ORIGINAL ARTICLE

DOI: 10.4274/eamr.galenos.2021.34713
Eur Arch Med Res 2022;38(1):56-60

Radiotherapy for Patients with Cancer and Connective Tissue Disease

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Abstract

Objective: This research aimed to evaluate acute and late toxicities of radiotherapy for patients with connective tissue disease (CTD).

Methods: A retrospective review was performed with the medical records of patients with a diagnosis of both cancer and CTD, who have undergone radiotherapy at our institution between January 2010 to December 2020. Acute and chronic adverse effects of radiotherapy were analyzed.

Results: The mean age of the patients at time of RT was 58 years (45-74) and 50 years (35-68) at CTD diagnosis. Fourteen of patients were female (77.7%). Primary tumor location was as; breast 8 (44.7%), cervix 2 (11.1%), rectum 2 (11.1%), prostate 2 (11.1%), brain 1 (5.5%), lung 1 (5.5%), larynx 1 (5.5%) and endometrium 1 (5.5%). Nine patients (50%) had Behçet's disease, 5 (28%) systemic lupus erythematosus, 2 (11%) systemic sclerosis and 2 (11%) dermatomyositis. Patients in the curative group receiving higher doses of radiation have experienced more acute toxic effects than the others. Thirteen (72%) patients had any grade 1 and 6 (33%) patients had any grade 2 acute toxicities while only 3 (17%) patients with cervical and brain cancers had chronic grade 2 hematological toxicity due to concomitant chemoradiotherapy. The most common acute toxicities were radiation dermatitis, nausea, fatigue and diarrhea. No acute or chronic toxicities higher than grade 2 were recorded. There was not any interruption occured during radiotherapy treatment because of acute toxicities and all patients completed their prescribed course of radiotherapy.

Conclusion: With new radiotherapy techniques there was no increased incidence of acute and chronic risk of toxicity observed and radiotherapy was generally well-tolerated for patients with CTD during the treatment and follow-up. Individualizing treatment strategy for each patient will help improve the results for this group of patients with increased treatment efficacy and decreased toxicity.

Keywords: Connective tissue diseases, adverse effects radiotherapy, toxicity radiotherapy, collagen vascular diseases, complications

INTRODUCTION

Connective tissue diseases (CTD) are a group of autoimmune diseases,including systemic lupus erythematosus (SLE), systemic sclerosis (SS), dermatomyositis (DM), polymyositis, rheumatoid arthritis (RA) and Behçet's disease (BD) that have potential to affect multiple organ systems leading to diverse clinical conditions like renal dysfunction alongside vasculitis, malar or discoid rash, arthritidies, serositis and ulceration (1). Symptoms appear in flares with active and non-active phases of disease with relapsing and remission course, which require different therapeutic approaches including non-steroidal anti-inflammatory drug (NSAID), systemic glucocorticoids, antimalarials and cytotoxic drugs (2).

Inflammatory reactions at the organs with a tendency of elevated immunologic response and poor wound healing affected the decision of radiotherapy (RT) for CTD known as relative contraindication for years because of the possibility of increased toxicity. Early publications of several case reports, with severe radiation-induced toxicity in the setting of CTD after receiving radiation treatment have taken place in the scientific literature

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Received: 18.06.2021
Accepted: 15.11.2021

Cite this article as: Kandemir Gürsel Ö, Dönmez Yılmaz B. Radiotherapy for Patients with Cancer and Connective Tissue Disease. Eur Arch Med Res. Eur Arch Med Res 2022;38(1):56-60

(3-10). Regarding these case reports, the American College of Radiology published guidelines defined CTD as a relative contraindication to breast conservation treatment (11). Although previous studies with case series about RT toxicities for patients with CTDs are heterogeneous in terms of tumor type, anatomical region, radiation site, radiation dose and therapeutic modalities; several relatively large and homogeneous retrospective studies have been published suggesting that RT of CTD patients have a toxicity risk potency which should be held carefully (12-17). While one matched control study did not observe any increased risk of complications in patients with CTD (18), two matched control studies concluded that patients with SS have a significantly increased incidence of complications differing from the rest of CTD (19,20). In an other aspect, there are studies suggesting an increased risk of developing malignancies with CTD that leads RT as a component of multimodality treatment and it is essential forming strategies for this group of patients (21,22). Our goal was to evaluate a 10 year's period of our data of CTD patients with cancer who received RT for assessing both acute and chronic treatment toxicity by presenting a retrospective study.

METHODS

We identified patients by electronically searching a central computer database with ICD-10 codes (23) for the diagnosis of both cancer and CTD between January 2010 to December 2020. Patients who were indicated RT cross-referenced with records from the department of radiation oncology. RA and patients who have diagnosis of CTD after the completion of RT were excluded from our search. Medical records were reviewed for the following characteristics: Age, sex, CTD type, date of CTD diagnosis, concurrent medications, date of cancer diagnosis, primary of cancer site and dose schedule of RT, acute and late toxicity, pattern of failure, and survival.

Toxic effects were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events v 5.0 (24) (Table 1). Symptoms that developed within 90 days from the start of radiation were considered acute toxicities, while those that occurred later than 90 days were considered chronic toxicities.

This study was conducted in accordance with the ethical standards provided by the Helsinki Declaration and informed consent documents, obtained before treatment from each patient are available in patient files. This study was accepted by the Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital (date: 07.06.2021, decision no: 227).

Table 1. Common terminology criteria for adverse events version 5.0 grading scale

Grade 1	Mild adverse event	Asymptomatic or mild symptoms intervention not indicated
Grade 2	Moderate adverse event	Minimal, local or non-invasive intervention indicated
Grade 3	Severe or medically significant but not immediately life-threatening	Hospitalization or prolongation of hospitalization indicated, disabling, limiting self care
Grade 4	Life-threatening consequences	Urgent intervention indicated
Grade 5	Death related to adverse event	Death related to adverse event

Statistical Analysis

During the evaluation of the study data, descriptive statistical methods such as mean, median, frequency, ratio, minimum and maximum value were used.

RESULTS

The mean age of the patients at time of RT was 58 years (45-74) and 50 years (35-68) at CTD diagnosis. Fourteen of 18 patients were female (77.7%). Primary tumor location was as; breast 8 (44.7%), cervix 2 (11.1%), rectum 2 (11.1%), prostate 2 (11.1%), brain 1 (5.5%), lung 1 (5.5%), larynx 1 (5.5%) and endometrium 1 (5.5%). CTD subtypes were nine patients (50%) BD, 5 (28%) SLE, 2 (11%) SS and 2 (11%) DM. Most seen CTD symptoms were arthritis, skin lesions, oral ulcerations, uveitis, genital ulcerations, renal and neurologic disorders (Table 2). For CTD treatment; twelve patients were medicated NSAIDs, 6 patients with colchicine, 5 patients with hydroxychloroquine and 3 patients with corticosteroids. At the time of analysis 15 (83%) patients were alive and 3 (17%) patients had died; two because of lung metastasis, one because of SLE nephritis with a median follow-up time of 4.05 years (range, 1.2-9.7 years).

All patients were evaluated carefully and discussed in tumor council for indication of RT and consulted with their rheumatologists for phase, current CTD treatment and individual recommendation. Patients received 18 courses of RT with external beam radiation therapy (EBRT), one course of intraoperatif boost RT and three courses of intracavitary brachytherapy after EBRT. Three patients had concomitant chemoradiotherapy. All EBRT was administered with megavoltage linear accelerators and ten patients treated with conformal while 8 patients with intensity modulated radiotherapy (IMRT). RT treatment characteristics are summarized in Table 3.

Table 2. Demographic, rheumatologic and tumor characteristics of patients	
Criteria	**Value (n=18) %**
Demographic	
Sex	
Female	14 (77.7)
Male	4 (22.3)
Age, y, median (range)	
At radiotherapy	58 (45-74)
At CTD diagnosis	50 (35-68)
Primary tumor location	
Breast	8 (44.7)
Cervix	2 (11.1)
Rectum	2 (11.1)
Prostate	2 (11.1)
Brain	1 (5.5)
Lung	1 (5.5)
Larynx	1 (5.5)
Endometrium	1 (5.5)
CTD type	
Behçet's disease	9 (50)
Systemic lupus erythematosus	5 (28)
Systemic sclerosis	2 (11)
Dermatomyositis	2 (11)
CTD symptoms	
Arthritis	7 (38.8)
Skin lesions	6 (33.3)
Oral ulcerations	5 (27.7)
Uveitis	3 (16.6)
Genital ulcerations	1 (5.5)
Renal disorders	1 (5.5)
Neurologic disorders	1 (5.5)
CTD: Connective tissue diseases	

Table 3. Characteristics of radiotherapy	
Treatment criteria	**Value (%)**
Intent of treatment per radiotherapy course	
Definitive	17 (94)
Palliative	1 (6)
Anatomical target	
Breast	8 (44)
Pelvis	7 (38)
Brain	1 (6)
Neck	1 (6)
Bone	1 (6)
Radiotherapy dose, median (range)	
Dose per fraction, Gy	2 (1.80-4.00)
No of fractions	30 (5-35)
Total dose, Gy	60 (20-70)

Thirteen (72%) patients had any grade 1 and 6 (33%) patients had any grade 2 acute toxicities while only 3 (17%) patients with cervical and brain cancers had chronic grade 2 hematological toxicity due to concomitant chemoradiotherapy. The most common acute toxicities were radiation dermatitis, nausea, fatigue and diarrhea. No interruption occurred during RT treatment because of acute toxicities and all patients completed their prescribed course of RT. Patients in the receiving higher doses of radiation have experienced more acute toxic effects than the others as expected. No acute or chronic toxicities higher than grade 2 were recorded (Table 4).

Table 4. Acute and chronic adverse events		
	Acute adverse events	**Chronic adverse events**
Grade 1		
Behçet's disease	7/9	1/9
Systemic lupus erythematosus	3/5	0/5
Systemic sclerosis	2/2	0/2
Dermatomyositis	1/2	0/2
Total	13 /18	1/18
Grade 2		
Behçet's disease	3/9	1/9
Systemic lupus erythematosus	1/5	1/5
Systemic sclerosis	1/2	0/2
Dermatomyositis	1/2	1/2
Total	6/18	3/18

DISCUSSION

The management of RT for patients with CTD has always known as challenging approach for radiation oncologists requiring an additional attention. In this retrospective study, cancer patients with CTD completed their treatment with acceptable toxicity so that we suggest RT can be performed safely for this group of patients.

Similarity between CTD and malignancy as TGF-β has been shown to be a key molecular component, which is responsible for effective wound healing and is commonly disrupted at the pathophysiology of both groups; wound healing is impaired in severe CTD (25). At the same time localized fibrosis and inflammation, mediated by TGF-β, can be intensified by RT which reactivates systemic CTD (26) and it could be difficult to manage the complexity of pro-inflammation promotion of RT in patients with autoimmune disease (27).

Lin et al. (28) studied with 73 CTD patients and concluded that although they appear to predispose to a greater risk of late RT toxicity, treatment is generally well tolerated, with a relatively low incidence of severe acute or late toxicity but CTD subtype, the site of irradiation, RT dose and the use of concurrent chemotherapy should be carefully evaluated. In a review Wo and Taghian (29), commented that although numerous case reports reported increased risk of acute and late toxicities; a large retrospective series stay controversial in this patient population. Ma evaluated cervical cancer patients with SLE treated by IMRT

that was generally well tolerated by decreasing the prescribed dose to the normal tissues and established that SLE was not a risk factor for radiation complications (14). Chen et al. (20) showed that CTD subtype like scleroderma with a significantly increased incidence of complications after breast-conserving surgery and radiation therapy and different organ involvement, radiation dose and the use of immunosuppressants might be risk factors for severe complications from radiation treatment. Hölscher et al. (30) concluded in a review that although there are some methodological problems with the studies there can be association with an increased risk of late radiation-induced reaction and CTD patients. Unlike these studies acute toxicity were more recorded than chronic toxicity in our study.

With an international systematic review and meta-analysis, Lin et al. (31) evaluated toxicity after radiotherapy in patients with historically accepted contraindications to treatment (CONTRAD) briefly analyzing 417 patients and suggested that CTD is not an absolute contraindication and should not prevent RT for curable cancer therapy. Our patients had all RT with exact indication and did not compromised of their oncology treatment because of CTD.

Shah et al. (32) from two centers, in a retrospective study of scleroderma patients with breast cancer, showed no significant acute skin toxicity from radiation, but approximately 50% chronic radiation-induced cutaneous fibrosis localized to the field of radiation. Benk et al. (33) suggested that RT have been inappropriately withheld from patients with SLE with cancer for fear of severe late complications traditionally and should always be taken to consideration if indicated. Lee et al. (26) recommended a national record system of registration for toxicity recording to understand true incidence of CTD patients being referred for RT at different centers. They also suggested close liaison with the rheumatologist during the decision of indication, monitoring acute effects, reducing the total dose by >10%, considering smaller treatment volumes, conventional fraction sizes and caution with concurrent chemoradiotherapy (26). In our group similar to late retrospective studies which were treated with new RT techniques there was no increased incidence of acute or late complications observed and RT was generally well tolerated for patients with CTD during the treatment and follow-up. Individualizing treatment strategy for each patient will help improve the results for this group of patients. Although its retrospective nature, data were evaluated carefully from well-recorded toxicity profile from patient files and treatment charts.

Study Limitations

The most significant limitation of this retrospectively designed study is small sample size with heterogeneous patient population and RT treatment schedules but it should be taken consideration that as CTD patients receiving RT is a rare group for a single institution. Further multi-institutional studies may help to enlarge the study group with detailed analysis of toxicities

CONCLUSION

Factors including CTD subtype and disease activity, site of irradiation, RT dose, technique and the use of concurrent chemotherapy can increase the risk of toxicity and should be considered carefully. While interfering RT, a multidisciplinary discussion including rheumatologist should be administered between the treating modalities. Recent advances in RT have shown superiority in decreasing the prescribed dose to the normal tissues with decreased toxicity for all groups of cancer patients. Even in the presence of a CTD, RT with modern techniques is generally well tolerated, with a relatively low incidence of severe acute or late toxicity so that CTD patients will not be excluded from RT regimens when indicated because of the risk of toxicities.

Ethics

Ethics Committee Approval: This study was accepted by the Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital (date: 07.06.2021, decision no: 227).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.K.G., B.D.Y., Concept: Ö.K.G., Design: Ö.K.G., B.D.Y., Data Collection or Processing: Ö.K.G., B.D.Y., Analysis or Interpretation: Ö.K.G., Literature Search: Ö.K.G., B.D.Y., Writing: Ö.K.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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