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REVIEW

Radiotherapy in Patients with Autoimmune Diseases: Risks, Evidence, and Management Strategies

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Abstract

Autoimmune diseases affect a substantial proportion of the global population, and affected individuals carry an elevated lifetime risk of developing various malignancies. When radiotherapy is indicated for cancer treatment in these patients, clinicians face the challenge of balancing oncological efficacy against the heightened risk of radiation-induced toxicity in tissues already compromised by chronic immune dysregulation. This review synthesizes the current evidence on the use of radiotherapy in patients with pre-existing autoimmune conditions, including systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, dermatomyositis, inflammatory bowel disease, and multiple sclerosis. We examine the pathophysiological basis for increased radiosensitivity in autoimmune disease, encompassing impaired DNA repair mechanisms, aberrant cytokine signaling, compromised tissue homeostasis, and the confounding effects of immunosuppressive therapy. The evidence from retrospective cohort studies, case series, and institutional analyses is critically appraised, highlighting that connective tissue disorders, particularly systemic sclerosis and systemic lupus erythematosus, are associated with significantly elevated rates of severe acute and late toxicities, while other autoimmune conditions may confer more moderate risk. Management strategies are discussed in detail, including pre-treatment multidisciplinary assessment, individualized dose and fractionation modifications, advanced radiation delivery techniques to minimize normal tissue exposure, and coordinated immunosuppressive medication management. The role of emerging biomarkers for predicting individual radiosensitivity and the potential impact of modern radiation technologies such as intensity-modulated radiotherapy, stereotactic body radiotherapy, and proton therapy in mitigating toxicity are also reviewed. This article provides a comprehensive framework for evidence-based decision-making to optimize outcomes for autoimmune disease patients requiring radiotherapy in the Asia Pacific region and beyond.

Keywords: Radiotherapy- Autoimmune diseases- Radiosensitivity- Toxicity- Systemic sclerosis- Cancer management

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Introduction

Autoimmune diseases constitute a heterogeneous group of disorders characterized by aberrant immune responses directed against self-antigens, resulting in chronic inflammation and tissue damage across multiple organ systems [1]. These conditions collectively affect approximately 5–10% of the global population, with prevalence rates varying considerably across geographic regions, ethnicities, and sex [2]. In the Asia Pacific region, the epidemiological landscape of autoimmune diseases presents distinctive features, with notable variations in the prevalence of specific conditions such as systemic lupus erythematosus (SLE), which demonstrates particularly high incidence among East and Southeast Asian populations [3].

Patients with autoimmune diseases carry a well-documented elevated risk of developing various malignancies. This increased cancer susceptibility arises from a complex interplay of chronic immune activation, the use of immunosuppressive medications, shared genetic susceptibility loci, and disease-specific pathological processes [4]. Epidemiological data indicate that individuals with rheumatoid arthritis (RA) have an

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increased risk of lymphoproliferative disorders, patients with inflammatory bowel disease (IBD) face elevated colorectal cancer risk, and those with dermatomyositis exhibit particularly striking associations with a range of solid tumors [5, 6]. Consequently, radiation oncologists will inevitably encounter patients with concurrent autoimmune disease in their clinical practice.

Radiotherapy remains a cornerstone of modern oncological treatment, employed with curative or palliative intent in approximately 50% of all cancer patients during the course of their disease [7]. The therapeutic efficacy of ionizing radiation derives from its capacity to induce lethal DNA damage in tumor cells, primarily through the generation of double-strand breaks and the formation of reactive oxygen species [8]. However, the biological effects of radiation are not confined to malignant tissue; adjacent normal tissues inevitably receive some degree of radiation exposure, leading to acute and late toxicities that define the therapeutic window of radiation treatment.

The intersection of radiotherapy and autoimmune disease represents a clinical scenario of considerable complexity. Theoretical and empirical evidence suggests that pre-existing autoimmune conditions may amplify the detrimental effects of radiation on normal tissues through several mechanisms, including impaired DNA damage repair pathways, dysregulated inflammatory responses, compromised microvascular integrity, and the concurrent use of immunosuppressive agents that may themselves alter radiosensitivity [9, 10]. The seminal concern is that irradiating tissues already subject to chronic immune-mediated injury may precipitate disproportionately severe toxicities, potentially necessitating treatment interruptions, dose reductions, or premature cessation of therapy, all of which compromise oncological outcomes.

Despite the clinical importance of this issue, the evidence base informing the management of autoimmune disease patients requiring radiotherapy remains limited, consisting predominantly of retrospective studies, case series, and expert consensus rather than prospective randomized trials [11]. The historical guidance from the American College of Radiology, which once listed connective tissue diseases as relative contraindications to radiotherapy, has been progressively refined as more nuanced data have emerged [12]. Nevertheless, considerable uncertainty persists regarding which specific autoimmune conditions confer the greatest risk, the magnitude of excess toxicity, and the optimal strategies for risk mitigation.

This review aims to provide a comprehensive synthesis of the current evidence on radiotherapy in patients with autoimmune diseases. We examine the pathophysiological mechanisms underlying increased radiosensitivity, critically appraise the clinical data stratified by specific autoimmune condition, and delineate practical management strategies encompassing multidisciplinary assessment, treatment planning modifications, and supportive care approaches. The review also addresses emerging technologies and biomarkers that may improve the therapeutic ratio in this vulnerable patient population, with particular attention to considerations relevant to the Asia Pacific context.

Pathophysiological Basis for Increased Radiosensitivity in Autoimmune Diseases

Understanding the biological mechanisms by which autoimmune diseases potentiate radiation-induced tissue injury is essential for rational clinical decision-making. The increased radiosensitivity observed in autoimmune disease patients is multifactorial, involving interconnected pathways at the molecular, cellular, and tissue levels.

Impaired DNA Damage Repair

Ionizing radiation exerts its cytotoxic effects primarily through the induction of DNA double-strand breaks, the most lethal form of DNA damage [8]. The cellular response to such damage involves the coordinated activation of multiple repair pathways, including homologous recombination and non-homologous end joining. Several autoimmune conditions are associated with intrinsic defects in DNA repair capacity. In SLE, antibodies directed against components of the DNA repair machinery, including anti-Ku and anti-DNA-PKcs antibodies, may functionally compromise the non-homologous end joining pathway [13]. Furthermore, polymorphisms in DNA repair genes such as XRCC1 and XRCC3 have been reported at elevated frequencies in patients with autoimmune diseases, potentially impairing the efficiency of base excision repair and homologous recombination, respectively [14]. These pre-existing deficiencies in DNA repair may render normal tissues more susceptible to radiation-induced genomic damage, resulting in enhanced cell death and tissue injury.

Dysregulated Inflammatory and Cytokine Responses

Radiation-induced tissue damage triggers an acute inflammatory response characterized by the release of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and transforming growth factor-beta (TGF-β) [15]. In patients with autoimmune diseases, the baseline inflammatory milieu is already significantly perturbed, with chronically elevated levels of many of these same mediators. The superimposition of radiation-induced inflammation upon this dysregulated background may generate a synergistic amplification of the inflammatory cascade, resulting in exaggerated acute tissue damage [16]. Moreover, the persistent activation of pro-fibrotic pathways, particularly through TGF-β signaling, is central to the pathogenesis of late radiation toxicity and is also a hallmark of several autoimmune conditions, most notably systemic sclerosis (SSc) [17]. This convergence of pro-fibrotic signaling may explain the particularly severe fibrotic complications observed when patients with SSc undergo radiotherapy.

Microvascular Dysfunction

Radiation-induced vascular injury, characterized by endothelial cell damage, intimal fibrosis, and progressive luminal narrowing, constitutes a major pathogenic mechanism underlying late radiation toxicity [18]. Many autoimmune diseases, particularly SSc,

SLE, and vasculitides, are associated with pre-existing microvascular dysfunction, including endothelial activation, impaired vascular repair, and obliterative vasculopathy [19]. The combination of radiation-induced and autoimmune-mediated vascular damage may produce synergistic microvascular compromise, accelerating tissue ischemia, fibrosis, and necrosis. In SSc, where Raynaud phenomenon reflects the severity of underlying microvascular disease, this pathological synergy is clinically evident in the dramatically elevated rates of severe radiation-induced fibrosis and soft tissue necrosis reported in irradiated fields [20].

Effects of Immunosuppressive Therapy

The majority of patients with active autoimmune diseases receive immunosuppressive medications, many of which possess radiosensitizing properties. Methotrexate, a folate antagonist widely used in RA and other conditions, inhibits DNA synthesis and repair and has been associated with enhanced radiation mucositis and dermatitis in clinical reports [21]. Cyclophosphamide, employed in severe SLE and vasculitis, is itself a DNA-alkylating agent with additive DNA-damaging effects when combined with radiation [22]. Biologic agents targeting TNF-α, while reducing inflammation, may theoretically impair normal tissue recovery by suppressing the adaptive immune responses necessary for tissue repair [23]. Conversely, some immunosuppressive agents, including corticosteroids, may attenuate the acute inflammatory component of radiation toxicity, creating a complex pharmacological interplay that is difficult to predict in individual patients [24].

Aberrant Fibrotic Remodeling

Late radiation toxicity is predominantly characterized by progressive fibrosis of irradiated tissues. The pathogenesis involves sustained activation of fibroblasts, excessive deposition of extracellular matrix components, and impaired matrix remodeling [25]. Autoimmune conditions associated with fibrotic phenotypes, notably SSc and to a lesser extent SLE with skin involvement, may predispose to accelerated and more severe radiation-induced fibrosis. The shared involvement of the TGF-β/Smad signaling axis in both autoimmune fibrosis and radiation fibrosis suggests a mechanistic convergence that compounds tissue injury in affected patients [17, 26].

Clinical Evidence by Autoimmune Disease

The clinical evidence regarding radiotherapy outcomes in patients with specific autoimmune diseases is reviewed below, with attention to the quality and limitations of available data.

Systemic Sclerosis

SSc represents the autoimmune condition most consistently associated with severe radiation toxicity, and it has historically been regarded as a near-absolute contraindication to radiotherapy by many radiation oncologists [12]. The pathophysiological features of SSc, including widespread microvascular obliteration, dermal and visceral fibrosis, and impaired tissue repair, create an inherently hostile environment for radiation tolerance. Retrospective analyses have demonstrated that patients with SSc who receive radiotherapy experience significantly elevated rates of severe late toxicities, including grade 3–4 fibrosis, soft tissue necrosis, and joint contracture in irradiated fields [27, 28]. In a landmark systematic review by Lin et al. [29], approximately 50% of SSc patients treated with radiotherapy developed severe late complications, compared with background rates of 5–10% in the general population. The risk appears particularly pronounced for truncal and extremity irradiation, where the fibrotic predisposition of SSc is most evident. However, it is important to note that not all SSc patients experience catastrophic outcomes, and some series have reported acceptable toxicity profiles with carefully planned treatment, particularly for breast irradiation using modern techniques [30]. The diffuse cutaneous variant of SSc appears to confer greater risk than the limited cutaneous variant, although the data are insufficient for definitive stratification [31].

Systemic Lupus Erythematosus

SLE is a prototypical systemic autoimmune disease with the potential to affect virtually every organ system. The relationship between SLE and radiation toxicity has been evaluated in several retrospective studies, with somewhat heterogeneous results. Early case reports raised significant concerns regarding severe acute and late toxicities in SLE patients receiving radiotherapy, including severe mucositis, radiation pneumonitis, and accelerated fibrosis [32]. However, larger retrospective series have provided a more nuanced picture. A study by Chen et al. [33] evaluating 80 SLE patients who received radiotherapy found an overall rate of severe toxicity of approximately 15–20%, which was elevated compared with matched controls but substantially lower than the rates reported for SSc. The risk appeared to correlate with disease activity at the time of irradiation, with patients receiving active immunosuppressive therapy for disease flares demonstrating higher toxicity rates [34]. Notably, SLE patients treated with breast or pelvic radiotherapy using conventional fractionation generally tolerated treatment reasonably well, suggesting that the risk, while real, may be manageable with appropriate precautions [9].

Rheumatoid Arthritis

RA is the most prevalent inflammatory autoimmune condition and therefore the autoimmune disease most commonly encountered in radiation oncology practice. The evidence regarding RA and radiation toxicity is generally reassuring. Multiple retrospective studies have demonstrated that RA patients tolerate radiotherapy without significantly elevated rates of severe toxicity, although modest increases in mild to moderate acute reactions have been reported in some series [35, 36]. A large institutional analysis by Gold et al. [27] found no statistically significant increase in grade 3 or higher toxicity among RA patients compared with the general population. However, caution is warranted in patients

receiving concurrent methotrexate, which may potentiate mucositis and dermatitis, particularly in head and neck and upper gastrointestinal irradiation fields [21]. Additionally, RA patients with joint involvement adjacent to irradiation fields may experience exacerbation of articular symptoms [37].

Inflammatory Bowel Disease

IBD, encompassing Crohn disease and ulcerative colitis, presents specific challenges when pelvic or abdominal radiotherapy is required, as the already inflamed gastrointestinal mucosa may exhibit heightened radiosensitivity. Clinical evidence supports this concern: retrospective studies have demonstrated elevated rates of acute gastrointestinal toxicity, including severe diarrhea, proctitis, and bowel perforation, in IBD patients receiving pelvic radiotherapy [38]. Willett et al. [38] reported that approximately 30% of IBD patients treated with pelvic radiotherapy developed severe acute gastrointestinal complications requiring treatment modification, compared with approximately 10% in the general population. The risk appears to be particularly pronounced in Crohn disease, where transmural inflammation and skip lesions may create focal areas of extreme radiosensitivity. Late complications, including stricture formation and fistulization, are also more frequent. For irradiation of sites distant from the gastrointestinal tract, IBD patients do not appear to carry significantly elevated risk [38].

Dermatomyositis and Polymyositis

The inflammatory myopathies, particularly dermatomyositis, present a unique clinical scenario because of the strong association between dermatomyositis and underlying malignancy, which may necessitate radiotherapy as part of cancer treatment [6]. The cutaneous manifestations of dermatomyositis, including photosensitivity and skin fragility, raise theoretical concerns regarding enhanced radiation dermatitis. Clinical data, while limited to case reports and small series, suggest an increased risk of severe skin reactions and potentially of radiation-induced myositis when treatment fields encompass skeletal muscle already affected by inflammatory myopathy [39]. However, the evidence base is insufficient to draw firm conclusions, and management must be individualized.

Multiple Sclerosis

Multiple sclerosis (MS) is a demyelinating autoimmune disease primarily affecting the central nervous system. When cranial or spinal radiotherapy is indicated in MS patients, there are theoretical concerns regarding enhanced neurotoxicity and potential exacerbation of demyelination [40]. The clinical evidence, derived predominantly from case reports, provides conflicting signals: some patients tolerate cranial irradiation without neurological deterioration, while others experience significant exacerbation of MS symptoms following treatment [40]. The risk may be modulated by disease activity, the extent of pre-existing demyelinating burden, and the specific neuroanatomical relationship between the irradiation field and existing plaques. For radiotherapy targeting sites distant from the central nervous system, MS does not appear to confer appreciable excess risk [11].

Other Autoimmune Conditions

Less extensive data are available for other autoimmune diseases, including Sjögren syndrome, ankylosing spondylitis, autoimmune thyroiditis, psoriasis, and autoimmune hepatitis. Sjögren syndrome may predispose to enhanced salivary gland toxicity during head and neck irradiation, with accelerated xerostomia [41]. Ankylosing spondylitis, while historically treated with spinal irradiation in the pre-biologic era, does not appear to significantly increase toxicity from therapeutic irradiation at other sites [42]. Overall, the principle that autoimmune conditions involving the same organ system as the irradiation target carry the greatest risk applies broadly across the spectrum of autoimmune diseases.

Management Strategies

The management of autoimmune disease patients requiring radiotherapy demands a systematic, multidisciplinary approach that balances oncological imperatives with the mitigation of excess toxicity risk. A summary of the toxicity risk stratified by autoimmune disease is presented in Table 1. The proposed management algorithm is illustrated in Figure 1. The following strategies represent current best practices informed by

Table 1. Summary of Radiotherapy Toxicity Risk by Autoimmune Disease

Autoimmune Disease	Toxicity Risk Level	Key Toxicities	General Recommendation
Systemic sclerosis	Very High	Severe fibrosis, necrosis, contracture	Avoid if possible; if essential, modern techniques with dose reduction
Systemic lupus erythematosus	Moderate–High	Mucositis, pneumonitis, enhanced fibrosis	Proceed with caution; manage disease activity; monitor closely
Rheumatoid arthritis	Low–Moderate	Mild increase in acute reactions	Generally safe; caution with concurrent methotrexate
Inflammatory bowel disease	High (pelvic RT)	Severe GI toxicity, perforation, stricture	Avoid pelvic RT if possible; advanced techniques to spare bowel
Dermatomyositis	Moderate–High	Severe dermatitis, myositis	Individualize; monitor skin and muscle carefully
Multiple sclerosis	Moderate (cranial RT)	Demyelination exacerbation	Avoid cranial fields near plaques; standard risk for distant sites
Sjögren syndrome	Moderate (H&N RT)	Accelerated xerostomia	Parotid-sparing techniques essential

RT, radiotherapy; GI, gastrointestinal; H&N, head and neck.

Table 2. Immunosuppressive Medications and Radiotherapy Interactions

Medication	Mechanism of Interaction	Potential Toxicity	Management Recommendation
Methotrexate	Impaired DNA synthesis and repair	Enhanced mucositis, dermatitis	Consider dose reduction or hold during RT to mucosal sites
Cyclophosphamide	DNA alkylation; additive damage	Myelosuppression, mucosal injury	Avoid overlap with RT delivery
TNF-α inhibitors	Suppressed tissue repair signaling	Uncertain; potentially impaired healing	Continue with close monitoring; case-by-case decision
Corticosteroids	Anti-inflammatory; impaired wound healing	Reduced acute inflammation; delayed healing	Continue at lowest effective dose
Mycophenolate mofetil	Antiproliferative; impaired cell renewal	Possible enhanced mucosal toxicity	Monitor closely; adjust based on toxicity
Rituximab	B-cell depletion	Uncertain RT interaction	Continue; monitor for immune-related complications

RT, radiotherapy; TNF-α, tumor necrosis factor-alpha.

available evidence and expert consensus.

Multidisciplinary Pre-treatment Assessment

Prior to initiating radiotherapy, a comprehensive multidisciplinary evaluation involving radiation oncology, rheumatology or relevant subspecialty, and medical oncology is essential [11]. The assessment should characterize the specific autoimmune diagnosis, current disease activity, extent of organ involvement, the presence of active flares versus stable remission, and the complete immunosuppressive medication regimen. Disease-specific considerations must be evaluated: the subtype and extent of SSc, the serological activity of SLE, the mucosal status in IBD, and the neurological burden in MS. This evaluation serves to stratify individual risk and inform subsequent treatment planning decisions. A documented record of baseline organ function, including pulmonary function tests for thoracic irradiation, dermatological assessment of the skin in planned irradiation fields, and relevant organ-specific biomarkers, provides an essential reference for monitoring treatment-related changes [33].

Individualized Dose and Fractionation Strategies

For patients identified as being at elevated risk of radiation toxicity, modifications to standard dose-fractionation regimens may be warranted. Hypofractionation, which delivers larger daily fractions over a shorter overall treatment time, may be considered with caution in selected clinical scenarios, as larger fraction sizes are generally associated with increased late effects; however, the shorter overall treatment course may benefit patients with progressive autoimmune disease [43]. Conversely, hyperfractionation or modest dose reductions have been proposed as strategies to reduce late toxicity,

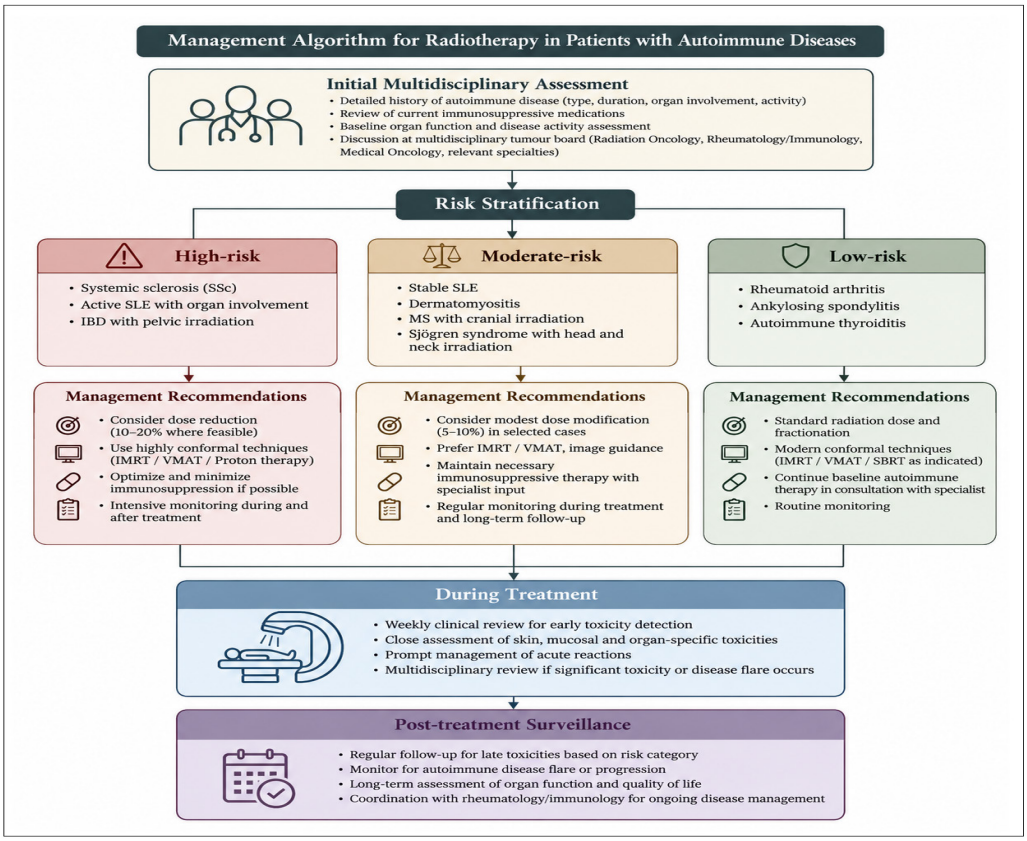

Figure 1. Algorithm for the Proposed Management Approach

although the impact on oncological efficacy must be carefully weighed [44]. In practice, the most common approach involves the use of standard fractionation with reduced overall dose when feasible, though robust evidence supporting specific dose reduction thresholds is lacking. For patients with SSc or other high-risk conditions requiring curative-intent radiotherapy, treatment decisions should be made on a case-by-case basis, weighing the risk of severe toxicity against the consequences of under-treatment [11].

Advanced Radiation Delivery Techniques

Modern radiation technologies offer substantial opportunities to minimize normal tissue exposure, which is particularly valuable in autoimmune disease patients. Intensity-modulated radiotherapy (IMRT) enables precise sculpting of dose distributions to conform to target volumes while reducing dose to adjacent organs at risk [45]. Volumetric modulated arc therapy (VMAT) provides similar conformality with improved treatment delivery efficiency. These techniques are now standard of care for many treatment sites and should be preferentially employed in autoimmune disease patients.

Stereotactic body radiotherapy (SBRT) delivers highly focused radiation in a small number of fractions with steep dose gradients, dramatically reducing the volume of normal tissue exposed to significant radiation doses [46]. For appropriately selected tumors, SBRT may offer a favorable therapeutic ratio in autoimmune disease patients by limiting the radiation exposure of surrounding tissues. However, the higher per-fraction doses inherent to SBRT raise theoretical concerns regarding late effects in tissues with impaired repair capacity, and prospective data in autoimmune populations remain scarce.

Proton beam therapy, by virtue of the Bragg peak effect, deposits minimal exit dose beyond the target volume, offering a dosimetric advantage over photon-based techniques in terms of integral dose to normal tissues [47]. Although data specifically evaluating proton therapy in autoimmune disease patients are extremely limited, the physical properties of proton beams make them an attractive option for reducing toxicity in this population, particularly for thoracic, abdominal, and cranial irradiation sites. The limited availability and higher cost of proton therapy, especially in the Asia Pacific region, currently restrict its widespread application [48].

Management of Immunosuppressive Medications

The management of immunosuppressive therapy during radiotherapy requires careful coordination between the radiation oncologist and the treating rheumatologist or immunologist. The decision to continue, modify, or temporarily suspend immunosuppressive medications must balance the risk of radiation toxicity potentiation against the risk of autoimmune disease flare [49]. A summary of common immunosuppressive agents and their interactions with radiotherapy is provided in Table 2.

General principles include the following: methotrexate should be used with caution during radiotherapy, particularly when treatment fields include mucosal surfaces, and temporary dose reduction or interruption may be considered in consultation with the rheumatologist [21]. Cyclophosphamide and other alkylating agents should ideally not overlap with radiotherapy delivery due to additive DNA-damaging effects [22]. Biologic agents, including TNF-α inhibitors and B-cell depleting therapies, have uncertain interactions with radiation and may be continued with close monitoring unless clinical circumstances suggest otherwise [23, 50]. Corticosteroids may have a dual role, potentially mitigating acute radiation-induced inflammation while also contributing to impaired wound healing; their continuation at the lowest effective dose is generally recommended [24]. A planned approach to medication management, documented prior to treatment initiation, reduces the risk of ad hoc decisions during therapy.

Supportive Care and Monitoring

Proactive supportive care is integral to the management of autoimmune disease patients during radiotherapy. Aggressive prophylactic skin care, including emollient application and avoidance of irritants, is recommended for all patients and is particularly important for those with dermatological autoimmune conditions [51]. For patients receiving pelvic radiotherapy with concurrent IBD, close collaboration with gastroenterology and the early initiation of antidiarrheal and mucosal protective agents may reduce acute toxicity [38]. Weekly clinical assessments during treatment, with a low threshold for imaging or laboratory investigation of emerging symptoms, enable early detection and management of complications. Post-treatment surveillance should be intensified in autoimmune disease patients, as late toxicities may manifest months to years following irradiation and may be difficult to distinguish from progression of the underlying autoimmune condition [10].

Emerging Approaches and Future Directions

Biomarkers for Radiosensitivity Prediction

The ability to prospectively identify autoimmune disease patients at the highest risk of radiation toxicity would represent a major advance in clinical management. Several candidate biomarkers are under investigation. Assays measuring the efficiency of DNA double-strand break repair, such as the gamma-H2AX foci assay, have demonstrated potential for predicting individual radiosensitivity in preliminary studies [52]. The clonogenic survival assay of skin fibroblasts remains a research tool for assessing intrinsic radiosensitivity, although its clinical applicability is limited by the time required for cell culture [53]. Circulating cytokine profiles, including baseline levels of TGF-β, IL-6, and TNF-α, may provide accessible and rapidly obtainable indicators of fibrotic propensity and inflammatory predisposition [54]. Genetic polymorphisms in DNA repair genes and radiation-responsive genes represent another avenue for risk stratification, with several candidate single-nucleotide polymorphisms identified in population studies, though validation in autoimmune disease cohorts is needed [55].

Radiogenomics and Precision Medicine

The burgeoning field of radiogenomics seeks to identify genetic determinants of radiation response that can be integrated into clinical decision-making [56]. Genome-wide association studies have identified several loci associated with radiation toxicity susceptibility in the general population, and the integration of autoimmune disease-specific genetic information with radiogenomic data may enable the development of composite risk models with improved predictive accuracy [57]. Machine learning approaches combining clinical variables, genomic data, dosimetric parameters, and autoimmune disease characteristics hold promise for individualized toxicity prediction, although prospective validation studies are required [58].

Immunotherapy-Radiotherapy Interactions

The increasing use of immune checkpoint inhibitors in oncological practice introduces an additional layer of complexity for autoimmune disease patients requiring combined modality treatment. Checkpoint inhibitors carry significant risks of exacerbating autoimmune disease, and their combination with radiotherapy may further amplify both anti-tumor immune responses and autoimmune toxicity [59]. The abscopal effect, whereby radiation at one site induces immune-mediated regression at distant sites, is of particular scientific interest but also raises concerns regarding the potential for widespread immune activation in patients with pre-existing autoimmune dysregulation [60]. The management of autoimmune disease patients receiving concurrent radiotherapy and immunotherapy remains a rapidly evolving area requiring careful multidisciplinary oversight.

Image-Guided and Adaptive Radiotherapy

Advances in image guidance and adaptive radiotherapy allow real-time monitoring and adjustment of treatment plans in response to anatomical changes and treatment-related tissue alterations. Daily image-guided radiotherapy using cone-beam computed tomography enables precise target localization and margin reduction, minimizing unnecessary irradiation of normal tissues [61]. Adaptive radiotherapy, in which treatment plans are modified during the course of treatment based on observed changes in tumor volume and normal tissue geometry, may be particularly valuable for autoimmune disease patients in whom early tissue reactions necessitate replanning to avoid escalating toxicity [62]. The incorporation of functional imaging modalities, such as positron emission tomography and magnetic resonance imaging, into the adaptive planning process may further enhance the ability to balance tumor control with normal tissue protection [63].

Considerations for the Asia Pacific Region

The management of autoimmune disease patients requiring radiotherapy in the Asia Pacific region is shaped by several region-specific factors. The prevalence and phenotypic expression of autoimmune diseases vary across Asian populations, with SLE being notably more common and often more severe in East and Southeast Asian patients compared with Western populations [3]. Genetic variations in drug-metabolizing enzymes and DNA repair genes among Asian populations may influence both autoimmune disease susceptibility and radiation sensitivity, although specific data linking these polymorphisms to clinical outcomes in the context of concurrent autoimmune disease and radiotherapy are lacking [3]. Access to advanced radiation technologies, including IMRT, SBRT, and proton therapy, varies widely across the region, with high-resource centers in Japan, South Korea, Australia, and Singapore contrasting with more limited availability in many lower-income settings [64]. The development of region-specific clinical guidelines and prospective registry studies would significantly enhance the evidence base for managing this complex patient population in the Asia Pacific context.

In conclusion, radiotherapy in patients with autoimmune diseases requires careful consideration of the complex interplay between radiation biology and immune dysregulation. The evidence indicates that the risk of radiation toxicity is not uniform across autoimmune conditions: SSc carries the highest risk and warrants the greatest caution, while RA and many other conditions confer more modest excess risk that can generally be managed with appropriate precautions. The fundamental principles of management include comprehensive multidisciplinary assessment, individualized treatment planning with advanced radiation technologies to minimize normal tissue exposure, coordinated immunosuppressive medication management, and proactive supportive care with enhanced surveillance. The integration of emerging biomarkers, radiogenomic approaches, and adaptive treatment strategies holds promise for further improving the therapeutic ratio in this vulnerable population. Prospective, multicenter studies incorporating standardized toxicity assessment and long-term follow-up are urgently needed to strengthen the evidence base and enable the development of robust clinical guidelines, particularly within the Asia Pacific region where the burden of autoimmune disease and cancer converges in a context of evolving oncological infrastructure.

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Conflict of Interest

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References

1. Davidson A, Diamond B. Autoimmune diseases. The New England Journal of Medicine. 2001 08 02;345(5):340-350. https://doi.org/10.1056/NEJM200108023450506
2. Cooper GS, Bynum MLK, Somers EC. Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases. Journal of Autoimmunity. 2009;33(3-4):197-207. https://doi.org/10.1016/j.jaut.2009.09.008
3. Lau CS, Yin G, Mok MY. Ethnic and geographical differences in systemic lupus erythematosus: an overview. Lupus. 2006;15(11):715-719. https://doi.org/10.1177/0961203306072311
4. Franks AL, Slansky JE. Multiple associations between a broad spectrum of autoimmune diseases, chronic inflammatory diseases and cancer. Anticancer Research. 2012 04;32(4):1119-1136.
5. Simon TA, Thompson A, Gandhi KK, Hochberg MC, Suissa S. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. Arthritis Research & Therapy. 2015 08 15;17(1):212. https://doi.org/10.1186/s13075-015-0728-9
6. Hill CL, Zhang Y, Sigurgeirsson B, Pukkala E, Mellemkjaer L, Airio A, Evans SR, Felson DT. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. Lancet. 2001 01 13;357(9250):96-100. https://doi.org/10.1016/S0140-6736(00)03540-6
7. Delaney G, Jacob S, Featherstone C, Barton M. The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. Cancer. 2005 09 15;104(6):1129-1137. https://doi.org/10.1002/cncr.21324
8. Lomax ME, Folkes LK, O'Neill P. Biological consequences of radiation-induced DNA damage: relevance to radiotherapy. Clinical Oncology (Royal College of Radiologists (Great Britain)). 2013 Oct;25(10):578-585. https://doi.org/10.1016/j.clon.2013.06.007
9. Pinn ME, Gold DG, Petersen IA, Osborn TG, Brown PD, Miller RC. Systemic lupus erythematosus, radiotherapy, and the risk of acute and chronic toxicity: the Mayo Clinic Experience. International Journal of Radiation Oncology, Biology, Physics. 2008 06 01;71(2):498-506. https://doi.org/10.1016/j.ijrobp.2007.10.014
10. Morris MM, Powell SN. Irradiation in the setting of collagen vascular disease: acute and late complications. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 1997 07;15(7):2728-2735. https://doi.org/10.1200/JCO.1997.15.7.2728
11. Giaj-Levra N, Sciascia S, Fiorentino A, Fersino S, Mazzola R, Ricchetti F, et al. Radiotherapy in patients with connective tissue diseases. Lancet Oncol. 2016;17(3):e109-e17. https://doi.org/10.1016/s1470-2045(15)00417-9
12. Ross JG, Hussey DH, Mayr NA, Davis CS. Acute and late reactions to radiation therapy in patients with collagen vascular diseases. Cancer. 1993 06 01;71(11):3744-3752. https://doi.org/10.1002/1097-0142(19930601)71:11<3744::aid-cncr2820711144>3.0.co;2-c
13. Reeves WH, Lee PY, Weinstein JS, Satoh M, Lu L. Induction of autoimmunity by pristane and other naturally occurring hydrocarbons. Trends in Immunology. 2009 09;30(9):455-464. https://doi.org/10.1016/j.it.2009.06.003
14. Bassi C, Xavier D, Palomino G, Nicolucci P, Soares C, Sakamoto-Hojo E, et al. Efficiency of the DNA repair and polymorphisms of the xrcc1, xrcc3 and xrcc4 DNA repair genes in systemic lupus erythematosus. Lupus. 2008;17(11):988-95. https://doi.org/10.1177/0961203308093461
15. Schaue D, Kachikwu EL, McBride WH. Cytokines in radiobiological responses: a review. Radiation Research. 2012 Dec;178(6):505-523. https://doi.org/10.1667/RR3031.1
16. Mavragani IV, Laskaratou DA, Frey B, Candéias SM, Gaipl US, Lumniczky K, Georgakilas AG. Key mechanisms involved in ionizing radiation-induced systemic effects. A current review. Toxicology Research. 2015 08 11;5(1):12-33. https://doi.org/10.1039/c5tx00222b
17. Varga J, Abraham D. Systemic sclerosis: a prototypic multisystem fibrotic disorder. The Journal of Clinical Investigation. 2007 03;117(3):557-567. https://doi.org/10.1172/JCI31139
18. Hauer-Jensen M, Denham JW, Andreyev HJN. Radiation enteropathy--pathogenesis, treatment and prevention. Nature Reviews. Gastroenterology & Hepatology. 2014 08;11(8):470-479. https://doi.org/10.1038/nrgastro.2014.46
19. Guiducci S, Giacomelli R, Cerinic MM. Vascular complications of scleroderma. Autoimmunity Reviews. 2007 09;6(8):520-523. https://doi.org/10.1016/j.autrev.2006.12.006
20. Varga J, Haustein UF, Creech RH, Dwyer JP, Jimenez SA. Exaggerated radiation-induced fibrosis in patients with systemic sclerosis. Jama. 1991;265(24):3292-5.
21. Kharfan Dabaja MA, Morgensztern D, Markoe AM, Bartlett-Pandite L. Radiation recall dermatitis induced by methotrexate in a patient with hodgkin's disease. Am J Clin Oncol. 2000;23(5):531-3. https://doi.org/10.1097/00000421-200010000-00020.
22. Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, Shank B, Solin LJ, Wesson M. Tolerance of normal tissue to therapeutic irradiation. International Journal of Radiation Oncology, Biology, Physics. 1991 05 15;21(1):109-122. https://doi.org/10.1016/0360-3016(91)90171-y
23. Brix N, Tiefenthaller A, Anders H, Belka C, Lauber K. Abscopal, immunological effects of radiotherapy: Narrowing the gap between clinical and preclinical experiences. Immunological Reviews. 2017 Nov;280(1):249-279. https://doi.org/10.1111/imr.12573
24. Gutierrez-Dalmau A, Campistol JM. Immunosuppressive therapy and malignancy in organ transplant recipients: a systematic review. Drugs. 2007;67(8):1167-1198. https://doi.org/10.2165/00003495-200767080-00006
25. Straub JM, New J, Hamilton CD, Lominska C, Shnayder Y, Thomas SM. Radiation-induced fibrosis: mechanisms and implications for therapy. Journal of Cancer Research and Clinical Oncology. 2015 Nov;141(11):1985-1994. https://doi.org/10.1007/s00432-015-1974-6
26. Denton CP, Khanna D. Systemic sclerosis. Lancet. 2017 Oct 07;390(10103):1685-1699. https://doi.org/10.1016/S0140-6736(17)30933-9
27. Gold DG, Miller RC, Pinn ME, Osborn TG, Petersen IA, Brown PD. Chronic toxicity risk after radiotherapy for patients with systemic sclerosis (systemic scleroderma) or systemic lupus erythematosus: Association with connective tissue disorder severity. Radiother Oncol. 2008;87(1):127-31. https://doi.org/10.1016/j.radonc.2007.11.031
28. Chen AM, Obedian E, Haffty BG. Breast-conserving therapy in the setting of collagen vascular disease. Cancer J. 2001;7(6):480-91.
29. Lin A, Abu-Isa E, Griffith KA, Ben-Josef E. Toxicity of radiotherapy in patients with collagen vascular disease. Cancer. 2008 08 01;113(3):648-653. https://doi.org/10.1002/cncr.23591
30. Dragun AE, Harper JL, Olyejar SE, Zunzunegui RG, Wazer DE. The use of adjuvant high-dose-rate breast brachytherapy in patients with collagen vascular disease: A collaborative

experience. Brachytherapy. 2011;10(2):121-7. https://doi.org/10.1016/j.brachy.2010.05.001.
31. Shaikh PM, Singh SA, Alite F, Vargo JA, Emami B, Wu MJ, et al. Radiation toxicity in patients with collagen vascular disease: A meta-analysis of case-control studies. Int J Radiat Oncol Biol Phys. 2021;111(5):1214-26. https://doi.org/10.1016/j.ijrobp.2021.08.006.
32. Olivotto IA, Fairey RN, Gillies JH, Stein H. Fatal outcome of pelvic radiotherapy for carcinoma of the cervix in a patient with systemic lupus erythematosis. Clin Radiol. 1989;40(1):83-4. https://doi.org/10.1016/s0009-9260(89)80040-6
33. Diao K, Chen YH, Catalano PJ, Lee S, Milani N, Killoran JH, et al. Radiation toxicity in patients with collagen vascular disease and intrathoracic malignancy treated with modern radiation techniques. Radiother Oncol. 2017;125(2):301-9. https://doi.org/10.1016/j.radonc.2017.10.002
34. Fleck R, McNeese MD, Ellerbroek NA, Hunter TA, Holmes FA. Consequences of breast irradiation in patients with pre-existing collagen vascular diseases. Int J Radiat Oncol Biol Phys. 1989;17(4):829-33. https://doi.org/10.1016/0360-3016(89)90074-6
35. Lin D, Lehrer EJ, Rosenberg J, Trifiletti DM, Zaorsky NG. Toxicity after radiotherapy in patients with historically accepted contraindications to treatment (contrad): An international systematic review and meta-analysis. Radiother Oncol. 2019;135:147-52. https://doi.org/10.1016/j.radonc.2019.03.006.
36. Wo J, Taghian A. Radiotherapy in setting of collagen vascular disease. Int J Radiat Oncol Biol Phys. 2007;69(5):1347-53. https://doi.org/10.1016/j.ijrobp.2007.07.2357
37. Bijlsma JW, Hachulla E. EULAR Textbook on Rheumatic Diseases. 2nd ed. London: BMJ Publishing Group; 2015.
38. Willett CG, Ooi CJ, Zietman AL, Menon V, Goldberg S, Sands BE, et al. Acute and late toxicity of patients with inflammatory bowel disease undergoing irradiation for abdominal and pelvic neoplasms. Int J Radiat Oncol Biol Phys. 2000;46(4):995-8. https://doi.org/10.1016/s0360-3016(99)00374-0
39. Huang PY, Zhong ZL, Luo DH, Mai HQ, Chen MY, Li YX, et al. Paired study of 172 cases of nasopharyngeal carcinoma with or without dermatomyositis. Acta Otolaryngol. 2014;134(8):824-30. https://doi.org/10.3109/00016489.2014.913312
40. Miller RC, Lachance DH, Lucchinetti CF, Keegan BM, Gavrilova RH, Brown PD, et al. Multiple sclerosis, brain radiotherapy, and risk of neurotoxicity: The mayo clinic experience. Int J Radiat Oncol Biol Phys. 2006;66(4):1178-86. https://doi.org/10.1016/j.ijrobp.2006.06.014
41. Mavragani CP, Moutsopoulos HM. Sjögren syndrome. Cmaj. 2014;186(15):E579-86. https://doi.org/10.1503/cmaj.122037.
42. Weiss HA, Darby SC, Doll R. Cancer mortality following x-ray treatment for ankylosing spondylitis. Int J Cancer. 1994;59(3):327-38. https://doi.org/10.1002/ijc.2910590307.
43. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The uk standardisation of breast radiotherapy (start) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol. 2013;14(11):1086-94. https://doi.org/10.1016/s1470-2045(13)70386-3.
44. Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, Bentzen SM, Bliss JM, et al. The uk standardisation of breast radiotherapy (start) trial b of radiotherapy hypofractionation for treatment of early breast cancer: A randomised trial. Lancet. 2008;371(9618):1098-107. https://doi.org/10.1016/s0140-6736(08)60348-7.
45. Intensity-modulated radiotherapy: Current status and issues of interest. Int J Radiat Oncol Biol Phys. 2001;51(4):880-914. https://doi.org/10.1016/s0360-3016(01)01749-7.
46. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, Fakiris A , et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. Jama. 2010;303(11):1070-6. https://doi.org/10.1001/jama.2010.261.
47. Mohan R, Grosshans D. Proton therapy - present and future. Adv Drug Deliv Rev. 2017;109:26-44. https://doi.org/10.1016/j.addr.2016.11.006.
48. Liao Z, Lee JJ, Komaki R, Gomez DR, O'Reilly MS, Fossella FV, Blumenschein GR ,et al. Bayesian adaptive randomization trial of passive scattering proton therapy and intensity-modulated photon radiotherapy for locally advanced non-small-cell lung cancer. J Clin Oncol. 2018;36(18):1813-22. https://doi.org/10.1200/jco.2017.74.0720.
49. Holroyd CR, Seth R, Bukhari M, Malaviya A, Holmes C, Curtis E, Chan C ,et al. The british society for rheumatology biologic dmard safety guidelines in inflammatory arthritis. Rheumatology (Oxford). 2019;58(2):e3-e42. https://doi.org/10.1093/rheumatology/key208.
50. Burmester GR, Bijlsma JWJ, Cutolo M, McInnes IB. Managing rheumatic and musculoskeletal diseases - past, present and future. Nat Rev Rheumatol. 2017;13(7):443-8. https://doi.org/10.1038/nrrheum.2017.95.
51. Salvo N, Barnes E, van Draanen J, Stacey E, Mitera G, Breen D, Giotis A, et al. Prophylaxis and management of acute radiation-induced skin reactions: A systematic review of the literature. Curr Oncol. 2010;17(4):94-112. https://doi.org/10.3747/co.v17i4.493.
52. Olive PL, Banáth JP. Phosphorylation of histone h2ax as a measure of radiosensitivity. Int J Radiat Oncol Biol Phys. 2004;58(2):331-5. https://doi.org/10.1016/j.ijrobp.2003.09.028.
53. Burnet NG, Nyman J, Turesson I, Wurm R, Yarnold JR, Peacock JH. Prediction of normal-tissue tolerance to radiotherapy from in-vitro cellular radiation sensitivity. Lancet. 1992;339(8809):1570-1. https://doi.org/10.1016/0140-6736(92)91833-t.
54. Anscher MS, Chen L, Rabbani Z, Kang S, Larrier N, Huang H, Samulski TV, et al. Recent progress in defining mechanisms and potential targets for prevention of normal tissue injury after radiation therapy. Int J Radiat Oncol Biol Phys. 2005;62(1):255-9. https://doi.org/10.1016/j.ijrobp.2005.01.040.
55. Barnett GC, Coles CE, Elliott RM, Baynes C, Luccarini C, Conroy D, Wilkinson JS, et al. Independent validation of genes and polymorphisms reported to be associated with radiation toxicity: a prospective analysis study. The Lancet. Oncology. 2012 01;13(1):65-77. https://doi.org/10.1016/S1470-2045(11)70302-3
56. West CM, Barnett GC. Genetics and genomics of radiotherapy toxicity: towards prediction. Genome Medicine. 2011 08 23;3(8):52. https://doi.org/10.1186/gm268
57. Kerns SL, Fachal L, Dorling L, Barnett GC, Baran A, Peterson DR, Hollenberg M, et al. Radiogenomics Consortium Genome-Wide Association Study Meta-Analysis of Late Toxicity After Prostate Cancer Radiotherapy. Journal of the National Cancer Institute. 2020 02 01;112(2):179-190. https://doi.org/10.1093/jnci/djz075
58. Rosenstein BS, West CM, Bentzen SM, Alsner J, Andreassen CN, Azria D, Barnett GC, et al. Radiogenomics: radiobiology enters the era of big data and team science. International Journal of Radiation Oncology, Biology, Physics. 2014 07 15;89(4):709-713. https://doi.org/10.1016/j.

ijrobp.2014.03.009
59. Abdel-Wahab N, Shah M, Lopez-Olivo MA, Suarez-Almazor ME. Use of Immune Checkpoint Inhibitors in the Treatment of Patients With Cancer and Preexisting Autoimmune Disease: A Systematic Review. Annals of Internal Medicine. 2018 01 16;168(2):121-130. https://doi.org/10.7326/M17-2073
60. Ngwa W, Irabor OC, Schoenfeld JD, Hesser J, Demaria S, Formenti SC. Using immunotherapy to boost the abscopal effect. Nature Reviews. Cancer. 2018 05;18(5):313-322. https://doi.org/10.1038/nrc.2018.6
61. Jaffray DA. Image-guided radiotherapy: from current concept to future perspectives. Nature Reviews. Clinical Oncology. 2012 Dec;9(12):688-699. https://doi.org/10.1038/nrclinonc.2012.194
62. Sonke J, Aznar M, Rasch C. Adaptive Radiotherapy for Anatomical Changes. Seminars in Radiation Oncology. 2019 07;29(3):245-257. https://doi.org/10.1016/j.semradonc.2019.02.007
63. Thorwarth D. Functional imaging for radiotherapy treatment planning: current status and future directions-a review. The British Journal of Radiology. 2015 07;88(1051):20150056. https://doi.org/10.1259/bjr.20150056
64. Abu Awwad D, Shafiq J, Delaney GP, Anacak Y, Bray F, Flores JA, et al. Current and projected gaps in the availability of radiotherapy in the asia-pacific region: A country income-group analysis. Lancet Oncol. 2024;25(2):225-34. https://doi.org/10.1016/s1470-2045(23)00619-8.