Effect of lymph node density in the prognosis of patients after pancreatic cancer resection

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Background
Pancreatic cancer has the worst prognosis of all gastrointestinal malignancies. Lymph node metastasis is a powerful determinant of prognosis. The ratio between the number of affected lymph nodes and the total number of examined lymph nodes is known as lymph node density (LND). LND has proved clinically important in other gastrointestinal malignancies. Our main objective was to identify the role of LND in the prognosis of patients after pancreatic cancer resection.
Patients and methods
Our study included 30 patients who underwent pancreatic cancer resection from 2010 to 2015. Pathological reports and medical records were retrieved retrospectively for tumor-specific data and patient-specific data (age, sex, and presence of diabetes mellitus). LND was calculated as the number of metastatic lymph nodes divided by the total number of lymph nodes examined. Survival time was calculated from the date of operation to the date of death.
Results
Patients with LND less than 0.2 have a probability of 1-year survival of 98% and 3-year survival of 62%, which is better than those with LND more than 0.2 (P=0.001).
Conclusion
LND was significantly related to survival outcome after pancreatic cancer resection, as patients with LND more than or equal to 0.2 displayed a poor prognosis.

Keywords:
lymph node density, prognosis, pancreatic cancer, survival

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Background

Pancreatic malignant tumor is the 12th most common cancer worldwide [1]. In the United States, it accounts for ~3% of all cancers. It is considered the fourth leading cause of cancer-related death for both men and women in the United States [2]. In Egypt, the incidence of pancreatic cancer is estimated to be 2.3% in males and 1.4% in females [3].

Patients with pancreatic cancer have a very poor prognosis. Unfortunately, the resectability rate of pancreatic is still relatively low. However, even after potentially curative resection, actuarial 5-year survival is reported in the range between only 15 and 25% in most series [4].

Prognostic outcome of patients with resected pancreatic cancer is related to various factors such as stage of tumor, tumor grade, tumor size, lymph node status, and safety margin status [5]. Multiple studies have shown that lymph node involvement alone in pancreatic cancer is a poor prognostic factor [6].

Lymph node density (LND) has been demonstrated to be a more powerful predictor of survival in patients with gastrointestinal malignancies [7].

Numerous retrospective studies have mentioned that the total number of positive nodes identified, the total number of negative nodes identified, and the ratio of positive to total lymph nodes assessed after pancreatic cancer resection all correlate with survival [8–10].

Recently, few authors investigated the role of LND instead of the nodal status alone in pancreatic cancer, demonstrating that this has a significant influence on prognosis in patients undergoing pancreatic resection [11,12].

Many studies have identified that LND is a valuable prognostic factor in patients with pancreatic cancer [13]. However, the cutoff values of LND are inconsistent in different studies. LND more than or equal to 0.2, 0.15, and 0.1 have all been reported as independent poor predictive factors [14,15].

The current study aims to assess the prognostic value of lymph node ratio (LNR) postoperatively in patients after pancreatic cancer resection surgery.

Patients and methods

Patients

The current retrospective survival analysis study was conducted at the Surgery Department in Suez Canal University Hospital, in the period between 2010 and 2015, after the approval of the Research Ethical Committee (REC), Faculty of Medicine, Suez Canal University was obtained. This study has been reviewed by our research ethics committee in Faculty of Medicine, Suez Canal University, at its meeting on March 21, 2016, with reference number 2758. The written consent from all cases are reported in this study.

A total of 30 patients who underwent surgical resection either pancreaticoduodenectomy or distal pancreatectomy for pancreatic cancer were included in the study.

The selection of the patients in this study was done according to the following criteria.

Inclusion criteria

All patients who underwent curative surgical resection in the period between 2010 and 2015.

Exclusion criteria

The following were the exclusion criteria:

(1) Patients with advanced cancer involving the head of the pancreas and treated with palliative bypass surgery.
(2) In-hospital mortality.
(3) Patients with positive surgical resection margins.

Procedure

The surgical procedures performed were open pancreaticoduodenectomy (classical Whipple procedure) for tumors located in the pancreatic head or uncinate process and distal pancreatectomy or splenopancreatectomy for tumor located in the pancreatic body or tail associated, with standard lymphadenectomy (level I lymph nodes).

Pancreaticogastrostomy was the routine reconstruction procedure after pancreaticoduodenectomy and was carried out by performing anastomosis between the pancreatic parenchyma stump and posterior gastric wall after a transverse full-thickness incision was made on the posterior wall of the stomach with a length of at most 2 cm, to ensure tight adherence with continuous seromuscular purse-string sutures (proline 3–0) and multiple internal gastric mucosal interrupted sutures after identification of pancreatic duct to ensure patency.

A standard lymphadenectomy entailed removal of nodes at the duodenum and pancreas and on the right side of the hepatoduodenal ligament, the right side of the superior mesenteric artery (SMA), and the anterior and posterior pancreaticoduodenal lymph nodes.

The operative specimen was immersed in neutral buffered formalin 10% with marking of common bile duct margin; the gallbladder was submitted in a separate container. Specimen underwent standard histopathological evaluation by multiple qualified pathologist, and reporting was done according to the College of American Pathologists (CAP) reporting protocol [16].

Medical records were reviewed retrospectively. The following data were collected from each patient record: age, sex, presence of diabetes mellitus, tumor characteristics, total number of lymph nodes harvested, and lymph node status.

Patients were subclassified according to age into either younger than 65 years old or older than 65 years old, as 65 years was the mean age of the patients in our study.

Tumor characteristics included tumor size either smaller than 3 cm or larger than 3 cm; tumor location in either head or body/tail; histologic grade, which was categorized into two groups, low grade or moderate/high grade; and perineural invasion.

The total number of examined lymph nodes and the number of histologically positive metastatic lymph nodes within each surgical specimen were recorded. LND was calculated as the number of metastatic lymph nodes divided by the total number of lymph nodes examined.

Cancer staging was based on pathologic findings referenced to the sixth edition of the AJCC guidelines for pancreatic exocrine cancer. TNM staging was performed according to the AJCC staging system [17].

Patients were divided according to lymph node status into two groups (N0 and N1). Patients with N1 disease were subclassified according to lymph node ratio into

two groups using the cutoff values of 0.2, either less 0.2 or equal and more than 0.2, as it is a common cutoff used in previous studies [8,9,15,18].

Survival time was calculated from the date of operation to the date of death. Both 1- and 3-year actuarial survival rates were considered in the study, but the 5-year actuarial survival could not be applied, as last year of including cases was 2015.

Statistical analysis

Statistical analysis was conducted using statistical package for the social sciences, version 21.0 software (IBM Corp., in Armonk, NY, USA). *P* value less than 0.05 was considered as statistically significant. The Kaplan–Meier method was used for survival analysis.

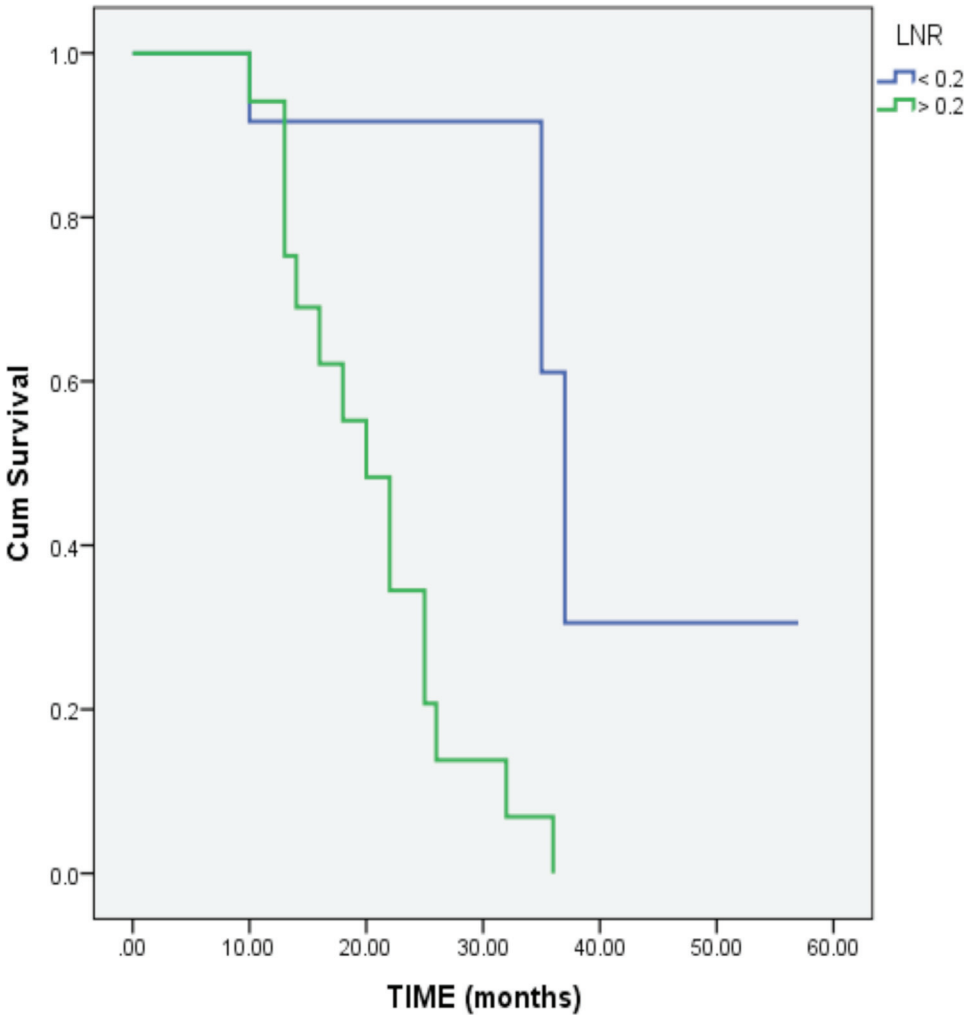
Results

A total of 45 patients who were suspected to have pancreatic cancer and explored from 2010 to 2015 were included. Of them, 40 patients were diagnosed to have pancreatic carcinoma, one patient had duodenal tumor, and four patients had cholangiocarcinoma. Five patients experienced in-hospital mortality; three patients were in the advanced stage at time of operation, and two of them showed positive surgical margin (Flow chart 1).

Our study included 30 cases with pancreatic carcinoma, comprising 18 (60%) males and 12 (40%) females. Patients' age ranged from 48 to 68 years, with a mean age of 56±6.5 years. A total of 26 (87%) patients were younger than 65 years and four (13%) patients were older than 65 years. Moreover, 21 (70%) patients were diabetic, whereas nine (30%) patients were nondiabetics (Table 1).

The mean size of tumors was 3 cm and ranged from 1.3 to 7 cm. In 12 (40%) patients, tumor was smaller than 3 cm, whereas in 18 (60%) patients, tumor was larger than 3 cm. A total of 21 (70%) patients

Flow Chart 1



Study group.

had tumors located at the head of pancreas, six (20%) patients had tumors at the body, and three (10%) patients had tumors at the tail of pancreas. In addition, 12 (40%) cases were high grade, whereas 18 (60%) cases were moderate. However, no cases (0%) showed low grade of differentiation. Two (7%) patients were stage I pancreatic carcinoma, whereas 28 (93%) patients were stage II. Only 30% of the studied cases showed evidence of perineural invasion whereas the rest 70% did not show any evidence of perineural invasion (Table 2).

Table 1 Patients' characteristics

Variables	Cases [*n* (%)]
Sex	
Male	18 (60)
Female	12 (40)
Age (years)	
<65	26 (87)
≥65	4 (13)
Diabetes	
No	9 (30)
Yes	21 (70)

Table 2 Results of the preoperative laboratory workup

Preoperative workup	Mean±SD (range)
Hemoglobin level (g/dl)	10±0.9 (8.9–13)
Serum albumin (g/dl)	3.3±0.3 (2.6–3.8)
Serum bilirubin (mg/dl)	8.5±4.8 (2.6–16.5)
Tumor marker CA19-9 (U/ml)	728±672 (45–2758)

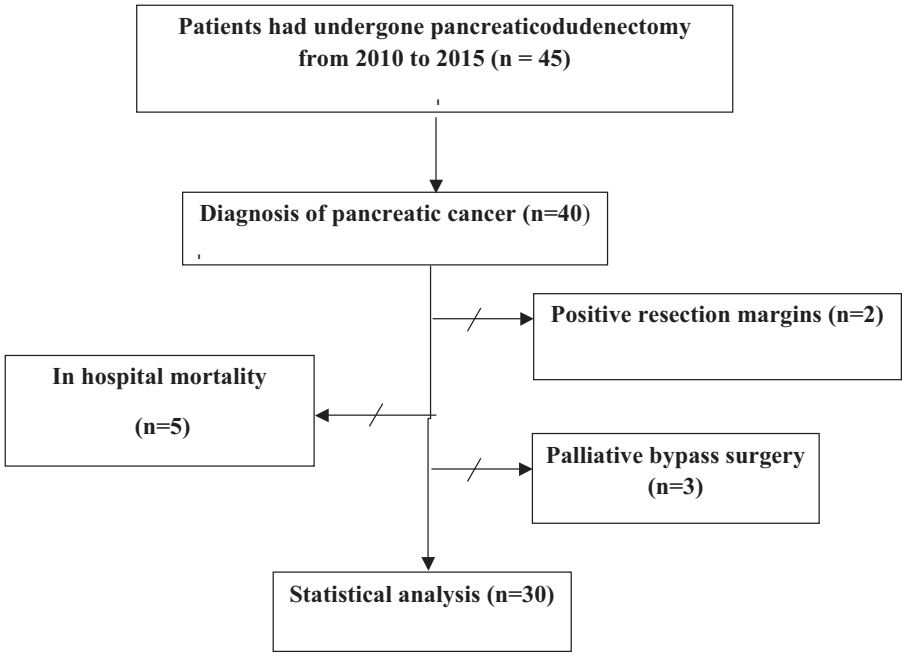
Our study showed that the mean hemoglobin level was 10±0.9 g/dl, ranging from 8.9 to 13 g/dl; the mean serum albumin level was 3.3±0.3 g/dl, ranging from 2.6 to 3.8 g/dl; mean serum bilirubin level was 8.5 ±4.8 mg/dl, ranging from 2.6 to 16.5 mg/dl; and the mean CA19-9 level was 728±672 U/ml, ranging from 45 to 2758 U/ml (Table 3).

The number of detected lymph nodes ranged from 9 to 23 lymph nodes, with a mean of 15±3 lymph nodes. In 10% of the cases, the number of examined lymph nodes was less than 12 lymph node, whereas in 90% of the cases, the number of examined lymph nodes was more than 12 lymph nodes. The cutoff value of LND was 0.2, and the study showed that 60% of the cases had LND more than o equal to 0.2, whereas 40% of the cases had LND less than 0.2 (Fig. 1).

The average follow-up was 20.5 months (median, 17 months; range, 9–57 months). The median survival was 25 months. The overall actuarial 1- and 3-year survival rates were 80 and 18%, respectively. Univariate analysis demonstrated that sex, age, nodal status, and LND significantly predict the prognosis ($P<0.05$) in patients with pancreatic carcinoma after resection as shown in Table 4.

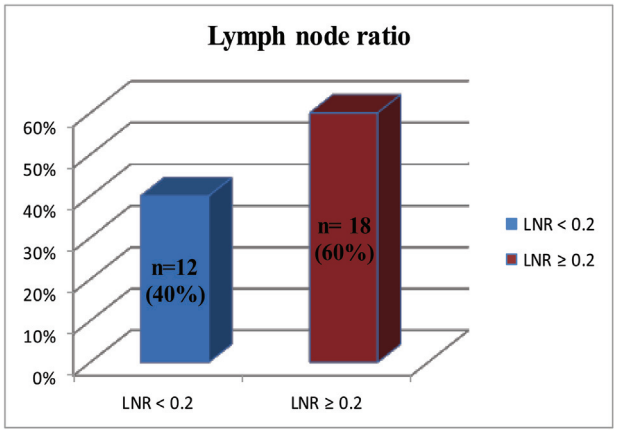
Our study showed that the patients with lymph node negative results have a probability of 1- and 3-year survival rate of ~100%, whereas the patients with

Fig. 1



Distribution of patients according to lymph node ratio (LND). LND, lymph node density.

Fig. 2



Influence of LND on actuarial survival (Kaplan–Meier analysis). LND, lymph node density.

lymph node positive results have a probability of 1-year survival rate of 80% and 3-year survival rate of 18%.

It was found that patients with LND less than 0.2 have a probability of 1-year survival of ~98% and 3-year survival of ~62%, whereas the patients with LND more than or equal to 0.2 have a probability of 1-year survival of ~88% and 3-year survival of ~8%, as shown in Fig. 2.

Discussion

A total of 30 patients with pancreatic cancer were recruited in the current study, including 18 males and 12 females, with an average age of 56±6.5 years old. This is closely related to Zhan *et al.* [19] whose study included 53 males and 30 females, with an average age of 61.7±10.7. The higher incidence of men with pancreatic cancer is explained by the fact that men are slightly more likely to develop pancreatic cancer than women, owing to the higher tobacco use in men, which increases pancreatic cancer risk [20]. Moreover, this is compatible with the results of cancer incidence in Egypt which showed that pancreatic cancer is estimated to be 2.3% in males and 1.4% in females [3].

In the present study, 21 (70%) patients had tumors located at the head of pancreas, six (20%) patients had tumors at the body, and three (10%) patients had tumors at the tail of pancreas. These findings are compatible with the data from a study which stated that ~75% of all pancreatic carcinomas occur within the head or neck of the pancreas, 15–20% occurs in the body of the pancreas, and 5–10% occurs in the tail [21].

We have found that the number of detected lymph nodes ranged from 9 to 23 lymph nodes, with a mean of 15±3. In 10% of the cases, the number of examined lymph nodes was less than 12 lymph nodes, whereas in 90% of cases, the number of examined lymph nodes was more than 12 lymph nodes.

This is confirmed by a study of large population-based analysis that demonstrated that a correct lymphadenectomy is obtained by an evaluation of at least 12 lymph nodes [12].

Table 3 Tumor characteristics

Variables	Cases [*n* (%)]
Tumor location	
Head	21 (70)
Body-tail	9 (30)
Tumor size (cm)	
<3	12 (40)
≥3	18 (60)
Tumor grade	
High	12 (40)
Moderate	18 (60)
Low	0 (0)
TNM staging	
I	2 (7)
II	28 (93)
Perineural invasion	
Yes	9 (30)
No	21 (70)

Table 4 Factors predictive of survival after resection using univariate analyses

Variables	*P* value
Sex	
Male	0.02*
Female	
Age (years)	
< 65	0.003*
Diabetes	
No	0.6
Yes	
Tumor size (cm)	
<3	0.076
≥3	
Degree of differentiation	
High	0.35
Moderate	
Low	
TNM staging	
I/II	0.07
III	
LNR	
<0.2	0.001*
Total number of examined lymph nodes	
<12	0.33
≥12	

**P* value less than 0.05, statistically significant. LNR, lymph node ratio.

Our results are contrary to Zhan *et al.* [19] who found that 72% of cases with the number of examined lymph nodes was less than 12 lymph nodes, whereas in 28% of cases, it was more than 12 lymph nodes. This can be rationalized by the fact that retrieval of the lymph nodes depends not only on the scope of the lymphadenectomy but also on how thorough the pathological examination is.

This study showed that 27 (90%) patients had positive nodal disease, whereas three (10%) patients had no nodal involvement. This is closely to Pawlik *et al*. [8], Riediger *et al*. [22], and House *et al.* [18]. However, these findings were in contrast to Chen *et al*. [23] and Zhan *et al.* [19] who found that 36% of the patients had positive nodal disease, whereas 64% of the patients had no nodal involvement.

There is no agreement on the best cutoff value for LNR. Sierzega and colleagues used 0, 0–0.199, and more than 0.2. Slidell and colleagues and Pawlik and colleagues used categories of LNR less than 0.2, 0.4, and more than 0.4, whereas House and colleagues used 0.18 as a cutoff value. Ashfaq *et al*. [15] indicated that LND cutoff of 0.1 was statistically significant for survival discrimination [8,9,12,18].

In our study, we used LND with cutoff value of 0.2, as it is a common cutoff used in many of the previous studies. It showed that 60% cases with LND more than 0.2, whereas 40% cases with LND less than 0.2. This is in contrast to Zhan *et al.* [19] who found that 21% of cases with LND more than 0.2, whereas 79% of cases with LND less than 0.2.

We found that the median survival was 25 months. The overall 1- and 3-year survival rates were 80 and 18%, respectively. This is different from Zhan *et al.* [19] who found that the median survival was 20 months, and the overall 1- and 3-year survival rates were 58.6 and 42.7%, respectively.

Our study revealed that patients with lymph node negative results have a probability of 1- and 3-year survival rates of ~100%, whereas the patients with lymph node positive results have a probability of 1-year survival of 80% and 3-year survival of 20%.

La Torre *et al.* [24] found that 3-year survival probability in patients with node negative and node positive results was 70 and 30%, respectively.Riediger *et al*. [22] demonstrated that the nodal status per se did not correlate with survival. The reason for this phenomenon is the fact that patients with one single metastatic node had the same survival as node negative patients.

Multiple studies found that lymph node status is imperfect as the sole predictor of survival, as it is unable to predict survival exactly. This could be explained by incomplete lymphadenectomy or inadequate histopathologic examination, potentially missing or leaving metastatic nodes, resulting in the phenomenon of stage migration [10,15,22].

The current study found that patients with LND less than 0.2 have a probability of 1-year survival of about 98% and 3-year survival of ~62%, whereas patients with LND more than or equal to 0.2 have a probability of 1-year survival of ~88% and 3-year survival of ~8%. Our results seem to be in concordance with Zhan *et al.* [19], but the difference was that patients with LNR more than or equal to 0.2 in their study had a probability of 3-year survival approaching 10%.

On the contrary, Riediger and colleagues found that patients with LNR less than 0.2 have a probability of 3-year survival of ~30%, whereas in patients with LND more than or equal to 0.2 of less than 10%. Moreover, they found that patients with LND more than or equal to 0.3 had clearly the worst outcome with an actuarial survival reaching zero at 3 years [22].

Studies demonstrated that LND represents a stronger independent prognostic indicator than the absolute number of affected lymph nodes [8,9].

In the current study, we were able to demonstrate a relationship between LND and survival outcome. We demonstrated that patients with LND more than or equal to 0.2 displayed poor prognosis, as reported by recent studies [14,25].

The current study has several limitations to be considered. Small sample size makes it difficult to draw firm conclusions about the role of lymph node status, the possibly effect of adjuvant chemotherapy on the course of the disease is not accounted for, and follow-up period is limited.

Conclusion

We were able to demonstrate a relationship between LND and survival outcome, as patients with LND more than or equal to 0.2 displayed poor prognosis. We found that LND represents an important prognostic factor in patients after resection of pancreatic cancer.

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All authors read and approved the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

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