Neoadjuvant Chemotherapy Efficacy and Safety in Borderline Resectable Pancreatic Cancer

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The current study was designed to investigate the safety and effectiveness of neoadjuvant therapy in patients with borderline resectable pancreatic cancer. The study was a retrospective case control with propensity score similarity. From January 2017 to June 2022, data regarding 70 patients who had received radical resection of pancreatic cancer at the department of hepatobiliary and pancreatic surgery of first affiliated hospital of Huzhou university was acquired. The neoadjuvant therapy group consisted of 35 patients who underwent neoadjuvant therapy before surgery. Patients who received extensive surgical resection were included in the control group directly. The effect of the neoadjuvant therapy group was evaluated before the operation and serum tumor markers carcinoembryonic antigen, cancer antigen 125 and cancer antigen 19-9 levels were compared before and after neoadjuvant therapy. Comparative analyses of perioperative surgical variables, postoperative pathological symptoms and postoperative complications were performed between both groups. Among the patients without complete remission or progressive disease after neoadjuvant therapy, 13 cases (37.14 %) were evaluated as partial response and 22 cases (62.86 %) were assessed as stable disease. After neoadjuvant therapy, serum levels of cancer antigen 19-9, cancer antigen 125 and carcinoembryonic antigen indexes revealed a significant (all $p<0.05$) downward trend. There were no statistically significant differences (all $p>0.05$) between the two groups regarding surgery type, operation duration, intraoperative blood loss, number of cases requiring blood transfusion, or postoperative hospital stay. Neoadjuvant treatment patient's tumor diameters and the number of removed lymph nodes were significantly less ($p<0.05$) than those of the control group and their R0 resection rates were significantly greater ($p<0.05$) than those of the control group. There was no substantial variation in the frequency of complications between both groups ($p>0.05$). Preoperative neoadjuvant therapy for patients with minimally resectable pancreatic cancer can lower tumor marker levels. Moreover, it can produce a specific curative impact without raising surgical risk levels and boosting the R0 resection rate, which is safe and appropriate.

Key words: Neoadjuvant therapy, R0 resection rate, borderline resectable pancreatic cancer, chemotherapy

Only about 20 % of pancreatic cancer patients are surgically resectable at diagnosis, 30 % are borderline resectable and locally advanced, and 50 % have metastasized[1]. Radical resection for localized pancreatic cancer remains the only cure and if R0 resection can be achieved, significantly improves patient survival[2]. The 5 y survival rate is less than 40 % in clinical practice and some resectable patients are vulnerable to early recurrence and poor prognosis following direct surgical therapy. Analysis of these patients is almost all related to minimal postoperative lesions[3,4]. Therefore, the preoperative evaluation and treatment selection of pancreatic cancer patients is essential. Both the 2021 Chinese Pancreatic Cancer Guidelines and the National Comprehensive Cancer Network of the United States recommend preoperative neoadjuvant therapy for resectable patients with a precise pathological diagnosis and high-risk factors such as a significant increase in extreme pain, a considerable loss of weight, presumed metastasis of regional lymph nodes, a large tumor size and Cancer Antigen (CA) 19-9[5,6]. Prospective clinical investigations of neoadjuvant chemotherapy and chemoradiotherapy for borderline resectable pancreatic cancer have revealed promising applicability potential.

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More studies are still needed to provide evidence for the promotion of neoadjuvant chemotherapy[7]. In order to assess the clinical effectiveness of neoadjuvant therapy, individuals with resectable pancreatic cancer who were hospitalized at First affiliated Hospital of Huzhou University were recruited as study participants. Clinical data including the current study examined 70 participants with borderline resectable pancreatic cancer who were diagnosed at First affiliated Hospital of Huzhou University's Department of Hepatobiliary and Pancreatic Surgery between January 2017 and June 2022. Inclusion criteria were radical surgical resection of pancreatic cancer; initial preoperative evaluation as resectable pancreatic cancer; postoperative pathological diagnosis of pancreatic ductal adenocarcinoma and no tumor-related treatment before surgery. Exclusion criteria were patients with radical resection combined with distant metastases resection; patients with other malignant diseases and heart, lung and kidney diseases and incomplete clinical data. Following evaluation, 35 cases of patient populations with borderline resectable pancreatic cancer who had previously received neoadjuvant treatment were preferred for the study's neoadjuvant therapy group. They were matched in a 1:1 ratio based on propensity scores and radical surgical resection was appointed simultaneously. The control group consisted of 35 individuals with pancreatic cancer. The Ethics Committee at First affiliated Hospital of Huzhou University approved this study and the participants and their families were informed of its purpose and requested to complete a consent form. The control group was (59.48±7.13) y old, comprised of 23 males and 12 females, whereas the neoadjuvant therapy group was (57.16±6.67) y old, with 19 males and 16 females, 15 pancreatic head cancers and 20 pancreatic tail tumors. Pancreatic head cancer affected 11 people and pancreatic tail cancer affected 24 individuals. The general data did not significantly differ (all $p>0.05$) between both groups. Neoadjuvant therapy including the following modified FOLFIRINOX regimen was administered to 35 participants in the neoadjuvant therapy group before surgery; on the 1st d of each course of treatment, intravenous injection of fluorouracil (400 mg/m^2), folinic acid (400 mg/m^2), irinotecan (135 mg/m^2), intravenous infusion of oxaliplatin (68 mg/m^2), followed by continuous infusion of fluorouracil (2400 mg/m2) for 46 h, 2 w as a cycle[8]. If the patient can tolerate it, 8 cycles of FOLFIRINOX will be arranged and abdominal CT re-examination will be performed after the 4th (about 2 mo) and 8th (about 4 mo) FOLFIRINOX chemotherapy. Preoperative imaging to assess neoadjuvant therapy's effects (RECIST1.1 standard, defined as Progressive Disease (PD), Stable Disease (SD), Partial Response (PR) and Complete Response (CR)); the levels of tumor markers Carcinoembryonic Antigen (CEA), CA 125 and CA19-9 prior to and following neoadjuvant therapy were compared. Comparing the perioperative parameters between the two treatment populations, including the amount of blood lost during surgery, the procedure's duration, the frequency of cases where a blood transfusion was necessary and the length of the postoperative hospital stay; the postoperative pathological conditions of the two groups were compared; R0 resection rate, number of resected lymph nodes, tumor diameter, T stage and degree of differentiation and comparing the incidence of adverse outcomes between the two groups. For statistical analysis, Statistical Package for the Social Sciences (SPSS) (v.6.0) statistical software was employed. The t-test was utilized to compare two groups of normally distributed measurement data expressed as x±s. Enumeration data were represented as the percentage of cases, and the Fisher test or Chi-square (χ^2) test was employed to compare groups. The statistically significant threshold was defined as a $p<0.05$. Imaging efficacy evaluation after neoadjuvant therapy showed that there were no patients with CR or PD, 13 cases (37.14 %) were evaluated as PR and 22 cases (62.86 %) were assessed as SD. Compared the changes of CEA, CA125 and CA19-9 index levels before and after treatment in the neoadjuvant therapy group, it was found that the serum CA19-9, after neoadjuvant therapy CA125 and CEA index levels showed a significant downward trend. The discrepancy was significant statistically ($p<0.0001$) as shown in Table 1. The type of procedure, length of the operation, intraoperative blood loss, number of patients needing blood transfusions and length of postoperative hospital stay did not significantly differ (all $p>0.05$) between the two groups as shown in Table 2. There was no discernible difference ($p>0.05$) in tumor differentiation or pathological T stage between both groups. In the neoadjuvant therapy group, the tumor diameter and the number of resected lymph nodes were considerably less than in the control group ($p<0.05$) and the R0 resection rate was significantly greater than in the control group ($p<0.05$, Table 3). In terms of postoperative complications, including abdominal infection, abdominal bleeding, puncture drainage and incision infection, the difference between both groups was insignificant statistically ($p<0.05$, Table 4). For

individuals with locally advanced pancreatic cancer and borderline resectable, domestic and foreign guidelines recommend neoadjuvant therapy to control or shrink tumors and micro metastases, reduce vascular invasion, increase R0 resection rate and reduce postoperative tumor recurrence and metastasis, thereby prolonging patient survival rate[9]. Compared with direct surgery, patients undergoing neoadjuvant chemotherapy can improve their preoperative physical strength and surgical tolerance through physical conditioning and tumor reduction during chemotherapy and may remove some potential patients with rapid tumor progression or minimal distant metastases may be excluded. According to a recent meta-study analysis, individuals who had neoadjuvant chemotherapy accompanied by surgical resection had a significantly longer survival rate than those who underwent surgery alone[10]. Neoadjuvant chemotherapy for pancreatic cancer can enhance the R0 resection rate of pancreatic cancer surgery, revolutionize the therapies for locally advanced pancreatic cancer and minimize postoperative complications with high significance in incidence and prolongation of long-term survival time, according to an increasing number of studies[11-13]. The current guidelines mostly recommend the AG regimen or the modified FOLFIRINOX regimen for the choice of neoadjuvant therapy. In this study, individuals in the neoadjuvant chemotherapy group received the modified FOLFIRINOX regimen. It has been proved that peripheral blood CA19-9, CA125 and CEA have high sensitivity and specificity and are commonly used clinical indicators for diagnosing and treating pancreatic cancer[14,15]. In recent years, the development of neoadjuvant therapy has triggered the exploration of CEA, CA125 and CA19-9 to evaluate the efficacy of neoadjuvant therapy. Ye *et al.*[16] showed that serum CA19-9 is of great value in determining the effect of neoadjuvant therapy in patients with pancreatic cancer and may be an appropriate prognostic indicator to guide treatment decisions. Kato *et al.*[17] found that serum CEA level >7.2 μg/l after neoadjuvant therapy in patients with locally advanced pancreatic cancer was the only independent risk factor for Overall Survival (OS). In neoadjuvant therapy, preoperative CA125<32.8 kU/l was associated with better progression-free survival and OS after treatment[18]. In the study by Marsh *et al.*[19], the curative effect of imaging evaluation after neoadjuvant therapy was 5 % CR and 14 % PR, the median tumor diameter decreased from 30 mm to 22 mm ($p<0.05$) and CA19-9 decreased from 68 U/ml decreased to 31 U/ml ($p<0.05$). The findings demonstrated no CR and PD cases after neoadjuvant therapy, 37.14 % PR and 62.86 % SD; after neoadjuvant therapy, CA19-9, CA125 and CEA showed a significant downward trend compared with before treatment, indicating that patients with pancreatic cancer underwent surgery. Neoadjuvant therapy can benefit to a certain extent. A phase I investigation assessing the acceptability and efficacy of neoadjuvant therapy in patients with resectable pancreatic cancer was discontinued early due to an unexpected rise in intraoperative complications[20]. This study compared the perioperative surgical indicators of patients with neoadjuvant therapy and those who underwent direct surgery. No statistically significant differences were found between both groups in terms of surgery type, operation time, intraoperative blood loss; number of intraoperative blood transfusion cases and postoperative hospital stay, indicating that radical resection of pancreatic cancer after neoadjuvant therapy is generally safe and does not increase the risk of complications. The tumor diameter and the number of lymph nodes removed were significantly lower in the neoadjuvant chemotherapy group than in the control group. The R0 resection rate was 100 %, substantially higher than that in the control group, demonstrating that neoadjuvant. In addition, we compared the postoperative pathological conditions of the two groups. The pathological advantage of the treatment group, neoadjuvant therapy can obtain a specific effect. According to thorough research, preoperative chemotherapy-induced peritumoral fibrosis may lessen the likelihood of postoperative pancreatic fistula. However, side effects from chemotherapy may impair the healing of postoperative incisions and raise the risk of postoperative abdominal infection[21]. Neoadjuvant therapy did not appear to have any limitations and had good safety.

TABLE 1: CHANGES OF SERUM CA19-9, CA125 AND CEA BEFORE AND AFTER NEOADJUVANT THERAPY

Variable	Pre-neoadjuvant therapy (n=35)	Post-neoadjuvant therapy (n=35)	t	p
CA19-9 (U/ml)	246.43±37.25	197.19±28.57	6.205	<0.0001
CA125 (U/ml)	65.28±13.45	40.52±10.16	8.690	<0.0001
CEA (ng/ml)	15.29±4.11	10.61±3.08	5.391	<0.0001

TABLE 2: COMPARES PERIOPERATIVE SURGICAL MARKERS BETWEEN THE TWO PATIENT POPULATIONS

Variable	Neoadjuvant therapy group (n=35)	Control group (n=35)	χ^2/t	p
Operation type (Laparoscopy/laparotomy) (n)	3 (8.57)/32 (91.43)	5 (14.29)/30 (85.71)	0.5645	0.7096
Operation time (min)	276.86±69.51	258.16±74.58	1.085	0.2817
Intraoperative blood loss (ml)	353.18±161.39	338.49±173.64	0.3666	0.7151
Number of cases requiring blood transfusion (n)	14 (40.00)	11 (31.43)	0.5600	0.6183
Postoperative hospital stay (d)	14.61±6.28	16.13±6.72	0.9777	0.3317

TABLE 3: POSTOPERATIVE PATHOLOGICAL CONDITIONS

Variable	Neoadjuvant therapy group (n=35)	Control group (n=35)	χ^2/t	p
Tumor diameter (mm)	29.12±13.08	35.81±14.26	2.045	0.0447
Differentiation (n %)			1.507	0.3261
Medium to advanced	24 (68.57)	19 (54.29)		
Low	11 (31.43)	16 (45.71)		
T stage (n %)			1.850	0.3965
T1	11 (31.43)	12 (34.29)		
T2	18 (51.43)	13 (37.14)		
T3	6 (17.14)	10 (28.57)		
Number of resected lymph nodes	10.57±4.06	13.32±5.49	2.383	0.0200
R0 resection rate (n %)	35 (100.00)	31 (88.57)	4.242	0.0394

TABLE 4: COMPARES THE TWO GROUPS INCIDENCE OF POSTOPERATIVE COMPLICATIONS

Complications	Neoadjuvant therapy group (n=35)	Control group (n=35)	χ^2	p
Postoperative abdominal infection (n %)	5 (14.29)	3 (8.57)	0.5645	0.4524
Postoperative abdominal bleeding (n %)	0 (0.00)	2 (5.71)	2.059	0.1513
Postoperative puncture drainage (n %)	3 (8.57)	4 (11.43)	0.1587	0.6903
Incision infection (n %)	1 (2.86)	2 (5.71)	0.3483	0.5551

This study's findings on the frequency and incidence of postoperative complications between the two groups were further revealed. In conclusion, preoperative neoadjuvant therapy can lower tumor marker levels and produce specific curative effects for individuals with borderline resectable pancreatic cancer while reducing surgery-related risks and boosting the R0 resection rate, which has good safety.

Author's contributions:

Xiaowei He and Yinyuan Zheng contributed equally to this work.

Conflict of interests:

The authors declared no conflict of interests.

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