Patterns of Local-regional Failures after Adjuvant Chemotherapy in Resected Pancreatic Cancer without adjuvant radiation therapy: Implication for Irradiation Volumes Design

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Research

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Abstract

In the present study, we aimed to assess the patterns of recurrence in pancreatic cancer patients, following surgical resection and adjuvant chemotherapy in the absence of adjuvant radiation, for optimal irradiation volumes design encompassing the majority of local recurrences. Isolated local regional recurrence (LRR) was defined as LR (local recurrence) and/or regional recurrence (RR) without distant metastasis (DM). The Fine and Gray competing risks regression analysis was performed to identify prognostic factors associated with isolated LRR. A total of 85 male and 29 female patients were included, 95 (83.3%) of the 114 patients had recurred. Most patients recurred at LRR (n=36, 37.9%), and isolated LR was seen in 23 patients (24.2%). The median time between the end of the treatment and initial recurrence was 9.8 months (2.2-71). Competing risks analysis demonstrated that surgery combined with vascular resection (HR 2.44, 95% CI: 1.40–4.27, $p=0.002$) and R1 resection status (HR 3.96, 95% CI: 2.23-7.02, $p<0.0001$) significantly increased the risk of developing isolated LRR. The most common site of specific LRR were observed in the lymph node regions (LN) No. 14p (30.5%), followed by pancreas or tumor bed (23.7%), LN No.16b1 (23.7%), celiac artery (22%), and superior mesenteric artery (22%). In conclusion, the risk of developing isolated LRR in patients with PDAC who underwent curative resection and adjuvant treatment remains high, especially for patients received surgery combined with vascular resection or R1 resection. Adjuvant radiotherapy for tumor bed/vessels and involved regional nodes including partially the region No.16 is recommended for this patient population.

Introduction

Although pancreatic ductal adenocarcinoma (PDAC) only accounts for 2.5% (458,918 newly diagnosed PDAC) of all new cancer cases worldwide in 2018, it is one of the most fatal malignancies, with a total of 432,242 patients died annually [1]. Surgical resection with negative margins (R0) is the only potentially curative treatment for PDAC, but only a minority of these patients (15–20%) are eligible for resection at the initial diagnosis. For patients after microscopically pathologically complete removal of tumor (R0), the vast majority of these patients would relapse within 2 years. CONKO-001 trials, the first phase III randomized trials investigating the effects of adjuvant gemcitabine chemotherapy in resected PDAC, demonstrated that the use of adjuvant gemcitabine for 6 months compared with observation alone resulted in increased overall survival as well as disease-free survival, which supporting the use of adjuvant chemotherapy in this settings [2, 3]. However, the CONKO-005 trial investigating the combination of chemotherapy and a targeted therapy in the adjuvant treatment of PDAC found that gemcitabine combined with erlotinib failed to improve disease-free survival (11.4 vs. 11.4 months) or overall survival (24.5 vs. 26.5 months) over gemcitabine alone, although there was a trend toward long-term survival in favor of combination therapy (5-year OS: 25% vs. 20%) [4]. While another ESPAC-4 trial found that the adjuvant combination of gemcitabine and capecitabine was superior to gemcitabine alone group (median OS, 28 versus 25.5, hazard ratio 0.82 [95% CI 0.68–0.98], $p=0.032$) [5]. Based on these high-quality clinical evidence, curative surgery resection in combination with adjuvant chemotherapy is regarded as the standard treatment regimen for resectable PDAC [6, 7]. However, the long-term survival of

this patient population remains poor, with 5-year overall survival of 25%. Clearly, more efficient treatments are still needed to optimizing adjuvant strategies in this settings.

In the ESPAC-4 trial[5], approximately 50% resected PDAC patients received adjuvant chemotherapy would develop local recurrence, which is the most common site of relapse. In addition, nearly 25% patients in CONKO-005 trial would develop isolated local recurrence. As a result, the addition of radiotherapy to adjuvant therapy in PDAC might reduce local recurrence and improve survival. Indeeds, several randomized clinical trials have been conducted to investigate the role of adjuvant chemoradiotherapy in PDAC patients, but the results is controversial [8–12]. One possible explanation for this finding is that there is no agreement on the definition of irradiation volumes and the irradiation strategies vary among these trials. In addition, there is no published studies to optimizing the irradiation volumes based on the recurrence patterns of PDAC patients. Therefore, we use the Fine and Gray competing risks regression analysis to clearly define the risk factors for LRR and optimize the irradiation volumes in resected PDAC after adjuvant chemotherapy.

Patients And Methods

We used an institutional pancreatic tumor registry to identify all patients who received adjuvant chemotherapy between January 2008 and December 2013. Pancreatoduodenectomy or distal pancreatectomy was performed according to the tumor location. The staging was established according to AJCC TNM classification, 7th edition. Adjuvant chemotherapy regimens were mainly based on gemcitabine (G), as following: (1g/m² d 1, 8 and 15 every 4 weeks) for 6 months. We excluded the patients who received less than 2 courses of adjuvant chemotherapy or those who received radiotherapy before. Clinical follow-up and enhanced computed tomography (CT) scan were performed every 2-3 months during adjuvant chemotherapy and after completion of therapy. Patients without evidence of recurrent disease in 2 years after surgical resection were evaluated every 6 months. The development of a new low-density mass was considered as tumor recurrence by scheduled CT scan. Recurrent lymph nodes were defined as short axis> 1cm, abnormal round morphology, heterogeneity, or central necrosis[13]. The recurrence were confirmed by PET-CT or multidisciplinary review if necessary. Tissue biopsy confirmation was rarely obtained. The present study procedures were approved by the Ethical Committee of Rui Jin Hospital affiliated medicine school of Shanghai Jiao Tong University, all subjects provided written informed consent.

Recurrence patterns were categorized as local, regional recurrence or distant metastasis(LR,RR,DM)[14]. LR was defined as recurrence in the region of tumor bed (including the remnant pancreatic) and involved local vessel (the superior mesenteric artery (SMA), celiac trunk (CT), portal vein (PV), inferior vena cava (IVC), etc. RR was defined as recurrence in lymph nodes within regional pancreatic lymph node drainage region and the retroperitoneal region. Lymph node station numbers was adopted by the Japan Pancreas Society (JPS) staging system to more accurately describe the location of lymph nodes[15, 16]. DM was defined as recurrence in the liver, lungs, omentum, or other distant organs (include ascites). The isolated LRR includes LR, RR, or simultaneous LR and RR without DM. Any DM included DM only. Whether or not

there is LR or RR. Only first sites and time of initial recurrence on imaging were documented. After the diagnosis of recurrence, the treatment was determined by the multidisciplinary team according to patient's performance status and disease progression level. Second-line systemic chemotherapy or chemo radiotherapy regimens were typically employed.

Statistical analysis

Overall survival (OS) was defined as the time from the date of surgery to death, censoring patients who were alive on the date of last follow-up. Progression-free survival (PFS) was measured from operation date to whichever the date of the first recurrence or of the last follow-up. Descriptive statistics were used to summarize the study data. Continuous variables were expressed as the median and range, and categorical variables as a number and percentage. We used the Kaplan-Meier method to analyze survival time and the Log-rank test to compare the isolated LRR and any DM group. Cox proportional hazard model is used to identify significant prognostic factors of PFS and isolated LRR. For any DM is a competing risk event which prevent isolated LRR from occurring and the Fine-Gray's model were used to further assess the effect of patient demographic, clinical, pathologic factors on isolated LRR. Statistical analyses were performed using IBM SPSS Statistics for Mac, version 23.0. (SPSS, Chicago, IL). Fine-Gray's model analysis is performed in R 3.4.3 using the crr package. Statistical significance established at $P < 0.05$, all statistical tests were 2-sided.

Results

Patients' outcome

Between January 2008 and February 2013, a total of 310 patients with pancreatic cancer received chemotherapy. After excluding patients without surgery ($n=119$) or without radical resection ($n=16$), other histology than adenocarcinoma ($n=18$), as well as those with intraoperative radiotherapy ($n=4$), and those receiving less than 2 courses of chemotherapy ($n=16$) or developing recurrence before adjuvant chemotherapy ($n=23$), we studied 114 patients with PDAC treated with curative surgery plus adjuvant chemotherapy considered eligible for investigating the patterns of the failure.

Recurrence Incidence

After a median follow-up of 42 months (range, 3-92.3), 95 of 114 patients (83.3%) developed recurrence. LR occurred in 23 patients (24.2%), RR in 20 (21.1%), DM in 16 (16.8%), LR with RR in 16 cases (16.8%), RR with DM in 12 patients (12.6%), LR with DM in 1 case (1.1%), LR and RR with DM in 7 patients (7.4%). Figure 1 showed the rate of isolated LRR and any DM per 6-month follow-up period after surgery . The incidence of isolated LRR and any DM was 31.6%, and 23.7% in the first year, 14% and 7% in the second year, 6.1% and 0.9% in the third year respectively.

Survival Analysis

The median time between the end of the treatment and initial recurrence was 9.8 months (range, 2.2-71). Of all 114 patients, median OS time was 30.8 months (95% confidence interval [CI] 26.8-34.9) and the median PFS was 11 months (95% CI 9-13)(figure 2a and 2b). In the LRR group, the OS was significantly longer (median OS, 31.5 months; 95% CI, 28.2-34.8) than in patients presented with DM (median OS, 14.6 months)($p<0.0001$). The 2-year and 5-year survival rate in isolated LRR group was 75.9% and 11.1% in comparison with DM group: 30.5% and 0%.

The median PFS in isolated LRR group was 10.2 months (95% CI, 8.8-11.7) significantly longer than in any DM group 7.1 months (95% CI, 4.6-9.6) ($p=0.019$). Actuarial 1-year and 2-year rates of PFS of patients with isolated LRR was 42.3% and 14.7%, as compared with 25.0% and 2.8% in patients with any DM. (Figure 2c and 2d)

Prognostic Factors for Isolated LRR and PFS

The univariable and multivariable analyses for risk factors for PFS and isolated LRR are shown in Table 1 and Table 2. Positive resection margins (HR 1.76, 95% CI: 1.26–3.63, $p=0.005$) and poor differentiation (HR 2.07, 95% CI: 1.31–3.28, $p=0.002$) were correlated with worse PFS. Adjuvant treatment courses more than 6 cycles was associated with improved PFS (HR 0.51, 95% CI: 0.33–0.80, $p=0.003$). The predictive factors of isolated LRR, obtained by Cox proportional hazard model univariate and multivariate analysis, was only R1 resection status (HR 3.86, 95% CI: 2.09-7.16, $p<0.0001$). Considering the competitive risk event, we adopted competing risk analysis to adjust the risk factor assessment. The analysis demonstrated that surgery combined with vascular resection (HR 2.44, 95% CI: 1.40–4.27, $p=0.002$) and R1 resection status (HR 3.96, 95% CI: 2.23-7.02, $p<0.0001$) increased risk of isolated LRR. Cumulative incidence curves for patients presented with or without vascular resection are statistically different for isolated LRR ($p=0.025$) and any DM ($p=0.021$), the cumulative incidence curves for resection status were not significantly different for any DM ($p=0.1$) but are highly significant for LRR ($p<0.0001$, figure 3).

Recurrence sites

In the 59 patients with only LRR, the major recurrent sites were No.14p lymph nodes(30.5%), remnant pancreas or tumor bed(23.7%), No.16b1 lymph nodes (23.7%),CA(22.0%), SMA(22.0%), and No. 9(20.3%),12p(15.3%),14d(13.6%) lymph nodes. In the any DM of patients also had some local- regional recurrence, mainly of No.16b1(33.3%), 12p(19.4%), 16a2(19.4%), 14p(16.7%),14d(16.7%) and No. 9(16.7%)lymph nodes, SMA(16.7%), CA(11.1%).For all patients with relapse, the susceptible involved sites are No.16b1(27.4%), 14p(25.3%) lymph nodes, SMA(20.0%), No. 9(18.9%), CA(17.9%), 12p(16.8%),remnant pancreas or tumor bed(15.8%), No.14d(14.7%), 16a2(10.5%) lymph nodes (Table 3.)

Discussion

Although adjuvant chemotherapy in resected PDAC patients can significantly improve overall survival in comparison with observation, the majority of these patients would eventually develop local recurrence with or without distant metastasis. Since not all PDAC patients recur in the same manner, understanding the

pattern, timing, and implications of recurrence is critical to the planning of adjuvant strategies. In addition, clinicopathologic risk factors for predicting failure patterns could potentially allow individualized and more effective adjuvant therapy strategies[17, 18]. However, to our best knowledge, there is no published studies to specially investigate the risk predictor factors for isolated LRR in PDCA patients by using competing risk regression model, and the patterns of local regional recurrence of lymph node are remains undetermined. As a result, we conduct the present study to clearly define the patterns of recurrence and identify the risk factors for isolated LRR, in order to optimize the irradiation volume and perform individualized treatments.

A total of 114 patients are included for analysis. In consistent with previously published data, 95 of 114 patients (83.3%) develop recurrence after a median follow-up of 42 months, and the isolated local recurrence is observed in 23 patients(24.2%). Previously published data also demonstrated that the prognosis of patients with local recurrence is better than that of distant metastasis [19–21]. In the present study, we also found that the interval of patients developing isolated LRR is significantly longer than those recurred with any DM after the adjuvant chemotherapy. This may be explained for this finding is that micro-metastasis might exist before the surgical resection of primary tumor [22–24]. As a result, local treatment options such as re-resection and radiotherapy could be considered to for those isolated LRR patients to improve the survival.

Adjuvant chemotherapy can also improve the local control rate[25, 26]. However, with the completion of the chemotherapy, it is hypothesized that the local-regional problem will emerge as the main challenge. In consistent with this hypothesis, our study demonstrates that the incidence of isolated LRR is significantly higher than that of DM after completion of adjuvant chemotherapy. Although most patients with PDAC would die from distant metastases, the mortality after local recurrence is still 20%. And the natural evolution is the development of hepatic metastases after the local recurrence[27]. Therefore, the avoiding of the LRR becoming a secondary source of DM, it may be an important reason for application radiochemotherapy following adjuvant chemotherapy after curative surgery.

In order to reduce post-operative recurrence, increasingly radical surgery with extended lymph node dissection and combined with vascular resection has been explored but the efficacy is debated [28–31]. The combination with vascular resection improved the prognosis of patients in comparison with not resected tumors [32, 33]. This surgery is associated with higher probability of positive surgical margins [34–36]. Furthermore, tumor involving arterial structures (especially T4 tumor) recur rapidly, even after an apparent R0 resection[36]. In our series, the vascular resection is associated with a higher risk of isolated LRR as previously reported in the literature [37, 38]. However, this phenomenon is masked by the decline of distant metastasis rate after vascular resection when analyzed by the cox regression model. There are two types of vascular involvement after vascular resection: neoplastic vessel invasion on histopathology and inflammatory adhesion[35]. Mierke et. al. reported that patients who had inflammatory adhesion has a lower distant metastasis rate than those who had tumor infiltration and those without vascular resection[39]. Thus, the involvement of peripancreatic vessels seems to be an indicator of unfavorable

tumor topography [40]. One of the limitations of our retrospective study is that it can not provide the proportion of inflammatory adhesion in those patients with vascular resection.

Positive surgical margin (R1 resection) is a major adverse prognostic factor of disease-free survival(DFS) for resectable PDAC[27, 41, 42] though lack of consensus on definition of margin status[43]. The definition of positive margin in our institution is the directed involvement of tumor at any of the edges of the resection specimen. In our study, R1 resection rate was about 20% and R1 status was a significant predictor of isolated LRR but not significantly increase rates of any DM in PDAC patients after received adjuvant chemotherapy. Systemic chemotherapy was still effective for decreasing recurrence in R1 patients, with small benefit as previously reported [44]. Our study shows that after chemotherapy, local-regional problems become the focus of attention in patients with R1 resection. Therefore the idea of this work is that the loco regional radiotherapy with careful volume definition and delineation after attentive analysis of the patterns could be alternative for this population of patients. We have shown that the remnant pancreas or tumor bed was the common site of recurrence (23.7%) and it must be included in the target volume of irradiation. Miyazaki et al. reported 13/67(19%) patients with isolated local recurrence in the remnant pancreas[45]. Of the many major vessels near the pancreas, the most likely to relapse is the SMA and the CA. This occurs not only due to their features easy to directly involved from the primary tumor but also the practical difficulties for surgical clearance, and radiation oncologists have attached vital importance to them from the era of two dimensional radiotherapy treatment to modern radiotherapy[46–48].

So far, several studies optimizing the adjuvant radiotherapy field for pancreatic cancer have been published [47–49]. However, these studies generally use the Cox regression model to identify the risk factors for LRR. In the present study, we use the competing risks regression model to define the risk factors and comprehensively investigate the recurrence patterns of regional lymph nodes. We believe that the understanding based on vascular anatomy may make easier to delineate, however, for the analysis of lymph node metastasis, there is a lack of uniformity. Thus, we used JPS stage system to study the recurrence of the peritoneal lymph nodes, and we find that nodal metastasis is commonly involved in No.14p, No.16b1, No. 9 and No. 12p. The outcome is consistent with the pathological results after surgery[50], besides the lymph nodes around the pancreas, the regional lymph nodes are mainly involved in group No.9, No.12 group, No.14 group. Furthermore, para-aortic lymph node (No.16) metastasis, regarded as distant metastasis rather than regional lymph node and classified as pM1 stage, is found in 37 of 114 patients (32.4%) after adjuvant chemotherapy, which approximately involved 14–18% at the time of resection[51–54]. No.16 is classified into four groups according to JPS system (16a1, 16a2, 16b1, 16b2). In the present study, No.16b1 is frequently involved (27.4% of all recurrences). Especially, in any DM group, No.16b1 is involved more frequently with the recurrence of tumor bed apparently decreased (2.8%) compared to the isolated group. A recent meta-analysis also confirmed that the status of lymph node para-aortic (No.16) metastases had a significant prognostic value[53]. Our study suggests that the optimal radiotherapy volume may include not only the tumor bed and vessels but also involved regional nodes including partially the region No.16 (Figure. 4).

The findings of present study should be interpreted with some caution due to the following limitations: (1) first of all, our study is a single institute retrospective studies, and selection bias is unavoidable, the true impact of adjuvant chemotherapy on recurrence patterns of pancreatic cancer could be underestimated in this study; (2) secondly, the sample size for our study might be relatively small to evaluate all patterns of recurrences, although the median follow-up time is longer than three years. The strength of this study is that we only include resectable pancreatic cancer received with adjuvant chemotherapy, and patients, who initially diagnosed with “borderline resectable” pancreatic cancer and received neoadjuvant therapy, are excluded for analysis, while this patient cohort is generally included for analysis in several published studies [11, 33–36], as a result, the clinical heterogeneities of the present is relative small than previous publication.

Conclusion

In conclusion, the risk of developing isolated LRR in patients with PDAC who underwent curative resection and adjuvant treatment remains high, especially for patients received surgery combined with vascular resection or R1 resection. Adjuvant radiotherapy for tumor bed/vessels and involved regional nodes including partially the region No.16 is recommended for this patient population.

Abbreviations

LRR, local regional recurrence; RR, regional recurrence; DM, distant metastasis; LR, local recurrence; LN, lymph node; PDAC, pancreatic ductal adenocarcinoma; G, gemcitabine; CT, computed tomography; SMA, superior mesenteric artery; CT, celiac trunk; PV, portal vein, IVC, inferior vena cava; OS, Overall survival; PFS, Progression-free survival;

Declarations

Ethics approval and consent to participate

The present study procedures were approved by the Ethical Committee of Rui Jin Hospital affiliated medicine school of Shanghai Jiao Tong University. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants included in the study.

Consent for publication

Not applicable.

Availability of supporting data

All data included in this study are available upon request by contact with the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' information

Conceived and designed the experiments: Jiayi Chen. Performed the experiments: Shengguang Zhao and Wei-xiang Qi. Analyzed the data: Shengguang Zhao. Contributed reagents/materials/analysis tools: Wei-Xiang Qi. Wrote the paper: Jiayi Chen and Youlia Kirova.

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Tables

Due to technical limitations, Tables 1-3 are only available as a download in the supplemental files section

Figures

Figure 1

Rate of isolated LRR and any DM per 6-month follow-up period after surgery

Figure 2

Overall and progression-free survival of patients with PDAC after adjuvant chemotherapy. (a) Overall survival of all patients (n = 114). (b) Progression-free survival of all patients (n=114). (c) Overall survival of patients with recurrence (n=95) separated into isolated LRR (n=59) and any DM (n = 36) subgroups according to recurrence status. (d) Progression-free survival isolated LRR (n=59) compared with any DM (n = 36).

Figure 3

Predicted cumulative incidence curves of isolated LRR and any DM for resection margin status, and whether combined vascular resection

Figure 4

Suggestion of the optimal irradiation volumes design

Supplementary Files

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