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ORIGINAL ARTICLE

Prognostic Role of Log Odds of Lymph Nodes After Resection of Pancreatic Head Cancer

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Abstract
Introduction Nodal status is a strong prognostic factor after resection of pancreatic cancer. The lymph node ratio (LNR) has been shown to be superior to the pN status in several studies. The role of log odds of the ratio between positive and negative nodes (LODDS) as a suggested new indicator of prognosis, however, has been hardly evaluated in pancreatic cancer.
Methods Prognostic factors for overall survival after resection for cancer of the pancreatic head were evaluated in 409 patients from two institutions (prospectively maintained databases). The lymph node status, LNR, and LODDS were separately analyzed and independently compared in multivariate survival analysis.
Results The median numbers of examined and positive lymph nodes were 16 and 2, respectively. Actuarial 3- and 5-year survival rates were 29 and 16 %. All three classifications of nodal disease significantly predicted survival in the entire group ($n = 409$), in patients with free resection margins ($n = 297$), and in patients with <12 examined nodes. In multivariate analysis, however, both LNR and LODDS were equally superior to the nodal status. In node-negative patients ($n = 110$), LODDS could not identify subgroups with different prognosis.
Conclusion Both LNR and LODDS are superior to the classical nodal status in predicting prognosis in resected pancreatic cancer. However, LODDS has not shown any advantage over LNR in our series, neither in the entire patient group nor in the subgroups with free margins, negative nodes or a low number of examined nodes. Therefore, the use of LODDS to predict the outcome after resection of pancreatic head cancer cannot be recommended.

Keywords Pancreatic cancer · Resection · Survival · Prognostic factors · Lymph node ratio · LogODDS lymph nodes

Introduction

Locoregional lymph node metastasis is a well-known and important prognostic factor in patients with (resected) pancreatic cancer. A sufficient lymphadenectomy is considered as gold standard during potentially curative resection for pancreatic cancer. The lymph node ratio (LNR; number of involved nodes divided by the number of examined nodes) has been shown by several groups to be superior to the nodal status per se in predicting overall survival after surgery [1, 2].

In recent years, several studies have reported that the so called log odds of positive lymph nodes (LODDS) may be superior to the nodal status or even the LNR in various malignancies [3–5]. The LODDS are defined as the log of the ratio between the number of positive and the number of negative lymph nodes (when at least one lymph node is sampled). The LODDS, therefore, evaluate the number of examined nodes in a different manner than the LNR. By including the number of examined negative nodes in a logarithmic model, the LODDS potentially may define subgroups of node-negative patients with different prognosis (which is not the case in pN and LNR models).

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In one retrospective analysis of 143 patients after resection of pancreatic cancer, the prognostic relevance of LODDS has been shown to be comparable to LNR in the entire study group but even superior in the subgroup of nodal negative cases [6].

The aim of our study is to evaluate the prognostic role of LODDS after potentially curative resection in 409 patients with pancreatic cancer. We have merged the data of two departments with largely identical treatment standards and database documentation in surgery for pancreatic cancer [7].

Patients and Methods

The outcome of 409 patients undergoing oncological pancreatic resection for pancreatic head cancer was evaluated. The procedures were performed by a group from the University hospital in Freiburg, Germany (since 1994; $n = 313$) or by two surgeons in the Humboldt-hospital in Berlin, Germany (since 2007; $n = 96$). The two surgeons performing the procedures in the second institution (Berlin) were initially trained in the first institution (Freiburg) with common scientific experience [2, 7]. Data collection was performed using the same database structures.

Only patients with a postoperative follow-up of at least 3 months were included in our study to exclude a potential bias of perioperative mortality on oncological prognostic factors.

Surgical Technique and Perioperative Treatment

All patients underwent routine pre-operative work-up including a contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). In general, if metastases were found on preoperative imaging, patients were not eligible for curative resection. Arterial infiltration (>180° circumference) or complete occlusions of the superior-mesenteric/portal vein were further contraindications for (primary) resection. Involvement of/tumor contact to the portal vein alone did not contraindicate surgery. More than one-third of the patients in our series underwent portal vein resection. Further perioperative techniques have been published in detail before [7, 8].

The standard pancreatic head resections for pancreatic head masses were either a Kausch-Whipple procedure (Whipple) or a pylorus-preserving pancreatico-duodenectomy (PPPD) with reconstruction as pancreaticojejunostomy (PJ) or pancreaticogastrostomy (PG). Total pancreatectomy was performed in 6 % of the cases.

A standard lymphadenectomy along the right side of the superior mesenteric artery, the hepatoduodenal ligament, and the celiac trunc/upper pancreatic margin was performed in almost all cases. In a few selected, an extended lymphadenectomy was undertaken in order to achieve a complete resection.

After initial intraoperative frozen section analysis, all specimens underwent further routine histopathological examination.

Classification of Nodal Involvement

The absolute numbers of examined and the numbers of positive nodes were always documented in our databases. For this study, three different classifications were used to further evaluate the prognostic role of nodal involvement: The *N-status* was defined as positive (pN+) by the existence of at least one positive lymph node. The LNR was calculated as the ratio between positive and examined lymph nodes. For further subgroup analysis, LNR was then categorized into three groups: LNR < 0.1, LNR 0.1 to 0.199, and LNR ≥ 0.2. The *LODDS* were defined as log ((positive nodes + 0.5)/(negative nodes + 0.5)). The summand ".5" was added to avoid undefined logarithms. LODDS were then categorized into three or four subgroups for further analysis (see "Results" and Tables 2 and 4).

Neoadjuvant and Adjuvant Therapy

A smaller percentage of patients underwent neoadjuvant therapy for locally advanced disease ($n = 22$; 5.4 %). Sixteen patients received neoadjuvant chemoradiation (various chemotherapies; radiation between 45 and 56 Gy) or neoadjuvant chemotherapy (various protocols). Postoperative adjuvant treatment of all patients was heterogeneous. In the early study period, patients did not routinely undergo adjuvant treatment after curative resection. After publication of randomized trials, most patients underwent adjuvant chemotherapy after margin negative resection [9, 10].

Patients with positive resection margins were preferentially treated with postoperative chemoradiation or additive chemotherapy, some of them in prospective multicenter studies.

Data Collection, Follow-Up, and Statistical Analysis

Data were gained by analysis of our prospectively maintained institutional databases. For this study, the selected patients of the two databases were merged for final exploratory and statistical analyses.

Long-term survival status was assessed by contacting the general practitioners and/or oncologists of the patients, or by the regional cancer registries. SPSS software (IBM SPSS Statistics, last version used: 23.0; Armonk, NY USA: IBM Corp.) for Windows was used for data management and analysis. Overall survival was analyzed by the Kaplan–Meier method, with a log-rank test for the comparison of subgroups. Multivariate survival analysis was performed by the Cox proportional hazard model (forward selection strategy using a likelihood ratio statistic; inclusion p value = 0.1) including the report of relative risks and their 95 % confidence interval.

Since overlapping prognostic scores (pN status, LNR, LODDS) were used in our analyses, multivariate survival analysis (Cox regression) was performed in different steps/ models with the inclusion of only one of these scores each time in order to prevent multicollinearity.

Results

Clinical and Pathological Characteristics (*n* = 409)

Median age of all patients was 67 years (31–89). The most frequently performed procedure was a PPPD (*n* = 319; 78 %). Overall morbidity was 51 % (*n* = 209). The median number of examined lymph nodes was 16, and the median number of positive lymph nodes was 2. Median LNR was 0.11, and median LODDS were -0.81 (Table 1). Seventy-three percent of the patients were node-positive, and 27 % had positive margins (almost all microscopic) in the final pathological report. The median number of examined lymph nodes was 15 in node-negative patients and 17 in node-positive patients ($p < 0.01$). In node-negative patients, 27 % had less than 12 examined nodes whereas in node-positive cases, only 18 % had less than 11 nodes evaluated ($p < 0.02$).

Table 1 Clinical and morphologic features of 409 patients with resected pancreatic adenocarcinoma

Age (median; range)	67.4 (31–89)
Gender	
Female	204 (50 %)
Male	205 (50 %)
Hospital (*n*/%)	
Freiburg	313 (77 %)
Berlin	96 (23 %)
Type of resection	
Whipple	47 (12 %)
PPPD	319 (78 %)
Pancreatectomy	26 (6 %)
Laparoscopic pancreatoduodenectomy	17 (4 %)
Blood transfusion during surgery[a]	137 (34 %)
Vein resection	157 (38 %)
Overall morbidity	209 (51 %)
Positive nodes (*n*/%)	300 (73 %)
Number of examined lymph nodes (median; IQR)	16 (10)
Number of positive lymph nodes (median; IQR)	2 (4)
LNR (lymph node ratio) (median; IQR)	0.11 (0.25)
Log odds (median; IQR)	−0.81 (0.79)

[a] Some parameters were not available in selected cases (see numbers)

IQR interquartile range

Long-Term Survival of all Patients (*n* = 409)

Univariate Survival Analysis (Table 2)

The median survival of all patients was 1.75 years. Cumulative 3- and 5-year survival rates were 29 and 16 %, respectively. Cumulative survival did not differ between the two study institutions ($p = 0.77$). Median survival increased to 2.0 years in case of free margins ($p < 0.01$). In univariate analysis, intraoperative blood transfusion, mesenterico-portal vein resection, poor grading, and all three classifications of nodal disease (N-status, LNR, LODDS; Fig. 1) significantly influenced survival. Five-year survival was 12 % in nodal positive patients. Cumulative survival, however, was clearly lower in patients with LNR ≥ 0.2 (3 %) or LODSS > −0.5 (6 %). In the subgroup of patients with the highest percentage of involved nodes (LODSS > 0), median postoperative survival was clearly below 1 year.

Multivariate Survival Analysis (Table 3)

In multivariate survival analysis of the entire patient group (three different models for N-status, LNR, LODDS), tumor grading, resection margin, and nodal disease independently predicted survival in all models. Positive nodes were associated with a 1.4-fold risk of poor outcome ($p < 0.02$) whereas the subgroups of LNR and LODDS showed a better discrimination for survival (relative risk between the subgroups 1.78–2.16; all $p < 0.001$, Table 3). Multivariate reanalysis of LNR and LODDS as continuous variables did not show any superiority of LODDS over LNR (Table 3).

Subgroup Analysis of Margin Negative Patients (*n* = 297)

To exclude a potential bias of the (strong prognostic marker) resection margin, univariate and multivariate survival analysis was again performed in the subgroup of 297 patients with negative margins. Median survival in this subgroup was 2.0 years with a 3- and 5-year actuarial survival of 34 and 18 %, respectively. In univariate analysis, vein resection, grading, and N-status were significant predictors of long-term survival (Table 4) in those patients with free margins. As for the entire study group, LNR and LODDS, again, were strong prognostic factors in univariate analysis (Table 4 and Fig. 2).

In multivariate survival analysis of patients with negative margins, tumor grading, vein resection, and nodal disease (again the three different models for N-status, LNR, LODDS) independently predicted survival. Positive nodes

Table 2 Univariate survival analysis after resection of pancreatic cancer ($n = 409$)

Parameter	n	Median survival (years)	3-year survival (%)	5-year survival (%)	p
Hospital					
Freiburg	313	1.74	28.1	17.2	0.77
Berlin	96	1.79	30.4	11	
Age					
<70 years	253	1.79	26.5	12.6	0.49
≥70 years	156	1.64	32.6	20.0	
Gender					
Female	204	1.80	27.4	17.2	0.88
Male	205	1.75	30.0	12.8	
Introperative blood transfusion[a]					
Yes	137	1.25	22.0	14.4	<0.02
No	251	2.00	33.6	15.1	
Vein resection					
Yes	157	1.80	19.2	6.9	0.02
No	250	1.75	34.7	20.2	
Grading[a]					
G1/2	237	1.92	31.0	17.3	<0.01
G3/4	164	1.25	22.3	9.2	
T stage[a]					
T1/2	41	2.17	34.4	14.4	0.30
T3/4	365	1.75	28.0	15.0	
Neoadjuvant therapy					
Yes	22	1.32	34.1	34.1	0.53
No	387	1.75	28.4	14.3	
Resection margin					
Negative	297	2.0	34.4	18.0	<0.001
Positive	112	1.22	13.7	8.2	
Nodal status					
Negative	109	2.42	42.6	23.7	<0.001
Positive	300	1.50	23.3	11.9	
LNR					
<0.1	189	2.32	38.9	22.0	<0.001
0.1 to 0.199	88	1.83	29.9	15.1	
≥0.2	132	1.05	11.6	3.3	
No. of examined nodes					
<12	86	1.5	29.2	17.9	0.81
≥12	323	1.8	28.5	14.4	
Complications					
Yes	209	2.89	32.4	16.8	0.28
No	200	2.63	24.8	13.3	
Log odds models					
Log odds (three groups)					
<−1.0	149	2.33	41.0	21.5	<0.001
−1.0 to −0.5	141	1.83	29.3	15.7	
>−0.5	119	1.05	10.6	6.4	
Log odds (four groups)					
<−1.0	149	2.33	41.0	21.5	<0.001
−1.0 to −0.5	141	1.83	29.3	15.7	
>−0.5 to −0.001	98	1.07	9.5	7.1	
>0	21	0.85	18.3	-	

[a] Some parameters were not available in selected cases (see numbers)

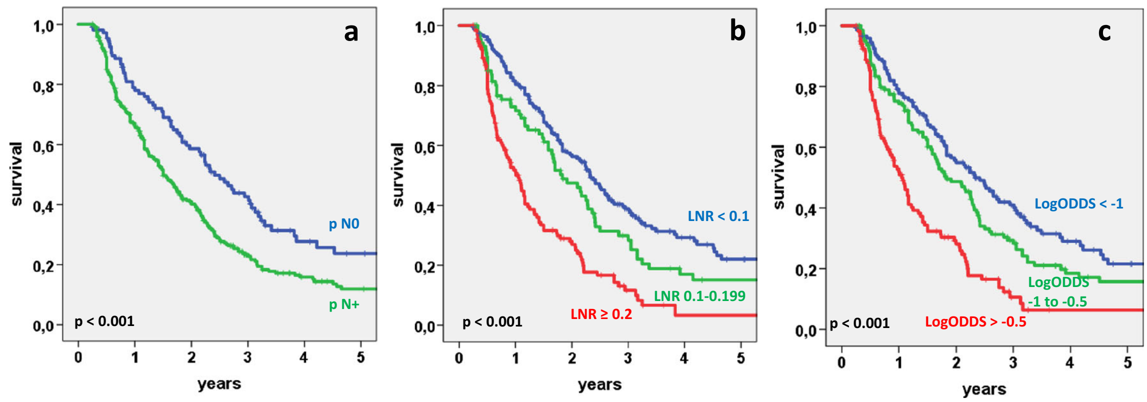


Fig. 1 Kaplan–Meier analysis of long-term survival after resection of pancreatic head cancer in 409 patients. Prognostic influence of different classifications of nodal disease. **a** Nodal status (pN0 vs pN+), **b** lymph node ratio, **c** log odds of positive nodes (three subgroups)

(pN+) were associated with a 1.6-fold risk of poor outcome ($p < 0.01$) whereas the subgroups of LNR and LODDS, again, showed a better prediction for survival (relative risk between the subgroups 2.35–3.07; all $p < 0.001$, Table 5). As in the entire patient group, separate reanalysis of LNR and LODDS as continuous variables did not show any superiority of LODDS over LNR.

Subgroup Analysis of Patients with <12 Examined Nodes (n = 86)

Since the nodal status per se (i.e., pN0 vs pN+) and the LNR do not directly consider the number of examined nodes, the LODDS have also been suggested to be a better prognostic indicator by also considering the number of negative nodes

Table 3 Results of multivariate survival (Cox regression) analysis after resection of pancreatic cancer

Parameter	*p*	Relative risk	95 % confidential interval
Model 1 with nodes (+/−)			
Blood transfusion during surgery (yes/no)	(0.07)		
Grading (G1/2 vs G3/4)	0.003	1.45	1.13–1.85
Resection margin	0.002	1.51	1.16–2.00
Nodal status (positive vs negative)	0.013	1.43	1.07–1.9
Model 2 with LNR			
Vein resection (yes/no)	(0.06)		
Grading (G1/2 vs G3/4)	0.01	1.38	1.08–1.92
Resection margin	0.019	1.38	1.06–1.81
LNR			
<0.1			
0.1 to 0.199	<0.001	2.16	1.63–2.87
≥0.2)	<0.001	1.85	1.33–2.57
LNR (continuous)[a]	<0.001	4.48	2.27–8.85
Model 3 with log odds			
Blood transfusion during surgery (yes/no)	(0.10)		
Grading (G1/2 vs G3/4)	0.004	1.43	1.12–1.82
Resection margin	0.019	1.39	1.05–1.82
Log odds			
<−1.0			
−1 to −0.5	<0.001	2.08	1.53–2.85
≥−0.5	<0.001	1.78	1.38–2.39
Log odds (continuous)[a]	<0.001	1.67	1.30–2.14

[a] Separate models with continuous variables

Table 4 Univariate survival analysis after resection of pancreatic cancer in patients with negative resection margins ($n = 297$)

Parameter	*n*	Median survival (years)	3-year survival (%)	5-year survival (%)	*p*
All with negative resection margins	297	2.0	34.4	18.0	
Hospital					
Freiburg	228	1.97	34.2	20.1	0.83
Berlin	69	2.10	34.9	14.1	
Age					
<70 years	179	1.97	31.6	14.5	0.45
≥70 years	118	2.07	38.8	24.3	
Sex					
Female	154	1.97	33.1	20.2	0.85
Male	143	2.09	35.8	14.8	
Introperative blood transfusion *					
Yes	90	1.75	27.7	17.9	0.10
No	196	2.14	37.9	17.1	
Neoadjuvant therapy					
Yes	12	2.75	46.7	46.7	0.30
No	285	1.97	33.9	17.0	
Vein resection					
Yes	103	1.83	22.6	6.8	0.03
No	194	2.10	40.1	23.2	
Grading					
G1/2	168	2.15	38.4	21.3	<0.01
G3/4	121	1.63	25.1	9.9	
T *					
T1/2	35	2.42	41.4	17.3	0.33
T3/4	259	1.92	33.4	17.8	
Nodal status					
Negative	93	2.75	47.4	27.3	<0.001
Positive	204	1.68	28.1	13.4	
LNR					
<0.1	152	2.65	45.5	26.4	<0.001
0.1 to 0.199	62	2.17	38.3	16.9	
≥0.2	83	0.92	9.9	2.5	
No. of examined nodes					
<12 LN	61	1.83	39.3	23.7	0.78
≥12 LN	236	2.0	32.9	16.4	
Log odds models					
Log odds (three groups)					
<−1.0	122	2.75	47.8	26.6	<0.001
−1.0 to −0.5	100	2.25	36.6	17.1	
>−0.5	75	0.92	6.9	3.5	
Log odds (four groups)					
<−1.0	122	2.75	47.8	26.6	<0.001
−1.0 to −0.5	100	2.25	36.6	17.1	
>−0.5 to −0.001	64	1.07	5.8	2.9	
>0	11	0.65	24.0	-	

Some parameters were not available in selected cases (see numbers)

[6]. We, therefore, compared the (univariate) influence of LNR and LODDS on survival in the subgroup of 86 patients with less than 12 examined nodes. As already shown for the entire group and for patients with free margins, the survival curves of the LNR groups and the LODDS groups were almost identical (Fig. 3).

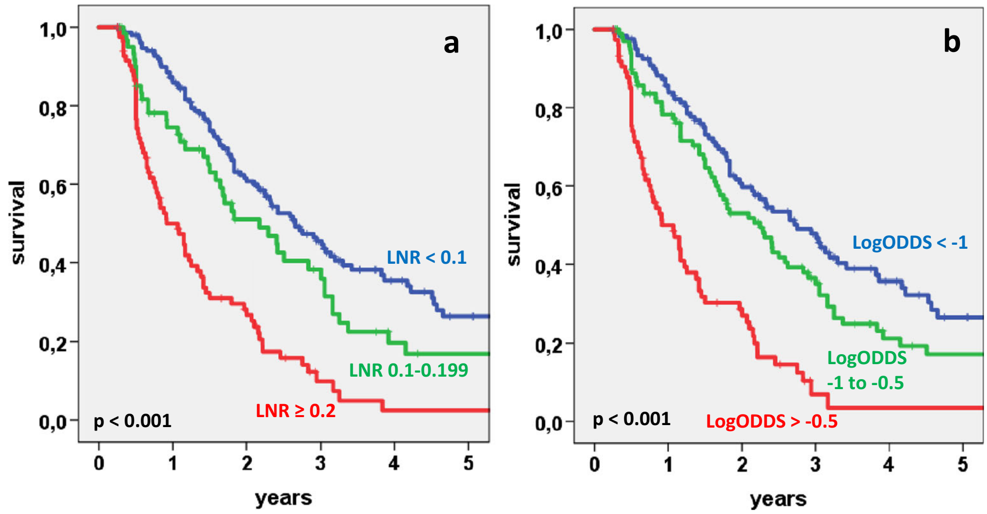


Fig. 2 Actuarial survival after resection of pancreatic head cancer in 297 patients with free resection margins. Prognostic influence of lymph node ratio (**a**) and log odds of positive nodes (**b**)

Subgroup Analysis of Node-Negative Patients (n = 109)

As for patients with a low number of examined nodes, LODDS have also been proposed to potentially identify subgroups with different prognosis in node-negative patients (by including the number of examined nodes). In the subgroup of 109 node-negative patients, different comparative analyses of LODSS classes (LODDS < −1 v. ≥−1; LODDS < −1.2 vs ≥−1.2; LODDS < −1.5 vs ≥−1.5) did not reveal any prognostic influence of LODDS on survival in node-negative patients (log-rank p value between 0.65 and 0.87; data not shown).

Discussion

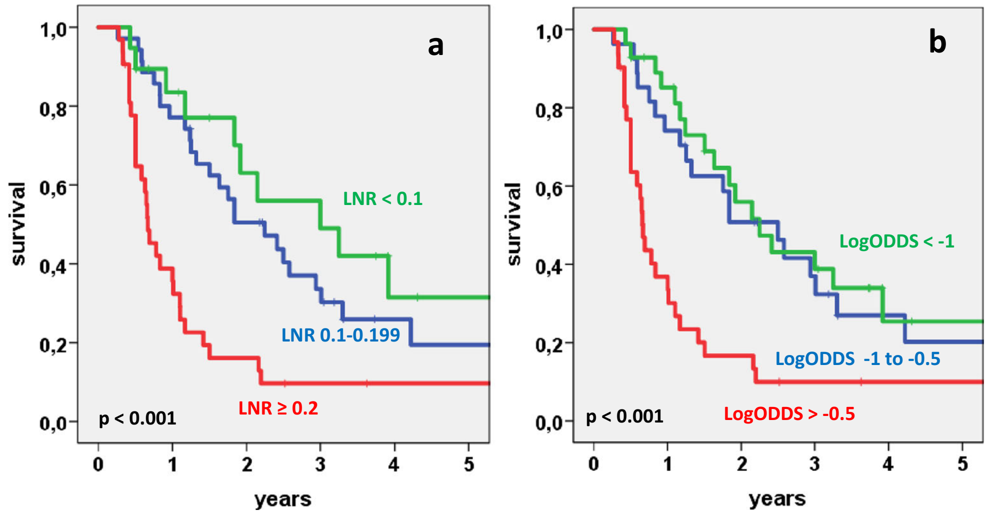
Lymph node involvement is one of the strongest factors influencing prognosis after resection of pancreatic cancer [11, 12]. Several groups reported that the LNR is a more powerful

Table 5 Results of multivariate survival (Cox regression) analysis after resection of pancreatic cancer with negative resection margins ($n = 297$)

Parameter	p	Relative risk	95 % confidential interval
Model 1 with nodes (+/−)			
Vein resection (yes/no)	0.02	1.39	1.05–1.86
Grading (G1/2 vs G3/4)	<0.01	1.52	1.15–2.02
N (N0/N+)	<0.01	1.56	1.14–2.12
Model 2 with LNR			
Vein resection (yes/no)	0.02	1.43	1.07–1.91
Grading (G1/2 vs G3/4)	<0.01	1.45	1.09–1.93
LNR			
<0.1			
0.1 to 0.199	<0.001	2.92	2.12–4.03
≥0.2	<0.001	2.35	1.59–3.47
LNR (continuous)[a]	<0.001	9.5	4.37–20.68
Model 3 with log odds			
Vein resection (yes/no)	0.03	1.39	1.04–1.85
Grading (G1/2 vs G3/4)	<0.01	1.53	1.67–2.04
Log odds			
<−1.0			
−1 to −0.5	<0.001	3.07	2.16–4.37
≥−0.5	<0.001	2.46	1.73–3.48
Log odds (continuous)[a]	<0.001	2.05	1.54-2.74

[a] Separate models with continuous variables

Fig. 3 Actuarial survival after resection of pancreatic head cancer in 86 patients with less than 12 examined lymph nodes. Comparison of lymph node ratio (a) and log odds of positive nodes (b)



prognostic parameter than nodal disease per se [1, 13]. This fact was also demonstrated in an earlier report by our group [2]. In recent years, the log odds of positive nodes have been suggested as an even better prognostic parameter in various malignancies like gastric, breast, and colon cancer [3, 5, 14]. Several theoretical advantages of the LODDS over the pN status or the LNR have been proposed [3, 6, 15]. By considering the number of negative nodes, LODDS can discriminate between subgroups with different prognosis in node-negative patients (which may be a result of the so-called stage migration). In addition, LODDS may provide further prognostic information in patients with identical LNR values but different numbers of examined nodes (e.g., LNR 0.1 in patients with 1/10 metastatic nodes or 2/20 metastatic nodes).

In gastric cancer, for example, LODDS have been shown to be superior to LNR and N-status, especially in the case of insufficient lymphadenectomy [3, 15, 16]. In colon cancer, LNR and LODDS have been significantly predictive whereas only LODDS have been powerful in case of negative nodes or insufficient lymphadenectomy [4, 14]. Moreover, LODDS have been meaningful in nodal positive patients as they allow a more precise grouping of patients [17].

To our knowledge, only one study published in 2014 evaluated the role of LODDS after (margin-free) resection of pancreatic cancer in a relatively small patient group ($n = 143$) [6]. In that study, LNR and LODDS were more powerful predictors of survival than the pN status. The authors also stated that LODDS were superior to LNR in the subgroup of node-negative patients.

In our study, we evaluated the outcome after resection of more than 400 pancreatic head cancers. All included patients had sufficient follow-up information and data on nodal involvement. As in our previous analysis, LNR was clearly a better discriminating prognostic factor than the mere presence of nodal involvement per se (pN0 vs pN+) in univariate and multivariate analysis. In our series, LODDS (evaluated in three or four subgroups) were also a strong predictive factor but did not show any superiority to LNR. When comparing LNR and LODDS, the curves of actuarial survival analysis and (in multivariate analysis) the relative risks/odds ratios were almost identical. This was the case not only in the entire study group but also in the subgroup of R0 patients, thus excluding a potential bias of resection margin.

The suggested advantages of LODDS in patients with a low number of examined nodes or in node-negative patients could not be confirmed in our series. In the subgroup analysis of patients with less than 12 nodes examined, LNR and LODDS again showed absolutely comparable survival curves. Furthermore, LODDS subgroup analysis did not reveal any prognostic value in node-negative patients. This was still the case when trying different cutoff values to define the LODDS subclasses.

There may be several theoretical reasons why LODDS did not improve the outcome prediction as compared to LNR: The

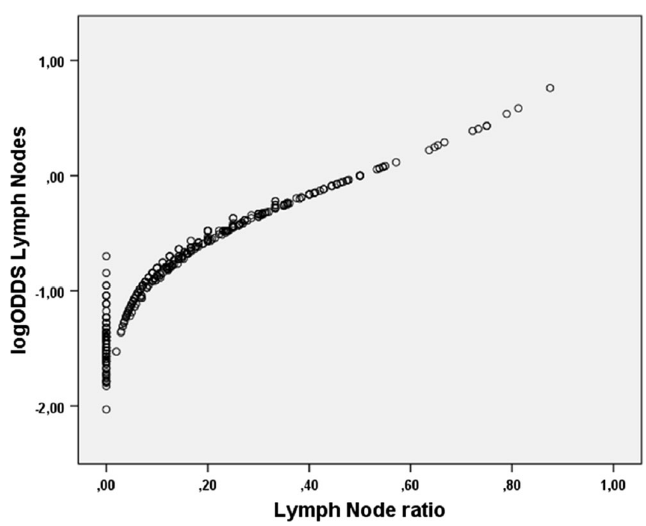


Fig. 4 Scatter plot of the relationship between lymph node ratio and log odds of nodes in 409 resected pancreatic head cancers. Please note the different log odds values in cases with LNR of zero (representing node-negative patients)

classification of the LODDS subgroups was strongly correlated to the LNR subgroups leading to comparable predictive values of the corresponding subgroups. However, LODDS was not superior to LNR when both parameters were independently analyzed in the Cox regression analysis as continuous variables. Prognostic values also did not change when we tried other cutoffs between the LODDS groups. In addition, the relationship between LNR and LODDS was rather linear above LNR of around 0.1 (i.e., in patients with a higher nodal burden, see Fig. 4).

Because the number of examined lymph nodes in node-negative patients was lower than in node-positive cases, it is theoretically possible that a certain "stage migration" effect exists in our evaluations. However, since the number of examined nodes did not show any influence on survival rates (p 0.78–0.81; Tables 2 and 4), we believe that this possible effect did not relevantly influence our results. This is further supported by the lack of an additional prognostic power of LODDS in node-negative patients (thus excluding a prognostic difference between node-negative patients with different numbers of negative nodes).

Conclusions

Both LNR and log odds of lymph nodes are strong prognostic factors after resection of cancer of the pancreatic head. Both classifications are superior to the nodal status in predicting survival. In contrast to published reports on colon, gastric, or breast cancer, LODDS did not show any additional advantage over LNR in our relatively large series, neither in the entire patient group nor in the subgroups with free margins, negative nodes or low numbers of examined nodes. Therefore, the use of LODDS to predict the outcome after resection of pancreatic head cancer cannot be recommended.

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