Chapter 3

Lymphadenectomy in Pancreatic Cancer Surgery

Daniel Kostov

Department of Surgery, Naval Hospital of Varna, Bulgaria

*Corresponding Author: Daniel Kostov, Department of Surgery, Naval Hospital of Varna, Bulgaria, Email: danielkostov@abv.bg

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Abstract

Pancreatic cancer is one of the most aggressive malignancies with poor rates of survival. Lymph node involvement in pancreatic adenocarcinoma is a key prognostic factor. We present the operative technic and the volume of the standard lymph node dissection, as well as our own experience with this type of operation. Pancreaticoduodenectomy with standard lymphadenectomy including at least 15 lymph nodes should be the procedure of choice in adenocarcinoma of the pancreatic head. Extended lymphadenectomy should not be applied routinely in patients with pancreatic cancer requiring pancreaticoduodenectomy or distal pancreatectomy. The radical antegrade modular pancreato-splenectomy is recommended for cancer location in the body or tail. Lymph node ratio $\geq 0.2$ is an independent adverse prognostic factor, which is powerful and useful for prognostic assessment for pancreatic cancer. We establish a directly proportional correlation between the presence of metastatic lymph nodes independently of their number and the development of local recurrence and distant metastases. The most commonly affected by metastasis are lymph nodes around superior mesenteric artery (station 14) and anterior pancreatic nodes (station 13). Pancreatic cancer should be managed as a systemic disease, even in patients with evidence of only local or regional disease; consequently, any effort for local control can have little effect on survival. This finding confirms the fact that the biology of the disease remains the most important determining factor affecting the final
outcome, despite the progress in surgical technique and systemic therapy.

**Introduction**

Pancreatic cancer (PC) treatment is an interdisciplinary challenge as this tumor entity is still characterized by a poor prognosis, with long-term survival less than 6% [1-3]. PC causes about 20 million deaths worldwide each year with an increasing incidence rate [4]. Nowadays it is the fourth leading cause of death among cancers, and is one of the common gastrointestinal malignancies. Although recent advances in chemotherapy have made an impact on PC treatment, the surgical resection still remains the only hope for cure of this lethal disease [5,6]. However, the PC easily invades to adjacent organs, especially to the surrounding major vasculatures, due to its malignant behavior and the anatomical location of the pancreas. Less than 20% of patients who present with PC have resectable tumors because of local invasion, together with frequent occurrences of distant metastasis[7]. The Cancer Statistics Review (2002–2008) from the US Surveillance Epidemiology and End Results showed that 53% of all patients with PC had concomitant distant metastases at the time of diagnosis; only 15–20% of the remaining patients were eligible for potentially curative resection, and up to 25% were staged as having locally advanced disease and thus were potentially “inoperable” because of involvement of
surrounding major vessels [8].

Pancreatic resections for malignant disease processes, are some of the most technically challenging operations performed by surgeons. Difficulties with PC include the increased frequency of regional or distant lymph node involvement, positive resection margins in the pancreas itself and in the retroperitoneal tissues [9]. Despite the recent advances in imaging, staging, adjuvant therapy, aggressive surgery, and downstaging by neoadjuvant therapy, there is no improvement in the overall survival of these patients. Randomized controlled trials of surgical resection followed by adjuvant therapy demonstrate disease relapse rates of >70% [10] while autopsy series of patients after resection show local and distant failure rates of 75% and 88%, respectively [11]. Only 30%-40% of pancreatectomies achieve actual R0 resection, even in experienced hands, because of the early spread into and along the neural sheaths [12].

Standardization of surgical procedures and centralization of pancreatic surgery in high-volume institutions guarantees the best patient’s care, a mortality of 0.7%-3% and a morbidity of 36%-41% [13]. Median overall survival of primarily resectable patients ranges between 20 and 24 months, while survival in locally advanced, non-metastatic PC is 9-13 months only. However, in patients who are suitable for resection, five-year survival rates of 25% are possible, which underlines that surgery offers the only
chance of cure and long-term survival [14].

Pancreaticoduodenectomy (PD) is the only effective treatment for cancers of the pancreatic head region. The major goals that must be achieved during pancreatic resection include reduced postoperative hemorrhaging and operation time, because integrated resection of the pancreatic head is the most difficult step of radical PD in patients with invasion or oppression of the portal vein and superior mesenteric vein by the tumor. The extent of the cancer to the regional lymph nodes is a powerful prognostic factor after resection independently from cancer histology [15]. For this reason, lymphadenectomy is considered a crucial step of PD for pancreatic head cancer. In 2014, a consensus meeting of the International Study Group on Pancreatic Surgery (ISGPS) in Verona on the definition and the prognostic role of lymphadenectomy during PD for cancer stated that: (i) the use of the nomenclature for nodal stations based on the classification of the Japanese Pancreas Society [21-16] is recommended; (ii) an extended lymphadenectomy does not improve the oncological outcome of patients and should not be associated with PD for cancer; (iii) lymphadenectomy should include the removal of the hepatoduodenal ligament nodes (stations 5, 6, 12b1, 12b2, 12c), nodes along the hepatic artery (station 8a), the posterior surface of the pancreatic head (station 13a and 13b), the superior mesenteric artery (SMA) (14a right lateral side, 14b right lateral side) and nodes of the
anterior surface of the pancreatic head (stations 17a and 17b) [17].

Whereas operable cancers of the pancreatic body and tail are less common than those of the pancreatic head, distal pancreatectomy (DP) is the only effective treatment for cancers of the pancreatic body and tail. DP has been the standard procedure for these cancers for decades. However, the recurrence rate after DP has remained high [18-20]. Lymphadenectomy during pancreatectomy for patients with pancreatic adenocarcinoma in the body or tail includes nodes in stations 10 in the hilum of the spleen, 11 along the splenic artery, and 18 along the inferior border of the body and tail of the pancreas. Lymph node station 9 is only suggested to be included in the resection when tumors are confined to the area of the body of the pancreas [17].

Today, standardization of surgical procedures and centralization of pancreatic surgery in high volume institutions guarantees the best patient care and mortality rates below 5%. This chapter summarizes the current state of lymphadenectomy in surgery for pancreatic adenocarcinoma with focus on standard lymphadenectomy. We studied the lymph node involvement in patients with resectable P-C undergoing PD or DP with standard lymphadenectomy.
Standard Lymphadenectomy

Lymphadenectomy in Pancreaticoduodenectomy

The standard lymphadenectomy formulated by the ISGPS based on the literature and expert opinions is a guide for surgeons when operating on patients with resectable pancreatic adenocarcinoma. Compelling evidence-based reports, both randomized, controlled trials and meta-analyses, show no benefit to performing an extended lymphadenectomy [10,11,21-29]. Extended lymphadenectomy has a harmful impact on patients undergoing oncological PD compared with standard lymphadenectomy. A standard lymphadenectomy should include supra- and infrapyloric nodes (stations 5,6), nodes to the right of the hepatoduodenal ligament (stations 12b1, 12b2, and 12c), anterior and posterior pancreatico-duodenal nodes (stations 17a, 17b, 13a, and 13b), nodes to the right of the SMA (stations 14a and 14b), and anterior to the common hepatic artery (station 8a) (Figure 1). Lymphnode stations 13 and 17 are embedded within the pancreaticoduodenal-groove, and therefore are always resected with the specimen (Figure 2).

The standard lymphadenectomy includes lymph node stations 5, 6, 8a, 12b, and 12c found in the hepatoduodenal ligament. Lymphadenectomy should extend up to the level of the right hepatic artery as it crosses over to the right liver to adequately clear the hepatoduodenal liga-
ment (Figure 3 and Figure 4).

**Figure 1:** Volume of the standard lymphadenectomy during PD in patients with pancreatic head adenocarcinoma.
Figure 2: Lymph node stations 13 and 17 are embedded within the specimen– tumor (1), d. choledochus (2), duodenum (3).

A complete resection of the lymph nodes around the SMA as part of an extended lymphadenectomy has not been shown to be beneficial for the patient and leads to more morbidity, in particular postoperative diarrhea, and is not indicated. Diarrhoea, as assessed up to 4 months after surgery, was markedly more common in patients in whom nerve tissue surrounding the SMA was cleared circumferentially. By contrast, in studies in which only the right lateral aspect of the nerve plexus was dissected, no impact on intestinal transit was observed. Only lymph node stations along the right side of the SMA (stations 14a and 14b) should be resected in a standard lymphadenectomy during PD (Figure 5, Figure 6 and Figure 7). Complete resection around the SMA is not indicated. Nodes around the celiac trunk should not be resected.
Figure 3: Lymph node dissection in the hepatoduodenal-ligament: left gastric artery (1), proper hepatic artery (2), common hepatic artery (3), portal vein (4), interrupted common hepatic duct (5) and an aberrant right hepatic artery (6) of Michels’ type III.

Pawlik et al. demonstrated that less than 12 nodes retrieved in N0 disease resulted in poorer overall survival and Tomlinson and colleagues highlighted that $\geq 15$ nodes were required to confer a survival advantage in N0 disease [30,31]. The number of lymph nodes required to minimize the risk of the stage migration phenomenon is proposed to be between 10 and 15 [32,33]. The American Joint Committee on Cancer (AJCC) TNM classification and the Royal College of Pathologist of United Kingdom have set 12 and 15 lymph nodes, respectively, as the minimal number to be collected at surgery and these figures
were utilized to create categorical variables for the survival analysis [34,35]. The standard lymphadenectomy should regularly provide ≥15 lymph nodes to ensure adequate pathologic staging of the disease [17].

**Figure 4:** Lymph node dissection in the hepatoduodenal ligament: left gastric artery (1), left hepatic artery from which the artery for segment 4 (2) arises, common hepatic artery (3), portal vein (4), interrupted common hepatic duct (5), aberrant right hepatic artery of Michels’ type VIII (6), accessory left hepatic artery (7) and gastroduodenal artery (8).
Figure 5: Lymphadenectomy along the right side of the SMA (2): mesenterico-portal vein (1) and an aberrant right hepatic artery extending from the SMA (2).

The number of positive lymph nodes was shown to have an important impact on long-term outcome. In patients with one positive node, long-term survival was equal to patients with an N0 stage, whereas two or more positive nodes were associated with a significantly poorer survival, regardless to the total number of positive nodes. This observation was similarly made in DP with a cutoff level of three or more positive nodes. These results underline the importance of lymph node dissection, as in case of only one or two positive nodes the radical removal leads to a dramatically improved prognosis, compared to
patients with residual tumor manifestation or merely palliative therapy.

Figure 6: Lymphadenectomy along the right side of the SMA (3): portal vein (1), superior mesenteric vein (2) and an aberrant common hepatic artery extending from the SMA (3).

Very important prognostic factor is the number of harvested lymph nodes and the ratio of positive to total examined lymph nodes that is, the lymph node ratio. Lymph node ratio is a commonly used term initially introduced to characterize lymphatic tumor load and create a prognostic parameter independent from the rough estimation N0 vs. N1 or the overall number of positive lymph nodes. Usually the number of 0.2 is accepted as the separation level that indicates poor survival. Lymph node ratio > 0.2, together with vascular or perineural invasion, and a positive resection margin are all independent prognos-
tic factors in determining long-term survival in patients undergoing resection for periampullary tumors [36-39].

**Figure 7:** Lymphadenectomy along the right side of the SMA (2): portal vein (1), superior mesenteric vein (2) and an aberrant common hepatic artery extending from the SMA (3).

**Lymphadenectomy in Distal Pancreatectomy**

Lymph node involvement in tumors located in the body or tail of the gland is most frequently observed in the lymph nodes attached to the pancreas in the resected specimen. Standard lymphadenectomy during pancreatectomy for patients with pancreatic adenocarcinoma in the body or tail includes lymph nodes in stations 10 in the hilum of the spleen, 11 along the splenic artery, and 18 along the inferior border of the body and tail of the pancreas (Figure 8) [17].
**Figure 8:** Standard lymphadenectomy in tumors located in the body or tail of the pancreas (lymph node stations 10, 11, 18).

**Figure 9:** A tumor localized at the boundary between the body and tail of the pancreas.
**Figure 10:** A tumor localized at the boundary between the body and tail of the pancreas.

Lymph node station 9 is only suggested to be included in the resection when tumors are confined to the area of the body of the pancreas (Figure 9, Figure 10, Figure 11 and Figure 12). In patients undergoing left-sided pancreatectomy for malignant neoplasms, splenectomy is indicated to ensure adequate excision of the primary tumor and lymph nodes.

Two or three positive nodes were not associated with an impairment of the prognosis but had an equal survival to those patients with an N0 situation. A routine removal of the directly attached and peripancreatic nodes is a highly important part of the resection to achieve best oncological
outcome. In contrast, a more extended lymphadenectomy cannot be recommended from the available data, as this is, comparable to the setting of pancreatic head resection, associated with an increase in morbidity without proven oncological benefit.

**Figure 11:** A tumor (yellow circle) localized in the body of the pancreas. The lymphadenectomy includes lymph nodes in station 9 (lymph nodes around the celiac artery)–a.gastroduodenalis (1), common hepatic artery (2), a.gastricasinistra (3), a.lienalis (4).

**Lymphadenectomy in Total Pancreatectomy**

From the oncological point of view, a multifocal pancreatic cancer as well as multiple metastases in the pancreas are indications for a primary total pancreatectomy. This procedure may be necessary to achieve a tumor-free
reseption margin and R0 situation in centrally localized tumors of the pancreatic body. The removal of the gland as an en bloc pancreatectomy should be performed to avoid pancreatic transection with the risk of tumor cell spilling. The volume of lymph node dissection in total pancreatectomy combines a standard lymphadenectomy in PD and DP.

**Figure 12:** A specimen from a tumor located in the body of the pancreas in the center of the tumor is visible a ductus pancreaticus.

**Prospective Study**

We studied the rate of metastatic lymph nodes according to their localization in patients with resectable pancreatic head adenocarcinoma, undergoing PD with standard lymphadenectomy [40]. Medical records of 116 consecutive patients treated for pancreas head adenocarcinoma at Naval Hospital of Varna, Bulgaria, between January 2004 and December 2012 were analyzed. Patients underwent a
classical Whipple’s procedure or pylorus preservation with standard lymphadenectomy. Pancreatogastrostomy in our modification was the preferred anastomotic technique [41]. Tumors were staged after resection according to the 7th edition of the American Joint Committee on Cancer Staging Manual [42]. Postoperatively, 82 (70.6%) patients received adjuvant 5-fluorouracil or gemcitabine-based regimens, including radiation as a component of adjuvant therapy. The follow-up from the date of surgery for all the patients was at least 18 months long. Only 48 (41.3%) patients are followed-up for 5 years and this prospective study still goes on. Postoperatively, they were evaluated according to their history and physical examination, serum carbohydrate antigen 19-9 (CA 19-9) levels, and CT scans of the chest, abdomen and pelvis every 3-6 months for 3 years and, subsequently, once annually. We studied the frequency of the lymph node involvement in all these patients, the lymph node stations most commonly affected by metastases after standard lymphadenectomy as well as the interdependence between the frequencies of the regional nodal metastases and the local/distant recurrence. Categorical variables were compared using chi-squared analysis. Continuous data were expressed as the median and range and compared using the Mann-Whitney test. Survival analysis was performed using the Kaplan-Meier method, and differences in survival were compared using the log-rank test. The significance parameter was set at P<0.05. Statistical analysis was performed using SPSS.
version 17.0 (SPSS, Inc., Chicago, IL, USA).

Figure 13: Interdependence between the frequencies of regional nodal metastases and local/distant recurrences.

Morbidity and mortality rates after PD are 53.4% (n=62) and 5.1% (n=6), respectively. The number of retrieved lymph nodes in the standard lymphadenectomy is ≥15. Among the 116 patients who have undergone PD, 81 (69.8%) patients are lymph-node positive. Recurrence data are available for 110 of them. The overall recurrence rate is 75.4% (83 patients) during the follow-up period. Clinicopathologic data are presented in Table 1.

The lymph-node areas most affected are station 13 (n=24), 17 (n=17) and 14 (n=13), followed by stations 12 (n=5) and 8a (n=2) (P=0.016) (Table 2).
Figure 14: Median disease-free survival and median overall survival after pancreatic resection in patients with and without lymph node.

Lymph-node involvement is significantly associated with the development of local recurrence. The latter occurs in 20% (n=22) of patients. Lymph-node involvement affects local recurrence rates, which occur in 20 of 75 (26.6%) and in two of 35 (5.7%) patients with and without lymph-node involvement, respectively (P=0.024) (Figure 13).
Table 1: Clinical and pathologic features of 116 PC patients submitted to PD.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Without lymph-node metastases (n=35)</th>
<th>With lymph-node metastases (n=81)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td>0.343</td>
</tr>
<tr>
<td>female</td>
<td>11 (31.4)</td>
<td>22 (27.1)</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>24 (68.5)</td>
<td>59 (72.8)</td>
<td></td>
</tr>
<tr>
<td>Age, years, median (range)</td>
<td>63 (28-73)</td>
<td>61 (36-72)</td>
<td>0.152</td>
</tr>
<tr>
<td>Postoperative adjuvant therapy, n (%)</td>
<td>28 (80.0)</td>
<td>54 (66.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preoperative CA 19-9, U/ml, median (range)</td>
<td>41 (&lt;1-1135)</td>
<td>181 (&lt;1-6010)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Surgical procedure, n (%)</td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Whipple’s procedure</td>
<td>28 (80.0)</td>
<td>53 (65.4)</td>
<td></td>
</tr>
<tr>
<td>pylorus preservation</td>
<td>7 (20.0)</td>
<td>28 (34.5)</td>
<td></td>
</tr>
<tr>
<td>Vascular resection, n (%)</td>
<td>8 (22.8)</td>
<td>10 (12.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tumour size, cm, median (range)</td>
<td>2.5 (1-6)</td>
<td>3.0 (1.8-8)</td>
<td>0.005</td>
</tr>
<tr>
<td>Tumour stage, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T1</td>
<td>4 (11.4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>2 (5.7)</td>
<td>22 (27.2)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>29 (82.8)</td>
<td>59 (72.8)</td>
<td></td>
</tr>
<tr>
<td>Histologic differentiation, n (%)</td>
<td></td>
<td></td>
<td>0.235</td>
</tr>
<tr>
<td>good</td>
<td>1 (2.8)</td>
<td>4 (4.9)</td>
<td></td>
</tr>
<tr>
<td>moderate</td>
<td>13 (37.1)</td>
<td>34 (42.0)</td>
<td></td>
</tr>
<tr>
<td>poor</td>
<td>21 (60)</td>
<td>43 (53.1)</td>
<td></td>
</tr>
<tr>
<td>Resection margin, n (%)</td>
<td></td>
<td></td>
<td>0.543</td>
</tr>
<tr>
<td>R0</td>
<td>20 (57.1)</td>
<td>46 (56.8)</td>
<td></td>
</tr>
<tr>
<td>R1</td>
<td>14 (40.0)</td>
<td>32 (39.5)</td>
<td></td>
</tr>
<tr>
<td>R2</td>
<td>1 (2.8)</td>
<td>3 (3.7)</td>
<td></td>
</tr>
<tr>
<td>Recurrence, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.018</td>
</tr>
<tr>
<td>local recurrence</td>
<td>2 (5.7)</td>
<td>20 (24.7)</td>
<td></td>
</tr>
<tr>
<td>distant recurrence</td>
<td>10 (28.5)</td>
<td>51 (62.9)</td>
<td></td>
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</table>

Distant metastases occur in 55.4% (n=61) of patients. Regional nodal metastases from primary tumor correlate with the development of distant metastases, which occur in 68% (51 of 75) and 28.5% (10 of 35) of patients with and without positive regional lymph nodes, respectively (P=0.011). Vascular resection, margin status, T-stage and tumor size do not correlate with recurrence patterns. Postoperative radiation has not affected local recurrence rates. The 18-month survival estimates for lymph-node positive
group is 56% (n=42) but for lymph-node negative one - 80% (n=28), respectively. Median disease-free survival from the date of surgery is 8,5 months (95% CI 6,4-18) in 75 patients with and 14,0 months (95% CI 11,1-18) in 35 patients without lymph-node metastases, respectively (P = 0,022) (Figure 14).

**Table 2: Distribution of lymph-node metastases.**

<table>
<thead>
<tr>
<th>Variable (nodal station)</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node metastases in one nodal station</td>
<td></td>
</tr>
<tr>
<td>5 – suprapyloric</td>
<td>0</td>
</tr>
<tr>
<td>6 – infrapyloric</td>
<td>0</td>
</tr>
<tr>
<td>8a – nodes anterior to the common hepatic artery</td>
<td>2</td>
</tr>
<tr>
<td>12 b1, b2, c – nodes to the right of the hepatoduodenal ligament</td>
<td>5</td>
</tr>
<tr>
<td>13 a, b – posterior pancreaticoduodenal nodes</td>
<td>24</td>
</tr>
<tr>
<td>14 a, b – nodes to the right of the superior mesenteric artery</td>
<td>13</td>
</tr>
<tr>
<td>17 a, b – anterior pancreaticoduodenal nodes</td>
<td>17</td>
</tr>
<tr>
<td>Lymph-node metastases in two or more nodal stations</td>
<td>20</td>
</tr>
</tbody>
</table>

Median overall survival from the date of surgery was 12 months (95% CI 10,4-18) in 75 patients with and 17 months (95% CI 15,3-18) in 35 patients without lymph-node metastases, respectively (P=0,035).

**Conclusion**

PD with standard lymphadenectomy including at least 15 lymph nodes should be the procedure of choice in adenocarcinoma of the pancreatic head. Extended lymphadenectomy should not be applied routinely in patients with PC requiring PD or DP. The radical antegrade modular pancreateo-splenectomy is recommended for cancer location in the body or tail. Lymph node ratio ≥ 0.2 is an
independent adverse prognostic factor, which is powerful and useful for prognostic assessment for pancreatic cancer. The illusion of ‘localized’ disease is betrayed by the high frequency of regional and distal nodal involvement, positive pancreatic and/or retroperitoneal margins following resection, and the presence of distant micrometastases that commonly become clinically apparent shortly after surgery. We establish a directly proportional correlation between the presence of metastatic lymph nodes independently of their number and the development of local recurrence and distant metastases. PC should be managed as a systemic disease, even in patients with evidence of only local or regional disease; consequently, any effort for local control can have little effect on survival. This finding confirms the fact that the biology of the disease remains the most important determining factor affecting the final outcome, despite the progress in surgical technique and systemic therapy.

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References


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