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Resected Pancreatic Cancer With N2 Node Involvement Is Refractory to Gemcitabine-Based Adjuvant Chemotherapy

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Abstract

Lymphatic metastasis is a major determinant of the outcome of resected pancreatic cancer. Gemcitabine-based adjuvant chemotherapy can improve the outcome of resected pancreatic cancer. However, the efficacy of gemcitabine against pancreatic cancer stratified by nodal involvement is unclear. In this study, patients who had undergone curative resection of pancreatic adenocarcinoma (612 cases) were included. The efficacy of adjuvant gemcitabine-based regimen, stratified by nodal status (negative, positive) or N substage (N0, no nodal involvement; N1, 1-3-node involvement; N2, ≥4-node involvement), was examined. Both the node-negative (hazard ratio [HR] = 0.62, 95% confidence interval [CI], 0.44-0.87, $P = .006$) and node-positive subgroups (HR = 0.45, 95% CI, 0.33-0.62, $P < .001$) benefited from gemcitabine-based adjuvant chemotherapy. Patients with N0 (ie, the node-negative subgroup) or N1 (HR = 0.36, 95% CI, 0.25-0.52, $P < .001$) disease benefited from gemcitabine-based chemotherapy. However, patients with N2 tumors (HR = 0.95, 95% CI, 0.50-1.78, $P = .867$) had poor response to gemcitabine-based treatment. Therefore, we postulate that resected pancreatic cancer with N2 node involvement is refractory to gemcitabine-based adjuvant chemotherapy. A more intensive adjuvant regimen may be required for N2 subgroup patients.

Keywords

pancreatic adenocarcinoma, adjuvant chemotherapy, resected, gemcitabine, lymph metastasis

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Introduction

Pancreatic cancer is an extremely lethal neoplasm whose incidence has risen in recent decades.[1,2] In 2019, the estimated number of new pancreatic cancer cases in the United States was 56 770, whereas deaths from pancreatic cancer were estimated at 45 750.[1] Although major advances have recently been made in treating pancreatic cancer, total resection is still the only curative option.[3,4] Approximately 20% of patients are diagnosed at a localized stage and are candidates for curative resection.[2,5] However, for patients who have undergone curative resection, the 5-year survival rate is only ~20%.[3,6] Regional and distant recurrences lead to failure of curative operation.[3] Therefore, methods to identify the risk factors of recurrence and to provide therapeutic strategies are urgently needed to improve the outcome of patients with resected pancreatic cancer.[2]

Lymphatic metastasis is one of the most important risk determinants for the recurrence of resected pancreatic cancer.[6-12] The American Joint Committee on Cancer's (AJCC)

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TNM classification of nodal substage has been modified from the nodal status in the 7th edition (N0, node negative; N1, node positive) to nodal involvement with details on the number of positive nodes in the 8th edition (N0, no regional node involvement; N1, 1-3-regional node involvement; N2, ≥4-regional node involvement).[13-15] This modification implies that the degree of lymph node involvement has an important impact on the patients' prognosis, which has also been validated in previous reports.[13,14] The importance of lymph node involvement may guide therapeutic strategies, especially for adjuvant treatment.[16] Mounting evidence has shown that adjuvant chemotherapy can improve the prognosis of patients with resected pancreatic cancer and prevent recurrence.[7,17-22] An adjuvant gemcitabine-based regimen has been well established for these patients.[7,16,19] However, the efficacy of gemcitabine-based adjuvant chemotherapy against pancreatic cancer stratified by the degree of lymph node involvement is unclear.

In this study, 612 patients with curatively resected pancreatic adenocarcinoma who were subjected to either gemcitabine-based adjuvant chemotherapy (453 cases) or close observation (159 cases) were included. The efficacy of the adjuvant gemcitabine-based regimen was determined by Cox proportional hazard regression model stratified by the degree of lymph node metastasis.

Materials and Methods

Patients and Data Collection

Data on patients with pancreatic cancer between May 2003 and April 2017 were retrieved from a large, prospectively constructed database. Data on age, sex, date of diagnosis, major treatments, tumor location, size, differentiation, nerve invasion, vascular invasion, lymph node involvement, and serum carbohydrate antigen 19-9 (CA19-9) levels were collected. The inclusion criterion was that all patients should be pathologically confirmed as having pancreatic adenocarcinoma. All patients underwent curative resection with a microscopically negative margin (R0). Sufficient information was needed from all patients to allow for accurate staging using the 8th edition AJCC TNM classification.[15] The exclusion criteria were as follows: patients with nonadenocarcinoma histologies, such as intraductal papillary mucinous neoplasm and pancreatic endocrine tumors; patients who had received nongemcitabine-based adjuvant chemotherapy; patients who had received adjuvant radiotherapy or for whom information on major treatments were unavailable; patients with locally advanced tumors or metastatic neoplasms; and patients with no information on nodal involvement. The study was approved by the institutional review board of the Fudan University Shanghai Cancer Center. Written informed consent was obtained from all patients. All data were cross-checked for inconsistencies by G.L. and Z.F.

The chemotherapy group was defined as patients who had undergone curative resection and gemcitabine-based adjuvant chemotherapy (gemcitabine monotherapy or gemcitabine-based combined chemotherapy). Gemcitabine was delivered according to the following regimen: 1000 mg/m^2 over 30 minutes, weekly for 3 weeks every 28 days. Adjuvant chemotherapy was initiated within 2 months after curative resection. Chemotherapy was discontinued if severe toxic effects occurred despite dose reduction or if the patients refused to receive further chemotherapy. Severe toxic effects may justify a dose reduction of 25%. Granulocyte colony-stimulating factor was recommended for patients with severe neutropenia. The observation group included patients who had undergone curative resection and were under close follow-up without adjuvant chemotherapy or radiotherapy. The term "node-positive" defined tumors in any number of regionally involved lymph nodes, and the term "node-negative" defined tumors without regionally involved lymph node. All tumors were staged according to the 8th edition AJCC staging classification. According to the 8th AJCC staging system, N0 was defined as no regional node involvement; N1, as 1-3-node involvement; and N2, as ≥ 4-node involvement.

Statistical Analysis

All statistical analyses were performed using the STATA 12.0 software package (StataCorp LP, College Station, Texas). Continuous variables were compared using the rank-sum test stratified by chemotherapy and regional lymph node involvement. Categorical variables were compared using the Pearson χ^2 test. The primary end point was overall survival, which was evaluated from the date of diagnosis to the date of last follow-up or the date of death. Patients were followed up for at least 18 months if they were still alive. Survival between groups was analyzed by Kaplan-Meier curve analysis and compared using the log-rank test. The Cox proportional hazard regression model was used to examine the prognostic value of chemotherapy and nodal involvement. Hazard ratio (HR) and 95% confidence interval (CI) were calculated. A 2-sided *P* value less than .05 was considered statistically significant.

Result

Patients' Characteristics

In total, 612 patients who underwent curative resection for pancreatic adenocarcinoma were included, with a median overall survival of 16.9 months (Table 1). The median age was 62 years, with 60.1% of patients being younger than 65 years. Less than half (43.5%) of the patients were female. Nearly 60% (59.6%) of the patients had a tumor located at the head of the pancreas. The mean tumor diameter was 3.3 cm. More than 60% (63.3%) of the patients had well-differentiated or moderately differentiated tumors. The majority (84.3%) of tumors had nerve invasion, and a minority (26.1%) had vascular invasion. Nearly 80% (76.9%) of patients had serum CA19-9 levels higher than 37 U/mL.

Among 64 patients with N2 tumors, stage T2 (64.1%) was more common than stage T1 (10.9%) or T3 (25.0%). Among these patients, 21.4% had no disease relapse and 78.6% had disease relapse. Sites of recurrence included local recurrence

Table 1. Baseline Characteristics of Patients With Curative Resected Pancreatic Cancer Divided by Adjuvant Chemotherapy.

Characteristic	Total (n = 612)	Chemotherapy (n = 453)	Observation (n = 159)	*P*
Median survival (months)	16.9	20.0	11.6	<.001
Age (median [range], years)	62 (30-84)	61 (30-83)	64 (37-84)	<.001
<65 (%)	368 (60.1)	290 (64.0)	78 (49.1)	
≥65 (%)	244 (39.9)	163 (36.0)	81 (50.9)	
Gender				.273
Male (%)	346 (56.5)	262 (57.8)	84 (52.8)	
Female (%)	266 (43.5)	191 (42.2)	75 (47.2)	
Location				.551
Head (%)	365 (59.6)	267 (58.9)	98 (61.6)	
Body and tail (%)	247 (40.4)	186 (41.1)	61 (38.4)	
Size (SD, cm)	3.3 (1.4)	3.3 (1.4)	3.4 (1.6)	.721
Differentiation[a]				.738
Well, moderate (%)	381 (63.3)	284 (63.7)	97 (62.2)	
Poor (%)	221 (36.7)	162 (36.3)	59 (37.8)	
Nerve invasion[b]				.754
Yes (%)	511 (84.3)	379 (84.6)	132 (83.5)	
No (%)	95 (15.7)	69 (15.4)	26 (16.5)	
Vascular invasion[c]				.034
Yes (%)	157 (26.1)	106 (23.8)	51 (32.5)	
No (%)	445 (73.9)	339 (76.2)	106 (67.5)	
Lymph metastasis				.092
Yes (%)	273 (44.6)	193 (42.6)	80 (50.3)	
No (%)	339 (55.4)	260 (57.4)	79 (49.7)	
N substage				.186
N0 (%)	339 (55.4)	260 (57.4)	79 (49.7)	
N1 (%)	209 (34.2)	150 (33.1)	59 (37.1)	
N2 (%)	64 (10.5)	43 (9.5)	21 (13.2)	
CA19-9[d]				.913
<37 U/mL (%)	140 (23.1)	103 (23.0)	37 (23.4)	
≥37 U/mL (%)	466 (76.9)	345 (77.0)	121 (76.6)	

Abbreviations: CA19-9, carbohydrate antigen 19-9; SD, standard deviation.
[a]Ten cases had unknown information of tumor differentiation.
[b]Six cases had unknown information of nerve invasion.
[c]Ten cases had unknown information of vascular invasion.
[d]Six cases had unknown information of serum CA19-9 levels.

(45.5%), liver (45.5%), other intra-abdominal areas (30.3%), lung (24.2%), and bone (3.0%). Among N2 patients who had undergone adjuvant chemotherapy, 80.0% of tumor relapses occurred during chemotherapy. All of these patients died from pancreatic cancer.

Comparison Between the Chemotherapy Group and the Observation Group

In this cohort, 453 (74.0%) patients received gemcitabine-based adjuvant chemotherapy and 159 (26.0%) patients underwent close observation. The chemotherapy group had a better prognosis than did the observation group in terms of overall survival (median survival, 20.0 vs 11.6 months, $P < .001$ by a log-rank test, Figure 1A). The chemotherapy group was younger than the observation group (median age, 61 vs 64 years, $P < .001$ by a rank-sum test, Table 1). A statistical difference in vascular invasion between the chemotherapy (23.8%) and observation groups was also observed (32.5%, $P = .034$). There was no difference between the chemotherapy and observation groups in sex ($P = .273$), location ($P = .551$), size ($P = .721$), differentiation ($P = .738$), nerve invasion ($P = .754$), regional lymph node involvement ($P = .092$), N substage ($P = .186$), or serum CA19-9 levels ($P = .913$). Chemotherapy was determined to be an independent variable in prognosis (HR = 0.53, 95% CI, 0.42-0.66; $P < .001$).

T stage was a prognostic factor for patients who had undergone curative chemotherapy (T1, reference; T2, HR = 1.67, 95% CI, 1.24-2.25, $P = .001$; T3, HR = 2.09, 95% CI, 1.49-2.93, $P < .001$ by a univariate analysis). Adjuvant chemotherapy was effective in patients with T2 cancer (HR = 0.48, 95% CI, 0.36-0.63, $P < .001$ by a univariate analysis) or T3 cancer (HR = 0.61, 95% CI, 0.39-0.94, $P = .026$) but not T1 cancer (HR = 0.69, 95% CI, 0.38-1.25, $P = .219$).

Regional Lymph Node Involvement and Adjuvant Chemotherapy

In this study, 44.6% of patients had regional lymph node involvement (N1, 1-3 nodes involvement, 34.2%; N2, ≥4 nodes

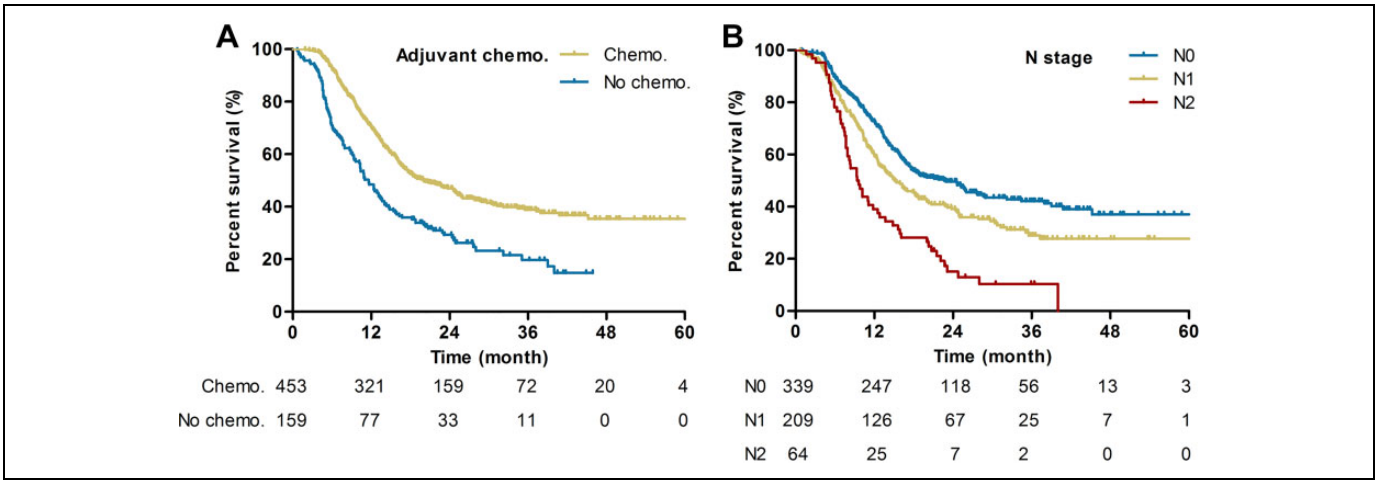

Figure 1. Kaplan-Meier estimates of overall survival divided by adjuvant chemotherapy (A) and AJCC nodal stage (B). Patients who underwent gemcitabine-based adjuvant chemotherapy had better outcome than patients without chemotherapy ($P < .001$ by a log-rank test). Survival curves were well separated by nodal stage ($P < .001$). AJCC indicates American Joint Committee on Cancer.

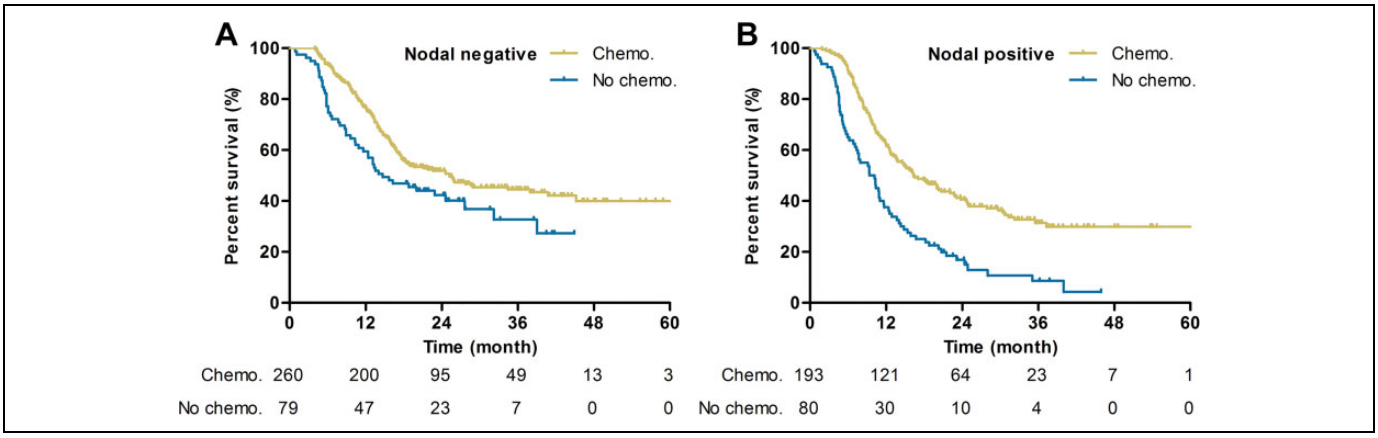

Figure 2. Kaplan-Meier estimates of overall survival divided by nodal status and adjuvant chemotherapy. Patients who underwent adjuvant chemotherapy had better outcome than patients without chemotherapy for both node-negative ($P = .015$ by a log-rank test, A) and node-positive patients ($P < .001$, B).

involvement, 10.5%). The median overall survival was 22.9 months in the N0 group, 15.2 months in the N1 group, and 9.4 months in the N2 group. Positive regional node involvement was an independent poor prognostic factor of outcome (HR = 1.47, 95% CI, 1.19-1.81, $P < .001$, Figure 1B) when adjusted for age, sex, location, size, differentiation, nerve invasion, vascular invasion, and CA19-9. Chemotherapy was shown to be an independent prognostic factor in both the node-negative subgroup (HR = 0.62, 95% CI, 0.44-0.87, $P = .006$, Figure 2A) and the node-positive subgroup (HR = 0.45, 95% CI, 0.33-0.62, $P < .001$, Figure 2B). The prognostic value of chemotherapy in N1 patients and N2 patients in the node-positive subgroup was further analyzed. For N1 patients, chemotherapy was found to be an independent prognostic factor on multivariable analysis (HR = 0.36, 95% CI, 0.25-0.52, $P < .001$, Figure 3A). However, in N2 patients, no statistical significance was found between the chemotherapy group and the observation group (HR = 0.95, 95% CI, 0.50-1.78, $P = .867$, Figures 3B and 4).

Discussion

The role of lymph metastasis in guiding adjuvant chemotherapy for resected pancreatic cancer is unclear. In this study, 612 patients who underwent curative resection of pancreatic adenocarcinoma and were subjected to either gemcitabine-based chemotherapy (453 cases) or close observation (159 cases) were included. Both gemcitabine-based adjuvant chemotherapy (HR = 0.53, 95% CI, 0.42-0.66; $P < .001$) and nodal status (HR = 1.47, 95% CI, 1.19-1.81, $P < .001$) were shown to be independent prognostic factors. Moreover, the node-negative (HR = 0.62, 95% CI, 0.44-0.87, $P = .006$) and node-positive subgroups (HR = 0.45, 95% CI, 0.33-0.62, $P < .001$) were found to have benefited from gemcitabine chemotherapy. Patients with N0 (no

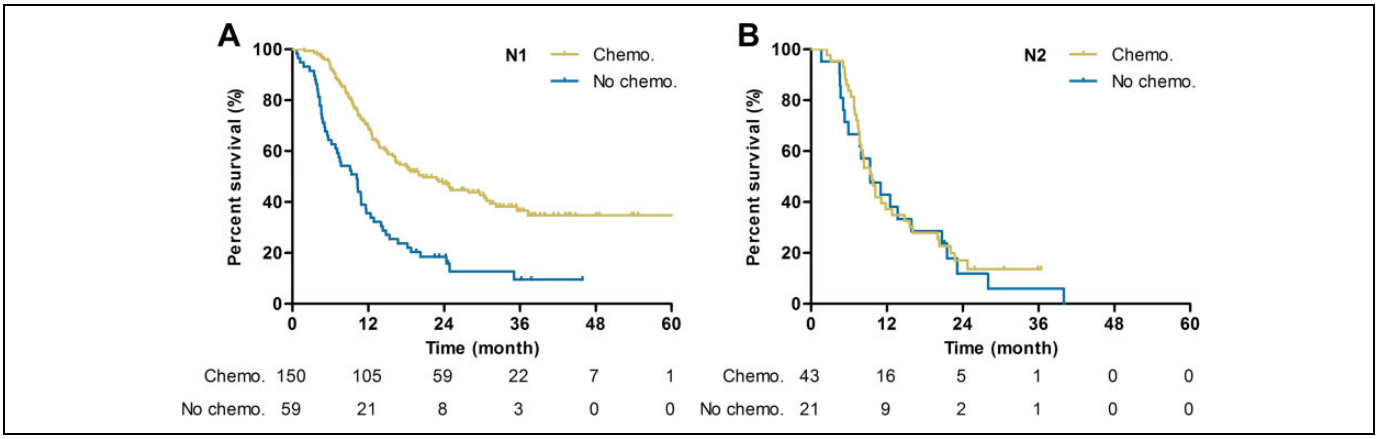

Figure 3. Kaplan-Meier estimates of overall survival divided by nodal stage and adjuvant chemotherapy in node-positive patients. For the N1 subgroup (1-3 involved nodes), patients who underwent adjuvant chemotherapy had better outcomes than patients without chemotherapy ($P < .001$ by a log-rank test, A). However, for the N2 subgroup (≥4 involved nodes), no difference in outcome was observed between patients who underwent chemotherapy and patients who did not undergo chemotherapy ($P = .715$, B).

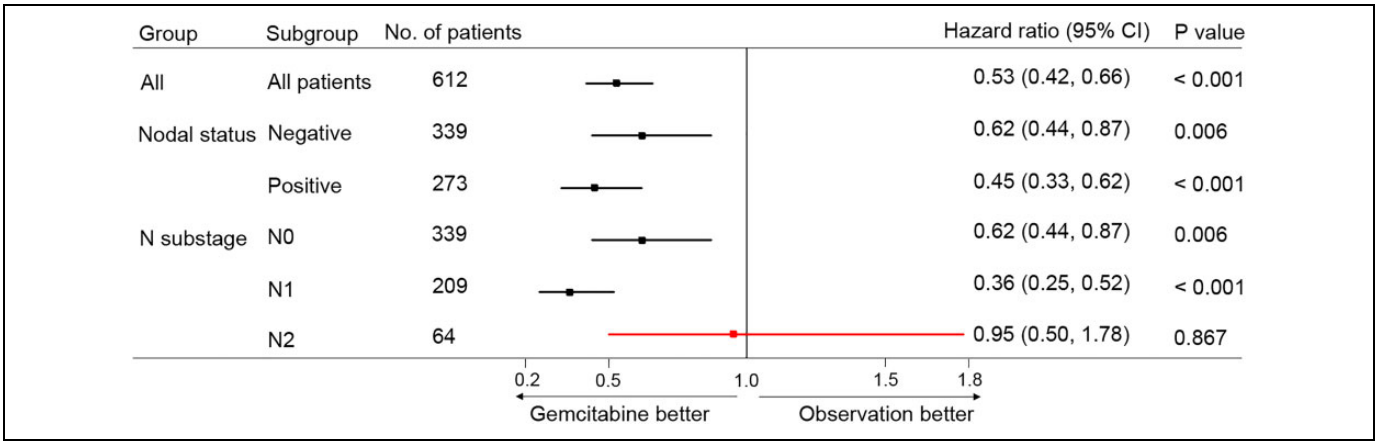

Figure 4. Forest plot of the treatment effect on overall survival in subgroup analyses stratified by adjuvant chemotherapy and lymph metastasis. Gemcitabine-based adjuvant chemotherapy was an independent prognostic factor in the whole cohort, the node-negative (or N0) subgroup, the node-positive subgroup, or the N1 subgroup, while the N2 subgroup was refractory to gemcitabine-based regimen.

node involvement, as in the node-negative subgroup) or N1 (1-3 nodes involvement, HR = 0.36, 95% CI, 0.25-0.52, $P < .001$) disease showed a favorable response to gemcitabine-based adjuvant chemotherapy. However, patients with N2 disease (≥4 nodes involvement, HR = 0.95, 95% CI, 0.50-1.78, $P = .867$) showed a poor response to gemcitabine-based treatment. Our results therefore suggest that resected pancreatic cancer with N2 nodal involvement is refractory to gemcitabine-based adjuvant chemotherapy. A more intensive adjuvant regimen may be required for the N2 subgroup.

Gemcitabine-based chemotherapy is one of the gold standard adjuvant regimens for resected pancreatic cancer patients.[16,19,21] In the CONKO-001 study, patients who received adjuvant gemcitabine were found to have prolonged overall survival compared with the observation group (median overall survival, 22.8 vs 20.2 months, HR = 0.76, $P = .01$).[17] The European Study Group for Pancreatic Cancer 3 trial included patients who had undergone curative resection for pancreatic ductal adenocarcinoma and had received either adjuvant gemcitabine or fluorouracil plus folinic acid. The median survival was 23.6 months for patients who received gemcitabine and 23.0 months for patients who received fluorouracil plus folinic acid (HR = 0.94, $P = .39$), indicating that both gemcitabine and fluorouracil plus folinic acid could be applied in patients with resected pancreatic cancer.[18] It is currently recommended that all patients with resected pancreatic cancer receive adjuvant chemotherapy. Patients with different risks of cancer recurrence may extract various degrees of benefit from adjuvant chemotherapy. It is therefore important to examine the efficacy of adjuvant chemotherapy in patients stratified by different risks of tumor recurrence.

Regional lymph node metastasis is one of the most important risk factors for the recurrence of resected pancreatic cancer.[6-12] Patients with regional lymph node involvement have a worse outcome than that in patients without node involvement.[6,8,11,15,23] Honselmann et al[24] showed that the time to

recurrence was longer for the node-negative group (16 months) than for the node-positive group (10 months, $P < .001$). Morales-Oyarvide et al[25] found that the median overall survival of the node-negative patients with resected pancreatic adenocarcinoma was significantly higher than that of the node-positive patients (training set, 33.9 vs 20.1 months, $P = .016$; validation set, 42.3 vs 17.4 months, $P < .001$). This study confirms that nodal status (HR = 1.47, $P < .001$) is an independent prognostic factor. Therefore, for resected pancreatic cancer, patients with different degrees of lymph node metastasis may benefit differently from adjuvant chemotherapy.

Previous clinical trials have evaluated the efficacy of different adjuvant chemotherapy regimens stratified by lymph node status.[19-21] The CONKO-001 study showed that both the node-negative group (HR = 0.63, 95% CI, 0.40-0.97) and node-positive group benefit from gemcitabine (HR = 0.81, 95% CI, 0.63-1.06),[17] which was confirmed in the current study. Neoptolemos et al[20] performed a phase 3, multicenter, randomized clinical trial to evaluate the efficacy of gemcitabine and capecitabine compared with gemcitabine alone for patients with macroscopic resected pancreatic cancer. Hazard ratio was 0.83 (95% CI, 0.49-1.39) in the node-negative group and 0.84 (95% CI, 0.69-1.02) in the node-positive group, indicating a potentially better efficacy of gemcitabine plus capecitabine than that of gemcitabine alone for patients with positive node.[20] Another study by Conroy et al[22] demonstrated that a modified FOLFIRINOX regimen (oxaliplatin, irinotecan, leucovorin, fluorouracil) had better efficacy than gemcitabine alone for patients with resected pancreatic cancer (HR for death, 0.64, $P = .003$). In a stratified analysis, patients with positive nodes (HR = 0.54, 95% CI, 0.42-0.69) had a better response to FOLFIRINOX than those with negative nodes (HR = 0.89, 95% CI, 0.53-1.49).[22] These studies suggest that lymph node status may affect the response of pancreatic cancer to different adjuvant chemotherapy regimen.

Several studies found that patients with N2 regional nodes metastasis had worse prognosis than N0 and N1 patients for resected pancreatic cancer.[5,12,13] Asano et al showed that the median overall survival was 56 months in the N0 group, 34 months in the N1 group, and 20 months in the N2 group for patients with pancreatic head ductal adenocarcinoma who underwent pancreaticoduodenectomy.[6] Lowder et al[9] found that N2 staging was correlated with postoperative CA19-9 levels ($P = .044$) and systemic recurrence ($P < .001$), indicating that extensive lymph node involvement may be associated with occult systemic disease. In this study, patients with N0 ($P = .006$) or N1 ($P < .001$) disease were susceptible, while patients with N2 disease ($P = .867$) were resistant to gemcitabine-based adjuvant chemotherapy. This suggests that resected pancreatic cancer with N2 nodal metastasis is refractory to gemcitabine-based treatment.

In this study, the median survival time of patients with resected pancreatic cancer was 16.9 months. Previous epidemiology studies have shown that patients with pancreatic cancer in China have worse prognosis than patients in most other countries (mortality to prevalence ratio, 0.85 in China, 0.70 in the United States, 0.56 in South Korea, 0.55 in Germany, and 0.40 in Japan).[2,26] The possible reasons behind this phenomenon are largely unknown and should be clarified.

The current study is mainly limited by its retrospective design. Another limitation lies in that the study is based on data from a single institution. Prospective randomized multicentric clinical trials are urgently needed to confirm our findings. Future clinical trials should assess the efficacy of adjuvant treatment stratified by the degree of lymph node involvement (N0, N1, N2) and not just by lymph node status (positive, negative).

Authors' Note

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Ethics Committee of Fudan University, Shanghai Cancer Center (050432-4-1805C). Informed consent was obtained from all individual participants included in the study. C.L., H.C., and K.J. contributed equally to this work.

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