ORIGINAL ARTICLE

Does the surgical waiting list affect pathological and survival outcome in resectable pancreatic ductal adenocarcinoma?

Giovanni Marchegiani, Stefano Andrianello, Giampaolo Perri, Erica Secchettin, Laura Maggino, Giuseppe Malleo, Claudio Bassi & Roberto Salvia

Department of General and Pancreatic Surgery, The Pancreas Institute, University of Verona Hospital Trust, Italy

Abstract

Background: High-volume centers have to deal with long surgical waiting-lists leading to a potential delay in treatment. This study assessed whether a longer time from diagnosis to surgery worsened pathological and survival outcomes in resectable pancreatic ductal adenocarcinoma (PDAC).

Methods: A retrospective analysis of patients treated for resectable PDAC. Difference in size between preoperative CT-scan and specimen, pathological features, the rate of vascular and R1 resections as well as recurrence and survival were analyzed depending on the waiting time using a 30-day cut-off.

Results: Waiting more than 30 days for surgery was associated with an increase in tumor size on specimen when compared with CT-scan (+3 vs. +1 mm, p = 0.04). T and N status, rate of vascular resection, grading, perineural and lymphovascular infiltration, and R1 rates did not differ between groups, as well as tumor recurrence (48.8% vs. 48.9%, p = 0.5) and survival (31 vs. 29 months, p = 0.7). For PDAC < 20 mm, waiting less than 30 days improved overall survival (p = 0.02).

Conclusion: The duration of the surgical waiting-list did not affect pathological features and survival. Delayed surgery was associated with increased cancer size on the specimen. However, surgery should not be delayed for PDACs < 20 mm as this may negatively affect the prognosis.

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Correspondence

Claudio Bassi, General and Pancreatic Surgery, The Pancreas Institute, University of Verona Hospital Trust, P.le Scuro 10, 37134 Verona, Italy. E-mail: claudio.bassi@univr.it

Introduction

After decades of a lack of significant improvement in survival outcome following curative resection for pancreatic ductal adenocarcinoma (PDAC), systemic therapy[1,2] combined with more extensive and radical surgery[3,4] have resulted in significant improvement in prognosis.[5] Surgery still represents the only potentially curative treatment[6] and the role of the institutional case load has been reinforced by recent evidence.[7,8] High-volume centers ensure the best results in terms of surgical technique, postoperative complication management and follow-up strategies. However, substantial patient referral to these tertiary care centers may result in surgical waiting list prolongation.[7,9–11] The Italian national health care system recommends that patients with an overt or suspected malignancy must be operated within 30 days from surgical consultation. However, depending on the actual resources available, this threshold can be exceeded.

A delay in the surgical treatment of solid tumors has been already shown to adversely affect tumor stage and survival outcomes for lung, breast, colorectal and bladder cancers.[12–16] With regards to PDAC, as the doubling time is known to be extremely rapid,[17] a time-effective treatment appears to be of outmost importance. However, specific data regarding the potential impact of delaying the surgical treatment are lacking.

The aim of the present paper is to evaluate the impact of delayed surgical treatment on tumor size and other pathological predictors of prognosis and on overall survival in patients with resectable PDAC.

Methods

Data from patients who underwent standard pancreatic resection for pathologically confirmed PDAC from 2010 to 2014 were identified from the prospectively maintained database of the Department of General and Pancreatic Surgery – The Pancreas

Institute, University of Verona Hospital Trust. The study was approved by the local Institutional review board. Patients undergoing palliative and loco-regional ablation procedures were excluded. Due to the specific endpoints of the study, only patients with a minimum follow-up of 12 months were included. Moreover, all patients lacking preoperative clinical data and computed tomography (CT) images for review were excluded. Patients who had undergone neoadjuvant chemotherapy were also excluded, as surgery was strictly scheduled between 4 and 6 weeks after the last administration of the systemic therapy in these cases. Moreover, tumor size measured at CT after chemotherapy significantly lacks accuracy.[18] Post-operative follow-up was carried out through regular cross-sectional imaging, laboratory test and clinical check-ups at discrete time intervals. Data included demographics, clinical presentation, preoperative cross-sectional imaging, intra-, post-operative, and pathology. Of note, the date of scheduling for surgery was obtained on the same day the patient was placed on the waiting list by the surgeon after evaluation for suspected pancreatic malignancy. The primary endpoint was defined as the increase in tumor size between preoperative CT and pathology. Tumor size was reported as the greatest diameter recorded for both. Secondary outcomes were defined as the rate of R1 resections according to the American College of Pathologists Guidelines,[19] the status of pathological predictors of outcome and TNM according to the AJCC 7th Edition,[20] disease recurrence and overall survival rates.

Statistical analysis was performed using SPSS ver. 20 (SPSS, Inc., IBM, Chicago, IL). Categorical variables were reported as frequencies, continuous variables as median with range or mean with standard deviation, if appropriated. Statistical differences were detected using Chi-square test, Student t-test or Mann–Whitney test, when appropriated. Prognostic factors were evaluated through univariate analysis. Survival was estimated by Kaplan–Meier methods. Differences in survival were tested with the log-rank test. Macroscopically incomplete R2 resections were excluded from survival analysis since, independently from surgical wait time or from any other feature, are associated with a poor prognosis. All p values < 0.05 were considered statistically significant.

Results

A total of 1264 pancreatic resections were performed during the study period, and 531 patients with a diagnosis of PDAC were considered eligible for the study. After excluding patients treated with neoadjuvant chemotherapy or radiotherapy (n = 80), those without complete pathological data and/or preoperative CT (n = 115), and those without accurate data regarding the surgical list wait time (n = 119), the final study population consisted of 217 patients. Their features are shown in Table 1. Reasons for waiting more than 30-days included: need for a complete diagnostic work-up in patients without a typical appearance of malignancy at CT, need for severe and prolonged jaundice relief with endoscopic and/or percutaneous biliary stent placement, patient choice and the variable length of the surgical waiting list during the study period. Median follow-up after surgery was 15 months. The features of the study population are shown in Table 1 and are stratified by surgical waiting time using a 30-day cut-off. Patients who waited for more than 30 days had a greater increase in size of the tumor between preoperative scan and pathology but no differences in terms of R1 or R2 and vascular resection rates were found between the groups. Pathological features including T, N, grading, perineural and lymphovascular invasion were similar between the two populations. Post-operatively, patients of both groups had equivalent access to adjuvant therapies and experienced similar tumor recurrence rates. Similar results were found after expanding the cut-off to 45 days (<45 days vs. >45 days; 154 vs. 63 patients). Patients who waited less than 45 days were confirmed to have a reduced difference in tumor size between preoperative CT and surgical specimen. Of note, the median overall survival was similar (31 vs. 29 months, p = 0.2). Results remained similar after expending the cut-off to 60 days (<60 days vs. >60 days; 187 vs. 30 patients). However, no differences in tumor size increase between CT and surgical specimen were found in this scenario (+2 vs. +2, p = 0.8).

Fig. 1 demonstrates the overall survival stratified for preoperative waiting time. Patients with R2 resections (n = 9) where excluded from the survival analysis given their poor prognosis conferred by the presence of macroscopic cancer residual. No significant difference in the median overall survival was found between those who waited less and more than 30 days (31 vs. 29 months, p = 0.7). Similar results were found for PDAC of the head (31 vs. 28 months, p = 0.2) and of the body-tail (33 vs. 27 months, p = 0.8). After stratifying patients by tumor size, no difference in survival was found for PDAC > than 20 mm at preoperative CT (Fig. 2, 30 months for both <30 days vs. >30 days, p = 0.4). However, a significant difference was found for tumors < 20 mm (n = 84) (Fig. 3), since the median survival of patients operated before 30 days (n = 42) was not reached at the moment of the analysis compared to 28 months of those operated after 30 days (n = 42) (p = 0.02). With regards to pathological features of PDAC < 20 mm at diagnosis, T and N status, perineural and lymphovascular infiltration, grading, vascular resection and R1 resection rate did not differ between > and <30 days groups. However, patients who waited less than 30 days had a reduced rate of nodal metastatic spread (71.4 vs. 85%, p = 0.02).

Table 2 displays the uni- and multivariate analysis for predictors of survival. Nodal metastasis, grading and tumor size were found to be independent predictors of survival, whereas the surgical waiting time did not result as a significant factor in both analyses.

Discussion

The exceptionally aggressive biological behavior of pancreatic ductal adenocarcinoma (PDAC) raises several relevant issues