CASE REPORT

Rare long-term survivors of pancreatic adenocarcinoma without curative resection

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Abstract

Long-term outcome data in pancreatic adenocarcinoma are predominantly based on surgical series, as resection is currently considered essential for long-term survival. In contrast, five-year survival in non-resected patients has rarely been reported. In this report, we examined the incidence and natural history of ≥ 5-year survivors with non-resected pancreatic adenocarcinoma. All patients with pancreatic adeno-carcinoma who received oncologic therapy alone without surgery at our institution between 1995 and 2009 were identified. Non-resected ≥ 5-year survivors represented 2% (11/544) of all non-resected patients undergoing treatment for pancreatic adenocarcinoma, and 11% (11/98) of ≥ 5-year survivors. Nine patients had localized tumor and 2 metastatic disease at initial diagnosis. Disease progression occurred in 6 patients, and the local tumor bed was the most common site of progression. Six patients suffered from significant morbidities including recurrent cholangitis, second malignancy, malnutrition and bowel perforation. A rare subset of patients with pancreatic cancer achieve long-term survival without resection. Despite prolonged survival, morbidities unrelated to the primary cancer were frequently encountered and a close follow-up

is warranted in these patients. Factors such as tumor biology and host immunity may play a key role in disease progression and survival.

Core tip: Five-year survival in patients with pancreatic cancer without curative resection is rare and has not been well described in the literature. At our institution from 1995 to 2009, non-resected ≥ 5-year survivors represented 2% (11/544) of all non-resected patients with pancreatic adenocarcinoma, and 11% (11/98) of ≥ 5-year survivors. These patients were mostly younger than 70 years of age, had excellent performance status and responded favorably to chemotherapy but suffered significant morbidities such as biliary sepsis. We speculate that tumor biology and host immunity play important roles on disease progression and survival.

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States and has one of the worst five-year survival rate of any cancer[1]. Several large population-based studies indicated an overall 5-year survival rate less than 5% and median overall survival of 3 to 6 mo[2-5]. Although a recent Surveillance, Epidemiology, and End Results (SEER) database demonstrated a steady increase in the 5-year survival rates from 3.1% to 4.4% to 6.9% over the three decades from 1981 to 2010[6], long-term survival rate compared with other malignancies still remains very low.

Currently, complete surgical resection is considered essential for potential cure for pancreatic cancer and management is benchmarked on the outcomes of resection. As a result, the vast majority of long-term survivors are described in surgical series, and the reported 5-year actual survival rate after resection ranges from 12% to 27%[7-23].

Although the prognosis for patients with unresectable disease is dismal with a median overall survival of 9 mo for locally advanced disease and 3 to 6 mo for metastatic disease[24], there is some evidence of long-term survival for patients with non-resected pancreatic cancer in the literature. The original paper published by the Gastrointestinal Tumor Study Group examining the role of chemoradiation in locally advanced pancreatic cancer suggested the possibility of long-term survival without surgery for a small subset of patients[25]. Furthermore, the most recent SEER database also displayed a small (2.1%) 5-year survival rate for stage IV pancreatic cancer patients[26]. Unfortunately, clinical details about such patients are lacking from the medical literature.

In this case series, we report the incidence and natural history of non-resected ≥ 5-year survivors with biopsy-proven pancreatic adenocarcinoma treated with oncologic therapy alone without curative resection between January 1995 and December 2009.

CASE REPORT

Eleven non-resected ≥ 5-year survivors represented 2% (11/544) of all non-resected patients with pancreatic adenocarcinoma who received treatment at our institution from 1995 to 2009, and 11% (11/98) of all ≥ 5-year survivors (Figure 1).

Histopathological evaluation

The original histopathology slides of all patients were re-reviewed by a single faculty gastrointestinal pathologist to confirm the presence of pancreatic adenocarcinoma. Additionally, autoimmune pancreatitis, neuroendocrine tumors and tumors arising from the bile duct, gallbladder and duodenum were excluded. Endoscopic ultrasound-guided FNA (EUS-FNA) for cytology of a pancreatic mass (4) or lymph node (1) was performed in 5 patients, endoscopic retrograde cholangiopancreatography (ERCP) brushing of the pancreatic/bile duct for cytology in 2, computed tomography (CT)-guided core needle biopsies of a pancreatic mass in 2 and laparoscopic biopsies of a liver mass (1) and a pyloric implant (1) in 2.

Clinical characteristics

Clinical characteristics of the 11 non-resected patients are described in Tables 1-3. The median age was 62.7 years (54.2-69.5). All of them had an ECOG score of 0 or 1, normal serum albumin level and tumor in the head of the pancreas. Neutrophil-to-lymphocyte ratio (NLR) in the peripheral blood ranged from 1.5 to 14.2. Pain, weight loss or jaundice were present in about half of the patients. Nine patients with localized tumor were treated with combined chemoradiation, of whom 6 received the Virginia Mason protocol therapy consisting of interferon-alpha-2b, 5-fluorouracil (5-FU), cisplatin and radiotherapy. Two patients with metastatic disease were treated with gemcitabine and docetaxel[26].

Six patients suffered from significant morbidities leading to frequent hospitalizations. Recurrent cholangitis occurred in 5 patients (patients 4, 6,
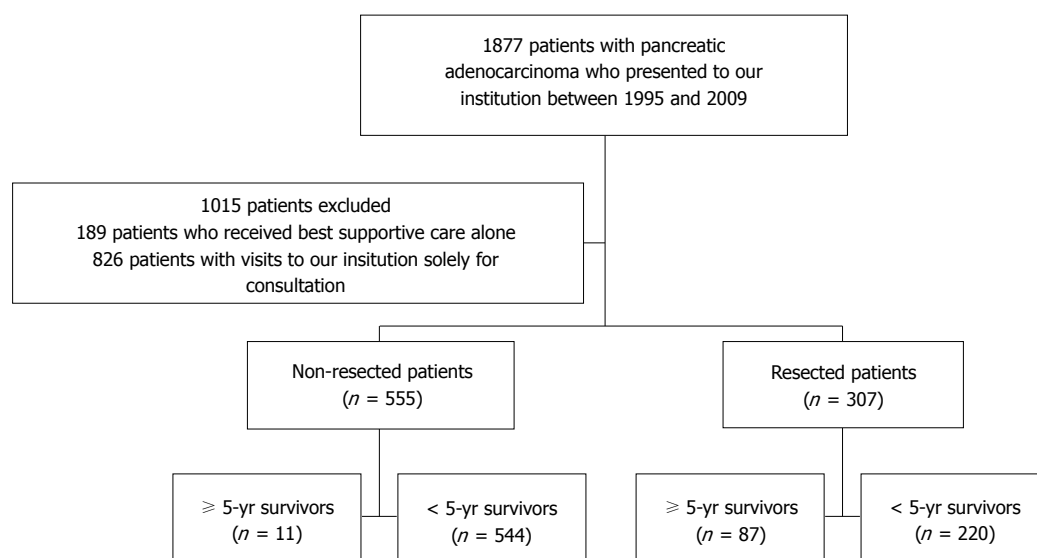
Figure 1 Treatment for pancreatic adenocarcinoma from 1995 to 2009, and 11% of all ≥ 5-yr survivors.

Table 1 Clinical characteristics of 11 non-resected ≥ 5-year survivors *n* (%)	
Baseline characteristics	
Age (yr)	62.7 (54.2-69.5)
Male gender	7 (64)
ECOG ≤ 1	11 (100)
BMI (kg/m^2)	27.2 (24.2-27.9)
DM	2 (18)
Smoking[1]	6 (55)
Pancreatic head tumor	11 (100)
Biliary stent[2]	7 (64)
Presenting symptoms and signs[2]	
Pain[3]	5 (45)
Weight loss[4]	6 (55)
Jaundice	6 (55)
Laboratory values[2]	
Ca 19-9 (U/mL)	72 (33.9-397.1)
Abnormal Ca 19-9	8 (73)
Bilirubin (mg/dL)	4.1 (0.5-11.4)
Abnormal bilirubin	6 (55)
Albumin (g/dL)	4.2 (4.0-4.9)
Abnormal albumin	0 (0)
Resectability[5]	
Resectable	0 (0)
Borderline resectable	2 (18)
Unresectable	7 (64)
Metastatic	2 (18)
AJCC staging[5]	
1	0 (0)
2	2 (18)
3	7 (64)
4	2 (18)

[1]History of cigarette smoking with 5 yr of diagnosis; [2]At the time of initial diagnosis; [3]Persistent abdominal or back pain; [4]Self-reported weight loss of > 10%; [5]Staging CT scan was re-reviewed by an experienced pancreas cancer surgeon who had no involvement in the original care of the patients. Continuous variables are shown as median (interquartile range). Categorical variables are shown as % (number). BMI: Body mass index; CT: Computed tomography.

7, 8 and 11 in Tables 2 and 3). These patients underwent frequent biliary drainage *via* ERCP and/or percutaneous transhepatic biliary drainage (PTBD). Two patients developed small bowel perforations (patient 7 due to an erosion at the site of previously placed duodenal stent, and patient 9 following ERCP). Two patients developed gastric outlet obstruction during the course of the disease (patients 4 and 7), thought to be due to therapy-induced peritumoral scarring. Both were treated with endoscopic duodenal stent placement and/or bypass surgery. One of them (patient 7) had a minimal response to endoscopic and surgical interventions and subsequently developed severe malnutrition, necessitating long-term enteral feeding and total parenteral nutrition. The patient also had an issue with chronic pain and was treated with narcotics administered *via* intrathecal pump. Second malignancies were observed in 2 patients, one with bladder cancer (patient 8), and the other with breast cancer as well as hypernephroma metastatic to the bone (patient 6). Five remaining patients (patients 6, 7, 8, 9 and 11) had uneventful progress in the setting of indolent disease.

Disease progression

Disease progression was observed in 6 patients (1 with local progression only, 5 with systemic with or without local progression). Five of those patients experienced disease progression within the first 3 years after diagnosis. Local tumor bed was the most common site of progression. To date, no patient has survived longer than 10 years and the longest overall survival is 8.6 years.

DISCUSSION

To our knowledge, this is the first series of non-resected ≥ 5-year survivors with pancreatic adenocarcinoma. There are 3 case reports of patients with unresectable pancreatic cancer surviving at least 4 years[27-29]

Table 2 Clinical characteristics of 11 non-resected ≥ 5-year survivors

Patient	Age (yr)	Gender	ECOG	BMI (kg/m²)	Pain	Weight loss	Jaundice	DM	Smoking	Biliary stent	CA19-9 (U/mL)	NLR	Tumor location	AJCC Staging	Initial therapy	Duration of initial therapy (mo)
1	52.3	Female	0	20.8	Yes	No	No	No	No	No	2183.1	2.5	Head	2	VM CRT, GD	9
2	61.6	Male	0	28	No	Yes	Yes	No	No	Yes	200	3.4	Head	3	GD, VM CRT	12
3	62.7	Female	0	24.1	Yes	Yes	No	No	Yes	No	72	1.5	Head	3	GD[1], 5-FU + R[1]	8[1]
4	48.3	Male	0	26.7	No	No	No	No	No	No	9.8	2.2	Head	3	VM CRT, DT	10
5	51.7	Male	0	28	No	Yes	Yes	No	No	Yes	38.8	14.2	Head	3	GD, VM CRT	4
6	66.6	Female	0	21.7	Yes	Yes	Yes	Yes	Yes	Yes	661	4.7	Head	3	VM CRT, GD	8
7	56	Female	0	24.3	Yes	Yes	Yes	No	Yes	Yes	29	1.2	Head	3	VM CRT, GD	10
8	65.4	Male	0	27.8	No	No	Yes	No	Yes	Yes	156.8	10.1	Head	2	GD[1], 5-FU + R[1]	6[1]
9	81	Male	0	27.8	No	Yes	No	No	Yes	Yes	19.3	7.7	Head	4	GD	12
10	72.5	Male	0	27.2	Yes	No	No	No	Yes	Yes	40	2.7	Head	3	5-FU + R	6
11	76.5	Male	0	29.1	No	No	Yes	Yes	No	Yes	594.2	6.4	Head	4	GD	12

[1]Neoadjuvant therapy. NLR: Peripheral blood neutrophil-to-lymphocyte ratio; GD: Gemcitabine and doxetaxel; 5-FU + R: 5-fluorouracil and radiotherapy; VM CRT: Virginia Mason Protocol chemoradiation regimen consisting of interferon-alpha-2b.

and a report of a long-term survivor treated with 57 courses of gemcitabine where the exact survival was not reported[30]. The paucity of such reports is related to the fact that non-resected long-term survivors are exceedingly rare and the literature on long-term survival is focused heavily on patients undergoing resection.

Our study shows that there is a small subset of patients with unresectable pancreatic cancer who can survive at least 5 years. The 11 ≥ 5-year survivors represent only 2% of all non-resected patients undergoing treatment for pancreatic adenocarcinoma from 1995 to 2009 at our institution, and 11% of all ≥ 5-year survivors (Figure 1). The majority of our long-term survivors were younger than 70 years of age, exhibited excellent performance status and had tumors in the head of the pancreas. These were previously identified as favorable prognostic factors in pancreatic cancer[31-33]. Most of our patients were also overweight or obese, supporting the fact that obesity is associated with increased risk of developing pancreatic cancer[34-36]. On the other hand, obesity has also been shown to confer a survival advantage to patients with diseases associated with wasting, such as pancreatic cancer[37,38].

The majority of our non-resected survivors had locally advanced unresectable disease, and all of these patients received chemoradiation (Tables 2 and 3). Chemoradiation in locally advanced pancreatic cancer is thought to improve local disease control but has been investigated with conflicting results[25,39-42]. A selective strategy of first providing chemotherapy followed by chemoradiation has been proposed to minimize radiation-induced toxicities in patients with rapidly progressive tumors during initial chemotherapy and some studies have shown improved outcomes in patients who complete initial chemotherapy and subsequent chemoradiation[38,42,43]. At our institution, induction chemotherapy with gemcitabine and

docetaxel followed by consolidative chemoradiation consisting of interferon-alpha-2b, 5-FU, cisplatin and radiotherapy has been used for patients with locally advanced unresectable disease who do not experience disease progression during induction therapy. The interferon-based regimen is also used as adjuvant therapy in resected patients, which we have previously reported[26].

It is noteworthy that 6 survivors suffered significant morbidities including recurrent cholangitis, liver abscess, malnutrition, second malignancy and small bowel perforation (Tables 2 and 3). In 4 out of 6 patients who died, death was not related directly to tumor: patient 6 died from a perforated duodenal ulcer and sepsis unrelated to tumor; patients 7 and 8 had recurrent biliary sepsis; patient 10 developed sepsis due to bacterial peritonitis in the setting of ascites. Long-term survivors often possess structural alterations to the pancreaticobiliary anatomy, are frequently exposed to endoscopic interventions and receive immunosuppressive therapies, making them susceptible to treatment-induced complications and infections. Hence, a close long-term follow-up is often indicated in these patients.

With regard to disease progression, 6 of the 11 non-resected long-term survivors experienced disease progression. Five of these received second-line therapy and responded favorably, even though 3 of these patients were given a regimen identical to the initial therapy (Tables 2 and 3). These tumors may exhibit characteristics that render them susceptible to cytotoxic effects of chemotherapy. Interestingly, tumor progression occurred most commonly in the local tumor bed which is similar to what has been observed in resected patients - when disease recurrence occurs 5 years after the surgery, it is more often local than distant[18]. Long-term survivors, whether or not resected, may have less propensity to develop distant

Table 3 Clinical characteristics of 11 non-resected ≥ 5-year survivors

Patient	Time to initial progression (mo)[1]	Site of initial progression[1]	Therapy used for progression	Alive	Overall survival (yr)[2]	Cause of death	Clinical progress
1	15.3	Supraclavicular lymph node	5-FU + R	Yes	8.6	N/A	Recurrence in the supraclavicular lymph node was treated with 5-FU and radiotherapy. No further therapy was required and the patient remains alive 8.6 yr after diagnosis
2	37.1	Peritoneum	GD	Yes	5.9	N/A	Prophylactic double bypass surgery was performed at diagnosis. Initial chemotherapy was interrupted by ischemic bowel but completed subsequently. Peritoneal recurrence was treated with GD intermittently over 2.5 yr. The patient remains alive 5.9 yr after diagnosis
3	N/A	N/A	N/A	Yes	5.7	N/A	Resection was attempted however aborted due to occluded common hepatic artery. No major medical issues following initial chemoradiation was noted and the patient remains alive 5.7 yr after diagnosis
4	N/A	N/A	N/A	Yes	5.6	N/A	After initial therapy, patient developed gastric outlet and biliary obstruction requiring endoscopic and radiology interventions. Patient then received salvage therapy for 4 mo with gemcitabine-based combination therapy. This was later stopped as imaging demonstrated stable disease. The patient remains alive 5.6 yr after diagnosis
5	N/A	N/A	N/A	Yes	5.5	N/A	Patient has a remarkable family history of cancers in multiple family members and *BRCA2* gene mutation. Initial therapy was stopped prematurely due to financial issue. GD was re-commended as maintenance therapy for 5 mo. No further therapy was required afterwards and the patient remains alive 5.5 yr after diagnosis
6	N/A	N/A	N/A	No	8.4	Perforated duodenal ulcer and sepsis	Patient's progress was hampered by recurrent cholangitis requiring multiple biliary interventions and second malignancies (breast cancer at 5 yr after the initial diagnosis of pancreatic cancer, recurrent hypernephroma metastasizing to the bone at 7 yr after the initial diagnosis)
7	87.3	Local, mesenteric lymph node, peritoneum	Palliation	No	7.5	Biliary sepsis	After initial therapy, patient developed gastric outlet and biliary obstruction treated with endoscopic stent placement and double bypass surgery. The patient suffered from chronic pain and malnutrition necessitating supplemental feeding and narcotics *via* intrathecal pump, respectively. Seven years after the diagnosis, the patient developed bowel perforation at the site of previously placed duodenal stent and died from sepsis
8	N/A	N/A	N/A	No	6.4	Biliary sepsis	The tumor was resectable but cirrhosis discovered incidentally at laparoscopy precluded patient from resection. The patient developed bladder cancer (2 yr after diagnosis) treated with resection and chemotherapy, and chronic renal failure due to glomerulonephritis (6 yr after diagnosis) requiring hemodialysis. The patient underwent multiple interventions for recurrent cholangitis
9	37.1	local, liver	GD	No	6.4	Disease progression	ERCP at the time of diagnosis was complicated by perforated duodenal diverticulum requiring surgery for the repair of perforation and double bypass surgery at the same time. GD was used intermittently to treat disease progression over 5 yr until death
10	33.6	local	GD	No	6.2	Sepsis due to ascitic fluid infection/ peritonitis	Prophylactic double bypass surgery was performed at diagnosis. Patient was later treated with GD and investigational monoclonal antibody therapy for local and peritoneal recurrence, respectively
11	27.8	Lung	GD	No	5.2	Disease progression	Patient experienced recurrent cholangitis and liver abscess requiring multiple biliary interventions

[1]Disease progression was defined as the presence of recurrent tumor in the pancreas (local) or development of new metastatic focus in a distant organ (systemic) coinciding with patient's symptom and/or rise in Ca 19-9. Time to initial progression was measured from initial diagnosis (the date with the first pathological evidence of pancreatic adenocarcinoma) to the date of first progression; [2]Overall survival was calculated from initial diagnosis to the date of death. The actual date of death was confirmed in all patients by assessing the cancer registry. N/A: Not applicable; GD: Gemcitabine and doxetaxel; 5-FU + R: 5-fluorouracil and radiotherapy.

metastases.

Long-term survival in our non-resected patients implies that the survival may be determined by factors other than the stage of the cancer and treatment, such as tumor biology and host immunity. The tumors in long-term survivors may have a lower number of cancer-initiating cells (aldehyde dehydrogenase-high), cells that possess properties of self-renewal, tumor initiation, and differentiation[44]. Other studies have shown a poorer prognosis in patients who have more mesenchymal tumors, which express vimentin, fibronectin, and N-cadherin[45,46], suggesting that long-term survivors may have tumors with more epithelial features. Although many gene amplifications and deletions, epigenetic changes and proteomic abnormalities have been identified, the biology of pancreatic cancer is still poorly understood. Of particular interest in this regards is that patient 5 (Tables 2 and 3) had a remarkable family history of breast and gastrointestinal cancer and a BRCA2 mutation, a phenotype known to possess unusual sensitivity to PARP-1 inhibitors and platinum based drugs[47,48].

On the other hand, there has been increased interest in the role of host immunity in the outcomes of pancreatic cancer. α-Enolase (ENO1) is an enzyme expressed on the surface of pancreatic cancer cells responsible for cell migration and metastasis. A recent study showed that there was a decreased number of ENO1-specific T helper 17 cells, which have anti-tumor effector function, in patients with pancreatic cancer. Conversely, elevated levels of ENO1-specific regulatory T cells, which lead to the inhibition of the effector T cells and promotes tumor progression, were noted in pancreatic cancer patients[49]. These results may be relevant for the design of novel immunotherapies for pancreatic cancer, include passive immunotherapeutic approaches, such as the use of effector cells generated in vitro, and active immunotherapeutic strategies, whose goal is to stimulate an antitumor response in vivo, by means of vaccination[50].

In addition, the presence of a systemic inflammatory response has been postulated as having prognostic significance in malignancy and high NLR was independently associated with worse outcome in pancreatic cancer[51]. In our small cohort of survivors, a wide range of NLR was observed and further validation in a large population of patients with pancreatic cancer would be useful to determine its predictability in long-term survival.

There are several limitations to our study. Firstly, as our institution is a tertiary referral center, patients may not be an accurate representation of the average patient population. There may be a tendency for patients who are younger with good performance status to be referred and selected for treatment (referral and selection bias). Secondly, histology subtypes and lymphocyte infiltrations in the tumors of the long-term survivors are unknown due to the inadequacy of FNA samples. However, all specimens from the 11 non-resected survivors were re-reviewed by a pathologist to confirm the presence of adenocarcinoma and exclude autoimmune pancreatitis, neuroendocrine tumors and cancers arising from the bile duct, gallbladder and duodenum. In addition, every CT scan used to clinically stage patients in the 11 non-resected survivors was re-reviewed by an experienced pancreas cancer surgeon who had no involvement in the original care of the patients. Thirdly, our study population was predominantly Caucasian and additional studies in patients of other ethnic background are warranted. Lastly, we do not have detailed data for non-resected patients who survived less than 5 years for comparison, which may allow us to identify predictors of long-term survival.

In conclusion, a rare subset of patients with pancreatic adenocarcinoma achieve long-term survival without resection. However, morbidities unrelated to disease were frequently encountered and a close long-term follow-up is warranted in these patients. Our series implies that factors other than the stage of the disease such as tumor biology and host immunity may play a key role in the outcome of patients afflicted with pancreatic cancer. Continued investigation of clinical and molecular prognostic markers is therefore needed in the future.

COMMENTS

Case characteristics
The authors report eleven patients with pancreatic adenocarcinoma who did not undergo curative resection, were treated with oncologic therapy alone and survived 5 years or more.

Clinical diagnosis
Patients presented with pain, weight loss and/or jaundice. Seven patients required biliary stent placement due to obstructive jaundice at the time of initial presentation.

Laboratory diagnosis
The median serum Ca 19-9 was 72 U/mL and 8 patients had a raised Ca 19-9 at the time of diagnosis. Serum bilirubin was raised in 6 patients at the time of diagnosis.

Imaging diagnosis
Staging computed tomography (CT) scan was performed in all patient. CT scans were re-reviewed by an experienced pancreas cancer surgeon who had no involvement in the original care of the patients.

Pathological diagnosis
Patients had biopsy-proven pancreatic adenocarcinoma. The original histopathology slides of all patients were re-reviewed by a single faculty gastrointestinal pathologist to confirm the presence of pancreatic adenocarcinoma.

Treatment
All patients received chemotherapy or chemoradiation, including gemcitabine and docetaxel combination, 5-fluorouracil (5-FU) and radiotherapy or Virginia Mason Protocol chemoradiation regimen consisting of interferon-alpha-2b, 5-FU, cisplatin and radiotherapy. Six patients experienced disease progression, in whom 5 received second-line therapy and responded favorably. Six patients suffered from significant morbidities including recurrent cholangitis, second

malignancy, malnutrition and bowel perforation. These patients required frequent endoscopic and radiological interventions.

Experiences and lessons

A rare subset of patients with pancreatic adenocarcinoma achieve long-term survival without resection but morbidities unrelated to the primary cancer were frequently encountered and a close long-term follow-up is warranted in these patients.

Peer-review

This manuscript report clinical features of long-term survivors of pancreatic adenocarcinoma without curative resection. This case series are well written. The features of long-survivors are detailed.

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