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Scientific Article

The role of bone marrow and spleen irradiation in the development of acute hematologic toxicity during chemoradiation for esophageal cancer

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Abstract

Purpose: The purpose of this study was to determine the impact of splenic and thoracic bone marrow irradiation on hematologic toxicity in the setting of chemoradiation therapy for esophageal cancer.

Methods and materials: We analyzed 60 patients with carcinoma of the distal esophagus or gastroesophageal junction who received concurrent chemoradiation in the preoperative or definitive setting. Dosimetric and volumetric parameters were calculated for the spleen, thoracic spine, and posterior ribs. The primary endpoint was grade ≥3 hematologic toxicity (HT3+). Associations were assessed using logistic and linear regression models.

Results: Twenty-one patients (35%) experienced HT3+, including 18 patients with leukopenia and 5 with thrombocytopenia. Higher spleen V5-V20 was correlated with a lower risk of HT3+ on multivariable analysis (odds ratio: 0.83 per 10 cm^3 increase in V10; $P = .013$). A dose-dependent decrease in spleen volume was observed after radiation therapy, and a greater decrease was independently associated with a lower risk of HT3+ (odds ratio: 0.93 per 1% volume decrease; $P = .014$). Dosimetric parameters of the thoracic spine were not significantly associated with HT3+.

Conclusions: A greater decrease in spleen size after radiation therapy and a higher spleen V5-V20 were independently associated with a lower risk of severe hematologic toxicity. Splenic irradiation may mitigate leukopenia associated with chemoradiation therapy.

Introduction

Since the publication of the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study, neoadjuvant chemoradiation therapy has been firmly established as the standard of care for locally advanced, resectable esophageal

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and gastroesophageal junction (GEJ) cancer.[1] However, morbidity associated with chemoradiation can be significant, particularly with respect to hematologic toxicities. In the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study, leukopenia (60%) and thrombocytopenia (54%) were quite common, and 8% of patients experienced a grade ≥3 hematologic toxic effect of any type.[2] Several potential factors contribute to these findings, including chemotherapy-related and radiation-related effects on hematopoiesis.

Several studies have previously investigated radiation dose to the bone marrow and its effect on acute hematologic toxicity for various disease sites, including anal, cervical, and thoracic.[3-5] However, radiation therapy for esophageal cancer is unique from the aforementioned sites because the spleen, which is an additional hematopoietic organ, is often within the radiation field. The spleen is known to serve several functions, including serving as a reservoir for lymphocytes, platelets, and potentially other cell types.[6]

The effects of radiation on the normal functions of the spleen remain largely unknown, and the organ is not routinely designated as an organ at risk with applicable dosimetric constraints. One recent study found a dose-dependent decrease in spleen size after postoperative radiation therapy for gastric cancer.[7] However, the clinical significance of this finding has not been clearly elucidated. The current study investigates the relationship between changes in blood cell counts and dosimetric parameters of the spleen and thoracic bone marrow, specifically among patients who received treatment to the distal esophagus or GEJ, given the anatomic level of the spleen. An improved understanding of the role of the spleen in acute hematologic toxicity and its relation to bone marrow suppression after radiation therapy may allow for improved design of radiation therapy fields to minimize adverse hematologic events.

Methods and materials

Patient selection

In this study, which was approved by the Institutional Review Board of Stanford University, we conducted a retrospective analysis of 60 patients with stage IB-IV adenocarcinoma or squamous cell carcinoma of the distal esophagus or GEJ who received concurrent chemoradiation in the preoperative or definitive setting at our institution between January 2007 and February 2015. Patients with metastatic disease were included if they received high-dose radiation therapy to the primary tumor, as per our institutional practice described later. Patients underwent computed tomography (CT) of the thorax, whole-body positron emission tomography/CT, and upper endoscopy with endoscopic ultrasound as part of the routine staging process. Treatment planning CT imaging from the T1 to L1 vertebral levels and encompassing the entire spleen was required for the analysis. Follow-up data were collected from the first 2 surveillance CT scans performed for each patient after the initial treatment planning scan.

Treatment planning

Radiation treatment was delivered using a 3-dimensional conformal or intensity modulated radiation therapy (IMRT) technique, primarily via volumetric modulated arc therapy. Our institutional practice for IMRT is to treat the elective regional nodal basins to a dose of 45 Gy at 1.8 Gy per fraction with a simultaneous integrated boost to the primary tumor and to treat any gross nodal disease to 50 to 54 Gy at 2 Gy per fraction. The initial clinical target volume (CTV) receiving 45 Gy includes the primary tumor with a 3 to 4 cm margin along the mucosa, elective periesophageal nodes, and any grossly involved lymph nodes. For tumors in the distal esophagus or GEJ, the celiac axis and perigastric nodes within the 3 to 4 cm mucosal margin are also included. The CTV receiving the boost includes the primary tumor and grossly involved nodes with a 1 to 2 cm margin. Our normal tissue constraints for IMRT plans typically include a total lung mean dose <12 Gy, total lung V20 <15%, and heart mean dose <25 Gy. Chemotherapy was delivered concurrently with radiation therapy in all cases. The majority of patients received weekly carboplatin and paclitaxel[2] but additional drug regimens included 5-fluorouracil, capecitabine, cisplatin, oxaliplatin, and trastuzumab. Respiratory gating was typically used for distal esophageal tumors to account for any significant organ motion.

Dosimetric parameters

For each patient, the thoracic spine, posterior ribs, and spleen were delineated on the treatment planning CT scan by a trained radiation oncologist. The thoracic spine was contoured as the vertebral bodies, transverse processes, and posterior elements from the T1 to L1 vertebral levels, inclusive. The posterior ribs included the T1 to T12 ribs from the costovertebral joint to the midscapular line bilaterally. Dose volume histogram data were generated in MIM (version 6.5.7, MIM Software Inc.; Cleveland, OH) and the following data were recorded for each structure: volume; mean dose; and absolute and relative volume receiving at least 5 (V5), 10 (V10), 15 (V15), 20 (V20), 30 (V30), and 40 Gy (V40).

Laboratory data

Complete blood counts with differential, including white blood cell (WBC), absolute neutrophil, hemoglobin, and platelet counts, were obtained within 1 week prior to the