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Conditional survival analysis for patients with intraductal papillary mucinous neoplasms (IPMNs) undergoing curative resection☆

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ABSTRACT

Background: Conditional survival (CS) analysis represents a novel method that may provide more clinically relevant perspectives to cancer management compared to conventional survival analysis. The purpose of this study was to evaluate conditional survival for patients with intraductal papillary mucinous neoplasms (IPMNs) undergoing curative resection.

Methods: A retrospective search of the Surveillance Epidemiology and End Results (SEER) database was performed. Three-year conditional survival (i.e. probability that a patient will survive an additional 3 years if they have already survived x years) was calculated using the formula $3\text{-}CS(x)=OS(x+3)/OS(x)$, where OS represents overall survival.

Results: Overall, 1303 patients were identified, with mean age of 65.2 ± 12.2 years. 3-CS at 1, 3 and 5 years after diagnosis was 35.8%, 47.5% and 44.7%. Patients with stage III/IV disease demonstrated small differences in 3-CS at 1–3 years after diagnosis compared to patients with stage I/II disease (I/II: 35.1%–46.9%, III/IV: 22.1%–42.3%, *d* range 0.09–0.28), while their 3-CS was superior at 4–5 years after diagnosis (I/II: 41.5%–45.7%, III/IV: 57.9%–64.7%, *d* range 0.24–0.47). Differences in 3-CS based on tumor grade displayed a different pattern, with small differences at 1–3 years after diagnosis (well-differentiated (WD)/moderately-differentiated (MD): 34.6%–50%, poorly-differentiated (PD)/undifferentiated (UD): 23.2%–40%, *d* range 0.18–0.24), before becoming prominent at 4–5 years after diagnosis (WD/MD: 50%–51.7%, PD/UD: 24.1%–30%, *d* range 0.4–0.55).

Conclusions: Conditional survival for patients with IPMNs undergoing resection improves over time, especially for patients with high-risk features. This information may be used to provide individualized approaches to surveillance and treatment.

Introduction

Intraductal papillary mucinous neoplasms (IPMNs) are rare pancreatic cystic tumors, comprising an estimated 24% of all pancreatic cystic tumors and 0.5–9.8% of all exocrine pancreatic tumors [1,2]. These tumors are increasingly diagnosed incidentally at early stages due to the advents in axial imaging, but may later progress to invasive tumors [3,4]. IPMNs are characterized by the intraductal proliferation of mucin-producing cells, often forming papillary formations and leading to cystic dilation of the pancreatic ducts [5]. The first International Consensus Guidelines regarding the management of these tumors were published in 2006 and revised in 2012 [6,7]. Based on these guidelines, IPMNs are sub-categorized into main-duct (MD-IPMN), branch-duct (BD-IPMN) and mixed types based on their origin, with MD-IPMN more commonly being malignant and consequently resection of MD-IPMNs is generally recommended for all surgically fit patients. In contrast, surgical resection of BD-IPMNs is more selectively indicated due to a lower incidence of malignancy [7].

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Conventional survival curves estimate patients' expected survival based on clinical characteristics at baseline and may not accurately reflect long-term survival, especially for high-risk groups, such as patients with distant metastatic disease, where likelihood of death is highest during the first few years after diagnosis. In contrast, conditional survival (CS) analysis provides novel, more clinically relevant perspectives in tailoring treatment and surveillance approaches, by also considering the changing survival likelihood after certain time has elapsed from diagnosis. The greatest benefit of employing CS in clinical practice is bestowed on patients with high-risk clinical features at baseline that may benefit from more aggressive treatment or less frequent surveillance if they have survived beyond certain time points, at which point their expected survival is no different from that of patients without these high-risk features. CS is particularly interesting for IPMNs, whose long-term prognosis is superior to that of pancreatic adenocarcinomas with a reported 5 year survival after resection of up to 60% compared to 34.5% for adenocarcinomas, and therefore these patients may benefit from more aggressive treatment strategies in the long run if their expected survival is deemed adequate [8,9]. In addition, no evidence-based recommendations exist at the moment regarding surveillance intervals after resection and CS analysis may serve as the basis for these recommendations. Finally, CS is also helpful for the purpose of patient education by providing estimates of expected survival after a certain number of years have passed from the time of diagnosis. The purpose of this study is to determine CS estimates for patients with IPMNs that underwent curative surgery, as well as determine the impact of high-risk clinical features on CS.

Methods

A retrospective analysis of the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database between 1996 and 2013 was undertaken. The SEER program has been collecting information since 1973 and is estimated to encompass 28% of the population in the United States [10]. Only patients that were diagnosed after 1996 were included, due to the first definition by the World Health Organization that year [11]. Cases were selected based on pancreatic location and ICD-O-3 (International Classification of Disease for Oncology, 3rd Edition) histological classification. The following ICD-O-3 codes were included, based on previous studies that employed the same database: 8050, 8260, 8450, 8453, 8471, 8480, 8481, and 8503 [12–16]. Only patients that underwent cancer-directed surgery were included. In situ tumors and those without positive histologic diagnostic confirmation were excluded from the analysis. To avoid the inclusion of IPMNs that were incidentally discovered during pancreatic resection for other aggressive tumors (e.g. pancreatic adenocarcinoma), patients with concurrent malignant pancreatic tumors were also excluded.

The following parameters were assessed for each patient: age at diagnosis, sex, tumor grade, operative management, AJCC TNM stage, disease-specific survival (DSS) and overall survival (OS). AJCC stages were coded based on the 7th edition staging system. T stage was derived from variables “CS tumor size (2004+)”, “CS extension (2004+)”, “EOD 10 – size (1988–2003)” and “EOD 10 – extent (1988–2003)”. N stage was derived from AJCC stage and “Regional nodes positive (1988+)”. M stage was derived from AJCC stage and “SEER historic stage A”. The study was exempted from Institutional Review Board approval, due to SEER's inclusion of unidentifiable patient information. The extent of resection (i.e. partial or total pancreatectomy) was not specified for some patients and these were designated as “Not specified”.

Statistical analysis

Survival univariate analysis with the log-rank test and multivariate analysis using Cox proportional hazards model were performed. Only variables significant on univariate analysis were included in multivariate analysis. Age was tri-chotomized (<50 years, 50–69 years and ≥70 years) based on the relevance of these age groups for clinical decision-making. Poorly-differentiated and undifferentiated tumor grades were grouped together for the survival analysis due to a low number of undifferentiated tumors. Statistical tests employed two-tailed p-values and 0.05 was used as a threshold of significance. All statistical tests were performed on SPSS v.24 (IBM Corp., Armonk, NY).

Given that a patient has already survived x years after diagnosis, the y-conditional survival is defined as the probability that a patient will survive an additional y years. Three-year conditional survival (3-CS) estimates were calculated using the formula $CS(x)=OS(x+3)/OS(x)$, where OS(x) represents patients' OS 3 years after diagnosis. In this way, eight-year survival data were used to calculate 3-CS up to 5 years after diagnosis. Standardized differences in conditional survival between subgroups were established based on the formula $(P2-P1)/\sqrt{[P(1-P)]}$, employed in similar analyses [17–19]. A d-value $<|0.1|$ indicates very small differences, $|0.1| \leq d < |0.3|$ indicates small differences, $|0.3| \leq d < |0.5|$ indicates moderate differences and $|0.5| \leq d$ indicates considerable differences. For comparison of 3-CS estimates, age was dichotomized at 70 years, whites and blacks (taken together due to similar survival on multivariate analysis) were compared to patients of other races, AJCC I/II stages to III/IV stages, AJCC T1/T2 stages to T3/T4 stages and well-differentiated (WD)/moderately-differentiated (MD) tumors grades to poorly-differentiated (PD)/undifferentiated (UD) ones.

Results

Overall, 1303 patients were identified based on the aforementioned criteria. Mean age at diagnosis was 65.2 ± 12.2 years, 53.3% of patients were males and 46.6% were females. Whites constituted the majority of the cohort (1101 [84.5%]) and most tumors were located at the head (800 [61.4%]), followed by the tail (190 [14.6%]) and body (78 [6%]). Most patients underwent partial pancreatectomy (1061 [81.4%]), while 166 (12.7%) underwent total pancreatectomy (Table 1). Patients were followed for up to 17 years, with median follow-up of 20 months.

Factors associated with DSS

On univariate analysis, age, race, tumor grade and AJCC stage were associated with DSS. Multivariate analysis showed that race (black vs. white: HR 0.94, 95% CI: 0.67–1.33, p = .726, non-black-non-white vs. white: HR 0.57, 95% CI: 0.38–0.87, p = .009), tumor grade (MD vs. WD: HR 1.41, 95% CI: 1.11–1.8, p = .005, poorly-differentiated PD/UD vs. WD: HR 2.04, 95% CI: 1.56–2.66, p < .001) and AJCC stage (II vs. I: HR 3.33, 95% CI: 2.23–4.98, p < .001, III vs. I: HR 6.04, 95% CI: 3.65–10.01, p < .001, IV vs. I: HR 6.81, 95% CI: 4.31–10.76, p < .001) were independent risk factors of DSS (Table 2).

Comparison of OS and CS

Regarding the entire cohort, 3-CS improved over time, while OS decreased. For example, OS at 2 years after diagnosis was 45.6% and decreased to 19.4% at 5 years after diagnosis. In contrast, 3-CS at 2 years (i.e. the probability of surviving an additional 3 years after having survived 2 years) was 42.6%.

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