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”ways decreasing) or Type B (“B”idirectional) exponential decay model (Fig. 1)
  - Y(t)=a*exp(-βt)
  - 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

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.

<table>
<thead>
<tr>
<th>Model Parameters</th>
<th>Baseline CA19-9 Normalizers (n=52)</th>
<th>Baseline CA19-9 Non-normalizers (n=34)</th>
<th>Total (n=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>21</td>
<td>12</td>
<td>33</td>
</tr>
<tr>
<td>Female</td>
<td>31</td>
<td>22</td>
<td>53</td>
</tr>
<tr>
<td>Median Age (years)</td>
<td>66 (IQR: 53-70)</td>
<td>61 (IQR: 56-69)</td>
<td>61 (IQR: 56-69)</td>
</tr>
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<td>Chemotherapy</td>
<td>FOLFOX</td>
<td>GEM/ABR</td>
<td>FOLFOX/ABR</td>
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<td>BR</td>
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<td>24</td>
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</tr>
<tr>
<td>Resectable</td>
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<td>27</td>
</tr>
<tr>
<td>Locally Advanced</td>
<td>13</td>
<td>21</td>
<td>34</td>
</tr>
</tbody>
</table>

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Fig. 1. CA19-9 Prediction Model Design: Patients with CA19-9 levels decreasing during the initial period (1; 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

- 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.

Acknowledgements
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References