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Fractionated dosage of radioiodine for the ablation of low-risk differentiated thyroid cancer has no impact on survival

Short title: Fractionated dosage of radioiodine for the ablation of thyroid cancer

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Abstract

Introduction: Due to a limited number of hospital beds dedicated to radioiodine therapy (RIT) in some countries, a fractionated dose of radioiodine may be considered as the ablation therapy of differentiated thyroid cancer (DTC). The aim of the study was to compare the late effects of ablation therapy with single and fractionated doses of radioiodine in patients with DTC.

Material and methods: Patients with low-risk DTC referred to our institution 5–16 weeks after thyroidectomy, treated with 2.2 GBq of ¹³¹I, either in a single dose (2.2 GBq, group 1) or in two fractions (1.1 GBq+1.1 GBq administered with a 24 h interval, group 2), were retrospectively included. Clinical outcome of the treatment and overall survival (OS) was evaluated.

Results: Eighty-three patients treated with single dose and 186 patients treated with fractionated dose of radioiodine were included. Mean duration of follow-up was 11.4 vs. 10.9 years, respectively ($p = ns$). There were no significant differences between the groups in male-to-female ratio, age at the time of the first RIT, proportion of papillary thyroid cancers, volume of the thyroid tissue, and thyroid-stimulating hormone and thyroglobulin levels before first RIT. RIT was repeated in 55.4% and 54.8% of patients from group 1 and 2, respectively ($p = ns$). There were no significant differences including the course and outcomes of the treatment between the groups, measured by: cumulative dose of ^{131}I , mean number of ^{131}I administrations, and mean thyroglobulin concentration at follow-up. Also, the overall survival did not differ significantly between the groups. Probability of five-year OS was 98.6% for patients treated with single and 99.5% with fractionated dose of ^{131}I , 10-year OS was 98.6 and 97.1%, respectively, and 15-year OS was 95.5 and 92.9%, respectively ($p = ns$).

Conclusions: In the long-term follow-up, radioiodine ablation therapy with fractionated doses in low-risk DTC patients is equally effective as with a single dose.

Key words: *thyroid cancer, differentiated thyroid cancer, radioiodine, fractionated dose, survival*

Introduction

The standard post-operative treatment of patients with DTC includes radioiodine therapy (RIT). It is aimed at total ablation of thyroid remnants, eradication of potential metastases [1], and the increase in post-treatment whole body scan sensitivity for detection of asymptomatic metastases, as well as improvement of diagnostic accuracy of thyroglobulin monitoring [2, 3]. Both former and current guidelines recommend administration of the radionuclide in one dose with subsequent isolation of patients in appropriate therapy wards, in accordance with local regulations of radiation protection. In some regions experiencing deficits of isolation beds in relation to increasing DTC morbidity, attempts were undertaken to improve treatment accessibility by applying lower activities of ^{131}I in order to avoid hospitalisation in RIT-dedicated wards. A temporary situation of that kind occurred at our centre in 1999-2000 when patients with low-risk DTC had to be treated with fractionated doses of RIT.

Though suboptimal, this treatment method proved as effective as regular RIT with one dose of 2.2 GBq in our early evaluation [4].

Aim of the current study was to retrospectively evaluate the late treatment outcome in this unique patient cohort, diagnosed with DTC almost 15 years ago. It was expected that the

results would provide interesting data for the ongoing discussion on the optimal dosage of RIT in patients with low-risk DTC.

Material and methods

Subjects

Patients with DTC, who underwent total thyroidectomy between 1999 and 2003, were included in the study. At 5–16 weeks after surgery they were admitted to our institution for ablation RIT. The treatment was performed under endogenous TSH stimulation (TSH > 30 mU/L) achieved by withdrawal of L-thyroxin medication for 4–6 weeks.

The following inclusion criteria were used:

- no signs of regional lymph node involvement in histopathological evaluation, ultrasound (US), and whole-body scan (WBS);
- no signs of distant metastases in WBS, chest radiography, or computed tomography;
- no invasion of neoplasm extending the thyroid capsule.

Patients with following exclusion criteria were not included in the study:

- ineffective TSH concentration elevation (< 30 mU/l);
- the volume of remaining thyroid parenchyma > 2 ml;
- initially recognised distant metastases;
- RIT used in palliative setting;
- lacking follow-up data.

According to the RIT protocol used in our institution, patients were treated with standard activity of 2.2 GBq ^{131}I . L-thyroxine administration was discontinued 5–6 weeks before RIT. Before the initial radioiodine administration, standard biochemical examinations (TSH, Tg, anti-Tg), US, chest radiography, and WBS were performed in all subjects.

Ultrasound examination

US of the neck was performed by an experienced endocrinologist. The examination included thyroid remnant volume measurement and bilateral inspection of cervical lymph nodes for the detection of potential metastases. Fine-needle aspiration biopsy was performed in every case of malignancy suspicion.

Laboratory measurements

TSH concentration during the initial evaluation was analysed with the use of immunofluorometric assay. At the end of follow-up TSH was measured using electrochemiluminescent method with a third-generation kit presenting sensitivity ≤ 0.005 IU/mL.

Tg concentration was measured by Tg-DYNOtest (Brahms, Germany) at the initial evaluation and using electrochemiluminescent method during follow-up.

Radioiodine uptake test

Twenty-four hours after oral administration of diagnostic ^{131}I (1 MBq) radioiodine, activity in the neck region was measured with the use of a Nucline gamma camera (Mediso, Hungary).

Whole-body diagnostic scan

WBS with the use of a Varicam gamma camera (Elscont, Israel) was performed 44–46 h after the administration of 74–111 MBq ^{131}I . It was viewed and interpreted by two experienced nuclear medicine specialists.

Radioiodine therapy

RIT was performed 2–4 h after WBS, ca. 48 h after administration of the diagnostic dose mentioned above. All the subjects included in the study were treated with an equal total dose of 2.2 GBq. Patients included in group 1 received the total radioiodine activity in one administration. In patients from group 2, the dose was divided into two fractions of 1.1 GBq administered twice, with an interval of 24 h.

Post-treatment WBS

According to a standard protocol, 7–10 days after the treatment, post-treatment whole-body scan was performed in order to identify possible locoregional or distant metastases that had not been disclosed before. As explained previously, patients with locoregional and distant metastases were excluded from the study.

Follow-up period

In all of the subjects, the therapy with L-thyroxine (L-T₄) was initiated later, with the recommendation of a gradual increase of the total daily dose, with the aim of TSH

suppression. 6–8 months after the initial RIT, with the period of at least four weeks LT₄ withdrawal, the subjects were admitted for an early follow-up evaluation with performance of the same procedures as those performed at the baseline. The next control visits were then repeated 12 and 36 months after RIT, followed by the next control visits performed approximately two years later.

Statistical analysis

The calculations were performed using Statistica 10 from StatSoft. A *P* level of less than 0.05 was considered statistically significant. Significance of the differences between medians was evaluated using Mann-Whitney test, between means — using *t* test for independent samples. Comparison of numbers of patients with and without particular features in two groups was performed using Fisher's exact test. Overall survival (OS) of the patients was compared using Cox-Mantel test.

Results

In total 269 patients were included in the study: 83 patients treated with single dose and 186 patients treated with fractionated dose of radioiodine. A comparison of group characteristics at the time of diagnosis is shown in Table I. There were no statistically significant differences concerning age, proportion of genders, percentage of papillary thyroid cancers (PTC), volume of thyroid remnants measured with ultrasonography (USV), radioiodine uptake (RIU), thyroglobulin (Tg), and TSH.

Data on the clinical course and treatment outcome in both groups is shown in Table II and III. There were no significant differences between groups concerning duration of the follow-up, number of RIT courses, cumulated dose of radioiodine, and Tg at the end of follow-up. These data show that the course of disease and subsequent management was equal in both groups.

OS did not differ significantly between the groups. Probability of five-year OS was 98.6% for patients treated with single and 99.5% with fractionated dose of ¹³¹I, and 10-year OS was 98.6 and 97.1%, respectively (*p* = 0.54) (Fig. 1). Among patients treated with fractionated dose of ¹³¹I, 11 persons were lost from follow-up in five years (5.9%) and 37 in

10 years (19.9%). Among patients treated with a single dose of ^{131}I , seven patients were lost from follow-up in five years (8.4%), and 22 in ten years (26.5%). Kaplan-Meier survival curves are presented in Figure 1.

Discussion

RIT has been widely used as a standard method for ablation of thyroid remnants and potential metastases in subjects treated for DTC [5]. The presented study concentrates on radioiodine treatment of patients with low-risk thyroid cancer. The indications to the ablation therapy in such patients have never been clear. Currently, experts of the American Thyroid Association do not recommend radioiodine ablation treatment in patients with low-risk differentiated thyroid carcinoma, in their recent management guidelines [6]. Their opinion is not always shared by other groups. The management guidelines of the Polish Group for Endocrine Tumours are in favour of routine indications to radioiodine ablation also in patients staged T1b-T2N0M0, based on the positive experience of the Polish centres [7]. Because the presented patient cohort was qualified to radioiodine ablation as early as in 1999-2003, the clinical practice at that time was influenced by the previous guidelines of 1996 that recommended use of 29.9–100 mCi of ^{131}I for thyroid remnant ablation [8].

Although recommended activities of radioiodine have been a matter of discussion, it seems undebated that the target activity should be administered in one dose. It is important not only for practical reasons but also mainly due to the thyroid stunning phenomenon that is expected to decrease iodine uptake following the application of ionising radiation to the thyroid cells [9]. It could be hypothesised that administering a fractionated dose of radioiodine causes a similar effect: reduced uptake of second and eventually further fractionated doses. However, some authors claim that the stunning effect is not relevant in clinical practice [9–11]. Amin et al. compared patients who received a diagnostic dose of ^{131}I (185 MBq) in order to perform WBS about 11 days before the administration of the ^{131}I ablation dose. Although the uptake of the therapeutic dose of radioiodine was lower in patients who underwent the WBS, there was no significant difference in the ablation success rate evaluated on the basis of post-therapeutic WBS, Tg level, and neck sonography [12].

The amount of data on the topic of the effectiveness of treatment of DTC with fractionated doses of radioiodine instead of a single equivalent dose is very limited. Arad et

al. described comparable effectiveness of treatment with single and fractionated doses of radioiodine administrated at one-week intervals [13]. This finding was confirmed by a study performed in our centre on a larger group of patients [4]. Also, Wang et al. reported good effectiveness of treatment with fractionated doses [14]; however, there was no control group described. To our knowledge, the present study is the first comparison of late effects of ablation therapy of thyroid cancer with the use of fractionated dosage of radioiodine.

Our previous study did not indicate any significant differences in early clinical outcomes between the groups [4]. The present, extended analysis also did not reveal any dissimilarities in the course and outcome of the treatment during approximately 10 years of follow-up. A similar percentage of patients required second administration of radioiodine; patients in both groups required the same number of subsequent radioiodine administrations and received similar cumulative dose. At the end of the follow-up the concentration of thyroglobulin was similar in both groups. The overall survival in 10 years of observation did not differ significantly.

In the present study, the long-term efficacy of initial treatment with single and fractionated doses of radioiodine was compared. We have compared patients with DTC, who received a single dose of 2.2 GBq ^{131}I (group 1), with patients who received two doses of 1.1 GBq each, administered with a 24-hour interval (group 2). No significant differences between the two groups were found regarding age, sex, type of thyroid cancer, presence of metastases, USV, Tg, and TSH before the radioiodine administration. Both groups included low-risk patients with no signs of extra-thyroid disease spread. In compliance with the procedure guidelines valid at the time of diagnosis, all these patients were assigned the dose of 2.2 GBq ^{131}I . Selection of treatment method (one or two doses) was dependent only on the logistic issues (i.e. availability of the appropriate sewage system in the ward) and was not influenced by medical or social factors. Thus, it may be concluded that the assignment to the groups was practically random.

Although both methods of RIT were carried out at our institution in different time intervals (before and after installation of the radioactive sewage system), no technical bias should be expected because the management guidelines of thyroid cancer did not change during the study and all the diagnostic procedures were performed using the same equipment, with equal standard parameters of laboratory and imaging data. Moreover, the evaluation of the patients was performed by the same team of co-workers.

According to our results, there were no significant differences in the clinical course and outcomes between the groups. Though suboptimal, in low-risk patients with differentiated thyroid carcinoma the treatment with fractionated doses of ^{131}I administered in 24-hour intervals can be considered an equivalent alternative to the treatment with a single dose.

Table I. Comparison of the groups at the pretherapeutic evaluation — before the first administration of radioiodine

	Group 1 (single dose)	Group 2 (fractionated dose)	P
Number of patients	83	186	
Age (mean \pm SD)	44.6 \pm 12.8	46.8 \pm 14.8	0.24
Gender — % of women	88.0	90.9	0.51
Papillary thyroid cancer (%)	85.5	84.9	1.0
USV [cm ³] (mean \pm SD)	0.64	0.86	0.06
RIU — % (mean \pm SD)	4.8 \pm 4.8	6.2 \pm 6.3	0.09
TSH [mU/l] (mean \pm SD)	71.7 \pm 35.1	73.6 \pm 44.4	0.75
Tg [ng/l] (median)	3.8	5.4	0.32

Abbreviations: TSH — thyroid-stimulating hormone; USV — volume of thyroid remnants measured with ultrasonography; RIU — radioiodine uptake; Tg — thyroglobulin; SD — standard deviation

Table II. Comparison of the clinical outcomes between the groups

	Group 1 (single dose)	Group 2 (fractionated dose)	P
Duration of the follow-up (mean \pm SD)	11.4 \pm 2.3	10.9 \pm 3.2	0.22
Duration of the follow-up (mean \pm SD)	8.0 \pm 3.6	7.8 \pm 2.6	0.68
Number of iodine administrations (median)	2.0	2.0	0.77
Cumulated dose of ^{131}I administrated during follow-up (mean \pm SD)	203.2 \pm 240.8	189.4 \pm 186.0	0.60
Thyroglobulin at the end of follow-up (median)	0.66	1.12	0.14

Table III. Total number of RIT courses administered to patients from both groups

Number of RIT courses	Group 1	Group 2	P
1	100%	100%	1.00
2	55.4%	54.8%	1.00
3	30.1%	27.4%	0.66
4	10.8%	11.8%	1.00
5	7.2%	7.0%	1.00
6	3.6%	2.2%	0.68

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Comparison of overall survival in patients treated with single and fractionated dose of 131-I

