Implantable Cardioverter Defibrillator for the Primary Prevention of Sudden Cardiac Death among Patients With Cancer

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Data are limited regarding the characteristics and outcomes of patients with cancer who are found eligible for primary defibrillator therapy. We performed a single-center retrospective analysis of patients with preexisting cancer diagnoses who become eligible for a primary prevention implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT) defibrillator. Multicenter Automatic Defibrillator Implantation Trial−ICD (MADIT-ICD) benefit scores were calculated. The study included 75 cancer patients at a median age of 73 (interquartile range 64, 81) years at heart failure diagnosis. Active cancer was present in 51%. Overall, 55% of the cohort had coronary artery disease and 37% were CRT eligible. We found that 48%, 49%, and 3% of cohorts had low, intermediate, and high MADIT-ICD Benefit scores, respectively. Only 27% of patients underwent primary defibrillator implantation. Using multivariate analysis, indication for CRT and intermediate/high MADIT-ICD Benefit categories were found as independent predictors for implantation (odds ratio 8.42 p <0.001 and odds ratio 3.74 p = 0.040, respectively). During a median follow-up of 5.3 (interquartile range 4.5, 7.2) years, one patient (5%) with a defibrillator had appropriate shock therapy and 2 patients (10%) had bacteremia. Of 13 patients with CRT defibrillator−implants, one patient was admitted for heart failure exacerbation (8%). Using a time-varying covariate model, we did not observe statistically significant differences in the survival of patients with cancer implanted versus those not implanted with primary defibrillators (hazard ratio 0.521, p = 0.127). In conclusion, although primary defibrillator therapy is underutilized in patients with cancer, its relative benefit is limited because of competing risk of nonarrhythmic mortality. These findings highlight the need for personalized cardiologic and oncologic coevaluation. **© 2022 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2023;191:32−38)**

Patients with cancer may become eligible for primary prevention defibrillator therapy because of either cancer-related cardiomyopathy or non-cancer-related conditions with a contemporary estimate rate of 4.8% implantations in patients with cancer.[1] However, this is most likely an underestimation of the true number of patients with cancer who fulfill the guidelines' recommendations criteria for primary defibrillator therapy, as published data suggest that patients with cancer are often deprived of various invasive procedures,[2,3] at times inappropriately. Recently, Younis et al[4] published the multicenter Automatic Defibrillator Implantation Trial−implantable cardioverter defibrillator (MADIT-ICD) benefit score which is a clinical score aiming to identify patients who are more likely to benefit from primary prevention defibrillator therapy through an assessment of individualized predicted risk for life-threatening ventricular arrhythmias and the competing risk of nonarrhythmic mortality. Although a well-established nonarrhythmic mortality risk factor,[5] cancer was not included in the proposed model as it was not studied in the MADITs. This study has several aims: first, to describe the clinical characteristics of patients with a preexisting cancer diagnosis who become eligible for primary defibrillator therapy. Second, to evaluate the clinical predictors for primary defibrillator implantation in this population, and finally, to evaluate the incidence of appropriate device therapy and device-related complications in patients with cancer implanted with primary prevention defibrillators.

Methods

Single-center retrospective analysis for the years 2015 to 20 of adult patients with cancer who fulfill the society guideline recommendation for primary defibrillator therapy. Eligibility for primary prevention ICD (or cardiac resynchronization therapy defibrillator based on electrocardiographic features) was based on European Society of

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Cardiology Heart Failure (HF) Guidelines requiring evidence of symptomatic HF of an ischemic or nonischemic etiology and a left ventricular ejection fraction (LVEF) ≤ 35% despite at least 3 months of optimal medical therapy, and estimated survival of longer than 1 year.[6] The latter was estimated for each individual patient by oncologic evaluation based on published prognostic data. Only patients with preexisting cancer diagnoses at the time of the index echocardiography study were included in this study. Patients who fulfilled society's guideline recommendation for secondary prevention defibrillators were excluded as well.

MADIT-ICD benefit scores (overall, ventricular tachycardia/ventricular fibrillation [VT/VF], and nonarrhythmic mortality scores) were calculated using the online calculator. The overall MADIT-ICD Benefit score categories are defined as low benefit Group 1 to 25, intermediate benefit Group 26 to 75, and high benefit Group 76 to 100.[4]

Data regarding patients' co-morbidities, cardiac disease, cause of death, cancer type, staging, and given therapies were retrieved from patients' electronic medical records. The study protocol was approved by the Rabin Medical Center Institutional Review Board.

Continuous variables were presented as median and interquartile range. Categorical variables were presented as number (%). A *t* test was used to compare the value of continuous variables, which are deemed to have a normal distribution between study groups, and the Wilcoxon test was used for non-normal distribution variables. Fisher's exact test was used to compare the value of categorical variables between study groups. We used logistic regression analysis to define the potential independent predictors for the implantation of primary defibrillator therapy. Prespecified covariates that were included as potential predictors for implantation were electrocardiographic indication for CRT, intermediate or high versus low MADIT-ICD Benefit category, coronary artery disease, and active cancer. A Cox proportional hazard model, where implantation status was treated as a time-varying covariate, was used to analyze the effect of implantation on survival from HF diagnosis. Two-sided p values <0.05 were considered statistically significant.

Results

The study included 75 patients with a preexisting diagnosis of cancer who were diagnosed with symptomatic HF and an LVEF ≤35% despite at least 3 months of guideline-directed medical therapy and with an estimated prognosis of longer than 1 year (Figure 1). Patients' baseline characteristics are presented in Table 1. The median age at HF diagnosis was 73 (interquartile range [IQR] 64, 81) years with no gender predilection. A total of 41 patients (55%) had a history of coronary artery disease, 88% of which had a previous acute myocardial infarction. All study patients were treated with at least 2 guideline-directed HF medical therapy drugs. Overall, 28 patients (37%) had an indication for CRT implantation based on electrocardiographic features.

The most frequent cancer diagnoses in our cohort were breast (16%), lung (13%) bladder (11%), and colorectal (11%) cancer (Figure 2). A total of 17% of patients had hematologic malignancies. Of the patients with cancer, 51% (n = 38) had an active cancer disease while being diagnosed with HF and 8% had concurrent systemic metastases. The mean time from cancer diagnosis to HF diagnosis was 5.6 ± 8.52 years. In total, 24% of the patients (n = 18) have been treated with anthracyclines-based regimens and 2 patients received immune-checkpoint inhibitor therapy. Only 8% (n = 6) of patients underwent thoracic irradiation.

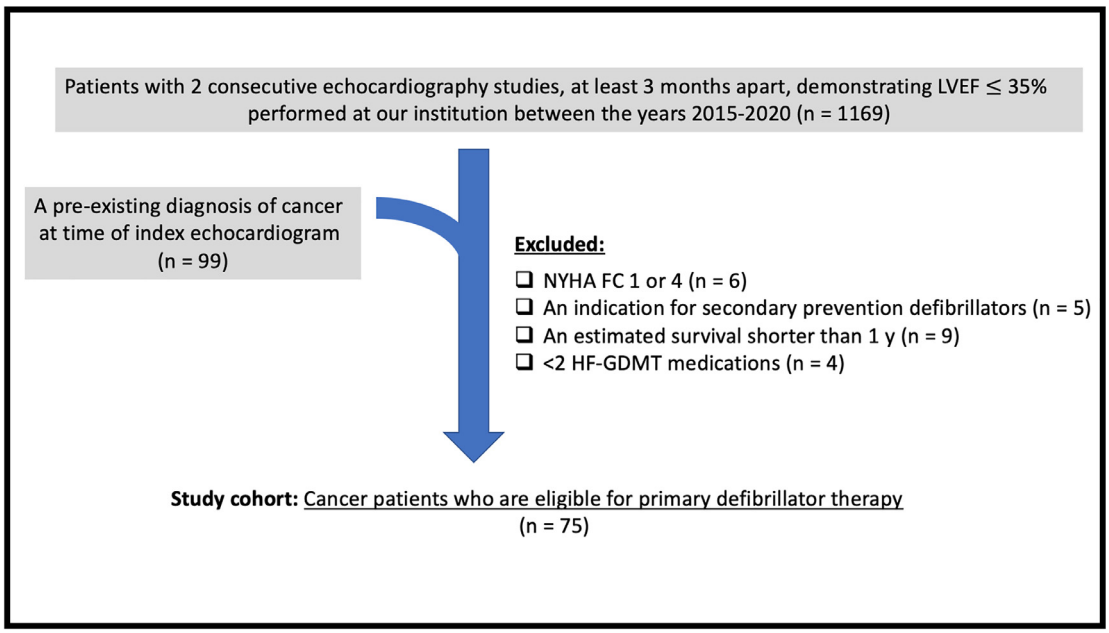

Figure 1. Study flow-chart. Eligibility for primary prevention defibrillator was based on ESC-HF Guidelines requiring evidence of symptomatic HF of an ischemic or nonischemic etiology and an LVEF ≤35% despite at least 3 months of optimal medical therapy, and an estimated survival of longer than 1 year. GDMT = guideline-directed medical therapy; NYHA FC = New-York Heart Association Functional Class.

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Table 1
Baseline characteristics of cancer patients who are found eligible for primary defibrillator therapy

	All patients (n=75)	Defibrillator not implanted (n=55)	Defibrillator implanted (n=20)	p- value
Age at cancer diagnosis	67 (60, 74)	67 (60, 73)	68 (60, 77)	0.624
Age at HF diagnosis	73 (64, 81)	73 (64, 82)	72 (65, 79)	0.813
Time from cancer diagnosis to HF diagnosis (years, mean± SD)	5.62± 8.52	6.2 ± 9.62	4.04 ± 4.02	0.957
Sex (females)	29 (39)	24 (44)	5 (25)	0.184
BMI (Kg/m^2)	25 (23, 29)	26 (23, 29)	25 (23, 29)	0.811
Smoker (%)	21 (28)	13 (24)	8 (40)	0.252
COPD (%)	7 (9)	6 (11)	1 (5)	0.666
Hypertension (%)	36 (48)	28 (51)	8 (40)	0.444
Diabetes mellitus (%)	22 (29)	15 (27)	7 (35)	0.572
CVA/TIA (%)	6 (8)	4 (7)	2 (10)	0.659
CAD (%)	41 (55)	30 (55)	11 (55)	0.794
Prior myocardial infarction (%)	36 (48)	25 (45)	11 (55)	0.602
Atrial fibrillation (%)	16 (21)	10 (18)	6 (30)	0.341
Documented NSVT (%)	3 (4)	1 (2)	2 (10)	0.530
NYHA functional class (%)				0.860
1	0	0	0	
2	43 (57)	32 (58)	11 (55)	
3	29 (39)	20 (36)	9 (45)	
4	0	0	0	
SBP at rest (mmHg)	124 (110, 136)	125 (109, 140)	118 (111, 130)	0.179
HR at rest (beats per minute)	76 (66, 88)	78 (67, 94)	71 (63, 77)	0.040
Electrocardiographic indication for CRTD implantation (%):	28 (37)	14 (25)	14 (70)	0.001
CLBBB (%)	19 (68)	9 (64)	10 (71)	
CRBBB (%)	4 (14)	2 (14)	2 (14)	
Pacemaker-dependent (%)	5 (18)	3 (21)	2 (14)	
LVEF by echocardiography	25 (20, 30)	25 (20, 30)	26 (22, 30)	0.539
Cancer characteristics				
Active cancer (%)	38 (51)	28 (51)	10 (50)	1.000
Cancer metastases (%)	6 (8)	4 (7.3)	2 (10)	1.000
Anthracycline-based regimen chemotherapy (%)	18 (24)	13 (24)	5 (25)	0.499
Thoracic radiation (%)	6 (8)	5 (9)	1 (5)	1.000
HF-medications				
ACE-I or ARBs	61 (81)	46 (84)	15 (75)	0.504
ARNI's	10 (13)	6 (11)	4 (20)	0.442
Beta-blockers	72 (96)	52 (95)	20 (100)	0.560
MRA's	35 (47)	24 (44)	11 (55)	0.439
SGLT-2 inhibitors	4 (5)	3 (5)	1 (5)	1.000
Hydralazine and/or nitrates	13 (17)	8 (15)	5 (25)	0.314

Data are presented as mean± SD, median (25th, 75th quartiles) or as percentages, as appropriate.

ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BMI = body mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CRTD = cardiac resynchronization therapy defibrillator; CVA = Cerebrovascular accident; HF = heart failure; HR = heart rate; ICD = implantable defibrillator; LBBB = bundle branch block; MRA = mineralocorticoid receptor antagonists; NSVT = nonsustained ventricular tachycardia; NYHA = New-York Heart Association; RBBB = right bundle branch block; SBP = Systolic blood pressure; SGLT-2 inhibitors = sodium-glucose cotransporter-2 inhibitors; TIA = transient ischemic attack; VF = ventricular fibrillation; VT = ventricular tachycardia.

MADIT-ICD Benefit scores were retrospectively calculated for each patient to assess the theoretical potential benefit of primary ICD therapy. We found that 48%, 49%, and 3% of our patients from cancer cohort had low (1−25) intermediate,(26−75) and high (>75) MADIT-ICD benefit scores, respectively. The median ICD benefit score, VT/VF score, and nonarrhythmic mortality score were 42 (IQR 20, 54), 15 (IQR 11, 15), and 9 (IQR 9, 12), respectively (Table 2).

A total of 27% of study patients (n = 20) were implanted with a primary defibrillator (Figure 2). The median time from HF diagnosis to device implantation in our cohort was 1.3 (IQR 0.6, 2.7) years. Compared with patients with cancer not implanted with a primary defibrillator, patients with cancer who were implanted with a primary defibrillator were more likely to have an indication for CRT (70% vs 27%, p = 0.001) and to have a tendency to higher MADIT-ICD VT/VF scores (15 vs 11, p = 0.052) (Tables 1, 2). Patients with cancer implanted versus those not implanted with a defibrillator had similar rates of cardiovascular comorbidities (including coronary artery disease) and comparable malignancy status (Table 3). By multivariate analysis, we found that an indication for CRT therapy and being in the high and intermediate versus low MADIT-ICD Benefit

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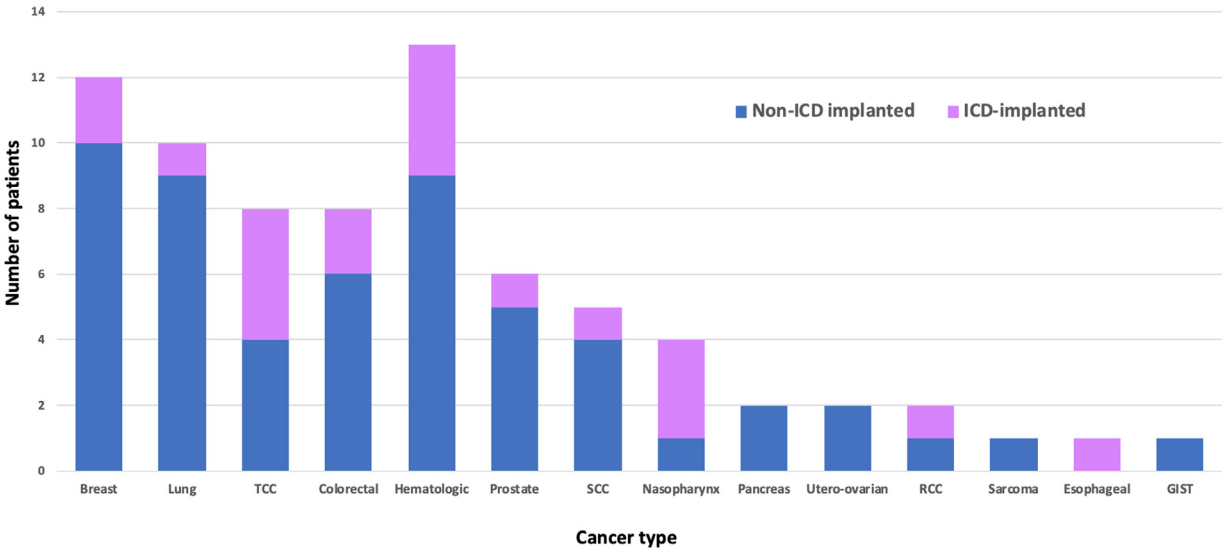

Figure 2. Cancer type distribution among study cohort stratified by defibrillator implantation status. GIST = gastrointestinal stromal tumor; RCC = renal cell carcinoma; SCC = squamous cell carcinoma; TCC = transitional cell carcinoma.

Table 2
Baseline MADIT-ICD Benefit score values of cancer patients who are eligible for primary defibrillator therapy

	All patients (n=75)	Defibrillator not implanted (n=55)	Defibrillator implanted (n=20)	p- value
MADIT-ICD Benefit overall score	42 (20, 54)	25 (20, 54)	50 (24, 60)	0.139
VT/VF Score	15 (11, 15)	11 (11, 15)	15 (11, 15)	0.052
Non-arrhythmic Mortality Score	9 (9, 12)	12 (9, 12)	9 (9, 12)	0.056

MADIT-ICD Benefit scores (overall, VT/VF and non-arrhythmic mortality scores) were calculated using the online calculator (https://is.gd/madit).
ICD = implantable defibrillator; VF = ventricular fibrillation; VT = ventricular tachycardia.

Table 3
Baseline predictors for primary defibrillator implantation in cancer patients by univariate and multivariate analyses

	Univariate analysis		Multivariate analysis	
	OR 95% confidence intervals	p- value	OR 95% confidence intervals	p-value
Age (per 1 year)	0.99 (0.95, 1.04)	0.793		
Sex (females vs. males)	0.46 (0.15, 1.40)	0.171		
LVEF (per 1-point reduction)	1.03 (0.95, 1.12)	0.510		
Electrocardiographic indication for CRT	5.83 (1.92, 17.78)	<0.001	8.42 (2.48, 28.62)	<0.001
Intermediate or high vs. low MADIT-ICD Benefit category	2.69 (0.91, 7.94)	0.074	3.74 (1.07, 13.11)	0.040
Coronary artery disease	0.81 (0.29, 2.28)	0.695	0.69 (0.21, 2.31)	0.584
Active cancer	0.97 (0.35, 2.67)	0.945	0.89 (0.27, 2.94)	0.846
Metastases	1.15 (0.11, 11.83)	0.904		
Anthracyclines-containing regimens	0.92 (0.28, 3.08)	0.893		
Thoracic radiation	0.71 (0.09, 5.32)	0.736		

CRT = cardiac resynchronization therapy; ICD, = implantable defibrillator; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; LVEF = left ventricular ejection fraction.
*Intermediate benefit Group 26 to 75 = high benefit Group 76 to 100; MADIT-ICD Benefit score categories = low benefit Group 1 to 25.

categories were independent predictors for the defibrillator implantation (odds ratio 8.42, p <0.001 and OR 3.74, p = 0.040, respectively; Figure 3, Table 3).

After 1-year follow-up, the median LVEF among the study population (n = 54 patients alive) increased from 25% to 30% (IQR 25, 35)%. During a median follow-up of 2.6 (IQR 0.78, 4.70) years, 48 patients (64%) died. Causes of death were determined in 26 patients (57% of deaths). Of them, 8 patients (31%) died from HF-related causes and 16 patients (62%) died from cancer-related causes. Malignant arrhythmias were identified as the cause of death in 2 patients (7%) who did not receive a defibrillator. Cancer-related death was the most commonly identified cause of death regardless of defibrillator status, yet with a lower prevalence among patients implanted versus not implanted (57% vs 80%, respectively). Patients with HF-related death versus cancer-related death had comparable MADIT-ICD Benefit scores (38 ± 20 vs 33 ± 20, respectively, p = 0.136).

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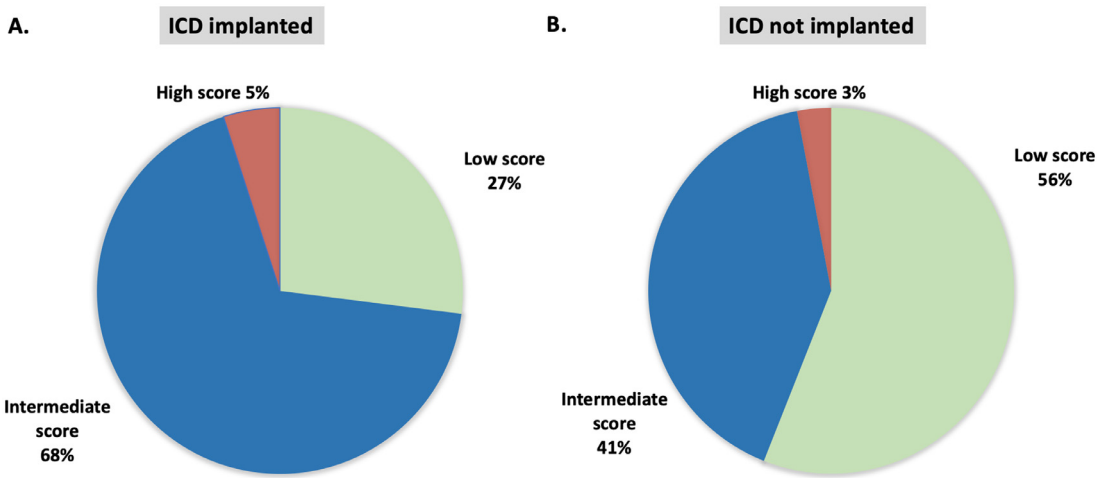

Figure 3. The distribution of baseline MADIT-ICD scores among cancer patients stratified by defibrillator implantation status (*A*) ICD implanted. (*B*) ICD not implanted.

During a median follow-up of 5.3 (IQR 4.5, 7.2) years, 11 patients with primary defibrillator implants (55%) had documented nonsustained VT events and 1 patient (5%) had an appropriate defibrillator shock. Overall, 2 patients (10%) had documented bacteremia during follow-up (methicillin-sensitive *Staphylococcus aureus* and *Escherichia coli* bacteremia) with no evidence of infective endocarditis. Device extraction was not required in either case. Of 13 patients with cardiac resynchronization therapy defibrillator implant, one patient was admitted for HF exacerbation (8%).

We analyzed patients' survival using a time-varying covariate model to account for the differences in the timing of device implantation. There was no statistically significant difference in the survival of patients implanted versus not implanted with primary defibrillators (hazard ratio 0.521, 95% confidence interval 0.23, 1.20, p = 0.127). Similar results were observed in a sensitivity analysis which included only patients with baseline coronary artery disease (hazard ratio 0.363, 95% CI 0.09 to 1.45, p = 0.151).

Discussion

This study evaluated the clinical characteristics of patients with a preexisting diagnosis of cancer (about half with active cancer) who were eligible for primary prevention defibrillator therapy based on the recommendation of European Society of Cardiology (ESC)-HF guidelines[6] (Figure 4). We found that approximately half of our cancer cohort had an ischemic cause as a possible etiology for their cardiomyopathy, and approximately a quarter of patients were previously exposed to anthracycline-based therapy. Importantly, we found that only 27% of primary defibrillator therapy-eligible patients underwent device implantation. Independent predictors for primary defibrillator implantation by multivariate analysis were an electrocardiographic indication for CRT and a higher MADIT-ICD Benefit scoring. Among patients who received a defibrillator, a low incidence of appropriate device therapy was reported (4%). The risk of bacteremia was low (10%) with no need for device extraction. By time-varying analysis, survival of patients with cancer was comparable between patients implanted versus not implanted with primary defibrillators with the most commonly identified cause of death being cancer-related mortality.

The implantation of defibrillators among patients with HF and LVEF $\leq$ 35% is the standard of care by the European Society of Cardiology (ESC) Guidelines for the primary prevention of sudden cardiac death,[6,7] yet pivotal studies have excluded patients with a preexisting diagnosis of cancer. Published data regarding primary defibrillator therapy and the occurrence of ventricular arrhythmias in patients with cancer are limited. Lalario et al[8] recently showed that patients with a chemotherapy-induced dilated cardiomyopathy had a higher incidence of all-cause mortality, but a lower incidence of malignant ventricular arrhythmic events compared with patients with idiopathic dilated cardiomyopathy (0% vs 4% rates of VT/VF, respectively). In our study, during a median follow-up of 5.3 years, only one patient (5%) with a defibrillator had an appropriate device therapy. Other studies have shown higher rates (29% to 32%) of appropriate device therapy and ventricular arrhythmias among patients with cancer when compared with patients who did not have cancer.[1,9] The discrepancies between studies are mostly attributed to differences in cohorts' characteristics including the indication for defibrillator therapy, cancer type and stage including cardiac and pericardial involvement, electrolytes' abnormalities, baseline cardiovascular co-morbidities, and drug toxicities.

To our knowledge, this is the first study to evaluate the rate of defibrillator implantation among patients with cancer who were found eligible for primary prevention defibrillator therapy. We found that only 27% of primary defibrillator therapy-eligible patients underwent device implantation. Several arguments advocating nonadherence to the guidelines should be discussed. First, as guidelines' recommendation require a minimum estimated survival of 1 year,[6] physicians may be reluctant to implant a defibrillator in a patient with a history of cancer, particularly when the disease is considered advanced or active. However, because of the rapid proliferation of novel anticancer

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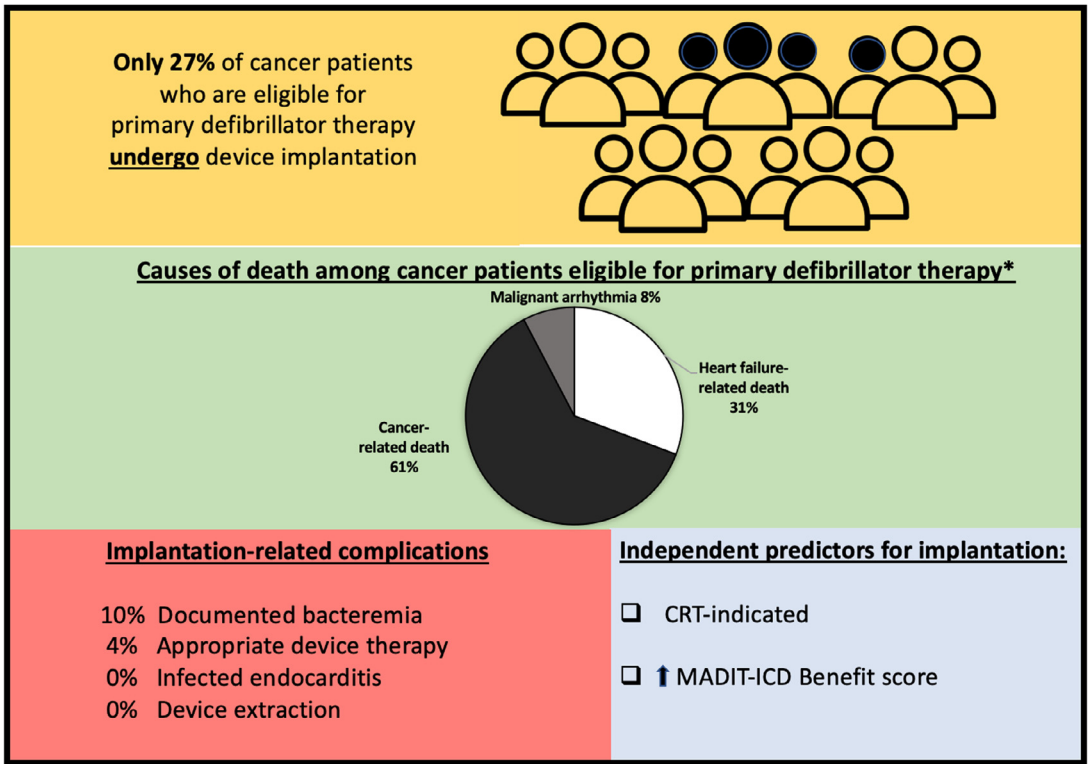

Figure 4. Central illustration. *Death causes were missing in 43% of cohort.

therapies, many patients, including those presenting with metastatic disease, are expected to live longer than several years. In our cohort, active cancer disease did not display as a negative predictor for the implantation of primary defibrillators. This may be the result of an established and readily-available cardio-oncology service at our medical center that intersects these 2 disciplines. Second, the benefit of primary defibrillator therapy for the prevention of sudden cardiac death is considered lower in patients with nonischemic versus ischemic etiology.[6,10] As many patients with cancer suffer from nonischemic causes of cardiomyopathy (such as anthracycline or trastuzumab-induced cardiomyopathy or immune checkpoint−induced myocarditis), the potential benefit from primary prevention defibrillators may be attenuated. This was demonstrated in this study by the low number of appropriate device therapies during patients' follow-ups. To note, although patients with nonischemic cardiomyopathy have a higher potential for LV systolic recovery,[11] the majority of patients with cancer in our study did not significantly improve their LVEF at 1-year follow-up beyond the cutoff for primary prevention defibrillator therapy. Third, a possible drawback of device implantation in patients with cancer is the risk of developing continuous bacteremia which may require device extraction. Patients with cancer are at a higher risk of developing bacteremia compared with the general population because of an increased prevalence of indwelling catheters and immunosuppressive states and prolonged stay at hospital facilities.[1,12] A meta-analysis that investigated the different baseline risk factors for the occurrence of cardiac implantable electronic device infection found an odds ratio of 2.23 (95% CI 1.26 to 3.95) for cancer.[13] However, newer prophylactic techniques that may lower the rate of device-related infections, including in the cancer population, are available nowadays.[12] None of the subjects in our cohort presented with continuous bacteremia and/or required device extraction during long-term follow-up.

Predictors for the implantation of primary defibrillators among patients with cancer were an electrocardiographic indication for CRT and a higher MADIT-ICD Benefit score (which also includes CRT as one of its items). These findings are important from an HF perspective as the MADIT-CHIC study previously showed that in patients with chemotherapy-induced cardiomyopathy the use of CRT was associated with improvement in LVEF after 6 months.[14] Nevertheless, our findings suggest that the MADIT-ICD Benefit score does not optimally identify the patients with cancer' sub-population that is more likely to experience malignant ventricular arrhythmias and to benefit from defibrillator implantation. We found that cancer, rather than cardiac causes, was the most commonly identified cause of death in our cohort and that the incidence of sudden cardiac death (2 patients) or appropriate defibrillator therapies (1 patient) were relatively low (a total of 3 of 75 patients, 4% of cohort). These findings underscore the need to include cancer as a predictor for nonarrhythmic mortality in primary defibrillator therapy benefit/futility scores such as the MADIT-ICD Benefit model.

Importantly, although the study's design is observational, we believe there is a causal relationship between the low rate of appropriate device therapies in patients with cancer and the higher rate of cancer-related mortality on

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one hand, and the underutilization of primary defibrillators in this population on the other. However, as the life expectancy of patients with cancer is on the rise, one should expect a greater future benefit from primary prevention therapies. There is currently an unmet need in the cancer patient population for a risk stratification algorithm that will assist health caregivers in referring the appropriate patients to primary defibrillator therapy. Such a tool should account for other known prognostic and arrhythmogenic parameters, such as the extent of the myocardial scar as evident by cardiac magnetic resonance imaging, the patient's tendency for electrolyte disturbances, and the use of antineoplastic drugs with known arrhythmogenic properties.

This study has several limitations. First, our study is limited by its relatively small sample size and single-center nature possibly limiting generalizability. Second, death causes were missing in 43% of the cohort despite our efforts to retrieve data from personal electronic records. Larger-scale studies are required to verify our findings.

In conclusion, we suggest that primary defibrillator therapy should not be routinely denied to patients with a cancer diagnosis and that the decision to implant a defibrillator should be individualized for each patient following coevaluation by cardiology and oncology healthcare providers. Moreover, we found that potential defibrillator utility in patients with cancer is only partially portrayed in the MADIT-ICD Benefit tool, thus underscoring the need for a tailored risk stratification algorithm for patients with cancer who are found eligible for primary sudden cardiac death prevention.

Disclosures

The authors have no conflicts of interest to declare.

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