

Gastrointestinal Side Effects of the Radioiodine Therapy for the Patients with Differentiated Thyroid Carcinoma Two Days after Prescription

Mehran Pashnehsaz¹, Abbas Takavar^{1,2}, Sina Izadyar³, Seyed Salman Zakariaee¹, Mahmoud Mahmoudi⁴, Reza Paydar⁵, Parham Geramifar²

¹Departments of Medical Physics and Biomedical Engineering, ³Nuclear Medicine and ⁴Statistical in Medicine, Tehran University of Medical Sciences, ²Nuclear Medicine, Research Institute for Nuclear Medicine, Shariati Hospital, ⁵Department of Radiation Sciences, Faculty of Allied Medicine, Iran University of Medical Sciences, Tehran, Iran

Abstract

Iodine-131 (I-131) therapy is one of the conventional approaches in the treatment of patients with differentiated thyroid carcinoma (DTC). The radioiodine agents also accumulate in the other organs that cause pain and damage to the patients. Radioiodine therapy is associated with various gastrointestinal (GI) toxicities. In this study, GI side effects of the radioiodine therapy were investigated. GI toxicities of the radioiodine therapy were studied in 137 patients with histologically proven DTC in Jun–Nov 2014. All the patients were treated by radioiodine agents in the research institute of Shariati Hospital, Tehran, Iran. The patients were examined 48 h after prescription (before discharge) and their GI side effects were registered. Correlation of the age, gender, administered dose, administered dose per body weight as the independent factors, and GI side effects were analyzed using the Pearson correlation test with Statistical Package for the Social Sciences (SPSS) version 20. Regression coefficients and linearity of the variable were investigated by MATLAB software. Line fitting was performed using MATLAB curve-fitting toolbox. From the subjects, 38 patients had GI complaints (30.4%). Significant factors influencing GI side effects were dose per body weight and administered doses. There was no significant correlation between age and gender as the independent parameters and GI complaints. The most prevalent GI side effect was nausea that occurs in 26.4% of the patients. From the results, it could be concluded that the GI side effects could be prevented by administering a safe radioiodine dose value less than 5,550 MBq.

Keywords: Gastrointestinal (GI) side effects, radioiodine therapy, short-term side effects, thyroid cancer

Introduction

Iodine-131 (I-131) therapy is one of the conventional therapeutic approaches in the treatment of patients with differentiated thyroid carcinoma (DTC). I-131 eliminates the residual tumor cells after surgery and prevents cancer from returning.^[1] This therapeutic method also can be

effective for distant metastases.^[2-6] In I-131 decay chart, 84% of the emitted rays are beta and the remaining rays are gamma. The mean energy of the gamma and beta rays are 364 keV and 192 keV, respectively.^[7]

Radioiodine agent is commonly administered by the oral route and excreted by the renal system.^[8] The International Commission on Radiological Protection (ICRP) recommended a biokinetic model for the iodine distribution in the human body that was divided into five

Address for correspondence:

Dr. Sina Izadyar,
Department of Nuclear Medicine, Faculty of Medicine, Tehran
University of Medical Sciences, Tehran, Iran.
E-mail: sizadyar@yahoo.com

Access this article online

Quick Response Code:



Website:
www.wjnm.org

DOI:
10.4103/1450-1147.174703

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Pashnehsaz M, Takavar A, Izadyar S, Zakariaee SS, Mahmoudi M, Paydar R, *et al.* Gastrointestinal side effects of the radioiodine therapy for the patients with differentiated thyroid carcinoma two days after prescription. *World J Nucl Med* 2016;15:173-8.

compartments.^[9] the recommended model of the iodine distribution in the human body is shown in Figure 1. After administration of radioiodine, initially I-131 was accumulated in the stomach. Then it was absorbed by the body fluids and reached to the thyroid tissue. In hyperthyroidism treatments, I-131 is mostly uptake by thyroid cells, and it causes the destruction of thyroid cells by beta particles.^[10-12]

The physical half-life of I-131 is approximately 8.01 h^[7] but its biological half-life is variable. The biological half-life of the I-131 depends on many factors such as age,^[13,14] gender, weight, blood thyroid stimulating hormone (TSH) [recombinant human (rhTSH)], thyroid tissue remaining after surgery, metabolic factors, and metastasis.^[15-17] The effective half-life of the I-131 could be calculated by its physical and biological half-lives. The mean value of the effective half-life for I-131 is ranged from 14 to 16 h.^[15-17]

I-131 is commonly employed for thyrotoxicosis and thyroid cancer treatments. Administered radioiodine agent for hyperthyroidism is ordinary less than 1,000 MBq.^[10-12] Higher magnitudes of the I-131 (more than 3,000 MBq) could be utilized for treating the large volume of thyroid.^[10-12] For thyroid cancer treatment, the initial prescribed dose is about 3,000 MBq and this value increased to 8,000 MBq for the treatment of metastases.^[10-12]

The radioiodine agents also accumulate in other organs, such as stomach, salivary glands, and bladder, which cause pain and damage to the patients. Different types of the gastrointestinal (GI) toxicity are classified in the report of the common terminology criteria for adverse events (CTCAE) v 3.0. Radioiodine therapy is associated with various GI toxicities including GI complaints, salivary gland swelling with pain, change in taste, and headache

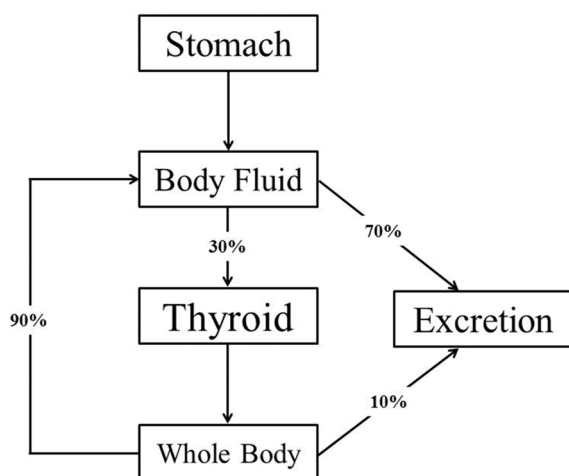


Figure 1: Biokinetic model for the iodine distribution in a standard healthy man. The model was recommended by ICRP-30

that have been listed in grade 1 of the GI side effects.^[18,19] Grade 1 included negligible clinical consequence of GI side effects such as nausea, diarrhea, and vomiting.^[20] Iodine therapy might cause long-term effects such as secondary solid tumors,^[21] leukemia,^[22,23] adverse effects on fertility and reproduction^[24-28] and etc.^[8,29]

In this study, GI side effects of the radioiodine therapy including nausea, heartburn, diarrhea, and vomiting were investigated for different iodine doses. Threshold dose for radioiodine agent to prevent these GI side effects was studied and the correlation of the effective factors (such as gender and age) with observed side effects were evaluated.

Materials and Methods

Patients and protocols

In this study, 137 patients with histologically proven DTC were studied in Jun–Nov 2014. All the patients were treated by radioiodine agents in the research institute of Shariati Hospital, Tehran, Iran. The patients were examined and their basic information such as gender, age, weight, smoking history, and history of GI diseases were registered. For each patient, a proper radioiodine dose was determined by the physician. The patients were quarantined 2 days after the I-131 administration. They were examined 48 h after the prescription (before discharge), and their GI side effects were registered.

Twelve patients were excluded from the study due to their history of GI disease. Fifteen patients were smokers (11 men and 4 women). The patient's age was 44.94 ± 14.92 years (mean \pm standard deviation, range 18–86 years). Only 23 patients were men and 81.6% of the patients were women. The ages of the men ranged 30–78 years with the mean age of 52.22 ± 13.20 years (mean \pm standard deviation). The ages of the women ranged 18–86 years with the mean age of 43.29 ± 14.86 years (mean \pm standard deviation).

Single treatment was used for 84 patients and 42 patients were treated by combined treatments (two or more therapy methods).

Statistical analysis

Correlation of the independent factors, such as age, gender, administered dose (MBq), and administered dose per body weight (MBq/kg), and GI side effects were analyzed using the Pearson correlation test with Statistical Package for the Social Sciences (SPSS) version 20 (SPSS Inc, Chicago, USA). The correlation analysis measures the relationship between two parameters such as the frequency of GI

side effects and the administered dose. The correlation coefficients indicate how the change in the independent parameter (i.e., administered dose) could change the dependent parameter (i.e., GI side effects). The correlation coefficient ranged from -1.0 to + 1.0.

The regression coefficients and linearity of the variable were investigated by MATLAB software (ver. 2012a, The MathWorks TM, Natick, Massachusetts, USA). Line fitting was performed using MATLAB curve-fitting toolbox.

In this study, the GI side effects of the 3,700 MBq, 4,625 MBq, 5,550 MBq, 6,475 MBq, and 7,400 MBq radioiodine doses were investigated. Studied GI side effects include nausea, heartburn, diarrhea, and vomiting.

Results and Discussion

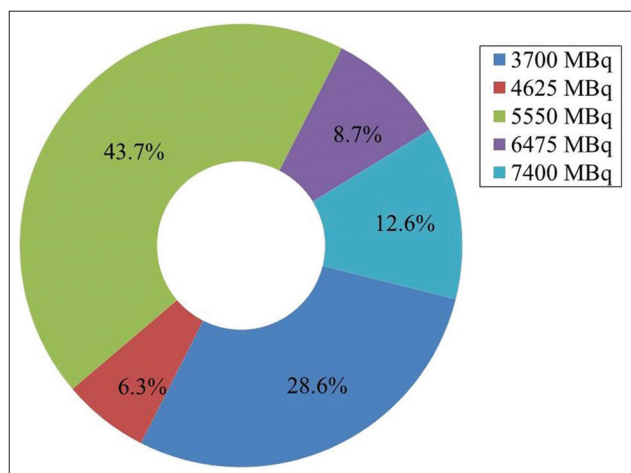
The prescribed iodine doses of 3,700 MBq, 4,625 MBq, 5,550 MBq, 6,475 MBq, and 7,400 MBq were administered to 36 (31 women and 5 men), 7 (6 women and 1 men), 55 (44 women and 11 men), 11 (6 women and 5 men), and 16 (15 women and 1 men) patients, respectively. For each administered dose, the percentage of the number of patients is shown in Graph 1.

Out of all the subjects, 38 patients had GI complaints (30.4%). And out of these 38 patients, 8, 2, 18, 5, and 5 patients were given 3,700 MBq, 4,625 MBq, 5,550 MBq, 6,475 MBq, and 7,400 MBq iodine doses, respectively. For each administered dose, the frequency of the GI complaints is shown in Graph 2. Frequency of the GI side effects increased smoothly in the range of 3,700–6,475 MBq iodine doses. GI complaints decrease in 7,400 MBq iodine dose that was opposed to the expectations. It could be attributed to the type of metastases and their responses to the 7,400 MBq iodine dose. In patients with prescribed

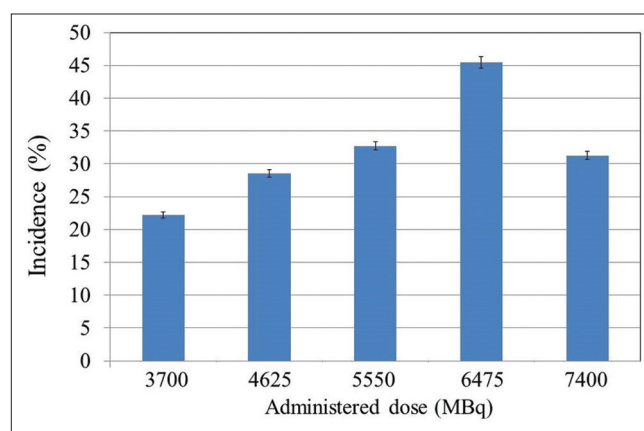
7,400 MBq doses, variety of distant metastases of different sizes and types exist (than patients with lower doses). For correlation analysis between administered I-131 doses and GI side effects, Pearson correlation was 0.173. There was a weak correlation between gender and GI complaints. The patients with 7,400 MBq iodine doses were excluded from the sample population, as a result the Pearson correlation reached to 0.210 that is significant at the 0.05 level ($P < 0.05$). Frequencies of the GI side effects for administered iodine doses were listed in Table 1. Percentage of different GI side effects for observed GI complaints were listed in Table 2. The sum of the percentage values in Table 2 was larger than 100% because there was more than one symptom in some patients. For some patients, all GI side effects were registered. The most prevalent GI side effect was nausea that occurs in 26.4% (33 patients) of the patients. Nausea was registered in 86.84% of the observed GI side effects.

The linearity of the GI toxicities versus the increased dose of I-131 was investigated for the sample population with and without the patients with 7,400 MBq iodine dose. Frequencies of the GI side effects versus administered doses were plotted by MATLAB curve-fitting. A linear line was fitted to these points using MATLAB software. The results of the line fittings based on the linear model (for sample population with and without of patients with 7,400 MBq iodine dose) are shown in Graph 3. The regression value and indication parameters of the fitted lines are listed in Table 3. The better line could be achieved using the power function model. The fitted lines based on the power function model (for sample population with and without the patients with 7,400 MBq iodine dose) are shown in Graph 4. The regression value and indication parameters of the power function models are listed in Table 4.

For both of fitting models, higher regression values were obtained by excluding the patients with 7,400 MBq iodine doses. By excluding the patients with 7,400 MBq



Graph 1: The percentage of the number of patients in each administered dose



Graph 2: The frequency of the observed symptoms for administered doses

Table 1: Frequency of the observed GI toxicity for administered iodine doses

| Gastrointestinal symptoms | Number of patients in each administered dose | | | | | Number of incident symptoms | Percentage of the incident symptoms (%) |
|---------------------------|--|-----------|-----------|-----------|-----------|-----------------------------|---|
| | 3,700 MBq | 4,625 MBq | 5,550 MBq | 6,475 MBq | 7,400 MBq | | |
| Heartburn | 6 | 1 | 5 | 1 | 4 | 17 | 13.6 |
| Nausea | 5 | 2 | 16 | 5 | 5 | 33 | 26.4 |
| Diarrhea | 2 | 0 | 3 | 0 | 2 | 7 | 5.6 |
| Vomiting | 1 | 0 | 0 | 0 | 1 | 2 | 1.6 |

Table 2: Frequency of the heartburn, nausea, diarrhea, and vomiting in the gastrointestinal complaints

| Gastrointestinal symptoms | Ratio of the observed symptoms (%) |
|---------------------------|------------------------------------|
| Heartburn | 44.74 |
| Nausea | 86.84 |
| Diarrhea | 18.42 |
| Vomiting | 5.26 |

Table 3: Regression value and indication parameters of the fitted lines in the linear model

| | Equation | R |
|---|-------------------------|---------|
| The sample population including the patients with 7,400 MBq iodine dose | $Y=0.0037772(X)+11.082$ | 0.64939 |
| The sample population excluding the patients with 7,400 MBq iodine dose | $Y=0.0079841(X)-8.3752$ | 0.97196 |

Table 4: Regression value and indication parameters of the fitted lines in the power function model

| | Equation | R |
|---|-----------------------------------|---------|
| The sample population including the patients with 7,400 MBq iodine dose | $Y=0.025575(X+1227.7)^{0.80876}$ | 0.69274 |
| The sample population excluding the patients with 7,400 MBq iodine dose | $Y=3.0432E-10(X+5556.1)^{2.7353}$ | 0.98275 |

iodine doses, the frequencies of the GI side effects were increased linearly with the increase in iodine dose.

The frequencies of the GI toxicities in different dose per body weight (MBq/kg) are shown in Graph 5. For correlation analysis between administered dose per body weight (MBq/kg) and GI side effects, Pearson correlation was 0.147. There was a weak significant correlation between administered dose per body weight (MBq/kg) and GI complaints. The patients with 7,400 MBq iodine doses were excluded from the sample population, as a result the Pearson correlation reached to 0.189 that is significant at the 0.05 level ($P < 0.05$). The frequency of the GI toxicities did not change linearly versus dose per body weight.

For correlation analysis between gender and GI side effects, Pearson correlation was 0.144. There was a weak correlation between gender and GI complaints. The correlation of the age and GI complaints were also studied. For this analysis, age was divided into eight groups. The

results of this correlation analysis are shown in Graph 6. For correlation analysis between gender and GI side effects, Pearson correlation was -0.117. There was a weak negative correlation between age and GI complaints.

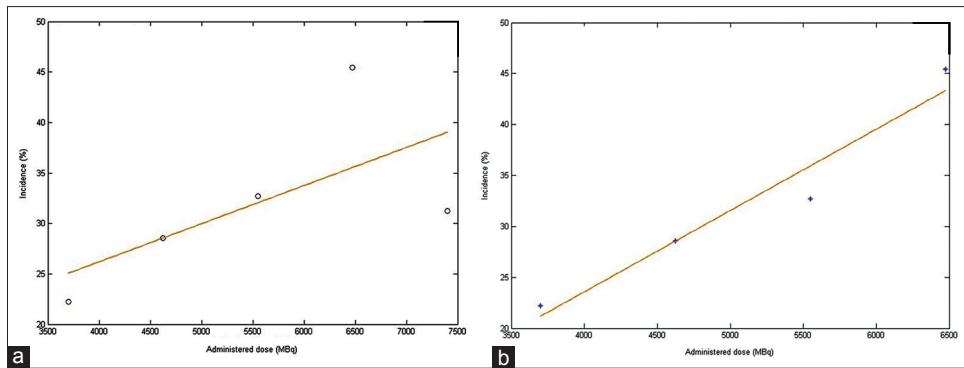
In the study by Kita *et al.*, 71 patients with differentiated carcinoma were studied to evaluate the short-term side effects occurring within 96 h after radioiodine-131 therapy for DTC. In this study, GI complaints, salivary gland swelling with pain, change in taste, and headache were observed in 65.2%, 50%, 9.8%, and 4.4% of the patients, respectively. They reported that in GI complaints, frequency of appetite loss, nausea, and vomiting were 60.9%, 40.2%, and 7.6%, respectively. They concluded that TSH values and dose per body weight are the most significant factors in the incidence of GI complaints.^[19]

In the study by Van Nostrand *et al.*, side effects of rational dose I-131 therapy for metastatic well-differentiated thyroid carcinoma were investigated in 15 patients. In this study, the incidence of immediate side effects, short-term GI, and salivary complaints were 80%, 66.67%, and 60%, respectively. For intermediate side effects, the incidence rates of GI and salivary complaints were 0% and 20%, respectively.^[18]

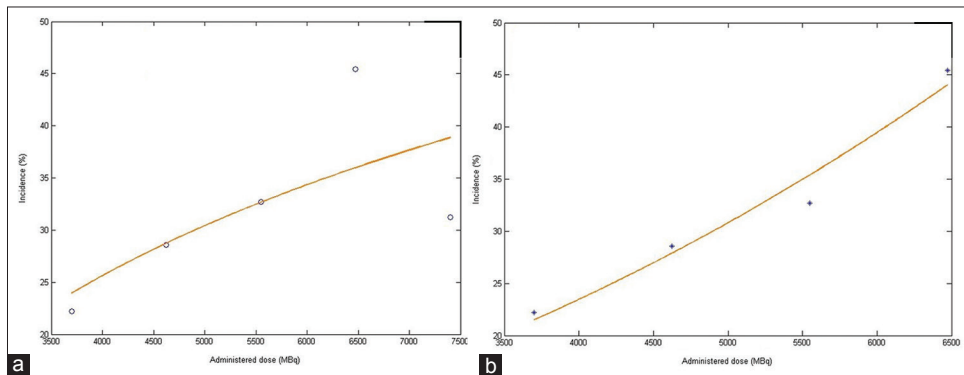
In Alexander's study, intermediate and long-term side effects in 203 patients after high-dose radioiodine treatment due to DTC were evaluated. They reported that the frequency of intermediate side effects (taste changes and sialadenitis) increase with the increase in dose (or cumulative activity).^[29] They also reported that there was no correlation between administered doses and transient alopecia. Transient alopecia was observed in 28.1% of the patients with at least 3,700 MBq iodine dose. Transient thrombocytopenia and leukopenia were also reported after I-131 administration.^[29-31] The obtained percentages of the GI side effects were in fair agreement with other studies.^[18,19,29]

Conclusion

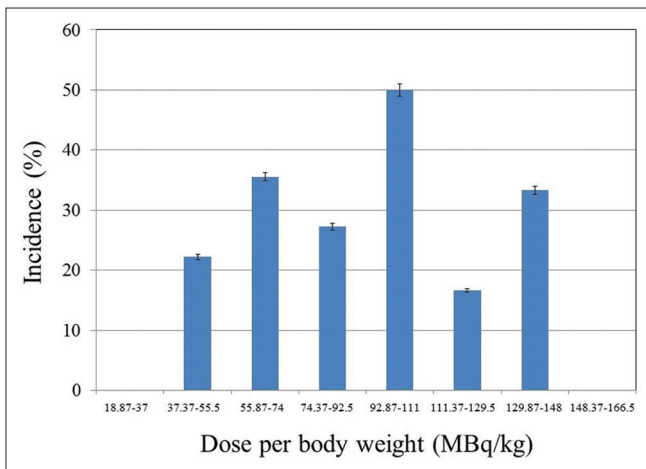
In this study, the GI side effects of the different radioiodine doses were investigated. A significant correlation was found between the administration



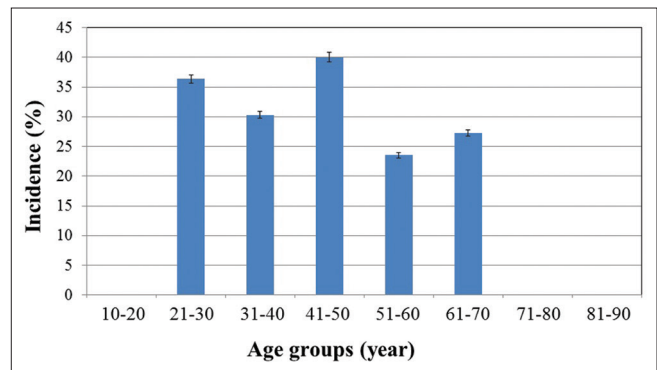
Graph 3: Fitted lines based on the linear model. (a) The sample population including the patients with 7,400 MBq iodine doses. (b) The sample population excluding the patients with 7,400 MBq iodine doses



Graph 4: Fitted lines based on the power function model. (a) The sample population including the patients with 7,400 MBq iodine doses. (b) The sample population excluding the patients with 7,400 MBq iodine doses



Graph 5: The frequency of GI side effects versus doses per body weights (MBq/kg)



Graph 6: The frequency of GI side effects in each age group

doses and administered dose per body weight (MBq/kg) as the independent parameters and GI complaints. Significant factors influencing GI side effects were dose per body weight and administered doses. There was no significant correlation between age and gender as the independent parameters and GI complaints. The most prevalent GI side effect was nausea that occurs

in 26.4% (33 patients) of the patients. From the results, it could be concluded that the GI side effects could be prevented by administering a safe radioiodine dose value less than 5,550 MBq.

Financial support and sponsorship

Research affairs of the Tehran University of Medical Sciences.

Conflicts of interest

There are no conflicts of interest.

References

- Baskin HJ, Cobin RH, Duick DS, Gharib H, Guttler RB, Kaplan MM, *et al.*; American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. *Endocr Pract* 2002;8:457-69.
- Samaan NA, Schultz PN, Hickey RC, Goepfert H, Haynie TP, Johnston DA, *et al.* The results of various modalities of treatment of well differentiated thyroid carcinomas: A retrospective review of 1599 patients. *J Clin Endocrinol Metab* 1992;75:714-20.
- DeGroot LJ, Kaplan EL, McCormick M, Straus FH. Natural history, treatment, and course of papillary thyroid carcinoma. *J Clin Endocrinol Metab* 1990;71:414-24.
- Chow SM, Law SC, Mendenhall WM, Au SK, Chan PT, Leung TW, *et al.* Papillary thyroid carcinoma: Prognostic factors and the role of radioiodine and external radiotherapy. *Int J Radiat Oncol Biol Phys* 2002;52:784-95.
- Chow SM, Law SC, Mendenhall WM, Au SK, Yau S, Yuen KT, *et al.* Follicular thyroid carcinoma: Prognostic factors and the role of radioiodine. *Cancer* 2002;95:488-98.
- Taylor T, Specker B, Robbins J, Sperling M, Ho M, Ain K, *et al.* Outcome after treatment of high-risk papillary and non-Hurthle-cell follicular thyroid carcinoma. *Ann Intern Med* 1998;129:622-7.
- Lyra M, Andreou M, Georgantzoglou A, Kordolaimi S, Lagopati N, Ploussi A, *et al.* Nuclear Medicine Therapy -Radioisotopes Production and Dosimetry. Available from: http://www.medimaging.gr/tutorials/booklet%20Radionuclide_therapy.pdf. [Last accessed on 2015 Aug 12].
- Chow SM. Side effects of high-dose radioactive iodine for ablation or treatment of differentiated thyroid carcinoma. *J HK Coll Radiol* 2005;8:127-35.
- de Klerk JM, de Keizer B, Zelissen PM, Lips CJ, Koppeschaar H. Fixed dosage of 131I for remnant ablation in patients with differentiated thyroid carcinoma without pre-ablative diagnostic 131I scintigraphy. *Nucl Med Commun* 2000;21:529-32.
- Directorate General Environmental, Nuclear Safety and Civil Protection. European Commission: Radiation Protection 97, Radiation Protection Following Iodine 131 Therapy (Exposures due to Out Patients or Discharged in Patients). Geneva; 1998. Available from: https://ec.europa.eu/energy/sites/ener/files/documents/097_en.pdf. [Last accessed on 2015 Aug 12].
- International Commission on Radiological Protection (ICRP 60), Recommendations of the International Commission on Radiological Protection. *Annals of the ICRP* 21 (1-3). Oxford: Pergamon Press; 1991.
- Rosário PW, Reis JS, Barroso AL, Rezende LL, Padrão EL, Fagundes TA. Efficacy of low and high 131I doses for thyroid remnant ablation in patients with differentiated thyroid carcinoma based on post-operative cervical uptake. *Nucl Med Commun* 2004;25:1077-81.
- Dant JT, Richardson RB, Nie LH. Monte Carlo simulation of age-dependent radiation dose from alpha-and beta-emitting radionuclides to critical trabecular bone and bone marrow targets. *Phys Med Biol* 2013;58:3301-19.
- Cristy M, Eckerman KF. Specific absorbed fractions of energy at various ages from internal photon sources. Health and Safety Research Division: ORNL/TM-8381/V1. Available from: <http://crpk.ornl.gov/documents/tm8381v1.pdf>. [Last accessed on 2015 Aug 12].
- Remy H, Borget I, Leboulleux S, Guilabert N, Lavielle F, Garsi J, *et al.* 131I effective half-life and dosimetry in thyroid cancer patients. *J Nucl Med* 2008;49:1445-50.
- Menzel C, Kranert WT, Döbert N, Diehl M, Fietz T, Hamscho N, *et al.* rhTSH stimulation before radioiodine therapy in thyroid cancer reduces the effective half-life of (131) I. *J Nucl Med* 2003;44:1065-8.
- North DL, Shearer DR, Hennessey JV, Donovan GL. Effective half-life of 131I in thyroid cancer patients. *Health Phys* 2001;81:325-9.
- Van Nostrand D, Neutze J, Atkins F. Side effects of "rational dose" iodine-131 therapy for metastatic well-differentiated thyroid carcinoma. *J Nucl Med* 1986;27:1519-27.
- Kita T, Yokoyama K, Higuchi T, Kinuya S, Taki J, Nakajima K, *et al.* Multifactorial analysis on the short-term side effects occurring within 96 hour after radioiodine-131 therapy for differentiated thyroid carcinoma. *Ann Nucl Med* 2004;18:345-9.
- Kavanagh BD, Pan CC, Dawson LA, Das SK, Li XA, Ten Haken RK, *et al.* Radiation dose-volume effects in the stomach and small bowel. *Int J Radiat Oncol Biol Phys* 2010;76(Suppl):S101-7.
- Rubino C, De Vathaire F, Dottorini ME, Hall P, Schwartz C, Couette JE, *et al.* Second primary malignancies in thyroid cancer patients. *Br J Cancer* 2003;89:1638-44.
- Shimon I, Kneller A, Olchovsky D. Chronic myeloid leukaemia following 131I treatment for thyroid carcinoma: A report of two cases and review of the literature. *Clin Endocrinol (Oxf)* 1995;43:651-4.
- Jokic VS, Kocovska MZ. New technique for effective dose estimation using Monte Carlo simulation for the patients undergoing radioiodine therapy. *Measurement* 2013;46:795-802.
- Dottorini ME, Lomuscio G, Mazzucchelli L, Vignati A, Colombo L. Assessment of female fertility and carcinogenesis after iodine-131 therapy for differentiated thyroid carcinoma. *J Nucl Med* 1995;36:21-7.
- Vini L, Hyer S, Al-Saadi A, Pratt B, Harmer C. Prognosis for fertility and ovarian function after treatment with radioiodine for thyroid cancer. *Postgrad Med J* 2002;78:92-3.
- Smith MB, Xue H, Takahashi H, Cangir A, Andrassy RJ. Iodine 131 thyroid ablation in female children and adolescents: Long-term risk of infertility and birth defects. *Ann Surg Oncol* 1994;1:128-31.
- Sarkar SD, Beierwaltes WH, Gill SP, Cowley BJ. Subsequent fertility and birth histories of children and adolescents treated with 131I for thyroid cancer. *J Nucl Med* 1976;17:460-4.
- Hyer S, Vini L, O'Connell M, Pratt B, Harmer C. Testicular dose and fertility in men following I (131) therapy for thyroid cancer. *Clin Endocrinol (Oxf)* 2002;56:755-8.
- Alexander C, Bader JB, Schaefer A, Finke C, Kirsch CM. Intermediate and long-term side effects of high-dose radioiodine therapy for thyroid carcinoma. *J Nucl Med* 1998;39:1551-4.
- Menzel C, Grünwald F, Schomburg A, Palmedo H, Bender H, Späth G, *et al.* "High-dose" radioiodine therapy in advanced differentiated thyroid carcinoma. *J Nucl Med* 1996;37:1496-503.
- Dorn R, Kopp J, Vogt H, Heidenreich P, Carroll RG, Gulec SA. Dosimetry-guided radioactive iodine treatment in patients with metastatic differentiated thyroid cancer: Largest safe dose using a risk-adapted approach. *J Nucl Med* 2003;44:451-6.