Radiological Evaluation of Radiation-Related Left Lung Damage Following Gastric Cancer Radiotherapy

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ABSTRACT

Radiation-induced lung injury (RILI) is one of the most important complications in thoracic tumors. After gastric radiotherapy left lung can be negatively affected in a variable severity depending on several factors due to the close anatomic location. In this study, radiotherapy planning computerized tomography data of 35 gastric cancer patients were evaluated retrospectively in terms of radiation-induced lung injury radiologically. Our aim is to investigate the correlation between the dosimetric data and radiologic changes of the left lung in the treatment field with computerized tomography images in 3-6 months after RT. Median values of treatment volumes, for left lung V25, mean (D mean) and maximum (D max) doses were evaluated via dose-volume histogram. Factors that may contribute to damage such as age, concomitant chemotherapy, radiotherapy technique, surgery and tumor location were also analyzed. RILI was detected in 51.4% of patients. These were parenchymal changes in 71.2%, a decrease in lung volume in 22.8%, pleural changes in 22.7%. RILI development was significantly higher in patients undergoing boost ($p< 0.05$).

Keywords: Gastric cancer, Radiotherapy, Lung-radiotherapy effects

INTRODUCTION

Radiotherapy (RT) is an important component of gastric cancer (GC) treatment. Abdominal region RT is associated with dose-limiting toxicity of various normal structures. Clinical target volume (CTV) delineation for adjuvant RT for GC depends on the primary tumor area and status of lymph node metastasis which is quite a large field. In clinical practice, the lung is not considered as a dose-limiting organ GC radiotherapy. However, we can see radiologic changes in patients' follow-up coputirezed tomography images, especially in the adjacent left lung area, that can be confused with metastasis.

Radiation-induced lung injury (RILI) is one of the major complications encountered especially in the case of radiotherapy for thoracic tumors and breast cancer.[1,2,3] The stomach is also in a close layout with left lung. Radiotherapy can cause inflammatory damage in the alveolar epithelium and capillary endothelium which is often asymptomatic.[4] In radiological follow-up, RILI can be seen as radiation pneumonitis (RP) in the early period (< 6 months) and/or radiation-induced lung fibrosis in the late period (> 6 months).[1,2] Fay et al reported RP occurred 6 weeks to 11 months after RT onset.[1]

In this study, we aimed to investigate the necessity of considering the left lung as a risky adjacent organ in gastric radiotherapy. We also wanted to lay emphasis on the misdiagnosis of radiation changes as metastasis leading to superfluous exams and/or treatment.

METHODS

The radiotherapy planning computerized tomography data and thoracic CT images 3 - 6 months after RT of 35 patients with gastric cancer treated between January 2012 and October 2018 were evaluated retrospectively. The current study was conducted according to the principles put forth by the Helsinki Declaration and Good Clinical Practice guidelines. Ethical approval was obtained from Süleyman Demirel University Clinical Research Ethical Committee.

Statistical Analysis

All analyses were performed on SPSS v20. Descriptive statistics are presented with frequency, percentage, mean and standard deviation. Relationships between categorical variables were evaluated with Person ChiSquare and Fisher's Exact Test. The normality assumption of numerical data was checked with the Shapiro Wilks Test. Numerical data of 2 groups were evaluated by Mann Whitney U Test. $p< 0.05$ was considered statistically significant. Patient characteristics are presented in Table 1.

Table 1. Patient Characteristics

Patient Characteristics	Number of patients n (%)
Median age (range)	61 (range: 42-90)
Surgery	
No	2 (6%)
Subtotal gastrectomy	19 (54%)
Total gastrectomy	14 (40%)
Concomitant Chemotherapy	
Yes	32 (91%)
No	3 (9%)
Radiotherapy technique	
3DCRT	25 (71%)
FIF-IMRT	10 (29%)
Total RT dose	
5040-5400cGy (single volume)	15 (43%)
5040cGy (2 volume/boost)	20 (57%)
V25< 10% (left lung)	24 (69%)
V25> 10% (left lung)	11 (31%)

Radiotherapy: Each patient was simulated with an individual vacuum bed for immobilization. They were positioned with hands overhead. CT of both lungs from apex to diaphragm with 2.5 mm slice thickness was performed for RT planning with

Computed Tomography Simulator (GE-Lightspeed 64, GE, USA). RT technique was three-dimensional conformal radiotherapy (3DCRT) in 25 patients and field-in-field intensity-modulated radiation treatment (FIF-IMRT) in 10 patients. Treatment planning was done via Eclipse 10.0.

While 33 (94%) of the patients received adjuvant RT, 2 (6%) patients who were considered as inoperable, underwent definitive RT. The whole lung was contoured as a high-risk organ on the RT-planning CT-scan. Dosimetrically, median values of treatment volumes (CTV, PTV), left lung mean (D mean), maximum (D max) doses, volume of lung receiving 25 Gy (V25 Gy) were examined. CTV was included gastric tumor bed/remnant stomach, regional lymphatics and anastomosis region. Planning target volume (PTV) was constructed by adding 1 cm to CTV in alldirections. The daily fraction dose was 180-200 cGy, 15 patients (43%) received 5040-5400 cGy in a single volume, and 20 patients (57%) received 540 cGy additional dose after 4500 cGy.

In this study, radiological changes in the adjacent (left) lung were evaluated by a radiologist in the control CT / PET-CT images 3-6 months after the treatment. In addition, the opposite (right) lung were also evaluated in terms of dosimetric data. The contribution of treatment volumes and lung volumes with radiation-related lung damage was examined via a dose-volume histogram. The dose-volume histogram features of the patients are presented in Table 2.

Table 2. Dose-volume histogram feature of patient	
Dose-volume	**Mean Dose**
Left Lung D mean	603cGy (range: 4-1357cGy)
Left Lung D max	4799cGy (range: 103- 5416cGy)
CTV	557cc (range: 372-1518 cc)
PTV	1193cc (range: 647-2996 cc)

RESULTS

Tumor location was proximal (cardia) in 10 (28.6%), distal (antrum, pylori) in 19 (54.3%), and corpus in 6 (17.1%). Surgery was performed in all patients except 2 patients. Therefore, RT was performed as definitive in 2 patients (6%) and adjuvant in 33 patients (94%). The ratio of 3DCRT and FIF- IMRT techniques was 71% and 29%, respectively. RT was applied as a single volume in 15 patients (43%), and boost was added in 20 patients (57%). In addition, the target volumes (CTV, PTV) of the patients were quite variable (Table 2).

Posttreatment RILI was detected in 18 of patients (51.4%) in the ipsilateral lung. In addition, RILI was detected in 50% of the 18 patients (9 patients) in the opposite lung basal segment (right posterior-basal segment and right paravertebral lung segment) (Table 3).

Radiologic changes were ground glass opacity in 12 patients (34.2%), consolidation in 8 patients (22.8%), air bronchogram in 4 patients (11.4%), loss of volume in 8 patients (22.8%), pleural thickening in 5 patients (14.2%), and pleural effusion in 3 patients (8.5%). Moreover, pre-existing bronchiectasis revealed progression in control CT images of 1 patient (2.8%) (Table 4).

Most of the patients who developed lung damage were in the corpus and distal locations (2 proximal, 4 corpus, 3 distal). We did not find a statistically significant relationship between tumor localization and RILI ($p > 0.05$). In subgroup analysis, RILI was detected in 66.7% of corpus-located tumors, 50% of proximally located tumors and 47.4% of distally located tumors ($p > 0.05$).

RILI development was observed more with 3DCRT technique compared to FIF-IMRT technique (for ipsilateral lung; 12 (66.7%) and 6 (33.3%), for opposite lung; 5 (56%) and 4 (44%), respectively) ($p > 0.05$). Due to the fact that the number of patients in 3DCRT and IMRT techniques is not equal and our current number of patients is low, no statistically significant difference was found in terms of lung damage.

Table 3. Factors affecting the development of Radiation-induced lung injury		
Factors	**RILI / number of patients (%)**	**p**
Operation		
Subtotal gastrectomy	11 (61.1%)	
Total gastrectomy	7 (38.9%)	0.38
Technique		
3DCRT	12 (66.7%)	
FIF-IMRT	6 (33.3%)	0.71
Chemotherapy		
Yes	17 (94.4%)	
No	1 (5.6%)	0.6
V25> 10%		
Yes	8 (44.4%)	
No	3 (17.6%)	0.14
Boost		
Yes (20 patients)	13 (65%)	
No (15 patients)	5 (33%)	< 0.05

RILI= Radiation-induced lung injury

Although 44% of the radiologically damaged patients had V25> 10% for the lung, no patients had symptomatic RP. Table 2 shows the CTV and left lung dose-volume values. No statistically significant association was found between RP development and dose-volume values.

Although the treatment volume (CTV, PTV), age, operation, concomitant chemotherapy were observed as factors related with a higher incidence of damage, it was not statistically significant. However, RILI development was significantly higher in patients undergoing boost ($p < 0.05$). RILI developed in 13 patients (65%) who underwent additional boost and it was bilateral in 7 (53%) of them. In patients without boost RILI development was seen in 5 (33%) patients. It was bilateral in 2 (40%) patients. Table 3 shows the factors affecting RILI development.

Table 4. Frequency of each sub-type of lung damage

Lung change	Number of patient n (%)
Parenchymal	
Ground-glass opacities	12 (34.2%)
Consolidation	8 (22.8%)
Air bronchogram	4 (11.4%)
Progression in pre-existing bronchiectasis	1 (2.8%)
Volume reduction	8 (22.8%)
Pleural reactions	
Thickening	5 (14.2%)
Effusion	3 (8.5%)

DISCUSSION

To our knowledge, the current study is the first study to evaluate lung damage after radiotherapy of gastric cancer. Most of the studies about RILI are in thoracic irradiation, especially lung cancer. We know that RILI has been considered a limiting factor for patients requiring thoracic radiation. Recurrent and strong lung injuries result in permanent radiological scarring often referred to as fibrosis.[5] RILI is common but generally asymptomatic.

Veiga et al. evaluated the lung damage in 3 categories on CT after chemoradiotherapy as parenchymal changes (consolidation, ground-glass opacities, bronchiectasis/reticulation), lung volume reduction, pleural changes (thickening, effusion) which are reported in 100%, 96%, 82% of patients, respectively.[6] These results are quite high because of patients with lung cancer. In addition, they also made their evaluations 12 months after chemoradiotherapy. Of course, we do not expect such high values in our study. In our study, parenchymal change, lung volume reduction, pleural changes were 71.2%, 22.8%, 22.7%, respectively. There is no similar study that we can compare our work exactly. However, we believe that these data for stomach cancer are too high to be overlooked.

Radiation dose and patient-related risk factors play an important role in the development of damage; Older age, presence of comorbidity, sequential chemotherapy, disease located in mid-lower lung increased the risk of RP.[7]

In many studies, it was emphasized that RP development was more common in lower lobe lung irradiation.[8,9] Kong et al. reported that this may be attributed to better oxygenation, perfusion and ventilation of lower lobe.[10] In our study, the lower lobe was already in the RT area due to the neighborhood with the lung. Considering the studies showing that the lower lobe is riskier in terms of RP development compared to other regions, the importance of our study increases. In addition to ipsilateral lung lobe, damage in the contralateral lung can not be ruled out. the opposite lung lobe damage is too much to ignore.

The use of drugs with known pulmonary toxicity, such as bleomycin, actinomycin D, adriamycin, cyclophosphamide, mitomycin C and vincristine, combined with radiotherapy further strengthens the toxicity of radiotherapy.[11] Direct DNA damage and the formation of reactive oxygen species are the mostly blamed underlying mechanism.[4] In this study, since most patients were given chemotherapy, a statistically significant relationship could not be established between RILI development and chemotherapy.

Another important factor which contributes to the damage is tumor location. As we know, the stomach is apportioned into three parts (fundus, body, antrum). On the left, it abuts on the diaphragm. The location of the tumor is important in determining the treatment volumes in RT of GC. Especially, in proximal tumors, the upper limit of RT area has to be kept wide. During two-dimensional traditional RT applications in the past, the treatment area was specifically determined by reference of bones. A large area was treated, roughly between the T10-L3 vertebrae, including the left hemidiaphragm. In the following years, innovations in both RT devices and planning techniques led to a reduction in treatment volume. Guidelines for postoperative irradiation define individualized target volume based on location, extent of the primary tumor (T-stage), and nodal involvement (N-stage).[12] At proximal gastric/ esophagogastric junction lesions, a 3 to 5 cm margin of distal esophagus should be included. Therefore, for tumors in esophagogastric junction and cardia/proximal one-third of the stomach, the lower lobe of the left lung is commonly more broadly within the irradiation fields. Accordingly, lung dose-volume parameters should be strongly considered for these patients. In our study, the tumor placement of our patients was mostly in the corpus and distal locations. Therefore, RILI development was high in that group. However, when we performed subgroup analysis (patients were evaluated within themselves), RILI was less in those with distal location ($p > 0.05$).

In addition to tumor placement, treatment volume, Dmean, total dose delivered,fractionation schedule are also a risk for lung damage formation.[13,14] In our study, no significant correlation was found between RILI development and dose-volume data.

Target volumes (CTV, PTV) of these patients are large and quite variable.[15] In the study, while the minimum observer variation was found at the border with the liver and the left kidney, the greatest differences were seen at the cranial and caudal parts. In particular, the large variation at the cranial part of the CTV has been attributed to the attempt of including part of the diaphragm and periesophageal nodes into the CTV. Particularly, the target volume for postoperative radiotherapy is troublesome. In our study, the target volumes (Table 2) of the patients were quite variable for the same reasons, but, we did not observe a significant result between treatment volume and damage. Also, RILI was not detected in 2 patients who underwent definitive RT. We thought that this may be due to better definition of the treatment volume as well as the distal location of the tumor.

The effects of lung irradiation can be seen in the form of early radiation toxicity, typically occurring within hours to a few days after RT exposure and late radiation toxicity that occurs months to years after treatment, including tissue fibrosis, necrosis, atrophy and vascular injury.[16,17]

CT is quite sensitive in the diagnosis.[18,19] Thin-section CT shows homogeneous consolidation 2-3 weeks after treatment and solid consolidation after doses higher than 50Gy.[20] Various cells and molecules are involved in pathophysiology this process. Type 2 pneumocytes, alveolar macrophages, endothelial cells, and fibroblasts are considered to be targets of pulmonary radiation.[21] Krengli et.al evaluated lung changes with highresolution computed tomography in 3 and 9 months before and after adjuvant RT in operated breast cancer patients.[22] The effect was observed in the alveolar-capillary barrier and smallest airway branches at 3 months and only partial recovery was seen 9 months after RT. In addition, they reported minimizing the lung volume receiving > or = 25 Gy (V25) could reduce pulmonary toxicity. In our study, we observed RILI development in the first 3-6 months after treatment which we can call early period, and at a rate that we can accept high.In addition, it would be better if we evaluate the changes to be observed in the RILI area (recovery or progression), in the chronic period. However, the follow-up of the patients was irregular.

Several clinical, radiological and functional criteria were used to form RILI scoring systems. Parenchymal changes are reported to occur after doses of about 40 Gy and higher.[23] Furthermore, preexisting radiological interstitial lung abnormalities have also been associated with an increased risk of ≥ grade 3 RP.[24] In our study, boost (additional dose after 45Gy treatment is found to significantly correlated with RILI. We know, loco-regional failures occur usually in the region of the gastric remnant, anastomosis and/or duodenal stump. Therefore, in clinical practice, we evaluate patients individually and increase the dose to such high-risk areas for recurrence with boost technique. So, it is not unexpected to detect lung damage in the left lung lower lobe (approximate boost region) more prominently.

Conclusion

RT is one of the important steps of treatment in stomach cancer. Especially the left lung lower lobe is included in the RT field while it is adjacent to the stomach leading to radiation damage. Also, it can be misdiagnosed as metastasis in patients follow. Although there is no similar study in the literature, as seen from our results, the damage rate is remarkable. Therefore, we recommend especially left lung to be considered in terms of radiation toxicity in patients who received RT for gastric cancer.

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