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Cohort Study

Survival in resectable pancreatic ductal adenocarcinoma with para-aortic lymph node dissection: A retrospective study in Vietnamese population

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ABSTRACT

Background: Pancreatic ductal adenocarcinoma (PDAC) has a high recurrence rate and poor outcome. Lymph node (LN) metastasis, especially para-aortic LN (PALN), is an important prognostic factor. PALN assessment through sampling with frozen-section analysis is a validated method. Our aim was to evaluate the prognostic impact of PALN on overall survival (OS) in patients who underwent standard pancreaticoduodenectomy, lymphadenectomy with PALN sampling, as well as to identify other prognostic factors for survival.

Methods: Our retrospective study included 89 PDAC patients undergoing radical resection with PALN sampling. The patients were classified into PALN(+) (n = 11) and PALN(−) (n = 78). Univariate and multivariate analyses of 1-year and 3-year OS and Kaplan-Meier model were used.

Results: OS after 1-year for PALN(+) and PALN(−) was 18.2 and 56.4%, after 3-year was 15.4% and 0%, respectively. Tumor differentiation, LN metastasis (LN(−), LN(+) PALN(−), LN(+) PALN(+)) were significant prognostic factors in both univariate and multivariate analyses for 1-year OS, and neural invasion (PN) was the solely significant factor for 3-year OS ($p < 0.05$). Kaplan-Meier estimate showed that OS of PALN(+) and PN (+) was significantly lower than the negative group, respectively ($p < 0.05$). No statistical difference in OS was seen between LN(−) and LN(+) PALN(−); and between LN(+) PALN(−) and PALN(+) ($p = 0.107$). Patients with PN (−) PALN(+) had similar OS compared to PN (+) PALN(−) ($p > 0.05$).

Conclusion: PDAC had a poor outcome despite treatment with radical resection. Further follow-up should be conducted to determine the role of surgery in PALN(+)and PN invasion.

1. Introduction

Pancreatic cancer (PC), mostly pancreatic ductal adenocarcinoma (PDAC), is the seventh most common cause of global cancer-related death due to late diagnosis and its aggressiveness [1]. GLOBOCAN 2018 estimates of incidence and mortality for pancreatic cancer was 458,918 and 432,242 respectively [2]. Radical surgery (pancreaticoduodenectomy with standard lymphadenectomy) combined with (neo)adjuvant chemotherapy is the gold standard for PC; however, only 15–20% of cases are classified as "resectable". Despite the development of early screening, advanced medical imaging, surgical techniques, and chemotherapy; the 5-year overall survival (OS) rose from 0.9% in 1975 to just around 9% in all-stages and 20% after curative resection [1,3,4]. Among several prognostic factors for poor outcome, lymph node metastasis has been shown to predict the worst outcome, which accounted for 65–86% of cases [5–7].

LN metastasis was classified as N1 by Union for International Cancer Control as N1/N2 for regional nodes and N3 (distant LNs), which is also expressed as M1 by the Japanese Pancreas Society (JPS) with the difference in defining the role of PALN [8]. PALN received LN in the right half of the pancreas, which originates from LN in common hepatic artery, superior mesenteric artery, and dorsal pancreatic route [9]. A recent meta-analysis showed that PALN(+) is a poor prognostic factor

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Abbreviations

CA125	Cancer Antigen 125
CA199	Carbohydrate Antigen 199
CEA	Carcinoembryonic Antigen
HR	Hazard Ratio
JPS	Japanese Pancreas Society
LN	Lymph node
LNR	Lymph node ratio
OS	Overall survival
PALN	Para-aortic lymph node
PC	Pancreatic cancer
PN	Perineural
SMA	Superior mesenteric artery
TNM	Tumor Node Metastasis

and was a contradiction for radical surgery on JPS's recommendation [8]. However, some studies have demonstrated that sub-groups with PALN(+) may still benefit from radical surgery [10–12]. Thus, early identification of positive PALN is one of the main priorities [13].

PALN sampling with frozen-section analysis has been proved as an acceptable method with high sensitivity, specificity and could be performed systematically to evaluate LN metastasis and PALN in specific [5,14]. Our primary aim was to evaluate the prognostic impact of PALN(+) on OS in patients with PDAC treated by pancreaticoduodenectomy, standard lymphadenectomy with PALN sampling. We also aimed to assess the prognostic factors for survival in pancreatic head cancer.

2. Materials and methods

Registration and ethics: Research Registry number is stated, in accordance with the declaration of Helsinki. Unique identifying number: researchregistry6635 (https://www.researchregistry.com/browse-the-registry#home/registrationdetails/60436fd7ebcf41001bdeb209/).

2.1. Patients and methods

From Schwarz's publication, HR 1.91 was used for calculating sample size. With a power of 0.8 and type I error of 5%, at least 80 fatal events are required to be significant [5,15]. Five-year OS after radical resection was 7%, and a minimum of 86 patients should be recruited [16]. Patients were recruited into the study if they agree to participate and 1) underwent pancreaticoduodenectomy, standard lymphadenectomy, and PALN sampling; 2) did not have second cancer or metastasis; 3) were not previously treated with neoadjuvant; and 4) did not have serious complications or life-threatening medical conditions. We excluded patients with recurrent pancreatic cancer or without relevant medical record information (status of each LN station's metastasis, complications). From the clinical database, 97 patients who underwent pancreaticoduodenectomy and para-aortic lymph node sampling at VietDuc University hospital from January 2013 to August 2020 were recruited in the study. Among these patients, follow-up was lost for eight patients; therefore, 89 patients were included for analysis. Our retrospective study was approved by Hanoi Medical University Institutional Ethical Review Board (No NCS10/BB-HĐĐĐ).

Information on demographic characteristics (age, sex, BMI, symptoms) was collected from medical records. Physical examination, laboratory results (CA 19–9, CEA), staging based on TNM seventh edition classification [17]. LN station metastasis (total, positive LN), perineural (PN) invasion, differentiation, and resection margin were reviewed. Operative and post-operative parameters (operation time, vascular resection, complications), and adjuvant chemotherapy were collected. This study has been reported in line with the STROCSS criteria [18,19].

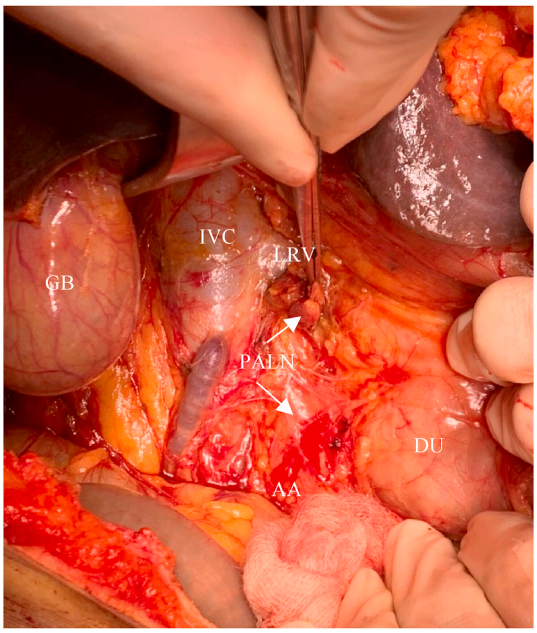


Fig. 1. Illustration of PALN sampling technique.

2.2. Operation procedure

Para-aortic lymph node (LN 16) were taken and sent for frozen-section procedure after kocherization by harvesting the lymphocellular aortocaval tissue lied below the left renal vein (Fig. 1) [5]. Standard pancreaticoduodenectomy and standard lymphadenectomy were performed (dissected LN 13 and 17 (peripancreatic), LN8 (hepatic artery), LN12 (hepatoduodenal), LN5 and 6 (supra/infra-pyloric), 14b and 14c (SMA)), PV/SMV was resected if needed [20]. A piece of 1*1*0.2 cm PALN sample was firstly frozen by Hematoxylin Eosin (Shandon Cryotome, Thermo Scientific, UK) and the remaining tissue was embedded by paraffin and stained later for double-checking. All samples were assessed and reviewed by experienced pathologists. Follow-up was conducted via telephone interviews with close relatives and examinations were conducted in the nearest provincial medical center at least once a year (see Fig. 2).

2.3. Statistical analysis

Patients were classified based on PALN status. The primary endpoint was overall survival, measured as the number of months from the operation until the latest follow-up or death. We used student's t-test for continuous variables, non-parametric test for median parameter, and $\chi 2$ test or Fisher's exact test for categorical variables. OS and survival probabilities were calculated by the Kaplan-Meier curves using the log-rank test. Univariate regression, Bayesian model averaging and multivariate regression by Cox proportional hazards model were used for prognosis. A p-value of ≤ 0.05 for two-tail was considered statistically significant. The analyses were performed using SPSS 25.0 64 bit for Windows (IBM Corporation, USA).

3. Results

Eight patients were lost for follow-up, a total of 89 patients were included in the study. Study population and operative characteristics are described in Table 1. We categorized patients into two groups: 78 patients (87.6%) with PALN(−) and 11 patients (12.4%) with PALN(+). In general, there were no significant differences in age (58 vs 54), sex ratio, pre-operative CA 19–9, and complications between the two groups ($p > 0.05$). Approximately 45% of the patients underwent chemotherapy.

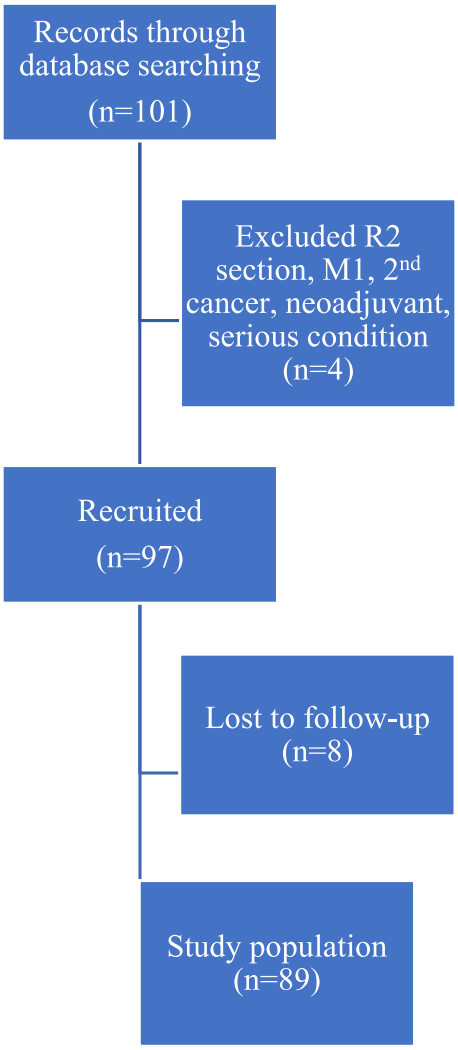


Fig. 2. Study protocol.

Survival time of patients with PALN(+) was shorter than PALN(−) (20.8 ± 19.9 vs 9.5 ± 5.2 months, respectively) ($p < 0.001$). The 1-year, 3-year and 5-year survival rates were 56.4%, 15.4% and 6.4% for PALN(+) and 18.2%, 0% and 0% for PALN(−), respectively. Histopathological characteristics are shown in Table 2. Most patients with PALN(−) had T-stage of III (70.5%) while 45.5% were in stage IV in PALN(+) group. No significant differences were seen regarding tumor differentiation and neural invasion. Patients with PALN(+) had more R1 margin than patients with PALN(−). PALN(+) group was found to have more LN(+) and higher LNR (calculated as positive LN/total LN) as compared to PALN (−) group.

Table 1
Patient and operative characteristics.

Variables	PALN(−)	PALN(+)	P value
Patients (n)	78	11	–
Age (mean ± SD)	58.0 ± 11.2	54.0 ± 9.8	0.2
Male: Female	1.6:1	4.5:1	0.32
Weight loss (%)	19 (24.1)	4 (36.3)	0.63
Pre-op CA 19–9 > 115 U/ml	48 (61.5)	4 (36.4)	0.19
Operative time (mean ± SD)	355.7 ± 96.7	370.6 ± 82.4	0.63
PV/SMV resection	10 (12.8)	3 (27.3)	0.42
Complications			
- POPF	9 (11.5)	2 (18.1)	0.89
- PPH	10 (12.8)	1 (9.1)	0.89
- Diarrhea	6 (7.7)	1 (9.1)	0.66
Adjuvant chemotherapy	36 (46.2)	5 (45.5)	1.0
OS (months)	20.8 ± 19.9	9.5 ± 5.2	**<0.0001**
OS 1-y	44 (56.4)	2 (18.2)	**0.024**
OS 3-y	12 (15.4)	0 (0)	0.35
OS 5-y	5 (6.4)	0 (0)	1.0

*PV: Portal vein, SMV: Small mesenteric vein, PPH: Post pancreatectomy hemorrhage.

Table 2
Histopathological characteristics.

Variables	PALN(−)	PALN(+)	P value
T stage			0.19
- 1,2	10 (12.8)	1 (9.1)	
- 3	55 (70.5)	5 (45.5)	
- 4	13 (16.7)	5 (45.5)	
Neural invasion	39 (50)	8 (72.7)	0.21
Differentiation (%)			0.66
- High	6 (7.7)	0 (0)	
- Moderate	35 (44.8)	5 (45.5)	
- Low, none	37 (47.5)	6 (54.5)	
Resection status			**0.007**
- R0	67 (85.9)	7 (63.6)	
- R1	11 (14.1)	4 (36.4)	
Median of examined LN (IQR)	8 (8)	16 (13)	0.136
Median of positive LN (IQR)	1 (2)	5 (7)	**0.001**
LN ratio			**<0.0001**
- ≥0,2	17 (21.8)	9 (81.8)	
- <0,2	61 (78.2)	2 (18.2)	

Table 3
Prognostic factors of 1-year and 3-year OS for pancreatic ductal adenocarcinoma.

Factor	OS 1-year			OS 3-year		
	HR	95% CI	P-value	HR	95% CI	P-value
Univariate analysis						
Age (<60, ≥60)	0.638	0.271–1.499	0.302	1.422	0.394–5.130	0.591
Sex (M, F)	0.616	0.256–1.479	0.278	0.756	0.219–2.611	0.658
CA 19–9 (<115, ≥115 U/ml)	0.674	0.289–1.573	0.362	1.004	0.292–3.450	0.994
CEA (<5, ≥5 ng/ml)	0.660	0.270–1.617	0.364	0.962	0.264–3.498	0.953
Tumor size (<2, ≥2 cm)	1.083	0.356–3.292	0.889	3.000	0.770–11.682	0.113
Differentiation (G1, G2, G3-4)	2.462	1.178–5.145	**0.017***	2.633	0.990–7.006	0.052[+]
Neural invasion (N/Y)	1.263	0.548–2.910	0.583	7.031	1.442–32.287	**0.016***
Mesopancreas invasion (N/Y)	2.256	0.392–13.001	0.362	0.764	0.081–7.167	0.814
Portal vein invasion (N/Y)	2.895	0.531–15.787	0.219	>1000	–	0.999
Resection status (R0, R1)	1.765	0.570–5.461	0.324	2.444	0.291–20.517	0.410
LN (LN-, LN+ 16-, LN+ 16+)	3.272	1.584–6.759	**0.001***	2.547	0.870–7.459	0.088[+]
Examined LN ≥ 15 (N/Y)	1.368	0.547–3.420	0.503	1.278	0.317–5.155	0.731
Positive LN ≥ 3 (N/Y)	2.292	0.764–6.871	0.139	>1000	–	0.998
LNR > 0,2 (N/Y)	1.705	0.677–4.291	0.258	2.264	0.460–11.135	0.315
Adjuvant chemotherapy (Y/N)	1.389	0.601–3.209	0.442	1.200	0.355–4.053	0.769
Multivariate analysis						
Age (<60, ≥60)	0.324	0.091–1.159	0.083[+]	2.497	0.440–14.168	0.302
CEA (<5, ≥5 ng/ml)	0.758	0.256–2.243	0.617	0.516	0.097–2.741	0.437
Differentiation (G1, G2, G3-4)	3.028	1.286–7.132	**0.011***	2.711	0.880–8.352	0.082[+]
Neural invasion (N/Y)	0.734	0.246–2.187	0.578	12.908	1.621–102.806	**0.016***
LN (LN-, LN+ 16-, LN+ 16+)	5.944	1.925–18.360	**0.002***	1.509	0.289–7.876	0.625
Examined LN ≥ 15 (N/Y)	1.019	0.286–3.631	0.977	0.319	0.036–2.852	0.307
Positive LN ≥ 3 (N/Y)	1.291	0.234–7.131	0.770			
LNR > 0,2 (N/Y)	0.356	0.066–1.924	0.230	1.289	0.105–15.776	0.843
Adjuvant chemotherapy (Y/N)	3.203	1.020–10.058	**0.046***	1.234	0.244–6.258	0.799

Among all study participants, 46 (51.7%) and 12 (13.5%) survived after 1 year and 3 years, respectively. The 90-day mortality was 5.7%, mainly due to severe malnutrition, the median OS was 12 months. Prognostic factors associated with 1-year and 3-year overall survival are demonstrated in Table 3. In univariate analysis, tumor differentiation and lymph node metastasis were associated with poor prognosis in patients with PDAC after 1 year (HR = 2.462, p < 0,05) and neural invasion was the only significant prognostic factor after 3 years (HR = 7.031, p = 0.015). Multivariate analyses showed similar results, with an additional significant factor of adjuvant chemotherapy in 1-year OS.

Kaplan-Meier analysis showed that OS of PALN(+) and PN(+) patients was significantly worse than PALN(−) and PN (−) patients, respectively (Fig. 3a and c). However, no statistical difference in OS was found between LN(−) and LN(+) PALN(−); between LN(+) PALN(−) and LN(+) PALN(+) (p = 0.107) (Fig. 3b). Patients with PN (−) PALN (−) were found to have no significant difference in OS than PN (−) PALN (+) and no significant difference was found between LN(−) and LN(+) PALN(−) (Fig. 3c). Patients with PN (−) PALN(−) were found to have a worse prognosis compared to PN (+) PALN(−) while patients with PN (−) PALN(+) had similar OS compared to PN (+) PALN(−) (Fig. 3d).

4. Discussion

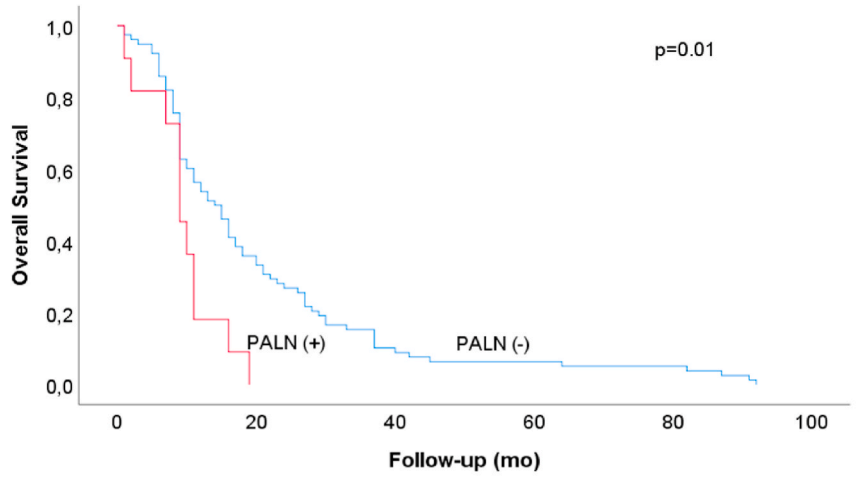
Among all study subjects, the 5-year overall survival was 5.6%, and no patient with PALN(+) survived after 3 years. Tumor differentiation, PALN(+), and adjuvant chemotherapy were found to be poor predictors for OS 1-year while PN invasion was the only poor indicator for 3-year OS. OS of patients with LN(−) was not statistically significant different than LN(+) PALN(−) (p = 0.067). No significant difference was found in survival between LN(+) PALN(−) and LN(+) PALN(+) (p = 0.107); PALN(+) PN(−) and PALN(−) PN(+) (p > 0.05).

PALN receives LN in the right half of the pancreas, which first starts from the common hepatic route (upper), superior mesenteric artery (middle and lower), then flows to node A (right side of the celiac trunk and superior mesenteric artery), which could easily be identified, before moving to node B right behind [9,21]. Liu et al. showed that patients with PALN(+) and locally advanced PC had similar OS, which was worse than patients with PALN(−) [22]. A study by Marchese et al. showed better prognosis of patients with PALN(+) who underwent chemotherapy alone compared to PALN(+) group that was treated with curative surgery [23]. Besides, no research determines the role of chemotherapy alone compared with pancreatectomy and adjuvant chemotherapy for PALN(+) [12,23,24].

Some authors pointed out that some groups of PALN(+) may benefit from curative surgery (i.e., CA12-5 <18.62 U/ml or LNR <0.25) [10,24]. CA12-5 (mucin-16) was the factor of metastatic invasion and chemotherapy resistance [25,26]. But Chen et al. did not show the survival of PALN(−) and CA12-5 <18.62 U/ml compared to others, and also for patients with LNR <0.25, which could make the interpretation inconclusive. Thus, a convincing conclusion for optimal treatment for PALN(+) has not been achieved [24]. Early identification of PALN(+) should be routinely conducted, by laparotomy or open surgery PALN sampling before deciding to take a radical surgery [5,14,23].

In our study, no patient with PALN(+) survived more than 3 years. Perineural invasion was the only prognostic factor for 3-year OS, which could mean that PN was associated with long-term survival and the pathway for metastasis. Guilia et al. suggested that PN invasion could be presented in epineural, perineural, and endoneural space, occur in 70–98% of cases with PDAC, and could present early stage of cancer development [27,28]. Ozaki et al. showed three mechanisms for local recurrence in pancreatic cancer, i.e. direct extension, LN metastasis, and extrapancreatic perineural invasion [29]. Studies showed a correlation between LN metastasis and PN invasion. Tanaka, Ozaki suggested that LN metastasis could trigger PN invasion, which may lead to peritoneal dissemination, higher recurrence rate [30,31]. A possible mechanism was that LN metastasis creates a lymphatic satellite around the nerve, which then breaks and invades the nerve membrane [29,32]. Autophagy helps tumor cells survive within nerve tissue, avoid apoptosis and promote tumor cell proliferation [33]. Another mechanism was lymphangiogenesis, which helps to spread tumor cells to the nervous system [34].

The neural invasion should be further investigated for improving survival. Level III mesopancreas dissection, including right semicircle of SMA plexus (from 11 to 5 o'clock), en bloc mesopancreas, the common trunk of inferior pancreaticoduodenal artery might be a promising solution, with R0 resection up to 93% and 5-year OS of 26% [35,36].



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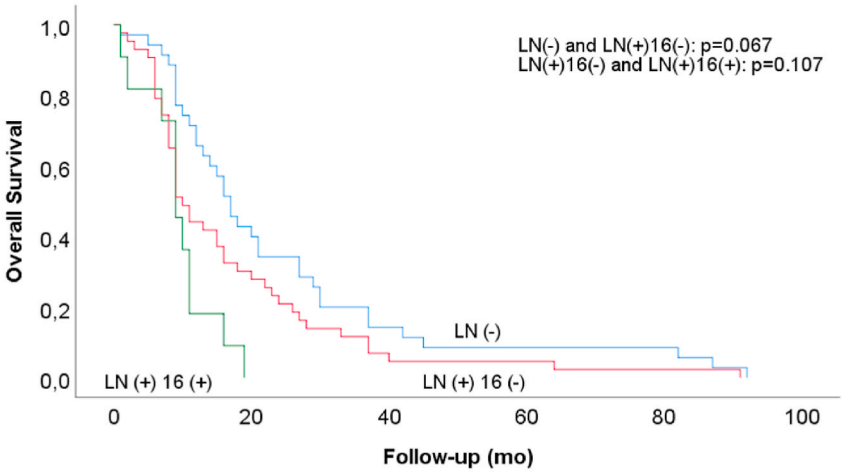

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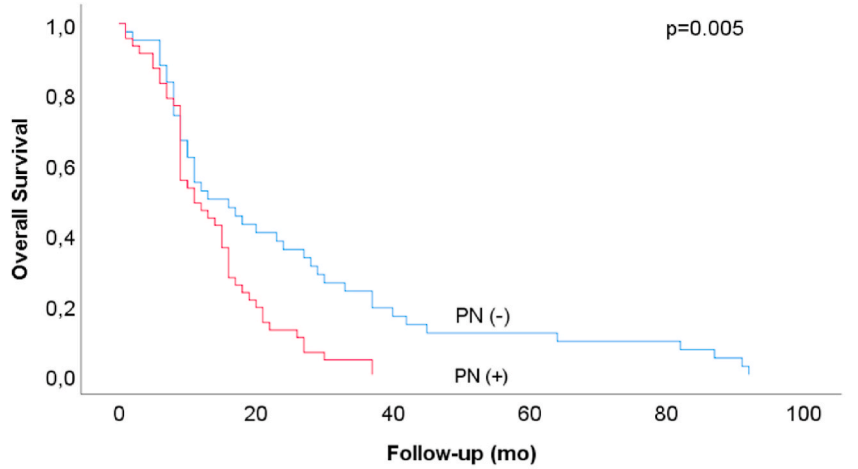

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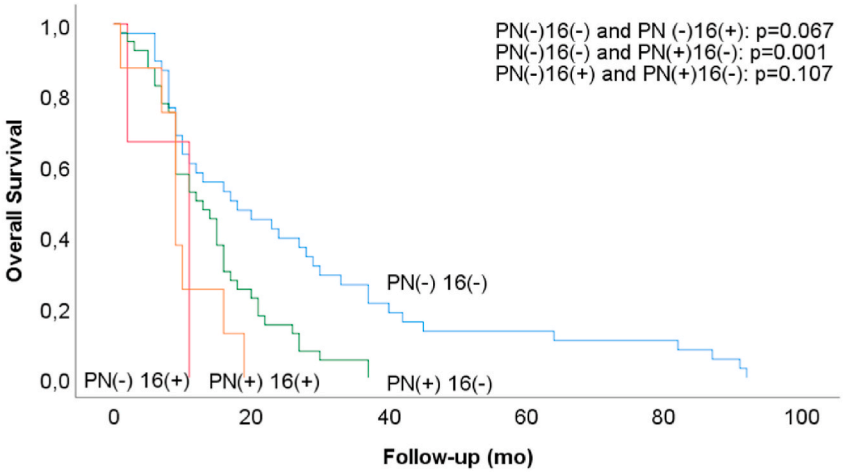

d

Fig. 3. Kaplan-Meier analysis of survival (3a: OS of PALN(−) and PALN(+); 3b: OS of LN(−), LN(+) PALN(−) and LN(+) PALN(+); 3c: OS of PN(−) and PN(+); 3d: PN(−) PALN(−), PN(−) PALN(+), PN(+) PALN(−) and PN(+) PALN(+)).

However, 76% of patients could suffer postoperative diarrhea [37]. Thus, a balance between the level of dissection and preservation should be further studied.

Our study has some limitations. First, the retrospective design with a non-large sample size may lead to recall or measurement biases, and could not draw a definitive conclusion. Moreover, patients were treated in several departments in our hospital with different strategies, which might affect the analyzed data. Further investigation with longer follow-up should be performed to determine the role of PALN, PN and develop a comprehensive treatment strategy for patients with PDAC.

5. Conclusion

Patients with pancreatic ductal adenocarcinoma had poor outcomes despite having a comprehensive treatment. Para-aortic lymph node and perineural invasion were among the two worst prognostic factors. Further studies should determine whether curative surgery can still be a part of the treatment strategy in pancreatic cancer with PALN(+).

Ethical approval

Research studies involving patients require ethical approval. Please state whether approval has been given, name the relevant ethics committee and the state the reference number for their judgement.

Sources of funding

None.

Author contribution

Lan Thi Nguyen, Hung Van Nguyen: Contributed equally to this work; Designed the study, did the data collection, the data analysis, the writing paper. Dang Hai Do: Did the analysis Khiem Thanh Nguyen, Anh Tuan Do: Designed the surgical procedure. Ha Hoang Pham, Chinh Duc Nguyen: Revised the manuscript.

Consent

The written informed consent was obtained from the recruited patients.

Registration of research studies

1. Name of the registry: Research Registry.
2. Unique Identifying number or registration ID: researchregistry6635.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#home/registrationdetails/60436fd7ebcf41001bdeb209/

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

None.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.102361.

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