



Outcomes of Lymph Node Dissection for Non-metastatic Pancreatic Neuroendocrine Tumors: A Propensity Score-Weighted Analysis of the National Cancer Database

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ABSTRACT

Background. Although the National Comprehensive Cancer Network (NCCN) guidelines recommend use of lymph node dissection (LND) in patients with pancreatic neuroendocrine tumors (pNETs) > 2 cm, there is limited evidence to support the association between use of LND and overall survival (OS).

Methods. Patients with resected pNETs were identified in the National Cancer Database (2004–2014). The inverse probability of treatment weighting (IPTW) method was used to reduce the selection bias. IPTW-adjusted Kaplan–Meier curves and Cox proportional hazards models were used to compare OS of patients in different treatment groups.

Results. A total of 2664 patients diagnosed met the study entry criteria. Of these, 2132 patients (80.6%) received LND, with a median of nine nodes removed. Positive nodes were identified in 28.0% of patients who underwent LND. IPTW-adjusted Kaplan–Meier analysis showed that median

OS was similar between the LND and LND-omitted groups (152.8 vs. 147.3 months; $p = 0.61$). In IPTW-adjusted Cox proportional hazards regression analysis, LND was not associated with an OS benefit (hazard ratio [HR] 1.15, 95% confidence interval [CI] 0.94–1.42; $p = 0.18$). The results were consistent across subgroups stratified by clinical T and N stages. Among patients with lymph node metastasis, the number of removed nodes (NRN) above the median was not associated with an improved OS (HR 0.82, 95% CI 0.60–1.13; $p = 0.22$).

Conclusions. LND had no additional therapeutic benefit among patients undergoing resection for pNETs. The present findings should be considered when managing patients with resectable pNETs.

Pancreatic neuroendocrine tumors (pNETs) are a relatively rare and heterogeneous group of tumors, accounting for only 1–2% of all pancreatic malignancies.^{1,2} The rate of lymph node metastasis (LNM) of pNETs has been reported as high as 38%.³ Although the clinical significance of LNM on prognosis is still debated,^{4–9} current guidelines incorporate lymph node status.^{10,11} The National Comprehensive Cancer Network (NCCN) guidelines recommend total removal of regional lymph nodes for larger pNETs (> 2 cm) and consideration of lymph node dissection (LND) for tumors < 2 cm.¹¹ The North American Neuroendocrine Tumor Society (NANETS) guideline requires routine LND for all pNETs.¹²

Standardized LND is associated with improved rates of local recurrence and overall survival (OS) for some tumor types^{13,14}; however, the benefit of LND during

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pancreatectomy for patients with pNETs remains controversial. Krampitz et al. reported that lymph node metastases significantly reduced disease-related survival,⁶ but whether the removal of nodal metastases translates into survival benefit was not answered. Two previous population-level studies found that LND did not improve prognosis in patients with pNETs ≤ 2 cm in size.^{15,16} However, the LN invasion rates are so low that the benefit of LND may be difficult to demonstrate in these patients.^{3,17} In addition, the therapeutic role of LND in patients with clinical or pathologic lymphadenopathy has not been studied previously. Moreover, the lack of therapeutic value of LND might be partly due to inadequate evaluations of lymph nodes.^{18–23}

Given the limitations of these previous studies, we performed a comprehensive analysis to examine the effect of LND on OS of patients with pNETs, using the National Cancer Database (NCDB). Inverse probability of treatment propensity-score weighting (IPTW) was employed to reduce the selection bias.

METHODS

Database and Patient Population

The NCDB is a nationwide hospital-based cancer registry that serves as a comprehensive surveillance resource for cancer care in the US. The NCDB includes approximately 75% of new cancers in the US and collects data from more than 1400 hospitals that have cancer treatment programs accredited by the American College of Surgeons Commission on Cancer. Data are coded and reported based on the Facility Oncology Registry Data Standards Manual. This study was granted Duke University Institutional Review Board exemption as no patient, physician, or hospital identifiers were examined.

Between 2004 and 2014, patients with pNETs undergoing curative-intent resection were identified. pNETs were identified based on International Classification of Diseases for Oncology, Third Edition (ICD-O-3) morphological codes 8150–8153, 8155–8157, 8240–8243, 8246, 8249,²⁴ and topographical codes C25.0–C25.9. Exclusion criteria included patients in whom this was not the only cancer diagnosis; patients with high-grade pNETs (grade codes 3 or 4) or tumor grade unknown; patients with clinical or pathological presence of distant metastases; patients with incomplete clinical stage or prognosis information; patients undergoing resection for palliative intent; patients who underwent treatment outside of the reporting facility; and patients who had unknown LND status. Patients who died within 90 days following surgery were

also excluded because of this period's significance as a legitimate measure of surgical quality.²⁵

Study Variables

Patient-related information included age at diagnosis, sex, year of diagnosis, insurance status, Charlson–Deyo comorbidity score, and zip-code-based income levels. Tumor data included tumor location, grade, clinical T stage, clinical N stage, and number of positive lymph nodes. The T stage was harmonized into the American Joint Commission on Cancer (AJCC) 8th edition.²⁶ Specifically, T1 is a tumor limited to the pancreas, < 2 cm in size; T2 is a tumor limited to the pancreas, 2–4 cm; T3 is a tumor limited to the pancreas, > 4 cm, or invading the duodenum or common bile duct; and T4 is a tumor invading the adjacent structures. Treatment-related factors included types of treatment facilities, receipt of LND, number of lymph nodes examined, surgical approach, margin status, unplanned 30-day readmissions, and length of hospital stay. LND was defined using a combination of the variables for scope of LN surgery and number of nodes examined by the pathologist. All patients whose surgical procedure was initiated by a laparoscopic or robot-assisted approach were categorized as having undergone minimally invasive surgery.

Statistical Analysis

Under the missing at random assumption, we first performed multiple imputation by chained equations to impute missing data for income (0.2% missing), types of treatment facilities (5.0%), insurance type (1.3%), tumor location (7.1%), surgical approach (22.7%), margin status (1.9%), unplanned 30-day readmissions (0.7%), and length of hospital stay (3.9%). We generated 30 complete datasets for subsequent analyses.²⁶

We compared the baseline characteristics between patients who underwent LND (LND group) with patients who did not (LND-omitted group). The balance in covariates was assessed using the standardized difference (SD) approach. An SD of 0.1 denotes meaningful imbalance in the factors between the two groups. In an attempt to eliminate the selection bias, the observed differences in baseline covariates between the two intervention groups were adjusted using the IPTW method. Specifically, we first estimated, in each imputed dataset, the propensity score, i.e. the conditional probability of receiving LND, using a logistic-regression model that included predictor variables that had been selected on the basis of their a priori possibility of confounding the relationship between receipt of LND and survival (age, sex, comorbidity score, income, insurance type, facility type, tumor location, year

of diagnosis, clinical T and N stages, tumor grade, and surgical approach). The estimated propensity scores from the 30 imputed datasets were then combined according to Rubin's rules,²⁷ and were used to weight each patient with the aim of balancing the characteristics between the two groups.

The adjusted Kaplan–Meier curves and log-rank test based on inverse probability weights were computed to compare OS between the LND and LND-omitted groups. In addition, univariate weighted Cox proportional hazards models were used to estimate the IPTW-adjusted hazard ratio (HR) of the LND versus LND-omitted groups. We further performed subgroup analyses to investigate the IPTW-adjusted HR according to the clinical T and N stages following the previously described methodology. If post-weighting balance cannot be achieved in a certain subgroup, multivariate Cox regression models were subsequently used to perform additional covariance adjustment.

We further conducted exploratory analyses to determine the impact of the extent of LND on OS among patients with pathologically proven LNM. As the current guidelines do not define the threshold of lymph nodes required for staging, we adopted the median number of removed nodes (NRN) as the cut-off value. OS between patients with different NRN levels was compared using the methods previously described.

In this study, all statistical analyses were performed using R version 3.5.1 (R Core Team 2018, Vienna, Austria). Statistical analyses were two tailed and a p -value < 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

In total, 2644 patients met the study entry criteria, of whom 2132 patients (80.6%) received LND. The baseline characteristics of eligible patients before and after propensity score matching, stratified by receipt of LND, are listed in Table 1. In multivariable logistic regression analysis, open surgery, moderately differentiated or pancreatic head tumor, and advanced T stage were significantly associated with the likelihood of receiving LND (Table 2). After IPTW adjustment, SD for all characteristics were < 0.1 , indicating that the weighted population in the two groups were subsequently comparable (Table 1). In the weighted study population, LND was associated with longer hospital stay after surgery compared with LND omission (mean 9.2 vs. 8.0 days).

Among patients undergoing LND, the median NRN was nine (interquartile range [IQR] 4–16). Results of multivariable logistic regression analysis based on unweighted patients demonstrated that academic facility, being diagnosed between 2010 and 2014, moderately differentiated or pancreatic head tumor, higher T stage, and cN0 disease were all significantly associated with $\text{NRN} > 9$ (Table 2). Metastatic nodal disease was detected in a total of 597 patients (28.0%). The LNM rates were 9.5%, 20.6%, 40.0%, and 50.7% for patients with clinical T1, T2, T3, and T4 disease, respectively ($p < 0.001$). A total of 1931 patients had cN0 disease, 538 of whom had LNM, similar to the LNM rate among those with cN + disease (27.9% vs. 29.4%; $p = 0.65$)

Overall Survival (OS) for the Matched Cohort: Lymph Node Dissection (LND) Versus LND Omitted

IPTW-adjusted Kaplan–Meier analysis showed that median OS was similar between the LND and LND-omitted groups (152.8 vs. 147.3 months; $p = 0.61$ in the IPTW-adjusted log-rank test) (Fig. 1). The 5- and 10-year IPTW-adjusted rates of OS were 91.2% and 67.0% for the LND group; and 89.5% and 72.0% for the LND-omitted group, respectively. In IPTW-adjusted univariate Cox proportional hazards regression analysis, LND was not associated with OS benefit (HR 1.15, 95% CI 0.94–1.42; $p = 0.18$). Subgroup analysis according to clinical T and N stages demonstrated no survival benefit after LND across subgroups (Table 3).

OS for the Matched Lymph Node Metastasis Cohort: Number of Removed Nodes (NRN) ≤ 9 Versus $\text{NRN} > 9$

The baseline characteristics of patients with LNM, stratified by NRN level, were balanced after matching (electronic supplementary Table). More than nine lymph nodes removed was associated with greater positive LN yield (mean 4.0 vs. 2.2) after weighting. IPTW-adjusted Kaplan–Meier analysis showed that median OS was similar between $\text{NRN} > 9$ and $\text{NRN} \leq 9$ (136.2 vs. 149.9 months; $p = 0.55$ in the IPTW-adjusted log-rank test) (Fig. 2). The 5- and 10-year IPTW-adjusted rates of OS were 85.2% and 67.0% for the $\text{NRN} > 9$ group, and 85.6% and 72.3% for the $\text{NRN} \leq 9$ group, respectively. $\text{NRN} > 9$ was not associated with OS benefit in IPTW-adjusted Cox proportional hazards regression analysis (HR 0.82, 95% CI 0.60–1.13; $p = 0.22$).

TABLE 1 Selected baseline characteristics between the LND and LND omitted groups, before and after weighting

	Unweighted study population [<i>n</i> (%)]			Weighted study population, %		
	LND [<i>n</i> = 2132 (80.6%)]	LND omitted [<i>n</i> = 512 (19.4%)]	Standardized difference	LND	LND omitted	Standardized difference
Age, years [mean (SD)]	58.3 (11.9)	59.2 (12.3)	0.074	58.5 (11.9)	58.4 (12.6)	0.002
Male	1079 (50.6)	249 (48.6)	0.020	51.1	50.2	0.009
Income, US\$						
< 38,000	317 (14.9)	76 (14.9)	< 0.001	14.9	14.8	0.001
38,000–47,999	533 (25.1)	118 (23.1)	0.020	24.3	27.0	0.023
48,000–62,999	536 (25.2)	139 (27.2)	0.020	25.7	26.2	0.005
> 62,999	740 (34.8)	178 (34.8)	< 0.001	34.7	32.0	0.027
Facility type						
Academic	1312 (64.8)	296 (60.7)	0.043	64.7	67.7	0.030
Community Cancer Program	484 (23.9)	130 (26.6)	0.027	23.8	22.1	0.017
Integrated Network	229 (11.3)	62 (12.7)	0.016	11.5	10.2	0.013
Insurance status						
Medicaid/others	144 (6.9)	29 (5.7)	0.011	6.6	7.3	0.007
Medicare	686 (32.7)	183 (36.0)	0.033	33.4	34.9	0.015
No insurance	57 (2.7)	13 (2.6)	0.001	2.7	2.3	0.004
Private	1214 (57.8)	283 (55.7)	0.021	57.3	55.5	0.018
Charlson–Deyo score						
0	1517 (71.2)	372 (72.7)	0.015	71.4	70.9	0.005
1	485 (22.7)	107 (20.9)	0.019	22.4	22.1	0.002
≥ 2	130 (6.1)	33 (6.4)	0.003	6.2	7.0	0.008
Year of diagnosis: 2010–2014	1642 (77.0)	401 (78.3)	0.013	77.3	77.8	0.004
Clinical T stage						
T1	642 (30.3)	297 (58.5)	0.280	35.8	37.0	0.012
T2	587 (27.7)	146 (28.7)	0.011	27.8	26.7	0.011
T3	354 (16.7)	32 (6.3)	0.104	14.7	14.9	0.002
T4	535 (25.3)	33 (6.5)	0.187	21.7	21.3	0.003
Clinical lymph node-positive	201 (9.4)	48 (9.4)	< 0.001	9.4	10.3	0.009
Tumor location						
Pancreatic body/tail	1041 (52.5)	326 (68.9)	0.167	55.8	58.1	0.023
Pancreatic head	696 (35.1)	80 (16.9)	0.183	31.5	28.6	0.029
Others	245 (12.4)	67 (14.2)	0.016	12.7	13.3	0.006
Open surgery	1085 (66.1)	215 (53.6)	0.134	64.8	61.8	0.030
Well-differentiated	364 (17.1)	47 (9.2)	0.107	84.5	85.3	0.009
Length of hospital stay, days, [mean (SD)]	9.3 (10.1)	6.7 (6.1)	0.318	9.2 (10.4)	8.0 (8.1)	0.136

LND lymph node dissection, *SD* standardized difference

DISCUSSION

The optimal management for resectable pNETs remains controversial, ranging from observation of small tumors to resection with or without LND.^{11,12} Currently there is no level 1 evidence demonstrating a therapeutic effect of LND in patients with pNETs ≤ 2 cm.^{15,16} As the risk of nodal metastasis increases in larger tumor sizes, LND is recommended by the NCCN for lesions larger than 2 cm in size.¹¹ However, LND may be associated with increased

operative time, higher blood loss, inclusion of splenectomy, complicated postoperative recovery, and increased risk for lymphocele development. Therefore, risks and benefits for LND need to be weighed carefully. In this analysis, LND was not associated with improved survival of patients with pNETs, regardless of T stage and nodal status.

Lymph nodes are often not or inadequately sampled in patients with pNETs. In a large international multi-institutional analysis, Rindi et al. reported that only 335 of 1072

TABLE 2 Multivariable logistic regression model predicting receipt of LND and NRN level in the unweighted study population

	LND versus LND omitted			NRN ≤ 9 versus NRN > 9		
	OR	CI	<i>p</i> value	OR	CI	<i>p</i> value
Age (per year)	1.0	0.99–1.01	0.98	1.0	0.99–1.01	0.98
Male	0.95	0.77–1.17	0.66	0.89	0.74–1.07	0.20
Income, US\$						
< 38,000	1			1		
38,000–47,999	1.14	0.81–1.60	0.44	1.02	0.76–1.38	0.86
48,000–62,999	0.93	0.67–1.29	0.65	0.72	0.53–1.17	0.33
> 62,999	1.11	0.80–1.53	0.51	1.0	0.75–1.33	0.98
Facility type						
Academic	1			1		
Community Cancer Program	0.83	0.65–1.06	0.12	0.44	0.29–0.68	< 0.001
Integrated Network	0.73	0.54–1.01	0.06	0.78	0.45–1.35	0.35
Insurance status						
Medicaid/others	1			1		
Medicare	0.88	0.54–1.41	0.61	0.83	0.56–1.27	0.42
Private	0.87	0.55–1.35	0.56	1.40	0.70–1.46	0.95
No insurance	0.67	0.32–1.43	0.29	1.04	0.55–2.0	0.90
Charlson–Deyo score						
0	1			1		
1	1.15	0.90–1.49	0.27	1.06	0.69–1.65	0.68
≥ 2	0.93	0.62–1.45	0.75	1.21	0.82–1.79	0.33
Year of diagnosis: 2010–2014	1.16	0.90–1.49	0.24	1.81	1.45–2.26	< 0.001
Clinical T stage						
T1	1			1		
T2	1.75	1.38–2.22	< 0.001	1.24	0.98–1.58	0.07
T3	4.45	3.03–6.74	< 0.001	1.91	1.44–2.55	< 0.001
T4	7.09	4.89–10.59	< 0.001	1.95	1.52–2.50	< 0.001
Clinical lymph node-positive	1.07	0.76–1.53	0.70	0.70	0.51–0.96	0.026
Tumor location						
Pancreatic body/tail	1			1		
Pancreatic head	2.12	1.62–2.79	< 0.001	2.76	2.24–3.42	< 0.001
Others	1.05	0.78–1.42	0.77	1.79	1.34–2.38	< 0.001
Open surgery	1.31	1.05–1.62	0.015	1.31	1.06–1.60	0.013
Well-differentiated	0.63	0.44–0.87	0.007	0.73	0.57–0.94	0.011

LND lymph node dissection, NRN number of removed lymph nodes, OR odds ratio, CI confidence interval

(31%) patients had lymph nodes assessed.¹⁸ In other retrospective studies, the utilization of lymphadenectomy ranged from 62.9 to 77%.^{21–23} Parekh et al. further reported that 52% of patients with pNETs who had lymph nodes sampled had five or fewer lymph nodes identified based on single-institutional data.²² In our study of 2664 patients from a national database, 80.6% of patients underwent LND, with a median number of nine lymph nodes removed. This rate is higher than that previously reported, probably because more patients with locally advanced disease were included in the present study.

The decision to perform LND and its extent were associated with various factors. Not surprisingly, patients with pancreatic-head-located or advanced T-stage disease

were more likely to receive LND and had more lymph nodes removed. LND was less likely to be performed in a minimally invasive surgery, and fewer nodes were retrieved with a minimally invasive surgery. Our study also indicated greater numbers of nodes removed among university hospitals than among community hospitals. Interestingly, more lymph nodes were retrieved since 2010, perhaps because surgeons attached more importance to LND after the release of the first pNETs staging system by the NCCN in that year.²⁸

Although LNM was detected in 28% of the included patients, LND did not lead to an improvement of outcomes. Indeed, the median OS was 152.8 and 147.3 months for patients with or without LND, respectively ($p = 0.61$).

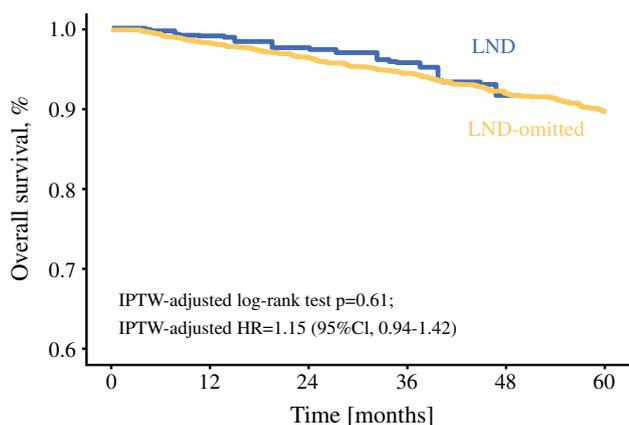


FIG. 1 IPTW-adjusted Kaplan–Meier analysis of overall survival according to LND status. *LND* lymph node dissection, *IPTW* inverse probability of treatment weighting

TABLE 3 Hazard ratio for the LND versus LND omitted groups in subgroups stratified by clinical T and N stages

	LND versus LND omitted		
	<i>n</i>	HR	95% CI
T1	886	1.45	0.42–1.13
T2	746	1.96	1.38–2.77
T3	378	2.38	1.41–4.0
T4	530	0.97	0.69–1.35
N0	2136	0.91	0.73–1.12
N1	234	0.49	0.21–1.13

HR hazard ratio, *CI* confidence interval, *LND* lymph node dissection

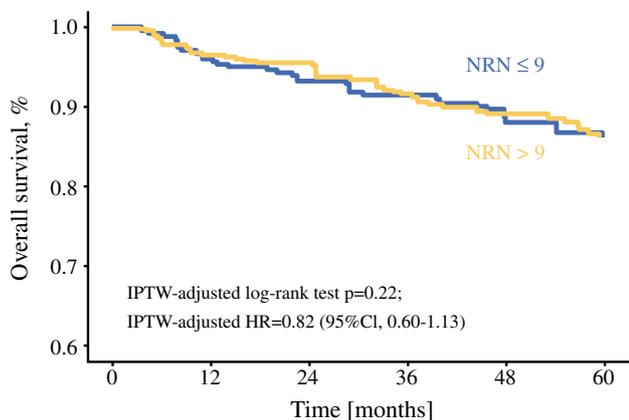


FIG. 2 IPTW-adjusted Kaplan–Meier analysis of overall survival according to the NRN. *NRN* number of removed nodes, *IPTW* inverse probability of treatment weighting, *HR* hazard ratio, *CI* confidence interval

However, we would refrain from concluding that LND can be routinely omitted for all patients with pNETs, and more selective decision making may be reasonable. Those with adverse tumor biology are potential candidates who can benefit from removing occult nodal diseases. However, the

result applied to all clinical T stages, even though advanced T stage was significantly correlated with an increasing probability of having LNM. Moreover, the results suggested a higher HR for death in T2/T3 patients undergoing LND, which might be attributed to the morbidities associated with LND in these subgroups. Some would also suggest that LND be reserved for patients with clinically N + disease, but the incidence of LNM was similar between patients with or without clinical evidence of lymph node positivity, and the results demonstrated that patients with clinically suspicious lymph nodes did not benefit from LND. Although we could not evaluate whether the omission of LND adversely affects the survival of patients with LNM, all patients with pathologically proven nodal diseases should certainly have undergone LND. However, NRN, as an indicator of LND extent, had no protective effect on OS in LN-positive patients also. The present findings show that the benefit of aggressive lymphadenectomy may have limited therapeutic value for patients with resectable pNETs.

The value of LND for prognosis may also be limited. Some researchers have argued that lymph node status does not improve staging.^{7–9} Krampitz et al. suggested that the 10-year OS for those with no metastases or lymph node metastases was similar in 326 patients undergoing surgery for pNETs.⁶ By analyzing 3851 patients who underwent pNET resection from the NCDB database, Bilimoria et al. concluded that nodal status was not an independent predictor of survival.⁷ Recently, Ellison et al. developed a novel staging system, entirely based on grade, to predict OS. The inclusion of lymph node involvement did not improve the model’s prognostic ability.⁹ Additionally, as imaging modalities improve, the prognostic value of nodal involvement may be further diminished.^{29–31}

Finally, in addition to being limited as a prognostic and therapeutic tool, LND also plays a minimal role in adjuvant therapy decision making.³² Systemic treatment recommendations are mostly based on grade (Ki-67, mitotic count and differentiation) rather than nodal status.^{11,12} Therefore, taken together, our present findings, as well as those of other studies, suggest that the value of routine LND for resectable pNETs may be limited.

There are limitations that should be considered in the interpretation of this analysis. First, the study population analyzed was developed from Commission on Cancer-accredited hospitals, thus there is likely heterogeneity in patient selection. Although patients were matched based on factors that could have influenced treatment choice in an attempt to minimize bias, unknown confounders still represent a source of bias. Second, our study was limited by the absence of several variables in the database, such as mitotic counts and Ki67, thus the grading of tumors in the NCDB is by tumor differentiation rather than on numerical

cut-offs of proliferation. Finally, there is no coding for local or distant recurrence in the NCDB database; therefore, recurrence patterns or recurrence-free survival could not be analyzed.

CONCLUSIONS

Based on the data retrieved from the NCDB database, LND is not associated with improved OS in patients with pNETs. Since a prospective randomized trial is unlikely to be feasible, a multicenter retrospective study may be of great value to provide further guidance on the role of LND in patients with resectable pNETs.

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