PRECISION IMAGE ANALYSIS

Patient Dropout Rate Reduction Through the Use of Cardiac MRI as a Secondary Endpoint to Echo

VP OF STRATEGIC RELATIONSHIPS – CNMT, RT(N)

Christian Teague has been involved in radiology for over 20 years. It was over that period of time that he was able to gain vast experiences in diagnostic imaging as well as research. He managed imaging data throughout the world both in a HIPPA compliant, as well as Part 11 compliant manner. After graduating from Loma Linda Medical University with an emphasis in Nuclear Medicine he began his career working at large research hospitals such as UCLA Medical Center where he became accustomed to the world of research.

Cardiac Toxicity monitoring through imaging needs to be improved. Current trends show a new way to solve an old problem. Patients who are at risk of dropout due to drug induced Cardiac Toxicity should have access to new techniques.

Christian Teague and Jason Lin of Precision Image Analysis

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Thanks to the recent advancements in cancer treatment and research, the number of cancer survivors continues to increase, allowing more patients improved outcomes and a better quality of life. However, many of these cancer survivors are now at risk of developing cardiac disorders due to cardiotoxicity as a side effect of the chemotherapeutic drugs used to treat these cancers Cardiotoxicity is damage to the heart that reduces its ability to function normally, and can result in cardiac complications such as a drop in left ventricular ejection fraction (LVEF), cardiomyopathy, myocarditis, and congestive heart failure[1,2].

In the case of clinical trials, a significant decline in a patient's LVEF, particularly below the lower bound threshold of 50%, the patient may no longer be eligible to continue participation in the clinical trial. Such patient dropouts not only deprive patients of the potential benefits of novel therapeutic treatments, but also waste time, money, and effort of all stakeholders involved in the trial. In the United States, the estimated total cost of patient recruitment is estimated at $1.89

billion[3]. However, the average dropout rate across all clinical trials is approximately 30%. Thus, the total economic loss attributed to recruitment by patient dropout alone easily exceeds $600 million[3]. For cardiovascular clinical trials, the estimated average cost per-patient in 2013 was $20 thousand[4]. Accordingly, an economic imperative exists to effectively address patient dropout rates and more efficiently use critical resources. More importantly, decreasing the dropout rate would be beneficial for the patients as well, enabling them to continue to receive therapeutic treatment and enhancing their chances of improved outcome.

To reduce the dropout rate in potential cardiotoxic drug studies, it is important to monitor the cardiac function of patients and ensure that the LVEF is evaluated accurately. The current standard of cardiac monitoring is based on the assessment of LVEF via multi -gated acquisition (MUGA) scans or echocardiograms[5]. The advantages

of echocardiography include itsnoninvasiveness and perceived low imaging cost. However, a critical disadvantage lies in its high variability, and low repreducibility of LVEF measurements. ln clinical practice, cardiotoxicity is defined as a 5 to 10% decrease in LVEF from its baseline, which is equivalent to the interobserver variability of echocardiography, as shown in Figure 1[5,6].

Figure 1. Interobserver and Intraobserver Reproducibilities for Left Ventricular Ejection Fraction*

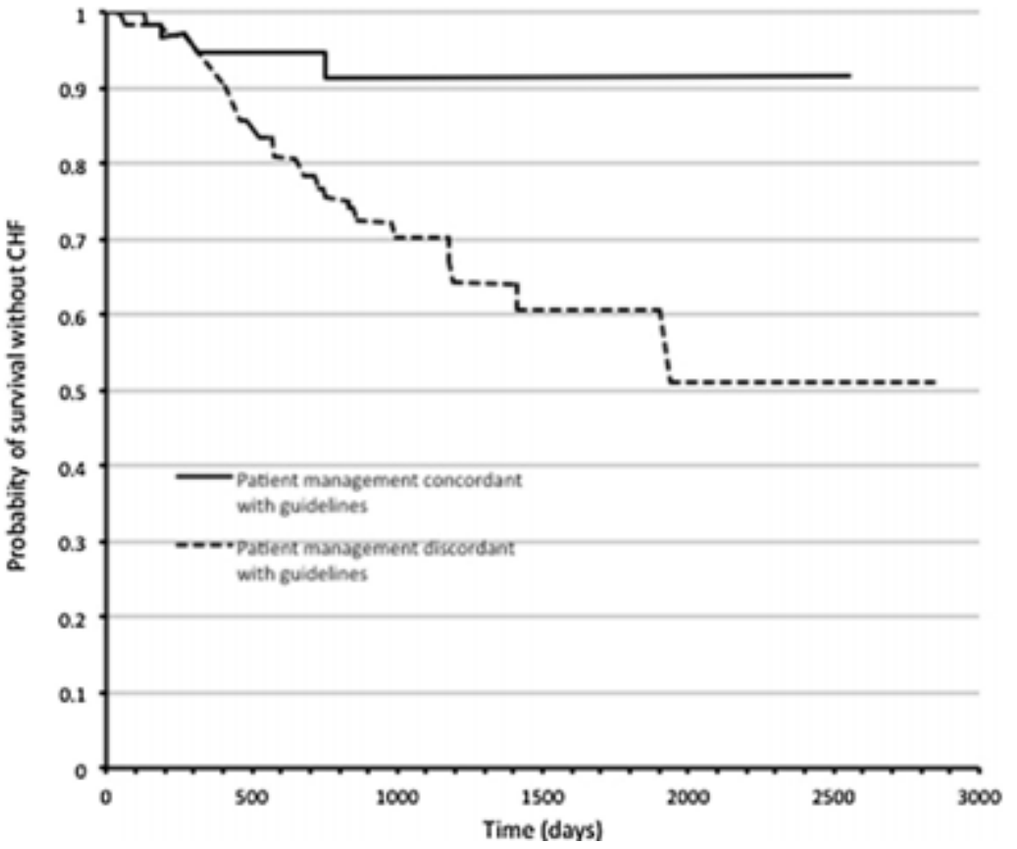
	Volumetric MRI	Biplane MRI	Volumetric Echocardiography	Biplane Echocardiography
Interobserver				
Variability (%)	3.6	13.4	8.3	17.8
Mean ± SD (%)	0.5 ± 1.5	−1.4 ± 5.9	−0.1 ± 3.8	1.3 ± 8.8
SEE	1.6	4.3	3.7	9.2
r^2	0.99	0.94	0.96	0.82
Intraobserver				
Variability (%)	5.1	13.0	6.9	13.4
Mean ± SD (%)	−1.1 ± 2.1	−2.0 ± 5.6	−0.4 ± 3.1	−0.9 ± 6.8
SEE	2.1	5.4	3.3	6.7
r^2	0.99	0.91	0.97	0.90

*Systematic differences between LVEF measurements are summarized. There were no statistically significant differences ($p > 0.10$) for all comparisons.

SD = standard deviation; SEE = standard error of the mean; MRI = magnetic resonance imaging.

Recent clinical research investigations have shown that more advanced imaging modalities can detect cardiotoxicity earlier and more accurately, potentially saving these patients from developing irreversible cardiac complications[7]. In a study conducted by Schwartz et al, LVEF assessed by highly reproducible methods resulted in significant improvements in outcome and lower incidence of clinical heart failure as shown in Figure [7,8]. In addition, many experts have promoted the use of multi-modality imaging in the diagnosis and management of cardiotoxicity during cancer therapy.

Figure 2[7,8]. Utilizing imaging management recommendations published by Shwartz et al[8], there was a significant decrease in the development of clinical heart failure in patients treated with anthracyclines.



However, due to the additional costs, a routine multi-modality approach would not be feasible as a clinical trial endpoint. A proposed alternative would be to use cardiac magnetic resonance (CMR) imaging as a secondary endpoint in combination with echocardiography. CMR is currently the gold standard for measuring LV volumes and LVEFs, as it has the greatest accuracy and reproducibility determining LV function. In support of this approach, an expert consensus report by the American Society of Echocardiography and the European Association of Cardiovascular Imaging suggested that CMR be the preferred technique for LVEF quantification when echocardiography approaches the 50% LVEF threshold[9]. With CMR as a secondary endpoint for LV EF, clinical trials can maintain higher confidence in their LV functional assessments for patients approaching the LVEF = 50% threshold. The greater accuracy of CMR can ensure that patients are not needlessly dropped out of clinical trials, thus reducing costs and the need to recruit more patients.

As well-established imaging modalities, echocardiography and MUGA are still most commonly used primary diagnostic exams when assessing cardiotoxicity. However, the rapid advancements in CMR have demonstrated its potential for earlier and more accurate detection of cardiotoxicity, with CMR highly recommended as a complementary assessment to echocardiography during clinical trials. An integrated approach of using both echocardiography, and CMR in a subset of patients, will enable clinicians to make the appropriate choice regarding the discontinuation of anti-cancer therapy for patients, thus potentially reducing cardiotoxicity effects and improving patient outcomes.

CREDITS

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REFERENCES

1. Csapo, M., Lazar L., Chemotherapy-Induced Cardiotoxicity: Pathophysiology and Prevention. Clujul Medical. 2014;87(3):135-142.
2. Albini, A., Pennesi, G., Donatelli, F., Cammarota, R., De Flora, S., & Noonan, D. M. (2010). Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. J Natl Cancer Inst 102, 14–25.
3. Nuttall, A. Considerations for Improving Patient Recruitment into Clinical Trials (2012).
4. Battelle Technology Partnership Practice. Biopharmaceutical Industry-Sponsored Clinical Trials: Impact on State Economies, March 2015.
5. Avelar, E., Strickland, CR., Rosito, G., Role of Imaging in Cardio-Oncology. Curr Treat Options Cardiovasc Med. 2017 Jun;19(6):46.
6. Chuang, M., et al., Importance of Imaging Method Over Imaging Modality in Noninvasive Determination of Left Ventricular Volumes and Ejection Fraction. JACC. February 2000:477-84.
7. Russell, R., et al., The Role and Clinical Effectiveness of Multimodality Imaging in the Management of Cardiac Complications of Cancer and Cancer Therapy. Journal of Nuclear Cardiology. June 01, 2016;23:856-84.
8. Schwartz RG, McKenzie WB, Alexander J, et al Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy: Seven-year experience using serial radionuclide angiocardiography. Am J Med 1987; 82:1109-18.
9. Plana, JC., et al., Expert Consensus for Multimodality Imaging Evaluation of Adult Patients During and After Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. European Heart Journal – Cardiovascular Imaging (2014); 15:1063-1093.