Pathologic Evaluation of Treated Pancreatic Ductal Adenocarcinoma and Its Clinical Implications

PRESENTED BY

Huamin Wang, M.D., Ph.D., FCAP
Disclosure of Relevant Financial Relationships

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I reported no relevant financial relationships
CONTENTS

• Brief introduction and rationale for neoadjuvant therapy for pancreatic ductal adenocarcinoma (PDAC)

• Tumor regression grading of treated PDAC

• Prognostic significance of tumor (ypT), lymph node (ypN) stage, and other histopathologic parameters of treated PDAC

• Conclusions

• Progress report of the Neoadjuvant Working Group of PBPS
Pancreatic Cancer Is One of The DEADLIEST CANCERS

- 3\textsuperscript{rd} leading cause of cancer death in the US
- Estimated New Cases in 2019: 56,770
  Estimated Deaths in 2019: 45,750
- Five survival rate: 8.5\%

The overall cancer death rate in the United States fell by 25% from 1990 to 2014.

Source: SEER Cancer Statistics Review (CSR) 1975-2014

cancer.gov
Projected Cancer Deaths in the US

PDAC Has Poor Response to Target Therapy

Median Overall Survival
- GemErlo: 24.5 months
- Gem: 26.5 months
Management of PDAC Patients at MD Anderson Cancer Center

- Pancreatic ductal adenocarcinoma (PDAC) is a systemic disease at the time of diagnosis

- Multidisciplinary approach, which is heavily biased towards neoadjuvant therapies, is used to the patients with potentially resectable PDAC
Potential Benefits of Neoadjuvant Therapy

- Better tolerated by patients
- Provides early treatment of micrometasis
- Selection for patients who would benefit the most from surgery
- Potentially reduces tumor volume and increases likelihood of resectability/complete resection
Preoperative Gemcitabine-Based Chemoradiation for Patients With Resectable Adenocarcinoma of the Pancreatic Head

• 36 y/o man with unresectable PDAC after exploratory laparotomy an outside hospital
• At MDACC, he received neoadjuvant Gemcitabine and cisplatin for 4 months and 30 Gy in 10 fractions
• CA19-9: 192 U/ml to 21 U/ml and underwent R0 pancreaticoduodenectomy at our institution
• Disease-free: 30 months after surgery
Increase in Neoadjuvant Therapy for PDAC

18,243 patients from National Cancer Database (1998 to 2011)

- The use of neoadjuvant therapy increased from 4.3% to 17.0%
- Patients who received neoadjuvant therapy were more likely to have negative margins, negative lymph nodes, and lower 30-day mortality and readmission rates
- Now neoadjuvant therapy has become the standard of care for patients with borderline resectable PDAC

Challenges in Pathologic Evaluation of Posttherapy Pancreatectomies For PDAC

- AJCC stages (8th edition): Posttherapy tumor (ypT) and lymph node metastasis (ypN)
- Tumor response to therapy (tumor regression grade)
- Other histopathologic parameters such as margins of resection, tumor grade, LVI, PNI, tumor invasion into SMV/PV etc.
CAP Tumor Regression Grading System

- Grade 0: No viable cancer cells (complete response)
- Grade 1: Single cells or rare small groups of cancer cells (near complete response)
- Grade 2: Residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells (partial response)
- Grade 3: Extensive residual cancer with no evident tumor regression (poor or no response)
Evans Grading System for Tumor Response to Therapy

- Grade I: Little (<10%) or no tumor cell destruction
- Grade IIa: Destruction of 10%-50% of tumor cells
- Grade IIb: Destruction of 51%-90% of tumor cells
- Grade III: Few (<10%) viable-appearing tumor cells
- Grade IV: No viable tumor cells

Complete pathologic response,
CAP Grade 0
Evans Grade IV
CAP Grade 1
Evans Grade III
CAP Grade 3
Evans Grade I
Study Population

223 patients between 1999 and 2007
- Histologically confirmed PDAC
- Completed neoadjuvant therapy
- Underwent pancreaticoduodenectomy (PD)

Age (years)
- Median: 62.9
- Range: 38.5-85.4

Gender
- Female 93 (42%)
- Male 130 (58%)
Grading of Residual Tumor

<table>
<thead>
<tr>
<th>CAP Grading (N=223)</th>
<th>Evan Grading (N=223)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>Grade IV</td>
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<tr>
<td>6 (2.7%)</td>
<td>6 (2.7%)</td>
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<tr>
<td>Grade 1</td>
<td>Grade III</td>
</tr>
<tr>
<td>36 (16.1%)</td>
<td>36 (16.1%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Grade IIb</td>
</tr>
<tr>
<td>124 (55.6%)</td>
<td>124 (55.6%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Grade Ila</td>
</tr>
<tr>
<td>57 (25.6%)</td>
<td>39 (17.5%)</td>
</tr>
<tr>
<td></td>
<td>Grade I</td>
</tr>
<tr>
<td></td>
<td>18 (8.1%)</td>
</tr>
</tbody>
</table>
CAP Grading and Survival

CAP Grade 0
CAP Grade 1
CAP Grade 2
CAP Grade 3

P=0.02

P=0.001

Disease-free Survival
Overall Survival
Evans Grading and Survival

- Overall Survival
- Disease-free Survival

Graphs showing survival rates for different Evans grading stages.

P-values:
- Disease-free Survival: P=0.02
- Overall Survival: P=0.004
## Multivariate Survival Analysis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of Patients</th>
<th>Disease-free Survival</th>
<th>Overall Survival</th>
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<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>p value</td>
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<td><strong>Pathologic Tumor Stage</strong></td>
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<tr>
<td>ypT0-ypT1-ypT2 (ref)</td>
<td>20</td>
<td>1.00</td>
<td></td>
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<tr>
<td>ypT3</td>
<td>203</td>
<td>2.95 (1.34, 6.50)</td>
<td>0.007</td>
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<tr>
<td></td>
<td></td>
<td>3.35 (1.20, 9.37)</td>
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<td><strong>Margin</strong></td>
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<td>Positive</td>
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<td>1.35 (0.84, 2.17)</td>
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<td></td>
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<td>1.52 (0.95, 2.43)</td>
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<td><strong>Lymph Nodes</strong></td>
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<td>95</td>
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<td>Positive</td>
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<td>1.57 (1.10, 2.26)</td>
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<td><strong>Extend of Residual Tumor</strong></td>
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<td>Response Group 1 (ref)</td>
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<td>Response Group 2</td>
<td>181</td>
<td>1.43 (0.90, 2.28)</td>
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<td></td>
<td></td>
<td>1.89 (1.09, 3.28)</td>
<td>0.01</td>
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</tbody>
</table>

Chatterjee et al. Cancer 2012
Validation Study Population

• 167 PDAC patients who completed neoadjuvant therapy and pancreaticoduodenectomy at our institution between 2008 to 2012
• 83 women and 84 men
• Median age: 65 years, range: 35 - 85 years
Validation Study of the CAP Grading System

We Propose A Modified 3-tier CAP Grading System

- Grade 0  No viable cancer cells
- Grade 1  Minimal residual cancer cells (single cells or small groups of cancer cells, <5% viable residual carcinoma)
- Grade 2  ≥5% viable residual carcinoma

Chatterjee et al. Cancer, 2012
Interobserver Concordance Using Different Tumor Regression Grading Systems

Four GI pathologists at University of Toronto used the CAP, Evans, new MDA regression grading systems to grade 14 selected cases

- CAP grading system: Consensus reached in 2/14 cases
- Evans grading system: Consensus reached in 1/14 cases
- New MDA grading system: Consensus reached in 11/14 cases
Regional lymph node (pN)
- **NX**: Regional nodes cannot be assessed
- **N0**: No regional nodal metastasis
- **N1**: Metastasis in one to three regional lymph nodes
- **N2**: Metastasis in four or more regional lymph nodes

Primary tumor (pT)
- **pTX**: Cannot be assessed
- **pT0**: No evidence of primary tumor
- **pTis**: Carcinoma in situ
- **pT1**: ≤ 2 cm  
  - **pT1a**: ≤ 0.5 cm  
  - **pT1b**: > 0.5 cm and < 1 cm  
  - **pT1c**: 1 – 2 cm
- **pT2**: > 2 cm and ≤ 4 cm
- **pT3**: >4 cm
- **pT4**: Tumor involves the celiac axis or the superior mesenteric artery regardless of size

AJCC Staging for Pancreatic Cancer, 8th Edition
### Correlations Between the ypT stage and Clinicopathologic Factors

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ypT0</th>
<th>ypT1</th>
<th>ypT2</th>
<th>ypT3</th>
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<td>85</td>
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<td>Fluoropyrimidine-based chemoradiation</td>
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<td>26</td>
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<td>Gemcitabine-based chemoradiation</td>
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<td>Chemo + gemcitabine-based chemoradiation</td>
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<td>38</td>
<td>55</td>
<td>5</td>
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<td>Chemo + Fluoropyrimidine-based chemoradiation</td>
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<td>10</td>
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<td>23</td>
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<td>ypT3</td>
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<td>ypN stage by AJCC 7th edition</td>
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<td>82</td>
<td>85</td>
<td>8</td>
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<td>70</td>
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<td>ypN stage by AJCC 8th edition</td>
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<tr>
<td>Negative (ypN0)</td>
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<td>82</td>
<td>85</td>
<td>8</td>
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<td>1-3 positive nodes (ypN1)</td>
<td>1</td>
<td>50</td>
<td>71</td>
<td>20</td>
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<tr>
<td>≥ 4 positive nodes (ypN2)</td>
<td>0</td>
<td>20</td>
<td>47</td>
<td>6</td>
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</table>

**Total number of patients: 398**
Tumor (ypT) Stage and Survival in PDAC Patients Who Received Neoadjuvant Therapy

 ypT0, n=9
 ypT1, n=152
 ypT2, n=203
 ypT3, n=34

 P<0.001
Patients with ypT1a and ypT1b have better survival than those with ypT1c and ypT2 tumors.
ypT1a and ypT1b Have Better Survival Than ypT1c in Patients With ypT3 Based on AJCC 7th Edition
Lymph Node (ypN) Stage And Survival in Treated PDAC Patients

**Disease-free Survival**
- ypN0, n=183
- ypN1, n=142
- ypN2, n=73

**Overall Survival**
- ypN0, n=183
- ypN1, n=142
- ypN2, n=73

P<0.0001
## Multivariate Cox Regression Analysis of Disease-free and Overall Survival

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients</th>
<th>Disease-free survival</th>
<th>Overall survival</th>
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<tbody>
<tr>
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<td>HR (95% CI)</td>
<td>p value</td>
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<tr>
<td>Tumor differentiation</td>
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<tr>
<td>Well-moderate (reference)</td>
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<tr>
<td>Poor</td>
<td>146</td>
<td>1.29 (1.01-1.65)</td>
<td>0.04</td>
</tr>
<tr>
<td>Margin status</td>
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<tr>
<td>Negative (reference)</td>
<td>358</td>
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<tr>
<td>Positive</td>
<td>31</td>
<td>1.28 (0.84-1.95)</td>
<td>0.25</td>
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<tr>
<td>CAP Tumor regression Grade</td>
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<tr>
<td>1 (reference)</td>
<td>54</td>
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<tr>
<td>2 and 3</td>
<td>335</td>
<td>1.48 (1.01-2.16)</td>
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<td>ypT stage</td>
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<td>ypT1 (reference)</td>
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<td>ypT2</td>
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<td>1.21 (0.93-1.57)</td>
<td>0.15</td>
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<tr>
<td>ypT3</td>
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<td>1.46 (0.95-2.25)</td>
<td>0.08</td>
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<tr>
<td>ypN stage</td>
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<td></td>
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<tr>
<td>Negative (ypN0, reference)</td>
<td>175</td>
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<tr>
<td>1-3 positive nodes (ypN1)</td>
<td>141</td>
<td>1.54 (1.17-2.04)</td>
<td>0.002</td>
</tr>
<tr>
<td>≥ 4 positive nodes (ypN2)</td>
<td>73</td>
<td>2.58 (1.88-3.53)</td>
<td>0.00</td>
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</table>
Study Summary

• New ypT and ypN stages better stratify survival than the ypT and ypN stages in AJCC 7th edition for PDAC patients who underwent PD after neoadjuvant therapy

• 1.0 cm is better cutoff for ypT2 in treated PDAC patients
Superior Mesenteric Artery (SMA) Margin (Retroperitoneal or Uncinate Margin)
The Distance of SMA Margin
Distance of SMA Margin and Survival

- **P<0.001**

Graphs showing disease-free survival and overall survival by distance from SMA margin and MOR status.
Distance of SMA Margin and Survival

Liu & Wang et al. USCAP 2015

Am J Surg Path

Distance of SMA Margin and Survival

Liu & Wang et al. USCAP 2015

Am J Surg Path

Distance of SMA Margin and Survival

Liu & Wang et al. USCAP 2015

Am J Surg Path
Vascular Invasion of PDAC Mimicking PanINs
Tumor Invasion Into Muscular Vessel and Survival

Vascular Invasion in Infiltrating Ductal Adenocarcinoma of the Pancreas Can Mimic Pancreatic Intraepithelial Neoplasia: A Histopathologic Study of 209 Cases

Hong, Seung-Mo; Goggins, Michael; Wolfgang, Christopher; Schulick, Richard; Edil, Barish; Cameron, John; Handra-Luca, Adriana; Herman, Joseph; Hruban, Ralph [American Journal of Surgical Pathology. 36(2):235-241, February 2012]

With vascular invasion (N=137)
- Median survival: 15.3 mo
- 1-year survival rate, 66.0%
- 3-year survival rate, 14.2%

Without vascular invasion (N=72)
- Median survival: 25.1 mo
- 1-year survival rate, 67.8%
- 3-year survival rate, 31.7%
Pancreateicoduodenectomy with SMV/PV Resection
No involvement of SMV/PV

Tumor involves the tunica adventitia of SMV/PV
Tumor invades into the tunica media of SMV/PV

Tumor invades into the lumen of SMV/PV
Tumor Involvement of SMV/PV and Survival

- Invading into the lumen
- SMV/PV negative
- No vein resection
- Involving adventitia
- Involving media or intima

Disease-free Survival

Overall Survival

P=0.0001
Tumor Involvement of SMV/PV and Survival

Cancer 2012 Aug 1;118(15):3801-11
CONCLUSIONS

• New ypT and ypN stages, tumor regression grade, SMA margin, vascular invasion and tumor involvement of SMV/PV are importance prognostic factors for Treated PDAC patients

• We propose a modified 3-tier CAP tumor regression grading system
  Grade 0: No residual carcinoma
  Grade 1: Minimal (<5%) residual carcinoma
  Grade 2: ≥ 5% residual carcinoma
CONCLUSIONS

• Our study suggests that tumor size cutoff for ypT2 should be 1.0 cm for treated PDAC patients

• Tumor at ≤1.0 mm from SMA margin should be considered as positive (R1) in posttherapy pancreaticoduodenectomy specimens
Neoadjuvant Working Group of Pancreatobiliary Pathology Society

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University of Texas MD Anderson Cancer Center
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Dr. Runjan Chetty (Co-Chair)
University of Toronto
Canada

Dr. Mojgan Hosseini
University of California San Diego, USA

Dr. Irene Esposito
Heinrich-Heine University of Duesseldorf, Germany

Dr. Yoko Matsuda
Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Japan

6:00 am in San Diego
8:00 am in Houston
9:00 am in Toronto
3:00 pm in Germany
10:00 pm in Tokyo
Tumor Size Measurement (ypT) for Treated PDAC

To provides accurate ypT stage, gross measurement of tumor size should be corroborated with histologic assessment.
Sampling of the Treated PDAC

- The entire tumor bed and/or suspicious areas, especially when tumor is small (3.0 cm or less), should be entirely submitted with mapping for histologic examination.

- For tumor with complete or near complete pathologic response (<5% viable tumor), entire pancreas, common bile duct and ampulla of Vater should be submitted to rule out possible tumor foci missed on gross examination.
Multiple Microscopic Foci of Residual Viable Tumor Cells In Treated Tumor Bed, Multifocality?
Residual viable tumor may be scattered as multiple microscopic foci of viable tumor cells in the treated tumor bed.

Currently, there are no criteria or definitions for the multifocality of residual viable tumor in the same tumor bed. Therefore, measurement of the sizes of individual viable tumor foci in the same tumor bed seems to be arbitrary and difficult.

There is no available data on the clinical significance for the tumor size (ypT stage) measured by adding the sizes of individual viable tumor foci in the same tumor bed.
Measuring Size of Residual Carcinoma by Histology

Single focus of viable tumor cells
Measuring Size of Residual Carcinoma by Histology

Single focus of viable tumor cells

Multiple foci of viable tumor cells
Measuring Size of Residual Carcinoma by Histology

Deyali et al. Am J Surg Pathol 41(8), 2017
Modify the Current Four-tier CAP Tumor Regression Grading System to a Three-tier Grading System

• TRG 0, No viable tumor after entire pancreas submitted for histology

• TRG 1, < 5% viable tumor cells (single cells, rare individual glands or rare small groups of tumor cells after histologic examination of entire tumor bed or entire pancreas)

• TRG 2, ≥ 5 % viable tumor cells
Gross of Patch SMV/PV Resection in Pancreaticoduodenectomy

- Carefully ink the peripheral margin of the vein patch
- Carefully take the tips 1 and 2 by pulling the vein wall and summit the tips in one cassette
- Submit the rest of the vein with underlying tumor (perpendicular)
Gross of Segmental SMV/PV Resection in Pancreaticoduodenectomy

- Carefully take a thin rim of the vein at each end (margin) of the resected vein by pulling the vein wall and summit both margins in one or two cassettes.
- Section perpendicularly to the vein axis into the underlying tumor.
- Submit the rest of the vein with underlying tumor.
Reporting of SMV/PV Status in Pancreaticoduodenectomy

• Whether or not the vein is involved by the tumor

• If MSV/PV is involved, report depth of tumor invasion into the vein: tunica adventitia (tumor cells invade perivascular soft tissue at ≤1.0 mm from the tunica media of the vein), tunica media or lumen

• Report the vein margins
Future Directions

• Clinical significance for the presence and grading of tumor regression in lymph node metastasis
• Evaluation of additional parameters, such as residual tumor index, Ki-67 in residual cancer cells etc. for inclusion into future regression grading and staging systems
• Clinical implications of other histological features of post-treatment changes in tumor, tumor microenvironment, and adjacent pancreas
Poll: When measuring the tumor size for treated pancreatic cancer in a pancreatectomy specimen, which of the following is the most appropriate approach?
THANK YOU