El- Shanshoury H., / Vol. 06 / Issue 01/ 2018 / 1 – 7.

Research Article

Available Online at: www.ijphr.com
An African Edge Journal

International Journal of Pharmaceuticals and Health care Research

SJ Impact Factor – 5.546

ISSN: - 2306 – 6091

FOLLICULAR THYROID CARCINOMA: SECOND PRIMARY NEOPLASM IN PATIENT RECEIVED EXTERNAL BEAM RADIOTHERAPY FOR CONGENITAL RETINOBLASTOMA; A CASE STUDY

*El- Shanshoury H

Lecturer in Radiation Safety Department, Nuclear and Radiological Regulatory Authority, Cairo, Egypt. PhD, M.D in Laser Sciences (Department of Medical Applications of Laser), National Institute of Laser Sciences, Cairo University, Cairo, Egypt

Abstract

Background

Second primary neoplasms (SPNs) are a recognized late effect of treatment for childhood cancer. Thyroid SPNs can develop after exposure to low-dose radiation, due to the radio-sensitivity of the thyroid gland. The risk of radiotherapy-related secondary cancers in children with congenital retinoblastoma has led to reduced use of external beam radiotherapy (EBRT) as a treatment. Recently, tumor reduction with chemotherapy with or without focal surgery is most commonly undertaken and EBRT is avoided as much as possible and is considered only as the last treatment option prior to enucleation.

Case presentation

A 17 year old female patient was presented to our clinic with a painless mass in the neck of insidious onset and progressive course for two months duration. Subsequently she was diagnosed as having a thyroid swelling on the left lobe which is clinically a solitary nodule. The patient was running the routine laboratory investigations and Complete Blood Count which were all normal. Neck ultrasound examination, Color Doppler interrogation and Fine Needle Aspiration Cytology (FNAC) revealed follicular neoplasm.

The patient scheduled for surgical hemi-thyroidectomy of the left lobe. Histopathological examination was done revealing follicular carcinoma of the thyroid gland. By taking history from the patient family, the patient had got a past history of congenital retinoblastoma with external beam radiotherapy since she was six months.

Conclusion

This case study emphasizes that the high risk of second cancers in congenital retinoblastoma is significantly influenced by treatment. External beam radiotherapy has the strongest effect. Clinicians need to be particularly aware of the risks of low-dose exposure after radiation fields administered to areas adjacent to the thyroid region.

Keywords: Second primary Neoplasm; Childhood cancer; External beam radiotherapy; Congenital retinoblastoma.

Received on- 26.01.2018; Revised and accepted on- 03.02.2018; Available online- 10.02.2018

Author for Correspondence:
El- Shanshoury H
Email: hala.elshanshoury@yahoo.com

Introduction

Retinoblastoma is a childhood tumor with excellent survival rates in developed countries, but late effects are a major concern. Cumulative incidence ratios were significantly raised after external beam radiotherapy compared with patients who received enucleation or focal treatment. This impact of radiotherapy has been reported previously in large American, UK, and Dutch cohorts (1,2). Almost all children with bilateral retinoblastoma are heterozygous for an oncogenic alteration of the *RB1* gene (germline mutations). By contrast, oncogenic alterations of the *RB1* gene are confined to the tumor (somatic mutations) in most children with isolated unilateral retinoblastoma. As the risk of second primary malignancy (SPM) depends vastly on laterality and family history, it is to be expected that genetic factors influence the type and incidence of SPM in addition to treatment-related factors. In fact, in a recent study it was found that risk of SPM is higher in bilateral retinoblastoma survivors with a presumed inherited germline mutation compared to patients who had a germline mutation of de novo origin(3). In addition to the oncogenic *RB1* alteration, treatment intensity and modality carry a substantial impact on SPM development. External beam radiotherapy (EBRT) has been described as a major risk factor for later development of SPM (1).

External beam radiotherapy (EBRT), a modality of treatment used to control congenital retinoblastoma (RB), was found to save globes and vision. However, this modality carries the risk of developing secondary cancers in children and this may itself be a threat to the patient and mandate follow up for life (4). However, the use of EBRT was found to increase the lifelong risk of secondary cancers in children with constitutive RB1 mutations. It was also found to affect the growth of the soft tissue and bone around the eye. At present, radiotherapy is usually performed when all other treatments have failed or when tumors are large and cannot be controlled by focal surgery. Control of congenital retinoblastoma by saving vision and eye were well established goals regardless of whether RB is unilateral or bilateral. Focal surgical treatment, such as cryotherapy, thermotherapy, or laser therapy, can control the tumor, save vision, and preserve cosmesis when tumors are at an early stage (5). Alarmingly, the highest incidence rate of second cancers was found in the group of congenital retinoblastoma survivors with combined or metachronous chemotherapy and external beam radiotherapy. This finding is consistent with data from an American cohort of congenital retinoblastoma survivors when chemotherapy consisting of alkylating agents raised the risk to develop sarcoma in children who had been irradiated for treatment of retinoblastoma. The incidence of second cancer after chemotherapy without radiotherapy was low (6).

.

Childhood cancer survivors are at an increased risk of late effects of treatment, including the development of second primary neoplasms (SPNs) including thyroid cancer as the thyroid gland is a highly radiosensitive organ (7).Thyroid cancer has been frequently reported as a second primary neoplasm(SPN) after treatment for childhood cancers including Hodgkin's disease, neuroblastoma and other malignancies that involve radiation to the neck region (8-10).

This case study highlighted the relatively high risk of thyroid cancer in survivors of childhood cancer, particularly those treated at a young age, and its presentation early in the period of surveillance after completion of treatment. Clinicians need to be particularly aware of the risks of low-dose exposure after radiation fields administered to areas adjacent to the thyroid region.

Case Report

A 17 year old female patient was presented to our clinic with a painless mass in the neck of insidious onset and progressive course for two months duration. The patient gave a past history of congenital retinoblastoma with external beam radiotherapy since she was six months. Clinical examination revealed a thyroid swelling on the left lobe which is clinically a solitary nodule; not tender, around 3x4 cm, oval in shape, firm in consistency with no palpable lymph nodes over the neck, no displacement of the carotid pulses, and no recent change in the patient voice. The patient was running the routine laboratory investigations including hormonal profiles (T_3, T_4, free T_3, free T_4, and TSH) which were totally within normal limits. Complete Blood Count shows normal values too. Neck ultrasound examination revealed slightly enlarged the left thyroid lobe with a well-defined hypoechoeic focal mass lesion of about

17x23x25mm in diameters seen at its mid pole, with no calcifications or cystic changes. Color Doppler interrogation of the examined thyroid parenchyma revealed perinodular hyper vascularity apart from normal vascularity of the rest of the gland. No other nodules were noticed and the right lobe was normal. The patient performed Fine Needle Aspiration Cytology (FNAC) which revealed follicular neoplasm. Follicular neoplasm is a terminology that implies a possibility of either follicular adenoma or follicular carcinoma. The differentiation by FNAC is impossible and a tissue biopsy is a must. The patient scheduled for surgical hemi-thyroidectomy of the left lobe. A routine procedure was performed. Histopathological examination was done and the final diagnosis was established as follicular carcinoma of the thyroid gland fig. no. 01(11). Detailed history from the patient family as regard her retinoblastoma diagnosis was taken. She is the third in row child of the family to harbor the congenital retinoblastoma. She was diagnosed at age of 6 months and it was bilateral disease. The patient received vision preserved strategy. She is treated by chemotherapy(carboplatin, vincristine sulfate, and etoposide phosphate) as a primary mode of treatment in reducing tumor bulk, followed bylocal approaches treatment with external beam radiotherapy with radiation doses of 4000-4500 cGy used with 200 cGy fractions. She also received laser therapy to the eye that can be used for final tumor control with preservation of vision and eye. The patient lost follow up at age of 12 years because of psychological burden and anxiety.

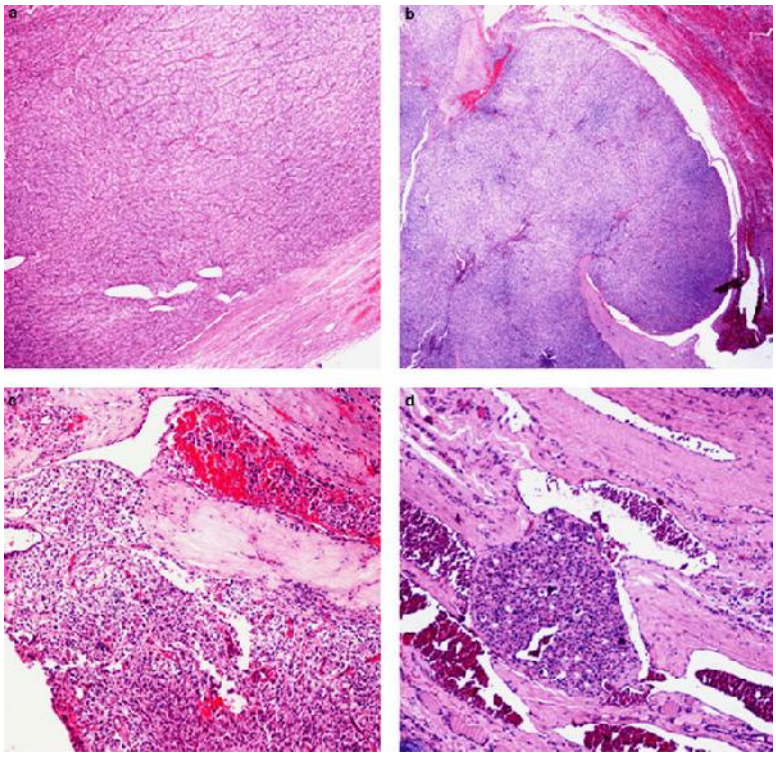

Fig. No. 01: *Histological appearance of a minimally invasive, angioinvasive, follicular thyroid carcinoma. (**a**) Microfollicular/solid pattern of growth of the neoplasia surrounded by a thick capsule (HE, × 4), (b) displaying, focally, capsular invasion (HE, × 4) and (**c** and **d**) vascular invasion (HE, × 100).*

Discussion

Second cancer occurrence is not limited to a specific age group and tumors may develop at various sites(12). Radiotherapy has been shown to increase risk for second cancers, particularly sarcomas within the radiation field, in several patient cohorts in the United States, United Kingdom, and the Netherlands(13-15).

Past studies of cancer incidence and mortality have revealed increased risks for secondary cancers in congenital RB patients, especially after radiotherapy. However, radiotherapy is still an important treatment option in patients with advanced intraocular stages and when there is a possibility of saving the eyeball and vision (16).

Reports from studies of survivors of the Chernobyl accident have reported a high risk of thyroid cancer in children as a consequence of exposure to low dose radiation (17-20). As a result thyroid carcinoma is a complication of irradiation even when the tissue lies outside the radiation field where the gland is exposed to scatter irradiation. The radio sensitivity of thyroid tissue coupled with the increased vulnerability of the pediatric gland accounts for the high incidence of thyroid carcinoma in childhood cancer survivor cohorts as well as children who were exposed to radioactive contamination after the Chernobyl nuclear accident in 1986 (17-20). Childhood cancer survivors who were under the age of 5 at the time of exposure to radiation therapy are reported to be at greatest risk and the risk remains comparatively higher for those under the age of 10 compared to older age groups (21).

Before 1960, external-beam energies were orthovoltage x-rays (35%). After 1960, energies were 22 to 23 MV betatron (34%), megavoltage photons (14%), and cobalt-60 (60Co) gamma rays (8%). Tumor doses to the affected eye ranged from 15 to 115 Gy (average, 48 Gy), with the highest doses delivered from orthovoltage external-beam radiation machines. Kleinerman etal lists the distribution of scatter radiation doses from orthovoltage and betatron external beam for a typical Rb treatment for a 1-year-old patient as shown in table no. 01 (1).

Table No. 01: Radiation Scatter Doses After a Typical Treatment for Retinoblastoma for *a 1-Year-Old Patient*

	Type of External-Beam Treatment	
Organ Site†	**Orthovoltage‡ Dose (Gy**	**Betatron§ Dose (Gy)**
Brain (average)	3.60	1.60
Pineal gland	4.00	1.40
Eye plus orbit Untreated side Treated side	 18.2 60.0	 34.5 45.0
Nasal region	34.0	3.20
Head and neck (soft tissue) Untreated side Treated side	 9.00 22.0	 5.50 11.0
Facial bones	27.5	8.00
Salivary glands¶	4.25	1.60
Thyroid (average left and right)	2.00	0.90
Breast (average left and right)	0.40	0.40
Upper trunk	0.60	0.45
Lung (average left and right)	0.45	0.40
Kidney (average left and right)	0.13	0.28
Stomach	0.18	0.36
Pancreas	0.16	0.33
Liver	0.16	0.24
Colon	0.10	0.25
Bladder	0.07	0.19
Uterus	0.08	0.20
Rectum	0.07	0.19
Total active bone marrow	1.20	1.00

Dose administered 50 Gy each to lateral and nasal field (4 cm _ 4 cm) for orthovoltage and 50 Gy to one lateral field for betatron.
†Organs listed in descending order of distance from the treated eye.
‡Half-value layer _ 1.9 mm Cu.
§23 MV photons.
¶Includes partotid, submaxillary, submandibular, and sublingual glands.

The traditional therapeutic dose of EBRT is 40–50 Gy; however, successful tumor control has been reported with doses less than 36 Gy (22). Patients treated with EBRT after cytoreduction with chemotherapy and repeated focal surgical therapies may be at greater risk for eye complications, while cytoreduction modalities may place patients at greater risks of vascular complications and drug toxicity (23). A lower dose of radiation may be considered when radiotherapy is used as a consolidation treatment followed by other treatment modalities. The rates of enucleation and therapeutic radiotherapy were reported to be significantly lower in patients treated with chemotherapy plus low-dose prophylactic planned EBRT than chemotherapy alone (24).

Children's Cancer and Leukaemia Group [CCLG—formally the United Kingdom Children's Cancer Study Group (UKCCSG)] guidelines in the United Kingdom recommend annual palpation of the thyroid gland if the survivor has been treated with radiation that includes the thyroid (neck, spine, mantle, mediastinum, total body irradiation). If the palpation is abnormal, then an ultrasound scan is recommended (25).

The US Children's Oncology Guidelines (COG) also recommend yearly thyroid palpation followed by ultrasound or fine needle aspiration if there is an abnormality. COG guidelines recommend that thyroid examination starts 5 years after treatment for childhood cancer, with high risk groups being those treated for childhood cancer at a young age, female sex, with radiation directly involving the thyroid area or total body irradiation, with the risk of thyroid cancer increasing to a maximum after treatment with radiation of 30 Gy and decreasing thereafter (26).

The use of EBRT to treat RB has decreased dramatically over the past four decades, more than for other types of pediatric cancer. According to the National Cancer Institute's Surveillance, Epidemiology, and End Results database of the nine original tumor registries (SEER-9), the use of EBRT for RB has declined from 30% of treatments in the period from 1973 to 1976 to 2% in the period from 2005 to 2008 (27).

Expert consensus recommends that radiotherapy is indicated when other means of saving the eye, such as chemotherapy and focal therapy, have failed. When radiotherapy is used, modern high-precision radiotherapy is recommended to minimize the dose to the orbital bones, and proton beam therapy (PBT) could be an excellent treatment option. PBT can be used in combination with chemotherapy as a local treatment modality, consolidating the effect of chemoreduction, or as salvage treatment after other therapeutic modalities. Depending on the location of the tumor within the eye, proton beam dosimetry can minimize the dose to the orbital bone. Careful selection of patients may contribute to high cure rates with good vision and good cosmesis without the need for long-term chemotherapy and may reduce chemotherapy- and radiotherapy-associated complications (28).

Due to the more frequent use of chemotherapy in the 1990s, the international classification of RB (ICRB) system was designed to better predict responses to chemotherapy. Although ICRB system is based on tumor size and location, it also classifies tumors by the presence or absence of subretinal and vitreous seeds, as well as by the extent of retinal involvement, indicated as the percentage of the total retinal area (7, 29).

Systemic chemoreduction has replaced radiotherapy as a vision-preserving therapy since 1996. However, there are plausible concerns that chemotherapeutic agents, especially topoisomerase inhibitors and alkylating agents may also induce second cancers. Combining radiotherapy with the alkylating agent triethylenemelamine was recently shown to raise the risk for bone tumors and leiomyosarcoma above the risk for radiotherapy alone in retinoblastoma survivors. The impact of systemic chemotherapy without radiotherapy on the incidence of second cancers in patients with congenital retinoblastoma remains less defined (30).

In recent decades, treatment recommendations and techniques have been changed specifically to reduce late effects, and the follow-up time is shortest for patients that received modern treatment. Thus, it is to be expected that incidence of second cancers will be lower in the future.

Conclusion

In an effort to avoid radiotherapy-related toxicity, including secondary malignancy, chemotherapy,

which was formerly used only for RBs with extraocular extension or systemic metastasis, is now regarded as a primary treatment modality, even in patients with locally advanced intraocular RB, to reduce tumor size prior to focal therapies. The use of EBRT in RB patients previously treated with multiple rounds of systemic and local chemotherapy, with or without focal surgery, may yield poorer treatment outcomes than its previous *de novo* use, as evaluated by cure and eye complication rates.

References

1. Kleinerman RA, TuckerMA, Tarone RE, et al. (2005): Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: An extended follow-up. *J Clin Oncol*.;23(10):2272–2279.
2. Marees T, Moll AC, Imhof SM, de Boer MR, Ringens PJ, van Leeuwen FE(2008): Risk of second malignancies in survivors of retinoblastoma: More than 40 years of follow-up. *J Natl Cancer Inst*; 100(24):1771– 1779.
3. Kleinerman RA, Yu CL, Little MP, Li Y, Abramson D, Seddon J, Tucker MA (2012): Variation of second cancer risk by family history of retinoblastoma among long-term survivors. J ClinOncol; 30:950–957.
4. Halperin EC, Constine LS, Tarbell NJ, Kun LE (2012): Pediatric Radiation Oncology. Philadelphia: Wolters Kluwer Health.
5. Abramson DH. Retinoblastoma: saving life with vision (2014): Annu Rev Med;65:171-84.
6. MacCarthy A, Bayne AM, Brownbill PA, et al. (2013): Second and subsequent tumours among 1927 retinoblastoma patients diagnosed in Britain 1951–2004. *Br J Cancer*; 108(12):2455–2463.
7. Wong JR, Morton LM, Tucker MA, et al. (2014): Risk of subsequent malignant neoplasms in long-term hereditary retinoblastoma survivors after chemotherapy and radiotherapy. *J ClinOncol*.;32(29):3284–3290.
8. Vathaire F,Hawkins M,Campbell S,Oberlin O,Raquin MA,Schlienger JY,Shamsaldin A,Diallo I,Bell J,Grimaud E,Hardiman C, Lagrange JL, et al (1999): Second malignant neoplasms after a first cancer in childhood: temporal pattern of risk according to type of treatment. Br J Cancer; 79: 1884–93.
9. Tucker MA,Jones PH,Boice JD,Jr,Robison LL,Stone BJ,Stovall M,Jenkin RD,Lubin JH,Baum ES,Siegel SE, Meadows AT, Hoover RN, et al (1991): Therapeutic radiation at a young age is linked to secondary thyroid cancer. The Late Effects Study Group. Cancer Res; 51: 2885–8.
10. AcharyaS, SarafoglouK, LaQuagliaM, LindsleyS, GeraldW, WollnerN, TanC,Sklar C (2003): Thyroid neoplasms after therapeutic radiation for malignancies during childhood or adolescence. Cancer; 97: 2397–403.
11. Jen-Der L and Tzu-Chieh C (2006): Follicular thyroid carcinoma: From diagnosis to treatment. *Endocrine Journal*, 53(4), 441-448.
12. Woo KI, Harbour JW (2010): Review of 676 second primary tumors in patients with retinoblastoma: Association between age at onset and tumor type. *Arch Ophthalmol*.; 128(7):865–870.
13. Abramson DH, Ellsworth RM, Kitchin FD, Tung G (1984): Second nonocular tumors in retinoblastoma survivors. Are they radiation-induced? *Ophthalmology*; 91(11):1351–1355.
14. Moll AC, Imhof SM, Schouten-Van Meeteren AY, Kuik DJ, Hofman P, Boers M (2001): Second primary tumors in hereditary retinoblastoma: A register-based study, 1945–1997: Is there an age effect on radiationrelated risk? *Ophthalmology*; 108(6):1109–1114.
15. Wong FL, Boice JD Jr, Abramson DH, et al. (1997): Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. JAMA 278: 1262- 1267.
16. Fontanesi J, Pratt CB, Hustu HO, Coffey D, Kun LE, Meyer D (1995): Use of irradiation for therapy of retinoblastoma in children more than 1 year old: the St. Jude Children's Research Hospital experience and review of literature. Med PediatrOncol;24:321-6.
17. Williams D (2008): Twenty years' experience with post-Chernobyl thyroid cancer. Best Pract Res ClinEndocrinolMetab;22:1061–73.
18. Davis S, Stepanenko V, Rivkind N, Kopecky KJ, Voillequ_e P, Shakhtarin V, Parshkov E, Kulikov S, Lushnikov E, Abrosimov A, Troshin V, Romanova G, et al (2004): Risk of thyroid cancer in the Bryansk Oblast of the Russian Federation after the Chernobyl Power Station accident. Radiat Res;162:241–8.

19. Boice JD, Jr (2005): Radiation-induced thyroid cancer–what's new? J Natl Cancer Inst;97:703–5; Review.
20. Boice JD, Jr (2006): Thyroid disease 60 years after Hiroshima and 20 years after Chernobyl. JAMA;295:1060–62.
21. Sigurdson AJ, Ronckers CM, Mertens AC, Stovall M, Smith SA, Liu Y, Berkow RL, Hammond S, Neglia JP, Meadows AT, Sklar CA, Robison LL, et al. (2005): Primary thyroid cancer after a first tumour in childhood (the Childhood Cancer Survivor Study): a nested case-control study. Lancet;365:2014–23.
22. Shields CL, Fulco EM, Arias JD, Alarcon C, Pellegrini M, Rishi P, et al. (2013): Retinoblastoma frontiers with intravenous, intra-arterial, periocular, and intravitreal chemotherapy. Eye (Lond);27:253-64.
23. Shields CL, Ramasubramanian A, Thangappan A, Hartzell K, Leahey A, Meadows AT, et al (2009):Chemoreduction for group E retinoblastoma: comparison of chemoreduction alone versus chemoreduction plus low-dose external radiotherapy in 76 eyes. Ophthalmology; 116: 544-51.
24. Jairam V, Roberts KB, Yu JB (2013): Historical trends in the use of radiation therapy for pediatric cancers: 1973-2008. Int J RadiatOncolBiolPhys; 85:e151-5.
25. United Kingdom Children's Cancer Study Group. Late effects group practice statement. Therapy based long term follow up (Thyroid). Second edition, 2005. Available at: http:/ /www.ukccsg.org/ public/ follow up/ Practie Statement/10.pdf. Accessed February 18, 2009.
26. Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Available at: http://www.survivorshipguidelines.org/pdf/LTFUGuidelines.pdf. Accessed February 18, 2009.
27. Canadian Retinoblastoma Society. National Retinoblastoma Strategy Canadian Guidelines for Care (2009): Stratégiethérapeutique du rétinoblastome guide cliniquecanadien. Can J Ophthalmol; 44 Suppl 2:S1-88.
28. Dimaras H, Kimani K, Dimba EA, Gronsdahl P, White A, Chan HS, et al.(2012): Retinoblastoma. Lancet; 379:1436-46.
29. Dimaras H, Dimba EA, Gallie BL (2010): Challenging the global retinoblastoma survival disparity through a collaborative research effort. Br J Ophthalmol; 94:1415-6.
30. Balmer A, Munier F, Zografos L (2003): Centenary of the first radiotherapy treatment of retinoblastoma (Hilgartner, 1903) [in French] J FrOphtalmol 26:1089–1096.

Indexed by - Scientific index, Research bible, Jour–Informatics, Google Scholar, Inno-space.org, Cosmos: Germany

Registered & Approved by:
ISSN International Centre, Bibliographic Data Section, 45 rue de Turbigo, 75003 Paris, France.