Case Report

Pulmonary metastases in pancreatic cancer, is there a survival influence?

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Abstract: Pancreatic cancer is known to be one of the most lethal cancers. The majority of patients present with advanced stage disease, making curative approach unachievable. In untreated patients, the median survival does not exceed 6 months in metastatic disease and 10 months in locally advanced disease. Furthermore, the 5-year survival rate remains poor even in patients with early stage disease who are surgical candidates. The detrimental outcome is related to the high potency of developing metastasis which can be detected at diagnosis, when the disease progresses or relapses after surgery. Although the liver is the most common site of pancreatic cancer metastases, the cancer can escape the liver in some cases and metastasize to the lung or other distant organs. The involvement of some sites not others might reflect subgroups of this cancer with different molecular backgrounds. Identifying these groups may have utility in determining prognosis and stratifying treatment for patients.

Keywords: Pancreatic cancer pulmonary metastases; pancreatic cancer; gemcitabine; nab-paclitaxel

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In spite of the advances in chemotherapy and immunotherapy, oncologist are still not able to provide good news for patients with pancreatic cancer, which is known to be one of the most deadly cancers and ranked as the fourth cause of cancer related death in both Europe and United States (1,2). Overall survival remains poor either in metastatic disease or in patients with early-stage disease who have undergone apparent curative surgery (3).

During the last decade, pancreatic cancer incidence rates increased by 0.9% per year among white men, white women, and African American men, while rates remained stable for African American women and men and women of all other major racial and ethnic groups (4). Mortality rate remains high because most patients are diagnosed with metastatic disease at first presentation. Pancreatic metastases can arise in any organ site but are mostly detected in abdominal sites. In an autopsy series, the liver was found to be the most common site of metastasis, followed by the peritoneum and lung. Adrenal and bone metastases consistently account for ~10% of metastatic disease from pancreatic cancer (5,6). In some cases, metastases can spread bypassing the liver through portosytemic shunt to extra-abdominal organs which is more often seen if the tumor is in the body or tail of the pancreas (7,8). The overall survival in metastatic settings is known to be less than 6 months without treatment but the data from different studies doesn't distinguish the survival based on the sites of metastasis.

In this report, we are presenting five patients with pancreatic cancer who developed pulmonary metastases and in whom we observed longer than expected survival.

Case 1

A 69-year-old male with moderately differentiated pancreatic cancer pT3N1MX diagnosed in 05/2012 and underwent Whipple procedure 06/2012 followed by three cycles of gemcitabine/nab-paclitaxel and gemcitabine based chemoradiation. The patient decided against any post radiation chemotherapy due to generalized weakness. He remained in remission until a follow up CT scan in 04/2014 showed evidence

of bilateral pulmonary metastatic disease. These metastatic lesions improved in size after initiating doublet chemotherapy consisting of gemcitabine and nab-paclitaxel.

Case 2

A 64-year-old female presented to her PCP in Dec 2011 complaining of recurrent episodes of diffuse pruritus, dark urine and abdominal discomfort. Her work up including abdominal CT scan revealed intrahepatic and extrahepatic biliary ductal dilation to the level of the pancreatic head, but no mass could be visualized. She had ERCP which revealed distal bile duct stricture. A subsequent MRCP revealed minimal pancreatic duct dilation, but no mass. After discussing her case at MDTB, a decision was made to proceed with Whipple resection in 10/2012. The surgical pathology revealed invasive pancreatic adenocarcinoma, 3.2 cm in greatest length, with 15/23 positive lymph nodes. She was started on adjuvant chemotherapy, chemoradiotherapy then chemotherapy with no evidence of local recurrence. The surveillance follow up images in 03/2014 showed several new pulmonary nodules. The constellation of the abnormalities with new significant rise in CA19-9 was worrisome for relapsed disease with pulmonary metastases. Chemotherapy was restarted and CA19-9 normalized with stable appearance of the lung lesions.

Case 3

A 60-year-old male presented with painless jaundice and 15-pound weight loss over 3 months in 08/2011. He was diagnosed with pancreatic adenocarcinoma stage IIB (pT2N1Mx) and underwent Whipple surgery in 08/2011 followed by adjuvant therapy consistent of two cycles of gemcitabine, gemcitabine based chemoradiation and post-radiation gemcitabine. He had no evidence of disease for two years post therapy then his CA19-9 started to rise and a follow up CT scan in 02/2014 revealed several new and enlarging pulmonary nodules, highly suspicious for pulmonary metastatic disease. He was commenced on chemotherapy consisting of gemcitabine and nab-paclitaxel. He received six cycles with a good response.

Case 4

A 51-year-old female originally presented in 08/2011 with severe right sided mid epigastric abdominal pain. CT at that time revealed a 2.7 cm × 3.1 cm mass in the uncinated process which appeared to infiltrate the surrounding fat and SMA. The work up including CA19-9 was normal and ×2 EUS which were unsuccessful for tissue diagnosis. She underwent exploratory laporatomy with biopsy of pancreatic mass that revealed well-differentiated adenocarcinoma with perineural invasion. This patient was not a surgical candidate, was started on gemcitabine and nab-paclitaxel followed by gemcitabine based chemoradiation then gemcitabine/nab-paclitaxel for 11 cycles finished in 12/2012. The patient had a good response to treatment. Although the follow up images showed stable appearance of the ill-defined pancreatic head and uncinated process mass, there was progression of multiple pulmonary nodules which was concerning for metastatic disease. The patient preference was to hold on chemotherapy and to continue with monitoring with serial CT scans.

Case 5

A 55-year-old female presented initially with epigastric discomfort in 11/2010, described it as fullness, gas-type discomfort. Underwent an ultrasound which showed 2.7 cm pancreatic head mass. Follow-up CT revealed 3.6 cm × 2.6 cm pancreatic body mass encasing the superior mesenteric artery and, likely, the common hepatic artery, with occlusion of the portal vein. She was initially considered a non-surgical candidate and started on gemcitabine/nab-paclitaxel, followed by gemcitabine/RXT then eight cycles of gemcitabine plus nab-paclitaxel. Her CA19-9 normalized and follow up CT scans showed response to treatment with no POD. The patient underwent subtotal distal pancreatectomy and abdominal lymphadenectomy. The final pathology was significant for a pathologic complete response. Post-surgery, she was on active surveillance until a follow up CT scan was concerning for POD with pulmonary metastasis and this was also associated with new increasing CA19-9 levels. She was restarted on gemcitabine and nab-paclitaxel with good response to treatment.

Discussion

In these five cases, the first three patients presented with resectable disease initially and underwent pancreaticoduodenectomy while the other two patients had locally advanced borderline resectable disease. One of the patients with locally advanced disease was able to have subtotal distal pancreatectomy and abdominal lymphadenectomy after receiving neoadjuvant chemo-chemoradiation-chemotherapy with complete radiological and pathological response. All five patients

developed lung metastases at approximately two years after the initial first treatment approach and they are still alive (29, 35, 39, 39 and 48 months respectively from initial diagnosis). At the time of this report, all patients still appear to have stable disease.

Different studies have been conducted to identify the prognostic factors for survival in patients with pancreatic cancer. Almost all of these studies included patients with locally advanced disease regardless of whether they were surgical candidates. Although 15-20% of patients are able to undergo surgery for local disease (9), survival in this group of patients is determined by negative prognostic factors including positive resection margin, tumor size, positive peritoneal cytology, positive lymph nodes or lymph node ratio and elevated preoperative and postoperative CA19-9 levels (10-12). The 5-year survival after pancreaticoduodenectomy is about 25 to 30 percent for node-negative and 10 percent for node-positive disease (13-15). One study looked at the 10 years survival in patients after surgical resection of the tumor and determined that DNA content (ploidy level), pathologic tumor size, and lymph node metastases were the strongest prognostic indicators for long-term patient survival. At 10 years, only 7% of the patients with diploid cancers were alive, whereas none of the patients with aneuploid carcinomas had survived (P=0.0001) (16). However, the results from these studies did not distinguish subtypes of disease and whether there is any impact on survival based on the sites of relapsed disease. Pancreatic cancer is known as a fast growing and fatal malignancy with wide spread metastases being responsible for 70% of cancer related deaths and appears to be related to either late diagnosis or early dissemination of disease to distant organs. To improve the survival and treatment outcome especially with the lack of novel agents, efforts have been undertaken to understand the histology and biology of disease at different stages of progression.

Pancreatic cancer has been shown to be a genetically evolving and heterogeneous disease (17-19). This malignant evolution is the result of accumulating cytological atypia in well-defined precursor lesions in the pancreas called pancreatic intraepithelial neoplasia (PanIN) arising from a stem cell-like/progenitor cell population within the pancreas. As a result, little is known about the mechanisms responsible for cancer progression given the diversity of clonal populations isolated from patient biopsies (20). Interestingly, Lacobuzio-Donahue looked at the clinical and molecular features of advanced stage disease and was able to provide evidence that advanced pancreatic cancer is composed of distinct morphologic and genetic subtypes with significantly different patterns of metastasis which did not correlate with clinicopathologic features of these patients at initial diagnosis or their treatment history (21). A study instituted by Gastrointestinal Cancer Rapid Medical Donation Program (GICRMDP) evaluated the clonal relatedness of different carcinoma samples within an individual with metastatic disease by analyzing genetic alterations from distinct samples in the same patient. They found that the genetic heterogeneity of metastases is reflected by what is within the primary carcinoma (22). Also in this study, they classified the detected mutations into two categories, the founder mutations category which includes identical mutations found in all samples (which are the known driver mutations for pancreatic cancer) and the progressor mutations category which corresponds to mutations found in a subset of the samples for each patient. To determine the nature of the genetic heterogeneity of different clones, a subsequent study was done to examine the proteomic consequences across pancreatic cancers by studying the cells isolated from various sites in the same individual. This revealed distinct pattern of both overall proteome expression and tyrosine kinase activities across the three different metastatic lesions suggesting personalized therapy may be needed in patients with metastatic disease by administrating a combination of agents aimed at targeting the features of different subclones (23).

The group of patients we present had only pulmonary metastasis with remarkable prolonged survival, which could be related to subclonal mutations. We believe that a better understanding of the genetic progression in pancreatic cancer can enable identifying different subtypes of this cancer, with pathognomonic behavior and methods of progression which can aid in stratifying patients for different treatment regimens. Furthermore, distinguishing the sites of metastases might have an impact on the TNM staging and the overall survival in the metastatic setting.

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