Feasibility of pancreaticoduodenectomy with synchronous liver metastasectomy for oligometastatic pancreatic ductal adenocarcinoma - A case-control study

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\textbf{ABSTRACT}

\textbf{Background:} Resection of pancreatic ductal adenocarcinoma (PDAC) with synchronous liver metastasectomy is still a matter of debate. We aimed to evaluate the feasibility of synchronous resection of PDAC and liver metastases for curative intent at a high-volume surgical center.

\textbf{Methods:} Patients who underwent pancreaticoduodenectomy (PD) with synchronous liver metastasectomy (M1 resection group, n=50) were matched 1:1 based on tumor and nodular stage, age, gender, body mass index and concomitant disease with two control groups (M0 resection and M1 no resection). The M0 resection group included patients who underwent PD without metastases. The M1 no resection group included patients with liver metastases who underwent palliative bypass or exploratory laparotomy without resection followed by palliative and adjuvant therapies.

\textbf{Results:} M1 resection group had a longer operation time, larger intraoperative blood loss, and longer postoperative hospital stay than other two groups. R0 resection rate of M1 resection group was similar to that of M0 resection group (92% vs. 94%, p=1.000). Postoperative complications were comparable between the groups. The overall median survival in M1 resection, M0 resection, and M1 no resection group was 16, 30, and 6 months, respectively. Cumulative survival rates for 1-, 2-, and 3-year of the M1 resection, M0 resection, and M1 no resection group were 63.8%, 29.0%, and 6.7%; 94.0%, 74.4%, and 25.1%; 24.0%, 2.0%, and 0%, respectively. The survival of M1 resection group was worse than that of M0 resection group (p=0.009), however significantly much better than that of M1 no resection group (p=0.001). Univariate analysis showed carcinoembryonic antigen >8 ng/ml and non-R0 resection were associated with death. Multivariate analysis revealed that M1 resection group had improved survival compared with M1 no resection group.

\textbf{Conclusions:} PD with synchronous liver metastasectomy for oligometastatic PDAC is safe and feasible, it might provide survival benefits for selected patients.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignant tumors with a poor prognosis [1]. Surgery remains the best hope for cure, which may provide a long-term survival opportunity for patients. However, about half of the patients have distant metastases at the time of diagnosis, which is generally considered unsuitable for curative resection [2]. At present, systemic chemotherapy is the standard treatment for M1 patients [2,3]. Nevertheless, progress in surgical safety has led to the consideration of more aggressive surgical methods.

Resection of PDAC with synchronous metastasectomy continues to be attempted, among which liver metastasectomy accounts for the largest proportion [4], but leading to highly controversial results. Many studies showed no survival benefits from surgical resection to PDAC and synchronous liver metastases [5,6]. However, more recent studies suggested that primary tumor resection with liver metastasectomy following effective systemic chemotherapy could prolong survival for some of these patients, and might be considered in carefully selected patients [7–10]. Whereas, due to the small amount of examined cases and the heterogeneity of retrospective analyses, it is still difficult to derive objective recommendations. Herein, we aim to reevaluate the
feasibility of synchronous resection of PDAC and liver metastases for curative intent at a high-volume surgical center.

2. Materials and methods

2.1. Patients

Patients with PDAC who were treated by pancreaticoduodenectomy (PD) between June 2009 and November 2018, were candidates for study inclusion. Patients were included if they underwent curative-intent PD with liver metastasectomy (wedge resection, segmentectomy, or hemihepatectomy) regardless of whether they had undergone neoadjuvant chemotherapy or not. Patients with extrahepatic metastases, cholangiocarcinoma, neuroendocrine tumors, periampullary cancer, or other primary cancer history were excluded. The local Research Ethics Committee approved the study protocol.

2.2. Therapeutic strategy

Preoperative contrast-enhanced computed tomography and magnetic resonance imaging were used as baseline assessment for staging and tumor resectability in all patients. Tumor resectability criteria was adopted according to NCCN guidelines in our center [2]. We performed endoscopic or percutaneous ultrasound guided biopsy for histological diagnosis in those distant metastases detected. Treatment strategies and surgical indications were decided in a multi-disciplinary treatment (MDT) meeting for each patient. FOLFIRINOX or gemcitabine-based chemotherapy was regarded as the first-line therapeutic option for most M1 patients. Upon effective neoadjuvant chemotherapy, primary tumor resection with synchronous liver metastasectomy was proposed based on a MDT review. Preoperative biopsy was not routinely performed in patients with resectable disease. For preoperatively assessed M0 patients, if intraoperatively found liver metastasis, resection still proceeded in some oligometastatic cases (≤3 metastatic tumors total in liver) followed by postoperative adjuvant chemotherapy.

2.3. Study design

A retrospective, case–control study was conducted at a high-volume hepatobiliary and pancreatic surgical center. Patients with hepatic oligometastatic PDAC who underwent PD and synchronous liver metastasectomy (M1 resection group) were compared with two control groups (M0 resection and M1 no resection). Cases of M1 resection group were matched at a 1:1 ratio based on primary tumor and nodal stage, age, gender, body mass index and concomitant disease with two control groups (Table 1, Table 2). The M0 resection control group included patients who underwent PD without metastases. The M1 no resection control group included patients with liver metastases who underwent palliative gastroenterostomy, or choledochojunostomy, or both, or just abdominal exploration without tumor resection, followed by definitive palliative chemotherapy and other adjuvant therapies. Management decisions of all patients were discussed at a MDT meeting. Blood test, operative details, postoperative complications, and prognosis records were compared between groups. All patients underwent physical examination, laboratory tests and image examinations for follow-up at 1, 3 and then at 3-month intervals post discharge. Special personnel were responsible for a 3-month regular telephone follow-up. All subsequent treatments, quality of life and survival time of the patients were investigated and recorded. The date of last follow-up was November 2019. This work has been registered at http://www.researchregistry.com (unique identifying number: researchregistry5665).

2.4. Statistical analysis

Data were analyzed using SPSS 22.0 (IBM, Armonk, NY, USA). Quantitative variables were presented as median and range, and compared by Student’s t-test or Wilcoxon’s test followed by Mann-Whitney U test according to data distribution. Discrete categorical variables were expressed as number and percentage, and analyzed by chi-square test or Fisher exact test, as applicable. Survival were calculated from the date of diagnosis to the time of death or last follow-up. The survival of patients were analyzed by Kaplan-Meier method, and survival curves between groups were assessed using log-rank test. The risk factors associated with survival were determined by univariate and multivariate analysis using Cox regression. A two-tailed p-value <0.05

Table 1
Baseline demographics and clinicopathologic characteristics.

| Characteristics | M1 resection | M0 resection | M1 no resection | p-Value | p-Value |
|-----------------|--------------|--------------|-----------------|---------|---------|
|                  |              |              |                 |         |         |
| Male, n (%)      | 39 (60)      | 28 (56)      | 37 (74)         | 0.685   | 0.137   |
| Age (years), median (range) | 63 (40–81) | 63 (41–79) | 63 (47–81) | 1.000 | 0.984   |
| BMI, median (range) | 20.80       | 21.36        | 20.69           | 0.506   | 0.927   |
| CA 19-9 at diagnosis, U/ml, median (range) | 1451 (2–12000) | 1549 (24–11876) | 2912 (2–12000) | 0.859 | 0.157   |
| CEA at diagnosis, ng/ml, median (range) | 8.6 (1.3–117.9) | 5.5 (1.1–48.1) | 6.2 (1.6–23.8) | 0.409 | 0.448   |
| Resectable, n (%) | 43 (86)      | 46 (92)      | NA              | 0.525   | NA      |
| Borderline resectable | 7 (14) | 4 (8) | NA | NA       |
| Tumor differentiation, n (%) | 36 (72) | 33 (66) | NA | NA      |
| Poor | 14 (28) | 17 (34) | NA | NA |
| Moderate-well | 3.6 (1.5–9.5) | 3.5 (1.1–8.5) | 3.1 (1.2–14.0) | 0.893 | 0.175 |
| Nodal status, n (%) | 34 (68) | 34 (68) | 33 (66) | 1.000 | 0.852   |
| R0 resection, n (%) | 46 (92) | 47 (94) | NA | 1.000 | NA     |

BMI, body mass index; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; NA, not applicable.
Similar to that of M0 resection group (92% vs. 94%, p = 0.009). Multivariate analysis showed that M1 no resection group increased the risk of death compared with the M1 resection group (p = 0.001; Fig. 1, Table 3). Further, univariate analysis showed that carcinoembryonic antigen (CEA) > 8 ng/ml and non-R0 resection were positively associated with death (Table 3). Multivariate Cox regression revealed that M1 no resection group increased the risk of death compared with the M1 resection group (4.091 [95% CI, 2.410–6.943], p = 0.001), while M0 resection group decreased the risk of death compared with the M1 resection group (0.271 [95% CI, 0.092–0.814], p = 0.010).

### 3. Results

A total of 702 patients underwent PD for PDAC in our center during this period. 88 cases combined with metastasectomy, among which 50 cases were PD with synchronous liver metastasectomy (M1 resection group), matched for certain criteria with 50 cases in the M0 resection group, and 50 in the M1 no resection group. Baseline demographics and clinicopathologic variables were comparable between the groups (Table 1). In the M1 resection group, the liver metastases surgery consisted of hepatic resection for 45 (90%) patient and hepatic resection plus radiofrequency ablation (RFA) for 5 (10%; Table 2).

### 3.1. Surgical risks

M1 resection group had a longer operation time than M0 resection group (430 vs. 388 min, p = 0.046) and M1 no resection group (430 vs. 174 min, p = 0.000), and had a larger intraoperative blood loss than other two groups (Table 2). R0 resection rate of M1 resection group was similar to that of M0 resection group (92% vs. 94%, p = 1.000). Postoperative complications were comparable between the groups, except for differences in postoperative pancreatic fistula (M1 resection vs. no resection, p = 0.016; Table 2). Moreover, postoperative hospital stay of M1 resection group was longer than that of M0 resection group (21 vs. 18 days, p = 0.047) and M1 no resection group (21 vs. 13 days, p = 0.000).

### 3.2. Adjuvant/palliative therapies

41 (82%) patients received adjuvant treatment in M1 resection group, the other 9 (18%) patients who were misconceived as M0 preoperatively, whereas liver metastasis detected during the abdominal exploration, still underwent PD with synchronous liver metastasectomy as the tumor resectability was good. While only 4 (8%) received neo-adjuvant treatment in the M0 resection group. All the M1 patients received adjuvant/palliative chemotherapy, apart from poor general condition of 3 and 4 patients in resection group and no resection group respectively. The adjuvant/palliative therapies of three groups were listed in Table 2.
body/tail showed no benefit between the comparison (14 vs. 15 months, p = 0.486) [16]. However, another study by Yang J et al. showed that 23 patients with PDAC and liver metastases resection had a median survival of 11.4 months, suggesting surgery for liver metastases is not feasible for most patients [5]. Shrikhande SV et al. reported that 11 M1 PDAC patients who underwent pancreatic resection with liver resection achieved patients with baselined CEA ≤ 8 ng/ml; 3. primary PDAC with achievable metastasis: 1. liver oligometastases with good resectability excluding extrahepatic metastasis [7-15]; 2. good response to neoadjuvant chemotherapy [8-10], especially the reduction of carbohydrate antigen 19-9 is more than 50% from the baseline value [8], and baselined CEA no more than 8 ng/ml; 3. primary PDAC with achievable R0 resection [8,10,12,15]; 4. good performance status for surgery. In this study, although we enrolled 9 patients who underwent surgical resection without neoadjuvant chemotherapy, it should not be encouraged because it might increase the associated potential risk.

Our study still has many limitations. Although we strived to minimize the selection biases by carefully case matching for tumor stage, nodular stage, age, gender, BMI and comorbid disease, the intrinsic drawbacks of retrospective study objectively existed. Moreover, metastatic volume and metastatic burden might be different between M1 resection group and M1 no resection group, which might lead to the survival difference. Another limitation of this study is that the chemotherapy regimens and durations were not included in the analysis.

Due to the limitations of the research type and the heterogeneity of the existing evidence, whether aggressive surgery is beneficial is still a matter of debate. And the current data cannot draw a definite final conclusion. Thus, a prospective multicenter, randomized, controlled phase III trial (Clinical Trials.gov identifier: NCT03398291) activated by the Chinese Study Group for Pancreatic Cancer (CSPAC), called CSPAC-1, is currently under way [16].

5. Conclusions
PD with synchronous liver metastasectomy for oligometastatic PDAC is safe and feasible, it might provide survival benefits, especially in R0 resection achieved patients with baselined CEA ≤ 8 ng/ml, combined with effective neoadjuvant chemotherapy.

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Ethical approval
The Research Ethics Committee of the First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang Province, China approved this study. And the reference number is 2019-1496.
Consent
The patients have provided permission to publish the features of their cases. Written informed consents were acquired and the identities of the patients have been protected.

Author contribution
Yi Shao and Jiaojiao Feng analyzed the data and wrote the manuscript. Zhenhua Hu and Shusen Zheng designed the study, commented on and revised the manuscript. Yi Shao, Zhenhua Hu, Jian Wu, Min Zhang, Yan Shen and Shusen Zheng built the patient database. All authors read and approved the final manuscript.

Registration of research studies
Registry used: Research registry.
Name of the registry: Feasibility of pancreaticoduodenectomy with synchronous liver metastasectomy for oligometastatic pancreatic ductal adenocarcinoma - a case-control study.
Unique Identifying number or registration ID: researchregistry5665.
Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#home/registrationdetails/5ed5b57e1fcac40016edb9ef/

Guarantor
Yi Shao; Shusen Zheng.

Declaration of competing interest
The authors declare no conflict of interest.

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