MAYO CLINIC PROCEEDINGS: DIGITAL HEALTH

ORIGINAL ARTICLE

Predicting Tolerance to Anthracycline Chemotherapy Using Electrocardiogram-Based Artificial Intelligence in Sarcoma

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Abstract

Objective: The objective of this study was to understand the utility of artificial intelligence-enabled electrocardiogram (AI-ECG) to assess the tolerability of anthracycline chemotherapy.

Patients and Methods: From December 18, 2006 to October 15, 2020, we identified adults with sarcoma who were treated with anthracycline chemotherapy at our institution who had an ECG within 1 year prior to treatment initiation. Utilizing previously defined AI-ECG nomograms, we obtained age and ejection fraction (EF) predictions. Changes in AI-ECG age were correlated with chemotherapy tolerance (the rates of dose reductions, treatment delays, and early discontinuation). We measured the sensitivity and specificity of the ECG to predict an EF of less than 50% or 35% prior to treatment and compared how changes in the AI-ECG EF prediction related to changes in echocardiography-based EF.

Results: Forty patients met the eligibility criteria. Sixty-eight percent of the patients were men. The median age was 56.5 years (18-76 years). We did not find differences in chemotherapy tolerance between patients who had an elevated or decreased ECG age. There was a trend `toward higher rates of dose reductions in patients with high ECG aging (odds ratio, 5.13; P=.32). The AI-ECG low EF prediction had a sensitivity of 100% and a specificity of 94% to isolate patients with an EF of less than 50% prior to treatment. Two patients' EF decreased more than 10% after treatment, and both cases showed significant increases in the low EF prediction.

Conclusion: Overall, AI-based predictions on ECG tracings could be a way to monitor for decreases in EF during treatment with anthracycline chemotherapy. We recommend further studies to evaluate AI-ECG aging as a marker for chemotherapy tolerance.

Anthracycline-based chemotherapy is the first-line systemic treatment for most bone and soft tissue sarcomas.[1,2] However, treatment related cardiovascular adverse effects can lead to poor treatment tolerance and require close monitoring.[3] Although the incidence rate of anthracycline-induced cardiomyopathy remains debated, cumulative doses above 200 mg/m^2 raise the risk of developing long-term toxicities.[3] In the setting of sarcoma, these cumulative doses are commonly met, with treatment regimens exceeding 400 mg/m^2.[4] As a result, modern sarcoma trials have incorporated dexrazoxane as a cardioprotectant and ejection fraction (EF) monitoring to mitigate or identify anthracycline-induced cardiomyopathy, respectively.[5]

Currently, physician estimate of performance status (either by the Eastern Cooperative Oncology Group performance status or Karnofsky performance status) is used to predict the tolerance of treatment.[6,7] Although these models are pragmatic, they are limited by interobserver variation along with an inability to predict organ-specific toxicities.[6,7]

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There have been several attempts to improve the Eastern Cooperative Oncology Group performance status and the Karnofsky performance status to predict who will tolerate cancer-directed therapies.[6,7] However, more research is needed to define ways to predict chemotherapy tolerability and, in the case of anthracycline-related cardiotoxicity, reduce the financial burden incurred by incorporating cardioprotectants or increased left ventricular (LV) function monitoring.

One exciting area of development is using artificial intelligence (AI) to develop novel models of risk stratification for tolerance to chemotherapy.[8] Previous studies have shown that age as predicted from convolutional neural network predictions from electrocardiogram (ECG) tracings could serve as a marker for "biological" health.[9] Additional studies have shown that a similar framework can predict patients who have decreased left ventricular ejection fraction (LVEF) or are at risk of decreased LVEF in the future.[10]

We aimed to assess the utility of AI-enabled ECG (AI-ECG) predictions of age and EF to assess the tolerability of anthracycline-based chemotherapy. We hypothesize that patients with extreme increases in AI-ECG age (ie. large differences between AI-ECG-predicted age and chronological age) or accelerated ECG aging will have poor tolerance to therapy. We also hypothesize that the AI-ECG-based EF prediction may identify those at risk for anthracycline-induced decreases in LVEF.

PATIENTS AND METHODS

Patient Selection and Chart Review

We identified adults (aged $\geq$ 18 years) with sarcoma who were treated with an anthracycline at Mayo Clinic Rochester from 2006 to 2020 and had an ECG within 1 year prior to treatment initiation. We selected the ECG closest to the start date of anthracycline chemotherapy unless there were more than 180 days between the ECG and pretreatment echocardiogram, in which case the ECG closest to the echocardiogram was selected.

The electronic medical record was reviewed to capture patient and cancer demographics, treatment history (including lifetime dosages of anthracycline), tolerance of treatment (defined as rates of dose reductions, treatment delays, and early discontinuation of chemotherapy), cardiac comorbidities (hypertension, diabetes, heart failure, history of myocardial infarction, obesity, BMI greater than 30, and hyperlipidemia), and echocardiogram reports. ECGs were also collected for the 1-year period after completion of anthracycline-based treatment. We selected the ECG closest to the end date of anthracycline chemotherapy unless there were more than 180 days between the ECG and post-treatment echocardiogram, in which case, the ECG closest to the echocardiogram was selected. AI-ECG predictions for age and EF were also collected for each patient. The neural networks and validation of these AI-ECG predictions have been previously described.[9,10]

This study was reviewed and approved by the Mayo Clinic Institutional Review Board and a Health Insurance Portability and Accountability Act waiver was approved (ID 23-007295 8/17/2023).

Outcomes

Echocardiograms were selected within 1 year of treatment initiation or discontinuation. Left ventricular ejection fraction was abstracted for each pretreatment and post-treatment echocardiogram. In accordance with American College of Cardiology guidelines for monitoring chemotherapy-related LV systolic dysfunction, the global longitudinal systolic strain was abstracted for each pre- and post-treatment echocardiogram.[11] LV strain less than -18% was defined as normal, strain -16 to -18% was defined as borderline, and strain greater than -16% was defined as abnormal.

Age deviation was defined as the difference between the patient's chronologic age and AI-ECG-predicted age. Extreme age deviation was defined as a difference of ± 7.4 years between the chronologic age and AI-ECG-predicted age.[12] We defined the rate of ECG aging as (Δ AI-ECG age before and after treatment)/(Δ chronological age before and after treatment). A high aging rate was defined as a ratio greater than 1, and a low aging rate was defined as less than 1. Tolerance of treatment was compared between patients with

extreme age deviations along with high and low ECG aging.

We measured the sensitivity and specificity of the AI-ECG prediction for a low EF with a threshold of 0.256 to predict an EF of less than 50% or 35% prior to treatment.[10,13] We then compared how numeric changes in the AI-ECG-low EF prediction before and after treatment related to changes in the pre- and post-treatment echocardiogram-based EF. An ECG-echocardiogram pair was considered valid if the 2 studies were within 180 days.

Statistical Analyses

Welch 2 sample *t* tests with unequal variance were used to compare means between the 2 groups. For chemotherapy outcomes with AI-ECG age deviation, we completed a binomial logistic regression accounting for biological age (dose reductions, treatment delays, and early discontinuation of chemotherapy). Odds ratios (OR) were calculated as the e^{β} for the respective independent variable in the model. For accelerated aging outcomes, ORs and *P* values were calculated using Fisher exact tests (dose reductions, treatment delays, and early discontinuation of chemotherapy). Kaplan-Meier survival curves with a Cox-proportional hazards regression model were used to compare overall survival (OS) and relapse-free survival (RFS) between the relevant groups. All statistical analysis was completed in R (4.3.2). The code used to perform analysis will be available upon reasonable request.

RESULTS

AI-ECG-Predicted Age Trends With Chronologic Age but Not Chemotherapy Tolerance

Forty patients (27 men; 67.5%) were included in the study. The median age at diagnosis was 56.5 years (range: 18-76 years). Most patients had localized disease (n=33, 82.5%), and the mean cumulative anthracycline dose was 215 mg/m^2 (Table 1). The most common anthracycline-based regimes were doxorubicin/ifosfamide (n=15, 37.5% of patients)

TABLE 1. Patient Demographics and Clinical Characteristics

Characteristics	N (%)
Total patients	40 (100)
Male	27 (67.5)
Female	13 (32.5)
Age at diagnosis	
Mean	51.73 ± 17.48
Median	56.5
Range	18-76
Metastatic vs localized	
Localized	33 (82.5)
Metastatic	7 (17.5)
Pathology	
Osteosarcoma	12 (30)
UPS	6 (15)
Ewing sarcoma	4 (10)
Myxofibrosarcoma	3 (7.5)
Sarcoma NOS	3 (7.5)
Chondrosarcoma	2 (5)
Leiomyosarcoma	2 (5)
Pleomorphic RMS	2 (5)
Alveolar soft part sarcoma	1 (2.5)
Myxoid liposarcoma	1 (2.5)
Pleomorphic sarcoma	1 (2.5)
Pleomorphic liposarcoma	1 (2.5)
Spindle cell sarcoma	1 (2.5)
Synovial sarcoma	1 (2.5)
Medical comorbidities	
Hypertension	22 (55)
Diabetes	6 (15)
History of heart failure	2 (5)
History of myocardial infarction	2 (5)
Obesity (BMI>30)	20 (50)
Hyperlipidemia	17 (42.5)
Radiation treatment	
Yes	28 (70)
No	12 (30)
Surgery	
Yes	34 (85)
No	6 (15)
Cumulative anthracycline dose (mg/m^2)	
Mean	214.53 ± 140.47
Median	180
Range	30-525
Received dexrazoxane	
Yes	4 (10)
No	36 (90)

Abbreviations: NOS, not otherwise specified; RMS, rhabdomyosarcoma; UPS, undifferentiated pleomorphic sarcoma.

and doxorubicin/cisplatin/mitomycin (n=12, 30% of patients) (Supplemental Table, available online at https://www.mcpdigitalhealth.org/). Four patients (10% of patients) received dexrazoxane with anthracycline (Table 1). Three patients received dexrazoxane due to previous treatment with anthracyclines or concerns due to high cumulative doses of anthracycline. One patient received dexrazoxane due to a history of heart failure with reduced EF that had recovered from LVEF prior to treatment initiation. The median pretreatment LVEF was 64 %, and the median post-treatment LVEF was 57.5 %. Two patients (5%) had borderline LV strain, and 2 patients (5%) had abnormal LV strain prior to anthracycline therapy. Two patients (5%) had borderline LV strain, and 1 patient (2.5%) had abnormal LV strain after completion of anthracycline therapy (Table 2).

The difference between AI-ECG age and chronological age had a normal distribution around 0 (Figure 1A), and the gap between AI-ECG age and chronological age was affected by the baseline chronologic age (Figure 1B), such that younger patients were predicted to be older and older patients were predicted to be younger. After adjusting for chronologic age, we did not find a relationship between having a higher predicted AI-ECG age prior to treatment (ie. being predicted to be older than chronologic age) with a subsequent need for anthracycline dose reductions (OR, 0.25; P=.45), treatment delays (OR, 1.20; P=.91), or early discontinuation of chemotherapy (OR, 1.0; P>.99).

TABLE 2. Echocardiogram Characteristics

Echocardiogram characteristics	N (%)
Total echocardiograms	
Pretreatment	37 (93)
Post-treatment	14 (35)
Pretreatment EF	
Mean (%)	62.7 ± 6.1
Median (%)	64
Post-treatment EF	
Mean (%)	55.5 ± 8.4
Median (%)	57.5
Pretreatment LV Strain	
Borderline	2 (5)
Abnormal	2 (5)
Post-treatment LV Strain	
Borderline	2 (5)
Abnormal	1 (2.5)

Abbreviations: EF, ejection fraction; LV, left ventricle.
Normal LV strain < −18%; borderline LV strain −16 to −18%; abnormal LV strain > −16%.

ECG Aging Trends With Cumulative Anthracycline Dose Trends

Twenty-four patients (60%) had ECGs within 1 year of treatment completion, allowing for the calculation of ECG aging rates. Unlike pretreatment ages, we did not find a significant relationship between chronological age and the ECG aging rate through treatment (Supplemental Figure, available online at https://www.mcpdigitalhealth.org/). We found a strong trend between increased cumulative anthracycline dose in patients with accelerated ECG aging (Figure 2A). Although there was no difference between rates of dose reductions (OR, 5.13; P=.32), treatment delays (OR, 0.32; P=.59), or early discontinuation of chemotherapy (OR, 0.86; P>.99) between patients who had high or low ECG aging, there was a trend toward higher rates of dose reductions in patients with high ECG aging.

We then tested if there was a relationship between OS (Figure 2B) or RFS Figure 2C) between patients with accelerated aging versus those who did not. There was no difference in OS or RFS between the ECG aging groups (Figure 2B, C).

AI-ECG Prediction of Decreased EF Correlates With Echocardiogram-Based EF

There were 37 and 12 patients who had echocardiograms obtained before and after treatment, respectively. Of these patients, 35 patients had a corresponding ECG within 180 days of the pretreatment echocardiogram and 6 corresponding ECGs with the pre- and post-treatment echocardiograms.

The AI-ECG prediction of low EF had a sensitivity of 100% and a specificity of 94% to isolate patients with an EF of less than 50% prior to treatment. There were no cases of an EF less than 35% prior to treatment to calculate the sensitivity, but the specificity of the low EF prediction was 92%. Of the 6 patients who had ECGs and echocardiograms prior to and after

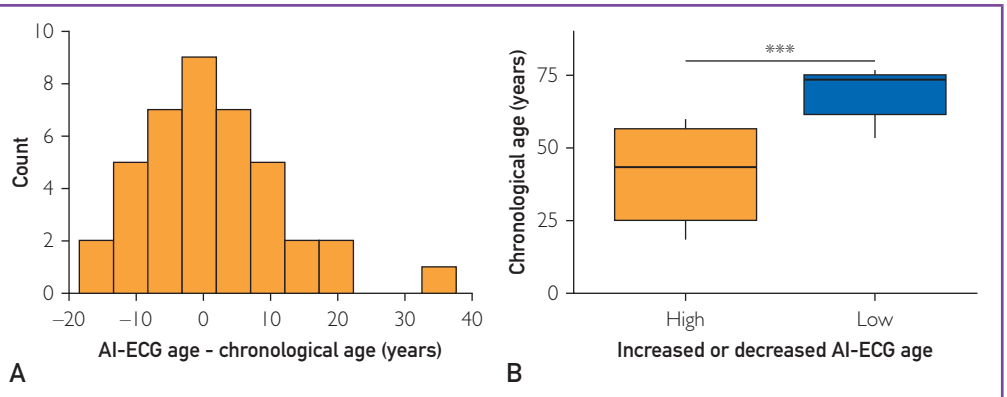

FIGURE 1. AI-ECG prediction of age varies with chronologic age. (A) Distribution of the difference between AI-ECG-predicted age and chronologic age prior to anthracycline chemotherapy. (B) Average chronologic age between patients that have an AI-ECG age greater than or less than the chronologic age, respectively. Delta cutoff 7.4 years. ***P<.001.

treatment, the average change in EF was −6.5%. Four of these patients did not have a significant change in EF after treatment (<10%), and 2 patients showed a greater than 10% decrease in EF (Figure 3A).

Interestingly, the 2 patients who had a significant decrease in EF were the only 2 patients who had a corresponding increase in the AI-ECG prediction of a decreased EF (>0.2; Figure 3B). Of note, neither of these patients received left chest radiation therapy as part of their treatment. One of the patients did receive dexrazoxane due to a history of heart failure with reduced EF. The other 4 patients did not show a significant change in either EF or in the AI-ECG prediction of low EF (Figure 3A, B). One of these patients received dexrazoxane due to concerns regarding cumulative anthracycline dose.

DISCUSSION

We found that discrepancies between AI-ECG age and chronological age do not predict tolerance to anthracycline-based chemotherapy.

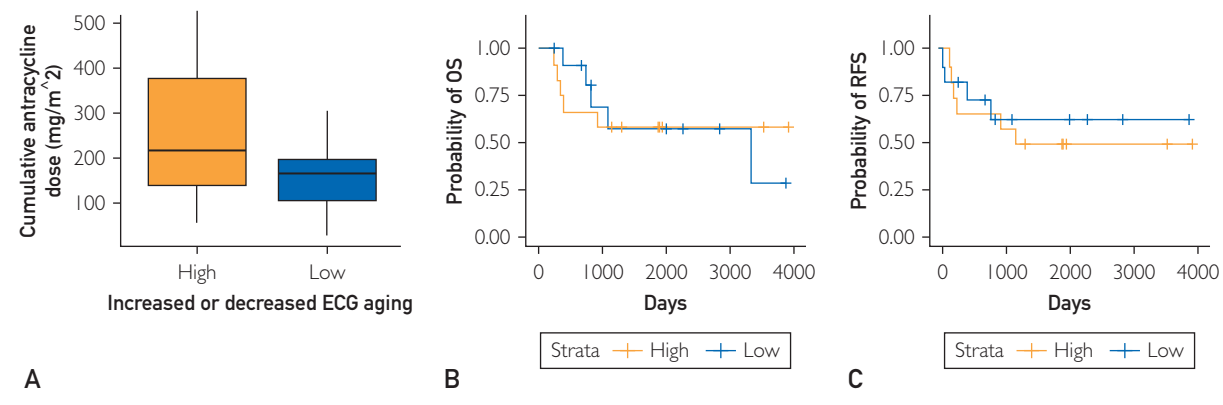

FIGURE 2. ECG aging rate trends with cumulative anthracycline dose but not OS or RFS. (A) Cumulative anthracycline dose between patients categorized into increased ECG aging (>1) or decreased ECG aging (<1), P=.06. (B) Kaplan-Meier curve for overall survival (OS) between the increased and decreased ECG aging groups, P=.98. (C) Kaplan-Meier curve for relapse-free survival (RFS) between the increased and decreased ECG aging groups, P=.67.

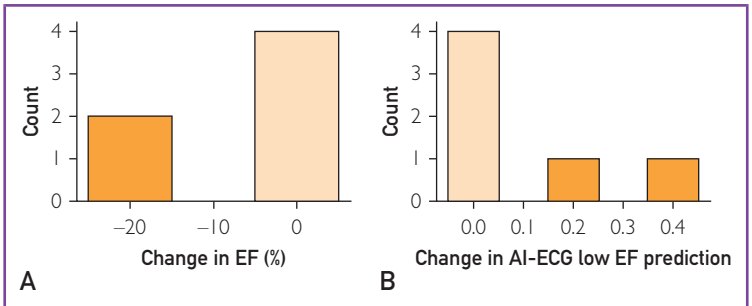

FIGURE 3. Changes in AI-ECG predictions of low EF isolate patients with decreased EF after treatment. (A) Histogram of EF changes after treatment with anthracycline-based chemotherapy. (B) Changes in the low EF AI-ECG prediction after treatment with anthracycline-based chemotherapy. Highlighted bars in A-B correspond to cases where EF decreased more than 10% after treatment.

Although large discrepancies between the AI-ECG age and biological age have been shown to predict cardiovascular outcomes in a general population[12] and in patients with a Lamin A/C mutation,[14] we did not see this trend in our patient population. One potential explanation could be that poor tolerance to the treatment regimens could be encapsulated more so by noncardiac toxicities from either the anthracycline or the other chemotherapy agents, which may be hard to capture with ECG data. Another interpretation is that "biological" age relative to chronological age prior to treatment is not predictive of tolerance to chemotherapy.

We did find that rates of ECG aging through treatment, rather than prior to treatment, had stronger predictive values for patients requiring dose reductions, although this will need to be tested with a larger cohort to further investigate significance. Interestingly, we did find strong trends between cumulative anthracycline dose, which is well known to increase the risk of cardiovascular adverse effects[3] and the rates of ECG aging. Although there have been case reports studying ECG aging rates,[9] we are not aware of previous studies investigating this in the context of chemotherapy tolerance. There is ongoing work to define if and how cancer-directed therapies can affect biological aging.[15–18] Although further studies are needed, this could represent a cost-effective option to monitor and study the rates of biological aging in the setting of cancer-directed therapies.

We did find that predictions of low LVEF based on ECG tracings performed well in isolating patients with low EF prior to treatment. Interestingly, we also found that patients who experienced significant decreases in EF after treatment also had a corresponding increase in the low EF predictor. This is in line with recent work showing that the AI-ECG low LVEF prediction increased in breast cancer patients who experience anthracycline-induced cardiotoxicities.[19,20] Additional work has shown that AI-ECG predictions can isolate patients at risk for anthracycline-related cardiotoxicities and decrease LVEF after treatment with anthracyclines in patients with breast cancer and non-Hodgkin lymphoma.[21] In accordance with this work, our study suggests that AI-based predictions of low EF from ECG tracings could be used as a screening method to risk stratify patients who are at risk of developing significant decreases in EF during treatment with anthracyclines. Interestingly, there are well-defined ECG changes that occur in patients who develop anthracycline-related cardiotoxicities, such as T wave flatting, that theoretically could be identified by an AI algorithm.[22] As there is not a well-defined way to screen patients at risk of developing decreases in LVEF besides repeat cardiac imaging, these data suggest a potential solution through AI-ECG, which may be less resource-intensive.

Our study should be interpreted in the setting of its limitations. First, this is a retrospective single-center study, which is inherently limited in being able to extract causal relationships. We also selected patients who had ECGs on file. As this is not a standard test to obtain prior to therapy, there is the risk of selection bias. Additionally, the original AI-ECG age algorithm was developed on a general patient population, not necessarily a "healthy" patient population.[9] Therefore, the underlying AI-ECG predicted age could be accounting for some level of illness that could affect the predictive value of the prediction. The mean cumulative anthracycline dose was only 215 mg/m^2, which is lower than the cumulative dose of 450 mg/m^2 that patients with advanced soft tissue sarcomas typically receive.[4] The lower cumulative dose, and thus lower

cardiotoxicity risk, may limit the interpretation of these results. We also found a significant relationship between the AI-ECG-predicted age and the patient's chronological age, which has also been described in previous studies.[23] Although we controlled for this in our models, this may introduce a co-founder into the analysis. Finally, we set the gap between a valid ECG-echocardiogram pair as 180 days. Although the patients did not receive additional anthracycline chemotherapy between these intervals, there may have been changes in clinical status between these time points that may be unaccounted for.

CONCLUSION

Discrepancies between AI-ECG-predicted age and chronological age do not predict tolerance to anthracycline-based chemotherapy. The rates of ECG aging could be a marker of tolerance to therapy requiring dose reductions, but additional studies are required. The AI-ECG prediction of low EF could be a potential way to monitor for a decrease in LVEF during treatment with anthracyclines.

POTENTIAL COMPETING INTERESTS

Mayo Clinic has a financial interest related to this research. This research has been reviewed by the Mayo Clinic Conflict of Interest Review Board and is being conducted in compliance with Mayo Clinic Conflict of Interest policies.

ETHICS STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Mayo Clinic. HIPAA waiver was approved after review by the Institutional Review Board of Mayo Clinic (ID 23-007295 8/17/2023).

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at https://www.mcpdigitalhealth.org/. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AI,** artificial intelligence; **AI-ECG,** artificial intelligence-enabled electrocardiogram; **ECG,** electrocardiogram; **EF,** ejection fraction; **LV,** left ventricular; **LVEF,** left ventricular ejection fraction; **OR,** odds ratio

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