Surgery for pancreatic cancer

Andrew Smith
12 September 2018
Leeds Regional Study Day
Pancreatic Surgery

- Range of pancreatic surgery
  - Pre-op preparation
  - Post op complications
  - guidelines

- Advances in pancreatic surgery
Pancreatic Cancer Presentation - Q cancer risk score

- GP EMIS system (14 million)
- Has identified most common symptoms for each cancer
- Can provide a % risk

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk factors</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Age, sex, smoking, deprivation, COPD, prior cancers</td>
<td>Haemoptysis, appetite loss, weight loss, cough, anaemia</td>
</tr>
<tr>
<td>Gastro-oeso</td>
<td>Age, sex, smoking status</td>
<td>Haematemesis, appetite loss, weight loss, abdo pain, dysphagia</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Age, sex, alcohol, family history</td>
<td>Rectal bleeding, appetite loss, weight loss, abdo pain, change bowel habit, anaemia</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Age, sex, type 2, chronic pancreatitis</td>
<td>Dysphagia, appetite loss, weight loss, abdo pain, abdo distension, constipation</td>
</tr>
<tr>
<td>Ovarian</td>
<td>Age, family history</td>
<td>Rectal bleeding, appetite loss, weight loss, abdo pain, abdo distension, PMB, anaemia</td>
</tr>
<tr>
<td>Renal</td>
<td>Age, sex, smoking status, prior cancer</td>
<td>Haematuria, appetite loss, weight loss, abdo pain, anaemia</td>
</tr>
</tbody>
</table>
Early diagnosis

- Familial Pancreatic Cancer (FPC)
  - ≥2 first degree relatives
  - 1 case within a syndrome

- Hereditary Pancreatitis (HP)
  - ‘True’ PRSS1
  - ‘Neg All’
  - Familial Idiopathic Pancreatitis (FIP)

Regional Centres
Liverpool Only
Risk of Pancreatitis
(6.8%)
Early diagnosis
Education

BMJ Learning

You are currently not logged in to BMJ Learning.

1 hour ★★★★☆ (1) All audience...

Start module Add to portfolio

Pancreatic adenocarcinoma

RCGP Learning
Essential CPD for primary care
Pancreatic Surgery History

• 1912 Walter Kausch first to describe removal of the pancreas and duodenum

• 1935 Alan Oldfield Whipple – described 3 patients undergoing combined duodenal and pancreatic resections

• 1990s Yorkshire – in hospital PPPD mortality 28%
Operations for Pancreatic tumours

Classic Procedures
• Whipple / PPPD
• Distal (left sided pancreatectomy) +/- Spleen
• Total Pancreatectomy

Pancreas Sparing Procedures
• Central Pancreatectomy
• Enucleation
Operations for Pancreatic tumours

• Whipple / PPPD
Operations for Pancreatic tumours

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  - Ennucleation

- Ennucleation

b  hepatic duct
a  hepatic artery
c  mucinous cyst
p  pancreatic head
Pre-operative preparation

**Diagnosis and Staging**

- CT – Chest/abdo/pelvis – triple phase pancreas
- PET CT
- +/- Histology ERCP + brushings and bx, EUS + FNA/B
- +/- pre-operative biliary drainage vs Fast track

**Patient Factors**

- Overall fitness - co-morbidity. CPEX test
- Pain control
- Nutrition – Pre-op PERT, supplements
- If jaundiced - correct clotting
Pre-operative preparation

Communication and Consent

Outpatient clinic - allow adequate time
Use of visual aids

Consent in clinic – not on day of surgery

Patient information – local, national eg PCUK

Support
CNS
Contact numbers
Post Whipple complications

• Mortality 1 - 3% - 90 day mortality
• Morbidity ~ 50%

• Early complications
  • Post operative pancreatic fistula
  • Bleeding
  • Leaks from the other joins
  • Infection – wound /chest
  • Pancreatic insufficiency
  • Diabetes

• Late complications
  • Pancreatic insufficiency
  • Diabetes
  • Incisional hernia
  • Recurrent disease
Pancreatic Fistula (POPF) - Incidence

• POPFs result in additional procedures, life threatening complications, increased length of stay

• 15 - 30% PPPDs

• 40 - 50% Distal / left sided pancreatectomy
Postoperative pancreatic fistula: An international study group (ISGPF) definition

Claudio Bassi, MD, a Christos Dervenis, MD, b Giovanni Butturini, MD, a Abe Fingerhut, MD, c Charles Yeo, MD, d Jakob Izbicki, MD, e John Neoptolemos, MD, f Michael Sarr, MD, g William Traverso, MD, h and Marcus Buchler, MD, i for the International Study Group on Pancreatic Fistula

Definition, a Verona, Italy; Athens, Greece; Poissy, France; Baltimore, Md; Liverpool, United Kingdom; Hamburg, Germany; Rochester, NY; Seattle, Wash; and Heidelberg, Germany

any drainage fluid > 3-times elevated amylase

Bassi et al., Surgery 2005
POPF - Patient Factors

Significant increase in POPF incidence:

General

• BMI - high associated with increased POPF

Pancreas Gland

• Duct Size < 3mm

• Soft Gland texture

Wada, Surgery 2006
Yeo, Ann Surg 2000
Suzuki, Arch Surg 2002
Winter, J Gastroint Surg 2008
Pre-op Biliary Drainage

Mumtaz, Cochrane Database Syst Rev, 2007, CD 006001

↓ post op complications
No change in POPF rate

- Van der Gaag, NEJM, 2010, 362, 129

RCT, 202 patients

<table>
<thead>
<tr>
<th></th>
<th>Complications</th>
<th>PJ leak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Surgery</td>
<td>37%</td>
<td>11/94</td>
</tr>
<tr>
<td>Biliary Drainage</td>
<td>47%</td>
<td>8/102</td>
</tr>
</tbody>
</table>
POPF - Somatostatin and analogues

- Gurasamy, *Cochrane Database SR, 2012, CD008370*

19 trials, 2245 pts

- **all complications**  
  RR 0.69, 95% CI 0.60 – 0.79

- **pancreatic POPF**  
  RR 0.63, 95% CI 0.52 – 0.77

? Clinically significant fistulas
POPF - Surgeon’s Operative Volume

High Volume Surgeon (HVS) > 12 PPPD’s / yr
POPF rate  HVS  vs  LVS,
          24.1%  vs  32.4%, p=0.03

No overall difference in mortality

Pecorelli, J Gastrointest Surg, 2012
POPF - Classic Whipples vs PPPD

465 pts
No significant difference in POPF rate
OR 0.86, 95% CI 0.46 – 1.81

Diener, Cochrane Database Syst Review, 2008 CD006053
Pancreaticojejunostomy, PJ

vs

Pancreaticogastrostomy, PG

Meta-analysis of pancreaticojejunostomy versus pancreaticogastrostomy reconstruction after pancreatectoduodenectomy

A. McKay¹, S. MacLachnie¹, F. R. Sutherland¹, O. F. Bathu¹, C. Doig², J. Dott¹,², C. M. Vollmer Je³
and E. Dixon¹

Departments of ¹Surgery and ³Community Health Sciences, University of Calgary, Calgary, Canada and ²Department of Surgery, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

Clinical surgery–International

Pancreaticojejunostomy versus pancreaticogastrostomy: systematic review and meta-analysis

Moritz N. Wente, M.D., M.Sc.¹, Shailsh V. Shrikhande, M.D.¹, Michael W. Müller, M.D.², Markus K. Diener, M.D.³, Christoph M. Seiler, M.D., M.Sc.³, Helmut Friess, M.D.³, Markus W. Bächler, M.D.³,⁴,⁵

³Department of General, Visceral and Trauma Surgery, University of Heidelberg, Heidelberg, Germany
⁴Department of Gastro-intestinal Surgical Oncology, Tata Memorial Hospital, Mumbai, India

British Journal of Surgery 2006; 93: 929–936
POPF - Pancreatic Duct Stent

- Xong, *BJS*, 2012,
  16 studies, 1726 patients

  No change POPF rate

However, Ext vs Int stent

  No effect on clinical outcome

  External stent: ↓ POPF, ↓DGE, ↓post-op morbidity
POPF - Timing of Drain Removal

Bassi, Ann Surg, 2010

Amylase < 5000 POD  #1, #3
USS negative      POD  #3

POPF, p = 0.0001
Extended pancreatectomy in pancreatic ductal adenocarcinoma: Definition and consensus of the International Study Group for Pancreatic Surgery (ISGPS)

Werner Hartwig, MD, Charles M. Vollmer, MD, Abe Fingerhut, MD, Charles J. Yeo, MD, John P. Neoptolemos, MD, Mustapha Adham, MD, Alex Anderf-Stenberg, MD, Helen C. Gordon, MD, Charles H. Bains, MD, Max Brandt, MD, Richard Charnley, MD, Kevin G. Gordon, MD, Jeannice Fernandez-Cruz, MD, Hermann Friesen, MD, Dieter J. Germer, MD, Glenn W. Imrie, MD, Keith D. Lillemoe, MD, Mirando N. Milosevic, MD, Marco Moncada, MD, Shuvalakshmi S. Bhaskaran, MD, Yogesh K. Vashist, MD, Jakob R. Eicheni, MD, and Markus W. Buechler, MD, for the International Study Group on Pancreatic Surgery, Munich, Hamburg, and Heidelberg, Germany, Philadelphia, PA, Pittsburgh, PA, and New York, NY, USA, for the International Study Group on Pancreatic Surgery, Anchorage, AK; London, UK; Nashville, TN; and Honolulu, HI, USA, for the International Study Group on Pancreatic Surgery, Sydney, Australia; and for the International Study Group on Pancreatic Surgery, Shanghai, China.
Pancreatic cancer in adults: diagnosis and management

NICE guideline
Published: 7 February 2018
nice.org.uk/guidance/ng85
Post Whipple complications

• Mortality 1 - 3%
• Morbidity ~ 50%

– Early complications
  – Post operative pancreatic fistula
  – Bleeding
  – Leak from the other joins
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  – Diabetes
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  – Recurrent disease
Advances for PPPD/Whipples

Artery first Approach

- Now accepted that venous resection can and should be undertaken
- Resectability should be dictated by whether the SMA is involved
- Also allows early control
SMA technique

2 approaches depending on pre-operative and initial findings

• Borderline SMA
  • Direct dissection onto SMA
  • POSTERIOR approach

• SMA clear
  • including known venous involvement
  • MEDIAL UNCINATE approach
Posterior Approach Technique

- Left side of patient
- Midline incision
- Wide Kocher’s maneuver
  - Release ligament of Treitz
- Incise perivascular connective tissue at the origin of the SMA
- Dissect caudally
- Attachments between SMA and pancreas divided
Medial Uncinate First Technique

Caudal dissection

Dissection along PV and SMV

complete retrograde mobilisation of the pancreatic head
Artery first & PV resection

• PV resection is last manouvre in artery first approach

• Excellent control

• Can easily perform end to end reconstruction without the need for a graft
## SMA first alone improves resection margins

- SMA demonstrated improved LN yield & negative margins

<table>
<thead>
<tr>
<th></th>
<th>Classical N=77</th>
<th>SMA-first N=77</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node yield (median)</td>
<td>21 (5-50)</td>
<td>28 (13-50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>R0 resection</td>
<td>14 (18%)</td>
<td>27 (35%)</td>
<td>0.042</td>
</tr>
<tr>
<td>Posterior margin R1</td>
<td>37 (48%)</td>
<td>32 (42%)</td>
<td>0.547</td>
</tr>
<tr>
<td>Anterior margin R1</td>
<td>11 (14%)</td>
<td>12 (16%)</td>
<td>0.835</td>
</tr>
<tr>
<td>Artery margin R1</td>
<td>37 (48%)</td>
<td>33 (43%)</td>
<td>0.633</td>
</tr>
</tbody>
</table>
Fast Track Surgery
Natural History Pancreatic Cancer

• PDAC tumorigenesis 20 yrs

• Later stages rapid
  • 14 months T1 to T4

Gut 2015; 64: 1783 – 1789
Impact of delay between imaging and treatment in patients with potentially curable pancreatic cancer

S. Sanjeevi¹, T. Ivanics⁴, L. Lundell², N. Kartalis³, Å. Andrén-Sandberg², J. Blomberg², M. Del Chiardo² and C. Ansorge²

¹Department of Surgical Gastroenterology, Karolinska University Hospital, and Divisions of ²Surgery and ³Radiology, Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institute, Stockholm, Sweden, and ⁴Department of Surgery, Mayo Clinic, Rochester, Minnesota, USA

Correspondence to: Dr C. Ansorge, K53, Karolinska Institute, Karolinska University Hospital, 14186 Stockholm, Sweden (e-mail: christoph.ansorge@ki.se)

Median IR interval was 42 days

Unresectability rate = 0, IR interval < 22 days

Cut off 32 days, unresectability rate 13 v 26.2% ; HR 0.42, P = 0.021
Fast Track surgery

Preoperative Biliary Drainage for Cancer of the Head of the Pancreas

PBD complications 47%
Surgery complications ES 39% vs PBD 74%, P< 0.001

No evidence of improved survival
Leeds Pancreas Pathology Protocol

Described By Caroline Verbeke in 2006

More accurate analysis of the specimen

Despite radical surgery 80% have positive margins - R1
Survival following surgery and adjuvant therapy – ESPAC 4 data

Median OS = 25.5 months (95% CI: 22.7–27.9)
Median OS = 28.0 months (95% CI: 23.5–31.5)

HR = 0.82 (95% CI: 0.68–0.98); p = 0.032

CI = confidence interval; HR = hazard ratio; OS = overall survival
Neoadjuvant Therapy

Preoperative radiochemotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC): A randomized, controlled, multicenter phase III trial of the Dutch Pancreatic Cancer Group

Geertjan van Tienhoven, radiation oncologist, AMC, Amsterdam

Eva Versteijne 1, Mustafa Suerk 2, Karin B Groothuis 3, Olivier R Busch 4, Bert A Bonsing 5, Ignace H de Hingh 6, Sebastiaan Festen 7, Gj J A Patijn 8, Judith de Vos -Geelen 9, Aelko H Zwijderman 10, Cornelius J Punt 11, Casper H van Eijck 2

1 Radiation Oncology, Academic Medical Center, Postbus 22660, 1105 AZ, Amsterdam, the Netherlands.
3 Clinical Research Department, Netherlands Comprehensive Cancer Organization (NKI), Postbus 1281, 5501 BG, Nijmegen, The Netherlands.
4 Surgery, Academic Medical Center, Postbus 22660, 1105 AZ, Amsterdam, the Netherlands.
5 Surgery, Leiden University Medical Center, Postbus 9600, 2330 RA, Leiden, The Netherlands.
6 Surgery, Catharina Hospital, Postbus 1331, 5600 EA, Eindhoven, The Netherlands.
7 Surgery, OLVG, Postbus 9500, 1080 HM, Amsterdam, The Netherlands.
9 Internet Medicine, Division of Medical Oncology, GROW - School for Oncology and Developmental Biology, Maastricht UMC+, The Netherlands.
10 Clinical Epidemiologic Biostatistics, Academic Medical Center, Postbus 22660, 1105 AZ, Amsterdam, The Netherlands.
11 Medical Oncology, Academic Medical Center, Postbus 22660 1105 AZ, Amsterdam, The Netherlands.

Presented By Geertjan Van Tienhoven at 2018 ASCO Annual Meeting
**Baseline characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Immediate surgery (n=127)</th>
<th>Preop. Radiochemotherapy (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range)</strong></td>
<td>67 (37-81)</td>
<td>65 (33-80)</td>
</tr>
<tr>
<td><strong>WHO PS 0-1</strong></td>
<td>94%</td>
<td>92%</td>
</tr>
<tr>
<td><strong>Location pancreatic head</strong></td>
<td>88%</td>
<td>87%</td>
</tr>
<tr>
<td><strong>Borderline resectable</strong></td>
<td>46%</td>
<td>53%</td>
</tr>
</tbody>
</table>

Presented by Geertjan Van Tienhoven at 2018 ASCO Annual Meeting
Overall survival (ITT)

Preliminary: 149/176 events

Median survival:
13.7 vs 17.1 months
HR 0.74
p=0.074
Subset analysis

Patients after R0/R1 resection

For comparison with observational studies and adjuvant trials

Median OS: 16.8 vs 42.2
Results

Tumor Regression: Implications

Patients categorized into 3 subgroups:

- Complete or near complete response
- Moderate response
- Minimal response

Results

<table>
<thead>
<tr>
<th>Tumor Regression: Implications</th>
<th>Complete Response</th>
<th>Moderate Response</th>
<th>Minimal Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA mths</td>
<td>23 (48%)</td>
<td>10 (21%)</td>
<td>15 (31%)</td>
</tr>
<tr>
<td>38.0 mths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.0 mths</td>
<td></td>
<td></td>
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</tr>
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</table>

P = 0.011
P = 0.03
Transforming research and treatment approaches for Pancreatic Cancer

PRECISION-Panc

Improving outcomes through a dynamic research & development platform for Precision Medicine
Impact neoadjuvant Rx - More complex surgery

GLASGOW GRADING FOR WHIPPLES
1. Virgin Whipple
2. Post CBD stent Whipple
3. Acute Pancreatitis post CBD stent Whipple
4. Whipple for Chronic Pancreatitis
5. Neoadjuvant Whipple
### Falling resection numbers

<table>
<thead>
<tr>
<th>Year</th>
<th>Aberdeen</th>
<th>Inverness</th>
<th>Dundee</th>
<th>Edinburgh</th>
<th>Glasgow</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>16</td>
<td>7</td>
<td>9</td>
<td>28</td>
<td>39</td>
<td>99</td>
</tr>
<tr>
<td>2015</td>
<td>19</td>
<td>7</td>
<td>5</td>
<td>42</td>
<td>35</td>
<td>75</td>
</tr>
<tr>
<td>2016</td>
<td>13</td>
<td>2</td>
<td>2</td>
<td>35</td>
<td>23</td>
<td>75</td>
</tr>
</tbody>
</table>

Data from Scottish HPB Cancer Network
Volume and outcomes

Hospital experience

HOSPITAL VOLUME AND SURGICAL MORTALITY IN THE UNITED STATES


Birkmeyer JD et al., NEJM 2002
Volume and outcomes

Individual surgeon’s experience

Surgeon Volume and Operative Mortality in the United States

John D. Birkmeyer, M.D., Therese A. Stukel, Ph.D., Andrea E. Siewers, M.P.H., Philip P. Goodney, M.D., David E. Wennberg, M.D., M.P.H., and F. Lee Lucas, Ph.D.

"Practice makes perfect"

Birkmeyer JD et al., NEJM 2003
Surgeon Volume and Outcome

9116 PDs

HES data

2 to 31 PDs / surgeon / year

Proficiency relationship between surgeon volume and mortality
Surgeon volume

Mortality Rate

- Low: 4.4% (P<0.001)
- Med: 2.94%
- High: 2.94%
Surgeon Volume

- Surgeon volume increased, mortality rate decreased, no evidence of a plateau at the top end with 31 PDs per annum
- Each additional case reduces the 30 day mortality odds by 4.1%
- No recommendation for minimum case numbers
For better outcomes, would patients be willing to travel further?

- 75 mins longer to reduce risk of complications by 1%
- 5 hours longer to reduce risk of death after surgery by 1%
- 3 hours longer to have specialist 24/7 surgical cover
Questions ?