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Metastatic Disease to the Pancreas and Spleen

Shayna L. Showalter, Eric Hager, and Charles J. Yeo

Isolated metastases to the pancreas and spleen are a rare occurrence. When they are diagnosed, pancreatic metastases are most often from renal cell carcinoma, lung cancer, and breast cancer. The most common source of splenic metastases is gynecological in origin; the overwhelming majority is ovarian. If extensive staging studies reveal these metastases to be isolated, then curative resection may be warranted. This review will demonstrate that long-term survival may be achieved in patients with isolated metastases and a prolonged disease-free interval.
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Autopsy data demonstrate that metastases to the pancreas and spleen are common. However, in a large majority of cases, these lesions represent diffuse spread of a primary cancer to these and other sites. Isolated metastases to these organs are a rare clinical event. Herein, we review the literature on the most common primary tumors that metastasize to the pancreas and spleen. We will discuss the nature of each primary cancer, the general course of disease that leads to distant spread, and the treatment options for metastases to the pancreas and spleen, with a focus on isolated lesions.

METASTATIC DISEASE TO THE PANCREAS

The pancreas is a site of metastatic spread from a multitude of different primary neoplasms. One example is illustrated in Figure 1. Autopsy data show that 3% to 12% of all patients with diffuse metastatic disease have pancreatic involvement.[1-5] In a review of 4,955 autopsies, Adsay et al found that 81 patients had metastatic disease with spread to the pancreas. This study demonstrated that the most common primary malignancies that metastasize to the pancreas include lung, stomach, colon, and esophageal cancers and lymphoma (Table 1).[6]

A review of the literature, involving the surgical pathology of 355 solitary metastases to the pancreas, demonstrated that the five most common cancers with isolated metastases to the pancreas include renal, lung, breast, colon, and melanoma (Table 2).[7,8] These data are supported by a single-institution report of 1,050 fine-needle aspiration (FNA) biopsies of pancreatic lesions.[9] Volmar et al identified 20 metastases: nine from renal cell carcinoma, three from lung carcinoma, two from breast carcinoma, one from prostate carcinoma, and one from a gastrointestinal stromal tumor.[9]

The definitive diagnosis of secondary pancreatic lesions is often difficult because the presenting clinical picture may be similar to that of primary pancreatic cancer or the patient may be entirely asymptomatic. Patients with metastases to the pancreas usually are identified in one of three ways: the pancreatic lesion is discovered during initial metastatic work-up, the lesion is identified during routine follow-up after resection of the primary cancer, or the patient presents with symptoms secondary to the pancreatic lesion. In a review of patients with pancreatic metastases, Minni et al found that 22% of the patients with secondary pancreatic neoplasms

presented with synchronous lesions at the time of their primary diagnosis.[7] Hiotis et al reported that 69% of the patients with isolated metastatic disease to the pancreas were asymptomatic at the time of presentation.[10] Radiologic findings that arouse suspicion for metastatic disease to the pancreas rather than a primary neoplasm include hypervascularity of lesions, absence of lymphadenopathy, and multicentricity.[11,12] As seen with primary pancreatic neoplasia, patients with secondary malignancies can present with painless jaundice, early satiety, epigastric pain, and gastrointestinal bleeding.

Resectional options depend on the type of primary tumor, location of the metastasis, and the extent of disease. When a patient presents with widely metastatic disease, most investigators agree that there is no role for pancreas-focused metastectomy. Surgical treatment options depend on the physical location of the metastasis and include pancreaticoduodenectomy, distal pancreatectomy, total pancreatectomy, central pancreatectomy, and, rarely, enucleation. A discussion of specific tumors metastatic to the pancreas follows.

Renal Cell Carcinoma

Renal cell cancers (RCCs) are relatively uncommon malignancies. Approximately 51,000 new cases were diagnosed in 2007, accounting for only 3% of all newly diagnosed cancers.[13] Only 10% of patients with RCC present with the classic triad of gross hematuria, flank pain, and a palpable mass. However, presenting symptoms are notoriously variable with this disease, and can include anemia, microscopic hematuria, and the sudden onset of a varicocele.[14] Many lesions are now discovered as asymptomatic incidental findings on imaging. The most important prognostic factors relate to the gross size and extent of the primary lesion, and the presence of metastatic disease. Patient survival varies with disease stage. The estimated 5-year survival approximates over 80% for organ-confined localized disease, and 0% to 20% for metastatic disease.[15]

Ultrasound in conjunction with computed tomography (CT) scan is the modality of choice for identifying renal masses.[16] With the increasing use of abdominal CT and ultrasound, there has been an increase in the detection of incidental RCCs.[17] Current medical treatment of disseminated RCC is improving but remains disappointing, and, therefore, the diagnosis of early stage RCC is the key to substantially improving survival.

Surgery is the only treatment modality for RCC that has the possibility of cure. For patients found to have a single suspicious renal mass, the treatment of choice is nephrectomy, with postoperative surveillance. Traditionally, radical nephrectomy, including Gerota's fascia and the associated adrenal gland, is performed to ensure appropriate resection. Recently, there has been a move away from radical surgery, and more RCCs are being treated with adrenal-sparing, laparoscopic or partial nephrectomy. Adjuvant therapy following surgery is still unproven, and has included interferon-alpha, radiation therapy, and autologous tumor vaccines.[18,19]

Approximately 25% of newly diagnosed patients will have either locally advanced or widely metastatic cancer which is not amenable to surgery.[20,21] The most common sites of RCC metastases are the lung, lymph nodes, bone, liver, brain, ipsilateral adrenal, contralateral kidney, and pancreas.[22]

Although medical options are disappointing with widely metastatic RCC, they are often explored when surgical intervention is not indicated.[20] Current medical treatment for metastatic RCC includes chemotherapy, targeted therapy, and immunotherapy. Response rates of metastatic disease to chemotherapeutics and surgical intervention are generally poor. In 1993, a trial

of approximately 3,600 patients placed on single- or double-drug chemotherapy regimens demonstrated an average response rate of only 5.5%.[23] When compared to monotherapy, double-drug chemotherapy has been shown to produce a slightly higher response rate, but many patients are not able to tolerate the increased side effect profile.[24] Recently there has been enthusiasm for immunotherapy in the treatment of metastatic RCC. Because RCC evokes an immune response, it was theorized that cytokines could be useful in treatment regimens, a theory based on the innate properties of cytokines to stimulate the immune system. Initially, the targeted use of cytokines showed promising results. However, their use has not been associated with a significant survival advantage in the majority of studies with advanced RCC.[25-27] Newer targeted agents now widely used to treat metastatic RCC include sorafenib and sunitinib.

A review of surgical pathology reports reveals RCC to be the most common cancer associated with solitary metastasis to the pancreas (Table 2).[7,9] In general, evidence of pancreatic metastases in cancer patients represents diffuse systemic disease. Of note, RCC is more commonly associated with isolated metastatic disease to the pancreas, and therefore these lesions are potentially more amenable to surgery.[28] Autopsy data from patients who succumbed to RCC identified metastases to the pancreas in approximately 1.75% of patients.[29] After resection of the primary tumor, recurrence is often delayed a number of years. In a review of patients with metastatic RCC, Sellner et al reported only 12% of pancreatic metastasis to be synchronous with the primary renal tumor.[30] In fact, most patients who presented with pancreatic metastasis from RCC did so an average of 9.2 years after initial resection (Table 3).[5,31-35] Thus, patients must be followed closely for evidence of disease spread, since those with recurrence tend to be asymptomatic and are often diagnosed only during follow-up imaging. It is interesting to note that a literature review by Wente et al found there to be a slight predilection for pancreatic metastasis from a left kidney primary (58%), although this left-sided predilection is not supported in all series.[11]

Metastasectomy at the time of nephrectomy provides a survival benefit over nephrectomy alone for patients found to have synchronous, solitary metastatic lesions.[31,35] Surgical options for pancreatic metastasis must be carefully planned and individualized to each patient. Resection must aim to achieve clear margins, while leaving as much healthy pancreatic parenchyma as possible. Total pancreatectomy is therefore the last resort for resection, and carries a higher postoperative morbidity than segmental resection alone.[28] A review of patients who underwent pancreatic resection yielded a 5-year survival post-pancreatectomy between 53% and 75% (Table 3). Patients with widely metastatic disease or who choose not to have surgical intervention can expect a 5-year survival of only 5% to 30%.[35,36] It is likely that surgical intervention for solitary pancreatic metastasis from RCC provides a survival benefit, although such benefit may be due to both the extent of disease and the surgical resection.[5,20,33,37,38]

Lung Cancer

Lung cancer is the most common cause of cancerrelated death in the United States.[13] Lung cancer is typically classified as either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC: squamous cell carcinoma, adenocarcinoma, and large cell carcinoma), based on pathologic parameters.

SCLC, which represents 14% of all new lung cancers, is an aggressive disease characterized by rapid doubling time and the early development of widespread metastases. Ninety-five percent of all SCLCs can be linked to tobacco use. Although considered to be

highly responsive to chemotherapy and radiotherapy, SCLC usually relapses quickly, and more than 95% of patients will eventually die of the disease.[39] Because patients typically present with disseminated disease, treatment is usually focused on systemic therapy, not surgery. In the occasional case where SCLC presents as a solitary pulmonary nodule (T1N0M0 or T2N0M0), surgical resection may be considered, in addition to systemic chemotherapy.[40]

NSCLCs, which represent 85% of lung cancers, are differentiated based on histopathology. Surgical resection continues to be the primary treatment for NSCLC patients who present with localized, resectable disease. Adjuvant chemotherapy is also recommended for patients with completely resected early-stage NSCLC.[41,42] Because metastatic spread is typically considered a contraindication to surgery with a curative intent, aggressive efforts must be made to detect nodal disease, mediastinal spread, and distant metastases prior to surgical resection.

The most common sites of metastatic spread from primary lung cancer include the brain, bone, liver, adrenal glands, and skin. Within the abdomen, metastases from lung cancer are most commonly found in the liver, adrenal glands, abdominal lymph nodes, and kidneys.[43] Pancreatic metastases from lung primaries are found infrequently in patients with widely disseminated disease; these lesions are discovered most often during autopsy (see Table 1). In a retrospective study of 22 patients with pancreatic metastases, Moussa et al found four patients with primary lung cancer.[8] The median time to diagnosis of the metastatic lesion in the pancreas was 4.5 months after discovery of the primary lung lesion. Two of the patients were diagnosed by surveillance, and the other two were diagnosed after the development of jaundice. At the time that the pancreatic lesions were identified, all of the patients had diffuse metastatic disease, local recurrence, or local spread. Congruent with the treatment of all metastatic lung cancers, these patients were not treated with surgical metastectomy. Two of the patients were treated with palliative billary stents for tumor-associated obstructive jaundice. Isolated pancreatic metastases from lung cancer are extremely rare. Combined data from institutional reviews of patients with apparently isolated metastases to the pancreas revealed that 30% of the patients had primary lung cancer.[5,10] The pancreatic lesions were found incidentally, or secondary to jaundice or gastrointestinal bleeding. In a single-institution review, Hiotis et al found that three of the 16 patients who underwent pancreatic resection for isolated metastases to the pancreas had a primary lung cancer.[10] These patients underwent either distal pancreatectomy or pancreaticoduodenectomy. Although this study demonstrated a slight increase in the disease-free interval in the patients with primary renal cell carcinoma, there was not a significant long-term survival advantage after pancreatic metastasectomy for patients with a primary lung cancer. At the end of the study, two of the three patients with lung cancer were dead of disease, and the third was alive with disease. Z'graggen et al reported that four of their 10 patients with isolated pancreatic metastases had primary lung cancer. There was a median interval of 70 months between treatment of the primary lung cancer and identification of the metastases. Surgery for these patients served to provide a definitive diagnosis of the lesion, as well as to palliate obstructive symptoms. The tumors were not resected with curative intent.[5] These data suggest that unlike RCC, patients with lung cancer with apparent solitary metastatic spread to the pancreas have a poor prognosis and do not routinely benefit from metastectomy.

Breast Cancer

Breast cancer, one of the most prevalent cancers found in women today, ranks third in overall cause of cancer death in the United States. It is estimated that in 2007, more than 178,000

women in the United States were diagnosed with breast cancer, and another 40,000 died of the disease.[13] Ten percent of women with breast cancer will have metastatic disease at the time of presentation.

Breast cancer most commonly spreads to the liver, brain, adrenals, lung, ovary, and bone. The evaluation of a patient with suspected metastatic disease should include extensive full body imaging and a bone scan. The median survival for patients with widely metastatic disease is approximately 18 to 24 months. The 5-year survival has been reported to be as low as 5% to 10%.[44-47] Although stage IV breast cancer is generally not a surgical illness, many studies have shown a survival benefit to metastasectomy of solitary lesions, especially those found in the liver and lung.[48-52]

Metastasis to the pancreas from breast cancer usually occurs in the setting of diffusely metastatic multiorgan disease. Isolated pancreatic involvement in breast cancer is uncommon, although there are a few published series. In a study of 333 cases of isolated metastasis to the pancreas, Minni et al reported that only 25 (8%) were from a breast primary.[7] Of note, an analysis of autopsy data from 707 patients who died of metastatic breast cancer demonstrated that 13% had pancreatic involvement.[53] This indicates that although isolated metastases to the pancreas are uncommon, the pancreas may be involved in widely metastatic breast cancer. Breast cancer patients with pancreatic involvement present with symptoms typical of pancreatic lesions including jaundice, weight loss, and abdominal pain.[54-56] Jaundice in the presence of a history of breast cancer is usually an ominous sign, indicating diffuse hepatic involvement and an average life expectancy of only 1 month.[57-59] However, imaging is very important in these patients, as extrahepatic bile duct obstruction by a metastatic lesion to the periampullary region, while rare, can mimic diffuse hepatic metastases, and can be palliated with a biliary endoprosthesis.

The average latency period between the treatment of a primary breast cancer and the identification of a pancreatic recurrence is approximately 74 months (Table 4).[52,54-60] It has been hypothesized that such a long latency may indicate a slow-growing tumor, more amenable to either curative or palliative surgery.[5] While controversial, surgical resection of pancreatic metastasis from breast primaries, in conjunction with chemotherapy, hormonal therapy (for receptor positive tumors), and radiation therapy may improve survival in carefully selected individuals.[5,54-60]

Colon Cancer

Colon cancer is highly prevalent in Western societies. The mortality from colon cancer accounts for 10% of all cancer deaths, ranking second only to lung cancer. [13] The incidence of colon cancer increases with age, yielding an average lifetime risk of 5%.[61] Over the past 20 years there has been an improvement in the 5-year survival rate. This is generally attributed to earlier detection and improved chemotherapeutics.[62] As the risk factors for colon cancer have become better defined, so have the guidelines for screening and surveillance, leading to a reduction in advanced disease at initial presentation. Of all patients diagnosed with colon cancer, approximately 5.5% to 12% will have locally advanced disease, while another 30% to 40% will have metastatic disease at initial diagnosis.[63]

Pancreatic metastasis from colon cancer most often occurs secondary to local invasion from primaries involving either the transverse or right colon. Extensive, en bloc resection of locally advanced colon cancer has been studied and found to improve prognosis, and in

some cases to provide a definitive cure.[64-66] A recent review of the literature found the 5-year survival of patients who had an incomplete, margin-positive resection to vary between 0% and 23%, while patients undergoing en bloc resection faired significantly better, with a survival of 16% to 45% at 5 years.[67-69] For patients with locally advanced but node-negative disease, 5-year survival rates can approach 76% for en bloc resection.[70] There have been numerous case reports of patients undergoing colectomy plus pancreaticoduodenectomy for pancreas-invading colon cancer. In 1994, Curley et al reported 12 patients who underwent extensive en bloc resection (colon and pancreas), and found the median survival for all 12 patients to be 32 months.[66] Of note, three of these patients had lymph node–positive disease and died early. Berrospi et al reported three patients who underwent en bloc resection (colon and pancreas), and were alive at 10, 30, and 113 months post-resection.[65]

Malignant Melanoma

Melanoma, the most fatal of all skin cancers, is a leading cause of cancer-related death in the United States.[13] The incidence of melanoma is rapidly increasing. Melanoma microstaging depends on the thickness of the lesion (Breslow classification), or the level of invasion (Clark classification).[71,72]

The most common sites of distant disease spread from melanoma are lung, liver, brain, bone, and the gastrointestinal tract. Visceral metastases occur in 20% of patients as the first site of disease spread. Stage IV melanoma is generally incurable and surgical intervention is reserved for palliation. In rare cases, there is a survival advantage for the surgical resection of isolated distant metastases. This has been shown after complete resection of solitary metastases to the lung, hollow viscus organs of the gastrointestinal tract, and the adrenal glands.[73]

As previously mentioned, malignant melanoma is commonly associated with metastatic disease to the hollow organs of the gastrointestinal tract. Rarely, metastatic lesions are found in the pancreas. In a large review of patients with intra-abdominal metastatic melanoma from the M.D. Anderson Cancer Center, 16% of the patients had metastatic disease in the pancreas however, all of these were accompanied by other intra-abdominal metastases).[74] In a review of a number of patients with metastatic lesions to the pancreas, melanoma accounted for 2.5% to 15% of all cases.[4,6,8-10,64,75]

There are only limited data specific to the resection of malignant melanoma to the pancreas. In a retrospective review by Wood et al of 60 patients with melanoma metastatic to solid intra-abdominal organs, 44 patients underwent complete resection of disease in single or multiple organ sites.[73] Eight of these patients had secondary lesions in the pancreas. Six of the eight underwent complete resection, with a 5-year survival rate of 50%. Two of the eight had palliative surgery, with a 5-year survival rate of 0%. Overall, patients undergoing complete resection had a significant survival advantage when compared to both non-operative patients and patients who underwent partial resection only. This review is the first to demonstrate improved survival by the complete resection of multiple organ site metastases from melanoma. These results are supported by the M.D. Anderson data, which report increased symptom-free and overall survival in highly selected patients able to undergo complete resection of abdominal metastases from melanoma.[74]

METASTATIC DISEASE TO THE SPLEEN

The spleen is a relatively frequent site of metastasis in disseminated cancer.[76] Berge et al found the spleen to be the tenth most common site of metastasis, with an incidence of neoplastic involvement in 7.1% of autopsy cases of cancer patients.[77] Although splenic involvement is seen fairly often, isolated metastases to the spleen are exceedingly rare. In 2001, Agha-Mohammadi et al reported a series of 54 patients, and found the most common primary neoplasms to be gynecologic (61%), colorectal (15%), lung (9%), and stomach (4%) (Table 5).[78] Several hypotheses have been proposed to explain the low incidence of isolated metastatic spread to the spleen. It is believed that the spleen possesses an innately hostile environment for malignant invasion and residence. The reticuloendothelial system may help to inhibit the initial phase of tumor cell seeding.[79] If a malignant nidus is established, the contraction of the spleen may expunge the cells.[80] Lack of afferent lymphatics also may provide some protectionto the spleen[81] and may explain the typical lack of splenic hilar lymph node involvement seen in isolated metastatic lesions.[82] A typical splenic metastasis is shown in Figure 2.

Patients presenting with splenic metastases do so with a widely variable clinical picture. Agha-Mohammadi et al found that only 21% of patients presented with symptoms of pain, splenomegaly, or weight loss.[78] In contrast, there have been dramatic reports of spontaneous splenic rupture from tumor burden, with a high morbidity rate.[83,84] In most patients, splenic involvementis detected through routine follow-up imaging. The challenge for the clinician is to discern the relatively rare finding of splenic metastasis from the more common primary splenic pathology, such as abscess, hemangioma, or infarct.[85] Imaging, tumor markers, and FNA all are used to diagnose splenic lesions,with acceptable risks.[86] When an isolated metastasis is confirmed, most investigators agree that a splenectomy should be performed to prevent further metastatic seeding and to avoid possible splenic rupture.[78,87]

Splenectomy has been performed both laparoscopically and via laparotomy. Most authors support using an open approach when operating for malignant conditions. The laparoscopic method is limited in these cases because it is frequently necessary to remove metastases in other locations and because the spleen is often large. However, for truly isolated metastases to the spleen, laparoscopic splenectomy represents a reasonable approach.

Gynecologic Cancers

The majority of reported cases of isolated splenic metastases are represented by gynecologic cancers. In an extensive review of all cases of solitary splenic metastasis, Agha-Mohammadi and Calne found 61% to be associated with gynecologic primaries, with the majority being ovarian cancer. As with other cancers, splenic involvement from ovarian or endometrial cancers typically signifies late disseminated disease. Isolated lesions are rare, with only 33 reported cases.[78]

Ovarian cancer patients are closely followed with CT scanning and measurement of the tumor marker CA-125. Both of these modalities are useful in the diagnosis of recurrence and splenic metastases. Case reports of splenectomy during both primary cytoreductivesurgery and secondary debulking are increasingly frequent in the literature.[88] It is essential to thoroughly examine the abdomen and pelvis for peritoneal carcinomatosis, and to perform multiple biopsies to exclude microscopic peritoneal dissemination. Splenectomy for isolated lesions is viewed as a relatively safe procedure that can lead to a prolonged disease-free interval, prior to the possibility of disseminated recurrence of ovarian cancer.[89]

Lung Cancer

Lung cancer is one of the most common non-gynecologic cancers that metastasize to the spleen. Overall, the total proportion of lung cancers that metastasize tothe spleen is low. Satoh et al performed a retrospective analysis of 997 patients with lung cancer.[90] Only 1.2% of these patients were identified to have synchronousor metachronous splenic metastases. These lesions were diagnosed via CT scan. This study found that SCLC is the most likely to metastasize to the spleen, and that squamous cell carcinoma is the least likely to doso. All 12 patients in this study were found to have disseminated disease elsewhere at the time of the diagnosis of splenic involvement.

In a retrospective analysis of 92 patients with secondary nonlymphoid splenic tumors recorded over a25-year period, the lung was the primary tumor site in 21%. Four of these 92 patients had apparent isolated splenic metastases; one of the four represented a primary lung adenocarcinoma.[91] In a meta-analysis of all cases of solitary metastases to the spleen, primary lung cancer accounted for 11%. Splenic metastases originated from bronchioalveolar carcinoma, adenocarcinoma, SCLC, and pulmonary carcinoid primary tumors. [78]

Table 6 reviews the small number of reported cases of isolated splenic metastases from a primary lung cancer.[91-100] These reports underscore that all types of lung cancer have been found in the spleen, including a carcinoid tumor. The indication for splenectomy generally has been to avoid potential complications such as painful splenomegaly, splenic vein thrombosis, and rupture. As with any metastasectomy from a lung primary, there is no evidence that splenectomy increases survival.

Colon Cancer

Isolated splenic metastases from colon cancer are extremely rare. Most patients with metastasis to the spleen from colon cancer have widely metastatic disease.An autopsy review showed that of 1,019 patients with colon cancer, 21 had splenic metastasis but all were associated with diffuse disease.[77] In 2001, Okuyama et al performed a world literature search and reported only 29 cases of isolated splenic metastases from colon cancer primaries.[101] The average patient presented with splenic metastasis 29 months after the initial colon cancer diagnosis. Most of the patients presented with increased CEA found by routine blood work. Of the 29 patients reported, 28 were treated with a splenectomy and had an estimated 1-year survivalof 86.6% (with a median survival of 66 months). There is currently no long-term follow-up in these patients and, thus, the survival benefit is not known. There are, however, documented cases of splenic rupture if surgical intervention is not pursued.[102] Thus, even without a documented survival advantage, splenectomy should be entertained.

Malignant Melanoma

Melanoma has been found to metastasize to the spleen, usually in cases of disseminated disease. In the review by Aga-Mohammadi et al, melanoma accounted for only one of the reported cases of solitary splenic metastases.[77] In a review of 25 patients with abdominal metastases, Gutman et al found that the spleen was involved in 15% of cases.[74]

Because patients with visceral metastases have a poor prognosis, and solitary metastases to the spleen are uncommon, surgery with curative intent is rarely undertaken in these patients. The rationale for splenectomy is similar to the previous discussion of complete resection of metastases to the pancreas. There are reports that complete resection does increase overall and disease-free survival rates.[73,74] In the review by Wood et al of 60 patients with intra-abdominal solid organ metastases from melanoma, 11 were found to have splenic involvement. All of these patients underwent splenectomy with curative intent. Five-year survival data are unfortunately

not available for this group of patients.[73] In a single-institution review of 113 patients found to have splenic metastases secondary to melanoma, 15 patients underwent splenectomy.[103] Seven of the 15 were thought to have a solitary lesion. Median survival after splenectomy was 11 months for all 15 patients; however, the subgroup of 7 patients with isolated metastases had a median survival of 23 months. Median survival of the non-surgical group was only 4 months. Although these small retrospective reviews cannot be used to extrapolate general treatment for patients with metastatic melanoma, there may be a survival advantage for the surgical resection of isolated splenic metastases.

Breast Cancer
Isolated splenic metastasis from breast cancer is exceeding rare. In a review of 92 patients with secondary splenic metastases, Lam and Tang found four patients with primary breast cancer.[91] Among the population with breast cancer, there have been few case reports of isolated splenic metastasis.[91,104-107] Of the five reported cases, two patients presented with idiopathic thrombocytopenic purpura, one with a splenic mass by routine ultrasound, and two with abdominal pain and splenomegaly. The patients all had a splenectomy with favorable short-term outcomes.

Gastric Cancer
While direct splenic invasion from gastric carcinoma may occur, discontiguous splenic metastases from gastric cancer are uncommon. Lam and Tang report 16% of metastatic tumors to the spleen to be secondary to gastric cancer.[91] Agha-Mohammadi et al found only one case of gastric cancer with a solitary metastasis to the spleen in their extensive literature review.[78]

Yamanouchi et al reviewed all reported cases of isolated metachronous and synchronous splenic metastases from gastric cancer, identifying a total of 11 patients. This review demonstrated that in the majority of cases, the primary tumors are located in the upper to middle third of the stomach. Gastric cancer is thought to metastasize to the spleen via the splenic artery, because there have been few reports of nodal metastases at the hilum or of tumor embolism in the splenic vein. It is important to remember that the blood flow from the stomach does not reach the spleen directly but rather through the systemic circulation. Therefore, in most cases there are likely to be undetectable micrometastases in other organs.[108] As with other primary cancers, gastric cancer that metastasizes to the spleen is treated with splenectomy.

Renal Cell Carcinoma
Splenic metastases from a renal cell primary are rare, but they do represent 1.8% of all splenic metastases in autopsy data.[91] Usually splenic involvement is via direct invasion from the left kidney.[109] To the best of our knowledge, there have been no more than a few isolated case reports of RCC metastasizing to the spleen.[109-111] These patients were treated successfully with splenectomy, and the patients were disease free at follow-up.

CONCLUSION
Isolated metastases to pancreas and spleen occur rarely. Most often these metastases are associated with disseminated disease. The most common primaries with isolated pancreatic metastases include renal cell carcinoma, lung cancer, and breast cancer. On the other hand, the most common primaries associated with splenic metastases are gynecologic—primarily

ovarian. Review of the literature shows that in appropriate patients with isolated metastases and prolonged disease-free interval, long-term survival can be achieved with resection of these metastases.

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Table 1. Incidence of Pancreatic Metastasis: Autopsy Data

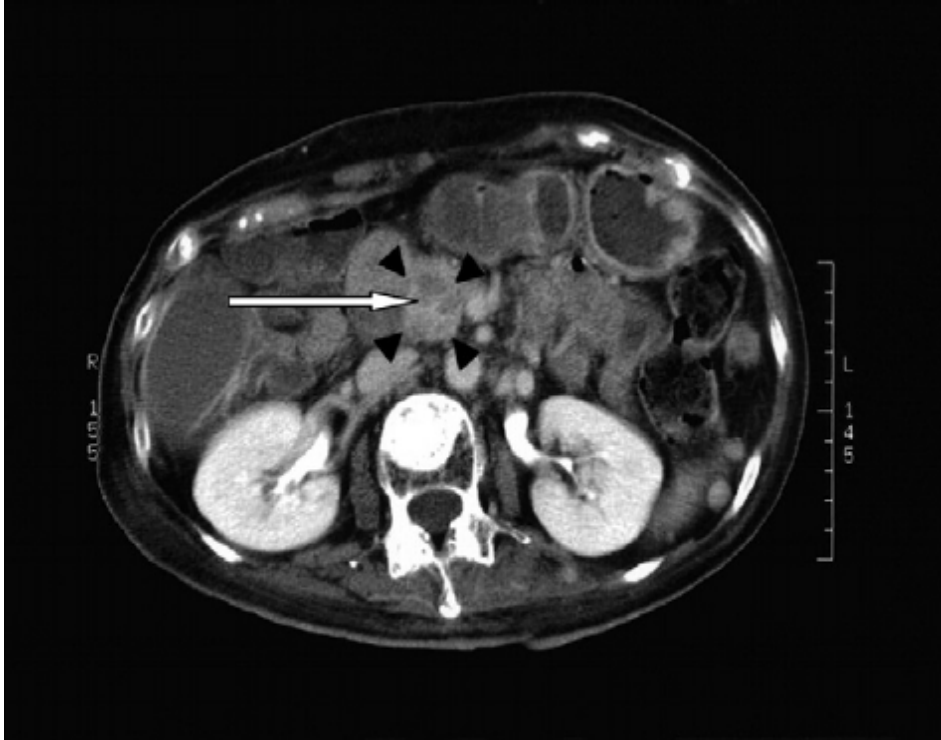| Autopsy Pathology	
Type of Primary Cancer	% of Cases (n = 81)
Lung	34
Stomach	10
Colon	5
Lymphoma	5
Esophagus	4
Renal	4
Unknown carcinoma	4
Breast	3
Liver	2
Melanoma	2
Sarcoma	2
Mesothelioma	2
Multiple myeloma	1
Ovary	1
Rectum	1
Urinary bladder	1

Modified with permission.[6]

Figure 1. CT scan of breast cancer metastatic to the pancreas. The white arrow points to the hypervascular lesion, which is outlined by the dark arrowheads.

Table 2. Incidence of Isolated Pancreatic Metastasis: Surgical Pathology Data

	Surgical Pathology
Type of Cancer	No. of Cases (N = 355)
Renal	160
Lung	53
Breast	29
Colon	26
Melanoma	12
Sarcoma	10
Ovarian	8
Lymphoma	6
Biliary tract	6
Hepatocellular	5
Leiomyosarcoma	5
Esophageal	4
Gastric	4
Thyroid	4
Other	23

Table 3. Summary of Pancreatic Resections for Renal Cell Carcinoma

Authors	N	Median Age (yr)	Median Recurrence Time of RCC (mo)	Median Follow-up After Surgery (mo)	5-Year Survival	Surgery			
						Whipple	Segmental Resection	Distal Pancreatectomy	Total Pancreatectomy
Sohn et al[31]	10	63	102	8	75%	6	0	2	2
Wente et al[11]	15	61	86	10	?	3	2	7	3
Law et al[28]	14	64	83	32	75%	7	0	5	2
Z'graggen et al[5]	2	?	191	20	?	0	0	0	2
Ghavamian et al[32]	11	68	108	50	72%	Not reported	Not reported	Not reported	Not reported
Tuech et al[33]	5	58	78	49	68%	5	0	0	0
Bassi et al[34]	17	64	126	33	53%	2	6	7	2
Summary	74	63	110	28.8	68.6%	23	8	21	11

Table 4. Pancreatic Involvement in Breast Cancer—Interval and Symptoms

Authors	N	Average Latency Time (mo)	Symptoms
Minni et al[7]	25	90	Jaundice, weight loss
Azarelli et al[55]	1	48	Jaundice
Crippa et al[54]	3	36,60,84	Jaundice, pain, weight loss
Nomizu et al[56]	1	80	Jaundice and fatigue
Pappo et al[57]	1	0	Jaundice
Popp et al[58]	7	40	Jaundice
	(N = 38)	74	—

Table 5. Incidence of Splenic Metastasis: Surgical Pathology Data

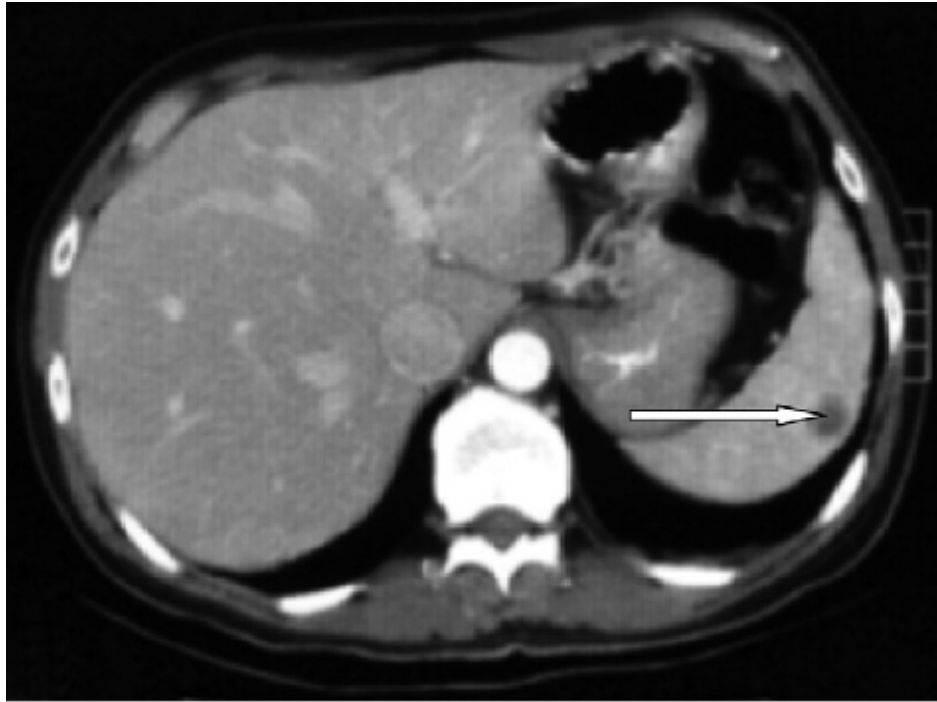|	Surgical Pathology
Type of Cancer	No. of Cases (N = 54)
Gynecologic	33
Colorectal	8
Lung	5
Stomach	2
Esophageal	1
Breast	1
Other	4

Modified with permission.[78]

Figure 2. CT scan of lung cancer metastatic to the spleen. The white arrow points to the hypodense mass.

Table 6. Review of All Reported Cases of Isolated Splenic Metastases From Primary Lung Cancer

Author	Tumor Type	Interval Between Primary Tumor and Metastases	Presenting Symptom or Mode of Diagnosis	Treatment	Follow-up
Klein et al, 1987[92]	Bronchioalveolar	20 mo	Painful splenomegaly	Splenectomy	Death 49 mo after splenectomy
Edelman and Rotterdam, 1990[93]	Poorly differentiated adenocarcinoma	Synchronous	Asymptomatic: CT at initial metastatic work-up	Splenectomy	—
Macheers and Mansour, 1992[94]	Undifferentiated large cell	Synchronous	Asymptomatic: found on CT at time of diagnosis of primary	Splenectomy w/o thoracotomy	Death 1 month after initial diagnosis
Gupta and Havey, 1993[95]	Hilar neoplasm	Synchronous	Splenic rupture followed by diagnosis of primary	Splenectomy	Death- 8 weeks after splenectomy
Kinoshita et al, 1995[96]	Squamous cell	14 months	Follow-up CT	Splenectomy	Death 27 months after splenectomy
Takada and Takami, 1998[97]	Bronchopulmonary carcinoid	8 years	LUQ pain	Splenectomy	No recurrence at 8 years
Lam and Tang, 2000[91]	Adenocarcinoma	—	—	—	Death secondary to metastatic disease
Massarweh and Ohinga, 2001[98]	Poorly differentiated adenocarcinoma	Synchronous	Splenic rupture	Splenectomy	—
Schmidt and Smith, 2004[99]	Adenocarcinoma	25 months	Asymptomatic- Routine follow-up CT	Splenectomy	No recurrence at 2 years
Pramesh et al, 2004[100]	Non-small cell	After 2 cycles of chemotherapy	Asymptomatic: repeat CT	No splenectomy, palliative radiotherapy	—

Abbreviation: LUQ, left upper quadrant; CT, computed tomography.