Critical issues in pathologic evaluation of pancreatic ductal adenocarcinoma resected after neoadjuvant treatment: a narrative review

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Background and Objective: Preoperative neoadjuvant therapy (NAT) is increasingly used in the treatment of patients with potentially resectable pancreatic ductal adenocarcinoma (PDAC). Because NAT often induces heterogeneous tumor response and extensive fibrosis both in tumor and adjacent pancreatic tissue, pathologic assessment of posttherapy pancreatectomy specimens is challenging. A limited number of studies examined the optimal grossing and sampling methods, tumor response grading (TRG), and the prognostic value of posttherapy tumor (ypT) and lymph node (ypN) stages of treated PDAC patients. In this review, we will provide an overview of the current status and critical issues in pathologic evaluation of PDAC resected after NAT.

Methods: In PubMed, Google Scholar and Web of Science, we reviewed existing English literature (published up to December 2021) highlighting the most recent ones using electronic databases and authors' experience to outline the challenging aspects and new perspectives on pathologic assessment of the treated PDAC.

Key Content and Findings: The recent recommendations from the Pancreatobiliary Pathology Society (PBPS) provide the much-needed guidelines for systematic and standardized pathologic evaluation and reporting of treated PDAC for optimal patient care. For treated PDAC, tumor size measured by gross and radiology is not reliable. Histologic validation of tumor size on consecutive mapping sections is recommended for accurate ypT stage. A tumor size of 1.0 cm seems to be a better cutoff for ypT2 for treated PDACs. The published data suggested that the MD Anderson Cancer Center (MDA) TRG system is easy to use, has a better interobserver agreement and better correlation with patient prognosis compared to the College of American Pathologists (CAP) and Evans grading systems and may be used as an alternative TRG system for the CAP cancer protocol.

Conclusions: Systemic and standardized grossing and sampling are essential for accurate pathologic evaluation and reporting for optimal care of PDAC patients who received NAT. Future studies on optimal sampling and integration of histopathology with artificial intelligence (AI), molecular and immunohistochemical markers are needed for better and personalized care of treated PDAC patients.

Keywords: Pancreatic ductal adenocarcinoma (PDAC); neoadjuvant therapy (NAT); pathologic staging; tumor response grade; survival

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Introduction

Pancreatic cancer is a highly aggressive and lethal malignancy with a 5-year survival rate of 10.8% (1,2). The annual incidence of pancreatic cancer has increased worldwide with 495,773 new cases in 2020 (3). Pancreatic cancer is projected to be the second most common cause of cancer-related death in the United States by 2030 (4). Despite recent progresses made in surgical and medical oncology fields including immunotherapy and targeted therapies, there is no significant improvement in patient prognosis for pancreatic cancer in the last four decades (5). Surgical resection provides the only potential cure for patients with pancreatic ductal adenocarcinoma (PDAC). However, only 15–20% of PDAC patients are qualified for surgery with curative intent at the time of diagnosis due to the lack of specific symptoms at the early stage of disease and the lack of effective methods for early diagnosis (6).

The multidisciplinary neoadjuvant therapy (NAT) approach is more commonly used to treat PDAC patients with potentially resectable disease. According to the current National Comprehensive Cancer Network (NCCN) guideline, NAT is currently the standard of care for PDAC patients with borderline resectable and high-risk resectable disease, and selected patients with locally advanced disease (7). NAT improves both disease-free and overall survival in PDAC patients with resectable and borderline resectable disease (8-11). Because NAT often induces a heterogenous response in different tumor areas and extensive fibrosis in the tumor and in the adjacent pancreatic and peripancreatic tissue, pathologic evaluation of posttherapy pancreatectomy specimens is challenging (12). Accurate pathology assessments, such as pathologic staging, tumor response grading (TRG), status of resection margins, tumor invasion of superior mesenteric vein/portal vein (SMV/PV) and/or other organs are important in selecting postoperative adjuvant treatment and in predicting the prognosis of PDAC patients (13-19). However, systemic and standardized grossing protocol and pathologic examination of treated PDAC are lacking. In this review, we will provide an overview of the current status and critical issues in pathologic evaluation of PDAC resected after NAT. The recent recommendations from the Pancreatobiliary Pathology Society (PBPS) on the optimal grossing and sampling methods, tumor size measurement, TRG systems, and evaluation of lymph node metastasis are discussed. We present the following article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-21-175/rc).

Methods

A comprehensive literature search of electronic databases was performed on the 5th of December 2021 and updated in March of 2022, including PubMed, Google Scholar, and Web of Science without restrictions regarding time of publication or study design. Only articles in English language were selected. The search keywords used in the title/abstract were ('pancreas' OR 'pancreatic') AND ('cancer' OR 'carcinoma') AND ('neoadjuvant'). The retrieved list of references was reviewed for relevance to this review article. The specific search strategy for this narrative review is summarized in *Table 1*.

Discussion

Measurement of tumor size and sampling of pancreatectomy specimens of treated PDAC

Posttherapy tumor (ypT) stage for ypT1-ypT3 PDAC is entirely based on tumor size in the American Joint Committee on Cancer (AJCC) staging system (8th edition): ypT1 tumor ≤2 cm (ypT1a ≤0.5 cm, ypT1b >0.5 cm and <1 cm, and ypT1c ≥1 cm and ≤2 cm), ypT2 tumor >2 cm and ≤4 cm, and ypT3 tumor >4 cm (20). Accurate tumor size measurement for treated PDAC is, however, extremely difficult. Identification of tumor and tumor borders, and measurement of tumor size of treated PDAC by gross examination is often inaccurate due to the highly invasive nature of PDAC, which commonly invades beyond the grossly identified tumor area into adjacent pancreas, peripancreatic tissue, duodenum, or other organs. This difficulty is also due to the heterogenous response in different regions of the tumor, and severe fibrosis in both tumor and adjacent pancreatic/peripancreatic tissue secondary to NAT. This is particularly true for PDAC patients who showed marked responses to NAT, in which the residual tumor may not be identifiable on gross examination, but microscopic foci of residual carcinoma are typically present on histologic examination. Therefore, the tumor size should be validated and measured by histologic examination rather than gross measurement alone based on the current College of American Pathologists (CAP) cancer protocol and International Collaboration on Cancer Reporting (ICCR) guidelines (21,22). To accurately measure the tumor size histologically, the PBPS recently

Table 1 The literature search strategy

Items	Specifications
Date of search	5th December 2021
Databases and other sources searched	PubMed, Google Scholar, Web of Science
Search terms used	('pancreas' OR 'pancreatic') AND ('cancer' OR 'carcinoma') AND ('neoadjuvant')
Timeframe	Up to December 2021
Inclusion and exclusion criteria	English literature included only
Selection process	MT and HW searched the list of references and reviewed them to select the relevant articles for this narrative review
Any additional considerations	Not applicable

recommended that consecutive mapping sections across the largest dimension of the treated tumor bed or whole mount sections of the tumor with pancreas should be submitted (23). Microscopically, the final tumor size should be measured as the largest dimension of the tumor bed that is bound by viable tumor cells, including intervening non-neoplastic pancreatic tissue and stroma, on the reassembled consecutive sections or whole mount sections (23). This method is also being used for measuring the tumor size in breast cancer specimens after NAT (24).

Currently, there are significant variations among different institutions in grossing and sampling of pancreatectomy specimens resected for PDAC after NAT (25). Standardized grossing protocol and adequate sampling are essential for accurate pathologic evaluation and systemic reporting for these complex specimens (26,27). However, the optimal sampling method for treated PDAC specimens remains to be determined. Recently the PBPS recommended the submission of entire tumor for small tumors of 2.0 cm or less and generous sampling of larger tumors of >2.0 cm (at least 2 sections per cm of the tumor should be sampled) for histologic examination (23). The PBPS also recommended that the entire pancreas, peripancreatic tissues, bile duct, ampulla of Vater, accessory ampulla if present, along with the duodenum neighboring the pancreas must be examined histologically before a case can be classified as a complete pathologic tumor response (23). A similar liberal sampling approach should also be considered for the cases, in which only minimal tumor is identified in the initial representative sections. Additional sampling may reveal a significant amount of residual carcinoma in these cases, which is not identified during the initial gross examination due to the presence of therapy-induced fibrosis and the heterogeneous response to therapy within the tumor.

In addition to the mapping sections, other sections in a post-therapy pancreaticoduodenectomy specimen are the same as those treatment-naïve PDAC cases and include all lymph nodes, common bile duct margin (entirely submitted), pancreatic neck margin (entirely submitted), uncinate margin (preferably perpendicular sections, entirely submitted), proximal gastric or duodenal margin (1 section), distal small bowel margin (1 section), vascular groove (at least 1 section closest to the tumor), posterior free surfaces (at least 1 section from the closest tumor), anterior free surfaces (at least 1 section from the closest tumor), tumor in relation to common bile duct, ampulla of Vater, duodenum and other organs if present, and uninvolved pancreas (minimum 1 section). For cases with SMV/PV resection, the vein margins and the remaining portion of the resected vein should be submitted to evaluate vein margins, tumor involvement of the SMV/PV and the depth of tumor invasion into the vein (17,26). For distal pancreatectomies: pancreatic resection margin (entirely submitted), anterior surfaces with closest tumor (at least one section from the closest tumor), posterior surfaces with closest tumor (at least one section from the closest tumor), uninvolved pancreas proximal to the tumor, uninvolved pancreas distal to the tumor, tumor to adjacent organs (if present, spleen, kidney, stomach, respectively). A minimum of 12 lymph nodes is required for accurate ypN stage according to the current AJCC/Union for International Cancer Control (UICC) Staging Manual and CAP protocol (12,28).

Correlation of post-therapy tumor size measured by radiology and by pathology

After the completion of NAT, PDAC patients routinely undergo CT scans using pancreatic protocol to evaluate

tumor response, clinical stage and resectability of the tumor (29-32). We previously showed that the post-therapy changes of the tumor/pancreatic parenchyma interface compared to the pre-therapy CT scans predicts tumor response to therapy (32), and that reduction of tumor volume measured by CT scans can independently predict major pathologic response (30). Recently, we showed that post-therapy tumor size measured by radiology correlated positively with pathologic tumor size and TRG in 343 PDAC patients who completed NAT before pancreaticoduodenectomy (33). However, our study did not find any correlation between tumor size measured by post-therapy CT-scan and that reported by pathology in 27 patients who had a tumor that was 1.0 cm or less. Among the eight PDAC patients with complete pathologic response, only two showed no detectable tumor by radiology. The other six patients (75%) showed a tumor size ranging from 0.6 to 2.5 cm by post-therapy CT scan. On the other hand, among 25 patients with no detectable tumor by radiology after NAT, only 2 (8%) patients showed complete pathologic response. Tumor size measurement based on posttherapy CT scans understaged treated PDAC in 92% (23/25) patients. Therefore, no radiologically identifiable tumor by post-therapy CT scan is not reliably an indicator of complete pathologic response for PDAC patients who received NAT. For patients whose post-therapy tumor is 1.0 cm or less, tumor size measured by radiology is not a reliable predictor for pathologic tumor size (34).

Histologic grading of tumor response for treated PDAC

Histologic TRG in post-therapy resection specimens for PDAC is an important indicator of tumor sensitivity or resistance to the neoadjuvant regimens, which could be used to guide the selection of adjuvant treatment after surgical resection (35). Recent studies showed that the TRG is a predictor of survival in PDAC patients who received NAT and pancreatectomy (26,27,36-39). Multiple grading systems have been in use or proposed for pathologic evaluation of tumor response of PDAC to NAT. The most widely used systems are the CAP grading system (28), Evans grading system (40), and the MD Anderson Cancer Center (MDA) grading system (41). The more recently proposed grading schemes include the Japanese Pancreas Society (JPS) (42), Royal North Shore (RNS) (38), and the Area of Residual Tumor (ART) (43). The criteria for these grading systems are listed in *Table 2*. Although currently there is no international consensus on which is the best TRG system that is clinically relevant and practical, emerging data suggested that the CAP and MDA TRG systems are the most widely accepted grading systems. The CAP system for PDAC, based on a modified Ryan scheme (46), was initially proposed to assess pathologic response in neoadjuvant-treated rectal carcinomas. As part of the CAP cancer protocol for exocrine carcinoma of the pancreas, the CAP grading system is widely used in the United States and North America.

Several studies have investigated and compared the prognostic significance of the CAP, Evans, and MDA TRG systems in PDAC patients receiving NAT (36-39). The results from these studies consistently showed no significant differences in either disease-free survival or overall survival between the patients with CAP grades 2 and those with grade 3, or among Evans grades I, IIa, and IIb. In comparison, the 3-tier MDA TRG system showed significant correlations with both disease-free and overall survival as well as significant correlations with the pathologic tumor and nodal stages, status of resection margins, and post-operative recurrence (26,41,47).

Other important criteria for an optimal TRG system are the good interobserver agreement among the pathologists and the ease of application in daily practice. Kalimuthu *et al.* (48) investigated the interobserver agreement on MDA, CAP, and Evans grading systems among four gastrointestinal pathologists. The highest concordance was observed using MDA grading system (78.6%, 11/14 cases), followed by CAP grading system (14.3%, 2/14 cases), and Evans grading system (7.1%, 1/14 cases). They concluded that the MDA system not only has more consistency and reproducibility but also is simple for daily practice. Similar findings on the interobserver agreement were also reported by Matsuda *et al.* and Chou *et al.* between two pathologists who reviewed two large cohorts of treated PDAC in their studies. In the study by Matsuda *et al.*, the concordant rates between two pathologists were 96% for the MDA TRG, 72% for the CAP TRG, and 59% for Evans TRG. The interobserver concordance (κ value) were 0.65, 0.5, and 0.34 for the MDA, CAP, and Evans TRG systems, respectively (43). The interobserver concordance between two pathologists was also the highest for MDA system (κ =0.691) in Chou's study (38) compared to the CAP system (κ =0.431) and Evans system (κ =0.307). These studies showed that the MDA TRG system is more reproducible than the CAP or Evans TRG systems. The published interobserver concordant rates using the CAP

Table 2 TRG systems for treated PDAC

Grading systems	Criteria/definition
Major systems	
Evans *et al.* (40)	
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	<10% viable-appearing tumor cells
Grade IV	No viable tumor cells
The CAP (28)	
Grade 0	No viable residual tumor
Grade 1	Single cells or small groups of cancer cells
Grade 2	Residual cancer with evident tumor regression, but more than single cells or rare groups of cancer cells
Grade 3	Extensive residual cancer with no evident tumor regression
The MDA (41)	
Grade 0	No residual tumor
Grade 1	Minimal (<5% residual tumor in treated tumor bed)
Grade 2	≥5% tumor in treated tumor bed
Others	
Ishikawa *et al.* (44)	
Grade 1	One-third or less severely degenerated cancer cells
Grade 2	One-third to two-thirds severely degenerated cancer cells
Grade 3	More than two-thirds severely degenerated cancer cells
White *et al.* (45)	
Large	>90% viable tumor cells
Moderate	10–90% viable tumor cells
Small	<10% residual, scattered foci, or no residual tumor cells
The JPS (42)	
Grade 1a	Estimated residual rate ≥90%
Grade 1b	Estimated residual rate ≥50% and <90%
Grade 2	Estimated residual rate ≥10% and <50%
Grade 3	Estimated residual rate <10%
Grade 4	No viable tumor cells
ART (43)	
Grade 0	No remaining viable tumor cells
Grade 1	Spanning ≤1 4× the objective lens field
Grade 2	Spanning >1 and ≤2 4× the objective lens fields
Grade 3	Spanning >2 and ≤3 4× the objective lens fields
Grade 4	Spanning >3 4× the objective lens fields
RNS (38)	
Grade 1	≤10% of tumor bed area occupied by viable tumor
Grade 2	11–75% of tumor bed area occupied by viable tumor
Grade 3	>75% of tumor bed area occupied by viable tumor

TRG, tumor response grading; PDAC, pancreatic ductal adenocarcinoma; CAP, College of American Pathologists; MDA, MD Anderson Cancer Center; JPS, Japanese Pancreas Society; ART, Area of Residual Tumor; RNS, Royal North Shore.

Table 3 Interobserver concordance for the CAP and MDA grading systems

Author, year	Number of cases	Number of pathologists	Number (percentage) of consensus cases
Kalimuthu *et al.*, 2017	14	4	CAP: 2 (14.3%)
			MDA: 11 (78.6%)
Insilla *et al.*, 2020	29	2	CAP: 21 (72.4%)
			MDA: 26 (89.7%)
Matsuda *et al.*, 2020	97	2	CAP: 70 (72.2%)
			MDA: 93 (95.9%)
Chou *et al.*, 2021	147	2	CAP: 97 (66.0%)
			MDA: 135 (91.8%)
Kameyama *et al.*, 2021	30	8	CAP: 4 (13.3%)
			MDA: 25 (83.3%)

CAP, College of American Pathologists; MDA, MD Anderson Cancer Center.

and MDA systems are shown in *Table 3*. Similar to these reports, a recent large study on interobserver agreement from the International Study Group of Pancreatic Pathologists (ISGPP), in which tumor response of 50 treated PDAC cases was graded by reviewing digitalized hematoxylin and eosin (H&E) slides by 18 international gastrointestinal/pancreatic pathologists using the CAP and MDA systems, also showed that the MDA TRG has much better interobserver agreement than that for the CAP system (personal communication). These studies clearly demonstrated that the MDA system is easy to apply in daily practice and has better interobserver agreement among pathologists compared to the CAP and Evans systems. The PBPS recently recommended that the 3-tier MDA grading system may be adopted as an alternative grading system for treated PDAC in the CAP cancer protocol (23).

Both the CAP and the MDA grading systems have strengths and weakness. The major strengths of CAP grading system include: (I) it is a 4-tier system, which provides more stratifications of tumor responses to NAT. (II) As part of the CAP cancer protocol, the CAP grading system is widely used for treated PDAC in the US and North America. The major weaknesses for CAP grading systems include: (I) it uses subjective and descriptive terms, including "single cells or rare small groups of cancer cells" for grade 1, "residual cancer with evident tumor regression, but more than single cells or rare groups of cancer cells" for grade 2, or "extensive residual cancer with no evident tumor regression" for grade 3. When applying these subjective grading criteria in daily practice, subjective interpretation may vary significantly among the practicing pathologists, which have been demonstrated by the poor interobserver agreements in multiple studies as shown in *Table 3*. (II) The published data failed to show prognostic difference for patients with CAP grade 2 compared to those with CAP grade 3 (38,41,43,47). In comparison, the MDA grading system uses quantitative criteria: "No residual carcinoma", "<5% residual tumor in treated tumor bed" and "≥5% residual tumor in treated tumor bed" for grade 0, 1 and 2 tumor response, respectively. The use of objective and quantitative criteria makes the MDA grading system easy to apply, reduces the variations of interpretation by different pathologists, and leads to significantly better interobserver agreements compared to the CAP grading system in multiple studies (*Table 3*). More importantly, the MD Anderson grading system has been shown to correlate with patient survival and other clinicopathologic parameters (41,47). The weakness of the MDA grading system is that it is a 3-tier grading system and classifies >80% of treated PDAC patients as grade 2 based on the published data (38,41,47). Another potential argument against MDA grading system is that some studies have not shown a good separation of survival between the MDA grade 0 and grade 1, which could be due to: (I) some cases in these studies were classified as MDA grade 0 based on representative sampling, not complete submission of the entire pancreas and adjacent tissue (38). Without complete sampling of entire pancreas and adjacent tissue, microscopic residual tumor can be easily missed in these cases. (II) Patients with MDA grade 0 are rare and, therefore, the number of patients with MDA

grade 0 is small in the published studies, which reduce the statistical power when compared to MDA grade 1.

Critical issues regarding the pathologic staging for post-therapy PDAC patients

The AJCC staging system for PDAC (8th edition) is mainly based on the clinicopathologic and survival data from treatment-naïve PDAC patients (20). Few studies examined the prognostic significance of ypT and ypN stages of treated PDAC patients (16,18,37). A recent study of 398 PDAC patients treated with NAT and pancreaticoduodenectomy by Chatterjee *et al.* (37) showed that the ypT and ypN stages using the AJCC 8th edition performed better in predicting both disease-free and overall survival compared to the AJCC 7th edition. More importantly, their study suggested for the first time that a tumor size of 1.0 cm is a better cut-off for ypT2 for treated PDAC since patients with ypT1c had similar disease-free and overall survival to those with ypT2, but significantly shorter survival compared to those with ypT1a and ypT1b disease (27,37). Future studies are warranted to validate this newly proposed cut-off size of 1.0 cm for ypT2 for treated PDAC (49).

Lymph node metastasis (pN stage), the number of lymph nodes examined, and the ratio of number of positive verse total number of lymph nodes are important prognosticators in both treatment-naïve PDAC patients and those who received NAT (16,50-52). Similar to the primary PDAC, variable degrees of response to NAT may also present in the metastatic carcinoma in lymph node(s). Although studies on clinical significance of tumor response of lymph node metastasis or micrometastasis in lymph node(s) for PDAC patients who received NAT are lacking, the PBPS recommended that the presence of any viable tumor cells in a lymph node should be regarded as positive as a positive lymph node, and that isolated tumor cell category should be avoided for treated PDAC cases (23). It is important to cut deeper sections of the suspected lymph node(s) with or without immunohistochemical stain for pan-cytokeratin to document the presence of rare tumor cells when a lymph node shows features of treatment response, including fibroinflammatory response and/or mucin but not viable tumor cells, particularly when other lymph nodes from the case are negative.

Future prospective in the pathology of treated PDAC

Pathologic examination of treated PDAC specimens is challenging. The recent recommendations from the PBPS provide the much-needed guidelines for systematic and standardized pathologic evaluation and reporting for optimal patient care. Future studies are needed to address the following questions: (I) which is a better method for sectioning the pancreas: the bivalving versus the axial sectioning method, and what is the optimal sampling method for pancreatectomy specimens for treated PDAC? Since very limited data on these topics are available in the literature, future prospective and/or retrospective international/multi-institutional studies on these topics will facilitate the development of better systemic and standardized protocols for gross examination and sampling of treated PDAC. (II) The current TRG systems for treated PDAC do not incorporate the response of metastatic tumor in lymph node(s). How to integrate the response of metastatic tumor in lymph node(s) with response of the primary tumor to develop a new and better TRG system is a challenging but interesting topic for future studies. (III) A recent study showed that the artificial intelligence (AI)-based assessment of residual cancer is feasible and could be developed into a promising tool to evaluate the response of PDAC to treatment (53). Integration of histopathologic parameters with AI-based approaches and molecular and/or immunohistochemical markers may provide better predictive and prognostic markers for PDAC patients who have received NAT.

Summary

In conclusion, systemic and standardized grossing and sampling are essential for accurate pathologic evaluation and reporting for optimal care of PDAC patients who received NAT. The tumor size measurement by gross and radiology is often inaccurate for treated PDAC; histologic validation of tumor size on consecutive mapping or whole mount sections should be performed for a more accurate ypT stage. A tumor size of 1.0 cm seems to be a better cutoff for ypT2 for treated PDACs. The currently available data suggest that the MDA TRG system is easy to use and has a better interobserver agreement and better correlation with patient prognosis compared to the CAP and Evans grading systems. Future studies on optimal sampling and integration of histopathology with AI, molecular and immunohistochemical markers may be needed for better and personalized care of treated PDAC patients.

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