Polish Journal of Medical Physics and Engineering
The Journal of Polish Society of Medical Physics
ISSN 1898-0309, doi: 10.2478/pjmpe-2018-0021

December 2018
Vol 24, Issue 4

Scientific Paper

Developing of predictive models for pneumonitis with forward variable selection and LASSO logistic model for breast cancer patients treated with 3D-CRT

Maede HASAN ABDALI[1], Karim KHOSHGARD[2,a], Abdolazim SEDIGHI PASHAKI[3]

[1]*Student Research Committee, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran*

[2]*Department of Medical Physics, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran*

[3]*Department of Radiation Oncology, Mahdieh Radiotherapy and Oncology Charity Center, Hamedan, Iran*

[a]*E-mail address: khoshgardk@gmail.com*

(received 3 November 2017; revised 19 April, 29 June and 30 October 2018; accepted 31 October 2018)

Abstract

Purpose: To develop a multiple logistic regression model as normal tissue complication probability model by least absolute shrinkage and selection operator (LASSO) technique in breast cancer patients treated with three-dimensional conformal radiation therapy (3D-CRT), we focused on the changes of pulmonary function tests to achieve the optimal predictive parameters for the occurrence of symptomatic radiation pneumonitis (SRP).

Materials and methods: Dosimetric and spirometry data of 60 breast cancer patients were analyzed. Pulmonary function tests were done before RT, after completion of RT, 3, and 6 months after RT. Multiple logistic regression model was used to obtain the effective predictive parameters. Forward selection method was applied in NTCP model to determine the effective risk factors from obtained different parameters.

Results: Symptomatic radiation pneumonitis was observed in five patients. Significant changes in pulmonary parameters have been observed at six months after RT. The parameters of mean lung dose (MLD), bridge separation (BS), mean irradiated lung volume (ILV_{mean}), and the percentage of the ipsilateral lung volume that received dose of 20 Gy (IV20) introduced as risk factors using the LASSO technique for SRP in a multiple normal tissue complication probability model in breast cancer patients treated with 3D-CRT. The BS, central lung distance (CLD) and ILV in tangential field have obtained as 23.5 (20.9-26.0) cm, 2.4 (1.5-3.3) cm, and 12.4 (10.6-14.3) % of lung volume in radiation field in patients without pulmonary complication, respectively.

Conclusion: The results showed that if BS, CLD, and ILV are more than 23 cm, 2 cm, and 12%, respectively, so incidence of SRP in the patients will be considerable. Our multiple NTCP LASSO model for breast cancer patients treated with 3D-CRT showed that in order to have minimum probability of SRP occurrence, parameters of BS, IV20, ILV and especially MLD would be kept in minimum levels. Considering dose-volume histogram, the mean lung dose factor is most important parameter which minimizing it in treatment planning, minimizes the probability of SRP and consequently improves the quality of life in breast cancer patients.

Key words: radiation therapy; radiobiological model; breast cancer; pneumonitis.

Introduction

Many technical improvements such as three-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT), image guide radiation therapy (IGRT) and etc. have been developed for optimizing conventional radiotherapy (RT). Despite efforts to reduce the irradiated volume of normal tissues, radiation doses received by these organs are unavoidable. Pulmonary complications (PCs) as a major side effect in breast cancer RT have remained. Lung inflammation due to radiotherapy is termed radiation pneumonitis and occurs generally 4 to 12 weeks after radiation therapy. It doesn't usually have characteristic clinical symptoms, although in some cases, it can be accompanied with symptoms of cough, dyspnea, fever and chest pain [1].

Reducing the radiation absorbed dose in normal tissues during breast cancer radiotherapy reduces PCs probability and improves quality of life of patients. Various anatomical and physiological tests such as computed tomography, X-ray images [2] and pulmonary function tests (PFTs) [3,4] are used to assess pulmonary complications. However, decrease in the level of pulmonary functional parameters such as forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) after six months and one year after RT have been shown in the previous studies [4,5]. In contrast, Fragkandrea *et al*. reported no significant decrease in PFTs, and also no significant differences were noted between mean values of FVC and FEV1 in before and three months after RT and also between before and six months after RT [4]. Since the breast cancer is more common disease among women, improving the RT techniques and consequently reducing the incidence of pulmonary complications after RT is important. There are different results in assessment of irradiated lung's function after RT in former studies [6-10]. Bridge separation (BS) as an effective parameter was averagely in treatment planning of breast cancer and it was defined by Taylor *et al*. [5]; BS greater than 22 cm in tangential fields, will led to significant dose inhomogeneity in the breast when treatment is done with 6-MV or lower energy photons. mean BS and some other parameters can effect on the dose volume histograms in breast cancer RT [11]. We conducted a study to assess the effect of the mean central lung distance (CLD), mean BS as well as irradiated lung volume (ILV) parameters as dosimetric and clinical factors in pulmonary complications during the three and six- months follow-up.

Modeling the normal tissue probability complication in RT is done to describe relationship between absorbed dose and possible side effects in normal tissues [7]. Based on a proper radiobiological model an accurate estimation of the tumor control probability and NTCP can be obtained for acceptance or rejection of a treatment plan. Some researchers have investigated predictive parameters based on dose volume histograms, such as mean lung dose (MLD) [12-14] and percentage of ILV that receives more than given dose (IVx) for induction of symptomatic radiation pneumonitis (SRP). However, the most of these studies have done on lung cancer patients [6,14]; in a study, univariate logistic regression model has been used for predicting the PCs in breast cancer patients; it has shown that dosimetric parameters of MLD and IV19 have the significant relation with PCs [12].

Least absolute shrinkage and selection operator (LASSO) method, selection operator and mean Bayesian model have been used by Xu *et al.* [8] for creation NTCP models in xerostomia after 3D-CRT for head and neck cancer patients. LASSO method also recommended by Lee *et al*. [9] for investigating the multivariate regression NTCP modeling in breast cancer patients treated by IMRT technique. Radiation pneumonitis in breast cancer patients have not been considered in such models after six months follow up. Therefore in present study, we developed for the first time a multiple logistic regression model as NTCP model using LASSO method in breast cancer patients who treated with 3D-CRT with focusing on the changes of pulmonary function tests (ΔPFTs) followed up in six months. We also examined the geometrical parameters of treatment plan such as CLD and BS moreover to DVHs parameters in this model.

Methods

Patients

This prospective analysis 60 patients ages 32 to 71 years, (mean age: 47 years) (**Table 1**) with stages II, III (based on American Joint Committee on Cancer (AJCC) [15]) breast cancers who were referred to Mahdeih Radiotherapy Center in Hamedan, Iran between March 2015 and July 2016 were included. All of the patients, 30 patients with left and 30 patients with right breast involvement, were undergone modified radical mastectomy (MRM) or mastectomy. All patients had received prior chemotherapy with a same regimen of 8 steps, one month before radiotherapy. Also patients with smoking addiction, background lung or heart diseases were previously excluded from study. The parameters including CLD, BS, and ILV in tangential field were obtained from the treatment plans. Information of the patients is included in the **Table 1**. The Common terminology criteria CTC Version 2.0 were used for defining the pneumonitis [16].

Table 1. Demographic, clinical, and treatment characteristics of patients.

Characteristic of patients			
Age (years)		**T stage**	
Mean	47	T1	7(13.73%)
Range	32-71	T2	28(54.90%)
Std. Deviation	8.57	T3	16(31.37%)
Tumor site		**N stage**	
Left	25(49%)	N0	7 (13.7%)
Right	26(51%)	N1	19(37.2%)
Surgery		N2	22 (43.3%)
Mastectomy	27(53%)	N3	3 (5.8%)
Modify radical mastectomy	24(47%)	**Ipsilateral lung dose (cGy)**	
		Max	3235.69
Ipsilateral lung volume (cm^3)		Min	68.81
Mean	1253.5	Mean	722.38

Radiation therapy

Radiation therapy of the patients was done using 6-MV and 15-MV photon beams produced by a linear accelerator (Primus, Siemens, Germany). CT images were obtained using a single-slice CT-scan unit (Sensation, Siemens, Germany) transverse slices with thickness of 8 mm. Treatment planning of RT based on the CT-scan slices for the patients was performed using the Core-PLAN (version 3.5.0.5, Seoul C & J Co., Seoul, South Korea) treatment planning system (TPS). Dose delivery technique was SAD for delivering 2 Gy/d in 5 consecutive days per week. A sample of the breast cancer treatment planning is shown in **Figure 1**. The chest wall in the patients with mastectomy and whole breast in the patients with modified radical mastectomy (MRM) were outlined as clinical target volume (CTV) and also CTV+1cm margin were outlined as Planning Target Volume (PTV); also left and right lungs volumes were separately contoured as the organ at risk (OAR) structures. A part of ipsilateral lung volume of all patients was within the tangential radiation field.

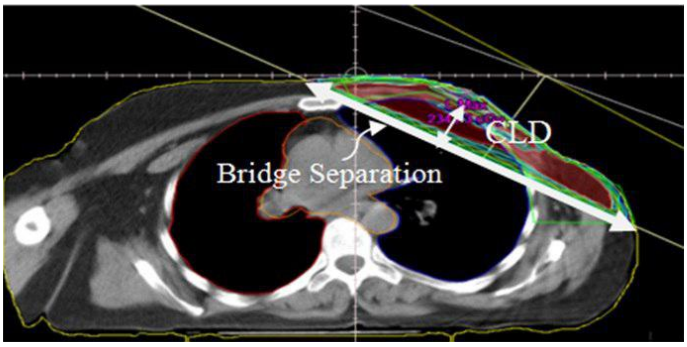

Figure 1: Central lung distance (CLD) and bridge separation (BS) parameters in treatment plan.

Dose calculations were carried out using equivalent tissue to air ratio (ETAR) algorithm. The absorbed dose received by the ipsilateral lung was derived from the patients' treatment plans. CLD parameter which defined as the perpendicular distance from the posterior tangential field edge to chest wall [11] was measured. Also, the percentage of lung volume which is within the tangential field was calculated. Definition of CLD and BS parameters are shown in **Figure 1**.

The prescribed dose to the PTV was 50 Gy in 25 fractions. A number of 11 patients (18.33%) received five more fractions as a boost using 6 MV or 15 MV photon beams or 15 MeV electron beams to the tumor bed. All patients treated with tangential opposed fields, with an anterior supraclavicular field. Furthermore internal mammary node (IMN) radiation field using photon or electron beams in addition to tangential and supraclavicular fields was used for 6 patients (10%). Postaxillary field was used in 9 patients (15%) too. Tangential fields were defined in treatment planning, in which the minimum lung volume would be within radiation field while having an appropriate coverage of dose to PTV. This will led to maximum protection of surrounding normal tissues [11].

Evaluation of pulmonary functional parameters

Pulmonary function tests (PFTs) parameters of the patients were measured using a spirometer (ZAN spirometer). All relevant pulmonary function parameters were measured. All of these pulmonary function tests were done for 51 patients before and after completion of radiotherapy, 3 and 6 months afterwards. Since 9 patients had not completely PFTs, therefore they excluded of this study. The Common terminology criteria CTC Version 2.0 from the National Cancer Institute [16] were used in pneumonitis definition.

Statistical analysis

Paired t-test was used to compare the obtained results of PFTs between before RT and three time points after RT (including end of RT, 3 months after RT, and 6 months after RT). The PFTs differences were estimated with the 95% confidence intervals. P-values less than 0.05 were considered statistically significant.

We also obtained dose-volume predictive factors with the univariate logistic NTCP model for investigation probability SRP.

At second step, we used the multiple logistic regression model as NTCP model to fit on the data (**Equation 1**) and forward selection method for model building was applied to determine the significant risk factors among candidate parameters [17].

$$\mathrm{NTCP} = (1 + e^{-S})^{-1} \quad S = \beta_o + \sum_{i=1}^{p} X_i \beta_i + \varepsilon \qquad \text{Eq. 1}$$

where S is response level, β_o is intercept, p is the number of candidate risk factors, X_i and β_i are different risk factors and their corresponding regression coefficients, respectively and ε is the random error of the model. The candidate factors were including 8 clinical and 9 dosimetric factors and two plan-related factors.

The clinical candidate factors were age, total dose, tumor site, radiation energy, irradiation of IMNs, surgery method, T stage, and N stage. The dosimetric candidate factors were the PTV volume, PTV dose, mean, min and max dose delivered to the ipsilateral lung, the percentage of the ipsilateral lung volume that received doses of 10–40 Gy at selected steps (IV10–IV40). The plan-related factors were CLD and BS parameters. According to the dosimetric factors, high values of correlations were expected between related variables, such as PTV dose. Therefore, these related variables were considered as grouped variables; ipsilateral lung dose, PTV dose, the percentage of the ipsilateral lung volume that received doses of 10–40 Gy at selected steps (IV10–IV40). Therefore, to avoid the collinearity problem, the list of dosimetric and clinical candidate risk factors was determined based on the results of correlation analysis before fitting the model. In addition, a penalized multiple logistic regression model with LASSO penalty was fitted on the entire list of risk factors including 19 variables to compare the optimum number of selected risk factors with the result of initially fitted model. The LASSO is a shrinkage method to select subset variables by imposing a penalty on the size of regression coefficients [18]. The LASSO estimate is defined by:

$$\hat{\beta}^{lasso} = \mathrm{argmin}_{\beta} \sum_{i=1}^{n} \left(y_i - \beta_0 - \sum_{j=1}^{p} x_{ij}\beta_j\right)^2$$

$$\text{Subject to } \sum_{j=1}^{p} |\beta_j| \le t \qquad \text{Eq. 2}$$

Where the n is the number of samples, and t is a parameter controlling the degree of penalty that can be determined by cross-validation.

After building the model, odds ratios and 95% confidence intervals (95% CIs) were calculated for all of selected risk factors. For performance of prediction of response, the area under the receiver operating characteristics curve (AUC) was calculated. Statistical analyses were performed by SPSS 16 and R programming software 3.2.2.

Results

Demographic, clinical, and treatment characteristics of the patients are shown in **Table 1**. After completion of RT, 46 (90.1%), 5 (9.8%) of patients had pulmonary functional changes of grades 0, 1 respectively. Patients with grade 1 are those who had the symptomatic pneumonitis [16].

The patients without SRP were classified in group 0 (n = 46) and those with SRP were in group 1 (n = 5). Table 2 shows the means (±SD) and P-values for the pulmonary functional tests. As can be seen in the **Table 2**, obvious fall in FEV1 and FVC parameters in all patients occurred during of follow-up period. Totally, FVC and FEV1 values have decreased about 9.24% and 3.06% after 6 months of RT, respectively. However, statistically significant changes have been observed at six months after RT.

Information of 19 initial clinical and dosimetric variables is tabulated in **Table 3** for each radiation pneumonitis (RP) group. In this study, the mean irradiated lung dose for 51 patients with breast cancer was achieved 722.38 cGy.

Table 2. Results of spirometry in all patients; pulmonary functional tests were done at different times including: before RT, at end of RT, 3 months after RT, and 6 months after RT.

Spirometry parameters			Pairs	Mean differences	95% Confidence Interval of the Difference		P-value
					Lower	Upper	
FEV1	**Mean**	**SD**					
Before RT	84.56	13.44	FEV1 (Before RT) - FEV1 (End of RT)	-1.117	-3.39	1.16	0.33
End of RT	85.68	12.78	FEV1 (Before RT) - FEV1 (3 months after RT)	0.74	-1.84	3.33	0.56
3 months after RT	83.82	1.6	FEV1 (Before RT) - FEV1 (6 months after RT)	3.05	0.2	5.91	0.036
6 months after RT	81.50	10.81					
FVC	**Mean**	**SD**					
Before RT	90.9	13.75	FVC (Before RT) - FVC (End of RT)	-0.62	-4.96	3.71	0.77
End of RT	91.52	17.1	FVC (Before RT) - FVC (3 months after RT)	2.33	-1.29	5.96	0.20
3 months after RT	88.56	12.41	FVC (Before RT) - FVC (6 months after RT)	9.23	5.56	12.9	p <0.001
6 months after RT	81.66	9.35					

Table 3. Clinical and dosimetric data of patients with (Group 1) and without (Group 0) Symptomatic Radiation Pneumonitis (SRP); which considered as clinical and dosimetric variables for the predictive model in which these variables were chosen as candidate risk factors for SRP.

	Clinical/ Dosimetric data		No. of patients in Group 0 (total=46) (Frequency %)	No. of patients in Group 1 (total=5) (Frequency %)
Clinical parameters	**Internal mammary node (IMN)**	No	41 (89.1%)	4 (80%)
		Yes	4 (8.7%)	1 (20%)
	Energy (MV)	6	18 (39.1%)	1 (20%)
		6&15	28 (60.9%)	4 (80%)
	T stage	1	4 (8.7%)	3 (60%)
		2	27 (58.6%)	1 (20%)
		3	14 (30.4%)	2 (20%)
	N stage	0	7 (15.2%)	0 (0%)
		1	17 (36.9%)	2 (40%)
		2	19 (41.3%)	3 (6.5%)
		3	3 (15.3%)	0 (0%)
	Tumor site (Left/Right)	Left	23 (50%)	3 (60%)
		Right	23 (50%)	2 (40%)
	Surgery	Mastectomy	23 (50%)	4 (80%)
		MRM	23 (50%)	1 (20%)
	Age (years) (Mean±SD)		47.1±9.4	46.8±9.8
Dosimetric parameters	**Total dose (cGy) (Mean±SD)**		5289.47±497.99	5318.18±476.73
	Ipsilateral lung dose (cGy)	Minimum	59.71	82.11
		Mean (MLD) ±SD	721.16±381.91	771.96±402.87
		Maximum	3131.16	3450.80
	CLD (cm) (Mean±SD)		2.38±0.87	2.43±0.7
	Bridge separation (cm) (Mean±SD)		23.48±2.52	21.93±2.12
	PTV volume (cm^3) (Mean±SD)		1135.4±480.45	945.54±531.05
	PTV dose (cGy) (Mean±SD)		2615.66 ±1349.03	2770.04±1419.11
	Irradiated lung volume (cm^3) (Mean±SD)	Mean	1243.55±184.78	1343.42±264.02
		IV10	24.35±13.12	22.99±13.55
		IV20	15.10±11.08	13.32±8.89
		IV30	4.84±7.87	6.11±8.67
		IV40	1.78±3.47	3.01±5.07

Table 4. Correlation between CLD and ILV parameters with tumor site and type of surgery.

		Central Lung Distance (Mean± SD)	Irradiated Lung Volume (Mean± SD)	P-value
Tumor site	Left	2.69±0.7	12.85±3.66	0.14
	Right	2.28±0.86	7.87±2.12	0.29
Surgery type	Mastectomy	2.51±0.82	11.4±1.93	0.16
	Modified radical mastectomy	2.28±0.85	8.5±2.17	0.28
All patients		2.40±0.82	10.06±2.95	0.07

Table 5. Coefficients of the final multiple logistic regression model as the NTCP model.

Variable	B	P-value	EXP	95% CI for EXP(B)
Bridge Separation	-0.284	0.024	0.752	[0.58-0.96]
Irradiated lung volume	1.24	0.001	2.10	[0.67- 2.30]
IV20	1.25	0.024	1.56	[0.46- 2.04]
Mean lung dose	0.75	0.04	1.31	[0.26- 1.49]
Constant	5.9	0.038	365.03	

Table 6. Area under the receiver operating characteristic curve and 95% confidence interval for four effective risk factor including mean lung dose, bridge separation, irradiated lung volume, and IV20.

Variable	Area	P-value	95% confidence interval
Mean lung dose	0.815	0.021	0.709- 0.920
Bridge Separation	0.385	0.400	0.089- 0.682
Irradiated lung volume	0.524	0.862	0.312- 0.736
IV20	0.698	0.145	0.548- 0.848

We have shown the mean CLD and irradiated lung volume for irradiated right or left side patients in comparison to tumor site and surgery in **Table 4**. This table presented that no considerable differences in mean CLD and ILV parameters were observed between patients irradiated on the left side and those irradiated on the right side; this is consistent with results of Tokatli *et al*. [19]. Furthermore, we found no significant differences between mentioned parameters and surgery type. Therefore, can be verified that significant relation not exist between the mean central lung distance (CLD) and irradiated lung volume (P = 0.07).

In order to estimate the threshold values for mean CLD and mean BS parameters for patients without SRP, pair wise comparisons with groups (0 and 1) were done. It was revealed that the threshold values were 2.38 cm and 23.48 cm, respectively. Based on the results of correlation analysis, there were significant correlation within dosimetric parameters groups ($P < 0.05$). Therefore, relevant dosimetric variables including ipsilateral MLD and PTV dose were included in initial multiple logistic NTCP model. Furthermore, the IV20 among the IV10 to IV40 values, which had strongest Spearman correlation coefficient in univariate logistic regression, was selected as one of the candidate risk factors. The variables of mean BS (B = -0.28), ILV (B = 1.24), IV20 (B = 1.25) and MLD (B = 0.75) were obtained as results of fitted multiple logistic NTCP model with forward variable selection and LASSO logistic model.

For each patient the NTCP value can be calculated using the logistic regression as mentioned in **Equation 2**:

$$NTCP = (1 + e^{-S})^{-1} \quad \text{Eq. 3}$$

Where S = 5.9 - 0.284×Bridge separation + 1.24×irradiated lung volume + 1.25×IV20 + 0.75×mean lung dose.

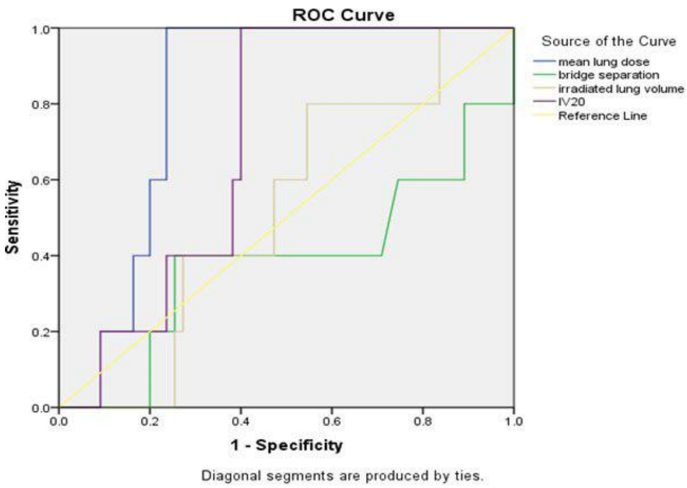

Figure 2: The receiver operating characteristic curves (ROC) of the final logistic NTCP model for four risk factor (including IV20, mean lung dose, irradiated lung volume, bridge separation) for symptomatic radiation pneumonitis in breast cancer patients treated with 3D-CRT.

The final logistic NTCP model was built based on the result of forward selection technique (based on likelihood ratio test) and the final LASSO logistic model for symptomatic radiation pneumonitis was resulted based on 5-folds cross-validation and AUC. The coefficients of selected variables for the final multiple logistic NTCP model have been presented in **Table 5**. The AUC values for the final logistic NTCP and LASSO models are exactly alike. Therefore, we reported just results of the multiple logistic NTCP model. **Figure 2** shows the ROC curve of four risk factors for the multiple logistic NTCP model. For each variable, the area under ROC curve was calculated as diagnostic test accuracy index; the variables with high diagnostic accuracy are shown in **Table 6**. As can be seen in ROC curve, MLD and IV20 risk factors have high value of area under curve; however, only the MLD parameter was statistically significant (P value<0.05).

Discussion

In our study, a decrease of 9.24% and 3.06% in FVC and FEV1 parameters, respectively were occurred after six months. Also, in another study, an apparent decrease after 6–16 weeks of radiotherapy in these parameters was observed [19]. Based on literatures, radiation induced pneumonitis usually occurs 4 to 12 weeks after completion of radiation therapy [1,2]. Since that, a relatively small volume of lung (averagely 12.4% ± 1.8%) was irradiated by tangential fields, about 8.3% of patients who were treated with 3D-CRT technique, indicated SRP after six months of RT in our study. Tokateli *et al*. [19] implied that two patients of 20 patients (10%) with average irradiated volume of lung tissues 6.4% ± 2 had shown mild SRP. In their study, irradiated lung volume had significant relationship (P = 0.02) with incidence of pneumonitis. Rancati *et al*. have reported that ipsilateral mean lung dose (MLD) in breast cancer patients treated with 3D-CRT is in a range of 2.5–18 Gy with median of 12 Gy; they also have reported that 16.6% of patients had shown grade ≥ II of pulmonary toxicity [1]. Furthermore, Lee *et al*. reported 33.3 % incidence of SRP with a median lung dose of 20.52 Gy in breast cancer patients after hybrid IMRT [9]. In our study, the ipsilateral MLD had range of 0.29–15 Gy with a median dose of 6.8 Gy.

Also there were no statistically significant differences between mean CLD and irradiated lung volumes in the patients with different surgeries (**Table 4**). In some previous studies, chest X- ray radiography or CT- scan images [1,20] has been used for evaluating the radiation-induced complications of lung; however, we used pulmonary functional tests as physiological tests [13], because of more protection against ionizing radiation in patients. Among patients with SRP, four patients had been underwent mastectomy; and irradiated lung volume for these patients were more than patients who had been underwent modified radical mastectomy. Despite the limited number of these patients, there was significant relation between radiation-related injury (SRP) and surgery type (mastectomy).

Our results showed, if mean CLD and mean BS values are lower than 2.38 cm and 23.48 cm, respectively, patients will protect from SRP. Jaen *et al*. reported 86.5% and 94% of mean basal values for FVC and FEV1 (before 3D-CRT) in 39 patients with breast cancer, respectively. Also, they found no significant differences between these values with age, smoking history or previous chemotherapy [21]. In consistency to this study, we found average values of 90.8% and 84.9% for the FVC and FEV1 parameters in all patients, respectively before RT.

Symptomatic pneumonitis after breast radiotherapy is important issue and must be considered. It is essential to develop an appropriate NTCP model to predict probability of SRP in breast cancer patients in treatment planning softwares. Early NTCP models, which are limited to Lyman-Kutcher-Burman (LKB model) and univariate logistic regression models [22] were based on dose volume histograms (DVH based).

These models derived from dose distributions in the target/OAR volumes. According to the such models, IV20 [13], equivalent uniform dose (EUD), and the MLD, have been reported as predictive parameters for inducing pneumonitis [1,23]. Dosimetric and clinical factors (as the predictive parameters for OAR complications) in breast cancer patients treated with 3D-CRT have not been assessed and reported based on logistic regression LASSO model in literatures yet. In other words, evaluating of relations of ΔPFTs and radiation-induced injury with considering dosimetric and clinical parameters were the main objectives in this study using the NTCP models.

In present study, we introduced parameters of MLD, BS, ILV, and IV20 as risk factors using the LASSO technique for SRP in a multiple normal tissue complication probability model in breast cancer patients treated with 3D-CRT. This model can provide the optimal number of reliable predictive parameters for the occurrence of symptomatic radiation pneumonitis. Lee *et al*. [9] had shown that IV20, energy, age, BMI and T-stage are the risk factors for SRP in breast cancer patients after hybrid IMRT. It has been recommended that 3D-CRT-based models are more useful for prediction of xerostomia in patients who treated with 3D-CRT than those treated with IMRT [24], and therefore IMRT-based NTCP models cannot be used for 3D-CRT patients. Although Ling *et al*. [25] reported no differences in dose delivered to lung and heart tissues between 3D-CRT and IMRT techniques, but we found incidence of SRP in 8.3% of 3D-CRT treated breast cancer patients in contrast to 33.3% of the incidence in Lee *et al*. [9], in which patients had been treated with IMRT. Regarding to AUC values, MLD was the greatest risk factor for symptomatic radiation pneumonitis in present study; in the other words, this parameter can be mainly considered for prediction of pneumonitis. Predictive power of the mentioned and also other relevant parameters could be checked and improved by increasing the sample size (the number of patients) in future works.

Conclusion

Symptomatic radiation pneumonitis is observable in breast cancer patients who are treated with 3D-CRT. Our results indicated that pulmonary function changes occur at about six months after RT.

The MLD, BS, ILV, IV20 parameters are as significant risk factors to predict the SRP in our multiple NTCP LASSO model; among these parameters, the MLD is the most important predictive parameter for SRP in breast cancer patients. Considering and minimizing these key parameters specially MLD factor as low as possible in treatment planning, can avoid or reduce the radiation related damages and consequently improved the quality of life in breast cancer patients.

Acknowledgement

The authors gratefully acknowledge the research council of Kermanshah university of medical sciences (Grant Number 93454) for the financial support. This work was performed in partial fulfillment of the requirements for the master of science degree of Maede Hasanabdali, in the faculty of medicine, Kermanshah university of medical sciences, Kermanshah, Iran. This study also is carried out with the collaboration of Mahdieh Radiotherapy Center in Hamedan, Iran. Hence, we would like to express our special thanks to all the members of staff at this center, especially Mr. Mohammad Hadi Gholami for providing us the technical and clinical support.

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