Nodal Spread and Extent of Lymphadenectomy in Hepatobiliary and Pancreatic Cancer

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• Pancreatic adenocarcinoma
  • Pancreaticoduodenectomy
  • Distal pancreatectomy

• Cholangiocarcinoma
  • Intrahepatic
  • Extrahepatic

• Gallbladder cancer
Pancreatic adenocarcinoma
Introduction

- Lymph node status of patients with resectable pancreatic ductal adenocarcinoma is an important predictor of survival
- Whether survival benefits of extended lymphadenectomy is disputed
- No true definition of the optimal extent of the lymphadenectomy
Randomized Controlled Trials

- 4 RCT (in 6 papers) analyzed the results of extended versus standard lymphadenectomy but failed to find better outcomes in patients undergoing extended Ln dissection
- Trials difficult to compare since classification of Ln stations, and definition of standard or extended lymphadenectomy widely vary.
- There is no level I evidence on optimal lymphadenectomy
- 2013: consensus meeting ISGPS

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Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: A consensus statement by the International Study Group on Pancreatic Surgery (ISGPS)

Kennis / Ervaring / Zorg

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Farnell et al. Surgery 2005; 138: 618-630

Tol et al. Surgery 2014, 156(3): 591-600
**Table 1** Study characteristics of the four randomized clinical trials comparing standard versus extended lymphadenectomy during pancreaticoduodenectomy

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Multi-center</td>
<td>Single center</td>
<td></td>
<td>Multi-center</td>
</tr>
<tr>
<td>No. of patients</td>
<td>Standard: 40</td>
<td>Extended: 41</td>
<td>Standard: 40</td>
<td>Extended: 51</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection type</td>
<td>PP or DG</td>
<td>PP</td>
<td>DG</td>
<td>PP, SP, DG</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sequential</td>
<td>En bloc</td>
</tr>
<tr>
<td>Node dissection</td>
<td>En bloc</td>
<td>Sequential</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LN stations removed</td>
<td>LN5, 6, 8, 12, 13, 17</td>
<td>LN12⁵, LN12⁶, LN12⁷, LN12⁸, LN12⁹, LN12¹₀</td>
<td>LN3, 4, 6, 8, 9, 11, 12, 13, 14, 15, 16, 17</td>
<td>LN13, 17</td>
</tr>
<tr>
<td>Operating time (min)</td>
<td>372</td>
<td>354</td>
<td>378</td>
<td>426</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>396</td>
<td>547</td>
</tr>
<tr>
<td>No. of LNs removed</td>
<td>13.3 (1–35)*</td>
<td>17*</td>
<td>15 (3–13)*</td>
<td>13.3 (4–30)*</td>
</tr>
<tr>
<td></td>
<td>19.8 (3–76)*</td>
<td>28.5*</td>
<td>36 (6–74)*</td>
<td>40.1 (15–81)*</td>
</tr>
<tr>
<td>N+ status</td>
<td>24 (60 %)</td>
<td>24 (59 %)</td>
<td>(82 %)</td>
<td>32 (63 %)</td>
</tr>
<tr>
<td></td>
<td>(82 %)</td>
<td>(77 %)</td>
<td>(95 %)*</td>
<td>30 (60 %)</td>
</tr>
<tr>
<td>R0 resection</td>
<td>29 (72.5 %)</td>
<td>32 (78 %)</td>
<td>(80 %)*</td>
<td>48 (94 %)</td>
</tr>
<tr>
<td></td>
<td>80/44/23 (75/34/13 %)</td>
<td>77/44/29 (73/38/29 %)</td>
<td>(83)</td>
<td>45 (90 %)</td>
</tr>
<tr>
<td>Adjuvant treatment</td>
<td>IORT (10)</td>
<td>CRT (81)</td>
<td>CRT (83)</td>
<td>CRT</td>
</tr>
<tr>
<td></td>
<td>IORT (9)</td>
<td>CRT (125)</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>2 (5 %)</td>
<td>6 (4 %)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2 (5 %)</td>
<td>3 (2 %)</td>
<td>1 (3 %)</td>
<td>1 (2 %)</td>
</tr>
<tr>
<td>1-, 3-, 5-Year</td>
<td>80/44/23 (75/34/13 %)</td>
<td>77/44/29 (73/38/29 %)</td>
<td>82/41/16 (73/38/29 %)</td>
<td>78/28/16 (54/18/6)</td>
</tr>
<tr>
<td>survivals (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median survival</td>
<td>11.2</td>
<td>30.0</td>
<td>19.9</td>
</tr>
<tr>
<td></td>
<td>(months)</td>
<td>16.7</td>
<td>28.0</td>
<td>13.8</td>
</tr>
</tbody>
</table>


*a* Significant differences between the two groups

*a* Nodes in the lower hepatoduodenal ligament

*b* Nodes in the right hepatoduodenal ligament for LN12, on the superior mesenteric artery for LN14
Lymph drainage pathways

Identification of the Lymphatic Drainage Pathways from the Pancreatic Head Guided by Indocyanine Green Fluorescence Imaging during Pancreaticoduodenectomy

Seiko Hirono, Masaji Tani, Manabu Kawai, Ken-Ichi Okada, Motoki Miyazawa, Atsushi Shimizu, Kazuhisa Uchiyama, Hiroki Yamaue

Dig Surg 2012;29:132–139

- Indocyanin green fluorescence imaging
- Identification of seven pathways:
  - Along anterior or posterior pancreaticoduodenal arcade
  - Running obliquely down behind the SMV
  - Reaching the left side of the SMA
  - Running upward between SMV and SMA
  - Along the middle colic artery towards transverse colon
  - Reaching para-aortic region
  - Reaching hepatoduodenal ligament

| Table 2. Lymphatic drainage pathways in the patients injected with ICG into the anterior surface of the uncinate process of the pancreas |
|---|---|---|---|---|---|
| No. | Anterior pancreaticoduodenal arcade | Behind the SMV | Left side of the SMA (11, 12, 13 regions) | Longitudinally upward between the SMV and SMA | Origin of the middle colic artery toward the transverse colon | PA region | Hepatoduodenal ligament |
| 1 | o | o | o | o | o | x | x |
| 2 | o | o | o | o | o | x | x |
| 3 | o | o | o | o | o | x | x |
| 4 | o | o | o | o | o | x | x |
| 5 | o | o | o | o | o | x | x |
| 6 | o | o | o | o | o | x | x |
| 7 | o | o | o | o | o | x | x |
| 8 | o | o | o | o | o | x | x |
| 9 | o | o | o | o | o | x | x |
| 10 | o | o | o | o | o | x | x |

| Table 3. Lymphatic drainage pathways in the patients injected with ICG into the posterior surface of the uncinate process of the pancreas |
|---|---|---|---|---|---|
| No. | Posterior pancreaticoduodenal arcade | Behind the SMV | Left side of the SMA (11, 12, 13 regions) | Longitudinally upward between the SMV and SMA | Origin of the middle colic artery toward the transverse colon | PA region | Hepatoduodenal ligament |
| 11 | o | o | x | o | o | x | x |
| 12 | o | o | x | o | o | x | x |
| 13 | o | o | x | o | o | x | x |
| 14 | o | o | x | o | o | x | x |
| 15 | o | o | x | o | o | x | x |
| 16 | o | o | x | o | o | x | x |
| 17 | o | o | x | o | o | x | x |
| 18 | o | o | x | o | o | x | x |
| 19 | o | o | x | o | o | x | x |
| 20 | o | o | x | o | o | x | x |
Classification for nodal stations in pancreatic surgery

Pancreaticoduodenectomy: Standard or extended lymphadenectomy?

- 2 meta-analyses
  - Michalski: 3 RCT
  - Iqbal: 15 studies: 3 RCT, 3 prospective non-randomized trials, nine retrospective series

- Conclusion:
  - No benefit of extended lymphadenectomy

- Consensus:
  - Extended lymphadenectomy is not recommended and might be associated with more morbidity such as diarrhea and weight loss.
Which Ln stations should be included in standard lymphadenectomy for pancreatic ductal carcinoma?

- No discussion: 13 and 17 since they are embedded in the pancreaticoduodenal groove
- Only Ln 14 a and 14 b should be included in standard lymphadenectomy since extended lymphadenectomy is not beneficial and leads to more morbidity
- Nodes around the coeliac trunk (Ln 9) should not be resected
How high should resection go into hepatoduodenal ligament?

- Should be resected:
  - Ln 5 (suprapyloric)
  - Ln 6 (infrapyloric)
  - Ln 8a (anterosuperior of common hepatic artery)
  - Ln 12b and 12c (along bile duct)
- Resection should extend to the level where the right hepatic artery crosses over to the right liver
- Discussion:
  - Ln 8p (posterior of common hepatic artery)
  - Some surgeons resect this node as part of the resection field
Extent towards left gastric artery, splenic artery and aorta in pancreaticoduodenectomy?

- Should not be resected in PD:
  - Ln11 and Ln 7
- Discussion on Ln 16
  - Some studies reported no difference in patients with or without positive para-aortic Ln’s
  - Other studies reported poorer survival rates in positive Ln’s
  - Positive 16b1 did not have effect on survival
- Consensus
  - Routine resection of station 16 is not recommended
  - Some surgeons include 16b1 in the resection field
Conclusion for pancreaticoduodenectomy

- A standard lymphadenectomy in pancreaticoduodenectomy should include: Ln stations 5, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a, 14b, 17a and 17b
- Discussion: Ln 8p and 16b1
• Studies on lymphadenectomy in distal pancreatectomy are scarce
• The most recent study on distribution of metastatic Ln’s reporting the greatest incidence of nodal involvement, included stations 8, 11, 14, 16
• But no study could provide evidence on survival benefit related to extended lymphadenectomy
• Consensus: no evidence to support extended lymphadenectomy of 8, 14, 16
Distal pancreatectomy

• Discussion:
  • Ln 9, some surgeons resect this Ln station especially when the lesion is a pancreatic corpus tumor, others don’t

• Conclusion for distal pancreatectomy:
  • Should include: Ln 10, 11, 18
  • Discussion: Ln 9
  • Splenectomy is indicated to ensure adequate excision primary tumor and Ln’s
Which nodal stations should undergo frozen section?

- Positive Ln’s can influence management during pancreatectomy and the strategy towards adjuvant or palliative treatment.
- Should positive Ln’s beyond the resection field be considered as metastatic disease?
- Should the surgeon continue with the resection if possible to achieve R0 resection?
Ln’s beyond the standard resection field: consensus

- In patients with preoperative proven positive Ln’s outside the standard resection field, surgical exploration is not recommended.
- When a suspicious Ln is discovered beyond the standard resection field, it should be removed and sent for frozen section.
- Positive Ln’s around coeliac trunk (9), left of superior mesenteric artery (14c, 14d) and caudal to the mesocolon are considered metastatic, pancreaticoduodenectomy should be abandoned.
- Positive Ln’s in position 16 during pancreaticoduodenectomy, resection should be continued.
- Decision to abandon resection depends also on comorbidity, age, local ingrowth into main vessels and markedly increased CA 19.9.
Minimal number of Ln’s retrieved during pancreaticoduodenectomy

• Several articles have discussed
  • the prognostic value of the number of harvested Ln’s
  • The Lymph Node Ratio: positive / total Ln ‘s examined
• A minimum of 12-15 Ln’s should be retrieved
• A LNR > 0.2 was an independent negative predictor of survival.

Sierzega et al. Pancreas 2006; 33: 240-245
Pawlik et al. Surgery 2007; 141: 610-618
Sahin et al. Pancreas 2011; 40: 1029-1033
Impact of lymph node ratio on survival in patients with pancreatic and periampullary cancer

J. A. M. G. Tol, L. A. A. Brosens, S. van Dieren, T. M. van Gulik, O. R. C. Busch, M. G. H. Besselink, and D. J. Gouma

Table 4 Multivariable Cox regression analysis of 3-year survival following pancreatoduodenectomy in 350 patients with pancreatic cancer

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>$P$</th>
<th>$\beta$</th>
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<tbody>
<tr>
<td>Male sex</td>
<td>1.21</td>
<td>0.299</td>
</tr>
<tr>
<td>R1 resection margin</td>
<td>1.55</td>
<td>0.022</td>
</tr>
<tr>
<td>Metastasis</td>
<td>1.36</td>
<td>0.607</td>
</tr>
<tr>
<td>Tumour differentiation</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Well (grade 1)</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td>Moderate (grade 2)</td>
<td>1.20</td>
<td>0.597</td>
</tr>
<tr>
<td>Poor (grade 3)</td>
<td>2.78</td>
<td>0.003</td>
</tr>
<tr>
<td>Perineural growth</td>
<td>1.02</td>
<td>0.907</td>
</tr>
<tr>
<td>Angioinvasion</td>
<td>1.25</td>
<td>0.263</td>
</tr>
<tr>
<td>LNR*</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>$0$</td>
<td>1.00 (reference)</td>
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</tr>
<tr>
<td>$\leq 0.18$</td>
<td>1.12</td>
<td>0.689</td>
</tr>
<tr>
<td>$&gt; 0.18$</td>
<td>1.75</td>
<td>0.012</td>
</tr>
<tr>
<td>No adjuvant therapy</td>
<td>1.54</td>
<td>0.045</td>
</tr>
</tbody>
</table>

LNR $\leq 0.18$ median survival 26 months  
LNR $> 0.18$ median survival 16 months

Table 5 Multivariable Cox regression analysis of 3-year survival following pancreatoduodenectomy in patients with distal common bile duct cancer and periampullary cancer

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>$P$</th>
<th>Hazard ratio</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice</td>
<td>–</td>
<td>1.93 (1.07, 3.48)</td>
<td>0.030</td>
</tr>
<tr>
<td>R1 resection margin</td>
<td>1.22</td>
<td>0.412</td>
<td>2.68 (1.75, 4.10)</td>
</tr>
<tr>
<td>Tumour category</td>
<td>0.505</td>
<td></td>
<td>0.667</td>
</tr>
<tr>
<td>T1</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>1.04 (0.51, 2.13)</td>
<td>0.912</td>
<td>0.76 (0.40, 1.42)</td>
</tr>
<tr>
<td>T3</td>
<td>0.70 (0.35, 1.41)</td>
<td>0.323</td>
<td>1.04 (0.57, 1.99)</td>
</tr>
<tr>
<td>T4</td>
<td>0.94 (0.29, 3.07)</td>
<td>0.914</td>
<td>0.99 (0.38, 2.74)</td>
</tr>
<tr>
<td>M1 category</td>
<td>3.35 (0.43, 26.31)</td>
<td>0.251</td>
<td>–</td>
</tr>
<tr>
<td>Tumour differentiation</td>
<td>0.003</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Well (grade 1)</td>
<td>1.00 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate (grade 2)</td>
<td>1.62</td>
<td>0.430</td>
<td></td>
</tr>
<tr>
<td>Poor (grade 3)</td>
<td>3.30 (1.02, 10.60)</td>
<td>0.046</td>
<td></td>
</tr>
<tr>
<td>LNR</td>
<td>4.51 (2.03, 10.05)</td>
<td>&lt; 0.001</td>
<td>7.82 (3.96, 15.55)</td>
</tr>
<tr>
<td>Overall morbidity</td>
<td>0.77 (0.49, 1.22)</td>
<td>0.270</td>
<td></td>
</tr>
</tbody>
</table>


Kennis / Ervaring / Zorg
Cholangiocarcinoma
NCCN guidelines

- Intrahepatic cholangiocarcinoma
  - Resectable → resection and consider lymphadenectomy

- Principles of surgery
  ‘A portal lymphadenectomy is reasonable since this provides relevant staging information’
  ‘Lymph node metastases beyond the porta hepatis … contraindicate resection’
  ‘Gross lymph node metastases to the porta hepatis portend a poor prognosis and resection should only be considered in highly selected cases’
Lymphadenectomy in the staging and treatment of intrahepatic cholangiocarcinoma: a population-based study using the National Cancer Institute SEER database

Clancy J. Clark¹, Christina M. Wood-Wentz², Kaye M. Reid-Lombardo³, Michael L. Kendrick⁴, Marianne Huebner⁵ & Florencia G. Que¹

HPB 2011, 13, 612-620

- N= 4893
- Only 13.5 % had lymphadenectomy
- Worse 5 year survival in case of positive nodes (8.4% versus 25.9%)
- Clinical benefit of lymphadenectomy in ICC remains unknown
Intrahepatic cholangiocarcinoma

Treatment and Prognosis for Patients With Intrahepatic Cholangiocarcinoma
Systematic Review and Meta-analysis

Michael N. Mavros, MD; Konstantinos P. Economopoulos, MD; Vangelis G. Alexiou, MD, PhD; Timothy M. Pawlik, MD, MPH, PhD

- **Review**
  - n= 4756
  - 82% had major hepatectomy, 67% lymphadenectomy, 34% had Ln metastases
  - Predicting shorter OS = large tumor size, multiple tumors, lymph node metastases and vascular invasion

- **Meta-analysis**
  - n= 2132
  - Predicting shorter OS = older age, larger tumor size, multiple tumors, lymph node metastases, vascular invasion and poorer differentiation
Intrahepatic cholangiocarcinoma

N= 449

Lymphadenectomy performed in 55%

30% had Ln metastases

Associated with worse outcome: median survival 30 m versus 24 m

Other factors associated with adverse prognosis include positive margin status, multiple lesions and vascular invasion
NCCN guidelines

• Extrahepatic cholangiocarcinoma
  • Hilar cholangiocarcinoma
    Principles of surgery:
    • ‘Exploration … distant lymph nodes beyond the porta hepatis … contraindicate resection’
    • ‘Regional lymphadenectomy of the porta hepatis is carried out.’

• Distal Cholangiocarcinoma
  Principles of surgery:
  • Cfr. Pancreatic head resection
Perihilar Cholangiocarcinoma

Does the extent of lymphadenectomy, number of lymph nodes, positive lymph node ratio and neutrophil-lymphocyte ratio impact surgical outcome of perihilar cholangiocarcinoma?

Abdul R. Hakeem, Gabriele Marangoni, Stephen J. Chapman, Richard S. Young, Amit Nair, Ernest L. Hidalgo, Giles J. Toogood, Judy I. Wyatt, Peter A. Lodge and K.R. Prasad


- 5 year OS for node-positive status was 10 %, whereas for node-negative status OS was 41%
- There was no difference between OS and DFS
- Patients with more than 20 Ln’s removed had worse 5 year OS than patients with less than 20 Ln’s removed
  - Trend towards more postoperative complications
  - In group > 20 Ln’s removed, 30 day mortality was 13 % versus 3%
Perhilar and intrahepatic cholangiocarcinoma

Patterns and Prognostic Significance of Lymph Node Dissection for Surgical Treatment of Perhilar and Intrahepatic Cholangiocarcinoma

Lymph nodal metastases was one of the strongest predictors of survival

- Consensus on the extent of lymphadenectomy is still not available
- Recommend to retrieve more Ln’s to better stage patient
Gallbladder carcinoma
• Resectable disease → radical cholecystectomy
  + part of liversegment IV B and V
  + lymphadenectomy
  +/- bile duct excision depending on frozen section
Conclusion: Lymphadenectomy in HPB cancer

- Pancreaticoduodenectomy
  - A standard lymphadenectomy in pancreaticoduodenectomy should include: Ln stations 5, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a, 14b, 17a, and 17b
  - Discussion: Ln 8p and 16b1
- Distal Pancreatectomy
  - Should include: Ln 10, 11, 18
  - Discussion: Ln 9
  - Splenectomy is indicated to ensure adequate excision of primary tumor and Ln’s
- Cholangiocarcinoma and gallbladder carcinoma
  - No consensus on the extent, only staging