Pathology of Treated Pancreatic Ductal Adenocarcinoma and Its Clinical Implications

Teddy Sutardji Nagaria, MD, PhD; Hua Wang, MD, PhD; Deyali Chatterjee, MD; Huamin Wang, MD, PhD

• Context.—Preoperative neoadjuvant therapy has been increasingly used to treat patients with potentially resectable pancreatic ductal adenocarcinoma (PDAC). Neoadjuvant therapy often induces extensive fibrosis in tumor, adjacent pancreatic parenchyma, and peripancreatic tissue. Histopathologic evaluations and histologic tumor response grading (HTRG) of posttherapy pancreatectomy specimens are very difficult and challenging. Studies on prognostic significance of posttherapy pathologic staging, optimal system for HTRG, and other pathologic parameters in treated PDAC patients are limited.

Objective.—This review is to provide a timely update of the prognostic values of posttherapy pathologic staging, HTRG, and other pathologic parameters in PDAC patients who received neoadjuvant therapy and pancreatectomy resection.

Data Sources.—Systemic review of major studies on pathologic evaluation and its clinicopathologic implications in treated PDAC patients.

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies, with a 5-year survival rate of 8.5%.² The prognosis and survival for patients with PDAC have not changed significantly in the past 4 decades despite significant advances in surgical oncology and developments in new oncologic therapeutic strategies, such as targeted therapy and immunotherapy.²,³

Preoperative neoadjuvant therapy has been increasingly used to treat patients with potentially resectable PDAC. Neoadjuvant therapy has been shown to improve resectability in patients with borderline resectable PDAC and to provide a survival benefit in patients with locally advanced disease.⁴ At MD Anderson (MDA) Cancer Center (Houston, Texas), a multidisciplinary neoadjuvant approach is routinely used to treat all patients who have potentially resectable PDAC, except those who have contraindications to or refuse neoadjuvant therapy. The potential advantages of the neoadjuvant therapy approach for patients with PDAC are listed in Table 1. The neoadjuvant therapy approach provides a window of 3 to 6 months to observe the tumor behavior/biology while the patients are being treated with chemotherapy or chemoradiation therapy. The tumor responses to neoadjuvant therapy are clinically evaluated by comparing the pretherapy and posttherapy computerized tomography scans or magnetic resonance imaging. Only patients who have no evidence of disease progression or metastasis and no contraindications to major surgery are selected to receive pancreatic resection with curative intent. Therefore, the selected patients may benefit the most from pancreatectomy.

Systemic pathologic examination and reporting of posttherapy pancreatectomy specimens are important not only for postoperative care, but also for the prognosis of PDAC patients.⁴,⁵,⁶ Because neoadjuvant therapy often induces extensive fibrosis in the adjacent pancreatic parenchyma and peripancreatic soft tissue, histopathologic evaluations of posttherapy pancreatectomy specimens, such as pathologic stage based on the current American Joint Committee on Cancer (AJCC) staging manual, histologic tumor response grading (HTRG), tumor involvement of superior mesenteric artery, and other pathologic parameters in treated PDAC patients are limited.

Conclusions.—Systemic pathologic examination, histologic tumor regression grading, pathologic evaluation of the margins, tumor involvement of superior mesenteric vein/portal vein, accurate pathologic staging, and reporting of posttherapy pancreatectomy specimens provide highly valuable prognostic information for postoperative patient care. Our findings suggest for the first time that tumor size of 1.0 cm, instead of 2.0 cm, is a better cutoff for ypT2 in PDAC patients. The newly proposed 3-tier MDA HTRG system not only has proved to be an independent prognostic marker for PDAC patients who received neoadjuvant therapy and pancreatectomy, but also improves interobserver agreement among pathologists in evaluation of tumor response. This grading system should be considered in future editions of the College of American Pathologists protocol for PDAC.

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vein/portal vein (SMV/PV), status of resection margins, etc, are often very difficult and challenging. In this review, we will focus on the prognostic values of these histopathologic parameters and the challenges in pathologic evaluations of posttherapy pancreatectomy specimens.

**PROGNOSTIC SIGNIFICANCE OF THE POSTTHERAPY PATHOLOGIC STAGE IN PDAC PATIENTS**

The current AJCC staging system for PDAC (8th edition) uses only tumor size in maximum dimension for pT1 to pT3: pT1, tumor 2 cm or less (subdivided into pT1a ≤0.5 cm, pT1b >0.5 cm and <1 cm, and pT1c ≥1 cm and ≤2 cm); pT2, tumor greater than 2 cm and 4 cm or less; and pT3, tumor greater than 4 cm. The pT4 definition remains the same as that in the 7th edition and is defined as tumor involving the celiac axis, superior mesenteric artery (SMA), and/or common hepatic artery, irrespective of tumor size. The current AJCC staging system also subclassifies N stage into N0 (no lymph nodes [LNs] involved), N1 (1–3 positive LNs) and N2 (≥4 positive LNs). However, both the current and previous AJCC staging systems are based on clinical and survival data from PDAC patients who did not receive neoadjuvant therapy. Few studies have examined the prognostic significance of posttherapy pT and pN stages of PDAC. Using a large cohort of 240 PDAC patients who received neoadjuvant therapy and pancreatectoduodenectomy, Estrella et al showed that posttherapy T stage based on the 7th AJCC staging system was an important prognostic factor in their patient population. In addition, they subclassified LN-positive patients into 2 groups: one with 1 to 3 positive LNs, and the other with 4 or more positive LNs. They found that the group with 1 to 3 positive LNs had better disease-free and overall survival than those with 4 or more positive LNs by univariate and multivariate analyses.

Their findings have been incorporated into the pN classification for PDAC in the 8th AJCC Cancer Staging Manual. Recently Chatterjee et al showed that the 8th AJCC ypT and ypN stages are independent factors for both disease-free and overall survival in a large cohort of 398 PDAC patients who received neoadjuvant therapy and pancreatectoduodenectomy. Similar to findings, patient populations who did not receive neoadjuvant therapy, Chatterjee et al reported that the 8th AJCC ypT stage performed better in predicting patient survival than the 7th AJCC ypT stage. More importantly, Chatterjee et al showed that patients with ypT1c had shorter survival than those with ypT1a and ypT1b, but similar survival to those with ypT2. Their findings suggest for the first time that tumor size of 1.0 cm, instead of 2.0 cm, is a better cutoff for ypT2 in PDAC patients. More studies are needed to confirm their findings.

It is important to note that accurate tumor size measurement (ypT stage) in posttherapy pancreatectomy specimens is extremely difficult and may be impossible in some cases. Neoadjuvant therapy induces extensive fibrosis in both tumor and adjacent pancreatic tissue, which often makes the gross identification of tumor border and gross measurement of tumor size inaccurate, especially for those patients who had good responses to neoadjuvant therapy. In addition, residual viable PDAC cells often invade into the adjacent pancreatic/peripancreatic tissue beyond the treated tumor area/tumor bed identified grossly. Thus, the gross measurement of tumor size may be either larger or smaller than the actual tumor size. The current College of American Pathologists (CAP) protocol recommends that gross measurement of tumor size be validated by microscopic examination for PDAC. In order to validate the tumor size by histology, systemic tumor mapping across the largest possible tumor/tumor bed area and generous sampling of the possible tumor area are highly recommended. When no tumor is grossly identified in a pancreatectomy specimen, systemic submission of the entire pancreas with peripancreatic soft tissue, bile duct, ampulla of Vater, and peripancreatic duodenal wall is ideal to rule out any microscopic residual carcinoma. In cases that have major pathologic responses, the tumor bed is often overrun by fibrosis with only scattered microscopic foci of residual viable tumor cells, defined as tumor cells that have intact cytoplasmic membrane, cytoplasm, and intact nuclei based on histologic examination on hematoxylin-eosin–stained slides. For these cases, some investigators proposed to measure the maximal linear dimension of each tumor focus and then calculate the sum of the maximal linear dimension as the final tumor size. However, there are no reported criteria or minimal distance to define separate microscopic tumor foci in the same treated tumor bed. Based on the study by Chatterjee et al, a practical approach for the tumor size in these cases is to measure the largest dimension of the entire area of treated tumor bed that is bound by viable tumor cells (Figure 1, A through C). This approach was adopted from the recommendations of an international working group for the standardized pathologic evaluation of postneoadjuvant breast cancer, and is in line with the recommendation from the current CAP cancer protocol for pancreatic exocrine tumor.

The current AJCC N stage is a robust prognostic factor for survival in both treated and treatment-naive PDAC patient populations. The number of examined LNs and the ratio of number of positive to number of examined LNs have also shown to be prognostic factors in PDAC patients in previous studies. The importance of examining adequate number of LNs from pancreatectomy specimens for accurate N stage cannot be overemphasized. For accurate N stage, a minimum of 12 LNs from pancreatectomy specimens should be examined according to the 8th AJCC Cancer Staging Manual and CAP protocol, whereas the International Study Group on Pancreatic Surgery recommends that a minimum of 15 be examined. Because neoadjuvant therapy often shrinks peripancreatic LNs, dissecting an adequate number of LNs in posttherapy pancreatectomy specimens may be difficult. Careful examination and complete submission of the peripancreatic fat and retroperitoneal soft tissue should be performed to maximize the number of LNs in pancreatectomy specimens. Some institutions use the orange-peeling method to increase the yield of LN harvest in pancreatectoduodenectomy specimens.

| Table 1. Potential Benefits of Neoadjuvant Therapy for Pancreatic Cancer |
|-------------------------------------------------|
| Selection for patients who would benefit the most from surgery |
| Better tolerance by patients compared with postoperative adjuvant therapy |
| Increased resectability of borderline resectable tumors |
| Providing early treatment of micrometastasis |
| Potential reduction in tumor volume, and increased likelihood of resectability/complete resection |

Pathology and Prognostic Factors of Treated PDAC—Nagaria et al

Arch Pathol Lab Med—Vol 144, July 2020

839
HISTOLOGIC TUMOR RESPONSE GRADING OF PDAC TO NEOADJUVANT THERAPY

Pancreatic ductal adenocarcinoma is characterized by extensive desmoplastic stroma and often infiltrates into adjacent pancreatic tissue beyond the grossly identifiable tumor area. Among patients with untreated PDAC, there is significant variation in the percentage of PDAC tumor cells and the ratio of tumor cells to stroma. In addition, neoadjuvant therapy−induced fibrosis in the tumor and adjacent pancreatic tissue obscures the boundary of treated tumor bed. Therefore, histopathologic evaluation of tumor response to neoadjuvant therapy (ie, HTRG) for treated PDAC is often subjective and very difficult. There are several major grading systems of tumor regression/response for PDAC in posttreatment pancreatectomy specimens (Table 2) 23–27. The current CAP HTRG system for PDAC is adopted from a modified Ryan scheme, which was originally proposed for treated rectal cancer. The same grading scheme and criteria are also used for reporting tumor response/regression of all carcinomas of the gastrointestinal tract, including carcinoma of the esophagus, esophagogastric junction, stomach, rectum, and anus. The clinical significance of this grading system has not been validated in PDAC patients who received preoperative neoadjuvant therapy. Recently Chatterjee et al 28 examined the clinical and prognostic significance of HTRG in 223 PDAC patients who received neoadjuvant therapy and pancreatectoduodenectomy using both the Evans and CAP grading systems. They found that patients with complete pathologic response (CAP grade 0 or Evans grade IV) or minimal residual tumor (CAP grade I or Evans grade III) had better disease-free and overall survivals than those with CAP grades 2 and 3 or Evans grades IIa, IIb, and I. However, there were no differences in either disease−free or overall survival between the patients with CAP grade 2 and those with grade 3. 28 There were also no differences in disease−free or overall survival among the patients with Evans grades I, IIa, and IIb. Although the number of patients who had complete pathologic response (CAP grade 0) was small in their study, patients with CAP grade 0 response had better disease-free and overall survival than those with CAP grade 1 response (P < 0.01). Based on their findings, they proposed a new 3-tier MDA grading system (modified CAP grading system): grade 0, no residual carcinoma; grade 1, patients with minimal residual carcinoma (single cells or small groups of cancer cells, < 5% residual carcinoma cells in the treated tumor bed); and grade 2, patients with 5% or more residual carcinoma cells in the treated tumor bed (Figure 2, A through D). 28 The clinical and prognostic significance of this newly proposed 3-tier MDA grading system was validated by Lee et al 6 in another large cohort of 167 PDAC patients who received neoadjuvant therapy and pancreatectoduodenectomy. The disease-free and overall survival curves stratified by CAP and MDA HTRG of 398 treated PDAC patients, which combined the cohorts from above−mentioned studies, are shown in Figure 3, A through D. The new MDA HTRG system correlated significantly with ypT and ypN stages, resection margin status, and tumor recurrence after resection. 6,28 A recent study 29 of pathologic tumor response in borderline resectable PDAC patients from the Cleveland Clinic Foundation showed similar results, although the correlation of HTRG and overall survival was not statistically significant, which may be because of a small patient population.

Reliability and reproducibility of an HTRG system are very important for daily practice. The MDA HTRG not only has proved to be a highly valuable prognostic factor for clinical care of patients, but also improves interobserver agreement among pathologists. Recently, Kalimuthu et al 30 examined the interobserver concordance rate among 4 gastrointestinal pathologists using CAP, Evans, and the new MDA grading system. They found concordant grading in 11 of 14 cases (79%) using the MDA grading system, compared with 2 of 14 (14%) for the CAP grading system and 1 of 14 (7%) for the Evans grading system. 30 Therefore, the new 3-tier MDA grading system is simple and easy for pathologists to apply, and produces a more consistent and reproducible histologic grading for tumor response in pancreatectomy specimens from patients who have received neoadjuvant therapy.

Recently Panni et al 31 examined the prognostic value of residual tumor index (RTI), which is calculated as a product of the percentage of residual viable tumor and tumor bed proportion.
size in centimeters, in a cohort of 105 PDAC patients who received neoadjuvant therapy and pancreatectomy. They subgrouped their patients into RTI low, RTI mid, and RTI high using RTI cutoffs of 0.2 and 2.0, respectively. They found that RTI was a predictive marker for both recurrence-free and overall survival in their patient populations. However, accurate measurement of RTI is difficult, and RTI may have a limited use in routine pathologic reporting given the above-mentioned difficulties in accurate measurement of tumor size and the percentage of residual viable tumor for treated PDAC.

Another important issue is how to measure the tumor regression of metastatic PDAC in LNs. Tumor regression of LN metastasis alone or in combination with tumor regression of primary PDAC may prove to be a valuable parameter in measuring overall response to neoadjuvant therapy, and this may affect the prognosis of PDAC patients who have received neoadjuvant therapy. Future studies to integrate tumor regression grade of primary PDAC and nodal metastasis are needed.

**PROGNOSTIC SIGNIFICANCE OF SMA MARGIN IN POSTTHERAPY PANCREATICODUODENECTOMY SPECIMENS**

Microscopically negative resection margins (R0 resection) are important indicators of high-quality surgery. Pancreatic ductal adenocarcinoma patients with R1 resection (microscopically positive resection margin[s]) have shorter survival than those with R0 resection. The pancreatic resection margin and the common bile duct margin are routinely submitted en face and are often evaluated by intraoperative frozen sections in most institutions. However, the method to evaluate the SMA margin (also known as the uncinate or retroperitoneal margin) varies among different institutions. Some submit representative section(s) of SMA margin either en face or perpendicularly, whereas others submit the entire SMA margin for histologic examination. Moreover, some authors and studies include the posterior free surfaces as a margin as well. At MDA, we routinely submit the entire SMA margin using perpendicular sections for all pancreatoduodenectomy specimens because microscopic tumor invasion into fibroadipose tissue or perineural spaces close to the SMA margin cannot be reliably identified by gross examination. In our practice, the SMA margin is strictly defined as the uncinate surgically dissected margin, not the posterior free surface, which is in line with the current CAP cancer protocol for pancreas exocrine.

Local recurrence of PDAC after pancreatoduodenectomy often occurs in the area corresponding to the SMA margin. For patients who have undergone pancreatectomy for treatment-naïve PDAC, positive SMA margin is associated with increased risk of local recurrence and distant metastasis. In a study of a large cohort of 411 PDAC patients who received neoadjuvant therapy and pancreatoduodenectomy, Liu et al. showed that patients with positive margins had median disease-free and overall survival of 11.9 and 24.1 months, respectively, which are significantly shorter than those with negative margins (median disease-free and overall survival of 15.9 and 37.3 months, respectively). Among the 379 margin-negative patients in this study, there was no difference in either disease-free or overall survival between the margin-positive group and those with an SMA margin of 0 to 1.0 mm. These data support the CAP and European definition of a positive SMA margin as the presence of tumor cells at 1 mm or less from the treated tumor bed.

### Table 2. Major Histologic Tumor Response Grading Systems for Treated Pancreatic Ductal Adenocarcinoma

| Grading System | Based On | Grade | Description |
|----------------|----------|-------|-------------|
| Proposed by Ishikawa et al | % SDCCs | 1 | One-third or less SDCCs |
| | | 2 | One-third to two-thirds SDCCs |
| | | 3 | More than two-thirds SDCCs |
| Evans | % Tumor cell destruction | 1 | Little (<10%) or no tumor cell destruction |
| | | 1a | Destruction of 10%–50% of tumor cells |
| | | 1b | Destruction of 51%–90% of tumor cells |
| | | 3 | Few (<10%) viable-appearing tumor cells |
| | | 4 | No viable tumor cells |
| Proposed by White et al | % Viable tumor cells | Large | >90% viable tumor cells |
| | | Moderate | 10%–90% viable tumor cells |
| | | Small | <10% residual tumor cells, scattered foci of tumor cells, or no residual tumor cells |
| College of American Pathologists | Degree of radiation-induced fibrosis and regressive changes in the tumor | 0 | No viable cancer cells (complete response) |
| | | 1 | Single cells or rare small groups of cancer cells (near complete response) |
| | | 2 | Residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells (partial response) |
| | | 3 | Extensive residual cancer with no evident tumor regression (poor or no response) |
| MD Anderson | % Viable tumor cells | 0 | No viable cancer cells (complete response) |
| | | 1 | Minimal residual carcinoma (single cells or small groups of cancer cells, <5% viable residual carcinoma in the treated tumor bed) |
| | | 2 | 5% or more viable residual carcinoma cells in the treated tumor bed |

Abbreviation: SDCCs, severely degenerated cancer cells.
the SMA margin. They also showed that patients with an SMA margin of greater than 5.0 mm survived longer than those with an SMA margin of 1.0 to 5.0 mm and that longer distance of SMA margin correlated with smaller tumor size, lower ypT and AJCC stages, better tumor response grading to neoadjuvant therapy, and less frequent LN metastases and recurrences.\textsuperscript{11} Similar findings were reported in a recent study\textsuperscript{33} of 531 patients from US and European cancer centers that showed patients with an SMA margin of 1 mm or greater had better survival compared with those with 0 mm clearance (hazard ratio, 0.71; \(P < .01\)), but there was no difference in survival between patients with a margin clearance of less than 1 mm and those with 0 mm SMA margin clearance (HR, 0.93; \(P = .60\)). Therefore, complete examination of perpendicular sections of the SMA margin and accurate microscopic measurement of the distance of tumor clearance to SMA margin are important for postoperative management and prognosis of PDAC patients. An SMA margin clearance of 1 mm or greater is a better predictor of a complete margin-negative resection in PDAC patients who have undergone pancreaticoduodenectomy.

\textbf{CLINICAL IMPLICATIONS OF TUMOR INVOLVEMENT OF SMV/PV}

The current National Comprehensive Cancer Network guideline recommends neoadjuvant chemotherapy and/or radiation therapy before surgery for patients with borderline resectable PDAC,\textsuperscript{34} which is defined based on the potential tumor resectability as tumor abutment or short-segment occlusion of the SMV/PV, short-segment involvement of the hepatic artery or its branches, or less than 180° abutment of the SMA.\textsuperscript{35} Therefore, it is not uncommon to have simultaneous segmental or tangential/patch resection of SMV/PV with pancreaticoduodenectomy in PDAC patients who have received neoadjuvant therapy. However, there is no standardized protocol for the histologic evaluation of tumor involvement of resected SMV/PV, and in some cases the status of vein involvement may be overlooked and not reported in the final pathology report. In these cases, because of close proximity of the tumor to the vein wall, therapy-induced fibrosis involving the tunica adventitia of SMV/PV is often present and difficult to differentiate from the fibrosis of treated tumor bed after neoadjuvant therapy.

\begin{figure}
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\caption{A, Representative micrograph shows extensive fibrosis in the tumor bed, but no viable carcinoma cells present (College of American Pathologists [CAP] grade 0 and MD Anderson [MDA] grade 0). B, Tumor bed with extensive fibrosis and rare individual tumor cells and one small tumoral gland (CAP grade 1 and MDA grade 1). C, Residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells (>5% viable tumor cells in treated tumor bed; CAP grade 2 and MDA grade 2). D, Extensive residual cancer with no evident tumor regression (>5% viable tumor cells in treated tumor bed; CAP grade 3 and MDA grade 2) (hematoxylin-eosin, original magnifications \(\times40\) [A, B, and D] and \(\times20\) [C]).}
\end{figure}
Therefore, a clear definition of histologic tumor involvement of SMV/PV is needed, especially for those cases with tumor cells invading the perivascular soft tissue of SMV/PV. In a study by Wang et al., the tumor involvement of the tunica adventitia of SMV/PV was defined as tumor cells invading perivascular soft tissue at 1.0 mm or less from the tunica media of the vein with fibrosis extending to the tunica media of the vein. In their cohort of 225 PDAC patients who received neoadjuvant therapy and pancreaticoduodenectomy, 85 patients had SMV/PV resection and 57 (67%) had histologic tumor involvement of SMV/PV (18 patients with tumor involving the tunica adventitia, 35 with tumor invasion into the tunica media or intima, and 4 with tumor invasion into the lumen of SMV/PV). Histologic tumor involvement of SMV/PV was associated with significant shorter disease-free and overall survivals (9.2 and 27.6 months, respectively), compared with those with no tumor involvement of SMV/PV (15.9 and 35.7 months, respectively). In addition, histologic SMV/PV involvement by tumor is also associated with more blood loss during surgery, larger tumor size, higher frequencies of margin-positive resection, and more frequent recurrence and distant metastasis compared with those who had no SMV/PV involvement. By multivariate analysis, histologic tumor involvement of SMV/PV was an independent predictor of both disease-free and overall survivals in their cohort. These findings have been recently validated by 2 large independent studies, a multicenter study of 406 patients and a study of 127 patients who underwent pancreatectomy with vein resection. Both studies showed similar adverse association between histologic tumor involvement of SMV/PV and patient survival.

Figure 3. Correlations of the College of American Pathologists (CAP) and MD Anderson (MDA) tumor regression grading with disease-free and overall survival in 398 patients who received neoadjuvant therapy and pancreaticoduodenectomy. The survival curves are constructed using the Kaplan-Meier method and the log-rank test is used to evaluate the statistical significance of differences. Kaplan-Meier curves for disease-free (A and C) and overall survival (B and D) are stratified by CAP (A and B) and MDA tumor regression grading (C and D). There is no difference in either disease-free ($P = .94$) or overall survival ($P = .84$) between the group with CAP grade 2 response and that with CAP grade 3 response. Patients with CAP grade 0 or 1 response have significantly better disease-free ($P < .001$) and overall survival ($P < .001$) than those with CAP grade 2 or 3.
with tumor invasion of the tunica adventitia, vein wall, or lumen of the SMV/PV was observed by Wang et al. Their findings are similar to the findings from a recent meta-analysis of 310 patients who had the reported depth of tumor invasion into SMV, in which the depth of tumor invasion into SMV/PV was not found to be associated with patient survival after pancreaticoduodenectomy. Based on the discussion above, it is critically important for pathologists to pay close attention to the vein groove of the pancreaticoduodenectomy specimen during gross examination to identify the resected SMV/PV and the vein margins, which may be tiny and not marked or labeled in the specimen. At MD Anderson Cancer Center, the resected segment or patch of SMV/PV is entirely submitted for all cases with the underlying tumor to document tumor involvement of the vein. The vein margins are carefully inked. For segmental vein resection, the superior and inferior vascular margins are submitted en face, and the rest of the vein is submitted using cross section of the vein perpendicular to the tumor. For vein patch resection, the tips of the vein are submitted separately after inking, and the rest of the vein patch with perpendicular vein margin and underlying tumor are submitted in a fashion similar to a skin ellipse. Histologic evidence of tumor cell invasion of SMV/PV is reported as present or absent. If present, invasion to which layer of the vessel—lumen, tunica media, or perivascular soft tissue (tunica adventitia), which is defined as tumor invasion to 1.0 mm or less from tunica media—and margin status of vein resection are also reported in the final pathology report. Recently Prakash et al. examined the significance of tumor cells present at vein edge/margin in 127 patients who underwent pancreatectomy with vein resection, of whom 114 (90%) received neoadjuvant therapy. They found that the presence of tumor cells at the vein edge/margin was not associated with survival and local recurrence. It is possible that the presence of tumor cells at the inked vein margin may not reflect the true positive margins of veins because of retraction artifact of the muscular wall of the vein after incision. More studies are needed to examine the optimal way for vein margin evaluation and to determine the clinical importance of vein resection margin.

In summary, systemic pathologic examination, HTRG, pathologic evaluation of the margin status, tumor involvement of SMV/PV, accurate pathologic staging, and reporting of posttherapy pancreaticoduodenectomy specimens provide highly valuable prognostic information for postoperative patient care. Our findings suggest for the first time that tumor size of 1.0 cm, instead of 2.0 cm, is a better cutoff for ypT2 in PDAC patients. The newly proposed 3-tier MDA HTRG system not only has proved to be an independent prognostic marker for PDAC patients who received neoadjuvant therapy and pancreatectomy, but also improves interobserver agreement among pathologists in the evaluation of tumor regression/response. This grading system should be considered in future editions of the CAP protocol for PDAC.

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Pathology and Prognostic Factors of Treated PDAC—Nagaria et al
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