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The occurrence of malignant thyroid lesions in patients after radioiodine treatment due to benign thyroid diseases

Występowanie zmian nowotworowych w tarczycy u pacjentów po leczeniu radiojodem z powodu zmian łagodnych

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Abstract

Introduction: Radioiodine treatment (RT) of benign thyroid diseases is a well-known, safe, and effective treatment. In a group of patients after RT, who remained in long-term follow-up, sporadic cases of malignant thyroid lesions occurred. The aim of the study was to estimate how often it happened despite the exclusion of malignancy before RT.

Material and method: A group of 4314 patients (7438 person-years) underwent RT and subsequently were followed-up for 1–8 years (mean 20.69 months). Apart from thyroid function estimation, if needed, fine needle aspiration biopsy (FNAB) of the thyroid or neck focal lesions was performed based on ultrasonographic or clinical examination. Patients with pathological FNAB were analyzed and histopathologically verified.

Results: In 12 out of 4314 cases (0.27%) suspicious FNAB results were found. Suspicious thyroid lesion results were found in 9 patients (8 F, 1 M), aged 46–73 (average 56 years) followed up for 3–57 months after RT: papillary cancer in two patients, Hürthle cell tumour in one patient, and suspicious cells in two patients (with benign lesions on postoperative histopathology). Two patients refused surgery (a suspicion of papillary cancer in one case and suspicious cells in FNAB in the second case). A follicular tumour in FNAB was suspected in two cases (no data about the first, and the second with lung cancer was not operable). In the remaining 3 cases FNAB revealed lymph node metastases due to other cancers.

Conclusions: Malignant thyroid lesions in patients after RT due to benign thyroid diseases are seldom detected. However, periodical clinical and ultrasonographic evaluation is recommended. **(Pol J Endocrinol 2010; 61 (5): 454–457)**

Key words: *hyperthyroidism, thyroid neoplasm, Graves' disease, nodular goiter, ^{131}I therapy*

Streszczenie

Wstęp: Leczenie radiojodem (RT, *radioiodine treatment*) chorób łagodnych tarczycy jest uznaną, bezpieczną i skuteczną metodą. W grupie chorych po RT, pozostających pod wieloletnią obserwacją autorów pracy, czasami zdarzały się przypadki zmian nowotworowych w tarczycy. Postanowiono ocenić jak często, mimo wykluczenia zmian złośliwych w tarczycy przed leczeniem, może się to zdarzyć w dłuższym okresie obserwacji.

Materiał i metody: Grupa 4314 chorych (7438 osobolat) po RT pozostawała następnie pod obserwacją od 1–8 lat (śr. 20,69 miesięcy). W trakcie badań kontrolnych, oprócz oceny czynności tarczycy, wykonywano między innymi biopsję aspiracyjną cienkoigłową (BAC) zmian ogniskowych w tarczycy lub zmian na szyi, do której kwalifikowano ultrasonograficznie lub klinicznie (pojawienie się zmiany palpacyjnej). Pacjentów z nieprawidłowym BAC analizowano i weryfikowano histopatologicznie.

Wyniki: U 12 z 4314 (0,27%) chorych stwierdzono w BAC zmiany podejrzane. Zmiany w tarczycy znaleziono u 9 osób (8 K, 1 M) w wieku 46–73 lat (śr. wieku 56 lat), 3–57 miesięcy po RT. Raka brodawkowatego stwierdzono u dwóch osób, guz z komórek Hürthle'a u jednej osoby, cytologicznie podejrzane komórki u dwóch osób (histopatologicznie zmiany łagodne). Dwie chore nie zgodziły się na leczenie operacyjne: jedna z podejrzeniem raka brodawkowatego, a druga z komórkami cytologicznie podejrzanymi w BAC. Guzek pęcherzykowy był podejrzany u 2 chorych: o jednej z nich nie ma danych, drugi chory został zdyskwalifikowany do leczenia operacyjnego tarczycy z powodu współistniejącego rozpoznania raka płuca. U pozostałych 3 osób stwierdzono zmiany przerzutowe w okolicznych węzłach chłonnych z powodu innych nowotworów.

Wnioski: Zmiany nowotworowe w tarczycy u pacjentów po RT z powodu zmian łagodnych zdarzają się sporadycznie, ale wskazana jest okresowa ocena kliniczna i ultrasonograficzna tych chorych. **(Endokrynol Pol 2010; 61 (5): 454–457)**

Słowa kluczowe: *nadczynność tarczycy, nowotwory tarczycy, choroba Gravesa-Basedowa, wole guzkowe, leczenie ^{131}I*

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Introduction

Benign thyroid diseases constitute one of the oldest indications for radionuclide therapy. For more than 60 years ^{131}I has been applied for diffuse and nodular hyperthyroidism. It may also be used for large non-toxic goitres if patients are not eligible for surgery. Its efficacy is beyond discussion and many studies have shown the safety of such therapy [1–5]. However, prior to qualification for radioiodine therapy (RT), patients should be carefully screened for possible malignancy. According to generally accepted practice, one year follow-up at a nuclear medicine department is recommended [6, 7]. Some papers concerning long-term cancer risk in hyperthyroid patients treated with radioiodine have been published recently [8, 9]. In a group of patients after RT, who remained in our long-term follow-up, sporadic cases of malignant thyroid lesions occurred. The aim of the study was to estimate how often it can happen in long-term follow-up despite the exclusion of malignancy before the RT.

Material and methods

A group of 4314 patients underwent RT in the years 2000–2008 due to TNG, GD, or in a few cases enlarged non-toxic goiter. The diagnosis of the type of hyperthyroidism was based on clinical data, ultrasonography examination, radioiodine uptake, thyroid scintigraphy, and thyroid function laboratory measurements. In the whole group, thyroid malignancy was excluded and the same means of therapeutic dose calculation based on the Marinelli formula was performed.

The present analysis covers 7438 person-years with a mean follow-up time of 20.69 months (range 3–84 months) after commencing RT. Patients were supposed to be at obligatory follow-up for one year after the treatment at a nuclear medicine out-patient clinic, but many of them continued for up to 8 years.

During routine checking procedure, as well as thyroid function estimation, a FNAB of the focal lesions in the thyroid or in the neck was performed based on ultrasonography or clinical examination (if a new palpable nodule occurred). Patients with pathological FNAB were analyzed and histopathologically verified.

Results

In 12 out of 4314 cases (0.27%), suspicious lesions were found in FNAB. Lesions in the thyroid were found in 9 patients (8 F, 1 M), aged 46–73 (average 56 years) and followed-up for 3–57 months after RT. Detailed information about FNAB-positive patients is shown in Table I.

Table I. *Characterics of FNAB-positive patients*

Tabela I. *Charakterystyka chorych z dodatnim wynikiem biopsji aspiracyjnej cienkoiglowej*

Pt	Age (yrs)/sex	Diagnose	Time since elapsed RT(months)	AD (Gy)	FNAB	Histopathology
1	73/F	TNG	39	250	Suspicious cells*	Papillary cancer
2	46/F	GB	57 (I dose) 48 (II dose)	150 250	Papillary cancer*	Papillary cancer
3	48/F	GB	28	ND	Suspicion of Hürthle cell tumour**	Hürthle cell adenoma
4	63/F	TNG	3	250	Atypical polymorphic cells, histopathology required***	Normal
5	48/F	TNG	4	300	Follicular tumour? Follicular cancer? Hyperplastic nodule?*	Normal
6	55/F	TNG	33	150	Papillary cancer or lesion after treatment*	Refused to be operated
7	45/F 46/F	TNG	26 (I dose) 38 (II dose)	250 250	Suspicious cells*	Refused to be operated
8	53F	TNG	35	200	Follicular tumour	ND
9	72M	GB	26	200	Follicular tumour	Advanced lung cancer
10	54M 61M	GB	82 (I dose) 2 (II dose)	ND 150	Squamous cell cancer***	Not operated (lung cancer)
11	66M	TNG	72	ND	Metastases from squamous cell cancer***	Not operated
12	70M	GB	25	200	Non microcellular cancer***	Not operated (lung cancer)

Pt — patient number, F — female, M — male, Gy — Grey; Indication for FNAB of the lesion for the biopsy: *Enlargement of the lesion in sonography examination; **New lesion in sonography examination; ***Palpable lymph node

Papillary cancer was confirmed histopathologically in two cases: in patient number 1 with a toxic nodular goiter (TNG), 39 months after RT, and in patient number 2 with Graves-Basedow (GB) disease, 48 months after the second course of RT (the first dose was administered nine months earlier). In patient 1 with TNG, the absorbed dose for the whole thyroid volume was 250 Gy. In patient 2 with GB, the cumulated absorbed dose was 400 Gy. The dose was 150 Gy at the first approach, followed by 250 Gy in 9 monthly intervals due to the persistence of hyperthyroidism.

In the third patient with GB (patient 3) 28 months after RT a Hürthle cell tumour was diagnosed and postoperative histopathology showed Hürthle cell adenoma.

In that particular case, we have no data about the absorbed dose. In patients 4 and 5 with TNG, four and three months after RT, FNAB revealed suspicious cells and the histopathology examination showed benign lesions.

Patient 6 with TNG, who received 150 Gy, had a suspicion of papillary cancer 33 months after RT. Patient 7 with diagnosis of TNG had suspicious cells in FNAB performed 38 months after RT with 250 Gy as the thyroid absorbed dose. Patient 6 and patient 7 did not agree to surgery and until now are in good health.

Follicular tumours were suspected in patients 8 and 9. There is no data about the postoperative histopathology of patient 8 with TNG and FNAB performed 35 months after RT. Patient 9 with GB and FNAB, 26 months after RT, was not qualified for surgery due to diagnosis of lung cancer. The absorbed dose in the last two cases was 200 Gy each.

In the remaining 3 cases, metastases in neck lymph nodes were found due to other cancers (squamous cell carcinoma in patients 10 and 11 and from an unknown cancer in patient 12). Patient 10 received two courses of RT. An enlarged lymph node was found 82 months after the first course (2 months after the second I^{131} administration). Patients 11 and 12 had enlarged nodes diagnosed 72 and 25 months after RT, respectively.

Discussion

The main target of radionuclide treatment in benign thyroid disease is both immunogenic (GD) and non-immunogenic hyperthyroidism (TNG). Large non-toxic goitre may be taken into consideration as well, especially if contraindicated for surgery. In the majority of papers, the thyroid function impairment (hypothyroidism less often than hyperthyroidism) is regarded as a factor which makes thyroid cancer less possible. However, this assumption is not correct if no autonomous nodule is stated.

There is no strict recommendation concerning the protocol of imaging and follow-up for patients previously treated [7, 10]. Many reports in literature point out the safety of RT [1–5, 11]. However, a nuclear medicine practitioner, when treating a hyperthyroid patient with radioiodine, has to keep in mind the possible occurrence of malignancy prior to the treatment and should be concerned with the proper follow-up after the end of therapy [6]. The authors of this paper have also described their own experiences in proper selection of patients for RT [12, 13]. Now we have attempted to discover how often thyroid gland cancer occurs despite the appropriate preselection before RT at our outpatient clinic.

The majority of the FNABS performed were done more than 24 months after the treatment. Patients 4 and 5 (interval 3 and 4 months after RT, respectively) probably showed false positive FNAB results caused by the radionuclide treatment itself. The postoperative histopathology in both cases was normal. The absorbed dose in all cases was applied according to the protocols [14–17].

The absorbed doses proposed for GB and TNG could be as high as 300 Gy if whole thyroid volume is taken into account. In fact, the risk of thyroid cancer is lower at thyroid ablative doses.

Regardless of the fact that RT is considered as a generally safe procedure [2], some publications point out increased cancer incidence among hyperthyroid patients in comparison to matched control groups. Metso et al. showed an increased stomach, kidney, and breast cancer risk in these patients [8, 9]. They found that cancers occurred 5 years from RT. Similar conclusions were drawn 16 years earlier by Holm et al. In their study, significantly elevated risks were discovered for cancers of the stomach, kidney, and brain among 10-year survivors [18]. As to the mortality increase, it is underlined in Lucignani's comment on Metso's findings: hyperthyroidism is a serious condition, so increased mortality can be tailored with hyperthyroidism per se [9].

Indeed, the risk of death due to endocrine and metabolic disorders, as well as circulatory diseases, was significantly greater in ^{131}I-treated patients in relation to the general population in a publication presented by Franklyn [19]. In this paper, there was no explanation regarding the underlying endocrine disorders treated by RT, and no data on the absorbed doses of ^{131}I that were given. However, the reader can find the range of administered activity of radioiodine (45% of the whole cohort received more than 480 MBq).

Contrary to previous conclusions, Ron et al. state in their paper that ten years after ^{131}I treatment for adult hyperthyroidism no risk of an increase in total cancer mortality was found. Among patients with GB, thyroid cancer mortality was increased, but not significantly,

after five or more years of follow-up. There was a relationship between the number of ^{131}I treatments, dose, and overall cancer mortality. Among patients with toxic nodular goiter, there was no relationship between the ^{131}I activity given and cancer mortality (but the number of cases was not large, and confidence intervals were wide) [20]. Hermus noticed that patients treated with radioiodine due to toxic nodular goiter "have an increased risk of thyroid carcinoma, because the paranodular tissue may receive sub-lethal mutagenic doses of radiation". But in his conclusion, the author underlines that "in a large follow-up study, the risk of thyroid carcinoma was not increased and the risk of carcinoma elsewhere was not increased or only marginally increased" [5].

A retrospective study performed by Angusti et al. analyzed a group of 6647 patients who underwent RT. Thyroid cancer was revealed in 10 (0.15%) patients exclusively with TNG. The time between treatment and cancer diagnosis ranged from 2 to 14 years (median 7.5 years). As no case of thyroid cancer in GD patients has been found, the authors concluded that RT is safe for GD. For TNG patients, attention must be focused on the presence of nodules with suspicious ultrasound pattern [21].

In a paper which described the evolution of anaplastic cancer six years after successful RT of toxic adenoma, Górowski outlined some hypotheses: cancer may evolve from paranodular tissue, may be an occult lesion with moderate malignancy or increased radiosensitivity, or may evolve de novo [22].

Lucignani notices in his editorial that the reported thyroid cancer occurrence after RT is not based on evidence-based medicine [9]. However, the proper and regular follow-up of patients treated with radioiodine is recommended. Apart from physical examination, the sequence of follow-up ultrasonography and FNAB examination is crucial.

Conclusions

Malignant thyroid lesions in patients after RT due to benign thyroid diseases are seldom detected but not excluded. Periodical clinical and ultrasonographic evaluation is recommended.

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