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The Brescia International Multidisciplinary Consensus Guidelines on the Optimal Pathology Assessment and Multidisciplinary Pathways of Non-Pancreatic Neoplasms in and Around the Ampulla of Vater (PERIPAN)

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ABSTRACT

Importance: The lack of multidisciplinary workflow guidelines and clear definitions and classifications for neoplasms in and around the ampulla of Vater results in inconsistencies affecting patient care and research.

Objective: The PERIPAN international multidisciplinary consensus group aimed to standardize the multidisciplinary diagnostic workflow and achieve consensus on definitions and classifications in order to ensure proper classification and optimal diagnostic assessment and consequently to improve patient care and future research.

Design: An international team of 43 experts (pathologists, surgeons, radiologists, gastroenterologists, oncologists) from 12 countries identified knowledge gaps, reviewed 37061 articles, and proposed recommendations using the Scottish Intercollegiate Guidelines Network methodology (SIGN), including the Delphi methodology and the AGREEII tool for quality assessment and external validation.

Results: The 38 consensus questions and 51 recommendations provide guidance on the following key aspects: I. More specific anatomic criteria for the definition of what qualifies as "ampullary" neoplasms, their distinction from duodenal and common bile duct tumors, and clinicopathologic characteristics of anatomic subsets; II. Avoidance of the confusing term "periampullary" for final classification; III. Refined definitions of intestinal, pancreatobiliary and mixed subtypes, and introduction of rare histologic subtypes; IV. The use and limitations of immunohistochemical and molecular profiling; V. Biopsy acquisition; VI. Clinical information required for accurate pathology assessment of biopsies and ampullectomy specimens; VII. Key items to be included in pathology reports of endoscopic specimens.

Conclusions and Relevance: Recognition of the Brescia PERIPAN guidelines will allow a more accurate classification of true ampullary cancers and their differentiation from other "periampullary" tumors. This will have significant implications for endoscopic interpretation and management, staging, pathologic diagnosis and therapeutic evaluation as well as oncologic treatment of various anatomic and histologic subsets of ampullary tumors. This will enhance the quality of both clinical care and future research in this complex medical field.

1 | Background and Aims

Pancreatic and biliary cancers are highly lethal malignancies, and they represent currently the third leading cause of cancer-related mortality in the Western world; they are expected to become the second in a few years [1]. As a part of the pancreatobiliary tract, cancers of the ampulla are often considered together with pancreatic cancer [2–4], although the cancers arising specifically from the ampulla are increasingly being recognized to have distinctive characteristics [5]. On the other hand, the periampullary region is a highly complex area where multiple anatomical structures and different epithelia converge, and it has been difficult to standardize what is to be classified as ampullary origin, thus leading to highly variable views on the nature of the tumors arising in this region [6]. Endoscopic findings of the cancers occurring in the ampulla and its vicinity are also highly variable; however unlike in the rest of the gastrointestinal tract, it has not been possible to glean out the significance of different growth patterns due to the lack of standardized definitions and classifications [5]. Nevertheless, it is increasingly recognized that the different growth patterns may be a reflection of differences in site specific origin and are associated with different carcinoma types and histologic subtypes [4, 7]. Further complicating the picture is that pancreatic ductal adenocarcinomas (PDACs), common bile duct carcinomas (intrapancreatic/periampullary cholangiocarcinomas) [8] and carcinomas arising from the non-ampullary duodenum [9], all of which are etiopathogenetically distinct processes, can secondarily involve the ampulla [10, 11]. All of these cancers are primarily defined based on anatomical criteria, however, different studies have taken different approaches to this issue [12]. Lack of consensus definitions has also hampered proper endoscopic classification of tumors as ampullary versus others. Moreover, being a transitional organ, the ampulla exhibits a high degree of versatility in the histologic types of carcinomas it generates, including pancreatobiliary and intestinal subtypes and a whole host of different entities [13]. However, there has not been a standardized approach to these, and it is debated whether morphology or immunohistochemistry should be used as the primary source in this classification [5, 14]. The lack of consensus and standardization regarding the classifications, definitions, and techniques that are used for the pathology diagnosis of these cancers results in worldwide divergence in daily practice. This in turn may lead to impaired patient care and incomparability of the study results.

Over the years, different disciplines have developed their own approaches to ampullary cancers. However, divergent terminology and criteria employed by different disciplines have impeded the advancements in this arena. For example, in the literature, the term "periampullary" has been used highly variably, in some studies referring to all cancer types removed by pancreatoduodenectomy, whereas, in others, to refer only to the ampulla of Vater and its

immediate vicinity. In addition, with the rise of personalized medicine and consequently the increasing need for accurate diagnosis and characterization of the tumor, close multidisciplinary collaboration has become critical. The complexity of the endoscopic and radiologic repertoire of cancers in this region, as well as the challenges in diagnosing and staging neoplasms, along with the diversity of treatment options, and the differences in prognosis, require a concerted multidisciplinary approach [15].

The PERIPAN group was established to have interdisciplinary communication between experts and develop guidelines applicable not only to the pathology assessment and diagnosis but also to the entire clinical team that is involved in the diagnostic and therapeutic part of the patient pathway, including gastroenterologists, radiologists, oncologists, and surgeons. Toward this goal, an international group of experts from pertinent disciplines was brought together to undertake a critical appraisal of the current state with a detailed analysis of the literature, to identify the gaps and inconsistencies in daily practice and to accordingly devise recommendations that address the issues related to standardized terminology, classification and approaches.

2 | Materials and Methods

2.1 | The PERIPAN Methodology

The PERIPAN guidelines were developed using a combination of several well-established and widely used methodologies. To provide a structured approach to literature review and evidence reporting, the Scottish Intercollegiate Guidelines Network (SIGN) [16], a widely used framework for developing high-quality evidence-based clinical practice guidelines, was applied. For topics where recommendations relied on expert opinion due to limited evidence, the DELPHI methodology was applied to achieve structured consensus [17, 18]. To systematically assess the strength of these recommendations, the widely adopted Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology was implemented [19]. Finally, to safeguard the quality and integrity of the process, the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool was utilized, and a jury committee of independent researchers with expertise in guideline development overviewed the entire process. The final guidelines were presented in an open-access format, allowing for public voting during a meeting at the Loggia hall in the Brescia city council on both the recommendations and the overall quality of the process [20]. The methodology was conducted through a transparent process of (1) defining the scope, (2) selecting renowned experts in the field, (3) identifying key clinical questions, (4) conducting systematic literature reviews and critical appraisal of the evidence, (5) developing recommendations, (6) developing agreement among the experts, and (7) external review and validation of the guidelines by stakeholders such as patients, healthcare professionals, and organizations.

2.2 | Creation of the PERIPAN Expert Panel and Committees

The development of the PERIPAN consensus guidelines was initiated by the International Study Group on Non-Pancreatic Periampullary Cancer (ISGACA, www.isgaca.com). The initiator, the ISGACA consortium, consulted the International Study Group of Pancreatic Pathologists (ISGPP) to serve as the steering committee. The ISGPP, composed of globally recognized experts in pancreatic pathology, formed an expert panel through a series of structured meetings and extended invitations to additional specialists based on their clinical expertise, academic contributions, and relevant publications. To ensure a comprehensive multidisciplinary approach, experts from all relevant specialties were independently invited through the ISGPP. Overall, the PERIPAN workforce represented 12 countries in America, Australasia and Europe (Supporting Information S1: Table S1) from five different disciplines, including pathology, surgery, oncology, radiology and gastroenterology.

2.3 | Literature Review and Identification of Gaps

The Steering Committee identified gaps and inconsistencies in daily practice, drafted the consensus questions and identified the experts eligible for the Expert Panel, Expert Multidisciplinary (MDT) Committee, and Research Team (see Supporting Information S1: Table S1). Systematic literature reviews were conducted in collaboration with a clinical librarian to collect and summarize all available evidence related to the consensus questions. All experts involved were allocated to teams anonymously to formulate evidence-based recommendations for the consensus questions (see Figure 1).

The systematic literature review included 10 different web searches in PubMed, Embase, and Web of Science (see Supporting Information S1: Table S2). In total, 59,797 articles were identified of which, after deduplication, 37,061 articles were screened for eligibility. An additional 23 articles were included in the manual reference search of included articles. In total, 229 articles were selected to assist the Expert Panel and Expert MDT Committee in answering the 38 consensus questions with recommendations. Several consensus questions were answered with more than one recommendation, resulting in 51 recommendations.

2.4 | Pre-Meeting Committee Preparations and Consensus Analysis

The DELPHI methodology was used for the development of agreement. Briefly, in several rounds of structured surveys, the experts voted “agree” or “disagree” for each of the consensus questions and recommendations [18]. When voting “disagree”, the expert provided a concise explanatory comment. If agreement did not reach 80%, the recommendation was revised by the responsible expert team according to the comments, and the process was repeated.

Three DELPHI rounds were conducted to reach 80% consensus on the recommendations. In the first, second and third DELPHI rounds, a consensus rate of ≥ 80% was achieved for 33/57, 19/24 and 4/5 of the recommendations (6 recommendations were combined with another recommendation), respectively, so that 50 of the 51 recommendations reached ≥ 80% agreement. The single recommendation that did not reach ≥ 80% agreement was

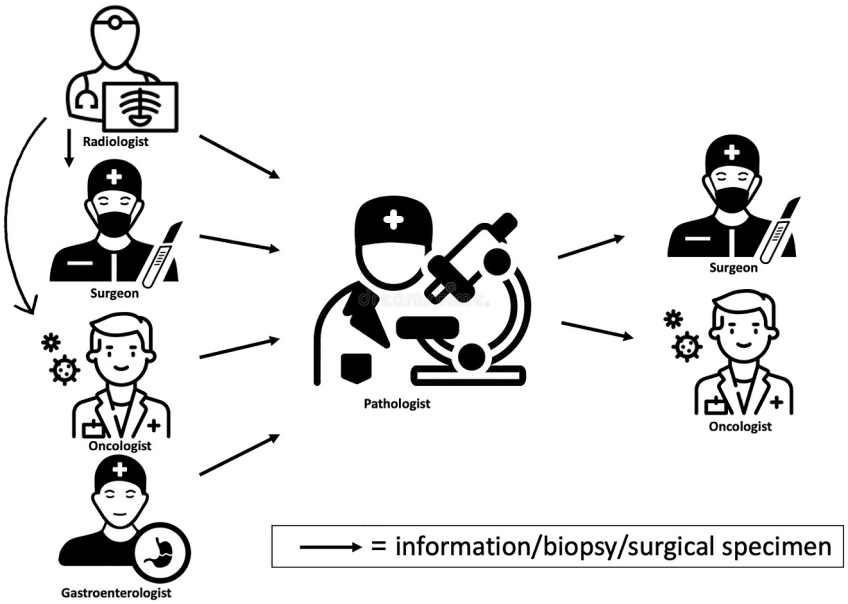

FIGURE 1 | Multidisciplinary workflow. The schematic figure represents the multidisciplinary workflow for neoplasms in the periampullary region, as it is practiced in most countries. It includes radiologists, surgeons, oncologists, gastroenterologists and pathologists. All arrows indicate the transfer of information, tissue biopsy, or surgical specimen. All multidisciplinary recommendations are related to one of the arrows in the figure. Optimal Multidisciplinary workflow is essential for patient treatment and care.

discussed at the final expert meeting (see below), which resolved differences of opinion and led to a final agreement. Several recommendations were fine-tuned linguistically. Eventually, the recommendations were graded following the GRADE methodology, resulting in a score that indicated the strength of the recommendations (strong or weak) and the quality of the evidence (high, moderate, low, or very low) based on the available data.

2.5 | PERIPAN Consensus Meeting

The created consensus recommendations were presented during the PERIPAN 2023 conference in Brescia, Italy, March 23–24, 2023, a meeting open to all individuals considering participation at which 31 of the experts participated personally. During this meeting, an independent Jury Committee who had not been involved in the pre-meeting preparations evaluated the quality of the process by calculating a "Quality Score" using the AGREE II tool [20]. This tool provides a standardized method for assessing the development process of clinical practice guidelines and consists of 23 items grouped into six domains: scope and purpose, stakeholder involvement, development rigor, presentation clarity, applicability, and editorial independence. Finally, the conference audience (all involved experts + all attendees) could vote "agree" or "disagree" for each consensus recommendation to assess the external audience agreement.

3 | Key Questions, Recommendations and Discussion

The PERIPAN guidelines consist of 38 consensus questions with 51 recommendations. The full guideline document, including questions, recommendations, evidence grading, comments, and proposed actions, can be found in the supplementary material as PERIPAN Consensus guidelines ("PERIPAN Consensus Guidelines", see Supporting Information S2). A summary limited to the consensus questions and recommendations of both the pathology part (21 consensus questions with 34 recommendations) and MDT part (17 consensus questions with 17 recommendations) is provided in Tables 1 and table 2, respectively. The key issues that are addressed in the guidelines are presented below.

3.1 | Definition of Neoplasm of "Ampullary" Origin and Distinction From Other "Periampullary" Neoplasms

- Ampullary carcinoma is defined as a carcinoma arising from any segment of the ampulla of Vater, including the ampullary duodenum (duodenum facing surface of the ampulla), as well as the intra-Oddi tips of the common bile duct and main pancreatic duct. If present, the precursor of the lesion is typically in the ampulla of Vater.
- Distal cholangiocarcinoma is defined as a carcinoma that has its (epi)center in the common bile duct between the junction of the cystic duct with the common hepatic duct and the ampulla of Vater (above the Oddi muscle and duodenal muscularis) with no or minimal involvement of the ampullary structures.
- Duodenal carcinoma is defined as a carcinoma that has its (epi)center in the non-ampullary duodenum. The (epi)center should not involve the ampulla, but minimal involvement of the ampulla by the peripheral edges of invasive or non-invasive neoplasia is accepted.

TABLE 1 | Summary of recommendations—pathology recommendations.

Topic	Consensus question	Recommendations	Level of evidence	Form of recommendation
Topic 1: Anatomy-based definition of periampullary cancers				
CQ1.1	What is the anatomical definition of ampullary carcinoma?	Ampullary carcinoma is defined as a carcinoma arising from any segment of the ampulla of Vater. If present, the precursor of the lesion is typically in the ampulla of Vater; however, occasionally incidental dysplastic lesions independent from the main lesion can be seen in the pancreas or bile duct in cases with ampulla of Vater carcinoma, which does not preclude ampullary origin.	Low	Strong (upgraded by the experts)
CQ1.2	What is the anatomical definition of distal cholangiocarcinoma?	Distal cholangiocarcinoma is defined as a carcinoma that has its (epi)center in the common bile duct between the junction of the cystic duct with the common hepatic duct and the ampulla of Vater (above the Oddi muscle), with no or minimal involvement of the ampullary structures.	Low	Strong (upgraded by the experts)
CQ1.3	What is the anatomical definition of (non-ampullary) duodenal carcinoma?	Duodenal carcinoma is defined as a carcinoma that has its (epi)center in the non-ampullary duodenum. The (epi)center should not involve the ampulla, but involvement of the ampulla by the peripheral edges of invasive or non-invasive neoplasia is accepted.	Low	Weak
CQ1.4	Can "papillary adenocarcinoma" be defined as a separate anatomical entity?	The term "papillary adenocarcinoma" should be avoided when describing the invasive component of an ampullary adenocarcinoma.	Low	Weak
CQ1.5	Which tumors are included in the definition "periampullary tumor"?	The term "periampullary" should be avoided in the postoperative setting, including in surgical pathology reports and reporting to cancer databases, as pathologic examination can specify the specific location of the tumor. Prior to resection, if imaging or other modalities cannot identify the (epi)center of the tumor, the term "periampullary" may be used as a descriptor.	Low	Strong (upgraded by the experts)
Topic 2: Site-specific precursor lesions				
CQ2.1A	How to define ampullary precursor lesions?	A diagnosis of ampullary precursor lesion can be made when the (epi)center of the precursor lesion is located in the ampulla of Vater.	Low	Strong
CQ2.1B		Ampullary precursor lesions can be subclassified as adenoma when they involve the duodenal surface of the ampulla, or IAPN when they involve the lumen of the ampullary channel(s)/ducts. If both compartments are involved, the subtyping should be based on the predominant component.	Low	Strong

(Continues)

TABLE 1 | (Continued)

Topic	Consensus question	Recommendations	Level of evidence	Form of recommendation
CQ2.1C		Ampullary precursor lesions can be subclassified into intestinal, pancreatobiliary, or mixed/hybrid subtypes by their direction of epithelial differentiation based on microscopic and/or immunohistochemical features. This subtyping is important especially when an invasive carcinoma is present.	Low	Strong
CQ2.1D		Pancreatic intraepithelial neoplasia (PanIN) should not be regarded as an ampullary precursor lesion.	Low	Strong
CQ2.2A	How can the presence, location, and subtype of a precursor lesion in a specific ampullary anatomical compartment provide evidence for the origin of an ampullary carcinoma?	The location of a precursor lesion in the vicinity of the ampulla should be considered when determining whether a carcinoma is ampullary or not. Precursor neoplasms growing along the lumen of the ampulla (IAPN) or present on the duodenal surface of the major papilla, at the tip of the ampullary opening into the duodenum (adenoma), qualify as ampullary precursor lesions.	Low	Weak
CQ2.2B		Ampullary carcinomas can be of intestinal, pancreatobiliary, mixed or tubular-NOS subtype. Hence, the histologic subtype does not determine whether an invasive carcinoma is ampullary or not.	Low	Strong
Topic 3: Anatomical variations in the periampullary region				
CQ3.1	What are the definitions of the relevant anatomical variations?	The anatomic variations that are studied for their association with ampullary cancer include: Low union (cystic duct joining the common hepatic duct inside the pancreas or within 5 mm of the pancreatic border), diverticula, pancreaticobiliary maljunction/anomalous union of pancreaticobiliary ducts, choledochal cyst, and pancreas divisum.	Moderate	Weak
Topic 4: Histological subtypes of ampullary cancer				
CQ4.1	Which type of ampullary adenocarcinoma should be classified into subtypes?	An attempt should be made to classify tubular type adenocarcinomas as pancreatobiliary or intestinal.	Expert opinion	
CQ4.2	On which part of the tumor should ampullary subtype analysis be performed?	Histologic subtyping of ampullary carcinoma should be based on the invasive component of the tumor rather than the preinvasive component. If there is no invasive carcinoma, this should be clarified.	Expert opinion	
CQ4.3A	How to define the pancreatobiliary subtype?	The pancreatobiliary subtype resembles pancreatic ductal adenocarcinoma and is characterized by more widely separated and relatively smaller and simpler glands lined by cuboidal or low columnar cells	Low	Weak

(Continues)

TABLE 1 | (Continued)

Topic	Consensus question	Recommendations	Level of evidence	Form of recommendation
		without nuclear stratification or elongation.		
CQ4.3B		Compared to intestinal subtype tubular adenocarcinoma, the pancreatobiliary subtype is typically more likely to express MUC1 and CK7 and less likely to express CDX2, MUC2, and CK20, but none of these markers are entirely specific or sensitive individually or in combination.	Low	Weak
CQ4.4A	How to define the intestinal subtype?	The intestinal subtype can be defined morphologically by tall columnar cells with nuclear elongation and stratification, and with large glandular or cribriform architecture. A further clue is dirty intraluminal necrosis.	Low	Weak
CQ4.4B		Compared to pancreatobiliary subtype tubular adenocarcinoma, the intestinal subtype is typically more likely to express MUC2, CDX2 and CK20 and less likely to express MUC1 and CK7. None of these markers are entirely specific or sensitive individually or in combination.	Low	Weak
CQ4.5A	How to define the mixed subtype?	For ampullary tubular-type adenocarcinomas that have morphologically distinct areas with unequivocal intestinal and pancreatobiliary components, classification as "mixed subtype" is advisable (the lesser component should comprise at least 30% of the tumor).	Low	Weak
CQ4.5B		In cases with mixed histologic features of the invasive carcinoma, it is preferable to give estimates of the percentage/ proportions of the different components (see CQ 4.3 and 4.4) of the carcinoma, if possible.	Low	Weak
CQ4.6A	Which other histologic subtypes are to be taken into consideration and how are they defined?	For tubular adenocarcinomas in which a definitive determination cannot be made as to intestinal versus pancreatobiliary (previously called hybrid subtype), the term tubular-NOS subtype is recommended. For such cases, it is advisable to document which lineage is favored overall, or if there are recognizably distinct components, to provide the percentage (and/or size of different components) in a comment. If available, it is also advisable to use immunohistochemical support.	Low	Weak
CQ4.6B		Medullary carcinoma, as defined in the colon, should be reported if recognized. Testing for mismatch repair deficiency is indicated.	Expert opinion	

(Continues)

TABLE 1 | (Continued)

Topic	Consensus question	Recommendations	Level of evidence	Form of recommendation
CQ4.6C		Carcinomas with individual cell or cord-like infiltration with or without signet-ring cell morphology should be classified as in the upper GI tract as "poorly cohesive carcinoma with/without overt signet ring cell formation".	Expert opinion	
CQ4.6D		Invasive micropapillary carcinoma is defined by the presence of small, closely packed micropapillary clusters without fibrovascular cores, lying within clefts and showing inverse cellular polarity in which the luminal surface of the cells (and the markers they express, e.g., MUC1) are facing the stroma rather than the center.	Low	Weak
CQ4.6E		"Gastric type" adenocarcinomas is closely related to the pancreatobiliary subtype, and more studies are needed to clarify the diagnostic criteria and characteristics.	Low	Weak
CQ4.6F		Undifferentiated carcinomas (high-grade pleomorphic carcinomas without glandular formations) do not contain osteoclastic giant cells. Undifferentiated carcinomas with rhabdoid phenotype are to be reported as a separate entity, since they appear to have different biologic characteristics.	Expert opinion	
Topic 5: Molecular and immunohistochemical analyses				
CQ5.1	What are the most important classification techniques for the distinction between the various periampullary tumor entities? (Morphology, immunohistochemical or histochemical markers, next-generation sequencing)	Classification is based on morphology but may be supported by immunohistochemistry (IHC) and molecular markers.	Low	Weak
CQ5.2	What is the role of tumor markers/ immunohistochemistry for the classification of tumor types or the definition of subgroups?	Tumor morphology is the key for identification of the various subtypes of ampullary carcinoma (intestinal, pancreatobiliary, mixed, tubular-NOS), and immunohistochemistry should be seen as a support, especially, in case of poorly differentiated carcinomas.	Low	Weak
CQ5.3	What is the role of tumor markers/ immunohistochemistry in relation to prognosis or chemotherapeutical response?	Historical studies on prognosis and chemotherapy response suffer from inconsistent definitions of ampullary carcinoma. Hence, the role of immunohistochemistry/tumor markers related to prognosis or treatment response is still unclear. Further studies (with the use of standardized definitions) are needed.	Low	Weak

(Continues)

TABLE 1 | (Continued)

Topic	Consensus question	Recommendations	Level of evidence	Form of recommendation
CQ5.4	Should mismatch repair (MMR) deficiency testing be performed and reported routinely?	MMR-testing should become a reflex test when diagnosing ampullary carcinoma since the prevalence of MMR deficiency is comparable to that of colorectal cancer and is also independent on the subtype. Preferably, MMR-testing should follow immediately after the diagnosis or, if possible, should be provided together with the final pathology report.	Low	Weak
Topic 6: T-stage classification				
CQ6.1	How to differentiate, in the presence of intra-ampullary neoplasia, true invasive growth from intraductal spread to accessory/pre-existent periampullary glands?	In the absence of lympho-vascular invasion and/or perineural invasion, the differentiation between true invasion and intraductal extension can be distinguished based on the architectural features (haphazardly arranged glands) and desmoplastic stroma reaction.	Low	Strong
Topic 7: Lymph node metastasis				
CQ7.1A	Has the minimum lymph node yield for non-pancreatic periampullary cancer been established, and if so, what should be done if a lower number of lymph nodes has been examined?	In clinical practice, lymph nodes are sampled before the definitive identification of the cancer origin. Therefore, it is recommended to adhere to the same minimum lymph node yield as for pancreatic cancer, until robust evidence specific to non-pancreatic periampullary cancers has been established.	Low	Strong (upgraded by the experts)
CQ7.1B		If the lymph node count in an individual case is lower than the minimum lymph node yield, the gross specimens (pancreatoduodenectomy specimen and separately submitted lymph node stations, if available) should be revisited and additional tissue samples examined.	Low	Weak
Topic 8: Future				
CQ8.1	What should be reported during pathology examination in order to collect valuable information for future studies?	A standardized protocol exists, the standardized college of american pathologists (CAP) protocol [1]; however, the PERIPAN workforce has developed the PERIPAN-PathologyReportTemplate, which expands the CAP protocol to enhance future studies.[2] It is recommended to follow one of these formats. [1]: CAP protocol for ampullary cancer [30] [2]: PERIPAN-PathologyReportTemplate [31]	Expert opinion	

3.1.1 | Ampullary Cancer

For the purpose of tumor location-based classification, the ampulla of Vater is defined as the intra-Oddi compartment of the distal common bile duct (CBD) and pancreatic duct, as well as the papilla of Vater (see Figure 2). The latter is the region where these ducts open to the duodenum, including the duodenum-facing surface of this promontory. As such, based on

TABLE 2 | Summary of recommendations—Multidisciplinary team (MDT) recommendations.

Topic and CQ	Consensus question	Recommendations	Level of evidence	Form of recommendation
MDT topic 1: Biopsy acquisition:				
CQ MDT 1.1	Which and how many biopsies should be taken during the diagnostic phase for optimal pathology assessment?	Targeted biopsies of viable abnormal or suspicious tissue should be the goal of tissue sampling. The number of biopsies is secondary to the quality of the sample but a minimum of three biopsies is recommended.	Expert opinion	
MDT Topic 2: Information for the pathologist required for biopsy assessment:				
CQ MDT 2.1	Which radiological information is helpful for optimal pathology assessment of the biopsy material?	Essential information includes: — The size of the lesion — The location of the lesion, that is, the relation to the duodenum, common bile duct and pancreas. — Presence/absence of intracanalicular growth Optional: — Dilation of the common bile duct and/or dilation of the pancreatic duct.	Expert opinion	
CQ MDT 2.2	Which clinical (surgical, oncological, endoscopy) information is key for pathology assessment of the biopsy material?	Essential information includes: — Previous local procedures — Size of the lesion — Location of the lesion with respect to the ampullary channel, bile duct and duodenum — Previous local procedures Highly recommended: — Hereditary predisposition, familial and personal cancer history Optional: — Endoscopic aspect of the lesion — If it has been decided that the patient will not undergo surgery, this should be explicitly stated, such that the pathologist can perform immunohistochemical and/or molecular tests that may be relevant to treatment.	Expert opinion	
MDT Topic 3: Ampullectomy				
CQ MDT 3.1	Which information can be provided by pathology examination of ampullectomy specimens?	The pathology assessment should follow the synoptic report for pathological examination of ampullectomy specimens which includes: — The presence of invasive carcinoma — The evaluation of resection margins — The presence of lymphatic/vascular/perineural invasion — The presence of tumor budding — The grade of differentiation — Depth/size of invasion	Expert opinion	

(Continues)

TABLE 2 | (Continued)

Topic and CQ	Consensus question	Recommendations	Level of evidence	Form of recommendation
MDT Topic 4: Perioperative specimen handling				
CQ MDT 4.1	Which lymph nodes should be marked in the surgical specimen following pancreatoduodenectomy for a non-pancreatic periampullary tumor.	All lymph node stations beyond the standard lymphadenectomy as recommended by ISGPS should be marked by the surgeon.	Expert opinion	
CQ MDT 4.2	Should the lymph nodes be collected in separate containers?	If lymph nodes are removed separately from the main specimen or if extra regional lymph nodes are excised (extended lymphadenectomy), these should be marked and collected separately by the surgeon.	Expert opinion	
CQ MDT 4.3	Which type of energy devise can be used or should be avoided for surgical dissection?	Regardless of the type of energy device used, tissue damage that would interfere with adequate pathology examination should be avoided, whenever feasible and as long as it does not compromise patient safety.	Expert opinion	
CQ MDT 4.4	Should the specimen be marked by the surgical team and if so, which surfaces and/or structures should be marked?	The surgeon should mark the specimen whenever there is something out of the norm.	Expert opinion	
MDT Topic 5: Logistics of perioperative specimen handling				
CQ MDT 5.1	What is the preferred time interval in which the specimen should reach the pathologist/pathology department?	As soon as the specimen is removed, ideally, it should be transported to the pathology department fresh for biobanking and proper processing for diagnostic evaluation.	Expert opinion	
CQ MDT 5.2	What is the maximum length of time before the specimen should be placed in formalin to prevent autolysis?	The specimen should be transported to the pathology department, processed and fixed in formalin as soon as possible (within 30 min)	Expert opinion	
CQ MDT 5.3A	If it is not possible to achieve the advised time interval, how to preserve the specimen to minimize autolysis?	If the specimen cannot be delivered to the pathology lab promptly and if it cannot be properly handled by the lab immediately upon removal, it should be placed in a refrigerator.	Expert opinion	
CQ MDT 5.3B	Should the specimen be sectioned/opened by the surgeon/non-pathologist before preserving?	Specimens should not be sectioned/opened by non-pathology personnel. If pathology personnel are not available, the specimen should be refrigerated. Specimens should not be placed in formalin as a whole.	Expert opinion	
MDT Topic 6: Information to the pathologist required for post-operative specimen assessment.				
CQ MDT 6.1	Which radiological information can be useful for specimen assessment?	Useful radiological information includes: Site of the lesion, size of the lesion, presence of venous/arterial involvement, anatomical variations (biliary, arterial, venous), previous pancreatitis, suspicious lymph nodes, additional benign or premalignant lesions of the periampullary region, preoperative sampling if performed in a different center, neoadjuvant treatment, prior history of cancer.	Expert opinion	

(Continues)

TABLE 2 | (Continued)

Topic and CQ	Consensus question	Recommendations	Level of evidence	Form of recommendation
CQ MDT 6.2	Which surgical/oncological information is useful for specimen assessment?	Key clinical information includes: Preoperative sampling if performed in a different center, neoadjuvant treatment, additional lymph node sampling, previous pancreatitis/cholangitis, biliary stent, relevant genetic disease, prior history of cancer, and serum tumor markers. The surgeon should report on any resected structures, including vessels that are not part of the routine surgical specimen, and how these have been labeled.	Expert opinion	
MDT Topic 7: Biopsy assessment				
CQ MDT 7.1	Which information should be reported on biopsy samples?	High-risk features, such as poorly cohesive nature, vascular invasion, histological typing and invasive/noninvasive should be reported.	Expert opinion	
CQ MDT 7.2	Is there a need for a subtype classification and biomarkers from the biopsy?	Subtyping and biomarker assessment on biopsy material should be done only if it may influence subsequent treatment.	Expert opinion	
MDT Topic 8: Specimen assessment				
CQ MDT 8.1	What specific information for the surgeon and oncologist should not be missed?	Pathology should be reported using a standardized synoptic report including the key data items recommended by major reputable published protocols (for example CAP, RCPA, RCPath data sets).	Expert opinion	

the exact localization and macroscopic appearance, which can mostly be determined on endoscopy and pathology grossing, ampullary tumors can be assigned to three distinct subsets, which also distinguish them from other periampullary cancers:.

1. Tumors arising on the wall of the very distal tips (intra-Oddi components) of the CBD and pancreatic duct are referred to as the "ampullary-ductal" subset of ampullary cancer (Figure 3) [5]. In essence, these are the ampullary-wall counterparts of PDAC and CBD carcinoma, respectively (see below). Although these typically form only minimal abnormalities from the duodenal perspective and can look underwhelming to endoscopists, they often form small cancers underneath the ampullary-duodenum. Biopsy acquisition from this subset of ampullary cancers may be problematic as these tumors are often represented minimally on the ampullary-duodenal surface as seen on endoscopy. Moreover, these cancers are often fairly small and of pancreatobiliary histological subtype, making it difficult to recognize them also on microscopy. Of note, although often small, these are characteristically highly infiltrative carcinomas and as such typically not amenable to ampullectomy (Figure 3).
2. Tumors arising from the mucosa of the intra-Oddi compartment of the CBD and pancreatic duct or common ampullary channel, and are characterized by adenomatous neoplastic growth within the ampulla are termed "intra-ampullary papillary tubular neoplasms" (IAPN) [7] (Figure 4), similar to their counterparts in the pancreas (intraductal papillary mucinous neoplasms, IPMNs) and the bile duct (intraductal papillary neoplasms, IPNBs). Similar to IPMN and IPNB, IAPN may transform into invasive adenocarcinoma. Because of their predominantly intra-ampullary growth, IAPNs typically result in a bulging ampulla that is readily identifiable endoscopically from a duodenal perspective [7]. However, as intact and unremarkable ampullary-duodenum often overlies the intra-ampullary mass, endoscopic biopsies may miss the lesion.
3. Tumors arising from the duodenal surface of the ampulla, which typically engulf the ampullary orifice eccentrically, are referred to as the "ampullary-duodenal" subset (previously also called "periampullary duodenal"; Figure 5) [5]. Ampullary-duodenal carcinomas often arise from adenomas of the ampullary-duodenum and form vegetating tumors that are readily recognizable on endoscopic examination.

In the Brescia consensus meeting, it was agreed that the above-described subsets are considered of ampullary origin and that every attempt should be made to assign tumors to one of these subsets based on endoscopic and pathological correlation. However, this may not be possible in some cases, which are then classified as "mixed" or "NOS" (Not Otherwise Specified) type ampullary cancer.

3.1.2 | Distal Common Bile Duct Carcinoma

A distal common bile duct carcinoma (intrapancreatic cholangiocarcinoma) [8] has its (epi)center in the CBD with no or minimal ampullary involvement. By definition, the (epi)center of this group is above the Oddi musculature and the band of duodenal muscularis. These cancers typically do not cause any significant abnormality in the ampulla and thus are not diagnosable endoscopically unless they invade the proximal non-ampullary duodenum directly. The concentration/circumferential arrangement surrounding the CBD above the Oddi sphincter is the defining and common characteristic. In small tumors, involvement of the pancreatic duct is typically tangential.

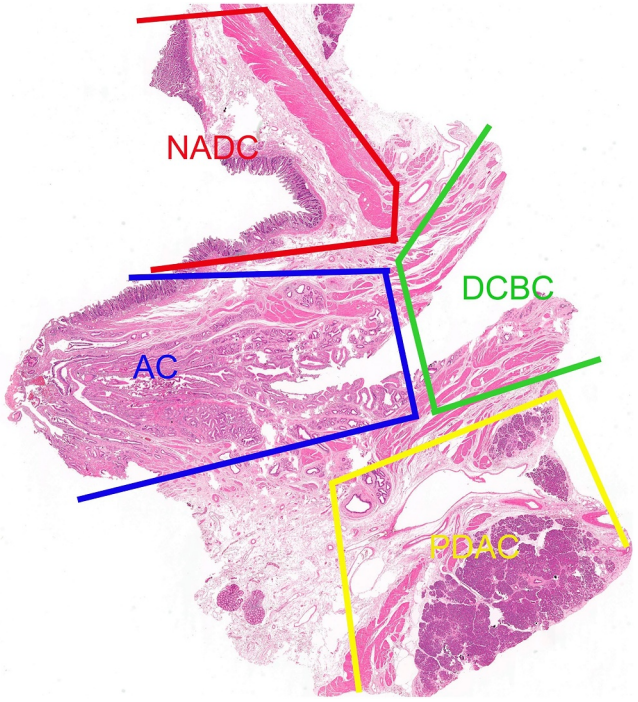

FIGURE 2 | Periampullary region. The ampulla refers to the area where the common bile duct and the main pancreatic duct meet, forming a channel known as the intra-Oddi compartment (IOC), as well as the papilla of Vater, that is, the area where the channel opens to the duodenum. Cancers that have their (epi)center in this region are regarded as ampullary cancer (AC). Indicated in the figure are the regions in which non-ampullary duodenal cancers (NADC), distal common bile duct cancers (DCBC) and pancreatic ductal adenocarcinomas (PDAC) have their (epi)center.

3.1.3 | Duodenal Carcinoma

Duodenal carcinoma has its (epi)center in the non-ampullary duodenum (Figure 6). Involvement of the ampulla is minimal and tangential, leaving much of the ampullary circumference uninvolved. As such, sparing of most of the ampulla itself endoscopically or grossly is the main criterion that distinguishes this group from ampullary cancers [9, 21, 22]. In some studies, some distance from the ampulla has been suggested [23–25]; however, in the Brescia consensus meeting, endoscopic and/or histological preservation of most of the ampulla was favored as the main criterion (see Figure 6).

Currently, widely varying criteria to define duodenal carcinoma and to distinguish it from ampullary carcinoma are being used. Consistent application of the recommended criteria will allow comparative studies of ampullary and duodenal cancers and their precursors.

For the accurate diagnosis of biopsy specimens, correlation with the endoscopic findings is of great value. As adenomatous neoplasms from the ampullary-duodenum and IAPN may look similar histologically, endoscopic findings may be key to reaching the correct diagnosis and management decision.

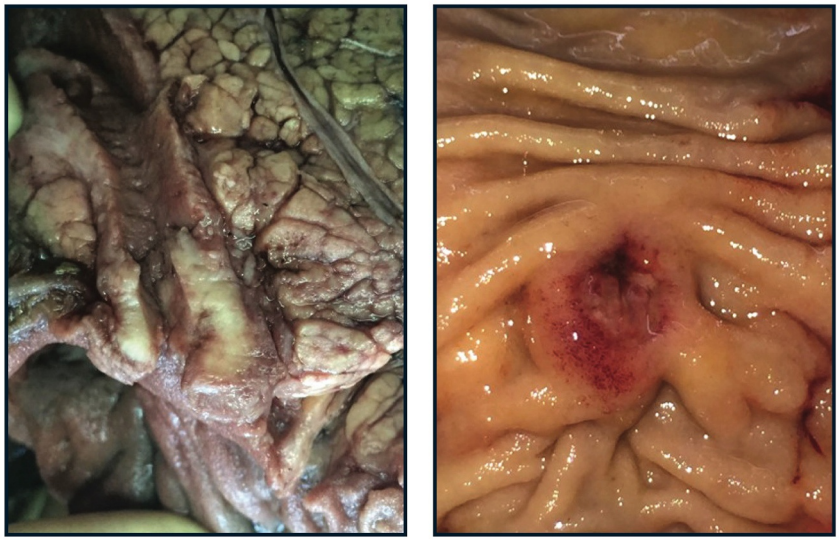

FIGURE 3 | Carcinoma of ampullary origin. Tumors arising on the wall of the very distal tips (intra-Oddi components) of the CBD and pancreatic duct (left), and tumors arising from the duodenal surface of the ampulla, which typically engulf the ampullary orifice eccentrically (right), are referred to as of ampullary-ductal origin.

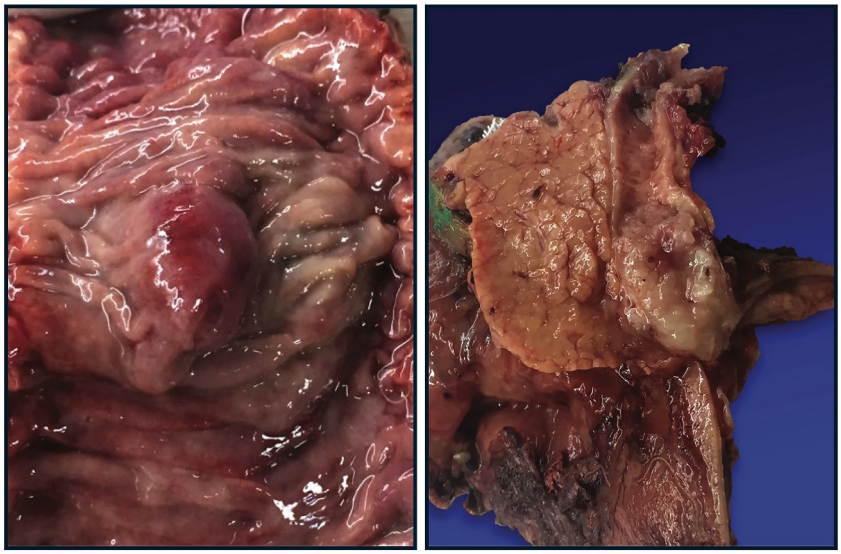

FIGURE 4 | Intra-ampullary papillary tubular neoplasm (IAPN). From an endoscopist's (duodenal luminal) perspective, the ampulla shows a mucosa-covered bulge (left), which is due to an adenomatous neoplasm within the ampulla (i.e., IAPN). The picture on the right illustrates the cut section of the ampulla with a tan beige polypoid mass filling the very distal (intraampullary) ends of the CBD and pancreatic duct. On histological examination, a microscopic focus of invasive carcinoma was identified.

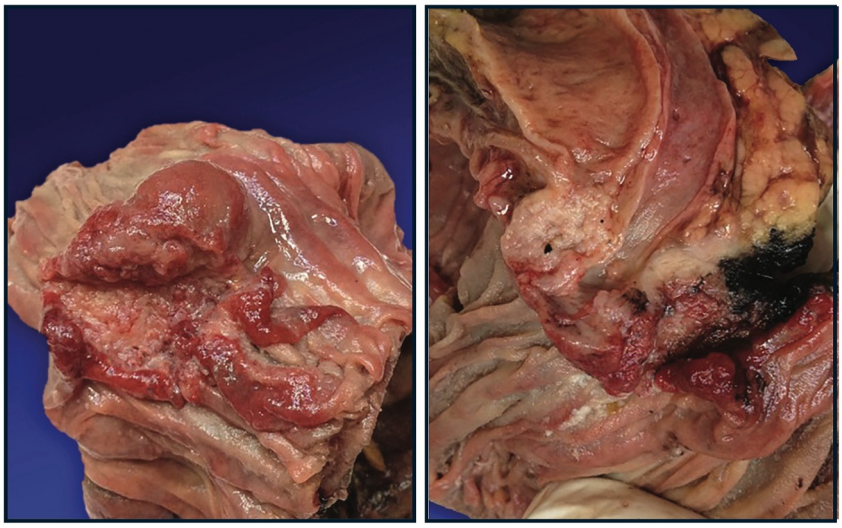

FIGURE 5 | Carcinoma of ampullary-duodenal origin. Ampullary cancer of ampullary-duodenal origin is characterized by an ulcero-vegetating mass in the region of the ampulla that is readily identified on endoscopy (left). The ampullary orifice is engulfed eccentrically in this lesion. A cut section of the ampulla illustrates that both the CBD and pancreatic duct open into the lesion (right), with tumor surrounding the orifices of both ducts in the ampullary duodenum.

For surgical resection specimens, careful and proper grossing of the specimens by experienced personnel familiar with the anatomy of the area and the above definitions is crucial for the determination of the cancer origin. Specimen photography is advisable in order to verify and compare with the microscopic findings.

The diagnosis of pancreatic cancer located in the periampullary region is made by default, when none of the above criteria specific for the diagnosis of ampullary, distal bile duct, or duodenal cancer are met.

3.2 | The Term "Periampullary Tumor"

The term "periampullary" should be avoided in the post-operative setting, including in surgical pathology reports and reporting to cancer databases, as pathologic examination can specify the specific location of the tumor. Prior to resection, if imaging or other modalities cannot identify the (epi)center of the tumor, the term "periampullary" may be used as a descriptor.

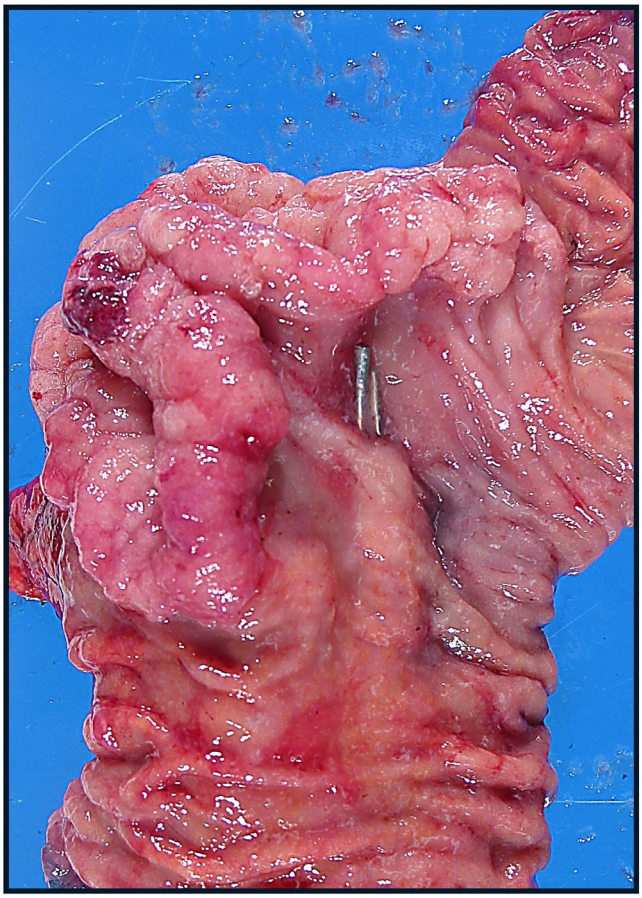

FIGURE 6 | Non-ampullary duodenal cancer. Probes inserted into the common bile duct (CBD) and pancreatic duct demonstrate that the ampullary orifice in the duodenum is completely spared. The tumor is located more than 1 cm away from the ampulla, confirming its classification as non-ampullary. It is staged as a duodenal, not ampullary, carcinoma. Compare with Figure 5.

The term "periampullary cancer" has been used highly variably, ranging from those strictly confined to the ampulla of Vater, to all tumors that can be removed by pancreatoduodenectomy, including ordinary PDAC [3, 4, 11, 26, 27]. Accordingly, it is advisable to avoid this term to prevent confusion [28]. However, it is acknowledged that this term is useful during preoperative assessment of a lesion that can be removed by pancreatoduodenectomy, that is at a time when the precise origin of the tumor may not be easy to determine. For surgeons' purposes, as all of these are resected with the same pancreatoduodenectomy operation, this term has some practical pre-operative value. However, if this term is to be used clinically or in a publication, it should be clarified in which meaning it is used. Moreover, the PERIPAN guidelines recommend that the term "periampullary cancer" should be avoided in the postoperative setting. Indeed, in the vast majority of cases, the cancer origin can be identified by pathological examination of the surgical specimen [29]. Although it may occasionally be difficult to make a definite decision on the origin of a large cancer with extensive involvement of the ampulla and duodenum and/or distal CBD. On a resection specimen, pathologists are required to make a final judgment based on the gross-microscopic correlation regarding the (epi)center of the tumor and relevant precursor lesions, should these be present. Along those lines, endoscopists also ought to make every attempt at determining the origin of a tumor as ampullary versus non-ampullary duodenal, CBD, or pancreatic, as both the diagnostic tests used as well as the oncologic treatment protocols employed are significantly different for cancers arising from each of these sites. For example, routine mismatch repair testing is warranted for the former two [4, 30], whereas it is not warranted for the latter two.

3.3 | Histologic Subtypes of Ampullary Carcinoma

- An attempt should be made to classify tubular type adenocarcinoma of the ampulla of Vater as pancreatobiliary or intestinal.
- Histological subtyping of ampullary carcinoma should be based on the invasive component of the tumor rather than the pre-invasive component. If there is no invasive carcinoma, this should be clarified.
- The pancreatobiliary subtype resembles pancreatic ductal adenocarcinoma and is characterized by more widely separated and relatively smaller and simpler glands lined by cuboidal or low columnar cells without nuclear stratification or elongation.
- The intestinal subtype can be defined morphologically by tall columnar cells with nuclear elongation and stratification and large glandular or cribriform architecture. A further clue is dirty intraluminal necrosis.
- For ampullary tubular-type adenocarcinomas that have morphologically distinct areas with unequivocal intestinal and pancreatobiliary components, classification as "mixed subtype" is advisable (the lesser component should comprise at least 30% of the tumor).
- For tubular adenocarcinomas in which a definitive determination cannot be made as to intestinal versus pancreatobiliary (previously called hybrid subtype), the term tubular-NOS subtype is recommended. For such cases, it is advisable to document which lineage is favored overall, or if there are recognizably distinct components, to provide the percentage (and/or size of different components) in a comment. If available, it is also advisable to use immunohistochemical support.
- A number of other rare histologic types of ampullary carcinoma should be recognized and considered separately.

It has long been presumed that ampullary carcinomas displaying the morphology of intestinal-type cancers behave more like colon cancers biologically, and conversely, those that resemble pancreatic/biliary cancers behave like pancreatic cancer, that is, aggressively.

This impression was further substantiated in studies of "periampullary cancers", many of which unfortunately included conventional PDACs. However, studies focusing strictly on

ampullary cancers with careful exclusion of adjacent PDACs and CBD cancers revealed that ampullary cancers not uncommonly exhibit mixed/hybrid features [13, 31]. Moreover, this study showed that the survival advantage of intestinal-type ampullary cancer over pancreatobiliary-type ampullary cancer may not be as striking as presumed. Nevertheless, even in this study, data indicate behavioral differences. With the recommended refined criteria that define ampullary cancer and its subtypes and distinguish it from the neighboring cancers in this consensus manuscript, there will be a better chance to conduct studies based on standardized cohorts to clarify questions about biological and clinical differences.

It has been shown in many studies that about 25%–44% of all ampullary cancers are not classifiable as pancreatobiliary or intestinal due to the "mixed" or "hybrid" nature of the tumor. Mixed subtype refers to tumors containing discernible intestinal and pancreatobiliary components (or others), where the lesser component should comprise at least 30% of the tumor. It is acknowledged that 30% is an arbitrary cut-off that requires reevaluation in future studies. At present, it is preferable to provide estimates of the percentage/proportions of both components in the pathology report.

A substantial number of the tubule-forming adenocarcinomas of the ampulla are unclassifiable as intestinal or pancreatobiliary because they exhibit hybrid features, that is, the neoplastic tubules have non-committal morphology. For these cases, the PERIPAN consensus guidelines recommend the term tubular-NOS subtype (Not Otherwise Specified). Pathologists are encouraged to report in a comment the favored lineage (e.g., "tubular-NOS subtype but with predominantly pancreatobiliary features") whenever possible. It is also advisable to perform immunohistochemistry for the same purpose (see below). The subjectivity in the classification of such cases as well as the possibility of changes in the final diagnosis in an endoscopic biopsy versus a full tumor examination should be acknowledged.

As a versatile region, the ampulla gives rise to a whole host of different carcinoma types that are tubular or non-tubular. In addition to those acknowledged in the WHO classification [32], PERIPAN consensus guidelines provide more refined definitions and recognize additional rare carcinoma types such as medullary [33], micropapillary, gastric-type, rhabdoid, osteoclastic carcinoma (see Supporting Information S2). These should be recognized and considered separately from the more common tubular adenocarcinomas of intestinal, pancreatobiliary, mixed, or NOS subtypes.

Of note, the majority of ampullary cancers of the *ampullary-duodenal* subset (those arising from the duodenal surface of the ampulla; Figure 5) are of the intestinal subtype. In contrast, as expected, most ampullary cancers of the *ampullary-ductal* subset (which endoscopically present as subtle ulcerations or dimple like elevations; Figure 4) prove to be of pancreatobiliary subtype [7]. In other words, from an endoscopic perspective, it is the less impressive and more subtle tumors that prove to be of pancreatobiliary subtype and thus warrant even more careful attention.

3.4 | Immunohistochemical and Molecular Analyses

- Immunohistochemical markers may have some value in confirming the lineage of a tubular carcinoma of the ampulla of Vater (pancreatobiliary vs. intestinal), but subtyping is ultimately based on morphology.
- Compared to the intestinal subtype, the pancreatobiliary subtype is typically more likely to express MUC1 and CK7 and less likely to express CDX2, MUC2, and CK20. Conversely, the intestinal subtype tubular adenocarcinoma is typically more likely to express MUC2, CDX2 and CK20 and less likely to express MUC1 and CK7. None of these markers are entirely specific or sensitive individually or in combination.
- Mismatch repair (MMR) deficiency analysis should become a reflex test when diagnosing ampullary carcinoma, independent of the subtype.
- Some immunohistochemical markers have been advocated as independent prognosticators which requires further analysis.

Immunohistochemical and molecular markers have been shown to correlate with morphological subtypes and may thus aid in diagnosing periampullary cancers [34]. However, as the ampulla lies at the crossroad of three distinct anatomical structures (pancreatic and biliary ducts, duodenum), it is not surprising that considering the relative commonness of mixed and hybrid morphology, ampullary carcinoma may present with a range of immunohistochemical and molecular profiles as well. As mentioned previously, due to lack of standardized definition of what qualifies as ampullary cancer (and common inclusion of other "periampullary cancers" including PDACs and cholangiocarcinomas in the analysis), it has been difficult to glean the immunophenotype of the true ampullary cancers. Nevertheless, combination panels of IHC markers are considered to be of some use in establishing the cell lineage in ampullary carcinoma. While different combinations of IHC markers have been proposed, some using a rather complex weighting formula [35, 36], it should be noted that the application of these markers in daily practice is fraught with challenges. For example, different studies have used different thresholds (1, 5, 10, 20 or 50%) to classify a marker expression level as "positive" [30, 35, 37]. Also, overlap of IHC profiles is common, such that many cases remain unclassifiable even after detailed IHC scrutiny [14, 35]. Equally important, the prognostic relevance of these markers in properly defined true ampullary cancers could not be verified. Therefore, the PERIPAN consensus group determined that more studies are needed to develop specific protocols for this purpose before a specific recommendation can be issued. However, at the same time, it is well established in the literature that expression of CDX2, MUC2 and CK20 is significantly more common in ampullary cancer of the intestinal subtype while MUC1 and CK7 are substantially more common in the pancreatobiliary subtype. A relatively complex formula was proposed by Ang et al. in a well-defined true ampullary cancer

cohort, which classifies cases as intestinal if positive with CDX2 or CK20 or MUC2 and MUC1 negative, or, if positive for all CDX2/MUC2/CK20 even if MUC1 is positive [35]. It classifies cases as pancreatobiliary if MUC1 is positive and both MUC2 and CDX2 are negative. Unfortunately, the prognostic relevance of this profile was not provided in this study, and it could not be verified in the study by Xue, Reid et al. [14] Moreover, even this formula still leaves more than a quarter of the cases as "ambiguous". Nevertheless, in cases with hybrid/uncertain morphology, these formulas can be employed to "favor" one lineage.

Historical studies on prognosis and response to chemotherapy in (peri)ampullary carcinomas suffer from inconsistent pathological diagnosis. However, recent studies consistently show that ampullary carcinomas harbor MMR-deficiency in rates comparable to those of colorectal carcinomas, independent of the subtype [38–40]. Considering MMR-deficiency has been shown in virtually every organ cancer to identify a subset with different behavior and differential vulnerability to targeted therapies, including candidacy for immunotherapy, it is important that testing for MMR, which detects deficiency in close to one in 6 ampullary cancers, is an integral part of patient management. Therefore, reflex testing of MMR - based on immunohistochemistry or PCR - in ampullary cancers is recommended [33].

Various other markers are under investigation for the prognostication of ampullary cancer. Among these is MUC5AC, which has been found to be an independent prognostic factor regardless of the histologic subtype [14]. Further studies are needed to verify the prognostic role of MUC5AC and other markers.

3.5 | Biopsy Acquisition

- Targeted biopsies of viable abnormal or suspicious tissue should be the goal of tissue sampling.

The number of biopsies is secondary to the quality of the sample, but a minimum of three biopsies is recommended to allow optimal pathology assessment.

Tumors of the ampulla are usually easily accessible for direct endoscopic biopsy sampling. However, pathology-based diagnostic accuracy is suboptimal, with the false-negative rate being high (20%–30%), especially for the differential diagnosis between adenoma and adenocarcinoma [41, 42]. As this is mainly due to sampling bias, that is, the area of adenocarcinoma in the context of an adenoma not being represented, acquisition of biopsy material from the accurate site is key and more important than the actual number of biopsies [43, 44]. In case of hard-to-reach, deep-seated lesions that are located intra-ampullary—typically ampullary-ductal carcinoma or IAPN—and may be covered by intact or ulcerated mucosa, EUS-FNB is recommended. EUS-FNA or brushings, which are still commonly used in current diagnostic practice, may be considered in combination with EUS-FNB as an attempt to increase the diagnostic yield in difficult cases. However, as the cytological distinction between reactive atypia and truly neoplastic atypia may be extremely challenging, biopsy material—obtained by direct endoscopy or EUS-FNB—is clearly preferred, also because it allows immunohistochemical and molecular analysis for diagnostic purposes.

3.6 | Essential Information Required for the Pathology Assessment of Biopsy Material

- Essential information includes size and exact site of the lesion, presence/absence of intracanalicular growth, and previous local procedures.
- Provision of relevant information on hereditary predisposition and familial and personal cancer history is highly recommended.
- Information on the endoscopic aspect of the lesion is helpful.
- If it is decided that the patient will not undergo surgery, this should be explicitly stated so that immunohistochemical and/or molecular tests that may be relevant to treatment can be performed.

During the PERIPAN conference, it was discussed which clinical information—regarding patient-related aspects, imaging, endoscopy findings, or patient management decisions—should be consistently provided to the pathologists. The information listed above was considered essential to ensure optimal pathology assessment in terms of diagnostic accuracy and additional analysis that may be relevant to patient management. Moreover, it may reduce the time spent by pathologists, trying to retrieve missing information from the electronic patient record and may avoid unnecessary investigations or analyses, saving time and resources. Particularly important is precise information on the site of the lesion in relation to the duodenum, ampullary channel, CBD, pancreatic duct and pancreas, and the presence or absence of intracanalicular growth. Endoscopists are encouraged to make an attempt to classify an ampullary lesion as ampullary-duodenal (forming visible pathologic changes on the duodenal surface of the ampulla), or whether the lesion is more inside the ampulla. It is recommended that gastroenterologists notate if the lesion shows the features of an IAPN [7], based on the presence of an elevated ampulla covered with relatively preserved ampullary-duodenal mucosa (Figure 4), as this will guide both the evaluation and management of the specimen. Similarly, if a cancer of ampullary-ductal origin (Figure 3) is suspected based on the endoscopic findings of a more subtle ulcerated (dimple-like) lesion characteristic of this type, then this should be mentioned as it will allow the pathologists to obtain deeper sections of the tissue to investigate subtle cancer cell growth. For practical purposes, it is also recommended that it should be stated if biopsies stem from a patient who will not undergo surgery, so

that immunohistochemical and/or molecular tests that may be relevant to treatment can be performed without any delay. This underscores the importance of effective multidisciplinary communication between gastroenterologists, surgeons, pathologists and oncologists in determining whether theranostic tests including immunohistochemistry for histological subtyping as well as MMR are to be performed on the biopsy specimen or can be performed later when the surgical resection specimen is available. The routine use of standardized lists of information items will improve the quality and efficiency of tertiary patient care. Moreover, uniform data collection will also support the adoption of artificial intelligence technology, which depends on uniform data input [45].

3.7 | Essential Information on Biopsies and Ampullectomy Specimens Provided by the Pathology Report

- For biopsy samples and ampullectomy specimens, information on the presence of high-risk features is essential: the presence of noninvasive neoplasia/invasive carcinoma, histological type of carcinoma (including poorly cohesive nature), grade of differentiation, lymphatic/vascular/perineural invasion, and tumor budding.
- Subtyping and biomarker assessment of biopsy material should be done only if it may influence subsequent treatment.
- For ampullectomy specimens, the depth/size of invasion and status of the resection margins (separately for the invasive—if present - and non-invasive component of a lesion) should be reported in addition to the above-mentioned features.
- The use of standardized synoptic reporting is highly recommended.

While reporting on the nature of a lesion, that is, noninvasive neoplasm or invasive carcinoma, and traditional high-risk features such as lymphatic, vascular and perineural invasion are uncontroversial, the inclusion of tumor budding prompted discussion among the experts. Tumor budding has increasingly received attention as a prognostic marker, not only for colorectal cancer where it is now used as a determinant in management algorithms but also for esophageal and gastric carcinoma and PDAC. Recent studies show that tumor budding is also relevant for ampullary cancer, as it is commonly present, and high-budding (defined as $\geq$ 3 budding foci per x200 field) is an independent predictor of overall survival, with a stronger prognostic impact than tumor stage and lymph node metastasis. Hence, to improve prognostication of invasive ampullary carcinoma, especially on biopsy material and ampullectomy specimens in which T- and N-stage cannot be appreciated, reporting on tumor budding is recommended. However, it is acknowledged that in biopsies, the invasive tumor front, where tumor budding ideally should be assessed, may not be represented. In ampullectomy specimens, it is recommended to report the size of the invasive carcinoma as well as the margin status.

An attempt at histologic subtyping of ampullary carcinoma in a biopsy is recommended if the patient may not undergo (primary) surgery and information on the subtype may affect treatment. However, it should be taken into consideration that due to tumor heterogeneity, the subtype identified in the biopsy may not be representative for the entire tumor, especially since about 40% of ampullary carcinomas show a mixed/hybrid phenotype [11]. Therefore, if the patient is to undergo resection, subtyping is preferentially performed on the surgical specimen, along with MMR testing.

4 | Limitations

The Delphi methodology is considered the best option to reach consensus, but limitations of this methodology include the difficulty of capturing all key issues in the literature during questionnaire development, the importance of ongoing willingness of panelists to participate, and the risk of skewed data due to the lack of participation by those who are less confident about the topic [46, 47]. Second, although the aim of the PERIPAN initiative was to provide guidelines for all non-pancreatic cancers in the periampullary region, more recommendations relate to ampullary cancer than to CBD or duodenal cancer. This imbalance could indicate a higher degree of uncertainty and stronger need for guidance regarding ampullary cancer and its different subtypes. For that reason, and considering that the declared aim of the PERIPAN initiative was to improve consistent, standardized and high-quality reporting, the relative predominance of recommendations regarding ampullary cancer was accepted.

5 | Final Comments

Existing literature reveals significant inconsistency in the classification and definition of periampullary cancers, which limits the comparability of research and treatment strategies. Historically, periampullary cancers were grouped as a single entity, but recent stringently defined studies have established that the classification of “periampullary” cancers as PDAC, distal cholangiocarcinoma, duodenal adenocarcinoma, and ampullary adenocarcinoma, based on the anatomical localization, not only reflects different biology (and possibly also different etiopathogenesis), but also has significant implications for diagnosis and management. The lack of consensus definition and standardization of documentation together with high interobserver variability have hindered consistent conclusions across studies, particularly regarding patient management, including the management efficacy of adjuvant chemotherapy, all of which remain highly controversial due to these inconsistencies. Standardizing these definitions will improve study comparability and enable more targeted treatment strategies.

The PERIPAN guidelines are the first international consensus guidelines on the standardization of the definition of what qualifies as ampullary cancer, the distinction of the latter from other “periampullary” cancers, as well as the multidisciplinary diagnostic workflow and pathology diagnosis. The major strength of the PERIPAN initiative is that the guidelines address

a topic that currently lacks substantial evidence. For a considerable part of the consensus questions, there are fairly limited data published in the literature, such that most of the recommendations are supported only by a low level of evidence. This highlights the early stage at which our knowledge of periampullary cancer stands. However, ever-improving endoscopic imaging and surgical techniques have brought ampullary cancers to the forefront. While this will bring new perspectives, it also necessitates a more nuanced approach to the tumors of this small but complex region. The lack of international consensus on key aspects related to the pathology diagnosis of periampullary cancers explains why data from various studies and centers are currently difficult to compare, which is an obstacle to any research to improve patient care. This reflects the very motivation for the PERIPAN guidelines. In a field where decisions are predominantly driven by expert opinion, having all the experts come together to create consensus-based recommendations is crucial. This consensus-driven approach based on rigorous methodology provides the highest level of evidence available at present and serves as a foundation for future research.

The process involved 43 experts from 12 countries who represented all relevant disciplines, that is, pathology, surgery, radiology, gastroenterology and oncology. This multidisciplinary international approach ensures the development of comprehensive guidelines that are tailored to the current multidisciplinary organization of tertiary health care, yet accounts for geographical differences in logistics and resources in order to allow for global applicability. It also results in the use of a common language and the development of common understanding, which facilitates a more robust implementation of the guidelines as an integral part of the patient pathway. As such, these guidelines can serve as a model for a multidisciplinary approach to guideline development for other diseases and clinical teams.

By embracing the PERIPAN guidelines on a global scale, consistency in terms of primary diagnosis of the cancer entity, tumor subtyping, staging, and multidisciplinary workflow can be improved. This will enhance the quality of both clinical care and future research in this complex medical field.

Author Contributions

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that supports the findings of this study are available in the supplementary material of this article.

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