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Fahad Waqar
Department of Cardiovascular Analytics Group, Islamabad, Pakistan

Ayesha Sultan
Department of Cardiovascular Analytics Group, Islamabad, Pakistan

Romeet Raja Bathija
Department of Cardiovascular Analytics Group, Islamabad, Pakistan

Amin Mehmoodi
Department of Medicine, Ibn e Seena Hospital, Kabul, Afghanistan, amin.doctor21@gmail.com

Jahanzeb Malik
Department of Cardiovascular Analytics Group, Islamabad, Pakistan

REVIEW ARTICLE

Cardiovascular Interventions in Patients With Active and Advanced Malignancy: An Updated Review

Fahad Waqar [a], Ayesha Sultan [a], Romeet R. Bathija [a], Amin Mehmoodi [b,*], Jahanzeb Malik [a]

[a] Department of Cardiovascular Analytics Group, Islamabad, Pakistan
[b] Department of Medicine, Ibn e Seena Hospital, Kabul, Afghanistan

Abstract

In the context of active, advanced malignancies, the recommendation for invasive cardiac interventions is grounded primarily in evidence from trials focused on specific cardiovascular conditions. However, the inclusion of individuals with advanced malignancies in these trials has historically been limited, and the intricate interplay between cancer and cardiovascular disease poses unique challenges for treatment decisions. In this comprehensive review, we delve into the complex landscape of invasive cardiac interventions and their applicability in patients with active, advanced cancer. Our analysis encompasses a range of cardiovascular scenarios, including ST-segment elevation myocardial infarction, non−ST-segment elevation acute coronary syndromes, multivessel coronary disease, severe symptomatic aortic stenosis, and cardiomyopathy. We critically examine the available data and evidence, shedding light on the benefits and potential risks associated with invasive cardiac procedures in the presence of advanced malignancies. Acknowledging the competing risk of mortality posed by advanced cancers, we delve into the contemporary survival expectations for patients across various types of active, advanced malignancies. By synthesizing current literature and exploring cardiovascular interventions within these populations, we aim to establish a well-informed framework. Our ultimate goal is to provide clinicians with a rational guide for making nuanced clinical recommendations regarding the utilization of invasive cardiac interventions in the challenging context of active, advanced cancer.

Keywords: Invasive cardiac interventions, Active advanced malignancies, Cardiovascular disease, Survival expectations, Shared decision-making

1. Introduction

In the realm of medical interventions for individuals facing complex health challenges, invasive cardiac procedures have shown their potential to reduce both the risk of mortality and the burden of illness in carefully selected patients.[1] These procedures have particularly proven beneficial for those experiencing acute coronary syndromes, severe valvular disease, heart failure, and ventricular arrhythmias.[2] Nonetheless, it is important to note that the success of these interventions has largely been established through randomized trials that have excluded patients grappling with active, advanced malignancies − such as those with ongoing treatments for advanced solid organ cancers or incurable hematologic neoplasms with a guarded prognosis.[3] This exclusion of individuals with such complex medical conditions has resulted in a dearth of direct clinical trial data that can guide decision-making regarding the potential risks and benefits of invasive cardiovascular procedures for this specific patient population.[4] Concurrently, the field of cancer therapy has witnessed revolutionary developments, with the emergence of targeted biological therapies and immunologic treatments.[5] These groundbreaking advancements have translated into substantial improvements in survival rates for many patients contending with advanced cancers. As these precise and personalized cancer treatments continue to evolve, not only has event-free survival increased, but overall survival as well.[6] However, this progress has introduced a new set of challenges − individuals are now at an elevated risk

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* Corresponding author.
E-mail address: amin.doctor21@gmail.com (A. Mehmoodi).

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of experiencing adverse cardiovascular outcomes, both as a consequence of cancer therapy-related cardiovascular toxicity and unrelated cardiac issues.[7] Given this complex landscape, healthcare providers have been hesitant to refer patients with active, advanced cancer for invasive cardiac procedures. The prevailing concern has been that the patient's life might be cut short by cancer before any potential benefit from the cardiac intervention can be realized. Nevertheless, the increasing life expectancy of many patients with advanced cancer has begun to challenge this previously held notion.[8] In light of the limited availability of clinical trial data on invasive cardiac interventions for patients dealing with active, advanced cancer, an evidence-based approach to decision-making necessitates a nuanced understanding of the patient's projected cancer-specific survival.[9] If the estimated duration of survival exceeds the time required to derive benefit from an invasive cardiac procedure, one could extrapolate that the individual is likely to gain advantages from the cardiac intervention.[10] With this goal in mind, our objective is to provide a comprehensive summary of the current body of evidence to facilitate informed decision-making for patients with common metastatic cancers or malignancies that carry a poor prognosis, but are also eligible for specialized cancer treatments. This comprehensive approach involves integrating the existing literature on invasive cardiac procedures in the general population with the specific context of cancer patients. A pivotal consideration when dealing with patients who have active, advanced cancer is the presence of competing risks, primarily the risk of succumbing to cancer before the potential benefits of a cardiac intervention can be realized.

2. Literature review

We identified invasive cardiac interventions that have received strong endorsements based on robust evidence from high-quality randomized, controlled trials. These endorsements stem from the clinical guidelines established by the American College of Cardiology for various cardiovascular conditions, including heart failure, coronary artery revascularization, valvular heart disease, and ventricular arrhythmias, along with the prevention of sudden cardiac death. Specifically, we focused on interventions that garnered a Class 1 recommendation, indicating a strong endorsement, and were supported by Level of Evidence: A, denoting high-quality evidence from at least one well-conducted randomized, controlled trial. These included scenarios such as ST-segment elevation myocardial infarction (STEMI) with or without multivessel coronary artery disease, non-ST-segment elevation acute coronary syndrome (NSTE-ACS), chronic coronary artery disease involving multiple vessels, severe aortic stenosis, and the utilization of an implantable cardioverter-defibrillator (ICD) for primary prevention against sudden cardiac death, as well as cardiac resynchronization therapy (CRT). In addition to relying on the Level of Evidence: A for substantiating these recommendations, we embarked on a supplementary literature review that specifically delved into the applications of coronary revascularization, transcatheter aortic valve replacement (TAVR), ICD usage, and CRT within the context of cancer populations. From the array of papers published over the years, we incorporated the most insightful findings in a narrative fashion.

3. Primary percutaneous coronary intervention in STEMI

When it comes to treating STEMI, recent studies have shown that primary percutaneous coronary intervention (PCI) has led to decreased in-hospital mortality rates from 10.8% to 7.7%.[11] This approach demonstrates improved odds of short-term survival compared to thrombolytic therapy.[12] Moreover, primary PCI has been associated with a reduced risk of reinfarction and stroke, offering patients better outcomes in terms of health.[13] Even if extending life isn't the primary focus, primary PCI can enhance the quality of life and alleviate symptoms, which is crucial from a patient-centered perspective.[14] Interestingly, individuals with cancer are more susceptible to ischemic heart disease than those without.[15] A distinct feature noted through optical coherence tomography is that patients with cancer experiencing a heart attack may display different plaque characteristics, particularly a higher occurrence of plaque erosion in the culprit lesion.[16,17] This has prompted speculation that cancer or its treatments might trigger biological changes that make individuals more prone to heart attacks. These effects are likely multifaceted and intricate, involving factors like inflammation and prothrombotic states related to cancer or its treatments, the lesser-known implications of clonal hematopoiesis of indeterminate potential, shared risk factors such as smoking, obesity, physical inactivity, and diabetes, as well as the impact of cancer therapies like fluoropyrimidines and radiotherapy on coronary arteries.[18] In the context of patients who have active, advanced cancer and are primarily hospitalized due to STEMI, data suggests that in-hospital mortality is lower among those who undergo PCI

compared to those who do not.[19] Although there might be a degree of selection bias in these observations, it implies that if extending life aligns with a patient's healthcare goals, primary PCI should be seriously considered, especially if it can be conducted promptly. Nonetheless, the available information regarding the impact of primary PCI on the quality of life in patients with active, advanced cancer is limited. Additionally, observational studies that explore the benefits of primary PCI within this patient group might be compromised by selection bias, as patients with advanced cancer might not have been offered coronary angiography due to incongruence with their care goals or perceived clinical futility. In cases of STEMI where primary PCI is performed on the main artery responsible for the STEMI, subsequent PCI procedures targeting other affected arteries have demonstrated reductions in cardiovascular death and recurrent heart attacks.[20] This approach has also led to an improvement in the quality of life concerning angina-related symptoms over a median follow-up period of 3 years. Fig. 1 shows specific considerations when undertaking invasive procedures in patients with active cancer.

4. Strategy for NSTE-ACS

The guidelines for managing patients with Non-ST Segment Elevation Acute Coronary Syndrome (NSTE-ACS) recommend a routine invasive strategy to proceed to revascularization.[21] This approach has been supported by a meta-analysis of randomized trials that compared routine invasive strategies with selective invasive strategies.[22] The analysis demonstrated a reduction in nonfatal outcomes among patients with NSTE-ACS. Over a follow-up period of 6–24 months, there was a decrease in the combined rate of death or myocardial infarction in the routine invasive group compared to the selective invasive group. This reduction was primarily driven by a decrease in the incidence of myocardial infarction. However, there was no significant reduction in mortality. The routine invasive approach also led to fewer instances of rehospitalization and moderate to severe angina. Regarding the timing of intervention, two large randomized trials showed similar outcomes for patients undergoing cardiac catheterization either early (within 24 h) or later (24–72 h) after NSTE-ACS onset.[23–25] If PCI is performed, a radial approach (through the wrist) is preferable based on a patient-level meta-analysis of randomized trials comparing radial versus femoral (through the groin) access for coronary angiography.[26] The radial approach was associated with reduced mortality and major bleeding, which is particularly relevant for patients with cancer who are at a higher risk of bleeding complications. Following PCI for NSTE-ACS, dual antiplatelet therapy is typically recommended for at least 12 months.[27] However, in patients with active, advanced cancer, the decision to undergo routine cardiac catheterization should be carefully

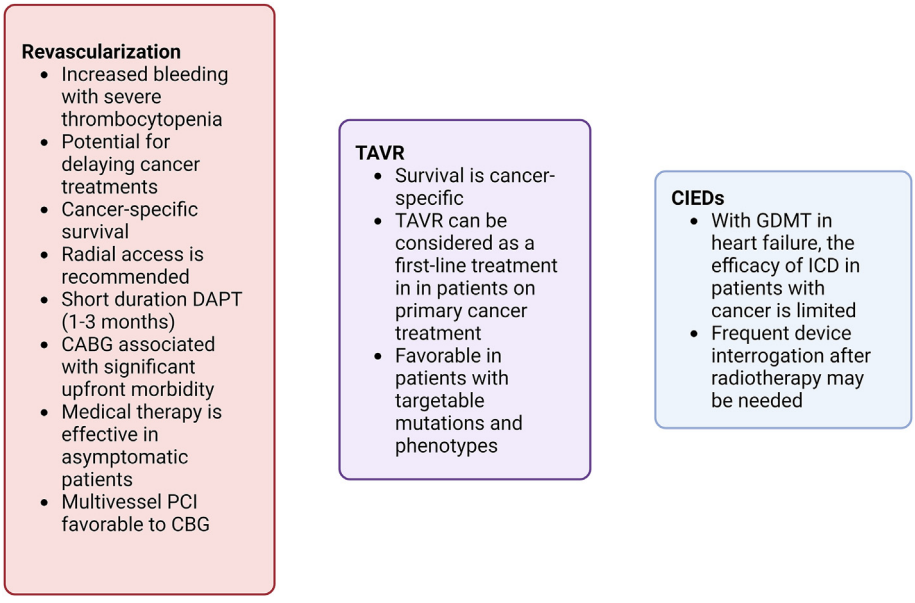

Fig. 1. Specific considerations for invasive procedures in cancer. Legend: DAPT (dual antiplatelet); CABG (coronary artery bypass graft); PCI (percutaneous coronary intervention); TAVR (transcutaneous aortic valve replacement); GDMT (guideline directed medical therapy); ICD (implantable cardioverter defibrillator).

considered, especially if these treatments are not aligned with the patient's overall goals of care. The available research on managing patients with cancer and NSTE-ACS largely comes from single-center retrospective studies or analyses of administrative databases.[28] These studies have limitations, such as limited information on cancer stage and treatments, potentially biased patient selection for cardiac catheterization, and methodological challenges.

5. Multivessel or left main coronary artery disease

Patients who have cancer often undergo diagnostic or staging imaging, which can incidentally reveal vascular issues like coronary artery disease due to the discovery of vascular calcification. When dealing with left main stenosis, revascularization might be considered either to alleviate angina symptoms or to enhance prognosis.[29] In cases where the coronary anatomy is suitable, percutaneous revascularization for left main stenosis could be a viable option.[30] It has been found to have comparable mortality rates to coronary artery bypass graft (CABG) surgery but without the upfront complexities associated with a sternotomy.[31] For individuals with stable multivessel coronary disease, revascularization might not necessarily reduce the risk of death or heart attack when combined with optimal medical therapy.[32] However, it can alleviate angina symptoms in those with stable coronary artery disease and inducible myocardial ischemia. Therefore, for patients who have active and advanced cancer and asymptomatic coronary artery disease, focusing on optimal medical therapy might be appropriate.[33] On the other hand, those with symptomatic multivessel coronary disease could potentially benefit from coronary revascularization. When considering a revascularization strategy, the decision between a PCI and CABG needs careful evaluation. A pooled analysis of data from 12 randomized trials comparing CABG with PCI in non-acute myocardial infarction patients showed similar 30-day mortality rates for both approaches.[34] However, at the 5-year follow-up, patients who underwent CABG had better survival rates compared to PCI. This difference was particularly notable for patients with diabetes, where CABG demonstrated better outcomes.[35] For patients with active, advanced cancer and multivessel coronary disease, especially those with diabetes, CABG might be a consideration if there's a reasonable expectation of 5-year survival. It's important to balance the modest long-term benefits of CABG against the greater immediate morbidity associated with the procedure. Some patients with incurable cancers might be hesitant to undergo CABG due to the upfront challenges it presents, such as the sternotomy, which could disrupt their cancer treatment plans. Managing multivessel or left main coronary disease in patients with active, advanced malignancies necessitates a comprehensive, patient-centered approach.[1] This involves collaboration among various specialists, including interventional cardiologists, cardiac surgeons, and oncologists/hematologists, often under the umbrella of cardio-oncology. When making recommendations, factors such as the patient's cancer prognosis, past and potential future cancer treatments, symptoms, preferences, and the technical feasibility of different revascularization approaches should all be taken into account. In instances where surgical risk is deemed high, PCI might be a viable alternative, potentially offering improved health status without excessive risk.[36]

6. Antiplatelet therapy

Following an episode of acute coronary syndrome, medical guidelines recommend the continuation of DAPT for at least 12 months.[37] However, the approach is flexible, as transitioning to P2Y12 inhibitor monotherapy might be acceptable after 1–3 months of DAPT.[38] This transition could be especially relevant if there's a high risk of bleeding or if active bleeding is already present. While current meta-analyses suggest that discontinuing DAPT early might not increase the risk of ischemic events, these findings could be limited by their statistical power.[39] Nevertheless, the balance of benefits and risks in this population leans toward monotherapy, considering the potential for bleeding complications. Patients with advanced cancer undergoing PCI are likely to face higher bleeding rates due to bleeding from tumors themselves or thrombocytopenia, which can be caused by various factors related to cancer and its treatments. For instance, chemotherapy recipients might experience thrombocytopenia, with varying severity depending on the specific treatment.[40] Additionally, thrombocytopenia is often observed following hematopoietic stem cell transplantation. In cases of hyperproliferative thrombocytopenia, platelet counts below certain thresholds are associated with an increased risk of bleeding.[41] On the other hand, cancer itself can create a prothrombotic state, potentially leading to an elevated risk of stent thrombosis after PCI.[42] Consequently, a personalized approach to antiplatelet therapy becomes essential for these patients. The available evidence guiding the use of antiplatelet regimens in patients with both acute

coronary syndrome and thrombocytopenia is limited.[43] Recent studies, such as the MASTER DAPT trial, have taken a unique approach by including patients with specific platelet count levels and cancer types associated with high bleeding risk.[44] This trial explored the feasibility of abbreviated antiplatelet therapy and found that stopping DAPT and continuing with antiplatelet monotherapy might not increase the risk of adverse cardiac or cerebral events. Instead, it led to lower rates of clinically significant bleeding. To address concerns about potential ischemic events following early reduction of antiplatelet therapy intensity after complex PCI procedures, a pooled analysis of multiple trials revealed that P2Y12 inhibitor monotherapy after 1−3 months had comparable mortality and ischemic event rates as standard DAPT. In terms of specific platelet count thresholds, experts recommend aspirin for platelet counts above 10,000/mm^3, clopidogrel monotherapy for counts above 30,000/mm^3, and more potent DAPT with prasugrel or ticagrelor for counts above 50,000/mm^3.[45] However, these recommendations lack concrete evidence, and alternative thresholds have been suggested by other experts. For instance, clopidogrel monotherapy might be considered for platelet counts between 50,000/mm^3 and 100,000/mm^3.[46]

7. Aortic stenosis

Transcatheter Aortic Valve Replacement (TAVR) has emerged as an effective intervention for individuals with severe symptomatic aortic stenosis, particularly for those who are considered unsuitable candidates for surgical aortic valve replacement due to high surgical risk or comorbidities.[47] A significant trial has demonstrated the benefits of TAVR over standard care in such patients.[48] In this landmark trial, patients with severe symptomatic aortic stenosis were randomized to receive either TAVR or standard care when surgical valve replacement was deemed unsuitable due to a high predicted probability of death at 30 days or serious irreversible conditions. The results indicated that TAVR led to a reduction in mortality, with a hazard ratio (HR) of 0.55 and a 95% confidence interval (CI) of 0.40−0.74. Moreover, the combined outcome of death or hospitalization was also favorably impacted by TAVR, as evidenced by an HR of 0.46 (95% CI: 0.35−0.59). Importantly, at the 12-month mark, a higher proportion of surviving patients who underwent TAVR showed improvement in heart failure symptoms or were asymptomatic when compared to those receiving standard care. The trial's findings hold significant implications for patients with active and advanced malignancies who suffer from severe symptomatic aortic stenosis. It suggests that those who have both conditions, particularly if their expected noncardiac survival is greater than 12 months, are likely to benefit from TAVR.[49] This information guides clinical decision-making in these complex cases. However, studies exploring TAVR in patients with cancer have yielded mixed results.[50,51] Some of these investigations have indicated higher mortality rates among individuals with cancer who underwent TAVR, as opposed to those without cancer.

8. Clinical implications

Like the transformation seen in the management of human immunodeficiency virus (HIV), where what was once a fatal disease has now become a chronic condition with multiple treatment options and extended survival, the strategies for managing individuals with active, advanced malignancies have also evolved over the past few decades.[52] This shift in cancer management has led to increased survival rates, prompting a re-evaluation of how cardiovascular disease is addressed in this population. It's crucial to acknowledge that cancer survival rates have progressively improved, necessitating a reconsideration of the management of cardiovascular issues, which could potentially become a significant cause of morbidity and mortality among these patients. As new paradigms for cancer treatment, such as targeted molecular therapies and immunotherapies, emerge and demonstrate efficacy in reducing mortality, it becomes essential to incorporate real-time cancer survival data into management decisions.[53] Cardiologists need to stay informed about these advancements as they assess the risks and benefits of invasive cardiac interventions. While providing an exhaustive summary of prognosis and improvements in all types of advanced cancers isn't feasible, some common malignancies illustrate the changing landscape. In non-small cell lung cancer (NSCLC), increasing life expectancy among patients may make cardiovascular disease a significant concern due to shared risk factors, notably smoking.[54] As NSCLC treatment and prognosis evolve, primary PCI is generally recommended for those with advanced NSCLC. Hormone-sensitive disease in advanced prostate cancer responds to androgen deprivation therapy (ADT), and newer inhibitors have improved survival.[55] However, hormonal therapies can increase cardiovascular risk factors, emphasizing the importance of implementing invasive approaches in eligible individuals with metastatic prostate cancer. Survival rates are also improving for advanced

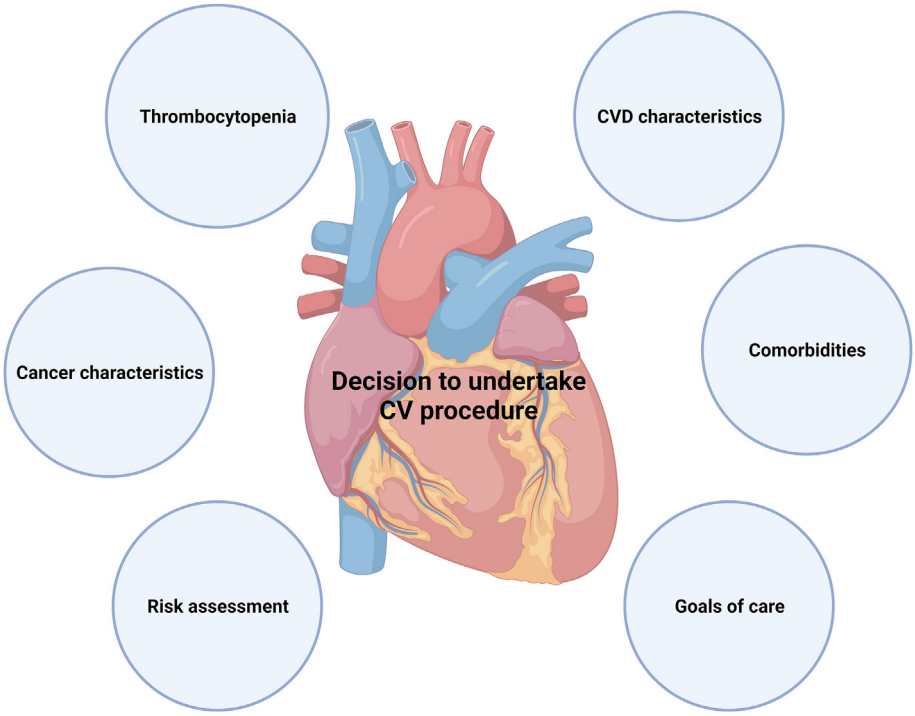

Fig. 2. Factors influencing the decision for invasive procedures in cancer.

breast cancer due to targeted therapies. However, these therapies, along with anthracycline-based treatments, may elevate cardiovascular risk. Cardiac interventions like CRT and PCI are suitable for some breast cancer patients.[56] The appropriateness of an invasive cardiac intervention depends on the patient's prognosis. Interventions with immediate impact, like primary PCI for STEMI, are more likely to benefit patients with advanced cancer.[57] Fig. 2 shows the decision of risks and benefits of invasive CV procedures in patients with cancer.

9. Conclusion

In conclusion, patients who find themselves facing the dual challenges of advanced cardiac conditions and active cancers should be active participants in shared decision-making processes with their healthcare teams, including both cardiologists and oncologists. While the evidence regarding the benefits of invasive cardiac procedures in individuals with advanced cancers remains limited, the importance of informed decision-making cannot be overstated. Healthcare providers have a crucial role in presenting patients with a comprehensive overview of contemporary data, focusing on factors such as cancer survival rates and the potential impact and timing of benefits from invasive cardiac interventions. The synthesis of this information empowers patients to make well-informed choices that align with their individual circumstances, preferences, and treatment goals.

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Conflict of interest

The authors declare no conflict of interest.

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