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Effect of complications on oncologic outcomes after pancreaticoduodenectomy for pancreatic cancer

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ABSTRACT

Background: Although adjuvant therapy (AT) is a necessary component of multimodality therapy for pancreatic ductal adenocarcinoma (PDAC), its application can be hindered by post-pancreaticoduodenectomy (PD) complications. The primary aim of this study was to evaluate the impact of post-PD complications on AT utilization and overall survival (OS).
Methods: Patients undergoing PD without neoadjuvant therapy for stages I-III PDAC at a single institution (2007-2015) were evaluated. Ninety-day postoperative major complications (PMCs) were defined as grade ≥3. Records were linked to the Kentucky Cancer Registry for AT/OS data. Early AT was given <8 wk; late 8-16 wk. Initiation >16 wk was not considered to be AT. Complication effects on AT timing/utilization and OS were evaluated.
Results: Of 93 consecutive patients treated with surgery upfront with AT data, 64 (69%) received AT (41 [44%] early; 23 [25%] late). There were 32 patients (34%) with low-grade complications and 24 (26%) with PMC. With PMC, only six of 24 patients (25%) received early AT and 13 of 24 (54%) received any (early/late) AT *versus* 35 of 69 (51%) early AT and 51 of 69 (74%) any AT without PMC. PMCs were associated with worse median OS (7.1 *versus* 24.6 mo, without PMC, $P < 0.001$). Independent predictors of OS included AT (hazard ratio [HR]: 0.48), tumor >2 cm (HR: 3.39), node-positivity (HR: 2.16), and PMC (HR: 3.69, all $P < 0.02$).
Conclusions: Independent of AT utilization and biologic factors, PMC negatively impacted OS in patients treated with surgery first. These data suggest that strategies to decrease PMC and treatment sequencing alternatives to increase multimodality therapy rates may improve oncologic outcomes for PDAC.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) among all stages has a 5-y survival of only 7.7%.[1] Current guidelines for anatomically resectable PDAC recommend surgical resection for patients who are clinically operable followed by planned adjuvant therapy (AT) with chemotherapy with or without chemoradiation.[2-7] Completion of 6 mo of AT has clearly been shown to improve overall survival (OS) in patients with resected PDAC; so these patients should all be offered AT as part of the multimodality treatment plan.[8] Postoperative complications can contribute to increased mortality after major resections of gastrointestinal cancers[9-14] as well as delay the administration, or cause the omission of, AT and could potentially reduce survival in this manner.[15,16] Patients with PDAC are particularly vulnerable to this problem because of the high inherent risk of their operations. Many patients with delayed healing or major complications never make it to their intended AT.[17] In PDAC patients undergoing upfront surgery, one recent study suggested that the observed OS in patients with postoperative major complications (PMCs) was similar to patients who received chemotherapy alone or those who had no surgery.[14] Although there are increasing data corroborating the negative effect of major complications on oncologic outcomes, this concept is not universally accepted by all surgeons.[18] Nor has it led to widespread changes in treatment sequencing for PDAC, where surgery-first remains the default pathway nationally.[14]

In this context, this retrospective study was designed to evaluate the effect of major complications after PD on AT use and on OS for patients with PDAC treated with surgery upfront. We hypothesized that postoperative complications would decrease the use of AT and be associated with lower OS compared with those with minor or no complications.

Patients and methods

This retrospective single-institution study was approved by the University of Kentucky Institutional Review Board. Electronic medical records were reviewed for all resected patients with stages I-III PDAC from 2007 to 2015, who underwent surgery first treatment sequencing with pancreaticoduodenectomy (PD) at the University of Kentucky. Patients were excluded if they had missing data on AT administration or if they had received neoadjuvant therapy (which was rarely used at a rate of 2.2% of all resected Kentucky PDAC patients before 2013).[7] The variables extracted from the medical records included demographics, perioperative clinicopathologic data, intraoperative details, postoperative morbidity and mortality, and short-term and long-term oncologic outcomes including AT initiation. The Kentucky Cancer Registry (KCR), a statewide database that is part of the Surveillance Epidemiology and End Results (SEER) registries and tracks cancer outcomes data for the population of Kentucky, was used for OS data for these patients, all of whom had their operation at the University of Kentucky. Mandatory reporting by all acute care hospitals in Kentucky and their outpatient facilities to the KCR were required starting in 1991. As a result, KCR has been able to provide high-quality data on more than 25,000 new cases of cancer each year since 1995.[19]

Complications and AT

Post-PD major complications were defined as complications with a Clavien-Dindo grade $\geq$3 and recorded up to 90 d after surgery.[20] "Early" AT was defined as any chemotherapy or radiation therapy administered $\leq$8 wk postoperatively, "late AT" was administered 8-16 wk postoperatively, and "no AT" was administered >16 wk or not at all postoperatively. The cutoff of 16 wk was chosen based on the time interval definition of AT from the American College of Surgeons Commission on Cancer.

Outcomes

Patients were categorized into those with and without major complications. When patients had more than one complication, they were grouped based on the highest level complication, including perioperative death as a grade 5 complication in an intent-to-treat analysis of all resected patients. We then compared the timing and use of AT between these patients. This study also sought to evaluate if demographics, socioeconomic factors, pathology, use of AT, and postoperative outcomes were independent predictors of OS. In a post hoc analysis, we excluded grade 5 complications to measure the impact of only survivable grade 3-4 major complications.

Statistical analyses

Descriptive statistics were carried out for the demographic and clinical factors. Bivariate analysis was used to assess differences between outcomes and those patients with and without major postoperative complications. Kaplan–Meier estimates were used to generate survival curves and median OS. Log-rank tests were used to identify statistical significances of survival curves. Multivariate Cox regression models were used to identify significant factors of OS. Proportional hazard assumption and model fit statistics were examined. All tests were two-sided, and statistical significance was defined as $P < 0.05$. All statistical analyses were calculated using SAS 9.4 (Cary, NC). To exclude the impact of the five patients who died in the immediate postoperative period, we performed an additional OS analysis on the remaining patients with grade 0-4 complications.

Results

Patients and complications

Of 104 total patients identified, 93 (89.4%) met inclusion criteria with sufficient follow-up information. Five patients were excluded for incomplete records and six for insufficient details on AT within 4 mo. The majority ($n = 75$, 80.6%) had stage II pancreatic cancer (Table 1). Fifty patients (53.8%) were