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Radiation therapy with elective lymph node irradiation for breast cancer: dosimetric study and impact on cardiovascular risk and second neoplasms

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SUMMARY

OBJECTIVE: The aim of this study was to perform dosimetric analysis of radiotherapy (RT) plans with or without elective nodal irradiation (ENI) and estimate whether the increase in mean doses (MDs) in the heart and lungs with ENI may lead to late side effects that may surpass the benefits of treatment.

METHODS: The dosimetric analysis of 30 treatment plans was done with or without ENI. The planning and dose-volume histograms were analyzed, and the impact on the mortality of cardiovascular and lung cancer was estimated based on the correlation of the dosimetric data with data from population studies.

RESULTS: RT with ENI increased the doses in the lungs and heterogeneity in the plans compared to breast-exclusive RT. When the increase in MDs is correlated with the increase of late side-effect risks, the most important effect of ENI is the increased risk of lung cancer, especially in patients who smoke (average increase in absolute risk=1.38%). The increase in the absolute risk of cardiovascular diseases was below 0.1% in the all the situations analyzed.

CONCLUSIONS: ENI increases the heterogeneity and the doses at the lungs. When recommending ENI, the risks and benefits must be taken into account, considering the oncology factors and the plan of each patient. Special attention must be given to patients who smoke as ENI may lead to a significant increase in MD in the lung and the increased risk of radiation-induced lung cancer may surpass the benefits from this treatment.

KEYWORDS: Radiotherapy. Breast cancer. Lymphatic irradiation. Dosimetry. Smoking.

INTRODUCTION

Breast cancer is the second most common type of cancer in women and represents the fifth most frequent cause of death due to cancer. According to the data from the World Health Organization, 2.1 million new cases had occurred in 2018[1].

The role of radiotherapy (RT) after conservative breast cancer surgery is well established. This treatment leads to overall survival rates similar to those after isolated mastectomy of early-stage tumors[2,3]. Compared with conservative surgery alone, adjuvant RT decreases local and regional relapse rates, incidence of distant metastases, and cancer-specific mortality[3-5].

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Axillary lymph node metastases have important prognostic value in patients with breast cancer. It is known that elective nodal irradiation (ENI) can reduce local relapse rates, distant metastases, and cancer-specific mortality[6]. However, this treatment has side effects, and a higher incidence of cardiovascular diseases (CVDs) and secondary neoplasms may occur with increased doses to the heart and lung[7,8]. The risk of CVD is approximately four times higher in women who smoke than in the general population, whereas the risk of lung cancer is up to 20 times higher[9]. The combined effect of tobacco, smoking, and radiation exposure can significantly increase the mortality rate in these patients.

The objective of this study was to perform a dosimetric analysis of RT plans for patients with breast cancer receiving adjuvant treatment with the three-dimensional (3D) conformal RT with and without ENI. Furthermore, it aimed to estimate whether increasing the doses to organs at risk because ENI could lead to an increase in the absolute risk of death due to cardiovascular causes or lung cancer and minimize the potential benefits of this treatment.

METHODS

We performed dosimetric analyses of RT plans involving 3D conformal RT in patients with breast cancer with or without ENI.

Contouring of the target volumes and risk structures was conducted by a single radiation oncologist, according to the recommendations of the Radiation Therapy Oncology Group. Furthermore, 30 plans were prepared for 10 patients in three situations: RT of the breast alone, RT of the breast and the supraclavicular fossa (SCF), and RT of the breast, SCF, and internal mammary chain (IMC). Tangent fields were planned using the field-in-field technique for homogenization; the IMC was treated with a wide tangent field and the SCF with direct fields, with eventual addition of a posterior field for better coverage, if necessary.

The planning and dose-volume histograms were analyzed, and their effects on mortality due to CVD and lung cancer were estimated on a case-by-case basis in the three analyzed situations based on the correlation found between dosimetric and population study data[10]. It was considered that every gray (Gy) of increase in the mean dose (MD) to the lung and heart contributes to 11 and 4% increase in the relative risk of death due to lung cancer and CVDs, respectively. The absolute risks of death from lung cancer in smokers and nonsmokers are 4 and 0.3%, respectively, whereas those in smokers and nonsmokers are 1 and 0.3%, respectively (Table 1).

Statistical analysis was performed using nonparametric Friedman's test, and a significance level less than or equal to 0.05 was considered significant. The MDs to the heart and lungs of the 10 patients in the three situations being studied were used in the calculation to reduce the effect of individual anatomical variations.

Table 1. Cardiovascular and lung cancer risks.

Absolute risk of death (nonsmoking patients)	Lung cancer: 0.3% CVDs: 0.3%
Absolute risk of death (smoking patients)	Lung cancer: 4% CVDs: 1%
Increased relative risk of death for every 1-Gy increment in the mean dose	Lung cancer: 11% CVDs: 4%

CVDs: cardiovascular diseases.

RESULTS

Thirty plans were prepared based on the computed tomography scans of 10 different patients in three situations: only the left breast as the target volume; the SCF and the left breast as the target volumes; and the SCF, IMC, and left breast as the target volumes. The effect on planning target volume (PTV) coverage, heterogeneity, and doses to organs at risk were analyzed in all the plans.

Irradiation of the SCF, IMC, or both did not compromise breast PTV coverage because 95% of this volume received at least 95% of the prescription dose in all analyzed situations for the same minimum dose delivered to 95% of the PTV (D95). Heterogeneity indices were also not compromised because there was no difference between the PTVs that received 108 and 112% of the prescribed dose. In the 10 plans with IMC irradiation, at least 95% of the volume of the IMC PTV received a dose greater than or equal to 40 Gy. A mean incidental dose close to 73.4% of the prescription was administered to the IMC PTV even to plans that did not aim to cover this volume (Table 2).

In the 10 plans with breast treatment alone, the averages of the mean total lung dose (total lung MD), MD to the ipsilateral lung (lung MD), percentage of the lung receiving a 5-Gy dose (lung V5), percentage of the lung receiving a 10-Gy dose (lung V10), and percentage of the lung receiving a 20-Gy dose (lung V20) were 4.97 (3.60–5.90) Gy, 10.66 (8.5–12.20) Gy, 33.67% (26.0–38.0%), 23.44% (19.0–27.0%), and 18.08% (15.0–21.0%), respectively. In the same plans, the averages of the MD to the heart (heart MD), percentage of the heart receiving a 15-Gy dose (heart V15), and percentage of the heart receiving a 25-Gy dose (heart V25) were 3.31 (1.50–4.4) Gy, 4.06% (0–6%), and 3.12% (0–5%), respectively (Table 2).

Table 2. Dosimetric analysis of the averages of the 10 plans in the three analyzed situations (nonparametric Friedman's test).

Dosimetric analysis		Mean	p-value	Comparison between groups	Adjusted p-value
Heart MD (Gy)	No IMC	3.3100	0.027	No IMC/no drainage	1
	With IMC	4.0600		No IMC/with IMC	0.133
	No drainage	3.3100		No drainage/with IMC	0.133
	Total	3.5600			
Heart V15 (%)	No IMC	0.0406	0.895		
	With IMC	0.0560			
	No drainage	0.0406			
	Total	0.0457			
Heart V25 (%)	No IMC	0.0312	0.895		
	With IMC	0.0445			
	No drainage	0.0312			
	Total	0.0356			
Total lung MD (Gy)	No IMC	7.0600	<0.001	No IMC/no drainage	0.057
	With IMC	8.1100		No IMC/with IMC	0.133
	No drainage	4.9700		No drainage/with IMC	<0.001
	Total	6.7133			
Lung MD (Gy)	No IMC	15.0600	<0.001	No IMC/no drainage	0.076
	With IMC	17.2300		No IMC/with IMC	0.076
	No drainage	10.6600		No drainage/with IMC	<0.001
	Total	14.3167			
Lung V5 (%)	No IMC	0.5093	<0.001	No IMC/no drainage	0.057
	With IMC	0.5528		No IMC/with IMC	0.133
	No drainage	0.3367		No drainage/with IMC	<0.001
	Total	0.4663			
Lung V10 (%)	No IMC	0.3568	<0.001	No IMC/no drainage	0.076
	With IMC	0.4136		No IMC/with IMC	0.076
	No drainage	0.2344		No drainage/with IMC	<0.001
	Total	0.3349			
Lung V20 (%)	No IMC	0.2738	<0.001	No IMC/no drainage	0.076
	With IMC	0.3281		No IMC/with IMC	0.076
	No drainage	0.1808		No drainage/with IMC	<0.001
	Total	0.2609			
IMC mean (Gy)	No IMC	36.6800	<0.001	No IMC/no drainage	1
	With IMC	47.4700		No IMC/with IMC	0.02
	No drainage	36.6800		No drainage/with IMC	0.02
	Total	40.2767			
IMC V40 (%)	No IMC	0.5708	<0.001	No IMC/no drainage	1
	With IMC	0.8486		No IMC/with IMC	0.02
	No drainage	0.5708		No drainage/with IMC	0.02
	Total	0.6634			

No IMC: plan without the internal mammary chain and only breast and SCF; With IMC: plan with full drainage, including the IMC; No drainage: plan with the breast alone and no drainage; MD: mean doses; IMC: internal mammary chain.

In the 10 plans with SCF irradiation, the averages of total lung MD, ipsilateral lung MD, lung V5, lung V10, and lung V20 were 7.06 (6.30–8.10) Gy, 15.06 (13.7–16.70) Gy, 50.9% (46–54%), 35.68% (33–38%), and 27.38% (24–31%), respectively. In the same plans, the averages of heart MD, heart V15, and heart V25 were 3.31 (1.50–4.4) Gy, 4.06% (0–6%), and 3.12% (0–5%), respectively (Table 2).

In the 10 plans that included full lymphatic drainage and the IMC, the averages of ipsilateral lung MD, lung V5, lung V10, and lung V20 were 8.11 (6.70–9.80) Gy, 17.23 (15.4–19.90) Gy, 55.28% (49–60%), 41.36% (37–46%), and 32.81% (29–37%), respectively. In the same plans, the mean values of heart MD, heart V15, and heart V25 were 4.06 (1.60–6.0) Gy, 5.6% (0–11%), and 4.45% (0–9%), respectively (Table 2).

Compared with the 10 plans in which only the breast PTV was treated, IMC irradiation increased the MDs, V15, and V25 to the heart, whereas SCF irradiation, with or without the IMC, increased the doses in the lung (Table 2). The values of total lung MD, ipsilateral lung MD, lung V5, lung V10, and lung V20 showed a statistically significant difference via the Friedman's nonparametric test when the plans irradiating the breast alone were compared with those with full lymphatic drainage irradiation ($p<0.001$) (Table 2).Considering the absolute risk of death due to lung cancer or CVD in smokers and nonsmokers, the increase in the relative risk of death for every Gy increment in the mean heart and lung dose (Table 1), and the increase in the mean lung and heart doses after analysis of the 30 plans (Table 2), we estimated that irradiation of the SCF and IMC may increase the risk of death due to lung cancer and CVD in smoking patients by 1.38 and 0.03%, respectively, and that in nonsmokers by 0.1 and 0.01%, respectively.

DISCUSSION

Better systemic treatments have decreased the mortality risk due to breast cancer, local therapy plays a key role in this scenario[11]. A meta-analysis of the Early Breast Cancer Trialists' Collaborative Group showed that RT after conservative surgery or mastectomy is associated with a 20% gain in overall recurrence-free survival at 10 years and an 8.5% decrease in breast cancer mortality at 15 years in patients with lymph node involvement[5,6].

Elective lymph node irradiation represents a key component in the treatment of breast cancer. The IMC is affected in approximately 28–52%[12] of patients with positive axillary lymph nodes. The EORTC 22922 and NCIC MA.20 studies have demonstrated a reduction in the risk of distant metastases with SCF and IMC irradiation[13,14]. At present, the National Comprehensive Cancer Network recommends the inclusion of the IMC in patients with four or more compromised lymph nodes, whereas the ASCO-ASTRO-SSO recommends elective irradiation of the lymphatic drainage in patients with positive lymph nodes after conservative surgery or mastectomy[15]. However, there is no consensus regarding IMC irradiation owing to increased doses to organs at risk[16,17], as demonstrated in this study, as well as the possible side effects of treatment.

There is an association between smoking and breast cancer[18-20], and a meta-analysis with approximately 40,000 patients showed that cigarette smoking increased mortality due to cancer and other causes[20]. In addition, smoking can increase the risk of side effects related to RT, such as CVD and RT-induced secondary neoplasms, particularly in patients with lung cancer[10]. Several studies have correlated the risks of side effects from RT with doses to at-risk organs[21,22]. Taylor et al.[10] estimated a 4 and 11% increase in the relative risk of death due to CVD and lung cancer for every Gy increase in the MDs to the heart and lungs, respectively. In the dosimetric analysis of our study, the increase in the risk of death due to CVDs was less impacted by the inclusion of the elective irradiation of the lymphatic drainage, even in smoking patients. However, the impact of lymph node irradiation on the risk of death due to lung cancer was more significant. We found that compared with the treatment of the breast or chest wall alone, SCF and IMC irradiation may increase the mean risk of death due to lung cancer by 1.38% in smoking patients, which could considerably minimize the oncological benefits of this treatment.

There are other factors that influence the dose distribution in RT planning, such as the technique chosen, positioning, and individual anatomy of the patient. Furthermore, there are ways to reduce doses to risk organs via biofeedback, breath-holding, or prone positioning techniques[21,22]. These techniques can be used either alone or in combination to reduce doses to the lungs and heart and consequently the risk of death due to lung cancer and CVDs; however, their use was outside the scope of this study and was, therefore, not analyzed.

CONCLUSIONS

Smoking status and an increase in the MDs to the heart and lungs are factors that should be considered in the indication of ENI, particularly when this treatment is not mandatory, as in the case of patients with 1–3 compromised axillary lymph nodes. It is important to weigh the risks and benefits of this treatment because an increase in the MDs to the heart and particularly to the lungs of smoking patients can increase the mortality due to other causes and can minimize the oncological benefits of the treatment.

AUTHORS' CONTRIBUTIONS

AAPM: Data curation, Writing – original draft. **PMM:** Data curation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **CQT:** Conceptualization, Methodology, Writing – review & editing. **ACAP:** Conceptualization, Methodology, Writing – review & editing. **FBM:** Conceptualization, Methodology, Writing – review & editing. **RCF:** Conceptualization, Methodology, Writing – review & editing. **MJC:** Conceptualization, Methodology, Writing – review & editing. **MLGS:** Conceptualization, Methodology, Writing – review & editing. **DGC:** Conceptualization, Methodology, Writing – review & editing. **GRMG:** Conceptualization, Project administration, Supervision, Writing – review & editing.

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