

Predicative Meaning of Radioiodine Pharmacokinetics Indices for Evaluation of Radioablation Efficacy of Thyroid Residuum in Patients with Differentiated Thyroid Cancer

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Abstract: *Background:* The radioiodine ablation (RIA) of thyroid residuum in patients with differentiated thyroid cancer (DTC) is an important stage of complex treatment. The aim of RIA is the elimination of potential foci of DTC and creating conditions for monitoring of the patients. Prognosis of the efficacy of RIA is important for further planning of the complex treatment. The aim of the study was to improve a prognosis of RIA of thyroid residual tissue (TRT) in patients with DTC using scintigraphic data about ^{131}I kinetics, that reflect a radioresistance of a thyroid tissue. *Material and Methods:* The results of RIA of TRT in 62 patients were analyzed. During radioiodine therapy (RIT) the elimination halftime of ^{131}I from TRT in time interval 3–6 days after administration of therapeutic activities was determined, and the focal radiation adsorbed doses (FRAD) in TRT were calculated. *Results:* It was determined that values $T_{1/2} \geq 4.0$ days may indicate on the high probability of the incomplete RIA of TRT at FRAD within 50–500 Gy, while values $T_{1/2} \leq 1.9$ days – on the radiosensitivity of the thyroid tissue and the great probability of the complete RIA. *Conclusions:* During RIT of DTC the elimination halftime of iodine-131, determined on time interval 3–6 days after the administration of therapeutic activities may be used as one of predicative indices of RIA efficacy. Since the elimination halftime of the radiopharmaceutical reflects the individual natural radiosensitivity of TRT, this approach may be applied in studies of the radioresistance of a normal human tissue.

Keywords: Differentiated Thyroid Cancer, Radioiodine Therapy, Radioiodine Ablation, Residual Thyroid Tissue, Prognosis of Radioiodine Ablation Efficacy

1. Introduction

The conventional tactics of treatment of the differentiated thyroid cancer (DTC) consists of three basic components – thyroidectomy, radioiodine therapy (RIT) and suppressive thyroid hormone therapy [1-3]. The first course of RIT is directed on a radioablation of the thyroid residual tissue (TRT) after thyroidectomy and evaluation of spreading of the tumor process. The aim of a radioiodine ablation (RIA) is the elimination of potential foci of DTC and creating conditions for monitoring of the patients [4-6]. RIA may reduce the risk of recurrence, development metastases, and long-term mortality from DTC [7-9]. The efficacy of RIA is depended from several factors: values of focal radiation adsorbed doses (FRAD), which created in TRT, mass of TRT, a

radioresistance of thyroid tissue, an adequacy of the suppressive hormonal therapy, and some other [10, 11].

As rule, the prognosis of results of RIA is made on the bases of FRAD; the efficacy of first RIA increased progressively with enlarging of FRAD in TRT. Creation of FRAD in 300 Gy ensures the positive effect of first course of RIT in 81% of all patients and in 86% of all parts of TRT [12]. In the same time, it was determined that FRAD at least in 300 Gy, 300–700 Gy, and more than 700 Gy created practically almost equal efficacy of RIA – 83–86% [13].

The similar results were received by C. Bal et al.: in range of FRAD in TRT 300–1300 Gy the efficacy of RIT fluctuated within 74–78% [14]. Thus, the increasing of FRAD more than 300–400 Gy did not results to further significant enlarging of the efficacy of RIA. Probably, in first

turn this was connected with high individual radioresistance of thyroid tissue. In these cases for complete devitalization of TRT the repeated courses of RIA are realized. Prognosis of the efficacy of RIA is important for further planning of the complex treatment.

The aim of the study was to improve the prognosis of efficacy of RIA using indices of elimination halftime of iodine-131 from TRT. It is known, that the maximal accumulation of the radiopharmaceutical is observed one day after administration of the therapeutic activity, rarely 2–3 days. As a rule, beginning from the fourth day the elimination of iodine-131 occurs; its speed depends, in certain extent, on a degree of decline in the functional activity of thyrocytes, which is dependent from the radiation damage. Based on this, the radioiodine elimination halftime, defined in time interval 3–6 days, was selected as an index of the efficacy of first RIA, which reflects the radioresistance of TRT.

2. Materials and Methods

The results of complex treatment of 62 patients aged 34–68 years (47 females, 15 males) with DTC were analyzed. Stage T₁₋₂N₀M₀ was determined in 23 (37.1%) patients, T₃₋₄N₀M₀ – in 25 (40.3%), T₁₋₂N₁M₀ – in 8 (12.9%), T₃₋₄N₁M₀ – in 6 (9.7%). The papillary thyroid cancer was diagnosed in 44 (71.0%) cases, follicular – in 12 (19.3%), mixed forms – in 6 (9.7%). All patients had TRT only.

Diagnostic scintigraphy with 70–80 MBq of iodine-131 was realized for all patients following 4–6 weeks after a thyroidectomy. Scintigraphic investigations were made on gamma camera «MB 9200» with operation software «Microsegams 9201» («Gamma», Hungary) and single photon emission tomograph "E. CAM 180" with software package "Syngo 2.0" ("Siemens Medical Solutions, Inc.", USA). Based on the results of diagnostic scintigraphy, RIA of TRT with calculated or empirical activities ranged 1.8–4.8 GBq were executed. On the fourth day after administration of therapeutic activities the suppressive therapy with L-thyroxine was prescribed. Control scintigraphies were made in 6 months after RIA of TRT.

For determination of the activity in TRT, scintigraphies were made daily, beginning in the second day after administration of therapeutic activity during 6–7 days at equal parameters of registration. The elimination halftime of iodine-131 from TRT on time interval between 3 and 6 days was calculated according to formula (1) [15]:

$$T_{1/2} = 0.693(T_1 - T_2) / |\ln(N_1) - \ln(N_2)|, \quad (1)$$

where T_{1/2} – elimination halftime of iodine-131, days;

N₁ and N₂ – counts in "region of interest" of TRT in time T₁ and T₂.

FRAD in TRT were estimated according to recommendations of the Committee on Medical Internal Radiation Dose using formula (2) [16]:

$$D_{\text{ther}} = 0.1187 \int A(t) dt / m, \quad (2)$$

where D_{ther} – FRAD after RIA, Gy;

∫A(t)dt – integral of activity in TRT, MBq×h;

m – mass of TRT, g.

The integral of activity was calculated as square under the activity-time curve. Building of the activity-time curve and calculation of the integral of activity were made using a packet of programs "CurveExpert 1.34".

For determination of the activities in TRT was used the phantom of thyroid gland. The mass of TRT was determined proceeding from the volume of radioiodine distribution determined at the scintigraphy. Specific weight of thyroid tissue was accepted 1 g/cm³. For calculation of the value of TRT was used ellipsoid model (3) [17]:

$$V = \pi a b c / 6, \quad (3)$$

where V – volume of TRT, cm³;

a, b, c – diameters of ellipsoid, cm.

Linear sizes of diameters were determined using cutting of background. The value of cutting in percents from maximal count in TRT was determined using phantom measuring.

Statistical analysis of data was executed with using packets of programs "Statistica 6.0", "SPSS 8.0 for Windows".

3. Results and Discussion

In 13 patients (10 females, 3 males aged 36–67 years) with 22 parts of TRT, which had an incomplete RIA after first RIA, the mean T_{1/2} determined in time interval 3–6 days was 3.96±0.26 days. In this group FRAD ranged 49.8–819.2 Gy; the mean value was 171.4±40.4 Gy.

In group from 49 patients (37 females, 12 males aged 38–69 years) with 93 parts of TRT which had the complete RIA the mean T_{1/2} consisted 1.92±0.14 days. In this group FRAD ranged 36.0–787.6 Gy, the mean value – 170.2±14.0 Gy. The difference between the mean T_{1/2} in groups was significant (p<0.05). Taking into account the mean values, as prognostic indices T_{1/2} ≥ 4.0 days for incomplete RIA, and T_{1/2} ≤ 1.9 days for complete RIA were accepted.

These criteria were used for prognosis of the efficacy of first course of RIA in 52 patients with FRAD in TRT ranged 50–500 Gy. Among 17 patients (13 females, 4 males aged 34–68 years) with 26 parts of TRT, who had T_{1/2} ≥ 4 days incomplete RIA were in 13 patients (76.5%) and in 22 parts of TRT (84.6%). The mean FRAD in this group was 179.3±36.4 Gy.

In group from 35 patients with 59 parts of TRT (27 females, 8 males, aged 38–63 years), who had T_{1/2} ≤ 1.9 days (mean FRAD – 186.1±17.9 Gy), the complete RIA was in 30 patients (85.7%) and in 52 (88.2%) parts of TRT. Hence, in range of FRAD 50–500 Gy positive predicative value of the incomplete RIA at T_{1/2} ≥ 4 was 76.5% and complete RIA at T_{1/2} ≤ 1.9 days – 85.7%.

Thus, the elimination halftime of iodine-131 may be, in certain extent, the index of radiosensitivity of the thyroid tissue and predicative factor of the efficacy of RIA, because one of the factors, which determined a speed of the elimination of radioiodine from TRT, is a decline of the

functional activity of thyrocytes and their death as result of a radiation damage in first hours and days after administration of therapeutic activity – the effect of thyroid selfstunning. Prolonged elimination halftime of iodine-131 is possible only when the thyroid selfstunning is minimal as result of high radioresistance of thyroid tissue. It's necessary to note, that this dependence saves in sufficiently large range of FRAD from several dozens to several hundreds grays.

Since TRT is represented mainly by normal thyroid tissue, this simple approach to the assessment of natural individual radioresistance may be used in studies of radioresistance of normal human tissue.

Following clinical cases may illustrate the possibility of using these predicative indices.

Woman, 39 years old. Diagnosis: differentiated thyroid cancer, papillary form, $T_2N_1M_0$, condition after definitive thyroidectomy, right dissection of the neck. Diagnostic scintigraphy with 73 MBq of $Na^{131}I$ was performed: residuum thyroid tissue of right and left lobes of thyroid gland. RIT with 4720 MBq was executed. At scintigraphy with therapeutic activity 2 parts of TRT with volumes 2.1 and 1.6 cm^3 were diagnosed, FRAD were 231.1 and 81.7 Gy, respectively. The halftimes of elimination of iodine-131 from TRT determined on time interval 3–6 days consisted 4.65 and 4.4 days, respectively. On fourth day after administration of therapeutic activities the suppressive hormone therapy with 200 mcg/day of L-thyroxine was prescribed. In 6 months on control scintigraphy TRT was diagnosed again. Repeated RIT with 4360 MBq was performed. On following control scintigraphies TRT was not registered, the results of determination of thyroglobulin were negative.

Man, 46 years old. Diagnosis: differentiated thyroid cancer, infiltrative papillary form, $T_2N_1M_0$, condition after right hemithyroidectomy with isthmus and subtotal resection of left lobe of thyroid gland. Diagnostic scintigraphy with 73 MBq of $Na^{131}I$ was performed: TRT, volume 5.6 cm^3 . Level of thyroglobulin in blood was 77.7 mcg/l. RIT with 4720 MBq was executed. The scintigraphy with therapeutic activity diagnosed TRT only, FRAD was 819.2 Gy. The halftime of elimination of iodine-131 from TRT was 4.6 days. On fourth day after administration of therapeutic activities the suppressive hormone therapy with 300 mcg/day of L-thyroxine was prescribed. In 6 months the control scintigraphy was performed: TRT. Repeated RIT with 2360 MBq was performed. On following control scintigraphies TRT was not registered, the results of determination of thyroglobulin were negative.

Thus, in these clinical observations the elimination halftime of iodine-131 from TRT indicated on the high radioresistance of thyroid tissue, which caused the necessity of repeated RIA, despite on sufficiently high FRAD in TRT after the first radioablation.

TRT usually consists of normal thyroid tissue, but the metastases of DTC may inherit some degree of the radioresistance of the normal source tissue. Probably, the indices of eliminations halftime of iodine-131 may be used as additional prognostic factors in RIT of the regional and distant metastases. Further research is needed in this

direction.

4. Conclusion

During RIT of DTC the elimination halftime of iodine-131 from TRT determined on time interval 3–6 days after the administration of therapeutic activities may be used as one of predicative indices of efficacy of first RIA. Values $T_{1/2} \geq 4$ days may indicate on the high probability of the incomplete radioablation of TRT at FRAD 50–500 Gy, while values $T_{1/2} \leq 1.9$ days – on the high probability of the complete RIA.

Since these predicative indices reflect the natural individual radioresistance of the normal thyroid tissue, they may be used in studies of the human radioresistance.

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