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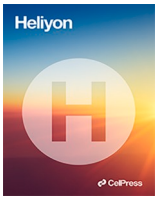

Research article

Is chemotherapy beneficial? A retrospective study of chemotherapy in patients with invasive intraductal papillary-mucinous carcinoma

Yonghao Ouyang [b,1], Pengpeng Liu [c,1], Lihua Chu [d], Yi Xiao [b], Hong Zhu [c], Qiang hao [c], Caihua Zhang [a,*]

[a] Department of Gastrointestinal, Xuzhou Central Hospital, Xuzhou 221000, China
[b] Research Institute of General Surgery, Jinling Hospital, Nanjing 210000, China
[c] Department of Hepatobiliary, Xuzhou Central Hospital, Xuzhou 221000, China
[d] Jinggangshan University, Ji'an 343000,China

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ABSTRACT

Background and aim: Whether chemotherapy can improve the prognosis of invasive intraductal papillary-mucinous carcinoma (IPMC) still remains unclear. The aim of this study is to observe the difference in survival time of patients with invasive IPMC receiving or not receiving chemotherapy.

Methods: 117 patients with invasive IPMC were included in The Surveillance, Epidemiology, and End Results (SEER) database. These patients were subsequently divided into two subgroups according to whether they received chemotherapy or not: the non-chemotherapy group (patients who did not receivechemotherapy, N = 58), the chemotherapy group (patients who received chemotherapy, N = 59). The overall survival (OS) and cancer specific survival (CSS) of two treatment groups were evaluated.

Results: Before adjusting for pathology grade, the Kaplan-Meier analysis showed that the difference of survival time is not significant between non-chemotherapy group and chemotherapy group ($P > 0.05$), but the land-mark analysis showed that short-term death risk of the chemotherapy group is significantly lower than non-chemotherapy group ($P < 0.05$). After adjust the pathology grade, survival time of the chemotherapy group is significantly longer than non-chemotherapy group ($P < 0.05$). Univariate and multivariate Cox regression showed that chemotherapy was an independent prognostic protective factor for invasive IPMC ($P < 0.05$). Land-mark analysis showed that short-term death risk of the chemotherapy group is significantly lower than non-chemotherapy group in N1-N2 subgroup ($P < 0.05$).

Conclusion: Chemotherapy is an independent protective factor IPMC, especially reducing the risk of short-term death for IPMC patients with lymph node metastasis.

* Corresponding author. Gastrointestinal Surgery, Xuzhou City Central Hospital, Xuzhou 221000, China.
E-mail address: zch1985724@163.com (C. Zhang).
[1] These authors contributed equally to this work.

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1. Introduction

Intraductal papillary-mucinous neoplasms (IPMNs) are mucin-producing cystic lesion involving the main pancreatic duct or its collaterals. According to the origin site, IPMN can be divided into the side branch ducts (BD-IPMN), in the main duct (MD-IPMN), or in both (mixed type IPMN) [1]. With the increasing resolution of modern imaging devices, the diagnostic rate of intraductal mucinous cystic tumors (IPMN) is also increasing [1,2]. Although the National Comprehensive Cancer Network (NCCN) considers intraductal papillary-mucinous carcinoma (IPMC) as a subtype of PDAC [3], studies have shown that characteristics of IPMC distinct from colloid pancreatic ductal adenocarcinoma (cPDAC) [4].

For therapy, Most IPMNs are non-malignant lesions with a favorable prognosis after surgery treatment [4,6]. The malignancy rate of the main duct IPMNs (MD-IPMNs) was up to 70 % [7]. Moreover, IPMN is predominantly asymptomatic and has the potential to develop to IPMC make it a great challenge for world [5]. According to the spectrum of neoplastic transformation of IPMNs can be divided into low-grade dysplasia (LGD), high-grade dysplasia (HGD), and IPMC [8,9]. It is generally believed that IPMC has a better prognosis than conventional pancreatic ductal adenocarcinoma (PDAC), but this advantage seems to exist only in the absence of lymph node metastasis [10]. Surgery is the primary strategy for IPMC. Although surgery has greatly improved the prognosis of IPMC patients, the problems of tumor recurrence and poor prognosis persist [7]. Moreover, the rate of radical surgery is lower in IPMC patients [11]. Surgery combined with adjuvant chemoradiation is the standard treatment for pancreatic adenocarcinoma. The addition of chemo-radiotherapy can often improve the prognosis of pancreatic adenocarinoma [12]. In past studies, Fogliati et al. concluded that Neo-adjuvant therapy (NAT) did not differ between IPMC and cPDAC [4,13]. However, the low number of IPMC patients receiving NAT may be biased. Song et al. believed that patients with lymph node-negative invasive pancreatic cystic neoplasms (iPCN) who underwent surgery did not have clinical benefit from chemotherapy or radiotherapy [11]. But they did not analyze for IPMC and may introduce bias due to other iPCN subtypes. Therefore, whether chemotherapy can improve the prognosis of IPMC remains controversial, and randomized controlled experiments are difficult to implement due to the rarity of IPMC [7,14,15].

SEER is a clinical database that collects cancer incidence, prevalence, and survival data from the US Cancer Registry, which covers approximately 34.6 % of the US population [16]. Therefore, this study conducted the analysis of the effect of chemotherapy on the prognosis of invasion IPMC patients using the SEER database.

2. Materials and methods

2.1. Data collection

We downloaded the invasive IPMC (ICD-O-3 8453/3) data from the SEER database from 2000 to 2020 using SEER*Stat version 8.4.0 and screened out the IPMC subjects for this study by the following exclusion criteria (Fig. 1): (1) Characteristic data (race, gender, marital status and income) were not clear; (2) Stage of tumor was unspecified; (3) Treatment modalities (primary tumor resection, surgery of distant metastasis, chemotherapy and radiotherapy)were not specific; (4) The sites of metastasis were unclear. And the inclusion criteria were: Complete patient characteristics, treatment modalities, and survival data were available.

We enrolled information on age, race, gender, pancreatic site, pathologic grade, T stage, N stage, TNM stage, treatment modalities, metastasis status, marital status, income and survival data. Then these patients were divided into two groups: non-chemotherapy (N =

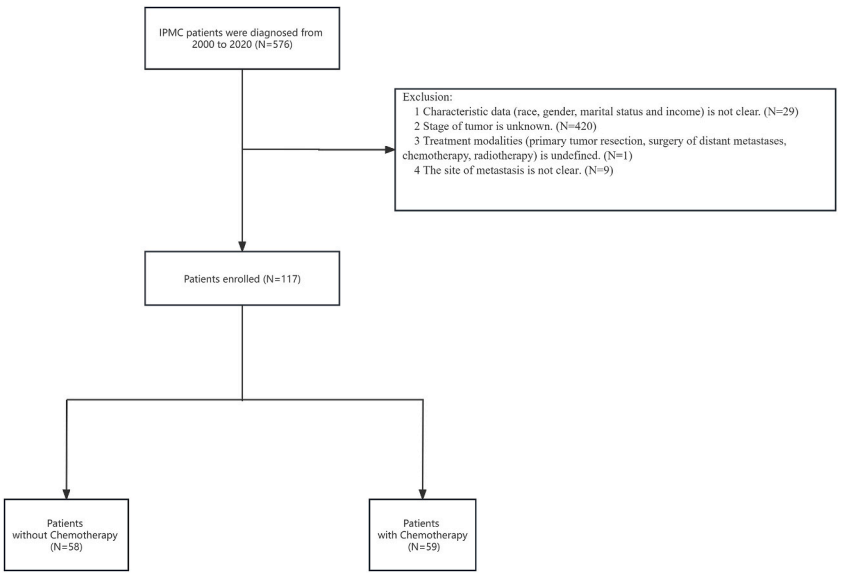

Fig. 1. Flowchart of the study participants.

58) and chemotherapy group (N = 59).

2.2. Statistical analysis

Statistical analyses of this study were performed exclusively using R language 4.1.1, including rms, survival, ggplot2 and survminer. $P < 0.05$ was regarded as statistically significant. The Kaplan-Meier curve was used to estimate the survival time in different groups, and the log-rank test was used to analyze the differences between the curves. Univariate and multivariate Cox regression were used to screen for independent prognostic factors for IPMC. We included factors with $P < 0.10$ in the univariate Cox regression in the multivariate Cox regression, and factors with $P < 0.05$ in the multivariate Cox regression were indicated as independent prognostic factors. Land-mark Analysis was used to observe short- and long-term mortality risk or to reduce time bias.

3. Results

3.1. Baseline information

A total of 117 patients with IPMC were included in our study (Table 1), of which 58 (49.6 %) were in the non-chemotherapy group and 59 (50.4 %) in the chemotherapy group. In the included population, 87.2 % were elderly patients with IPMC. There was a totally statistical difference in N stage ($P < 0.05$).

Table 1
The baseline information for IPMC patients.

Charateristics	Non-Chemotherapy group (N = 58)	Chenotherapy group (N = 59)	χ^2	P
Age			0.058	0.810
≤60	7 (12.1 %)	8 (13.6 %)		
>60	51 (87.9 %)	51 (86.4 %)		
Gender			0.687	0.407
Female	30 (51.7 %)	26 (44.1 %)		
Male	28 (48.3 %)	33 (55.9 %)		
Race			Fisher exact test	0.480
White	49 (84.5 %)	50 (84.7 %)		
Black	2 (3.4 %)	0 (0.0 %)		
Other	7 (12.1 %)	9 (15.3 %)		
Site			2.180	0.336
Head	25 (43.1 %)	30 (50.8 %)		
Body and tail	12 (20.7 %)	15 (25.5 %)		
Other	21 (36.2 %)	14 (23.7 %)		
Grade			1.424	0.232
G1-G2	24 (41.4 %)	31 (52.5 %)		
G3-G4	5 (8.6 %)	13 (22.0 %)		
T			1.776	0.183
T1-T2	38 (65.5 %)	35 (59.3 %)		
T3-T4	13 (22.4 %)	21 (35.6 %)		
N			22.265	<0.001
N0	46 (79.4 %)	26 (44.1 %)		
N1-N2	6 (10.3 %)	31 (52.5 %)		
Stage			0.146	0.703
I-II	45 (77.6 %)	44 (74.6 %)		
III-IV	13 (22.4 %)	15 (25.4 %)		
PTR			3.921	0.077
No	19 (32.8 %)	10 (16.9 %)		
Yes	39 (67.2 %)	49 (83.1 %)		
Radiotherapy			3.001	0.083
No	55 (94.8 %)	49 (83.1 %)		
Yes	3 (5.2 %)	10 (16.9 %)		
Liver metastasis			Fisher exact test	0.490
No	53 (91.4 %)	56 (94.9 %)		
Yes	5 (8.6 %)	3 (5.1 %)		
Other metastasis (except for liver)			2.604	0.707
No	50 (86.2 %)	56 (94.9 %)		
Yes	8 (13.8 %)	3 (5.1 %)		
Income			Fisher exact test	0.321
≤54,999	4 (6.9 %)	4 (6.9 %)		
55,000–74,999	22 (37.9 %)	15 (25.3 %)		
>74,999	32 (55.2 %)	40 (67.8 %)		
Marital_status			0.414	0.520
No	24 (41.4 %)	21 (35.6 %)		
Yes	34 (58.6 %)	38 (64.4 %)		

3.2. Survival analysis for all invasive IPMC patients

By Kaplan-Meier analysis, we observed the difference in prognosis between non-chemotherapy group and chemotherapy group. The results showed that the difference of survival time (OS or CSS) was not significant between non-chemotherapy group and chemotherapy group ($P > 0.05$, Fig. 2A and B). However, we could observe a change in the slope of Kaplan-Meier curve at 8 months. Thus, we set 8 months as the landmark to perform landmark analysis. The results of landmark analysis showed that the risk of death in the chemotherapy group significantly reduce comparing to the non-chemotherapy group during the short-term ($P < 0.05$, Fig. 2C and D).

3.3. Screening the independent risk factors

Due to the heterogeneity of data between non-chemotherapy group and chemotherapy group, we screened for independent prognostic risk factors that could affect the survival time of patients, aiming to identify features of different distributional characteristics that could significantly affect the prognosis of patients. Therefore, after excluding samples with missing data, we performed a univariate and multivariate Cox regression analysis. The univariate results showed that male (vs. female, OS: 0.46[0.20–1.04], P = 0.061; CSS: 0.45[0.19–1.06], P = 0.069), G1-G2 (vs. G3-G4, OS: 2.10[0.93–4.74], P = 0.074; CSS: 2.18[0.92–5.17], P = 0.077), T1-T2 (vs. T3-T4, OS: 2.11[0.97–4.57], P = 0.059; CSS: 2.41[1.06–5.50], P = 0.036), N0 (vs. N1-N2, OS: 2.38[1.05–5.40], P = 0.038; CSS: 2.61[1.09–6.27], P = 0.032), stage I-II (vs. stage III-IV, OS: 4.19[1.72–10.26], P = 0.002; CSS: 4.50[1.80–11.23], P = 0.001), primary

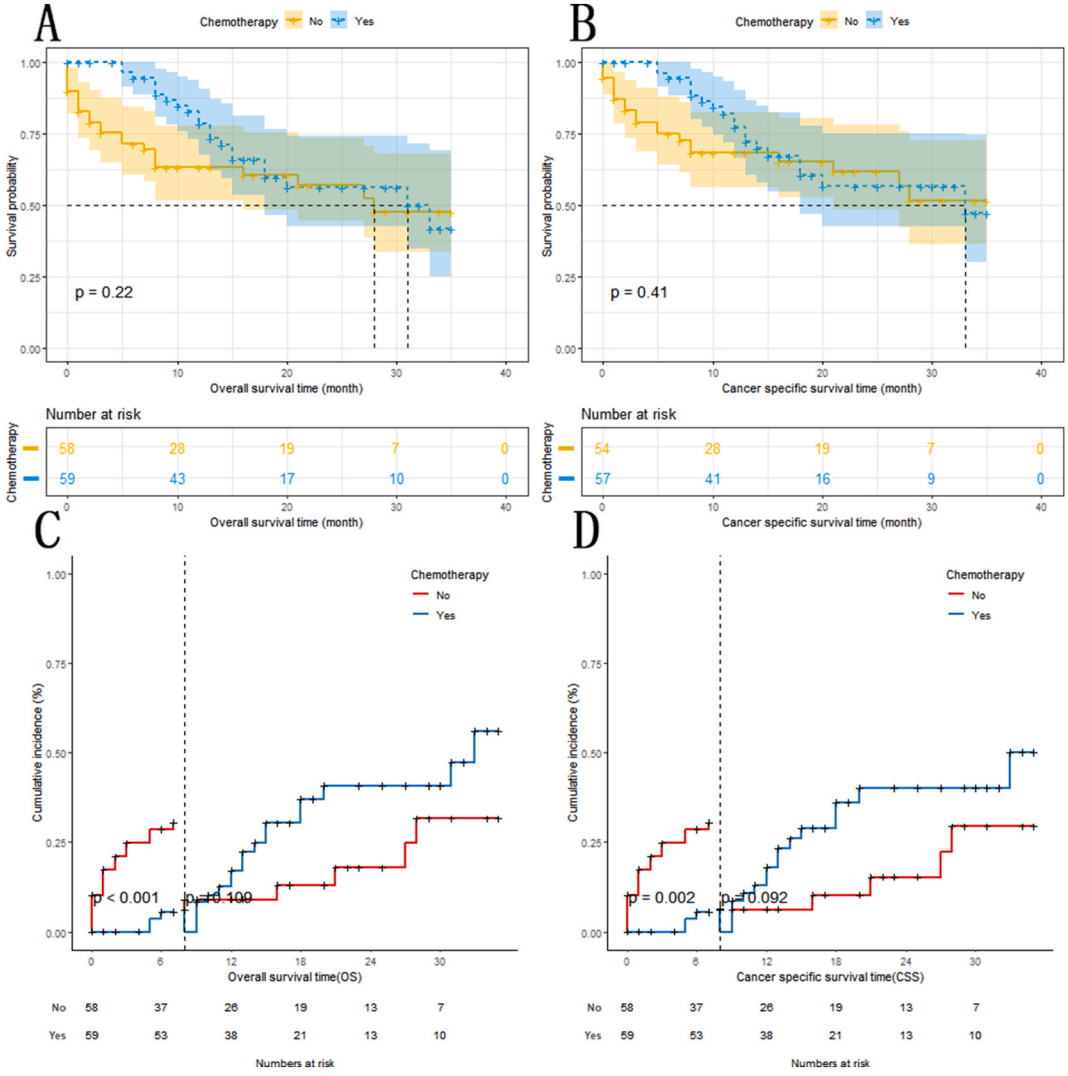

Fig. 2. The survival analysis for IPMC patients A: Kaplan-Meier analysis for OS of IPMC patients; B: Kaplan-Meier analysis for CSS of IPMC patients; C: Landmark analysis for OS of IPMC patients; D: Landmark analysis for CSS of IPMC patients.

tumore resection (PTR) yes (vs. no, OS: 0.07[0.02–0.26], P < 0.001; CSS: 0.07[0.02–0.26], P < 0.001), chemotherapy yes (vs. no, OS: 0.41[0.18–0.89], P = 0.025; CSS: 0.42[0.18–0.96], P = 0.039), liver metastasis yes (vs. no, OS: 5.23[1.54–17.78], P = 0.008; CSS: 5.60 [1.63–19.25], P = 0.006), other metastasis yes (vs. no, OS: 4.94[1.45–16.82], P = 0.011; CSS: 5.26[1.53–18.12], P = 0.008) are

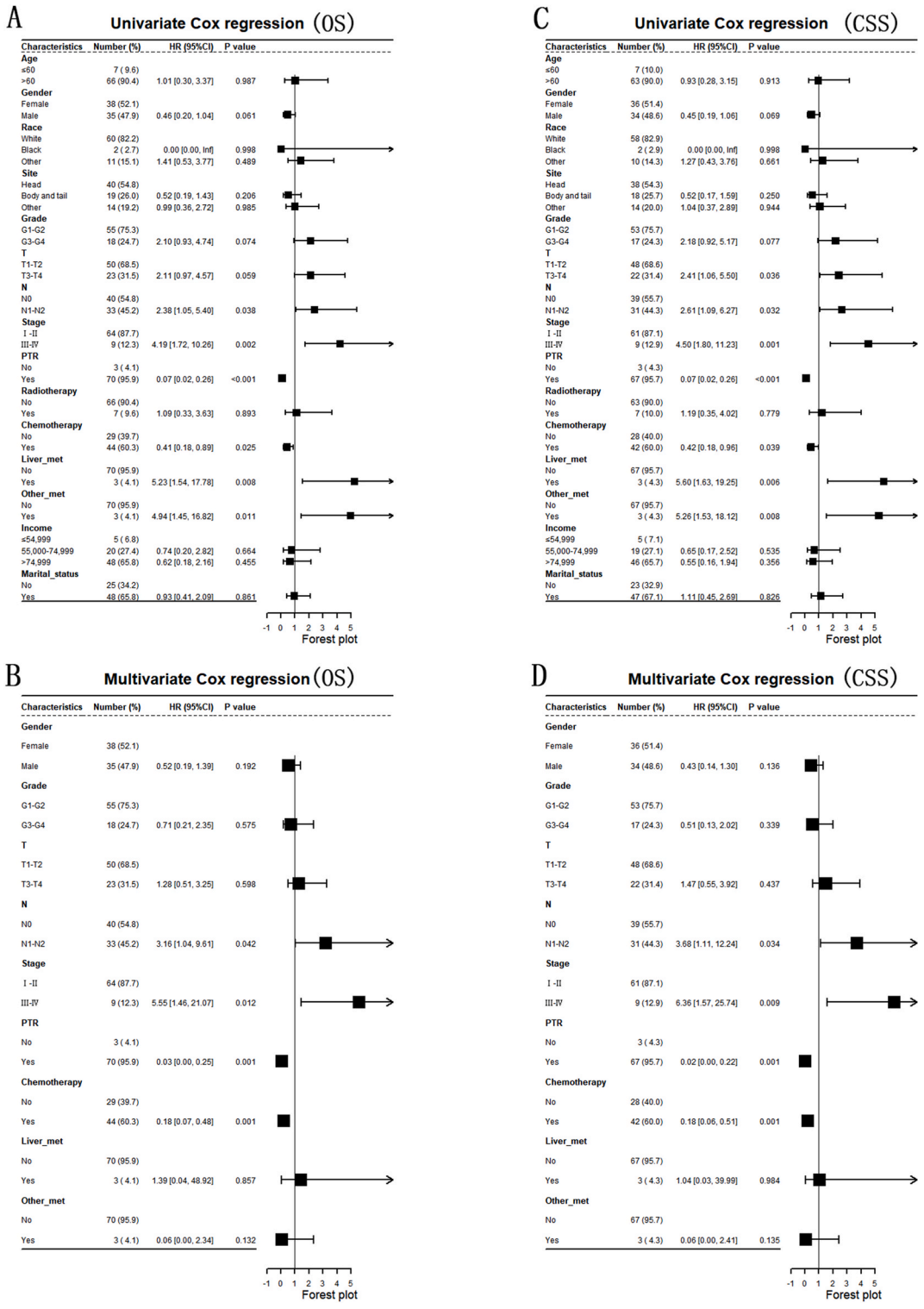

Fig. 3. Cox analysis for IPMC patients A: Univariate Cox analysis for OS of IPMC patitens; B: Univariate Cox analysis for CSS of IPMC patients; C: Multivariate Cox analysis for OS of IPMC patients; D: Multivariate Cox analysis for CSS of IPMC patients.

prognostic factors (Fig. 3A–C). Subsequently, we included these prognostic factors into multivariate Cox analysis, which showed that N0 (vs. N1-N2, OS: 3.16[1.04–9.61], P = 0.042; CSS: 3.68[1.11–12.24], P = 0.034), stage I-II (vs. stage III-IV, OS:5.55[1.46–21.07], P = 0.012; CSS: 6.36[1.57–25.74], P = 0.009), PTR yes (vs. no, OS: 0.03[0.00–0.25], P = 0.001; CSS: 0.02[0.00–0.20], P = 0.001), chemotherapy yes (vs. no, OS: 0.18[0.07–0.48], P = 0.001, CSS: 0.18[0.06–0.51], P = 0.001) were the independent prognostic factors (Fig. 3B–D). The results showed that the prognosis of patients who received chemotherapy was significantly better than that of patients who did not receive chemotherapy.

3.4. Kaplan-Meier analysis after adjusting pathological grade

According to the results of Cox analysis and pairwise comparative χ^2 test, we found that N stage was a non-independent prognostic factor (Fig. 3A). Unknown pathologic grading may bias the results. Thus, we performed Kaplan-Meier analysis after adjusting for pathological grading to eliminate the samples with unknown pathological grade. The results of Kaplan-Meier analysis showed that the prognostic of chemotherapy group was better than non-chemotherapy group ($P < 0.05$, Fig. 4A and B).

3.5. Subgroup analysis

According to the results of Cox analysis and pairwise comparative χ^2 test, we found that N stage was an independent prognostic factor (Fig. 3) and physicians seem to prefer patients with lymphatic metastasis for chemotherapy. Previous studies have shown that IPMC patients with lymph node metastasis have a significantly worse prognosis than IPMC patients without lymph node metastasis, and their survival rate is close to that of PDAC patients [10]. Therefore, we performed Kaplan-Meier analysis for different N stage. The results showed that patients who received chemotherapy had a better prognosis than those who did not receive chemotherapy, but statistical differences was not significant ($P > 0.05$, Fig. 5A–D).

To further investigate the effect of chemotherapy on the short-term and long-term risk of death, we performed the landmark analysis (the landmark was set at 12 month) for patients with lymph node metastases. We found that the short-term risk of death was lower in the chemotherapy group than in the non-chemotherapy group (Fig. 5E and F).

4. Discussion

IPMC is an uncommon subtype of PDAC that evolved primarily from IPMN. IPMC has been reported to account for approximately 10 % of the resected pancreatic cancers of ductal origin [17]. As with conventional PDAC, abdominal pain, weight loss, and jaundice are the most common symptoms [17]. However, the difference between the carcinogenic effect of IPMC and PDAC may result in different sensitivities to chemotherapy [7]. The need for adjuvant chemotherapy for IPMC remains controversial. The European Study Group on Pancreatic Cystic Neoplasms recommended adjuvant chemotherapy for IPMC [18]. However, the revised Fukuoka consensus guidelines do not recommend adjuvant chemotherapy for patients with IPMC [19]. Therefore, an analysis of whether chemotherapy can improve the outcome of IPMC patients is warranted. Although several studies have explored the efficacy of adjuvant therapy on IPMC in the past, the number of IPMC patients receiving chemotherapy is small due to the controversial nature of chemotherapy. Most studies combined chemotherapy and other adjuvant therapies as a whole object in the IPMN population for analysis. Marchegiani et al. compared the survival of 19 patients with surgical plus chemotherapy and surgery alone, and showed that adjuvant therapy could

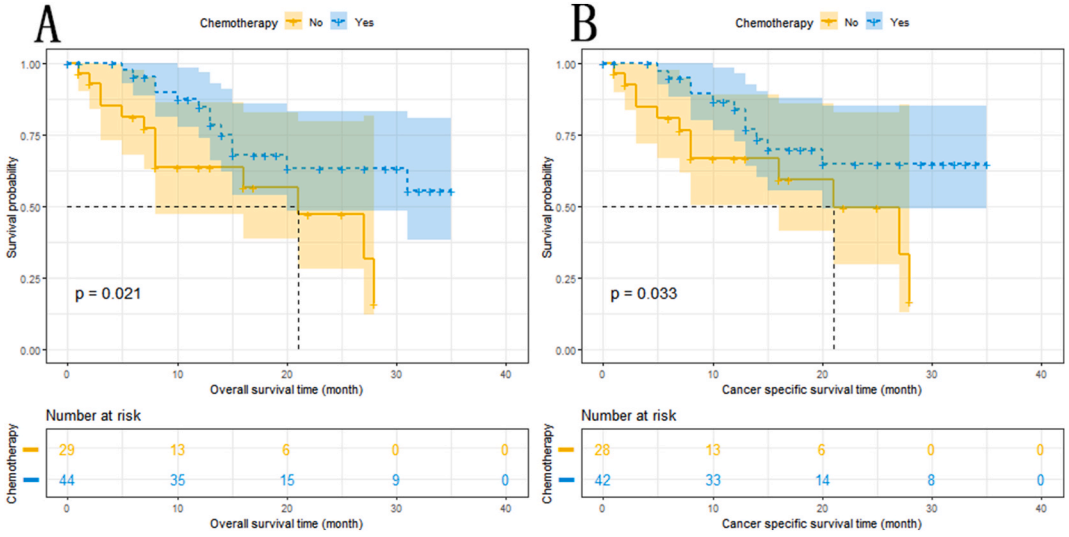

Fig. 4. Kaplan-Meier analysis for IPMC patients after adjusted pathological grade A: Kaplan-Meier analysis for OS of IPMC patients after adjusted pathological grade; B: Kaplan-Meier analysis for CSS of IPMC patients after adjusted pathological grade.

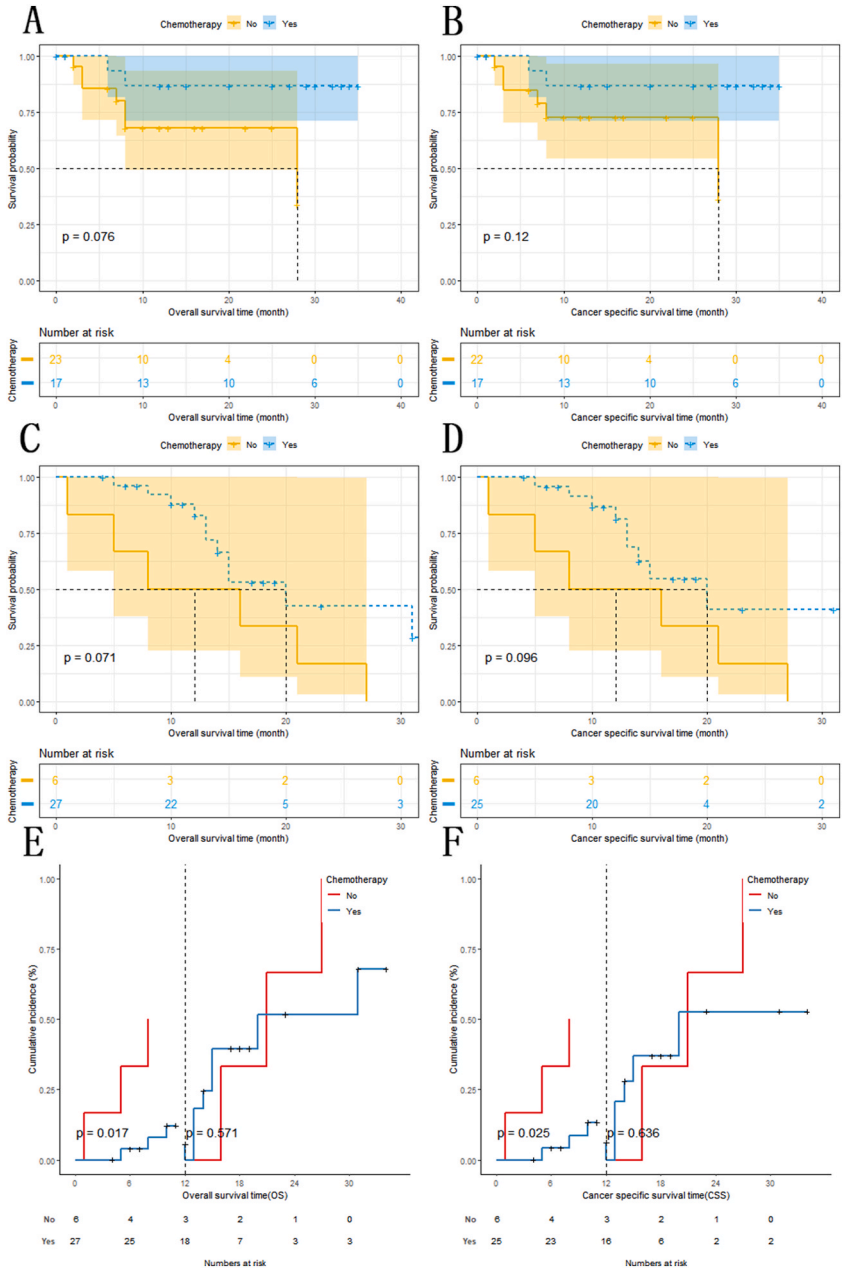

Fig. 5. The survival analysis for IPMC patitens in different stage N subgroup A: Kaplan-Meier analysis for OS of IPMC patients with N0; B: Kaplan-Meier analysis for CSS of IPMC patients with N0; C: Kaplan-Meier analysis for OS of IPMC patients with N1-N2; D: Kaplan-Meier analysis for CSS of IPMC patients with N1-N2; E: Landmark analysis for OS of IPMC patients with N1-N2; F: Landmark analysis for CSS of IPMC patients with N1-N2.

improve the prognosis of patients with lymph node metastasis [20]. However, the number of patients with adjuvant chemotherapy was small, and the number of patients who received concurrent radiation in the adjuvant chemotherapy group was significantly more than the surgery-only group, which may result in bias. Although the study by McMillan et al. included a sufficiently large number of IPMC patients receiving adjuvant therapy, the study treated chemotherapy and other adjuvant therapies as a whole subject, which did not allow for a better observation of the efficacy of chemotherapy [21]. The study by Duconseil et al. mainly compared cPDAC and IPMC, and did not have a detailed description of the baseline data of IPMC, which may introduce bias [22].

In this study, we used patients receiving chemotherapy and no chemotherapy as the main contrast objects to observe the efficacy of chemotherapy in IPMC. A total of 58 patients without chemotherapy and 59 patients receiving chemotherapy were included in this study. We found that IPMC mostly occurred in older patients, which is similar to previous reports [23,24]. Furthermore, we observed

differences N stage between the two groups. Similarly, the study of Alexander et al. found a higher rate of lymph node positivity in patients receiving chemoradiotherapy [25]. In the study of Marchegiani et al., the proportion of lymph node metastases treated with surgical plus chemotherapy was up to 62.3 %, which was significantly higher than 38.6 % in the surgical group [20]. McMillan et al. also showed a higher proportion of lymph node metastases in the adjuvant treatment group [21], Above study suggests that clinicians may prefer to choose IPMC with lymph node metastasis for chemotherapy. Unlike Baine et al. and Sachs et al., our results do not support the association of marital status and family income with the prognosis of IPMC [26–29]. Therefore, the marital status and family income were included in the analysis of this study. However, differences in marital status and income between non-chemotherapy group and chemotherapy group were not observed in our study. To compare the prognosis of the non-chemotherapy group and chemotherapy groups, we performed Kaplan-Meier analysis and landmark analysis. Kaplan-Meier analysis showed no significant difference in survival time between non-chemotherapy group and chemotherapy group ($P > 0.05$). This seems to be similar to the conclusions obtained in Turrini et al [30]. Nevertheless, in our landmark-analysis, we observed a significantly lower risk of short-term mortality in chemotherapy group than non-chemotherapy ($P < 0.05$). To make a more intuitive judgment of the efficacy of chemotherapy on IPMC, univariate and multivariate Cox regression was performed. We found that for OS and CSS, chemotherapy was an independent protective factor independent of N stage, TNM stage, and PTR. This is consistent with the Cox regression results of adjuvant therapy in node-positive patients [25]. In the study of McMillan et al., the adjuvant therapy can improved the OS with AJCC TNM stage II or III/IV, positive lymph node status, positive margins, and poorly differentiated tumors [21]. Caponi et al. found that disease-free survival was longer in patients receiving adjuvant chemotherapy with gemcitabine, which is consistent with our conclusions [31]. However, The study of Rodrigues et al. found that adjunctive therapy do not prolong survival time for IPMC patients (was associated with a worse prognosis even in the N0 subgroup) [32]. This may be related to the higher T stage, N stage and more perineural, lymphovascular invasion of adjunctive therapy group in the study of Rodrigues et al. The N0 and N1-N2 component ratios, which are independent risk factors for IPMC, were different between the non-chemotherapy and chemotherapy groups. Previous studies reported that the survival of IPMC patients with lymph node metastasis was significantly shorter than that of IPMC patients without lymph node metastasis [10]. Thus, we set N0 and N1-N2 subgroups to analyze the efficacy of chemotherapy. Kaplan-Meier showed that the differences in OS and CSS between non-chemotherapy group and chemotherapy group for IPMC patients with stage N1-N2 was not significant ($P < 0.05$). But the landmark analysis showed that chemotherapy can reduce the short-term death risk of IPMC patients with stage N1-N2, which has the same conclusion shared with most of the studies on adjuvant therapy [21,31,33,34]. In a previous study, Mungo et al. compared 267 patients receiving adjuvant therapy with 225 patients without adjuvant therapy and found that adjuvant therapy improved the prognosis of patients in N1 stage, but had no significant impact on the prognosis of patients in N0 stage [33]. Besides, the study of McMillan et al. believed that adjuvant therapy can improve IPMC patients with lymphoma metastasis, but not in IPMC patients without lymphoma metastasis [21]. This is in agreement with our results. However, these studies combined chemotherapy and radiotherapy as adjuvant therapy and could not intuitively observe the efficacy of chemotherapy. Although the prognosis of chemotherapy group was better than non-chemotherapy in the N0 subgroup, there was no statistical difference between the two groups ($P > 0.05$). Due to the good prognosis of N0 stage patients, longer-term follow-up data were not available in the SEER database, leading to the inability of landmark analysis to observe short-term and long-term outcomes. Therefore, we judged that chemotherapy was an independent protective factor IPMC, especially reducing the short-term risk of death in IPMC patients with lymph node metastasis.

The strengths of this study are: (1)This study is based on SEER database, which provides sufficient samples for rare diseases. (2) This study compared the effects of different treatment modalities on patient prognosis by Kaplan-Meier analysis, Cox regression analysis and landmark analysis. (3) This study reduced the bias caused by the uneven distribution of etiologic characteristics between the non-chemotherapy and chemotherapy groups by subgroup analysis. (4) The efficacy of chemotherapy on IPMC alone was studied with chemotherapy as the only observation.

However, there are some imperfections in this study: (1) This experiment may bring bias to retrospective studies. (2) We were unable to obtain detailed information about treatment regimens (whether the patients had received immunotherapy, the sequence between chemotherapy and splenectomy, and the specific chemotherapy regimen remains unknown). (3) Based on the information provided in the SEER database, we cannot distinguish between the subtypes of IPMC, namely tubular and colloid. However, There have been reports indicating that the lymph node involvement is an important biological surrogate that could guide patient selection for adjuvant therapy [35]. (4) Since IPMC patients with N0 had a significantly longer survival time than patients with N1-N2 and the SEER database has a shorter follow-up period for IPMC patients with N0, we were unable to observe short-term and long-term outcomes by landmark analysis. (5) Due to the rarity of the disease, only a relatively small number of IPMC patients with N0 stage were included in this study. More multicenter comparative studies are still needed for further validation.

In conclusion, we demonstrated that the efficacy of chemotherapy in patients with IPMC through the SEER database. We observed that chemotherapy was an independent protective factor for IPMC patients and showed a significant improvement in short-term outcomes for N1-N2 patients. However, long-term follow-up with large sample sizes is still needed for the efficacy of chemotherapy in N0 patients.

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Ethical approval

The study did not require approval from the ethics review committee.

Data and code availability statement

The data supporting the conclusions of this article will be made available by SEER database (https://seer.cancer.gov/data-software/).

CRediT authorship contribution statement

Yonghao Ouyang: Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Methodology, Formal analysis, Data curation. **Pengpeng Liu:** Writing – review & editing, Data curation. **Lihua Chu:** Writing – review & editing. **Yi Xiao:** Writing – review & editing. **Hong Zhu:** Writing – review & editing. **Qiang hao:** Writing – review & editing. **Caihua Zhang:** Writing – review & editing, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] M.G. Keane, E. Afghani, A review of the diagnosis and management of premalignant pancreatic cystic lesions, J. Clin. Med. 10 (2021) 1284.
[2] M. Moris, M.D. Bridges, R.A. Pooley, et al., Association between advances in high-resolution cross-section imaging technologies and increase in prevalence of pancreatic cysts from 2005 to 2014, Clin. Gastroenterol. Hepatol. 14 (4) (2016) 585–593.
[3] M.A. Tempero, M.P. Malafa, M. Al-Hawary, et al., Pancreatic adenocarcinoma, version 2.2021, NCCN clinical practice guidelines in oncology, J Natl Compr Canc Netw 19 (4) (2021) 439–457.
[4] A. Fogliati, A. Zironda, G. Fiorentini, et al., Outcomes of Neoadjuvant Chemotherapy for Invasive Intraductal Papillary Mucinous Neoplasm Compared with de Novo Pancreatic Adenocarcinoma, Ann. Surg Oncol. 31 (4) (2024 Apr) 2632–2639.
[5] V. Djordjevic, D. Knezevic, B. Trotovsek, et al., Navigating intraductal papillary mucinous neoplasm management through Fukuoka consensus vs. European evidence-based guidelines on pancreatic cystic neoplasms-A study on two European centers, Cancers 16 (11) (2024 Jun 6) 2156.
[6] C.E. Cauley, J.A. Waters, R.P. Dumas, et al., Outcomes of primary surveillance for intraductal papillary mucinous neoplasm, J. Gastrointest. Surg. 16 (2) (2012) 258–266.
[7] Z.V. Fong, C.F. Castillo, Intraductal papillary mucinous adenocarcinoma of the pancreas: clinical outcomes, prognostic factors, and the role of adjuvant therapy, Viszeralmedizin 31 (1) (2015 Feb) 43–46.
[8] M. Tanaka, C. Fernández-del Castillo, T. Kamisawa, J.Y. Jang, P. Levy, T. Ohtsuka, et al., Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas, Pancreatology 17 (2017) 738–753.
[9] O. Basturk, S.M. Hong, L.D. Wood, N.V. Adsay, J. Albores-Saavedra, A.V. Biankin, et al., A revised classification system and recommendations from the Baltimore Consensus Meeting for neoplastic precursor lesions in the pancreas, Am. J. Surg. Pathol. 39 (2015) 1730–1741.
[10] L. Mas, R.M. Lupinacci, J. Cros, J.B. Bachet, F. Coulet, M. Svrcek, Intraductal papillary mucinous carcinoma versus conventional pancreatic ductal adenocarcinoma: a comprehensive review of clinical-pathological features, outcomes, and molecular insights, Int. J. Mol. Sci. 22 (13) (2021 Jun 23) 6756.
[11] Y. Song, Z. Li, H. Cui, J. Xu, et al., Clinical characteristics and survival prediction of surgical patients with invasive pancreatic cystic neoplasm: a large retrospective study over two decades, World J. Surg. Oncol. 21 (1) (2023) 261.
[12] W. Park, A. Chawla, E.M. O'Reilly, Pancreatic cancer: a review, JAMA 326 (9) (2021 Sep 7) 851–862.
[13] A Fogliati, A Zironda, G Fiorentini, et al., Outcomes of Neoadjuvant Chemotherapy for Invasive Intraductal Papillary Mucinous Neoplasm Compared with de Novo Pancreatic Adenocarcinoma, Ann Surg Oncol 31 (4) (2024) 2632–2639.
[14] S. Hirono, H. Yamaue, Surgical strategy for intraductal papillary mucinous neoplasms of the pancreas, Surg. Today 50 (1) (2020 Jan) 50–55.
[15] E. Ohno, A. Balduzzi, S. Hijioka, et al., Association of high-risk stigmata and worrisome features with advanced neoplasia in intraductal papillary mucinous neoplasms (IPMN): a systematic review, Pancreatology 24 (1) (2024 Feb) 48–61.
[16] K.M. Doll, A. Rademaker, J.A. Sosa, Practical guide to surgical data sets: surveillance, Epidemiology, and End results (SEER) database, JAMA Surg 153 (6) (2018) 588–589.
[17] L. Mas, R.M. Lupinacci, J. Cros, J.B. Bachet, F. Coulet, M. Svrcek, Intraductal papillary mucinous carcinoma versus conventional pancreatic ductal adenocarcinoma: a comprehensive review of clinical-pathological features, outcomes, and molecular insights, Int. J. Mol. Sci. 22 (13) (2021) 6756.
[18] European Study Group on Cystic Tumours of the Pancreas European evidence-based guidelines on pancreatic cystic neoplasms, Gut 67 (5) (2018) 789–804.
[19] M. Tanaka, C. Fernández-del Castillo, T. Kamisawa, J.Y. Jang, P. Levy, T. Ohtsuka, et al., Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas, Pancreatology 17 (5) (2017) 738–753.
[20] G. Marchegiani, S. Andrianello, C. Dal Borgo, et al., Adjuvant chemotherapy is associated with improved postoperative survival in specific subtypes of invasive intraductal papillary mucinous neoplasms (IPMN) of the pancreas: it is time for randomized controlled data, HPB (Oxford) 21 (5) (2019) 596–603.
[21] M.T. McMillan, R.S. Lewis, J.A. Drebin, et al., The efficacy of adjuvant therapy for pancreatic invasive intraductal papillary mucinous neoplasm (IPMN), Cancer 122 (4) (2016) 521–533.
[22] P. Duconseil, J. Périnel, A. Autret, et al., Resectable invasive IPMN versus sporadic pancreatic adenocarcinoma of the head of the pancreas: should these two different diseases receive the same treatment? A matched comparison study of the French Surgical Association (AFC), Eur. J. Surg. Oncol. 43 (9) (2017) 1704–1710.
[23] S. Partelli, C. Fernandez-Del Castillo, C. Bassi, et al., Invasive intraductal papillary mucinous carcinomas of the pancreas: predictors of survival and the role of lymph node ratio, Ann. Surg. 251 (3) (2010) 477–482.
[24] S. Hirono, M. Tani, M. Kawai, et al., Treatment strategy for intraductal papillary mucinous neoplasm of the pancreas based on malignant predictive factors, Arch. Surg. 144 (4) (2009) 345–350.
[25] B.M. Alexander, C. Fernandez-Del Castillo, D.P. Ryan, et al., Intraductal papillary mucinous adenocarcinoma of the pancreas: clinical outcomes, prognostic factors, and the role of adjuvant therapy, Gastrointest Cancer Res 4 (4) (2011) 116–121.
[26] A.V. Neale, B.C. Tilley, S.W. Vernon, Marital status, delay in seeking treatment and survival from breast cancer, Soc. Sci. Med. 23 (3) (1986) 305–312.
[27] A.A. Aizer, M.H. Chen, E.P. McCarthy, et al., Marital status and survival in patients with cancer, J. Clin. Oncol. 31 (31) (2013 Nov 1) 3869–3876.

[28] M. Baine, F. Sahak, C. Lin, et al., Marital status and survival in pancreatic cancer patients: a SEER based analysis, PLoS One 6 (6) (2011) e21052.
[29] E. Sachs, V. Jackson, U. Sartipy, Household disposable income and long-term survival after pulmonary resections for lung cancer, Thorax 75 (9) (2020 Sep) 764–770.
[30] O. Turrini, J.A. Waters, T. Schnelldorfer, et al., Invasive intraductal papillary mucinous neoplasm: predictors of survival and role of adjuvant therapy, HPB (Oxford) 12 (7) (2010) 447–455.
[31] S. Caponi, E. Vasile, N. Funel, et al., Adjuvant chemotherapy seems beneficial for invasive intraductal papillary mucinous neoplasms, Eur. J. Surg. Oncol. 39 (4) (2013) 396–403.
[32] C. Rodrigues, T. Hank, M. Qadan, et al., Impact of adjuvant therapy in patients with invasive intraductal papillary mucinous neoplasms of the pancreas, Pancreatology 20 (4) (2020 Jun) 722–728.
[33] B. Mungo, C. Croce, A. Oba, et al., Controversial role of adjuvant therapy in node-negative invasive intraductal papillary mucinous neoplasm, Ann. Surg Oncol. 28 (3) (2021) 1533–1542.
[34] M.J. Swartz, C.C. Hsu, T.M. Pawlik, et al., Adjuvant chemoradiotherapy after pancreatic resection for invasive carcinoma associated with intraductal papillary mucinous neoplasm of the pancreas, Int. J. Radiat. Oncol. Biol. Phys. 76 (3) (2010) 839–844.
[35] Z.V. Fong, C.F. Castillo, Intraductal papillary mucinous adenocarcinoma of the pancreas: clinical outcomes, prognostic factors, and the role of adjuvant therapy, Viszeralmedizin 31 (1) (2015) 43–46.