Specialised care in patients undergoing pancreatoduodenectomy

Tol, J.A.M.G.

Citation for published version (APA):
Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma

J.A.M.G. Tol
D.J. Gouma
C. Bassi
C. Dervenis
M. Montorsi
M. Adham
A.A. Sandberg
H.J. Asbun
M. Bockhorn
M.W. Büchler
K.C. Conlon
L.F. Cruz
A. Fingerhut
H. Friess
W. Hartwig
J.R. Izbicki
K.D. Lillemoe
M.N. Milicevic
J.P. Neoptolemos
S.V. Shrikhande
C.M. Vollmer
C.J. Yeo
R.M. Charnley
for the International Study Group on Pancreatic Surgery

Surgery 2014 Sep;156(3):591-600
ABSTRACT

Introduction
Lymph node status of patients with resectable pancreatic ductal adenocarcinoma is an important predictor of survival. Survival benefit of extended lymphadenectomy during pancreatectomy is, however, disputed, and there is no true definition of the optimal extent of the lymphadenectomy. The aim of this study was to formulate a definition for standard lymphadenectomy during pancreatectomy.

Methods
During a consensus meeting of the International Study Group on Pancreatic Surgery, pancreatic surgeons formulated a consensus statement based on available literature and their experience.

Results
The nomenclature of the Japanese Pancreas Society was accepted by all participants. Extended lymphadenectomy during pancreatoduodenectomy with resection of lymph nodes along the left side of the superior mesenteric artery, around the celiac trunk, splenic or left gastric artery showed no survival benefit compared to a standard lymphadenectomy. No Level I evidence was available on prognostic impact of positive para-aortic lymph nodes. Consensus was reached on selectively removing suspected lymph nodes outside the resection area for frozen section. No consensus was reached on continuing or terminating resection in case these nodes were positive.

Conclusion
Extended lymphadenectomy cannot be recommended. Standard lymphadenectomy for pancreatoduodenectomy should strive to resect lymph node stations no. 5, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a, 14b, 17a and 17b. For cancers of the body and tail of the pancreas removal of stations 10, 11 and 18 is standard. Furthermore, lymphadenectomy is important for adequate nodal staging. Both pancreatic resection, in relatively fit patients or non-resectional palliative treatment were accepted as acceptable treatment in case of positive lymph nodes outside the resection plane. This consensus statement could serve as a guide for surgeons and researchers in future directives and new clinical studies.
INTRODUCTION

The optimal lymphadenectomy during pancreatectomy for pancreatic adenocarcinoma is disputed. Although the lymph node (LN) status of patients with resectable pancreatic ductal adenocarcinoma is an important predictor of survival, the actual survival benefit of an extended lymphadenectomy compared to a standard lymphadenectomy is limited. Four randomized controlled trials (RCT) analysed extended versus standard lymphadenectomy during pancreaticoduodenectomy and failed to find better outcomes in patients undergoing an extended resection 1-6. However, nomenclature, definitions and classifications of LN stations and standard or extended lymphadenectomy vary widely in the four RCTs which make it difficult to compare the results between the studies and to analyse which lymphadenectomy is preferred. During a consensus conference in 1999, an agreement was reached on which LN nomenclature should be used and definitions for standard and extended lymphadenectomy were formulated 7. Notwithstanding, there is still ongoing discussion regarding the extent of lymphadenectomy and what consequences positive lymph nodes in specific stations will have when discovered during an operation. Due to the persistent controversy on this topic and absence of Level I evidence on the optimal lymphadenectomy, an expert panel prepared and participated in a consensus conference of the International Study Group on Pancreatic Surgery (ISGPS) in April 2013 to evaluate the current literature on the definitions and to discuss the extent of a standard lymphadenectomy and related issues. In this consensus document, the term “standard lymphadenectomy” is used to define the extent of the lymphadenectomy and the nodal stations that should be removed in patients undergoing resection for suspected or confirmed pancreatic ductal adenocarcinoma. This type of lymphadenectomy might also be appropriate in patients with peripancreatic cancers and cystic neoplasms with malignant potential. To determine this, studies first need to present data using the same definition for lymphadenectomy to enable an accurate comparison and to start new clinical trials.

The aim of this consensus statement was to guide surgeons in their decision-making and prevent unnecessary extended procedures from being performed. Furthermore, this consensus statement can prevent the disparity in classification of lymphadenectomy that is found today.

METHODS

A computerized search of the PubMed and Embase database was made using the following terms: “pancreatic cancer”, “pancreatic adenocarcinoma”, “surgery”, “radical lymphadenectomy”, “extended lymphadenectomy”, “complications”, “para-aortic”, “lymph nodes”, and “nodal staging”. Publications of rated in descending order of level of evidence: systematic reviews and meta-analyses, prospective (randomized) studies, major publications from high-volume centers and existing consensus reports; however case-studies were excluded. Only studies published
in English were included. References of the included articles were hand-checked to ensure no relevant studies were missed. The search was performed in February 2013.

All relevant literature and a summary of the extracted data were reviewed by the study group (DJG, CB, CD, MM, RMC) of the International Study Group Pancreatic Surgery (ISGPS) which resulted in a first draft of the consensus definition and preparation of the statement. During the international consensus meeting attended by members of the ISGPS, the first draft was discussed. A final consensus statement on the definition of standard lymphadenectomy in pancreatic surgery was formulated and agreed by all cosignatories using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines.

RESULTS AND CONSENSUS STATEMENTS

Nomenclature for nodal stations in pancreatic surgery

Both the Union International Contre le Cancer (UICC) criteria and the Japanese Pancreas Society rules have been described in all Level I RCTs. During the European consensus meeting in 1999, the nomenclature of the Japanese Pancreas Society was selected and specification of the lymphadenectomy during pancreatoduodenectomy was described thereafter. There now seems to be general acceptance to use the “classification of pancreatic carcinoma” proposed by the Japanese Society, as summarized in Figure 1.

Consensus statement

Based on the above-mentioned RCTs and the detailed nature of the classification, the use of the nomenclature for nodal stations based on the classification of the Japanese Pancreas Society (Japan Pancreas Society. Classification of pancreatic carcinoma. 2nd English ed. Tokyo: Kanehara & Co. Ltd.: 2003) was agreed on by all conference members and was strongly recommended.

Extended or standard lymphadenectomy?

The extent of lymphadenectomy in patients with pancreatic adenocarcinoma during pancreatoduodenectomy as well as for left-sided pancreatectomy will be discussed separately.

Lymphadenectomy during pancreatoduodenectomy was described in two older cohort studies showing improved 5-year survival rates in patients who underwent standard lymphadenectomy compared to non-radical lymphadenectomy. Three RCTs published afterwards reported no survival benefit, and no arguments could be presented based on the evidence of these studies to support the role of extended lymphadenectomy during pancreatoduodenectomy. A similar conclusion was underlined again in two meta-analyses, the first from Michalski et al. in which three RCTs were analysed and the second from Iqbal et al., in which both RCTs and cohort studies were included (Figure 2), both of which showed no benefit of extended lymphadenectomy. These conclusions are in accordance with the fourth RCT from Japan showing no benefit in long-term survival after
extended lymphadenectomy in patients with resectable pancreatic head adenocarcinoma. However, the definition of lymphadenectomy varied between the RCTs. The pancreatic cancer registry of the Japan Pancreas Society analyzed 32,619 records and showed a significantly poorer survival in patients who underwent resection with a D1 lymphadenectomy compared to D2 and D3, however, no survival advantages were seen between D2 versus the more extended D3 resections.
Consensus statement

The performance of an extended lymphadenectomy during pancreatoduodenectomy, as described in the four RCTs, was not of any proven benefit and should not be performed. Although the definition of extended lymphadenectomy varied between the RCTs, none of the trials reported a survival benefit in patients undergoing the more extended lymphadenectomy. Moreover, an extended lymphadenectomy might be associated with undesirable consequences, such as chronic diarrhea and associated weight loss.

Which local lymph nodes should be included in standard lymphadenectomy during pancreatoduodenectomy in patients with pancreatic ductal adenocarcinoma?

Table 1 depicts the differences found in the literature when comparing the different RCTs accompanied with the outcomes after lymphadenectomy. During the consensus conference, all lymph nodes were discussed and no consensus could be reached by reviewing the available literature. Consensus on including LN stations 13 and 17 in the standard lymphadenectomy was reached beforehand because these nodes are imbedded within the pancreaticoduodenal groove, and therefore are always resected with the specimen. Lymph nodes around the SMA, celiac trunk, hepatoduodenal ligament, splenic artery, left gastric artery, and interaorto-caval are discussed below.

- **Should lymph nodes of the complete SMA (LN 14) or only right lateral SMA be included?**
- **Should the lymph nodes around the celiac trunk (LN 9) be included?**

According to the four RCTs, only LN along the right lateral side of the SMA should be resected during standard lymphadenectomy. This is the area in which recurrence is most common, and positive lymph nodes are most likely to be detected. A complete resection of the LN 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. Generally, clearance of the LN and tissue at the right site of the SMA (dissection plane) is helpful to allow...
Chapter V

Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma

Complete resection of the uncinate process of the pancreas. Similarly, there are no data that show a survival benefit when lymph nodes around the celiac trunk are removed, and therefore, extending the lymphadenectomy to include station 9 is not indicated (Table 1).

<table>
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Lymph nodes resected, n (mean) 13 20 15 27 15 36 13 40

Margin free resection (R0), % 73 78 88 95 76 82 94 45

Morbidity, % 34 40

Mortality, % 5 5 5.4 3.4 0 3 0 2

$ indicates resection of the right lateral side of that particular lymph node

$¥ indicates resection of that particular lymph node station

$¥¥ indicates resection of the right lateral side of that particular lymph node

$excluding severe diarrhea

Table 1 Differences in lymph node and nerve plexus dissection, median number of resected lymph nodes, margin free resection, morbidity and mortality in four randomized controlled trials assessing the value of extended lymphadenectomy during pancreateoduodenectomy for pancreatic adenocarcinoma.
Consensus statement
Only LN stations along the right side of the SMA (LN 14a and 14b) should be resected in a standard lymphadenectomy during pancreatoduodenectomy. Complete resection around the SMA is not indicated. Nodes around the celiac trunk should not be resected.

• How high should the resection go into the hepatoduodenal ligament (LN 5, 6, 8 and 12)?
The hepatoduodenal ligament includes LN stations, from a more proximal location, No. 12, to a more distal location, No. 8 and No. 6 toward the duodenum. When reviewing the LN stations resected in the four RCTs, a standard lymphadenectomy should include: 5, 6, 8a, and 12b and c (Table 1). Whether to resect lymph node 8p was discussed extensively during the consensus conference.

Consensus statement
All conference members agreed on dissecting LN stations 5, 6, 8a, 12b and 12c found in the hepatoduodenal ligament. Considering the results of the RCTs and the extensive discussion during the conference meeting, no strong recommendation could be formulated on routine resection of LN 8p, however, some members resect this node as part of the resection plane. Lymphadenectomy should go up to the level of the right hepatic artery (classic anatomy) as it crosses over to the right liver in order to adequately clear the hepatoduodenal ligament.

• Should lymph nodes around the splenic (LN 11) and left gastric (LN 7) artery be included?
Reviewing the LN dissection during pancreatoduodenectomy in the four RCTs, dissection of LN around the splenic and left gastric artery (No. 11 and 7) was not performed in the standard procedure during pancreatoduodenectomy (Table 1).

Consensus statement
Resection of LN stations of the splenic and left gastric artery is not recommended during pancreatoduodenectomy. These nodal stations should not be part of a standard lymphadenectomy.

• Should para-aortic lymph nodes (LN16) be included, in particular the lymph nodes at the posterior side of the pancreas between the aorta and inferior vena cava (16b1)?
Several studies reported the prognostic impact of positive para-aortic lymph nodes on survival in patients with pancreatic ductal adenocarcinoma after pancreatoduodenectomy 18–22. Some studies showed no difference in survival between patients with or without positive para-aortic lymph nodes undergoing resection 19,21. Other studies reported poorer survival rates in patients with positive para-aortic lymph nodes and summarized the outcomes found in several studies leading to the conclusion that the prognosis of patients with positive para-aortic lymph nodes was extremely poor (Figure 3) 18,20.
There was an extensive discussion about LN 16b1; some members include this LN routinely within the resection plane. Data on lymphatic drainage pathways has shown that LN 16b1 is an important node in the major lymphatic drainage route \(^{23,24}\) but a study of positive lymph nodes in stations 8a and 16b1 found that positive 16b1 lymph nodes did not have an effect on survival (p=0.185) \(^{22}\). Nevertheless there is no Level I evidence available concerning the impact on survival. It should also be noted that almost all of the available studies emanated from Asian centers.

**Consensus statement**

Based on the poor prognosis of patients with positive para-aortic lymph nodes, routine resection of lymph node station 16 was not recommended. No consensus however, was reached on LN 16b1 due to variation in the literature and different expert opinions during the consensus conference. Some members resect this node because they include it in the resection plane; however, no strong recommendation could be formulated on dissecting LN 16b1 routinely.

**Final definition of a standard lymphadenectomy during pancreatoduodenectomy in patients with pancreatic ductal adenocarcinoma**

After evaluating all the available literature and the expert opinions during the consensus meeting, a clear definition of a standard lymphadenectomy was reached, although no strong recommendation could be given on resecting LN 8p and 16b1 routinely: a standard lymphadenectomy should include LN stations 5, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a right lateral side, 14b right lateral side, and 17a and 17b (Figure 4).

**Definition of standard lymphadenectomy during left-sided pancreatectomy in patients with pancreatic ductal adenocarcinoma in the body or tail area**

Studies on lymphadenectomy during left-sided pancreatectomy for body and tail tumors are scarce. A study from 1997 described LN involvement in 30 specimens. The greatest incidence of LN involvement was around the splenic artery (LN station 11), aorta (LN station 16), SMA (LN station 14), and celiac trunk (LN station 9) \(^{25}\). Another study reported similar findings with the greatest incidence of involvement seen in nodes around the splenic artery, along the inferior border of
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...the body and tail of the pancreas, and along the common hepatic artery. The authors suggested that extended lymphadenectomy, including the para-aortic, celiac and superior mesenteric lymph nodes, might improve prognosis. The most recent study on distribution of metastatic lymph nodes reporting the highest incidence of nodal involvement included stations 8, 11, 14 and 16, but, no study could provide evidence on a survival benefit related to extended lymphadenectomy. Therefore there is no current evidence to support an extended lymphadenectomy of stations 8, 14, and 16 during left-sided pancreatectomy. The consensus meeting in 1999 included LN no. 9, 10, 11 and 18 in a standard lymphadenectomy. During the consensus in 2013 discussion among the experts on LN 9 revealed that some members of the consensus conference resect this lymph node station, particularly when the tumor is close to the celiac axis in the body of the pancreas, while others do not. No consensus could be reached.

Another technical approach designed to dissect more lymph nodes is to extend the resection by performing a left-sided pancreatectomy with en bloc resection of the celiac axis. Preoperative coil embolization of the common hepatic artery in order to develop collateral pathways and performing a left-sided pancreatectomy with en bloc resection of the celiac axis, together with the surrounding lymph nodes, has been described in several studies. This procedure has also

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**Figure 4:** Standard lymphadenectomy during pancreateoduodenectomy in patients with pancreatic ductal adenocarcinoma includes:

- No. 5, suprapyloric lymph nodes
- No. 6, infrapyloric lymph nodes
- No. 8a, lymph nodes in the anterosuperior group along the common hepatic artery
- No. 12b and 12c, lymph nodes along the bile duct and around the cystic duct
- No. 13a, lymph nodes on the posterior aspect of the superior portion of the head of the pancreas
- No. 13b, lymph nodes on the posterior aspect of the inferior portion of the head of the pancreas
- No. 14, lymph nodes along the right lateral superior mesenteric artery
- No. 17a, lymph nodes on the anterior surface of the superior portion of the head of the pancreas
- No. 17b, lymph nodes on the anterior surface of the inferior portion of the head of the pancreas
been described without preoperative coil embolization of the common hepatic artery and was compared to a standard left-sided pancreatectomy, but, no survival benefit was reported\textsuperscript{29}. In order to improve the visibility of the posterior extent of the resection, a different operative approach to tumors of the body and tail of the pancreas by means of an antegrade procedure, was described in 2003\textsuperscript{30}. Long-term results were promising, but no formal trial has been conducted with standard left-sided pancreatectomy\textsuperscript{31}.

\textit{Consensus statement}

Standard lymphadenectomy during pancreatectomy for patients with pancreatic ductal adenocarcinoma in the body or tail includes lymph nodes no. 10 hilum of the spleen, no. 11 splenic artery, and no. 18 along the inferior border of the body and tail of the pancreas. LN 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 5).

Members of the consensus conference also agreed that in patients undergoing left-sided pancreatectomy for malignant tumors, splenectomy is indicated to ensure adequate excision of the primary tumor and lymph nodes. The lack of consensus and no available Level I evidence on the benefit of extending the resection weakens this consensus statement.

\textbf{Figure 5}: Standard lymphadenectomy during left-sided pancreatectomy in patients with pancreatic ductal adenocarcinoma includes:

- No. 10, lymph nodes at the splenic hilum
- No. 11, lymph nodes along the proximal and distal splenic artery
- No. 18, lymph nodes along the inferior margin of the pancreas

No. 9, lymph nodes around the celiac artery (suggested only in tumors in the area of the corpus)
Which nodal stations should undergo frozen section during pancreatoduodenectomy?

Whether a lymphadenectomy could be extended by selectively removing suspected lymph nodes beyond the resection area for frozen section was discussed during the consensus conference. This procedure should provide more information on the nodal status of the patient. Furthermore, positive lymph nodes can subsequently influence the ultimate management during the pancreatoduodenectomy, as well as the potential for adjuvant or palliative treatment. What consequences will these positive lymph nodes have? Should positive lymph nodes be considered as metastatic disease or should the surgeon continue with the resection if possible in order to attempt to achieve an R0 resection?

Consensus statement

If during operation, a suspicious lymph node is discovered beyond the standard lymphadenectomy resection area, it should be removed and sent for frozen pathologic examination. Ideally, however, any suspicious lymph node should be detected on preoperative imaging and biopsied prior to operation. Operative exploration is not normally recommended in patients with proven positive lymph nodes outside the standard resection field. In contrast, if positive nodes are discovered outside the boundary of a standard resection during operation for a tumor confined to the head of the pancreas, there was still a consensus to consider nodes along the left side of the SMA in particular inferior to the mesocolon or around the celiac axis, beyond the classic resection margin, to be metastatic lymph nodes. When LN station 16 is found to be positive during operation, most members of the consensus conference would continue with resection in order to achieve optimal treatment. Deciding to abandon resection or to continue the procedure should also depend on other variables, such as comorbidity and age of the patient, local ingrowth of tumor into the main vessels, or a markedly increased level of CA 19-9 preoperatively, which is considered a relevant prognostic parameter. These combined factors might lead to a change in strategy concerning resection or a palliative bypass procedure. Both strategies were considered to be appropriate in selected situations.

Lymphadenectomy for nodal staging and minimal number of lymph nodes retrieved during pancreatoduodenectomy

Lymph node status is an important prognostic factor and is crucial in the pathologic examination of the resected specimen. A standard lymphadenectomy is also important for staging the patient’s disease, and therefore, as part of the multimodal therapy for pancreatic adenocarcinoma. Several articles have discussed the prognostic value of the number of harvested lymph nodes and the ratio of positive to total examined lymph nodes, i.e. the lymph node ratio (LNR). Increased survival has been reported in patients in whom a greater number of lymph nodes were harvested. Some studies reported this survival benefit in N0 patients, probably due to a more accurate classification of the N0 group; others only reported benefit in N1 patients. However, other studies were contradictory and did not find the number of LN to be a predictor of survival. During
the consensus meeting the importance of a minimum number of harvested lymph nodes was stressed such that the pathologic N status would be accurate, a minimum of 12 or 15 LN was believed to be important. The LNR was considered an important predictor for poor survival. The greater the LNR, the worse the prognosis for the patients. A LNR>0.2 was a negative independent predictor of survival.\textsuperscript{35–43}

The more lymph nodes examined, the less chance of underestimating the N stage.\textsuperscript{39} The number of LN harvested and examined pathologically and the LNR is, therefore, dependent on both the surgeon performing the lymphadenectomy and the pathologist examining the specimen. Furthermore, the body mass index (BMI) of the patient influences the lymph node yield, although another study did not found a correlation between BMI and lymph node yield.\textsuperscript{44,45}

**Consensus statement**

The description of standard lymphadenectomy, as described herein, should regularly provide around 15 lymph nodes to assure an adequate pathologic staging of the disease. Furthermore, to be able to adequately stage the patient, the total number of LN and the LNR are important, and should be regularly reported in the pathologic analysis. In addition, the role of neo-adjuvant therapy should be mentioned during examination of the specimen. After preoperative chemotherapy or chemo-radiotherapy, pathologists may find fewer LN; in this case, a total of less than 15 LN should be accepted.

**GENERAL DISCUSSION**

The standard lymphadenectomy formulated by the ISGPS members based on the literature and expert opinions is a guide for surgeons when operating on patients with resectable pancreatic ductal adenocarcinoma. The diversity of extent and site of lymphadenectomy described in the literature makes it difficult to compare results and analyse the optimal procedure. There are many potential advantages in adopting this consensus statement, including new clinical trials which can generate evidence for the appropriate treatment in the case of positive distant lymph nodes. Compelling evidence-based reports, both RCTs and meta-analyses, show no benefit to performing an extended lymphadenectomy. Despite the variation in definition of lymphadenectomy, this consensus states that extended lymphadenectomy should not be performed. What consists of a standard lymphadenectomy was made clear in this consensus proposal, although there was no general agreement on the exclusion of LN stations 16b, the posterior para-aortic lymph node and lymph node station 8p. Final consensus was reached on lymph nodes which were not included in the standard lymphadenectomy but situated nearby the resection plane; when lymph nodes could be incorporated easily into the resection plane, dissection was justified.

Selective removal of suspected lymph nodes has not been reported to influence survival. The potential advantage or importance of this practice and the consequences of tumor positive nodes
beyond the resection area remains unknown. Consensus was reached on positive nodes along the left side of the SMA or around the celiac axis positioned beyond the resection area and are considered to be metastatic lymph nodes. Some conference members however, resect positive para-aortic nodes found at the time of resection, in selected patients. Deciding to continue or cease the operation should depend on other characteristics, such as comorbidity and age of the patients, local ingrowth of tumor into the main vessels and the presence of markedly increased serum tumor markers such as CA 19-9. Both resection and bypass were accepted as being plausible treatments for patients with these areas of metastatic lymph nodes.

Although an R0 resection is always reported to be the only chance of long-term survival in patients with pancreatic ductal adenocarcinoma, this treatment modality alone is not sufficient and should be combined with some form of adjuvant chemotherapy with or without radiotherapy. While the appropriate lymphadenectomy is an important therapeutic maneuver, it is only a part of the multi-modal treatment of these patients.

This consensus statement should serve as a guide, although it is clear that patient characteristics and other factors that influence the postoperative course and long term results will influence the surgeon’s decision-making. Adoption of this statement will provide the most optimal lymphadenectomy and should ensure accurate reporting of techniques and outcomes of pancreatectomy for ductal adenocarcinoma of the pancreas. It will enable accurate comparisons of studies using the same definition for lymphadenectomy and the start of new clinical trials.
REFERENCES


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