Radiotherapy and Oncology 87 (2008) 127—131
www.thegreenjournal.com

Connective tissue disorder

Chronic toxicity risk after radiotherapy for patients with systemic sclerosis (systemic scleroderma) or systemic lupus erythematosus: Association with connective tissue disorder severity

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Abstract

No method reliably identifies which patients with connective tissue disorders are at greatest risk of radiotherapy-related complications. Building on our prior experience, we postulated that disease severity, as measured by the number of organ systems involved, may predict chronic radiation toxicity risk.

Keywords: Adverse effects; Connective tissue disorder; Radiotherapy; Scleroderma; Systemic lupus erythematosus; Systemic sclerosis

Certain connective tissue disorders (CTDs) may be a relative contraindication for radiotherapy. Numerous case reports describe possible long-term complications, some of which may be severe [2,3,6—8,16,17,20]. Retrospective studies of patients with CTDs who receive radiotherapy show inconsistent toxicity outcomes [4,12,14,18]. Some series indicate that patients with certain CTDs may have increased risk of chronic complications [4,12,14]. Moreover, a recent systematic review using pooled data from the literature suggests that patients with CTDs have increased risk of chronic radiation-induced normal tissue toxicity [10].

Systemic sclerosis (systemic scleroderma) is a CTD of particular concern because some series showed that it was associated with an increased incidence of chronic toxicity when compared with other CTDs [4,12,14]. We previously described a series of systemic sclerosis patients receiving radiotherapy (the largest series studied to date) and showed that severe chronic radiotherapy-related toxicity does not prohibit consideration of radiotherapy in appropriately selected patients [9]. In that series of 20 patients, 3 had chronic toxicity that was grade 3 or higher. On the basis of several retrospective series [4,12,14], radiotherapy-related toxicity in systemic lupus erythematosus (SLE) patients has been of less concern. However, case reports have documented considerable radiation toxicity in this group of patients [8,13], and a recent abstract describing patients with various CTDs suggested that severe toxicity may be most common in patients with SLE [1]. Our recent analysis showed that 4 of 17 evaluable patients with SLE experienced grade 3 or higher chronic toxicity after radiotherapy [15].

In general, there is a paucity of data regarding radiotherapy-related chronic toxicity in patients with CTDs, although some patients clearly experience striking and severe chronic complications. However, it is also clear that patients with severe adverse effects constitute only a small subset of patients with CTDs. From a practical standpoint, development of clinical criteria to identify patients with the greatest risk of chronic radiation toxicity would be advantageous. To this end, we report our experience treating patients with systemic sclerosis or SLE with radiotherapy and describe our efforts to identify patients at high risk of chronic radiotherapy-induced complications.

Materials and methods

Criteria for inclusion in the study included an unambiguous diagnosis of systemic sclerosis or SLE and treatment at Mayo Clinic (Rochester, Minnesota) with external radiotherapy (total external beam dosage, >10 Gy) or with brachytherapy (or both). The diagnosis of systemic sclerosis

Abbreviations: CI, confidence interval; CTD, connective tissue disorder; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

0167-8140/$ - see front matter doi:10.1016/j.radonc.2007.11.031

typically was made by a rheumatologist or dermatologist at our institution and was established on the basis of clinical, serologic, and histopathologic findings and the results of procedural and radiologic tests. We used the 1982 revised criteria [19] to establish the diagnosis of SLE.

Twenty patients with systemic sclerosis and 21 patients with SLE were consecutively treated with radiotherapy between January 1, 1980, and December 31, 2003. Their records were reviewed retrospectively. Specific details regarding these patients were reported previously [9,15]. Briefly, patients were selected by electronically cross-referencing the Mayo Clinic electronic database of patient diagnoses with medical records from the Department of Radiation Oncology. Approval for this study was obtained from the Mayo Clinic Institutional Review Board.

Chronic toxic effects were graded using the Common Terminology Criteria for Adverse Events, version 3.0 [5]. A toxic effect was classified as chronic if it occurred more than 30 days after completion of radiotherapy. If ambiguity existed regarding whether a toxic effect was due to radiotherapy or the CTD, it was considered to be caused by radiotherapy unless the toxic effect was evident before the start of radiotherapy and if no apparent increase in signs or symptoms of toxicity were noted after radiotherapy was complete.

Follow-up time was calculated as the time between the radiotherapy completion date and the date of final patient contact. CTD severity or extent was determined by the total number of organ systems involved (Table 1). For the 20 systemic sclerosis patients, 5 systems potentially were involved (skin, gastrointestinal, pulmonary, vascular, and renal systems). Musculoskeletal involvement (e.g., arthralgias or arthropathies, contractures, joint deformities) was not scored as a separate organ system, and no systemic sclerosis patient had cardiac involvement. For patients with SLE, 8 systems, defined by the 1982 revised criteria for the classification of SLE [19], potentially were involved (skin [malar rash, discoid rash, or photosensitivity], oral ulcers, arthritis, serositis, renal disorder, neurologic disorder, hematologic disorder, and immunologic disorder). If a patient had multiple dermatologic manifestations of SLE (e.g., malar rash and photosensitivity), it was scored as a single organ system.

The division of patients into high- and low-severity CTD groups was made at the 50th percentile of number of organ systems involved for each of the 2 groups of CTD patients. Low-severity CTD was defined as 2 to 3 organ systems involved for systemic sclerosis and 2 to 4 organ systems for SLE. High-severity CTD was defined as 4 to 5 organ systems involved for systemic sclerosis and 5 to 6 organ systems for SLE.

Statistical analysis

Standard Kaplan—Meier statistics were used in the actuarial analysis of chronic toxicity rates [11]. Log-rank testing was used to examine the difference between chronic toxicity rates for the high- and low-severity CTD groups. *P* values were calculated from two-sided tests. The statistical software used was JMP, version 5 (SAS Institute Inc., Cary, North Carolina).

Results

Clinical features (including occurrence of chronic toxicity) of the patients with systemic sclerosis ($n = 20$) or SLE ($n = 21$) are shown in Table 1. Chronic toxicity information was not available for 4 SLE patients; thus, only 17 SLE patients were evaluated for long-term complications. Eight of the 20 patients with systemic sclerosis were in the low-severity CTD group; in the SLE group, 11 of 17 evaluable patients were in the low-severity CTD group. The median follow-up period for survivors was 4.7 years for systemic sclerosis patients and 5.6 years for SLE patients.

For all patients, the 5- and 10-year chronic toxicity rates (any grade) were 52% (95% confidence interval [CI], 36—69%) and 64% (95% CI, 43—80%), respectively. For all patients, 5- and 10-year chronic toxicity rates for grades 3 and higher were 18% (95% CI, 7—38%) and 36% (95% CI, 16—63%), respectively.

Univariate analysis showed a significant difference in the risk of toxicity (any grade) for patients with high-severity CTD when compared with patients with low-severity CTD ($P = .006$). Fig. 1 displays the rate of chronic toxicity (any grade) for all patients with systemic sclerosis or SLE, stratified by CTD severity. For patients with low-severity CTD, the 5- and 10-year chronic toxicity rates for any grade were 41% (95% CI, 19—67%) and 52% (95% CI, 26—88%), respectively. For patients with high-severity CTD, 5- and 10-year chronic toxicity rates for any grade were 79% (95% CI, 52—93%) and 79% (95% CI, 52—93%), respectively.

Univariate analysis did not show a difference in rates of toxicity of grades 3 and higher when comparing patients with high- and low-severity CTD ($P = .56$). For patients with low-severity CTD, 5- and 10-year chronic toxicity rates for grades 3 and higher were 23% (95% CI, 5—59%) and 38% (95% CI, 12—74%), respectively. For patients with high-severity CTD, 5- and 10-year chronic toxicity rates for grades 3 and higher were 25% (95% CI, 9—51%) and 25% (95% CI, 9—51%), respectively.

Discussion

Details of acute and chronic radiotherapy-related toxicity in patients with systemic sclerosis or SLE who were treated at Mayo Clinic have been reported [9,15]. The current analysis combined the systemic sclerosis and SLE patient data and specifically analyzed the incidence of chronic toxic effects due to radiotherapy as a function of the severity of CTD (severity was measured by the number of organ systems involved).

In our previously published systemic sclerosis report, the severity of CTD, as measured by the number of involved organ systems, did not predict chronic radiation complications of any grade in a statistically significant manner [9]. However, we noted a trend in this group of 20 patients ($P = .15$). The trend toward statistical significance was stronger for our 17 evaluable lupus patients when the number of American Rheumatism Association criteria was used as a predictor of chronic toxicity ($P = .053$) [15]. It is not surprising that a statistically significant difference was not achieved, given the small number of patients. When the 2 datasets were combined for analysis ($N = 37$), the associa-