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Long-term Outcomes after Laparoscopic Distal Pancreatectomy for Renal Cell Carcinoma Metastasis in the Pancreas: A Single-Center Experience

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Abstract

Background: The aim of this study was to foster evidence, favoring laparoscopic distal pancreatectomy as a safe, patient friendly procedure, significantly prolonging survival in patients with metastases from renal cell carcinoma (RCC) to the pancreas.

Laparoscopic distal pancreatectomy (LDP) is becoming a standard of care for lesions in the body and tail of the pancreas. Yet its role in the treatment of renal cell carcinoma (RCC) metastases to the pancreas remains unclear.

Methods: From May 2002 to November 2021, perioperative and long-term oncological outcomes were recorded prospectively in 21 patients undergoing distal pancreatectomy resection for RCC metastases at Oslo University Hospital.

Results: In 21 resections, 17 (81 %) were performed laparoscopically, four by open surgical technique. Median follow-up was 59(19-136) months. Recurrence was detected in 12 (57.1%). Median recurrence-free survival was 51 months, while 3- and 5-year recurrence-free were 58.3 and 38.9 %, respectively. Overall survival at 3 and 5 years were 89.7 % and 72.1%, respectively. No significant differences were observed between the patients undergoing laparoscopic and open surgery.

Conclusion: Distal pancreatectomy for pancreatic metastases from RCC is associated with acceptable oncologic outcomes. LDP is a feasible and safe alternative to open approach. Careful selection in a multidisciplinary setting remains crucial.

INTRODUCTION

The pancreas is not a common site for metastasis, but renal cell carcinoma (RCC), which exhibits a capacity to spread to any part of the body (1), has a predilection to metastasize to the pancreas. RCC is the primary tumor of origin in approximately 55% of all metastases to the pancreas which are resected (2). Metastasis to the pancreas has a unique biology compared with other RCC metastatic sites, with more favorable survival after surgical resection. In 25 cases, operated in Copenhagen (3), five-year overall survival (OS) was 83.6%, disease free survival (DFS) 32.2% respectively. An article from Bordeaux reported five-year OS 92.8%, DFS 29.6% respectively, in altogether 42 resected patients (4). In this report, 19 (45.2%) lesions in the pancreas were multiple, and total pancreatectomy was performed in 18 cases. Despite favorable survival data after surgical resection, there is no consensus concerning resection versus targeted therapy, for example in the form of tyrosine kinase inhibitors(5).

Laparoscopic distal pancreatectomy (LDP) is becoming a standard of care in patients with lesions in the body and tail of the pancreas. Randomized trials have shown that LDP is associated with reduced blood loss, shorter hospital stay, faster recovery and better quality of life after surgery (6–8). At the same time, its role in the treatment of RCC is little studied.

The purpose of the present paper is to explore surgical outcomes and oncologic safety of LDP in patients with RCC.

METHODS

Study Population and Data collection

This is a single-center study including patients operated from May 2002 to November 2021 with distal pancreatectomy (DP) for metastasis to the pancreas from RCC.

All patients undergoing pancreatic surgery due to metastasis from RCC were prospectively recorded in a database at the Intervention Center, Oslo university hospital, after signature of informed consent. Number of metastases and location in the pancreas were recorded together with perioperative and long-term oncological outcome. Survival data was collected from the Norwegian National Population Registry. The study was approved by the hospital review board according to the guidelines provided by the Regional Ethics Committee.

Definitions

Extended pancreatectomy and multivisceral resections are defined in accordance with the criteria from the International Study Group for Pancreatic Surgery (ISGPS) (9), postoperative morbidity classified according to Clavien and Dindo(10). Grade ≥ 3 complications were considered severe. Postoperative pancreatic fistula was reported according to the 2016 update from the ISGPS (11). Mortality and readmission is reported in line with the “90 days from surgery” definition (12). Conversion was defined as laparotomy during LDP not related to specimen extraction.

Treatment

All patients were reviewed at a weekly multidisciplinary conference, attended by a radiologist, HPB-surgeon, gastroenterologist and oncologist. All pancreatic metastases were located in the body and/or tail and were considered operable with distal resection. The preferred surgical technique was laparoscopy, but in some cases had to be operated by open technique because no present surgeon had the required expertise at the time of the operation.

Statistics

Continuous variables are given as mean ± SD for normally distributed data, median and range for non-parametric numbers. Accordingly, two sample Student T-test was used to compare parametric data and two sample Mann-Whitney U-test for corresponding analysis of non-parametric numbers. Categorical parameters are given in numbers, and comparisons evaluated by Chi-square test or Fishers exact test.

The level of significance was set at $p < 0.05$ in two- sided test. Survival estimation was performed according to the Kaplan-Meier method using the log-rank test with the level of significance set at $p < 0.05$ (two-sided test).

RESULTS

The study included 21 patients with metachronous RCC metastasis, 17 operated laparoscopically, four with open technique. Demographic data, comorbidity and ASA score are shown in table 1. There were 13 men, 8 women with the mean age of age 65.6 (± 6.7) years. Median body mass index was 26.6. Median time from removal of the primary RCC to the pancreatic resection was 7.9 years. No metastases were synchronous with an interval approaching eight years between removal of the primary neoplasm in the kidney and the pancreatic resection (table 1).

Five patients underwent multivisceral resections due to local tumor invasion or metastatic spread to other organs. These included liver resection (n = 1), adrenalectomy (n = 1), left- sided hemicolectomy (n = 1), resection of retroperitoneal tumor and excision of a lesion from the abdominal wall (n = 1). Two patients underwent a spleen-preserving procedure in the laparoscopic group. No laparoscopic procedure was converted to open technique. Mean operative time was 178 minutes in the laparoscopic group versus 216 in the open, but this difference was not statistically significant (Table 2). The two groups were also comparable in terms of intraoperative results and postoperative outcomes (Table 2).

Complications were recorded in 9 (42.9%) patients including severe in 6 (28.6%) cases. The latter included pancreatic fistula requiring intervention (n = 4), multiorgan failure (n = 1) and anastomotic leakage after multivisceral resection (n = 1). The frequency of postoperative complications was significantly lower in patients undergoing LDP ($p = 0.021$, Table 2). Clinically relevant pancreatic fistula developed in 6 (28.6%) patients. There was one postoperative death in the above mentioned patient with multiorgan failure. Postoperative stay was almost twice as long after open than laparoscopic resection, but the difference was not statistically significant (p-value = 0.06) (Table 2).

Oncological outcome

Recurrence following surgery was detected in 12 (57.1%) patients after median follow-up 59 (19–136) months (Table 3). The most frequent location of recurrence was bone, in only four local recurrence was found in the pancreas. None of these was found suitable for re-resection. Those with bone metastasis received radiotherapy (n = 6), while chemotherapy was initiated in 5 patients.

Median recurrence-free survival was 51 months, 3- and 5-year recurrence-free survival were 58.3% and 38.9%, respectively. OS 3 and 5 years after LP were 89.7% and 72.1%, respectively. No significant differences were observed between patients undergoing laparoscopic and open surgery.

DISCUSSION

In the present cohort, all patients obtained radical removal of RCC metastases by DP. The latter are particularly a patient friendly procedure when performed laparoscopically (6–8), which was the case in 81% of our patients. Minimally-invasive DP is becoming routine in high volume centers worldwide (13, 14), while open surgery remains an available alternative in selected cases. DP is traditionally associated with lower risk of severe complications compared with pancreaticoduodenectomy and total pancreatectomy which imply increased risk of complications and may have long-term negative impact on patients' quality of life (15). In the published surgical series on resection of metastases in the pancreas, more than half of procedures were DP, while 29.9% were pancreaticoduodenectomies, 11.4% total pancreatectomies and 8.3% other procedures (enucleations etc) (16). At the same time, pancreatecticoduodenectomy and total pancreatectomy are also safe procedures when performed in high volume hospitals (17–19). Accordingly, the risk of complications itself is not a contraindication for resection of pancreatic metastasis from RCC, independent of location in the organ.

According to the present results OS 89.9% and 72.1% are achievable 3 and 5 years after DP for pancreatic metastases from RCC. This is in line with a recent review, presenting survival data from 346 pancreatectomies for RCC metastases, with median OS 8 years (16). Recurrence-free survival after 3 and 5 years in our cohort was 58.3% and 38.9% respectively, illustrating the fact that surgery was not curative in numerous patients, but significant survival benefit was obtained even when recurrence took place. Finally, our findings indicate the LDP is oncolgically sound alternative to its open counterpart.

The concept of oligometastases as a clinical state of limited metastatic disease is a matter of discussion (20), opening a window of opportunity for surgical and/or ablative therapy when the number of metastatic sites and extent of disease is limited. The case mix in this respect in published series of patients operated with pancreatic resection for RCC metastases, is varying. An illustrating example is the difference between the 42 patients from Bordeaux (4) and the present series. Multiple lesions were found in 45.2% of patients in the former, located in all parts of pancreas, whereas all cases in the present cohort had lesions in the pancreatic body or tail. This might reflect differences in tumor biology (21), and the variation has also profound consequences for choice of surgical method. Among 21 patients included in this study, preoperatively conceived oligometastatic disease, was in some cases shown to be more advanced than expected preoperatively, resulting in multivisceral resection in five cases. One of these patients died because of severe complications resulting in multiorgan failure, illustrating the downside of surgery and the uncertainty associated with therapeutic application of the concept oligometastatic disease (22, 23). The core question is therefore whether surgery is the treatment of choice in patients with oligometastatic RCC. A comprehensive longitudinal retrospective, non-interventional cohort study, including 4078 patients diagnosed with metastatic RCC in Norway from 1995–2018 has recently documented increased OS from 2.31 years to 4.51 years when checkpoint inhibitors are added to tyrosine kinase inhibitors (24). Further details on first, second and third line therapies are discussed in a Lancet Seminar (21), underlining that "robust evidence establishing the benefit of metastatectomy in RCC is insufficient". But toxicity and severe side effects is associated with most chemotherapy. Even if OS was twice as long after combined ICI and TKI treatment in the Norwegian cohort, the treatment was not curative and would have to go on to obtain stable disease. In a

recent RCT from Boston, investigating the effect of Cabozantinib plus Nivolumab and Ipilimumab in metastatic RCC, grade 3 and 4 adverse events were most frequent in the therapeutic arm (25), compatible with the notion that improved anti-tumor therapy also carry comprehensive toxicity. Accordingly, the role of surgery must be assessed with awareness of the fact that also the conservative treatment arm has severe downsides and a curative potential has not been documented. When radical surgery is possible, this is a good treatment option, and the burden of surgical complications must be considered.

The limitations of this paper are numerous. The number of patients is small, the retrospective analysis is a weakness and the recorded number of clinical parameters is not complete. Nevertheless, the present observational study has verified that only 57.1% of our patients had a documented recurrence after median six years, at the end of follow up. In view of that more than 40% of our cohort had a curative perspective at this time without any ongoing anti-tumor therapy. “The role of surgery in the management of isolated metastases to the pancreas” was the headline of a Lancet oncology paper almost ten years ago (26), underlining the favorable outcome of early reports on surgical resection. Even though the evidence favoring surgery is still not robust, accumulating data has over the years supported the hypothesis. The present results add into the accruing evidence.

Declarations

Author Contribution

T.J.J.T and M.A.S wrote the main manuscript text and figures. B.G.E and T.B came with valuable feedback, reviews and alterations. All authors reviewed the manuscript and contributed in this research article.

Data Availability

All sources to data used are given or referenced in the article.

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Tables

Tabell 1: Clinical data for 21 patients, operated with DP for RCC metastases.

Parameter	Total (n = 21)	Laparoscopic (n = 17)	Open (n = 4)	p-value
Age, years, mean (SD)	65.6 (6.7)	65,4 (7.3)	66.3 (3.6)	0.83
Body mass index, mean (SD), kg/m^2	26,6 (3.0)	25.6 (3.3)	25.9 (1.5)	0.87
Female gender, n	8	7	1	1.0
Comorbidity, n	18	14	4	1.0
Cardiovascular, n	6	3	3	0.053
Hypertension, n	8	7	2	1.0
Diabetes mellitus, n	2	2	0	1.0
Chronic renal failure, n	2	1	1	0.35
Total number of comorbidities, mean (SD)	1.4 (1,2)	1.6 (1.2)	0.6 (0.5)	0.08
ASA Score $\geq$ III	10	8	2	1.0
Years between operations, mean (SD)	7.9 (6.3)	8.3 (6.8)	6.8 (3.3)	0.68

Table 2: Procedures and postoperative outcome.

Parameter	Total (n = 21)	Laparoscopic (n = 17)	Open (n = 4)	p-value
Mulitivisceral resection, n	5	3	2	0.23
Spleen preservation, n	2	2	0	1.0
Blood loss, median (range) ml	80 (30-1700)	50 (30-1700)	100 (50-700)	0.53
Red blood cell transfusion, n	3	3	0	1.0
Operative time, median (SD), min	185 (54)	178 (55)	216 (38)	0.22
Grade B/C fistula, n	6	3	3	0.053
Morbidity, n	9	5	4	0.021*
Severe mobidity, n	6	3	3	0.053
90-day mortality, n	1	1	0	1.0
Readmission, n	2	1	0	1.0
Postoperative stay, median (range)	6 (1-38)	6 (1-23)	13 (4-38)	0.06

Table 3: Oncological outcome.

Parameter	Total (n = 21)	Laparoscopic (n = 17)	Open (n = 4)	p-value
Recurrence, n	12	10	2	1.0
Recurrence site, n				0.52
Pancreas				
Others	4	4	0	
	8	6	2	
Chemotheraphy, n	5	5	0	0.53
Radiotherapy, n	6	5	1	1.0
Recurrence-free survival				
Median (range) months	51 (20-81)	50 (19-80)	57 (17-97)	
3-year (%)	58.3 %	55.6 %	66.7 %	
5-year (%)	38.9 %	39.7 %	33.3 %	
Overall survival				0.91
Median (range) months	-	-	-	
3-year (%)	89.7 %	93.8 %	75 %	
5-year (%)	72.1 %	72.1 %	75 %	