Intraoperative Consultation of the Whipple Resection Specimen

Pathology Update
Faculty of Medicine, University of Toronto
November 15, 2014

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Objectives
• Review of anatomy, orientation of Whipple resection
• Variations in specimen dissection, reporting of Whipple specimens
• Does FS during Whipple resection improve outcome?
• Examples of FS in Whipple resections

Pancreas Anatomy

The Whipple Resection (Pancreaticoduodenectomy)

• Resection of tumours involving the head of pancreas
  – Partial or total pancreatectomy
  – Entire duodenum, distal stomach
  – Bile duct, gallbladder
  – May include portion of portal vein, SMV, SMA

The Whipple resection

• Neoplasms of
  – Pancreas
  – Peri-ampullary and ampullary regions
  – Second part of duodenum
  – Distal bile duct
• Chronic pancreatitis

Pancreatic ductal carcinoma

• Aggressive tumour with poor survival
• XRT and chemo limited benefit
• Resection only chance for cure
• Only 10-20% are deemed resectable
• 75-85% recur post resection (local & distant)
• Reported R1 resection rate 15-80%
• Role of FS in improving R0 rate and survival?
Margin status in Whipple

- Margin status is a key prognostic factor
- Reported R1 rates very variable, but outcomes similar
- Margin status is determined by
  - Surgeon – surgical technique
  - Pathologist – sampling and assessment of margins
- A low R1 rate may not be an indicator of high quality surgical technique, but suboptimal margin assessment by pathologist

The Whipple Specimen
Anatomical Relationships

The Whipple Specimen

Margin status in Whipple

- Variability in terminology of margins, grossing of specimen, pathological reporting
- Terminology of margins
  - Pancreatic neck, anterior
  - Uncinate, SMA, retroperitoneal
  - Posterior, retroperitoneal
  - Portal vein groove, medial

The Whipple Specimen

The Whipple Specimen

- Specimen dissection techniques
  - Axial slicing favored in Europe
    - More extensive assessment of margins, higher R1 rates
  - Opening of ducts favored in North America
    - Better anatomic orientation for ampullary tumours
- Definition of R1
  - 0 mm in North America
  - \(<=1\) mm in Europe
**True “positive” margin?**

- LVI, PNI
- Tumour in lymph node
- Detached tumour in lumen of duct
- At FS, report the presence of tumour cells and their location to surgeon
- Is revision required for margin?

**R1 rate and survival pancreatic carcinoma**

<table>
<thead>
<tr>
<th>Study</th>
<th># cases</th>
<th>R1/R2 rate (%)</th>
<th>R0/R2 median survival (months)</th>
<th>R0 median survival (months)</th>
</tr>
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<tbody>
<tr>
<td>Menon (2009)</td>
<td>27</td>
<td>82</td>
<td>14</td>
<td>&gt;55</td>
</tr>
<tr>
<td>Verbeke (2006)</td>
<td>26</td>
<td>85</td>
<td>11</td>
<td>37</td>
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<tr>
<td>Raut (2007)</td>
<td>360</td>
<td>17</td>
<td>22</td>
<td>28</td>
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<tr>
<td>Sohn (2000)</td>
<td>616</td>
<td>30</td>
<td>12</td>
<td>19</td>
</tr>
</tbody>
</table>

- R0 survival in studies with low R1 rate remain low similar to R1 group
- R0 survival in studies with high R1 rate is much higher than R1 group
- Implies studies with low R1 rate has many R0 cases that are really under sampled R1 cases
- In several institutions, modifying specimen dissection protocol increases R1 rate

**Effect of FS on survival**

- Hernandez J et al
  Survival after pancreaticoduodenectomy is not improved by extending resections to achieve negative margins
  Annuals of Surgery (2009) 250:76-80

- Mathur A et al
  Margin status impacts survival after Pancreateicoduodenectomy but negative margins should not be pursued
  The American Surgeon (2014) 80:353-360 (from U South Florida, Tampa, FL)

**Effect of FS on survival**

- Lad NL et al
  Is it time to stop checking frozen section neck margins during pancreaticoduodenectomy?

- Kooby DA et al
  Value of intraoperative neck margin analysis during Whipple for pancreatic adenocarcinoma. A multicenter analysis of 1399 patients.

**Kooby et al.**

Value of intraoperative neck margin analysis during Whipple for pancreatic adenocarcinoma.
Annuals of Surgery (2014), 260:494-503

- Multi-institutional retrospective analysis of cases from the Central Pancreas Consortium
- 1399 cases of pancreatic ductal adenocarcinoma with FS of neck margin
- Cases associated with IPMN excluded
- R0 > 1mm

**Distribution of cases by FS & PS neck margin status**

- Negative (FS-R0)
  n=1247 (89%)
- Positive (FS-R1)
  n=152 (11%)
- PS-R0
  n=1196
- PS-R1
  n=131
- FS-R1 to PS-R0
  n=72

**OS by margin status, all patients**

- **Overall Survival**
  - p<0.001
  - Median OS: 22.8 mos
  - PS-R0 any margin (n=1048)
  - PS-R1 any margin (n=351)

**OS stratified by neck margin status**

- **Overall Survival**
  - p<0.001
  - PS-R0 neck (n=1116)
  - PS-R1 neck (n=131)
  - FS-R1 to FS-R0 neck (n=72)

**OS stratified by neck margin status, negative uncinate margin patients only**

- **Overall Survival**
  - p=0.95
  - PS-R1 neck (n=63)
  - FS-R1 to FS-R0 neck (n=58)

**Effect of FS on Survival**

- Negative initial margin at FS correlates with better survival
- Revised negative margin after initial positive margin has same survival as those with unrevised positive margin
- Positive initial margin at FS is associated with
  - Larger tumour size
  - More node positivity
  - PV/SMA resection
  - Trend toward more frequent uncinate margin positivity

**FS of Whipple Specimen**

- Be prepared
  - History, radiological dx, previous biopsy / cytology
- Many cases have no prior tissue diagnosis
- Initial FS
  - In the “old days”, sample from tumour for “confirmation of malignancy”
  - From metastatic sites – liver, peritoneum, LN’s, if positive, may abort procedure
- FS margin assessment
  - separately submitted pieces
  - dissected from Whipple specimen
  - Ask surgeon which margin is needed!

**FS of Whipple Specimen**

- Whipple margins for FS
  - Bile duct margin
  - Pancreatic neck margin (if partial)
  - Uncinate margin
  - Vascular margin, if present
**Histological challenges**

- Pancreatic pathology difficult even on paraffin sections. FS artifacts add to difficulty.
- Tumour may be difficult to distinguish from chronic pancreatitis
- Tumour desmoplasia versus fibrosis
- Residual islets versus NET
- Inflammatory changes in bile duct from obstruction, stent

**Features favoring carcinoma**

- Disorganized duct distribution
- Variation in nuclear size $\geq 4:1$
- Incomplete duct lumen
- Disorganized stroma
- Single cell infiltration
- Cribriform glands
- Epithelial mitoses
- Necrotic glandular debris
- Large nucleoli
- Perineural invasion


**Pancreatic margin**

- Routinely sampled in most cases requiring FS
- Usually sectioned en face (shaved)
- Reported as positive if any tumour cells present on slide
- Report high-grade dysplasia in ducts if present
Case 1: FS - neck margin
- Atrophic ducts & residual islets
- Malignant
- High-grade dysplasia

Case 1: PS - neck margin
- Malignant

Case 1: FS - neck margin
- Atrophic ducts & residual islets

Case 2: FS - neck margin
- Benign
CASE 2
FS - neck margin
malignant

atrophic ducts & residual islets

CASE 2
FS - neck margin
bigger tumour focus present

malignant

CASE 3
FS - neck margin
IPMN in main duct

IPMN in main duct

surgeon proceeded with completion pancreatectomy

CASE 3
FS - neck margin
CASE 3  
**PS - distal pancreas**  
IPMN & adenocarcinoma in completion pancreatotomy

CASE 4  
**FS - neck margin**  
“cystic mucinous lesion”

CASE 4  
**FS - neck margin**  
“cystic mucinous lesion”

CASE 4  
**FS - neck margin**  
“cystic mucinous lesion”

CASE 4  
**PS - pancreas**  
IPMN & adenocarcinoma

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**Uncinate Margin**

- Area inked, removed and serially sectioned perpendicularly
  - May require many FS blocks
  - Often fatty, hard to cut on cryostat
- Is FS really needed?
  - Current surgical protocol specifies removal of all tissues around the SMA, so even if margin is positive on FS, no additional tissue can be removed.
CASE 5

FS - uncinate margin

malignant

case 5

PS - uncinate margin

malignant

case 5

CASE 5

FS - uncinate margin

malignant

case 5

PS - uncinate margin

malignant

case 5

tumour at inked surface

case 6

CASE 6

FS - uncinate margin

malignant

case 6

FS - uncinate margin

malignant

case 6
CASE 6  FS – revised uncinate margin

CASE 7  FS - uncinate margin

CASE 7  FS - uncinate margin

CASE 7  PS - uncinate margin

CASE 7  FS - uncinate margin

CASE 8  FS - uncinate margin
CASE 8 PS - uncinate margin

malignant negative at ink

Bile Duct Margin

- FS performed frequently, but seldom positive
- Usually provided as separate tissue piece
- Reactive changes common, especially if prior stent in place
- Normal intramural glands versus adenocarcinoma
- Look for tumour in nerves, LN's

Vascular Margin

- Uncommon FS
  - Segment of vessel (take end margins en face)
  - Patch of vessel (depending on size, may section en face circumferentially or serially section perpendicularly like skin ellipse)
- Ask surgeon if FS desired
- May take more vessel if positive
- May proceed to resection of vessel + graft

CASE 9 FS - PV margin

malignant

References

- Mather A et al. Margin status impacts survival after pancreaticoduodenectomy but negative margins should not be pursued. The American Surgeon 2014;80:353-360
- Verbeke CS, Menon KV. Refining resection margin status in pancreatic cancer. HPB 2009; 11:282-9