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Investigating the radiation dose to the cervical and thoracic esophagus from post-mastectomy adjuvant radiation therapy in breast cancer

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► ***Short report***

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ABSTRACT

Background*:** Radiation therapy (RT) plays a crucial role in breast cancer management. However, RT may inadvertently expose neighboring organs to potential adverse effects. This study aimed to quantitatively analyze the radiation dose delivered to the cervical and thoracic esophagus during RT, focusing on patients undergoing post-mastectomy adjuvant RT. ***Materials and Methods: This cross-sectional study included 100 breast cancer patients who underwent post-mastectomy adjuvant RT to the chest wall and supraclavicular field (SCF) using 3-Dimensional Conformal Radiation Therapy (3DCRT). The dosimetric parameters, including mean dose (D_{mean}), V5, V10 and V30, were estimated from dose-volume histogram (DVH) data for the cervical and thoracic esophagus. ***Results:*** The mean age of the patients was 54.01 (± 11.62) years. The Dmean (± SD) for the thoracic and cervical esophagus were 1.15 (± 0.52) and 3.06 (± 2.09), respectively, with statistically significant different doses between the thoracic and cervical esophagus (P-value < 0.001). The V5, V10, and V30 for the thoracic esophagus were zero; however, the V5, V10 and V30 for the cervical esophagus were 7.07 (± 15.83), 2.29 (± 8.04) and 0.29 (± 1.99), respectively. The V5 values were significantly higher than V10 (P-value < 0.001) and V30 (P-value < 0.001), while V10 and V30 did not differ significantly (P-value = 0.155). ***Conclusions:*** This study reveals distinct dosimetric patterns for the cervical and thoracic esophagus during RT. The thoracic esophagus received low radiation doses, whereas the cervical esophagus demonstrated higher doses and more significant variability. Findings emphasize the importance of meticulous treatment planning to minimize potential late radiation-induced complications, especially in the cervical region.

INTRODUCTION

Breast cancer accounts for the most prevalent malignancy among women, with an increasing incidence observed globally [1]. According to estimates, the global incidence of breast cancer is expected to increase by more than 46% in 2050 [2].

With advancements in treatment modalities over the years, radiation therapy (RT) stands as a cornerstone in the management of breast cancer, contributing to reduced local recurrence rates and improved overall survival [3]. RT has resulted in a reduction of the mortality risk associated with breast cancer after mastectomy [4,5]. Nonetheless, the therapeutic benefits of RT come with inherent risks to neighboring organs at risk (OARs) [6]. The critical determinants of late radiation-induced complications are closely linked to the dose received by OARs [6-9].

The esophagus, due to its proximity to the irradiated breast tissue, is particularly susceptible to potential adverse effects of RT [10,11]. Findings of a meta-analysis have shown that breast cancer RT is linked to an elevated risk of esophagus cancer five to fifteen years after the RT [12]. From an anatomical perspective, the esophagus is situated near the supraclavicular fossa nodes, primarily located towards the left side of the cervical spine. Therefore, this particular anatomical arrangement presents the possibility of exposing larger portions of the esophagus while applying RT guidelines for patients affected by nodal involvement. Accordingly, higher esophagus radiation doses have been reported for RT including a nodal region [13].

While previous studies have explored RT-induced adverse events, limited research has specifically focused on the radiation dose distribution to the cervical and thoracic esophagus, particularly among patients with nodal involvement. This is among the first studies to quantitatively analyze the distinct radiation dose delivered to the cervical and thoracic esophagus during RT for breast cancer treatment. By employing dosimetric techniques and leveraging comprehensive patient data, we aimed to provide insights into the spatial distribution of radiation

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doses within these esophageal regions.

MATERIALS AND METHODS

Study design and participants

This was a cross-sectional study performed at the radiation oncology ward of Afzalipour Hospital, an academic referral center located in Kerman, the largest province in southeast Iran. The studied population were female patients with pathologically confirmed breast cancer who had received post-mastectomy adjuvant RT to the chest wall and supraclavicular field (SCF) between July 2019 and July 2021. Patients were excluded if they had a history of other types of cancer or had a documented history of esophagitis, gastroesophageal reflux disease (GERD) or esophageal cancer. Using the formula for estimating the population mean, taking into account the mean esophageal dose in a previous study [13] and considering a 95% confidence interval and a 0.2 margin of error, the minimum sample size was calculated to be 78. One hundred patients were finally enrolled in the study. The protocols for this study have been approved by the Ethics Committee of Kerman University of Medical Sciences (Registration number: IR.KMU.REC.1401.249; Date of registration: 2023-01-21).

RT procedures

We retrospectively analyzed the treatment plans of post-mastectomy breast cancer patients who had undergone adjuvant RT of dose 50 Gray (Gy) in 25 fractions over five weeks to the chest wall and SCF via 3-Dimensional Conformal Radiation Therapy (3D CRT). All patients had been treated with 6 MV photon beams (Vitan Beam- SN3011, Varian Medical Systems, USA). The procedure of RT was as follows: the individuals were fixed on the breast board (Omni Board, Macro Medics, Netherlands) and skin wires were positioned along the medial and lateral borders. The medial border was positioned at the chest's midline, while the lateral border's placement was determined through a physical examination. The upper and lower borders were established at the lower extremity of the medial clavicular head and 2 centimeters beneath the breast fold, respectively. Computed tomography (CT) scans were performed employing 5 mm thick slices via Neosoft equipment (Neosoft Medical Solutions, Hun Nun Industrial Area, Shenyang, China). Subsequently, the obtained image datasets were transferred to the Eclipse RT treatment planning system (Varian Medical Systems, USA). The clinical target volume (CTV) was considered as the whole breast tissue, and the planning target volume (PTV) was constituted by the CTV with an additional extension of 0.5 to 1 cm margins [14]. The beam arrangement consisted of three half–beams block with two tangential beams and one anterior field. Field borders were delineated as follows: superior: 1 cm above the breast tissue (usually at the inferior aspect of the clavicle or the sternum manubrium joint), inferior: 2 cm beneath the inframammary line, medial: mid-sternum and lateral: mid-axillary line (figure 1). The position of the field borders was modified based on the location of the lumpectomy and areas at higher risk of recurrence.

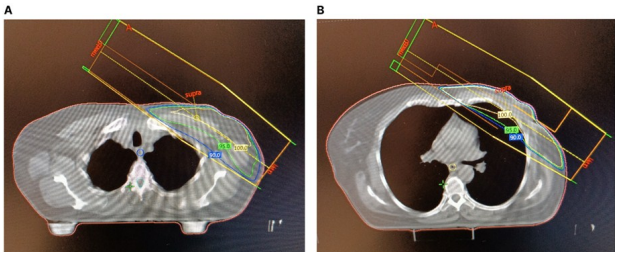

Figure 1. Planning images for cervical esophagus **(A)** and thoracic esophagus **(B)**.

Dosimetry assessments

The breast contouring guidelines of the Radiation Therapy Oncology Group (RTOG) were followed to delineate CTV and OARs. The esophageal volume was contoured from the inferior edge of the cricoid cartilage to the Carina. The upper part of the esophagus, which extends from the cricopharyngeal muscle to the thoracic inlet, was defined as the cervical esophagus. The thoracic portion was defined in the superior mediastinum, situated between the vertebral column and the trachea and extended from the suprasternal notch to the diaphragm. Dosimetric parameters received by the esophagus were estimated from dose-volume histogram (DVH) data. The mean dose (D_{mean}) and maximum dose (D_{max}) to the esophagus were evaluated. Moreover, the volume of the esophagus receiving at least 5 Gy (V_5), 10 Gy (V_{10}) and 30 Gy (V_{30}) were analyzed. Every patient was assigned two distinct plans: The tangential wedged beam (TWB) plan and the field-in-field (FIF) plan. The conventional TWB plans were created, incorporating suitable wedge angles to achieve the desired dose distribution. To formulate FIF plans, two open tangential beams were generated. The primary field size of FIF, the gantry angle and the collimator angle were identical to those utilized in the TWB. Nevertheless, in the FIF plans, the physical wedges were not utilized. Initially, the assessment was conducted without the incorporation of any beam modifiers. Subsequently, hot-dose regions were shielded by additional subfields.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) software (version 26.0. SPSS, Inc., USA) and R statistical software (4.3.2) were used for data analysis. The comparison of doses between cervical and thoracic esophagus was performed using a paired t-test. The effect size was reported using both Mean Difference (MD) and Hedge's g with

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corresponding 95% confidence intervals (95% CI). A repeated measure ANOVA followed by Tukey's HSD was utilized for the comparison of V_5, V_{10} and V_{30}. A p -value less than 0.05 was considered significant.

RESULTS

Data from 100 female patients were investigated. The mean age (± SD) of patients was 54.01 (± 11.62), ranging from 28 to 86 years old. Analyzing the dosimetric parameters received by the esophagus according to the DVH demonstrated that the D_{mean} (± SD) for the thoracic and cervical esophagus were 1.15 (± 0.52) and 3.06 (± 2.09), respectively, with statistically significant different doses between the thoracic and cervical esophagus (P-value < 0.001) (table 1).

Assessing the volume of the esophagus receiving at least 5 Gy (V_5), 10 Gy (V_{10}) and 30 Gy (V_{30}) demonstrated that no volume of thoracic esophagus received a minimum dose of 5 Gy as the V_5, V_{10} and V_{30} were zero for thoracic esophagus. The corresponding values for the cervical esophagus showed that the V_5, V_{10} and V_{30} were 7.07 (± 15.83), 2.29 (± 8.04) and 0.29 (± 1.99), respectively, with statistically different values between measurements (P-value < 0.001). Pairwise comparisons revealed significant differences between V_5-V_{10} (P-value < 0.001) and V_5-V_{30} (P-value < 0.001) but not between V_{10}-V_{30} (P-value = 0.155) (table 2).

Table 1. Dosimetric parameters received by the thoracic and cervical esophagus.

Dose	Mean (±SD)	Mean difference (95% CI)	Hedges' g effect size (95% CI)	P-value
Thoracic Esophagus Dose (Gy)	1.15 (±0.52)	1.91 (1.52, 2.31)	0.96 (0.72, 1.19)	<0.001
Cervical Esophagus Dose (Gy)	3.06 (±2.09)			

Gy: Gray, SD: Standard deviation, C.I: Confidence interval.

Table 2. Corresponding volumes of cervical esophagus receiving doses of 5, 10 and 30 Gy.

Volume	Mean (±SD)	ANOVA P-value	Pairwise comparison	Tukey's HSD P-value
V_5	7.07 (±15.83)	<0.001	**V_5-V_{10}**	<0.001
V_{10}	2.29 (±8.04)		**V_5-V_{30}**	<0.001
V_{30}	0.29 (±1.99)		**V_{10}-V_{30}**	0.155

Gy: Gray, V: Volume, SD: Standard deviation.

DISCUSSION

In this study, we separately analyzed the dosimetric parameters of the thoracic and cervical esophagus. Our results (table 1) demonstrated that the thoracic esophagus received a relatively low mean dose, indicating a well-controlled radiation exposure to the thoracic esophagus during RT. Furthermore, no volume of the thoracic esophagus received a minimum dose of 5 Gy, as indicated by V_5, V_{10} and V_{30} values being zero. Some studies have provided dose-volume predictors associated with esophageal complications following RT. For instance, findings of a study by Wang *et al*. on dose-volume predictors of radiation esophagitis in patients with breast cancer undergoing regional nodal RT suggested that maintaining the relative upper esophageal V_{25} lower than 20% and the absolute V_{35} lower than 0.27 mL was associated with decreased risk of radiation esophagitis [15]. However, studies assessing dosimetric parameters solely for the thoracic esophagus are scarce. As we observed zero values of V_5-V_{30} in the thoracic esophagus in our study, our findings suggest that analyzing lower values (e.g., V_2) might provide more accurate dose-volume predictors of radiation-induced esophageal outcomes, particularly when assessing the thoracic esophagus.

In contrast, the cervical esophagus received a significantly higher mean dose compared to the thoracic esophagus (table 1). Moreover, the volume receiving specific doses (V_5, V_{10} and V_{30}) for the cervical esophagus also showed higher mean values than the thoracic esophagus, representing the proportion of the cervical esophagus being exposed to radiation doses (table 2). The higher dose-volume parameters observed in the cervical esophagus compared to the thoracic esophagus can be attributed to the employment of the SCF in the treatment plan. The alignment of the SCF with the cervical esophagus leads to increased radiation exposure in this region, consequently resulting in higher corresponding dose values. In a study by West and colleagues on patients receiving supraclavicular nodal RT, the D_{mean} and D_{max} were reported to be 32.87 (± 7.4) and 50.32 Gy, respectively. Moreover, patients receiving a mean esophageal dose of 31 Gy or higher had a significantly higher incidence of grade 2 esophagitis [16]. Furthermore, the authors proposed that limiting the inclusion of the pharynx to less than 1 cm within the SCF could potentially lead to a reduction in the occurrence of esophageal toxicity [16]. Another study assessing the post-mastectomy intensity modulation radiation therapy (IMRT) of the chest wall and regional nodes demonstrated an esophageal D_{mean} value of 10.65 (± 2.43) and D_{max} of 40.61 (± 4.45) [17]. Moreover, findings from an older study by Lamart *et al.* indicated that treatment fields encompassing the SCF and/or internal mammary lymph nodes resulted in the highest radiation doses within three specific regions of the esophagus: Upper thoracic (32 Gy), middle thoracic (25 Gy) and cervical (median: 38 Gy). In contrast, other fields, including direct chest wall, axillary, and tangential fields, contributed significantly lower doses (nearly 2 Gy) to the esophagus [18]. Additionally, results of a systematic review of esophagus doses indicate that for RT including a nodal region, average esophagus doses

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were 11.4 Gy (range < 0.1–29.3) and maximum 34.4 Gy (range 3.4–51.3). Furthermore, in cases where RT included the treatment of lymph nodes, an average mean esophagus dose of 11.4 Gy has been associated with an almost two-fold increase in the risk of developing esophageal cancer [13].

Generally, 3D CRT has been associated with reduced esophageal adverse outcomes. Findings from a recent study underscore that the risk of grade 2 esophagitis was remarkably higher in patients undergoing IMRT (23.6%) as compared to patients receiving 3D CRT (10.9%) [19]. Moreover, dosimetric parameters, including esophageal D_{mean}, V_{10} and V_{20}, were higher in IMRT than in 3D CRT patients [19]. Although we did not have access to IMRT in our institution, these findings are in line with our study demonstrating that dose-volume parameters in patients undergoing 3D CRT planning are lower than those observed in other studies in IMRT. Furthermore, Bhaskaran and colleagues reported that contouring the esophagus as an organ at risk (OAR) during radiotherapy treatment for breast cancer led to a statistically significant reduction in the dose delivered to the esophagus [20]. This finding suggests that 3D CRT planning with esophagus delineation could serve as an effective approach to minimizing esophageal radiation dose [20].

Despite its contributions, this study had several limitations. First, the single-center nature of the study may restrict the generalizability of the findings to other treatment centers with varying protocols and techniques. Second, this study was conducted using a retrospective cross-sectional design and no follow-up of the patients was done to fully capture the long-term effects of radiation exposure on the esophagus. Third, our study encompassed patients with a high risk of nodal involvement who underwent a mastectomy. Analyzing the dosimetric data in patients with breast-conserving surgery who undergo RT warrants further research.

CONCLUSION

In conclusion, this study reveals distinct dosimetric patterns for the cervical and thoracic esophagus during RT, with significantly higher doses in the cervical esophagus. Given the absence of established dose thresholds for preventing secondary cancer risk in OARs and considering the enhanced survival outcomes of breast cancer patients with the utilization of RT, it becomes imperative to minimize radiation doses to all OARs.

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Ethicals approval: All study protocols have been conducted under approval of the Ethics Committee of Kerman University of Medical Sciences (Registration number: IR.KMU.REC.1401 ;249.Date of registration: 2023-01-21 .(Data were collected retrospectively using the clinical and imaging records, therefore the need for informed consent was waived by the ethics committee. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication: Not applicable.

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