A Nomogram for Predicting the Benefit of Adjuvant Therapy for Resected Pancreatic Ductal Adenocarcinoma

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Purpose/Objective

Given the poor long-term outcomes of resected pancreatic ductal adenocarcinoma (PDAC), the addition of adjuvant therapy is one avenue to improve survival and local control outcomes. There is no clear consensus regarding the optimal adjuvant therapy, which can consist of either chemotherapy and/or radiotherapy. Identifying which patients will benefit from adjuvant therapy and estimating the magnitude of this benefit remains challenging.

The specific aim was to create a web-based nomogram to facilitate individualized estimates of the potential survival benefit of adjuvant chemotherapy or chemoradiotherapy (CRT) for patients with resected PDAC.

Materials/Methods

We analyzed a prospectively collected cohort of patients (179) between 1996 and 2010 that underwent pancreaticoduodenectomy. Potential covariates analyzed included: age, sex, age, lymphadenectomy, nodal status, histology, margin status, LVSI, PNI. The primary endpoint was OS after surgery alone, with adjuvant chemotherapy alone, or with adjuvant CRT. Several types of multivariate survival regression models were constructed and compared. Forward stepwise variable selection was used to select the final covariates included in the model. Model performance was compared using the Akaike Information Criterion (AIC). The best performing model was internally validated for both discrimination (concordance index) and calibration (calibration curve) using bootstrap resampling.

Results

At the time of analysis, 82% of patients had already expired. The median survival for the entire cohort was 16.4 months. Median overall survival for patients who received no adjuvant therapy, adjuvant chemotherapy alone, and adjuvant CRT was 15.2, 12.6, and 20.8 months, respectively.
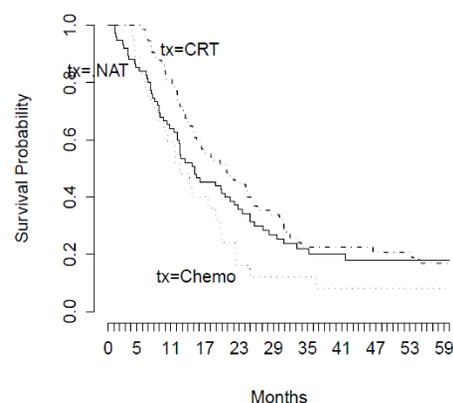

Figure 1. Kaplan Meier Curve- Overall Survival by Type of Adjuvant Treatment

When models were compared using the AIC, the log-logistic and lognormal survival models showed the best performance.

Table 1. Patient & Tumor Characteristics (N=179)

Median Age (range)	65	(26-83)	TNM Stage		
Female Sex (%)	89	(50%)	T1	35	(20%)
			T2	138	(77%)
LVSI			T3-T4	6	(3%)
Yes	69	(39%)			
No	66	(37%)	Number Positive Nodes		
Unknown	44	(25%)	0	66	(37%)
			1	31	(17%)
Perineural Invasion			2+	82	(46%)
Yes	143	(80%)			
No	19	(11%)	Grade		
Unknown	17	(9%)	G1	13	(7%)
			G2	92	(51%)
Margins			G3	59	(33%)
Positive	45	(25%)	Unknown	15	(8%)
Close (<1mm)	24	(13%)			
Negative	102	(57%)	Adjuvant Treatment		
Unknown	8	(4%)	None	75	(42%)
			Chemo alone	27	(15%)
			CRT	77	(43%)

Table 2. Gamel Boag Lognormal multivariate regression model parameters.

Covariate	Beta Coefficient	p-value
Intercept (β_0)	3.969	<.0001
tumor size > 2cm	-0.231	0.249
node positive	-0.681	0.003
margins positive	-0.633	0.005
perineural invasion	-0.509	0.040
chemo	0.564	0.310
chemoRT	0.304	0.254
margins * chemo	-0.226	0.592
margins * chemoRT	0.154	0.614
node * chemo	-0.109	0.852
node * chemoRT	0.288	0.362
log(σ)	-0.146	0.016

Figure 2. Example comparison of Log-Normal (LN) survival model curve (dotted) with actual Kaplan-Meier (KM) data (solid) for a T2N1 pancreatic CA pt with positive margins and positive perineural invasion.
Abbreviations:
KM: Kaplan-Meier
LN: Log-Normal
S: Surgery
C: Chemotherapy
CRT: Chemoradiotherapy
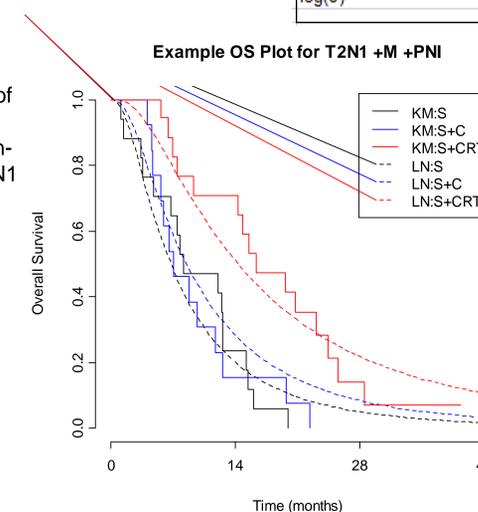
A web browser-based nomogram was built from the lognormal model that can make individualized estimates of survival benefit from adjuvant therapy. The concordance index of this model was 0.66.

Figure 3. Browser- based software application that calculates the potential benefit of adjuvant therapy for an individual patient. This browser can be assessed at
http://skynet.ohsu.edu/nomograms/pancreas

The model predicts that nodal status, margin status, and PNI are the most important factors predicting outcome and patients with positive nodes, positive margins, or PNI yield the most benefit from adjuvant CRT.

Conclusion

An online nomogram built from a parametric survival model can be used as a decision aid to predict and quantify the expected benefit from adjuvant chemotherapy or CRT for resected pancreatic cancer.