ORIGINAL ARTICLE

Estimating Radiotherapy-Induced Secondary Cancer Risk Arising from Brain Irradiation at High Energy: A Monte Carlo Study

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Abstract

Purpose: The present study aims to determine the whole-body out-of-field photon dose equivalents of high-energy conventional radiation therapy treatment. Also, it is tried to estimate the probability of fatal secondary cancer risk for the susceptible organs using a Monte Carlo (MC) code.

Materials and Methods: A Monte Carlo N-Particle eXtended (MCNPX)-based model of 18-MV Medical Linear Accelerator (LINAC) was created to calculate the out-of-field photon dose equivalent at the locations of fascinating organs in the mathematical female Medical Internal Radiation Dosimetry (MIRD) phantom. Then, the secondary malignancies risk was estimated based on out-of-field doses and radiation risk coefficients according to the National Council of Radiation Protection and Measurements (NCRP).

Results: The average photon equivalent dose in out-of-field organs was about 3.25 mSv/Gy, ranging from 0.23 to 37.2 mSv/Gy, respectively, for the organs far from the Planning Target Volume (PTV) (Rectum) and those close to the treatment field (Eyes). The entire secondary cancer risk for the 60 Gy prescribed dose to isocenter was obtained as 2.9987%. Here, the maximum risk among off-field organs was related to stomach (0.0805%), lung (0.0601%), and thyroid (0.0404%).

Conclusion: Regarding the estimated values for the probability of secondary cancer risk, it is suggested to perform a long-term follow-up of brain cancer patients regarding the prevalence of thyroid, stomach, and lung cancer after completing the treatment course.

Keywords: Brain Cancer; Radiotherapy; Peripheral Dose; Secondary Neoplasms; Monte Carlo.

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Frontiers in BIOMEDICAL TECHNOLOGIES

1. Introduction

The combination of surgery, radiotherapy, and chemotherapy is the standard treatment for malignant brain tumors [1, 2]. Radiotherapy increases the average survival time in patients with glioblastoma multiforme to 10-12 months, with a 3-year survival rate of 6-8% [3]. Radiation therapy is performed to deliver the total prescription dose to the target volume while sparing the critical structures. In this respect, the drawback of therapy outcome is peripheral radiation dose to healthy organs and tissues far away from the Planning Target Volume (PTV) [4]. Secondary dose chiefly arises from three sources: (a) leakage transmission radiation of Medical Linear Accelerator (LINAC) head, (b) scattered radiation spreads out of the collimator, and (c) scattered radiation with the patient. Although these three types are the main secondary radiation sources, leakage radiation has the least contribution for most clinically relevant treatment fields [5, 6].

Since secondary radiation dose to normal tissues may be associated with an increased risk of secondary malignancies [7-9], the long-term side effects of secondary radiation must be taken into account in treatment planning, especially when the patients live enough to manifest radiation-related adverse effects. Since risk estimation will be inevitably uncertain without accurate knowledge of the irradiated organs' absorbed dose [10], determining the out-of-field doses is a crucial prerequisite for risk estimation. Moreover, as the Treatment Planning System (TPS) underestimates out-of-field doses [11, 12], determining accurate peripheral doses requires applying other dose reconstruction methods, such as experimental measurements or Monte Carlo calculations. Measurements of out-of-field radiation dose to various critical organs have been reported for different brain radiation therapy methods. Most of these studies have focused on determining radiation dose to the specific head and neck nontarget structures outside the irradiated and target volume. However, according to the National Council of Radiation Protection (NCRP) [13], some organs at particular risk for fatal secondary malignancy were not intended in such studies. Besides, the risk of secondary cancer has not been comprehensively studied in the literature [14-18].

Majer *et al.* (2017) [14] reported the received dose by the brain, cranium, eyes, mandible, spine, thyroid, and clavicle in brain radiation. In another attempt, Foo *et al.* [15] tried to measure out-field organ dose, such as lenses, parotids, thyroid, and pituitary dose, by thermo-luminescence dosimeters. In a more comprehensive study, Taylor *et al.* [16] extended their investigation to the heart, lungs, kidneys, and gonads.

This research aimed to provide the pattern of secondary cancer risk using the whole-body dose distribution obtained from a simple simulation of brain treatment using mathematical phantom and modeled LINAC head.

2. Materials and Methods

The head of Varian Clinac 2100 C/D 18-MV, including target, a beryllium window, primary collimator, flattening filter, ion chamber, mirror, secondary collimator, jaws, and the upper circle, was simulated using MCNPX (2.6.0) code [19]. The geometry of the LINAC head was adapted from the manufacture available data and literature [20,21] (Table 1). Figure 1 presents the cross-section view of the model with details.

Table 1. The main parts of Varian 2100 CD 18-MV

Part	Material and Density (gr/cm^3)
Target	W: 19.30 Cu: 8.96
Primary Collimator	W: 19.30
Flattening Filter	Ta: 16.65 Fe: 7.86
Ion Chamber	Cu: 8.96 Kapton[a]: 1.42
Mirror	Al: 2.70 Mylar[b]: 1.39
Secondary Collimator	W: 19.30 Pb: 11.34
Jaw	W: 19.30
Upper Circle	Fe: 7.86

[a] 2.6% H, 69.1% C, 7.3% N and 21.0% O

[b] 4.2% H, 62.6 C and 33.2% O

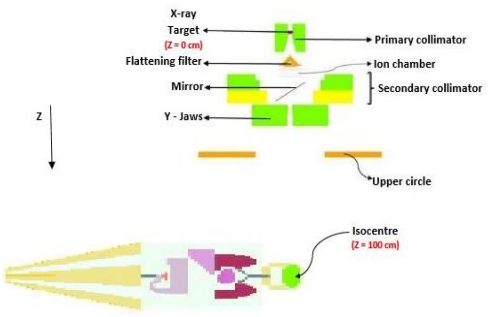

Figure 1. Geometrical model of Varian Clinac 2100 C/D 18-MV and mathematical MIRD Phantom simulated by MCNPX

The MC model used in this study had been precisely benchmarked with measured data by Chegeni *et al.* [21] and used for radiotherapy dose evaluation in several MC studies [21-23]. Briefly, Percentage Depth Dose (PDD) and dose profile for 4×4, 10×10, and 20×20 cm^2 field sizes were measured and calculated in a water phantom. Finally, the γ-index (3 mm, 3%) was used to compare measured and calculated dose distribution. Figure 2, which was extracted from Chegeni *et al.'s* study [21], confirms the above statements. The primary electron source model was characterized by a Gaussian energy spectrum centered at 18.3 MeV with an FWHM= 1.2 MeV and a Gaussian distribution in space with an FWHM = 0.14 cm. In this study, 1×10^9 electron histories were used for each simulation in forming valid confidence intervals calculations. Cross-section libraries of MCPLIB04 and EL03 were used for photon and electron transport calculations, respectively. The photon interactions include Rayleigh and Compton scattering, pair production, and the photoelectric effect. Elastic and inelastic collision, Bremsstrahlung, and annihilation interactions were considered for electron and positron. Further, the cut-off energy for photons and electrons was 0.01 and 0.7 MeV, respectively.

The absorbed dose of critical organs was calculated by applying the F6:E tally in the Medical Internal Radiation Dose (MIRD) [24] Phantom (Figure 1) under clinical conditions of brain tumor conventional radiation therapy. Accordingly, laterally opposed equally weighted beams under 5×5 cm^2 treatment fields were used to irradiate a piece of the brain as an imaginary tumor located in the midline. Finally, according to NCRP No.116 [13], the risk of induced second malignancy to interesting organs was estimated for the prescribed isocenter dose of 60 Gy. The total prescribed dose was chosen as the average of 15 previously treated patients with high-grade glioma.

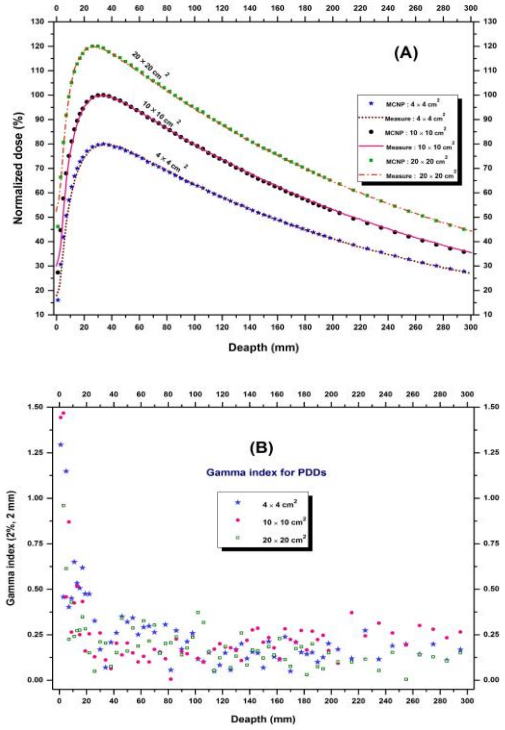

Figure 2. The credibility of the MC model used in this study (PDDs and profiles of the model benchmarked by Chegeni *et al.* [20])

3. Results

The secondary radiation dose values arising from brain radiation therapy for 27 out-of-field organs of a woman patient are summarized in Table 2 for 18-MV X-ray beams.

Table 2. Secondary doses (mSv per unit photon Gy delivered to isocenter) for midline brain radiation therapy (E= 18-MV)

Organ	Dose Equivalent (mSv/Gy)		
	Right lateral	Left lateral	Total
Brain	767.00	767.00	767.00
Cranium	229.00	228.00	228.50
Skin	10.20	10.20	10.20
Eye	36.70	37.80	37.20
Mandible and Teeth	14.50	14.60	14.55
Spine	1.77	1.79	1.78
Thyroid	8.18	8.67	8.42
Esophagus	1.20	1.37	1.28
Ribs	1.24	1.22	1.23
Thymus	0.69	0.65	0.67
Lungs	1.22	1.15	1.18
Heart	0.73	0.83	0.78
Breasts	0.98	0.97	0.98
Liver	1.77	0.73	1.25
Gall bladder	1.10	0.91	1.00
Spleen	0.69	1.88	1.28
Stomach	0.79	1.66	1.22
Pancreas	0.99	1.53	1.26
Adernals	0.41	0.40	0.40
Kidneys	0.97	1.00	0.98
Intestine	0.48	0.52	0.50
Colon	0.47	0.48	0.48
Pelvis	0.36	0.37	0.36
Ovaries	0.32	0.37	0.34
Uterus	0.33	0.32	0.32
Urinary bladder	0.26	0.29	0.27
Rectum	0.24	0.23	0.23
Reminder	354.00	354.00	354.00

These values are listed in the order of the distance from the primary field. All data were accepted if the R-value was less than 0.1 and all 10 statistical test results were satisfactory. The risk of secondary malignancies for the skin, stomach, liver, breast, ovary, urinary bladder, esophagus, lung, and thyroid was estimated using organ-specific risk coefficients (from NCRP 116 report) and reported in Table 3.

Table 3. The risk of second cancers based on organ's received dose during the high-energy brain radiotherapy (Risks are based on a prescribed dose to the target of 60 Gy)

Organ	Probability (%)
	18-MV
Skin	0.0122
Stomach	0.0805
Liver	0.0112
Breast	0.0117
Ovary	0.0020
Urinary bladder	0.0048
Esophagus	0.0230
Lung	0.0601
Thyroid	0.0404
Total	2.9987

4. Discussion

In this study, an adult MIRD phantom was simulated to out-of-field organ dose calculations, followed by estimating the risks of second radiation-related cancers. The MIRD phantom undergoing simulated brain radiation treatment by lateral opposed fields and high-dose photon beams were exposed to the tumor. Moreover, mediocre and low doses were exposed to neighboring tissues and the rest of the off-field body, respectively. As expected, organs such as the brain, cranium, and even skin near the PTV were partially inside the primary beam and received remarkably higher levels of radiation exposure than those situated far from the PTV. The average out-of-field organ dose was about 195 mGy.

Based on a study by Ruben *et al.* [25], out-of-field photon dose appears to be energy-independent for each treatment technique. Besides, Kry *et al.* [26] found the similarity of the secondary dose between high- and low-energy radiation treatments. Therefore, the results of the current study can be generalized to lower energies treatment with great confidence. In addition, Kry *et al.* concluded that the secondary photon doses differed considerably between the conventional and intensity-modulated radiation therapies. Consequently, the IMRT technique might raise or bate cancer risk for each organ than the conventional radiation therapy method applied in this research.

In [26], it was proven that the MC-calculated and measured doses were in good agreement. A few studies have focused on measuring the peripheral photon doses during brain irradiation. Foo *et al.* [15] measured secondary doses for three-field-vertexed (field size: 7×7 cm^2) left temporal lobe treatment with 6-MV X-rays. The thyroid dose was higher than reported by our study. This discrepancy may be due to using the vertex field in Foo *et al.'s* study. In a similar survey by Elmtalab and Abedi [27], the thyroid and lens doses in high-energy treatment were about 7 cGy and 46.5 cGy, respectively. Because of the more significant thyroid distance to the isocenter, the received dose was lower than our study's. Ahmadi *et al.* [28] evaluated 50 patients' thyroid radiation dose and reported that thyroid secondary radiation doses from whole-brain 6-MV 3D-CRT are 0.941 to 6.028 cGy. These results are in reasonably good agreement with the present research. Majer *et al.* [14] determined out-of-field organ dose in anthropomorphic pediatric (5 and 10 years old) phantoms, which received a brain 3D-CRT treatment, using radio photoluminescence and thermo-luminescent dosimeters. A pediatric phantom receives higher radiation doses than an adult one. Therefore, based on Majer *et al.* results, the likelihood of radiation-induced cancer was estimated significantly higher for children than for adults in the present research. Elmtalab *et al.* [29] reported the thyroid neutron dose equivalent of 12.3 mSv during brain 15-MV 3D-CRT, which is negligible compared to the photon dose received in the present study.

Although the results of the present study show that the dose of the organs is much less than the tolerance, secondary malignancies could happen (Table 2). The radiation-induced second cancer risk is highly organ dose-dependent. Gold *et al.* [30] showed that 14% of secondary cancers are outside the treatment volume. In another study, Diallo *et al.* [31] reported that 22% of secondary cancer occurred 5 cm away from the treatment field edge. According to Figure 3, the organs closer to the isocenter received a higher dose. Therefore, due to the

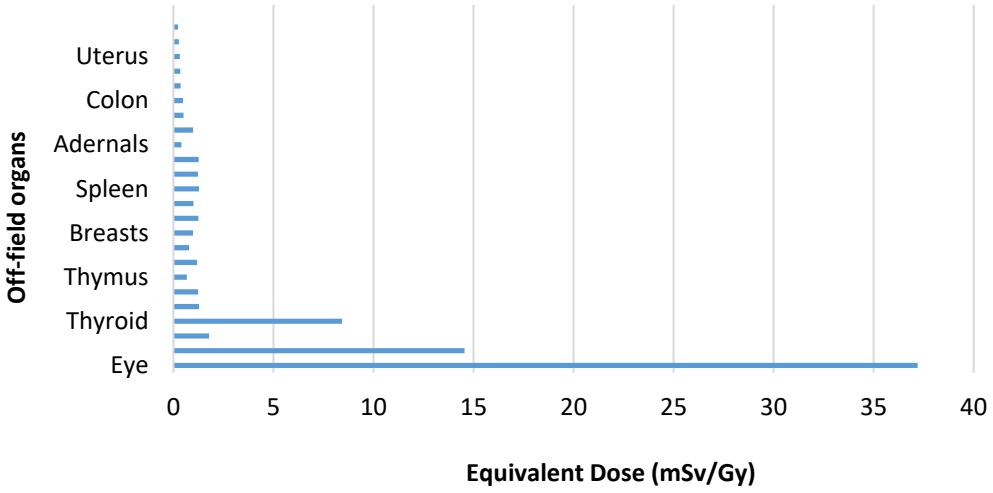

Figure 3. presents out-of-field dose distributions as a function of distance from the isocenter and dose reduction with increasing distance from the field edge (doses are shown for a target dose of 1Gy)

closer proximity of organs such as the thyroid, lungs, and stomach to the field edge, they are at increased risk of developing radiation-induced malignancies. Besides, there is less risk of malignancy in the ovary and urinary bladder located far from the treatment area.

Shore *et al.* (1992) [32] demonstrated that secondary malignancies could be caused by radiation even at doses as low as 10 cGy for thyroid treatment. Therefore, the received dose of thyroid and the risk of secondary cancer associated with it have already been mentioned in previous reports. The current study has found that the stomach and lungs were just as important as the thyroid during the brain tumor patients' follow-up. Therefore, it is necessary to pay more attention to these organs to alleviate the side effects of treatment.

The simulated lateral opposed fields used in this study may be combined with a vertex field in clinical conditions. The result is higher doses of the thyroid, which is due to the direction of radiation. Therefore, it is worthwhile investigating the risks of secondary cancer for different treatment plans in future research.

5. Conclusion

With the advancement in radiation oncology, cancer patients live long enough to experience the side effects of treatment. In this regard, follow-up data of the Cancer Survivor Study has shown that the incidence of radiation-induced malignancies was higher in brain tumor patients. Nevertheless, the quantifications of associated risk have not been comprehensive. The calculated risk values provided helpful information to identify susceptible organs to secondary cancer in this study. In patients undergoing brain radiation therapy, the stomach and lungs are at high risk for secondary cancer as the thyroid. Therefore, a careful long-term brain tumor survivors' follow-up regarding the development of thyroid, stomach, and lung cancer may be valuable for clinical radiation oncologists and epidemiologists. Furthermore, the measurement of whole-body scattered dose leads to improvements in shielding and dose optimization in radiation oncology.

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References

1- Juratli TA, Schackert G, Krex D "Current status of local therapy in malignant gliomas—a clinical review of three selected approaches.", *Pharmacol Ther*, 1;139(3):341-58, (2013).

2- NCCN Clinical Practice Guidelines in Oncology: Anaplastic Gliomas/Glioblastoma, (2018).

3- "Medical Research Council Brain Tumour Working Party Randomized trial of procarbazine, lomustine, and vincristine in the adjuvant treatment of high-grade astrocytoma: a Medical Research Council trial.", *J Clin Oncol*, 19(2):509-18, (2001).

4- Kry SF, Salehpour M, Followill DS, *et al.* "Out-of-field photon and neutron dose equivalents from step-and-shoot intensity-modulated radiation therapy." *Int J Radiat Oncol* Biol* Phys*, 62(4):1204-16, (2005).

5- Greene D, Chu GL, Thomas DW "Dose levels outside radiotherapy beams.", *The Br J Radiol*, 56(668):543-50, (1983).

6- Kase KR, Svensson GK, Wolbarst AB, et al. "Measurements of dose from secondary radiation outside a treatment field.", *Int J Radiat Oncol* Biol* Phys*, 9(8):1177-83, (1983).

7- Harrison RM "Introduction to dosimetry and risk estimation of second cancer induction following radiotherapy.", *Radiat Meas*, 57:1-8, (2013).

8- Newhauser WD and Durante M "Assessing the risk of second malignancies after modern radiotherapy.", *Nat Rev Cancer*, 11(6):438-48, (2011).

9- Hall EJ and Wuu CS "Radiation-induced second cancers: the impact of 3D-CRT and IMRT." *Int J Radiat Oncol* Biol* Phys*, 56(1):83-8, (2003).

10- Wang B and Xu XG, "Measurements of non-target organ doses using MOSFET dosemeters for selected IMRT and 3D CRT radiation treatment procedures.", *Radiat prot dosimetry*,128(3):336-42, (2008).

11- Howell RM, Scarboro SB, Kry SF, et al. "Accuracy of out-of-field dose calculations by a commercial treatment planning system." *Phys Med Biol*, 55(23):6999, (2010).

12- Kavousi N, Nedaie HA, Gholami S, Esfahani M, Geraily G. "Evaluation of dose calculation algorithms accuracy for eclipse, PCRT3D, and monaco treatment planning systems using IAEA TPS commissioning tests in a Heterogeneous Phantom.", *Iran J Med Phys*, 1;16(4):285-93, (2019).

13- Meinhold CB, Abrahamson S, Adelstein SJ, et al. "Limitation of exposure to ionizing radiation." *NCRP REP*, (116):1-86, (1993).

14- Majer M, Stolarczyk L, De Saint-Hubert M, et al. "Out-of-field dose measurements for 3D conformal and intensity-modulated radiotherapy of a paediatric brain tumour." *Radiat Prot dosimetry*, 176(3):331-40, (2017).

15- Foo ML, McCullough EC, Foote RL, et al. "Doses to radiation-sensitive organs and structures located outside the radiotherapeutic target volume for four treatment situations.", *Int J Radiat Oncol* Biol* Phys*, 27(2):403-17, (1993).

16- Taylor ML, Kron T, Franich RD "Assessment of out-of-field doses in radiotherapy of brain lesions in children.", *Inter J Radiat Oncol* Biol* Phys*, 79(3):927-33, (2011).

17- Di Betta E, Fariselli L, Bergantin A, Locatelli F, Del Vecchio A, Broggi S, Fumagalli ML. "Evaluation of the peripheral dose in stereotactic radiotherapy and radiosurgery treatments." *Med Phys*;37(7Part1):3587-94, (2010).

18- Miljanić S, Hršak H, Knežević Ž, Majer M, Heinrich Z. "Peripheral doses in children undergoing Gamma Knife radiosurgery and second cancer risk.", *Radiat Meas*, 1;55:38-42, (2013).

19- Hendricks, John S., et al. "MCNPX 2.6. 0 Extensions." *Los Alamos National Laboratory*, (2008).

20- Alem-Bezoubiri A, Bezoubiri F, Badreddine A, et al. "Monte Carlo estimation of photoneutrons spectra and dose equivalent around an 18 MV medical linear accelerator.", *Radiat Phys Chem*, 97:381-92, (2014).

21- Chegeni N, Karimi AH, Jabbari I, et al. "Photoneutron Dose Estimation in GRID Therapy Using an Anthropomorphic Phantom: A Monte Carlo Study." *JMSS*, 9(1):75, (2019).

22- Karimi AH, Brkić H, Shahbazi-Gahrouei D, et al. "Essential considerations for accurate evaluation of photoneutron contamination in radiotherapy.", *Appl Radiat Isot*, 145:24-31, (2019).

23- Karimi AH and Vega-Carrillo HR "Grid therapy vs. conventional radiotherapy–18 MV treatments: Photoneutron contamination along the maze of a linac bunker.", *Appl Radiat Isot*, 158:109064, (2020).

24- Han EY, Bolch WE, Eckerman KF "Revisions to the ORNL series of adult and pediatric computational phantoms for use with the MIRD schema." *Health Phys*, 90(4):337-356, (2006).

25- Ruben JD, Smith R, Lancaster CM, Haynes M, et al. "Constituent components of out-of-field scatter dose for 18-MV intensity-modulated radiation therapy versus 3-dimensional conformal radiation therapy: a comparison with 6-MV and implications for carcinogenesis.", *Int J Radiat Oncol* Biol* Phys*, 90(3):645-53, (2014).

26- Kry SF, Salehpour M, Titt U, et al. "Monte Carlo study shows no significant difference in second cancer risk between 6-and 18-MV intensity-modulated radiation therapy.", *Radiother Oncol*, 91(1):132-7, (2009).

27- Elmtalab S, Abedi I. "Investigating the out-of-field doses and estimating the risk of secondary thyroid cancer in high-grade gliomas radiation therapy with modulated intensity and 3D-conformal: a phantom study." *Int J Radiat Res*;19(3):569-74, (2021).

28- Ahmadi M, Tavakoli MB, Amouheidari A, et al. "Investigation of the absorbed dose and estimation of the risk of secondary thyroid cancer in whole-brain radiotherapy." *J Isfahan Med Sch*, 34(413):1590-1594, (2017).

29- Elmtalab S, Abedi I, Choopan-Dastjerdi M, et al. "Evaluation of the risk of secondary thyroid cancer caused by neutron dose equivalent from brain tumor 3D-conformal radiation therapy (3D-CRT)." *J Isfahan Med Sch*, 38(586):569-574, (2020).

30- Gold DG, Neglia JP, Potish RA, et al. "Second neoplasms following megavoltage radiation for pediatric tumors.", *Cancer*, 100(1):212-3, (2004).

31- Diallo I, Haddy N, Adjadj E, et al. "Frequency distribution of second solid cancer locations in relation to the irradiated volume among 115 patients treated for childhood cancer.", *Int J Radiat Oncol* Biol* Phys*, 74(3):876-83, (2009).

32- Shore RE "Issues and epidemiological evidence regarding radiation-induced thyroid cancer.", *Radiat Res*, 131(1):98-111, (1992).