CASE REPORT

Synchronous Liver Metastasis Should not be an Absolute Contraindication for Curative Pancreaticoduodenectomy: A Report of 3 Cases with Good Long-term Survival

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ABSTRACT

Background Ductal adenocarcinoma of the pancreatic head is an aggressive cancer with poor prognosis. Surgery offers the only means of cure but most patients are often inoperable at diagnosis due to concomitant metastasis. Although many authors have explored the role of surgery in these patients there is no reported long-term survival. **Case presentation** The salient features of the clinical presentation, surgical management and long-term outcomes of patients who underwent simultaneous pancreaticoduodenectomy and resection of liver metastases associated with peri-operative chemotherapy are presented and discussed. We report three patients who have survived more than five years after undergoing surgery with curative intent of metastatic pancreatic head adenocarcinoma. **Conclusion** The salient feature of these patients is that the metastases were limited to the liver with good response to chemotherapy. One patient in particular is considered to be cured. This strategy offers a chance of prolonged survival and even cure compared to palliative chemotherapy.

BACKGROUND

Pancreatic head ductal adenocarcinoma (PanCa) is an aggressive disease with dismal prognosis. Only 20% are operable at diagnosis and five-year disease-free survival in those undergoing pancreaticoduodenectomy (PD) is about 20% [1, 2, 3]. Locally advanced disease and presence of metastases are considered absolute contraindications for PD because there is no survival advantage over palliative chemotherapy [4, 5, 6]. With advancement in surgical techniques, peri-operative management and advanced chemotherapy regimens, some authors now debate the need to expand the resection criteria particularly for tumors with vascular involvement and incidentally detected liver metastasis [7, 8, 9, 10]. But five-year survival in patients with metastatic PanCa has not yet been reported [1, 8, 9, 10, 11]. We present three patients of metastatic PanCa who underwent curative-intent simultaneous resection of both primary and synchronous liver metastases.

Received June 22nd, 2020 - Accepted August 17th, 2020
Keywords Pancreaticoduodenectomy; Adenocarcinoma; Hepatectomy; Pancreatic cancer
Abbreviations PD Pancreaticoduodenectomy; PanCa Pancreatic head ductal adenocarcinoma; FU Fluorouracil; ypCR pathologic complete response; ECOG Eastern Cooperative Oncology Group; FOLFIRINOX Folinic acid, Fluorouracil, Irinotecan Hydrochloride and Oxaliplatin; CEA Carcinoembryonic Antigen; CA19-9 Cancer Antigen 19-9; CK7+ Cytokeratin 7+; OS Overall Survival
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CASE PRESENTATION

Patient 1: A 45-year-old man, with recent onset jaundice, was found to have a two-cm mass in the head of the pancreas with three nodules varying between 10 to 35 mm in segments 3, 4 and 7 of the liver on CT scan. Ultrasound-guided biopsy of the liver metastasis revealed CK7+ and CK20- poorly differentiated carcinoma compatible with bilio-pancreatic origin **(Figure 1)**. Neoadjuvant chemotherapy with 5-fluorouracil (5FU) and cisplatin (LV5FU2-P) regimen was initiated after endoscopic biliary drainage to alleviate jaundice. After six cycles the primary tumor had halved in size and the largest liver nodule decreased from 35 mm to 21 mm in size **(Figure 2)**. Tumor markers CA19-9 level decreased from 80 to 20 IU/mL (N<37 IU/mL) and CEA level remained within normal range (N<5 ng/mL). Considering the patient's young age, Eastern Cooperative Oncology Group (ECOG) performance status of 0 and excellent response to chemotherapy, PD with left lobectomy extended to segment 4 for two nodules and partial hepatectomy of a nodule in segment 7 was performed. Histopathology showed that the primary tumor and liver metastases were replaced by fibrotic scar with no viable tumor cells suggesting pathological complete

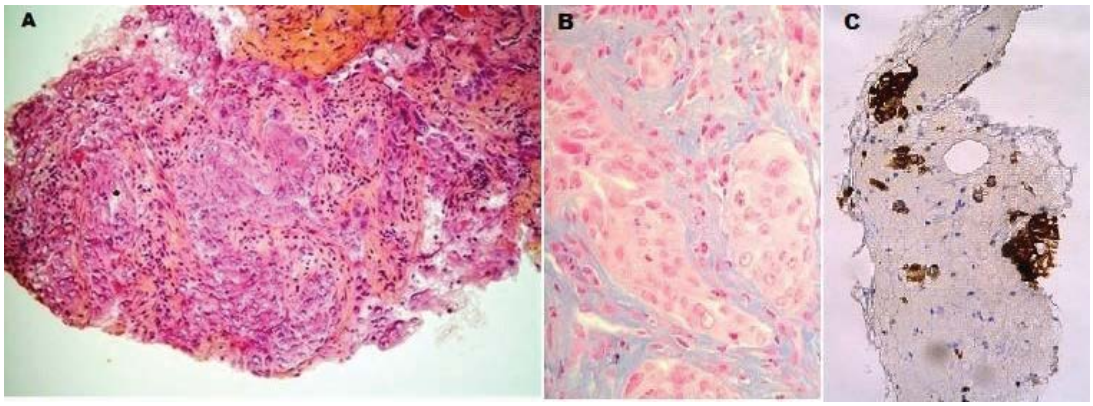

Figure 1. Histology of the preoperative biopsy of a liver nodule showing the metastasis from pancreatic adenocarcinoma (A – Hematoxylin-eosin-saffron staining, B –Alcian blue staining and C – CK 7 immunostaining).

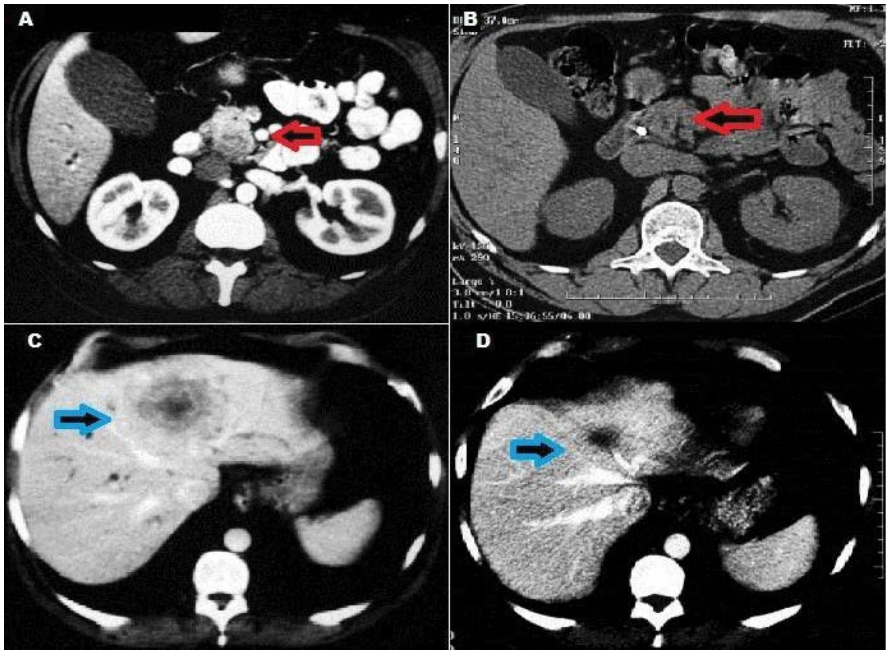

Figure 2. CT scan pictures showing the primary tumor in the head of pancreas and a metastasis in left lobe of liver, shown by arrows, before (A and C) and after chemotherapy (B and D).

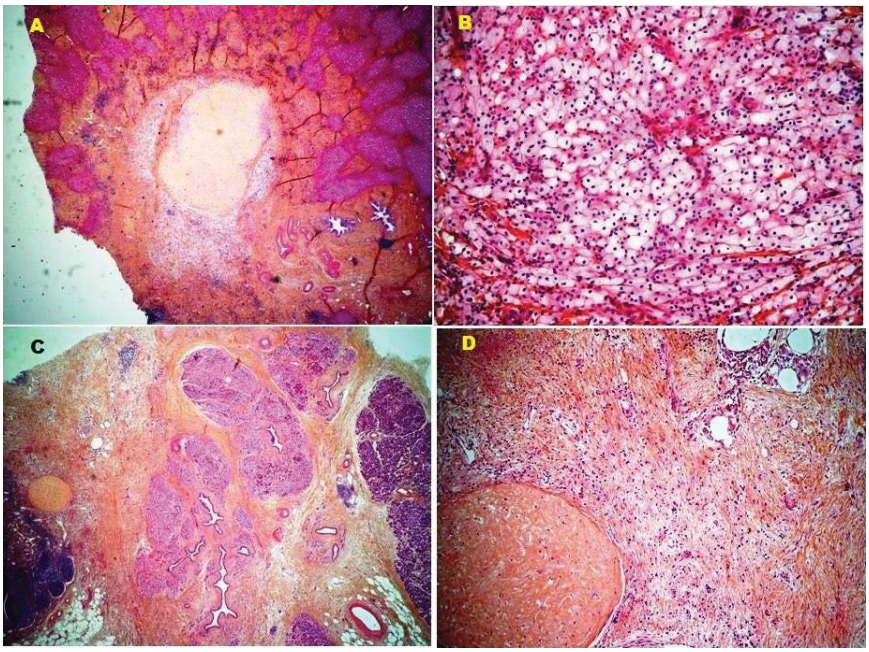

Figure 3. Histology of the resected liver metastasis (A and B) and pancreatic head primary tumor (C and D) showing only fibrotic scar with macrophage infiltration with no viable tumor cells (Hematoxylin-eosin-saffron staining).

response (ypCR) **(Figure 3)**. Three additional cycles of the same chemotherapy was administered postoperatively. At 15-year follow-up, the patient was doing well with no recurrence of the disease.

Patient 2: A 52-year-old woman presented with obstructive jaundice and CT scan confirmed a three-cm tumor of the head of the pancreas with two synchronous liver metastases in segments 7 and 8. CA19-9 was elevated at 139 IU/mL and CEA was normal. Considering the patient's young age and good general health (ECOG 0), resection of both the tumor locations was proposed. At laparotomy we found a four-cm tumor in the head of the pancreas with enlarged regional lymph nodes and four nodules in the liver. Simultaneous PD with multiple partial hepatectomies in segments 4, 5, 6 and 8 was performed. Histology revealed a well-differentiated PanCa infiltrating the peri-pancreatic adipose tissue with four liver metastases and three metastatic celiac and inter-aortocaval lymph nodes (pT3N1bM1). Six cycles of LV5FU2-P regimen was administered postoperatively. After 14 months of disease-free interval, the patient developed local recurrence in the liver with two nodules in segments 4 and 8. Chemotherapy was restarted with 5FU, folinic acid and gemcitabine. Due to poor tolerance, new regimen with gemcitabine-oxaliplatine (GEMOX) was introduced. After nine cycles, the disease was controlled for a year with disappearance of the liver nodules and normalization of CA19-9 level from 38.9 U/mL. After 28 months from the primary surgery, patient had a new progression with bilobar recurrence in liver and an additional eight cycles of chronomodulated GEMOX was administered. As the disease remained stable with no extrahepatic metastases and normal CA19-9 level, bisegmentectomy 7 and 8 with metastasectomies in segments 2 and 4 was performed under total vascular exclusion of the liver four years from the primary surgery. Histology revealed four out of five resected nodules to be metastatic from poorly differentiated PanCa (CK7+, CK19+, CK20-). Adjuvant chemotherapy could not be administered as the postoperative course was complicated by a biliary fistula and subphrenic abscess. At six months from the second hepatectomy the patient was commenced on GEMOX for recurrences in liver, lung and mesenteric lymph nodes. After six cycles, GEMOX was substituted by oral capecitabine plus erlotinib and the disease was controlled for another year. Subsequently the patient developed a new recurrence in the liver, which was treated by radiotherapy. Two years from the second hepatectomy and more than six years from the primary surgery, she developed new metastases in the vertebrae treated by external radiotherapy. The chemotherapy was subsequently changed to oral sorafenib and subsequently to sunitinib to achieve disease control. Eventually the patient succumbed to the disease at seven years and three months from PD.

Patient 3: A 73-year-old man in good physical health (ECOG 1) was referred to our hospital with a diagnosis of metastatic PanCa. CT scan revealed a 36 mm hypodense mass in the pancreatic head and a 9-mm hypodense lesion in segment 3 of liver. Endoscopic ultrasonography guided needle biopsy of the primary tumor confirmed the diagnosis of mucous-secreting PanCa. CA 19-9 level and liver function tests were normal. Neoadjuvant chemotherapy with gemcitabine–erlotinib was initiated. After four cycles of chemotherapy, there was a 50% reduction in the size of PanCa. PD combined with excision of the liver nodule was performed. Histology revealed poorly differentiated PanCa with no residual tumor cells in the liver nodule (pyT3N1M0). His post-operative course was complicated by Grade B pancreatic fistula and intra-abdominal collection treated by percutaneous drainage, antibiotics and total parentral nutrition. Six cycles of gemcitabine was administered postoperatively. After two and half years of disease-free interval, follow-up CT scan revealed a recurrence in segment 6 of the liver. A new chemotherapy regimen with 5FU, folinic acid, irinotecan and oxaliplatin (FOLFIRINOX) was commenced. Re-evaluation after 11 cycles showed a reduction in the size of the liver nodule from 15 mm to 9 mm. As the metastasis was unique and responding to chemotherapy, re-hepatectomy was performed for two nodules were found intra-operatively. Histology of the liver nodules showed fibrous scar without viable tumor cells suggesting ypCR. The patient received additional 11 cycles of FOLFIRINOX postoperatively. At the last follow up five years and three months from the first procedure and two years from the second procedure, the patient was disease-free and doing well.

DISCUSSION

Although many authors have debated the role of curative surgery in patients with metastatic PanCa, the current standard of care for these patients is palliative chemoradiation and best supportive care [2, 5, 9, 11]. Surgical resection is contraindicated in these patients and long-term survival has not yet been reported. We report, for the first time, three patients who have survived more than five years after undergoing surgery with curative intent of metastatic pancreatic head adenocarcinoma. In our report the treatment strategy consisted of neoadjuvant chemotherapy leading to ypCR and simultaneous surgical resection of the primary and secondary tumors. These principles have been well established in the treatment of other cancers notably metastatic colorectal cancer and not yet been validated in the treatment of metastatic PanCa [12, 13, 14]. Also there is no relevant data on ypCR to chemotherapy in metastatic pancreatic adenocarcinoma. However in locally advanced pancreatic head tumors undergoing neoadjuvant chemoradiotherapy, a 6%-12% ypCR has been reported in the resected tumors and a good tumor response has also been shown to be associated with better survival in resected patients [13, 14, 15]. In the first patient, an unexpected drastic reduction in the size of the primary tumor and metastases with normalization of tumor markers motivated us to attempt curative resection. The postoperative histology was even more surprising. Complete pathological response to chemotherapy is a very good prognostic factor and is associated with prolonged disease-free survival and cure

[16]. We can indeed question the role of surgery in this patient who had ypCR to chemotherapy. There are no imaging techniques available to diagnose ypCR accurately and therefore surgical resection remains the only option. In future, molecular/genetic analysis might help to identify such those who have less aggressive tumor biology and/or respond very well as observed in patients with BRCA 1/2 mutation undergoing platinum based chemotherapy for PanCa [17]. Another reason to justify resection after neoadjuvant chemotherapy is the discordant response as observed in the third patient who had ypCR in the liver metastasis and persistent viable tumor in the pancreatic primary. In the second patient, a multimodality strategy including repeated surgical resections of liver/lymph node metastases combined with multiple lines of postoperative chemotherapy and radiotherapy resulted in prolonged survival of seven years. Presence of lymph node disease in this patient would be considered as regional spread and was removed in totality during PD.

Simultaneous resection of the primary tumor and incidentally detected liver secondary has been shown to prolong the survival to a maximum of three years [1]. The prerequisite for this aggressive strategy should be a good response to primary chemotherapy as it was observed in all the three patients - in the first and third patient before and in the second patient after surgery. Rescue surgery after combination chemotherapy could improve the patient's overall survival (OS) in metastatic PanCa. A recent systematic review of surgical resection of synchronous liver-only metastases from pancreatic cancer demonstrated that median OS ranged from 7.6 to 14.5 months after upfront pancreatic/liver resection and from 34 to 56 months in those undergoing preoperative chemotherapy. Patients who undergo surgery after primary chemotherapy had to fulfill strict criteria: (1) good performance status, (2) >50% decrease or normalization in CA19.9 from baseline values, and (3) radiological down staging with no or limited residual metastases. Another interesting observation of this review was that surgery was performed after a median of 9.7-12 months from initial diagnosis. This test of time would enable surgeons to identify patients with less aggressive tumor biology and achieve a prolonged response before surgery [18]. Another review of 19 studies with 428 patients with metastatic pancreatic cancer who underwent surgical resection following favourable response to initial chemotherapy for liver metastases (N:343), lung metastases (N:57), and limited peritoneal dissemination (N:8) demonstrated an encouraging median overall survival of 34 months and 28 months in patients with synchronous liver metastases and peritoneum disease respectively. Although the authors were unable to suggest definitive criteria of surgical indication for patients with metastatic PanCa, they opined that the patients who responded favourably to initial chemotherapy for a certain period of time should be reviewed in multidisciplinary meeting and decision about surgery be taken after informed consent from patients [19].

CONCLUSION

In well-selected patients, aggressive onco-surgical strategy in the era of effective multi-agent chemotherapy would enable curative resection of metastatic PanCa and it could help improve the dismal prognosis associated with this disease. Patients with liver-only oligometastases (<5) with good biological (normalization or ≥ 50% decrease in CA 19-9 level) and radiological response (≥ 50% reduction in size) to primary combination chemotherapy for minimum of 3-6 months and good performance status (ECOG 0/1) would be ideal candidates for curative surgery after primary combination chemotherapy.

Conflicts of Interest

All named authors hereby declare that they have no conflicts of interest to disclose.

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