ISSN No:-2456-2165

Research Progress of Radiation-Induced Hypothyroidism Following Supraclavicular Radiotherapy for Breast Cancer Patients

Abdulkareem Qasem Moqbel[1,2*], Lina Jamal Hameed[3], Mustafa A.S. Dehwah[2*], Ram Prasad Chaulagain[4], Nand Lal[5]
[1]Department of Biochemistry and Molecular Biology, Cancer Center, Medical Research Institute, Southwest University, Chongqing 400716, China
[2]Department of Clinical Laboratory, Faculty of Medical and Health Science, Taiz University/AL-Turba branch, Yemen
[3]Department of Immunology, Heilongjiang Provincial Key Laboratory for Infection and Immunity, Harbin Medical University, Harbin 150081, China
[4]Department of Gastroenterology and Hepatology, The Second Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China
[5]Department of Physiology, School of Biomedical Sciences, Harbin Medical University, Harbin, Heilongjiang, China
[*]Corresponding author: Mustafa A.S. Dehwah

Abstract:- Radiotherapy (RT) is essential for treating cancer alongside chemotherapy and surgery, improving survival rates, and lowering local recurrence risk in high-risk breast cancer (BC) patients. However, it can lead to thyroid complications like hypothyroidism (HT), especially with higher radiation doses using traditional methods. Higher radiation doses to the thyroid, especially with conventional methods and exposure of the cervical region, increase the risk of HT. External radiation, particularly in the supraclavicular (SCV) and infra-clavicular nodal levels, poses a significant risk to the thyroid, a radiation-sensitive organ. Radiation's negative impact on the thyroid includes late and irreversible effects like atrophy, follicle, and vascular damage. Thyroid size, radiation dose, technique, and clinical factors (age, stage) influence these outcomes and toxicities. As a result, routine thyroid function assessment should be performed for BC patients after radiation. According to the reviewed articles, further study is needed to pinpoint variables and create advanced normal tissue complication probability (NTCP) models. Intensity-modulated radiotherapy (IMRT) must limit the dose to the thyroid to reduce the prevalence of HT. This review aims to outline SCV radiation's impact on thyroid function and factors related to radiation-induced hypothyroidism in breast cancer patients.

Keywords:- *Radiotherapy; Breast Cancer; Supraclavicular; Hypothyroidism.*

I. INTRODUCTION

Breast cancer (BC) is the leading global cancer among women, contributing significantly to cancer-related deaths in various countries [1]. In 2020, BC accounted for 11.7% of worldwide cancer cases, topping both incidence (159 out of 185 countries) and mortality (110 countries) [2].

Radiation therapy is crucial in treating various cancers. Standard BC treatment includes surgery, radiation, and systemic therapy tailored to stage and clinical presentation [3, 4]. Advancements in technology have heightened the importance of treatment planning in radiation therapy. Modern techniques protect essential organs and precisely target tumor areas with improved radiation delivery [5, 6].

Radiobiological models for normal tissue complication probability (NTCP) and TCP offer valuable tools to enhance treatment approaches. Oncology centers increasingly adopt patient-specific CT-based methods over standardized planning [7]. This shift aims to achieve precise target characterization and reduce radiation-induced side effects [7, 8]. The thyroid, a crucial organ, can be partly exposed to high-energy photon beams during BC radiation therapy. Its proximity to the gross tumor volume means it can fall within the treatment beam when irradiating supraclavicular (SCV) lymph nodes (Figure 1).

The thyroid is highly sensitive to radiation and is a critical endocrine organ near the SCV nodal area. Radiation exposure can lead to thyroid toxicity in both medical and occupational adults [9, 10].

High-risk BC patients benefit from external beam radiation therapy covering the breast and regional lymph nodes (axillary and SCV). This reduces accidental local recurrence and improves long-term survival [11, 12]. Whole breast radiation therapy reduces local recurrence risk by two-thirds; an additional boost lowers it by 50% [13]. Radiotherapy (RT) also enhances survival rates [14]. However, RT benefits are countered by adverse effects on surrounding structures, impacting patient's quality of life [15]. Radiation-induced toxicities to neighboring tissues can cause significant morbidity in cancer survivors [16]. Ionizing

radiation's most harmful impact is altering cell genetics risking cancer and functional issues in exposed tissues. BC patients receiving SCV radiation, particularly younger individuals, face a higher hypothyroidism (HT) incidence [17, 18].

HT, a known delayed consequence of external thyroid radiation, can emerge months to years post-RT. High radiation exposure designates the thyroid as an organ at risk [19]. Reduced thyroid volume due to radiation could contribute to this complication. Recent research by Huang et al. [20] Indicated that radiation-induced HT is more common in BC patients with smaller thyroid volumes. Prioritizing pre-RT HT risk assessment and post-RT risk reduction is vital for better patient quality of life, especially in growing BC survivorship concerns. This review aims to outline the impact of SCV radiation on thyroid function and reconsider factors tied to radiation-induced HT in BC patients. These include RT, thyroid volume, techniques, doses, clinical characteristics, and NTCP models.

II. RADIATION-INDUCED HYPOTHYROIDISM

Cancer patients receiving radiation to cervical or SCV lymph nodes often experience radiation-induced HT as an RT side effect [21, 22]. Table 1 compiles studies on radiation-induced HT post-treatment of BC. While initial research focused on RT-induced HT in head and neck cancer and lymphoma patients, the first instances in BC patients undergoing SCV radiation therapy were noted in the 1980s by Bruning et al. Subsequent studies further confirmed the connection between SCV-directed radiation and increased HT incidence [18, 23]. In a study by Huang et al., of 192 BC patients who received SCV lymph node RT, post-radiation HT incidence ranged approximately from 19.3% (overall patients) to 32% (patients with follow-up labs) at a median of 25 months (2-83 months range) after treatment [20].

Many studies indicate that SCV lymph node RT elevates HT in BC patients [23-25]. Additional research highlights radiation and chemotherapy as substantial hazards, leading to thyroid damage and HT in BC patients, as seen in studies by Huang et al. [26] and Smith et al. [21]. Some studies conducted by Choi et al. [17] and Falstie-Jensen et al. [27] establish that BC patients receiving chemotherapy and lymph node radiation face the most significant risk of HT development. A Korean study with 4073 BC patients undergoing varying RT dosages-2468 whole breast, 215 regional node irradiation (RNI) LV.4, and 1390 RNI-SCV-found higher HT risk post RNI-SCV compared to RNI-Lv 4 [17]. In a Danish study involving 44,574 BC patients and 203,306 matched controls, those who had chemotherapy and RT to local lymph nodes exhibited the highest HT incidence, with an HR of 1.74 (95% CI 1.50-2.02). Nodal radiation with or without chemotherapy in the BC cohort led to elevated HT risk compared to no such treatments [27]. In a recent study by Roberson et al. [28] on 61 BC patients who received SCV lymph node radiation, a post-SCV RT HT incidence of 27.9% was observed, with a median onset at 38.7 months. Cutuli et al. noted that 6.2% of BC patients undergoing RT, chemotherapy, and surgery experienced clinically symptomatic HT by the end of the initial treatment [29].

In another Korean study by Park et al. [30], BC patients receiving RT tended to have higher HT incidence than non-RT patients (HR = 1.248; 95% CI, 0.977-1.595). Adjusted risk was higher in RT -RT-receiving BC patients. A Canadian analysis of BC therapy from 2005 to 2009 revealed increased comorbidities post-treatment, including ischemic heart disease and HT, with an HT HR of 1.17 (95% CI: 1.09–1.26) [31]. A more extensive retrospective study by Huang et al. indicated through univariable analysis that reduced thyroid volume correlated with HT development in BC patients [32].

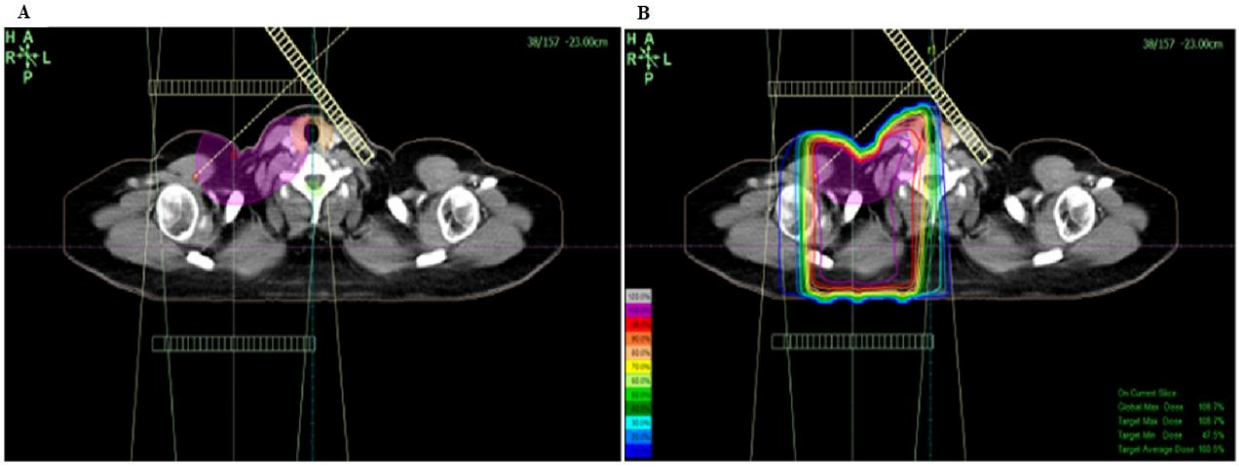

Fig 1. A, Radiation plan for the supraclavicular field. The thyroid gland is colored orange.
B, Dose distribution for supraclavicular field [33].

➢ *Chang of the thyroid gland (volume) after radiation*

Higher occurrence of post-radiation primary HT could relate to reduced thyroid volume caused by radiation, as observed in studies by Lin et al. [34] and Ishibashi et al. [35] [2018]. Local thyroid doses of 2 Gy or higher might lead to decreased thyroid volume due to radiation-induced microvascular and parenchymal damage, as noted by Lollert et al. [36]. Roberson et al. found that thyroid volume decrease occurs six months after SCV-directed radiation for BC. Their study indicates persistent thyroid atrophy for years post-radiation, becoming an independent risk indicator for HT. Within one year after treatment, thyroid volume reduction was evident; by four years, it decreased by 29.7% (range: 2.3-64.4%) [28]. Namdar et al. [37] of 32 BC patients observed that radiation-induced HT risk increases with higher mean thyroid gland doses at an 11.4-month median follow-up but decreases when thyroid volume surpasses 11.4 cc.

III. RADIOTHERAPY TECHNIQUES

Advancements in radiation therapy technology have led to lower side effect rates for BC patients undergoing irradiation. Three-dimensional conformal radiation therapy (3D-CRT) planning for SCV irradiation indicated improved target coverage in certain instances but also revealed higher radiation doses being absorbed by the thyroid [38]. Reinertsen et al. [2009] [39] divided 403 women undergoing SCV irradiation for BC into two groups based on treatment planning technique: conventional 2D RT or computed tomography (CT) based planning (CT-RT). Their study suggested that 3D-CRT might elevate post-treatment HT risk compared to traditional planning. Meanwhile, Nageeti et al. [40] observed that using a larger anterior SCV field angle to protect the spinal cord increased thyroid radiation at all doses, potentially elevating post-radiation thyroid damage.

Intensity-modulated radiotherapy (IMRT), the latest planning method, reduces unintended radiation exposure to non-target tissues. In contrast to 3D-CRT, IMRT may expose the thyroid gland to more low-dose radiation, as indicated by Chen et al. [41] and Dogan et al. [42]. Multiple studies have shown that thyroid-sparing IMRT can preserve thyroid function while maintaining primary tumor target coverage, as seen in research by Lu et al. [43], Kim et al., and Robin et al. [44]. Therefore, we recommend employing advanced techniques like IMRT, which adjusts radiation intensity based on tumor thickness and density, reducing thyroid gland dose and HT risk.

Table 1. Selected studies related to radiation-induced hypothyroidism after treatment of BC

Authors	N	Surgery involved	Median follow-up time	Radiotherapy type	Endpoint	Incidence risk of HT	Thyroid Dose per fraction (Gy)/total dose (Gy)	Related Risk factors of HT	Restrictions
Akyurek et al.+(2014)	28	MRM (19) BCS (9)	9 months	3D-CRT	SHT, Clinical HT	One year: 14% 2-years: 21%	50+10 (19) 50 (9)	D_{mean}, V20, V30 & V40	D_{mean}<36 Gy
Tunio et al.* (2017)	40	MRM (15) BCS (25)	52 months	3D-CRT	SHT, Clinical HT	Crude: 15%	2	VT, V30>50%	V30>50%
Johansen et al+. (2011)	32	MRM (12) BCS (4)	Not	3D-CRT	Biochem. HT, overt HT	Not reported	50 (13) 50+10 (3)	VT, V30	V30
Kikawa et al.* (2017)	42	Not reported		3D-CRT	SHT, Clinical HT	5-years Prevalence: SHT: 14.3% Clinical HT: 2.4%	2	VT< 8cm3	V30
Kanyilmaz etal.+ (1017)	243	MRM (146) BCS (97		3D-CRT	SHT, Clinical HT	Crude: 21% SHT: 11.9% Clinical HT: 9.1%	50 (135) 60 (82) 66 (26)	D_{mean}	D_{mean} > 21 Gy
Choi et al.+ (2020)	4073	MRM (12) BCS (4)		3D-CRT IMRT	SHT, clinical HT	3-year Incidence; RNI-SCL: 2.2% WB-alone groups: 0.8%;	50 in 25 to 28 and 40.05-42.56 in	younger age (<60 years), Anthracycline-based or	NA

							15 to 16 fractions	paclitaxel-based adjuvant chemotherapy and RNI fields	
Roberson et al.+ (2023)	61	MRM BCS	38.7 months	3D-CRT IMRT	SHT, clinical HT	Crude:27.9% SHT: 9.8% Clinical HT: 18.0%	44–50.4 in 1.8–2/ fraction	20 and 40 Gy, mean dose, postmenopausal, aromatase inhibitor and VT	VT, radiation dose of 20 Gy or higher.
Huang et al.+ (2021)	192	MRM (104) BCS (82)	25 months	3D-CRT IMRT	SHT, clinical HT	Incidence: All patients: 19.3%. SHT: 8.3%. Clinical HT: 10.9% Follow-up: 32%. SHT: 16%, Clinical HT: 16%,	44–50.4 in 1.8–2/ fraction	Smaller thyroids, mean dose, and VT less than 20 Gy	Less than 20 Gy
Farshchian et al.+ (2022)	21	BCS (12) MRM (9)		3D-CRT		3 months: 0% 6 months: 9.5%	50	Not associated with any factors	NA
Namdar et al.+ (2020)	32	BCS (5) MRM (26)		3D-CRT		One year: Incidence: 16.1%	2-50 or 2.66-42.56 in 5 days per week	Age, gender, chemotherapy, VT <11.4 cc,D_{mean}	D_{mean} > 27 Gy
Park et al.* (2022)	64080	MRM BCS		IMRT		1-year: 1.7% 5-years: 6.9% 8-years: 9.2%		Patient's age, mastectomy, and the long-time of cancer treatment. (Multivariate analysis)	NA
Falstie-Jensen et al * (2020)	1712					5-years Incidence: 1.8%		Patients who received RT to the lymph nodes with or without chemotherapy	NA

MRM: Modified Radical Mastectomy; BCS: Breast Conservation Surgery; Three-Dimensional Conformal Radiation Therapy (3D-CRT); Intensity-Modulated Radiation Therapy (IMRT); SCH: Subclinical Hypothyroidism; Biochem. HT: Biochemical Hypothyroidism; VT: Thyroid Gland Volume; D_{mean}: the mean dose to thyroid gland; NA; No Applicable; and WB: whole breast. +; Retrospective Methodology; *: Prospective Methodology

➢ *Dose-volume predictor for hypothyroidism in treatment BC*

While past studies explored dose-volume relationships for increased HT risk, the findings have been inconsistent. Tissue exposure and radiation dose are linked. A retrospective analysis of BC patients with SCV-directed RT found that thyroid volume decreased after six months. The reduction associated with clinical and subclinical HT onset. Patients receiving 40 Gy or higher doses exhibited a significant decrease in thyroid volume compared to lower dose recipients. The study highlighted a dose-dependent relationship between thyroid subvolume reduction and SCV-directed RT in BC patients [28]. Albuquerque et al. [45] found a correlation between the volume of thyroid volume irradiation and the occurrence of HT. The average thyroid volume in patients who acquired HT was 7 cc, compared to 10 cc in those who did not. Nageeti et al. [40] studied how varying SCV field angles impact thyroid dose absorption compared to spinal cord dose. Smaller angles (0°) correlated with lower thyroid absorption at all dose levels (15 Gy, 30 Gy, 50 Gy); max dose was 47.9 Gy at 0°. Thyroid volume influenced absorption mainly at high doses and angles ≤ 10°. As per Huang H et al. [20], among BC patients, sparing volume from receiving ≥20 Gy (CV20Gy[cc]) is the primary predictor for predicting HT. It's the top predictor in univariable analysis and the sole significant predictor apart from follow-up length in multivariable analysis. Namdar AM et al. [37] studied 62 breast and neck cancer patients who underwent 3D RT. HT was found in 17 of 62 patients over 11.4 months of median

follow-up. In BC patients, HT was more common when the thyroid mean dose surpassed 27 Gy.

Many studies show that varying radiation therapy dose levels, including mean dose [23, 25], V20 Gy [%][25], V30 Gy [%] [25, 46, 47], and V40 Gy [%] [25], are associated with higher chances of developing HT. Kanyilmaz et al. [23] and Tunio et al. [46] found that the mean dose to the thyroid gland (D_{mean}) > 21 Gy and V30 are predictors of HT. Kanyilmaz reported 3-year incidence rates of 10% and 3% for SCV RT and non-SCV RT patients, with D_{mean} values of 19.0 Gy and 13.2 Gy for HT and euthyroid groups [23]. Tunio showed, at 52 months, 15% with SCV RT and 5% without had HT. D_{mean} values were 25.8 Gy and 5.6 Gy, respectively. The V30 (>50%) was a significant predictor in the SCV radiation group [46]. Ansari et al. studied 64 BC individuals, finding an essential link between higher thyroid-absorbed doses and thyroid hormone changes [48].

Akyurk et al. prospectively analyzed thyroid conditions in 28 BC patients with a median follow-up of 25 months. In their investigation, V20-40 and D_{mean} of thyroid ≥ 36 Gy significantly influence the development of radiation HT; however, V_{mean} of the thyroid was unrelated to RHT development. Additionally, the prevalence of radiation HT in their patient population was 21% [25]. Kikawa et al. studied 42 BC patients with SCV radiation, finding that smaller thyroid volumes (<8 cm3) predicted a higher risk of radiation-induced HT in a 30-month follow-up. Smaller thyroid volumes were linked to clinical and subclinical HT [24]. Johansen et al. found that BC patients with small thyroid volumes are prone to HT post-RT due to limited thyroxin production capacity at doses under 30 Gy. No significant differences were found between V20 and V50 [47]. Farshchian et al. found no significant association between radiation-induced HT in BC patients after SCV region radiation therapy and thyroid gland volume or dose-volume parameters (including thyroid V10-50) [49]. Thyroid radiation exposure should be minimized in IMRT to reduce HT.

IV. OTHERS CLINICAL FACTOR

- *Age*

The literature suggests that the onset of RT-induced HT may be influenced by the patient's age and radiation exposure and that the thyroid gland radiosensitivity declines with advancing age [47]. Many studies suggest that post-RT HT in BC patients may be associated with factors such as chemotherapy and young age. Thyroid epithelium degradation is associated with an increased risk of HT [50, 51]. Due to thyroid epithelial deterioration, age may contribute to the higher prevalence of HT in the general population. In younger patients, a more comprehensive SCV field limit and more frequent use of harsh chemotherapy may explain the observed outcome variations. The Roberson et al. [28] and Farshchian et al. [49] investigations do not consistently support this connection.

- *Clinical stage*

The BC tumor-node-metastasis stage and radiation field are connected. The European Organization for Research and Treatment of Cancer 22922/10925 study showed that regional nodal irradiation significantly reduced BC mortality and recurrence in stage I-III cases [52, 53]. Consequently, the application of RT to the SCV region has expanded, extending from N2 to N1 disease cases [54]. Kanyilmaz's study revealed that surgery type, stage, nodal status, and RT field were significant predictors for HT in univariate analysis. However, multivariate regression analysis found no such correlation [23]. Advanced-stage patients require close monitoring for thyroid function tests.

- *Normal tissue complication probability modeling*

Given the inevitability of normal tissue exposure in external beam RT, comprehending the radiation tolerance levels of organs is vital for appropriate dose distribution and harm prevention. Increased radiation dose can lead to higher incidence and severity of radiation-induced damage. Radiobiological studies often depict the impact of radiation on normal and malignant tissues through dose-response curves. These curves illustrate the likelihood of specific responses, like radiation effects. Radiation therapy planning should incorporate restrictions on thyroid dosage to mitigate potential long-term HT effects.

Assessing NTCP is crucial for comparing treatment options and understanding how normal tissues respond to radiation therapy [55, 56]. To enhance treatment planning and minimize effects on adjacent normal tissue, accurate prediction of radiation responses is vital. NTCP models, based on radiobiological or dosimetric data, have emerged to evaluate complications. These models play a pivotal role when aiming for maximum treatment efficacy with specific goals [57]. It would be necessary to reduce iatrogenic diseases such as radiation-induced HT To improve the quality of life of cancer patients after radiation therapy [37].

In a 2021 study, Huang et al. investigated HT in BC patients after SCV RT. They established an NTCP model using a 15% cutoff at 5 years. The study revealed a strong link between a thyroid volume over 8.5 cc and receiving less than 20 Gy with increased HT risk. Comparing IMRT (n = 120) and 3D-CRT (n = 72) treatment modalities, IMRT showed higher minimum and mean thyroid doses, along with increased volume received at least 10 Gy (V10Gy) and V20Gy percentages and decreased thyroid volume receiving less than 10 Gy (CV10Gy[cc]) and 20 Gy (CV20Gy[cc]) volumes compared to 3D-CRT [20]. Conclusively, they suggest that maintaining CV20Gy [cc] at ≥ 8.5 cc could serve as a useful dosimetric reference to lower post-treatment HT risk, utilizing NTCP modeling with a 15% HT incidence threshold [20]. It's essential to factor in radiotherapy's impact on the thyroid gland when developing NTCP models for radiation-induced HT in BC patients.

V. CONCLUSION

This systematic review underscores radiation-induced HT as a standard long-term side effect, especially when the SCV region is directly irradiated. While RT is a routine BC treatment, its impact on thyroid radiation dosage can lead to thyroid atrophy, damage to small vessels, direct harm to follicles, and indirect damage to the vascular network. Thyroid gland size, absorbed radiation dose, RT technique, and clinical factors (like age and stage) influence radiation effects and their associated toxicities. High-risk patients, including those with greater thyroid dose, smaller thyroid volume, recent surgery, and younger age with advanced disease, should undergo regular thyroid function testing post-RT. While an optimal thyroid threshold isn't universally agreed upon, managing thyroid dose within the bounds of primary tumor coverage remains crucial. Existing studies suggest further research to define variables, develop multivariate models for NTCP, and elucidate the mechanism of radiation-induced HT while effectively constraining thyroid dose. In IMRT, controlling thyroid dose is vital to minimize radiation exposure and reduce the risk of HT. Additional research is needed to understand the mechanism of radiation-induced HT, the RT-HT link, early detection, and treatment strategies, reducing radiation-induced HT rates, and enhancing the quality of life for BC patients. A longitudinal study with recurrent thyroid assessments can validate the strength of the risk model.

- *Abbreviations*

Radiotherapy (RT); Breast cancer (BC); hypothyroidism (HT); Supraclavicular (SCV); Normal tissue complication probability (NTCP); Intensity-modulated radiotherapy (IMRT); Regional node irradiation (RNI); Three-Dimensional conformal radiation therapy (3D-CRT)

REFERENCES

[1]. Waks AG and Winer EP, Breast Cancer Treatment: A Review. JAMA 2019;321:288-300 DOI: 10.1001/jama.2018.19323.
[2]. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al., Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71:209-249 DOI: 10.3322/caac.21660.
[3]. Mirinezhad SK, Somi MH, Seyednezhad F, Jangjoo A, Ghojazadeh M, Mohammadzadeh M, et al., Influence of chemoradio therapeutic strategies and factors on the five yearssurvival of patients with esophageal cancer. Journal of Isfahan Medical School 2014;32:982-990.
[4]. Mohammadzadeh M, Faramarzi E, Mahdavi R, Nasirimotlagh B and Asghari Jafarabadi M, Effect of conjugated linoleic acid supplementation on inflammatory factors and matrix metalloproteinase enzymes in rectal cancer patients undergoing chemoradiotherapy. Integr Cancer Ther 2013;12:496-502 DOI: 10.1177/1534735413485417.
[5]. Mesbahi A and Dadgar H, Dose calculations accuracy of TiGRT treatment planning system for small IMRT beamlets in heterogeneous lung phantom. 2015.
[6]. Mesbahi A, Akcay D and Alikus ZA, The impact of residual geometric inaccuracies on normal organ doses in image guided-radiation therapy of prostate cancer using on-board kilovoltage Cone-Beam computed tomography. Iranian Journal of Medical Physics 2017;14:104-113.
[7]. Prabhakar R, Rath GK, Julka PK, Ganesh T, Joshi RC and Manoharan N, Breast dose heterogeneity in CT-based radiotherapy treatment planning. J Med Phys 2008;33:43-8 DOI: 10.4103/0971-6203.41191.
[8]. Charaghvandi RK, Yoo S, van Asselen B, Rodrigues A, van den Bongard D and Horton JK, Treatment constraints for single dose external beam preoperative partial breast irradiation in early-stage breast cancer. Clin Transl Radiat Oncol 2017;6:7-14 DOI: 10.1016/j.ctro.2017.06.003.
[9]. Park S, Lee DN, Jin YW, Cha ES, Jang WI, Park S, et al., Non-cancer disease prevalence and association with occupational radiation exposure among Korean radiation workers. Sci Rep 2021;11:22415 DOI: 10.1038/s41598-021-01875-2.
[10]. Sinnott B, Ron E and Schneider AB, Exposing the thyroid to radiation: a review of its current extent, risks, and implications. Endocr Rev 2010;31:756-73 DOI: 10.1210/er.2010-0003.
[11]. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al., Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;366:2087-106 DOI: 10.1016/s0140-6736(05)67887-7.
[12]. Van de Steene J, Soete G and Storme G, Adjuvant radiotherapy for breast cancer significantly improves overall survival: the missing link. Radiother Oncol 2000;55:263-72 DOI: 10.1016/s0167-8140(00)00204-8.
[13]. Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, et al., Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011;378:1707-16 DOI: 10.1016/s0140-6736(11)61629-2.
[14]. Buchholz TA, Radiotherapy and survival in breast cancer. Lancet 2011;378:1680-2 DOI: 10.1016/s0140-6736(11)61296-8.
[15]. Akın M, Ergen A, Unal A and Bese N, Irradiation doses on thyroid gland during the postoperative irradiation for breast cancer. J Cancer Res Ther 2014;10:942-4 DOI: 10.4103/0973-1482.137991.

[16]. Taylor C, Correa C, Duane FK, Aznar MC, Anderson SJ, Bergh J, et al., Estimating the Risks of Breast Cancer Radiotherapy: Evidence From Modern Radiation Doses to the Lungs and Heart and From Previous Randomized Trials. J Clin Oncol 2017;35:1641-1649 DOI: 10.1200/jco.2016.72.0722.
[17]. Choi SH, Chang JS, Byun HK, Son N-H, Hong C-S, Hong N, et al., Risk of Hypothyroidism in Women After Radiation Therapy for Breast Cancer. International Journal of Radiation Oncology, Biology, Physics 2021;110:462-472 DOI: 10.1016/j.ijrobp.2020.12.047.
[18]. Darvish L, Ghorbani M, Teshnizi SH, Roozbeh N, Seif F, Bayatiani MR, et al., Evaluation of thyroid gland as an organ at risk after breast cancer radiotherapy: a systematic review and meta-analysis. Clin Transl Oncol 2018;20:1430-1438 DOI: 10.1007/s12094-018-1875-7.
[19]. Pernas S, Tolaney SM, Winer EP and Goel S, CDK4/6 inhibition in breast cancer: current practice and future directions. Ther Adv Med Oncol 2018;10:1758835918786451 DOI: 10.1177/1758835918786451.
[20]. Huang H, Roberson J, Hou W, Mani K, Valentine E, Ryu S, et al., NTCP model for hypothyroidism after supraclavicular-directed radiation therapy for breast cancer. Radiother Oncol 2021;154:87-92 DOI: 10.1016/j.radonc.2020.09.003.
[21]. Smith GL, Smith BD, Giordano SH, Shih YC, Woodward WA, Strom EA, et al., Risk of hypothyroidism in older breast cancer patients treated with radiation. Cancer 2008;112:1371-9 DOI: 10.1002/cncr.23307.
[22]. Alterio D, Jereczek-Fossa BA, Franchi B, D'Onofrio A, Piazzi V, Rondi E, et al., Thyroid disorders in patients treated with radiotherapy for head-and-neck cancer: a retrospective analysis of seventy-three patients. Int J Radiat Oncol Biol Phys 2007;67:144-50 DOI: 10.1016/j.ijrobp.2006.08.051.
[23]. Kanyilmaz G, Aktan M, Koc M, Demir H and Demir LS, Radiation-induced hypothyroidism in patients with breast cancer: a retrospective analysis of 243 cases. Med Dosim 2017;42:190-196 DOI: 10.1016/j.meddos.2017.03.003.
[24]. Kikawa Y, Kosaka Y, Hashimoto K, Hohokabe E, Takebe S, Narukami R, et al., Prevalence of hypothyroidism among patients with breast cancer treated with radiation to the supraclavicular field: a single-centre survey. ESMO Open 2017;2:e000161 DOI: 10.1136/esmoopen-2017-000161.
[25]. Akyurek S, Babalioglu I, Kenan K and GOKCE SC, Thyroid dysfunction following supraclavicular irradiation in the management of carcinoma of the breast. Int J of Hema Oncol 2014;24:139-144 DOI: 10.4999/uhod.14234.
[26]. Huang J, Jin L, Ji G, Xing L, Xu C, Xiong X, et al., Implication from thyroid function decreasing during chemotherapy in breast cancer patients: chemosensitization role of triiodothyronine. BMC Cancer 2013;13:334 DOI: 10.1186/1471-2407-13-334.
[27]. Falstie-Jensen AM, Esen B, Kjærsgaard A, Lorenzen EL, Jensen JD, Reinertsen KV, et al., Incidence of hypothyroidism after treatment for breast cancer-a Danish matched cohort study. Breast Cancer Res. 2020;22:106 DOI: 10.1186/s13058-020-01337-z.
[28]. Roberson J, Huang H, Noldner C, Hou W, Mani K, Valentine E, et al., Thyroid volume changes following adjuvant radiation therapy for breast cancer. Clin Transl Radiat Oncol 2023;39:100566 DOI: 10.1016/j.ctro.2022.100566.
[29]. Cutuli B, Quentin P, Rodier JF, Barakat P and Grob JC, Severe hypothyroidism after chemotherapy and locoregional irradiation for breast cancer. Radiother Oncol. 2000;57:103-5 DOI: 10.1016/s0167-8140(00)00183-3.
[30]. Park J, Kim C, Ki Y, Kim W, Nam J, Kim D, et al., Incidence of hypothyroidism after treatment for breast cancer: A Korean population-based study. PLoS One 2022;17:e0269893 DOI: 10.1371/journal.pone.0269893.
[31]. Ng HS, Vitry A, Koczwara B, Roder D and McBride ML, Patterns of comorbidities in women with breast cancer: a Canadian population-based study. Cancer Causes Control 2019;30:931-941 DOI: 10.1007/s10552-019-01203-0.
[32]. Huang J, Walker R, Groome PG, Shelley W and Mackillop WJ, Risk of thyroid carcinoma in a female population after radiotherapy for breast carcinoma. Cancer 2001;92:1411-8 DOI: 10.1002/1097-0142(20010915)92:6<1411::aid-cncr1464>3.0.co;2-9.
[33]. Imani A, Mesbahi A, Jafari-Koshki T, Eghdam Zamiri R and Nasiri Motlagh B, Evaluation of the Radiobiological Models Predicting the Radiation-Induced Hypothyroidism in the Partially Irradiated Thyroid Gland of Patients with Breast Cancer. Int J Cancer Manag 2022;15:e119445 DOI: 10.5812/ijcm-119445.
[34]. Lin Z, Wu VW, Lin J, Feng H and Chen L, A longitudinal study on the radiation-induced thyroid gland changes after external beam radiotherapy of nasopharyngeal carcinoma. Thyroid 2011;21:19-23 DOI: 10.1089/thy.2010.0229.
[35]. Ishibashi N, Maebayashi T, Aizawa T, Sakaguchi M, Okada M and Matsushita J, Computed Tomography Density Change in the Thyroid Gland Before and After Radiation Therapy. Anticancer Res 2018;38:417-421 DOI: 10.21873/anticanres.12238.
[36]. Lollert A, Gies C, Laudemann K, Faber J, Jacob-Heutmann D, König J, et al., Ultrasound Evaluation of Thyroid Gland Pathologies After Radiation Therapy and Chemotherapy to Treat Malignancy During Childhood. Int J Radiat Oncol Biol Phys 2016;94:139-146 DOI: 10.1016/j.ijrobp.2015.09.016.
[37]. Namdar A, Sadeghi-Bazargani H, Mohammadzadeh M and Mesbahi A, Radiation-induced Hypothyroidism in Survivors of Head-and-Neck and Breast Cancers After 3-Dimensional Radiation Therapy: Dose-Response Models and Clinical-Dosimetric Predictors. Reports of

Radiotherapy and Oncology 2020;In Press: DOI: 10.5812/rro.102343.
[38]. Ung KA, Portillo M, Moran B, Kron T, Sawyer B, Herschtal A, et al., The dosimetric impact of supraclavicular nodal irradiation on the thyroid gland in patients with breast cancer. Pract Radiat Oncol 2013;3:e131-7 DOI: 10.1016/j.prro.2012.12.007.
[39]. Reinertsen KV, Cvancarova M, Wist E, Bjøro T, Dahl AA, Danielsen T, et al., Thyroid function in women after multimodal treatment for breast cancer stage II/III: comparison with controls from a population sample. Int J Radiat Oncol Biol Phys 2009;75:764-70 DOI: 10.1016/j.ijrobp.2008.11.037.
[40]. Nageeti T, Mahfouz M, Al Gaod M and Zatar R, Absorbed Radiation Dose in the Thyroid Gland Following Regional Nodal Irradiation for Breast Cancer. Int J Oncol Res 2018;1.
[41]. Chen F, Li J, Ai N, Zhang H, Li J and Zhu Y, Influence of 3D-CRT and conformal IMRT on thyroid function of patients with cervical and upper thoracic esophageal cancer and comparison of clinical efficacy. Oncol Lett 2019;17:3432-3438 DOI: 10.3892/ol.2019.9989.
[42]. Dogan N, Cuttino L, Lloyd R, Bump EA and Arthur DW, Optimized dose coverage of regional lymph nodes in breast cancer: the role of intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 2007;68:1238-50 DOI: 10.1016/j.ijrobp.2007.03.059.
[43]. Lu JY, Wu LL, Zhang JY, Zheng J, Cheung ML, Ma CC, et al., Improving target dose coverage and organ-at-risk sparing in intensity-modulated radiotherapy of advanced laryngeal cancer by a simple optimization technique. Br J Radiol 2015;88:20140654 DOI: 10.1259/bjr.20140654.
[44]. Robin TP, Amini A, Ryan N, Karam SD and Raben D, (P075) Thyroid Gland Sparing Radiotherapy in the Management of Head and Neck Cancer: A Single Institution Prospective Approach to Assess Feasibility, Safety, and Response. International Journal of Radiation Oncology, Biology, Physics 2017;98:E35.
[45]. Albuquerque K, Beall N, Shah K, Niemierko A and Bova D, Incidence and Predictors of Thyroid Dysfunction following Three-Dimensional Conformal Radiation Therapy (3D-CRT) to Low Neck as Component of Adjuvant Radiation in Women with Breast Cancer: Prospective Long Term Follow-Up. International Journal of Radiation Oncology, Biology, Physics 2009;75:S499.
[46]. Tunio MA, Al Asiri M, Bayoumi Y, Stanciu LG, Al Johani N and Al Saeed EF, Is thyroid gland an organ at risk in breast cancer patients treated with locoregional radiotherapy? Results of a pilot study. J Cancer Res Ther. 2015;11:684-9 DOI: 10.4103/0973-1482.167613.
[47]. Johansen S, Reinertsen KV, Knutstad K, Olsen DR and Fosså SD, Dose distribution in the thyroid gland following radiation therapy of breast cancer--a retrospective study. Radiat Oncol 2011;6:68 DOI: 10.1186/1748-717x-6-68.
[48]. Ansari L, Nasiri N, Aminolroayaei F, Sani KG, Dorri-Giv M, Abedi-Firouzjah R, et al., The Measurement of Thyroid Absorbed dose by Gafchromic™ EBT2 Film and Changes in Thyroid Hormone Levels Following Radiotherapy in Patients with Breast Cancer. J Med Signals Sens. 2020;10:42-47 DOI: 10.4103/jmss.JMSS_10_19.
[49]. Farshchian N, Amirifard N, Azar MHS, Heydarheydari S, Farshchian N and Haghparast A, Thyroid function following radiation therapy in breast cancer patients: risk of radiation-induced hypothyroidism. Rep Pract Oncol Radiother 2022;27:691-698 DOI: 10.5603/RPOR.a2022.0074.
[50]. Choi SH, Chang JS, Byun HK, Son NH, Hong CS, Hong N, et al., Risk of Hypothyroidism in Women After Radiation Therapy for Breast Cancer. Int J Radiat Oncol Biol Phys 2021;110:462-472 DOI: 10.1016/j.ijrobp.2020.12.047.
[51]. Mortezaee K, Ahmadi A, Haghi-Aminjan H, Khanlarkhani N, Salehi E, Shabani Nashtaei M, et al., Thyroid function following breast cancer chemotherapy: A systematic review. J Cell Biochem 2019;120:12101-12107 DOI: 10.1002/jcb.28771.
[52]. Poortmans PM, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, et al., Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer. N Engl J Med 2015;373:317-27 DOI: 10.1056/NEJMoa1415369.
[53]. Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, et al., Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med 2015;373:307-16 DOI: 10.1056/NEJMoa1415340.
[54]. Frasier LL, Holden S, Holden T, Schumacher JR, Leverson G, Anderson B, et al., Temporal Trends in Postmastectomy Radiation Therapy and Breast Reconstruction Associated With Changes in National Comprehensive Cancer Network Guidelines. JAMA Oncol 2016;2:95-101 DOI: 10.1001/jamaoncol.2015.3717.
[55]. A M, N R, M M, B NM and H OT, Comparison of Radiobiological Models for Radiation Therapy Plans of Prostate Cancer: Three-dimensional Conformal versus Intensity Modulated Radiation Therapy. J Biomed Phys Eng 2019;9:267-278 DOI: 10.31661/jbpe.v9i3Jun.655.
[56]. Mesbahi A, Rasouli N, Motlagh B and Mohammadzadeh M, Radiobiological Model-Based Comparison of Three-Dimensional Conformal and Intensity-Modulated Radiation Therapy Plans for Nasopharyngeal Carcinoma. Iranian Journal of Medical Physics 2017;14:190-196 DOI: 10.22038/ijmp.2017.22508.1213.
[57]. El Naqa I, Pater P and Seuntjens J, Monte Carlo role in radiobiological modelling of radiotherapy outcomes. Phys Med Biol 2012;57:R75-97 DOI: 10.1088/0031-9155/57/11/r75.