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FIRST TREATMENT ACTIVITY AND OUTCOME OF RADIOIODINE THERAPY IN THYROID CANCER PATIENTS WITH METASTASES IN LYMPH NODES: MATHEMATICAL CORRELATION AND CLINICAL IMPLICATIONS

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Aim: **The aim of the work was to estimate the strength of influence of the first ^{131}I activity on the outcome of the first course of radioiodine treatment as compared with other variables such as remnants volume, size and number of metastases in lymph nodes.** ***Patients and Methods:*** **68 adult patients with differentiated thyroid cancer have been treated with radioiodine after thyroidectomy. All patients had metastatic lesions in lymph nodes accumulating ^{131}I. Activities administered amounted from 1000 to 6000 MBq. From 1 to 4 courses of radioiodine therapy were necessary for total ablation of metastases and remnants. Logistic function has been used to describe the probability of the total ablation of metastases and thyroid remnants after the first course.** ***Results:*** **It was shown that the value of the first activity has the decisive influence on the treatment outcome. In patients included into analysis the outcome of the first course actually does not depend on level of radioiodine accumulation in pathological lymph nodes and effective half-time of ^{131}I excretion in remnants.** ***Conclusion:*** **As a result, in the case of metastatic lesions in lymph nodes accumulating radioiodine the first activity should not be less then 5000 MBq with the aim of minimizing the number of courses. Outcome of the treatment only slightly depends on such factors as histology, the number and the size of metastases in lymph nodes.**
***Key Words*: thyroid cancer, metastases, ^{131}I, kinetics.**

Question of correct choice of the first therapeutical activity in differentiated thyroid cancer after thyroidectomy is still under discussion. The decisions are often based on empirical approach. Several factors, such as thyroid remnants volume, the number and the size of pathological sites accumulating radioiodine, histology of the tumor may be taken into account in the choice of the activity value [1, 5]. Nevertheless the factors associated with ablation failure are not fully understood. In particular, it is not certain whether the use of activities higher than 3.7 GBq would result in any additional benefit [7]. Meanwhile several researches have been yet focused on the use of low activities for ablating the thyroid remnants upon thyroidectomy. Even the possibility of low activities fractionation by successive treatment courses is still discussed [6]. Standardized regimens of ^{131}I therapy in fact have several advantages over the attempts of individual selection of the activities based on accounting preliminary kinetics data [14, 15]. Either administering an empirically chosen fixed dose or using dosimetry — guided techniques, can achieve remnants ablation. Because of the technical and logistic difficulties, most centers have adapted the fixed dose or standard–dose technique for remnants ablation using ^{131}I [2]. In [8] the individual activity value A_0 was calculated for the cases without metastatic lesions and when only thyroid remnants were present. A_0 could be estimated based on the kinetics of ^{131}I distribution assessed in diagnostic scintigraphy. As a rule, in the case of metastases in lymph nodes revealed in diagnostic scintigraphy the therapeutical activities amounted approximately to 3600 MBq [13]. Nevertheless, the relative contribution of thyroid remnants size to the outcome of the first course of radioiodine treatment has not been yet established. It has not been also established which factors are more decisive in terms of the influence on treatment outcome, namely the first activity administered or thyroid remnants volume and the number and the size of metastatic lymph nodes.

The aim of the study was to estimate the relative contribution of the first activity to the outcome of the first course of radioiodine treatment as compared with other variables such as remnants volume, size and the number of metastases in lymph nodes.

PATIENTS AND METHODS

68 adult patients (aged from 46 to 76, 55 ± 7 in average) with differentiated thyroid cancer have been treated with radioiodine after thyroidectomy. Patients have been operated in different clinics in Ukraine. In every patient the scope of the surgery comprised resection of regional lymph nodes with possible metastases. Nevertheless, only patients with metastases in lymph nodes accumulating radioiodine have been enrolled into the study.

15 patients had follicular thyroid cancer, 40 — papillary, 12 — mixed form, in one patient histological data were not available. Therapeutical activities amounted from 1000 to 6000 MBq. From 1 to 4 courses of radioiodine treatment were necessary for total thyroid tissue ablation. If the first course failed, the following successive courses were appointed. 55 patients had full ablation of metastases and remnants after the first course of the treatment. The following parameters of ^{131}I kinetics in remnants and lymph nodes were measured in 25 random patients from the first day of treatment activity administration: the effective half- life in remnants and pathological lymph nodes and level of radioiodine

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accumulation in remnants in 24 h after activity administration. Calculations were made on gamma camera 6400 (Hungary) and SPECT E. Cam (Siemens).

Regression analysis has been applied for estimating the relative contribution of the first activity to the outcome of the first course of radioiodine treatment as compared with individual peculiarities of the patient such as thyroid remnants volume, number of lymph nodes metastases and histological type of the tumor. Logistic function was used in regression analysis for describing the probability of full metastases ablation after the first course.

RESULTS

For evaluating the relative contribution of the first activity on the outcome of the first course, the whole interval of the activities administered was divided in 1000 MBq subintervals. In every subinterval *p* has been calculated as the ratio of the number of patients with full thyroid tissue ablation after the first course of the treatment to the total number of patients being treated in such activity interval. *p* value as a function of activity is plotted in Fig. 1.

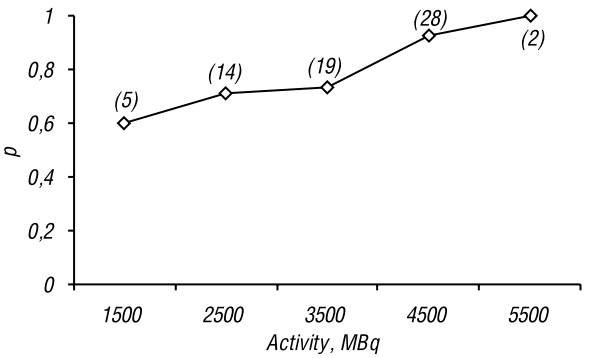

Fig. 1. *p* as a function of the first activity value *A*. The number of patients being treated in every activity ^{131}I interval is indicated in brackets.

From Fig. 1 it is obvious that the probability of full ablation of metastases and remnants increases with increasing value of the first activity. The relationship is approximated by linear function. p does not take the zero value throughout all the range of activities administered even in the lowest activity of 1100 MBq. This fact suggests that individual values of the optimal activity for each patient do exist.

p = 1 in the activity interval from 5000 MBq to 6000 MBq. The plotted function reflects the overall *p* increment with the increasing activity, not taking into account the individual features of each patient.

The total number of patients required one or more than one courses for complete ablation of remnants and metastases for every histology group is indicated in Table 1.

Table 1. The number of patients treated with 1 or > 1 courses in different histology groups

Total number of courses	Papillary cancer	Follicular cancer	Mixed form
1	33	11	11
> 1	7	4	1

From Table 1 it could be seen that the relative percentage of cases requiring more than 1 course, seems to be the same whatever the histological type of thyroid cancer.

For comparing the strength of the influence of parameters of radioiodine distribution in thyroid remnants and metastases on treatment outcome the regression analysis has been applied in 25 randomly selected patients.

Parameters of radioiodine distribution in thyroid tissue were as follows: average value of the first treatment activity A_{av} = 3631 MBq; effective half-time of radioiodine excretion in remnants T_{av} = 3.28 days; level of thyroid remnants accumulation relative to its background value in 24 h after activity administration σ_{av} = 25.68. In metastases in lymph nodes average value in 24 h after beginning of the treatment σ^{ln}_{av} = 12.06 (from 0.6 to 54). Effective half-life of ^{131}I excretion in lymph nodes in average was equal 2.7 $\pm$ 1.6 days (from 0.5 days to 6.19 days).

In 17 of 25 patients remnants and metastases were completely ablated after the first course of the treatment. 8 patients were subjected to several courses of radioiodine treatment.

In principle, the radioiodine therapy outcome may be reduced to two discrete values — 1 or 0 (ablation success or failure). Nevertheless, the outcome depends on several continuous parameters such as therapeutic activity, parameters of radioiodine distribution in thyroid tissue and other factors. All of them may be aligned in certain hierarchy depending on the strength of their influence on the outcome of the first course of the treatment. We have attempted to isolate those factors which are decisive ones and to clear up whether it is possible to indicate such activity value which could overcome the effects of individual factors such as the number and the size of metastatic lesions in lymph nodes.

Logistic function depending on measured parameters of radioiodine distribution in thyroid tissue was chosen as treatment outcome function of the first course. This function has two asymptotic values which were assigned as 1 — related to full metastases and remnants ablation after the first course or 0 — in case of the necessity of several courses of radioiodine treatment (the failure of the first course).

The normalization of the parameters to the average values allows us to compare their relative contribution to the treatment outcome:

$A_n = A / A_{av}$; $\sigma_n = \sigma / \sigma_{av}$

After the normalization of the parameters included into calculations, the function f of treatment outcome was determined (Statistics 5.5):

$$f = \exp(-3.2 + 4.46 \cdot A_n - 0.29 \cdot \sigma_n) / [1 + \exp(-3.2 + 4.46 \cdot A_n - 0.29 \cdot \sigma_n)] \quad (1)$$

$p = 0.04$.

f was equal 0.76 $\pm$ 0.18 in patients with total thyroid tissue ablation after the first course of the treatment;

and $f = 0.50 \pm 0.16$ in the case of the necessity of the several courses (upon failure of one course).

Fig. 2 shows the fraction of patients with the total thyroid tissue ablation after the first course in the every activity interval and f value for 25 randomly selected patients under study. *f* was calculated on the basis of equation (1); the mean value of σ for the patients treated in this activity interval and average activity value have been used in the calculations.

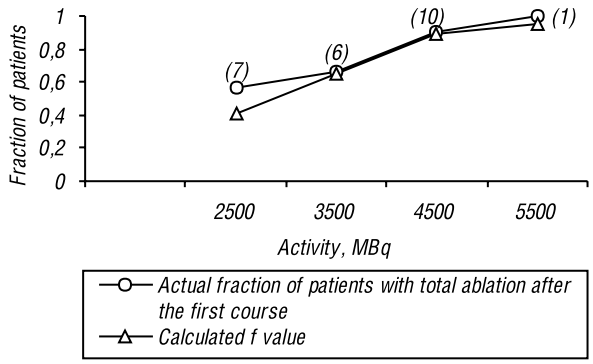

Fig. 2. The actual fraction of patients with total thyroid tissue ablation as compared with calculated *f* values in the treatment activity interval. The number of patients in every activity interval is indicated in the brackets

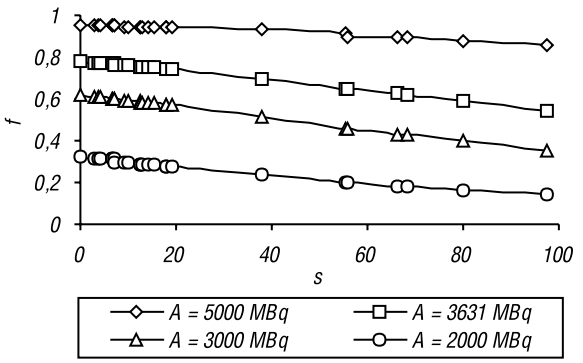

Fig. 3. f(σ) calculated at different activities value A_1 = 5000 MBq, A_2 = 3631 MBq (average value); A_3 = 3000 MBq; A_4 = 2000 MBq

It could be seen that calculated f values coincide with the fraction of the patients treated with not more then one course with the high accuracy.

From the equation (1) it could be concluded that the greater is remnants volume reflecting in σ, the greater treatment activity is necessary for increasing the probability of the treatment outcome after the first course (negative σ_n term of equation — 0.29). It should also bear in mind that σ reflects indirectly also the functional activity of thyroid remnants. According to our data % of radioiodine accumulation in remnants in 24 hours after activity administration correlates highly with σ (k = 0.8).

Activity value has the decisive influence on the treatment outcome as compared with σ (4.46 vs 0.29). Including other parameters (effective half-time of radioiodine excretion in remnants and metastatic lymph nodes, level of radioiodine accumulation in them) into analysis does not increase the confidence of the model (p = 0.04). Thus, treatment outcome does not depend on half-time of radioiodine excretion from remnants as well as level of radioiodine accumulation in lymph nodes (normal thyroid tissue is more radio resistant then lymph nodes [11]).

To assess the predictive strength of the model proposed, the relationship between *f* and the real values of σ has been plotted for different therapeutic activities.

In Fig. 3 the function *f(σ)* is represented under the assumption that all patients were given the same activity value (it could be plotted since σ does not correlate with activity value) –

A_1 = 5000 MBq;

A_2 = 3631 MBq (average value);

A_3 =3000 MBq;

A_4 =2000 MBq.

From Fig. 3 it could be seen that f > 0.7 at A = 5000 MBq. Thus, probability to pass only one course is rather high after administration of 5000 MBq. When the activity exceeds 5000 MBq, the individual clinical features do not appear to affect significantly on the outcome of the first course. Activity of 2000 MBq is insufficient whatsoever value of σ (f < 0.5). Nevertheless, in reality even one course may be sufficient in rather low activities approximately 1100 MBq.

With the aim to show the difference in the patterns of scintigramm in patients included into analysis three patterns of scintigram are given in Fig. 4, 5, 6.

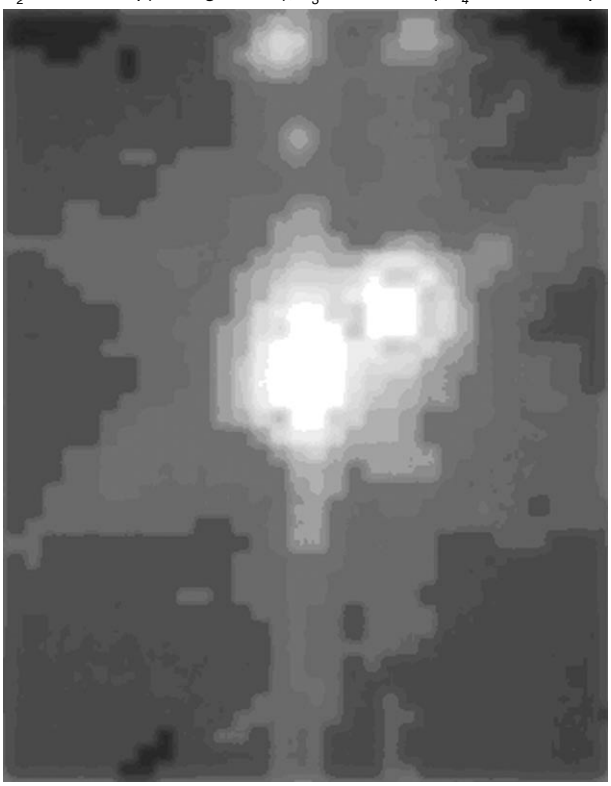

Fig. 4. Patient N. Follicular thyroid cancer. Thyroid remnants and metastases in lymph nodes of the neck are visualized on scintigram. The first activity was 3330 MBq

Patient N, Fig. 4, has undergone one course for total thyroid tissue ablation that coincided with the calculated value f of the proposed model.

In spite of the significant individual differences in the size of remnants, the number and the size of the affected lymph nodes, as shown in the scintigrams (Fig. 4–6) in all the cases the first radioiodine activity turned out to be decisive factor for radiotherapy outcome.

It is interesting to pay attention to the patients who were given several courses of the treatment but according to the model the total ablation should have taken place after the first course (4 patients) and *vise versa* — according to the model patients should have gone few courses but total ablation was revealed after the first course (2 patients). Thus, the model failed in 6 patients. 4 patients had follicular cancer, 2 — papillary one. No peculiar characteristics have been evident in scintigrams of these patients and individual σ values did not differ from σ_{av}. Upon analysis of the scintigrams of

these patients small remnants volume (σ =3.04 and σ = 7.16) and low level of ^{131}I accumulation in pathological lymph nodes were revealed in patients after one course (2 patients) in the first treatment activities A = 2364 MBq and A = 2368 MBq, while in the cases of the necessity of few courses activities were equal 3700 MBq in average but parameters of ^{131}I kinetics in remnants varied a little from average meanings. Thus, such results could rather be referred to individual radiosensitivity.

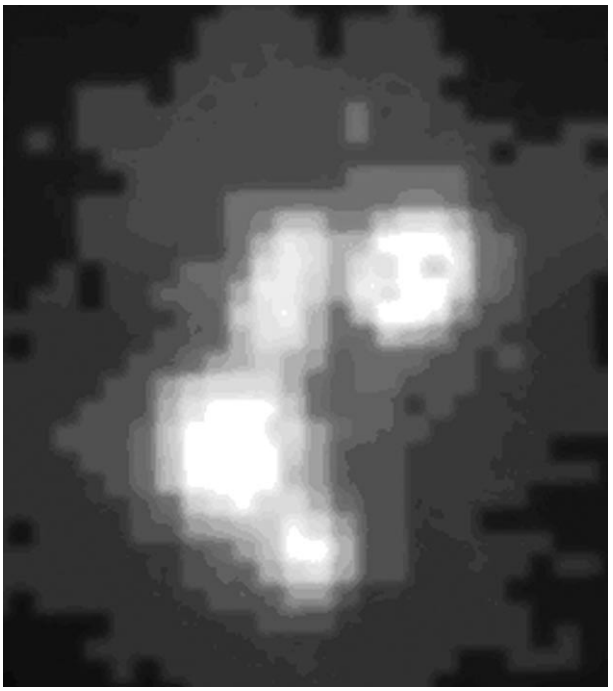

Fig.5. Patient Z. Papillary thyroid cancer. Thyroid remnants and metastases in lymph nodes are visualized. 2 courses of radioiodine treatment were necessary. 4300 MBq — the first therapeutical activity. According to the model total ablation should have take place after 1 course

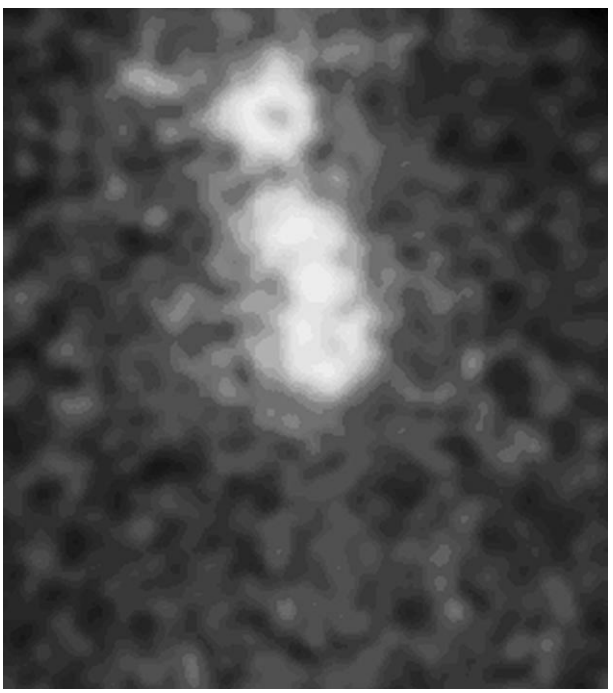

Fig. 6. Patient M. Papillary cancer of thyroid. Thyroid remnants and metastases in lymph nodes. First activity was 4500 MBq. Patient has undergone 1 course of the treatment which coincided with calculations

DISCUSSION

Activity value is the only variable parameter that could be changed during the treatment. As a rule, in the case of metastases in lymph nodes accumulating radioiodine the activities amount from 3600 to 7400 MBq [1]. There are cases when the volume of thyroid remnants after the surgery is large and thus pathological lymph nodes are not visualized during scintigraphy. Although ^{131}I accumulation in metastatic lymph nodes as a rule is less then in remnants (as well as $T_{effective}$), metastatic lymph nodes require less doses for their eradication – approximately 80 — 100 Gy as compared with 300 – 1000 Gy for remnants [12]. The higher radiosensitivity of the pathological thyroid tissue as compared to the normal one [10] may be helpful to explain the data cited above. May be due to the same difference in radiosensitivity, the volume of the remnants has decisive influence on the treatment outcome of the first course. The model proposed in this study states that the treatment outcome of the first course is determined by the first activity value and the level of ^{131}I accumulation in remnants but does not depend on T_{eff} in remnants. It is possible that predominant part of the dose (whether sufficient or not enough for ablation) is absorbed in remnants within the first day of the treatment.

The results of this analysis do not exclude the attempts of the individual approach to the treatment that could be useful in understanding the radiobiological effects of thyroid tissue ablation and ^{131}I distribution in remnants and metastases. Several researches are attempting to correlate the first treatment activity of radioiodine with the neck uptake in 24 or 48 h after administration of the low diagnostic activity (approximately 74 MBq). Meanwhile, effectiveness of 1100 MBq of ^{131}I in producing ablation did not correlate with ^{131}I uptake by the thyroid remnants, surgeon's estimate of remnant size, or dose delivered to the remnant, calculated using reasonable assumptions. These findings emphasize the difficulty of dosimetric measurements and calculations [4, 9, 14]. It was also shown that such factors as age, gender, tumor histology, stage, pre–therapy neck uptake of ^{131}I, diagnostic dose, TSH — level, ablation dose, time between diagnostic and therapeutic dose, etc. have rather low influence on the treatment outcome [7]. Nevertheless higher therapeutic activities are associated with higher rates of successful ablation, even when administered to patients with more advanced cancer.

Meanwhile, the optimal ^{131}I activity necessary to achieve total ablation of remnants and metastases remains uncertain [11].

Some authors indicate that to achieve ablation is more difficult with increasing individual percentage of ^{131}I uptake that confirms our data. Nevertheless, in [3] the conclusion has been made that in the percentages of successful ablation, there were no significant differences between ^{131}I activities of 3700–5500 MBq, 5500–6500 MBq, 6600–7300 MBq, and 7400 MBq or more. The 3700–5500 MBq ablative activity may furnish adjuvant therapy for occult metastases.

The results of our study suggest that therapeutical activities for treatment of thyroid cancer with metastases in lymph nodes should be not less then 5000 MBq if other restrictions are absent.

Within the activities exceeding 5000 MBq, the number and the volume of the affected lymph nodes as well as histology of the tumor do not appear to contribute substantially to the outcome of the treatment after the first activity administration in patients with metastases in lymph nodes. The choice of the activities exceeding 5000 MBq as well as those inferior to this value is rather doubtful.

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ВЛИЯНИЕ ТЕРАПЕВТИЧЕСКОЙ АКТИВНОСТИ I-131 НА РЕЗУЛЬТАТ РАДИОЙОДОТЕРАПИИ ДИФФЕРЕНЦИРОВАННОГО РАКА ЩИТОВИДНОЙ ЖЕЛЕЗЫ ПРИ МЕТАСТАТИЧЕСКОМ ПОРАЖЕНИИ ЛИМФОУЗЛОВ: МАТЕМАТИЧЕСКАЯ КОРРЕЛЯЦИЯ И КЛИНИЧЕСКОЕ ПРИМЕНЕНИЕ

Цель: **оценить влияние первой лечебной активности ^{131}I на результат радиойодотерапии по сравнению с размерами остаточной ткани щитовидной железы, количеством и размерами метастазов в лимфоузлах.** ***Материалы и методы:*** **68 больным с дифференцированным раком щитовидной железы проводили лечение радиойодом после тиреоидэктомии. У всех пациентов было выявлено патологическое накопление ^{131}I в пораженных лимфоузлах. Введенные активности принимали значение от 1000 до 6000 МБк. Для полного уничтожения тиреоидной ткани, включая метастатические очаги поражения, необходимо было провести от 1 до 4 курсов радиойодотерапии. Для оценки вероятности полного уничтожения метастазов и остаточной ткани после первого курса радиойодотерапии была выбрана логистическая функция.** ***Результаты:*** **результат применения I курса радиойодотерапии не зависит от уровня накопления ^{131}I в лимфоузлах, а также от эффективного периода полувыведения радиойода из остаточной ткани щитовидной железы.** ***Выводы:*** **у больных с дифференцированным раком щитовидной железы в случае наличия пораженных лимфоузлов, в которых накапливается радиойод, первая лечебная активность не должна быть меньше 5000 МБк — для уменьшения количества курсов радиойодотерапии до минимума. Результат применения радиойодотерапии слабо зависит от таких факторов, как гистология, а также от количества пораженных лимфоузлов и уровня накопления радиойода в них.**

Ключевые слова: **рак щитовидной железы, метастазы, ^{131}I, кинетика.**