Risk stratification of cardiac metastases using late gadolinium enhancement cardiovascular magnetic resonance: prognostic impact of hypo-enhancement evidenced tumor avascularity

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Abstract

Background: Late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR) is widely used to identify cardiac neoplasms, for which diagnosis is predicated on enhancement stemming from lesion vascularity: Impact of contrast-enhancement pattern on clinical outcomes is unknown. The objective of this study was to determine whether cardiac metastasis (CMET) enhancement pattern on LGE-CMR impacts prognosis, with focus on heterogeneous lesion enhancement as a marker of tumor avascularity.

Methods: Advanced (stage IV) systemic cancer patients with and without CMET matched (1:1) by cancer etiology underwent a standardized CMR protocol. CMET was identified via established LGE-CMR criteria based on lesion enhancement; enhancement pattern was further classified as heterogeneous (enhancing and non-enhancing components) or diffuse and assessed via quantitative (contrast-to-noise ratio (CNR); signal-to-noise ratio (SNR)) analyses. Embolic events and mortality were tested in relation to lesion location and contrast-enhancement pattern.

Results: 224 patients were studied, including 112 patients with CMET and unaffected (CMET-) controls matched for systemic cancer etiology/stage. CMET enhancement pattern varied (53% heterogeneous, 47% diffuse). Quantitative analyses were consistent with lesion classification; CNR was higher and SNR lower in heterogeneously enhancing CMET (p < 0.001)—paralleled by larger size based on linear dimensions (p < 0.05). Contrast-enhancement pattern did not vary based on lesion location (p = NS). Embolic events were similar between patients with diffuse and heterogeneous lesions (p = NS) but varied by location: Patients with right-sided lesions had threefold more pulmonary emboli (20% vs. 6%, p = 0.02); those with left-sided lesions had lower rates equivalent to controls (4% vs. 5%, p = 1.00). Mortality was higher among patients with CMET (hazard ratio [HR] = 1.64 [CI 1.17–2.29], p = 0.004) compared to controls, but varied by contrast-enhancement pattern: Diffusely enhancing CMET had equivalent mortality to controls (p = 0.21)

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Background
Nearly 17 million Americans are living with cancer [1], among whom cardiac metastases (C_M) bear a major impact on therapeutic decision-making and prognosis. Survival has markedly improved for patients with advanced (stage IV) cancer, resulting in a growing population at risk for C_M and its serious consequences. Data from our group and others have shown C_M to be common with advanced cancer, occurring in up to 20% of patients. [2–6] Embolic events—which can occur when lesions dislodge from the heart—are a leading source of morbidity and mortality among patients with C_M. Given that a growing array of new therapies and anticoagulants are available to potentially reduce risk, improved strategies to guide therapy and refine prognostic risk stratification for patients at risk for C_M are of substantial importance.

Cardiovascular magnetic resonance (CMR) has been well-validated for tissue characterization of cardiac masses. [2, 4, 7–12] Whereas neoplasms can vary in morphology, vascular supply is an intrinsic requirement for tumor growth and this property can be leveraged for diagnostic purposes. Using the technique of late gadolinium enhancement (LGE), CMR can identify neoplasms based on vascularity as manifested by presence of contrast-enhancement. [13] It is also known that neoplasms can vary in pattern of contrast enhancement on LGE-CMR, and that some lesions can include enhancing and non-enhancing components. [2–4] Consistent with this, pathology studies have shown that some neoplasms can have avascular foci (“tumor necrosis”)—a finding linked to aggressive tumor growth and adverse outcomes. [14] Impact of tumor avascularity—as manifested by contrast hypo-enhancement on LGE-CMR—has yet to be tested as a prognostic marker among patients with C_M.

This study encompassed a broad cohort of systemic cancer patients with C_M as well as controls (without C_M) matched for cancer etiology and stage. CMR was performed using a tailored protocol to assess presence and pattern of C_M enhancement—including standardized grading and quantitative analyses—as well as standardized assessment of lesion size and mobility. The goal was to test impact of C_M anatomic distribution and contrast enhancement pattern on embolic events and mortality.

Methods
Study population
The population was comprised of adults (≥18 years) with advanced (stage IV) systemic cancer and C_M, and controls without C_M, matched (1:1) for cancer diagnosis: Presence or absence of C_M was established using the reference of LGE-CMR, on which it was defined via established criteria as a discrete tissue prominence with vascularity as evidenced by contrast-enhancement. [2–4] Subjects with CMR-evidenced intracardiac thrombi were excluded.

Figure 1 provides a schematic of the research protocol. As shown, study participants were accrued at two tertiary care centers with dedicated cancer care programs (Memorial Sloan Kettering Cancer Center [MSKCC], Weill Cornell Medicine—New York Presbyterian Hospital, New York, New York, USA) that share an integrated CMR program. Clinical data were collected in a standardized manner, including cancer diagnosis and stage, anti-cancer and anticoagulant therapies, as well as clinically documented embolic events (pulmonary embolism (PE), cerebrovascular events (CVA), systemic [splenic, peripheral] emboli) within 6 months of CMR. Mortality was assessed to test prognosis in relation to anatomic and tissue characteristics of C_M.

This study entailed analysis of data acquired for clinical purposes between 2012 and 2020; no dedicated interventions were performed for research purposes. Ethics approval for this protocol was provided by the MSKCC and Weill Cornell Medicine institutional review boards, each of which approved a waiver of informed consent for analysis of pre-existing clinical data.

Imaging protocol
CMR was performed on commercial (1.5 T [87%], 3 T [13%]) scanners (General Electric Healthcare, Waukesha, Wisconsin, USA). Exams included electrocardiogram (ECG)-gated cine- and LGE components; both were obtained in contiguous left ventricular (LV) short (mitral annulus—apex) and long axis (2, 3, and 4 chamber) orientations. Cine-CMR utilized a balanced steady-state

Conclusions: Contrast-enhancement pattern and location of C_M on CMR impacts prognosis. Embolic events vary by C_M location, with likelihood of PE greatest with right-sided lesions. Heterogeneous enhancement—a marker of tumor avascularity on LGE-CMR—is a novel marker of increased mortality risk.

Keywords: Cardiovascular magnetic resonance, Cardio-oncology, Cardiac neoplasm
free precession (bSSFP) pulse sequence. LGE-CMR utilized an inversion recovery pulse sequence; images were acquired after gadolinium (0.2 mmol/kg) infusion (“long-TI” [600 ms] = 5–10 min, conventional [~ 300 ms] 10–30 min post contrast). Contrast administration entailed gadoterate meglumine (Dotarem, Guerbet, Villepinte, France) or gadopentetate dimeglumine (Magnevist, Bayer Schering Pharma, Berlin, Germany), which were respectively utilized in 53% and 47% of exams. Conventional and long inversion time (TI) LGE-CMR were used to discern presence and pattern of enhancement in CMET, concordant with prior methods validated by our group and others. [2–4, 9–11] Conventional LGE-CMR was acquired in all patients; additional breath holds for long TI imaging were tolerated in 92% (103/112) of patients with CMET.

Image analysis
CMET was identified on LGE-CMR based on lesion-associated vascularity in accordance with established qualitative (visual) criteria. [2–4] To test modifying impact of CMET tissue properties on cancer associated outcomes, lesions were further classified into two distinct categories—*diffuse enhancement* (homogenous contrast enhancement throughout lesion) or *heterogeneous enhancement* (enhancing and non-enhancing components within a lesion).

CMET were scored in a binary manner (present/absent), localized based on chamber (right atrium [RA], right ventricle [RV], left atrium [LA], left ventricle [LV]) or pericardial involvement, and classified as intra-cavitary (predominantly localized to cardiac chamber) or intramural (invading into myocardium). Intra-cavity lesions were further graded for lesion mobility, with highly mobile lesions classified as demonstrating dys-synchronous mobility in relation to adjacent myocardium. Figure 2 provides representative examples of CMET types, including heterogeneous and diffusely enhancing lesions with intra-cavity or intramyocardial involvement.

Quantitative analyses were used to assess magnitude of contrast enhancement within CMET. Concordant with established methods used by our group, [2, 4] aggregate signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) ratios were measured on the long TI LGE-CMR image on which the lesion was most prominent. Intra-cardiac lesion size (area, linear dimensions) was measured on cine-CMR datasets, which were co-localized with LGE-CMR for purpose of analyses. For patients with multiple CMET, the largest lesion was used for quantitative analysis and patient categorization (i.e. heterogeneous or diffusely enhancing). Ancillary analyses included quantification of cardiac chamber size and function, which were measured on cine-CMR using standard planimetry methods. [3]

Prognostic assessment
Electronic medical records were reviewed to assess embolic events (PE, CVA, systemic [i.e. splenic, peripheral] emboli) within 6 months of imaging, as well as all-cause mortality after CMR so as to test clinical events in relation to presence and type of CMET. All-cause mortality and embolic events were ascertained blinded to CMR analyses.

Statistical methods
Comparisons between groups with or without CMET, and between CMET subtypes (heterogeneous, diffusely enhancing) were made using Student’s t-tests (expressed as mean ± standard deviation) for continuous variables, and Chi-square or Fisher’s exact tests for categorical variables: Paired testing (t-tests or McNemar’s tests) was employed for matched case–control comparisons. Univariate logistic regression was used to test variables associated with mortality and embolic events; variables significantly associated with outcomes in univariate
analysis were then tested together in adjusted models. The Kaplan–Meier method was used to calculate survival; follow-up duration was reported as median with interquartile range (IQR). Cox proportional hazards models compared mortality risk between groups, including prognostic utility of CMET features. Calculations were performed using SPSS (Statistical Package for the Social Sciences, International Business Machines, Inc., Armonk, New York, USA). Two-sided \( p < 0.05 \) was deemed indicative of statistical significance.

**Results**

**Population characteristics**

The population comprised 224 adults with advanced (stage IV) systemic cancer undergoing CMR, including 112 patients with CMET as defined by LGE-CMR, and unaffected (CMET-) controls matched for primary cancer diagnosis and stage. Table 1 details population characteristics, together with comparisons between cancer patients with CMET and their respective controls. As shown, cancer diagnosis varied among patients with CMET: Sarcoma, lung, genitourinary, gastrointestinal cancers, and skin/melanoma comprised the leading primary cancer diagnoses, although the population also included patients with primary cancers not typically associated with CMET (e.g. endocrine, head/neck). Regarding anti-cancer regimen, patients with CMET were more likely to be treated with mediastinal radiation therapy and low molecular weight heparin (both \( p = 0.01 \)) but were otherwise similar with respect to matched controls. Of note, nearly half (49%) of patients with CMR-evidenced CMET had a subsequent change in anti-cancer medication regimen following CMR; 16% received new mediastinal/chest radiation within 3 months after imaging.

Regarding cardiac indices, cancer-matched controls referred for CMR were more likely to have adverse left sided chamber remodeling—as evidenced by lower LV ejection fraction and larger chamber size (both \( p < 0.01 \)), but groups had similar right sided structural and functional indices (\( p = \text{NS} \)).

**Cardiac metastasis location in relation to contrast enhancement**

Anatomic location of CMET varied (LV 32%  LA 22%  LA 22%  RA 30%  multi-chamber involvement 30%): Left and right sided chamber involvement were near equal in prevalence (50%, 58% respectively). Regarding CMET tissue properties, 53% of patients had heterogeneously enhancing lesions (enhancing and non-enhancing components on LGE-CMR), whereas 47% had diffusely enhancing lesions without non-enhancing components.
| Clinical characteristics       | Overall (n = 224) | $C_{MET}+$ (n = 112) | $C_{MET}^-$ Controls (n = 112) | $p^b$  |
|-------------------------------|------------------|----------------------|--------------------------------|--------|
| Age (years)                   | 58 ± 17          | 57 ± 16              | 58 ± 18                        | 0.68   |
| Gender (male)                 | 59% (133)        | 63% (71)             | 55% (62)                       | 0.23   |
| Body surface area (kg/m$^2$)$^a$ | 1.9 ± 0.3        | 1.9 ± 0.3            | 1.9 ± 0.3                      | 0.55   |
| Cancer etiologies$^b$         |                  |                      |                                |        |
| Sarcoma                       | 20% (44)         | 20% (22)             | 20% (22)                       |        |
| Lung                          | 16% (36)         | 16% (18)             | 16% (18)                       |        |
| Genitourinary                 | 15% (34)         | 15% (17)             | 15% (17)                       |        |
| Gastrointestinal              | 13% (28)         | 13% (14)             | 14% (14)                       |        |
| Skin/melanoma                 | 13% (28)         | 13% (14)             | 13% (14)                       |        |
| Lymphoma                      | 8% (18)          | 8% (9)               | 8% (9)                         |        |
| Endocrine                     | 8% (18)          | 8% (9)               | 8% (9)                         |        |
| Anti-cancer regimen           |                  |                      |                                |        |
| Chemotherapy                  |                  |                      |                                |        |
| Alkylating agent              | 44% (99)         | 46% (52)             | 41% (46)                       | 0.47   |
| Plant alkaloid                | 31% (70)         | 32% (36)             | 30% (34)                       | 0.88   |
| Antitumor antibiotics         | 21% (48)         | 21% (23)             | 23% (26)                       | 0.69   |
| Antimetabolites               | 31% (70)         | 35% (39)             | 27% (30)                       | 0.19   |
| Topoisomerase inhibitors      | 8% (17)          | 7% (8)               | 8% (9)                         | 1.00   |
| Anthracycline                 | 21% (46)         | 19% (21)             | 23% (26)                       | 0.41   |
| Monoclonal antibodies         |                  |                      |                                |        |
| Tyrosine kinase inhibitors    | 23% (51)         | 20% (22)             | 28% (31)                       | 0.21   |
| Other kinase inhibitors       | 4% (8)           | 2% (2)               | 6% (7)                         | 0.18   |
| Immunotherapy                 | 21% (47)         | 21% (24)             | 20% (22)                       | 0.84   |
| Radiation therapy             |                  |                      |                                |        |
| Mediastinal radiation         | 13% (28)         | 18% (20)             | 7% (8)                         | 0.01   |
| Other radiation               | 38% (84)         | 40% (45)             | 35% (39)                       | 0.49   |
| Anticoagulation therapy       |                  |                      |                                |        |
| Overall                       | 22% (50)         | 28% (31)             | 17% (19)                       | 0.07   |
| Low molecular weight heparin  | 24% (53)         | 32% (36)             | 16% (18)                       | 0.01   |
| Warfarin                      | 3% (6)           | 4% (4)               | 2% (2)                         | 0.69   |
| Direct Oral Anticoagulant     | 15% (34)         | 18% (20)             | 13% (14)                       | 0.26   |
| Cardiovascular disease risk factors |            |                      |                                |        |
| Hypertension                  | 43% (97)         | 41% (46)             | 45% (51)                       | 0.59   |
| Hyperlipidemia                | 31% (69)         | 28% (31)             | 34% (38)                       | 0.35   |
| Diabetes mellitus             | 14% (31)         | 11% (12)             | 17% (19)                       | 0.23   |
| Smoking                       | 38% (79)         | 31% (35)             | 39% (44)                       | 0.26   |
| Cardiopulmonary disease       |                  |                      |                                |        |
| Coronary artery disease       | 11% (24)         | 11% (12)             | 11% (12)                       | 1.00   |
| Atrial fibrillation/flutter    | 16% (35)         | 13% (14)             | 19% (21)                       | 0.27   |
| Pulmonary disease             | 6% (13)          | 3% (3)               | 9% (10)                        | 0.09   |
| Pulmonary hypertension        | 16% (36)         | 13% (14)             | 20% (22)                       | 0.17   |
| Cardiac morphology and function |                |                      |                                |        |
| Left ventricle                |                  |                      |                                |        |
| Ejection fraction (%)         | 61 ± 11          | 63 ± 8               | 59 ± 12                        | 0.004  |
| End-diastolic volume (mL)     | 124 ± 41         | 114 ± 34             | 131 ± 43                       | 0.002  |
| End-systolic volume (mL)      | 51 ± 29          | 42 ± 17              | 57 ± 32                        | < 0.001|
| Stroke volume (mL)            | 73 ± 21          | 72 ± 22              | 75 ± 21                        | 0.38   |
| Myocardial mass (gm)          | 118 ± 49         | 117 ± 55             | 116 ± 37                       | 0.83   |
Table 2 compares heterogeneously enhancing and diffusely enhancing CMET. As shown, lesions were similar with respect to anatomic distribution, as evidenced by equivalent patterns of chamber involvement and rates of intra-cavitary location (all \( p = \text{NS} \)). Regarding lesion size, heterogeneously enhancing lesions were larger, based on linear dimensions (\( p < 0.05 \)). Quantitative analyses were consistent with lesion classification, as evidenced by higher CNR (reflecting greater differences between enhancing and non-enhancing regions) and lower normalized SNR (reflecting impact of non-enhancing lesions on aggregate lesion signal intensity) in heterogeneously enhancing CMET (both \( p < 0.001 \) vs. diffusely enhancing CMET).

**Embolic events**

Embolic events (within 6 months of CMR) were assessed to test if presence of CMET impacted likelihood of clinical events, and whether this was modified by lesion location or tissue characteristics. A total of 33 embolic events occurred in the study population; events occurred at a median interval of 2 weeks from CMR [IQR 0.5, 9.5 weeks]. As shown in Table 3A, embolic events were over twofold more common among patients with CMET as compared to cancer matched controls (21% vs. 8%, \( p = 0.006 \)), including increased incidence of PE (13% vs. 5%, \( p = 0.08 \)); Embolic events occurred at a median interval of 2 weeks from CMR [IQR 0.5, 9.4 weeks].

Data shown in Table 3A also demonstrates that CMET location modified likelihood of clinical events: Whereas patients with right sided lesions had a more than three-fold increase in PE (20% vs. 6%, \( p = 0.02 \)), those with left sided lesions had near identical rates of PE compared to cancermatched controls (4% vs. 5%). Among patients with left sided lesions, CVA was more common compared to matched controls, although statistical differences between groups was not achieved in context of low clinical event rates (7% vs. 2%, \( p = 0.38 \)). Sub-group analyses limited to intracavitary CMET demonstrated a stronger association between lesion location and embolic event rates: Among patients with right sided intracavitary CMET, PE occurred in over one fourth of cases—a rate more than fourfold higher than in matched controls (27% vs. 7%, \( p = 0.01 \)). Two-thirds (8/12; 67%) of patients with right sided intracavitary CMET who developed PE had lesions graded as highly mobile on cine-CMR.

Notably, increased PE rates among patients with right sided CMET occurred despite frequent anticoagulation: Anticoagulant therapies (warfarin or direct oral anticoagulants) were more commonly utilized in patients with right sided CMET as compared to matched controls (33% vs. 15%, \( p = 0.02 \)), but were equivalent when among CMET patients with left sided involvement and controls (16% vs. 21%, \( p = 0.63 \)). Of note, 60% of patients with PE were on anticoagulation at the time of their clinical event (64% in CMET vs 50% in controls, \( p = 0.64 \)).

Regarding impact of CMET tissue characteristics on embolic events, Table 3B demonstrates that rates of PE were similar between patients with heterogeneous and diffusely enhancing lesions (\( p = \text{NS} \)), as were rates of left sided embolic events. Figure 3 reports PE rates among patients stratified by both lesion location and tissue characteristics: As shown, PE rates were highest among patients with intracavitary right ventricular lesions (\( p < 0.001 \) vs. other groups), whereas partitioning based on lesion tissue characteristics did not stratify event risk.
### Table 2 Anatomic and tissue properties of cardiac metastases

| Clinical characteristics | Heterogeneously enhancing CMET<sub>n = 59</sub> | Diffusely enhancing CMET<sub>n = 53</sub> | p   |
|--------------------------|-----------------------------------------------|-------------------------------------------|-----|
| **Cancer etiologies**    |                                               |                                           |     |
| Sarcoma                  | 24% (14)                                      | 15% (8)                                   | 0.25|
| Lung                     | 15% (9)                                       | 17% (9)                                   | 0.80|
| Genitourinary            | 19% (11)                                      | 11% (6)                                   | 0.28|
| Gastrointestinal         | 14% (8)                                       | 11% (6)                                   | 0.72|
| Skin/Melanoma            | 7% (4)                                        | 19% (10)                                  | 0.05|
| Lymphoma                 | 3% (2)                                        | 13% (7)                                   | 0.08|
| Endocrine                | 10% (6)                                       | 6% (3)                                     | 0.50|
| **Cardiovascular risk factors** |                                           |                                           |     |
| Hypertension             | 42% (26)                                      | 38% (20)                                  | 0.50|
| Hyperlipidemia           | 27% (16)                                      | 28% (15)                                  | 0.89|
| Diabetes mellitus        | 10% (6)                                       | 11% (6)                                   | 0.84|
| Smoking                  | 24% (14)                                      | 40% (21)                                  | 0.07|
| **Cardiopulmonary disease** |                                           |                                           |     |
| Coronary artery disease  | 12% (7)                                       | 9% (5)                                    | 0.68|
| Atrial fibrillation/flutter | 10% (6)                                      | 15% (8)                                   | 0.43|
| Pulmonary disease        | 3% (2)                                        | 2% (1)                                    | 1.00|
| Pulmonary hypertension   | 15% (9)                                       | 9% (5)                                    | 0.35|
| **Anatomic properties**  |                                               |                                           |     |
| Lesion location          |                                               |                                           |     |
| Left ventricle           | 36% (21)                                      | 28% (15)                                  | 0.41|
| Right ventricle          | 34% (20)                                      | 40% (21)                                  | 0.53|
| Left atrium              | 20% (12)                                      | 25% (13)                                  | 0.60|
| Right atrium             | 24% (14)                                      | 38% (20)                                  | 0.11|
| Pericardium              | 32% (19)                                      | 26% (14)                                  | 0.50|
| Left-sided               | 53% (31)                                      | 47% (25)                                  | 0.57|
| Right-sided              | 49% (29)                                      | 68% (36)                                  | 0.04|
| Bilateral                | 17% (10)                                      | 23% (12)                                  | 0.45|
| Multi-chamber            | 25% (15)                                      | 36% (19)                                  | 0.23|
| **Intra-cavity**         |                                               |                                           |     |
| Left ventricle           | 9% (5)                                        | 8% (4)                                    | 1.00|
| Right ventricle          | 22% (13)                                      | 25% (13)                                  | 0.76|
| Left atrium              | 17% (10)                                      | 21% (11)                                  | 0.61|
| Right atrium             | 17% (10)                                      | 26% (14)                                  | 0.22|
| Lesion number (1 | 2 | ≥ 3)  | 78% | 19% | 3% | 70% | 19% | 11% | 0.26|
| **Lesion size**          |                                               |                                           |     |
| Area (cm<sup>2</sup>)    | 16.0 ± 20.8                                   | 10.1 ± 16.0                               | 0.10|
| Perimeter (cm)           | 15.3 ± 11.3                                   | 13.3 ± 12.9                               | 0.39|
| Maximal length (cm)      | 5.1 ± 3.7                                     | 3.7 ± 2.8                                 | 0.02|
| Orthogonal length (cm)   | 3.0 ± 2.0                                     | 2.4 ± 1.8                                 | 0.11|
| Perimeter/min Length     | 5.0 ± 1.7                                     | 7.3 ± 8.8                                 | 0.06|
| Pericardial effusion     | 37% (22)                                      | 21% (11)                                  | 0.06|
| **Tissue properties**    |                                               |                                           |     |
| Contrast-to-noise ratio (CNR) | 20.5 ± 15.0                                   | 7.4 ± 9.1                                 | <0.001|
| Signal-to-noise ratio (SNR) | 33.1 ± 20.1                                   | 44.5 ± 41.2                               | 0.08|
| Blood pool normalized    | 0.6 ± 0.2                                     | 0.8 ± 0.3                                 | <0.001|
Table 4 demonstrates that increased PE risk among patients with right ventricular C\textsubscript{MET} was accompanied by impaired RV function, as evidenced by lower absolute RV ejection fraction (RVEF) and higher prevalence of RV dysfunction (both p < 0.05). Of note, among patients with RV C\textsubscript{MET}, RVEF was similar between those who had PE prior to, compared to those who had PE after CMR (51.0 ± 12.7% vs 53.5 ± 3.8%, p = 0.72)—consistent with the notion that event driven changes in RV systolic function were not responsible for observed associations between impaired RV function and PE. Data shown in Additional file 1: Table S1 tests both clinical and CMR parameters in relation to PE. As shown, both gastrointestinal cancer etiology and right sided C\textsubscript{MET} were each associated with increased likelihood of PE in univariate regression analysis, and each parameter remained associated with PE (p < 0.01) when the two parameters (gastrointestinal cancer etiology, right sided intracavitary C\textsubscript{MET}) were tested together in an adjusted model.

Mortality
Follow-up was performed for a median duration of 0.8 years [IQR 0.3–1.67], during which a total of 145 deaths occurred. Figure 4 provides Kaplan Meier survival curves for the overall cohort of C\textsubscript{MET} patients and cancer-matched controls, as well as for subgroups based on C\textsubscript{MET} tissue characteristics. As shown (a), mortality
risk was higher among CMET patients compared to controls (HR = 1.64 [CI 1.17–2.29], p = 0.004): Median survival after CMR was shorter among patients with CMET (9.7 months [IQR 4.0–21.7] vs. 15.1 months [5.4–60.3], p = 0.004), paralleled by increased 6-month (39% vs. 28%, p = 0.12) and 1 year (57% vs. 46%, p = 0.2) mortality.

Figure 4b demonstrates that mortality differed in relation to tissue characteristics of CMET: Whereas patients with diffusely enhancing CMET had near equivalent mortality to matched controls (p = 0.21), prognosis was worse among patients with heterogeneously enhancing CMET (p = 0.005)—including increased 6-month (44% vs. 26%) and 1 year (65% vs. 41%) mortality in respective case–control comparisons (both p < 0.05). As shown in Table 5, heterogeneously enhancing CMET conferred higher risk for mortality (HR 1.97 [CI 1.23–3.16], p = 0.005) than did number of lesions (HR 1.67 [CI 1.31–2.12], p < 0.001) or lesion size (1.11 per 10 cm [CI 0.53–2.33], p = 0.79). Additionally, whereas lymphoma was the sole cancer diagnosis associated with differential (improved) prognosis, an adjusted model analysis inclusive of this variable together with LGE-CMR tissue characterization data demonstrated heterogeneously enhancing CMET to remain associated with increased mortality (1.97 [CI 1.23–3.16], p = 0.005).

Discussion
To our knowledge, this is the first study to test LGE-CMR pattern of CMET as a prognostic marker in patients with systemic cancer, with focus on localized hypo-enhancement (a marker of tumor avascularity) as a novel marker of adverse prognosis. Results add to a growing body of literature by our group and others validating LGE-CMR in relation to histopathology and demonstrating clinical utility of this approach to guide diagnostic, prognostic, and therapeutic decision-making for patients with known or suspected cardiac masses. Key findings are as follows: First, among a broad cohort of advanced cancer patients, CMET contrast-enhancement pattern varied—prevalence of diffusely (47%) and heterogeneously enhancing CMET to have
more aggressive features, as evidenced by larger lesion size and lower SNR (as would be expected in context of tumor avascularity). Second, presence and distribution of CMET impacted likelihood of embolic events. Aggregate embolic events were higher among patients with CMET compared to cancer matched controls (21% vs. 8%, p = 0.006), CMET location modified likelihood of events: Whereas patients with right sided lesions had a threefold increase in PE (20% vs. 6%, p = 0.02), those with left sided lesions had near identical event rates to those of (CMET-) controls (4% vs. 5% p = 1.00). Embolic event rates did not vary in relation to CMET by tissue properties, as evidenced by equivalent rates of PE among patients with diffuse and heterogeneously enhancing right ventricular lesions. Third, mortality risk conferred by CMET varied in relation to contrast-enhancement pattern. During a median follow-up of 0.7 years [IQR 0.3–1.7], patients with and without diffusely enhancing CMET had equivalent mortality to controls (p = 0.21), whereas prognosis was worse among patients with heterogeneously enhancing CMET compared to controls matched for cancer etiology and stage (p = 0.005).

Our finding that heterogeneous lesion enhancement constitutes an adverse prognostic marker among patients with CMET is consistent with established concepts in tumor biology: Tumor necrosis—as would be expected to result in avascularity and thus impaired contrast uptake—is a known marker of aggressive phenotype: Uncontrolled oncogene driven proliferation of neoplastic cells exhausts oxygen supply from normal vasculature, resulting in localized hypoxia which upregulates production of angiogenic factors and triggers neovascularization. [15, 16] However, vessels formed in response to hypoxia lack normal physiological angiogenesis—providing a nidus for chaotic tumor architecture and vascular leakiness. Hypoxia alters cancer metabolism to foster survival during stress and drive malignant progression, resulting in resistance to anti-cancer

| Table 4 Cardiac remodeling in patients with and without right ventricular cardiac metastases |
|---------------------------------------------|---------------------------------------------|---------------------------------------------|
|                                             | Right ventricular CMET (n=41)               | Other CMET (n=71)*                          | p    |
| Cardiac morphology                          |                                             |                                             |      |
| Left ventricle                              |                                             |                                             |      |
| Ejection fraction (%)                        | 62 ± 8                                      | 64 ± 9                                      | 0.27 |
| Ejection fraction (<50%)                    | 10% (4)                                     | 9% (6)                                      | 1.00 |
| End-diastolic volume (mL)                   | 110 ± 33                                    | 117 ± 35                                    | 0.27 |
| End-systolic volume (mL)                    | 42 ± 17                                     | 42 ± 17                                     | 0.83 |
| Stroke volume (mL)                          | 68 ± 21                                     | 75 ± 23                                     | 0.12 |
| Myocardial mass (gm)                        | 130 ± 81                                    | 112 ± 37                                    | 0.19 |
| Right ventricle                             |                                             |                                             |      |
| Ejection fraction (%)                        | 52 ± 11                                     | 56 ± 8                                      | 0.048|
| Ejection fraction (<50%)                    | 34% (14)                                    | 16% (11)                                    | 0.03 |
| End-diastolic volume (mL)                   | 133 ± 41                                    | 129 ± 36                                    | 0.60 |
| End-systolic volume (mL)                    | 65 ± 30                                     | 57 ± 20                                     | 0.11 |
| Stroke volume (mL)                          | 68 ± 23                                     | 71 ± 23                                     | 0.54 |
| Atria                                       |                                             |                                             |      |
| Left atrial area (cm²)                      | 18.2 ± 5.7                                  | 19.5 ± 5.1                                  | 0.25 |
| Right atrial area (cm²)                     | 198 ± 6.7                                   | 18.7 ± 5.0                                  | 0.36 |
| Lesion characteristics                      |                                             |                                             |      |
| Anatomic properties                         |                                             |                                             |      |
| Area (cm²)                                  | 9.5 ± 12.4                                  | 13.3 ± 19.7                                 | 0.27 |
| Perimeter (cm)                              | 14.3 ± 14.0                                 | 13.6 ± 10.5                                 | 0.79 |
| Maximal Length (cm)                         | 4.1 ± 2.7                                   | 4.6 ± 3.9                                   | 0.43 |
| Orthogonal Length (cm)                      | 2.3 ± 1.5                                   | 2.9 ± 2.2                                   | 0.09 |
| Perimeter/Min Length                        | 7.2 ± 8.3                                   | 5.6 ± 4.7                                   | 0.18 |
| Tissue properties                           |                                             |                                             |      |
| Heterogenous Enhancement                    | 49% (20)                                    | 55% (39)                                    | 0.53 |
| Contrast to Noise Ratio (CNR)               | 13.5 ± 14.8                                 | 14.8 ± 13.8                                 | 0.64 |
| Signal-to-Noise Ratio (SNR)                 | 468 ± 46.9                                  | 335 ± 17.0                                  | 0.10 |
| Blood pool normalized                       | 0.7 ± 0.3                                   | 0.6 ± 0.3                                   | 0.007|

* Inclusive of left ventricular, left atrial, and right atrial cardiac metastases
therapy and accelerated tumor growth. Consistent with this, magnetic resonance imaging (MRI) studies focused on extra-cardiac areas—including neurologic and renal cancers—have associated contrast hypo-enhancement (tumor necrosis) with chemotherapeutic resistance and increased mortality. [14, 17, 18].

Regarding embolic events, our data demonstrated CMET location to be strongly associated with outcomes—as evidenced by increased rates of PE among patients with RV intracavitary CMET. Our finding that embolic events were equivalent between patients with diffuse and heterogeneous CMET is not unexpected, given that avascular components were typically centrally located within lesions and would thus be unexpected to provide a nidus for embolization. Regarding mechanism, our data demonstrated patients with RV CMET to have lower RV systolic function than those with CMET in other locations (p < 0.05)—possibly due to mechanical tumor effects or treatment related (i.e. radiation-induced) cardiac injury. Based on this, it is possible that localized stasis could contribute to development of super-imposed thrombosis on neoplastic lesions—providing a nidus for embolic events. Whereas heterogeneous enhancement (as would be expected in context of tumor with superimposed thrombus) was not identified as a risk factor for embolic events, it is possible that micro-thrombi developed prior to or following the time of CMR, or that spatial resolution of LGE-CMR was insufficient for diagnostic detection. It is also possible that emboli stemmed from tumor dislodgement rather than primary thrombotic processes or from insufficient anticoagulation—concepts supported by the fact that nearly two-thirds (63%) of CMET patients were on anticoagulation at the time of clinical events, as well as recent data showing high embolic event rates in non-cancer [10, 19] and cancer populations [20] with cardiac thrombus treated with anticoagulants. Future research, including imaging using high resolution 3D LGE-CMR [21] and prospective trials testing relative efficacy of anticoagulant regimens or targeted resection in cancer patients with CMET+ are necessary to further test these concepts.

Limitations
Several limitations should be noted. First, whereas our study encompassed a broad cohort of cancer patients undergoing CMR and clinical follow-up at two institutions, it should be recognized that embolic events were ascertained based on clinical documentation and/or diagnostic testing. In this context, it is likely that subtle clinical events were under-reported, or that clinical considerations may have influenced testing such that embolic...
### Table 5 Mortality predictors

| Clinical characteristics                        | Hazard ratios [95% CI] | p     |
|-----------------------------------------------|------------------------|-------|
| Age (years)                                   | 1.00 [1.00–1.01]       | 0.36  |
| Gender (male)                                 | 1.25 [0.88–1.76]       | 0.20  |
| Cancer etiologies                             |                        |       |
| Sarcoma                                       | 0.91 [0.61–1.37]       | 0.65  |
| Lung                                          | 1.45 [0.95–2.21]       | 0.08  |
| Genitourinary                                  | 1.12 [0.73–1.73]       | 0.59  |
| Gastrointestinal                              | 1.56 [0.96–2.54]       | 0.07  |
| Skin/melanoma                                  | 0.71 [0.41–1.20]       | 0.20  |
| Lymphoma                                      | 0.40 [0.19–0.86]       | 0.02  |
| Endocrine                                     | 0.62 [0.31–1.22]       | 0.16  |
| Cardiovascular risk factors                   |                        |       |
| Hypertension                                  | 0.98 [0.70–1.35]       | 0.86  |
| Hyperlipidemia                                 | 1.00 [0.70–1.44]       | 0.99  |
| Diabetes mellitus                             | 0.87 [0.52–1.46]       | 0.59  |
| Smoking                                       | 1.01 [0.71–1.41]       | 0.98  |
| Cardiopulmonary disease                       |                        |       |
| Coronary artery disease                       | 1.36 [0.84–2.21]       | 0.21  |
| Atrial fibrillation/flutter                    | 1.16 [0.74–1.82]       | 0.52  |
| Pulmonary disease                              | 0.86 [0.41–1.77]       | 0.67  |
| Pulmonary hypertension                        | 1.33 [0.86–2.06]       | 0.20  |
| Cardiac morphology                            |                        |       |
| Left ventricle                                 |                        |       |
| Ejection fraction (< 50%)                     | 1.01 [0.99–1.03]       | 0.21  |
| Ejection fraction (≥ 50%)                     | 0.82 [0.50–1.36]       | 0.44  |
| End-diastolic volume                          | 1.00 [0.99–1.00]       | 0.06  |
| End-systolic volume                           | 0.99 [0.99–1.00]       | 0.07  |
| Right ventricle                                |                        |       |
| Ejection fraction (< 50%)                     | 1.02 [1.00–1.04]       | 0.09  |
| Ejection fraction (≥ 50%)                     | 0.84 [0.57–1.26]       | 0.40  |
| **CMET**Lesion Characteristics                |                        |       |
| **CMET** (presence vs. absence)†              | 1.64 [1.17–2.29]       | 0.004 |
| Anatomic properties                            |                        |       |
| Lesion number                                 | 1.67 [1.31–2.12]       | <0.001|
| Multiple lesions                              | 1.94 [1.23–3.06]       | 0.004 |
| Lesion size (maximal diameter [per 10 cm])    | 1.11 [0.53–2.33]       | 0.79  |
| Lesion size (area [per 10 cm²])               | 0.99 [0.85–1.15]       | 0.88  |
| Intra-cavitary lesion                          | 1.27 [0.81–1.97]       | 0.30  |
| Tissue properties                              |                        |       |
| Heterogeneous enhancement                     | 1.97 [1.23–3.15]       | 0.005 |
| Diffuse enhancement                           | 1.36 [0.84–2.21]       | 0.21  |
| Adjusted multivariate model†                  |                        |       |
| Lymphoma (cancer etiology)                    | 0.44 [0.11–1.79]       | 0.24  |
| Heterogeneous enhancement                     | 1.97 [1.23–3.16]       | 0.005 |

* Comparison between cancer patients with CMR-evidenced cardiac metastases and cancer-matched controls
† Regression analysis performed incorporating lymphoma (sole cancer associated with differential (improved) prognosis) and **CMET** heterogeneous enhancement together in an adjusted model (no additional variables included in adjusted models)

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**Conclusions**

Location and contrast-enhancement pattern of **CMET** impact clinical outcomes, with RV lesion location associated with PE and heterogeneous enhancement conferring increased mortality. Given current findings, future research is warranted to test anticoagulant strategies in cancer populations, whether adverse prognosis conferred by heterogeneous lesion enhancement stems from accelerated tumor growth, and whether tailored therapies—paired to lesion tissue characteristics—improves clinical outcomes for cancer patients with **CMET**.
Abbreviations
bSSFP: Balanced steady-state free precession; CI: Confidence interval; C-MET: Cardiac metastasis; CMR: Cardiovascular magnetic resonance; CNR: Contrast-to-noise ratio; CVA: Cerebrovascular events; ECG: Electrocardiogram; HR: Hazard ratio; IQR: Interquartile range; L.A: Left atrium/left atrial; LGE: Late gadolinium enhancement; L.V: Left ventricle/left ventricular; MRI: Magnetic resonance imaging; PE: Pulmonary embolism; RA: Right atrium/right atrial; RV: Right ventricle/right ventricular; RVEF: Right ventricular ejection fraction; SNR: Signal-to-noise ratio; TI: Inversion time.

Supplementary Information
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Additional file 1: Supplementary Table 1.

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Authors’ contributions
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Availability of data and materials
Study data can be made available to other researchers for purposes of reproducing the results of this study on request (contingent on approval of the Memorial Sloan Kettering Cancer Center and Weill Cornell institutional review boards and assurance of data de-identification).

Ethics approval and consent to participate
This study entailed analysis of data acquired for clinical purposes between 2012 and 2020; no dedicated interventions were performed for research purposes. Ethics approval for this protocol was provided by the Memorial Sloan Kettering Cancer Center and Weill Cornell institutional review boards.

Consent for publication
Not applicable.

Competing interests
The authors disclose no relevant competing interests relevant to this research.

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