Iranian Journal of Medical Physics

ijmp.mums.ac.ir

Dosimetric Study of Tissue Heterogeneity Correction for Breast Conformal Radiotherapy

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ARTICLE INFO

Article type:
Original Article

Article history:
Received: May 27, 2018
Accepted: Sep 13, 2018

Keywords:
Breast Cancer
Conformal Radiotherapy
Heterogeneity Correction
Photon Energies
Treatment Planning

ABSTRACT

Introduction: Heterogeneity correction is an important parameter in dose calculation for cancer patients where it may be cause inaccuracy in dose calculation as a result of different densities of patients. This study studied the impact of dose calculation of breast cancer patients with and without heterogeneity correction.
Material and Methods: Twenty breast cancer patients were treated with Three-Dimensional Conformal Radiotherapy(3DCRT). Dose calculations were performed using two modes: Fast Photon mode for homogeneity and Fast Photon Effective Path length for heterogeneity with two photon energies. Monitor Units(MU), Modulation Factor, Dose Volume Histograms(DVH) and quality indices were used to evaluate the effect of heterogeneity correction on dose calculation and investigate the mechanism of this effect in the low and high energies.
Results: Heterogeneity correction compared to without it showed significant reduction in MU and modulation factor at 6MVand 10MV ($p<0.05$). Dosimetric parameters derived from DVH were significantly lower for Planning Target Volume (PTV) with homogeneity versus heterogeneity ($p<0.05$) as D_{95}% (95.1%vs93.7%) and V_{95}%(95.3%vs89%) for 6MV while max Dose and D_2 increased. Also the dose for organs at risk exhibited an increase with heterogeneity correction. Quality indices were be worst with heterogeneity correction with a significant difference ($p <0.05$). The differences between the dose with heterogeneity correction and without it in 6MV and 10MV were as follows: ΔD_{95}% (4.4%vs3.4%;P=0.001) and ΔV_{95}%(4.76%vs4.5%;P=0.001).
Conclusion: non-use of the heterogeneity correction can be cause to deliver under or overdose dose to the target volume. Tissue heterogeneity correction had an impact on dose calculation for breast cancer patients and this impact was more effective for the low energy.

►*Please cite this article as:*
Sinousy DM, Attalla EM, Hanafy MS, Abouelenein HS, Abdelmajeed M, Osama M. Dosimetric Study of Tissue Heterogeneity Correction for Breast Conformal Radiotherapy. Iran J Med Phys 2019; 16: 179-188. 10.22038/ijmp.2018.31579.1374.

Introduction

Treatment planning includes many steps such as patient imaging, tumor staging, image acquisition for treatment planning, localization of tumor and healthy structures, optimal beam placement, and treatment simulation and optimization [1]. Dose calculation (optimization) is one of the main steps in radiotherapy performed using computerized treatment planning systems. Dose calculation in radiotherapy is performed using different calculation methods integrated in the treatment planning system (TPS). There are two calculation methods, one of them is the homogeneous method where TPS assumes the patient has homogenous tissue density as water (without heterogeneity correction), and while the other is the heterogeneous method where TPS takes into consideration the different densities of the tissues (with heterogeneity correction).

Heterogeneity correction is often based on the relative electron densities obtained from computed tomography (CT) scan and used for density difference between air spaces, lung, water density or bony tissue consistent with Radiation Therapy Oncology Group (RTOG). The principle of heterogeneity correction is firstly to calculate the dose distribution inside a medium of homogeneous water-equivalent composition, and then to add the heterogeneity correction factor. This factor creates changes to the uncorrected distribution to account for the differences in tissue densities [2-5].

Breast cancer irradiation involves the inclusion of some lung tissue within the treatment volume, and the amount of lung organ within the tangential breast fields caused a reduction in the dose received by the target volume because the lung is considerably low density. Thus it has a great influence on dose distributions in breast cancer treatment planning.

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A Number of studies have assessed the impact of tissue heterogeneity correction and different algorithms on the radiation treatment planning for breast cancer patients showing a large impact on the dose calculation for patients [6-10].

Several studies have evaluated the impact of heterogeneity correction on dose calculation for external photon beam therapy [11-14]. Others have investigated the influence of lung density on planning for thoracic treatments such as the lung [15-16], based on which the influence of lung density on the treatment planning for breast cancer can be determined. Fraass et al (1988) reported the influence of lung volume on dose distribution in patients treated with tangential beams [17]. Marian et al (1999) pinpointed the impact of heterogeneity-corrected dose distributions is more noticeable for lower energies [18].

This study was focused on dose calculation methods used in breast cancer patients with and without heterogeneity correction using different photon energies (6MVand10MV), assessment of the impact of tissue heterogeneity correction on the treatment plan for breast cancer and evaluating which energy is more effective in tissue heterogeneity correction.

Materials and Methods

Patient Characteristic

Twenty breast cancer patients (10 for the left side and 10 for the right side) undergoing radiotherapy were enrolled in this retrospective study prior to breast radiotherapy. The inclusion criteria included female gender, as well as undergoing conservative treatment (5 patient) or mastectomy (15 patient). Computed tomography (CT) scans were acquired for each patient with demarcating on the patient's skin using a colored marker according to the physician's instructions, then scan dataset were transferred to Prowess treatment planning system (TPS).

Planning Target Volume (PTV) and Organs at Risk (OARs) were delineated by a radiation oncologist, where PTV was defined according to the recommendations of ICRU (International Commission on Radiation Units and Measurements) Reports 50 and 62 [19-20] with a 1-cm margin around the clinical target volume (CTV).

Treatment planning

The patients were treated using three-dimensional conformal radiotherapy treatment (3DCRT) using 6 and 10 megavoltage (MV) photon beams. Dose calculation was performed in this study with superposition algorithm, which is integrated into Prowess Panther TPS (Version 5.01).

This algorithm includes two calculation methods: without heterogeneity correction (Fast Photon) and with heterogeneity correction (Fast Photon Effective-Path length). Fast photon calculates dose based on the measured data where no tissue heterogeneity is taken into account and the patients are treated as a uniform volume equivalent to water (Hounsfield Unit = 0.0). Fast Photon Eff. Path length is similar to Fast photon, except effective path length through tissue is taken into account while performing the calculations. Full correction uses the CT Image Hounsfield Unit numbers to correct the radiation path length.

For each patient, four treatment plans were generated for each case using exactly the same beam orientation, collimator, and accessories. For plan 1, dose was calculated using the Fast photon calculation method with 6 MV photon beam energy. For plan 2, the dose was calculated using the Fast Photon-Eff. Path length calculation method with the same photon energy. Then, these two plans were recalculated using the 10 MV photon beam energy.

For all the plans, the dose was prescribed at a single reference point as recommended by the ICRU reports 50 and 62 [19, 20]. All the patients were treated with hypo-fractionation protocol, where each patient received 40 Gy over 15 fractions (2.67 Gy/fx). Each treatment plan was evaluated based on target volume covered by 95% isodose line at least while OARs criteria were evaluated as follows: mean dose for the heart <26 Gy or V30<46%, ipsilateral lung mean dose equal to 13 Gy, 20 Gy and 24 Gy or V20 <=30% [21].

As shown in Figure 1, the green color shows PTV and the blue color shows 95% isodose line. In this case, the patient was treated with four treatment fields (two tangential beams and two segmentation beams). The patients were treated using Siemens PRIMUS and PRIMUS^{Plus} linear accelerator with 6 MV and 10 MV.

For each patient, to compare plan 2 that was calculated by heterogeneity correction with plan 1 that was calculated without heterogeneity correction for both photon energies, the following equation [15] was used to calculate the percentage difference where the dose in plan 1 was taken as the reference value.

$$\Delta\text{Dose}\ (\%) = \left(\frac{D2-D1}{D1}\right) *100 \qquad (1)$$

Where D_2 is the dose calculated with heterogeneity correction and D_1 is the dose without heterogeneity correction.

Treatment plan evaluation

For each patient, the comparison of MUs and modulation factors (mu/cgy) was performed between plans 1 and 2. Spatial isodose distribution, the 95%isodose lines, as a reference isodose line, and isodose line of maximum dose were compared between plans 1 and 2. For each PTV, the maximum dose (Max), D_2%, mean dose, the dose to 95% of the PTV volume (D_{95}), and the volume of PTV receiving at least 95% of the prescribed dose (V_{95}) were compared according to ICRU50 [19] using DVH. Quality indices were also calculated and compared.

The homogeneity index (HI) is used to compare dose homogeneity in PTV [22].

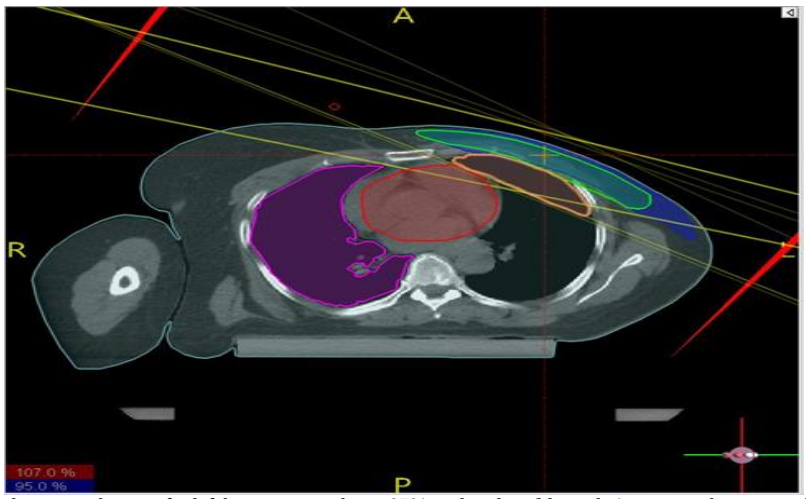

Figure 1. Computed tomography scan for left breast cancer shows 95% isodose line (blue color) covering the target volume (green color)

$$HI = \frac{D_{2\%} - D_{98\%}}{D_{Prescription}} \times 100 \quad (2)$$

Where $D_{2\%}$ and $D_{98\%}$ are doses received by 2% and 98% volume and are considered to be the maximum and minimum doses, respectively. HI = 0 (Zero) is the ideal value.

The conformity index (CI) is used to compare the degree of conformity of the prescribed dose. It was recommended by RTOG in 1993 [23] and described within ICRU report 62 [20].

CI is defined as the ratio of reference isodose volume to the target volume:

$$CI = \frac{V_{RI}}{TV} \quad (3)$$

Where V_{RI} is the volume receiving the reference isodose and TV is target volume.

Statistical analysis

Statistical analysis was carried out using paired samples t-test and Pearson correlation coefficient in SPSS, version 22. The data are presented as mean ± standard deviation (SD). P-value less than 0.05 was considered significant

Results

Monitor units (MUs) and Modulation factor (MU/cGy)

The heterogeneity calculations in plan 2 produced a lower number of monitor units than the homogeneity calculations in plan 1 for 6 MV and 10 MV. The mean differences in MU between homogeneity and heterogeneity corrections were, as follows: 2.94% ±1.22; P<0.05 for 6 MV and 2.16% ±0.96; P<0.05 for 10 MV.

Tables 1 and 2 illustrate this decreasing trend. The mean modulation factor for homogeneity was 2.30±0.38 MU/cGy (P<0.05), while for heterogeneity it declined to 2.23±0.37 MU/cGy (P<0.05) for 6 MV. For 10 MV, it also decreased with the heterogeneity correction, where the average was 1.89±0.26 MU/cGy (p<0.05) for homogeneity, and for heterogeneity it was 1.85±0.26 MU/cGy (p<0.05); Figure 2.

The correlation coefficients between the difference in MUs in each case and tumor volume were −0.05 for 6 MV and −0.02 for 10 MV.

Computed Tomography (CT) cuts evaluation

Figures 3 and 4 are computed tomography cuts for plan 1 with homogeneity correction and plan 2 with heterogeneity correction using 6MV and 10MV which they were illustrated that the 95% isodose line covered all the PTV in plan 1 with the homogeneity correction while in plan 2 with the heterogeneity correction there was a fraction of PTV that not covered with 95% isodose line.

Dose Volume parameters

The comparison of the doses delivered to PTV and OARs for the two plans (with/ without heterogeneity correction) is shown in tables 3 and, 4, in addition, to Figure 5 for 6 MV and tables 5, and 6 and Figure 6 for 10 MV. The results of the activation of the heterogeneity correction in Fast photon-Eff. Path length mode showed a decrease in D95%, V95%, and mean dose and a significant increase in max dose and D2% for each D95%, V95%, and mean dose, but there was no significant difference in max dose and D2 for the two photon energies. V_{20Gy} for ipsilateral lung, mean dose, and V_{30Gy} for the heart were higher for heterogeneity than homogeneity but this increasing was significant forV20Gy of ipsilateral lung and mean dose of the heart using 6 MV and also for V_{30Gy} and mean dose for the heart using10 MV, while it was non-significant for V30Gy of the heart using 6 MV and V20Gy of the lung using 10MV.

Table 1. The values of MU/fx and Modulation factor (MU/cGy) in addition to SD and P-value for Homogeneity and Heterogeneity using 6MV

	Homogeneity Mu/fx	Heterogeneity MU/fx	Homogeneity MU/cGy	Heterogeneity MU/cGy
Mean	615.5	597.5	2.30	2.23
SD	±102.2	±100.5	±0.38	±0.37
P-Value	P<0.05	P<0.05	P<0.05	P<0.05

Table 2. The values of MU/fx and Modulation factor (MU/cGy) in addition to SD and P-value for Homogeneity and Heterogeneity using 10MV

	Homogeneity Mu/fx	Heterogeneity MU/fx	Homogeneity MU/cGy	Heterogeneity MU/cGy
Mean	506	495	1.89	1.85
SD	±69	±68.7	±0.26	±0.26
P-Value	P<0.05	P<0.05	P<0.05	P<0.05

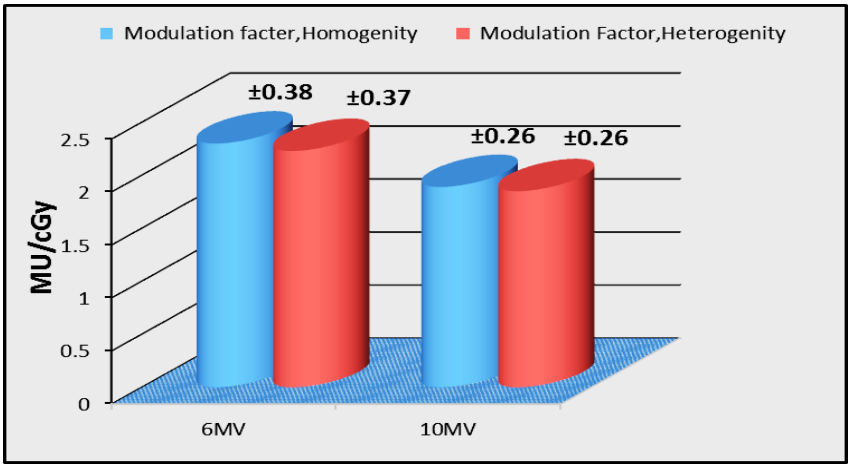

Figure 2. Comparison of modulation factor between homogeneity and heterogeneity plans for 6 MV and 10 MV.

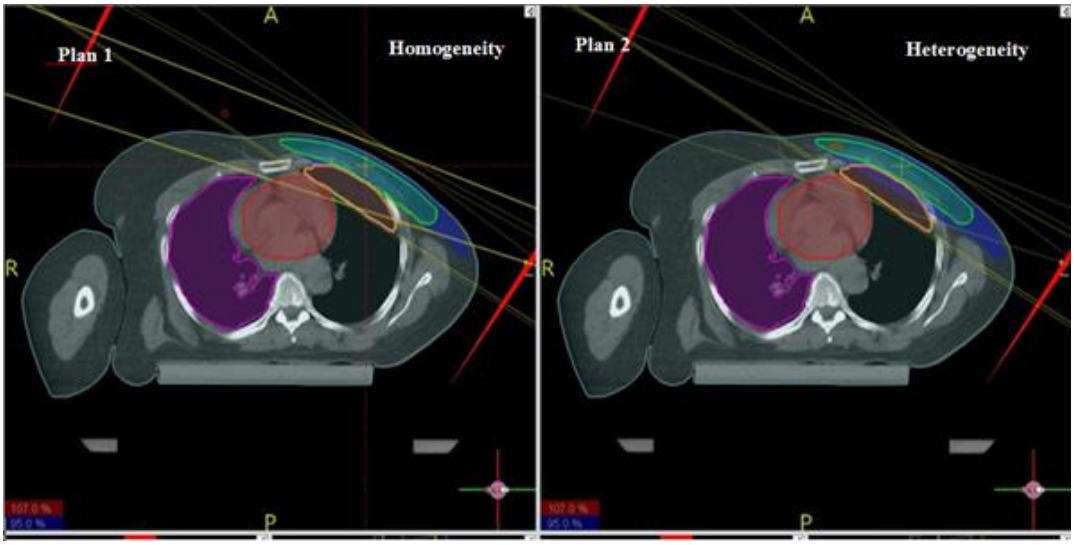

Figure 3. Computed tomography cuts with isodose distribution curves using 6 MV with the same beam configuration. The green color shows the planning target volume and the blue color shows 95% isodose line

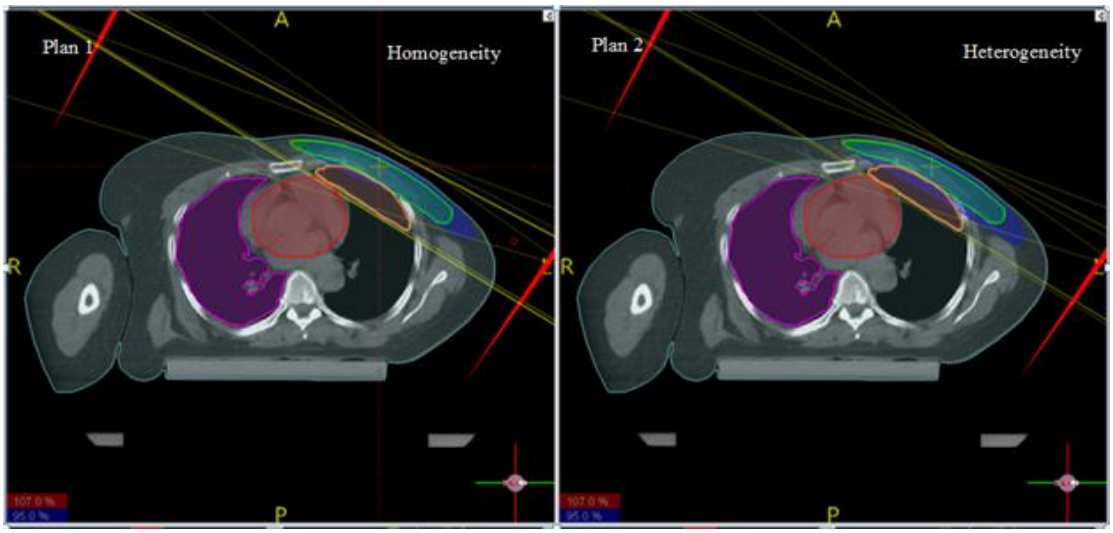

Figure 4. Computed tomography cuts with isodose distribution curves using 10 MV with the same beam configuration. The green color shows the planning target volume and the blue color shows 95% isodose line

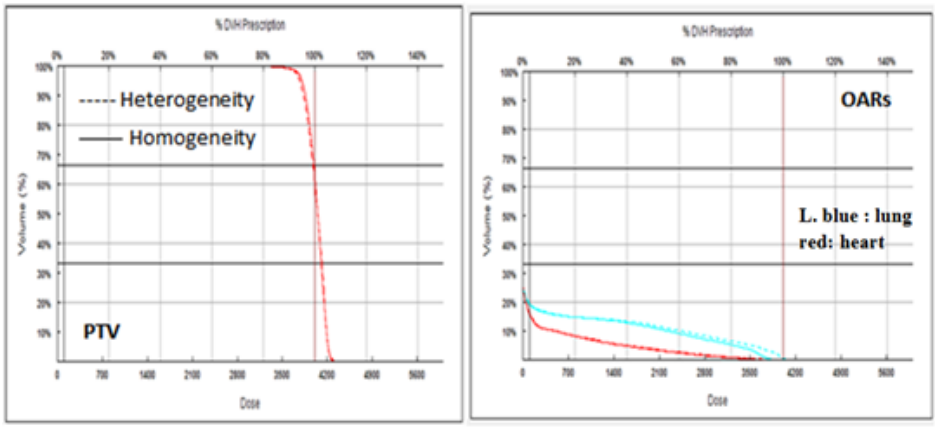

Figure 5. Dose volume histograms for planning target volume and organs at risk between homogeneity and heterogeneity plans using 6 MV.

Table 3. Parameters derived from dose volume histograms for the planning target volume (PTV). The results are dosimetric averaged over all the 20 analyzed cases using 6 MV. Δ is the difference of values between plan 2 and plan 1, SD is the standard deviation.

Plans	ΔDose %	Maximum Dose	Mean Dose	$D_{95\%}$	$V_{95\%}$	$D_{2\%}$
2 *vs 1*	average ± SD	0.84±2.25	0. 8±1.3	4.4±3.5	4.76±4.74	0.4±1.70
	P-Value	0.2	0.02	0	0.01	0.29

Table 4. Dosimetric parameters derived from dose volume histograms for organs at risk. The results are averaged over all the 20 analyzed cases using 6 MV. Δ is the difference of values between plan 2 and plan 1, SD is the standard deviation.

		Ipsilateral Lung	Heart	
Plans	ΔDose %	V_{20Gy}	Mean Dose	V_{30Gy}
2 *vs 1*	average ± SD	2.47±2.42	2.35±1.81	7.11±10.56
	P-Value	0	0.004	0.1

ΔDose% was calculated according to Equation 1. The D_{95}% is the dose delivered to 95% of the PTV. V_{95}% is the PTV volume receiving 95% of the prescribed dose. P-values were calculated using a paired samples t-test. P-value less than 0.05 was considered significant.

V_{20} and V_{30} Gy are defined as the volume fractions of both lungs receiving 20 Gy and the volume fractions of the heart receiving 30 Gy, respectively.

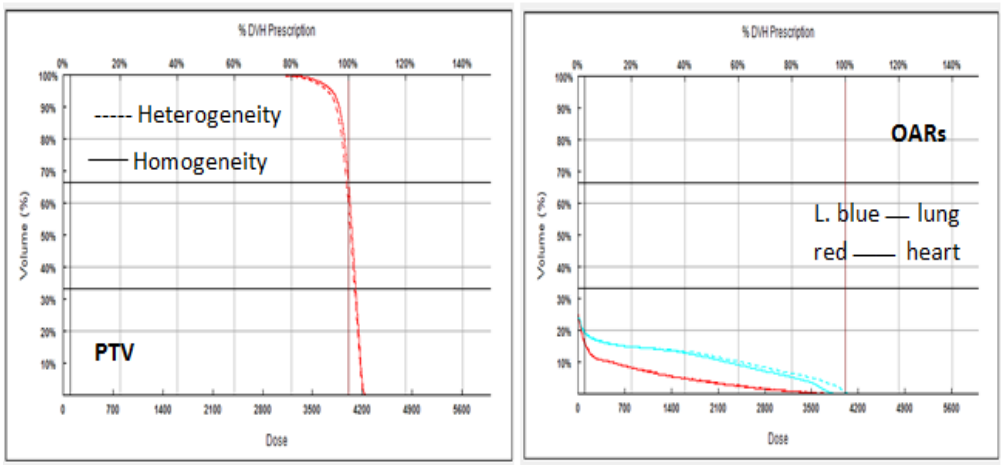

Figure 6. Dose volume histograms for planning target volume and organs at risk between homogeneity and heterogeneity plans using 10 MV.

Table 5. Dose-volume parameters derived from dose volume histograms for planning target volume; the results are averaged over all the 20 analyzed cases using 10 MV. Δ is the difference of values between plan 2 and plan 1, SD is the standard deviation.

Plans	ΔDose %	Maximum Dose	Mean Dose	$D_{95\%}$	$V_{95\%}$	$D_{2\%}$
2 *vs 1*	average ± SD	0.11±1.47	0.6±1.4	3.4±3.1	4.5±3.28	0.15±0.85
	P-Value	0.75	0.002	0	0.01	0.42

Table 6. Dose-volume parameters derived from dose volume histograms for organs at risk. The results are averaged over all the 20 analyzed cases using 10 MV. Δ is the difference of values between plan 2 and plan 1, SD is the standard deviation.

		Ipsilateral Lung	Heart	
Plans	ΔDose %	V_{20Gy}	Mean Dose	V_{30Gy}
2 *vs 1*	average ± SD	7.81±25.4	2.12±1.87	3.38±3.65
	P-Value	0.15	0.015	0.05

Table 7. The number of beams used in the treatment planning for the breast cases and its effect on heterogeneity correction

No of cases	7	13
No of beams	3	4
The effect of the heterogeneity	1.19%	1.66%

Table 8. The mean values of quality indices for planning target volume in plan 1 and plan 2 using 6 MV and 10 MV. Plan 1 for homogeneity and plan 2 for heterogeneity.

Energy	6MV		10MV	
Plans	CI	HI	CI	HI
Plan 1	0.95±0.003	0.14±0.02	0.89±0.04	0.20±0.04
Plan 2	0. 91±0.05	0.16±0.03	0.84±0.05	0.22±0.04
P-Value	0.01	0	0.015	0

Table 5 illustrates the difference between plan 1 and plan 2 for dose-volume parameters derived from DVHs for PTV using 10 MV. ΔDose% was calculated according to Equation 1. D_{95}% is the dose delivered to 95% of the target volume (PTV). V_{95}% is the PTV volume receiving 95% of the prescribed dose. P-values were calculated using paired samples t test.

Table 6 presents the difference between plan 1 and plan 2 for OARs using 10 MV. V_{20} and V_{30} Gy are defined as the volume fractions of both lungs receiving 20 Gy and the volume fractions of the heart receiving 30 Gy, respectively.

Table 7 demonstrates the comparison between the number of beams and the effect of heterogeneity correction on the coverage (D_{95}%), where seven patients were treated with 3 beams and 13 patients were treated with 4 beams, the average of the effect of heterogeneity correction was 1.19% and 1.66%, respectively.

Quality indices

Table 8 shows a reduction in HI (Homogeneity index) and CI (conformity index) with heterogeneity correction with a significant difference ($p<0.05$) between 6 MV and 10 MV.

The relationship between heterogeneity correction and photon energy

Figures 7 and 8 show the effect of heterogeneity correction in two different energies (high and low energies) excluding the effect of energy on the coverage. The comparison was performed by using the dosimetric parameters D_{95}% and mean dose, which caused the effect of heterogeneity correction be more effective in low energy (6 MV) than high energy (10 MV) (p=0.001 and p=0.004, respectively).

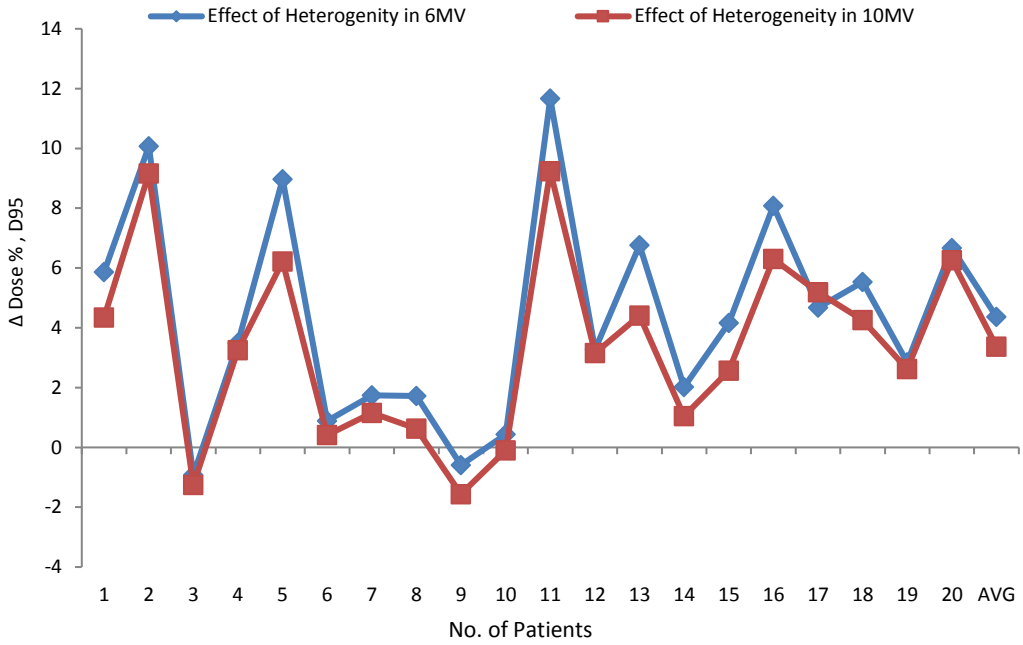

Figure 7. Chart for the effect of the heterogeneity correction in the two energies of 6 MV and 10 MV for the D_{95}% dosimetric parameter

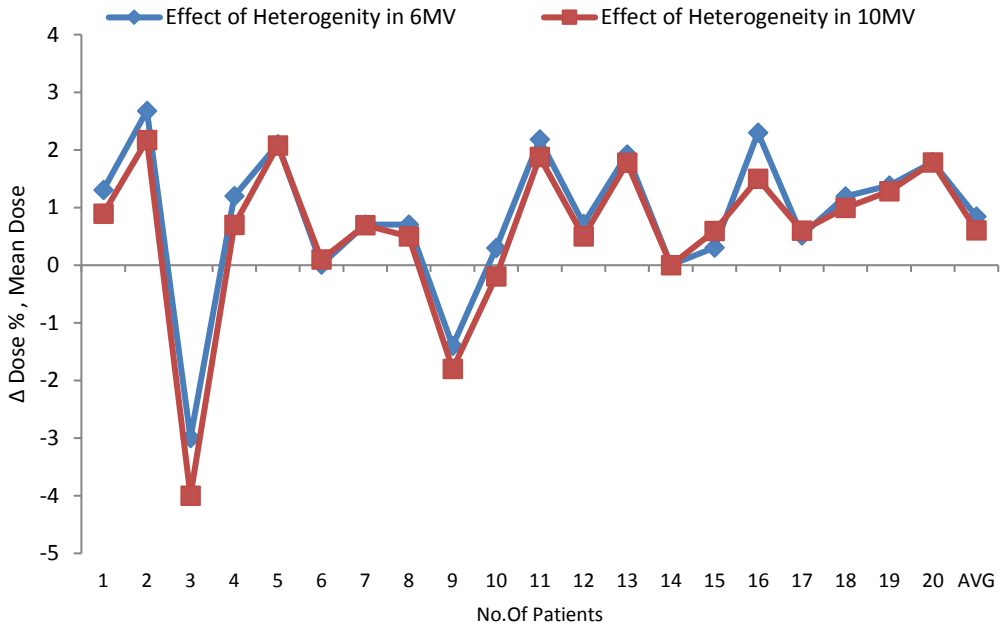

Figure 8. Chart for the effect of the heterogeneity correction in the two energies of 6 MV and 10 MV for the mean dose dosimetric parameter

Discussion

In radiation therapy, there is a wide range of dose calculation algorithms that are commercially accessible for heterogeneity corrections. Most dose calculation algorithms utilized for treatment planning do not represent all the lateral scatter effects in lung tissues and they just make longitudinal corrections, for example equivalent path length as the algorithm that was utilized in this study by Prowess TPS. Thus, they may create errors in dose estimation. Along these lines, more exact calculation methods are recommended in clinical radiation therapy planning, particularly for lung cancer

or any site encased by the lung, as the site that was utilized in this study (breast).

In our study, we reviewed the implications of changing the calculation method from Fast Photon without heterogeneity correction to Fast Photon-Eff. Path length with heterogeneity correction. In spite of some changes that may be observed in dose prescription or the doses to the tumor and some organs as a result of using heterogeneity correction, it is often the most accurate calculation method that can provide accurate absorbed dose that is close to the reality. Therefore, we suggest a sufficient number of cases for calculation with two different calculation methods and observing dose differences by changing the calculation method. Hence, we were able to provide clinicians with some recommendations to help with the adaption of the prescribed dose using new calculation methods.

The difference of tissue densities in breast cases introduced a difference between Fast Photon without heterogeneity correction and Fast Photon-Eff. Path length with heterogeneity correction. Breast cancer patients have a concave anatomy of the chest wall and whole breast, which represents an area of high dose inhomogeneity where a junction of three very different density tissues may be observed: lung (air), bone, and essentially water-equivalent tissue, for this reason, we selected this site in our study. Also this is the reason for showing a dosimetric impact on PTV and OARs as a result of using heterogeneity correction.

Also, we used two-photon energies to evaluate the impact of heterogeneity correction on dose distributions for different photon energies and to evaluate for which energy the impact of heterogeneity correction is more effective. The comparison between plan 1 without heterogeneity correction and plan 2 with heterogeneity correction showed that the number of MUs and modulation factors were significantly lower in plan 2 compared to plan 1 using 6MV and 10MV. MUs decreased with heterogeneity because Fast Photon-Eff. Path length calculation method takes into account every interaction occurring as the scattering dose and any absorbing dose of the different tissues through all the path length of the radiation beam within the tissues. Therefore, Fast Photon-Eff. Path length calculation method will deliver the dose with monitor units less than the Fast Photon calculation method.

In practice, clinical dose distributions are not uniform for the PTV due to variations in tissue densities. The spatial dose distribution and DVH showed that a large volume fraction of the PTV by the Fast Photon calculation method received the prescribed dose compared to the Fast Photon-Eff. Path length calculation method. This implies that Fast Photon tends to give a better PTV coverage. Nevertheless, the method with heterogeneity correction is closer to the reality [24]. Fast Photon-Eff. Path length increased the maximum dose which is usually in lung- overlapping regions or areas close to the lung.

The average values of D95%, V95%, mean dose, Dmax, and D2% associated with DVH without and with heterogeneity correction were 95.1% vs 93.7%, 95.3% vs 90.8%, 101% vs 100%, 109.7% vs 110.4%, and 106.4% vs 106.9%, respectively, for 6 MV. These values were 90.4% vs 88.1%, 88.8% vs 84.28%, 99% vs 98%, 107% vs 107.1%, and 104.6 % vs 104.4%, respectively, for 10 MV. From these results we can notice that maximum dose inside target volume increased (increasing in Dmax and D2% values) when taking into account heterogeneity correction, at the same time, the target coverage deteriorated (decreasing in D95%, V95%, and mean dose values).

These results are consistent with the clinical findings of Chaikh et al. (2014) [15], who concluded that the clinical results of the modification from the homogeneity plan to the heterogeneity plan were the reduction of delivered dose in monitor units for the PTVs, and with the findings of Fdhila et al. (2016) [8], who supported that MB algorithm (the heterogeneity correction for Pencil Beam Convolution algorithm) method reduced MU. However, our findings are inconsistent with those of Fdhila et al. (2016) [8], who supported the increment of dose to the target volume (lung and heart) when changed from PBC (homogeneity) to MB (heterogeneity) method. In this study, D95% for PTV decreased with heterogeneity, which could be due to the delineation of PTV above the ribs. Thus, PTV did not include any parts of the lung. Accordingly, in the heterogeneity correction method, the rib bones absorbed some of the radiation causing dose reduction to PTV, whereas causing increase in isodose lines that pass the lung, which can be the reason for increased doses to the lung and the heart (OARs).

The influence of heterogeneity correction in breast cancer cases is not more dominant due to the volume of the lung included in radiation beams. In breast cancer cases, the treated region can be the breast tissue that could be a homogeneous site and the beam only passes through a small part of the lung through the tangential beam in the treatment plan. Also, there is another parameter that affects heterogeneity correction that is beam arrangements (Number of beams in every plan). Comparison of the number of beams and the effect of the heterogeneity correction on the coverage (D95%) showed that the average effect of heterogeneity on coverage for seven cases treated with three beams was 1.19% and for 13 cases treated with 4 beams was 1.66%. This indicates that the effect of heterogeneity correction increases as the volume of the lung included in the beam and the number of beams in the treatment plan increase.

Comparison of the quality indices between the two treatment plans revealed that with the heterogeneity correction PTV conformity CI significantly decreased, whereas the homogeneity index (HI) significantly increased. This means that CI and HI were far from the ideal value with the heterogeneity correction, where the ideal value for CI was equal to 1 and for HI equal to zero. Therefore, CI is worst with the heterogeneity correction because in heterogeneity correction the coverage decreased and the doses to OARs increased, also HI was worst with the heterogeneity correction

because in the plan with heterogeneity correction the coverage decreased and the maximum dose increased.

The results are consistent with the clinical findings of Chaikh et al. (2014) [15], who founded that CI decreased with heterogeneity correction, but our findings are inconsistent with their results in that they found that HI was the same for the two plans and CI and HI were not significantly different.

The tissue heterogeneity correction had a considerable impact on the dose distribution for the lower energy than the higher energy excluding the effect of energy on coverage. The effect of the buildup region for each energy, which increases with increasing energy. In breast cancer patients, PTV is usually included the skin region, which is affected by the dose gradient in buildup region Therefore, the effect of heterogeneity correction must be calculated first through calculating the difference in coverage between the plans with and without heterogeneity correction in each energy, secondly, the difference in coverage between the two energies (6 and 10 MV) in each calculation method should be calculated to understand the effect of energy on coverage only. Finally, the effect of energy on coverage should be subtracted from the effect of heterogeneity on the coverage. For example, the difference in values of D95% and mean dose between homogeneity and heterogeneity correction in 6 MV and 10 MV, respectively, were as follows: 4.4±3.5 vs 3.4±3.1 (p=0.001) and 0.8±1.3 vs 0.6±1.4 (p=0.004), respectively. The results are consistent with the findings of Ellen et al. (1999) [18], who found that the impact of heterogeneity correction was higher in low energies than in higher energies.

Conclusion

- This study shows that heterogeneity correction decreases target coverage and increases doses to OARs.
- The impact of heterogeneity correction on dose distribution depends on the used energy and the number of beams. Heterogeneity correction showed larger effect in the low energy than the higher energy.
- We recommend considering tissue heterogeneity correction while calculating the dose for breast cancer patients because of the difference between the calculated dose by TPS assuming the patient as water (in case of non-use of heterogeneity correction) and the actual dose delivered to the patient as a result of the variation in organ density.
- Neglect in using heterogeneity correction may lead to misalignment of dose calculation with the physician's dose prescription or the accepted plan. Thus, individual beam weights should be re-optimized to deliver the dose prescription as more accurate as possible and to give the most uniform dose considering patient heterogeneity calculations.

Acknowledgment

We would like to thank Meet Ghammr Oncology Center for cooperating with us in this study.

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