These efforts involved multidisciplinary experts in pathology, surgery, internal medicine, radiology, evidence-based medicine, and guideline methodology. The process followed the World Health Organization (WHO) Handbook for Guideline Development,¹³ the Institute of Medicine's definition of clinical practice guidelines,¹⁴ the Chinese Principles for Developing/Revising Clinical Guidelines (2022),¹⁵ and the WHO International Classification of Diseases (11th Edition),¹⁶ and incorporated the Appraisal of Guidelines for Research & Evaluation II (AGREE II) instrument and the Reporting Items for Practice Guidelines in Healthcare (RIGHT) statement.^{17,18} Through a systematic literature review, nationwide expert consultation, and a modified Delphi method featuring iterative voting and panel discussions, 11 key recommendations were developed for standardized specimen sampling and diagnostic reporting. Drafted and revised by the Department of Pathology of the First Affiliated Hospital of Naval Medical University, the finalized "Evidence-Based Guidelines for Standardized Pathologic Sampling and Diagnostic Reporting of Pancreatic Cancer in China" was registered on the International Practice Guidelines Registry Platform (PREPARE-2023CN491; www.guidelinesregistry.cn). Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology,¹⁹ evidence certainty was classified as high (A), moderate (B), low (C), or very low (D), and recommendations were classified as strong or weak.

Methods

The guideline was developed through a systematic evaluation of pathologic sampling and diagnostic reporting standards for pancreatic cancer, in accordance with the WHO Handbook for Guideline Development.¹³ This process integrated the Institute of Medicine's definition of clinical practice guidelines,¹⁴ the Chinese Principles for Developing/Revising Clinical Guidelines (2022) issued by the Chinese Medical Association,¹⁵ and the WHO International Classification of Diseases (11th Revision, ICD-11).¹⁶ Methodological rigor was further ensured by using the AGREE II instrument and following the RIGHT statement.^{17,18}

Supporting institutions of the guideline

The guideline was led by the National Clinical Research Center for Digestive Diseases (Shanghai), the Pancreatic Disease Committee of the Chinese Medical Doctor Association, and the

Chinese Journal of Pancreatology. The Department of Pathology at the First Affiliated Hospital of Naval Medical University served as the primary implementing body. Methodological support was provided by the GRADE China Center. This guideline is registered on the International Practice Guidelines Registry Platform (<http://www.guidelinesregistry.cn/>) under registration number PREPARE-2023CN491.

Target users and beneficiaries of the guideline

The guideline is intended primarily for pathologists and members of multidisciplinary teams involved in pancreatic disease management; patients with pancreatic cancer are the main beneficiaries.

Organizational framework for guideline development

The organizational structure for guideline development comprises five core components: Principal Clinical Expert, Lead Methodologist, Guideline Consensus Committee, External Review Panel, and Working Taskforce. The multidisciplinary team includes specialists in pathology, internal medicine, surgery, oncology, medical imaging, evidence-based medicine, and guideline appraisal methodologies.

Declaration of relationships and interests

The development of this guideline strictly adhered to the WHO Conflict of Interest Policy and ethical standards for guideline development. All core contributors, including invited experts and consultants participating in guideline meetings, completed declarations of interest. Following rigorous assessment using the WHO-standardized assessment instrument, no direct conflicts of interest related to this guideline were identified.

Formulation and prioritization of key questions

The guideline taskforce conducted a systematic literature search aligned with evidence-based medicine principles to identify key issues in pancreatic cancer specimen processing and diagnostic reporting. The search included published guidelines, systematic reviews, and original studies and identified 11 preliminary pathologic assessment questions. Through two modified Delphi rounds with institutional and national experts, followed by in-depth deliberations, the final questions evaluated in this guideline are summarized in Table 1.

Evidence retrieval

Systematic literature searches were conducted across four English databases (PubMed, Cochrane Library, Embase, Web of Science) and five Chinese databases (Wanfang Data, China National Knowledge Infrastructure, China Biology Medicine, VIP Database, Yimaitong). Additionally, searches were performed on key international clinical guideline websites, including the National Guideline Clearinghouse, the Scottish Intercollegiate Guidelines Network, the WHO, and the Guidelines International Network. Google was searched as a supplementary source. The search included records published before December 31, 2023, and was limited to English or Chinese publications. Furthermore, the reference lists of all included studies were searched to identify additional relevant literature.

Evidence screening and data extraction

Evidence for the 11 histopathologic questions was derived from three clinical guidelines, eight newly developed or updated

Table 1. Summary of key questions and recommendations with GRADE evidence ratings

Key questions	Recommendation strength	Evidence quality	Recommendations
1 How should resection margins and specimen surfaces be defined in pancreatic cancer specimens?	Strong	Moderate	• Pancreatoduodenectomy: margins include: proximal and distal gastrointestinal, pancreatic transection, SMA, and bile duct or hepatic duct; circumferential surfaces: anterior/posterior peripancreatic and SMV groove • Distal pancreatectomy: true margin includes pancreatic transection; specimen surfaces include anterior/posterior surfaces. • Note: SMV groove and anterior/posterior surfaces are not true surgical margins. • Complete circumferential sampling of the entire margin and surface planes is required.
2 How should sampling methods be selected for pancreatic cancer surgical specimens?	Strong	Moderate	• Pancreatoduodenectomy: serial transverse sections perpendicular to the long axis of the duodenum (for pancreatic head carcinoma only; not for ampullary or common bile duct tumors) • Distal pancreatectomy: serial sections through the maximum tumor diameter in the anteroposterior plane. • After neoadjuvant therapy: complete sampling mandatory when assessing pCR.
3 How should the histologic types and grades of pancreatic cancer be evaluated?	Weak	Low	• Histologic classification: use WHO 5th edition • Differentiation grading: use CAP criteria for PDAC • With precursor lesions: specify whether ductal adenocarcinoma arose from a precursor lesion; report histologic subtype and differentiation.
4 How should lymphovascular invasion be evaluated?	Strong	Moderate	• Record lymphatic and vascular invasion separately • For named vessels (celiac trunk, SMA, CHA, portal vein, SMV, splenic artery/vein): document invasion depth (adventitia, media, intima)
5 How should perineural invasion be evaluated?	Weak	Low	• Report perineural invasion status • Distinguish between intrapancreatic and extrapancreatic involvement when possible
6 How should the R1 resection margin be evaluated in pancreatic cancer?	Weak	very low	• R1 is defined as a microscopic tumor-to-margin distance of ≤ 1 mm
7 How should T stage be assessed?	Weak	Low	• Use AJCC/UICC 8th edition staging system • For IPMN/IOPN/ITPN/MCN-associated invasive carcinoma: stage according to invasive-component size only (not whole lesion) • After neoadjuvant therapy: large-section sampling recommended; document measurement method
8 How should N stage be assessed?	Strong	Moderate	• Use AJCC/UICC 8th edition staging system (Table 3) • Count lymph nodes with direct tumor invasion or metastasis as positive • Examine at least 12 lymph nodes for pancreaticoduodenectomy specimens
9 How should M stage be	Strong	Moderate	• M0: no distant metastasis

Table 1. Summary of key questions and recommendations with GRADE evidence ratings (*continued*)

Key questions	Recommendation strength	Evidence quality	Recommendations
assessed?			• M1: distant metastasis present • Peritoneal seeding or positive ascites: M1
10 How should tumor regression grading (TRG) be assessed after neoadjuvant therapy?	Strong	Low	• Use CAP or MD Anderson Cancer Center (MDACC) TRG systems
11 Should background lesions of pancreatic cancer be assessed?	Weak	Low	• Assess background lesions: PanIN, IPMN, ITPN, IOPN, MCN, chronic pancreatitis • These assessments support risk stratification and understanding of tumorigenesis

AJCC, American Joint Committee on Cancer; CAP, College of American Pathologists; CHA, common hepatic artery; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IOPN, intraductal oncocytic papillary neoplasm; IPMN, intraductal papillary mucinous neoplasm; ITPN, intraductal tubulopapillary neoplasm; MCN, mucinous cystic neoplasm; MDACC, MD Anderson Cancer Center; PanIN, pancreatic intraepithelial neoplasia; pCR, pathologic complete response; PDAC, pancreatic ductal adenocarcinoma; SMA, superior mesenteric artery; SMV, superior mesenteric vein; TRG, tumor regression grading; UICC, Union for International Cancer Control; WHO, World Health Organization.

systematic reviews, and 169 additional studies, including clinical trials, cohort studies, case-control studies, case series, and case reports. After establishing inclusion and exclusion criteria through consensus among the guideline working group, methodologists, and pathology experts, comprehensive training was provided to all working group members. The group then synthesized evidence screened by domain experts and submitted it to the Guideline Steering Committee. Literature screening and data extraction were performed independently by two investigators, with disagreements resolved through discussion or consultation with a third investigator.

Evidence quality assessment and grading

The methodological quality of systematic reviews and meta-analyses was evaluated using the A Measurement Tool to Assess Systematic Reviews tool.²⁰ For the included guidelines, the methodological quality was evaluated using AGREE II.²¹ Methodologically sound and relevant evidence was updated and used to formulate the guideline. Otherwise, the guideline working group updated or conducted systematic reviews or used other evidence. The same databases were searched when systematic reviews were updated or conducted. When systematic reviews were updated or conducted, the Cochrane risk-of-bias tool was used to assess randomized controlled trials.²² The GRADE approach was used to assess evidence certainty and recommendation strength.²³ According to GRADE, evidence certainty was classified as high (A), moderate (B), low (C), or very low (D), and recommendations as strong (1) or weak (2).

Formation of guideline recommendations

Based on the working group’s synthesis of national and international evidence, the first questionnaire was developed by selecting critical questions and terminology from pathology reports, and classifying evidence levels and recommendation grades. This questionnaire was then distributed to an expert panel for a Delphi-based survey via Wenjuanxing. Each recommendation within the survey was evaluated using a 5-point Likert scale (“Strongly

Agree,” “Mostly Agree,” “Partially Agree,” “Mostly Disagree,” “Strongly Disagree”). Recommendations achieving ≥75% consensus from experts (combining “Strongly Agree” and “Mostly Agree” responses) were adopted as formal guideline recommendations. The final guideline comprises 11 evidence-based recommendations with corresponding rationales.

External review

After consensus was reached on the recommendations, the initial guideline draft was prepared and submitted to the External Review Panel for evaluation. The external reviewers comprised pathology experts, clinical practitioners, and guideline methodology specialists.

Funding sources and their utilization

Primary funding was provided by the National Natural Science Foundation of China (NSFC) and the Shanghai Municipal Science and Technology Commission Innovation Action Plan, covering research expenditures, material costs, and activities required to develop the guideline.

Guideline dissemination and implementation

After publication, the guideline will be disseminated through three primary channels: (1) multimedia campaigns, (2) promotion at relevant academic conferences, and (3) targeted training on the guideline for pathologists and clinicians engaged in pancreatic disease management.

Results

The guideline development process yielded 11 formal recommendations. These encompass four critical domains: margin definition protocols, specimen sampling strategies, histopathologic tumor assessment standards, and pancreatic background pathology evaluation.

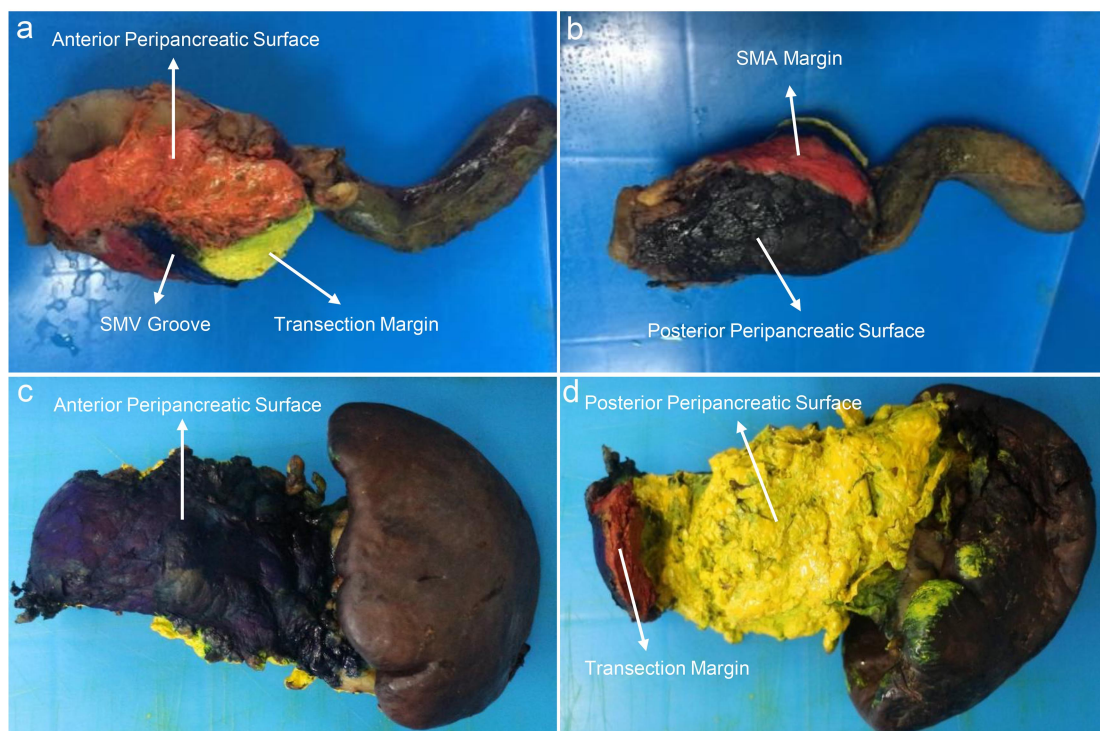


Fig. 1. Resection margins and specimen surfaces of pancreaticoduodenectomy and distal pancreatectomy specimens with color inking. (a, b) Pancreaticoduodenectomy specimen. (a) Anterior view showing the pancreatic transection margin (yellow), anterior peripancreatic surface (orange), and superior mesenteric vein (SMV) groove surface (blue). (b) Posterior view showing the posterior peripancreatic surface (black) and superior mesenteric artery (SMA) margin (red). (c, d) Distal pancreatectomy specimen. (c) Anterior view showing the pancreatic transection margin (orange) and anterior peripancreatic surface (blue). (d) Posterior view showing the pancreatic transection margin (orange) and posterior peripancreatic surface (yellow). SMA, superior mesenteric artery; SMV, superior mesenteric vein. Source: Original gross specimen photographs provided by the authors; all patient-identifying information has been removed.

How should resection margins and specimen surfaces be defined in pancreatic cancer resection specimens?

Recommendation 1: For pancreaticoduodenectomy specimens, surgical margins include (1) proximal and distal gastrointestinal margins, (2) pancreatic transection margin, (3) superior mesenteric artery (SMA) margin, and (4) bile duct or hepatic duct margin; circumferential surfaces comprise the anterior peripancreatic surface, posterior peripancreatic surface, and superior mesenteric vein (SMV) groove surface. For distal pancreatectomy specimens, the true surgical margin is the pancreatic transection margin, and the anterior and posterior peripancreatic surfaces are circumferential surfaces. The SMV groove and anterior and posterior peripancreatic surfaces are not classified as true surgical margins.²⁴⁻²⁷ Complete circumferential sampling of all margin and surface planes is required.

Quality of evidence: Moderate

Strength of recommendation: Strong

To standardize the nomenclature of resection margins in speci-

mens from pancreaticoduodenectomy and distal pancreatectomy, and clarify the definitions of the true surgical margins and their corresponding circumferential surfaces, this guideline establishes a standardized margin assessment protocol. This will not only support assessment of resection completeness (R0 status) for early-stage pancreatic cancer but also provide a standardized pathologic basis for assessing postoperative recurrence.

Resection margins and specimen surfaces in pancreaticoduodenectomy specimens

(1) The SMA (retroperitoneal/uncinate) margin, representing the most prognostically critical surgical margin, comprises a 3–4-cm soft-tissue zone in direct contact with the superior mesenteric artery. As shown in [Figure 1](#), this region contains dense perineural plexuses and lies close to the SMA; it is a frequent site of local recurrence at the uncinate tumor bed and therefore requires precise margin assessment.²⁷ This guideline recommends inking of the SMA margin plane followed by complete perpendicular sectioning of the entire inked surface for histologic examination, to enable accurate measurement of the closest tumor-to-margin distance.

(2) The pancreatic neck (transection) margin refers to the entire resection plane of the pancreatic stump. By performing complete sectioning parallel to the transected surface (with the cut surface

facing down), carcinoma identified microscopically at the inked plane indicates direct tumor involvement of the inked resection plane (tumor-to-margin distance, 0 mm).^{24,25} This records a tumor-to-margin distance and does not establish a separate R1 threshold; the SMA margin protocol may be used in routine practice. When the tumor is grossly ≤ 1 cm from the margin, the entire transection plane should be inked, followed by perpendicular sectioning toward the inked surface. All inked tissue blocks should undergo histologic examination, and the tumor-to-margin distance should be recorded to the nearest millimeter.

(3) The bile duct or hepatic duct margin constitutes the entire transection plane of the ductal stump. By performing complete sectioning parallel to the transected surface (with the mucosal surface facing down), microscopic identification of carcinoma at the inked plane indicates direct tumor involvement of the inked resection plane (tumor-to-margin distance, 0 mm).^{24,25} Alternatively, perpendicular sectioning may be adopted in accordance with the SMA margin protocol.

(4) Proximal and distal gastrointestinal margins represent the entire transection planes of the digestive tract. With complete sectioning parallel to the transected surface (with the transected surface facing down), the initial histologic section displays the true resection margin. Microscopic identification of carcinoma at this inked plane indicates direct tumor involvement of the inked resection plane (tumor-to-margin distance, 0 mm).^{24,25} Alternatively, perpendicular sectioning may be performed according to the SMA margin protocol.

(5) Portal vein margin: The status of the portal vein margin and the depth of tumor invasion into the venous wall are prognostically significant.²⁸ When a partial or complete segment of the portal vein is attached to the specimen, this must be explicitly documented. Both proximal and distal portal vein margins require histologic sampling. For blocks containing tumor-involved portal vein tissue, the entire venous wall thickness should be encompassed in the tissue section.

(6) Other circumferential surfaces

Posterior peripancreatic surface (excluding the SMA margin): This surface comprises the loose connective tissue spanning the entire posterior aspect of the pancreatic head, extending from the superior mesenteric artery (SMA) margin to the pancreatoduodenal groove. This surface requires complete sectioning (as a continuous plane rather than localized perpendicular sections) to determine the closest tumor-to-margin distance. When this surface is included with the SMA margin in the same tissue block, the two surfaces should be inked in different colors for precise margin orientation.

SMV groove: A smooth grooved impression (also termed the portal vein groove) on the posteromedial aspect of the pancreatic head, overlying the superior mesenteric vein (SMV). This surface should be completely sectioned as a continuous plane rather than localized perpendicular sections, consistent with the SMA margin protocol.

Anterior peripancreatic surface: This surface is defined as the entire ventral aspect of the pancreatic head extending from the SMV groove to the anterior pancreatoduodenal groove. Although not a true surgical resection margin, tumor invasion of this surface correlates with local recurrence and reduced survival, and therefore warrants histologic assessment.²⁹⁻³⁴ When adherent to

adjacent resected structures, these should be processed as additional circumferential margins with reporting of the closest tumor distance.

Collectively, these margins and pancreatic surfaces constitute the circumferential surfaces of the pancreaticoduodenectomy specimen (Fig. 1). Applying different-colored inks to individual margins and surfaces facilitates microscopic orientation.²⁴ Gross examination should document the closest tumor-to-margin distance, which should be confirmed histologically.

Resection margin and specimen surfaces in distal pancreatectomy specimens

(1) Proximal pancreatic (transection) margin: When the tumor is grossly ≤ 1 cm from this margin, the entire margin surface must be inked, followed by perpendicular sectioning toward the inked plane. All tissue blocks containing the inked margin require histologic examination with millimeter-level precision in documenting the tumor-to-margin distance. For tumors > 1 cm from the margin, sectioning parallel to the margin is permitted.

(2) Anterior peripancreatic surface: This surface reflects the relationship between the tumor and the soft tissue at the pancreatic anterior border. The tissue plane closest to the tumor must be sampled to assess surface involvement. The exact number of sections depends on the gross extent of tumor invasion.

(3) Posterior peripancreatic surface: This surface reflects the relationship between the tumor and the retroperitoneal soft tissue posterior to the pancreas. Tissue from the plane closest to the tumor must be sampled to assess surface involvement. The exact number of sections required depends on the gross extent of tumor invasion.

The distal pancreatectomy specimen should be evaluated for tumor involvement at the pancreatic neck margin and within the peripancreatic soft tissues surrounding the resection site (Fig. 1). Additionally, involvement of the splenic vessels (splenic artery and vein) and the spleen itself must be documented. The resection margins of the splenic vein and splenic artery should be sampled for histologic examination. The report should include the distance from the tumor to the closest resection margin or the specimen surface, and this distance must be confirmed microscopically.

How to select sampling methods for pancreatic cancer surgical specimens?

Recommendation 2: For pancreatoduodenectomy specimens, serial transverse sections perpendicular to the long axis of the duodenum are recommended for pancreatic head carcinomas; this method is not recommended for ampullary or common bile duct carcinomas. For distal pancreatectomy specimens, serial sections through the maximum tumor diameter in the anteroposterior plane (either perpendicular or parallel to the main pancreatic duct) should be used. Complete sampling of the entire lesion is mandatory when assessing pathologic complete response (pCR) in pancreatic cancer specimens after neoadjuvant therapy.

Quality of evidence: Moderate

Strength of recommendation: Strong

Currently, there are several approaches to sampling pancre-

aticoduodenectomy specimens.^{26,34-38} However, this guideline recommends sectioning perpendicular to the long axis of the duodenum using serial parallel sections (Fig. 2).³⁴ This method is straightforward to perform, as it does not require opening the common bile duct or the main pancreatic duct. However, it displays critical anatomical structures (such as the ampulla of Vater, common bile duct, and main pancreatic duct) within the same plane. Consequently, it is recommended by several cancer centers.^{39,40} This sectioning technique typically dissects the pancreaticoduodenectomy specimen into 8–10 sections. This approach allows detailed examination of the tumor characteristics, including its relationship to surrounding key anatomical structures and surgical margins.³⁵ A major advantage is that tumor extent can be measured in three dimensions and the relationship between the tumor and each surgical margin can be assessed in every section.⁴¹⁻⁴⁴

In distal pancreatectomy specimens, the splenic artery and splenic vein run along the posterosuperior border of the pancreas. This anatomical relationship allows for clear identification of the anterior peripancreatic and posterior peripancreatic surfaces, which should be inked to facilitate specimen orientation. The entire specimen may be serially sectioned in the anteroposterior plane, either parallel to the main pancreatic duct (Fig. 3a) or perpendicular to the main pancreatic duct (Fig. 3b).

For total pancreatectomy specimens, the pancreatic head can be sectioned serially using transverse sections (i.e., perpendicular to the long axis of the duodenum). The pancreatic body and tail may be sectioned serially either parallel to or perpendicular to the main pancreatic duct.

Before specimen dissection, samples should be obtained from the pancreatic duct margin, common bile duct margin, and both resection margins of the alimentary tract. Tissue blocks must encompass both tumor-involved anatomical structures (e.g., duodenum, ampulla of Vater, common bile duct, and peripancreatic soft tissues) and show the relationship between the tumor and its respective surgical margins. However, gross visual identification of precise tumor infiltration boundaries is often unreliable; therefore, extensive sampling of the tumor and adjacent margins is essential.^{42,45,46} When feasible, large-section embedding may clarify spatial relationships between the tumor, surrounding structures, and margins, while enabling more accurate measurement of the maximum tumor diameter.³⁹ Following neoadjuvant therapy, tumor tissue is frequently replaced by fibrosis, making it difficult to distinguish grossly residual tumor from treatment-related fibrotic areas and fibrosis associated with obstructive pancreatitis.⁴⁷ Extensive sampling is imperative for accurately evaluating both the extent of residual tumor and its proximity to margins. Crucially, assessment for pCR after neoadjuvant therapy requires submission and examination of the entire pancreatic specimen.^{39,48} Furthermore, retaining sequential images of gross sections (Fig. 4) provides useful documentation for multidisciplinary discussions regarding tumor origin and other key pathologic features. Standardized sampling may improve the accuracy and consistency of pathologic diagnosis and characterization of disease extent and biological behavior.

How to evaluate the histologic type and differentiation of pancreatic cancer?

Recommendation 3: For the histologic classification of pancreatic cancer, the fifth edition of the World Health Organization (WHO) Classification of Pancreatic Tumors is recommended. For grading histologic differentiation of pancreatic ductal adenocarcinoma, the College of American Pathologists (CAP) evaluation criteria are recommended. When pancreatic ductal adenocarcinoma is associated with precursor lesions, the report should state whether the ductal adenocarcinoma arose from a precursor lesion and should specify the histologic subtype and grade.

Quality of evidence: Low

Strength of recommendation: Weak

Pancreatic cancers covered by this guideline include pancreatic ductal adenocarcinoma, acinar cell carcinoma, and carcinomas arising from precursor lesions. The fifth edition of the WHO Classification of Digestive System Tumors provides a detailed classification of the histologic types for these categories of pancreatic cancer (Table 2).¹

Pancreatic ductal adenocarcinoma and its specific subtypes account for approximately 90% of pancreatic malignancies, while acinar cell carcinoma accounts for < 2% of pancreatic malignancies in adults. Accurate diagnosis of the specific subtypes of pancreatic ductal adenocarcinoma is crucial, as they differ in biological behavior, prognosis, and treatment strategies. When precursor lesions such as intraductal papillary mucinous neoplasm (IPMN), intraductal oncocytic papillary neoplasm (IOPN), intraductal tubulopapillary neoplasm (ITPN), and mucinous cystic neoplasm (MCN) are present in the background of pancreatic ductal adenocarcinoma, diagnosis requires determining whether the invasive carcinoma component has arisen from an intraductal tumor (IPMN, ITPN, IOPN) or MCN.^{49,50} Patients with ductal adenocarcinoma arising from MCN have a significantly better 5-year survival rate than those with ductal adenocarcinoma not arising from MCN.^{49,50} Both ductal adenocarcinoma arising from IPMN and IPMN with associated invasive carcinoma exhibit a more favorable prognosis and are more likely to be diagnosed at an early clinical stage than conventional ductal adenocarcinoma. Among invasive carcinoma subtypes, colloid carcinoma arising from IPMN has a better prognosis than ductal adenocarcinoma arising from IPMN.⁵¹⁻⁵⁴ Oncocytic carcinoma arising from IOPN has been associated with a particularly favorable prognosis, with a 5-year disease-specific survival rate of 100%.^{52,55,56} Patients with ITPN associated with invasive carcinoma have a 5-year survival rate of approximately 71%, which is significantly better than that of conventional ductal adenocarcinoma.⁵⁷⁻⁶⁰ Some rare subtypes have also been reported in the literature, including clear cell type,⁶¹⁻⁶³ oncocytic subtype,⁶⁴ ciliated cell type,⁶⁵ vacuole-rich type,⁶⁶ intestinal type,⁶⁷ microglandular type,⁶⁸ cystic type,⁶⁹ large duct type,⁷⁰ cystic papillary type,⁷¹ mucoepidermoid carcinoma,⁷² and non-mucinous glycogen-deficient cystadenocarcinoma.⁷³ With the advancement of molecular pathology, pancreatic carcinoma with SMARCB1/INI1 loss has also been reported in recent literature.^{74,75} Given the rarity of these tumor types and the limited research data available, their clinicopathologic significance requires further investigation. Standardized diagnosis of special

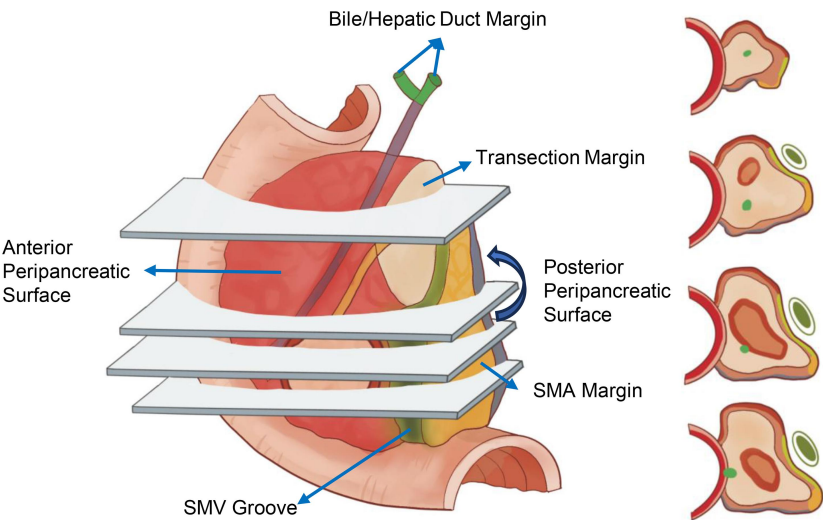


Fig. 2. Schematic diagram of the sectioning protocol for a pancreaticoduodenectomy specimen. SMA, superior mesenteric artery; SMV, superior mesenteric vein. Source: Original schematic illustration commissioned by the authors; no AI-generated content was used, and publication rights were obtained.

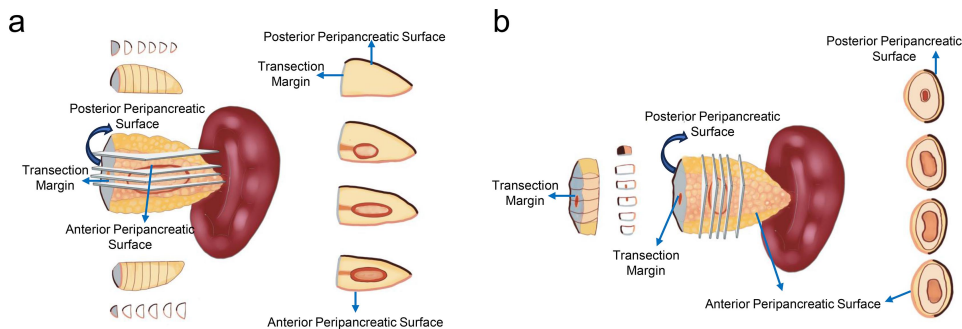


Fig. 3. Schematic diagram of sectioning protocols for distal pancreatectomy specimens. (a) continuous parallel sections parallel to the main pancreatic duct; (b) continuous parallel sections perpendicular to the main pancreatic duct. Source: Original schematic illustration commissioned by the authors; no AI-generated content was used, and publication rights were obtained.

histologic subtypes (e.g., colloid carcinoma and adenosquamous carcinoma) may help define subtype-specific screening sensitivity and provide a pathologic basis for developing individualized screening strategies.

Histologic differentiation holds significant prognostic value for pancreatic ductal adenocarcinoma.⁷⁶ WHO and CAP have established grading criteria that show high concordance and similar predictive value.^{1,77,78} The CAP system is simpler than the WHO criteria, as it does not require assessment of mucin production or mitotic figures, and is therefore more widely used. Accordingly, this guideline recommends using the CAP system for evaluating

the histologic differentiation of pancreatic ductal adenocarcinoma: Grade 1, > 95% of the tumor forms glandular structures; Grade 2, 50–95% of the tumor forms glandular structures; Grade 3, < 50% of the tumor forms glandular structures.

How to evaluate lymphovascular invasion?

Recommendation 4: Lymphatic and vascular invasion should be recorded separately. For invasion of named vessels (celiac



Fig. 4. Photo documentation of serial sections of a pancreatic gross specimen. CBD, common bile duct; PD, pancreatic duct. Source: Original gross specimen photograph provided by the authors; all patient-identifying information has been removed.

Table 2. Histologic types of pancreatic cancer in the WHO Classification of Digestive System Tumours, 5th edition (selected entities)

PDAC, NOS	8500/3
Colloid carcinoma	8480/3
Poorly cohesive carcinoma	8490/3
Signet-ring cell carcinoma	8490/3
Medullary carcinoma NOS	8510/3
Adenosquamous carcinoma	8560/3
Hepatoid carcinoma	8576/3
Large cell carcinoma with rhabdoid phenotype	8014/3
Carcinoma, undifferentiated, NOS	8020/3
Undifferentiated carcinoma with osteoclast-like giant cells	8035/3
Acinar cell carcinoma	8550/3
Acinar cell cystadenocarcinoma	8551/3
Mixed acinar-neuroendocrine carcinoma	8154/3
Mixed acinar-endocrine-ductal carcinoma	8154/3
Mixed acinar-ductal carcinoma	8552/3
Carcinoma arising from a precursor lesion	
IPMN with associated invasive carcinoma	8453/3
ITPN with associated invasive carcinoma	8503/3
IOPN with associated invasive carcinoma	8455/3
MCN with associated invasive carcinoma	8470/3

IOPN, intraductal oncocytic papillary neoplasm; IPMN, intraductal papillary mucinous neoplasm; ITPN, intraductal tubulopapillary neoplasm; MCN, mucinous cystic neoplasm; NOS, not otherwise specified; PDAC, pancreatic ductal adenocarcinoma; WHO, World Health Organization.

trunk, superior mesenteric artery, common hepatic artery,

portal vein, superior mesenteric vein, splenic artery, splenic

Lymphatic and vascular invasion are associated with poor prognosis in patients with pancreatic cancer, regardless of whether they have received neoadjuvant therapy.⁷⁹⁻⁸¹ According to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) eighth edition of the tumor-node-metastasis (TNM) staging system, and the National Comprehensive Cancer Network (NCCN) guidelines, these pathologic features should be recorded separately.

It is difficult to distinguish between small intratumoral lymphatic vessels and veins on routine histologic sections; the presence of accompanying small arteries can help identify venous invasion. Special stains, particularly elastic fiber stains, or immunohistochemical markers such as CD31, CD34, and D2-40, are helpful for differential diagnosis. Additionally, immunohistochemistry or special stains can identify vascular invasion that may be mistaken for pancreatic intraepithelial neoplasia (PanIN). Invasion of large, named vessels may help predict postoperative recurrence and 5-year survival in patients with pancreatic cancer, especially for the celiac trunk, superior mesenteric artery, and common hepatic artery, involvement of which affects TNM stage. The report should clearly indicate the presence or absence of invasion and specify the depth of invasion for these vessels.²⁷ For vessels not yet incorporated into the T stage, such as the portal vein, superior mesenteric vein, splenic artery, and splenic vein, it is also recommended to record the depth of invasion, because it may still have prognostic value for tumor metastasis, recurrence, and prognosis.^{28,82-89} Standardized documentation of lymphatic/vascular invasion, particularly precise assessment of the invasion depth in key named vessels, supports accurate staging and prognostic evaluation of advanced pancreatic cancer.

How to evaluate perineural invasion?

Recommendation 5: Perineural invasion should be reported, with intrapancreatic and extrapancreatic invasion distinguished when possible.

Quality of evidence: Low

Strength of recommendation: Weak

Perineural invasion is defined as tumor cell invasion into any of the three layers of a nerve or tumor cell encirclement of at least one-third of the nerve circumference.⁹⁰ Perineural invasion is a significant histologic feature of pancreatic cancer and an adverse prognostic feature associated with postoperative recurrence.^{81,91-95} The peripheral nerves in the pancreas are abundant and are classified into intrapancreatic nerves (within the pancreatic capsule) and extrapancreatic nerves (outside the capsule). Intrapancreatic perineural invasion is an important factor influencing the prognosis and recurrence of pancreatic cancer patients after surgery,^{92,96,97} and is correlated with extrapancreatic perineural invasion.⁹⁸ Intrapancreatic perineural invasion facilitates the spread of cancer cells along nerves to extrapancreatic nerves and soft tissues.^{99,100} Patients with extrapancreatic perineural invasion are more likely to experience recurrence and have a worse prognosis.¹⁰¹⁻¹⁰³ Perineural invasion is also associated with poor prognosis in patients who have received neoadjuvant therapy.^{104,105} Standardized assessment of perineural invasion may inform treatment decisions

and postoperative surveillance. Therefore, this guideline recommends separately recording intrapancreatic and extrapancreatic perineural invasion.

How to evaluate the R1 resection margin in pancreatic cancer?

Recommendation 6: R1 is defined as a microscopic tumor distance to the resection margin ≤ 1 mm. The ≤ 1 -mm criterion applies uniformly to all assessed true surgical resection margins and circumferential specimen surfaces; a distance of 0 mm denotes direct tumor involvement of the inked plane or surface and is not a separate margin-specific R1 threshold.

Quality of evidence: very low

Strength of recommendation: Weak

Although current international guidelines assess R status primarily using true surgical margins, such as the SMA margin, pancreatic transection margin, bile duct margin, and proximal/distal gastrointestinal margins,^{24,25,77,106} they also recommend assessing all surfaces of the resection specimen, including the anterior peripancreatic surface, posterior peripancreatic surface, and the SMV groove surface.^{25,106} Tumor involvement of these surfaces increases the risk of local tumor recurrence.^{30,44,107,108} Positive resection margins are also associated with poorer survival.¹⁰⁹⁻¹¹³ Numerous studies based on comprehensive and detailed pathologic examination protocols have found that evaluating all surfaces yields R1 rates $> 70\%$, which have been associated with survival.^{31,38,42,43,114-118} Therefore, this guideline recommends comprehensive sampling of all resection margins and surfaces, with microscopic confirmation of the shortest distance from the tumor to the margin or surface.

The definition of R0 and R1 in pancreatic cancer remains controversial. The ≤ 1 -mm criterion was originally derived from rectal cancer assessment protocols, where a tumor distance to the resection margin ≤ 1 mm was found to predict local recurrence and be associated with poorer survival.¹¹⁹⁻¹²³ Considering the more dispersed growth pattern of pancreatic ductal adenocarcinoma, some studies suggest that a larger distance (e.g., 1.5 mm) may offer greater prognostic discrimination;¹²³⁻¹²⁵ however, this has not been applied in routine diagnostic practice. Standardized assessment of the retroperitoneal margin is also necessary.¹²⁶ Furthermore, anatomically, the anterior surface of the pancreas is covered by peritoneum; therefore, involvement of the anterior surface should be recorded as direct surface penetration (0 mm).¹¹

In rare cases, no definitive tumor is identified in the pancreatic parenchyma, interstitial fibrosis, or adipose tissue within 1 mm of the resection margin, but tumor is present in lymph nodes, lymphatic or blood vessels, or perineural spaces within this range. Evidence is insufficient to determine whether such margins should be classified as R1. The UICC TNM staging system proposes that if tumor cells are found only within the lumina of vessels within 1 mm of the margin, this is classified as R0, whereas if the tumor adheres to or invades the vessel wall, it is classified as R1.¹¹⁴ Currently, evidence is insufficient to define involvement of lymph nodes or peripheral nerves within 1 mm of the margin; it is recommended to record and describe these findings in the

pathology report.

Additionally, the R1 definition of ≤ 1 mm is applicable only to pancreatic ductal adenocarcinoma. Evidence is insufficient to determine whether this definition applies to acinar cell carcinoma, which, unlike pancreatic ductal adenocarcinoma, typically does not exhibit a dispersed growth pattern. The closest distance should therefore be recorded from the tumor to the resection margin.

The definition of R1 margin distance in patients who have received neoadjuvant therapy remains uncertain.⁴⁸ First, following neoadjuvant treatment, selective sampling may lead to false-negative results in margin assessment. Second, the distance between tumor cells and the resection margin used to define R1 is also controversial. Some studies suggest that a closest tumor-to-margin distance > 2 mm is associated with a better prognosis.^{127,128} Standardized 1-mm margin assessment currently provides a relatively uniform benchmark for defining “radical resection,” helps determine the completeness of surgical intervention, and lays the foundation for subsequent evidence collection. It should be noted that whether 1 mm represents the optimal cutoff value remains uncertain and requires further clinical validation. Consequently, for surgically resected specimens following neoadjuvant therapy, this guideline recommends comprehensive margin evaluation through complete specimen sampling and large-section histopathology, with detailed documentation of the closest distance of residual tumor to the resection margin.

How to assess T stage?

Recommendation 7: T staging should be performed according to the AJCC/UICC 8th edition staging system. For invasive carcinoma associated with IPMN, IOPN, ITPN, or MCN, the T1–T3 stage should be assessed based on the largest dimension of the invasive component, not the size of the entire lesion. For surgically resected pancreatic specimens following neoadjuvant therapy, large-section sampling is recommended, and the method for measuring tumor size should be documented.

Quality of evidence: Low

Strength of recommendation: Weak

T staging should follow the AJCC/UICC 8th edition staging system (Table 3).²⁷ The staging of acinar cell carcinoma also follows the PDAC staging system. The designations “m,” “r,” and “y” indicate multiple primary tumors, recurrent tumors, and tumors assessed after neoadjuvant therapy, respectively.

Tumor size reflects primary tumor burden and is an important prognostic factor.¹²⁹ Because of the highly dispersed growth pattern of pancreatic cancer and pancreatic parenchymal atrophy and fibrosis, accurately defining the true tumor boundaries macroscopically is challenging.¹²³ Currently, most guidelines recommend using macroscopic tumor size measurement with microscopic confirmation.^{11,39,77,130,131} The T stage is assessed based on the maximum tumor diameter, as tumor size provides better prognostic stratification compared to the extent of peripancreatic invasion.^{112,132–135} Based on the maximum diameter, tumors are classified as T1 (≤ 2 cm), T2 (> 2 cm and ≤ 4 cm), and T3 (> 4 cm). T4 is defined by tumor invasion of the superior

mesenteric artery/celiac trunk/common hepatic artery, regardless of tumor size. T1 can be further subdivided into T1a (≤ 0.5 cm), T1b (> 0.5 cm and < 1 cm), and T1c (≥ 1 cm and ≤ 2 cm).²⁷ Tis includes PanIN-3, IPMN with high-grade dysplasia, ITPN with high-grade dysplasia, IOPN with high-grade dysplasia, and MCN with high-grade dysplasia.

In T staging, if more than one tumor is present, the number, location, and size of each tumor should be recorded in detail. However, this applies only to multiple tumors identifiable macroscopically, and not to tumors that appear as a single mass grossly but are multifocal microscopically.⁷⁷ For precursor lesions of PDAC with invasive carcinoma, including IPMN, IOPN, ITPN, and MCN with invasive carcinoma, the T1–T3 staging criteria are based on the maximum diameter of the invasive focus, not the size of the entire lesion.^{50,136} If the invasive foci are multifocal, it remains uncertain whether the T stage should be determined by the diameter of the largest invasive focus or the sum of multiple invasive foci. Therefore, in routine practice, a thorough evaluation is recommended. The number of invasive foci, the maximum diameter of each invasive focus, and the overall maximum diameter of the invasive foci should all be assessed to provide detailed pathologic data for future clinical research and development of more precise and standardized T-staging criteria.

For resected pancreatic cancer specimens following neoadjuvant therapy, current measurement methods are limited. After neoadjuvant treatment, tumor cells regress and are replaced by fibrous tissue. Particularly when tumor cells have largely regressed and the surrounding pancreatic tissue shows severe atrophy and fibrosis, it becomes more challenging to accurately identify the tumor boundaries macroscopically. Current T-staging criteria may not accurately stratify prognosis in these cases.¹³⁷ Therefore, more robust methods are needed to assess the actual tumor size after neoadjuvant therapy. Some studies have used microscopic confirmation of tumor boundaries together with gross images to delineate tumor borders and measure tumor size for T-stage assessment.¹³⁸ While this method is more accurate than direct macroscopic measurement, it is technically complex and still subject to significant error. Currently, the following two primary methods are recommended for tumor size assessment:

(1) Microscopic measurement of the maximum linear diameter of the entire area containing residual viable tumor cells, including non-neoplastic tissue (such as stroma and/or pancreatic parenchyma or other tissue structures) between tumor cells.

(2) Microscopic measurement of the maximum diameter of each tumor focus and summing these measurements.

Regardless of the measurement method, accurate assessment relies on precise sampling and adequate representation of the tumor’s maximum extent. Therefore, this guideline recommends using large-section sampling for surgically resected pancreatic specimens following neoadjuvant therapy to show the full extent of the tumor and its relationship to surrounding tissues, and to document the microscopic measurement method in the pathology report.

Tumor invasion into surrounding tissues includes involvement of peripancreatic soft tissues, the peritoneum (including the mesocolon, greater and lesser omenta), and the extrapancreatic biliary system. Tumors in the pancreatic head may also invade the duodenum (including the ampulla of Vater), while tumors in the

Table 3. American Joint Committee on Cancer (AJCC) TNM Staging of Pancreatic Cancer (8th ed., 2017)²⁷

TNM stage	Details
Primary tumor (T)	TX: Primary tumor cannot be assessed
	T0: No evidence of primary tumor
	Tis: Carcinoma in situ This includes high-grade pancreatic intraepithelial neoplasia (PanIN-3), intraductal papillary mucinous neoplasm with high-grade dysplasia, intraductal tubulopapillary neoplasm with high-grade dysplasia, intraductal oncocytic papillary neoplasm with high-grade dysplasia, and mucinous cystic neoplasm with high-grade dysplasia
	T1: Tumor ≤ 2 cm in greatest dimension
	T1a: Tumor ≤ 0.5 cm in greatest dimension
	T1b: Tumor > 0.5 cm and < 1 cm in greatest dimension
	T1c: Tumor 1–2 cm in greatest dimension
	T2: Tumor > 2 cm and ≤ 4 cm in greatest dimension
	T3: Tumor > 4 cm in greatest dimension
	T4: Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size
Regional lymph nodes (N)	NX: Regional lymph nodes cannot be assessed
	N0: No regional lymph node metastases
	N1: Metastasis in 1–3 regional lymph nodes
	N2: Metastasis in 4 or more regional lymph nodes
Distant metastasis (M)	M0: No distant metastasis
	M1: Distant metastasis

TNM, tumor-node-metastasis.

pancreatic body and tail may invade the stomach, transverse colon, spleen, and left adrenal gland. Although tumor invasion into surrounding tissues does not affect tumor staging, it should still be recorded in the pathology report. Standardized staging supports assessment of tumor extent and evaluation of downstaging and tumor shrinkage after neoadjuvant therapy and may inform comprehensive early-intervention strategies.

How to assess N stage?

Recommendation 8: Follow the AJCC/UICC 8th edition staging system (Table 3). Both direct tumor invasion and metastases are counted as positive lymph nodes. As many lymph nodes as possible should be retrieved, with at least 12 examined in pancreaticoduodenectomy specimens.

Quality of evidence: Moderate

Strength of recommendation: Strong

Lymph node status is an important prognostic factor in pancreatic ductal adenocarcinoma. Based on prognostic data, the classification is as follows: N0 (no regional lymph node metastasis), N1 (metastasis in 1–3 regional lymph nodes), and N2 (metastasis in 4 or more regional lymph nodes). All lymph nodes from the resec-

tion specimen should undergo histologic examination. Separately submitted regional lymph nodes should be reported independently.

The number of positive lymph nodes detected has been shown to correlate with patient survival, while insufficient lymph node sampling may lead to understaging of the N stage.¹³⁹⁻¹⁴³ The International Collaboration on Cancer Reporting, CAP, and the AJCC/UICC 8th Edition recommend that at least 12 lymph nodes be retrieved from pancreaticoduodenectomy specimens. Based on data from multiple studies, the Royal College of Pathologists (UK) recommends that at least 15 lymph nodes should be retrieved from pancreaticoduodenectomy specimens.^{141,142,144,145} In patients who have received neoadjuvant therapy, the number of retrieved lymph nodes often decreases and may fall below 15.¹⁴⁶ There is currently no consensus on the minimum number of lymph nodes to be retrieved from distal pancreatectomy specimens, and the benefit of extended lymphadenectomy remains uncertain.

Direct tumor invasion of lymph nodes is identified in up to 20% of pancreatic cancer resections. Some studies suggest that direct invasion does not represent true lymph node metastasis (i.e., spread via lymphatic vessels) and is prognostically equivalent to pN0.¹⁴⁷⁻¹⁴⁹ Other studies indicate that direct invasion is associated with outcomes similar to those of patients with true pN1 disease.^{150,151} In the UICC/AJCC 8th edition staging system, lymph nodes with direct tumor invasion are also counted as

positive lymph nodes.^{11,106} Additionally, some studies suggest that the lymph node ratio (the ratio of positive lymph nodes to the total number of lymph nodes examined) is also an effective prognostic indicator, with a ratio > 20% associated with poorer survival rates.^{109,152-160} Standardized lymph node evaluation supports precise risk stratification and individualized treatment in pancreatic cancer.

In both the AJCC/UICC TNM and the Japan Pancreas Society (JPS) systems, lymph nodes around the common hepatic artery are considered regional lymph nodes,¹⁰⁶ while para-aortic lymph nodes are not classified as regional. Survival is poorer in patients with positive para-aortic lymph nodes than in those without, and metastasis to para-aortic lymph nodes is considered distant metastasis (i.e., pM1)¹⁶¹⁻¹⁶³; however, this classification is not uniformly applied in clinical practice.

How to assess M stage?

Recommendation 9: Absence of distant metastasis is classified as M0, whereas the presence of distant metastasis is classified as M1. Peritoneal seeding and positive ascites are classified as M1.

Quality of evidence: Moderate

Strength of recommendation: Strong

A key aspect of M staging is that peritoneal seeding and positive ascites are classified as M1.^{27,164} Pathologic identification of M1 disease may help determine whether curative-intent intervention remains appropriate in screening-detected cases.

How to assess tumor regression grading (TRG) after neoadjuvant therapy?

Recommendation 10: The CAP and MD Anderson Cancer Center (MDACC) assessment systems are recommended to evaluate TRG after neoadjuvant therapy. Pathologic response assessment following neoadjuvant therapy may provide feedback on early intervention strategies and may support optimization of preoperative regimens and outcomes for screening-eligible populations.

Quality of evidence: Low

Strength of recommendation: Strong

The role of neoadjuvant therapy in improving the prognosis of pancreatic cancer patients has become increasingly important. When evaluating pancreatic cancer resection specimens after neoadjuvant therapy, TRG is typically assessed to evaluate the tumor's response to neoadjuvant therapy, thereby guiding subsequent adjuvant therapy and predicting patient prognosis. Currently, multiple TRG assessment systems are used for pancreatic cancer, including the Evans system, first proposed in 1992¹⁶⁵; the CAP system,¹⁶⁶ which is based on the grading system initially proposed by Ryan *et al.*¹⁶⁷ for evaluating neoadjuvant therapy response in rectal cancer, also known as the modified Ryan scheme; the MDACC system, based on the work of Chatterjee *et al.*¹⁶⁸; and the JPS system (Table 4).³⁴ Although no consensus

has been reached on the optimal assessment system, available evidence suggests that patients with complete or near-complete response have a better prognosis.¹⁶⁸ The AJCC 8th edition ypT stage after neoadjuvant therapy has also demonstrated prognostic significance and correlation with tumor regression grade.¹⁶⁹ The CAP assessment system is recommended by the NCCN guidelines. The Evans and JPS grading systems are specifically designed for PDAC and are commonly used in Japan.¹⁷⁰ The MDACC system is similar to CAP but uses a three-tier classification instead of a four-tier one. All four TRG assessment systems mentioned above are semiquantitative. Although all systems define complete regression similarly, the thresholds and criteria for assessing the degree of tumor regression differ, making it difficult to compare them directly.

Complete tumor regression, near-complete regression, partial regression, and no regression are important outcome indicators of neoadjuvant therapy. However, the reliability of histologic assessment for these outcomes remains uncertain. The main challenges lie in establishing reliable diagnostic criteria for complete regression and achieving reproducible assessments of varying degrees of regression. Therefore, extensive and comprehensive tissue sampling is crucial. Most studies, however, lack information on the extent of sampling. The limited published data indicate significant variability both within and between studies. A study based on complete embedding of the pancreas and surrounding tissues showed that only 2.5% of patients achieved complete tumor regression.¹⁷¹ In contrast, other studies that did not employ extensive sampling reported complete tumor regression in 10% to 33% of patients.¹⁷²⁻¹⁸¹ Consequently, accurate assessment of tumor regression requires extensive sampling of the lesional tissue. Particularly for evaluating complete tumor regression, it is essential to perform thorough sampling and histologic examination of the entire tumor bed and any adjacent macroscopically abnormal tissues.

Should background lesions of pancreatic cancer be assessed?

Recommendation 11: Background lesions of pancreatic cancer, such as PanIN, IPMN, ITPN, IOPN, MCN, and chronic pancreatitis, should be assessed.

Quality of evidence: Low

Strength of recommendation: Weak

In addition to focusing on the tumor itself, increasing attention is being given to background lesions associated with the tumor. PanIN is the most common precursor lesion of pancreatic ductal adenocarcinoma.¹⁸² Some studies suggest that the absence of accompanying PanIN may be associated with poorer postoperative survival.¹⁸³ If IPMN, ITPN, IOPN, or MCN are present, they should be noted in the pathology report, along with clarification of the degree of epithelial dysplasia and the relationship to pancreatic cancer.^{136,184} The NCCN guidelines also recommend documenting background lesions, such as the presence or absence of PanIN or chronic pancreatitis, in the diagnostic report. Standardized assessment and documentation of background lesions in pancreatic cancer may support patient risk stratification and individualized management, improve understanding of tumor

Table 4. Four commonly used international tumor regression grading assessment systems for pancreatic cancer

Assessment system	Tumor regression grade	Definition
Evans	Grade I	< 10% or no tumor cell destruction
	Grade IIa	Destruction of 10–50% of tumor cells
	Grade IIb	Destruction of 51–90% of tumor cells
	Grade III	Few (< 10%) tumor cells present
	Grade IV	No viable tumor cells present
CAP	Score 0	No viable cancer cells
	Score 1	Single cells or rare small groups of cancer cells
	Score 2	Residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells
	Score 3	Extensive residual cancer with no evident tumor regression
JPS	Grade 1a	Estimated residual tumor ratio $\geq 90\%$
	Grade 1b	Estimated residual tumor ratio $\geq 50\%$, < 90%
	Grade 2	Estimated residual tumor ratio $\geq 10\%$, < 50%
	Grade 3	Estimated residual tumor ratio < 10%
	Grade 4	No viable tumor cells
MDACC	Score 0	No residual carcinoma
	Score 1	< 5% residual carcinoma
	Score 2	$\geq 5\%$ residual carcinoma

CAP, College of American Pathologists; JPS, Japan Pancreas Society; MDACC, MD Anderson Cancer Center.

origin and biological behavior, and may inform early detection and prevention strategies.

Conclusions

Currently, there is a lack of standardized guidelines for pathologic sampling and diagnostic reporting of pancreatic cancer. Based on existing evidence from national and international sources, this working group has proposed six strong and five weak recommendations and developed a structured diagnostic reporting framework for pancreatic cancer. Drawing on many-years practical experience at Changhai Hospital, a practical pathology-examination report template is also provided for reference (Supplementary Table. 1). This approach may improve staging and survival prediction and guide postoperative treatment of pancreatic cancer. It enhances the completeness of reports, improves communication between pathologists and clinicians, and promotes consistency in pathologic reports across different institutions. Therefore, it may facilitate broader implementation.

Supporting information

Supplementary material for this article is available at <https://doi.org/10.14218/CSP.2026.00001>.

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Conflict of interest

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Author contributions

Conceptualization and framework development (HJ), figure design and visualization (HJ, YZ, YY), drafting the manuscript (YZ, YY), revision and content development (HJ, YY), critical review and academic oversight (JZ). All authors made substantial contributions to the study and approved the final manuscript.

Ethical statement

An institutional review board waiver of informed consent was obtained for the use of de-identified surgical gross pathology specimens in Figures 1 and 4. No patient-identifiable information is presented.

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References

- [1] Gill AJ, Klimstra DS, Lam AK, Washington MK. Tumours of the pancreas. WHO Classification of Tumours Editorial Board Digestive system tumours. 5th ed. Lyon, France; IARC; 2019:295-371
- [2] Fitzgerald TL, Hickner ZJ, Schmitz M, Kort EJ. Changing incidence of pancreatic neoplasms: a 16-year review of statewide tumor registry. *Pancreas* 2008;37(2):134–138. DOI: 10.1097/MPA.0b013e318163a329, PMID: 18665072.
- [3] Mizrahi JD, Surana R, Valle JW, Shroff RT. Pancreatic cancer. *Lancet* 2020;395(10242):2008–2020. DOI: 10.1016/S0140-6736(20)30974-0, PMID: 32593337.
- [4] Reni M, Balzano G, Zanon S, Zerbi A, Rimassa L, Castoldi R, *et al.* Safety and efficacy of preoperative or postoperative chemotherapy for resectable pancreatic adenocarcinoma (PACT-15): a randomised, open-label, phase 2-3 trial. *Lancet Gastroenterol Hepatol* 2018;3(6):413–423. DOI: 10.1016/S2468-1253(18)30081-5, PMID: 29625841.
- [5] Townend P, de Reuver PR, Chua TC, Mittal A, Clark SJ, Pavlakakis N, *et al.* Histopathological tumour viability after neoadjuvant chemotherapy influences survival in resected pancreatic cancer: analysis of early outcome data. *ANZ J Surg* 2018;88(3):E167–E172. DOI: 10.1111/ans.13897, PMID: 28318082.
- [6] Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. *N Engl J Med* 2014;371(22):2140–2141. DOI: 10.1056/NEJMc1412266.
- [7] Versteijne E, Vogel JA, Besselink MG, Busch ORC, Wilmink JW, Daams JG, *et al.* Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. *Br J Surg* 2018;105(8):946–958. DOI: 10.1002/bjs.10870, PMID: 29708592.
- [8] Versteijne E, Suker M, Groothuis K, Akkermans-Vogelaar JM, Besselink MG, Bonsing BA, *et al.* Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial. *J Clin Oncol* 2020;38(16):1763–1773. DOI: 10.1200/JCO.19.02274, PMID: 32105518.
- [9] Jang JY, Han Y, Lee H, Kim SW, Kwon W, Lee KH, *et al.* Oncological

- Benefits of Neoadjuvant Chemoradiation With Gemcitabine Versus Upfront Surgery in Patients With Borderline Resectable Pancreatic Cancer: A Prospective, Randomized, Open-label, Multicenter Phase 2/3 Trial. *Ann Surg* 2018;268(2):215–222. DOI: 10.1097/SLA.0000000000002705, PMID: 29462005.
- [10] Suker M, Beumer BR, Sadot E, Marthey L, Faris JE, Mellon EA, *et al.* FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. *Lancet Oncol* 2016;17(6):801–810. DOI: 10.1016/S1470-2045(16)00172-8, PMID: 27160474.
- [11] Verbeke C, Webster F, Brosens L, Campbell F, Del Chiaro M, Esposito I, *et al.* Dataset for the reporting of carcinoma of the exocrine pancreas: recommendations from the International Collaboration on Cancer Reporting (ICCR). *Histopathology* 2021;79(6):902–912. DOI: 10.1111/his.14540, PMID: 34379823.
- [12] N Kalimuthu S, Serra S, Dhani N, Hafezi-Bakhtiari S, Szentgyorgyi E, Vajpeyi R, *et al.* Regression grading in neoadjuvant treated pancreatic cancer: an interobserver study. *J Clin Pathol* 2017;70(3):237–243. DOI: 10.1136/jclinpath-2016-203947, PMID: 27681847.
- [13] World Health Organization. WHO handbook for guideline development. 2nd ed. World Health Organization; 2014.
- [14] Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice G. Clinical Practice Guidelines We Can Trust. Graham R, Mancher M, Miller Wolman D, Greenfield S, Steinberg E, editors. Washington (DC): National Academies Press (US); 2011.
- [15] Chen Y, Yang K, Wang X, Kang D, Zhan S, Wang J, *et al.* Guidelines for the Development and Revision of Clinical Practice Guidelines in China (2022 Edition) (in Chinese). National Medical Journal of China 2022;102(10):697–703. DOI: 10.3760/cma.j.cn112137-20211228-02911.
- [16] World Health Organization. International Classification of Diseases 11th Revision. 2018. Available from: <https://icd.who.int/browse/2018/mms/en>.
- [17] Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, *et al.* AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ* 2010;182(18):E839–E842. DOI: 10.1503/cmaj.090449, PMID: 20603348.
- [18] Chen Y, Yang K, Marušić A, Qaseem A, Meerpohl JJ, Flottorp S, *et al.* A Reporting Tool for Practice Guidelines in Health Care: The RIGHT Statement. *Ann Intern Med* 2017;166(2):128–132. DOI: 10.7326/M16-1565, PMID: 27893062.
- [19] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336(7650):924–926. DOI: 10.1136/bmj.39489.470347.AD, PMID: 18436948.
- [20] Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, *et al.* Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007;7:10. DOI: 10.1186/1471-2288-7-10, PMID: 17302989.
- [21] Wei D, Wang C, Xiao X, Chen Y, Yao L, Liang F, *et al.* A Guide to Appraisal of Guidelines Research & Evaluation (AGREE II) Instrument: Interpretation with Examples (in Chinese). *Chin J Evid Based Pediatr* 2013;8(4):316–319. DOI: 10.3969/j.issn.1673-5501.2013.04.017.
- [22] Higgins JP, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* version 5. 0.2. Chichester (UK): John Wiley & Sons; 2009.
- [23] Jaeschke R, Guyatt GH, Dellinger P, Schünemann H, Levy MM, Kunz R, *et al.* Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive. *BMJ* 2008;337:a744. DOI: 10.1136/bmj.a744, PMID: 18669566.
- [24] Tempero MA, Malafa MP, Benson III AB, Cardin DB, Chiorean EG, Christensen JA. Pancreatic Adenocarcinoma, version 1. 2023. 2023. Available from: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf.
- [25] Dhall D, Shi J, Allende DS, Jang KT, Basturk O, Adsay V, *et al.* Towards a More Standardized Approach to Pathologic Reporting of Pancreatoduodenectomy Specimens for Pancreatic Ductal Adenocarcinoma: Cross-continental and Cross-specialty Survey From the Pancreatobiliary Pathology Society Grossing Working Group. *Am J Surg Pathol* 2021;45(10):1364–1373. DOI: 10.1097/PAS.0000000000001723, PMID: 33899790.
- [26] Adsay NV, Basturk O, Saka B, Bagci P, Ozdemir D, Balci S, *et al.* Whipple made simple for surgical pathologists: orientation, dissection, and sampling of pancreaticoduodenectomy specimens for a more practical and accurate evaluation of pancreatic, distal common bile duct, and ampullary tumors. *Am J Surg Pathol* 2014;38(4):480–493. DOI: 10.1097/PAS.0000000000000165, PMID: 24451278.
- [27] Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, *et al.* *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017.
- [28] Fukuda S, Oussoultzoglou E, Bachellier P, Rosso E, Nakano H, Audet M, *et al.* Significance of the depth of portal vein wall invasion after curative resection for pancreatic adenocarcinoma. *Arch Surg* 2007;142(2):172–179; discussion 180. DOI: 10.1001/archsurg.142.2.172, PMID: 17309969.
- [29] Nagakawa T, Nagamori M, Futakami F, Tsukioka Y, Kayahara M, Ohta T, *et al.* Results of extensive surgery for pancreatic carcinoma. *Cancer* 1996;77(4):640–645. DOI: 10.1002/(SICI)1097-0142(19960215)77:4<640::AID-CNCR9>3.0.CO;2-K, PMID: 8616755.
- [30] Nagakawa T, Sanada H, Inagaki M, Sugama J, Ueno K, Konishi I, *et al.* Long-term survivors after resection of carcinoma of the head of the pancreas: significance of histologically curative resection. *J Hepatobiliary Pancreat Surg* 2004;11(6):402–408. DOI: 10.1007/s00534-004-0917-4, PMID: 15619016.
- [31] Verbeke CS, Menon KV. Redefining resection margin status in pancreatic cancer. *HPB (Oxford)* 2009;11(4):282–289. DOI: 10.1111/j.1477-2574.2009.00055.x, PMID: 19718354.
- [32] The Royal College of Pathologists. Minimum dataset for the histopathological reporting of pancreatic, ampulla of Vater and bile duct carcinoma. Standards and minimum datasets for reporting cancers. The Royal College of Pathologists; 2002.
- [33] Hruban RH, Pitman MB, Klimstra DS. *Tumors of the Pancreas*. Atlas of Tumor Pathology. 4th series, fascicle 6. Washington, DC: American Registry of Pathology; 2007.
- [34] Japan Pancreas Society. *Classification of pancreatic carcinoma*. 4th ed. Tokyo: Kanehara; 2017.
- [35] Campbell F, Verbeke CS. Specimen Dissection and Sampling. In: Campbell F, Verbeke C, editors. *Pathology of the pancreas - a practical approach*. 1st ed. London, UK: Springer-Verlag; 2013. DOI: 10.1007/978-1-4471-2449-8_3.
- [36] Soer E, Brosens L, van de Vijver M, Dijk F, van Velthuysen ML, Farina-Sarasqueta A, *et al.* Dilemmas for the pathologist in the oncologic assessment of pancreatoduodenectomy specimens: An overview of different grossing approaches and the relevance of the histopathological characteristics in the oncologic assessment of

- pancreatoduodenectomy specimens. *Virchows Arch* 2018;472(4): 533–543. DOI: 10.1007/s00428-018-2321-5, PMID: 29589102.
- [37] Shi J, Basturk O. Whipple Grossing in the Era of New Staging: Should We Standardize? *Diagnostics (Basel)* 2019;9(4):132. DOI: 10.3390/diagnostics9040132, PMID: 31569496.
- [38] Verbeke CS. Resection margins and R1 rates in pancreatic cancer--are we there yet? *Histopathology* 2008;52(7):787–796. DOI: 10.1111/j.1365-2559.2007.02935.x, PMID: 18081813.
- [39] Campbell F, Cairns A, Duthie F, Feakins R. Dataset for the Histopathological Reporting of Carcinoma of the Pancreas, Ampulla of Vater and Common Bileduct. 2019. Available from: <https://www.rcpath.org/asset/34910231-C106-4629-A2DE9AE6F87AC1>.
- [40] Björnstedt M, Franzén L, Glaumann H, Nordlinder H, Palmqvist R, Rissler P, *et al.* Gastrointestinal pathology-pancreas and periampullary region. Swedish Society for Pathology; 2020.
- [41] Verbeke CS, Gladhaug IP. Dissection of Pancreatic Resection Specimens. *Surg Pathol Clin* 2016;9(4):523–538. DOI: 10.1016/j.path.2016.05.001, PMID: 27926357.
- [42] Verbeke CS, Leitch D, Menon KV, McMahon MJ, Guillou PJ, Anthony A. Redefining the R1 resection in pancreatic cancer. *Br J Surg* 2006;93(10):1232–1237. DOI: 10.1002/bjs.5397, PMID: 16804874.
- [43] Esposito I, Kleeff J, Bergmann F, Reiser C, Herpel E, Friess H, *et al.* Most pancreatic cancer resections are R1 resections. *Ann Surg Oncol* 2008;15(6):1651–1660. DOI: 10.1245/s10434-008-9839-8, PMID: 18351300.
- [44] Chandrasegaram MD, Goldstein D, Simes J, Gebisi V, Kench JG, Gill AJ, *et al.* Meta-analysis of radical resection rates and margin assessment in pancreatic cancer. *Br J Surg* 2015;102(12):1459–1472. DOI: 10.1002/bjs.9892, PMID: 26350029.
- [45] Ohigashi H, Ishikawa O, Sasaki Y, Yamada T, Furukawa H, Imaoka S, *et al.* K-ras point mutation in the nerve plexuses around the superior mesenteric artery in resectable adenocarcinoma of the pancreatic head: distribution pattern and related factors. *Arch Surg* 2000;135(12):1450–1455. DOI: 10.1001/archsurg.135.12.1450, PMID: 11115351.
- [46] Kim J, Reber HA, Dry SM, Elashoff D, Chen SL, Umetani N, *et al.* Unfavourable prognosis associated with K-ras gene mutation in pancreatic cancer surgical margins. *Gut* 2006;55(11):1598–1605. DOI: 10.1136/gut.2005.083063, PMID: 16682430.
- [47] Chatterjee D, Katz MH, Rashid A, Estrella JS, Wang H, Varadhachary GR, *et al.* Pancreatic intraepithelial neoplasia and histological changes in non-neoplastic pancreas associated with neoadjuvant therapy in patients with pancreatic ductal adenocarcinoma. *Histopathology* 2013;63(6):841–851. DOI: 10.1111/his.12234, PMID: 24111684.
- [48] Verbeke C, Löhr M, Karlsson JS, Del Chiaro M. Pathology reporting of pancreatic cancer following neoadjuvant therapy: challenges and uncertainties. *Cancer Treat Rev* 2015;41(1):17–26. DOI: 10.1016/j.ctrv.2014.11.002, PMID: 25434282.
- [49] Campbell F, Verbeke CS. Intraductal Papillary Neoplasm. In: Campbell F, Verbeke CS, editors. *Pathology of the pancreas - a practical approach*. London, UK: Springer-Verlag; 2013. DOI: 10.1007/978-1-4471-2449-8_17.
- [50] Tanaka M, Fernández-del Castillo C, Adsay V, Chari S, Falconi M, Jang JY, *et al.* International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatology* 2012;12(3):183–197. DOI: 10.1016/j.pan.2012.04.004, PMID: 22687371.
- [51] Yamaguchi K, Kanemitsu S, Hatori T, Maguchi H, Shimizu Y, Tada M, *et al.* Pancreatic ductal adenocarcinoma derived from IPMN and pancreatic ductal adenocarcinoma concomitant with IPMN. *Pancreas* 2011;40(4):571–580. DOI: 10.1097/MPA.0b013e318215010c, PMID: 21499212.
- [52] Mino-Kenudson M, Fernández-del Castillo C, Baba Y, Valsangkar NP, Liss AS, Hsu M, *et al.* Prognosis of invasive intraductal papillary mucinous neoplasm depends on histological and precursor epithelial subtypes. *Gut* 2011;60(12):1712–1720. DOI: 10.1136/gut.2010.232272, PMID: 21508421.
- [53] Nakata K, Ohuchida K, Aishima S, Sadakari Y, Kayashima T, Miyasaka Y, *et al.* Invasive carcinoma derived from intestinal-type intraductal papillary mucinous neoplasm is associated with minimal invasion, colloid carcinoma, and less invasive behavior, leading to a better prognosis. *Pancreas* 2011;40(4):581–587. DOI: 10.1097/MPA.0b013e318214fa86, PMID: 21499213.
- [54] Yopp AC, Katabi N, Janakos M, Klimstra DS, D'Angelica MI, DeMatteo RP, *et al.* Invasive carcinoma arising in intraductal papillary mucinous neoplasms of the pancreas: a matched control study with conventional pancreatic ductal adenocarcinoma. *Ann Surg* 2011;253(5):968–974. DOI: 10.1097/SLA.0b013e318214bcb4, PMID: 21422912.
- [55] Marchegiani G, Mino-Kenudson M, Ferrone CR, Warshaw AL, Lillemoe KD, Fernández-del Castillo C. Oncocytic-type intraductal papillary mucinous neoplasms: a unique malignant pancreatic tumor with good long-term prognosis. *J Am Coll Surg* 2015;220(5):839–844. DOI: 10.1016/j.jamcollsurg.2015.01.051, PMID: 25840549.
- [56] Wang T, Askan G, Adsay V, Allen P, Jarnagin WR, Memis B, *et al.* Intraductal Oncocytic Papillary Neoplasms: Clinical-Pathologic Characterization of 24 Cases, With An Emphasis on Associated Invasive Carcinomas. *Am J Surg Pathol* 2019;43(5):656–661. DOI: 10.1097/PAS.0000000000001226, PMID: 30986801.
- [57] Basturk O, Adsay V, Askan G, Dhall D, Zamboni G, Shimizu M, *et al.* Intraductal Tubulopapillary Neoplasm of the Pancreas: A Clinicopathologic and Immunohistochemical Analysis of 33 Cases. *Am J Surg Pathol* 2017;41(3):313–325. DOI: 10.1097/PAS.0000000000000782, PMID: 27984235.
- [58] Suda K, Hirai S, Matsumoto Y, Mogaki M, Oyama T, Mitsui T, *et al.* Variant of intraductal carcinoma (with scant mucin production) is of main pancreatic duct origin: a clinicopathological study of four patients. *Am J Gastroenterol* 1996;91(4):798–800. PMID: 8677955.
- [59] Tajiri T, Tate G, Inagaki T, Kunimura T, Inoue K, Mitsuya T, *et al.* Intraductal tubular neoplasms of the pancreas: histogenesis and differentiation. *Pancreas* 2005;30(2):115–121. DOI: 10.1097/01.mpa.0000148513.69873.4b, PMID: 15714133.
- [60] Yamaguchi H, Shimizu M, Ban S, Koyama I, Hatori T, Fujita I, *et al.* Intraductal tubulopapillary neoplasms of the pancreas distinct from pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. *Am J Surg Pathol* 2009;33(8):1164–1172. DOI: 10.1097/PAS.0b013e3181a162e5, PMID: 19440145.
- [61] Tannous T, Perez Rodriguez AL, Mak AW, Tannous K, Keating M. Primary Clear Cell Carcinoma of the Pancreas: A Systematic Review. *Cureus* 2021;13(6):e15668. DOI: 10.7759/cureus.15668, PMID: 34150416.
- [62] Ray S, Lu Z, Rajendiran S. Clear cell ductal adenocarcinoma of pancreas: a case report and review of the literature. *Arch Pathol Lab Med* 2004;128(6):693–696. DOI: 10.5858/2004-128-693-CCDAOP, PMID: 15163226.

- [63] Kanai N, Nagaki S, Tanaka T. Clear cell carcinoma of the pancreas. *Acta Pathol Jpn* 1987;37(9):1521–1526. DOI: 10.1111/j.1440-1827.1987.tb02273.x, PMID: 3687432.
- [64] Papotti M, Cassoni P, Taraglio S, Bussolati G. Oncocytic and oncocytoid tumors of the exocrine pancreas, liver, and gastrointestinal tract. *Semin Diagn Pathol* 1999;16(2):126–134. PMID: 10452578.
- [65] Morinaga S, Tsumuraya M, Nakajima T, Shimosato Y, Okazaki N. Ciliated-cell adenocarcinoma of the pancreas. *Acta Pathol Jpn* 1986;36(12):1905–1910. DOI: 10.1111/j.1440-1827.1986.tb02255.x, PMID: 3825537.
- [66] Dursun N, Feng J, Basturk O, Bandyopadhyay S, Cheng JD, Adsay VN. Vacuolated cell pattern of pancreatobiliary adenocarcinoma: a clinicopathological analysis of 24 cases of a poorly recognized distinctive morphologic variant important in the differential diagnosis. *Virchows Arch* 2010;457(6):643–649. DOI: 10.1007/s00428-010-0978-5, PMID: 20931225.
- [67] Albores-Saavedra J, Simpson K, Dancer YJ, Hruban R. Intestinal type adenocarcinoma: a previously unrecognized histologic variant of ductal carcinoma of the pancreas. *Ann Diagn Pathol* 2007;11(1):3–9. DOI: 10.1016/j.anndiagpath.2006.06.008, PMID: 17240300.
- [68] Berho M, Blaustein A, Willis I, Sorace D, Suster S. Microglandular carcinoma of the pancreas: immunohistochemical and ultrastructural study of an unusual variant of pancreatic carcinoma that may closely resemble a neuroendocrine neoplasm. *Am J Clin Pathol* 1996;105(6):727–732. DOI: 10.1093/ajcp/105.6.727, PMID: 8659447.
- [69] Gupta N, Krishnan PV, Muzaffar J, Arora A, Anuradha S, Gondal R, *et al.* Cystic ductal adenocarcinoma of pancreas: an unusual variant. *Trop Gastroenterol* 2006;27(3):131–133.
- [70] Bagci P, Andea AA, Basturk O, Jang KT, Erbarut I, Adsay V. Large duct type invasive adenocarcinoma of the pancreas with microcystic and papillary patterns: a potential microscopic mimic of non-invasive ductal neoplasia. *Mod Pathol* 2012;25(3):439–448. DOI: 10.1038/modpathol.2011.181, PMID: 22056954.
- [71] Kelly PJ, Shinagare S, Sainani N, Hong X, Ferrone C, Yilmaz O, *et al.* Cystic papillary pattern in pancreatic ductal adenocarcinoma: a heretofore undescribed morphologic pattern that mimics intraductal papillary mucinous carcinoma. *Am J Surg Pathol* 2012;36(5):696–701. DOI: 10.1097/PAS.0b013e318249ce1c, PMID: 22367300.
- [72] Ma R, Yu YQ, Li JT, Peng SY. Mucoepidermoid carcinoma of the pancreas: a case report and a review of literature. *J Res Med Sci* 2012;17(9):886–889. PMID: 23826019.
- [73] Friedman HD. Nonmucinous, glycogen-poor cystadenocarcinoma of the pancreas. *Arch Pathol Lab Med* 1990;114(8):888–891. PMID: 2375664.
- [74] Hua Y, Soni P, Larsen D, Zreik R, Leng B, Rampisela D. SMARCB1/INI1-deficient pancreatic undifferentiated rhabdoid carcinoma mimicking solid pseudopapillary neoplasm: A case report and review of the literature. *World J Gastroenterol* 2020;26(36):5520–5526. DOI: 10.3748/wjg.v26.i36.5520, PMID: 33024402.
- [75] King DA, Rahalkar S, Bingham DB, Fisher GA. Pancreatic INI1-deficient undifferentiated rhabdoid carcinoma achieves complete clinical response on gemcitabine and nab-paclitaxel following immediate progression on FOLFIRINOX: a case report. *J Gastrointest Oncol* 2021;12(2):874–879. DOI: 10.21037/jgo-20-478, PMID: 34012674.
- [76] Adsay NV, Basturk O, Bonnett M, Kilinc N, Andea AA, Feng J, *et al.* A proposal for a new and more practical grading scheme for pancreatic ductal adenocarcinoma. *Am J Surg Pathol* 2005;29(6):724–733. DOI: 10.1097/01.pas.0000163360.40357.f1, PMID: 15897739.
- [77] College of American Pathologists (CAP). Protocol for the Examination of Specimens from Patients with Carcinoma of the Pancreas. 2021. Available from: https://documents.cap.org/protocols/Panc.Exo_4.2.0.2.REL_CAPCP.pdf.
- [78] Giulianotti PC, Boggi U, Fornaciari G, Bruno J, Rossi G, Giardino D, *et al.* Prognostic value of histological grading in ductal adenocarcinoma of the pancreas. Klöppel vs TNM grading. *Int J Pancreatol* 1995;17(3):279–289. DOI: 10.1007/BF02785825, PMID: 7642975.
- [79] Yamada M, Sugiyama T, Okamura Y, Ito T, Yamamoto Y, Ashida R, *et al.* Microscopic Venous Invasion in Pancreatic Cancer. *Ann Surg Oncol* 2018;25(4):1043–1051. DOI: 10.1245/s10434-017-6324-2, PMID: 29302820.
- [80] Garcea G, Dennison AR, Ong SL, Pattenden CJ, Neal CP, Sutton CD, *et al.* Tumour characteristics predictive of survival following resection for ductal adenocarcinoma of the head of pancreas. *Eur J Surg Oncol* 2007;33(7):892–897. DOI: 10.1016/j.ejso.2007.02.024, PMID: 17398060.
- [81] Chen JW, Bhandari M, Astill DS, Wilson TG, Kow L, Brooke-Smith M, *et al.* Predicting patient survival after pancreaticoduodenectomy for malignancy: histopathological criteria based on perineural infiltration and lymphovascular invasion. *HPB (Oxford)* 2010;12(2):101–108. DOI: 10.1111/j.1477-2574.2009.00140.x, PMID: 20495653.
- [82] Kanda M, Fujii T, Sahin TT, Kanzaki A, Nagai S, Yamada S, *et al.* Invasion of the splenic artery is a crucial prognostic factor in carcinoma of the body and tail of the pancreas. *Ann Surg* 2010;251(3):483–487. DOI: 10.1097/SLA.0b013e3181cf9171, PMID: 20101172.
- [83] Partelli S, Crippa S, Barugola G, Tamburrino D, Capelli P, D'Onofrio M, *et al.* Splenic artery invasion in pancreatic adenocarcinoma of the body and tail: a novel prognostic parameter for patient selection. *Ann Surg Oncol* 2011;18(13):3608–3614. DOI: 10.1245/s10434-011-1769-1, PMID: 21584836.
- [84] Kim BH, Kim K, Chie EK, Jang JY, Kim SW, Han SW, *et al.* Prognostic value of splenic artery invasion in patients undergoing adjuvant chemoradiotherapy after distal pancreatectomy for pancreatic adenocarcinoma. *Cancer Res Treat* 2015;47(2):274–281. DOI: 10.4143/crt.2014.025, PMID: 25544574.
- [85] Addeo P, Velten M, Averous G, Faitot F, Nguimpi-Tambou M, Nappo G, *et al.* Prognostic value of venous invasion in resected T3 pancreatic adenocarcinoma: Depth of invasion matters. *Surgery* 2017;162(2):264–274. DOI: 10.1016/j.surg.2017.03.008, PMID: 28576385.
- [86] Hamada Y, Nakayama Y. Aggressive venous invasion in the area of carcinoma correlates with liver metastasis as an index of metastasis for invasive ductal carcinoma of the pancreas. *Pancreatol* 2017;17(6):951–955. DOI: 10.1016/j.pan.2017.08.006, PMID: 28844697.
- [87] Song A, Liu F, Wu L, Si X, Zhou Y. Histopathologic tumor invasion of superior mesenteric vein/ portal vein is a poor prognostic indicator in patients with pancreatic ductal adenocarcinoma: results from a systematic review and meta-analysis. *Oncotarget* 2017;8(20):32600–32607. DOI: 10.18632/oncotarget.15938, PMID: 28427231.
- [88] Chen HY, Wang X, Zhang H, Liu XB, Tan CL. Mesenterico-portal vein invasion should be an important factor in TNM staging for pancreatic ductal adenocarcinoma: Proposed modification of the 8(th) edition of the American Joint Committee on Cancer staging

- system. *World J Gastroenterol* 2019;25(46):6752–6766. DOI: 10.3748/wjg.v25.i46.6752, PMID: 31857777.
- [89] Nakagohri T, Kinoshita T, Konishi M, Inoue K, Takahashi S. Survival benefits of portal vein resection for pancreatic cancer. *Am J Surg* 2003;186(2):149–153. DOI: 10.1016/s0002-9610(03)00173-9, PMID: 12885608.
- [90] Dunn M, Morgan MB, Beer TW. Perineural invasion: identification, significance, and a standardized definition. *Dermatol Surg* 2009;35(2):214–221. DOI: 10.1111/j.1524-4725.2008.34412.x, PMID: 19215258.
- [91] Hirai I, Kimura W, Ozawa K, Kudo S, Suto K, Kuzu H, *et al.* Perineural invasion in pancreatic cancer. *Pancreas* 2002;24(1):15–25. DOI: 10.1097/00006676-200201000-00003, PMID: 11741178.
- [92] Zhang JF, Hua R, Sun YW, Liu W, Huo YM, Liu DJ, *et al.* Influence of perineural invasion on survival and recurrence in patients with resected pancreatic cancer. *Asian Pac J Cancer Prev* 2013;14(9):5133–5139. DOI: 10.7314/apjcp.2013.14.9.5133, PMID: 24175789.
- [93] Schorn S, Demir IE, Haller B, Scheufele F, Reyes CM, Tiefrunk E, *et al.* The influence of neural invasion on survival and tumor recurrence in pancreatic ductal adenocarcinoma - A systematic review and meta-analysis. *Surg Oncol* 2017;26(1):105–115. DOI: 10.1016/j.suronc.2017.01.007, PMID: 28317579.
- [94] Di Martino M, Ielpo B, de Nova JLM, Muñoz EA, Santamaria C, Diago V, *et al.* Lymph Node Ratio, Perineural Invasion and R1 Resection as Independent Prognostic Factors in Pancreatic Adenocarcinoma: A Retrospective Cohort Study. *Surg Technol Int* 2020;36:82–88. PMID: 32190897.
- [95] Crippa S, Pergolini I, Javed AA, Honselmann KC, Weiss MJ, Di Salvo F, *et al.* Implications of Perineural Invasion on Disease Recurrence and Survival After Pancreatectomy for Pancreatic Head Ductal Adenocarcinoma. *Ann Surg* 2022;276(2):378–385. DOI: 10.1097/SLA.0000000000004464, PMID: 33086324.
- [96] Ozaki H, Hiraoka T, Mizumoto R, Matsuno S, Matsumoto Y, Nakayama T, *et al.* The prognostic significance of lymph node metastasis and intrapancreatic perineural invasion in pancreatic cancer after curative resection. *Surg Today* 1999;29(1):16–22. DOI: 10.1007/BF02482964, PMID: 9934826.
- [97] Shimada K, Nara S, Esaki M, Sakamoto Y, Kosuge T, Hiraoka N. Intrapancreatic nerve invasion as a predictor for recurrence after pancreaticoduodenectomy in patients with invasive ductal carcinoma of the pancreas. *Pancreas* 2011;40(3):464–468. DOI: 10.1097/MPA.0b013e31820b5d37, PMID: 21289526.
- [98] Kayahara M, Nagakawa T, Konishi I, Ueno K, Ohta T, Miyazaki I. Clinicopathological study of pancreatic carcinoma with particular reference to the invasion of the extrapancreatic neural plexus. *Int J Pancreatol* 1991;10(2):105–111. DOI: 10.1007/BF02924113, PMID: 1748826.
- [99] Nagakawa T, Kayahara M, Ueno K, Ohta T, Konishi I, Miyazaki I. Clinicopathological study on neural invasion to the extrapancreatic nerve plexus in pancreatic cancer. *Hepatogastroenterology* 1992;39(1):51–55. PMID: 1314766.
- [100] Nagakawa T, Kayahara M, Ueno K, Ohta T, Konishi I, Ueda N, *et al.* A clinicopathologic study on neural invasion in cancer of the pancreatic head. *Cancer* 1992;69(4):930–935. DOI: 10.1002/1097-0142(19920215)69:4<930::aid-cnrc2820690416>3.0.co;2-r, PMID: 1735083.
- [101] Takahashi T, Ishikura H, Kato H, Tanabe T, Yoshiki T. Intra-pancreatic, extra-tumoral perineural invasion (nex). An indicator for the presence of retroperitoneal neural plexus invasion by pancreas carcinoma. *Acta Pathol Jpn* 1992;42(2):99–103. DOI: 10.1111/j.1440-1827.1992.tb03082.x, PMID: 1314008.
- [102] Takahashi T, Ishikura H, Motohara T, Okushiba S, Dohke M, Katoh H. Perineural invasion by ductal adenocarcinoma of the pancreas. *J Surg Oncol* 1997;65(3):164–170. DOI: 10.1002/(sici)1096-9098(199707)65:3<164::aid-jso4>3.0.co;2-4, PMID: 9236924.
- [103] Takahashi S, Hasebe T, Oda T, Sasaki S, Kinoshita T, Konishi M, *et al.* Extra-tumor perineural invasion predicts postoperative development of peritoneal dissemination in pancreatic ductal adenocarcinoma. *Anticancer Res* 2001;21(2B):1407–1412. PMID: 11396223.
- [104] Chatterjee D, Katz MH, Rashid A, Wang H, Iuga AC, Varadhachary GR, *et al.* Perineural and intraneural invasion in posttherapy pancreaticoduodenectomy specimens predicts poor prognosis in patients with pancreatic ductal adenocarcinoma. *Am J Surg Pathol* 2012;36(3):409–417. DOI: 10.1097/PAS.0b013e31824104c5, PMID: 22301497.
- [105] Takahashi H, Ohigashi H, Ishikawa O, Gotoh K, Yamada T, Nagata S, *et al.* Perineural invasion and lymph node involvement as indicators of surgical outcome and pattern of recurrence in the setting of preoperative gemcitabine-based chemoradiation therapy for resectable pancreatic cancer. *Ann Surg* 2012;255(1):95–102. DOI: 10.1097/SLA.0b013e31823d813c, PMID: 22123160.
- [106] Brierley JD, Gospodarowicz MK, Wittekind C. *Skin tumours*. In: Sobin LH, Gospodarowicz MK, Wittekind C, Brierley JD, editors. *TNM Online*. Chichester (UK): John Wiley & Sons, Ltd; 2017. DOI: 10.1002/9780471420194.tnmc26.pub3.
- [107] Gnerlich JL, Luka SR, Deshpande AD, Dubray BJ, Weir JS, Carpenter DH, *et al.* Microscopic margins and patterns of treatment failure in resected pancreatic adenocarcinoma. *Arch Surg* 2012;147(8):753–760. DOI: 10.1001/archsurg.2012.1126, PMID: 22911074.
- [108] Frampton AE, Gall TM, Krell J, Ahmad R, Jiao LR. Is there a 'margin' for error in pancreatic cancer surgery? *Future Oncol* 2013;9(1):31–34. DOI: 10.2217/fon.12.175, PMID: 23252561.
- [109] Sierzega M, Popiela T, Kulig J, Nowak K. The ratio of metastatic/resected lymph nodes is an independent prognostic factor in patients with node-positive pancreatic head cancer. *Pancreas* 2006;33(3):240–245. DOI: 10.1097/01.mpa.0000235306.96486.2a, PMID: 17003644.
- [110] van Geenen RC, van Gulik TM, Offerhaus GJ, de Wit LT, Busch OR, Obertop H, *et al.* Survival after pancreaticoduodenectomy for periampullary adenocarcinoma: an update. *Eur J Surg Oncol* 2001;27(6):549–557. DOI: 10.1053/ejso.2001.1162, PMID: 11520088.
- [111] Lai CC, Wang SY, Liao CH, Hsu JT, Chiang KC, Yeh TS, *et al.* Surgical Margin Status of Patients with Pancreatic Ductal Adenocarcinoma Undergoing Surgery with Radical Intent: Risk Factors for the Survival Impact of Positive Margins. *In Vivo* 2018;32(6):1591–1597. DOI: 10.21873/invivo.11419, PMID: 30348721.
- [112] Moon HJ, An JY, Heo JS, Choi SH, Joh JW, Kim YI. Predicting survival after surgical resection for pancreatic ductal adenocarcinoma. *Pancreas* 2006;32(1):37–43. DOI: 10.1097/01.mpa.0000194609.24606.4b.
- [113] Crippa S, Ricci C, Guarneri G, Ingaldi C, Gasparini G, Partelli S, *et al.* Improved survival after pancreatic re-resection of positive neck margin in pancreatic cancer patients. A systematic review and network meta-analysis. *Eur J Surg Oncol* 2021;47(6):1258–1266. DOI: 10.1016/j.ejso.2021.01.001, PMID: 33487492.
- [114] Wittekind C, Compton CC, Greene FL, Sobin LH. TNM residual tumor classification revisited. *Cancer* 2002;94(9):2511–2516. DOI:

- 10.1002/cncr.10492, PMID: 12015777.
- [115] Erdmann J, van Eijck CH. Resection margin involvement and tumour origin in pancreatic head cancer (Br J Surg 2012; 99: 1036-1049). Br J Surg 2013;100(2):299. DOI: 10.1002/bjs.9011, PMID: 23239482.
- [116] Markov P, Satoi S, Kon M. Redefining the R1 resection in patients with pancreatic ductal adenocarcinoma. J Hepatobiliary Pancreat Sci 2016;23(9):523–532. DOI: 10.1002/jhbp.374, PMID: 27524388.
- [117] Menon KV, Gomez D, Smith AM, Anthoney A, Verbeke CS. Impact of margin status on survival following pancreatoduodenectomy for cancer: the Leeds Pathology Protocol (LEPP). HPB (Oxford) 2009; 11(1):18–24. DOI: 10.1111/j.1477-2574.2008.00013.x, PMID: 19590619.
- [118] Campbell F, Smith RA, Whelan P, Sutton R, Raraty M, Neoptolemos JP, *et al.* Classification of R1 resections for pancreatic cancer: the prognostic relevance of tumour involvement within 1 mm of a resection margin. Histopathology 2009;55(3):277–283. DOI: 10.1111/j.1365-2559.2009.03376.x, PMID: 19723142.
- [119] Wittekind C, Compton C, Quirke P, Nagtegaal I, Merkel S, Hermanek P, *et al.* A uniform residual tumor (R) classification: integration of the R classification and the circumferential margin status. Cancer 2009;115(15):3483–3488. DOI: 10.1002/cncr.24320, PMID: 19536900.
- [120] Leonhardt CS, Niesen W, Kalkum E, Klotz R, Hank T, Büchler MW, *et al.* Prognostic relevance of the revised R status definition in pancreatic cancer: meta-analysis. BJS Open 2022;6(2):zrac010. DOI: 10.1093/bjsopen/zrac010, PMID: 35301513.
- [121] Hartwig W, Werner J, Büchler MW. Prognosis of resected pancreatic cancer: is the refined resection margin status dispensable? Langenbecks Arch Surg 2012;397(6):859–860. DOI: 10.1007/s00423-012-0968-y, PMID: 22820875.
- [122] Weyhe D, Obonyo D, Uslar VN, Stricker I, Tannapfel A. Predictive factors for long-term survival after surgery for pancreatic ductal adenocarcinoma: Making a case for standardized reporting of the resection margin using certified cancer center data. PLoS One 2021;16(3):e0248633. DOI: 10.1371/journal.pone.0248633, PMID: 33735191.
- [123] Verbeke CS, Knapp J, Gladhaug IP. Tumour growth is more dispersed in pancreatic head cancers than in rectal cancer: implications for resection margin assessment. Histopathology 2011;59(6):1111–1121. DOI: 10.1111/j.1365-2559.2011.04056.x, PMID: 22175891.
- [124] Chang DK, Johns AL, Merrett ND, Gill AJ, Colvin EK, Scarlett CJ, *et al.* Margin clearance and outcome in resected pancreatic cancer. J Clin Oncol 2009;27(17):2855–2862. DOI: 10.1200/JCO.2008.20.5104, PMID: 19398572.
- [125] Jamieson NB, Chan NI, Foulis AK, Dickson EJ, McKay CJ, Carter CR. The prognostic influence of resection margin clearance following pancreaticoduodenectomy for pancreatic ductal adenocarcinoma. J Gastrointest Surg 2013;17(3):511–521. DOI: 10.1007/s11605-012-2131-z, PMID: 23297028.
- [126] Maksymov V, Hogan M, Khalifa MA. An anatomical-based mapping analysis of the pancreaticoduodenectomy retroperitoneal margin highlights the urgent need for standardized assessment. HPB (Oxford) 2013;15(3):218–223. DOI: 10.1111/j.1477-2574.2012.00561.x, PMID: 23374362.
- [127] Osipov A, Nissen N, Rutgers J, Dhall D, Naziri J, Chopra S, *et al.* Redefining the Positive Margin in Pancreatic Cancer: Impact on Patterns of Failure, Long-Term Survival and Adjuvant Therapy. Ann Surg Oncol 2017;24(12):3674–3682. DOI: 10.1245/s10434-017-6076-z, PMID: 28871564.
- [128] Gebauer F, Tachezy M, Vashist YK, Marx AH, Yekebas E, Izbicki JR, *et al.* Resection margin clearance in pancreatic cancer after implementation of the Leeds Pathology Protocol (LEPP): clinically relevant or just academic? World J Surg 2015;39(2):493–499. DOI: 10.1007/s00268-014-2808-4, PMID: 25270344.
- [129] Nix GA, Dubbelman C, Wilson JH, Schütte HE, Jeekel J, Postema RR. Prognostic implications of tumor diameter in carcinoma of the head of the pancreas. Cancer 1991;67(2):529–535. DOI: 10.1002/1097-0142(19910115)67:2<529::aid-cncr2820670235>3.0.co;2-3, PMID: 1985745.
- [130] The Royal College of Pathologists of Australasia (RCPA). Cancer of the Exocrine Pancreas, Ampulla of Vater and Distal Common Bile Duct. 2020. Available from: <https://www.rcpa.edu.au/getattachme nt/0e0524b6-32cb-491c-959f-4f60355d0509/Protocol-pancreatic-cancer.aspx>.
- [131] Wang H, Chetty R, Hosseini M, Allende DS, Esposito I, Matsuda Y, *et al.* Pathologic Examination of Pancreatic Specimens Resected for Treated Pancreatic Ductal Adenocarcinoma: Recommendations From the Pancreatobiliary Pathology Society. Am J Surg Pathol 2022;46(6):754–764. DOI: 10.1097/PAS.0000000000001853, PMID: 34889852.
- [132] Lim JE, Chien MW, Earle CC. Prognostic factors following curative resection for pancreatic adenocarcinoma: a population-based, linked database analysis of 396 patients. Ann Surg 2003;237(1):74–85. DOI: 10.1097/0000658-200301000-00011, PMID: 12496533.
- [133] Matsumoto G, Muta M, Tsuruta K, Horiguchi S, Karasawa K, Okamoto A. Tumor size significantly correlates with postoperative liver metastases and COX-2 expression in patients with resectable pancreatic cancer. Pancreatol 2007;7(2-3):167–173. DOI: 10.1159/000104241, PMID: 17592230.
- [134] Saka B, Balci S, Basturk O, Bagci P, Postlewait LM, Maithel S, *et al.* Pancreatic Ductal Adenocarcinoma is Spread to the Peripancreatic Soft Tissue in the Majority of Resected Cases, Rendering the AJCC T-Stage Protocol (7th Edition) Inapplicable and Insignificant: A Size-Based Staging System (pT1: ≤2, pT2: >2-≤4, pT3: >4 cm) is More Valid and Clinically Relevant. Ann Surg Oncol 2016;23(6):2010–2018. DOI: 10.1245/s10434-016-5093-7, PMID: 26832882.
- [135] Allen PJ, Kuk D, Castillo CF, Basturk O, Wolfgang CL, Cameron JL, *et al.* Multi-institutional Validation Study of the American Joint Commission on Cancer (8th Edition) Changes for T and N Staging in Patients With Pancreatic Adenocarcinoma. Ann Surg 2017;265(1):185–191. DOI: 10.1097/SLA.0000000000001763, PMID: 27163957.
- [136] Adsay V, Mino-Kenudson M, Furukawa T, Basturk O, Zamboni G, Marchegiani G, *et al.* Pathologic Evaluation and Reporting of Intraductal Papillary Mucinous Neoplasms of the Pancreas and Other Tumoral Intraepithelial Neoplasms of Pancreatobiliary Tract: Recommendations of Verona Consensus Meeting. Ann Surg 2016; 263(1):162–177. DOI: 10.1097/SLA.0000000000001173, PMID: 25775066.
- [137] Rowan DJ, Hartley CP, Aldakkak M, Christians KK, Evans DB, Tsai S, *et al.* Gross tumor size using the AJCC 8th ed. T staging criteria does not provide prognostic stratification for neoadjuvant treated pancreatic ductal adenocarcinoma. Ann Diagn Pathol 2020;46:151485. DOI: 10.1016/j.anndiagpath.2020.151485, PMID: 32172219.
- [138] Zhang ML, Kem M, Rodrigues C, Sandini M, Ciprani D, Hank T, *et al.* Microscopic size measurements in post-neoadjuvant therapy resections of pancreatic ductal adenocarcinoma (PDAC) predict patient outcomes. Histopathology 2020;77(1):144–155. DOI: 10.

- 1111/his.14067, PMID: 31965618.
- [139] Huebner M, Kendrick M, Reid-Lombardo KM, Que F, Therneau T, Qin R, *et al.* Number of lymph nodes evaluated: prognostic value in pancreatic adenocarcinoma. *J Gastrointest Surg* 2012;16(5): 920–926. DOI: 10.1007/s11605-012-1853-2, PMID: 22421988.
- [140] Ashfaq A, Pockaj BA, Gray RJ, Halfdanarson TR, Wasif N. Nodal counts and lymph node ratio impact survival after distal pancreatectomy for pancreatic adenocarcinoma. *J Gastrointest Surg* 2014;18(11):1929–1935. DOI: 10.1007/s11605-014-2566-5, PMID: 24916590.
- [141] Tomlinson JS, Jain S, Bentrem DJ, Sekeris EG, Maggard MA, Hines OJ, *et al.* Accuracy of staging node-negative pancreas cancer: a potential quality measure. *Arch Surg* 2007;142(8):767–723; discussion 773. DOI: 10.1001/archsurg.142.8.767, PMID: 17709731.
- [142] Schwarz RE, Smith DD. Extent of lymph node retrieval and pancreatic cancer survival: information from a large US population database. *Ann Surg Oncol* 2006;13(9):1189–1200. DOI: 10.1245/s10434-006-9016-x, PMID: 16955385.
- [143] Slidell MB, Chang DC, Cameron JL, Wolfgang C, Herman JM, Schulick RD, *et al.* Impact of total lymph node count and lymph node ratio on staging and survival after pancreatectomy for pancreatic adenocarcinoma: a large, population-based analysis. *Ann Surg Oncol* 2008;15(1):165–174. DOI: 10.1245/s10434-007-9587-1, PMID: 17896141.
- [144] Valsangkar NP, Bush DM, Michaelson JS, Ferrone CR, Wargo JA, Lillemoe KD, *et al.* N0/N1, PNL, or LNR? The effect of lymph node number on accurate survival prediction in pancreatic ductal adenocarcinoma. *J Gastrointest Surg* 2013;17(2):257–266. DOI: 10.1007/s11605-012-1974-7, PMID: 23229885.
- [145] Han SS, Jang JY, Kim SW, Kim WH, Lee KU, Park YH. Analysis of long-term survivors after surgical resection for pancreatic cancer. *Pancreas* 2006;32(3):271–275. DOI: 10.1097/01.mpa.0000202953.87740.93, PMID: 16628082.
- [146] Barrak D, Villano AM, Moslim MA, Hopkins SE, Lefton MD, Ruth K, *et al.* Total Neoadjuvant Treatment for Pancreatic Ductal Adenocarcinoma Is Associated With Limited Lymph Node Yield but Improved Ratio. *J Surg Res* 2022;280:543–550. DOI: 10.1016/j.jss.2022.08.002, PMID: 36096019.
- [147] Pai RK, Beck AH, Mitchem J, Linehan DC, Chang DT, Norton JA, *et al.* Pattern of lymph node involvement and prognosis in pancreatic adenocarcinoma: direct lymph node invasion has similar survival to node-negative disease. *Am J Surg Pathol* 2011;35(2):228–234. DOI: 10.1097/PAS.0b013e318206c37a, PMID: 21263243.
- [148] Byun Y, Lee KB, Jang JY, Han Y, Choi YJ, Kang JS, *et al.* Peritumoral lymph nodes in pancreatic cancer revisited; is it truly equivalent to lymph node metastasis? *J Hepatobiliary Pancreat Sci* 2021;28(10): 893–901. DOI: 10.1002/jhbp.940, PMID: 33735543.
- [149] Speichinger F, Dragomir MP, Schallenberg S, Loch FN, Degro CE, Baukloh AK, *et al.* Rethinking the TNM Classification Regarding Direct Lymph Node Invasion in Pancreatic Ductal Adenocarcinoma. *Cancers (Basel)* 2021;14(1):201. DOI: 10.3390/cancers14010201, PMID: 35008365.
- [150] Buc E, Couvelard A, Kwiatkowski F, Dokmak S, Ruszniewski P, Hammel P, *et al.* Adenocarcinoma of the pancreas: Does prognosis depend on mode of lymph node invasion? *Eur J Surg Oncol* 2014; 40(11):1578–1585. DOI: 10.1016/j.ejso.2014.04.012, PMID: 24923739.
- [151] Konstantinidis IT, Deshpande V, Zheng H, Wargo JA, Fernandez-del Castillo C, Thayer SP, *et al.* Does the mechanism of lymph node invasion affect survival in patients with pancreatic ductal adenocarcinoma? *J Gastrointest Surg* 2010;14(2):261–267. DOI: 10.1007/s11605-009-1096-z, PMID: 19937477.
- [152] Pawlik TM, Gleisner AL, Cameron JL, Winter JM, Assumpcao L, Lillemoe KD, *et al.* Prognostic relevance of lymph node ratio following pancreaticoduodenectomy for pancreatic cancer. *Surgery* 2007;141(5):610–618. DOI: 10.1016/j.surg.2006.12.013, PMID: 17462460.
- [153] Elshaer M, Gravante G, Kosmin M, Riaz A, Al-Bahrani A. A systematic review of the prognostic value of lymph node ratio, number of positive nodes and total nodes examined in pancreatic ductal adenocarcinoma. *Ann R Coll Surg Engl* 2017;99(2):101–106. DOI: 10.1308/rcsann.2016.0340, PMID: 27869496.
- [154] Mitsunaga S, Hasebe T, Iwasaki M, Kinoshita T, Ochiai A, Shimizu N. Important prognostic histological parameters for patients with invasive ductal carcinoma of the pancreas. *Cancer Sci* 2005;96(12): 858–865. DOI: 10.1111/j.1349-7006.2005.00128.x, PMID: 16367904.
- [155] Wentz SC, Zhao ZG, Shyr Y, Shi CJ, Merchant NB, Washington K, *et al.* Lymph node ratio and preoperative CA 19-9 levels predict overall survival and recurrence-free survival in patients with resected pancreatic adenocarcinoma. *World J Gastrointest Oncol* 2012;4(10):207–215. DOI: 10.4251/wjgo.v4.i10.207, PMID: 23444312.
- [156] Shamseddine AI, Mukherji D, Melki C, Elias E, Eloubeidi M, Dimassi H, *et al.* Lymph node ratio is an independent prognostic factor after resection of periampullary malignancies: data from a tertiary referral center in the middle East. *Am J Clin Oncol* 2014;37(1): 13–18. DOI: 10.1097/COC.0b013e31826b9c74, PMID: 23111358.
- [157] Riediger H, Keck T, Wellner U, zur Hausen A, Adam U, Hopt UT, *et al.* The lymph node ratio is the strongest prognostic factor after resection of pancreatic cancer. *J Gastrointest Surg* 2009;13(7): 1337–1344. DOI: 10.1007/s11605-009-0919-2, PMID: 19418101.
- [158] Robinson SM, Rahman A, Haugk B, French JJ, Manas DM, Jaques BC, *et al.* Metastatic lymph node ratio as an important prognostic factor in pancreatic ductal adenocarcinoma. *Eur J Surg Oncol* 2012; 38(4):333–339. DOI: 10.1016/j.ejso.2011.12.020, PMID: 22317758.
- [159] Yamamoto Y, Ikoma H, Morimura R, Konishi H, Murayama Y, Komatsu S, *et al.* The clinical impact of the lymph node ratio as a prognostic factor after resection of pancreatic cancer. *Anticancer Res* 2014;34(5):2389–2394. PMID: 24778048.
- [160] Berger AC, Watson JC, Ross EA, Hoffman JP. The metastatic/ examined lymph node ratio is an important prognostic factor after pancreaticoduodenectomy for pancreatic adenocarcinoma. *Am Surg* 2004;70(3):235–240; discussion 240. DOI: 10.1177/000313480407000309, PMID: 15055847.
- [161] Schwarz L, Lupinacci RM, Svrcek M, Lesurtel M, Bubenheim M, Vuarneisson H, *et al.* Para-aortic lymph node sampling in pancreatic head adenocarcinoma. *Br J Surg* 2014;101(5):530–538. DOI: 10.1002/bjs.9444, PMID: 24633831.
- [162] Paiella S, Malleo G, Maggino L, Bassi C, Salvia R, Butturini G. Pancreatectomy with Para-Aortic Lymph Node Dissection for Pancreatic Head Adenocarcinoma: Pattern of Nodal Metastasis Spread and Analysis of Prognostic Factors. *J Gastrointest Surg* 2015;19(9):1610–1620. DOI: 10.1007/s11605-015-2882-4, PMID: 26160322.
- [163] Doi R, Kami K, Ito D, Fujimoto K, Kawaguchi Y, Wada M, *et al.* Prognostic implication of para-aortic lymph node metastasis in resectable pancreatic cancer. *World J Surg* 2007;31(1):147–154. DOI: 10.1007/s00268-005-0730-5, PMID: 17171496.

- [164] Wittekind C, Greene FL, Hutter RVP, Sobin LH, Henson DE, editors. TNM Supplement: A Commentary on Uniform Use. 3rd ed. New York, NY: Wiley-Liss; 2003.
- [165] Evans DB, Rich TA, Byrd DR, Cleary KR, Connelly JH, Levin B, *et al.* Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. *Arch Surg* 1992;127(11):1335–1339. DOI: 10.1001/archsurg.1992.01420110083017, PMID: 1359851.
- [166] Washington MK, Berlin J, Branton P, Burgart LJ, Carter DK, Fitzgibbons PL, *et al.* Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum. *Arch Pathol Lab Med* 2009;133(10):1539–1551. DOI: 10.5858/133.10.1539, PMID: 19792043.
- [167] Ryan R, Gibbons D, Hyland JM, Treanor D, White A, Mulcahy HE, *et al.* Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. *Histopathology* 2005;47(2):141–146. DOI: 10.1111/j.1365-2559.2005.02176.x, PMID: 16045774.
- [168] Chatterjee D, Katz MH, Rashid A, Varadhachary GR, Wolff RA, Wang H, *et al.* Histologic grading of the extent of residual carcinoma following neoadjuvant chemoradiation in pancreatic ductal adenocarcinoma: a predictor for patient outcome. *Cancer* 2012;118(12):3182–3190. DOI: 10.1002/cncr.26651, PMID: 22028089.
- [169] Chatterjee D, Katz MH, Foo WC, Sundar M, Wang H, Varadhachary GR, *et al.* Prognostic Significance of New AJCC Tumor Stage in Patients With Pancreatic Ductal Adenocarcinoma Treated With Neoadjuvant Therapy. *Am J Surg Pathol* 2017;41(8):1097–1104. DOI: 10.1097/PAS.0000000000000887, PMID: 28614206.
- [170] Chinese Pancreatic Surgery Association; Chinese Society of Surgery; Chinese Medical Association; Zhao YP, Yang YM, Tian XD. Guidelines for the diagnosis and treatment of pancreatic cancer in China (2021) (in Chinese). *Zhonghua Wai Ke Za Zhi* 2021;59(7):561–577. DOI: 10.3760/cma.j.cn112139-20210416-00171.
- [171] Zhao Q, Rashid A, Gong Y, Katz MH, Lee JE, Wolf R, *et al.* Pathologic complete response to neoadjuvant therapy in patients with pancreatic ductal adenocarcinoma is associated with a better prognosis. *Ann Diagn Pathol* 2012;16(1):29–37. DOI: 10.1016/j.anndiagpath.2011.08.005, PMID: 22050964.
- [172] Strobel O, Berens V, Hinz U, Hartwig W, Hackert T, Bergmann F, *et al.* Resection after neoadjuvant therapy for locally advanced, "unresectable" pancreatic cancer. *Surgery* 2012;152(3 Suppl 1):S33–S42. DOI: 10.1016/j.surg.2012.05.029, PMID: 22770956.
- [173] Kang CM, Chung YE, Park JY, Sung JS, Hwang HK, Choi HJ, *et al.* Potential contribution of preoperative neoadjuvant concurrent chemoradiation therapy on margin-negative resection in borderline resectable pancreatic cancer. *J Gastrointest Surg* 2012;16(3):509–517. DOI: 10.1007/s11605-011-1784-3, PMID: 22183861.
- [174] Denost Q, Laurent C, Adam JP, Capdepon M, Vendrely V, Collet D, *et al.* Pancreaticoduodenectomy following chemoradiotherapy for locally advanced adenocarcinoma of the pancreatic head. *HPB (Oxford)* 2013;15(9):716–723. DOI: 10.1111/hpb.12039, PMID: 23458326.
- [175] Heinrich S, Schäfer M, Weber A, Hany TF, Bhure U, Pestalozzi BC, *et al.* Neoadjuvant chemotherapy generates a significant tumor response in resectable pancreatic cancer without increasing morbidity: results of a prospective phase II trial. *Ann Surg* 2008;248(6):1014–1022. DOI: 10.1097/SLA.0b013e318190a6da, PMID: 19092346.
- [176] Heinrich S, Pestalozzi BC, Schäfer M, Weber A, Bauerfeind P, Knuth A, *et al.* Prospective phase II trial of neoadjuvant chemotherapy with gemcitabine and cisplatin for resectable adenocarcinoma of the pancreatic head. *J Clin Oncol* 2008;26(15):2526–2531. DOI: 10.1200/JCO.2007.15.5556, PMID: 18487569.
- [177] Turrini O, Viret F, Moureau-Zabotto L, Guirmand J, Moutardier V, Lelong B, *et al.* Neoadjuvant chemoradiation and pancreaticoduodenectomy for initially locally advanced head pancreatic adenocarcinoma. *Eur J Surg Oncol* 2009;35(12):1306–1311. DOI: 10.1016/j.ejso.2009.06.005, PMID: 19576722.
- [178] Turrini O, Ychou M, Moureau-Zabotto L, Rouanet P, Giovannini M, Moutardier V, *et al.* Neoadjuvant docetaxel-based chemoradiation for resectable adenocarcinoma of the pancreas: New neoadjuvant regimen was safe and provided an interesting pathologic response. *Eur J Surg Oncol* 2010;36(10):987–992. DOI: 10.1016/j.ejso.2010.07.003, PMID: 20828979.
- [179] Calvo FA, Matute R, García-Sabrido JL, Gómez-Espí M, Martínez NE, Lozano MA, Herranz R. Neoadjuvant chemoradiation with tegafur in cancer of the pancreas: initial analysis of clinical tolerance and outcome. *Am J Clin Oncol* 2004;27(4):343–349. DOI: 10.1097/01.coc.0000071462.12769.35, PMID: 15289726.
- [180] Desai SP, Ben-Josef E, Normolle DP, Francis IR, Greenson JK, Simeone DM, *et al.* Phase I study of oxaliplatin, full-dose gemcitabine, and concurrent radiation therapy in pancreatic cancer. *J Clin Oncol* 2007;25(29):4587–4592. DOI: 10.1200/JCO.2007.12.0592, PMID: 17925553.
- [181] Gillen S, Schuster T, Meyer Zum Büschenfelde C, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med* 2010;7(4):e1000267. DOI: 10.1371/journal.pmed.1000267, PMID: 20422030.
- [182] Hruban RH, Adsay NV, Albores-Saavedra J, Compton C, Garrett ES, Goodman SN, *et al.* Pancreatic intraepithelial neoplasia: a new nomenclature and classification system for pancreatic duct lesions. *Am J Surg Pathol* 2001;25(5):579–586. DOI: 10.1097/00000478-200105000-00003, PMID: 11342768.
- [183] Hassid BG, Lucas AL, Salomao M, Weng C, Liu F, Khanna LG, *et al.* Absence of pancreatic intraepithelial neoplasia predicts poor survival after resection of pancreatic cancer. *Pancreas* 2014;43(7):1073–1077. DOI: 10.1097/MPA.0000000000000161, PMID: 24987871.
- [184] Basturk O, Hong SM, Wood LD, Adsay NV, Albores-Saavedra J, Biankin AV, *et al.* A Revised Classification System and Recommendations From the Baltimore Consensus Meeting for Neoplastic Precursor Lesions in the Pancreas. *Am J Surg Pathol* 2015;39(12):1730–1741. DOI: 10.1097/PAS.0000000000000533, PMID: 26559377.

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