RESEARCH PAPER

Correlation between gastric volume and organs at risk dose in adjuvant radiotherapy for left breast cancer

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ABSTRACT

Background: The role of the gastric volume on the dose-effect relationship for these organs has not been investigated. The aim of the study was to evaluate the correlation between gastric volume and dose-volume histogram (DVH) parameters of the heart, left lung and stomach during left breast cancer radiotherapy (RT).

Materials and methods: Ninety-nine left breast cancer patients who got adjuvant radiotherapy were included. Study was classified into two groups based on treatment field arrangements: 1) breast tangential fields only (T) and 2) breast tangential and supraclavicular fields (TS). Organs DVHs were extracted. Descriptive statistics, Pearson correlation, linear regression analyses, and receiver operating characteristic (ROC) analyses were performed.

Results: There is a direct but not significant correlation between the gastric volume and doses to the stomach and left lung. For a 100-cc increase in the gastric volume, the stomach maximum dose and the V_{50} increased by 3 Gy and 4%, respectively. For the left lung, V_4 and V_5 increased by 1% for TS cases. Considering ROC analysis results, one can make a decision for about 74% of patients due to their left lung DVH parameters, using gastric volume as a known input data. The correlation between gastric volume and heart dose was not significant.

Conclusions: The gastric volume of about 170 cc or less can result in lower dose to the stomach and ipsilateral lung during left breast cancer radiotherapy, especially for TS cases. To reach this gastric volume threshold, patients should be fast for 2 hours before the procedure of CT simulation and treatment.

Key words: breast cancer; gastric volume; heart dose; lung dose

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Introduction

In both developed and developing countries, breast cancer is still the most commonly diagnosed cancer among women, comprising 24.4% of all diagnosed malignancies among female cancer patients in Iran [1]. Various breast cancer management strategies exist based on the clinical and pathological characteristics of patients and tumors. Typically, a multidisciplinary approach is used, in which radiotherapy (RT) accounts for about 87% of breast cancers [2].

The technical advancement from 3D conformal radiotherapy (3D-CRT) to intensity-modulated

radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) has occurred for almost all treatment sites over the past two decades. IMRT provided superior dose conformity, especially for concave target volumes, and optimal dose sparing of adjacent normal tissues, but it might also increase the risk of radiation-induced secondary malignancies. Concerns about the secondary cancer of organs proximal to the fields, such as the contralateral breast, heart, and lung, have increased due to the higher low dose baths resulted from IMRT and VMAT [3]. Using the 3D-CRT technique, smaller volumes of normal tissues are potentially exposed to lower radiation dose than IMRT. However, due to its shorter planning time, there are still many cancer institutes that prefer the 3D-CRT technique for breast cancer radiotherapy, especially in high-loaded centers [4]. Furthermore, IMRT is still an expensive treatment procedure. In Iran, about 10,000 new cases of breast cancer are diagnosed every year which leads to overloaded public radiotherapy centers [5]. For all of these reasons, 3D-CRT is the first choice of breast cancer radiotherapy in Iranian centers. Moreover, conventional fractionation by 2 Gy/day and total dose of 50 Gy, with/without boost dose to the tumor bed, has been prescribed as the standard of care [6].

Lungs, heart, and stomach are the considered organs at risk (OARs) in radiotherapy of the left breast. Exposure of these critical structures to radiation may cause early and late sequelae. Because of increasing the general education level and stronger prevention policies, it is hoped that cancers can be detected in early stages, so treatments can be started as soon as the diagnostic procedures are completed. Today, higher overall survival of breast cancer patients is expected. In this regard, late side effects of radio-therapeutic interventions and limiting the risk of secondary cancer deserve more attention.

Excess absolute risk (EAR) term has been defined to represent the risk of developing a solid secondary cancer after radiotherapy. This concept can be estimated from the DVH of treatment planning [7]. Several risk models have been proposed to predict secondary cancer but still there is no accurate prediction due to the lack of follow-up and epidemiological data [3].

The risk of secondary cancer for the ipsilateral lung was even estimated higher than for the other proximal organs; it receives a higher dose in order to achieve a higher tumor control. Generally, known side effects of left breast RT included secondary lung malignancy, pneumonitis, lung fibrosis, cardiovascular diseases, and potential gastric complications [8–10]. The dose-effect relationship was directly proportional to: the higher the dose, the greater the complication rate. Studies indicate that pneumonitis (chronic or acute) and fibrosis have a direct correlation with radiation doses to the lung [11, 12].

Heart complication after radiotherapy of breast cancer has previously been studied. Two studies confirmed the probability of the coronary complications, including revascularization and myocardial infarction, increased linearly with the mean dose to the heart [13, 14]. The results of a cohort study proved that there was a significant dose-effect relationship between the probability of acute coronary events incidence and mean heart dose [15]. Cho et al. studied gastric complications after adjuvant radiotherapy for breast cancer. They concluded no chronic gastric complication was correlated with the radiation exposure during breast cancer irradiation [8]. Despite previous studies, the role of the gastric volume on the dose-effect relationship for the lung, heart, and stomach after the adjuvant left breast RT has not been investigated.

Therefore, to minimize the amount of low dose volume such as the known V_4 and V_5 (V_x referred to the volume receiving more than x Gy), as well as the mean and maximum dose should be assessed for proximal OARs. This may reduce the risk of secondary cancer and other complications [3, 7].

This study aimed to evaluate the correlation between the gastric volume and the dose-volume histogram (DVH) parameters of the stomach, left lung, and heart during adjuvant radiotherapy for left breast cancer. This study also made an effort to propose a protocol for patients' gastric preparation before the procedure of CT simulation and treatment if any relationship between the DVH parameter and gastric volume was confirmed.

Materials and methods

Study population

Treatment planning data of 99 patients during two years from February 2018 to January 2020 were studied, retrospectively. In this study partici-
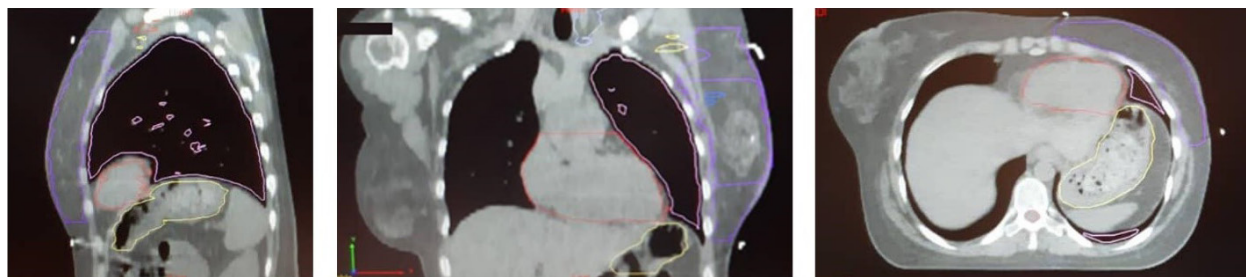
Figure 1. A sample of left breast case with her delineated organs

pants were patients treated by the 3D-CRT of the left breast cancer at Shohada-e Tarjish Hospital in Tehran, Iran. TNM and histological gradings were determined based on the National Comprehensive Cancer Network (NCCN) guidelines [16]. The patients were referred for postoperative irradiation based on their risk factors after mastectomy (MRM) or breast-conserving surgery (BCS) [17]. 83 of the included cases were BCS and the other 16 cases were MRM. The sampled population was classified into two groups according to the treatment field arrangements: 1) tangential (T) fields and 2) tangential/supraclavicular (TS) fields. All patients were set up in the supine position during CT simulations and radiotherapy treatments with the aid of a reproducible patient supporting system (AIO Breast'; Orfit; Belgium). For none of the considered cases electron beam was used and all were treated by the 6 MV photon beam of a Compact™ Linac (Elekta, Inc, Atlanta, USA). The treatment planning system was the ISOGray° Solution (DOSIsoft Ed. 4; France). The considered treatment phase in this study for BCS cases was justphase I (through which the whole breast was irradiated) without inclusion of any boost irradiation. Posterior axillary field was used for all the selected TS cases.

Contouring protocols

Sampled population involved patients with CT scan images covering the whole gastric volume. Left breast, chest wall, as well as auxiliary and supraclavicular lymph nodes were contoured based on the RTOG guideline [18]. Heart contour included the pulmonary artery and extended in the inferior direction to the apex [19]. The gastric volume contoured began at the gastro-esophageal junction (GEJ) and ended at the pyloric canal opened to the duodenum. The cardia, fungus, body or corpus,

antrum, and pylorus were included in the stomach structure [20, 21]. All delineated structures were reviewed by an expertise for consistency in contouring. A sample of a left breast case with its delineated organs has been illustrated in Figure 1.

Data collection

Treatment plans were evaluated in accordance with the national and international clinical protocols at the time of planning [22–26]. All of the dose constraints are according to QUANTEC. For example, for the lung: $V_{20} < 30$ %, for the heart: mean Gy, $V_{25} < 10\%$. All of the included patients were treated by the conventional dose-fractionation of 50 Gy in 25 fractions. The DVH parameters of the stomach, left lung, and heart were extracted from the approved treatment plans and used in the following statistical analyses. These parameters included the understudied organs V_x for different x Gy ranging from 4 Gy (as the low dose) to 50 Gy (as the prescription dose), their average/mean dose, and their maximum dose as presented in Table 1.

Statistical analysis

Descriptive statistics was used to describe included patients and treatment characteristics. Pearson correlation and linear regression analysis were used to investigate the relationship between the DVH endpoints of OAR (stomach; left lung; heart) and the gastric volume using a statistical significance level of 0.05 (p-value < 0.05). Receiver operating characteristic (ROC) analysis was also used to validate the results calculated by the two statistical models. The area under the curve (AUC) metric evaluated the classification performance of the ROC model and assisted in determining the threshold of the gastric volume, when a strong correlation with the DVH endpoint was confirmed

Table 1. Descriptive statistics for patients' dose-volume histogram (DVH) parameters

Organ		Volume (cc)				Volume (%)							Dose [Gy]	
						V_{45}	V_{50}	V_{55}					D_{Max}	D_{Mean}
Gastric	Min	69.00				0.00	0.00	0.00					0.00	0.64
	Max	984.00				21.50	5.50	0.00					51.97	16.30
	Mean	258.87				1.15	0.11	0.00					31.55	3.48
	SD	180.95				3.27	0.68	0.00					18.65	3.13
			V_4	V_5	V_8	V_{10}	V_{11}	$V_{12.5}$	V_{16}	V_{20}	V_{30}			D_{Mean}
Left lung	Min	441.00	13.40	10.30	6.00	4.90	4.40	4.00	3.20	2.50	1.50			2.60
	Max	1371.00	68.90	62.80	50.10	46.40	44.80	43.20	40.50	38.30	34.30			19.90
	Mean	915.36	44.49	39.80	31.74	28.95	27.93	26.73	24.79	23.12	20.29			12.88
	SD	183.76	13.16	12.27	10.28	9.56	9.30	9.00	8.53	8.10	7.45			4.03
						V_8	V_{10}	V_{16}	V_{20}	V_{25}	V_{30}			D_{Mean}
Heart	Min	250.00				3.05	2.67	2.06	1.74	1.53	1.23			1.60
	Max	1046.00				50.60	35.30	32.70	31.60	30.10	28.74			11.20
	Mean	539.65				15.63	14.71	12.81	12.07	11.97	10.72			8.58
	SD	141.68				7.92	7.01	6.62	6.42	8.14	6.03			11.00

V_x — the percent volume of organ receiving a dose of X Gy or more; D_{Max} — maximum dose to the OARs; D_{Mean} — mean dose of OARs; OAR — organ at risk

[27]. All of the statistical analyses were carried out in the IBM SPSS® Statistics (Version 23, IBM Crop.) Software.

Results

Descriptive statistics

Table 1 describes the statistics of the physical and dosimetric parameters of the three normal organs (stomach; left lung; heart) after the 3D-CRT of the left breast. The total sample size is 99: 51 cases were classified into the T group, and 48 cases into the TS group. Distribution of the patient's age ranged from 28 to 76, with the average age of 49 and standard deviation of 13. Categories of T1, T2, and T3 for staging of the primary tumor's size accounted for 46%, 19%, and 65%, respectively. Categories of N0, N1, N2, and N3 for staging of the spread to nearby lymph nodes accounted for 65%, 19%, 11%, and 5%, respectively. Histologic grading of G1, G2, and G3 for classification of cancer cells' growth and spread rates accounted for 21%, 65%, and 14%, respectively, of the total sample population. To be candidate for TS treatment patients had to have some indications; reported positive lymph nodes, categorized in T3 or T4 stages, not enough axillary lymph nodes were dissected or the result of sentinel biopsy was not convincing, and sometimes had medial lesions.

Correlation tests

Table 2 summarizes the Pearson's correlation and the linear regression results for potential correlation between the gastric volume and the dosimetric parameters (shown in Tab. 1) for the stomach, left lung, and heart. Separate results were shown in the table for the T and TS cases in each statistical test. Figures 2–4 show the linear regression models for the relationships between the gastric volume and the V_4 and V_5 of the left lung, and D_{Max} of the stomach, respectively. For all of them the p-value was less than 0.05 and statistically significant, as shown in Table 2. Separate plots of the regression model were shown in these figures for the T and TS groups for each corresponding dosimetric parameter.

Based on the obtained Pearson's correlation coefficients (R) in Table 2, there are direct but very weak to moderate correlations between the gastric volume and the dose received by the stomach, heart and left lung for these cases. Non-zero and positive regression coefficients mean that by any increase in gastric volume, the related DVH of the stomach, left lung, and heart will increase. However, this relationship was statistically significant just for V_4 and V_5 of left lung in TS cases (p-value < 0.05).

Moreover, Figures 2–4 were plotted to make an easier illustration and discern the correlations between the DVHs parameters and gastric volume. These figures and their trendlines slope give an in-

Table 2. Correlation between gastric volume and the stomach, left lung, and heart dose-volume histogram (DVH) parameters. T and TS cases are considered separately

Organ			Volume (%)										Dose [Gy]	
						V_{45}	V_{50}						D_{Max}	D_{Mean}
Gastric	R	T				0.31	0.49						0.31	0.27
		TS				0.12	0.03						0.27	0.09
	R.C.	T				0.01*	0.04						0.03**	0.00
		TS				0.00	0.00						0.03	0.00
	P-value	T				0.02	0.00						0.03	0.06
		TS				0.41	0.83						0.07	0.56
Left lung			V_4	V_5	V_8	V_{10}	V_{11}	$V_{12.5}$	V_{16}	V_{20}	V_{30}			D_{Mean}
	R	T	0.09	0.09	0.10	0.11	0.11	0.11	0.12	0.11	0.11			0.12
		TS	0.33	0.31	0.22	0.22	0.21	0.20	0.18	0.16	0.14			0.17
	R.C.	T	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00			0.00
		TS	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.00			0.00
	P-value	T	0.53	0.52	0.47	0.44	0.43	0.42	0.42	0.43	0.42			0.42
		TS	0.02	0.03	0.14	0.13	0.16	0.18	0.22	0.29	0.36			0.24
Heart					V_8	V_{10}	V_{16}	V_{20}	V_{25}	V_{30}				D_{Mean}
	R	T			0.03	0.03	0.04	0.04	0.29	0.01				0.05
		TS			0.05	0.08	0.08	0.09	0.09	0.09				-0.08
	R.C.	T			0.00	0.00	0.00	0.00	0.01	0.00				0.00
		TS			0.00	0.00	0.00	0.00	0.00	0.00				0.01
	P-value	T			0.83	0.81	0.78	0.80	0.04	0.94				0.72
		TS			0.76	0.60	0.59	0.56	0.53	0.54				0.59

V_x — the percent volume of organ receiving a dose of X Gy or more; D_{Max} — maximum dose to the delineated OAR; D_{Mean} — radiation doses averaged across delineated OAR; T — cases treated with tangential fields; TS — cases treated with tangential/supraclavicular fields; R — Pearson's Correlation; RC — regression coefficient; *by every 1 cc increase in gastric volume its V_{45} will increase by 0.01% and so on for the other RC obtained for OARs' V_x; **by every 1 cc increase in gastric volume its D_{Max} will increase by 0.03 Gy and so on for the other R.C. obtained for OARs' D_{Max} and D_{Mean}
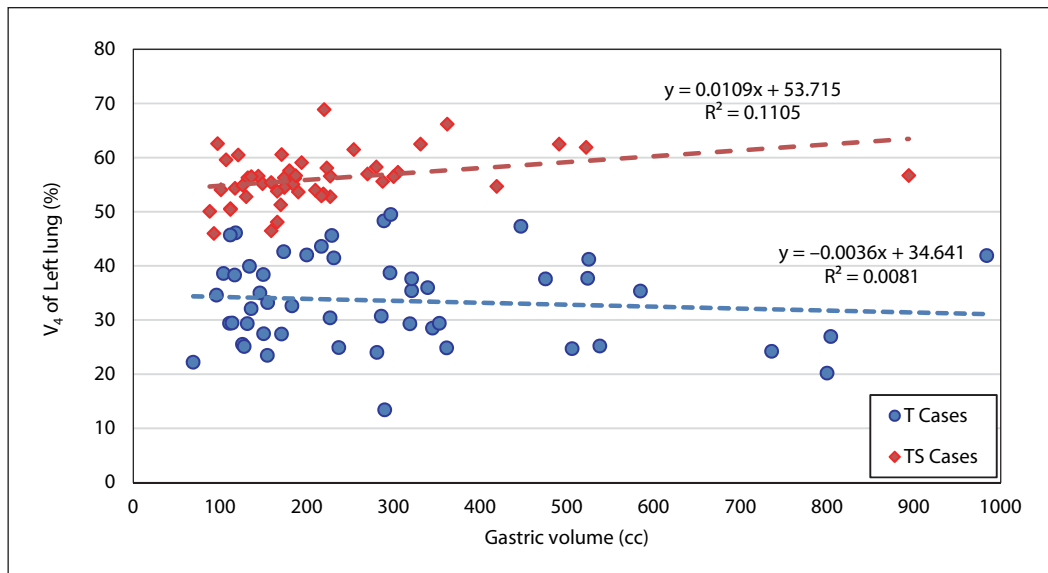

Figure 2. Correlation between gastric volume and V_4 of left lung
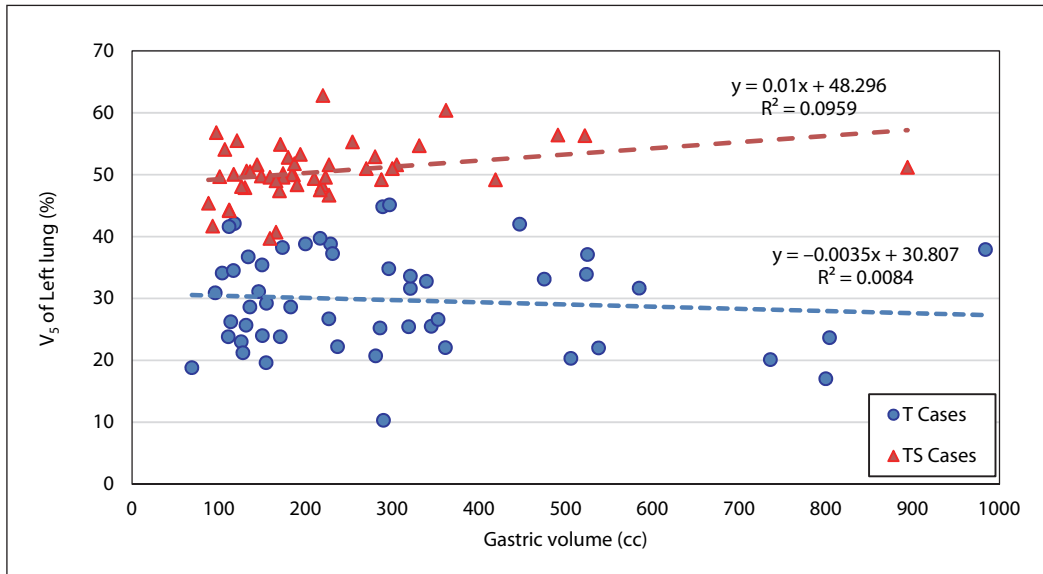
Figure 3. Correlation between gastric volume and V_5 of left lung
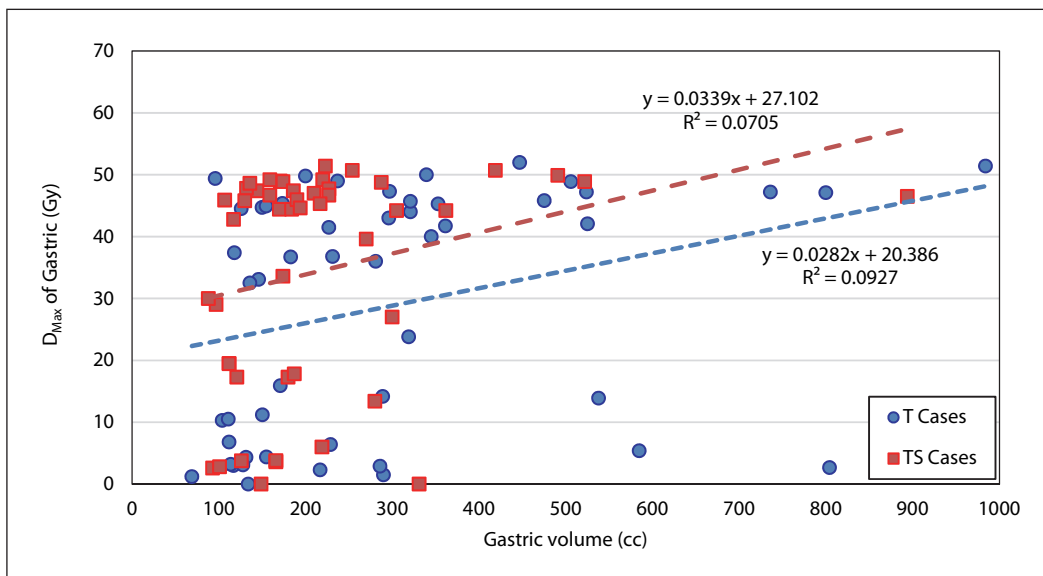

Figure 4. Correlation between gastric volume and D_{Max} of gastric

sight into the nature of the actual data, especially for the most significant results obtained from Table 2 (i.e. V_4, V_5 of the lung and D_{Max} of the stomach).

There is again a positive but weak to moderate association between maximum dose of the gastric volume and its volume for both T and TS groups. In each 100-cc increase in the gastric volume, its maximum dose would probably increase by 3 Gy, based on the obtained regression coefficients in Table 2.

There is no significant observed relationship between the gastric volume and heart dose during the left breast RT (Tab. 2). However, just for V_{25} of the heart in cases with tangential fields, there was a positive but not strong correlation with a reportable R.C. that can be explained as before (i.e. by increasing 100 cc of gastric volume, V_{25} of the heart would probably increase by 1%).

ROC analysis

Using the descriptive analysis of DVH parameters (Mean ± SD) in addition to dose constraints suggested in the protocols mentioned earlier

Table 3. Receiver operating characteristic (ROC) curve characteristics for dose-volume histogram (DVH) parameters

Organ			Volume (%)									Dose [Gy]
			V_4	V_5	V_8	V_{10}	V_{11}	$V_{12.5}$	V_{16}	V_{20}	V_{30}	D_{Mean}
Left lung	DVH threshold		> 50	> 50	> 35	> 35	> 35	> 30	> 25	> 25	> 20	> 15
	AUC	T	N	N	0.35	0.61	N	0.37	0.38	0.42	0.44	0.45
		TS	0.77	0.67	0.85	0.62	0.68	0.80	0.79	0.78	0.70	0.79
	Sensitivity	T	N	N	0.50	1.00	N	0.67	0.64	0.75	0.67	0.68
		TS	0.68	0.68	0.74	0.7	0.68	0.68	0.68	0.76	0.65	0.68
	Specificity	T	N	N	0.57	0.59	N	0.38	0.37	0.39	0.39	0.49
		TS	0.67	0.54	0.67	0.61	0.59	0.86	0.75	0.57	0.80	0.75
	Cutoff (cc)	T	N	N	290	288	N	172	172	172	172	228
		TS	163	173	154	177	170	168	162	146	168	162
Heart					V_8	V_{10}	V_{16}	V_{20}	V_{25}	V_{30}		D_{Mean}
	DVH threshold				> 25	> 25	> 20	> 15	> 10	> 10		> 4
	AUC	T			0.30	0.14	0.48	0.44	0.59	0.53		0.59
		TS			0.54	0.53	0.56	0.56	0.50	0.48		0.54
	Sensitivity	T			0.67	1.00	0.80	0.64	0.77	0.75		0.76
		TS			0.71	0.67	0.64	0.71	0.55	0.57		0.50
	Specificity	T			0.29	0.14	0.31	0.38	0.49	0.45		0.44
		TS			0.54	0.52	0.54	0.33	0.58	0.45		0.82
	Cutoff (cc)	T			150	117	150	172	172	172		148
		TS			182	182	182	154	182	172		275

V_X — the percent volume of organ receiving a dose of X Gy or more; D_{Mean} — mean dose of OARs; AUC — area under the curve; T — cases treated with tangential fields; TS — cases treated with tangential/supraclavicular fields; N — non reportable due to the low sample size

(QUANTEC, EMAMI, RTOG 1005, and NSABP B-51), DVH thresholds were selected for the ROC analysis (Tab. 3 and Fig. 5–7).

The ROC analyses between the gastric volume and its V_{45}, V_{50}, and V_{55} parameters resulted in no predictive ability of gastric volume for these DVH parameters. However, the resulted AUCs of analysis between gastric volume and its maximum dose were 0.77 (sensitivity = 0.80 and specificity = 0.61) and 0.65 (sensitivity = 0.61 and specificity = 0.64) for T and TS groups, respectively (Fig. 5). The cut-off point of gastric volume for T cases was about 230 cc and for TS cases was about 185 cc. These results were obtained after classification of D_{Max} into two binary groups of 0: $D_{Max} \leq 45$ Gy and 1: $D_{Max} > 45$ Gy, the tested state was 1. This analysis was also repeated for average dose of the stomach. For T cases no meaningful results were obtained after binary classification of the dose (0: $D_{Mean} \leq 10$ Gy and 1: $D_{Mean} > 10$ Gy). For the TS group and with the gastric volume cut-off point of about 220 cc, AUC was 0.59 with sensitivity and specificity of 0.67 and 0.69, respectively. Other reportable ROC curves for

the left lung and heart DVH parameters are illustrated in Figures 6 and 7 and the analyses detailed results are presented in Table 3.

Discussion

In different radiotherapy departments, based on their available image guidance facilities, such as electronic portal imaging device (EPID), cone-beam CT (CBCT) or even using MR-linac, several universal and/or local protocols are followed for patients' pre-simulation and pre-treatment preparation to reduce the radiation dose received by OARs and improve the adaptive treatment reproducibility [28]. However, there is no written preparation protocol for breast cancer irradiation regarding the gastric volume and, because of that, the high standard deviation of 181 cc (ranged from about 69 cc to 984 cc) for the gastric volume was achieved in Table 1.

In adjuvant RT of left-sided breast cancer, treating regional lymph node led to a remarkable increase in heart and lung doses [29]. Based on the recent systematic review by Anzar et al. MLD$_{ipsi}$ in
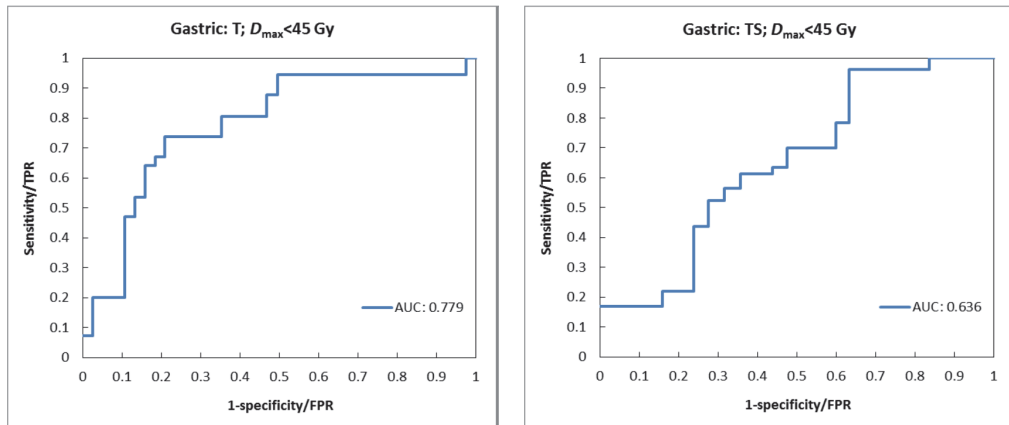
Figure 5. ROC analysis results of gastric volume predictability for its maximum dose. D_{Max} was classified into two binary groups; 0: Gastric $D_{Max} \leq 45$ Gy and 1: Gastric $D_{Max} > 45$ Gy and the tested state was 1. Left picture is for T (cases treated with tangential fields), and the right one for TS (cases treated with tangential/supraclavicular fields) groups
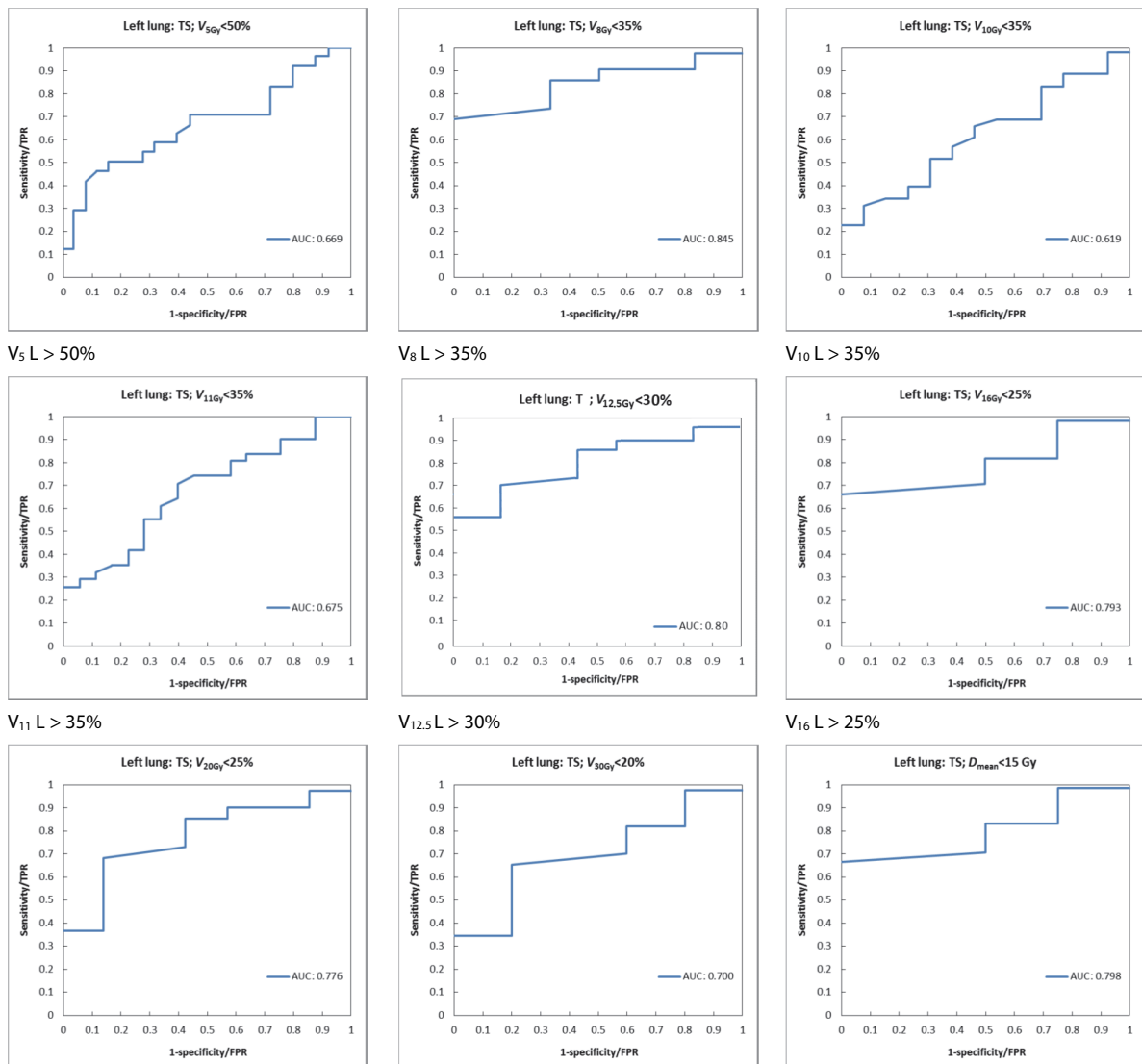

Figure 6. ROC analysis results of gastric volume predictability for left lung DVH parameters (L — left lung). T — cases treated with tangential fields; TS — cases treated with tangential/supraclavicular fields
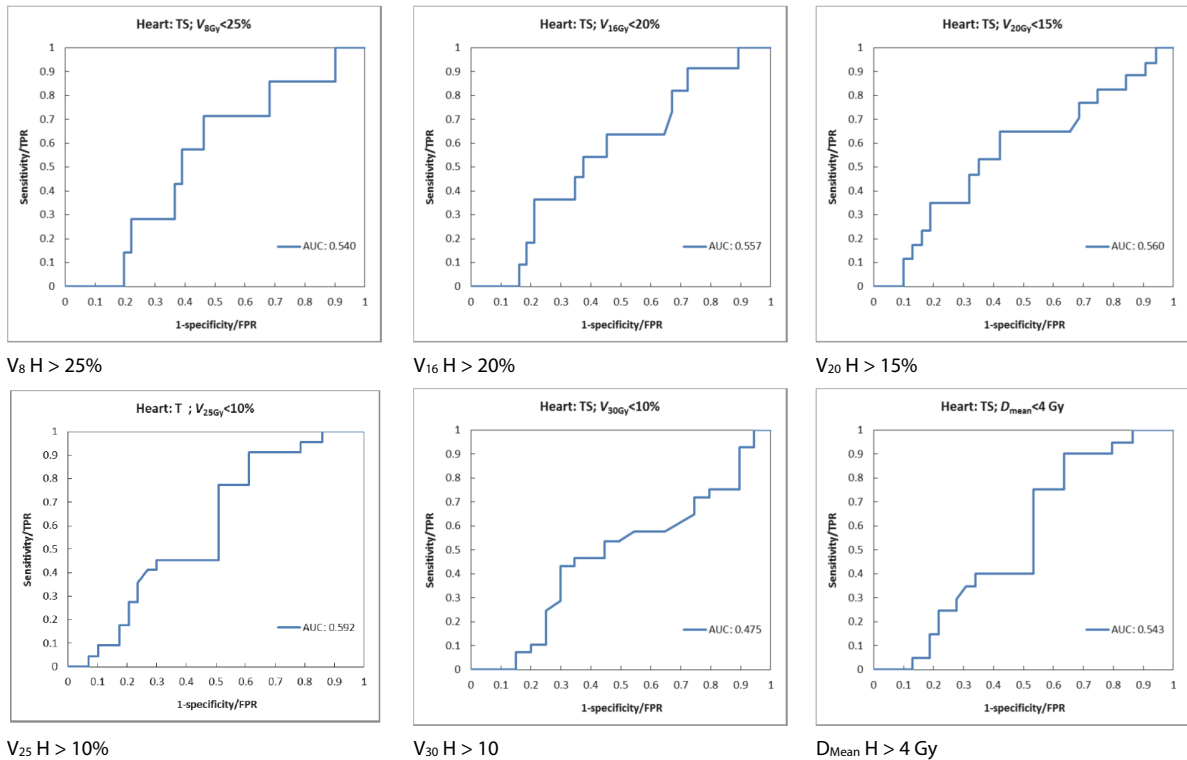
Figure 7. Receiver operating characteristic (ROC) analysis results of gastric volume predictability for heart dose-volume histogram (DVH) parameters. H — heart; T — cases treated with tangential fields; TS — cases treated with tangential/ /supraclavicular fields

breast radiotherapy with no breathing adaption in a supine position, it was 8.4 Gy for whole breast or/and chest-wall RT and 11.2 Gy when the axilla or/and supraclavicular fossa was irradiated [12]. That's why considered cases were classified into two groups of T and TS in the current study.

The mean ± SD of the left lung dose obtained 12.9 ± 4.0 Gy which was close to the data reported by Anzar MC et al. from their meta-analysis of conformal radiotherapy with tangent fields (10.9 ± 0.8 Gy) and IMRT (11.7 ± 1.1 Gy) [12]. Referring to the D_{Mean} definition, any fluctuation in the lung volume can influence the resultant mean dose. Mean ± SD of the left lung volume was 915.4 ± 183.8 cc for the cases being studied. Not following any breathing protocols during simulation can add more lung volume variations beside the intrinsic variation between different patients' anatomies. Therefore, high standard deviation could be due to the absence of any breathing protocols during patients' CT simulation.

Considering the recent publication by Cho WK et al., a five-year follow-up of breast cancer patients indicated that adjuvant RT is not a risk factor in late gastric cancer [8]. Despite the fact that the stomach

is considered as a radioresistant organ (maximum tissue tolerance dose with 5% rate of gastric complication in 5 years (TD 5/5) is 50 Gy based on Emami B. et al.), gastric ulceration risk would be 16% if it receives more than 50 Gy dose as reported by Brick IB et al. [26, 30]. For T cases, the regression coefficient (R.C.) was 0.04 (Tab. 2), which means that by increasing gastric volume in every 100 cc its V_{50} may increase by 4%. Therefore, fuller stomach increases the risk of gastric ulceration during left breast irradiation.

Based on Table 2, dependency of the ipsilateral lung volume that would receive low dose on the gastric volume is higher for TS cases than T ones. The apex of lung is irradiated to a higher dose by the tangential/supraclavicular RT fields and a higher correlation coefficient for TS was obtained compared to the T group referring to their Pearson coefficients (e.g. 0.09 for T *vs*. 0.33 for the TS cases' V_4). Using this direct correlation, the dose given to the lung can be managed better by controlling the gastric volume. For example, by considering regression coefficients of TS cases, one can conclude that an increase of 100 cc in gastric volume

may significantly raise V_4 and V_5 of the left lung by 1 percent (100 cc × 0.01 = 1) with p-value of 0.02 and 0.03, respectively. As mentioned, this correlation is much stronger in treatment of lymph node positive cases (TS) than the negative ones (T). The other DVH parameters of the left lung had a direct but moderate relationship with the gastric volume by approximately the same regression coefficients. However, the obtained associations were not strong (based on the calculated Pearson correlation coefficients) and not significant (based on the P-values) for this study population. Based on previous studies, such as Zhao H et al. and Drachman CB et al. review articles, radiation-induced secondary cancer is a concern that needs attention, especially in the irradiated organ volumes where the received dose from the primary fields exceeds 2.5 Gy [31, 32]. Furthermore, due to an individual patient data meta-analysis of 75 randomized trials, every 1 Gy increase in the mean dose of the lung during the radiotherapy of breast cancer, the risk of lung cancer increases by 11% after a decade from radiotherapy [12, 33]. However, there is no significant correlation (p-value > 0.05) between the mean dose of the left lung and the gastric volume in the current study. This randomized trial was performed by Taylor et al. and they also reported that the average of ipsilateral lung dose in modern breast radiotherapy was 9.0 Gy and the average of whole-lung dose was about 5.0 Gy. They also calculated the excess rate ratio (ERR) per Gy of whole-lung dose for incidence of lung cancer for two smoking and non-smoking groups. Based on their obtained ERR, the risk of mortality from radiation induced lung cancer is much higher in the smoking (from 9.4% to 13.8%) than nonsmoking group (from 0.5% to 0.8%). If the whole lung dose becomes higher, the excess risk will also be higher [33].

Based on previous studies, even a small heart dose can lead to cardiac disease as shown by the relative increase in this complication per gray [13]. There is a negative correlation [but weak and not significant (p-value > 0.05)] between the mean dose of the heart and the gastric volume for the current TS cases (by R.C. ≈ –0.01; by every increase of 100 cc in the gastric volume the heart mean dose may decrease by 1 Gy). Darby et al. reported the linear correlation coefficient between the rate of acute coronary events and heart mean dose (7.4% per 1 Gy) after radiotherapy of the left breast [14].

Van Den Bogaard et al. studied the relationship between acute coronary disease and the mean dose of the heart and indicated that its cumulative incidence increased by 16.5% per 1 Gy mean heart dose 9 years after this treatment [15]. Beaton et al. also assessed the cardiovascular disease (CVD) of women after 10 years of their left breast RT and checked if QUANTEC guidelines violation had any relationship with dying from this disease [9]. They concluded that the risk of death from CVD after 10 years of left breast RT is very low if the heart mean dose had been kept less than 3.3 Gy. However, weak correlation was detected between the heart dose and gastric volume in the current study.

AUC was approximately 0.77 for ROC analysis between the gastric volume and its maximum dose, which means that the gastric volume can classify about 77% of patients and specify whether their D_{max} of the stomach is more than 45 Gy or not (Fig. 5). Also, the sensitivity and specificity of 0.80 and 0.61 show that by possessing 185 cc as a cut-off point for gastric volume, the D_{max} of the stomach in 80% of patients can be predicted to be more than 45 Gy and in 61% of them to be less than 45 Gy.

The column V_4 of the left lung for TS cases in Table 3 can be interpreted based on the estimated indices. For this column, the AUC of 0.77 tells us that by considering the gastric volume one can truly classify about 77% of patients based on whether their left lung V_4 is more than 50% or not. The obtained sensitivity of 0.68 for TS cases with gastric volume cut-off of about 163 cc indicates that using this cut-off point, one can truly predict about 68% of patients' left lung V_4 parameters to be more than 50%. One the other hand, its specificity of 0.67 also indicates that by using this cut-off point it is predictable for about 67% of patients' V_4 of the stomach to be less than 50%.

Similar to V_4, using AUCs calculated for the other left lung DVH parameters of TS cases (Tab. 3), by knowing the gastric volume one can truly classify about 67%, 85%, 62%, 68%, 80%, 79%, 78%, 70%, and 79% of patients based on whether their left lung V_5, V_8, V_{10}, V_{11}, $V_{12.5}$, V_{16}, V_{20}, V_{30}, and D_{Mean} is more than 50%, 35%, 35%, 35%, 30%, 25%, 25%, 20%, and 15 Gy or not, respectively. Eventually, by using gastric volume data one may probably make a good prediction for about 75% (i.e. the average of all left lung DVH parameters' AUC) of these patients' left lung DVH parameters.

AUCs of T cases were almost less than 0.50, which means that by considering the gastric volume as a known data, DVH parameters of the ipsilateral lung can be foreseen for less than 50% of patients. However, just for V_{10} of the left lung in T cases, AUC obtained was 0.61, which means that by managing the gastric volume (with a cut-off point of about 288 cc) just for 61% of patients, one can truly predict whether left lung V_{10} is more than 35% or not.

AUC resulted from ROC analysis of TS cases, the V_8, V_{10}, V_{16}, and V_{20} parameters of the heart with thresholds of 25%, 25%, 20%, and 15% were about 0.54, 0.53, 0.56, and 0.56, respectively. For example, the column V_{10} of the heart with 25 Gy threshold can be explained so that just 53% of patients can be truly classified based on whether their heart V_{10} is less than 25 Gy or not. The sensitivity of 0.67 with 182 cc cut-off point for the gastric volume shows that for 67% of patients, V_{10} of the heart can be predicted to be less than 25 %. Nevertheless, the specificity of 0.52 shows that by using this cut-off point for 52% of patients, V_{10} of the heart can be predicted to be more than 25%, which is not reliable predictor data. Therefore, gastric volume is not a good predictor of the heart dose neither for TS nor for T cases. However, as a suggestion for future study, the heart's left descending artery (LAD) and left ventricle (LV) could also be delineated and assessed by having patients' CT scans acquired with a contrast agent to see if there is any correlation between their dose and gastric volume.

The average of all gastric volume cut-off points for the studied DVH parameters of the left lung and heart were 161 ± 12 cc and 176 ± 11 cc, respectively. Therefore, it can be concluded that the gastric volume of about 170 cc can result in an optimal situation for the stomach, left lung, and heart dose reduction during left breast cancer radiotherapy, especially with tangential plus supraclavicular fields. Based on the Hunt et al. study, 2 hours fasting can lead to an empty stomach [34]. There are also some previous studies that followed 2 hours fasting to reach a semi-empty stomach for radiotherapy purpose [35]. Therefore, considering about 2 hours fasting before CT simulation and every radiotherapy fraction can help patients reach this gastric volume and subsequent OARs' dose. In addition, by this gastric volume the control of

the risk of secondary cancer for the left lung would probably decrease, especially for TS cases, due to the reduction of its low dose.

Low statistical population can be named as the most limitation of current cross-sectional study. The non-uniformity of some ROC curves in Figures 5–7 with non-rounded shape was apparently due to the inadequate sample size in its related subgroup. The authors suggest a future prospective study on the DVH parameters of each mentioned OARs and follow up the related radiotherapy sequelae. Patients can be classified based not only on their T or TS prescribed treatment status but also based on their body surface area (BSA) which could lead to some bias to the current study results.

Eventually, to be able to suggest some recommendations as a patient preparation protocol for left breast cancer adjuvant radiotherapy, more multicentric randomized trial and meta-analysis studies are required. Image guided radiotherapy with cone beam CT or even MRI can give more reliable data about the exact position of soft tissues, like the stomach, during radiotherapy and its impact on the anatomical shift of its surrounding organs.

Conclusions

In this retrospective study, the effect of gastric volume on dose received by the stomach, heart, and left lung was evaluated during adjuvant radiotherapy of left breast cancer patients. Due to the obtained correlations, decreasing the gastric volume would reduce the ipsilateral lung mean dose. It also decreases the volumes that reach the low dose during left breast irradiation. This dose reduction may reduce the risk of patients' secondary lung cancer during the following decades of RT. The correlations between the gastric volume and heart DVH parameters was found non-significant. Maximum dose to the stomach is associated with its volume during RT. Any non-invasive interference that could reduce these OARs' dose would be appreciated during left breast radiotherapy.

Conflict of interest
There is no conflict of interest.

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