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Effect of Radiotherapy on Blood: A Systematic Review

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1. Background-Aim

Radiotherapy, a cornerstone in cancer treatment, utilizes ionizing radiation to selectively eradicate malignant cells. However, collateral damage to healthy tissues, particularly the hematopoietic system, is a significant concern. This can manifest as a marked decline in erythrocytes, leukocytes, and thrombocytes, leading to clinical conditions such as anemia, leukopenia, and thrombocytopenia. The underlying mechanisms include direct DNA damage, apoptosis, and altered cytokine signaling within the bone marrow microenvironment.

The primary objective of this review is to systematically investigate the hematological toxicities associated with radiotherapy, with particular emphasis on the temporal dynamics and magnitude of red blood cell, white blood cell, and platelet depletion. This analysis explores the dose-dependent and volume-dependent effects of radiation on hematopoietic tissues and the subsequent impact on patient morbidity and treatment outcomes.

Additionally, the review aims to delineate the role of inflammation and cytokine dysregulation in exacerbating hematopoietic injury. Further, it evaluates the efficacy of hematopoietic growth factors, such as granulocyte colony-stimulating factor (G-CSF), erythropoietin, and thrombopoietin mimetics, alongside transfusion support, as therapeutic strategies for mitigating hematological toxicities.

This research underscores the importance of personalized radiotherapy protocols that minimize hematopoietic toxicity, balancing the therapeutic benefits of tumor control with the preservation of hematological function. Ultimately, this work aims to contribute to the refinement of radiotherapy approaches and the development of prophylactic and supportive care strategies to enhance clinical outcomes in cancer treatment.

2. Materials & Methods

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The databases used in the study included Scopus and PubMed, with the search covering the period from November 2023 to the end of May 2024. VOSviewer software was employed for bibliometric analysis.

The initial search strategy utilized keywords such as "Hematology AND toxicity AND radiation," with searches performed across article titles, abstracts, and keywords. Following the initial screening of titles and abstracts, a secondary search was conducted using the terms "lymphopenia AND radiotherapy AND cancer," focusing specifically on article titles to enhance specificity. This process was repeated for a range of keywords associated with hematologic malignancies and their interactions with radiotherapy.

The inclusion criteria for the full-text review of selected articles were as follows: (1) articles published in English, (2) studies employing rigorous research methodologies such as clinical trials or meta-analyses, and (3) articles directly relevant to the study's topic. Exclusion criteria included studies unrelated to the hematologic effects of radiotherapy, those involving chemotherapy, inaccessible full texts, animal studies, letters, editorials, commentaries, and duplicate articles.

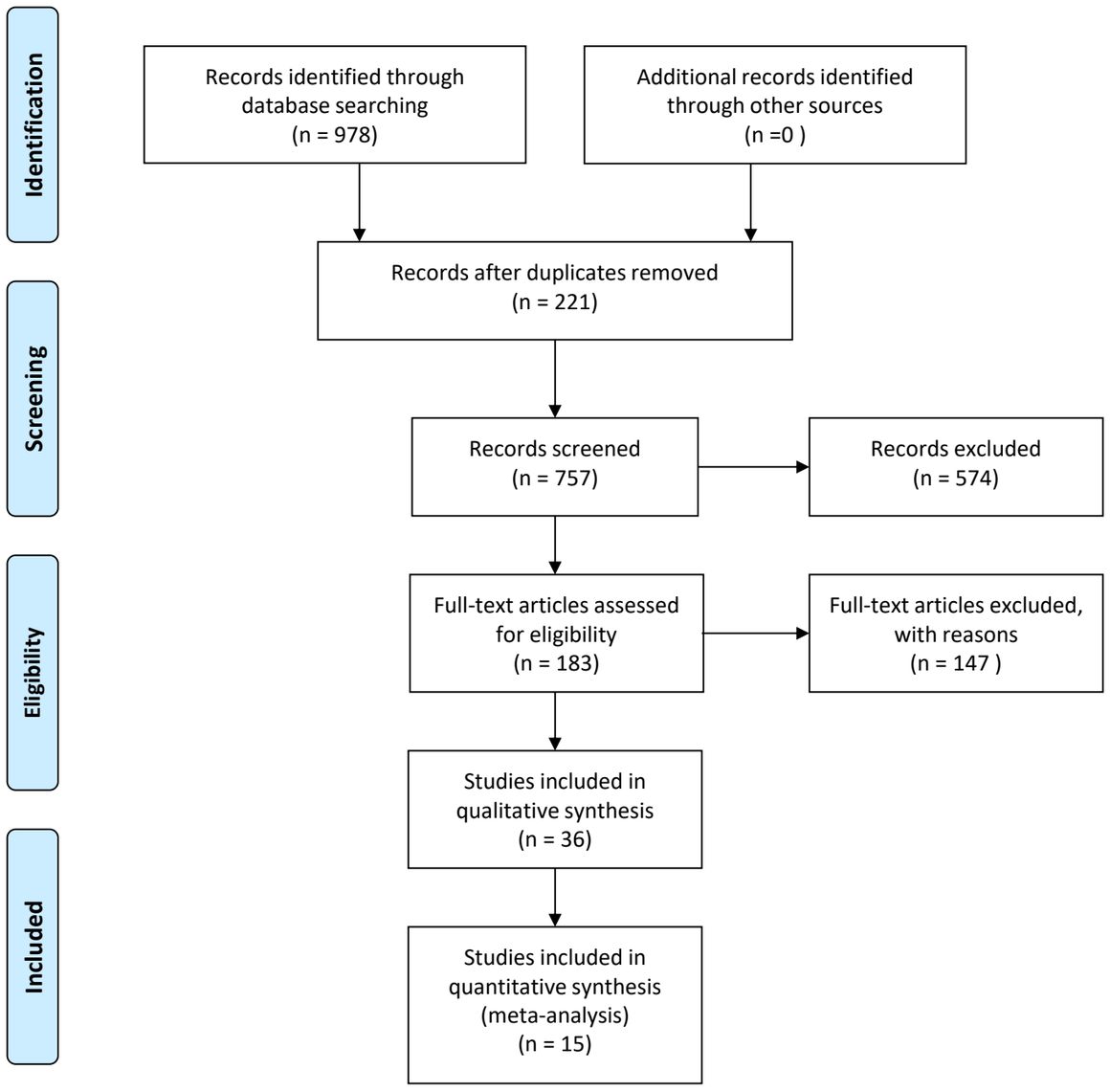
VOSviewer software was used to visualize the bibliometric data extracted from the selected studies. The analysis highlighted relationships between authors, countries, journals, keywords, and study characteristics. Different visualization techniques, including Network, Overlay, and Density visualizations, were employed to identify and illustrate relationships and patterns within the dataset.

VOSviewer
Visualizing scientific landscapes

Nees Jan van Eck and Ludo Waltman
Centre for Science and Technology Studies
Leiden University

Radiation therapy by Nick Youngson CC BY-SA 3.0Pix4free

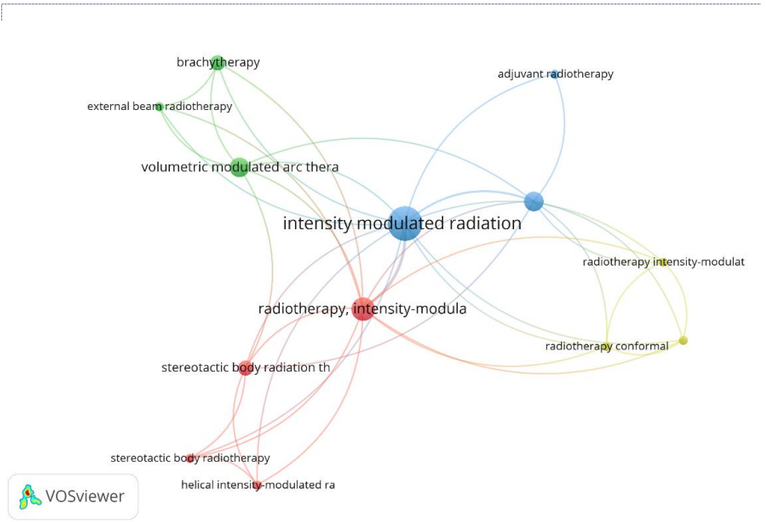
3. Results

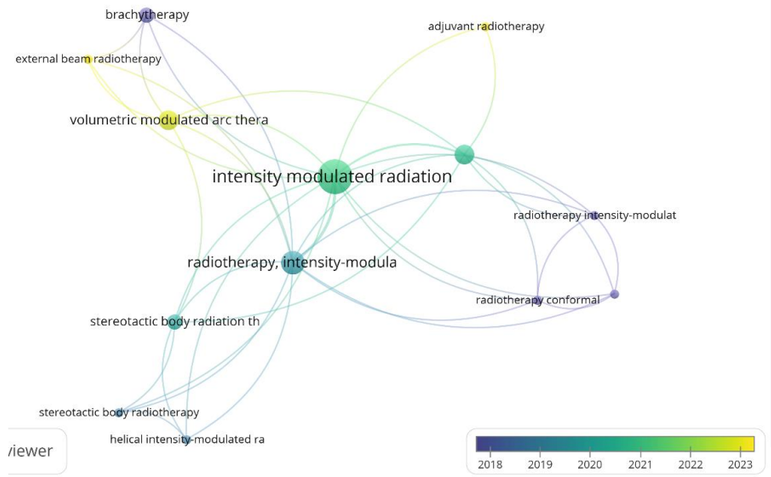


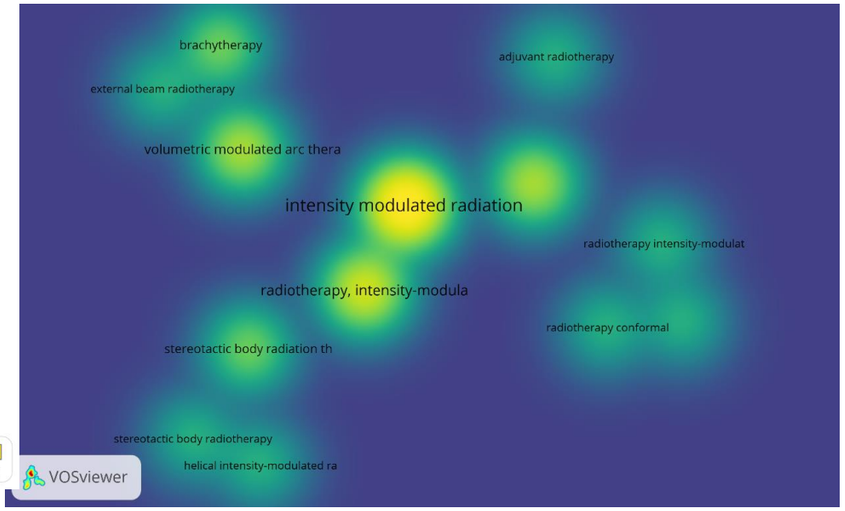
Based on the predefined selection and exclusion criteria, a total of 36 relevant articles were identified. Among these, 15 (41%) were original research articles, 19 (53%) were review articles, 1 (3%) was a conference paper, and 1 (3%) was a book chapter. The author demographics of these works were also analyzed, revealing that 166 (68%) of the authors were male, and 79 (32%) were female.

For the purposes of the systematic review and meta-analysis, only the original research articles were retained, with other types of publications (reviews, conference papers, and book chapters) excluded from the final dataset for the focus on empirical research. As a result, the final number of articles included in the systematic review and meta-analysis was 16.

3. Results





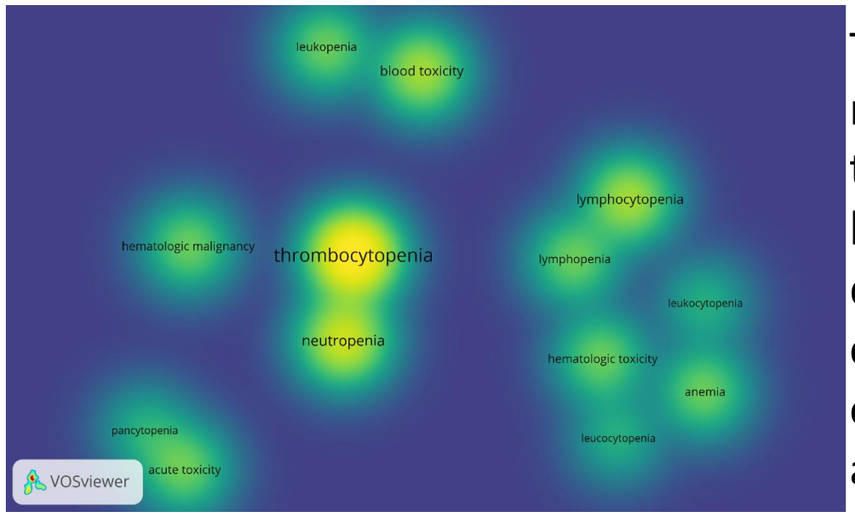


Network Visualization Map of Radiotherapy Types: This map highlights the relationships between various radiotherapy techniques, indicating that **Intensity Modulated Radiotherapy (IMRT)** and **Volumetric Modulated Arc Therapy (VMAT)** are the most frequently utilized methods. In contrast, **Helical Intensity Modulated Radiotherapy (H-IMRT)** appears with lower frequency, suggesting its relatively limited application compared to IMRT and VMAT in clinical practice.

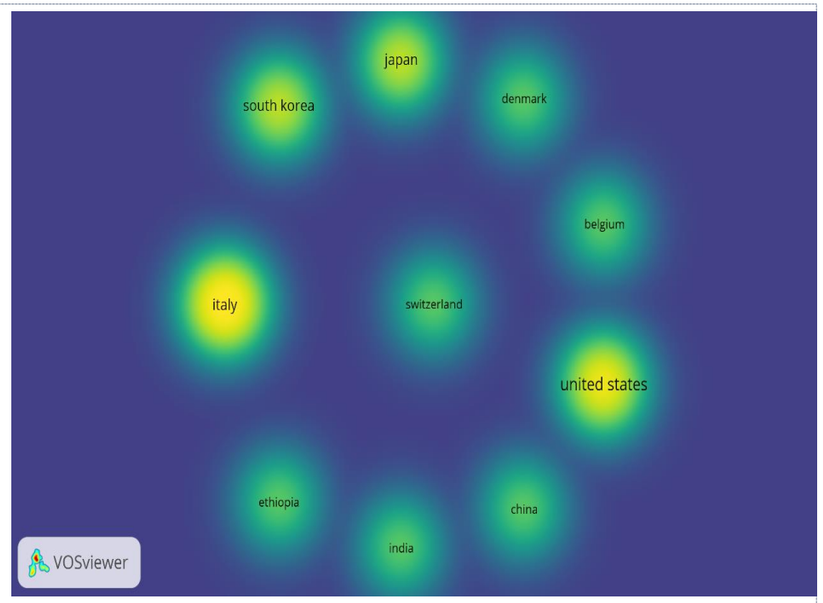
Overlay Visualization Map of Radiotherapy Types: The overlay map emphasizes the temporal evolution of radiotherapy techniques. IMRT is marked in teal, indicating its notable use in 2021. Meanwhile, **VMAT**, **External Beam Radiotherapy (EBRT)**, and **Adjuvant Radiotherapy** are shown in yellow, corresponding to the year 2023, reflecting their more contemporary relevance. **Brachytherapy**, shown in dark blue, is associated with earlier years, underscoring its longer historical use compared to newer techniques.

Density Visualization Map of Radiotherapy Types: The density map shows that IMRT and VMAT have the highest density, reflecting their widespread adoption in modern radiotherapy. **Conformal Radiotherapy** and **Stereotactic Body Radiotherapy (SBRT)** are represented with lower density, indicating they are less frequently employed relative to IMRT and VMAT.

3. Results



The most significant impacts of radiotherapy are neutropenia and thrombocytopenia, which are closely linked and commonly observed across different types of radiotherapy and cancers. Anemia, although related to other conditions like leukopenia, has a smaller and more



The **USA** is depicted as having the most significant international collaborations, particularly with **Switzerland**, which is among its closest research partners. In contrast, **Japan** exhibits fewer collaborative efforts with these countries. Switzerland's primary research collaborations are with **Italy**, **the USA**, and **Belgium**. In terms of publication output, the USA leads with the highest number of publications, followed by Switzerland.

Recent research activity, spanning from **2021 to 2024**, has been most prominent in the **USA**, **India**, and **Belgium**. In contrast, **Italy** demonstrated its primary research activity around **2010**.

High-density areas on the collaboration map indicate intense research activity and strong collaborative networks. The USA, Italy, **South Korea**, and Japan are represented with the highest density, reflecting their leading roles in research output and international collaborations. In contrast, other countries show lower density, suggesting either reduced research activity or fewer collaborations in the field.

4. Conclusions

Radiotherapy Site Maps indicate that the most frequently irradiated areas are the **breast**, **prostate**, and **bones**, which aligns with the high prevalence of cancers affecting these regions. These areas remained focal points of research from **2020 to 2023**, underscoring their sustained clinical significance. The high density for **breast cancer** and **bone tumors** highlights the frequent focus on both treatment and research in these areas. In contrast, **uterine cancer** appears less studied, with the majority of research concentrated in **2023**, suggesting that it may represent a more recent or underexplored area of interest.

From the studies analyzed, **Intensity Modulated Radiotherapy (IMRT)** and **Volumetric Modulated Arc Therapy (VMAT)** are identified as the most widely employed modern techniques. These methods have been extensively implemented between **2021 and 2023**. In contrast, **Stereotactic Body Radiation Therapy (SBRT)** and **Helical Intensity Modulated Radiotherapy (H-IMRT)** show lower density and less frequent use, suggesting the need for further clinical evaluation and study to match the prevalent use of IMRT and VMAT.

According to the analysis, **thrombocytopenia** is the most frequent and severe complication associated with radiotherapy. However, the **2021 overlay map** shows that its impact has diminished over time. In contrast, complications such as **acute toxicity** and **pancytopenia**, which appeared less prominent in earlier network maps, have gained prominence in recent years (**2023–2024**). Despite their rising significance, both acute toxicity and pancytopenia show lower density in the maps, potentially reflecting limited research or underreporting in the studies reviewed.

The **United States** leads in terms of publication output in the field of radiotherapy. However, **Italian authors** exhibit a higher degree of collaboration compared to their U.S. counterparts. This suggests that while the U.S. leads in overall publication volume, Italian researchers have established stronger collaborative networks. The country map shows that Italy's scientific activity peaked in **2010**, while the author map highlights increased collaboration in **2019**, suggesting that while most Italian publications were made around **2010**, significant collaborative efforts among authors emerged later, around **2019**.

5. References

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