



## **Lymph Node Size and Metastatic Infiltration in Adenocarcinoma of the Pancreatic Head**

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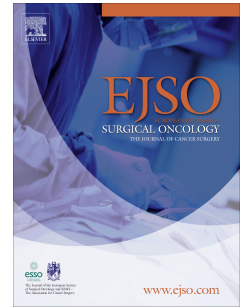
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## **Lymph Node Size and Metastatic Infiltration in Adenocarcinoma of the Pancreatic Head**

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Running Title: Pancreatic cancer lymph node size

**Abstract**

*Background:* Preoperative lymph node staging of pancreatic cancer by CT relies on the premise that malignant lymph nodes are larger than benign nodes. In imaging procedures Lymph nodes > 1cm in size are regarded as metastatic nodes. The extend of lymphadenectomy and potential application of neoadjuvant therapy regimens could be dependent on this evaluation.

*Patients and methods:* In a morphometric study regional lymph nodes from 52 patients with pancreatic cancer were analysed. The lymph nodes were counted, the largest diameter of each node was measured, and each node was analyzed for metastatic involvement by histopathological examination. The frequency of metastatic involvement was calculated and correlated with lymph node size.

*Results:* A total of 636 lymph nodes were present in the 52 specimens examined for this study (12.2 lymph nodes per patient). Eleven patients had a pN0 status, whereas 41 patients had lymph nodes that were positive for cancer. Five hundred twenty (82%) lymph nodes were tumor-free, while 116 (18%) showed metastatic involvement on histopathologic examination. The mean ( $\pm$  SD) diameter of the nonmetastatic nodes was 4.3 mm, whereas infiltrated nodes had a diameter of 5.7 mm ( $p=0.001$ ). Seventy-eight (67%) of the infiltrated lymph nodes and 433 (83%) of the nonmetastatic nodes were  $\leq 5$ mm in diameter. Of 11pN0 patients, 5 (45%) patients had at least one lymph node  $\geq 10$ mm, in contrast only 12 (29%) out of 41 pN1 patients had one lymph node  $\geq 10$  mm.

*Conclusion:* Lymph node size is not a reliable parameter for the evaluation of metastatic involvement in patients with pancreatic cancer.

## Introduction

Adenocarcinoma of the pancreas has the worst prognosis of all cancers, with a five year survival rate less than 3%, accounting for the fifth highest number of cancer related deaths in North America and Europe with rising incidence<sup>1,2</sup>. The only curative treatment for pancreatic cancer (PC) is complete resection which is possible in only 10 - 20% of patients<sup>3</sup> and associated with relatively constant 5-year survival rates of approximately 10-20% for the last 30 years<sup>4-6</sup>. To determine resectability and prognosis for the patient with pancreatic cancer, an accurate staging of the tumor, assessing the extent of local and distant disease, is necessary. Besides the location of the primary tumor and its infiltration of adjacent structures, the pretherapeutic staging includes assessment of lymph node infiltration. The surgical approach and planning of potential neoadjuvant therapy depend on these parameters. The preoperative evaluation of lymphatic infiltration is based on CT-scan, MRI or endosonography. Lymph nodes > 1cm in diameter are regarded as metastatic<sup>7-9</sup>. These data are based on the assumption that malignant nodes will be larger than benign nodes, and that smaller lymph nodes are more likely to be benign. Therefore, we measured the size of lymph nodes in specimens from 52 Patients to specify whether it is possible to differentiate malignant from benign lymph nodes in patients with pancreatic cancer by size.

## Materials and Methods

### *Patients*

The specimens included in this study were obtained from 52 patients, who underwent resection for pancreatic cancer between 1999 and 2003 in the Department of Surgery at the University of Cologne. Thirty two patients were male, 20 patients were female and their age ranged from 38 to 77 years (median age, 62 years). All patients were treated for adenocarcinoma of the pancreatic head. In 21 patients a Whipple procedure was performed, in 31 patients the pylorus was preserved. All patients underwent a regional lymphadenectomy around the duodenum and pancreas, including the lymph nodes on the right side of the hepatoduodenal ligament, the right side of the superior mesenteric artery, and the anterior and posterior pancreaticoduodenal lymph nodes. In no case was preoperative radiation or chemotherapy employed.

### *Lymph node Analysis*

A total of 636 lymph nodes were resected from 52 specimens. The material was fixed in 5% formaldehyde and was embedded in paraffin. The nodes were counted, and the maximal diameter of each node was measured after preparation with a slide gauge. A series of sections from six levels of each node was selected and stained with hematoxylin and eosin, and the periodic acid-Schiff reaction. All dissected lymph nodes were analyzed microscopically for metastatic infiltration. Histological findings

were classified by the TNM International Union Against Cancer Classification. To assess shrinkage due to fixation and staining, 36 lymph nodes from three pancreatic cancer specimens were measured before and after fixation with hematoxylin-eosin.

### *Statistical Analysis*

The relationship between lymph node size and presence of metastases was evaluated statistically. Continuous variables were expressed as the mean  $\pm$  SD and were analyzed using the Student t test. Frequencies were analyzed using the  $\chi^2$  test. A p value of  $< 0.05$  was considered to be significant. The mean shrinkage (95% confidence interval) was calculated. All calculations were performed using statistical software (SPSS 15.0; SPSS Inc; Chicago, IL).

### **Results**

The relative size of 36 lymph nodes (from three pancreatic cancer specimens) after fixation and staining was  $6.56 \pm 3.4$  mm compared with  $7.32 \pm 4.1$  mm before fixing and staining. Therefore the shrinkage factor (mean 0.6 mm; 96% confidence interval, 0.56 to 0.73) during lymph node preparation was estimated to be about 10%. No significant difference in the amount of shrinkage between metastatic and non metastatic lymph nodes of any size was seen.

Six hundred thirty-six lymph nodes were analyzed regarding size and metastatic infiltration. An average of 12.1 lymph nodes (range 8- 36) per specimen were found. One hundred sixteen (18%) showed metastatic infiltration while 520 nodes (82%) were free of tumor infiltration. Eleven patients (21%) were staged as pN0 while 41 (89%) patients showed lymphatic infiltration. The correlation of lymph node size and

metastatic involvement is shown in Table 1. The average size of tumor free lymph nodes was  $4.3 \pm 3.4$  mm (Fig. 1) while that of lymph nodes with metastatic involvement was  $5.7 \pm 4.1$  mm (Fig. 2). This difference was statistically significant ( $p=0.001$ ). Five-hundred-eleven lymph nodes were  $\leq 5$ mm in diameter. Seventy eight (15.3%) of these had tumor infiltration while 433 (85.7%) were tumor-free. One hundred twenty-five lymph nodes were  $> 5$ mm. Eighty seven of these (69.6%) had no metastatic involvement, while 38 (30.4%) contained metastases.

Regarding lymph nodes with histological signs of metastases ( $n=116$ ), 67% (78 lymph nodes) were  $\leq 5$ mm. Seventeen percent (87 lymph nodes) of the tumor free lymph nodes were  $> 5$ mm in size. Of 11 patients with pancreatic cancer and no histopathological sign of metastatic lymph node involvement, five (45.5%) patients had at least one lymph node that was  $>10$  mm. Thirty one (75.6%) of the patients with pN1 disease had no lymph node that was  $>10$ mm.



## Discussion

The accurate preoperative staging of pancreatic cancer is essential to specify the therapeutic regimen. Computer tomography has proven to be of diagnostic value to identify patients with advanced and unresectable tumors but its performance in evaluation of local tumor extension in patients with potentially resectable cancer is poor<sup>10-13</sup>. Furthermore image modalities like CT-scan, MR and transgastric endosonography are limited in their predictive value to differentiate benign lymph nodes from malignant ones<sup>14,15</sup>. In the pretherapeutic lymph node staging of pancreatic cancer, a correlation between lymph node size and metastatic infiltration is assumed. Most investigators have used short axis diameter of 10 mm for diagnosing nodal involvement<sup>8,9,16,17</sup>. Our study showed that in 86% of pN1 patients no lymph node was larger than 10 mm and the majority of nodes were smaller than 5 mm, whereas in 46% of pN0 patients at least one lymph node was larger than or equal 10 mm. This reflects the reported sensitivity and specificity of CT scan in the assessment of nodal metastases in pancreatic cancer which ranges from 14% to 37% and from 60% to 92% respectively<sup>8,9,14-16</sup>. The lack of correlation between lymph node size and metastatic infiltration has also been reported for other solid tumors. In a Japanese study regarding esophageal cancer, 36% of metastatic lymph nodes were <5 mm in diameter<sup>18</sup>. As we have demonstrated earlier in patients with gastric cancer, 55% of metastatic lymph nodes were  $\leq 5$ mm in diameter<sup>19</sup>. In patients with colorectal cancer 50 to 65% of metastatic lymph nodes were  $\leq 5$ mm in size<sup>20,21</sup>. Recently we also have shown that in NSCLC 44% of tumor infiltrated lymph nodes were <10 mm<sup>22</sup>. Additionally it has been shown that nodal micrometastasis is an independent prognostic factor also for pancreatic cancer<sup>23</sup>. This early form of nodal tumor spread is not detectable with preoperative image modalities.

Despite a significant difference in diameter between metastatic and tumor free lymph nodes the evaluation of lymph node metastasis in patients with pancreatic cancer by size is not accurate. An exact preoperative N-staging is therefore difficult to obtain. Presence of enlarged lymph nodes on CT-scan in patients with resectable pancreatic cancer is therefore no contradiction for surgical therapy.

**Table and figures legends**

Table 1: Size and numbers of infiltrated and tumor free lymph nodes

Figure 1: Size of tumor free lymph nodes (520 nodes); mean size  $4.3 \pm 3.4$  mm.

Figure 2: Size of metastatic involved lymph nodes (116 nodes) : mean size  $5.7 \pm 4.1$  mm.

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Table 1.

Lymph Nodes						
Lymph node	Total		With Metastasis		Tumor-free	
Size (mm)	No.	%	No.	%	No.	%
< 2	209	33	28	24	181	35
3-5	302	47	50	43	252	49
6-10	68	11	22	19	46	9
11-15	35	6	9	8	26	5
> 15	22	3	7	6	15	3
Total	636	100	116	100	520	100

