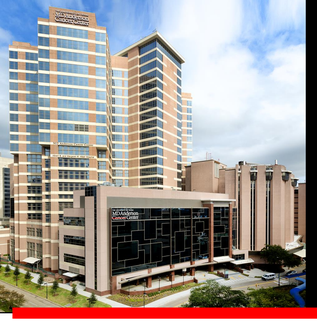

Mathematical Modeling of CA19-9 Normalization in Pancreatic Cancer Patients

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Introduction

Pancreatic cancer has shown little improvement in the 5-year survival rate since the 1970s (Rawla et. al. 2019)

CA19-9 is the most widely used biomarker for pancreatic cancer (Kleeff et. al. 2016)

Normalization of CA19-9, defined as levels < 40 U/mL, is associated with improved prognosis (Tzeng et. al. 2014)

We aimed to identify the trends of CA19-9 levels in patients with pancreatic cancer undergoing chemotherapy and develop a mathematical model that predicts outcomes to enhance treatment protocol.

Methods

- CA19-9 data was collected from 732 patients.
- Patients were selected for modeling if they met the following criteria (**Table 1**):
  - Baseline CA19-9 level above normalization (40 U/mL)
  - Normal bilirubin prior to therapy(<2.0 mg/dL)
  - No metastasis
  - Uninterrupted FOLFIRINOX or Gemcitabine/Abraxene for 6 months
  - 2+ CA19-9 measurements in addition to baseline
- CA19-9 data were fit to a Type A ("A"lways decreasing) or Type B ("B"idirectional) exponential decay model (**Fig. 1**)
  - $Y[t]=\alpha*\exp(\beta[t])$
  - Y(t): CA19-9 level at time t
  - T(0): Chemotherapy start date
  - A and β: Model parameters describing the shape of the response curve
- Model efficacy was compared to the "Ground Truth" (GT) presence or absence of CA19-9 normalization within 0-6 months
- ROC and Kaplan-Meier curves assessed model results
- Outcomes and patient trends were analyzed with Likelihood Ratio, Log Rank, and AUC tests

Patient Demographics

	CA19-9 Normalizers (n=34)	CA19-9 Non-normalizers (n=52)	Total (n=86)
Male	19	23	42
Female	15	29	44
Median Age [Range]	66 [31-83]	67.5 [45-86]	66.5 [31-86]
Gemcitabine/Abraxene	16	24	40
FOLFIRINOX	18	28	46
Borderline Resectabl (BR)	11	15	26
Locally Advanced (LA)	13	33	46
Resectable	10	4	14

Table 1. Patient Demographics: 86 patients met the criteria for inclusion. Patient counts are provided for normalizers and non-normalizers; categorized by sex, median age, type of chemotherapy, and type of PDAC.

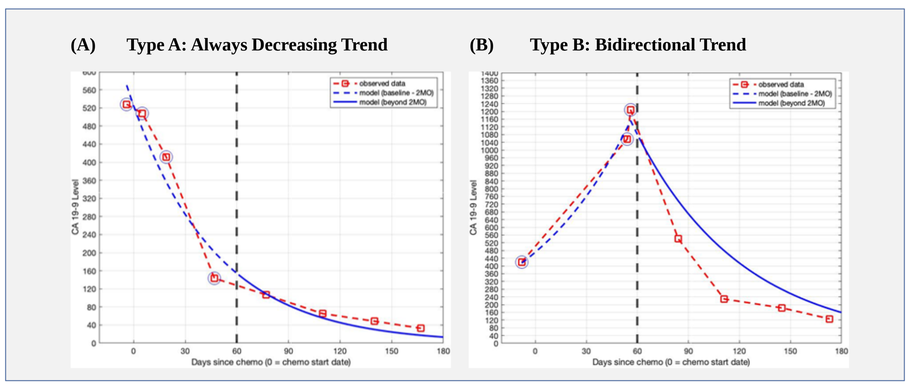
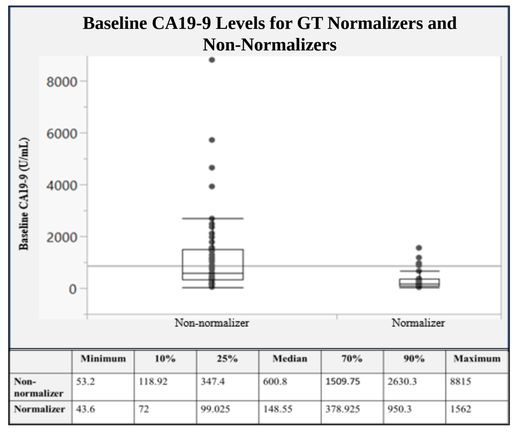


Fig 1. CA19-9 Prediction Model Design: Patients with CA19-9 levels decreasing during the initial period (t; 0-60) were fit to the Type A model (**A**). Patients with an increase in CA9-9 during the initial period followed by a decrease after T months were fit to the Type B model (**B**). Type B is a piece-wise defined curve where its first component has an increasing trend and the second has a decreasing trend of equal magnitudes with the turning point of f(t) as t=T.

Results



	Minimum	10%	25%	Median	70%	90%	Maximum
Non-normalizer	53.2	118.92	347.4	600.8	1509.75	2630.3	8815
Normalizer	43.6	72	99.025	148.55	378.925	950.3	1562

Fig 2. CA19-9 Normalization by Baseline Levels: Baseline CA19-9 levels were evaluated with respect to eventual normalization and non-normalization. Normalizers had a lower baseline CA19-9 (median 148.55 U/mL [range 43.6-1562]) compared to non-normalizers (median 600.8 U/mL [range 53.2-8815], ANOVA, p=0.0016).

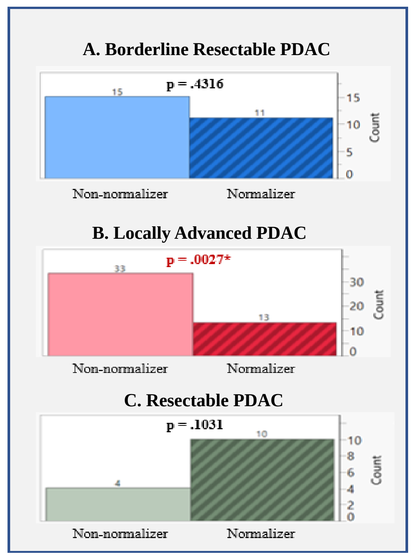
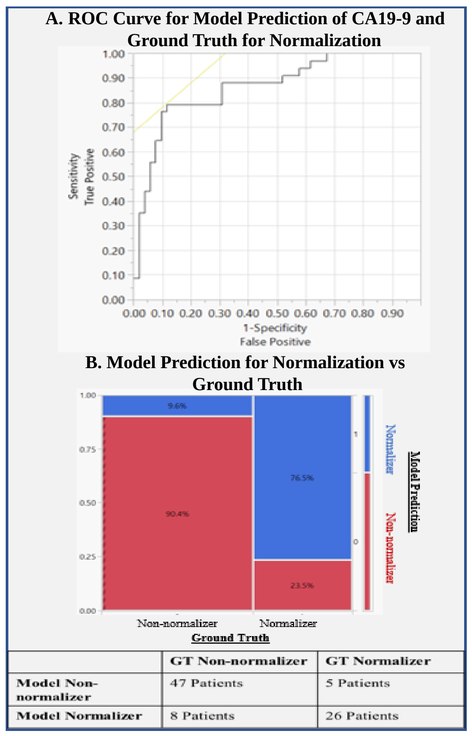


Fig 3. CA19-9 Normalization by Disease Class: Proportions of patients that normalized in each disease class were assessed with Likelihood Ratios to determine if type of PDAC affects CA19-9 normalization. 11 of 26 patients with BR PDAC **(A)** normalized (p =0.4316). 13 of 46 patients with LA PDAC **(B)** normalized (p=.0027). 10 of 14 patients with Resectable PDAC **(C)** normalized (p=.1031).



	GT Non-normalizer	GT Normalizer
Model Non-normalizer	47 Patients	5 Patients
Model Normalizer	8 Patients	26 Patients

Fig 4. Assessment of Model Accuracy: An ROC curve **(A)** for normalization of CA19-9 from the model's prediction within 6 months was generated to analyze model performance (AUC = .866). 73 of the 86 total patients had model results matching the GT presence or absence of normalization **(B)**.

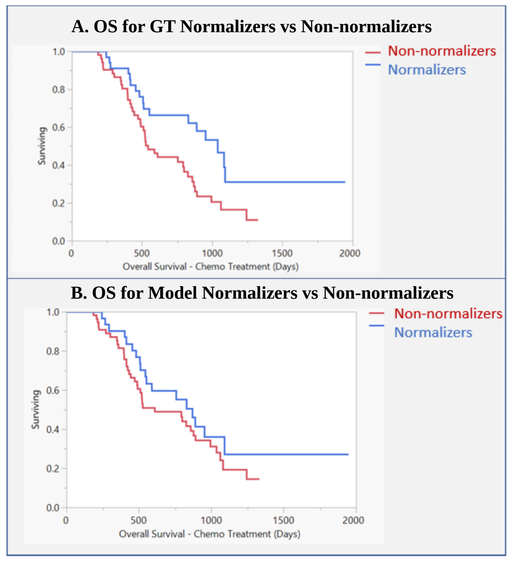


Fig 5. Kaplan-Meier Curves for GT and Model OS: Overall survival in days from the start of chemotherapy was plotted for normalizers and non-normalizers using GT and model responses. GT normalizers **(A)** had a median OS of 1037 days compared to 544 days for non-normalizers (Log rank, p= .0115). Model normalizers **(B)** had a median OS of 870 days compared to 611 days for non-normalizers (Log-rank, p=0.2441)

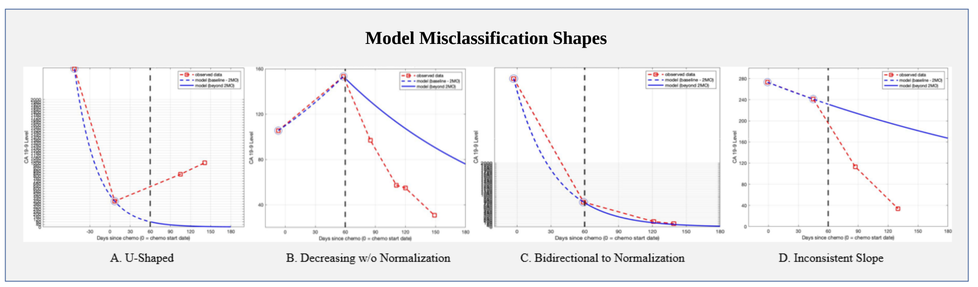


Fig 6. Visualization of Model Misclassification Shapes: 5 patients were misclassified as normalizers by the model: 2 demonstrated a "U-shaped" change in CA19-9 **(A)** and 3 decreased without normalization **(B)**. 8 patients were misclassified as non-normalizers by the model: 7 demonstrated a "bidirectional to normalization" change in CA19-9 **(C)** and 1 demonstrated an inconsistent rate of decline **(D)**.

- Normalizers displayed significantly lower baseline CA19-9 levels (p=.0016) compared to non normalizers (**Fig. 2**)
- Patients with LA PDAC are less likely to normalize (Likelihood Ratio, p=.0027) compared to patients with BR or Resectable PDAC (p > .05) (**Fig. 3**)
- Application of the model to predict CA19-9 normalization during 6 months of chemotherapy treatment accurately characterized 73 patients (AUC= .866) (**Fig. 4**)
- Although both the GT and model responses demonstrated longer median OS for normalizers compared to non-normalizers, the difference was only statistically significant for the GT patients (Log rank, p = .0115) (**Fig. 5**)
- Analysis of misclassifiers showed specific response patterns associated with the inaccurate model prediction (**Fig. 6**)

Conclusions

- The model performed well in predicting normalization for a small subset of patients but requires further refinement for enhanced prognostic capabilities and applications to more diverse patient profiles and CA19-9 response patterns.
- Ongoing work will examine additional parameters, test statistical models, and approach methods to account for continuous elevation of CA19-9.

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