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Use of imaging during symptomatic follow-up after resection of pancreatic ductal adenocarcinoma

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ABSTRACT

Background: Controversy exists whether follow-up after resection of pancreatic ductal adenocarcinoma (PDAC) should include standardized imaging for the detection of disease recurrence. The purpose of this study was to evaluate how often patients undergo imaging in a setting where routine imaging is not performed. Secondly, the pattern, timing, and treatment of recurrent PDAC were assessed.

Materials and methods: This was a *post hoc* analysis of a prospective database of all consecutive patients undergoing pancreatic resection of PDAC between January 2011 and January 2015. Data on imaging procedures during follow-up, recurrence location, and treatment for recurrence were extracted and analyzed. Associations between clinical characteristics and post-recurrence survival were assessed with the log-rank test and Cox univariable and multivariable proportional hazards models.

Results: A total of 85 patients were included. Seventy-four patients (87%) underwent imaging procedures during follow-up at least once, with a mean amount of 3.1 ± 1.9 imaging procedures during the entire follow-up period. Sixty-eight patients (80%) were diagnosed with recurrence, 58 (85%) of whom after the manifestation of clinical symptoms. Additional tumor-specific treatment was administered in 17 of 68 patients (25%) with recurrence. Patients with isolated local recurrence, treatment after recurrence, and a recurrence-free survival >10 mo had longer post-recurrence survival.

Conclusions: Even though a symptomatic follow-up strategy does not include routine imaging, the majority of patients with resected PDAC underwent additional imaging procedures during their follow-up period. Further prospective studies are needed to determine the actual clinical value, psychosocial implications, and cost-effectiveness of different forms of follow-up after resection of PDAC.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related mortality in Europe, with more than 43,000 deaths predicted for 2017.^{1,2} Due to late onset of symptoms, up to 80% of patients present with locally advanced or metastatic disease.³ Most prospective studies for advanced pancreatic cancer involve locally advanced disease, primary metastatic disease, and recurrent disease after surgery.⁴ It has been recently acknowledged, however, that survival outcomes for patients with recurrent disease can be superior when compared to locally advanced and primary metastatic disease, possibly warranting additional treatment for these patients.^{4,5}

Management of recurrent PDAC is less well established as it is for other stages of PDAC. Furthermore, controversy exists as to whether follow-up after pancreatic resection should include imaging testing for the diagnosis of recurrence.⁶⁻⁸ The European Society for Medical Oncology, for instance, only recommends symptomatic follow-up that concentrates on symptoms, nutrition, and psychosocial support without additional diagnostics for diagnosing recurrence.⁹

Adhering to the European guidelines, follow-up at our institution consists of regular checkups focusing on post-operative symptoms without imaging for the detection of recurrence. The purpose of this study was to evaluate how often patients undergo imaging in daily practice based on clinical suspicion of disease recurrence in a setting where routine imaging is not performed. Secondly, the pattern, timing, and treatment of recurrent PDAC resulting from symptomatic follow-up were assessed. Finally, potential predictive factors for extended survival after recurrence were evaluated.

Materials and methods

Patient selection

The primary source of information for this study was the prospective pancreatic surgery database of the UMC Utrecht Cancer Center Department of Surgery, which has been approved by our Institutional Review Board for data acquisition and query. Only patients undergoing pancreatic resection of PDAC between January 2011 and January 2015 were included for analysis. Patients with 30-d perioperative mortality were excluded.

Primary treatment

Resectability and staging were established using pancreatic protocol computed tomography (CT) and were discussed in a multidisciplinary setting. A team specialized in hepatobiliary and pancreatic surgeries performed all pancreatic resections. If their performance status allowed it, patients were offered adjuvant chemotherapy in the form of gemcitabine (1000 mg/m²) every 4 wk for six cycles following Dutch national guidelines based on the "ESPAC" and "CONKO" trials.¹⁰ All patients included in this study were considered resectable or borderline resectable and underwent upfront

surgery. Neoadjuvant therapy for resectable and/or borderline and/or locally advanced PDAC is a relatively recent development in the Netherlands and is generally only performed in the setting of current multi-institutional and national trials. Cancer stage was defined according to the seventh edition of the American Joint Committee on Cancer staging system.¹¹

Follow-up

Patient follow-up occurred at the outpatient clinic of our institution to a standardized schedule of visits. Following completion of all therapy, regular follow-up visits were scheduled at 3, 6, 9, 12, 18, and 24 mo, followed by yearly check-ups up to 5 y. After 5 y, patients were discharged from follow-up. The follow-up was performed by either an hepatopancreatobiliary surgeon or a medical oncologist and consisted mainly of an inquiry concerning postoperative symptoms and signs of endocrine and exocrine pancreatic insufficiency, followed by a physical examination and weight measurement. Imaging was explicitly not part of our standard follow-up protocol.

For this study, the actual use of imaging procedures was assessed to evaluate the results and implications of this follow-up protocol. Only those examinations ordered with a clear inquiry regarding tumor recurrence were included. Radiological or histological evidence was required for the diagnosis of recurrent disease. Only the first site of recurrence was documented, using four mutually exclusive categories. Local recurrence was defined as recurrence in the remnant pancreas or in the surgical bed, such as soft tissue along the celiac or superior mesenteric artery, aorta or around the pancreatojejunostomy site. Distant recurrence was defined as recurrence restricted to a single organ or site. When both isolated local recurrence and isolated distant recurrence were revealed simultaneously, recurrence was defined as "local + distant" recurrence. When multiple distant sites and/or carcinomatosis peritonei were revealed, recurrence was recorded as multiple. Records were further analyzed to determine the type of treatment received after detection of recurrence. Symptomatic recurrences were defined as those discovered due to a significant patient-initiated complaint that was new or had increased in severity or frequency.

Statistical analysis

Summary statistics were obtained using established methods. Patients were dichotomized based on whether recurrence occurred fewer or greater than 10 mo following surgery. This used cutoff point of 10 mo recurrence-free survival (RFS) was found to be the most significant value for showing differences in post-recurrence survival when using a minimum P-value approach to analyze our data and was similar to proposed cutoff in previously published surgical data.^{12,13} The proportion of patients receiving imaging procedures for each month of follow-up was calculated by dividing the amount of patients receiving one or more imaging procedure(s) for the detection of recurrence by the amount of uncensored patients. Censoring occurred at date of recurrence, death, or last follow-up if recurrence did not occur. Also, the median interval between surveillance imaging procedures was calculated for

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