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Radiation toxicity in patients with collagen vascular disease and intrathoracic malignancy treated with modern radiation techniques

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ABSTRACT

Background and purpose: There is concern that patients with collagen vascular disease (CVD) are at higher risk of developing radiation toxicity. We analyzed radiation toxicities in patients with intrathoracic malignancy and CVD treated using modern radiotherapy.

Materials and methods: This single-institution retrospective study included 31 patients with CVD and 825 patients without CVD treated from 1998 to 2014. Radiation esophagitis (RE) and radiation pneumonitis (RP) were scored by RTOG scales. RE was analyzed with logistic regression and RP with Cox regression.

Results: CVD patients experienced similar grade ≥3 RE compared to control patients (23% vs. 19%, $p = 0.64$) but more grade ≥3 RP (26% vs. 10%, $p = 0.01$). There was no significant association between CVD subtype and toxicities. In multivariate analysis, CVD and lung V20 >30% were associated with grade ≥3 RP. We identified V20 ≤30%, V5 ≤50%, and MLD ≤18 Gy as dose thresholds in patients with CVD. CVD patients with mild severity disease and only 1 organ system involved were at low risk for RP.

Conclusions: Patients with CVD may be at higher risk of RP. However, CVD patients may be offered curative thoracic RT with particular attention to risk-reduction strategies and maintaining recommended dose constraints as described in this study.

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Collagen vascular diseases (CVD) are a group of heterogeneous rheumatologic disorders that share clinical and pathologic features such as immune system dysregulation, development of autoantibodies, and widespread inflammation of connective tissues that can eventually lead to fibrosis and permanent tissue damage [1–3]. There is a long history of concern that patients with CVD are at higher risk of developing toxicity following treatment with radiotherapy (RT). It has been postulated that acutely, the reduced proliferation of early responding tissues such as mucosal surfaces caused by RT may worsen pre-existing susceptibility to inflammation and tissue injury in patients with CVD. Further, there is increasing evidence that an immune response characterized by production of cytokines and recruitment of immune cells following RT are important factors in tumor killing [4,5]. In the long-term, RT may cause additive obliteration of vasculature and proliferation of fibroblasts leading to tissue fibrosis, which are typical pathologic features observed in CVD [1–3].

The earliest clinical reports of toxicity in patients with CVD were case studies [6–12]. Since then, numerous retrospective reviews and matched case-control studies have demonstrated mixed results, with some finding no association between CVD and toxicity, others an increase in late toxicity, and others an increase in toxicity only for particular CVD subtypes such as scleroderma or systemic lupus erythematosus (SLE) [13–19]. In addition, there is a notable paucity of evidence regarding the impact of CVD severity, organ involvement, duration, and therapy on risk for toxicity [2,18]. A recent review article came to the conclusion that there is still insufficient evidence to provide a specific recommendation regarding the treatment of CVD patients with radiotherapy [2]. Further, existing studies on the topic describe patients with varying tumor and irradiation sites treated with outdated two-dimensional radiation techniques and lacking dosimetric covariates [2]. As a result, defining the true radiation toxicity profile of patients with CVD continues to present a challenge to clinicians [3,20,21].

We performed a retrospective review of patients with CVD and intrathoracic malignancy treated to curative doses with three-dimensional conformal radiation therapy (3D-CRT) or intensity modulated radiation therapy (IMRT) and compared their outcomes

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to control patients to determine whether patients with CVD treated with modern RT are at increased risk of radiation toxicity. We collected clinical and dosimetric covariates as well as metrics of CVD disease severity and therapy to explore the association between patient and treatment characteristics and risk of radiation toxicity in the setting of CVD.

Materials and methods

Patients

With institutional review board approval under a waiver of consent, we identified 36 consecutive patients with CVD and 1099 consecutive control patients with newly diagnosed intrathoracic malignancy (including adenocarcinoma, squamous cell carcinoma, small cell and large cell neuroendocrine, typical and atypical carcinoid, adenoid cystic, lymphoepithelioma, thymoma, and metastatic disease) treated with 3D-CRT or IMRT with curative intent (prescribed dose $\geq$45 Gy) from 1998 to 2014 at our institution. We excluded patients who were treated with stereotactic body radiotherapy (SBRT), received hypofractionated (>2 Gy/fx) radiotherapy, received total doses <24 Gy, or had previously received radiotherapy. Treatment with curative intent in patients with metastatic disease typically required (1) good performance status, (2) oligometastatic disease to one site only, (3) if the only site was brain then <4 brain lesions, and (4) intrathoracic disease that could be treated safely with RT while meeting dose constraints.

Clinical and radiation dosimetric covariates

Clinical covariates were retrospectively collected from medical records. Patient and tumor characteristics including age, sex, race, Eastern Cooperative Oncology Group (ECOG) performance status (PS), smoking status, pulmonary function tests (PFTs), chemotherapy, thoracic surgeries, and tumor, node, metastasis (TNM) classification system stage according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging manual were recorded [22]. Smoking status was categorized as: (1) never smoker, fewer than 100 lifetime cigarettes; (2) former smoker, quit >1 year prior to diagnosis; (3) current smoker, smoking at the time of diagnosis or quit <1 year ago. CVD-specific factors including symptoms, organ involvement, disease control status, duration, and timing and type of therapy were recorded. Disease was defined as well-controlled at the time of RT if symptoms were mild and not interfering with functioning. CVD severity was classified as (1) mild: symptoms relieved with NSAIDs or without therapy, (2) moderate: symptoms require steroids and/or immunosuppressant therapy, and (3) severe: end organ failure or severe symptoms not relieved by maximal medical therapy. Radiation dose and technique were retrieved from the Aria oncology information system while dosimetric parameters including mean lung dose, V5, and V20 and esophageal mean dose and V55 were determined from dose volume histograms (DVHs) calculated by the Eclipse treatment planning system (Varian Medical Systems).

Radiotherapy technique and follow-up

Radiation treatment planning was performed using 4D-CT planning to create an internal target volume (ITV) with a 5–7 mm clinical target volume (CTV) margin without elective nodal irradiation and a 5–7 mm planning target (PTV) margin. Patients treated prior to 2006–2008 were planned with either 3D-CT or partial 4D (end exhale-inhale scans). 3D-CRT or IMRT technique was used at the discretion of the treating clinician to meet normal tissue dose constraints. According to institutional guidelines, normal tissue dose constraints included lung V20 < 30%, lung V5 < 50%, mean lung dose <17 Gy, esophageal V55 < 30%, and esophageal mean dose <34 Gy. Variation was permitted per physician discretion as reflected in our ranges. Setup verification was performed using daily orthogonal X-rays for all patients, with adoption of weekly cone-beam CT more recently on patients treated after 2008–2010. Patients were seen in follow-up every 3–4 months after treatment for 2 years, every 6 months for the next 3 years, and every 1 year subsequently. Chest CT was obtained prior to each follow-up visit.

Endpoints

Our primary endpoints of radiation esophagitis (RE) and radiation pneumonitis (RP) were identified retrospectively from medical records. RE was graded using the Radiation Therapy Oncology Group (RTOG) Common Toxicity Criteria [23]. RP was graded using the RTOG/European Organization for Research and Treatment of Cancer (EORTC) Late Radiation Morbidity Scoring Schema [24]. The investigator, who was blinded to CVD status, independently reviewed notes and radiological imaging for each patient to determine a diagnosis and grade of RE and RP. Overall survival (OS) was obtained from medical records, social security death index (SSDI), and obituaries. Patterns of failure, comprising locoregional control (LRC; lobar or regional), freedom from distant metastases (FFDM), freedom from any recurrence (FFR; lobar, regional, or distant), and recurrence-free survival (RFS; survival without LRR or DM event) were determined from medical records.

Statistical analysis

Fisher's exact test and the Wilcoxon rank sum test were used to compare patient and treatment characteristics. All tests were two-sided. OS was calculated from RT start date to date of death or date last known alive. Patterns of failure were calculated from RT start date to the time of first failure or last disease assessment. The Kaplan–Meier method was used to characterize overall survival and patterns of failure. Statistical significance comparison was performed using the log rank test.

RE was analyzed as a time-independent variable. RP was analyzed as a time-dependent variable and calculated from the RT start date to a RP event or censored at the time of last follow-up or death. Logistic regression models were used to analyze grade $\geq$3 RE events and Cox proportional hazards models were used to analyze grade $\geq$3 RP events. CVD status and other important covariates were included in univariate analysis while prognostic variables and statistically significant covariates (p-value <0.05) were included in multivariate analysis.

Results

A total of 31 patients with CVD and 825 control patients without CVD were included in the analysis. Of the patients with CVD, 19 had rheumatoid arthritis (RA), 4 had systemic lupus erythematosus (SLE), 4 had scleroderma/CREST syndrome, 3 had Sjogren's syndrome, and 1 had mixed connective tissue disorder (MCTD). The median follow-up time was 55.3 months among all patients. The median age at the time of treatment was 64 years, 52% of patients were female, and 90% of patients had ECOG PS of 0–1 (Table 1). Forty-four percent of patients had lung adenocarcinoma and 42% had other non-small cell lung cancer (NSCLC) with 79% of patients having stage III or IV disease at the time of treatment. Patients were treated to a median total RT dose of 60 Gy at a median 2 Gy per fraction. Eighty-three percent of patients were treated with 3D-CRT, 13% with IMRT, and 4% with both. There was no significant difference in baseline, tumor, or treatment characteristics between patients with and without CVD other than sex (81% female and 51%

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