Predicting imminent disease progression in advanced colorectal cancer by a machine-learning algorithm

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Abstract #645

Background

In advanced cancers, predicting disease progression before its clinical manifestation enables an earlier switch to the next treatment line prior to deterioration in the patient's state, potentially improving survival. Yet, at present, serum tumor markers such as carcinoembryonic antigen (CEA) are poor indicators even of the current tumor state, and certainly cannot be used for forecasting future outcomes such as progression[1,2].

We developed a machine-learning algorithm alerting to approaching disease progression in patients with Colorectal Cancer (CRC), using longitudinal tumor marker input.

Methods & Results

Two types of datasets containing advanced CRC patients under standard-of-care 1st line treatment were collected (Tab. 1):

- **Clinical study data** obtained from control arms of 3 trials (FL-4/6, FL-Pan; derived from projectdatasphere.org);
- **Real-world evidence** obtained from Hadassah Medical Center (HMC).

Table 1. Data characteristics. Patients were eligible for the study if their individual data contained sufficient tumor response assessments and tumor marker measurements (as detailed in box below).

Data type	Clinical studies		Hospital-registry
Dataset (acronym)	FL-4/6	FL-Pan	HMC
Study (NCT identifiers)	NCT00272051 NCT00305188	NCT00364013	NCT02577627
Number of patients			
Total patients	756	935	132
Study-eligible patients	489	729	92
Age			
Median, years (range)	62 (22-83)	62 (27-82)	62 (24-89)
Gender			
Male / Female	283 / 206	471 / 258	52 / 40
Treatment			
FOLFOX	489	371	16
FOLFOX + Panitumumab	-	358	2
FOLFOX + Bevacizumab	-	-	24
FOLFIRI +/- Bevacizumab	-	-	14
Other regimens	-	-	36
Tumor assessments			
Progression events	175	251	32
Non-progression events	741	1818	142
Follow-up until progression			
Median, months	5.6	6.7	6.3
Number of tumor marker measurements			
CEA	1047	2400	313
CA19.9	-	-	224

Excluded patients:
- Patients with less than 2 tumor response assessments
- Patients with less than 3 tumor marker measurements

Excluded data:
- Early tumor marker measurements (<1 month after treatment onset)
- Late tumor marker measurements (post 1st line treatment)
- Treatment periods with sparse tumor marker measurements (>3 month between measurements)

References:
[1] Accordino MK et al. J Oncol Pract 2016;12(1):65-6, e36-43. [2] Holdenrieder S et al. Biomed Res Int. 2016; 9795269. [3] Kogan Y et al. J Clin Oncol 36, 2018 (suppl; abstr e21190).

Can Tumor Marker Values Directly Predict Progression?

Basic prediction potential of the tumor markers was examined by current methods:

- **Receiver operating characteristic (ROC) analysis** on marker values monitored in-treatment (Fig. 2);
- **ROC-derived classification trees** tested in a leave-one-out cross-validation process (Tab. 2); the marker value threshold was set to approximate 90% specificity.

Across the various datasets, CEA and CA19.9 values alone had poor predictive ability for progression **(Fig. 1, Tab. 2)**.

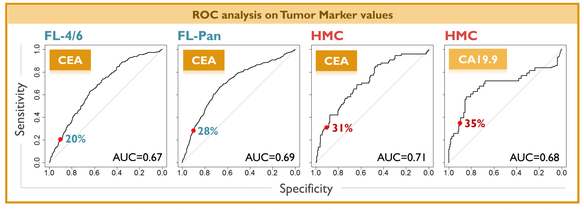

Figure 1. Tumor marker values as weak indicators for progression. ROC curves show the correlation between marker values and upcoming progressive disease (RECIST 1.1) in CRC patients. Sensitivity at points of 90% specificity is marked. AUC - area under curve.

Table 2. Poor performance of tumor marker value-based classification trees. Each classifier was derived from ROC analysis using one marker.

Dataset	FL-4/6	FL-Pan	HMC	HMC
Markers	CEA	CEA	CEA	CA19.9
Sensitivity	20.3%	28.1%	31%	37%
Specificity	90%	89.9%	89.5%	90%
Cohen's Kappa	0.12	0.2	0.23	0.29

With current methods, **tumor markers carry weak signals** and **are not useful** for indicating approaching progression

Algorithm Architecture

The algorithm was designed to process longitudinal tumor marker(s) and predict progression up to 3 months prior to radiological detection.

- **Modeling approach:** machine-learning using an R platform.
- **Training:** the Random Forest algorithm was trained using dynamic tumor marker features as input, and tumor assessment records (evaluated by RECIST 1.1) as output.
- **Testing**: leave-one-out cross-validation on the same dataset or separate testing on another dataset were performed, accuracy being evaluated separately for each test set.

Development of the Algorithm

Trained only on CEA values, the algorithm accurately pinpointed the majority of progression events in the clinical datasets **(Tab. 3)**.

	Cross-Validation		Testing	
Training dataset	FL-4/6	FL-Pan	FL-4/6	FL-Pan
Testing dataset	FL-4/6	FL-Pan	FL-Pan	FL-4/6
Sensitivity	57%	52%	68%	51%
Specificity	88%	90%	77%	93%
Positive Predictive Value	64%	54%	40%	72%
Negative Predictive Value	84%	90%	92%	83%
Accuracy	79%	83%	76%	81%
Cohen's Kappa	0.46	0.43	0.35	0.48

% of progression events accurately predicted (out of all observed progression events)

% of non-progression events accurately predicted (out of all observed non-progression events)

Table 3. Algorithm performance metrics after training/testing on clinical study CRC data.

The algorithm signals imminent progression at **high specificity and sensitivity**, and can prompt a timely switch to next line therapy

The algorithm predicts progression **at a suitable time** prior to clinical detection

Validation of the Algorithm

The clinical dataset-trained algorithm shows good performance also in real-world data **(Tab. 4)**.

Table 4. Algorithm testing on CRC patients in the Hadassah registry.

	Independent Testing	
Training dataset	FL-4/6	FL-Pan
Testing dataset	HMC	HMC
Sensitivity	70%	58%
Specificity	81%	88%
Positive Predictive Value	53%	61%
Negative Predictive Value	90%	87%
Accuracy	78%	81%
Cohen's Kappa	0.46	0.47

The algorithm uses **simple, accessible, low-cost markers,** and **enhances their value** for predicting progression

Multiple-Marker Algorithm

Combining CEA and CA19.9, the algorithm anticipates progression events at a high accuracy level (**Tab. 5**).

Table 5. Algorithm performance metrics in CRC patients using CEA and CA19.9 data.

	Cross-Validation
Training/Testing dataset	HMC (CEA + CA19.9)
Sensitivity	58%
Specificity	92%
Positive Predictive Value	65%
Negative Predictive Value	90%
Accuracy	86%
Cohen's Kappa	0.53

The algorithm can combine **multiple tumor markers** to produce an **even stronger progression signal** (better accuracy)

A New Paradigm for Algorithm-aided Clinical Practice

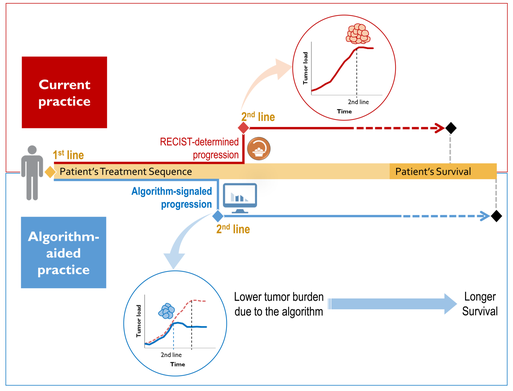

Figure 2. The concept underlying our algorithm. The algorithm provides an early alert of impending progression, allowing an earlier switch to 2nd line therapy, thus limiting the increase in tumor load, and ultimately extending survival of cancer patients.

Conclusions and Implications

- By machine-learning, we created a **new algorithm that amplifies weak signals from tumor markers** monitored during treatment, **to produce a strong alert of disease progression just before the tumor surges** (Fig. 2).
- The algorithm-amplified ability of CEA to predict progression in CRC complements our recent findings in non-small cell lung cancer, where CEA integrated with 4 other markers provides 91% specificity and 66% sensitivity in predicting progression, surpassing the low capacity of each separate marker.[3]
- Similarly, adding more markers is expected to boost the prediction capacity of the current algorithm for CRC.
- By **individually timing the therapy switch before disease deterioration**, the algorithm can **enhance the efficacy of 2nd line drugs**, thus **extending progression-free survival and overall survival rates** in cancer patients (Fig. 2).
- The paradigm of **algorithm-aided improvement of cancer treatment** can also be applied to further lines of therapy (e.g. 3rd line drugs) and additional indications.

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