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Role of palliative radiotherapy in cardiac metastasis: A review

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Abstract

Cardiac metastasis (CM) is a rare but clinically significant manifestation of advanced cancer, occurring when malignant cells originating from a primary tumor in a distant organ infiltrate and colonize the heart. This condition presents unique challenges in both diagnosis and treatment, often necessitating a multidisciplinary approach involving cardiology, oncology, and surgical teams. Understanding the mechanisms, clinical presentation, and management of CM is vital for health-care professionals to provide effective care and improve the quality of life for patients facing this challenging condition. Radiotherapy can be utilized as a primary treatment option for localized cardiac metastases or as part of a multimodal approach, often combined with surgery, chemotherapy, or other systemic therapies. In this review, we delve into the intricacies of CM, from its underlying causes to its clinical implications, and discuss the role of radiotherapy as a therapeutic option.

Keywords: Cardiac metastasis; Radiotherapy in heart; Palliative radiotherapy

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1. Introduction

Cardiac metastasis (CM) refers to the dissemination of cancer cells originating from a primary tumor located elsewhere in the body to the heart.[1] These metastatic cancer cells infiltrate and establish themselves within the heart, typically forming tumor growths or nodules. Although CM represents a secondary involvement of the heart by cancer, it can impair cardiac function and potentially lead to severe cardiovascular complications.[2] This condition, indicative of advanced cancer, is relatively rare compared to other sites of metastasis.[3]

Metastatic cardiac tumors, which affect the myocardium and pericardium, are infrequently encountered, with reported incidence rates in the range from 1.5% to 20% in autopsies conducted on cancer patients.[4] In general, CM occurs in approximately 10% of cases of non-cardiac malignancies. Among these cases, only 10% exhibit signs or symptoms of cardiac dysfunction unrelated to medical interventions. Consequently, clinically symptomatic cardiac involvement manifests in only around 1% of all malignancies.[5] While these metastatic lesions can potentially arise from a variety of malignant tumors, melanoma, lymphoma, and leukemia, as well as lung, breast, and esophageal carcinomas, are the primary culprits. It is noteworthy that the majority of secondary cardiac tumors (over 90%) typically remain asymptomatic, often evading clinical detection until after the patient's passing.[6]

The majority of CMs often remain clinically undetected, escaping notice until they have advanced to a stage where they significantly compromise cardiac function or are identified only during postmortem examinations.[7,8] Their presentation may include non-specific symptoms that can be challenging to differentiate from other cardiovascular disorders. For instance, right-sided obstructive tumors can lead to symptoms resembling right-sided heart failure, while left-sided obstructive tumors may result in pulmonary edema. In addition, myocardial metastasis can contribute to systolic dysfunction.[9] These metastatic lesions can also give rise to symptoms such as arrhythmias, chest pain, and, in severe cases, life-threatening conditions such as outflow obstruction and cardiac tamponade. Recognizing this condition is of paramount importance, as CMs can potentially cause disabling symptoms and even mortality if left untreated.[10]

2. Intricate pathways involved in the process of cardiac metastases

Various intricate pathways are involved in the process of CMs, which are discussed in detail as follows:

(i) Hematogenous spread: Cancer cells exploit the circulatory system to journey through the bloodstream, capitalizing on the heart's robust vascular supply for access. Metastasis through the bloodstream often leads to the development of secondary tumors within the myocardium or endocardium and is frequently associated with melanoma, lymphoma, and sarcoma.[7]

(ii) Lymphatic spread: Some malignant cells spread through the lymphatic vessels, possibly traversing regional lymph nodes to infiltrate the cardiac tissue. Dissemination through the lymphatic system commonly leads to the infiltration of tumors in the pericardium and epicardium, particularly observed in numerous epithelial tumors originating from the lung and breast.[11]

(iii) Direct extension: Neighboring tumors can directly encroach upon the heart or its protective pericardium, allowing cancer cells to breach these structures. Locally aggressive mediastinal and pleural tumors, such as mesothelioma, can directly invade the pericardial sac.[11]

(iv) Transvenous extension: Certain cancer types, such as renal or hepatic malignancies, utilize veins to ingress into the heart, frequently targeting the right atrium. Specific types of tumors, such as renal cell carcinoma and hepatocellular carcinoma, have the capability to spread into the inferior vena cava and advance into the right atrium through transvenous extension.[11]

(v) Implantation: Medical interventions bear the risk of inadvertently introducing primary tumor cells into the heart, leading to iatrogenic CMs.

Each of these avenues poses the potential for the formation of secondary cardiac tumors, imposing adverse effects on cardiac function and posing substantial risk for grave complications.

3. Pathways involved in CM

The diagnosis of CM can be diagnostically complex due to its widely variable clinical presentation, which may mimic primary endocardial tumors, vegetations, or organized thrombi, potentially leading to confusion during diagnosis.[12] Typically, diagnosis involves a combination of clinical evaluation, imaging studies, and histopathological analysis. An overview of the diagnostic process is discussed below:

(i) Clinical evaluation: Oncologists assess patients for symptoms suggestive of cardiac involvement, such as chest pain, shortness of breath, palpitations, or signs of heart failure. They also review the patient's medical history, including any previous cancer diagnoses and treatments.[13]

(ii) Imaging studies: Various imaging modalities are utilized to visualize cardiac structures and detect potential metastatic lesions:

- Echocardiography: Transthoracic echocardiography and transesophageal echocardiography can provide real-time images of the heart and its chambers, allowing for the detection of masses or abnormalities.[14]
- Computed tomography (CT) scan: Cardiac CT imaging provides detailed cross-sectional images of the heart and surrounding structures, aiding in the identification of masses, nodules, or infiltrative lesions.[15]
- Magnetic resonance imaging (MRI): Cardiac MRI offers high-resolution images of the heart, allowing for the visualization of both anatomical structures and tissue characteristics. The utilization of contrast-enhanced cardiac MRI is strongly advised for enhanced evaluation of cardiac masses, as it offers superior visualization of the pericardium, myocardial walls, and cardiac chambers, facilitating a more precise diagnosis.[16,17]
- Positron emission tomography-CT (PET-CT): PET-CT scans utilize a radioactive tracer to identify areas of increased metabolic activity, which may indicate the presence of cancerous lesions, including CMs.[18]

(iii) Biopsy: If imaging studies suggest the presence of CM, a biopsy may be performed to obtain tissue samples for histopathological analysis. This approach may involve minimally invasive techniques such as percutaneous biopsy guided by imaging modalities

such as CT or MRI, or it may require open surgical biopsy, depending on the location and accessibility of the suspected lesion.[19]

(iv) Additional evaluation: Depending on the primary cancer type and the extent of metastatic disease, additional tests such as blood tests, including tumor markers, and cardiac function assessments may be performed to evaluate overall health status and guide treatment planning.[16]

4. Treatment options

Despite notable advancements in treating metastatic malignancies, there is currently no established standard therapy for managing patients with CM. Due to the typically poor outcomes associated with widespread metastases, the decision on how and when to treat these patients remains a subject of debate. Treatment approaches often involve a combination of various options, including repeated palliative systemic treatments and, in rare instances, surgical removal.[20] Despite being linked to the terminal phase of a widespread disease, appropriate palliative care can significantly aid in symptom management, enhancing quality of life, averting further complications, and potentially extending survival in specific cases.

The approach to managing CMs is contingent upon the specific clinical presentation. In instances of cardiac tamponade, prompt intervention involves immediate pericardiocentesis. Ideally, this procedure is performed under fluoroscopy or echocardiography guidance. However, in situations of impending hemodynamic collapse, blind subxiphoid pericardiocentesis can be a life-saving intervention.[21]

Additional therapeutic strategies for managing malignant pericardial effusions encompass more definitive interventions. These strategies include subxiphoid or transthoracic pericardial windows and percutaneous tube pericardiostomy.[22] Arrhythmias induced by metastasis can occasionally be temporarily controlled through the administration of antiarrhythmic medications. In specific instances, radiofrequency ablation might also be considered as an option. However, managing arrhythmias becomes challenging when the conduction system is involved.[23]

Surgical resection is typically reserved for scenarios where the overall prognosis is favorable when complete removal is technically viable or in specific instances of intracardiac obstruction. Radiotherapy and chemotherapy can serve as valuable therapeutic modalities in managing select cases of CMs. Hence, it is crucial to engage a multidisciplinary team comprising various specialties in the assessment and treatment of patients diagnosed with CM.[24]

The utilization of palliative radiotherapy in managing these patients has been limited, primarily due to technical challenges that restrict the safe delivery of an effective radiation dose to the heart. In addition, concerns persist regarding the potential for radiation-induced toxicity.

Numerous case reports within the corpus of medical literature have meticulously detailed instances of CM. These reports serve as vital clinical annotations, highlighting the infrequent yet pivotal occurrences where cancers originating from various primary sites intricately disseminate and colonize the heart. The compilation of these clinical observations serves as a compendium, offering insights into the varied presentations, diagnostic challenges, and therapeutic dilemmas associated with CM. These reports stand as informative capsules, providing a clinical roadmap for navigating the intricacies of oncology, especially in understanding the nuanced impact of different cancers on the cardiac milieu.

In a seminal study conducted by Cham *et al.*[25] and published in *Radiology* in 1975, the impact of palliative radiotherapy on CM was investigated. This study focused on 38 cases involving patients with diverse primary cancers, all of whom received palliative radiotherapy. Notably, all the patients had advanced-stage metastatic disease, and a substantial proportion had previously undergone radiotherapy or chemotherapy. Although the sample size within each cancer subgroup was limited, efforts were made to establish potential correlations between the radiation dosage administered and treatment response. The findings from the study revealed intriguing outcomes across various cancer types. Among patients with breast cancer (16 individuals), 11 exhibited improvement, with response durations spanning from 2 to 36 months. In the subset of lung cancer patients (seven individuals), two showed improvement, with response durations ranging from 1 to 9 months. Remarkably, in patients with lymphoma and leukemia (seven individuals), six experienced improvements, with response durations lasting from 1 to 4 months.[25] This pivotal study by Cham *et al.*[25] laid the groundwork for subsequent investigations into the efficacy of radiotherapy for CM across different cancer types, serving as a catalyst for further research endeavors in this domain (Table 1).

5. Discussion

The incidence of CM fluctuates varies across various different autopsy series, showing with reported a range from 2.7% to 25% among individuals diagnosed with cancer.[36] CM ought to should be considered in a cancer patient with widespread disease if they present with abrupt and unexplained respiratory symptoms, chest pain,

Table 1. Compilation of various primaries with reported cardiac metastasis treated with palliative radiotherapy

Cancer type	Study	No. of cases	Prior RT	Dose	Response to RT
Lung adenocarcinoma	Lee *et al.*[26]	1	No	50 Gy/20 Fr	4 months
	Fotouhi Ghiam *et al.*[27]	2	No (1); Yes (1)	20 Gy/5 Fr; 6 Gy/1 Fr	3.5 months; died during treatment
	Jumeau *et al.*[28]	1	No	Cardiac SBRT 20 Gy single fraction followed by 66 Gy/33 Fr thoracic chemoradiation	Disease-free survival for 6 months
	Bonomo *et al.*[29]	8	No	SBRT 36 Gy/3 Fr	3 – 12 months
Sarcoma	Takenaka *et al.*[10]	9 (leiomyosarcoma [5], clear cell sarcoma [2], alveolar soft part sarcoma [1], undifferentiated pleomorphic sarcoma [1], alveolar rhabdomyosarcoma [1], synovial sarcoma [1])	No	-; 25 Gy/5 Fr; 45 Gy/15 Fr; 50 Gy/25 Fr; 60 Gy/30 Fr; immunotherapy; 60 Gy/30 Fr; 40 Gy/20 Fr; 32 Gy/16 Fr	-; 24 months; 13 months; 7 months; 18 months; 4 months; 8 months; 6 months; 5 months
	Fotouhi Ghiam *et al.*[27]	1	Yes (1)	50 Gy/25 Fr	7 months
	Bonomo *et al.*[29]	1	No	SBRT 36 Gy/3 Fr	3 – 12 months
Cervical Cancer	Lemus *et al.*[30]	2	Yes	28.8 Gy/16 Fr; 60 Gy/30 Fr	1 month; 7 months
Melanoma	Magnuson *et al.*[31]	1	No	45 Gy/25 Fr	6 months
	Balinski *et al.*[32]	23	No	5 patients received palliative RT (dose not specified)	10 months
Lymphoma	Fotouhi Ghiam *et al.*[27]	1	No	25 Gy/10 Fr	3 months
Rectal adenocarcinoma	Fotouhi Ghiam *et al.*[27]	2	No	20 Gy/5 Fr; 16 Gy/4 Fr	3 months; died during treatment
	Bonomo *et al.*[29]	5	No	SBRT 36 Gy/3 Fr	3 – 12 months
Esophageal cancer	Al-Mamgani *et al.*[4]	2	Yes	20 Gy/5 Fr	2.5 months
Thyroid cancer	Dasgupta *et al.*[33]	1	Yes	37.5 Gy/15 Fr	2 months
	Chen *et al.*[9]	2	no	35 Gy/10 Fr	4 months
Small cell carcinoma lung	Orcurto *et al.*[8]	1	No	60 Gy/30 Fr	Not reported
Renal cell carcinoma	Dhar *et al.*[34]	1	No	30 Gy/5 Fr	Stable disease for 2 months
Hepatocellular carcinoma	Aoki *et al.*[35]	1	No	June 2016 (30 Gy) and August 2017 (20 Gy)	42 months

Notes: Duration of response (from the completion of cardiac radiotherapy to cardiac tumor progression or death without tumor regrowth.
Abbreviations: C/T: Chemotherapy; Fr: Fraction; Gy: Gray; mo: Months; RT: Radiotherapy; SBRT: Stereotactic body radiation therapy.

tachycardia, arrhythmia, cardiomegaly, or signs indicative of heart failure. The tumors with the highest tendency of CM are melanoma, carcinomas of the breast and lung, and lymphoma.[37]

Cardiac radiotherapy is infrequently utilized in clinical practice, primarily due to the scarcity of clinically detectable cardiac tumors and concerns regarding potential radiation-induced toxicity to the heart.

However, many patients with CM may not be suitable candidates for surgery or chemotherapy due to factors such as unresectable tumors, compromised overall health, and the limited likelihood of a prompt and significant response from systemic therapy. Given these limitations and the potential effectiveness of radiotherapy across various tumor types, it becomes reasonable to consider palliative radiotherapy (RT) based on clinical and imaging findings, even without confirmed tissue diagnosis. Delaying palliative radiotherapy RT in severely symptomatic patients, either to obtain a tissue diagnosis for an undiagnosed primary tumor or to begin chemotherapy, could potentially deprive these individuals of an effective treatment that offers

symptom relief, with reported response rates reaching up to 60%.[7]

Indeed, several case reports and small case series have detailed diverse cardiac tumors, many of which exhibited symptomatic improvement or radiographic resolution subsequent to cardiac radiotherapy. While cardiac radiotherapy might not cure metastatic cancer, it has demonstrated advantageous effects concerning temporary local tumor control, alleviation of symptoms, and potential enhancement of quality of life quality.[38]

Radiotherapy targeting the thoracic region has been associated with various potential adverse effects on the heart, encompassing pericarditis, pericardial effusion, coronary artery disease, heart failure, arrhythmias, and valvular disease. The risk of these complications correlates with factors such as radiation dose, treatment duration, and the volume of tissue exposed to radiation. While most cardiovascular complications tend to manifest chronically, acute adverse effects of cardiac radiotherapy are relatively uncommon.[39] However, recent literature reports indicate that acute cardiac toxicities can emerge as early as 1 month after radiation exposure.[40,41]

Cuculich *et al*.[42] demonstrated the use of cardiac radiation for ventricular tachycardia ablation in five patients. Initially, observing there was an increase in ventricular tachycardia episodes, which subsequently became well controlled. Despite the potential for acute, subacute and chronic cardiac toxicities associated with radiation exposure in emergent situations, emergent radiotherapy remains reasonable, justified and necessary intervention to stabilise life threatening condition.[42] Therefore, while acknowledging the inherent risks, the immediate need for intervention often outweighs concerns about the acute, subacute, and chronic cardiac toxicities associated with radiation exposure.

6. Conclusion

Metastasis to the heart continues to present an ongoing formidable challenge in treatment challenge, often leading to a bleak prognosis despite available interventions. Determining the best optimal treatment strategy and the sequence of therapies necessitates an individualized approach, following predicated on comprehensive discussions within a multidisciplinary team. The efficacy demonstrated efficacy by palliative radiotherapy (RT) in alleviating clinical symptoms and achieving favorable local control underscores the necessity for further exploration of this treatment modality, either as a standalone therapy or in conjunction with surgery and/or chemotherapy.

The potential benefits observed from palliative radiotherapy RT advocate for its early consideration in managing patients with CM. It should no longer be relegated to a treatment of last resort, as has been customary in the past. Instead, its role should warrant reconsideration as an integral part of the initial management strategy for these patients.

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