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Original Research Article

The Impact of splenic irradiation during chemoradiation for Gastric and Gastroesophageal junctional cancers in the development of acute hematological toxicity

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ABSTRACT

Background : Spleen being in close proximity to radiation field in patients of gastric and gastroesophageal carcinomas treated with radiotherapy will inadvertently receive a part of the dose. The purpose of this study was to determine the impact of radiation dose and fractional volume of irradiated spleen in the setting of chemoradiation therapy for gastric and gastroesophageal junctional cancers on haematologic toxicity.

Materials and Methods: 40 patients with gastric and gastroesophageal junctional cancers who received concurrent chemoradiation were retrospectively analysed in the Department of Radiation oncology, Father Muller Medical College. Splenic dose-volume histogram (DVH) parameters were calculated as mean splenic dose (MSD) and percentage of splenic volume receiving 10 Gy (V10), 20 Gy (V20), 30 Gy (V30) and 40 Gy (V40) dose and correlated with clinical blood parameters. Mean, percentage, standard deviation and Student paired t-test were used to analyse the results.

Results: All the patients experienced haematological toxicities, including 7 patients with grade 3 leukopenia and 3 had grade 4 leukopenia, 19 with grade 2 thrombocytopenia and 4 had grade 3 thrombocytopenia, 28 with both leukopenia and lymphopenia. Mean dose to the spleen was 32 Gy (range 27–37). Higher spleen V10-V40 was correlated with leukopenia, lymphopenia and thrombocytopenia.

Conclusion: This dosimetric study demonstrates that splenic radiation was correlated with haematological toxicities, however role of chemotherapy as cause for toxicity could not be assessed as separate variable in this study. Future clinical correlational studies are needed to significantly determine the splenic dose constraints.

Key Messages: Radiation therapy for gastric and gastroesophageal carcinoma leads to significant dose to spleen causing an impact in acute haematological toxicities.

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1. Introduction

In upper abdominal malignancies, the use of concurrent chemoradiation has become a standard treatment option, either adjuvant to surgery or as a definitive treatment. Using radiation therapy comes with the risk of side effects and treatment planning with three dimensional or intensity modulated radiation therapy technique plays an important role in minimizing injury to organs at risk within or near

the target volume. Current treatment planning protocols evaluate dose to the heart, lung, liver, spinal cord, small bowel, and kidneys.

However, to our knowledge there are not many reports on the radiation dose received by the spleen or the potential sequelae to upper abdominal irradiation. The spleen being an hematopoietic organ, not only helps in a blood pathogen elimination and senile red blood-cell destruction but also in extramedullary hematopoiesis. The spleen plays a significant role in innate and

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adaptive immunity. Hyposplenism or splenectomy generally increases the future risk of infection or sepsis.^{1–3}

No study quantifies splenic radiation dose in the treatment of upper abdominal malignancies and no guidelines exist on the use of pneumococcal vaccination for patients having functional hyposplenism after receiving chemoradiation although it is a possibility.

The purpose of this study was to determine the impact of radiation dose and fractional volume of irradiated spleen in the setting of chemoradiation therapy for gastric and gastroesophageal junctional cancers on hematological toxicity.

2. Materials and Methods

A retrospective dosimetric study of 40 histologically proven squamous cell and adeno carcinoma with American joint committee on cancer staging criteria (AJCC) stage II, stage III gastric and gastroesophageal junctional cancers patients treated at the Department of Radiotherapy, Father Muller Medical College, Mangalore were considered after institution ethical clearance and patient participation consent.

The patients were immobilized in supine position with both arms raised and forearms kept under the head to avoid the arms coming in the radiation field. All patients underwent a planning CT with proper chest immobilization using all in one (AIO) carbon fiber base plate. During the CT scan, the flat AIO was placed over a curved CT Couch with the fiducial markers on single plane to fix the reference origin to simulate the treatment parameters. The 16 slice CT scan with 85 cm bore size was used. The Gross tumour volume (GTV) was delineated taking into consideration the endoscopy findings and the diagnostic CT scan images. Clinical target volume (CTV) was delineated to account for microscopic spread of disease covering the lymph node draining areas according to the tumour site. Planning target volume (PTV) of 0.5cm margin around CTV was considered as per institution protocol to account for movement and uncertainty in target delineation.

The spleen was contoured for each patient, and its corresponding dosimetry was calculated. Splenic dose-volume histogram (DVH) parameters were calculated as mean splenic dose (MSD) and percentage of splenic volume receiving 10 Gy (V10), 20 Gy (V20), 30 Gy (V30) and 40 Gy (V40) dose. Blood samples were obtained by venipuncture and were collected 0–3 days before the start of radiation therapy (RT), again once a week during RT and after RT (upto 3 months) to quantify the leukocytes, platelets and lymphocytes. Changes in the blood counts and minimum absolute lymphocyte count (ALCs) during RT were evaluated. The decrease in lymphocytes was quantified by the difference between the baseline values of the absolute peripheral lymphocyte before RT and the Min ALC during RT. All the hematological toxicity were graded

as per common toxicity criteria (CTC) version 2.0, Cancer Therapy Evaluation Program (CTEP).^{4,5}

2.1. Statistical analysis

The data was entered in the computer using the MS office excel sheet for statistical analysis. The mean along with standard deviation (SD) was calculated for each parameter. Student paired t test has been applied to find the significance of study parameters and to analyze the difference and level of significance between the splenic dose and the hematological toxicities. The results were also expressed in Percentage, Proportion, Mean and SD (Min-Max). The difference was considered significant if p value was less than 0.05. All calculations were done with SPSS version 19.

3. Results

The patient and tumour characteristics included in this study are listed in Table 1. The treatment characteristics of all the patients in the study are listed in Table 2.

For each patient, the minimum, mean and maximum splenic dose (Dmin, Dmean, Dmax) were recorded. To estimate dose-volume relationships to correlate with clinical hyposplenism, dose-volume at 10 Gy intervals were quantified. Dmean to the spleen was 32 Gy (range 27–37). Higher spleen V10-V40 was correlated with leukopenia, lymphopenia and thrombocytopenia. (Table 3)

All the patients experienced hematological toxicities (Table 4Figure 1), including

1. 7 Patients had grade 3 leukopenia and 3 had grade 4 leukopenia,
2. 19 had grade 2 thrombocytopenia, 4 had grade 3 thrombocytopenia and none of the patients had grade 4 thrombocytopenia.
3. 12 Had grade 3 lymphopenia and 6 had grade 4 lymphopenia.
4. Overall 28 patients had \geq grade 3 toxicity of both leukopenia and lymphopenia.

All the haematological toxicities appeared to increase along with the course of radiation therapy with a maximum increase appearing at 5th week. Lymphopenia appeared to be more significant compared to leucopenia and thrombocytopenia (Figure 2). On follow-up, 12 (30%) patients were alive. 19 patients survived less than 1-year. Median post-chemoradiation absolute lymphocyte count (620 cells/UL) was significantly lower than pre-chemoradiation absolute lymphocyte count (1460 cells/UL). The lymphocyte drop was found to be more evident than leukocyte and thrombocyte drop, as lymphocytes are more radiosensitive. Median V20, V30 and V40 were significantly higher in patients with leukopenia and thrombocytopenia compared to those without. Dose volume parameters of the spleen showed the highest correlation

with several toxicities like vomiting, anorexia, dehydration, hematological toxicity, fatigue, combined gastro-intestinal toxicity.

Correlation between Minimum absolute peripheral lymphocyte count (ALC) and spleen dosimetric variables were calculated. The peripheral blood lymphocytes decreased during radiation (from 1557.50 to 318.82 cells/ μ L)(Table 5). Spleen dosimetric variables, including the MSD, V20, V30 and V40, were significant factors correlated with the decrease in lymphocytes. Patients whose V30 < 30% and V40 < 20% performed better than those whose DVH was higher.

Table 1: Patient and tumor characteristics

Characteristics	Type	N	(%)
1.Age (years)	Median	55	
	Range	25 - 77	
2.Gender	Male	27	67.5%
	Female	13	32.5%
3.Tumor site	Stomach	25	62.5%
	GEJ	12	30%
4.Histology	Stomach + GEJ	3	7%
	Adenocarcinoma (mucinous/signet ring/medullary variant)	25	62.5%
5. Grade	Squamous cell ca	14	35%
	Both	1	2.5%
	Well differentiated	14	35%
	Moderately differentiated	15	37.5%
6.Staging	Poorly differentiated	11	27.5%
	T 1	3	7
	T 2	11	27.5
	T 3	19	47.5
	T 4	8	20
	N 0	5	12.5
	N 1	17	42.5
N 2	10	25	
N 3	9	22.5	

4. Discussion

The immune system plays an important role in cancer suppression and cancer prognosis. The effect of ionizing radiation therapy can lead to apoptosis of circulating lymphocytes, which lowers the antitumor effect of the immune response. Lymphocytes, being an effector cells in antitumor immunity, recognize and kill cancer cells and release cytokines to activate the host immune system.^{4,6} Chadha et al have demonstrated that peripheral lymphocytes tend to decrease during the course of radiation therapy (RT) because of their high radiation sensitivity.⁷

Traditionally the spleen is an ignored organ in radiotherapy, it recently has raised some interest with the onset of radio-immunotherapy. The minimum value of

Table 2: Treatment characteristics

		No of patients	%
NACT (8)	EOX (3 OR 4 cycles)	2	
	ECF	1	20%
	5FU+Cisplatin	2	
	Cisplatin + paclitaxel	3	
	Subtotal gastrectomy	Lap-6/radical-	
Surgery (31)		12 = 18	77.5%
	Near total gastrectomy	3	
	Total gastrectomy	7	
	Transhiatal oesophagectomy	2	
	Ivor lewis	1	
Radiotherapy schedule	Adjuvant -45Gy/25#	18	
	50.4Gy/28#	14	100%
	54Gy/30#	2	
	Definitive – 54Gy/27#	6	
Concurrent chemo	Capecitabine	24	60%
	Cisplatin	8	20%
	5FU + LV	2	5%
Radiation technique	Paclitaxel+cisplatin	6	15%
	3DCRT	26	65%
	IMRT	14	35%

Table 3: Spleendosimetry

	Median	Range
Spleen volume(cc)	156.35	87-299.4
D min (Gy)	8.8 Gy	1.8-16.1
D max(Gy)	39Gy	29.6-48.5
D mean(Gy)	32.3Gy	27-37.6
DVH V10	66.35%	32.7-100
V20	52.65%	30.7-94.9
V30	48.05%	21.3-74.8
V40	24.04%	11.7-36.4

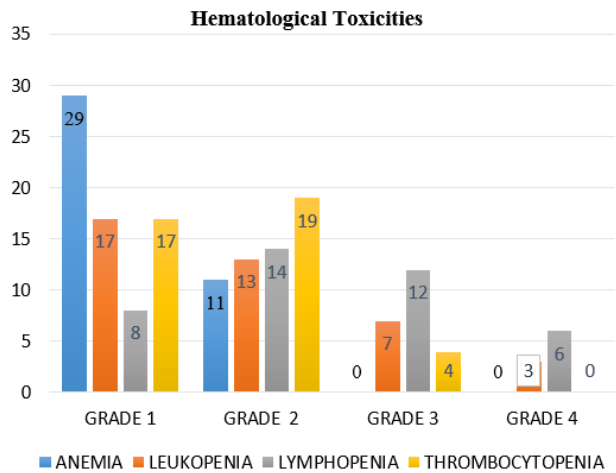


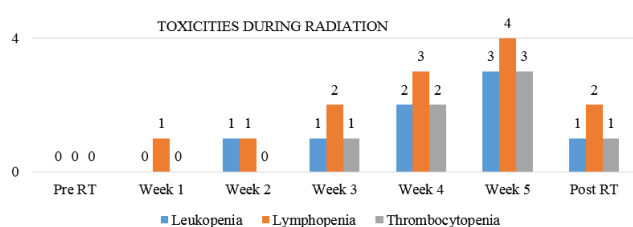
Fig. 1: Haematological toxicities

Table 4: Hematological toxicities

	Normal range	Grade 1	Grade 2	Grade 3	Grade 4
Anemia (Hb) g%	11-14	29	11	-	-
Leukopenia (TLC) cells/dl	>4000-11,000	17	13	7	3
Lymphopenia	<1500	8	14	12	6
\Thrombocytopenia (lakhs/dl)	1.5-5	17	19	4	-

Table 5: Minimum absolute lymphocytes (Min ALC) with mean dose to splenic irradiated volume (V10, V20, V30, V40- Volume of spleen receiving 10 Gy, 20Gy, 30Gy and 40Gy respectively)

Weekly cumulative splenic dose	Minimum absolute peripheral lymphocyte count (ALC) cells/UL
V10	756
V20	555
V30	468
V40	408

**Fig. 2:** Weekly toxicities during radiation therapy

absolute peripheral lymphocyte counts during RT treatment (Min ALC) has been proven to be a prognostic factor for tumour recurrence and overall survival in various cancers.^{8,9} In a study, by Liu et al, they verified the value of Min ALC in predicting survival in hepatocellular carcinoma (HCC) patients.^{10–12} Splenic damage may occur even at low radiation doses because of its exquisite radiosensitivity, resulting in transient reduction in platelet counts.^{13,14} Many peripheral blood lymphocytes pass through the spleen daily, and changes in the function of the spleen affects the counts of the lymphocytes in peripheral blood. Hence it was hypothesized that a radiation dose to the spleen would reduce the counts of peripheral blood lymphocytes.

The spleen irradiation dose observed had significantly correlated with a lower Min ALC during RT. Thus, splenic irradiation may contribute acutely to thrombocytopenia or pancytopenia in patients receiving concurrent chemoradiation and chronic splenic dysfunction may increase the risk of sepsis or pneumococcal pneumonia.^{15,16} Therefore, the maximum sparing for spleen irradiation during RT is recommended to preserve peripheral blood lymphocytes, which may decrease immunosuppression. Furthermore, we identified the predictive cutoff value of spleen dosimetric variables for the Min ALC to identify the spleen dosimetric constraints for clinical practice.

If a higher risk of toxicity exists, it may be worthwhile to consider pneumococcal vaccination prior to chemoradiation. In Hodgkin's disease, pneumococcal

vaccination is increasingly a routine for patients after splenectomy to avoid infection or sepsis.^{17,18} For gastrointestinal malignancies, we do not recommend routine vaccination but our data suggest it is worth further investigation to determine whether the spleen should be considered an organ at risk in patients receiving upper abdominal radiation therapy.

Our dosimetric study demonstrates that splenic radiation within a clinically relevant range (27-37 Gy) as measured, could lead to organ dysfunction. Future clinical correlational studies are needed to significantly determine splenic dose constraints⁵ and whether gastric and esophageal cancer patients have an elevated risk of pneumonia or sepsis after radiation therapy.

Limitations of our study was the role of chemotherapy as a cause for toxicity could not be assessed as a separate variable in this study and is therefore a major confounding factor, but radiation volume of spleen correlated with the severity of hematological toxicities. Use of varied target volumes, radiation doses and different radiation therapy techniques in the treatment are an another limitation of this study.

5. Conclusion

In chemoradiotherapy for gastric cancer and gastroesophageal junctional cancers, the spleen receives a high radiation dose. This results in a progressive, radiation dose-dependent hematological toxicity. Higher splenic doses increase the risk of developing severe post-radiation lymphopenia and thrombocytopenia. When clinically indicated, assessment of splenic DVHs prior to acceptance of treatment plans may minimize the risk of hematological toxicity. Future similar studies may help in framing dose constraint guidelines for splenic irradiation.

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8. Conflict of Interest

The authors declare they have no conflict of interest.

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