Long-Term Prognostic Value of ^{82}Rb PET/CT–Determined Myocardial Perfusion and Flow Reserve in Cancer Patients

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Myocardial flow reserve (MFR), derived from quantitative measurements of myocardial blood flow during PET imaging, provides prognostic information on patients with coronary artery disease (CAD), but it is not known if this also applies to cancer patients with a competing risk for mortality. **Methods:** To determine the prognostic value of MFR in patients with cancer, we designed a retrospective cohort study comprising 221 patients with known or suspected CAD (median age, 71 y; range, 41–92 y) enrolled between June 2009 and January 2011. Most patients were referred for perioperative risk assessment. Patients underwent measurement of myocardial blood flow at rest and during pharmacologic stress, using quantitative ^{82}Rb PET imaging. They were divided into early-stage versus advanced-stage cancer groups based on cancer histopathology and clinical state and were further stratified by myocardial perfusion summed stress score, summed difference score, and calculated MFR. Overall survival (OS) was assessed using the Kaplan–Meier estimator, and Cox proportional-hazards regression helped identify independent predictors for OS. **Results:** During a follow-up of 85.6 mo, 120 deaths occurred. MFR, summed difference score, and cancer stage were significantly associated with OS. In the age-adjusted Cox hazard multivariable analysis, MFR and cancer stage remained independent prognostic factors. MFR combined with cancer stage enhanced OS discrimination. The groups had significantly different outcomes ($P < 0.001$), with 5-y OS of 88% (MFR $\geq$ 1.97 and early-stage), 53% (MFR $<$ 1.97 and early-stage), 33% (MFR $\geq$ 1.97 and advanced-stage), and 13% (MFR $<$ 1.97 and advanced-stage). **Conclusion:** Independent of cancer stage, MFR derived from quantitative PET was prognostic of OS in our cohort of cancer patients with known or suspected CAD. Combining these 2 parameters enhanced discrimination of OS, suggesting that MFR improves risk stratification and may serve as a treatment target to increase survival in cancer patients.

Key Words: rubidium PET; quantitative myocardial perfusion imaging; myocardial flow reserve; cancer; survival

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An increasing number of adults with cancer also have coronary artery disease (CAD) (*1*). Therefore, it is important to monitor the cardiovascular health of cancer patients with risk factors for CAD or documented cardiovascular events. Cancer itself creates an immunocompromised and hypercoagulable milieu, which, in combination with potentially cardiotoxic cancer therapies, renders patients increasingly vulnerable to cardiac morbidity and mortality (*2,3*). Cardiotoxic culprits include mediastinal irradiation, fluoropyrimidines, alkylating agents, androgen deprivation therapy, and targeted therapies such as tyrosine kinase inhibitors.

Whereas SPECT and SPECT/CT myocardial perfusion imaging (MPI) is widely available and well established for evaluating cardiac risk in the general population (*4*), PET/CT MPI offers 2 major advantages (*5–7*): superior diagnostic accuracy and the ability to quantify myocardial blood flow at rest and during vasodilator stress and hence derive myocardial flow reserve (MFR). Although PET/CT MPI has prognostic value beyond routine clinical predictors for all-cause mortality and major adverse cardiovascular events (*8,9*), its prognostic value in patients with cancer (a major competing risk for death) is unclear. Therefore, we set out to evaluate the prognostic value of myocardial blood flow and MFR in patients with cancer and a suspected or known CAD comorbidity.

MATERIALS AND METHODS

Study Population

This was a retrospective investigation of consecutive patients with cancer who underwent rest–stress ^{82}Rb-chloride PET/CT MPI over a 20-mo period between June 2009 and January 2011. During this time, 1,233 patients were referred for MPI, including 236 who underwent ^{82}Rb-chloride PET MPI (19%) and 997 (81%) who underwent SPECT/CT MPI. MPI modality (PET vs. SPECT) was generally determined by logistic factors (e.g., availability of ^{82}Rb-chloride generator) rather than clinical criteria. Exclusion criteria for pharmacologic cardiac stress testing included acute myocardial infarction, unstable angina, overt heart failure, a history of severe asthma, or contraindications to vasodilation with adenosine, dipyridamole, or regadenoson (*10*). Fifteen patients were excluded because dynamic PET/CT datasets were not available for analysis. The final study population comprised 221 patients, most of whom were referred for perioperative risk assessment (Fig. 1). A detailed history was obtained from the patient, the referring clinician, and the center's electronic medical record before MPI PET/CT to define the cardiac risk factor profile. Lipid profiles were not available for all patients, as these are not a part of routine diagnostic evaluation. Clinical risk factors were scored and summed according to the risk assessment of Morise et al. for predicting cardiac events (*11*). The electronic medical record was reviewed to identify the incidence of cardiac catheterization, percutaneous revascularization, coronary artery bypass grafting, or cardiac death

Eligible patients (*n* = 236)
· Consecutive patients undergoing ⁸²Rb PET/CT rest & vasodilator stress myocardial perfusion imaging

Excluded patients (*n* = 15)
· Technically insufficient studies (e.g., dynamic images unavailable or corrupted; uninterpretable images due to artifacts)

Study population (*n* = 221)
· Pre-surgical cardiovascular risk assessment (*n* = 178)
· Pre-chemotherapy / pre-bone marrow transplant risk assessment (*n* = 9)
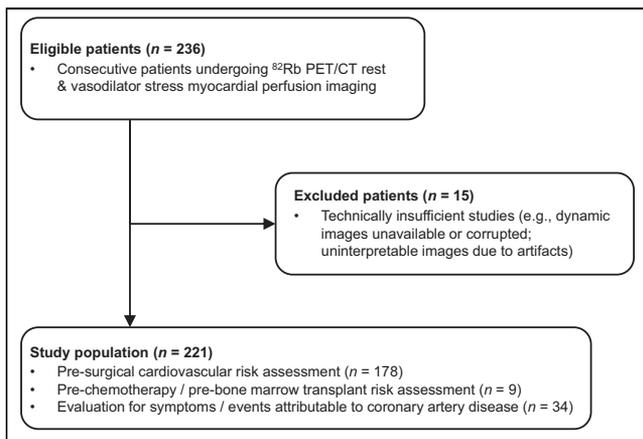· Evaluation for symptoms / events attributable to coronary artery disease (*n* = 34)

FIGURE 1. Flowchart of study patients.

within 90 d after ⁸²Rb-chloride PET/CT. Patient survival was accurately determined by scrupulous review of the electronic medical record. The institutional review board approved this retrospective, Health Insurance Portability and Accountability Act–compliant, single-institution study (institutional review board approval 11-150) and waived the requirement for informed consent. Data collection was finalized in December 2021. Details of the ⁸²Rb-chloride PET/CT rest–stress protocol, as well as details on image analysis, are shown in the supplemental materials (available at http://jnm.snmjournals.org) (*12–17*).

Cancer Status

The patients had a variety of primary cancers and disease stages (Supplemental Table 1). We divided the population into 2 groups, advanced-stage versus early-stage cancer, using an estimated cancer life expectancy based on historical 5-y survival rates at the time of ⁸²Rb PET/CT imaging. The advanced-stage cancer group was defined as patients with an expected 5-y survival rate of less than 50%, unknown primary cancer, or confirmed local recurrence or distant metastases within 3 mo after the ⁸²Rb PET/CT scan. The remaining patients were assigned to the early-stage cancer group. If patients had multiple primary cancers, staging was determined by the cancer with the lowest expected 5-y survival rate. Expected 5-y survival rates were based on the seventh edition of the *AJCC Cancer Staging Manual* (*18*). Lymphomas were staged according to the Ann Arbor classification.

Statistical Analysis

Data are expressed as mean ± SD, median and range, or frequency and percentage. The Welch 2-sample *t* test was used for comparison of normally distributed continuous variables between groups, whereas the Wilcoxon rank sum test was used for nonnormal variables. The Pearson χ^2 or Fisher exact test were used to compare categoric variables.

The Kaplan–Meier estimator was used to determine whether there was an association between clinical parameters or PET MPI and overall survival (OS), which was defined as the time from ⁸²Rb PET/CT until death from any cause. Patients who remained alive were censored at the last follow-up. The median follow-up time was calculated using the reverse Kaplan–Meier method (*19*). The dates of death and last follow-up were obtained from the electronic medical record. A log-rank test was performed to test for differences between survival curves. Hazard ratios and 95% CIs were calculated using univariable and multivariable Cox proportional-hazards regression models. To assess potential confounding effects on survival due to the retrospective nature of the study, multivariable analyses were performed as stepwise backward regression, with an entry probability for each variable set at 0.05. The final model was defined as the model after

variable selection, that is, after exclusion of variables that were not significant after adjustment. A sensitivity analysis was conducted by repeating the analysis on patients with both a normal summed stress score (SSS) (<4) and a normal summed difference score (SDS) (<3) only. Only a few missing values were observed, and a complete case analysis was conducted. Reported *P* values were 2-tailed; a *P* value of 0.05 or less was considered to indicate statistical significance. Statistical analysis was performed using SPSS (version 25) and R (version 6.3.0).

RESULTS

Patient Characteristics and Qualitative Assessment of Regional Perfusion

A flowchart summarizing patient selection is shown in Figure 1. Patient characteristics are detailed in Table 1. In total, 221 patients were included in the study. Most had at least an intermediate pretest probability for CAD (96.4%); 178 patients were referred for risk assessment before cancer surgery, 9 patients for risk assessment before undergoing chemotherapy or bone marrow transplantation, and 34 patients for evaluation of symptoms or signs attributable to coronary disease.

Myocardial Perfusion and Function

Abnormal stress perfusion (SSS ≥ 4) was observed in 52 of 221 patients (23.5%). Regional ischemia (SDS ≥ 3) was found in 46 patients (20.8%). In patients referred for symptoms, 14 of 34 (41.2%) showed evidence of ischemia, with an SDS of at least 3. Within 90 d after ⁸²Rb PET/CT, 7 patients underwent percutaneous coronary intervention, 1 patient underwent coronary artery bypass grafting, and 1 patient experienced cardiac death after myocardial infarction; all 9 patients had ischemia (SDS ≥ 3) on PET MPI.

A left ventricular ejection fraction of less than 50% was observed at rest in 26 patients (11.8%) and at stress in 22 patients (10.0%). An abnormal left ventricular ejection fraction reserve was observed in 24 patients.

Myocardial Blood Flow and MFR

Mean rest MBF was 1.01 mL/min/g (SD, 0.42), mean rest MBF after adjusting for RPP was 0.88 mL/min/g (SD, 0.32), and mean stress MBF was 1.93 mL/min/g (SD, 0.74). Mean MFR was 2.04 (SD, 0.74), and mean-adjusted MFR was 2.31 (SD, 0.85). Factors correlating with a low MFR (defined as an MFR lower than the median of 1.97) were a lower stress MBF (*P* < 0.001), a higher rest MBF or adjusted rest MBF (*P* < 0.001), a higher rest heart rate (*P* = 0.006), a lower stress ejection fraction (*P* = 0.002), and a higher SSS (*P* = 0.003) and SDS (*P* = 0.021, Table 2). In addition, a lower hemoglobin level (*P* < 0.001), a history of CAD (*P* < 0.001), an Agatston score classified as severe (score > 400, *P* < 0.001), and older age (*P* < 0.001) were all associated with a lower MFR (Table 2). However, stress heart rate, rest ejection fraction, body mass index, and type of vasodilator were not significantly associated with a low MFR.

Survival Outcome

The median follow-up time was 7.1 y (95% CI, 6.6–7.5 y). Median OS was 5.1 y (range, 14 d–8.8 y). During follow-up, 120 patients died. OS was significantly worse in patients with advanced-stage cancer than in those with early-stage cancer (adjusted hazard ratio, 4.06; *P* < 0.001; Supplemental Table 2). A higher stress MBF and lower rest MBF were both significantly associated with better OS in univariable analysis (*P* = 0.007 and 0.012, respectively). However, they were not entered in the multivariable model because of

TABLE 1
Demographics and Characteristics of Study Cohort (*n* = 221)

Characteristic	Data	Characteristic	Data
Age (y)	71 (41–92)	Vasodilator	
Age, binary		Dipyridamole	93 (42.1%)
<65 y	73 (33.0%)	Regadenoson	128 (57.9%)
≥65 y	148 (67.0%)	Heart rate (rest)	70.05 ± 13.15
Sex		Heart rate (stress)	87.44 ± 16.56 (2*)
Female	97 (43.9%)	Rest systolic blood pressure	140.60 ± 20.55
Male	124 (56.1%)	Stress systolic blood pressure	131.53 ± 22.53 (3*)
Height (cm)	168 (132–193)	Transient ischemic dilatation ratio	1.06 ± 0.15 (1*)
Weight (kg)	79 (36–161)	Stress MBF (mg/mL/min)	1.93 ± 0.74
Body mass index	27.82 (16.00–68.78)	Rest MBF (mg/mL/min)	1.01 ± 0.42
Body mass index, binary		Adjusted rest MBF (mg/mL/min)	0.88 ± 0.32
<30	136 (61.5%)	MFR	2.04 ± 0.74
≥30	85 (38.5%)	Adjusted MFR	2.31 ± 0.85
Stress LVEF (%)	71 (18–90) (1*)	Morise risk assessment	
Stress LVEF (%), binary	1*	Low (0–8)	8 (3.6%)
≥50	198 (90.0%)	Intermediate (9–15)	93 (42.1%)
<50	22 (10.0%)	High (>15)	120 (54.3%)
Rest LVEF (%)	66 (21–90) (1*)	SSS	
Rest LVEF (%), binary	1*	Normal (0–3)	169 (76.5%)
≥50	194 (88.2%)	Mild (*4–7*)	26 (11.8%)
<50	26 (11.8%)	Moderate (8–11)	8 (3.6%)
LVEF reserve	5 (-22–21) (1*)	Severe (≥12)	18 (8.1%)
Abnormal LVEF reserve	1*	Ischemia (SDS ≥ 3)	
Normal	196 (89.1%)	Abnormal	46 (20.8%)
Abnormal	24 (10.9%)	Normal	175 (79.2%)
Hemoglobin (g/dL)	12.40 (7.60–16.70) (4*)	Coronary calcium (Agatston score)	5*
Hemoglobin, binary	4*	None/minimal (0–10)	47 (21.8%)
≥10 g/dL	189 (87.1%)	Mild (11–100)	37 (17.1%)
<10 g/dL	28 (12.9%)	Moderate (101–400)	46 (21.3%)
Diabetes		Severe (>400)	68 (31.5%)
No	143 (64.7%)	Stent	9 (4.2%)
Yes	78 (35.3%)	Coronary artery bypass graft	9 (4.2%)
Dyslipidemia	157 (71.0%)	eGFR (mL/min/1.73 m²)	64 (22–109)
Hypertension	172 (77.8%)	eGFR, binary	
Smoker/former smoker	159 (71.9%)	≤60	96 (43.4%)
History of CAD	82 (37.1%)	>60	125 (56.6%)

*Unknown.
LVEF = left ventricular ejection fraction; MBF = myocardial blood flow; eGFR = estimated glomerular filtration rate.
Qualitative data are number and percentage; continuous data are median and range or mean ± SD.

collinearity with adjusted MFR. A lower adjusted MFR was significantly associated with a higher risk of death (increased by 3% for every 0.1-unit decrease in MFR); this translates to an increase in the risk of death of 17% when MFR decreases by 0.5 (*P* = 0.026). When stratifying MFR by quartiles, the 5-y survival rate for patients with an MFR of less than 1.45 was 22%, whereas for those with an MFR of more than 2.45 it was 73% (Supplemental Fig. 1). Other independent predictors of OS were age, history of

CAD, hemoglobin, and obesity (Supplemental Table 2). Therefore, MFR provided additional prognostic value to known clinical risk factors. Four risk categories were defined by stratifying the patients on MFR and cancer stage: patients with early-stage cancer and MFR ≥ 1.97; those with early-stage cancer and MFR < 1.97; those with advanced-stage cancer and MFR ≥ 1.97; and those with advanced-stage cancer and MFR < 1.97. These groups had significantly different outcomes, with 5-y OS of 88%, 53%, 33%, and

TABLE 2
Factors Contributing to Low MFR (All Patients)

Characteristic	MFR ≥ 1.97, n = 111	MFR < 1.97, n = 110	$P^{\dagger}$
Stress MBF (mg/mL/min)	2.14 (0.85–4.64)	1.57 (0.39–3.64)	<0.001
Rest MBF (mg/mL/min)	0.81 (0.40–2.25)	1.01 (0.48–2.61)	<0.001
Adjusted rest MBF (mg/mL/min)	0.77 (0.31–1.40)	0.88 (0.39–2.60)	<0.001
Heart rate (stress)	87 (52–126) (2*)	84 (51–141)	0.33
Heart rate (rest)	66 (44–102)	71 (42–112)	0.006
Ejection fraction (stress, %)	73 (40–90)	67 (18–90) (1*)	0.002
Ejection fraction (rest, %)	67 (27–90)	64 (21–86) (1*)	0.084
SSS	0.0 (0.0–21.0)	1.0 (0.0–40.0)	0.003
SDS	0.0 (0.0–9.0)	0.0 (0.0–26.0)	0.021
Hemoglobin (g/dL)	12.85 (7.60–16.70) (1*)	11.80 (7.60–15.60) (3*)	<0.001
Body mass index	28 (19–51)	27 (16–69)	0.26
Vasodilator			0.64
Dipyridamole	45 (41%)	48 (44%)	
Regadenoson	66 (59%)	62 (56%)	
History of CAD	29 (26%)	53 (48%)	<0.001
Coronary calcium (Agatston score)	(2*)	(3*)	<0.001
None/minimal (0–10)	32 (29%)	15 (14%)	
Mild (11–100)	25 (23%)	12 (11%)	
Moderate (101–400)	25 (23%)	21 (20%)	
Severe (>400)	25 (23%)	43 (40%)	
Stent	1 (1%)	8 (7%)	
Coronary artery bypass graft	1 (1%)	8 (7%)	
Age (y)	67 (44–92)	75 (41–90)	<0.001

*Unknown.

†Welch 2-sample t test, Wilcoxon rank sum test, Pearson χ^2 test; Fisher exact test.

MBF = myocardial blood flow.

Qualitative data are number and percentage; continuous data are median and range.

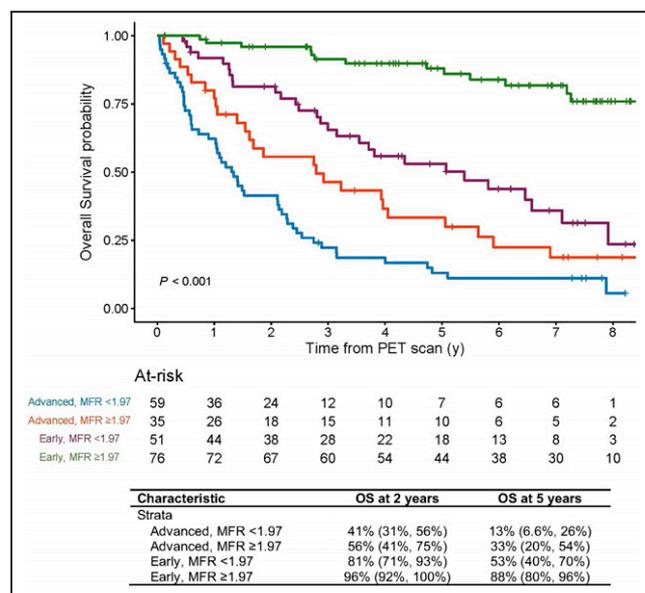| Characteristic	OS at 2 years	OS at 5 years
Strata		
Advanced, MFR <1.97	41% (31%, 56%)	13% (6.6%, 26%)
Advanced, MFR ≥1.97	56% (41%, 75%)	33% (20%, 54%)
Early, MFR <1.97	81% (71%, 93%)	53% (40%, 70%)
Early, MFR ≥1.97	96% (92%, 100%)	88% (80%, 96%)

FIGURE 2. Kaplan–Meier overall survival analysis stratified by MFR (<1.97 versus ≥1.97) and cancer stage (early versus advanced) in the overall cohort (n = 221).

13%, respectively (Fig. 2). Additional analyses classified by cancer staging and MFR are shown in Supplemental Table 3. When analysis was restricted to the 163 patients without regional perfusion abnormalities (SSS < 4 and SDS < 3), MFR still provided additional prognostic value for OS (Supplemental Fig. 2), with 5-y OS of 88%, 55%, 36%, and 15%, for patients with early-stage cancer and MFR ≥ 1.97; those with early-stage cancer and MFR < 1.97; those with advanced-stage cancer and MFR ≥ 1.97; and those with advanced-stage cancer and MFR < 1.97, respectively. Factors associated with OS in this restricted analysis of patients without regional perfusion abnormalities are listed in Supplemental Table 4.

DISCUSSION

This study demonstrated that MFR is an independent predictor of OS in a population of patients with active cancer, even after stratifying for cancer stage and regardless of the presence or absence of visual perfusion defects, suggesting that cardiovascular risk assessment and appropriate care remain paramount even in a population with significant competing morbidity.

PET-derived MFR is an established prognostic biomarker for the risk of major adverse cardiovascular events in the general population (5). In our cohort, we chose to focus on overall outcome

rather than limiting our investigation to these adverse events and cardiac-specific death. Given the complex nature of cancer care and follow-up, cardiac symptoms and events may be underestimated and erroneously ascribed to the underlying oncologic disease or therapy. On the other hand, OS is a robust and reliable outcome measure (20) and may indicate a holistic significance of impaired MFR beyond its association with cardiac health.

In a large study of over 4,000 patients (21), an MFR of less than 2.0 was an independent prognostic factor of all-cause mortality (hazard ratio, 1.72), with an average mortality of 4.4% per year during a median follow-up of 5.6 y (total mortality, 24.9%). In comparison, our patients had a higher all-cause mortality of 7.6% per year during a median follow-up of 7.1 y (total mortality, 54.3%). Although patient populations differ, MFR as an independent prognostic factor and the median values for MFR (1.97 vs. 2.0, respectively) were quite similar. In a study of 87 patients with breast cancer, those with an MFR in the lowest tertile had a higher cumulative incidence of MACE than those with an MFR in the highest tertile (22). In another study (23), an abnormal MFR remained predictive of cardiovascular death in patients with chronic kidney disease. Similarly, in a retrospective study of 198 patients with systemic inflammatory disorders, those in the lowest tertile of MFRs (defined as <1.65) experienced higher all-cause mortality than those in the highest tertile (hazard ratio, 2.4), regardless of other variables (24). In aggregate, these data suggest that a reduced MFR is a useful prognostic indicator even in the presence of significant noncardiac comorbidities. Accordingly, cardiac risk stratification should be performed in cancer patients with known or suspected CAD, and primary and secondary prevention strategies should be implemented to improve outcomes, similar to current practice in nonselected populations (25–28).

Previous epidemiologic studies have demonstrated that cardiovascular disease has a major impact on the long-term survival of cancer patients (29). Our study suggested that an impaired MFR during periods of stress may be a significant contributing factor. There are several potential ways in which cancer, by itself or by virtue of cancer therapy, may affect the cardiovascular system and control of vasomotion.

First, a recognized hallmark of cancer is the systemic inflammatory state (30,31), which may contribute to coronary microvascular dysfunction (32,33), akin to traditional cardiac risk factors (34). Inflammation-induced microvascular dysfunction is proposed to result from a reduction in microvascular nitric oxide bioavailability. The principal mechanism for the effect of nitric oxide on vasomotion is its binding to and activation of guanylate cyclase, increasing the production of cyclic guanosine monophosphate, which through second messengers promotes arterial smooth-muscle relaxation. Interestingly, phosphodiesterase 5 inhibition, preventing the breakdown of cyclic guanosine monophosphate, has recently gained interest as a potential anticancer therapy (35) beyond its established role as a systemic arterial vasodilator.

Another prevalent finding in cancer is autonomic dysfunction (36–39), a recognized contributor to abnormal MFR (40,41). The sympathetic nervous system can regulate the tumor microenvironment in multiple ways (42,43), and chronic activation of the sympathetic nervous system can promote cancer progression. β-adrenergic signaling, for instance, stimulates the transcription of proinflammatory cytokines and inhibits the transcription of interferons, thereby contributing to tumor progression and metastasis (42). Conversely, experimental inhibition of the sympathetic nervous system (44–46) has been shown to decrease tumor growth and improve outcomes.

Thus, impaired MFR, as seen in our study, may signify cancer-related coronary endothelial dysfunction or autonomic dysfunction. In contrast, cancer and CAD may simply coexist. Regardless of a causal link, our data suggest that cardiovascular risk assessment and appropriate care are important targets in the management of cancer patients.

This study had some limitations. It was retrospective, with potential deficiencies in the documentation of cardiovascular risk factors. It included only patients who were referred for MPI PET by their oncologist or cardiologist, which may introduce a selection bias. Its population was heterogeneous regarding age, cancer type, and treatment applied. Also, 11.8% had a resting left ventricular ejection fraction of less than 50%, and 31.5% had a coronary calcium score above 400. Nevertheless, none of these factors proved significant in the statistical analysis.

CONCLUSION

PET MFR is a strong, independent prognostic marker of OS, irrespective of cancer stage. Therefore, MFR assessment may contribute to better risk stratification and may serve as a treatment target to optimize cardiovascular care and improve survival in cancer patients. Prospective studies are warranted to validate this concept.

DISCLOSURE

KEY POINTS

QUESTION: Are cancer patients with abnormal myocardial blood flow and MFR, as derived from quantitative PET imaging, at higher risk for mortality, independent of their underlying disease?

PERTINENT FINDINGS: In a retrospective cohort study of 221 patients, we found that an abnormal MFR provides independent prognostic information; patients with an abnormal MFR had shorter survival, regardless of cancer type and stage.

IMPLICATIONS FOR PATIENT CARE: MFR improves risk stratification in cancer patients and may serve as a treatment target to increase their survival, suggesting a need for dedicated cardiac care in cancer patients, regardless of competing risk from their underlying disease.

REFERENCES

1. Schoormans D, Husson O, Oerlemans S, Ezendam N, Mols F. Having co-morbid cardiovascular disease at time of cancer diagnosis: already one step behind when it comes to HRQoL? *Acta Oncol.* 2019;58:1684–1691.
2. Abe J, Martin JF, Yeh ET. The future of onco-cardiology: we are not just "side effect hunters." *Circ Res.* 2016;119:896–899.
3. Gupta D, Pun SC, Verma S, Steingart RM. Radiation-induced coronary artery disease: a second survivorship challenge? *Future Oncol.* 2015;11:2017–2020.
4. Chang K, Sarkiss M, Won KS, Swafford J, Broemeling L, Gayed I. Preoperative risk stratification using gated myocardial perfusion studies in patients with cancer. *J Nucl Med.* 2007;48:344–348.
5. Murthy VL, Bateman TM, Beanlands RS, et al. Clinical quantification of myocardial blood flow using PET: joint position paper of the SNMMI Cardiovascular Council and the ASNC. *J Nucl Med.* 2018;59:273–293.

6. Weinstein H, Steingart R. Myocardial perfusion imaging for preoperative risk stratification. *J Nucl Med.* 2011;52:750–760.

7. Juárez-Orozco LE, Tio RA, Alexanderson E, et al. Quantitative myocardial perfusion evaluation with positron emission tomography and the risk of cardiovascular events in patients with coronary artery disease: a systematic review of prognostic studies. *Eur Heart J Cardiovasc Imaging.* 2018;19:1179–1187.

8. Murthy VL, Naya M, Foster CR, et al. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. *Circulation.* 2011;124:2215–2224.

9. Fukushima K, Javadi MS, Higuchi T, et al. Prediction of short-term cardiovascular events using quantification of global myocardial flow reserve in patients referred for clinical ^{82}Rb PET perfusion imaging. *J Nucl Med.* 2011;52:726–732.

10. Henzlova MJ, Duvall WL, Einstein AJ, Travin MI, Verberne HJ. ASNC imaging guidelines for SPECT nuclear cardiology procedures: stress, protocols, and tracers. *J Nucl Cardiol.* 2016;23:606–639.

11. Morise A, Evans M, Jalisi F, Shetty R, Stauffer M. A pretest prognostic score to assess patients undergoing exercise or pharmacological stress testing. *Heart.* 2007; 93:200–204.

12. Chow BJ, Dorbala S, Di Carli MF, et al. Prognostic value of PET myocardial perfusion imaging in obese patients. *JACC Cardiovasc Imaging.* 2014;7:278–287.

13. Pen A, Yam Y, Chen L, et al. Prognostic value of Rb-82 positron emission tomography myocardial perfusion imaging in coronary artery bypass patients. *Eur Heart J Cardiovasc Imaging.* 2014;15:787–792.

14. Arasaratnam P, Sadreddini M, Yam Y, et al. Prognostic value of vasodilator response using rubidium-82 positron emission tomography myocardial perfusion imaging in patients with coronary artery disease. *Eur J Nucl Med Mol Imaging.* 2018;45:538–548.

15. Rischpler C, Higuchi T, Fukushima K, et al. Transient ischemic dilation ratio in ^{82}Rb PET myocardial perfusion imaging: normal values and significance as a diagnostic and prognostic marker. *J Nucl Med.* 2012;53:723–730.

16. Lortie M, Beanlands RS, Yoshinaga K, Klein R, Dasilva JN, DeKemp RA. Quantification of myocardial blood flow with ^{82}Rb dynamic PET imaging. *Eur J Nucl Med Mol Imaging.* 2007;34:1765–1774.

17. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol.* 1990;15:827–832.

18. Edge SBBD, Compton CC, Fritz AG, Greene FL, Trotti A, eds. *AJCC Cancer Staging Manual.* 7th ed. Springer; 2010.

19. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials.* 1996;17:343–346.

20. Lauer MS, Blackstone EH, Young JB, Topol EJ. Cause of death in clinical research: time for a reassessment? *J Am Coll Cardiol.* 1999;34:618–620.

21. Gupta A, Taqueti VR, van de Hoef TP, et al. Integrated noninvasive physiological assessment of coronary circulatory function and impact on cardiovascular mortality in patients with stable coronary artery disease. *Circulation.* 2017;136:2325–2336.

22. Divakaran S, Caron JP, Zhou W, et al. Coronary vasomotor dysfunction portends worse outcomes in patients with breast cancer. *J Nucl Cardiol.* 2022;29:3072–3081.

23. Charytan DM, Skali H, Shah NR, et al. Coronary flow reserve is predictive of the risk of cardiovascular death regardless of chronic kidney disease stage. *Kidney Int.* 2018;93:501–509.

24. Weber BN, Stevens E, Perez-Chada LM, et al. Impaired coronary vasodilator reserve and adverse prognosis in patients with systemic inflammatory disorders. *JACC Cardiovasc Imaging.* 2021;14:2212–2220.

25. Mancini GBJ, Maron DJ, Hartigan PM, et al. Lifestyle, glycosylated hemoglobin A1c, and survival among patients with stable ischemic heart disease and diabetes. *J Am Coll Cardiol.* 2019;73:2049–2058.

26. Maron DJ, Mancini GBJ, Hartigan PM, et al. Healthy behavior, risk factor control, and survival in the COURAGE trial. *J Am Coll Cardiol.* 2018;72:2297–2305.

27. Solomon MD, Leong TK, Levin E, et al. Cumulative adherence to secondary prevention guidelines and mortality after acute myocardial infarction. *J Am Heart Assoc.* 2020;9:e014415.

28. Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med.* 2007;356: 830–840.

29. Sturgeon KM, Deng L, Bluethmann SM, et al. A population-based study of cardiovascular disease mortality risk in US cancer patients. *Eur Heart J.* 2019;40:3889–3897.

30. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. *Lancet Oncol.* 2014;15:e493–e503.

31. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell.* 2011; 144:646–674.

32. Schindler TH, Nitzsche EU, Olschewski M, et al. Chronic inflammation and impaired coronary vasoreactivity in patients with coronary risk factors. *Circulation.* 2004;110:1069–1075.

33. Recio-Mayoral A, Rimoldi OE, Camici PG, Kaski JC. Inflammation and microvascular dysfunction in cardiac syndrome X patients without conventional risk factors for coronary artery disease. *JACC Cardiovasc Imaging.* 2013;6:660–667.

34. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol.* 2013;62:263–271.

35. Cruz-Burgos M, Losada-Garcia A, Cruz-Hernández CD, et al. New approaches in oncology for repositioning drugs: the case of PDE5 inhibitor sildenafil. *Front Oncol.* 2021;11:627229.

36. Adams SC, Schondorf R, Benoit J, Kilgour RD. Impact of cancer and chemotherapy on autonomic nervous system function and cardiovascular reactivity in young adults with cancer: a case-controlled feasibility study. *BMC Cancer.* 2015;15:414.

37. Arab C, Vanderlei LCM, da Silva Paiva L, et al. Cardiac autonomic modulation impairments in advanced breast cancer patients. *Clin Res Cardiol.* 2018;107: 924–936.

38. Lakoski SG, Jones LW, Krone RJ, Stein PK, Scott JM. Autonomic dysfunction in early breast cancer: incidence, clinical importance, and underlying mechanisms. *Am Heart J.* 2015;170:231–241.

39. Teng AE, Noor B, Ajijola OA, Yang EH. Chemotherapy and radiation-associated cardiac autonomic dysfunction. *Curr Oncol Rep.* 2021;23:14.

40. Di Carli MF, Bianco-Batlles D, Landa ME, et al. Effects of autonomic neuropathy on coronary blood flow in patients with diabetes mellitus. *Circulation.* 1999;100: 813–819.

41. Zobel EH, Hasbak P, Winther SA, et al. Cardiac autonomic function is associated with myocardial flow reserve in type 1 diabetes. *Diabetes.* 2019;68:1277–1286.

42. Cole SW, Nagaraja AS, Lutgendorf SK, Green PA, Sood AK. Sympathetic nervous system regulation of the tumour microenvironment. *Nat Rev Cancer.* 2015; 15:563–572.

43. Zahalka AH, Arnal-Estapé A, Maryanovich M, et al. Adrenergic nerves activate an angio-metabolic switch in prostate cancer. *Science.* 2017;358:321–326.

44. Ben-Shaanan TL, Schiller M, Azulay-Debby H, et al. Modulation of anti-tumor immunity by the brain's reward system. *Nat Commun.* 2018;9:2723.

45. Melhem-Bertrandt A, Chavez-Macgregor M, Lei X, et al. Beta-blocker use is associated with improved relapse-free survival in patients with triple-negative breast cancer. *J Clin Oncol.* 2011;29:2645–2652.

46. Grytli HH, Fagerland MW, Fosså SD, Taskén KA. Association between use of β-blockers and prostate cancer-specific survival: a cohort study of 3561 prostate cancer patients with high-risk or metastatic disease. *Eur Urol.* 2014;65: 635–641.