Surgical resection of synchronous and metachronous metastases from pancreatic adenocarcinoma. Two case reports in the light of recent evidences


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Pancreatic ductal adenocarcinoma is the fourth leading cause of cancer-related mortality in the western countries for both men and women. Until in 2015, it remains one of the most challenging malignancies with a dismal prognosis and limited therapeutic options. The 5-year survival rate for pancreatic cancer is around 5%, which is the lowest among all different cancer sites. The poor prognosis of PDAC is largely attributed to delayed diagnosis due to nonspecific symptoms in the early stages of the disease, biological aggressiveness leading to rapid metastases, lack of effective screening methods, and resistance to radiation and chemotherapies.

In the event of metastases, patients were traditionally referred to palliative treatments. Thanks to continuous progresses in the surgical expertise, synchronous and metachronous metastases resections seem technically feasible nowadays. These reports describe 2 several clinical cases in which patients with Pancreatic Adenocarcinoma, and synchronous and metachronous liver metastases respectively, were treated with a surgical approach. Patients showed a better survival rate compared current data in the literature.

Our results, often in conflict with the guidelines and recent evidences, confirm the need for a new vision of the metastases “problem” in patients with Pancreatic Adenocarcinoma.

KEY WORDS: Metastases, Pancreatic Adenocarcinoma, Surgical resection

Introduction

Pancreatic Adenocarcinoma (PDAC), is still associated with a high mortality with a 5-year survival rate below 5% and morbidity for affected patients notwithstanding considerable progresses in diagnosis and both surgical pharmacological therapy1,2. This can be attributed to the fact that the only chance for cure is the complete surgical resection of the tumor, which, however, can only be performed in about 20% of all patients diagnosed (3); the remaining patients receive palliative treatment with very low survival rate. Resection is the only treatment that offers the potential of cure. Despite metastases from colorectal, gastric and neuroendocrine primary tumor and their treatment are widely reported, the literature has been rarely investigated the impact of localization and numbers of pancreatic metastases 4-8.
We describe 2 clinical cases of synchronous and metachronous liver metastases respectively treated with surgery, their natural history in light of recent scientific evidences.

Case Reports

CASE N. 1
A 63 year-old male patient with history of hypertension, dyslipidemia, chronic obstructive pulmonary disease (COPD) presented to our Department for an initial and nonspecific abdominal tenderness accompanied by itching and worse jaundice. Clinical evaluation revealed a palpable gallbladder (Courvoisier's sign) related to malignant obstruction of the lower common bile duct. The following data were collected: BMI 25; total bilirubin 5.3 mg/dl - indir. 0.9, CA 19-9 ≤ 200. EUS indicated the presence of neoplastic lesion in pancreatic head. Computed tomography (CT) scan with contrast revealed CT advanced PDAC (28 mm) with no extension to superior mesenteric artery (SMA) and initial enchasement of superior mesenteric vein (SMV) and presence of single liver metastasis in left lobe.

Without any indication for preoperative biliary drainage, patient underwent pancreaticoduodenectomy and liver wedge resection in segment 3 (S3). After laparotomy, en bloc pancreaticoduodenectomy with stomach and gallbladder was performed (Fig. 1); after routine intraoperative US for liver nodes detection, subsequent liver resection was performed. Pathologist's report was locally advanced PDAC with positive histology result moderately differentiated pancreatic ductal adenocarcinoma, infiltrating pancreatic head, peri-pancreatic tissues and Vater's papilla. 2 lymph nodes of 20 ones were metastatic. Resection margins of stomach and gallbladder were free. Stage III; TNM Classification: T3N1M1 - HEP- G2.

According to recent guidelines 9-11, the evaluation of resection margins was performed by intraoperative administration of cryostat on: 1) biliary tract; 2) pancreatic margin; 3) retroperitoneal margin. Patient underwent adjuvant chemotherapy (scheme GEM-OX (Gemcitabine - oxaliplatin)) for a total of VII cycles (6 months).

13 months after surgery, tumor markers (CA 19-9) had a huge increase and a control CT scan showed four liver and one-lung metastases. He died 19 months after surgery.

CASE N. 2
A 58-year-old female with astenia, fever, slight abdominal pain and initial jaundice presented to our Department. Hepatic function tests were significant for the elevations of total bilirubin 3.8 mg/dl (normal range 0.1–1.2 mg/dl) and alkaline phosphatase 454 U/l (normal range 30–125 U/l); CA19-9 levels were 226 mcg/ml (normal range 0–37 mcg/ml). Abdominopelvic CT scan revealed mass-form lesion (31 mm) in the head of the pancreas, compatible with locally advanced pancreatic carcinoma, with no extension to the SMA and SMV vessels and absence of detectable liver metastases, peripancreatic lymphnode enlargement. Patient underwent pancreaticoduodenectomy. After laparotomy, gastric wall en bloc resection was performed (Fig. 2). Pathologist's report was: "PDAC with positive histology for moderately differentiated mucinous adenocarcinoma, but also with focal aspects of signet-ring-cell infiltrating the pancreas and the main pancreatic duct; free gallbladder, gastric wall, adipose and tissues - vascular and free resection margins. 34 Lymphnodes free of cancer. TNM Classification: T3N0, G2, Stage IIA."

The patient started adjuvant chemotherapy with GEM-OX scheme (Gemcitabine - oxaliplatin) for a total of VII cycles (6 months).
Patient did not experience recurrence until the last follow-up of 48 months.

After about 4 years, radiological screening revealed a small pulmonary nodule in the right upper lobe described as: "opacity localized on the third segment of the right upper lobe, in the mantle; size is about 4 mm (Fig. 3)". The patient refused treatment and, after 7 months, CT showed, in addition to already known nodule increased in size (10mm), another node of 10 mm between two middle lobe pulmonary vessels. The patient underwent Whole Body PET: “hyperaccumulation of the tracer at the level of the anterior segment of the upper lobe (SUV 5.8) and the middle lobe (SUV 7.0) of the right lung. Accumulation of the tracer at abdominal-pelvic level, attributable, in first hypothesis, to intestinal nonspecific uptake. Nothing in the remaining segments”.

A biopsy for typing of formations was required and the patient underwent atypical lung resection of the right upper lobe. Pathologist’s report was: “secondary lung localization of moderately differentiated pancreatic adenocarcinoma with mucinous aspects, infiltrating the visceral pleura. No evidence of vascular and perineural invasion. Investigations of molecular morphology performed by IHC revealed: Cytokeratin 7+, Cytokeratin 20-, TTF/-, CDX2 -, Napsina -. Margins of resection free. The patient subsequently underwent superior right lung bilobectomy and lymphadenectomy.

Approximately 7 years from initial diagnosis and 3 months after second lung resection for metastatic metachronous PDAC, disease is currently in progression for the presence of bone metastases.

The patient is still surviving and she has recently started the second CHT line.

Discussion and Comments

Surgical resection of liver metastases from PDAC has not generally been acceptable, except some studies 5, 11-12: this is because, biologically, pancreatic tumors are inherently aggressive with poor long-term survival. According to the recent evidences several characteristics are required for treating pancreatic metastases with radical surgery: first, the primary cancer type should be associated with successful outcomes; second, the primary cancer site has been well controlled; third, the pancreatic metastases should be proven as isolated metastases; fourth, the pancreatic metastases should not involve invasion of the adjacent vessels, and the clinicians should consider the resectability of the metastasis; and fifth, the patient should be expected to be able to tolerate the operation 11,14.

Several studies have suggested that radical surgery is a favorable factor for the prognosis of patients with pancreatic metastases; other researchers believe that patients should not be treated surgically because the presence of multiple metastases indicates fatal generalized dissemination 15,16.

In this study we evaluated two kind of metastatic process in PDAC: synchronism and metachronism and their correlation with survival after a surgical approach.

Simultaneous pancreatic and liver resections are not generally recommended 8,17 because patients seem to have a higher complication rate than patients with multivisceral liver resections 18. However, several studies have shown that the presence of metastasis of a PDAC radical resection is possible and safe and that overall survival is comparable to patients who do not have metastatic disease 8,19,22.

In our first case report the survival time of patient with liver metastasis treated with synchronous surgical approach was 19 months compared with patient that not received surgical resection of liver metastases (11.4 months) and with patients receiving palliative chemotherapy who have a median survival time of approximately 5.4-8.4 months 23,24. According with these evidences, we believe that, in selected patients, concomitant resection of primary pancreatic tumor and synchronous hepatic metastases can be performed safely.

METACHRONOUS PANCREATIC METASTASES

Pancreatic recurrence diseases are usually treated with palliative operations, chemotherapy or radiotherapy, rather than radical operations. Adam and other authors found that hepatic metastases resection, after pancreatic surgery, may be warranted in those patients who demonstrate good tumor biology, and reported a 5-year survival of 20% in selected patients with liver metastases after resection for APDC (25-27). Kleeff et al published results of re-resection of localized recurrence for PDAC in a group of eight patients. Compared to a matched control group
of patients who did not undergo re-resection, median survival was significantly longer for patients undergoing re-resection (29 vs 14.5 months; P < 0.0001) (25, 28); other authors suggested that resection for recurrences of pancreatic cancer is feasible, safe, and associated with favorable survival outcome 29,30.

Our experience in metachronous pancreatic metastases (case report 2) showed a prolonged survival of the patient through surgical resection of metastatic lesions and subsequent medical therapy.

Conclusions

Localization and synchronism/ metachronism of pancreatic metastases are associated to different survivals in patients with PDAC. For this reason, as previously showed 13, M patients would require a “functional” grading to obtain a more correct therapeutic approach and prognostic evaluation. Future studies on large cohorts of patients with PDAC could confirm the data obtained in our study.

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References


