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Secondary Cancer Induction: Lifetime Attributable Risk Estimates Following Radioiodine Therapy Among Thyroid Cancer Female Survivors in Saudi Arabia

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Abstract: Radiation-induced second solid cancer (RISSC) is one of the critical late side effects of radiotherapy treatment of first cancer. The mechanism of second cancer incidence is not fully known yet. However, many elements contribute to the development of RISSC such as age at exposure, effective dose to the organ and surrounding tissues, treatment modalities and family history of cancer. The aim of this study is to provide long-term forecasts of second cancer prevalence among thyroid cancer female survivors in Saudi Arabia. The long-term harm resulting from radiation exposure or lifetime attributable risk (LAR) of RISSC after a radiation treatment of thyroid cancer was determined, between the age at exposure and up to 90 years, in a cohort of female cancer survivors whose age at treatment was in the range 15 to 76 years. Risk estimates varied significantly with age at exposure and effective organ dose. The results of the study clearly indicate a direct positive correlation between the patient's age at exposure and the induction of a thyroid secondary cancer. The chance of developing thyroid second cancer after radiotherapy is highest in those exposed as children. Furthermore, the radiation dose directly affects the emergence of secondary cancers.

Keywords: Second thyroid cancer; Radiotherapy; Organ dose; Second cancer incidence; Lifetime attributable risk

1. Introduction

The thyroid gland is an essential endocrine organ using iodine to secrete hormones that control vital functions in the human body such as heart rate, breathing, blood pressure, body temperature, menstrual cycle, metabolism. Thyroid cancer constitutes more than 90% of

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tumors of the endocrine system [1]. The highly treatable papillary and follicular malignant tumors are the most common thyroid cancers. However, the medullary and anaplastic cancers are more aggressive and difficult to cure because of their rapid metastasis [2].

The thyroid gland is extremely radiosensitive to the carcinogenic effects and highly prone to solid secondary malignancies [3,4]. Although it is not widespread, thyroid cancer was the first solid tumor found with a high occurrence amongst Japanese atomic bomb survivors [5] and population exposed to radioactive iodine from Chernobyl nuclear plant fallout [6] . Several studies showed that patients administrated with adjuvant radioiodine (RAI) presented an increase in the incidence of second thyroid sarcomas [7,8].

An ever-growing number of people in the world, diagnosed with cancer at some stage in their life, are now living normal life. In early January 2019, almost 17 million cancer survivors (8.1 million males and 8.8 million females) were alive in the United States and that number is likely to be over 22 million by January 2030 [9]. In 2012, 2.1 million cancer survivors were alive in the United Kingdom. An increase by roughly one million per decade of cancer survivors is estimated from 2010 to 2040 [10]. This number is expected to reach 4.0 and 5.3 million in 2030 and 2040, respectively. This tendency is a consequence of significant improvements in both treatment and better follow up of survivors of all malignant neoplasms combined over the past decade [11,12,13], to an increase in life expectancy and population ageing [14].

RISSC (other than metastasis) occurs following the cure of the first cancer. Numerous studies have showed that long-term survivors of childhood thyroid radiotherapy have an increased incidence of second cancer, mainly located inside or adjacent to the primary cancer treatment field after radiotherapy [4, 15,16]. Several Epidemiologic investigations identified a strong connection between external radiation exposure and a second thyroid cancer incidence [17,18,19]. For cancer survivors after radiotherapy treatment, especially survivors of childhood tumors, the risk of developing a second cancer over the course of their livelihood increases, as they are likely to live longer than older patients [20] (Travis et al., 2013). Radiation-associated solid tumors are the most common type of secondary malignancies observed in childhood cancer survivors. Life attributable risk at 30 years after childhood primary Hodgkin lymphoma and Ewing sarcoma treatment was higher for patients treated with radiotherapy than for those who receiving other types of treatment [21]. However, recent advances in radiotherapy modalities in the last decade, such as proton and heavy ions radiation therapy [22], pose a reduced risk of second cancer induction compared to conventional radiotherapy techniques due to the lower radiation exposure to healthy tissues surrounding the first tumor [23] [24].

1.1. Thyroid cancer types

Thyroid cancer is a tumor of the thyroid parenchymal tissue which consists of two main cell types, the follicular and the parafollicular cells. Thyroid cancer can be categorized in three main types:

- Differentiated thyroid carcinoma, including papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and Hurthle cell cancers. They arise from follicular cells of the thyroid and accounts for 80-85%, 10-15% and up to 5%, respectively of all thyroid malignancies [25].
- Medullary thyroid carcinoma arises from parafollicular cells and accounts for another 6% [26].

- Anaplastic thyroid carcinoma is rare (accounts for less than 1% of thyroid malignancies) and highly aggressive [27].

1.2. Biological pathways of thyroid cancer induction

Mutations to the *RET* proto-oncogene, occur in nearly 60% to 70% of PTC occurring after irradiation [28]. The remaining 40% to 30% are related to a point mutation in the *BRAF* gene [29]. Mutations of the *p53* tumor suppressor gene are associated with anaplastic thyroid carcinoma [30].

1.3.Risk factors of thyroid cancer

Numerous potential risk factors including genetic predisposition, exposure to therapeutic ionizing radiation, iodine deficiency or excess, family history of benign thyroid disease, as well as hormonal and reproductive factors can contribute to the prevalence of thyroid cancer which has risen all over the world in the last few decades [31, 32].

1.3.1. Gender related

Compared to males, females have a greater tendency to develop a radiation-induced second cancer (RISSC) [33,35]. This fact might be attributed to estrogen sex hormones level differences in men and women [35,36]. The α- and β-estrogen mediating receptors are over-expressed in women's thyroid cancer [37]. Sturniolo et al reported that frequency of PTC is nearly 3 times higher in females than in males [38]. Ron et al [39] found that the excess relative risk per Gy for female patients who were treated in their childhood for thyroid cancer with radiations was about twice that for males.

Age related

The excess relative risk per Gy of getting a future second cancer is higher during childhood and young adulthood exposure and decreases with increasing age at the time of radiotherapy [22, 40,41]. Buist and colleagues reported that over 17,000 women aged between 18 and 80 years, diagnosed with breast cancer and treated with radiotherapy, were followed up over 5-year period [42]. 4% of this cohort developed a second breast cancer and women who were over 80 years of age showed the lowest rate of second cancer (4%). The youngest age group, 17- 39 years showed the highest rate of incidence (9.7 %). In a pooled analysis of children under the age of 4 diagnosed with thyroid cancer and exposed to radiation, Veiga and colleagues showed a fivefold greater risk per Gy of developing a second thyroid cancer, relative to those aged 10–14 years [43]. In a similar study, a 10-fold higher risk per Gy was found for children between 0 and 1 year of age relative to those aged between 15 and 20 years [44]. Preston and colleagues estimated a decrease of 17% in the risk of getting a second cancer per decade increase in age at exposure [19].

1.3.2. Genetic factor

Recent progress in the human genome project led to the identification of several genetic variants that might induce the risk of thyroid carcinogenesis across different ethnicities [45]. For instance, the single nucleotide polymorphisms (SNPs) were confirmed to be directly linked to papillary thyroid carcinoma [46]. Furthermore, genetic factor appears to play an important role in the radiotherapy-related second cancer risk [20]. The RET proto-oncogene (located in chromosome number 10) mutation has been shown to play an important role in hereditary diseases among them the formation of medullary thyroid carcinoma [47].

1.3.3. Dietary iodine deficiency (or excess)

Zimmermann and Galetti [48] reported that iodine deficiency or excess act more as stimulators rather than as initiators of aggressive anaplastic thyroid carcinogenesis. Dietary iodine deficiency especially in childhood has been implicated as risk factor in thyroid cancer induction [49]. A meta-analysis revealed that a higher iodine intake (≥300 µg/day) and high consumption of sea fish and were reducing factors for all form of thyroid cancers [50].

1.3.4. Radiation exposure

Thyroid cancer was first linked to external radiation exposure in a 1969 study of the Nagazaki/Hiroshima atomic bomb survivors [51]. A huge increase in childhood thyroid cancer frequency was reported in contaminated areas around Chernobyl, 3-4 years after the nuclear accident in 1986, especially among infants and young adults [52, 53]. This was due to the thyroid gland intake of the main component of accident fallout radioiodine-131.

1.3.5. Lifestyle risk factors

High prevalence of thyroid cancer has been linked to the lifestyle of individuals. Physical activities [54], iodine nutritional status [55], smoking [56], obesity [57] and psychological stress [58] are potential risk factors for thyroid carcinoma development. However, the risk of thyroid cancer incidence was inversely associated and alcohol consumption [59,60,61]. Jiang and co-workers also reported that an increased frequency of seafood consumption was associated with a decreased prevalence of thyroid cancer [54].

1.4.Thyroid cancer in Saudi Arabia

In 2012, thyroid cancer was the ninth most common cancer between Saudi man (3.8%) and the second most common cancer among Saudi women (11.7%) after breast cancer (25.8%) with a male to female ratio of 0.3:1 [62, 63]. This type of cancer represents around 9% of all malignancies and 12% of all female malignancies in Saudi Arabia, which are significantly higher compared to the USA, where thyroid cancer represents only 2.9% of all malignancies and 4.6% of all female malignancies [62].

In this study we estimated the lifetime risks of developing a thyroid second cancer among Saudi female patients following a radiotherapy treatment of their thyroid using age and sex specific parameters set in the BEIR VII report [64]. Even though this report was used initially for atomic bomb survivors who were irradiated with one acute dose of less than 0.1 Gy, the BEIR VII risk models have been used to estimate lifetime cancer risk for high-dose exposures from radiotherapy in a numerous study [65, 66,67,68,69] . Sex- and age-related differences in the occurrence of the second cancer are examined.

2. Methodology

2.1 Data collection

Radioiodine therapy, using iodine-131 β-particle-emitter (192 keV), is strongly advocated in the treatment protocol for thyroid cancer patients [70,71,72]. Sodium Iodide-131 solution (NaI) is usually orally administrated to the patients. It is rapidly concentrated in the thyroid through Na^+/I^- membrane symporters, where it is oxidized to iodine and organified [73].

The retrospective cohort study included 77 female patients (ranged in age from 15 to 76 years) (Table 1), all from King Abdulaziz University Hospital (Jeddah, Saudi Arabia) Cancer Registry 2016-2018, with a confirmed first thyroid carcinoma. They were orally administrated with sodium iodide 131 in a liquid form which was generally well tolerated

with an activity of 30 to 200 mCi based on patient specific parameters such as the nature of the underlying condition, age, estimated thyroid tissue iodine uptake, thyroid size. Radiation exposure incurred from radioiodine was ascertained by the effective dose which quantifies the biologic effects of radiation absorbed by the anatomic region irradiated as determined by absorbed dose, radiation type, and concerned organ. The thyroid effective doses were calculated, based on the thyroid weighting factor of 0.04, and were approximately between 0.62 and 4.14 Sv. The dose selection was based on patient specific parameters such as the nature of the underlying condition, age, estimated thyroid tissue iodine uptake, thyroid size.

Table 1: Data of 77 female cases with thyroid cancer irradiated with known dose

#	Age at exposure (years)	Radioiodide Concentration (mCi)	Thyroid absorbed dose (Gy)	Thyroid effective dose (Sv)
1	15	150	155.4	3.11
2	16	100	103.6	2.07
3	20	100	103.6	2.07
4	21	200	207.2	4.14
5	22	100	103.6	2.07
6	22	150	155.4	3.11
7	23	100	103.6	2.07
8	23	100	103.6	2.07
9	23	100	103.6	2.07
10	24	150	155.4	3.11
11	25	100	103.6	2.07
12	26	150	155.4	3.11
13	26	100	103.6	2.07
14	26	100	103.6	2.07
15	27	100	103.6	2.07
16	27	30	31.08	0.62
17	27	100	103.6	2.07
18	27	30	31.08	0.62
19	28	100	103.6	2.07
20	29	100	103.6	2.07
21	29	150	155.4	3.11
22	29	100	103.6	2.07
23	30	100	103.6	2.07
24	30	150	155.4	3.11
25	31	150	155.4	3.11
26	32	100	103.6	2.07
27	32	50	51.8	1.04
28	33	100	103.6	2.07
29	33	150	155.4	3.11
30	33	100	103.6	2.07
31	33	150	155.4	3.11
32	34	100	103.6	2.07

Table 1: (Continued)

#	Age at exposure (years)	Radioiodide Concentration (mCi)	Thyroid absorbed dose (Gy)	Thyroid effective dose (Sv)
33	34	100	103.6	2.07
34	34	200	207.2	4.14
35	35	100	103.6	2.07
36	36	100	103.6	2.07
37	36	100	103.6	2.07
38	37	100	103.6	2.07
39	37	100	103.6	2.07
40	37	100	103.6	2.07
41	37	150	155.4	3.11
42	38	100	103.6	2.07
43	38	150	155.4	3.11
44	39	30	31.08	0.62
45	41	100	103.6	2.07
46	41	100	103.6	2.07
47	41	150	155.4	3.11
48	41	150	155.4	3.11
49	41	100	103.6	2.07
50	41	100	103.6	2.07
51	41	100	103.6	2.07
52	42	100	103.6	2.07
53	42	100	103.6	2.07
54	43	100	103.6	2.07
55	43	75	77.7	1.55
56	43	30	31.08	0.62
57	45	100	103.6	2.07
58	45	100	103.6	2.07
59	48	150	155.4	3.11
60	48	100	103.6	2.07
61	49	100	103.6	2.07
62	49	200	207.2	4.14
63	50	75	77.7	1.55
64	52	100	103.6	2.07
65	53	100	103.6	2.07
66	55	150	155.4	3.11
67	56	150	155.4	3.11
68	57	100	103.6	2.07
69	58	100	103.6	2.07
70	58	100	103.6	2.07
71	59	100	103.6	2.07
72	59	100	103.6	2.07
73	59	100	103.6	2.07
74	61	100	103.6	2.07
75	62	100	103.6	2.07
76	62	30	31.08	0.62
77	76	150	155.4	3.11

3. Secondary cancer risk calculation model

3.1.Calculating excess relative risk

To determine the LAR (total projected second cancer risk), the excess relative risk (ERR) was calculated in the present female patient cohort. The LAR for each patient is calculated from his exposure age to a period of up to 90 years.

The excess relative risk (ERR) of secondary solid cancer was calculated according to

$$ERR = \beta D e^{\gamma e^*}$$

$Where: D$ is the organ dose, e is the age at exposure, e^*= (e - 30) / 10 for e < 30 and 0 for e > 30 years; a is the attained age. a = age at exposure + latency period (between 5 and 10 years as reported[74,75,76] for the appearance of the thyroid cancer after radiation exposure. The biological parameters β and γ are the coefficients of the BEIR VII cancer risk model for the thyroid cancer and were based on the data obtained from the Hiroshima/Nagazaki atomic bomb survivors and Chernobyl nuclear accident irradiated people $\beta = 1.05$ and $\gamma = -0.83$. For all carcinogens, it is generally agreed that cancer risk increases with dose. There is no increase in risk in the absence of exposure. This means that ERR= 0 when D = 0.

The risk of secondary cancer during the course of the patient's life is given by the LAR

$$LAR = \left(\sum_{a}^{90} ERR.\lambda_a^s.\frac{S(a)}{S(e)} \right)$$

$S(a)$ is the probability of surviving until age a, and $\frac{S(a)}{S(e)}$ is the probability of surviving to age a conditional on survival to age e. λ_a^s is the baseline cancer rate, *i.e*. the cancer rate incidence in the absence of irradiation, which depends on sex (s) and attained age (a). Values of λ_a^s were taken from the Saudi National Health Information Center - Cancer Registry [77]. An average value of 44.6% for both males and females was taken for the value of $\frac{S(a)}{S(e)}$ [78].

4. Results and discussion

Figure 1 shows the age-specific incidence rate (AIR) for thyroid cancer among Saudi nationals (NHIC, 2015). This incidence is higher for female than male for all ages. For comperison purposes of the risk estimates, we computed the ERR/Gy for all patients as function of age at exposure and then deducted the LAR/Gy for each patient separately for every five years of attained age until the age of 90 years (Figure 2). Our results show that thyroid cancer survivors had an elevated LAR of developing a second cancer for all age groups, compared to the particular baseline cancer risks incidence (Figure 1). The LAR/Gy data show an inverse correlation with age at exposure with a kind of leveling off in the middle age. LAR/Gy decreased with increasing age at exposure from 324 (cancer cases per Gy per 100,000 people) for exposures at the age of 15 to 75 for exposures at age of 77.

Figure 3 shows a substantial increase of the LAR with dose for middle-aged patients (in their early 40's), *i.e* the risk of developing a second radiation-induced thyroid tumor increased almost linearly with the dose. A 3-fold increase in the dose induces a 3.2-fold increase in the LAR. This fact is consistent with earlier study [78].

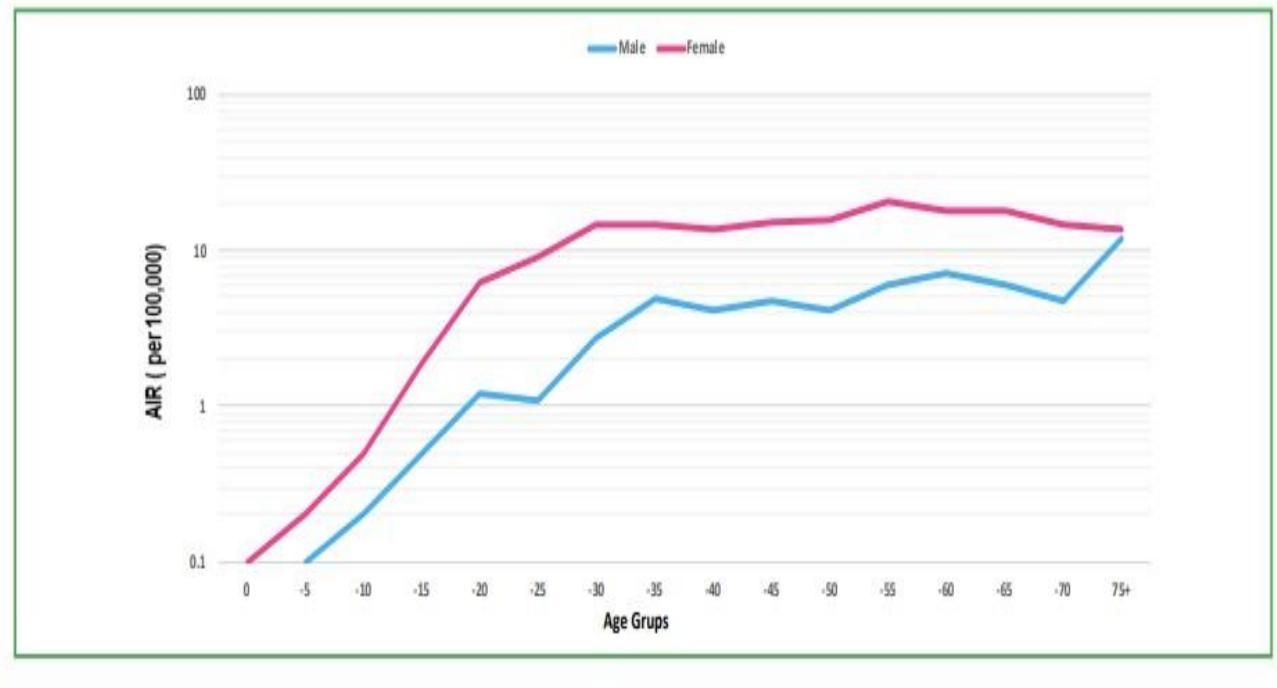

Figure 1: Age-Specific Incidence Rate (AIR) for thyroid cancer among Saudi nationals, 2015
*Saudi National Health Information Center - Cancer Registry [77]

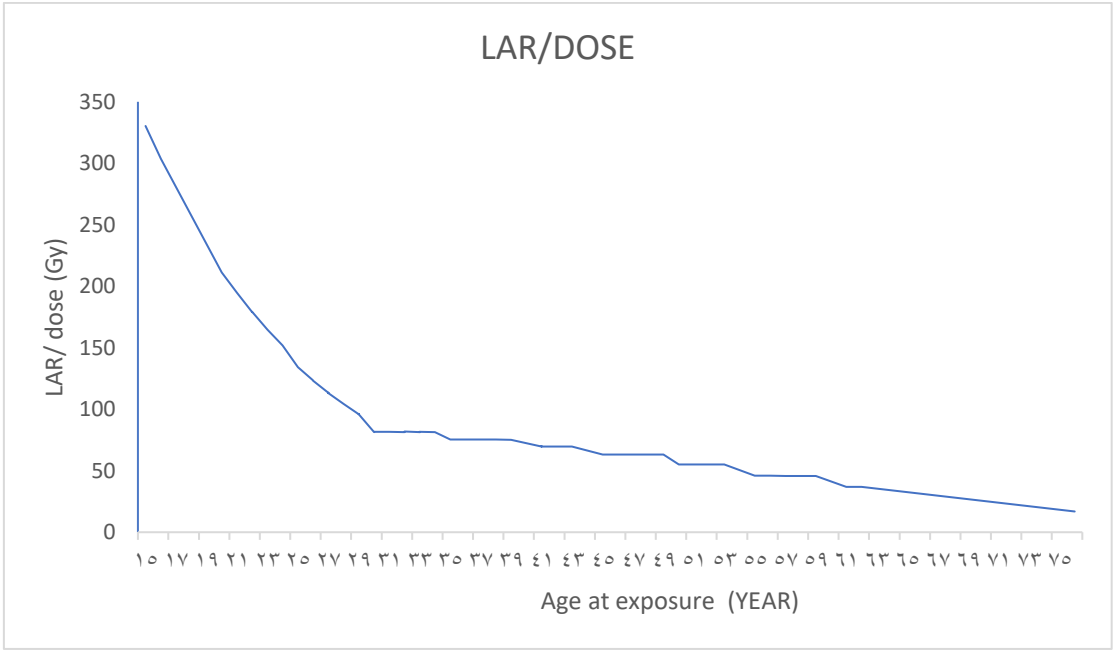

Figure 2: LAR/Gy vs age at exposure for all ages

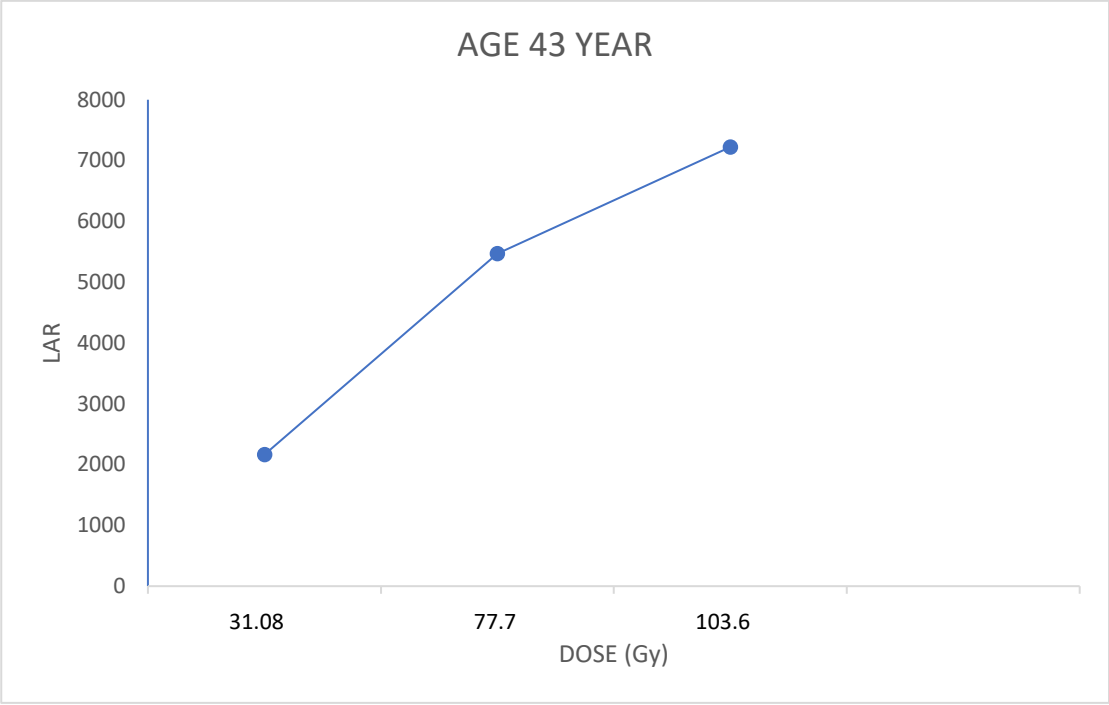

Figure 3: LAR vs radiation dose for middle aged patients

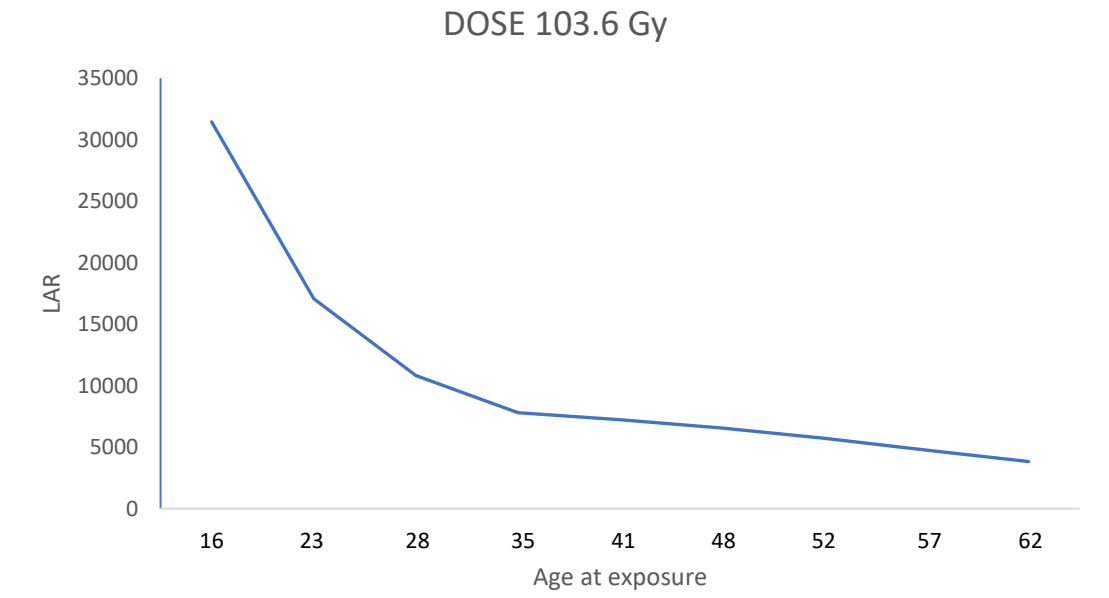

Figure 4: LAR vs age at exposure for fixed dose

For a given irradiation dose The LAR data show an inverse correlation with age at exposure with a kind of leveling off in the middle age (Figure 4). The fact that a higher

second thyroid cancer risk is observed amongst young patients is particularly due to longer residual life expectancy and various other aspects such as genetic predisposition, risk factor, etc. [80,81]. However, it should be noted that the decrease in LAR for people over the age of 50 is mostly owing to other risks – as people age, they have an ever-declining chance of living long enough to develop a radiation-induced cancer.

5. Conclusion

The late side effects of radiation therapy for tumors constitute a real challenge for decision makers in health care. Furthermore, it is clear from the results of this study that the dose of radiotherapy given to the patient directly affects the increase in the possibility of the emergence and formation of secondary cancers during the attained life of the patient after exposure to radiotherapy and her recovery from the primary injury. Saudi thyroid cancer female survivors have an increased risk of developing RISSC, particularly the younger age group (15 to 35 years old), when compared to the older age.

These findings may help provide the health service providers in the Kingdom of Saudi Arabia with valuable information on the impact of radioiodine-induced secondary thyroid cancer prevalence to develop a better surveillance strategy, as well as building a research bases on strategies to offset the risks of radiotherapy-associated secondary malignancies.

A healthy and balanced lifestyle after first cancer treatment (stopping smoking, reducing alcohol drinking, physical activities, healthy diet and weight loss) may be efficient in lowering the thyroid secondary cancer.

Ethics approval

We can confirm that this retrospective study involving patient diagnosed with thyroid cancer was approved by the Saudi National Committee on Bioethics (NCBE) in accordance with the ethical standards of the institutional and national research committee. Furthermore, informed consent obtained from each patient (or his/her legal representative) after being informed about the nature of research.

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الاستقراء للسرطان الثانوي: تقديرات المخاطر المتوقعة مدى الحياة بعد العلاج باليود المشع بين الناجيات من سرطان الغدة الدرقية في المملكة العربية السعودية

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المستخلص

يعتبر السرطان الصلب الثانوي الناجم عن الإشعاع (RISSC) أحد الآثار الجانبية المتأخرة الحرجة للعلاج الإشعاعي للسرطان الأول. آلية حدوث السرطان الثانوي غير معروفة بالكامل حتى الآن. ومع ذلك ، تساهم العديد من العناصر في نشوء السرطان الثانوي الناجم عن الاشعاع مثل العمر عند التعرض والجرعة الفعالة للعضو والأنسجة المحيطة وطرق العلاج والتاريخ العائلي للسرطان. الهدف من هذه الدراسة هو توفير توقعات طويلة الأجل لانتشار السرطان الثانوي بين الناجيات من سرطان الغدة الدرقية في المملكة العربية السعودية. تم تحديد الضرر طويل الأمد الناجم عن التعرض للإشعاع أو الخطر المتوقع مدى الحياة (LAR) من RISSC بعد العلاج الإشعاعي لسرطان الغدة الدرقية ، بين العمر عند التعرض وحتى ٩٠ عامًا ، في مجموعة من النساء الناجيات من السرطان اللائي تعرضن للعلاج. وكانت اعمارهن في حدود ١٥ إلى ٧٦ سنة. تختلف تقديرات المخاطر بشكل كبير مع تقدم العمر عند التعرض والجرعة الفعالة للأعضاء. تشير نتائج الدراسة بوضوح إلى وجود علاقة إيجابية مباشرة بين عمر المريض عند التعرض والتحريض على سرطان الغدة الدرقية الثانوي. تكون فرصة الإصابة بسرطان الغدة الدرقية الثاني بعد العلاج الإشعاعي أعلى عند أولئك الذين تعرضوا لها في سن الأطفال. علاوة على ذلك ، فإن جرعة الإشعاع تؤثر بشكل مباشر على ظهور السرطانات الثانوية.