

Prognostic Factors in Pancreatic Cancer

Åke Andrén-Sandberg

Department of Surgery, Karolinska University Hospital, Stockholm, Sweden

Abstract

Prognostic factors in pancreatic cancer have been a hot topic for the clinical pancreatology, and many studies have been involved in the field. The author reviewed the pancreatic abstracts of American Pancreas Club 2011, and summarized “highlight” of all the abstracts in prognostic factors in pancreatic cancer.

Keywords: Lymph nodes, Mortality, Pancreatic cancer, Perineural invasion, Resection margins, Statistical models

Address for correspondence: Dr. Åke Andrén-Sandberg, Department of Surgery, Karolinska University Hospital, Stockholm, Sweden.
E-mail: ake.andren-sandberg@karolinska.se

Introduction

Pancreatic cancer is a common cause of cancer death. Identification of defined patients based on prognostic factors may improve the prediction of survival and selection of therapy. However, pancreatic cancer is difficult to diagnose early, and the prognosis and treatment options depend on many factors, which significantly affect the quality of the life and survival. The article reviewed the prognostic factors influencing pancreatic cancer survival.

Analysis of Mortality

Although mortality rates from pancreatectomy have decreased worldwide, death remains an infrequent, but profound event at an individual practice level. Root-cause analysis is a retrospective method, commonly employed to understand the adverse events. It was evaluated whether the emerging mortality-risk tools sufficiently predicted and accounted for the actual clinical events that were often identified by root-cause analysis. It was assembled as a Pancreatic Mortality Study Group, which comprised of 32 pancreatic surgeons from 14 institutions

in four countries. Mortalities after pancreatectomy (30 and 90 days) were accrued from 2000–2010. For root-cause analysis, each surgeon deconstructed the clinical events preceding a death to determine the cause. It was further tested to see whether the mortality-risk tools (American Society of Anesthesiologists score (ASA), Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM), Charlson, National Surgical Quality Improvement Project (NSQIP)) could predict those patients who would die ($n=184$), and compared their prognostic accuracy against a cohort of resections in which no patient died ($n=630$). One hundred and eighty-four deaths (151 Whipples, 18 Distals, 15 Totals) were identified from 10,783 pancreatectomies performed by surgeons whose experience averaged 14 years. Overall 30- and 90-day mortalities were 0.92 and 1.71%. Individual institutional rates ranged from 0.3 to 4.7%. Only five patients died intraoperatively, while the other 179 succumbed at a median of 27 days. Mean patient age was 70 years (39% were >75). Eighty-nine percent of the cases were for malignancy, mostly pancreatic cancer (54%). Median operative time was 370 minutes and estimated blood loss was 750 cc (100–16,000). Vascular repair or multivisceral resections were required for 14 and 16%, respectively. Eighty-two percent had a variety of major complications before death. Eighty-four percent required Intensive Care Unit (ICU) care, 51% were transfused, and 36% were reoperated upon. Fifty-two died during the index admission, while another 9% died after re-admission. Almost half ($n=85$) expired between 31 and 90 days. Only 12% had autopsies. Operation-related complications contributed to 42% of the deaths, with pancreatic fistula

Access this article online

Quick Response Code:



Website:
www.najms.org

DOI:
10.4103/1947-2714.92893

being the most evident (16%). Technical errors (23%) and poor patient selection (16%) were cited by surgeons. Five percent of the deaths had associated cancer progression – all occurring between 31 and 90 days. Even after root-cause scrutiny, the ultimate cause of death could not be determined for 41 patients – most often between 31 and 90 days. Even as assorted risk models predicted mortality with variable discrimination from non-mortalities, they consistently underestimated the actual mortality events that were reported. Analysis with POSSUM illustrated the impact of operative performance on determining outcome. It was concluded that root-cause analysis suggested that risk-prediction should include, if not emphasize, operative factors related to pancreatectomy. Although risk models could distinguish between mortalities and non-mortalities in a collective fashion, they vastly miscalculated the actual chance of death on an individual basis.^[1]

Statistical Models

NSQIP represents an important step forward in acuity adjusted outcomes for a surgical patient. There is concern that such a large collection of operation types may result in inadequate predictive capabilities of the model based on procedures. For example, complex pancreatic procedures require a high degree of technical surgical acumen, yet maintain a high morbidity rate related to the procedure rather than the comorbidities. It was sought to establish the relative accuracy and validity of the NSQIP models from the perspective of complex pancreatic procedures. A combined data set of the NSQIP Public Use files (PUF) from 2005 to 2008 was created. NSQIP-generated predicted morbidities and mortalities were used to create the area under the receiver operator curve (AUROC) data. Complex pancreatic cases were flagged utilizing current procedural terminology (CPT) codes. In the four-year period analyzed, there were 7097 complex pancreatic procedures done, which were compared with 568,371 procedures that were not. It was found that the population level prediction model resulted in accurate proportions of complications. When viewed through the lens of the AUROC, which matched the prediction to the actual event at the individual level, the models were much less accurate in the complex pancreatectomy group. Procedures that were technically demanding and could have devastating morbidities not related to the pre-existing co-morbid conditions might not be adequately modeled by the existing NSQIP methodology.^[2]

Risk Score

It was developed and validated a preoperative risk score to predict the 30- and 90-day mortalities after pancreaticoduodenectomy (PD) or total pancreatectomy (TP). Data from consecutive patients ($n=1976$) who

underwent PD or TP, between 1998 and 2009, were obtained from a prospectively maintained institutional database. Multivariate logistic regression was used to develop a simple integer score in 70% of the patients (training cohort) randomly selected, and validated in the remaining 30% of the patients (validation cohort). Age, male gender, preoperative serum albumin, tumor size, total pancreatectomy, and a high Charlson score accurately predicted a 90-day mortality (AUC 0.78), while all these factors except the Charlson score, accurately predicted a 30-day mortality (AUC 0.79). On validation, the predicted and observed risks were not significantly different for 30-day (predicted 1.4% and observed 1%) and 90-day mortality (predicted 3.8% and observed 3.4%). Both scores maintained good discrimination (AUC of 0.74 and 0.73, respectively). The risk scores accurately predicted 30- and 90-day mortalities after pancreatectomy. They might help identify and counsel high-risk patients, support and calculate the net benefits of therapeutic decisions, and as propensity scores, could help control the selection bias in observational studies.^[3]

Resection Margins

The quality of the histopathological workup after oncological resection of pancreatic malignancies substantially has changed the role of surgery as the gold standard for radical tumor clearance over the past years. So far, a 20% incidence of R1 resections has been reported in literature. However, the development of standardized pathological workup protocols has dramatically increased the rate of R1 resections up to 80%. In one study, the incidence of R1 resections and their influence on survival after oncological resections of pancreatic cancer were investigated. A total of 265 pancreatic resections were performed from 2003 to 2010. Histology revealed ductal pancreatic adenocarcinoma in 97 patients (37%), which were included in the study. Various pre-, intra-, and postoperative variables, as well as our routine pathology report were assessed in detail. Follow-up data were obtained via telephone inquiry, directly from the patients, their relatives or their general practitioners. Pancreatic resection comprised of pylorus preserving or classical Whipple resection in 81, a distal resection in eight, and a total pancreatectomy in eight patients. R1-resections were present in 49(51%), R0 resections in 42(43%), R2-resections in four patients (4%), and in two patients the R-status could not be assessed. The percentage of R0 or R1 resections remained largely unchanged over the total study period. The R1 situation was located at the retroperitoneal resection margin in 76% ($n=37$), at the trans-section margin in 14% ($n=7$), and elsewhere in 10% ($n=5$) of the patients. Follow-up was performed for a median of 19 (range 1–75) months postoperatively. Survival was 60% in the R0-resected and 29% in the R1-resected group. Median survival

was 15 months (range 4–42) in R1-resections and 22 months in R0-resections (range 1–75). The 50% R1-resection rate in ductal pancreatic carcinoma indicated high quality routine pathological workup. The majority of the R1 resections were located at the retroperitoneal resection margin. It confirmed the impact of the detailed histopathological analysis on the survival data, after oncological resection of pancreatic cancer.^[4]

Perineural Invasion

Pancreatic ductal adenocarcinoma (PDAC) remains a deadly disease. Neoadjuvant chemoradiation identifies patients with favorable tumor biology, who would likely benefit most from surgery, and provides early treatment for the micrometastatic disease, thereby maximizing the rates of postoperative survival. A complete understanding of the factors associated with favorable survival is lacking in patients who receive neoadjuvant chemoradiation, prior to surgery. Correlation of perineural and blood vessel invasion with various clinicopathological parameters in this group of patients has been sought. Two trained surgical pathologists re-reviewed the surgical specimens of 86 patients with PDAC who received neoadjuvant chemoradiation followed by pancreaticoduodenectomy between 1999 and 2002. The histopathological parameters were assessed and recorded by one pathologist, to exclude observation bias. Blood vessel invasion was defined as the presence of intraluminal viable tumor cells within the vascular spaces lined by the endothelium, having a muscle wall. Perineural invasion was defined as extrapancreatic nerve involvement by the cancer cells, either outside the main tumor mass or at the periphery of the tumor. Blood vessel and perineural invasion were correlated with the overall survival, lymph nodal status, and other clinicopathological factors. The median survival of patients without blood vessel invasion was 34 months, and was significantly longer than that of patients with blood vessel invasion (22 months). Similarly, the median survival of patients without perineural invasion was longer than that of patients with invasion 36 months versus 22 months. Sixty-six percent of the 68 cases who did not show blood vessel invasion did not have nodal metastasis either. In contrast, 83% of the patients with vascular invasion had positive lymph nodes. The rate of nodal metastasis was lower in patients without perineural invasion than those with perineural invasion (36% vs. 58%). Both blood vessel and perineural invasion showed a significant correlation with the retroperitoneal resection margin status. However, there was no significant correlation of either blood vessel invasion or perineural invasion with other clinicopathological parameters, such as, age, gender, tumor size, grade (differentiation), and distant metastasis. It was concluded that perineural invasion and blood vessel invasion were

significantly adverse prognostic parameters of survival in patients with PDAC, who had received neoadjuvant treatment and pancreaticoduodenectomy. Blood vessel and perineural invasion also correlated significantly with nodal metastasis and the retroperitoneal resection margin status.^[5]

Lymph Nodes

Recent studies have offered conflicting views on the most accurate lymph node variable for predicting survival in patients with pancreatic cancer. The prognostic efficacy of the number of positive nodes (PNs) was compared with that of the lymph node ratio (LNR). The Surveillance, Epidemiology, and End Results (SEER) database of 10,254 patients and the MGH (Massachusetts General Hospital) database of 827 patients, resected for pancreatic cancer were reviewed for patient and tumor information. In each dataset, the patients were grouped in tertiles (33%) by the number of lymph nodes (LNs) examined. Accordingly, SEER patients were grouped into <6, 6–12, and >12 LNs. Higher numbers of LNs were evaluated at MGH and corresponding subgroups were <10, 10–16, and >17 LNs. The subsets were homogeneous in terms of patient's age at presentation, tumor size, stage, and site. There was a significant step-wise decrease in the LNR as the number of examined lymph nodes increased: SEER: 0.38 for <6 LNs versus 0.19 for >12 LNs, and MGH: 0.29 for <10 LNs versus 0.15 for >17 LNs. On univariate survival analyses, older age, tumor size, stage, tail tumors, node positivity, and higher LNR (>0.2) were associated with significantly worse survival. Multivariate analyses showed that LNR >0.2 was associated with worse survival in every subgroup and the hazard ratio (HR) increased proportionally when more LNs were examined: SEER, HR <6 LNs: 1.52, 6–12 LNs: 2.95, and >12 LNs 3.25. In the MGH series LNR >0.2 had an adverse effect on survival in all subsets except when <10 LNs were examined; HR: 1.37. The HR increased significantly with the number of nodes examined when at least 10 LNs were examined; 10–16 LNs: 1.61 and with >16 LNs: 2.17. When the LNR was replaced with the PNs in the Cox model, it was found that every positive node was associated with a much smaller increase in the risk of death compared to the LNR, regardless of the number of lymph nodes examined: 1.12 for SEER and 1.14 for MGH. Additionally, the HR was lower when more LNs were evaluated; SEER with >12 LNs: 1.07 and MGH with >16 LNs: 1.11. It was concluded that the contribution of the number of positive nodes to survival was relatively small, and the impact decreased further as more LNs were examined, probably representing stage migration. In contrast an LNR of >0.2 strongly correlated with survival and its power increased with more LNs examined. LNR provided a stronger and more accurate predictor of survival than the number of positive nodes.^[6]

Perioperative blood transfusions

Factors like nodal disease (lymph node ratio), resection margin, grading, and tumor size have been identified as prognostic factors in many series in pancreatic cancer. Overweight and adipositas has recently been suggested as a further (negative) prognostic factor. Perioperative complications and blood transfusions (blood-Tx) have been suggested to worsen prognosis in various cancers. The current experience after resection of pancreatic cancer (PaCa) was analyzed, with additional consideration of the above-mentioned parameters. The long-term outcome could be assessed in 270 patients after resection of pancreatic cancer (81% head, 13% distal, 6% total pancreatectomy), since 1995. Perioperative blood transfusions were given in 46%. One-third of the patients underwent additional mesentericoportal vein resection. Free margins were achieved in 71%. Seventy percent had nodal disease, and 45% had more than one positive node. Postoperative morbidity was 49% (any), 31% (surgical) or 10% (severe, requiring relaparotomy or mechanical ventilation), respectively. Overall five-year survival was 16% (16 true five-year survivors). In univariate analysis positive margins, more than one involved the node, poor grading (G3 / G4) and blood-Tx were associated with poorer survival. Other parameters like body mass index (BMI), tumor size, postoperative complications (all the above definitions), vein resection, gender, location of the pancreatic cancer resection (head / distal) or time period of surgery did not influence survival. In the multivariate (Cox) survival analysis again, the resection margin (RR 1.5), metastatic nodes (> one; RR 1.6), blood-transfusion (RR 1.3), and (borderline) grading, independently influenced the prognosis. It was concluded that long-term prognosis, after resection of pancreatic cancer, was not only influenced by 'established' tumor-related parameters, but also by perioperative blood transfusions.

This effect seemed to be independent of the perioperative complications or type / extent of the resection.^[7]

References

1. Vollmer CM, Sanchez NJ, Kent TS, Callery MP. A root-cause analysis of mortality following major pancreatectomy. American Pancreas Club, 45th Annual Meeting, May 6-7, 2011.
2. Shah R, Velanovich V, Syed Z, Swartz A, Rubinfeld I. Accuracy of the national surgical quality improvement project for modeling complex pancreatic operations. American Pancreas Club, 45th Annual Meeting, May 6-7, 2011.
3. Venkat KO, Puhan MA, Cameron JL, Eckhauser FE, Choti MA, Makary MA, *et al.* Predicting the risk of perioperative mortality in patients undergoing pancreatectomy: A novel scoring system. American Pancreas Club, 45th Annual Meeting, May 6-7, 2011.
4. Moritz K, Schuschian S, Schmidale M, Schwandner F, Alsfasser G, Prall F, *et al.* Incidence and influence of R1-status after oncological resection of pancreatic cancer. American Pancreas Club, 45th Annual Meeting, May 6-7, 2011.
5. Chatterjee D, Katz MH, Lee JE, Wolf RA, Varadhachary GR, Pisters PW, *et al.* Perineural and blood vessel invasion identified after neoadjuvant treatment correlates with poor prognosis in patients with pancreatic ductal adenocarcinoma. American Pancreas Club, 45th Annual Meeting, May 6-7, 2011.
6. Valsangkar NP, Bush DM, Michaelson JS, Fernandez del-Castillo C, Warshaw AL, Thayer SP. Predicting survival in pancreatic cancer: A comparison of lymph node ratio with number of metastatic nodes. American Pancreas Club, 45th Annual Meeting, May 6-7, 2011.
7. Keck T, Wellner U, Sick O, Hopt UT, Makowiec. Perioperative blood transfusions may influence prognosis after surgery for pancreatic cancer independent of complications or body mass index: Multivariate analysis of 270 resected patients. American Pancreas Club, 45th Annual Meeting, May 6-7, 2011.

How to cite this article: Andrén-Sandberg Å. Prognostic factors in pancreatic cancer. *North Am J Med Sci* 2012;4:9-12.

Source of Support: Nil. **Conflict of Interest:** None declared.

Announcement

"QUICK RESPONSE CODE" LINK FOR FULL TEXT ARTICLES

The journal issue has a unique new feature for reaching to the journal's website without typing a single letter. Each article on its first page has a "Quick Response Code". Using any mobile or other hand-held device with camera and GPRS/other internet source, one can reach to the full text of that particular article on the journal's website. Start a QR-code reading software (see list of free applications from <http://tinyurl.com/yzlh2tc>) and point the camera to the QR-code printed in the journal. It will automatically take you to the HTML full text of that article. One can also use a desktop or laptop with web camera for similar functionality. See <http://tinyurl.com/2bw7fn3> or <http://tinyurl.com/3ysr3me> for the free applications.