

# Clinical and Prognostic Relevance of Cardiac Wasting in Patients With Advanced Cancer



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## ABSTRACT

**BACKGROUND** Body wasting in patients with cancer can affect the heart.

**OBJECTIVES** The frequency, extent, and clinical and prognostic importance of cardiac wasting in cancer patients is unknown.

**METHODS** This study prospectively enrolled 300 patients with mostly advanced, active cancer but without significant cardiovascular disease or infection. These patients were compared with 60 healthy control subjects and 60 patients with chronic heart failure (ejection fraction <40%) of similar age and sex distribution.

**RESULTS** Cancer patients presented with lower left ventricular (LV) mass than healthy control subjects or heart failure patients (assessed by transthoracic echocardiography:  $177 \pm 47$  g vs  $203 \pm 64$  g vs  $300 \pm 71$  g, respectively;  $P < 0.001$ ). LV mass was lowest in cancer patients with cachexia ( $153 \pm 42$  g;  $P < 0.001$ ). Importantly, the presence of low LV mass was independent of previous cardiotoxic anticancer therapy. In 90 cancer patients with a second echocardiogram after  $122 \pm 71$  days, LV mass had declined by  $9.3\% \pm 1.4\%$  ( $P < 0.001$ ). In cancer patients with cardiac wasting during follow-up, stroke volume decreased ( $P < 0.001$ ) and resting heart rate increased over time ( $P = 0.001$ ). During follow-up of on average 16 months, 149 patients died (1-year all-cause mortality 43%; 95% CI: 37%-49%). LV mass and LV mass adjusted for height squared were independent prognostic markers (both  $P < 0.05$ ). Adjustment of LV mass for body surface area masked the observed survival impact. LV mass below the prognostically relevant cutpoints in cancer was associated with reduced overall functional status and lower physical performance.

**CONCLUSIONS** Low LV mass is associated with poor functional status and increased all-cause mortality in cancer. These findings provide clinical evidence of cardiac wasting-associated cardiomyopathy in cancer.

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## ABBREVIATIONS AND ACRONYMS

|              |   |
|--------------|---|
| <b>BSA</b>   | = body surface area   |
| <b>CRP</b>   | = C-reactive protein  |
| <b>ECOG</b>  | = Eastern Cooperative<br>Oncology Group                     |
| <b>IL</b>    | = interleukin   |
| <b>IVSd</b>  | = interventricular septal<br>thickness at end-diastole      |
| <b>LV</b>    | = left ventricular  |
| <b>LVEF</b>  | = left ventricular ejection<br>fraction                     |
| <b>LVIDd</b> | = left ventricular<br>internal diameter at end-<br>diastole |
| <b>PWd</b>   | = posterior wall thickness<br>at end-diastole               |
| <b>TNF</b>   | = tumor necrosis factor                                     |
| <b>T2DM</b>  | = type 2 diabetes<br>mellitus                               |

In advanced cancer, cachexia is frequently observed in 30% to 80% of patients, depending on the cancer type, stage, and comorbidities.<sup>1,2</sup> Cachexia is characterized by involuntary weight loss associated with loss of both skeletal muscle mass and fat tissue.<sup>3</sup> Other symptoms, such as fatigue, impaired physical performance, and dyspnea, are associated with cancer cachexia.<sup>4</sup> These symptoms are also frequently observed in chronic heart failure. There are multiple possible reasons for whole body wasting in cancer, including chronic and systemic inflammation (ie, cytokine mediated), neurohormonal alterations, metabolic dysregulation, and mitochondrial dysfunction.<sup>5,6</sup> All these pathophysiologic abnormalities may also affect the heart in cancer patients. In experimental models of cancer, cardiac wasting has been repeatedly observed,<sup>7,8</sup> and 1 study also documented this condition as a late-stage phenomenon in a rat cancer model with clinical features of advanced heart failure.<sup>9</sup> In human cancer patients, reductions of left ventricular (LV) mass have been described in 3 preliminary studies.<sup>9-11</sup>

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We previously proposed that cancer patients with advanced-stage disease develop *cardiac wasting-associated cardiomyopathy*.<sup>4</sup> Tumor-related wasting processes may cause many different structural and hemodynamic alterations in the cardiac milieu resulting in arrhythmias and clinical heart failure.<sup>4,12</sup> We hypothesized that cardiac wasting mainly occurs in advanced stages of different cancer types, and it is

enhanced by generalized body wasting and independent of systemic anticancer therapy (cardiotoxic or noncardiotoxic). Furthermore, we hypothesized that cardiac wasting may be associated with reduced functional outcomes and prognosis. From a methodologic point of view, LV mass adjustment for body surface area (BSA), which is currently the common mean for standardization,<sup>13</sup> may be misleading in advanced-stage cancer patients when assessing them for LV muscle wasting. Indeed, adjustment of LV mass for BSA may mask cardiac wasting, particularly when body weight is significantly reduced, which also reduces BSA values and results in small or no detectable changes of LV mass adjusted for BSA.

We hypothesized that LV mass adjustment for the square of the patients' height or unadjusted data should be used in patients with advanced-stage cancer instead of adjustment for BSA. Although BSA adjustment is needed in children, it is arguable whether it is needed in any other situations. For example, one could argue that BSA adjustment is also not needed in the evaluation of obesity-related heart failure, which could be considered the opposite problem of "cachexia-related heart failure" with regard to LV mass and its adjustment for frame size. We have designed this study to prospectively investigate the best metric(s) for quantifying cardiac wasting in patients with advanced-stage cancer, its pathophysiologic correlates, and prognostic implications.

## METHODS

**PATIENT GROUP.** Between September 2017 and October 2020, we prospectively examined 320 hospitalized cancer patients admitted to the oncology department of the Charité-Berlin University of

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**TABLE 1** Baseline Characteristics

|  | Healthy Control<br>Subjects<br>(n = 60) | All Cancer<br>Patients<br>(n = 300) | Heart Failure<br>Patients<br>(n = 60) | ANOVA<br>P Value <sup>a</sup> | Cachectic<br>Cancer Patients<br>(n = 87) | Noncachectic<br>Cancer Patients<br>(n = 213) | ANOVA<br>P Value <sup>b</sup> |
|--|---|-------------------------------------|---------------------------------------|-------------------------------|--|--|-------------------------------|
| <b>Clinical parameters</b>                   |   |                                     |                                       |                               |  |  |                               |
| Age, y                                       | 60 ± 8                                  | 62 ± 14                             | 62 ± 11                               | 0.40                          | 63 ± 14                                  | 62 ± 14                                      | 0.54                          |
| Female                                       | 36 (60)                                 | 154 (51)                            | 28 (47)                               | 0.22                          | 47 (54)                                  | 107 (50)                                     | 0.45                          |
| BMI, kg/m <sup>2</sup>                       | 25.7 ± 3.8                              | 24.8 ± 4.9 <sup>c</sup>             | 27.8 ± 5.3 <sup>d</sup>               | <0.001                        | 20.5 ± 2.4 <sup>c,e,f</sup>              | 26.6 ± 4.6 <sup>g</sup>                      | <0.001                        |
| Systolic BP, mm Hg                           | 137 ± 17                                | 128 ± 19 <sup>c,h</sup>             | 117 ± 19 <sup>f</sup>                 | <0.001                        | 121 ± 17 <sup>e,f</sup>                  | 131 ± 19 <sup>c,d</sup>                      | <0.001                        |
| Diastolic BP, mm Hg                          | 87 ± 10                                 | 78 ± 12 <sup>f,g</sup>              | 74 ± 13 <sup>f</sup>                  | <0.001                        | 76 ± 12 <sup>f,i</sup>                   | 79 ± 11 <sup>c,f</sup>                       | <0.001                        |
| Dyspnea under exertion                       | 3 (5)                                   | 146 (49) <sup>f</sup>               | 35 (58) <sup>f</sup>                  | <0.001                        | 48 (55) <sup>f</sup>                     | 98 (46) <sup>f</sup>                         | <0.001                        |
| <b>Cancer and anticancer therapy details</b> |   |                                     |                                       |                               |  |  |                               |
| Cancer stage III/IV                          | —                                       | 241 (80)                            | —                                     | —                             | 77 (89)                                  | 164 (77)                                     | 0.020                         |
| Solid cancer                                 | —                                       | 159 (53)                            | —                                     | —                             | 58 (67)                                  | 101 (47)                                     | 0.002                         |
| ECOG performance scale ≥3                    | —                                       | 81 (28)                             | —                                     | —                             | 40 (46)                                  | 41 (19)                                      | <0.001                        |
| First therapy line of anticancer therapy     | —                                       | 95 (32)                             | —                                     | —                             | 28 (32)                                  | 67 (32)                                      | 0.90                          |
| Previous cardiotoxic anticancer therapy      | —                                       | 125 (42)                            | —                                     | —                             | 43 (49)                                  | 82 (39)                                      | 0.081                         |
| Anticancer therapy naive                     | —                                       | 96 (32)                             | —                                     | —                             | 20 (23)                                  | 76 (36)                                      | 0.032                         |
| <b>Side diagnosis</b>                        |   |                                     |                                       |                               |  |  |                               |
| Anemia                                       | 9 (15)                                  | 251 (84) <sup>c,f</sup>             | 33 (55) <sup>f</sup>                  | <0.001                        | 85 (98) <sup>c,e,f</sup>                 | 166 (78) <sup>c,f</sup>                      | <0.001                        |
| Arterial hypertension                        | 25 (42)                                 | 133 (45) <sup>c</sup>               | 47 (78) <sup>f</sup>                  | <0.001                        | 30 (35) <sup>c,i</sup>                   | 103 (49) <sup>c</sup>                        | <0.001                        |
| Hypercholesterolemia                         | 38 (63)                                 | 96 (32) <sup>f,i</sup>              | 32 (53)                               | <0.001                        | 16 (18) <sup>c,f,k</sup>                 | 80 (38) <sup>f,d</sup>                       | <0.001                        |
| Type 2 diabetes mellitus                     | 1 (2)                                   | 40 (14) <sup>h,j</sup>              | 18 (30) <sup>f</sup>                  | <0.001                        | 7 (8) <sup>c</sup>                       | 33 (16) <sup>g,h</sup>                       | <0.001                        |
| Chronic kidney disease                       | 0 (0)                                   | 24 (8) <sup>c,d</sup>               | 18 (30) <sup>f</sup>                  | <0.001                        | 8 (9) <sup>h,j</sup>                     | 16 (8) <sup>c,d</sup>                        | <0.001                        |
| <b>Laboratory parameters</b>                 |   |                                     |                                       |                               |  |  |                               |
| Sodium, mmol/L                               | 141 ± 2                                 | 139 ± 4 <sup>f,g</sup>              | 140 ± 3                               | <0.001                        | 138 ± 4 <sup>f,i</sup>                   | 139 ± 4 <sup>f</sup>                         | <0.001                        |
| Potassium, mmol/L                            | 4.1 ± 0.3                               | 3.8 ± 0.4 <sup>c,f</sup>            | 4.3 ± 0.4 <sup>h</sup>                | <0.001                        | 3.9 ± 0.5 <sup>c,h</sup>                 | 3.8 ± 0.4 <sup>c,f</sup>                     | <0.001                        |
| Hemoglobin, g/dL                             | 14.4 ± 1.1                              | 11.1 ± 2.2 <sup>c,f</sup>           | 13.3 ± 2.0 <sup>h</sup>               | <0.001                        | 10.2 ± 1.8 <sup>c,e,f</sup>              | 11.5 ± 2.2 <sup>c,f</sup>                    | <0.001                        |
| Leukocytes, /nL                              | 6.1 ± 1.9                               | 8.1 ± 6.6 <sup>d</sup>              | 8.6 ± 2.5                             | 0.033                         | 7.9 ± 6.7                                | 8.2 ± 6.6                                    | 0.07                          |
| Platelets, /nL                               | 251 ± 55                                | 250 ± 131                           | 256 ± 79                              | 0.94                          | 249 ± 145                                | 250 ± 126                                    | 0.99                          |
| eGFR, mL/min/1.73 m <sup>2</sup>             | 86 ± 11                                 | 86 ± 23 <sup>c</sup>                | 63 ± 23 <sup>f</sup>                  | <0.001                        | 86 ± 26 <sup>c</sup>                     | 87 ± 22 <sup>c</sup>                         | <0.001                        |
| LDL, mg/dL                                   | 138 ± 36                                | 106 ± 40 <sup>f,i</sup>             | 98 ± 9 <sup>f</sup>                   | <0.001                        | 95 ± 42 <sup>f,k</sup>                   | 111 ± 39 <sup>c,f</sup>                      | <0.001                        |
| GOT, U/L                                     | 26 (22-28)                              | 26 (21-40)                          | 30 (21-39)                            | 0.12                          | 26 (19-48)                               | 26 (22-37)                                   | 0.23                          |
| Hs troponin T, ng/L                          | 5 (3-8)                                 | 11 (7-21) <sup>c,f</sup>            | 22 (12-45) <sup>f</sup>               | <0.001                        | 14 (8-26) <sup>f</sup>                   | 11 (6-17) <sup>c,f</sup>                     | <0.001                        |
| NT-proBNP, ng/L                              | 59 (42-143)                             | 281 (118-621) <sup>c,f</sup>        | 1,548 (572-8,179) <sup>f</sup>        | <0.001                        | 351 (169-742) <sup>c,f</sup>             | 244 (99-559) <sup>c,f</sup>                  | <0.001                        |
| CRP, mg/L                                    | 1 (1-3)                                 | 10 (3-33) <sup>f,g</sup>            | 4 (1-16) <sup>f</sup>                 | <0.001                        | 16 (3-50) <sup>f,i</sup>                 | 8 (3-26) <sup>f</sup>                        | <0.001                        |
| Interleukin-6, pg/mL                         | 2.5 (1.6-3.3)                           | 9.0 (4.0-23.3)                      | —                                     | <0.001                        | 19.0 (5.6-38.6) <sup>f,k</sup>           | 6.9 (3.2-18.4) <sup>f</sup>                  | <0.001                        |
| Interleukin-18, pg/mL                        | 0 (0.0-0.1)                             | 0.07 (0.0-0.18)                     | —                                     | <0.001                        | 0.12 (0.0-0.26) <sup>f,i</sup>           | 0.055 (0.00-0.16) <sup>h</sup>               | <0.001                        |
| Interleukin-10, pg/mL                        | 0.018 (0.010-0.479)                     | 0.396 (0.010-1.261)                 | —                                     | <0.001                        | 0.353 (0.010-1.23) <sup>f</sup>          | 0.396 (0.010-1.267) <sup>f</sup>             | 0.001                         |
| TNF, pg/mL                                   | 1.19 (1.04-1.35)                        | 1.94 (1.33-2.99)                    | —                                     | <0.001                        | 1.94 (1.40-2.92) <sup>f</sup>            | 1.95 (1.32-3.25) <sup>f</sup>                | <0.001                        |
| <b>Medications</b>                           |   |                                     |                                       |                               |  |  |                               |
| ACE inhibitors/ARBs                          | 13 (22)                                 | 77 (26) <sup>c</sup>                | 31 (52) <sup>f</sup>                  | <0.001                        | 17 (20) <sup>c</sup>                     | 60 (28) <sup>h</sup>                         | <0.001                        |
| ARNi   | 0 (0)                                   | 0 (0) <sup>c</sup>                  | 29 (48) <sup>f</sup>                  | <0.001                        | 0 (0) <sup>c</sup>                       | 0 (0) <sup>c</sup>                           | <0.001                        |
| Beta-blockers                                | 2 (3)                                   | 55 (18) <sup>c,h</sup>              | 57 (95) <sup>f</sup>                  | <0.001                        | 13 (15) <sup>c,d</sup>                   | 42 (20) <sup>c,h</sup>                       | <0.001                        |
| Anticoagulant agents                         | 1 (2)                                   | 11 (4) <sup>c</sup>                 | 20 (33) <sup>f</sup>                  | <0.001                        | 2 (2) <sup>c</sup>                       | 9 (4) <sup>c</sup>                           | <0.001                        |
| Diuretic agents                              | 2 (3)                                   | 54 (18) <sup>c,h</sup>              | 49 (82) <sup>f</sup>                  | <0.001                        | 11 (13) <sup>c</sup>                     | 43 (20) <sup>c,h</sup>                       | <0.001                        |
| Antidepressants                              | 1 (2)                                   | 41 (14) <sup>h</sup>                | 5 (8)                                 | 0.011                         | 12 (14) <sup>d</sup>                     | 29 (14) <sup>h</sup>                         | 0.027                         |
| Opioids                                      | 0 (0)                                   | 66 (22) <sup>c,f</sup>              | 1 (2)                                 | <0.001                        | 26 (30) <sup>c,f,i</sup>                 | 40 (19) <sup>c,f</sup>                       | <0.001                        |
| Corticosteroids                              | 0 (0)                                   | 99 (33) <sup>c,f</sup>              | 4 (7)                                 | <0.001                        | 22 (25) <sup>c,f</sup>                   | 77 (36) <sup>c,f</sup>                       | <0.001                        |

Values are mean ± SD, n (%), or median (IQR). P values for nominal variables refer to all comparison groups. <sup>a</sup>ANOVA P value/chi-square test for comparisons among cancer patients, healthy control subjects, and heart failure patients. <sup>b</sup>ANOVA P value/chi-square test for comparisons among cachectic cancer patients, noncachectic cancer patients, healthy control subjects, and heart failure patients. <sup>c</sup>P <0.001 vs heart failure patients. <sup>d</sup>P <0.05 vs control subjects. <sup>e</sup>P <0.001 vs noncachectic cancer patients. <sup>f</sup>P <0.001 vs control subjects. <sup>g</sup>P <0.05 vs heart failure patients. <sup>h</sup>P <0.01 vs control subjects; <sup>i</sup>P <0.05 vs noncachectic cancer patients. <sup>j</sup>P <0.01 vs heart failure patients. <sup>k</sup>P <0.01 vs noncachectic cancer patients.

ACE = angiotensin-converting enzyme; ANOVA = analysis of variance; ARB = angiotensin II receptor blocker; ARNi = angiotensin receptor-neprilysin inhibitor; BMI = body mass index; BP = blood pressure; BSA = body surface area; CRP = C-reactive protein; ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate; GOT = glutamic-oxaloacetic transaminase; hs = high-sensitivity; LDL = low-density lipoprotein; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TNF = tumor necrosis factor.

Medicine in Berlin, Germany. To be eligible for our study, all cancer patients needed the following: histologically proven, active cancer; age  $\geq 18$  years; willingness and ability to participate in a prospective study; and ability to sign the informed consent form themselves. Exclusion criteria for our study were as follows: 1) a different cancer diagnosis in the 5 years before study inclusion; 2) clinical signs of an acute infection or active antibiotic therapy; 3) a history or presence of significant cardiovascular disease (eg, coronary artery disease, myocardial infarction, severe cardiac valve dysfunction, or LV ejection fraction [LVEF]  $< 50\%$ ); or 4) the presence of severe chronic obstructive pulmonary disease at Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage  $> II^{14}$  (all GOLD stages were allowed in lung cancer). Patients with type 2 diabetes mellitus (T2DM) without cardiovascular complications and controlled arterial hypertension with blood pressure  $< 160/100$  mm Hg were not excluded. Cancer patients were allowed to be anticancer therapy naive or to have received cardiotoxic or noncardiotoxic anticancer therapy previously. Of the 320 cancer patients who were included in the study, 6 patients were excluded because of newly diagnosed LVEF  $< 50\%$  (according to the exclusion criteria of the study), and 14 cancer patients were excluded for insufficient echocardiographic images for LV mass calculations. The final study cohort comprised 300 cancer patients. Main reasons for hospitalization were as follows: systemic anticancer therapy administration ( $n = 123$ ); diagnostic examinations ( $n = 102$ ); worsening clinical condition ( $n = 38$ ); pain exacerbation ( $n = 13$ ); shortness of breath ( $n = 12$ ); and neurologic symptoms ( $n = 12$ ).

Sixty healthy control subjects of similar sex and age distribution were recruited. Healthy control subjects were free of significant cardiovascular disease and were generally healthy. T2DM and controlled arterial hypertension were not exclusion criteria.

For additional comparison, we also analyzed a control group of 60 patients from our hospital records with chronic heart failure and reduced ejection fraction (all with LVEF  $< 40\%$ ) according to the current guidelines of the European Society of Cardiology,<sup>15</sup> as well as available blood biomarkers and a well-documented echocardiogram in our departments' records. All heart failure patients were investigated in the same time span as the cancer patients, and they had similar sex and age distribution as the cancer patients.

**STUDY DESIGN.** All cancer patients and healthy control subjects were prospectively examined. All patients underwent the following: a detailed medical

history; physical examination, including determination of body weight, height, and BSA; blood samples for biomarker analyses; and a 12-lead resting electrocardiogram. For patient-reported outcomes and functional assessment, we used several instruments: the Eastern Cooperative Oncology Group (ECOG) performance scale,<sup>16</sup> the Karnofsky Index performance status,<sup>17</sup> EQ-5D-5L questionnaire,<sup>18</sup> the Visual Analogue Scale for appetite<sup>19</sup> and pain,<sup>20</sup>; and the Mini Nutritional Assessment.<sup>21</sup> The following functional assessment tests were all performed according to the respective standard protocols: maximum handgrip strength<sup>22</sup>; 4-meter gait speed<sup>23</sup>; 10-step stair-climbing power test<sup>24</sup>; and 6-minute walk test.<sup>25</sup>

All cancer patients were offered an echocardiographic follow-up examination within the first 12 months after study recruitment, but we aimed to conduct this examination within the first 6 months. Cancer patients were grouped by the presence of cachexia at baseline and were compared with healthy control subjects and patients with chronic heart failure. Cachexia was diagnosed when weight loss was  $\geq 5\%$  in the previous 12 months as reported by the patients and body mass index was  $< 24.0$  kg/m<sup>2</sup> at baseline (adapted from Fearon et al,<sup>26</sup> as well as recent clinical trials<sup>27</sup>). Advanced-stage cancer was defined as any of the following: stage III/IV, Union for International Cancer Control<sup>28</sup>; stage III/IV, Ann Arbor classification<sup>29</sup>; and stage III, Durie and Salmon classification.<sup>30</sup> Cardiotoxic anticancer agents were defined as drugs that can cause heart failure according to the most recent respective European Society of Cardiology guideline.<sup>15</sup> The study complied with the Declaration of Helsinki and was approved by the Charité Ethics Committee, and all patients gave their written informed consent.

**ECHOCARDIOGRAPHIC EXAMINATION.** A comprehensive 2-dimensional transthoracic echocardiographic examination was conducted and analyzed by 3 well-trained and experienced echocardiographers with standardized operating procedures. Additionally, all LV mass analyses were then validated by 2 independent and experienced echocardiographers who were not aware of the survival status of any participating study subject. We used a Vivid E90 machine (GE Healthcare) for echocardiograms and a Tomtec system for imaging analysis. Cardiac chamber quantification was performed according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.<sup>13</sup> The modified Simpson method was used to quantify end-systolic and end-diastolic LV volumes and for the biplane

calculation of the LVEF. LV diastolic function was evaluated according to the latest guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging in cancer patients and healthy control subjects (ie, only in subjects with LVEF  $\geq$ 50%).<sup>31</sup> Stroke volume was calculated as the product of the LV outflow tract area and the LV outflow tract time-velocity integral, and cardiac output was calculated by multiplying stroke volume by resting heart rate.<sup>32</sup> Speckle-tracking analyses were performed on 2-dimensional gray-scale acquisitions of the apical 4-chamber, 2-chamber, and long-axis views. LV global longitudinal strain was calculated as the mean of all segmental strain values of the apical views.

**LEFT VENTRICULAR MASS.** LV mass was calculated according to the Devereux formula<sup>33</sup> in all patients and control subjects. LV mass calculation was determined on the basis of linear measurements in 2-dimensional images of the parasternal long-axis views. For validation of the results, we additionally calculated LV mass with a second method: the area-length method<sup>34</sup> in the parasternal short-axis view at the level of papillary muscles. This was possible in 259 cancer patients (71 cachectic and 188 noncachectic), 59 healthy control subjects, and 59 heart failure patients. To assess the reproducibility of the 2 measurement methods, a Bland-Altman plot<sup>35</sup> was constructed to show limits of agreement. The coefficient of variability (expressed as a percentage) was calculated as the SD of the differences divided by the mean of the parameter under consideration.<sup>36</sup> Values of LV mass are provided as absolute values, as well as mass adjusted for height squared<sup>37</sup> and mass adjusted for BSA according to the DuBois formula.<sup>38</sup>

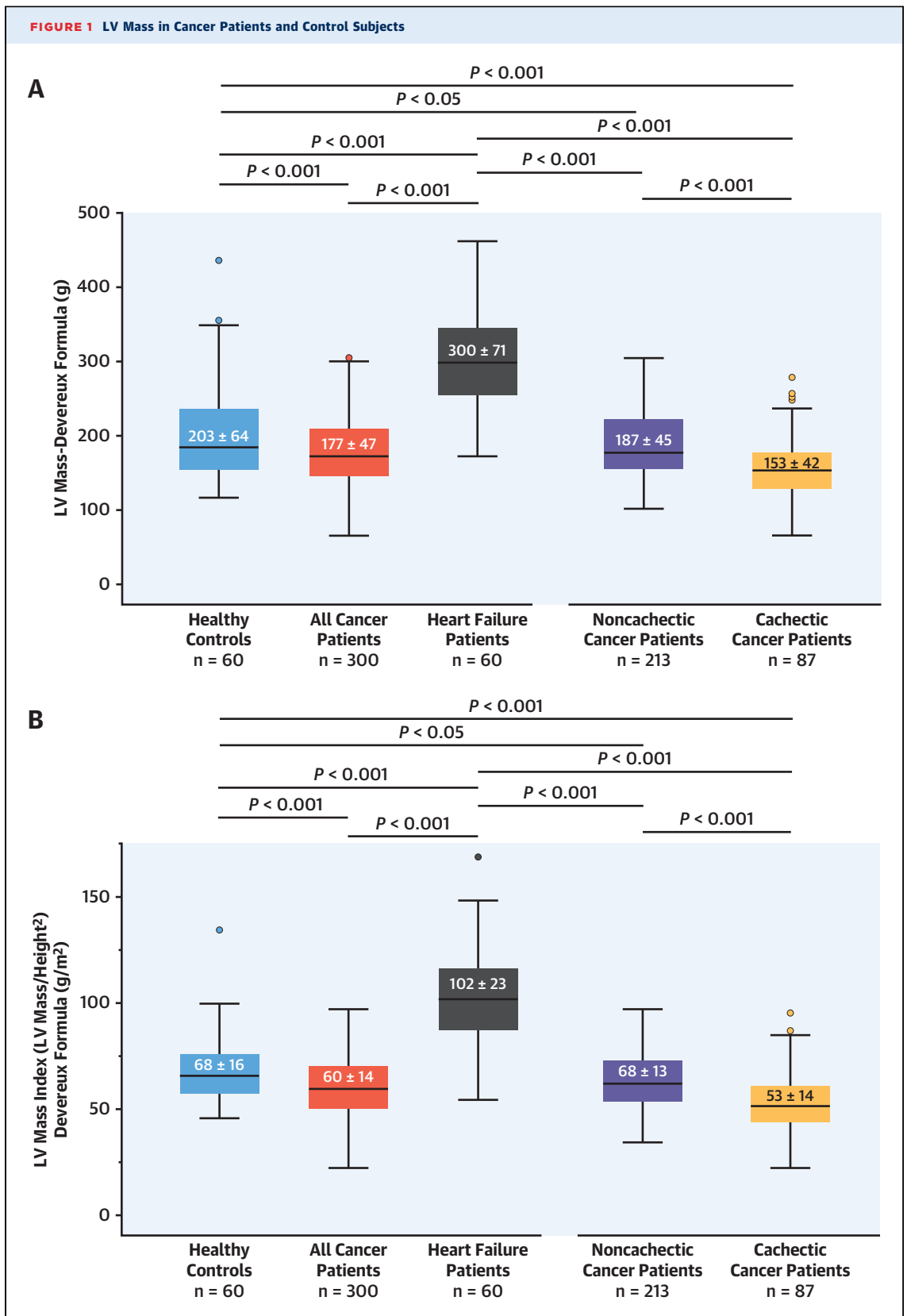
**STATISTICAL ANALYSIS.** We calculated that we needed to recruit 56 healthy control subjects to detect a difference in LV mass of 10% between healthy control subjects and 300 cancer patients (with 85% power at a 2-sided alpha of 5%), given a common pooled SD of healthy control subjects and cancer patients of LV mass of 32 g.<sup>39,40</sup> To increase the robustness of the data, we recruited 60 healthy control subjects (20% compared with the cancer group) and similarly chose to include another group of 60 patients with chronic heart failure with reduced ejection fraction for comparison. In addition, for power calculation of the number of repeat echocardiography assessments needed to detect a difference in LV mass of 10% (with 85% power at a 2-sided alpha of 5%), we assumed an SD of repeat LV mass assessments by echocardiography of 38 g.<sup>39</sup> On this

basis, we needed 88 cancer patients with repeat echocardiography.

The Kolmogorov-Smirnov test was used for assessment of normal distributions. One-way analysis of variance and the Fisher post hoc test were used as parametric tests, and mean  $\pm$  SD are displayed. The Mann-Whitney *U* test and the Kruskal-Wallis test were used as nonparametric tests, and median with IQRs are shown. The analysis of categorical variables was preferably conducted with the chi-square test. Only if 1 cell assignment in the contingency table was smaller than 5, the Fisher exact test was used. For survival analysis in cancer patients, we used a Cox proportional hazards regression model. In univariable and multivariable models for LV mass, sex was used as strata.<sup>13</sup> The multivariable models were adjusted for routinely assessed oncology care-focused parameters and for known prognostic variables for cancer patients: age (per 1 year); cancer stage (III-IV vs I-II); cancer group (each cancer group vs each other); ECOG performance scale (3-4 vs 0-2); time from diagnosis to study recruitment (per 3 months); cardiotoxic anticancer therapy (yes vs no vs anticancer therapy naive); and hemoglobin (per 1 g/dL). Additionally, these models were adjusted for the following important cardiovascular variables: N-terminal pro-B-type natriuretic peptide (ng/L, per 1 Ln increase); high-sensitivity troponin T (ng/L, per 1 Ln increase); estimated glomerular filtration rate (per 1 mL/min/1.73 m<sup>2</sup>); and the inflammatory marker C-reactive protein (CRP, mg/L, per 1 Ln increase). Univariable and multivariable HRs, 95% CIs, and *P* values are given. To verify the proportional hazard assumption, which was not found to be violated, the log-minus-log plots were visually inspected. Sex-specific cutpoints<sup>13</sup> (on the basis of the standardized log-rank test) with the most significant split were chosen to construct Kaplan-Meier cumulative survival plots for illustrative purposes and for further pathophysiologic analyses. The paired Student's *t*-test was used to compare echocardiographic parameters between the first and second echocardiograms. *P* <0.05 was considered statistically significant in all analyses. The data analysis for this paper was generated using SAS/STAT software version 9.4 (SAS Institute, Inc) and SPSS software version 26.0 (IBM Corp).

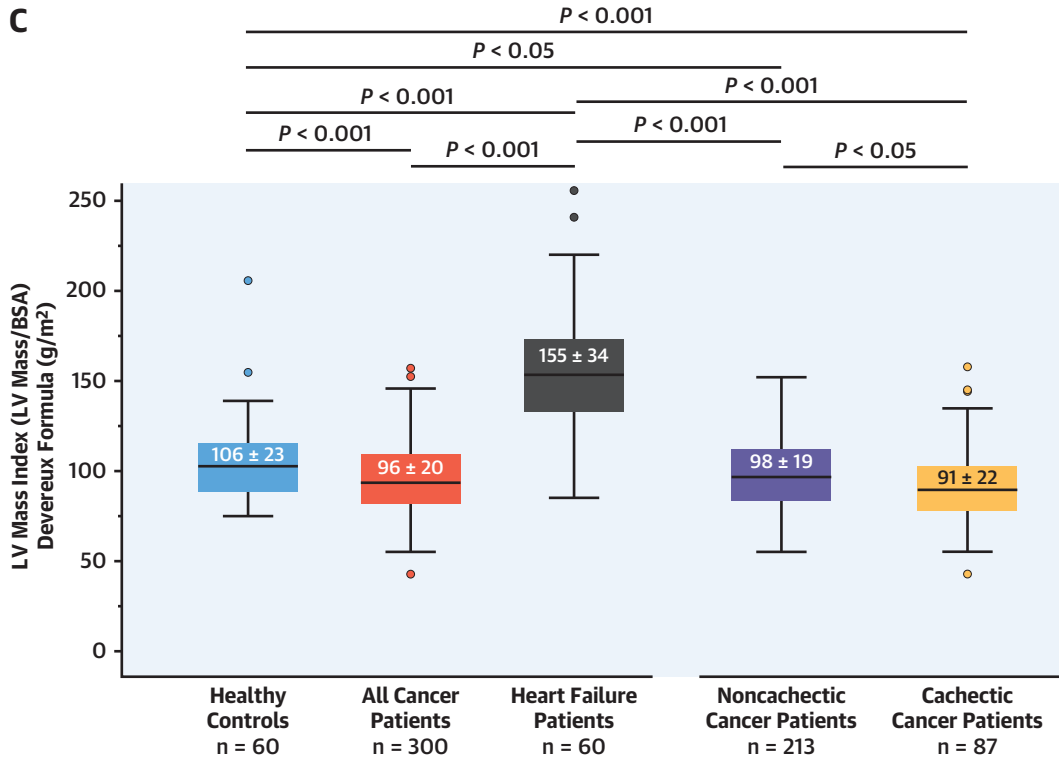
## RESULTS

**STUDY GROUP.** Cancer patients, healthy control subjects, and patients with chronic heart failure with reduced ejection fraction (LVEF <40%) were similar with respect to sex and age. Baseline characteristics



Continued on the next page

FIGURE 1 Continued



|  |          |          |          |          |
|--|----------|----------|----------|----------|
| LV Mass Index (LV Mass/Height <sup>2</sup> ) | 68 ± 16  | 60 ± 14* | 61 ± 13* | 60 ± 14* |
| LV Mass Index (LV Mass/BSA)                  | 106 ± 23 | 94 ± 21* | 97 ± 18* | 96 ± 21* |

and clinical features of our study patients are displayed in **Table 1**, and the distribution of cancer types is shown in **Supplemental Table 1**. Cancer patients had lower values of systolic and diastolic blood pressure, low-density lipoproteins, and hemoglobin in comparison with healthy control subjects. In addition, cachectic cancer patients (n = 87; 29%) had even lower values of systolic and diastolic blood pressure, low-density lipoproteins, and hemoglobin in comparison with noncachectic cancer patients. The frequency of previous cardiotoxic anticancer therapy was similar in cachectic and noncachectic cancer patients. Both cancer subgroups more frequently presented with dyspnea under exertion in comparison with healthy control subjects (**Table 1**), but with a frequency similar to that of patients with heart failure.

**ECHOCARDIOGRAPHIC EXAMINATION.** Cancer patients showed lower LV mass than healthy control subjects (with lower LV internal diameter at end-diastole [LVIDd] and posterior wall thickness at end-diastole [PWd]), and LV mass results remained significant after adjustment for BSA and height squared as calculated with Devereux formula. Cachectic cancer patients presented with lower LV mass, LV mass adjusted for height squared, and LV mass adjusted for BSA, interventricular septal thickness at end-diastole (IVSd), LVIDd, and PWd in comparison with noncachectic cancer patients, healthy control subjects, and heart failure patients (**Figures 1A to 1C**). Similar results were observed when the area-length method was applied for absolute and adjusted LV mass calculations (**Supplemental Table 2**), with a very high correlation (**Supplemental Figure 1**) and a coefficient of variability of 3.4% between both methods (**Supplemental Figure 2**).

Compared with findings in healthy control subjects, LV mass was reduced in a similar extent in anticancer therapy-naïve patients, in patients who had received noncardiotoxic therapy before, and in

patients previously treated with known cardiotoxic therapy (**Figure 1D**).

As a sensitivity analysis, we excluded all cancer patients and healthy control subjects receiving treatment with any cardiovascular medication and/or with T2DM. In this analysis, LV mass remained reduced in 151 cancer patients vs 41 healthy control subjects (**Supplemental Tables 3 and 4**).

Cancer patients presented with lower LVEF, stroke volume, stroke volume index, and cardiac output and with a higher heart rate and pulmonary artery systolic pressure in comparison with healthy control subjects (**Table 2**). Considering all cancer patients together, left and right atrium-related measures were not different compared with healthy control subjects (**Table 2**). This finding was also seen when patients or control subjects receiving any cardiovascular medication and/or having T2DM were excluded (**Supplemental Table 4**).

Cachectic cancer patients, analyzed separately vs noncachectic cancer patients, healthy control subjects, and heart failure patients, showed lower LV, left atrium, left atrial volume index, and right atrium cavity volume (**Table 2**). LVEF, global longitudinal strain, septal tissue Doppler velocity (septal e'), tricuspid annular plane systolic excursion, stroke volume, stroke volume index, and cardiac output were lower and heart rate was higher in cachectic cancer patients in comparison with noncachectic cancer patients.

**SURVIVAL ANALYSIS.** Patients were followed up from baseline to April 2021 (unless they died earlier) for a mean of 16 months (minimum 6 months, maximum 40 months). During follow-up, 149 (50%) patients died (1-year survival, 57%; 95% CI: 51%-63%). LV mass and LV mass adjusted for height squared as calculated with the Devereux formula were independent prognostic markers in multivariable Cox survival analysis (**Table 3**), with sex as strata and adjusted for age, cancer stage, cancer entity, ECOG

#### FIGURE 1 Continued

Box plots and comparisons of (A) absolute left ventricular (LV) mass; (B) left ventricular mass/height<sup>2</sup>; and (C) left ventricular mass/body surface area (BSA). (A to C) Data for healthy control subjects (n = 60), patients with cancer (n = 300), and patients with heart failure (n = 60). Cancer patients are additionally separated into noncachectic (n = 213) and cachectic (n = 87) categories. Cancer patients had lower absolute and relative (height<sup>2</sup>-adjusted and BSA-adjusted) left ventricular mass than healthy control subjects or heart failure patients. Cachectic cancer patients had lower left ventricular mass (absolute and relative) than noncachectic cancer patients, healthy control subjects, or heart failure patients. (D) Subgroups of cancer patients who were anticancer therapy naïve (n = 96), had noncardiotoxic anticancer therapy (n = 79), or had cardiotoxic anticancer therapy previously (n = 125) all had lower absolute and relative left ventricular mass compared with healthy control subjects. Left ventricular mass was calculated according to the Devereux formula; cachexia is defined as ≥5% weight loss in 12 months and body mass index <24.0 kg/m<sup>2</sup>; and body surface area was calculated according to the DuBois formula. Values are mean ± SD.



**TABLE 2** Baseline Echocardiographic Parameters

|  | Healthy Control Subjects (n = 60) | All Cancer Patients (n = 300) | Heart Failure (n = 60)   | ANOVA P Value <sup>a</sup> (All Cancer Patients vs Healthy Control Subjects vs Heart Failure) | Cachectic Cancer Patients (n = 87) | Noncachectic Cancer Patients (n = 213) | ANOVA P Value <sup>b</sup> (Cachectic vs Noncachectic Cancer Patients vs Healthy Control Subjects vs Heart Failure Patients) |
|--|-----------------------------------|-------------------------------|--------------------------|---|------------------------------------|--|--|
| LV mass, g   | 203 ± 64                          | 177 ± 47 <sup>c,d</sup>       | 300 ± 71 <sup>c</sup>    | <0.001  | 153 ± 42 <sup>c,d,e</sup>          | 187 ± 45 <sup>d,f</sup>                | <0.001   |
| LV mass index (LV mass/height <sup>2</sup> ), g/m <sup>2</sup> | 68 ± 16                           | 60 ± 14 <sup>c,d</sup>        | 102 ± 23 <sup>c</sup>    | <0.001  | 53 ± 14 <sup>c,d,e</sup>           | 63 ± 13 <sup>d,f</sup>                 | <0.001   |
| LV mass index (LV mass/BSA), g/m <sup>2</sup>                  | 106 ± 23                          | 96 ± 20 <sup>c,d</sup>        | 155 ± 34 <sup>c</sup>    | <0.001  | 91 ± 22 <sup>c,d,g</sup>           | 98 ± 19 <sup>d,f</sup>                 | <0.001   |
| IVSd, mm   | 10.7 ± 1.4                        | 10.5 ± 1.7                    | 10.8 ± 1.8               | 0.23  | 9.9 ± 1.7 <sup>e,h,i</sup>         | 10.7 ± 1.6                             | <0.001   |
| LVIDd, mm  | 46.9 ± 5.7                        | 44.8 ± 5.3 <sup>c,h</sup>     | 57.8 ± 6.1 <sup>c</sup>  | <0.001  | 42.9 ± 4.5 <sup>c,d,e</sup>        | 45.6 ± 5.5 <sup>d</sup>                | <0.001   |
| PWd, mm  | 9.8 ± 1.2                         | 9.4 ± 1.2 <sup>d,f</sup>      | 10.4 ± 1.5 <sup>f</sup>  | <0.001  | 9.1 ± 1.2 <sup>d,g,h</sup>         | 9.6 ± 1.2 <sup>d</sup>                 | <0.001   |
| LV end-diastolic apical length, mm                             | 73.8 ± 7.3                        | 73.8 ± 7.9 <sup>d</sup>       | 83.8 ± 8.0 <sup>c</sup>  | <0.001  | 71.3 ± 8.1 <sup>d,e</sup>          | 74.9 ± 7.5 <sup>d</sup>                | <0.001   |
| LV end-diastolic volume, mL                                    | 97 ± 28                           | 89 ± 29 <sup>d</sup>          | 167 ± 59 <sup>c</sup>    | <0.001  | 79 ± 29 <sup>d,h,j</sup>           | 93 ± 28 <sup>d</sup>                   | <0.001   |
| LV end-diastolic volume index (LVEDV/BSA), mL/m <sup>2</sup>   | 51 ± 11                           | 48 ± 14 <sup>d</sup>          | 86 ± 28 <sup>c</sup>     | <0.001  | 47 ± 16 <sup>d</sup>               | 49 ± 13 <sup>d</sup>                   | <0.001   |
| LA end-systolic volume, mL                                     | 49 ± 15                           | 44 ± 15 <sup>d</sup>          | 81 ± 36 <sup>c</sup>     | <0.001  | 36 ± 12 <sup>c,d,e</sup>           | 47 ± 15 <sup>d</sup>                   | <0.001   |
| LAVI (LAESV/BSA), mL/m <sup>2</sup>                            | 26 ± 6                            | 24 ± 7 <sup>d</sup>           | 41 ± 18 <sup>c</sup>     | <0.001  | 22 ± 7 <sup>d,f,g</sup>            | 24 ± 7 <sup>d</sup>                    | <0.001   |
| RA end-systolic volume, mL                                     | 36 ± 12                           | 33 ± 13 <sup>d</sup>          | 54 ± 24 <sup>c</sup>     | <0.001  | 28 ± 10 <sup>d,e,h</sup>           | 35 ± 14 <sup>d</sup>                   | <0.001   |
| RAVI (RAESV/BSA), mL/m <sup>2</sup>                            | 19 ± 6                            | 18 ± 6 <sup>d</sup>           | 28 ± 12 <sup>c</sup>     | <0.001  | 17 ± 6 <sup>d,f</sup>              | 18 ± 7 <sup>d</sup>                    | <0.001   |
| LV ejection fraction, %  | 68 ± 3                            | 64 ± 4 <sup>c,d</sup>         | 31 ± 6 <sup>c</sup>      | <0.001  | 63 ± 5 <sup>c,d,e</sup>            | 65 ± 4 <sup>c,d</sup>                  | <0.001   |
| LV GLS, %  | -19.4 ± 3.1                       | -18.6 ± 3.2 <sup>d</sup>      | -12.8 ± 2.4 <sup>c</sup> | <0.001  | -17.7 ± 3.1 <sup>c,d,e</sup>       | -18.9 ± 3.2 <sup>d</sup>               | <0.001   |
| Mitral septal e' velocity, cm/s                                | 8.6 ± 1.8                         | 8.2 ± 2.6 <sup>d</sup>        | 5.8 ± 2.4 <sup>c</sup>   | <0.001  | 7.7 ± 2.6 <sup>d,f,g</sup>         | 8.4 ± 2.6 <sup>d</sup>                 | <0.001   |
| Mitral lateral e' velocity, cm/s                               | 10.8 ± 2.5                        | 10.4 ± 3.7 <sup>d</sup>       | 7.4 ± 3.1 <sup>c</sup>   | <0.001  | 10.4 ± 4.4 <sup>d</sup>            | 10.4 ± 3.4 <sup>d</sup>                | <0.001   |
| Mitral E/e' mean   | 7.8 ± 1.6                         | 8.4 ± 2.6 <sup>d</sup>        | 14.9 ± 8.1 <sup>c</sup>  | <0.001  | 8.3 ± 2.8 <sup>d</sup>             | 8.5 ± 2.5 <sup>d</sup>                 | <0.001   |
| PASP, mm Hg  | 26 ± 4                            | 29 ± 8 <sup>d,h</sup>         | 35 ± 14 <sup>c</sup>     | <0.001  | 30 ± 8 <sup>d,f</sup>              | 29 ± 8 <sup>d,f</sup>                  | <0.001   |
| Normal diastolic function                                      | 60 (100)                          | 282 (94)                      | N/A                      | 0.052   | 81 (93)                            | 201 (94)                               | 0.075  |
| TAPSE, mm  | 25 ± 3                            | 25 ± 4 <sup>d</sup>           | 19 ± 4 <sup>c</sup>      | <0.001  | 23 ± 4 <sup>d,e,h</sup>            | 25 ± 3 <sup>d</sup>                    | <0.001   |
| Mitral valve regurgitation                                     |                                   |                               |                          | <0.001  |                                    |  | <0.001   |
| None/trivial   | 53 (88)                           | 237 (79) <sup>d</sup>         | 26 (43) <sup>c</sup>     |   | 66 (76) <sup>d</sup>               | 171 (80) <sup>d</sup>                  |  |
| Mild   | 6 (10)                            | 57 (19)                       | 18 (30) <sup>f</sup>     |   | 19 (23)                            | 38 (18) <sup>i</sup>                   |  |
| Moderate   | 1 (2)                             | 6 (2) <sup>d</sup>            | 16 (27) <sup>f</sup>     |   | 2 (2) <sup>d</sup>                 | 4 (2) <sup>d</sup>                     |  |
| Tricuspid valve regurgitation                                  |                                   |                               |                          | <0.001  |                                    |  | <0.001   |
| None/trivial   | 48 (80)                           | 225 (75) <sup>d</sup>         | 31 (52) <sup>h</sup>     |   | 59 (68)                            | 166 (78) <sup>d</sup>                  |  |
| Mild   | 12 (20)                           | 72 (24)                       | 18 (30)                  |   | 27 (33)                            | 45 (21)                                |  |
| Moderate   | 0 (0)                             | 3 (1) <sup>d</sup>            | 11 (18) <sup>c</sup>     |   | 1 (1) <sup>d</sup>                 | 2 (1) <sup>d</sup>                     |  |
| Stroke volume, mL  | 63 ± 14                           | 53 ± 14 <sup>c,d</sup>        | 41 ± 13 <sup>c</sup>     | <0.001  | 43 ± 10 <sup>c,e</sup>             | 56 ± 13 <sup>c</sup>                   | <0.001   |
| Stroke volume index (SV/BSA), mL/m <sup>2</sup>                | 33 ± 5                            | 29 ± 7 <sup>c,d</sup>         | 22 ± 7 <sup>c</sup>      | <0.001  | 26 ± 7 <sup>c,e,k</sup>            | 30 ± 7 <sup>c,d</sup>                  | <0.001   |
| Heart rate during echocardiography, beats/min                  | 65 ± 10                           | 76 ± 16 <sup>c</sup>          | 74 ± 15 <sup>c</sup>     | <0.001  | 81 ± 17 <sup>c,e,k</sup>           | 73 ± 14 <sup>c</sup>                   | <0.001   |
| Cardiac output, L/min  | 4.06 ± 1.05                       | 3.92 ± 1.16 <sup>c,d</sup>    | 3.08 ± 1.13 <sup>c</sup> | <0.001  | 3.50 ± 0.93 <sup>e,h,j</sup>       | 4.08 ± 1.19 <sup>d</sup>               | <0.001   |

Values are mean ± SD or n (%). P values for nominal variables refer to all comparison groups. <sup>a</sup>ANOVA P value/chi-square test for comparisons among cancer patients, healthy control subjects, and heart failure patients. <sup>b</sup>ANOVA P value/ chi-square test for comparisons among cachectic cancer patients, noncachectic cancer patients, healthy control subjects, and heart failure patients. <sup>c</sup>P <0.001 vs control subjects. <sup>d</sup>P <0.001 vs heart failure. <sup>e</sup>P <0.001 vs noncachectic cancer patients. <sup>f</sup>P <0.05 vs control subjects. <sup>g</sup>P <0.05 vs noncachectic cancer patients. <sup>h</sup>P <0.01 vs control subjects. <sup>i</sup>P <0.05 vs heart failure. <sup>j</sup>P <0.01 vs noncachectic cancer patients. <sup>k</sup>P <0.01 vs heart failure.

ANOVA = analysis of variance; BSA = body surface area according to the DuBois formula; E/e' = early diastolic filling velocity (E) over mitral annulus early diastolic tissue velocity (e'); GLS = global longitudinal strain; IVSd = interventricular septal thickness at end-diastole; LA = left atrium; LAEDV = left atrial end-diastolic volume; LAESV = left atrial end-systolic volume; LAVI = left atrium volume index; LV = left ventricular; LVIDd = left ventricular internal diameter at end-diastole; PASP = pulmonary artery systolic pressure; PWd = posterior wall thickness at end-diastole; RA = right atrium; RAVI = right atrium volume index; TAPSE = tricuspid annular plane systolic excursion.

performance scale, time from diagnosis to study recruitment, cardiotoxic anticancer therapy, and hemoglobin. LV mass adjusted for BSA was not a predictor of all-cause mortality. Similar results were found when the area-length method was used (Supplemental Table 5). The Kaplan-Meier curves, on the basis of the best sex-specific cutpoints for absolute and height squared -adjusted LV mass values (absolute: ≥151 g/≥210 g; height squared

-adjusted: ≥61 g/≥57g for female/male subjects), underlines the survival benefit of patients with higher LV mass (Figures 2A and 2B).

In additional analyses, 6-minute walking distance, stair-climbing power, maximum handgrip strength, ECOG performance scale, and Karnofsky performance status were significantly impaired in patients with prognostically relevant cardiac wasting (Table 4). Furthermore, we analyzed the prognostic value of left

**TABLE 3 Cox Regression Analyses for All-Cause Mortality in all 300 Cancer Patients**

|   | Univariable Analysis |                    | Multivariable Analysis        |                    |
|---|----------------------|--------------------|-------------------------------|--------------------|
|   | HR (95% CI)          | P Value            | HR (95% CI)                   | P Value            |
| LV mass – Devereux formula (per 20 g less)  | 1.12 (1.03-1.22)     | 0.010 <sup>a</sup> | 1.11 (1.00-1.22)              | 0.045 <sup>b</sup> |
| LV mass index (LV mass/height <sup>2</sup> ) (per 20 g/m <sup>2</sup> less)         | 1.34 (1.04-1.72)     | 0.025 <sup>a</sup> | 1.46 (1.10-1.94)              | 0.009 <sup>b</sup> |
| LV mass index (LV mass/BSA) (per 20 g/m <sup>2</sup> less)                          | 1.09 (0.91-1.31)     | 0.34 <sup>a</sup>  | –                             | –                  |
| Age (per 1 y)   | 1.02 (1.01-1.04)     | <0.001             | 1.01 (1.00-1.03) <sup>c</sup> | 0.120              |
| Sex (male vs female)  | 1.02 (0.74-1.40)     | 0.93               | –                             | –                  |
| Cancer stage (III-IV vs I-II)   | 4.87 (2.56-9.27)     | <0.001             | 1.74 (0.86-3.50) <sup>c</sup> | 0.122              |
| Cancer entity groups  | –                    | <0.001             | –                             | –                  |
| ECOG (per 1 grade increase)   | 1.91 (1.62-2.25)     | <0.001             | 1.47 (1.19-1.81) <sup>c</sup> | <0.001             |
| Time from diagnosis to recruitment (per 3 months)                                   | 1.01 (1.00-1.02)     | 0.002              | 1.00 (0.99-1.01) <sup>c</sup> | 0.755              |
| Cardiotoxic anticancer therapy (yes vs no vs anticancer therapy naive) <sup>d</sup> | –                    | <0.001             | –                             | –                  |
| Hemoglobin (per 1 g/dL)   | 0.91 (0.85-0.98)     | 0.013              | 1.01 (0.91-1.12) <sup>c</sup> | 0.800              |
| Ln NT-proBNP, ng/L (per 1 Ln increase)  | 1.26 (1.11-1.43)     | <0.001             | 1.15 (0.96-1.37) <sup>c</sup> | 0.130              |
| Ln hs troponin T, ng/L (per 1 Ln increase)  | 1.63 (1.35- 1.97)    | <0.001             | 1.26 (0.98-1.61) <sup>c</sup> | 0.071              |
| eGFR (per 1 mL/min/1.73 m <sup>2</sup> )  | 0.99 (0.98-1.00)     | 0.013              | 1.01 (1.00-1.02) <sup>c</sup> | 0.089              |
| Ln CRP, mg/L (per 1 Ln increase)  | 1.40 (1.25-1.55)     | <0.001             | 1.19 (1.04-1.36) <sup>c</sup> | 0.012              |

<sup>a</sup>Sex as strata. <sup>b</sup>Sex as strata and adjusted for age (per 1 year), cancer stage (III-IV vs I-II), cancer entity groups, ECOG (1-4), time from diagnosis to recruitment (per 3 months), cardiotoxic anticancer therapy (yes vs no vs anticancer therapy naive), hemoglobin (per 1 g/dL), log-transformed NT-proBNP, log-transformed hs troponin T, eGFR, and log-transformed CRP. <sup>c</sup>Data provided for the multivariable analysis, including LV mass – Devereux formula (additional data for LV mass/height<sup>2</sup> shown in Supplemental Table 9). <sup>d</sup>Significant subgroup differences: cardiotoxic anticancer therapy vs anticancer therapy naive: HR: 0.36 (95% CI: 0.22-0.59); *P* < 0.001; noncardiotoxic anticancer therapy vs anticancer therapy naive: HR: 0.38 (95% CI: 0.22-0.64); *P* < 0.001; multivariable: cardiotoxic anticancer therapy vs anticancer therapy naive: HR: 0.54 (95% CI: 0.33-0.88); *P* = 0.013; noncardiotoxic anticancer therapy vs anticancer therapy naive: HR: 0.86 (95% CI: 0.50-1.48); *P* = 0.589.

LV = left ventricular; other abbreviations as in Table 1.

atrial and right atrial volumes (absolute and adjusted for height squared, as well as for BSA). In univariable analyses, patients in the highest tertile of left and right atrial dimensions had the best prognosis, but in multivariable analyses, none of these findings were significant (Supplemental Table 6).

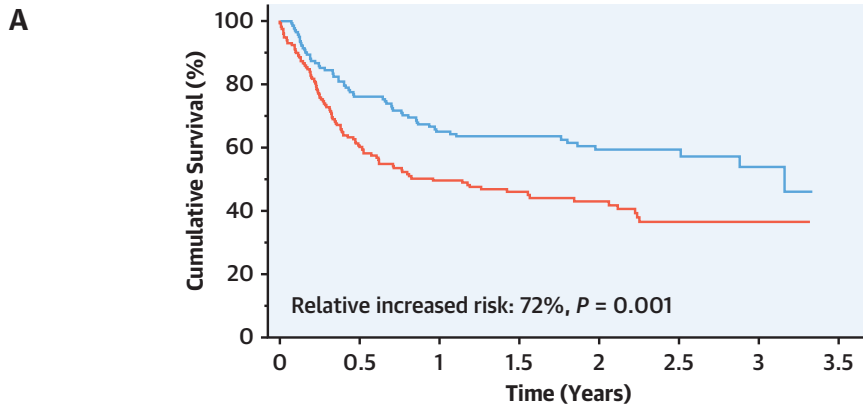
**ECHOCARDIOGRAPHIC FOLLOW-UP.** In total, 90 cancer patients received a second echocardiographic examination after 122 ± 71 days (baseline characteristics in Supplemental Table 7). LV mass was found to be reduced by 9.3% ± 1.4% in comparison with the first assessment (first assessment, 187 ± 48 g vs second assessment, 169 ± 48 g; *P* < 0.001) (Figure 3). Cancer patients with definite LV mass reduction (change ≥10.0%; average reduction of LV mass 20.3% ± 1.1%; *n* = 40; 44% of patients) showed lower values of IVSd, LVIDD, PWD, and stroke volume but higher resting heart rates at follow-up (Supplemental Table 8). In contrast, patients without LV mass reduction (change <5.0%; average increase of LV mass 3.5% ± 1.7%; *n* = 31; 34% of patients) had increased LVIDD and stroke volume and unchanged resting heart rates at follow-up. When patients with LV mass reduction ≥10% vs <5% at follow-up were compared for baseline results, a measure of inflammatory status—interleukin (IL)-6—was found to be significantly increased, and levels of CRP were nominally increased (Supplemental Table 7). Of note,

CRP, IL-1β, IL-6, IL-10, and tumor necrosis factor (TNF) were increased in cancer patients in general. IL-1β and IL-6 values were higher in cachectic vs noncachectic cancer patients (Table 1). IL-1β, IL-10, and TNF values were not found to be (more) increased in patients with subsequent LV mass reduction ≥10% vs <5% (Supplemental Table 7). The frequency of cardiotoxic anticancer therapy was similar in cancer patients with LV mass reduction ≥10% vs <5% (Supplemental Table 7).

## DISCUSSION

In this study, we have shown that patients with mostly advanced-stage active cancer presented with a lower absolute and indexed LV mass in comparison with healthy control subjects and patients with chronic heart failure. Compared with healthy control subjects, LV mass was reduced in a similar extent in anticancer therapy-naïve patients, in patients who had received noncardiotoxic anticancer therapy previously, and in patients who had previously received known cardiotoxic anticancer therapy. LV mass, stroke volume, blood pressure, and cardiac output were particularly low in cancer patients with whole body cachexia. Reduced LV mass, in absolute terms and adjusted for height squared, was an independent marker of poor survival in patients with cancer. However, when LV mass was adjusted for BSA, the

**FIGURE 2** Survival in Cancer Patients According to Sex-Specific LV Mass Cutoffs



LV Mass  $\geq 151$  g Females,  $\geq 210$  g Males (n = 142)

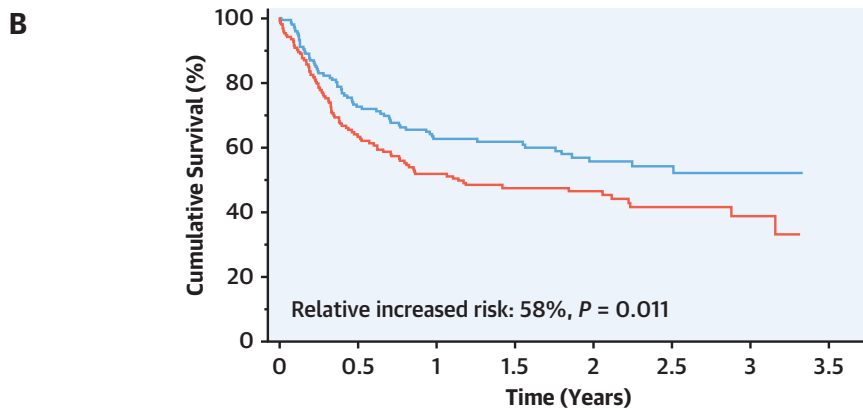
|                        |     |     |    |    |    |    |    |
|------------------------|-----|-----|----|----|----|----|----|
| At Risk                | 142 | 108 | 87 | 69 | 50 | 27 | 13 |
| Deaths                 | 0   | 34  | 50 | 51 | 55 | 55 | 57 |
| Cumulative Survival, % | 100 | 76  | 65 | 64 | 59 | 59 | 54 |

LV Mass  $< 151$  g Females,  $< 210$  g Males (n = 158)

|                        |     |    |    |    |    |    |    |
|------------------------|-----|----|----|----|----|----|----|
| At Risk                | 158 | 94 | 74 | 49 | 35 | 20 | 8  |
| Deaths                 | 0   | 64 | 79 | 84 | 88 | 92 | 92 |
| Cumulative Survival, % | 100 | 60 | 50 | 46 | 42 | 37 | 37 |

**LV Mass Split by Sex-Specific Cut-Offs**

● LV Mass  $\geq 151$  g Females,  $\geq 210$  g Males ● LV Mass  $< 151$  g Females,  $< 210$  g Males



LV Mass/Height<sup>2</sup>  $\geq 61$  g/m<sup>2</sup> Females,  $\geq 57$  g/m<sup>2</sup> Males (n = 146)

|                        |     |     |    |    |    |    |    |
|------------------------|-----|-----|----|----|----|----|----|
| At Risk                | 146 | 106 | 86 | 66 | 45 | 24 | 10 |
| Deaths                 | 0   | 40  | 54 | 55 | 61 | 62 | 63 |
| Cumulative Survival, % | 100 | 73  | 63 | 62 | 56 | 54 | 52 |

LV Mass/Height<sup>2</sup>  $< 61$  g/m<sup>2</sup> Females,  $< 57$  g/m<sup>2</sup> Males (n = 154)

|                        |     |    |    |    |    |    |    |
|------------------------|-----|----|----|----|----|----|----|
| At Risk                | 154 | 98 | 74 | 51 | 41 | 23 | 11 |
| Deaths                 | 0   | 56 | 73 | 79 | 81 | 84 | 85 |
| Cumulative Survival, % | 100 | 63 | 52 | 48 | 45 | 42 | 39 |

**LV Mass/Height<sup>2</sup> Split by Sex-Specific Cut-Offs**

● LV Mass/Height<sup>2</sup>  $\geq 61$  g/m<sup>2</sup> Females,  $\geq 57$  g/m<sup>2</sup> Males ● LV Mass/Height<sup>2</sup>  $< 61$  g/m<sup>2</sup> Females,  $< 57$  g/m<sup>2</sup> Males

The Kaplan-Meier curves are based on the best sex-specific cutpoints for (A) absolute left ventricular (LV) mass values (ie,  $< 151$  g/ $< 210$  g for female/male subjects) and (B) height<sup>2</sup>-adjusted left ventricular mass values (ie,  $< 61$  g/m<sup>2</sup>/ $< 57$  g/m<sup>2</sup> for female/male subjects). The results shown underline the increased mortality observed in patients with lower left ventricular mass. Left ventricular mass was calculated according to the Devereux formula.

**TABLE 4 Patient-Reported Outcomes and Functional Testing in Patients With and Without Prognostically Relevant Cardiac Wasting**

|  | LV Mass Index<br>(Mass/Height <sup>2</sup> )<br><61 g/m <sup>2</sup> in Women,<br><57 g/m <sup>2</sup> in Men<br>(n = 154) | LV Mass Index<br>(Mass/Height <sup>2</sup> )<br>≥61 g/m <sup>2</sup> in Women,<br>≥57 g/m <sup>2</sup> in Men<br>(n = 146) | P Value |
|--|--|--|---------|
| ECOG performance scale, points           | 1.8 ± 1.1  | 1.6 ± 1.1  | 0.033   |
| Karnofsky Index, %                       | 72 ± 19  | 77 ± 19  | 0.038   |
| EQ-5D-5L score (n = 123 vs 113)          | 0.755 (0.427-0.909)  | 0.830 (0.501-0.959)  | 0.066   |
| Visual Analogue Scale for appetite, mm   | 50 (29-75)   | 63 (31-84)   | 0.11    |
| Visual Analogue Scale for pain, mm       | 11 (0-40)  | 10 (0-40)  | 0.53    |
| Mini Nutritional Assessment, points      | 19.8 ± 4.4   | 21.3 ± 4.3   | 0.009   |
| Maximum handgrip strength, newton        | 266 ± 122  | 320 ± 157  | 0.001   |
| 4-m gait speed, ms                       | 1.08 ± 0.38  | 1.14 ± 0.37  | 0.001   |
| Stair-climbing power, W (n = 62 vs 68)   | 294 (238-413)  | 432 (330-523)  | <0.001  |
| 6-min walking distance, m (n = 61 vs 62) | 418 ± 94   | 455 ± 99   | 0.034   |

Values are mean ± SD or median (IQR). P values for nominal variables refer to both comparison groups.  
ECOG = Eastern Cooperative Oncology Group; LV = left ventricular.

prognostic significance of this parameter was masked. Interestingly, 6-minute walking distance, stair-climbing power, maximum handgrip strength, ECOG performance scale, and Karnofsky performance status were significantly impaired in patients with prognostically relevant cardiac wasting (**Central Illustration**). Loss of LV mass over time was associated with a reduction of stroke volume and an increase in resting heart rate. We suggest that these findings represent *cardiac wasting-associated cardiomyopathy* in cancer patients.

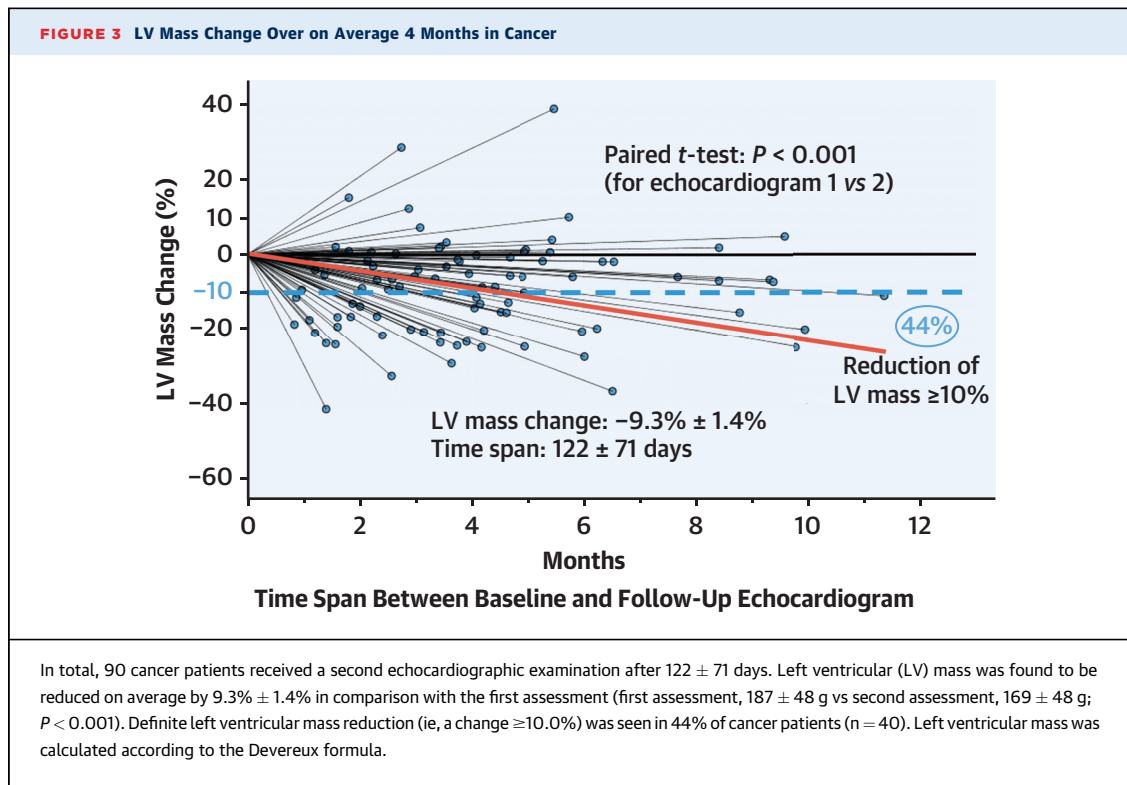
Cardiac wasting is known to occur at later stages in the progression of whole body cachexia in chronic illness.<sup>41</sup> Small hearts (with regard to mass and volume) have also been observed in patients with severe malnutrition (eg, in kwashiorkor<sup>42</sup> and in anorexia nervosa<sup>43,44</sup>). In heart failure, cardiac wasting is also known to occur.<sup>45</sup> Studies in preclinical models of cancer cachexia have shown that cardiac wasting is associated with increased proteolysis, fibrosis, and impaired cardiomyocyte ultrastructure.<sup>7</sup> It can be caused by different intrinsic factors such as oncometabolites, inflammatory cytokines, oxidative stress, and metabolic stress.<sup>4</sup> Biomarkers that have been linked to cardiac wasting in such models include inflammatory cytokines, the transforming growth factor- $\beta$  family, and nuclear factor- $\kappa$ B.<sup>5</sup> In the past, extensive research also focused on cellular oxidative stress and the increased inflammatory response in the cardiac milieu as a consequence of cardiotoxic anticancer drugs.<sup>15</sup> Therefore, we included cancer patients with or without previous cardiotoxic or noncardiotoxic anticancer therapy to investigate these possible effects in humans.

In humans, first data on cardiac wasting in cancer patients came from 2 retrospective studies reporting

data on 6 and 177 autopsy reports, respectively.<sup>9,10</sup> In the first study, the investigators found fibrotic changes in the cardiac muscle of cancer patients.<sup>9</sup> The second report suggested that patients with cancer-induced cachexia had a 19% lower LV mass compared with cancer patients without cachexia.<sup>10</sup> In addition, Kazemi-Bajestani et al<sup>11</sup> reported on 50 cancer patients with a focus on only 1 tumor entity (non-small cell lung cancer) and investigating patients before and after chemotherapy administration. These investigators documented the presence of cardiac wasting in patients with non-small cell lung cancer (9% during 4 months of follow-up) to a similar degree as seen here in a much larger cohort with different cancer entities. Cardiac wasting was found to be associated with changes in cardiac function as indicated by altered global longitudinal strain. These investigators did not assess the functional status of the patients with non-small cell lung cancer, and the study was not powered for prognostic assessments.

Our results, on the basis of 300 cancer patients without significant cardiovascular disease at baseline and different cancer types, demonstrate the presence of cardiac wasting, irrespective of the anticancer therapy status (naive, noncardiotoxic, cardiotoxic therapy). In addition, lower LV mass was associated with poor functional status, as well as an increased risk of all-cause mortality. Importantly, we show that in cancer patients, absolute LV mass and LV mass adjusted for height squared predict all-cause mortality, whereas LV mass adjusted for BSA does not.

In our analysis, the presence of reduced LV mass was accompanied by morphologic and functional cardiac abnormalities (ie, smaller cardiac cavities, thinner myocardial walls, and reduced systolic function) as a reflection of the underlying (cardiac)



wasting processes in cancer. Cancer cachexia is well known to be associated with an increased inflammatory response.<sup>46</sup> Cancer patients with vs without cardiac wasting identified in our echocardiographic follow-up had higher baseline levels of circulating IL-6 and nominally increased CRP (whereas IL-1 $\beta$  and TNF were not found to be increased). Moreover, patients with cardiac wasting at follow-up had reduced stroke volume and also increased resting heart rate. The latter could be considered a compensatory mechanism in this *cardiac wasting-associated cardiomyopathy*. The presence of anemia, low blood pressure, and raised heart rate, as well as mechanistic considerations of the changed physics of the heart as a pump when cardiac wasting develops,<sup>4</sup> may suggest the presence of a heart failure-like syndrome. Why these developments in *cardiac wasting-associated cardiomyopathy* do not lead to a compensatory increase in LV volumes we do not know; however, the lack of “material” (given the ongoing wasting processes) may simply put a limit to that pathophysiologic option. Of interest, the situation appears to be different in patients with chronic heart failure with reduced ejection fraction. They have the lowest blood pressure, the highest natriuretic peptide levels, and still by far the highest LV mass.

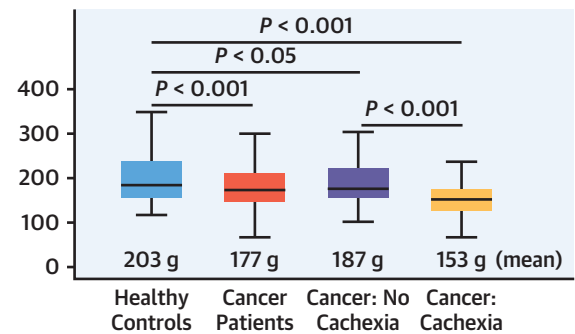
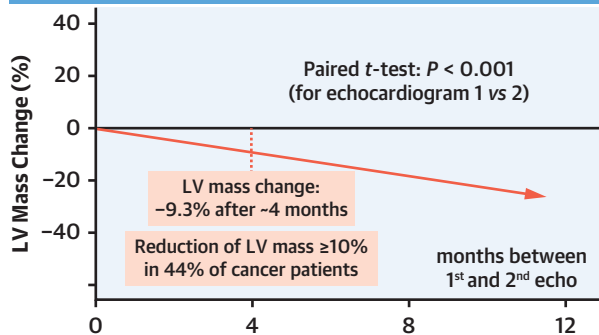
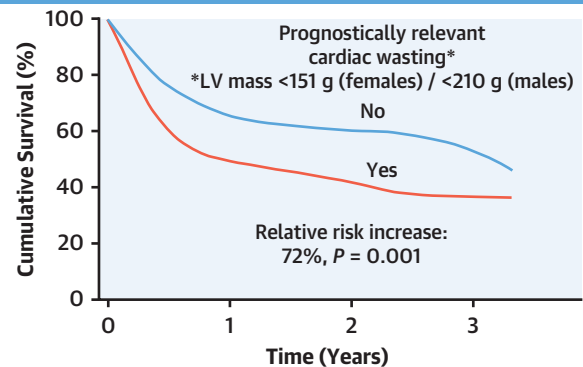
It is noteworthy that patients with vs without cardiac wasting during follow-up did not show whole

body cachexia at baseline more often. Hence, whole body cachexia and cardiac wasting may be occurring one after another in many cancer patients, but not in all. One also needs to consider whether the cardiac wasting (as seen in our study) is related to the general process of (skeletal) muscle wasting (ie, sarcopenia). The concept of sarcopenia was originally developed for muscle wasting in response to aging.<sup>47</sup> The concept is now also used for muscle wasting in any chronic illness, and then it is referred to as secondary (disease-mediated) sarcopenia vs primary (aging-associated) sarcopenia.<sup>48</sup> Sarcopenia is present in heart failure already when body weight overall is still stable.<sup>49</sup> This is the same in chronic cancer, where sarcopenia has even been described in obese cancer patients.<sup>50</sup> Hence, we hypothesize that the pathophysiology of cardiac wasting in cancer is independent of that of skeletal muscle wasting in cancer.

As seen in our study, the wasting processes affect the whole heart in some cancer patients. This is particularly evident in patients with cancer cachexia for the left ventricle and both atria (Table 2). In cancer patients without cachexia, however, LV mass is seen reduced, but LV volume is not changed, and left and right atrial dimensions are not reduced (Table 2). Whether the isolated observation of a somewhat lower LV mass already represents a “shrunken heart” in noncachectic patients could be debated. In

**CENTRAL ILLUSTRATION** Cardiac Wasting in Patients With Advanced Cancer**A** Patients With Prognostically Relevant Cardiac Wasting

|                             |   |
|-----------------------------|---|
| Maximum handgrip strength   | ↓ |
| Stair-climbing power        | ↓ |
| 6-minute walking distance   | ↓ |
| Mini Nutritional Assessment | ↓ |
| ECOG performance scale      | ↑ |
| Karnofsky Index             | ↓ |

**B** LV Mass in Healthy Controls and Cancer Patients**C** Change in LV Mass Over 4 Months (n = 90)**D** Kaplan-Meier Curves for Prognostically Relevant Cardiac Wasting According to LV Mass (n = 300)

Lena A, et al. *J Am Coll Cardiol.* 2023;81(16):1569-1586.

**(A)** Patients with prognostically relevant cardiac wasting have impaired functional status. **(B)** Box plots and comparisons of left ventricular mass are shown. Cancer patients in general and particularly cachectic cancer patients have lower left ventricular mass than healthy control subjects. **(C)** In total, 90 cancer patients received a second echocardiographic examination after  $122 \pm 71$  days. Left ventricular mass was found to be reduced by  $9.3\% \pm 1.4\%$  in comparison with the first assessment (first assessment,  $187 \pm 48$  g vs second assessment,  $169 \pm 48$  g;  $P < 0.001$ ). A definitive left ventricular mass reduction ( $\geq 10.0\%$ ) was seen in 44% of cancer patients. **(D)** Kaplan-Meier curves for overall survival on the basis of the best (sex-specific) cutpoints for mortality-predictive absolute left ventricular mass (ie, <151 g/<210 g in women/men),- showing the increased mortality observed in patients with lower left ventricular mass. Left ventricular mass calculated according to the Devereux formula. ECOG = Eastern Cooperative Oncology Group.

cachectic patients, when LV mass wasting is very significant and LV and atrial volumes are decreased, a “shrinking of the heart“ (ie, cardiac wasting) can be considered present in most of these patients. We suggest that possible increases in LV wall stress are the consequence of these wasting processes, not their cause.

There may be 2 reasons that cardiac wasting in cancer patients has not been adequately described before and has received little clinical and research attention so far. First, it is likely that cardiac wasting is a late onset phenomenon in cancer patients.<sup>4</sup> In chronic heart failure, 2 studies, using echocardiography and magnetic resonance imaging, respectively,

showed that body cachexia predates cardiac wasting, which is a very late phenomenon in heart failure patients.<sup>51,52</sup> If this is the same in cancer, cardiac wasting may develop particularly strongly once whole body cachexia is present because the heart may initially be better protected from wasting than skeletal muscle or fat tissue. Second, according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging, most large population studies have reported LV mass indexed only for BSA, which takes into account height and weight of the patient.<sup>13</sup> When cancer patients lose body weight overall (which is often the case in advanced cancer), BSA decreases as well, and in turn

the ratio of LV mass and BSA will increase. Therefore, adjusting LV mass for BSA may mask absolute declines in LV mass.

Overall, this explains why LV mass in absolute terms and LV mass/height<sup>2</sup> were independent prognostic markers, whereas LV mass/BSA was not. We therefore suggest not adjusting LV mass measurements in cancer patients for BSA, but preferably for height squared or to report only unadjusted data. We chose to raise height by the power of 2.0, as proposed by Lauer et al in 1994,<sup>37</sup> when investigating methods of “best” adjustment of LV mass in people free of cardiovascular disease. As we did here, Lauer et al<sup>37</sup> proposed adjusting LV mass not by BSA, but by a weight independent variable (ie, height to a non-integer power). Their model was developed in 1,101 patients with a logarithmic regression model trying to reduce differences between male and female patients and to be independent of obesity. The best fit results for which adjustments to use were (in their study) for women 1.91 and for men 2.12. In a pooled analysis, Lauer et al<sup>37</sup> found 1.97 to be the best noninteger to use. We selected adjusting by the power of 2.0 to make it practical for anyone to redo what we have done.

So far, very few preclinical studies investigating possible therapies for cancer associated cachexia or even cardiac wasting-associated cardiomyopathy exist. Our group (Springer et al<sup>9</sup>) has shown that bisoprolol (beta-blocker) or spironolactone (aldosterone receptor antagonist) could attenuate cardiac wasting in a rat model of liver cancer with severe cachexia (and cardiac wasting). The same group also reported that espidolol was able to attenuate cardiac wasting in this model.<sup>53</sup> Espindolol is now in development for cancer cachexia. In the ACT-ONE trial, espidolol was tested in cancer patients with cachexia caused by non-small cell lung or colorectal cancer, and it was associated with an increase in handgrip strength, body weight, and lean body mass.<sup>27</sup> The weight gain seen amounted to 4 kg in 4 months, which is much higher than is typical for racemic beta-blockers (typically 1-1.5 kg weight gain in 1 year in patients with heart failure).<sup>54</sup>

**STUDY LIMITATIONS.** Our study focused on hospitalized patients with mostly advanced cancer. These patients tend to have a globally reduced performance status and a reduced 1-year-overall-survival.<sup>4</sup> Furthermore, patients had several different cancer entities that represented a cross section of patients treated in a clinical oncology department, and we suggest that this can be considered a strength as well as a weakness of this study. Cancer stages may not be

comparable among cancer entities, but we also used clinical status markers (ECOG) for adjustment. The echocardiographic follow-ups were performed in a variable time frame (mostly within the first 2-7 months [range 1-12 months]). Clinically, a fully unified approach was not possible. Follow-ups were possible only in patients who were alive, and therefore some degree of a survivorship bias may be present. Patients with T2DM without cardiovascular complications and controlled arterial hypertension were not excluded. These diseases are known to be associated with LV hypertrophy and should not have negatively influenced the key results and, if anything, could even lead to some degree of underestimation of the frequency of cardiac wasting in these patients.<sup>55,56</sup> In future studies, it would also be desirable to assess the presence of increased myocardial wall stress in cancer patients with cardiac wasting-associated cardiomyopathy.<sup>4</sup> In addition, other factors such as prolonged immobility, malnutrition, and multiorgan dysfunction may have an impact on cardiac wasting.<sup>5</sup> Future studies could extend this research to patients with early-stage cancer and further investigate the role of physical activity and nutrition on cardiac wasting. Given that the rate of autopsies in cancer patients is generally very low, and the clinical presentation is often complex, and because patients often die at home or in hospice care, we used all-cause mortality for this study.<sup>57</sup> Nonetheless, further investigations on the specific cause of death in cancer patients are needed.

## CONCLUSIONS

Our study indicates that wasting of the left ventricle of the heart frequently occurs in patients with mostly advanced cancer. This cardiac wasting is associated with poor functional status of patients, as well as with increased all-cause mortality. We suggest that LV mass adjustment for BSA can mask this information, and adjustment for height squared appears more appropriate. We also suggest that these findings represent cardiac wasting-associated cardiomyopathy in cancer.

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## PERSPECTIVE

### COMPETENCY IN PATIENT CARE AND

**PROCEDURAL SKILLS:** Cardiac wasting is common among patients with advanced cancer, and it is associated with cachexia, poor functional status, and an increased risk of death. Adjustment of LV mass for height squared may be more appropriate than adjustment for BSA in this situation.

**TRANSLATIONAL OUTLOOK:** Further research is needed to understand the pathophysiology and clinical consequences of cardiac wasting in patients with advanced cancer and develop potential therapeutic interventions.

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**KEY WORDS** cancer, cardiac wasting-associated cardiomyopathy, cardiology, echocardiography, left ventricular mass

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**APPENDIX** For supplemental tables and figures, please see the online version of this paper.