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STATE-OF-THE-ART REVIEW

Cardiac Interventions in Patients With Active, Advanced Solid and Hematologic Malignancies

JACC: CardioOncology State-of-the-Art Review

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ABSTRACT

Invasive cardiac interventions are recommended to treat ST-segment elevation myocardial infarction, non–ST-segment elevation acute coronary syndromes, multivessel coronary disease, severe symptomatic aortic stenosis, and cardiomyopathy. These recommendations are based on randomized controlled trials that historically included few individuals with active, advanced malignancies. Advanced malignancies represent a significant competing risk for mortality, and there is limited evidence to inform the risks and benefits of invasive cardiac interventions in affected patients. We review the benefit conferred by invasive cardiac interventions; the periprocedural considerations; the contemporary survival expectations of patients across several types of active, advanced malignancy; and the literature on cardiovascular interventions in these populations. Our objective is to develop a rational framework to guide clinical recommendations on the use of invasive cardiac interventions in patients with active, advanced cancer. (J Am Coll Cardiol CardioOnc 2023;5:415–430) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Invasive cardiac interventions can reduce mortality and morbidity in selected patients with acute coronary syndromes, severe valvular disease, heart failure, and ventricular arrhythmias. However, randomized trials demonstrating improved cardiac outcomes have excluded patients with active, advanced malignancies, such as advanced solid organ cancers receiving ongoing treatment and incurable hematologic neoplasms with guarded prognosis. There is a paucity of direct clinical trial evidence to inform the risks and benefits of invasive cardiovascular interventions in these individuals.

In parallel with various seminal cardiovascular trials, there have been paradigm-changing developments in cancer therapies, including targeted biologic therapies and immunologic treatments. These have led to important improvements in survival in many patients with advanced cancers.[1,2]

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ABBREVIATIONS AND ACRONYMS

ADT = androgen deprivation therapy

CABG = coronary artery bypass graft

CRT = cardiac resynchronization therapy

DAPT = dual antiplatelet therapy

HER2 = human epidermal growth factor receptor-2

ICD = implantable cardioverter-defibrillator

NSCLC = non-small cell lung cancer

NSTEACS = non-ST-segment elevation acute coronary syndrome

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

TAVR = transcatheter aortic valve replacement

As targeted cancer therapies continue to evolve, event-free and overall survival has increased, placing individuals at increased risk of experiencing cancer therapy-related cardiovascular toxicity and also unrelated adverse cardiovascular outcomes as competing risks. Health care providers have been reluctant to refer patients with active, advanced cancer for invasive cardiac procedures because of the likelihood of succumbing to death from cancer before any benefit from the invasive cardiac intervention can be realized. However, longer life expectancy among many patients challenges this notion.

Given the limited clinical trial data on invasive cardiac interventions in patients with active, advanced cancer, an evidence-based approach to decision making in these individuals requires an understanding of the patient's expected cancer-specific survival. If the anticipated survival exceeds the length of time needed to derive benefit from an invasive cardiac intervention, then one might extrapolate that an individual is likely to benefit from the cardiac intervention. Our aim is to summarize the current data to guide decision making in patients with common metastatic cancers or malignancies with poor prognosis eligible for cancer-specific treatments (referred to as active, advanced cancer) who also have severe cardiovascular disease. To achieve this aim, we describe the evidence supporting invasive cardiac interventions in the general population, and we integrate the literature that exists for these interventions in cancer populations. A key consideration in patients with active, advanced cancer is the competing risk of cancer death, which may influence the patient's likelihood of benefitting from an invasive cardiac intervention. Thus, we describe the survival expectations for several of the most common cancers. We conclude by describing a conceptual framework that might be applied for cardiac decision making in this population. This framework incorporates cancer-related factors such as the need for uninterrupted cancer treatment; the risk of intervention-related complications in this population; and quality of life, which is magnified in importance as an outcome if longevity is limited.

HIGHLIGHTS

- Survival with both advanced malignancies and severe cardiovascular disease is increasing.
- The role of invasive cardiac interventions in patients with active, advanced cancer should be evidence-based and nuanced and requires cardio-oncology expertise and multidisciplinary input.
- Considerations include the: 1) magnitude of the benefit of the intervention vs the risk of adverse cardiovascular outcomes in the absence of the intervention; 2) cancer prognosis and need for uninterrupted treatment; 3) impact of thrombocytopenia (actual or anticipated); and 4) patient's goals of care.
- More research is needed to better understand outcomes in patients with active, advanced cancer undergoing invasive cardiac interventions.

LITERATURE REVIEW

We identified invasive cardiac interventions that are strongly recommended on the basis of high-quality randomized, controlled trial evidence from the American College of Cardiology clinical guidelines on heart failure,[3] coronary artery revascularization,[4] valvular heart disease,[5] and ventricular arrhythmias and the prevention of sudden cardiac death.[6] We included only invasive interventions with a Class 1 recommendation (ie, strongly recommended) supported by Level of Evidence: A (ie, of high quality based on at least 1 randomized, controlled trial). We included interventions shown to improve survival, quality of life, or both. By these criteria, we identified relevant recommendations for the invasive management of ST-segment elevation myocardial infarction (STEMI) with and without multivessel coronary artery disease, non-ST-segment elevation acute coronary syndrome (NSTEACS), multivessel chronic coronary artery disease, severe aortic stenosis, and ischemic cardiomyopathy using an implantable cardioverter-defibrillator (ICD) for the primary prevention of sudden cardiac death ± cardiac resynchronization therapy (CRT).

To complement the Level of Evidence: A supporting these recommendations, we also conducted a literature review specifically on coronary revascularization, transcatheter aortic valve replacement (TAVR), ICD, and CRT in cancer populations. The search strategy and full-text papers reviewed are described in the Supplemental Appendix. We excluded case reports, editorials, review articles, and studies with <100 patients. The most informative

findings from the papers published in the last 10 years are incorporated in a narrative manner.

PRIMARY PERCUTANEOUS CORONARY INTERVENTION FOR STEMI

After STEMI, contemporary in-hospital mortality rates of 3% to 6% have been reported after primary percutaneous coronary intervention (PCI),[7,8] which reduces the odds of short-term (4-6 weeks) mortality compared with thrombolytic therapy (pooled OR: 0.70; 95% CI: 0.58-0.85).[9] Moreover, primary PCI reduces the risk of reinfarction and stroke, with respective pooled ORs of 0.35 (95% CI: 0.27-0.45) and 0.46 (95% CI: 0.30-0.72), and can reduce symptoms and improve quality of life,[10] which may be important outcomes even if prolongation of life is not part of a patient's goals of care.

Ischemic heart disease occurs more frequently in patients with cancer than in those without cancer.[11] There is evidence from optical coherence tomography data that the plaque characteristics of patients with cancer having a myocardial infarction may differ from patients without cancer, with a higher rate of plaque erosion in the culprit lesion.[12] These observations raise the possibility that cancer or its treatment may have biologic effects that predispose to myocardial infarction. However, specific mechanisms are likely to be nuanced and diverse including inflammation and prothrombotic states related to the cancer or its treatment; the as-yet poorly defined effects of clonal hematopoiesis of indeterminate potential; shared determinants of health, such as smoking, obesity, physical inactivity, and diabetes; and cancer treatments such as fluoropyrimidines and radiotherapy affecting the coronary arteries.[13]

In patients with active, advanced cancer admitted primarily for STEMI, in-hospital mortality appears to be lower among those undergoing PCI than among those not undergoing PCI, although these data may be prone to selection bias.[14] This suggests that if prolongation of life is consistent with a patient's goals of care, primary PCI should be strongly considered if it can be performed in a timely fashion. There are scant data on the effects of primary PCI on quality of life in patients with active, advanced cancer, and observational studies of the benefit of primary PCI in this population are limited by potential selection bias in that patients with preterminal cancer may not have been offered coronary angiography if inconsistent with their goals of care or for reasons of clinical futility.

Following primary PCI of the culprit artery in patients with STEMI, staged PCI of nonculprit lesions with the goal of complete revascularization reduces cardiovascular death or myocardial infarction and improves angina-related quality of life during a median follow-up of 3 years.[15,16] In trials of complete revascularization, patients with a noncardiovascular life expectancy <5 years were excluded, which may have led to the exclusion of some patients with an active, advanced malignancy, so the implementation of this recommendation should be individualized in such patients.

ROUTINE INVASIVE STRATEGY FOR NSTEACS

A routine invasive strategy with intent to proceed to revascularization is recommended in the guidelines for patients with NSTEACS.[4] This recommendation is supported by a meta-analysis of randomized trials in which a routine invasive strategy was compared with a selective invasive strategy; it demonstrated a reduction in nonfatal outcomes in patients with NSTEACS.[17] During 6 to 24 months of follow-up, a reduction in death or myocardial infarction was observed in the routine invasive arms (pooled OR: 0.82; 95% CI: 0.72-0.93).[17] This was largely driven by a reduction in myocardial infarction (pooled OR: 0.75; 95% CI: 0.65-0.88); there was no reduction in mortality (pooled OR: 0.92; 95% CI: 0.77-1.09). Routine invasive approaches reduced rehospitalization (pooled OR: 0.66; 95% CI: 0.60-0.72) and moderate or severe angina (pooled OR: 0.77; 95% CI 0.68-0.87). With regard to the timing of intervention, 2 large, randomized trials have shown similar outcomes in patients advanced for cardiac catheterization early (within 24 hours) vs later (24-72 hours).[18,19] This suggests that in most patients with NSTEACS and cancer, there is time to have discussions with the patient and family regarding the goals of care as well as shared decision making regarding the risks and benefits of proceeding with invasive management.

Randomized, controlled trials of routine invasive approaches did not account for the competing risk of cancer death in patients with active, advanced malignancies. Among patients with cancer, contemporary administrative data suggest that in-hospital mortality may be similar in those managed medically for NSTEACS compared with invasive management.[14] Further data are needed to inform postacute outcomes in patients with active advanced cancer managed medically vs invasively. The clinical and research challenge lies in the great heterogeneity of cancers, cancer treatments, and corresponding prognoses.

If PCI is performed, a radial approach is preferable (**Table 1**). In a patient-level meta-analysis of

TABLE 1 Specific Considerations Before Undertaking Invasive Cardiac Interventions for Patients With Active, Advanced Malignancy

Intervention	Cancer-Specific Considerations	Mitigating Strategies
Primary PCI for STEMI	• Severe thrombocytopenia is associated with increased bleeding risk with antithrombotic therapy	• Radial arterial access is recommended • Shorten duration of DAPT to 1-3 months followed by SAPT
Routine invasive strategy for NSTEACS	• Expected cancer-specific survival • Potential for delaying cancer treatments • Thrombocytopenia may increase bleeding risk with antithrombotic therapy	• Radial arterial access is recommended • Shorten duration of DAPT to 1-3 months followed by SAPT
Revascularization of significant left main stenosis for stable ischemic heart disease	• Potential for delaying cancer treatments • Expected cancer-specific survival	• CABG is associated with significant up-front morbidity • In selected patients, PCI can be considered to improve survival and decrease angina
Revascularization for multivessel coronary disease for stable ischemic heart disease	• Potential for delaying cancer treatments • Expected cancer-specific survival	• Medical therapy for coronary disease is very effective, so CABG is only considered in highly selected, symptomatic cases refractory to medical therapy • Multivessel PCI is an alternative revascularization strategy to CABG
TAVR for symptomatic, severe, aortic stenosis	• Expected cancer-specific survival	• Because of its proven benefits in those with poor prognosis, TAVR should be considered in most cases on first-line cancer treatments and many on second-line treatments, especially with targetable mutations or phenotypes
ICD for the primary prevention of sudden cardiac death	• Expected cancer-specific survival • Obstruction of radiation delivery • Radiation to existing device	• Given the efficacy of heart failure pharmacotherapy, the lack of effect of ICDs on quality of life, and the competing risk of cancer death, the role of ICDs in patients with active, advanced cancer is limited • Device repositioning may be needed in specific cases • Device interrogation following radiation[54]
CRT for heart failure with EF <35% and wide QRS	• Distinguishing heart failure symptoms from other causes of dyspnea • Obstruction of radiation delivery • Radiation to existing device	• Careful clinical and echocardiographic evaluation; natriuretic peptide measurement to ascertain heart failure • Device repositioning may be needed in specific cases • Device interrogation following radiation[54]

The patient's goals of care are paramount in the decision to proceed with an invasive cardiac intervention.

CABG = coronary artery bypass surgery; CRT = cardiac resynchronization therapy; DAPT = dual antiplatelet therapy; EF = ejection fraction; NSTEACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; SAPT = single antiplatelet therapy; TAVR = transcatheter aortic valve replacement.

randomized trials comparing radial vs femoral access for coronary angiography, mortality (HR: 0.77; 95%: 0.63-0.95) and major bleeding (1.5% vs 2.7%; OR: 0.55; 95% CI: 0.45-90.67) were reduced using a radial approach.[20] Although there are no subgroup data by the presence of a malignancy, it is reasonable to extrapolate these benefits to patients with active, advanced cancer because they are likely to have a higher risk of bleeding than patients without cancer.

Following PCI for NSTEACS, dual antiplatelet therapy is usually recommended for ≥12 months (although P2Y12 monotherapy without aspirin may be acceptable after 1-3 months of dual antiplatelet therapy).[4] If these treatments are contraindicated or not consistent with the patient's goals of care in the setting of advanced, active malignancy, the role of routine cardiac catheterization is less certain. For this reason, the threshold to refer a patient with active, advanced cancer for early cardiac catheterization after NSTEACS differs from patients with STEMI, and the decision should be individualized, especially in those whose cancer is not responding to therapy and who are likely to have a shorter life expectancy (**Table 2**).

Existing research on the management of patients with cancer and NSTEACS is nearly exclusively from single-center retrospective studies or retrospective analyses of administrative databases (Supplemental Table 1). These studies contained few data on cancer stage or treatments, and the selection of patients for cardiac catheterization was likely biased toward those with a better perceived prognosis. Because of the methodological limitations of these study designs, few evidence-informed inferences can be made as to which patients are likely to benefit from an invasive approach in this context. In our opinion, patients who may be less likely to benefit from a routine invasive strategy include those with thrombocytopenia or who will require cancer therapies that will cause thrombocytopenia and those with cancer survival expected to be <6 months. Conversely, patients with persistent or recurrent ischemia, evidence of ischemia-driven hemodynamic instability, or a large burden of ischemic myocardium may be more likely to benefit from an early invasive approach.

TABLE 2 General Guidance on the Likely Benefit of Invasive Cardiac Interventions in Patients With Common Advanced Cancers With Consideration of Line of Cancer Therapy (First, Second, Third)

			Prostate Cancer		Breast Cancer			
Intervention	Non-Small Cell Lung Cancer	Colorectal Cancer	Hormone Sensitive	Castrate Resistant	HR or HER2 Positive	Triple Negative	Acute Myeloid Leukemia[a]	Multiple Myeloma
Primary PCI for STEMI	Should be performed in all cases with select exceptions (eg, patients near end of life or advanced directive)							
Invasive strategy for NSTEACS	First-line Rx: ✓ Second-line Rx: ±	First-line Rx: ✓ Second-line Rx: ±	✓	±	First-line Rx: ✓ Second-line Rx: ±	First-line Rx: ±	In complete remission ± refractory/ relapsed disease: ✗	First-line Rx: ✓ Second-line Rx: ±
Revascularization for multivessel CAD	First-line Rx (driver mutation): ± First-line Rx (no driver mutation): ✗	✗	✓	±	First-line Rx: ± Second-line Rx: ✗	First-line Rx: ± Second-line Rx: ✗	In complete remission ± Refractory/ relapsed disease: ✗	First-line Rx: ± Second-line Rx: ✗
TAVR for severe symptomatic AS	First-line Rx (driver mutation): ✓ First-line Rx (no driver mutation): ± Second-line Rx: ±	First-line Rx: ✓ Second-line Rx: ± Third-line Rx: ✗	✓	Starting newer hormonal Rx: ✓ Progression despite newer hormonal Rx: ±	First-line Rx: ✓ Second-line Rx: ±	First-line Rx: ✓ Second-line Rx: ✗	In complete remission ± Refractory/ relapsed disease: ✗	First-line Rx: ✓ Second-line Rx: ±
ICD for the primary prevention of sudden cardiac death	✗	First-line Rx: ± Second-line Rx: ✗ Third-line Rx: ✗	±	✗	First-line Rx: ± Second-line Rx: ✗	✗	✗	First-line Rx: ± Second-line Rx: ✗ Third-line Rx: ✗
CRT for the treatment of HF symptoms	First-line Rx (driver mutation): ✓ First-line Rx (no driver mutation): ± Second-line Rx: ±	First-line Rx: ± Second-line Rx: ✗ Third-line Rx: ✗	✓	±	First-line Rx: ✓ Second-line Rx: ±	First-line Rx: ✓ Second-line Rx: ±	In complete remission ± Refractory/ relapsed disease: ✗	First-line Rx: ✓ Second-line Rx: ✓ Third-line Rx: ±

Individual treatment decisions must be customized and may be influenced by goals of care, physical frailty, and comorbidities. Line of therapy (Rx) refers to the patient's current treatment regimen.
[a]Management should also take current or anticipated thrombocytopenia into consideration.

✓ = recommended; ± = consider in select cases; ✗ = not recommended; AS = aortic stenosis; CAD = coronary artery disease; CRT = cardiac resynchronization therapy; HER2 = human epidermal growth factor receptor-2; HF = heart failure; HR = hormone receptor; ICD = implantable cardioverter-defibrillator; NSTEACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TAVR = transcatheter aortic valve replacement.

LEFT MAIN OR MULTIVESSEL CORONARY DISEASE

Patients with cancer frequently undergo diagnostic or staging imaging that can lead to the identification of vascular disease, including coronary artery disease, through the incidental finding of vascular calcification.[21] Revascularization for left main stenosis may be considered to treat angina or to improve prognosis. In cases in which the coronary anatomy is suitable, percutaneous revascularization for left main stenosis may be a treatment alternative because it is associated with similar mortality rates to a coronary artery bypass graft (CABG)[22] without the up-front morbidity of a sternotomy.

Revascularization for stable multivessel coronary disease may not decrease the risk of death or myocardial infarction when performed in addition to optimal medical therapy.[23,24] However, revascularization can decrease angina in individuals with stable coronary artery disease and inducible myocardial ischemia.[25] Therefore, for patients with active, advanced cancer and asymptomatic coronary artery disease, optimal medical therapy alone is appropriate, whereas coronary revascularization can be considered for those with symptomatic multivessel coronary disease.

If a strategy of revascularization is pursued, the risks and benefits of PCI vs CABG need to be weighed. In a pooled patient-level analysis of 12 randomized trials comparing CABG with PCI (with stenting) in patients not presenting with acute myocardial infarction, 30-day mortality was 1.4% in the CABG group and 1.3% in the PCI group.[26] Patients undergoing CABG exhibited better survival at the 5-year follow-up when mortality rates were 9.2% in the CABG group and 11.2% in the PCI group (HR: 1.20; 95% CI: 1.06-1.37; $P = 0.0038$). A significant treatment interaction was noted for diabetes, with 5-year mortality rates among those with diabetes of 10.7% following CABG vs 15.7% following PCI (HR: 1.44; 95% CI: 1.20-1.74), whereas no difference between CABG

and PCI was observed among those without diabetes. Therefore, for patients with active, advanced cancer and multivessel coronary disease, especially among those with diabetes, CABG may be considered if there is a reasonable expectation of 5-year survival.

The modest long-term benefit of CABG should be weighed against the greater up-front morbidity. This may disincentivize some patients with incurable cancers from undergoing a sternotomy. CABG might also result in lengthy interruptions in cancer therapy.

The management of multivessel or left main coronary disease in patients with active, advanced malignancies should be discussed in a multidisciplinary and patient-oriented setting. In addition to patients and their social support, key stakeholders include interventional cardiologists, cardiac surgeons, and oncologists/hematologists. Cardio-oncology is important in bringing together these specialists. Factors to be considered when making recommendations include cancer-specific prognosis; past and potential future cancer therapies; patient symptoms, disabilities, and preferences; and the technical feasibility of minimally invasive CABG and percutaneous revascularization. In a large registry of patients with left main or multivessel coronary disease considered at prohibitively high surgical risk by a heart team, PCI was associated with mortality rates consistent with Society of Thoracic Surgeons and EuroSCORE II surgical risk scores but with improved health status.[27] However, the rates of advanced cancer in study participants were not reported. In all cases, care should be taken to ensure appropriate medical therapies are optimized for the secondary prevention of coronary artery disease.

ANTIPLATELET THERAPY CONSIDERATIONS

Following acute coronary syndrome, guidelines suggest dual antiplatelet therapy (DAPT) be continued for ≥12 months, although P2Y12 monotherapy may be acceptable after 1 to 3 months of DAPT.[4] In stable ischemic heart disease patients, DAPT may be changed to P2Y12 inhibitor monotherapy as early as 1 month if there is a high risk of or overt bleeding.[4] Although ischemic outcomes do not appear to be increased with early DAPT discontinuation in meta-analyses, they have been underpowered.[28] Nevertheless, the benefit-risk trade-off in this population likely favors monotherapy. Even a strategy of DAPT de-escalation from a potent P2Y12 inhibitor (prasugrel or ticagrelor) to the less potent clopidogrel may be associated with a higher bleeding risk than P2Y12 monotherapy.[29]

Bleeding rates after PCI are likely to be higher among patients with advanced cancer (Supplemental Table 1) because of bleeding from the tumor itself and/or secondary to thrombocytopenia, which may be caused by bone marrow infiltration, autoimmune mechanisms (eg, in chronic lymphocytic leukemia), or cancer treatments. In an analysis of administrative data, among 643,676 patients receiving myelosuppressive chemotherapy, the incidence of thrombocytopenia was 6.1% in cyclophosphamide recipients, 13.2% in carboplatin recipients, and 13.5% in gemcitabine recipients.[30] Thrombocytopenia is also unavoidable following hematopoietic stem cell transplantation, typically persisting from days 9 to 40.[31] In hypoproliferative thrombocytopenia, platelet counts <10,000/mm^3 are associated with an increased bleeding risk in patients with cancer; however, the association between the platelet count and bleeding risk is less clear for values 10,000to 50,000/mm^3.[32] On the other hand, cancer may also be associated with a prothrombotic state, and the risk of stent thrombosis after PCI may be higher in these patients compared with patients who do not have cancer.[33] Therefore, an individualized approach to antiplatelet therapy in these patients is recommended.

The evidence to inform the use of antiplatelet regimens following acute coronary syndrome in patients with thrombocytopenia is limited. In most clinical trials of DAPT, exclusion criteria included high bleeding risk, a contraindication to antiplatelet therapy, or “clinically important” thrombocytopenia.[34] However, specific platelet count thresholds were infrequently explicit. In the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38) trial in which prasugrel was compared with clopidogrel, a platelet count <100,000/mm^3 was an exclusion criterion.[35] In a systematic review of studies in which clinical outcomes stratified by the presence of thrombocytopenia were reported in patients undergoing PCI, thrombocytopenia (defined as platelet count <150,000/mm^3) was associated with higher in-hospital mortality (relative risk [RR]: 2.6, 95% CI: 1.7-3.8) and bleeding (RR: 2.4; 95% CI: 1.4-4.0) and also with higher late mortality (RR: 1.9; 95% CI: 1.2-2.9) and bleeding (RR: 1.7; 95% CI: 1.1-2.9).[36] Similar findings were also reported in a more recent systematic review, which also demonstrated increased adverse cardiovascular event rates (but not major bleeding) for those with thrombocytosis.[37] However, the degree of thrombocytopenia and the underlying cause are important when considering whether to advance patients for invasive therapies.

Mild or moderate thrombocytopenia, as a sole criterion, should not generally be used to exclude cancer patients from invasive management.

In the recent MASTER DAPT (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation with an Abbreviated versus Standard DAPT Regimen) trial, patients with acute or chronic coronary syndrome who had had successful PCI using a biodegradable sirolimus-eluting stent were randomized to immediately stop DAPT and continue antiplatelet monotherapy (abbreviated antiplatelet therapy) vs 6 months of dual antiplatelet therapy followed by monotherapy.[38] This trial is notable because a platelet count <100,000/mm^3 and nonskin cancers associated with a high bleeding risk (eg, gastrointestinal, urinary tract, and pulmonary) were specific inclusion criteria. At trial completion, the abbreviated antiplatelet therapy group did not appear to have an increase in adverse cardiac or cerebral events (HR: 0.99; 95% CI: 0.78-1.26), but this was associated with lower rates of clinically relevant bleeding (HR: 0.68; 95% CI: 0.55-0.84).

To allay concerns over ischemic events following early reduction in antiplatelet therapy intensity after a complex PCI, a pooled patient-level analysis of 5 randomized trials demonstrated that P2Y12 inhibitor monotherapy after 1 to 3 months had similar mortality and ischemic event rates as standard DAPT irrespective of procedural complexity.[39]

More broadly, 1 expert consensus statement suggested that aspirin can be prescribed for platelet counts >10,000/mm^3, DAPT with clopidogrel for platelets counts >30,000/mm^3, and DAPT with prasugrel or ticagrelor for platelet counts >50,000/mm^3.[40] However, no evidence to support these recommendations was provided, and other experts have recommended different thresholds based on the existing clinical trials. In the absence of bleeding, they suggest clopidogrel monotherapy be used after acute coronary syndrome for platelet counts between 50,000/mm^3 and 100,000/mm^3.[41] For platelet counts <50,000/mm^3, they recommend avoiding PCI and antiplatelet drugs. Existing or anticipated thrombocytopenia should be recognized when PCI and DAPT are considered in patients with advanced cancer.

SEVERE AORTIC STENOSIS

TAVR is an effective intervention for severe symptomatic aortic stenosis. In a landmark trial, patients with severe, symptomatic aortic stenosis who were considered unsuitable for surgical aortic valve replacement because of comorbidities (≥50% predicted probability of death at 30 days or a serious, irreversible condition) were randomly allocated to receive TAVR vs standard care.[42] TAVR reduced mortality (HR: 0.55; 95% CI: 0.40-0.74) and death or hospitalization (HR: 0.46; 95% CI: 0.35-0.59). At 12 months, 75% of the surviving patients in the TAVR group had mild heart failure symptoms or were asymptomatic compared with 42% of surviving patients receiving standard care ($P < 0.001$). The median survival in the standard care arm was approximately 12 months. This trial is highly relevant for patients with active, advanced malignancies because it suggests that those with severe, symptomatic aortic stenosis and an expected noncardiac survival >12 months are likely to benefit from TAVR (**Table 2**).

Some (but not all) studies of TAVR in patients with cancer suggest that mortality is higher than in TAVR recipients without cancer (Supplemental Table 1). However, these studies are limited because of their retrospective design with scarce data on the cancers or their treatment. Also, with no data on patients with severe, symptomatic aortic stenosis who were not offered TAVR because of an active, advanced malignancy, it is possible that the outcomes reported are influenced by selection bias.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS AND CARDIAC RESYNCHRONIZATION THERAPY

Several cancer therapies are associated with left ventricular dysfunction, which in some cases may result in heart failure. Left ventricular dysfunction may be reversible upon discontinuation of the offending cancer agent (eg, trastuzumab).[43,44] However, anthracyclines may result in heart failure with reduced ejection fraction during or after completion of cancer treatment, with partial or incomplete recovery of cardiac function. The risk of heart failure from anthracycline exposure is closely related to the cumulative dose administered.[45-47] Therefore, heart failure with reduced ejection fraction, caused either by cancer therapies or by other causes, can be a clinically important issue in patients with active, advanced cancer.

In the broader population of patients with heart failure with reduced ejection fraction, ICDs are effective at reducing the risk of sudden cardiac death. In a randomized trial, patients with symptomatic heart failure and left ventricular ejection fraction ≤35% received an ICD, amiodarone, or placebo.[48] The 5-year mortality rates were 36% in the placebo arm and 29% in the defibrillator arm. Survival

curves separated appreciably at approximately 2 years of follow-up.

Major trials of ICDs for both the primary and secondary prevention of sudden cardiac death did not specifically indicate cancer as an exclusion criterion.[48-51] However, these studies generally excluded patients with a nonarrhythmic medical condition making 1- or 2-year survival unlikely or with a high likelihood of death during the trial. Of note, the rates of cancer at baseline were not reported in any of these trials, so direct evidence of the trials' generalizability to patients with active, advanced cancer is lacking. Furthermore, since these landmark device trials, the efficacy of newer drugs for the treatment of heart failure, including sodium-glucose cotransporter 2 inhibitors and angiotensin receptor/neprilysin inhibitors, has been demonstrated. The use of these medications is associated with a reduced risk of death among patients with a cardiac implantable device.[52] Such data have prompted the role of primary prevention ICDs to be re-evaluated in the context of contemporary multidrug treatment for heart failure. Patients with active, advanced cancer should have heart failure therapies optimized before considering a cardiac implantable device because they may obviate the need for device implantation in this population where device benefits may be less clear.

Nonresynchronization ICDs may not improve quality of life or heart failure symptoms (with the possible exception of terminating ventricular tachycardia by antitachycardia pacing). Indeed, because of the risk of complications, such as infection and inappropriate shocks, ICDs may increase patient morbidity despite reducing mortality. Therefore, careful discussion with potentially eligible patients is needed to ensure their expectations from an ICD are well-informed (**Table 1**).

CRT in patients with moderate to severe heart failure, left ventricular ejection fraction ≤35%, and QRS duration ≥120 milliseconds (and additional echocardiographic indexes of dyssynchrony for QRS duration of 120 to 149 milliseconds) reduces mortality, heart failure hospitalization, and heart failure symptoms.[53] Kaplan-Meier curves between CRT recipients and controls diverge appreciably within months. The favorable effect of CRT on heart failure symptoms distinguishes it from an ICD. Therefore, cardiac resynchronization therapy using a biventricular pacemaker without defibrillator capabilities can be considered in eligible individuals when defibrillator therapy is not consistent with the patient's goals of care. However, distinguishing heart failure symptoms from symptoms related to advanced cancer can be challenging. Markers of left ventricular filling pressure, including echocardiographic indexes and N-terminal pro-B-type natriuretic peptide, may be helpful in evaluating the likely symptomatic benefit of CRT, although this approach requires prospective verification.

The implantation of a cardiac device in a patient with active, advanced cancer can have important implications. Ionizing radiation can damage cardiac devices.[54] In a cohort of 34,706 patients treated with radiotherapy, 261 (0.8%) had an implantable cardiac device. Of these 261 individuals, 3.4% required device repositioning because it obstructed the delivery of radiation, and 1.5% had inappropriate device function during radiotherapy.[55] A systematic review identified a pooled incidence of device malfunction of 6.6% (95% CI: 5.1%-8.4%) in 3121 patients.[56] The RR of device malfunction was higher when neutron-producing energies were delivered (pooled RR: 9.98; 95% CI: 5.09-19.60) and for ICDs/CRT defibrillators compared with pacemakers or CRT pacemakers (pooled RR: 2.07; 95% CI: 1.40-3.06). Also, thrombocytopenia and neutropenia caused by cancer therapy may increase the risk of bleeding and infection, respectively. Therefore, once a decision is made to proceed with an implantable cardiac device in a patient with active, advanced cancer, the timing of cancer treatments (ie, radiotherapy and chemotherapy in particular) needs to be incorporated into where and when the device is implanted.

A CONCEPTUAL FRAMEWORK FOR INVASIVE CARDIAC INTERVENTIONS IN PATIENTS WITH ACTIVE, ADVANCED CANCER

Analogous to the transformation that has occurred in human immunodeficiency virus, where a previously fatal disease has now become a chronic condition with numerous therapeutic options and a protracted course, management strategies and survival expectations have evolved for many individuals with active, advanced malignancies. It is crucial to recognize that over the past 3 decades in particular, cancer survival has progressively increased.[57,58] This change compels us to re-evaluate the management of cardiovascular disease, which may become an equally important cause of morbidity and mortality in this population. Appraisal of the role of an invasive cardiac intervention in a patient with active, advanced malignancy would be incomplete without consideration of the patient's cancer-specific prognosis.

New paradigms for cancer treatment, such as targeted molecular therapies and immunotherapies, have recently been proven to be effective at decreasing mortality. As these treatments are

TABLE 3 Therapeutic Milestones in Select, Common Advanced Malignancies and Associated Prognosis

Cancer	Milestone	Selected Data to Exemplify Contemporary Prognosis
Non-small cell lung	Targetable driver mutation (present in approximately two-thirds of cases)	The use of a targeted therapy is associated with a better median survival of 3.5 years (25th-75th percentile: 2.0-7.7 years) compared with an oncogenic driver not receiving targeted therapy, with median survival of 2.4 years (25th-75th percentile: 0.9-2.6 years).[69]
	Use of immune checkpoint inhibitors	In a randomized trial, among untreated patients with nonsquamous metastatic NSCLC, the checkpoint inhibitor, pembrolizumab, was compared with placebo (in addition to standard chemotherapy).[70] The median survival in pembrolizumab recipients was 22 (95% CI: 20-25) months vs 11 (95% CI: 9-14) months in the chemotherapy-only arm. Nearly 1 in 3 patients treated with pembrolizumab was alive at 5 years.
	Progression after chemotherapy	In a trial including patients with metastatic NSCLC with progression after first-line platinum-based chemotherapy, the median survival rates were 8 to 11 months.[71] In a randomized trial of crizotinib vs second-line chemotherapy, the respective median survival rates were 20 and 23 months.[72]
Colorectal	Use of biologic-targeted therapies	Among patients with metastatic colorectal cancer treated with FOLFIRI and randomized to receive cetuximab or bevacizumab, the median survival rates were 29 (95% CI: 24-37) months and 25 (95% CI: 23-28) months, respectively.[73] In another similar trial, the respective median survival rates were 30 and 29 months.[74]
	Need for second- or third-line therapy	Among those requiring second-line therapy, survival rates of 10 to 14 months have been reported.[75] The survival rates among those receiving third-line therapy are poor from 5 to 9 months.[76]
Prostate	Hormone-sensitive metastatic disease	Among men with metastatic prostate cancer who had received ADT for up to 12 weeks, the addition of the androgen receptor inhibitor enzalutamide led to an 80% 3-year survival (vs 72% 3-year survival in the control arm of this randomized trial).[77]
	Castrate-resistant disease	Outcomes are worse when the cancer acquires mutations enabling androgen-independent growth (metastatic castrate-resistant prostate cancer). In a randomized trial of enzalutamide among men with progressive metastatic prostate cancer despite castrate testosterone levels, 82% of enzalutamide recipients were alive at 18 months (vs 73% in the placebo group in which the median survival was 31 months).[78]
	Progression despite addition of androgen receptor signaling inhibitor	In a randomized trial among men with metastatic castrate-resistant prostate cancer with progression despite a new hormonal agent, the PARP inhibitor olaparib led to an improved median survival of 19 months compared with control (median survival 15 months).[79]
Breast	Survival with hormone receptor–positive vs –negative disease	In patients with advanced breast cancer, between 1990 and 2010, median survival increased from 21 (95% CI: 18-25) months to 38 (95% CI: 31-47) months.[64] Among those with estrogen receptor–positive vs –negative disease, survival rates increased from 32 (95% CI: 23-43) months to 57 (95% CI: 37-87) months and from 14 (95% CI: 11-19) months to 33 (95% CI: 21-51) months, respectively, during this time.
	CDK4/6 inhibitor addition to endocrine therapy for hormone receptor–positive disease	Among women with HR+/HER2-negative advanced breast cancer, the addition of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors to an endocrine therapy (eg, aromatase inhibitor or fulvestrant) backbone has led to significant improvements in progression-free (20-24 months) and overall survival (up to 64 months). In the MONALEESA-3 (Study of Efficacy and Safety of LEE011 in Men and Postmenopausal Women With Advanced Breast Cancer) trial, patients with HR+/HER2-negative advanced breast cancer receiving ribociclib and fulvestrant had a median overall survival of 54 months.[80]
	Progression despite CDK4/6 inhibition in hormone receptor–positive disease	Breast cancer progression despite CDK4/6 inhibition and in the absence of an actionable mutation (eg, PIK3CA) portends a poor prognosis, with survival rates generally <1 year.[81,82] Patients with endocrine-resistant advanced breast cancer have traditionally been offered single-agent systemic chemotherapy (eg, paclitaxel). There is an emerging role for antibody drug conjugates for patients with HR+/HER2 low (1+, 2+ ISH negative) advanced breast cancer who have endocrine-resistant disease and have progressed on at least 1 line of systemic chemotherapy (eg, T-DM1 is associated with a median survival of 24 months).[83]
	HER2-positive disease	In patients with advanced HER2-positive breast cancer, the traditional approach in the first-line setting has been dual HER2 blockade using trastuzumab and pertuzumab with a taxane with a median survival of 57 (95% CI: 50-72) months.[84]
	Progression despite trastuzumab and pertuzumab for HER2-positive disease	May be treated with T-DM1 with a median overall survival of 30 (95% CI: 26-34) months.[85] In a recent trial, trastuzumab-deruxtecan demonstrated superior progression-free survival (median 25 months) compared with T-DM1 (median 7 months) in the second-line setting.[86]
	Advanced triple-negative disease	Among patients with advanced triple-negative breast cancer, 20% to 40% will overexpress PD-L1.[87] In the KEYNOTE-355 trial, patients with advanced triple-negative breast cancer (first-line setting) who were strongly positive for PD-L1 were randomized to chemotherapy with the immune checkpoint inhibitor pembrolizumab or chemotherapy alone.[88] In the pembrolizumab group, the median overall survival was 23 months among pembrolizumab recipients vs 16 months among controls (HR: 0.73; 95% CI: 0.55-0.95).
	Advanced triple-negative disease not overexpressing PD-L1	Poor prognosis with median survival times of approximately 18 months[89]

Continued on the next page

TABLE 3 Continued

Cancer	Milestone	Selected Data to Exemplify Contemporary Prognosis
Acute myeloid leukemia	Following allogeneic SCT	Those undergoing SCT following complete remission have 3-year survival rates varying from 29% to 71% depending on their hemopoietic SCT comorbidity index.[90]
	Not undergoing allogeneic stem cell transplantation	In a study of adults <50 years of age who achieved a first complete remission and did not receive an allogeneic SCT who then relapsed but achieved a second complete remission, the 5-year survival rate was 34%.[91]
	Primary refractory disease or early relapse	Patients with primary refractory disease or with early relapse generally survive <1 year.[92]
	Not candidate for intensive chemotherapy	Survival is generally also <1 year in patients not considered candidates for intensive chemotherapy.[93]
Multiple myeloma	Autologous SCT	In 1 study of 494 patients undergoing autologous SCT within 12 months of myeloma diagnosis, those who relapsed within 12 months of the transplant had a median survival of 27 months, whereas those who relapsed >12 months after transplantation (or did not relapse at last follow-up) had a median survival of 91 months.[94]
	Refractory disease	Triple class refractory patients have a median survival of 8.6 months[95]; however, outcomes are expected to improve in the future with an increasing number of therapeutic options in this space including bispecific antibodies and 2 recent U.S. Food and Drug Administration–approved chimeric antigen receptor T-cell therapies.

ADT = androgen deprivation therapy; FOLFIRI = leucovorin, folinic acid, 5-fluoro-uracil and irinotecan; PARP = poly(adenosine diphosphate-ribose); PD-L1 = programmed death-ligand; SCT = stem cell transplantation; T-DM1 = trastuzumab emtansine; other abbreviations as in Table 2.

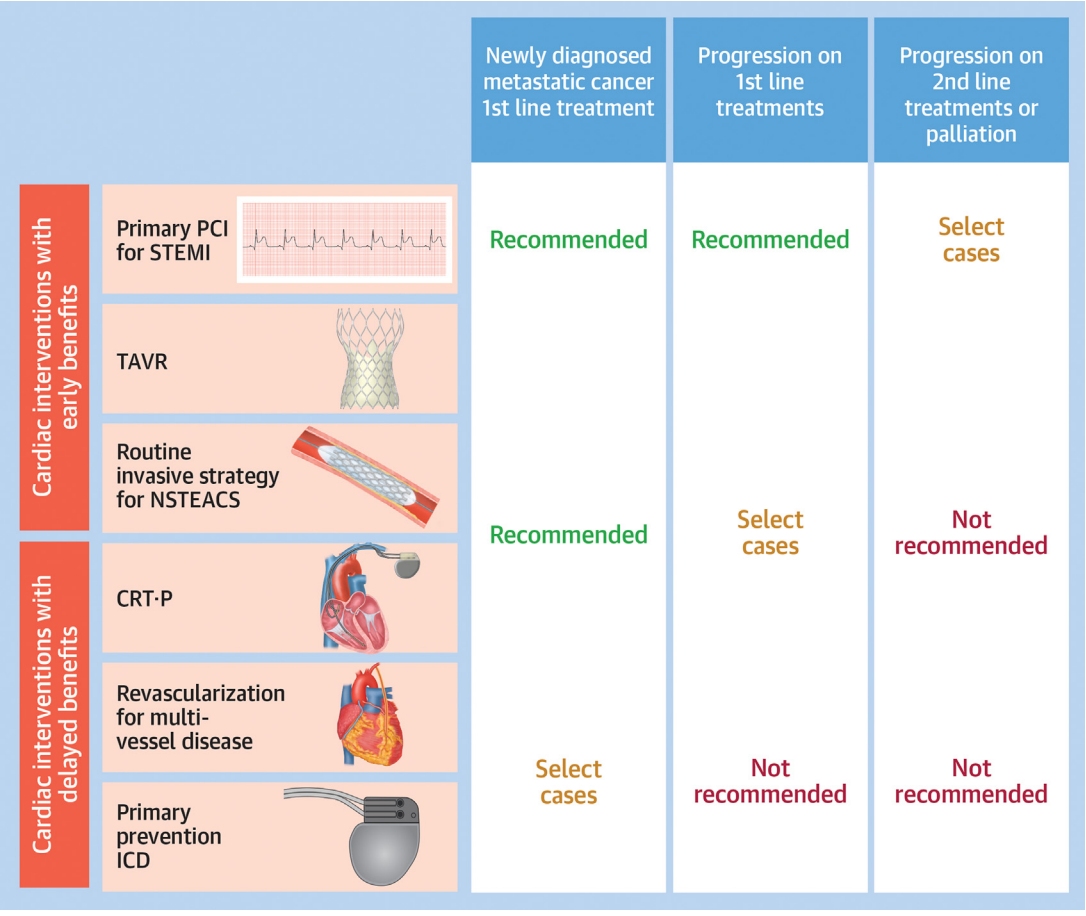
implemented and the pace of cancer research accelerates, there is a need for real-time cancer survival data to inform management recommendations, and cardiologists must be aware of these innovations when evaluating the risks and benefits of an invasive cardiac intervention. Although a detailed description of the prognosis for all cancers and stages is not feasible in any single publication, highlighting major therapeutic accomplishments for several of the most common malignancies can increase awareness that in many cases, active, advanced cancer is now a chronic disease. Select prognostic landmarks for these most common cancers are provided in Table 3 and are also described in the following paragraphs.

Increasing life expectancy in individuals with non-small cell lung cancer (NSCLC) may make cardiovascular disease an important health determinant in these patients. Cardiac disease affects 1 in 3 patients with lung cancer, likely because of shared risk factors, especially smoking.[59] Given the evolution in NSCLC treatment and prognosis and the high risk of coronary artery disease in this population, primary PCI is generally indicated in those with advanced NSCLC. In patients on first-line therapy for advanced NSCLC with an actionable driver mutation, an early invasive approach should be pursued in patients following NSTEACS and when TAVR or CRT are indicated. Primary prevention ICD and CABG for multivessel disease are less likely to offer substantial benefits in most patients with advanced NSCLC.

Initially, most patients with advanced prostate cancer have hormone-sensitive disease, which responds to androgen deprivation therapy (ADT). The development of newer inhibitors of androgen receptor signaling, which work downstream to the testosterone-suppressing effects of ADT, has led to further improvements in the survival of patients with metastatic prostate cancer. Hormonal therapies for prostate cancer can increase cardiovascular risk factors,[60] which are common in men with prostate cancer[61] and are frequently poorly controlled.[62] Consequently, those with metastatic prostate cancer have a 50% higher risk of cardiac death than similar-aged men without prostate cancer.[63] With the effective and growing number of therapies for metastatic prostate cancer, invasive approaches should be implemented in those with hormone-sensitive disease and STEMI, NSTEACS, severe symptomatic aortic stenosis, and when an ICD or CRT are indicated. Primary PCI and TAVR are also appropriate for those on androgen receptor signaling inhibitors for castrate-resistant disease, whereas invasive approaches to NSTEACS and CRT can be considered in these individuals.

Survival for individuals with advanced breast cancer is also improving.[64] Improved survival with advanced breast cancer is due at least in part to the development of treatments that target hormone receptor-positive and/or human epidermal growth factor receptor-2 (HER2)-positive disease. Compared with women without breast cancer, the risk of cardiovascular death in women with early-stage breast cancer is increased starting 7 years after diagnosis.[65] This is mostly related to the risk of heart failure caused by anthracycline and/or HER2-targeted therapies.[66] However, comorbidities, such as

CENTRAL ILLUSTRATION **The Continuum in Decision Making for the Role of Invasive Cardiac Intervention in Active, Advanced Cancers**



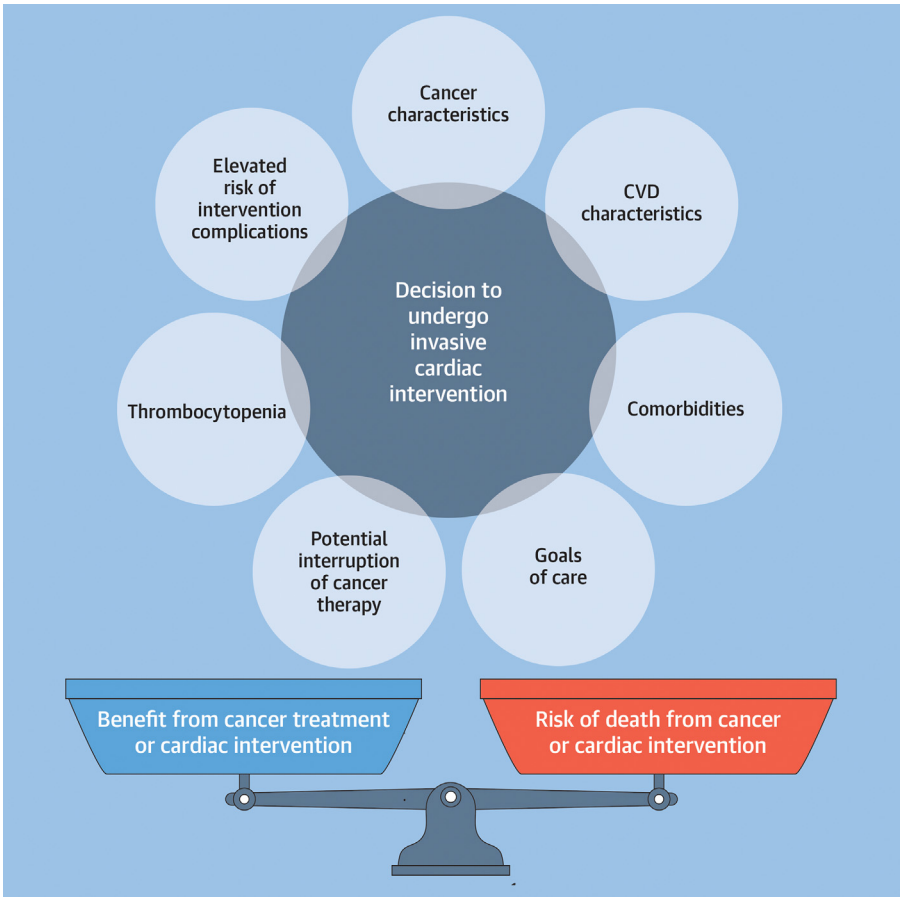
Leong DP, et al. J Am Coll Cardiol CardioOnc. 2023;5(4):415–430.

There is a continuum in the decision making with respect to the role of interventions in patients with advanced cancers. Cardiac interventions with earlier or larger benefits should be implemented in most patients, and interventions with delayed or modest benefit should only be offered in select cases. Recommended indicates that the intervention is advisable for most of the given cancer cases. Select cases indicates that the decision to offer the intervention needs to be highly individualized for the given cancer cases. Not recommended indicates that the intervention is generally not advisable for the given cancer cases. In all instances, individual circumstances need to be incorporated into the decision-making process as the evidence to guide these recommendations is limited. CRT-P = cardiac resynchronization therapy-pacemaker; ICD = implantable cardioverter-defibrillator; NSTEACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TAVR = transcatheter aortic valve replacement.

hypertension, diabetes, and dyslipidemia, are also likely to play a role in the risk of patients experiencing a cardiac event.[67] In the absence of strong data, CRT to treat symptoms of heart failure with reduced ejection fraction is reasonable in patients undergoing first-line therapy for advanced breast cancer who have a widened QRS complex. An ICD for the primary prevention of cardiac death can also be considered in select individuals undergoing first-line therapy, especially in the presence of a targetable cancer phenotype (hormone receptor + or HER2+). Percutaneous coronary and structural cardiac interventions are also appropriate in patients undergoing first-line therapy.

An exhaustive summary of the advances in and prognosis with all advanced cancers is beyond the

FIGURE 1 Factors Influencing the Decision to Undertake Invasive Cardiac Interventions



Decision making should incorporate information on the cancer and cardiovascular disease (CVD), comorbidities, patient goals of care, interruption of cancer therapies, thrombocytopenia, and the elevated risk of procedural complications.

scope of this paper. However, a rational approach to an invasive cardiac intervention depends on the likelihood that the intervention will be beneficial within the specific context of a patient's prognosis. Interventions with greater impact, such as primary PCI for STEMI, are more likely to help patients with advanced cancer (**Central Illustration**). Interventions whose benefits are realized after a longer lag or where there are good, less invasive alternatives might be unattractive in patients with active, advanced cancers and a life expectancy <2 years.

The notion of cancer cure needs to be contextualized. Although some malignancies are technically incurable, under certain circumstances, survival can be lengthy. For example, some patients with transplant-eligible multiple myeloma can survive over 10 years after their diagnosis. Thresholds where the benefit of an invasive intervention is likely to outweigh the risks also vary with cancer aggressiveness, the number of treatment lines the patient has been exposed to, and the duration of response to prior treatments.

Important considerations before invasive cardiac interventions in patients with active advanced malignancies (**Figure 1**) include the following: 1) minimal interruption to ongoing cancer treatment; 2) defining goals of care (quality of life vs life expectancy); 3) increased risk of thrombocytopenia; and 4) higher risk of complications such as bleeding observed after PCI (Supplemental Table 1).

There is increasing recognition of the importance of multimorbidity and physical frailty as prognostic factors in patients with active, advanced cancers and in patients with severe cardiovascular disease.[68]

Although outside the scope of this paper to review in detail, these patient characteristics should be considered when evaluating the risks and benefits of invasive cardiac interventions.

A treatment's effect on quality of life and patient goals of care are important factors when considering recommendations on invasive cardiac interventions. Decision making should be shared among the health care team, the patient, and the caregivers. ICDs for the primary prevention of cardiac death may lead to a modest absolute reduction in the risk of sudden death, but, importantly, they are unlikely to improve quality of life. Therefore, unless cancer survival expectations are prolonged (eg, newly diagnosed metastatic prostate cancer) and patients are highly motivated to avoid sudden cardiac death (accepting that the risk of eventual death from metastatic cancer may then be higher), primary prevention ICDs cannot be recommended in patients with active, advanced cancer.

CONCLUSIONS

Patients with advanced cardiac conditions and cancers should be involved in shared decision making with their health care team (eg, cardiologist/oncologist) when considering the role of invasive cardiac interventions. There is limited evidence on the benefits of invasive cardiac procedures in patients with advanced cancers. Health care providers must provide patients with a synthesis of contemporary data focused on cancer survival and the magnitude and time course of benefit from cardiac interventions. More research is needed to provide stakeholders with direct evidence to inform decision making on invasive cardiac interventions in patients with active, advanced cancers.

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KEY WORDS **cancer, cardio-oncology, dual antiplatelet therapy, implantable cardioverter-defibrillator, revascularization, survivorship**

APPENDIX **For a supplemental appendix and table, please see the online version of this paper.**