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Advancements in Radiation Therapy: Minimizing Cardiac Risks and Improving Cancer Treatment Outcomes

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Abstract

Over the past two decades, there has been a noticeable increase in cancer incidence and survivorship, mainly attributed to advancements in treatment modalities. One significant approach is radiation therapy (RT), utilized in 20-55% of cancer patients. Its fundamental principle involves either inhibiting the growth of cancer cells or inducing apoptosis. Historically, photon beam RT has been the primary choice for treatment. However, in recent years, proton beam therapy has emerged as a new option. This innovative method focuses more precisely on the tumor, minimizing damage to surrounding healthy tissues, such as the heart. Unfortunately, radiation to the heart remains a common complication of RT, particularly in patients with lymphoma, breast, lung, and esophageal cancer. The underlying cause lies in changes to the microvascular and macrovascular environment, which can lead to accelerated atherosclerosis and fibrosis of the heart's myocardium, pericardium, and valves. These complications may manifest days, weeks, or even years after RT, and several risk factors contribute to their occurrence. These factors include high radiation doses (>30 Gy), concurrent chemotherapy (especially anthracyclines), advanced age, pre-existing heart disease, and the presence of other cardiovascular risk factors. For physicians, understanding these mechanisms and risk factors is crucial, as it enables them to assess and monitor patients more effectively, with the goal of early detection and prevention of radiation-induced heart disease. Echocardiography, a noninvasive method that comprehensively evaluates the pericardium, heart valves, myocardium, and coronary arteries, is often the initial imaging tool used. Nevertheless, additional modalities like computed tomography, nuclear medicine, or cardiac magnetic resonance can provide valuable supplementary information. By employing a tailored approach to patient assessment and monitoring, healthcare professionals can mitigate the risks associated with radiation-induced heart disease, enhancing the overall care and well-being of cancer survivors.

Keywords: Radiation therapy; Photon beam therapy; Electron therapy, Proton therapy; Cardiac complications; Radiation-induced heart disease; Cancer treatment; Precision medicine, Cardiac screening, Cancer therapy

Introduction

The incidence and survivorship of cancer are on the rise globally. According to the International Agency for Research on Cancer (IARC) within the World Health Organization (WHO), which encompasses 185 countries, the estimated 5-year survival rate for certain cancers (such as breast, colorectal, and prostate) ranges from 51% to 71%. In the year 2020 alone, there were 19.3 million new cancer cases, resulting in 10 million deaths [1,2]. To combat this deadly disease, various treatment interventions have been developed, with radiation therapy (RT) being a prominent option, often used in conjunction with surgery and/or chemotherapy [3]. In the late 20th century, 20-55% of newly diagnosed cancer patients received RT, with nearly half of them receiving it with a curative intent, leading to improved survival rates [4-6]. The primary objective of RT is to damage the genetic material of cancer cells, thereby halting their growth and replication. This is achieved by exposing the targeted tissue to ionizing radiation, generating high-energy ions that disrupt the cells' proliferation and may induce apoptosis [7]. However, this approach also affects non-cancerous "healthy" cells, leading to detrimental effects. Although RT techniques have improved over time, the risk of collateral damage to healthy tissues and organs remains a concern [8]. One significant concern associated with thoracic RT is radiation-induced heart disease (RIHD). Patients treated for diseases like lymphoma, breast, lung, and esophageal cancer, among others, may develop RIHD years after treatment. The heightened risks for such patients compared to the general population include the development of accelerated ischemic heart disease and valvular and pericardial diseases [9,10]. It is crucial to comprehend the pathophysiology of RIHD, explore different techniques to enhance radiation delivery while minimizing tissue damage, understand various types of radiation, identify risk factors associated with RIHD, and establish early diagnosis methods for this condition.

Literature survey

Significant strides have been made in the field of radiation therapy (RT) since its inception in 1898. Initially, physicians solely relied on physical examinations to determine tumor margins. Unfortunately, this approach had drawbacks, as it often led to an underestimation of tumor size and disease progression. Furthermore, it made it challenging to ascertain whether there was tumor resolution during follow-up in patients. Another limitation during the early days of RT was the poor demarcation of 2D images, which hindered the precise localization and differentiation of tumors from surrounding soft tissue, deep tissue, or lymph nodes. Consequently, there was an inadequate estimation of tumor burden. Additionally, the methods used to assess the direction and penetration of radiation beams were inaccurate, resulting in unpredictable tumor coverage and exposure to nearby organs [11]. To address these issues, multileaf collimators were introduced. This technology involved movable leaves that could block certain radiation

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beams directed at healthy organs. However, this approach had limitations, as it was confined to geometrically shape rectangular fields that could not accurately cover the entire tumor contour and spare adjacent organs simultaneously [12]. Nonetheless, efforts continued to improve the technology, leading to the replacement of conventional 2D RT with 3D conformal RT, which was first introduced in 1965 by Takahashi et al. [13]. Three-dimensional RT utilized axial-computed tomography to precisely delineate the target tumor and adjacent organs, resulting in improved radiation dosage delivery. This breakthrough paved the way for the development of intensity-modulated RT (IMRT), which enhances 3D RT by modulating the dose delivered to each tissue to match specific prescription goals [14]. With the introduction of 3D RT, IMRT, and dose-reducing radiation equipment, standardization of protocols became possible, and RT has now achieved a higher level of accuracy while minimizing collateral radiation to adjacent organs [15]. The deep inspiration breath hold (DIBH) technique was introduced as a means to enhance the delivery of radiation therapy (RT). Widely adopted by radiation oncologists, DIBH has proven to be effective in significantly reducing radiation exposure to the heart and lungs [16]. The method involves utilizing the patient's natural respiratory process to shift internal organs into a more favorable position, ensuring more targeted RT against tumor cells and less exposure to adjacent tissues. During DIBH, patients are instructed to hold their breath until they achieve a predetermined abdominal elevation or height [17]. Numerous studies have demonstrated the efficacy of DIBH in reducing chest radiation. For instance, research involving patients receiving breast/chest wall RT showed that all those who used DIBH successfully met their therapeutic RT goals without exceeding the recommended daily radiation fraction doses for the heart. In contrast, 56% of patients without DIBH exceeded the safe radiation threshold for the heart [18]. Another study focusing on left-sided IMRT in breast cancer patients revealed that DIBH significantly reduced heart and lung radiation doses in six out of nine patients. Remarkably, the DIBH technique completely avoided heart radiation exposure in two subjects [19]. Radiation doses are measured in gray units (Gy), representing the amount of ionizing radiation absorbed per kilogram of tissue, with cumulative doses above 30 Gy and daily doses exceeding 2 Gy considered to increase the risk of radiation-induced heart disease (RIHD) [20]. A systematic review encompassing 10 studies and 268 patients found that DIBH reduced heart radiation doses by 38-67% and left anterior descending coronary doses by 31–71% compared to free breathing. However, DIBH does have some drawbacks. It requires patient education and training, which can take up to 30 minutes per session. Additionally, a greater number of staff members need to be trained in this technique. Despite these challenges, DIBH remains a valuable tool in RT, offering improved precision and reduced radiation exposure to critical organs, particularly the heart and lungs.

Pathophysiology

Traditional radiation therapy (RT) using photon beams can have significant impacts on the heart through both microvascular and macrovascular mechanisms [3]. These effects may give rise to various cardiac conditions, including valvular disease, pericardial disease, conduction abnormalities, cardiomyopathy, and accelerated coronary artery disease. The underlying pathophysiologic mechanism that is well understood involves macrovascular damage, leading to the earlier development of age-related atherosclerosis. This phenomenon is attributed to RT-induced endothelial damage in the coronary arteries, triggering an inflammatory response that releases numerous cytokines, which in turn activate macrophages and deposit lipoproteins. The formation of atherosclerotic plaques occurs similarly to traditional coronary artery disease but at an accelerated pace. A retrospective study focusing on 2168 women who underwent RT for breast cancer demonstrated that their risk of major coronary events increased by 7.4%. This risk elevation started five years after receiving RT and persisted for up to 30 years. The risk was higher for patients who received left-sided RT compared to right-sided RT. Preexisting cardiac risk factors and higher radiation doses were associated with a higher risk. Another systematic review, which included six studies spanning from 1996 to 2016 and involved patients with low risk of coronary artery disease (CAD) who received left breast/chest wall RT, found that cardiac exposure to radiation was linked to early myocardial perfusion defects. These defects were predominantly observed in the apical and anterolateral segments of the left ventricle (LV) and were not associated with changes in the ejection fraction. The review also highlighted that the presence of perfusion defects was strongly dependent on the radiation dose, and patients who underwent cardiac radiation-sparing techniques, such as deep inspiration breath hold (DIBH), experienced better outcomes. These findings emphasize the importance of minimizing radiation exposure to the heart during RT to reduce the risk of radiation-induced cardiac complications.

Radiation therapy: Radiation therapy (RT) is an essential treatment modality used to target tumors and improve survival rates. There are two primary methods of RT delivery: external beam radiation and internal radiation (brachytherapy). In this review, we will focus on external beam radiation, where high-energy rays (photons, protons, electrons, neutrons) are directed from outside the body to the tumor tissue. Traditional RT, also known as photon beam therapy, involves depositing energy throughout the entire path of the beam, which can affect surrounding tissues, such as the heart, surrounding the targeted tumor. To overcome this limitation, newer therapies utilizing particle beams (electrons, neutrons, and protons) have been explored. Electron beams have limited tissue penetration, making them suitable for superficial skin diseases like mycosis fungoides, cutaneous T-cell lymphoma, Sezary syndrome, Kaposi sarcoma, and inflammatory breast cancer. However, only a small subset of patients benefit from this approach due to its limited applicability. Neutron beams, on the other hand, are highly damaging and are generally avoided in clinical practice. Proton therapy has emerged as a promising option, providing optimal dosage delivery to cancer cells with minimal adverse effects on surrounding tissues. Protons can be precisely directed to reach a specific depth in the tissue, known as the Bragg peak effect, covering the entire length of the tumor. This approach minimizes radiation exposure to adjacent tissues while enabling higher RT doses to cancer cells, which would otherwise be challenging with photon therapy due to the increased risk of affecting nearby tissues and organs. However, the cost of proton beam therapy remains considerably high, making it unaffordable for many patients and institutions. As a result, photon beam therapy continues to be a viable therapeutic option for numerous cancer patients. Several studies focusing on patients with breast cancer, Hodgkin lymphoma, and pediatric malignancies like medulloblastoma have demonstrated a significant reduction in radiation doses to the heart when using proton therapy as compared to photon therapy. In a systematic review covering 13 studies conducted between 2002 and 2017, proton therapy was found to reduce the mean heart radiation dose by two- or three-fold in breast cancer patients compared to traditional RT. Another prospective study evaluating the mechanical function of the left ventricle (LV) in breast cancer patients, using 2D speckle tracking imaging, revealed compromised LV relaxation properties with photon therapy but preserved function with proton therapy. In patients with Hodgkin lymphoma, a systematic review incorporating 14 studies demonstrated that proton therapy resulted in a lower radiation weighted average compared to traditional 3D RT (by 3.57 Gy) and IMRT (by 2.24 Gy). Similarly, in pediatric patients with medulloblastoma, a study comparing proton and photon therapy revealed that the mean radiation heart dose was significantly lower with proton therapy (0.2 Gy) compared to photon therapy (10.4 Gy). While the long-term follow-up of patients receiving proton beam therapy is necessary to better define its adverse effects and relationship with cardiotoxicity. These findings highlight the potential benefits of proton therapy in minimizing the risk of radiation-induced heart complications in certain cancer populations.

Discussion

Despite the decline in radiation-induced heart disease (RIHD) cases over the past decade, it remains crucial for physicians to diligently assess its presence in every patient who has been exposed to heart radiation, particularly in those who received doses exceeding 30 Gy. It is prudent to screen these patients for traditional risk factors associated with coronary disease, including obesity, hypertension, dyslipidemias, diabetes, and smoking. Implementing appropriate lifestyle modifications and/or treatments is essential to mitigate potential cardiac complications. Failure to address and manage cardiac risks can compromise the life expectancy achieved through anticancer therapy. Increased morbidity and mortality stemming from cardiac complications, such as pericarditis, myocardial dysfunction, coronary artery disease, and valvular disease, can significantly impact patients' overall health and well-being. Therefore, vigilant monitoring and proactive interventions are necessary to safeguard the cardiac health of individuals undergoing radiation treatment for cancer.

Conclusion

'In conclusion, radiation therapy (RT) has come a long way since its inception in 1898, with significant advances improving its effectiveness and precision. Traditional RT, utilizing photon beam therapy, has been a valuable tool in eradicating targeted tumors and improving survival rates in cancer patients. However, it is not without its limitations, as it can also affect surrounding healthy tissues, including the heart. The introduction of newer therapies involving particle beams, such as electron and proton therapy, has shown promise in reducing radiation exposure to adjacent tissues while delivering optimal doses to cancer cells. Proton therapy, in particular, has demonstrated superior precision and lower adverse effects on surrounding organs, including the heart. Although proton beam therapy remains costly and may not be accessible to all patients, it represents a significant advancement in RT technology. Moreover, studies have highlighted the potential benefits of proton therapy in reducing radiation doses to the heart in patients with breast cancer, Hodgkin lymphoma, and pediatric malignancies. Proton therapy has shown promising results in minimizing the risk of radiation-induced heart disease (RIHD), a major concern when treating thoracic cancers. However, while the evidence is encouraging, continued long-term follow-up and evaluation of cardiac complications in patients receiving proton beam therapy are crucial to better define its safety and efficacy. Physicians must remain vigilant in assessing for the presence of RIHD, especially in patients exposed to heart radiation, and screen for traditional risk factors of coronary disease. Early detection and appropriate management of cardiac complications are vital to ensure that the benefits of anticancer therapy are not compromised by increased morbidity and mortality related to cardiac issues. In conclusion, ongoing research and advancements in radiation therapy techniques, such as proton therapy, offer hope for improved cancer treatment outcomes with reduced collateral damage to critical organs like the heart. This progress represents a significant step towards enhancing the quality of life for cancer survivors and enhancing their overall well-being. As technology and medical knowledge continue to advance, we can look forward to further improving the precision and effectiveness of radiation therapy, ultimately leading to better outcomes for cancer patients worldwide.

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Conflict of Interest

Author declares no conflict of interest.

References

1. Ahuja A, Blatt GL, Guterman LR, Hopkins LN (1995) Angioplasty for Symptomatic Radiation? Induced Extracranial Carotid Artery. Neurosurgery 36:399-403.
2. Ohta H, Sakai N, Nagata I, Sakai H, Higashi T, et al. (2001) Bilateral Carotid Stenting for Radiation-Induced Arterial Stenosis. No Shinkei Geka 29:559-563.
3. Mubarak NA, Roubin GS, Iyer SS, Gomez CR, Liu MW, et al. (2000) Carotid stenting for severe radiation-induced extracranial carotid artery occlusive disease. J Endovasc Ther 7:36-40.
4. Cohen JE, Rajz G, Lylyk P, Hur TB, Gomori JM, et al. (2005) Protected stent-assisted angioplasty in radiation-induced carotid artery stenosis. Neurol Res 27:69-72.
5. Stein JS, Jacobson JH (1993) Axillary-contralateral brachial artery bypass for radiation-induced occlusion of the subclavian artery. Cardiovasc Surg 1:146-148.
6. Guthaner DF, Schmitz L (1982) Percutaneous transluminal angioplasty of radiation-induced arterial stenosis. Radiology 144:77-78.
7. Julius HJ, Murray GB (1974) Axillary-Contralateral Brachial Artery Bypass for Arm Ischemia. Ann Surg 179:827-829.
8. Kretschmer G, Niederle B, Polterauer P, Waneck R (1986) Irradiation-induced changes in the subclavian and axillary arteries after radiotherapy for carcinoma of the breast. Surgery 99:658-663.
9. Becquemin JP, Gasparino LF, Etienne G (1994) Carotido-brachial artery bypass for radiation induced injury of the subclavian artery. The value of a lateral mid-arm approach. J Cardiovasc Surg 35:321-324.
10. Roche-Nagle G, Fitzgerald T, McNeaney P, Harte1 P (1997) Symptomatic Radiation-induced Upper Extremity Occlusive Arterial Disease. EJVES Extra 11:5-6.
11. Mellière D, Becquemin JP, Berrahal, Desgranges P, Cavillon (1997) Management of radiation-induced occlusive arterial disease: a reassessment. J Cardiovasc Surg 38:261-269.
12. Hans SS, Tuma (1989) Failure of Percutaneous Transluminal Angioplasty of Radiation-Induced Subclavian Artery Stenosis: Case Report. Vasc Endovasc Surg 23:235-239.
13. Yamanaka T, Fukatsu T, Satou H, Ichinohe Y, Komatsu H, et al. (2015) A case of radiation-induced subclavian artery stenosis treated with percutaneous transluminal angioplasty. J Cardiol Cases 12:61-64.
14. Yilmaz G, Ustundag S, Temizoz O, Sut N, Demir M, et al. (2015) Fibroblast Growth Factor-23 and Carotid Artery Intima Media Thickness in Chronic Kidney Disease. Clin Lab 61:1061-1070.
15. Kim PH, Kadkhodayan Y, Derdeyn CP, Moran CJ (2005) Outcome of carotid angioplasty and stenting for radiation associated stenosis. Am J Neuroradiol 26:1781-1788.
16. Houdart E, Mounayer C, Chapot R, Maurice JPS, Merland JJ (2001) Carotid stenting for radiation-induced stenosis. Stroke 32: 118-121.
17. Ting AC, Cheng SW, Yeung KM, Cheng PW, Lui WM, et al. (2004) Carotid stenting for radiation-induced extracranial carotid artery occlusive disease: efficacy and midterm outcomes. Endovasc Ther 11:53-59.
18. Thorleif E, Manfred H, Volker K (2013) Subclavian-axillary graft plus graft-

carotid interposition in symptomatic radiation-induced occlusion of bilateral subclavian and common carotid arteries. Vasa 42:223-226.

19. Hinchcliffe M, Ruttley MS, Rees GC (1995) Case report: percutaneous transluminal angioplasty of irradiation induced bilateral subclavian artery occlusions. Clin Radiol 50:804-807.
20. Lau WL, Leaf EM, Hu MC, Takeno MM, Kuro-o M, et al. (2012) Vitamin D receptor agonists increase klotho and osteopontin while decreasing aortic calcification in mice with chronic kidney disease fed a high phosphate diet. Kidney Int 82:1261-1270.