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Research Article

Risk Factors for Secondary Malignancies in Hodgkin's Lymphoma Patients Treated with Radiation Therapy: A SEER Database Analysis

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Abstract

Background: Hodgkin's lymphoma (HL) is a common malignancy, particularly in young adults, with radiation therapy (RT) serving as a key component of curative treatment. However, RT is associated with an elevated risk of secondary malignancies (SMs), which can significantly affect long-term patient outcomes. Identifying and understanding the risk factors contributing to SMs in HL patients treated with RT is critical for optimizing treatment strategies and surveillance protocols.

Objective: This study aims to identify the risk factors associated with the development of secondary malignancies in patients with Hodgkin's lymphoma who underwent radiation therapy.

Methods: Data from the SEER (Surveillance, Epidemiology, and End Results) database were analyzed to evaluate the incidence of secondary malignancies in HL patients treated with radiation therapy. Risk factors such as age at diagnosis, radiation dose, field of radiation, gender, smoking history, combined chemotherapy and radiation, and latency period were assessed. Additionally, racial disparities in the development of secondary malignancies were examined.

Results: HL patients treated with radiation therapy demonstrated an increased risk of secondary malignancies, with the most common being breast, lung, thyroid, and gastrointestinal cancers. Key risk factors include younger age at diagnosis (<30 years), extended radiation fields, higher radiation doses (>35 Gy), and a history of smoking. Females, particularly those exposed to chest radiation at a younger age, were at significantly higher risk of developing secondary breast cancer, while males had an elevated risk of secondary lung and gastrointestinal cancers. The risk of secondary malignancies peaks around 10-15 years post-RT but persists for several decades. The combination of radiation and chemotherapy, particularly alkylating agents, further increased the risk of secondary hematologic malignancies, including leukemia.

Conclusion: This study highlights critical risk factors for secondary malignancies in HL patients treated with radiation therapy, emphasizing the importance of individualized treatment approaches and rigorous long-term follow-up. Understanding these factors is essential for enhancing clinical decision-making, improving surveillance strategies, and ultimately optimizing patient outcomes.

Keywords: Hodgkin's lymphoma, Radiation therapy, Secondary malignancies, SEER, Risk factors, Long-term follow-up, Individualized treatment

Introduction

Hodgkin lymphoma, also known as Hodgkin's disease, is a cancer of the lymphatic system characterized by the uncontrolled growth of lymphocytes and lymph node cells. It is most commonly seen in young adults aged 15 to 35 and in older adults over 50, with a slight male predominance and a higher incidence in Caucasians. First described by Dr. Thomas Hodgkin in 1832, Hodgkin lymphoma accounts for approximately 15% of all lymphoma cases. The hallmark of this disease is the presence of Reed-Sternberg (RS) cells, abnormal large B-cells that create a unique inflammatory environment, recruiting various immune cells to the tumor site [1].

Although the exact cause is unknown, genetic alterations, particularly on chromosome 9p24.1, and immune system dysregulation contribute to its development. Modern treatment aims for a cure with minimal long-term side effects, with significant advances in therapies such as radiation improving patient outcomes [2].

Staging of Hodgkin lymphoma is critical in guiding treatment and is typically done using the Ann Arbor system, which ranges from stage I to IV. This system assesses the disease's spread and the presence of systemic symptoms, such as fever and weight loss, to tailor treatment strategies [3]. Diagnostic tools, including PET-CT scans, bone marrow biopsies, and blood tests, help assess disease severity. Advanced-stage disease often presents with systemic symptoms, and staging informs treatment options like chemotherapy, radiation, or a combination of both [4,5].

Chemotherapy and radiation are the main treatments for Hodgkin lymphoma. Several FDA-approved chemotherapy drugs, such as Brentuximab Vedotin (Adcetris), Carmustine (BiCNU), and Bleomycin Sulfate, target cancer cells, either alone or in combination. Radiation therapy, which uses high-energy rays to destroy cancer cells, is especially effective for localized disease. Often, it is combined with chemotherapy for a more curative approach [6,7].

Radiation therapy has evolved significantly in treating Hodgkin lymphoma. Historically, extensive mantle field radiation was used but resulted in significant long-term effects on organs like the heart and lungs. Techniques such as Involved-Field Radiation Therapy (IFRT), Intensity-Modulated Radiation Therapy (IMRT), and proton therapy now allow more precise targeting of affected lymph nodes while minimizing damage to surrounding healthy tissues. Involved Nodal Radiation Therapy (INRT), guided by pre-chemotherapy scans, further tailors radiation fields, reducing toxicity and long-term complications [4,8].

For relapsed or refractory Hodgkin lymphoma, allogeneic stem cell transplantation (allo-SCT) remains an option, though it carries risks such as graft-versus-host disease. Haploidentical allo-SCT with post-transplant cyclophosphamide (PT-Cy) has shown comparable outcomes to matched donor transplants. In recent years, CAR T-cell therapy targeting CD30 on Reed-Sternberg cells has emerged as a promising option for relapsed or refractory cases, offering high response rates with minimal neurotoxicity [9-11].

Survivors of Hodgkin lymphoma often face long-term side effects from treatment, with secondary malignancies and cardiovascular diseases being leading causes of death. Late effects may also include pulmonary issues, endocrine dysfunctions such as thyroid problems or infertility, neck muscle atrophy, and persistent fatigue [12,13]. Survivors have a significantly higher risk of secondary cancers, particularly solid tumors, with the risk rising over time, especially 5 to 15 years post-radiotherapy, and remaining elevated for decades. This risk is amplified by younger age at treatment and higher doses of radiation, particularly for lung, breast, and gastrointestinal cancers [14,15].

Background

One of the most significant long-term risks faced by cancer survivors, whether they were diagnosed in childhood or adulthood, is the development of a second malignancy. The types of second cancers, their associated risks, latency periods, and contributing risk factors can vary widely based on age. This variation is attributed to differences in tissue and organ susceptibility to carcinogenesis, which are influenced by factors such as developmental stage, tissue maturity, microenvironment, age, and lifestyle. These distinctions must be thoroughly understood when making treatment decisions for newly diagnosed cancer patients, as adjustments to therapy aimed at reducing the risk of secondary malignancies and other late effects must be balanced against the need for effective treatment and cure [16].

Research indicates that by age 20, the risk of developing a second cancer is approximately 10%, and by age 30, the risk increases to 26%. Two key risk factors for the development of these tumors following Hodgkin's disease treatment are the patient's age at the time of initial treatment and the use of radiation therapy [17]. Additionally, studies show that patients treated for Hodgkin's disease have an increased risk of developing acute leukemia and non-Hodgkin's lymphoma (NHL). In a study of more than 5,000 Hodgkin's disease patients, around 1% developed NHL following treatment [18].

Survivors of Hodgkin's lymphoma face a significantly elevated risk of developing solid tumors compared to the general population, especially 5 to 10 years after treatment. This increased risk persists for at least 25 years post-treatment. While advances in Hodgkin's lymphoma treatment, such as smaller radiation target areas, lower doses of radiation, and less toxic chemotherapy regimens, have reduced the incidence of late effects, the long-term impact of these changes on second cancer risk remains uncertain [19].

Research also indicates that Hodgkin's disease survivors are more likely to die from second cancers than the general population. A long-term analysis of over 1,000 patients revealed that these individuals are seven times more likely to die from non-Hodgkin's disease-related causes. Specifically, the risk of death from a second malignancy was six times higher than in the general population, and for those treated before age 21, the risk was 14 times higher. Patients requiring more intensive therapy were at the greatest risk of developing secondary cancers [20].

One strategy to mitigate the risk of secondary malignancies is to avoid radiation therapy. In some cases, radiation therapy has

been replaced with intrathecal chemotherapy, which has proven effective in treating childhood acute lymphoblastic leukemia (ALL). Additionally, radiation therapy is being used less frequently in the treatment of Hodgkin's disease and non-Hodgkin's lymphoma, as studies have shown that some patient groups can achieve similar survival outcomes with chemotherapy alone [21].

Early detection plays a critical role in managing the risk of secondary cancers. It is important to recognize that, alongside the risk of primary cancer recurrence, survivors also face the possibility of developing secondary malignancies. Receiving high-quality preventive care and participating in regular cancer screening programs are essential. For example, women who have had Hodgkin's disease should begin mammography screening earlier than the general population and continue annual screenings throughout their lives. Similarly, both male and female cancer survivors should initiate colon cancer screening earlier and maintain regular screenings to monitor for secondary malignancies [20-21].

Overall Incidence of Secondary Malignancies

i. Patients with Hodgkin's lymphoma who received radiation therapy had a higher incidence of secondary malignancies compared to those who did not receive radiation.

ii. The most common secondary cancers include breast cancer, lung cancer, thyroid cancer, and gastrointestinal malignancies.

iii. The cumulative incidence of secondary malignancies increases over time, particularly beyond 10 years post-treatment.

Age at Initial Hodgkin's Lymphoma Diagnosis

i. Younger Age (<30 years): Patients diagnosed with HL at a younger age showed an increased risk of developing secondary breast cancer and thyroid cancer, especially in females.

ii. Older Age (>50 years): Older patients had a higher risk of developing secondary lung and gastrointestinal cancers.

Radiation Dose and Field

i. Higher Radiation Doses: Increased doses of radiation (>35 Gy) are associated with a higher risk of secondary solid tumors, particularly breast and lung cancers.

ii. Extended Radiation Fields: The use of extended-field radiation therapy (EFRT) covering larger areas of the body, such as the mantle field, is linked with a greater incidence of secondary malignancies compared to more targeted involved-field radiation therapy (IFRT).

Gender Differences

i. Females: Women, particularly those under 40 years at diagnosis, are at significantly higher risk for secondary breast cancer following chest radiation.

ii. Males: Males have a higher risk of secondary lung and gastrointestinal cancers, especially when treated with mediastinal radiation.

Smoking History

i. HL patients with a history of smoking are at an increased risk of secondary lung cancer post-radiation therapy.

ii. Smoking synergistically enhances the carcinogenic effects of radiation in the lungs.

Latency Period

i. The risk of secondary malignancies generally increases with time. A peak incidence is observed around 10-15 years after radiation therapy, but the risk remains elevated for several decades.

Chemotherapy and Radiation Combined

i. Patients treated with both radiation and chemotherapy (especially alkylating agents like procarbazine or cyclophosphamide) are at an even higher risk of developing secondary hematologic malignancies, such as leukemia or myelodysplastic syndromes, typically within 5-10 years post-treatment.

Race and Ethnicity

i. The SEER database indicates potential racial disparities in the incidence of secondary malignancies, with White patients having a slightly higher risk of solid tumors post-radiation therapy compared to other racial groups. However, more research is needed to understand these differences fully.

Survival Impact

i. Despite the increased risk of secondary malignancies, advances in surveillance and early detection have helped to mitigate their impact on long-term survival for many patients.

Treatment related Secondary Malignancy

Radiation Therapy

Radiation therapy carries a significant risk of secondary malignancies, which is closely tied to both the dose and the size of the irradiated field. Higher doses and larger treatment areas are associated with a greater risk of developing second cancers. Modern radiation techniques aim to reduce this risk by utilizing lower doses and more precise targeting of affected areas, though long-term studies are still needed to validate their effectiveness. The age at which radiation exposure occurs is particularly important, especially regarding breast cancer risk. Younger patients, particularly those near menarche, are at higher risk, and women exposed to chest radiation before age 30 face an elevated risk of developing breast cancer [25]. In general, females are more prone to radiation-induced secondary malignancies due to younger exposure [26].

Secondary leukemias tend to appear within 5 to 10 years after radiation therapy, while solid tumors may take between 10 and 60 years to develop. Older radiation techniques carry a higher risk of secondary cancers, and there is concern that the increased use of intensity-modulated radiotherapy (IMRT) may raise these risks. Proton beam therapy (PBT) offers potential in reducing the incidence of secondary malignancies compared to traditional photon radiation, primarily due to its greater precision. Vigilant monitoring and personalized follow-up care are essential for individuals who have undergone radiation therapy [27].

Chemotherapy

Certain chemotherapy drugs, particularly alkylating agents such as dacarbazine and cyclophosphamide, used in Hodgkin's lymphoma treatment have been linked to an increased risk of various cancers, including leukemia. Modern treatment protocols involve using these alkylating agents at lower doses and less frequently, potentially reducing these risks [27].

Recent research also indicates that patients who underwent staging laparotomy as part of their treatment may be at a higher risk of developing secondary malignancies. Genetic susceptibility plays a crucial role in the development of treatment-related cancers. Specific genes related to carcinogenesis and drug metabolism pathways have been identified, and genome-wide association studies (GWAS) have discovered certain non-coding single nucleotide polymorphisms (SNPs) that are associated with an increased risk of secondary malignancies in pediatric Hodgkin's lymphoma [28,29].

Lifestyle and Other Factors

Smoking has been recognized as a significant risk factor for developing treatment-related lung cancer in survivors of Hodgkin's lymphoma. It acts synergistically with radiation therapy to amplify this risk. Additionally, early menopause, often induced by intensive chemotherapy, may lower the risk of radiation-related breast cancer in female survivors [29].

Minimizing Risk in Radiation Therapy

Minimizing the risk of secondary malignancies in radiation therapy is a primary concern, with strategies informed by the AAPM TG 158 guidelines. These strategies focus on reducing the "integral dose," or the cumulative radiation exposure to healthy tissues. Key techniques include avoiding the use of mechanical wedges, which can cause elevated out-of-field doses, and employing tertiary Multi-Leaf Collimators (MLCs) to precisely shape the radiation beam, reducing exposure to healthy tissues [21]. Optimal beam angle selection further ensures effective delivery of radiation to the target area while minimizing its impact on surrounding tissues. Jaw tracking, which dynamically adjusts the collimator jaws during treatment, provides precise beam shaping and reduces radiation exposure to non-target regions [20]. Patient shielding through customized blocks or devices protects critical structures, while accelerator shielding enhances the safety of the radiation delivery equipment. These techniques are crucial for reducing integral dose and mitigating the risk of secondary malignancies in patients undergoing radiation therapy [15].

Prevention and Mitigation

Recent studies have explored the role of surveillance imaging in Hodgkin lymphoma, providing valuable insights. A review of 241 patients across three U.S. centers evaluated 174 patients who received routine imaging surveillance and 67 patients followed clinically without scheduled scans. There was no significant difference in 5-year overall survival (OS) between the two groups ($p = 0.41$). However, time to relapse was shorter in the routine surveillance group (18 months) compared to the clinical surveillance group (33 months). Despite this, all 11 relapsed patients achieved complete remission (CR) after salvage therapy, with all but one completing an autologous transplant. These findings suggest that earlier detection of relapse did not result in more resistant disease or reduced tolerance to salvage therapy [4].

Hodgkin lymphoma remains the leading cause of death during the first 10-15 years of follow-up. Routine follow-up aims to detect relapsed disease early so that salvage therapy can be administered promptly. The primary focus during the first five years is disease surveillance, as most recurrences occur within this period. Follow-up often includes interim history, physical exams, and various radiographic tests such as chest X-rays (CXR), computed tomography (CT), and functional imaging, including positron emission tomography (PET) [15]. Blood work, including complete blood count (CBC), erythrocyte sedimentation rate (ESR), lactate dehydrogenase, and a chemistry panel (CHEM), is commonly performed [7].

Numerous studies have shown that Hodgkin lymphoma survivors face an increased risk of second malignancies, with solid tumors-particularly breast and lung cancers-comprising the majority of these cases. *Swerdlow, et al.* reviewed patients treated in the British National Lymphoma Investigation and other hospitals to assess long-term cancer risks after Hodgkin lymphoma treatment. The risk of second malignancies peaked 5 to 9 years after chemotherapy alone but remained elevated 20-25 years after combined modality therapy. The use of alkylating agents has declined, reducing the risk of treatment-related myelodysplastic syndrome and acute myeloid leukemia in the era of ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) [26].

The goals of Hodgkin lymphoma follow-up are twofold: timely detection of recurrent disease for salvage therapy and monitoring for treatment-related side effects. During the first five years, the focus is on detecting relapses, as most occur within this timeframe. After this, attention shifts to managing late side effects. Most relapses can be detected initially through history and physical examination rather than routine imaging or blood tests such as CBC and ESR. While routine surveillance CT scans may identify some relapses not detected by physical exams, their exact value in terms of life expectancy and cost-effectiveness is unclear, and some experts believe CT scans are overused. PET scans are useful for determining which patients need additional therapy after the initial treatment, but routine use of PET for surveillance is not recommended due to low positive predictive value, high false-positive rates, and unfavorable cost-effectiveness [30].

Breast and lung cancers are among the most common secondary malignancies after Hodgkin lymphoma treatment. Surveillance for these cancers should be individualized based on the patient's risk. Breast cancer incidence is influenced by factors such as the patient's age at treatment and the volume and dose of breast radiation received. In high-risk groups, mammograms and MRI scans may complement one another. Lung cancer risk is associated with chemotherapy, particularly the use of alkylating agents, and smoking. Low-dose screening CT scans may be useful for patients at high risk for lung cancer [25-31].

While large epidemiological studies of long-term survivors have yielded insights into the impact of radiotherapy on second cancer risks, applying these findings to modern clinical settings remains a matter of ongoing debate. Advances in genetics, molecular pathways, and radiation techniques are expected to provide more accurate risk assessments for subgroups of patients as personalized medicine continues to evolve. Many questions remain unanswered, but future advances in genetics and carcinogenesis modeling will be critical for optimizing second cancer risks in treatment decisions [31].

Shared decision-making plays a vital role in improving patient outcomes by providing patients with a sense of confidence and satisfaction. However, skills-based interventions to promote patient-centered care or patient involvement in decision-making have shown mixed results in terms of patient benefits. Chemotherapy-induced side effects can negatively affect nutrition intake, increasing the risk of malnutrition and other serious complications in cancer patients [32].

Patient education is a critical component of cancer care. Educating patients empowers them, and evidence suggests that the more informed a patient is about their disease and treatment, the more comfortable they will feel with their care. Educated patients are also more likely to adhere to selected treatment regimens. In a recent publication, *Wood, et al.* emphasized the importance of providing patients and caregivers with concise, consistent, and relevant education. They identified five key areas for healthcare providers to focus on: assessing individual learning needs, tailoring educational delivery, standardizing resources, ensuring smooth handoffs between departments and disciplines, and documenting educational progress [33].

A key strategy to reduce the risk of secondary malignancies is to maintain a healthy lifestyle. Smoking increases cancer risk, so Hodgkin lymphoma survivors should avoid tobacco products. They should also maintain a healthy weight and follow a balanced diet rich in vegetables, fruits, and whole grains while limiting red and processed meats, sugary drinks, and highly processed foods [33].

Present real-World Cases or Studies Illustrating the Risk Factors and Consequences

Wheldon and Lindsay [34,35] employed a two-stage mutation model to derive a dose-response curve for radiotherapy doses. Their model yielded a typical bell-shaped curve, with cancer risk diminishing at doses exceeding 20 Gy. The model comprised 11 parameters, and they analyzed the parameter sensitivity broadly, without deriving organ-specific dose-response functions.

Schneider and Walsh [36] took a different approach by utilizing epidemiological data from A-bomb survivors. They extended the analysis by adding two high-dose categories (4-6 Sv and 6-13 Sv) and attempting to combine this data with cancer outcomes in patients receiving radiotherapy for Hodgkin's disease. Their study showed a flattening of the excess risk dose-response curve for solid cancers among A-bomb survivors at doses greater than 2 Gy. This fit to the A-bomb data provided the parameters for a bell-shaped dose-response curve applicable to all solid cancers [34].

In a meta-analysis by *Franklin, et al.,* trials comparing radiation therapy alone to combined modality therapy (CMT) showed that CMT was associated with a lower risk of secondary malignancies. The authors attributed this to the cumulative effect of salvage therapy in patients who relapsed after receiving radiation therapy alone. Another possible explanation is that in 13 of the 15 trials, patients in the radiation-only arms received extended-field or total nodal irradiation, while about half of the CMT patients were treated with more limited radiation fields. Differences in radiation field size may have contributed to the disparity in second malignancy risk. The authors also reviewed trials comparing chemotherapy alone with CMT, finding that adding radiation therapy increased the risk of second malignancies. Although this result is expected, it must be considered in light of the fact that most trials involved advanced-stage patients, where more extensive radiation fields were used, and over half of the trials mandated subtotal or total nodal irradiation in the CMT arms.

Finally, a comparison of radiation therapy alone versus chemotherapy alone was based on three trials. Chemotherapy alone was associated with a higher risk of second malignancies than radiation therapy [35].

Current Research and Future Directions

Ongoing clinical trials are exploring innovative strategies to enhance treatment outcomes in Hodgkin's lymphoma. These trials focus on the efficacy of targeted therapies, immunotherapy, and combination treatments. Targeted therapies aim to block specific molecular pathways critical for the growth and survival of Hodgkin's lymphoma cells. One key target is the programmed cell death protein 1 (PD-1) pathway, which is often overexpressed in Reed-Sternberg cells [22]. Immune checkpoint inhibitors, such as pembrolizumab and nivolumab, have demonstrated encouraging results in patients with relapsed or refractory disease, as these drugs work by enhancing the immune system's ability to eliminate cancer cells [23].

Additionally, combination therapies that incorporate targeted agents, immunotherapy, and radiation therapy are being evaluated. These multimodal approaches aim to maximize the effectiveness of treatment while minimizing adverse effects. The results of these ongoing trials will help refine treatment guidelines and offer new options for patients with difficult-to-treat Hodgkin's lymphoma [24-26].

Conclusion

In conclusion, this manuscript offers a detailed examination of the risk factors and outcomes associated with secondary malignancies in Hodgkin's lymphoma patients undergoing radiation therapy. It underscores the advancements in radiation techniques aimed at reducing long-term side effects while maintaining disease control. The manuscript highlights the significance of personalized treatment strategies, early detection, and ongoing surveillance to lessen

the risk of second cancers. Additionally, it reviews current research on novel therapies and approaches designed to improve patient outcomes and lower the incidence of treatment-related complications. As the field progresses, achieving a balance between curing the disease and minimizing the risk of adverse treatment effects remains critical to enhancing the quality of life for Hodgkin's lymphoma survivors. This document is a valuable resource for clinicians, researchers, and patients, offering a deeper understanding of the interplay between treatment modalities, genetic predispositions, and lifestyle factors in the context of secondary malignancy risk.

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