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Radiotherapy in cancer and rheumathoid arthritis patients: cancer treatment or control of articular flares? We can achieve both

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Abstract. – OBJECTIVE: The study was aimed to investigate the role of radiotherapy (RT) as a risk factor for reactivation or worsening of symptoms in patients affected by rheumatoid arthritis (RA)

PATIENTS AND METHODS: This is a single-center retrospective observational study on RA patients who developed cancer requiring RT during the course of the disease. The control group consisted of RA patients with cancer who did not undergo RT. In both groups, the disease activity was evaluated at baseline and at 6 and 12 months through the DAS28 index. A relapse was defined as an increase of >20% in DAS28. A radiotherapist evaluated total and daily doses and timing of radiation. Acute and late toxicity was defined as events occurring within 90 days from the start and more than 90 days after the completion of RT, respectively.

RESULTS: Seventy-two RA patients (38F/34M; mean age: 70±9 years; mean disease duration: 13±9 years), 29 (40.2%) of whom received radiotherapy (mean age 72.9±9 years), were enrolled. The most frequent malignancies were breast (27.2%), thyroid (9.8%), and skin (7%). Between radio-treated and non-radio-treated patients, no significant differences in RA reactivation (6/29 vs. 17/43; p=0.12) or mean exacerbation time (6.7 ± 4.9 months compared to 6.4 ± 4.1 months; p=0.78) were found. Overall, RT was well tolerated with low rates of both acute and late toxicity.

CONCLUSIONS: In RA patients, RT was well tolerated and not associated with an increased risk of articular flares. Properly designed prospective clinical studies with a larger number of patients should be performed to confirm these data.

Key Words:
Radiotherapy, Rheumatoid arthritis, Cancer.

Introduction

Radiotherapy (RT) is the most common therapeutic option for cancer, as more than 60% of patients with solid tumors receive this treatment[1]. Radiation induces DNA damage in cells, known as the "target effect", which is primarily responsible for tumor growth control. As a consequence of the target effect, it was traditionally believed that RT had only immunosuppressive properties. In agreement with this assumption, after radiation treatment, the peripheral blood's lymphocyte levels are reduced[2]. However, it is now widely accepted that RT can also induce antitumor activity by stimulating the immune system, the so-called "nontargeted effect", although the ways by which radiation affects the immune system (i.e., total dose, daily dose, and timing) are not satisfactorily understood[3]. One of the recognized mechanisms related to the nontargeted effect is the ability of RT to enhance antigen presentation[4]. An immunomodulatory effect of radiation would be a potential therapeutic approach for cancer, considering the synergistic effect of checkpoint inhibitors[5]. On this basis, it is conceivable that an enhanced immune response might be associated with reactivation

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and/or worsening of symptoms in patients with autoimmune diseases undergoing RT.

Antigen-presenting cells play a key role in rheumatoid arthritis (RA), as they are crucial in triggering and/or maintaining the chronic inflammatory process[6]. The possible consequences of RT on the progression of RA as a result of its effects on the immune system are not yet fully known and defined, nor is whether RT could be responsible for the flare-up in the course of the disease and/or how often this occurs. The few available studies in the literature report conflicting results.

Our study's main objective was to verify whether RT has some influence on RA disease activity by retrospective analysis of a cohort of patients suffering from RA who developed cancer requiring RT treatment during the disease.

Patients and Methods

Patient Selection

This is a single-center retrospective observational study performed using criteria on the Preliminary Core Set of Domains and Reporting Requirements for Longitudinal Observational Studies in Rheumatology proposed by Wolfe et al[7]. All RA patients followed at the Rheumatology Unit of the University S. Anna Hospital of Ferrara, Italy, from January 2005 to December 2015 who developed cancer requiring RT during the course of RA were recruited. RT was performed at the Radiation Oncology Department of the University Hospital of Ferrara. Patients were identified by searching the available electronic medical records. Data were retrieved from the electronic database and clinical charts of patients.

From the total number of patients identified, those with incomplete histories or clinical data, and those who had neoplasms that appeared before the diagnosis of RA were excluded from the analysis. All recruited RA patients met the 1987 revised criteria for the classification of rheumatoid arthritis[8].

Of all selected RA patients, the following characteristics were analyzed: demographic data (age, sex, province of residence); date of diagnosis of RA; clinical and laboratory data (rheumatoid factor, anti-peptide citrullinated antibodies); date of cancer diagnosis and temporal relationship with RA; pharmacological therapy and disease activity of RA at the time of cancer diagnosis, the latter assessed through the Disease Activity Score on 28 Joints (DAS28) scale[9]; number and type of prior employed conventional DMARDs (cDMARDs) and biological drugs (bDMARDs); type of cancer, respective code according to the ICD classification and TNM staging and cancer therapy. After cancer diagnosis, in agreement with oncologists, patients treated with biological drug therapy discontinued bDMARDs. All RA patients continued drug therapy with low-dose steroids and/or cDMARDs according to the degree of disease activity and the "treat to target" strategy[10].

In all RA patients with cancer who underwent RT, the DAS28 was evaluated over 12 consecutive months [at the beginning of RT (T0) and after 6 (T6) and 12 (T12) months]. Remission of RA was defined as DAS28 <2.6; low disease activity >2.6 and <3.2; moderate >3.2 and <5.1; and high >5.1.

A relapse was defined as an increase of > 20% in DAS28 compared to the value at optimization. Radiation oncologists analyzed radiation delivery in terms of total dose, daily dose, and timing. The reactivation time was defined as the time that relapsed from the beginning of the RT up to the moment in which a modification of the treatment for the reactivation of the AR was requested. During radiation treatment, patients were monitored for adverse events, and visits included a clinical assessment and physical examination. Medical records were reviewed to evaluate and classify side effects and toxicity according to the National Cancer Institute (NCI) expanded Common Toxicity Criteria, version 3.0. Acute toxicity was defined as events occurring during radiotherapy to within 90 days of completion of radiotherapy, and late toxicity was defined as events occurring >90 days after radiotherapy completion.

As a control population, the group of RA patients with cancer for whom no RT treatment was required was evaluated. In these patients, the same evaluation of disease activity was performed within 12 months after the start of the specific therapy (surgical, chemotherapy, hormonal, etc.) at T0, T6, and T12. Data were anonymously analyzed and reported. The study was approved by the Ethical Research Committee of the University Hospital of Ferrara, Italy.

Data Analysis

Differences between groups were estimated according to the Kaplan-Meier method. Kaplan-Meier survival plots were used to determine and visualize differences in time-to-event data, with statistical significance ($p<0.05$) of differ-

ences evaluated by log-rank test. Continuous and categorical baseline variables were analyzed using *t*-tests and Fisher's exact tests, respectively, with significance set at α=5%. We did not perform multivariate analyses because the statistics became unstable due to the small sample size. SPSS 13.0 (SPSS for Windows, Rel. 13.0 2004. Chicago, IL, USA) was used for the analysis.

Results

Features of Patients at Baseline

Between 2005 and 2015, a total of 2,548 patients with RA were followed at the Rheumatologic Unit of University Hospital of Ferrara, Italy. A cancer diagnosis was made in 171 (6.7%) RA patients. Of these, 43 (25.1%) were excluded from the analysis because the cancer was diagnosed before the onset of RA (10.5±9.6 years). Of the remaining 128 (74.8%) in whom cancer was diagnosed after the onset of RA (8.6± 8.3 years), 56 (32.7%) were excluded because of insufficient data (lost to treatment or to follow-up), and 72 (42.1%) were included in the study protocol. The main baseline clinical and demographic data of patients finally included in the study are summarized in Table I. Considering all 128 RA patients in which cancer was diagnosed after the onset of RA, the main types of cancer were breast (27.2%), thyroid (9.8%), and cutaneous (7%) (1 melanoma and 8 NMSC). Pharmacological treatment of the 72 patients included in the study up to the time of cancer diagnosis is summarized in Table II (90.2% medium-low corticosteroids, 86.1% cDMARDs, 22.2% biological drugs (bDMARDs). Among the cDMARDs, the most commonly used drug was methotrexate (alone or associated with other cDMARDs), followed by hydroxychloroquine, leflunomide, and salazopyrin. Of the 72 recruited patients, 29 (40.2%; mean age: 72.9 ± 9 years) underwent RT as the standard of care, in addition to surgery, chemotherapy, hormonotherapy, or a combination of treatments as needed; the remaining 43 patients (48.2%) did not receive RT. In both groups, no patient received immune checkpoint inhibitor drugs. Radiotherapy was conventionally administered with a daily dose (1.8-2 Gy) in all patients except 5 (17.2%), in which a high daily dose (hypofractionated radiotherapy) between 5 and 8 Gy was used, with the total dose between 20 and 40 Gy. At the time of diagnosis of cancer, the mean DAS28-CRP was 2.25 (± 0.4 SD) for patients undergoing RT and 2.3 (± 0.9 SD) for those not radio-treated (p=0.78). Differences between the two groups regarding sex, DAS28-CRP, the use of cDMARDs/bDMARDs at the time of the diagnosis of cancer, and main treatments other than RT for cancer are reported in **Supplemental Digital Content I**. The types of cancer found in radio-treated and non-radio-treated patients are reported in **Supplemental Digital Content II**.

Table I. Main demographic data of the 72 recruited patients with RA and cancer.

Sex, n (%)	F: 38 (52.7%) M: 34 (47.3%)
Age, mean ± SD	70±9
Smokers, %	7.8%
RF+, %	46.2%
aCCP+, %	37.9%
Disease duration (years), mean ± SD	13±9

RF: Rheumatoid factor; aCCP: anti-cyclic citrullinated peptide antibodies;

Radiation-Related Toxicity

Globally, RT was well tolerated among patients. Only four patients (13.8%) experienced grade 3 acute toxicity: one patient had G3 mu-

Table II. Effect on nervous system and digestive system of subjects exposed to occupational lead (mean±SD).

Therapy	RA Patients n (%)	Number of DMARDs
cDMARDs (Methotrexate, Leflunomide, Salazopyrin, Hydroxychloroquine)	62/72 (86.1%)	-1 DMARD: 39/62 (62.9%) -Association of 2 DMARDs: 23/62 (37%)
bDMARDs	16/72 (22.2%)	-1 bDMARD: 10/16 (62.5%) -2 bDMARDs: 4/16 (25%)* -3 bDMARDs: 2/16 (12.5%)*
Corticosteroids, n (%)	65/72 (90.2%)	

cDMARDs: conventionals DMARDs; bDMARDs: biologic DMARDs; *patients who carried out a biologic switch/swap for ineffectiveness or adverse events

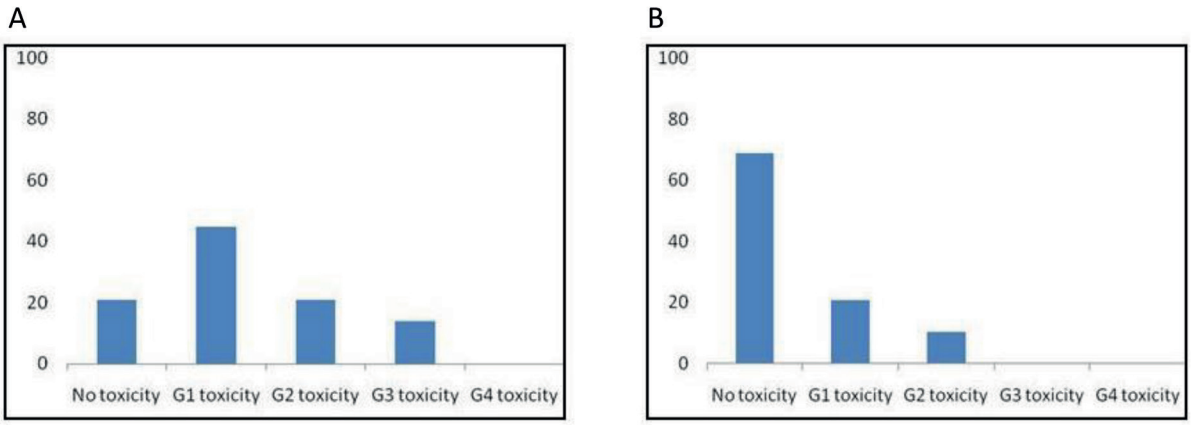

Figure 1. Distribution of acute toxicities (**A**) and late toxicities (**B**) by radiotherapy.

cositis during RT for non-small cell lung cancer, and three patients had G3 proctitis during RT for prostate cancer. No grade 4 or higher acute toxicity was observed. The late toxicity profile was also very favorable, with a low rate of grade 2 observed in 3 patients (10.3%) treated for prostate cancer. No grade 3 or higher late toxicity was evidenced. The rates of acute and late toxicities are listed in Figure 1.

Flare of Rheumatoid Arthritis

Based on DAS 28-CRP scores calculated at the start of RT, after 6 months, and after 12 months, relapse of RA occurred in 6 of the radio-treated patients (20.6%) (Figure 2) and 17 of the non-radio-treated (39.5%) (p=0.12) (Table III). In all patients, RA was pre-existing with respect to the onset of cancer.

In the 12-month observation period, the average exacerbation time was 6.7 (± 4.9) months among patients who underwent RT and 6.4 (± 4.1) months among patients not radio-treated (p=0.78). The actuarial overall relapse-free survival rates at 6 and 12 months were 82.8% and 79.3%, respectively (Figure 3A). Among relapsed patients, three (50%) were radio-treated with a daily dose ≥ 5 Gy. Of these, two (33.3%) had non-small cell lung cancer (daily dose: 8 Gy), and one

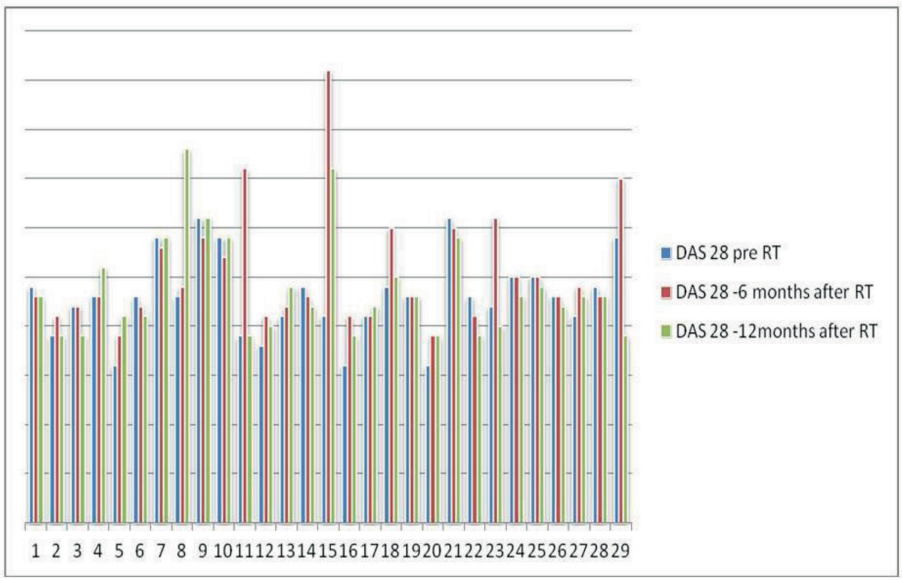

Figure 2. Variation in DAS 28 at 6 and 12 months after radiotherapy.

Table III. Exacerbation of the disease in the 12-month observation period in the two patient subgroups (with and without RT).

	RT n (%)	No RT n (%)
Relapse	29/72 (40.2%)	43/72 (59.7%)
(20.6%)	6/29 17/43 (39.5%)	p=0.12

cDMARDs: conventionals DMARDs; bDMARDs: biologic DMARDs; *patients who carried out a biologic switch/swap for ineffectiveness or adverse events

(16.7%) had gastrointestinal cancer (daily dose: 5 Gy). The other 3 relapses (33.3%) occurred in patients treated with conventional daily radiation doses. Of these, two were also treated with chemotherapy and had gastrointestinal cancer and small cell lung cancer, respectively, and one had breast cancer. The actuarial relapse-free survival in patients treated with a daily radiation dose ≥ 5 Gy is shown in Figure 3B.

A sub-analysis in radio-treated patients was performed to evaluate the possible influence of factors other than RT on exacerbation. The variables considered were sex, age, disease duration, anti-rheumatic therapy and disease activity at the time of cancer diagnosis, chemotherapy, total dose of RT, dose of each session, and number of radiotherapy sessions. The differences between the subjects who flared up and those who did not are reported in **Supplemental Digital Content III**.

Discussion

There is a well-known and complex relationship between rheumatic diseases and cancer. In addition to primary or secondary osteoarticular tumors and paraneoplastic forms (atypical rheumatic syndromes that may precede or follow the detection of a neoplasm), some well-defined rheumatic diseases, such as rheumatic polymyalgia, Sjogren's syndrome, systemic lupus erythematous, and RA, may be associated with cancer more frequently than others[11,12]. The pathogenetic mechanisms underlying this relationship are substantially unknown. One of the most reliable hypotheses is the influence of the inflammatory status on the risk of developing both hematological and solid tumors[12]. Furthermore, it has been ascertained that the activation of B and T lymphocytes against self-antigens also contributes to cancer development[13]. The onset of malignancy in the course of chronic inflammatory rheumatic disease seriously affects the patient's quality of life not only for the consequences inherent to neoplastic disease and its treatments but also for the possible discontinuation of anti-rheumatic therapy, with the consequent risk of exacerbation of the rheumatic disease itself. To date, one of the problems not yet fully resolved is whether patients with pre-existing rheumatic diseases undergoing RT can be at increased risk for flares of their underlying disease and whether there are differences in comparison with neoplastic patients who do not undergo RT[14,15]. Through its "target effect", RT induces DNA damage in cells, which is pri-

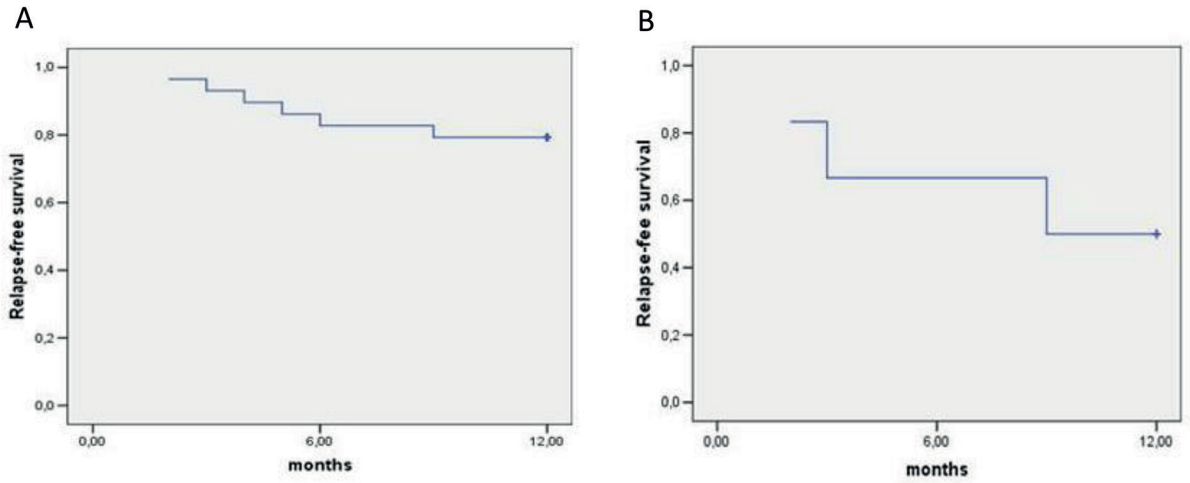

Figure 3. A, Actuarial overall relapse-free survival rates at 6 and 12 months in the 29 radio-treated patients. **B,** Actuarial relapse-free survival in patients treated with a daily radiation dose ≥ 5 Gy.

marily responsible for tumor growth control[16-21]. As a consequence, the classical radiobiological effects of RT are immunosuppressive[2]. Because of these properties, lymph node irradiation has been employed in non-treatable forms of RA[21-23]. All these empirical studies have used a conventional daily dose to achieve immunosuppression and to obtain symptom control. Despite some interesting results, the frequent associations with troublesome adverse effects do not make nodal irradiation a suitable standard treatment in patients with RA[22]. Recent reports[3-5,28-30] have shown that RT can also have an immunostimulatory effect, the so-called "nontargeted effect" or "abscopal effect", based on the ability of RT to enhance antigen presentation and to modify the tumor microenvironment, thus contributing to local and systemic antitumor responses. The radiotherapy can modulate the immune tumor microenvironment by debulking tumor cells, releasing tumor-associated antigens and stimulatory molecules, and increasing antigen presentation, thus enhancing antitumor immunity. This interaction of radiation and immunity is an intriguing link and experimentally demonstrates that the immunocompetence of the host affects the radiation response by comparing tumor growth between T-cell-deficient nude mice and immunocompetent wild-type mice[31]. Radiotherapy destroys implanted tumors in immunocompetent wild-type mice, while the same radiotherapy does not affect T cell-deficient nude mice. However, the interaction is complex because instead of achieving a local and systemic response to radiotherapy, cancer cells implement several mechanisms to escape immunity and avoid destruction. The same radiation treatment can have different effects. Radiation can upregulate PD-L1 expression in tumor cells[32], a negative ligand suppressing immunity. Immune drugs inhibiting the PD1-PD-L1 axis can also enhance the tumor activity of radiotherapy. It has been demonstrated a synergistic effect between immune checkpoint inhibitors and radiotherapy. Sharabi et al[33] demonstrated the ability of high-dose radiotherapy to induce endogenous antigen-specific immune responses when combined with an anti-PD1 checkpoint inhibitor.

Based on this effect, an increase in the immune response may be associated with reactivation and/or worsening of symptoms in patients with RA, which is closely linked to antigen-presenting cells that are crucial in triggering and/or maintaining the chronic inflammatory process[2].

To the best of our knowledge, our study is the first to analyze the effect of RT on RA. We found that within 12 months from the start of RT, 6 (20.7%) patients with RA and cancer experienced arthritic exacerbation. In 5 of these patients, the flare occurred early, within 6 months of the end of RT. Of the 6 patients, three received hypofractionated radiotherapy with a high daily dose ≥5 Gy, and three received a conventional daily dose of 1.8-2 Gy. However, in two of these last three cases, RT was delivered after chemotherapy. Although the number of RA patients treated with RT was significantly lower (approximately half) than that of those not treated with RT, these data appear quite interesting because it would seem that in patients who only perform RT, immunostimulation and a consequent flare of the disease may result mainly after a high daily radiation dose (≥ 5 Gy). Interestingly, Vanpouille-Box et al[30] described a model in which anticancer immunomodulation is regulated by an exonuclease (Trex1), whose primary function is activated by a single dose of radiation. According to this experimental study, a daily dose of 8 Gy increases the production of interferon type I and, therefore, could increase the possibility of obtaining systemic control of cancer with RT. This increased production of interferon could also explain RA relapses in the three patients who underwent RT with a daily dose ≥ 5 Gy, given the role of interferon in the pathogenesis of RA[34,35]. Moreover, it has been documented that a conventional daily dose of 1.8-2.0 Gy has mainly an immunosuppressive effect in RA, while a daily dose ≥5 Gy could have immunostimulating properties[23-26]. In this regard, the association of chemotherapy with RT might play an important role in acquiring immune stimulation. In fact, several preclinical and clinical studies[36-39] have demonstrated that cancer cell death caused by radiochemotherapy induces strong antitumor immune responses. Suppose further studies confirm these data. In that case, the most careful choice of both chemotherapy regimen and RT, as a daily dose and total dose, should be taken where possible as it could play a crucial role not only in obtaining the best results in cancer therapy but also in preventing RA flares. An important result of our study is that the comparison between radio-treated and non-radio-treated RA patients with cancer did not show significant differences in terms of RA exacerbation in a 12-month observation period. Interestingly, patients more likely to flare as a result of RT were those treated with biotechnological

drugs at the time of cancer diagnosis. A reasonable explanation for this association can be ascribed to the mandatory withdrawal of the biologic drug at the time of neoplasia diagnosis, while other conventional DMARDs, in most cases, do not need to be stopped. Furthermore, patients treated with biological drugs are generally affected by more severe disease. Another issue still to clarify is whether the presence of concomitant autoimmune disease, such as RA could facilitate the appearance of radiation toxicity in radio-treated patients. It could be argued that immune-related damage and radiation damage can act in a synergistic way, leading to an increased risk of radiotoxicity. In this regard, published studies have demonstrated conflicting results[13,40-42]. Ross et al[15] showed that patients with RA had a higher rate of late G3+ complications after definitive RT, even if the difference was not statistically significant. In the study by Lin et al[14] the rate of late toxicity was higher in patients with RA than in their matched controls (29.7% *vs.* 13.9%), but the rates of severe toxicity were comparable. Finally, Dong et al[40] showed that RT was well tolerated among women with breast cancer with RA, with a similar risk of grade 2+ toxicity compared to their matched cohort. We found that RT was well tolerated among patients with RA, with a low rate of grade 3 acute toxicity (13.8%) and no grade 4 or higher acute toxicity. Likewise, the late toxicity rate was low, with a low rate of grade 2 toxicity (10.3%) and no grade 3 or higher toxicity. On this basis, we can conclude that RA need not be considered as an absolute contraindication for RT.

It must be emphasized that the most frequent type of cancer found in RA patients in the observation period was breast cancer (21.8%), followed by thyroid (9.3%) and skin (7%) cancer. This result is in disagreement with that reported in the literature, where a higher frequency of lung cancer (increased risk of 64% compared to the risk of the general population) is reported in patients with RA, followed by thyroid and hematological malignancies, with breast cancer being less frequent[41-44]. This discrepancy is not surprising if one refers to the prevalence and incidence of individual tumors in Italy, where breast cancer has a higher prevalence (http://www.registri-tumori.it/PDF/AIOM2016/I_numeri_del_cancro_2016.pdf). Our study has some limitations due to its retrospective design and the small patient cohort. Moreover, the heterogeneity of the RT protocol, the ongoing therapy for RA, the different RA disease activities at the time of RT, and other concomitant therapies for cancer could have shadowed or influenced the independent role of RT as a risk factor for RA flares. However, a sub-analysis performed to specifically assess these aspects did not show significant differences between the subjects who flared up and those who did not. Finally, it should be acknowledged that radiotherapy itself can induce various complications, with clinical features that sometimes mimic typical manifestations of rheumatic disease that could be wrongly attributed to a flare of the disease. Regarding this point, a careful evaluation of patient history and a meticulous clinical chart review by two blinded expert rheumatologists should have extremely reduced, if not completely eliminated, this potential bias.

Conclusions

Our study shows that RT for cancer treatment in patients with RA does not significantly increase the risk of reactivation of arthritis. Therefore, RA does not seem to be a contraindication for RT to treat concomitant cancer. Further, properly designed prospective clinical studies with many patients are desirable to confirm these data and better clarify the most appropriate RT program in patients with RA.

Conflict of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Disclosure

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