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

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ABSTRACT

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.

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.

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.

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 metastasis 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

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List of abbreviations

PDAC	pancreatic ductal adenocarcinoma
PD	pancreaticoduodenectomy
MDT	multi-disciplinary treatment
RFA	radiofrequency ablation
CI	confidence interval
CEA	carcinoembryonic antigen
CSPAC	Chinese Study Group for Pancreatic Cancer

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 ($\leq$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 nodular 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 choledochojejunostomy, 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 reseciton	p-Value M1 resection vs. M0 resection	p-Value M1 resection vs. M1 no resection
Male, n (%)	30 (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 (17.48–25.48)	21.36 (16.65–26.08)	20.69 (17.58–26.35)	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
Tumor resectability, n (%)				0.525	NA
Resectable	43 (86)	46 (92)	NA		
Borderline resectable	7 (14)	4 (8)	NA		
Tumor differentiation, n (%)				0.517	NA
Poor	36 (72)	33 (66)	NA		
Moderate-well	14 (28)	17 (34)	NA		
Tumor size, cm, median (range)	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 (%)				1.000	0.832
N1	34 (68)	34 (68)	33 (66)		
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.

Table 2
Operative details, postoperative complications and adjuvant therapies for three groups.

Characteristics	M1 resection	M0 resection	M1 no reseciton	p-Value M1 resection vs. M0 resection	p-Value M1 resection vs. M1 no resection
Operative details					
Operation time,min, median (range)	430 (185–640)	388 (199–562)	174 (50–434)	0.046	0.000
Blood loss, ml, median (range)	500 (100–1500)	380 (100–1500)	150 (20–500)	0.038	0.000
Intraoperative transfusion, n (%)	8 (16)	9 (18)	0 (0)	0.790	0.006
Postoperative complications, n (%)					
Pancreatic fistula	9 (18)	7 (14)	1 (2)	0.585	0.016
Bleed	4 (8)	2 (4)	3 (6)	0.678	1.000
Delayed gastric emptying	6 (12)	5 (10)	2 (4)	1.000	0.269
Abdominal infection	5 (10)	3 (6)	1 (2)	0.715	0.204
Unplanned relaparotomy	1 (2)	1 (2)	0 (0)	1.000	1.000
Postoperative hospital stay, day, median (range)	21 (11–38)	18 (8–35)	13 (4–28)	0.047	0.000
Neoadjuvant chemotherapy (%)	41 (82)	4 (8)	NA	0.000	NA
Metastatic disease treatment, n (%)				NA	NA
Hepatic resection only	45 (90)	NA	NA		
Hepatic resection and RFA	5 (10)	NA	NA		
Adjuvant/palliative therapy, n (%)				0.007	0.467
None	3 (6)	14 (28)	4 (8)		
Adjuvant chemotherapy alone, n(%)	38 (76)	23 (46)	31 (62)		
Chemotherapy and RFA, n(%)	5 (10)	8 (16)	7 (14)		
Chemotherapy and RT, n(%)	4 (8)	5 (10)	8 (16)		

RFA, radiofrequency ablation; RT, radiotherapy; NA, not applicable.

was defined as statistical significance. The work has been reported in line with the STROCSS criteria [11].

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 Mo 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 neoadjuvant treatment in M1 resection group, the other 9 (18%) patients who were misconsidered 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 neoadjuvant 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.

3.3. Survival analysis

The overall median survival in M1 resection, M0 resection, and M1 no resection group was 16 months (95% confidence interval [CI], 14.7–17.3), 30 months (95% CI, 28.7–31.3), and 6 months (95% CI, 4.7–7.3), respectively (Fig. 1). Cumulative survival rates for 1-, 2-, and 3-year of the M1 resection group were 63.8%, 29.0%, and 6.7%, respectively; those of M0 resection group were 94.0%, 74.4%, and 25.1%, respectively; and in the M1 no resection group those were 24.0%, 2.0%, and 0%, respectively (Fig. 1). The long-term prognosis 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; 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,

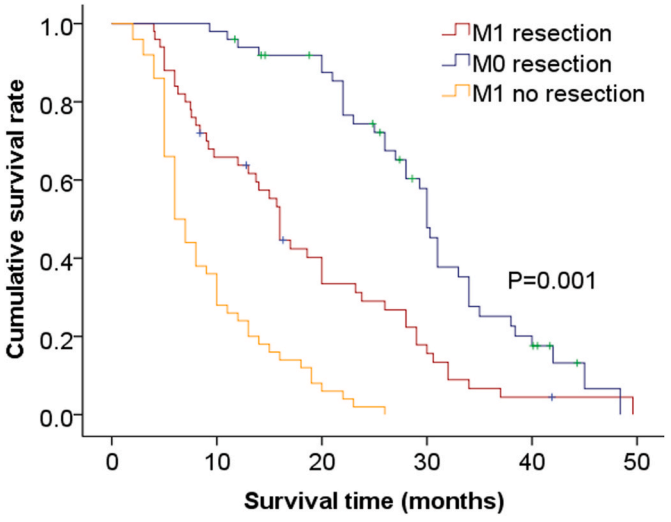

Fig. 1. Comparison of survival curves in the three groups by Kaplan-Meier method. M1 resection vs. M0 resection, p = 0.009; M1 resection vs. M1 no resection, p = 0.001; M0 resection vs. M1 no resection, p = 0.000.

Table 3
Univariate and multivariate Cox regression analysis for predictors of death.

Variables	Univariate HR (95%CI)	p-Value	Multivariate HR (95%CI)	p-Value
Gender (ref = female)	1.370 (0.949–1.977)	0.093		
Age (ref = ≤65 years)	0.881 (0.624–1.246)	0.474		
CEA (ref = ≤8 ng/ml)	1.718 (1.062–2.779)	0.027	0.851 (0.395–1.832)	0.680
CA 19-9 (ref = ≤300 U/ml)	1.190 (0.828–1.709)	0.348		
Lymph node metastasis (ref = N0)	1.147 (0.791–1.664)	0.470		
Non-R0 resection (ref = R0)	4.666 (2.059–10.577)	0.001	6.425 (2.049–20.150)	0.001
M0 resection (ref = M1 resection)	0.404 (0.260–0.626)	0.009	0.271 (0.151–0.486)	0.001
M1 no resection (ref = M1 resection)	3.619 (2.305–5.681)	0.001	4.091 (2.410–6.943)	0.000

HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9.

0.151–0.486], p = 0.009; Table 3).

4. Discussion

In spite of extensive research, PDAC remains a refractory cancer associated with poor prognosis [1]. For M1 patients with good performance status, palliative chemotherapy is the only routinely suggested treatment [2,3]. Due to the advances in surgical safety, aggressive surgeries for these patients are under persistently trying [4]. However, the benefit of surgery in such cases is still highly controversial. Shrikhande SV et al. reported that 11 M1 PDAC patients who underwent pancreatic resection with liver resection had a median survival of 11.4 months, although safe in selected patients, this approach cannot be generally recommended [5]. Zanini N et al. reported that the median overall survival after synchronous liver metastasectomy of 11 M1 PDAC patients was 8.3 months, suggesting surgery for liver metastases is not feasible for most patients [6]. Whereas, a large cohort study by Hackert T et al. showed that 85 patients with PDAC and liver metastases resection had a better median overall survival than exploration, resulting in a 5-year survival of 8.1%, concluding that this surgery might be superior to palliative treatment [12]. Further, a meta-analysis included 11 cohort studies with 1147 patients revealed that compared with non-surgical treatment (n = 930), hepatic resection (n = 217) was worth doing due to additional survival benefit (with a median survival of 9.9 months vs. 7.5 months) [13]. Moreover, a retrospective analysis of 6 European pancreas centers, involving 69 patients with PDAC and liver metastasis simultaneous resections, demonstrated that PDAC localized in the pancreatic head had a longer median overall survival than exploration (13.6 vs. 7 months, p < 0.001), while PDAC localized in the pancreatic body/tail showed no benefit between the comparison (14 vs. 15 months, p = 0.312) [14]. However, another study by Yang J et al. showed that 23 patients with body/tail PDAC and liver oligometastases synchronous resection had a better overall survival than systemic chemotherapy and palliative patients (16.1 vs. 7.6 months, p = 0.02; 16.1 vs. 4.3 months, p < 0.001; respectively) [15]. Besides, many case reports and small case series showed in highly selected M1 PDAC patients, after effective neoadjuvant chemotherapy, R0 resection combined multimodality treatment (adjuvant chemotherapy, radiotherapy, RFA, etc.) might provide long-term disease control and improve survival [7–10].

Our data showed that although M1 resection group prolonged operation time, enlarged blood loss and delayed postoperative hospital stay, postoperative complications were comparable among the groups, suggesting the safety of such procedure. The median overall survival of M1 resection group was much better than that of M1 no resection group (16 vs. 6 months, p = 0.001), and cumulative survival rates for 1-, 2-, and 3-year of the M1 resection group were much higher than that of M1 no resection group (63.8%, 29.0%, 6.7% vs. 24.0%, 2.0%, 0%; respectively; p = 0.001). Our results supported the survival benefits of synchronous resection in selected patients with liver oligometastatic PDAC, treated at a high-volume pancreatic cancer center. And we argued that surgery cannot be performed as an isolated treatment alone, but should be treated as an important part of the whole comprehensive multimodality treatments. We also recommended that all the management decisions should be made based on a MDT meeting.

Now, there is a question: who are these selected? Unfortunately, due to the lack of high-quality data and evidence support, there are no uniform standard criteria for patient selection. According to our experiences and literature reports, we consider that the appropriate criteria should include: 1. liver oligometastases with good resectability excluding extrahepatic metastasis [7,12–15]; 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 concomitant 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.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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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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