The Value & Limits of Resection in Pancreatic Cancer

Irinel Popescu, MD, PhD, FACS, FEBS

Center of General Surgery and Liver Transplant
Dan Setlacec

Fundeni Clinical Institute
Bucharest
Pancreatic Cancer

• An important health problem worldwide:
  - 4th leading cause of cancer related death in US
  - 5th leading cause of cancer related death in Europe
  - No significant decrease in cancer death rates for pancreatic cancer in the last 20 years

Jemal, CA Cancer J Clin, 2009; Ferlay, Eur J Cancer, 2010
Pancreatic Cancer

• **An aggressive disease**
  - Diagnosed at advanced stages
    • 90-95% locally/ systemically advanced
  - 5-year survival rates for all stages: < 5%

• **Surgery (i.e., pancreatectomy) represents the single hope for long-term survival**

• **Ductal adenocarcinoma:** > 90% of the patients

Pancreatic Cancer

- Invasive ductal carcinoma:
  - Papillary adk
  - Tubular adk
  - Adenosquamous carcinoma
  - Anaplastic carcinoma
    - Osteoclast-like giant cell type - better prognosis

Adapted from Classification of pancreatic cancer, Japan Pancreas Society, 2011
Invasive Ductal Adenocarcinoma
Tubular ADK

Pancreaticoduodenectomy specimen

Pancreaticoduodenectomy specimen
Invasive Ductal Adenocarcinoma
Osteoclast-like giant cell carcinoma

Ionescu & Dumitrascu, Chirurgia, 2005

Pancreaticoduodenectomy specimen
Invasive Ductal Adenocarcinoma
Adenosquamous carcinoma

Distal pancreatectomy specimen

Distal pancreatectomy specimen
Pancreatic Cancer - Assessment of resectability

Consensus Statement

1. Accurate radiographic assessment with high-quality 3-D imaging of the pancreas and associated mesenteric vessels is optimal for proper categorization of tumors according to potential resection status. Currently, the state-of-the-art imaging modality is multidetector CT with advanced volumetric processing techniques.
Resectable & Borderline Pancreatic Cancer

Consensus Statement

1. Tumors considered localized and resectable should demonstrate the following:
   a. No distant metastases.
   b. No radiographic evidence of SMV and portal vein abutment, distortion, tumor thrombus, or venous encasement.
   c. Clear fat planes around the celiac axis, hepatic artery, and SMA.

2. Tumors considered borderline resectable include the following:
   a. No distant metastases.
   b. Venous involvement of the SMV/portal vein demonstrating tumor abutment with or without impingement and narrowing of the lumen, encasement of the SMV/portal vein but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumor thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction.
   c. Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis.
   d. Tumor abutment of the SMA not to exceed >180° of the circumference of the vessel wall.
Pancreatic Cancer Surgery

Adapted from Dumitrascu & Stroescu, Textbook of Surgery (Editor: I. Popescu), in press
Pancreatic Cancer

Pancreatoc-oduodenectomy for pancreatic head cancer

Pancreatic Cancer

Distal pancreatectomy with splenectomy for pancreatic cancer of the body & tail

Pancreatic Cancer - Lymphadenectomy

Extensive lymphadenectomy - no survival benefit; increased morbidity rates

Michalski, Br J Surg, 2007
Pancreatic Head Cancer - Lymphadenectomy

**Standard Pancreatoduodenectomy**

En bloc resection of the following lymph node groups is performed.

<table>
<thead>
<tr>
<th>Node Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>12b1, 12b2, 12c</td>
<td>Lymph nodes of the right side of the hepatoduodenal ligament</td>
</tr>
<tr>
<td>13a, 13b</td>
<td>Posterior pancreaticoduodenal nodes</td>
</tr>
<tr>
<td>14a, 14b</td>
<td>Nodes to the right side of the superior mesenteric artery from the origin of the superior mesenteric artery at the aorta to the inferior pancreaticoduodenal artery</td>
</tr>
<tr>
<td>17a, 17b</td>
<td>Anterior pancreaticoduodenal nodes</td>
</tr>
</tbody>
</table>

In addition lymph nodes of the anterior-superior region of the common hepatic artery (8a) are removed separately.

**Current approach - STANDARD LYMPHADENECTOMY**

Pedrazzoli, Dig Surg, 1999
Distal Pancreatic Cancer - Lymphadenectomy

*Standard Left Pancreatectomy*

En bloc resection of the following lymph node groups is performed.

- 9 Celiac axis nodes
- 10 Nodes of the hilum of the spleen
- 11 Splenic artery lymph nodes
- 18 Nodes along the inferior border of the body and tail of the pancreas

**Current approach - STANDARD LYMPHADENECTOMY**
The “Artery First” Approach for Resection of Pancreatic Head Cancer

Jürgen Weitz, MD, Nuh Rahbari, MD, Moritz Koch, MD, Markus W Büchler, MD

* J Am Coll Surg, 2010

**Figure 2.** Intraoperative image demonstrating the origin of the superior mesenteric artery (*) from the aorta after incision of the peritoneum on the left side of the duodenojejunal flexure. The small bowel and the colon are displaced toward the head of the patient. IVC, inferior vena cava; LRV, left renal vein.

**Figure 3.** Intraoperative image demonstrating dissection of the superior mesenteric artery (red vessel loop) and the superior mesenteric vein (blue vessel loop) at the inframesocolic position. The proximal jejunum is marked with an asterisk.
Technical Refinements in Pancreatic Head Cancer Surgery – Posterior Approach

Pessaux, J Gastrointest Surg, 2006
Establishes invasion in the SMA, that signals an aggressive tumor biology and it is unlikely to be overcame by resection.
Technical Refinements in Pancreatic Head Cancer Surgery - Posterior Approach

- isolation of PV/SMV above and below of the tumour is made without its manipulation during dissection; a reduced time for venous reconstruction
Total Mesopancreas Excision in PHC

Pancreas

Total Meso–pancreas Excision: Key Point of Resection in Pancreatic Head Adenocarcinoma

Irinel Popescu, Traian Dumitrascu
Center of General Surgery and Liver Transplantation, Fundeni Clinical Institute, Fundeni Street no. 258, 022328, Bucharest, Romania

Hepato-Gastroenterology 2010; 57:1-6
Surgical technique and results of total mesopancreas excision (TMpE) in pancreatic tumors

M. Adham a,b,*, J. Singhirunnusorn a

* Department of Hepato-biliary and Pancreatic Surgery, Edouard Herriot Hospital, HCL, Lyon, France

Conclusion: Our procedure is feasible and safe in experienced hands. It is a description of a standardized method for TMpE that clearly shows an advantage in improving posterior clearance and R0 resection.

Appraisal of a total meso-pancreatoduodenectomy excision with pancreaticoduodenectomy for pancreatic head carcinoma

Y. Kawabata*, T. Tanaka, T. Nishi, H. Monma, S. Yano, Y. Tajima

Department of Digestive and General Surgery, Shimane University Faculty of Medicine, 89-1 En-yacho, Izumo, Shimane 693-8501, Japan

Conclusion: Our surgical technique, tMPDe, is safe and more radical when performing a PD and should be adopted when performing pancreatic surgery as a pathological cure for pancreatic head carcinoma.
Total Mesopancreas Excision

- Improved R0 resection rates
- Improved recurrence rates
- Improved survival?

Popescu & Dumitrascu, Hepatogastroenterology, 2011; Adham, EJSO, 2012; Kawabata, EJSO, 2012
Total Mesopancreas Excision


T. Dumitrascu
I. Popescu*

Center of General Surgery and Liver Transplantation, Fundeni Clinical Institute, Fundeni Street no. 258, 022328 Bucharest, Romania

EJSO 38 (2012) 725
Pancreatic Cancer Surgery Outcome

- **Curative-intent surgery:**
  - Postoperative mortality:
    - Past: 20%
    - Nowadays: < 5%
  - Postoperative morbidity: 15 – 60%
  - Safe even in elderly

Pancreatic Cancer Outcome

- **Median survival:**
  - 14 - 28 (resected patients)
  - 5.2 - 7.2 (unresected patients)

- **5-year survival:**
  - 12.5 % (resected patients)
  - 0 % (unresected patients)
Pancreatic Cancer

- Negative resection margins - the most important determinant of survival
  - R0 rates - 80%
  - R0 rates with standardized pathology - 20%
- R0 vs. R1: 26.5 – 37 mo vs. 11 – 15.4 mo

Pancreaticoduodenectomy
Standardized Pathology

Dumitrascu & Stroescu, Textbook of Surgery
(Editor: I. Popescu), in press

Jamieson NB. Ann Surg 2010
Pancreatic Head Cancer
Fundeni Clinical Institute 2002-2012

Overall Survival

Group
- NET Pancreatic Head (18 pts)
- ADK Ampulla of Vater (110 pts)
- ADK Duodenum (9 pts)
- ADK Pancreatic Head (156 pts)
+ censored
+ censored
+ censored
+ censored

ADK vs. NET Pancreatic Head, p < 0.001
ADK Pancreatic Head vs. ADK Ampulla of Vater, p < 0.001
ADK Pancreatic Head vs. ADK Duodenum, p = 0.047
ADK Ampulla of Vater vs. ADK Duodenum, p = 0.873, ns
ADK Ampulla of Vater vs. NET Pancreatic Head, p = 0.001
ADK Duodenum vs. NET Pancreatic Head, p = 0.004

Median OS - not reached
Median OS - 33 months
Median OS - 42 months
Median OS - 17 months

Time from surgery (months)
Pancreatic Cancer

Effect of Hospital Volume, Surgeon Experience, and Surgeon Volume on Patient Outcomes After Pancreaticoduodenectomy

A Single-Institution Experience

C. Max Schmidt, MD, PhD, MBA; Olivier Turrini, MD; Purvi Parikh, MD; Michael G. House, MD; Nicholas J. Zyromski, MD; Atilla Nakeeb, MD; Thomas J. Howard, MD; Henry A. Pitt, MD; Keith D. Lillemoe

Arch Surg. 2010;145(7):634-640

Table 2. Perioperative Outcomes According to Surgeon Experience

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Less Experienced Surgeons (&lt;50 PDs)</th>
<th>Experienced Surgeons (≥50 PDs)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgeons, No.</td>
<td>13</td>
<td>6</td>
<td>NA</td>
</tr>
<tr>
<td>PDs, No.</td>
<td>144</td>
<td>859</td>
<td>NA</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>4</td>
<td>3</td>
<td>.09</td>
</tr>
<tr>
<td>Morbidity, %</td>
<td>53</td>
<td>39</td>
<td>.001</td>
</tr>
<tr>
<td>Pancreatic leak, %</td>
<td>20</td>
<td>10</td>
<td>.03</td>
</tr>
<tr>
<td>Operating time, min (range)</td>
<td>458 (442-475)</td>
<td>335 (323-347)</td>
<td>.04</td>
</tr>
<tr>
<td>Intraoperative blood loss, mL (range)</td>
<td>1918 (2004-1832)</td>
<td>1101 (1056-1146)</td>
<td>.002</td>
</tr>
<tr>
<td>PV resection, No. (%)</td>
<td>3 (4)</td>
<td>68 (96)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Resected lymph nodes, No. (range)</td>
<td>11 (10-12)</td>
<td>10 (9-11)</td>
<td>.40</td>
</tr>
<tr>
<td>Positive margins, %</td>
<td>14</td>
<td>11</td>
<td>.06</td>
</tr>
</tbody>
</table>
Pancreatic Cancer

Fig. 1. Trends in in-hospital mortality (a) and complication rates (b), 1998 to 2006. Source: Simons et al., Journal of Gastrointestinal Surgery 2009: [26].

Witkowski, J Surg Oncol, 2013
Pancreatic Cancer

Fig. 2. One-year survival after pancreatectomy for pancreatic cancer. 1980s: 58%; 1990s: 68% (\(P = 0.02\) vs. 1980s); 2000s: 68% (\(P = 0.02\) vs. 1980s). Source: Winter et al., Annals of Surgical Oncology 2012: [20].

Fig. 3. Long-term survival after pancreatectomy for pancreatic cancer (1-year survivors). 1980s, median = 23.2 months; 1990s, median = 25.6 months; 2000s, median = 24.5 months. \(P\)-values compare the specified decade to the 1980s.
Pancreatic Head Cancer (PHC)

- PHC frequently extends directly into the retroperitoneal spaces (PV/SMV/SMA)

- Venous invasion is due to tumour location rather than an indicator for aggressive tumour biology
  - Rationale for PV/SMV resection
  - Arterial invasion - a sign of tumour aggressive biology?

- Incidence of PV/SMV resection during PD for PHC:
  - 2 - 77%

- Incidence of arterial resections during PD for PHC:
  - < 10%

PV/SMV Resection in PHC

FIGURE 3. Patients undergoing an R1 resection had an improved overall survival compared with those with LA unresectable tumors (median survival of 14 vs 11 months; \( P < 0.001 \)).

Kato, Hepatobiliary Pancreat Dis Sci, March 2013

Konstantinidis, Ann Surg, April 2013
PV/ SMV Resection in PHC

- PV/ SMV resection
  - Routinely
  - Selectively: most of surgical teams

PV/ SMV Resection in PHC

Should the Portal Vein Be Routinely Resected During Pancreaticoduodenectomy For Adenocarcinoma?

Olivier Turrini, MD,* Jacques Ewald, MD,* Louise Barbier, MD,* Djamel Mokart, MD,† Jean Louis Blache, MD,† and Jean Robert Delpero, MD*

PV/SMV invasion in PHC

Principles of PV/ SMV Resection in PD

- The management of PV/ SMV invasion depends on:
  - The site of tumour invasion
  - Length of venous resection
Principles of PV/ SMV Resection in PD

• Venous resection at a late stage in order to reduce time to venous reconstruction
  – Posterior approach facilitates

• Graft interposition vs. direct anastomosis
  – Direct anastomosis preferred

• Routine heparinization – controversial
Technical Principles

- Splenic vein reconstruction
  - Not routinely
  - Inferior mesenteric vein drainage in splenic vein (48-68%)
  - Potential left-side portal hypertension

Technical details

Figure 28-8.

Figure 4. Lateral resection of the portal vein (PV) in a pancreatic head cancer tumor (T) with limited invasion of the portal vein (intraoperative aspects). Of notice, the portal flow is not completely obstructed.


Moldovan, Dumitrascu & Popescu, Chirurgia, 2012
Technical details


Moldovan, Dumitrascu & Popescu, Chirurgia, 2012
Figure 3. (A) Invasion of the pancreatic head cancer into the portal vein (arrow), after complete removal of the retroportal lamina from the right side of the superior mesenteric artery (SMA) (intraoperative aspects) (PV – portal vein, RHA – replaced right hepatic artery). (B) Complete removal of the mesopancreas (PV – portal vein, SMA – superior mesenteric artery; CBD – common bile duct.)
Outcomes in PD with PV/SMV Resection for PHC

- **Morbidity**: 42% (6 – 67%) vs. 44%
  - Thromboses rate - 17%
    - No differences according to anticoagulation
    - Higher when synthetic grafts were used
    - On late onset - recurrence

- **Mortality**: 3.3 (0 – 14.3%) vs. 3.7%

- **5-year survival**: 12.3% (0 – 24%) vs. 17%
  - No differences vs. PD without PV/SMV resection

Outcomes in PD with PV/SMV Resection for PHC

- Median length of resected vein
  - 3.9 cm (range, 0 - 10 cm)

- Negative resection margins
  - 16.6% - 100%

- Histological proof of venous invasion
  - 21 - 100%

Outcomes in PD with PV/SMV Resection for PHC

Wang, Cancer, 2012;
PD for ADK Pancreatic Head

Fundeni Clinical Institute 2002 - 2012
183 pts

• With PV/ SMV resection: 53 pts (29%)
  - PV resection: 44 pts
  - SMV resection: 9 pts

• 30 day mortality: 10 pts (5.5%)
  - No PV/ SMV resection: 5/ 130 (3.8%)
  - With PV/ SMV resection: 5 / 53 (9.4%)

  » P = 0.156, ns
PD for ADK Pancreatic Head

Fundeni Clinical Institute 2002 - 2012
183 pts

- No survival data: 15 pts (8%)

- Type of PV/SMV resection (53 pts):
  - Lateral with venous suture: 8 pts (15%)
  - Segmental resection with reconstruction:
    • Without graft: 26 pts (49%)
    • With graft (Gore-Tex): 19 pts (36%)
PD for ADK Pancreatic Head

Fundeni Clinical Institute 2002 – 2012
183 pts

• Median survival – 17 months:
  - Without PV/ SMV resection: 17 months
  - With PV/ SMV resection: 16 months
    » P = 0.689, ns
PD for ADK Pancreatic Head
Fundeni Clinical Institute
2002 - 2012

Group
- PV/SMV resection (-) Median OS - 17 months
- PV/SMV resection (+) Median OS - 16 months
+ censored
+ censored

Overall Survival

Time from surgery (months)

p = 0.689, ns
PD with PV/SMV resection for ADK Pancreatic Head

N = 110
14.5 months median survival
55% 1-year survival rate
23% 2-year survival rate
23% 3-year survival rate
14% 5-year survival rate
5-year survival rate – not reported

N = 53
16 months median survival
51% 1-year survival rate
38% 2-year survival rate
23% 3-year survival rate
14% 5-year survival rate

Median follow-up 76 months
Median follow-up 8 months
Arterial Resections in PD for PHC

• Implies resection of SMA, CHA, HA ....

• Controversial in term of benefits

Mollberg & Buchler, Ann Surg, 2011
Posterior Approach PD

Establishes invasion in the SMA, that signals an aggressive tumor biology and it is unlikely to be overcame by resection.

Technical Aspects

Amano, J Hepatobiliary Pancreat Surg, 2009
Arterial Resections in PD for PHC

- **Morbidity:** 53.6% (16.7 - 100%)
  - Total pancreatectomy as a routine?
    - (M. Buchler)

- **Mortality:** 11.8 (0 - 45.5%)
  - Higher vs. PD without arterial resection

Mollberg & Buchler, Ann Surg, 2011
Arterial Resections in PD for PHC

- Negative resection margins
  - 13.3% - 100%

- Histological proof of arterial invasion
  - 0 - 100%
Outcomes in Arterial Resection for PHC

**Fig. 1** Kaplan–Meier survival curves for patients with pancreat adenocarcinoma who had pancreatic resection with arterial *en bloc* resection and reconstruction (group 1, 29 patients), pancreatic resection without vascular resection (group 2, 449 patients) or palliative bypass (group 3, 40 patients). $P = 0.028$, group 1 *versus* group 3; $P < 0.001$, group 2 *versus* group 3; $P = 0.152$, group 1 *versus* group 2 (log rank test)

Bockhorn & Izbicki, Br J Surg, 2010

**Fig. 4.** Comparison of survival curves of patients who underwent pancreatic resection with or without AR. No significant difference was found between the two groups ($P = 0.581$). Group AR+: —, group AR−: - - - -

Bachellier & Jaeck, J Surg Oncol, 2011

<table>
<thead>
<tr>
<th>TABLE V. Multivariate Cox Regression Analysis of Prognostic Factor for Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relative risk (95% CI)</strong></td>
</tr>
<tr>
<td><strong>$P$</strong></td>
</tr>
<tr>
<td>Perineural invasion (yes vs. no)</td>
</tr>
<tr>
<td>Number of resected lymph nodes ($\leq 15$ vs. $&gt;15$)</td>
</tr>
<tr>
<td>Arterial wall invasion (yes vs. no)</td>
</tr>
</tbody>
</table>
Conclusions: AR in patients undergoing pancreatectomy for pancreatic cancer is associated with a poor short and long-term outcome. Pancreatectomy with AR may, however, be justified in highly selected patients owing to the potential survival benefit compared with patients without resection. These patients should be treated within the bounds of clinical trials to assess outcomes after AR in the era of modern pancreatic surgery and multimodal therapy.

Arterial Resections in PD for PHC

Brasoveanu, Dumitrascu & Popescu, Chirurgia, 2009
Pancreatic Cancer

- Adjuvant chemotherapy with gemcitabine or 5FU/folinic acid is the current recommended gold standard in the management of resected pancreatic cancer
  - ESPAC 1 (5 FU)
  - CONKO-001 (Gemcitabine)
  - ESPAC 3 (Gemcitabine vs. 5 FU)
    » Less than 5 months
Survival Statistics Gone Awry
Pancreatic Cancer, a Case in Point

Birgir Gudjonsson, M.D., F.A.C.P., F.R.C.P.
The Medical Clinic, Reykjavik, Iceland.

Resections for pancreatic cancer have been performed for 65 years, with approximately 20,000 reported. A number of authors claim a 5-year survival rate of 30% to 58%. Review of the literature reveals only about 1,200 5-year survivors; however, 10 times as many individual resected survivors have been reported (in various countries), and nonresected survivors are overlooked. This high survival percentage is obtained by reducing the subset on which calculations are based and by using methods such as the Kaplan–Meier method, which produces higher figures as increasing numbers of patients are lost to follow-up. After adjustments, hardly more than 350 resected survivors could be found. Revision of statistical methods is urgently needed.
Take Home Messages

- Pancreatic cancer – dismal prognosis

- Resection is the single hope for long-term survival

- R0 resection margins the most important determinant of survival
Take Home Messages

• PV/ SMV involvement is no longer a contraindication for resection but arterial invasion yes

• Surgeon’s experience impact postoperative morbidity and mortality rates
  - Highly specialized centers and multidisciplinary teams for better outcome
Vă multumesc !