ORIGINAL ARTICLE

RESULTS OF THE ANALYSIS OF ONCOLOGICAL COMPLICATIONS OF ANTI-TUMOR TREATMENT IN PATIENTS WITH THYROID CANCER ON THE BASIS OF MATHEMATICAL ANALYSIS OF THE CATAMNESTIC DATA

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ABSTRACT

The aim: Identification of new, non-trivial knowledge on the prediction of thyroid recurrence on the basis of follow-up data from medical histories.

Materials and methods: The development of long-term oncological effects was studied on the catamnestic data of 157 patients diagnosed with thyroid cancer who were treated according to a standard scheme, including radical surgery, radioiodine therapy and hormone therapy.

Results: It is shown that the specificity of thyroglobulin as a cancer marker for thyroid cancer is not an unambiguous question and the probability of obtaining false-positive results on its basis is quite significant.

It is shown that violation of the recommended terms for special treatment (surgical and radioiodine therapy) can be used as a factor in the prognosis of relapse, and patients who received special treatment with violation of the terms for various reasons require careful attention and more careful examination. The dose of thyroxine that should be used to achieve suppression can be used as a marker of thyroid relapse: an excess of thyroxine levels of 2.8 μg / kg is an indicator of the risk of relapse in the future.

Statistically there was no significant effect on the prevention of long-term oncological complications by prolonging the duration of suppressive hormone therapy as a component of thyroid cancer treatment, but there are grounds to believe that prolonged suppression leads to increased cardiovascular and female genital complications.

Conclusions: the use of modern information technologies in relation to the arrays of catamnestic data of medical histories allowed to obtain additional knowledge to prevent the development of distant oncological complications resulting from thyroid cancer.

KEY WORDS: Differentiated thyroid cancer, long-term effects, Data Mining technology

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INTRODUCTION

Differentiated thyroid cancer (DTC) is the most common tumor of the endocrine system, and on average comprises 1.0 - 2.2% of all malignant neoplasms [1].

It is known that the prognosis of complete cure of differentiated thyroid cancer is quite favorable and reaches over 90% of 5, 10 and even 20 years of survival [2–4]. However, the number of recurrences and distant metastasis, which according to various authors [5,6] occur from 10 to 30%, encourage scientists to continue working towards optimizing the treatment of this disease.

State organization «Grigoriev Institute for Medical Radiology and Oncology of the National Academy of Medical Sciences of Ukraine» is one of the leading institutions of Ukraine for the treatment of the thyroid gland pathologies and has a large archive of paper medical histories starting from 1992 indexed in the official database. The availability of such a powerful source of information provides grounds for a more detailed analysis in order to obtain new knowledge about the course and consequences of thyroid cancer treatment. A possible way to conduct such an analysis is by using Data Mining, the purpose of which is to identify previously unknown non-trivial data that can be practically useful, available for new learnings and necessary for decision-making in various fields of human activity.

THE AIM

The aim of the present study was to identify new, non-trivial data about the prediction of thyroid recurrence based on catamnestic medical history of patients with thyroid cancer.

MATERIALS AND METHODS

The study included 157 medical histories of patients with thyroid cancer who underwent combined special treatment in the clinic from 1993 to 2020 and on the basis of which an appropriate electronic database (DB) which contained the

full amount of information from paper media was created.

The criterion for selecting medical histories for the database was either the appearance of any malignant disease one or more years after treatment, or the appearance of long-term therapeutic complications. The number of logical records about patients in the formed database was 463 units – one record for one consequence of each patient.

The database, in particular, contained information on the level of thyroglobulin (after surgery, before and after radioiodine therapy (RTI) and every next 6 months in the post-treatment monitoring phase), the dose of thyroxine (monitored every 3 months), the levels of thyroid-stimulating hormone (TSH) (every 2-3 months during treatment and post-treatment monitoring), the duration of suppressive hormone therapy (HST), the duration of non-compensated hypothyroidism (NHT), as well as information on age, weight, somatic complications, surgical complications, RT complications, etc. The state of suppression in patients was confirmed on the basis of TSH levels (0.1-0.5 mIU / l in the first three years after surgery and 0.1-1 mIU / l after).

For the high-risk group, the target baseline TSH level was below 0.1 mIU / L during the course of thyroxine suppressive therapy. For intermediate risk patients, the initial target TSH level was 0.1–0.5 mIU / L. For low-risk patients who received RTI after thyroidectomy and had a TG level lower than the limit of detection, the target TSH level was 0.5–2.0 mIU / L. For low-risk patients who received RTI after thyroidectomy and had low TG levels, the target TSH level was 0.1–0.5 mIU / L with monitoring for possible recurrence.

Among the patients there were 27 men (17.2%) and 130 women (82.8%). According to the histological structure, 126 (80.3%) people had papillary cancer and 25 people (16%) had follicular cancer. Papillary follicular cancer was diagnosed in 6 patients (3.7%). The most typical tumor volume ranged from 0,5 mm^3 to 8,2 mm^3. The age of patients in the general group ranged from 13 to 76 years with a median of 48 years and an interquartile range (IR) of 40 ÷ 56 years.

54 patients had oncological complications (OC), including: recurrences – 42 people (77,8 %), of which – local recurrences (in the area of the typical location of the thyroid gland) – 15 people (27,8 %), lymph nodes and / or lungs metastatic lesions (distant metastases in time (DMT) – 27 people (50 %), second cancers – 12 people (22,2 %). According to the stages of the cancer process, patients were distributed as follows: 1st stage – 13 (15,9 %) people, 2nd stage – 22 (40,7 %) people, 3rd stage – 14 (25,9 %) people, 4th stage – 5 (9,2 %) people. For the moment when OC appeared the age of the patients varied from 23 years to 76 years with IR = 42 – 63 years and a median of 51 year. The time when OC appeared was 62 months (median), varying from 10 months to 158 months (13 years), IR = 42 – 89 months.

In 12 patients (7.4%) no category of long-term effects of treatment was recorded, in 91 (58%) persons – only therapeutic complications.

The median total activity of ^{131}I was 4440 MBq, IR = 3050 – 7400 MBq.

The WizWhy package was used to conduct research and make hypotheses, which were then tested with the methods of non-parametric statistics. Statistical processing was performed using the software package Statistica Basic Academic 13 for Windows, (License Number: 139-956-866). The statistical significance of the results was assessed using Pearson's chi-squared test, Mann-Whitney test, Kruskal-Wallis test and median test.

The data are further presented as M (LQ; UQ), where M is the median of LQ is the lower quartile, UQ is the upper quartile.

RESULTS AND DISCUSSION

Thyroglobulin level (TG) was the first indicator that attracted attention based on the results of Data Mining on the array of catamnestic data on medical histories of patients with thyroid cancer. Against the background of suppressive therapy, this figure was different in patients with and without oncological complications in the future. The dependence was statistically significant (Mann-Whitney test, $p < 0,05$) (Fig.1).

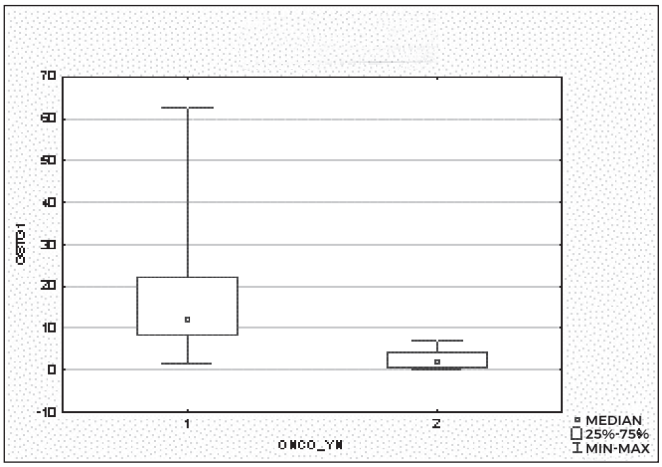
As can be seen from the figure, TG level was 11.7 (8.2; 22.1) ng / ml and ranged from 1.7 ng / ml to 62.5 ng / ml in patients with OC. In patients without OC, TG level was 2.1 (0.51; 4.4) ng / ml and ranged from 0.004 ng / ml to 11.9 ng / ml.

It is known that after removal of the thyroid gland, thyroglobulin is used as a tumor marker. Under favorable conditions, its level should be insignificant (at least <1 ng / ml and ideally go to 0 ng / ml). Our results regarding patients with OC correspond to well-known facts, but in some patients without oncological consequences in the future its level was quite significant and even reached the level of 11.9 ng / ml (Table I).

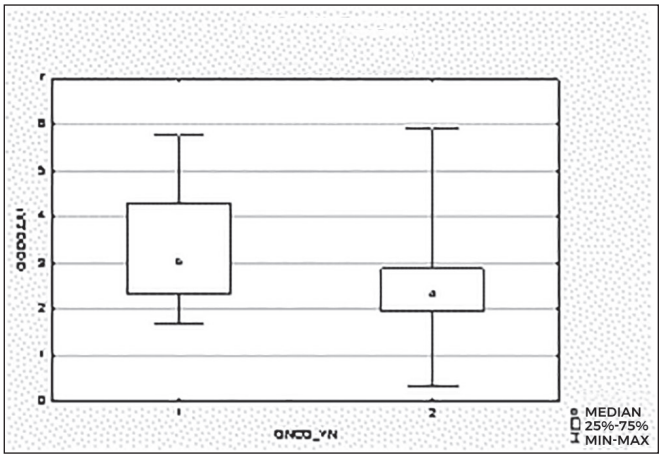
All the patients whose information is given in the table underwent regular examination after treatment and no signs of malignancy were detected.

The second indicator that attracted attention in terms of prognostic properties was the time of ablation: in patients with DMT it was 2.2 times higher than in patients without OC and was 19.5 (IR = 7.5 – 40, 5) months against 9 (IR = 5 – 22) ($p = 0.03$, Mann-Whitney test) (Fig. 2).

Thus, there are grounds to believe that if the time of ablation of thyroid tissue during the RNT exceeds the limit of 20 months it is an unfavorable factor for the appearance of distant metastases. Delay of the ablation, in our opinion, may be associated first with non-radical surgical treatment, as evidenced by the presence of residual thyroid tissue (more than 1 cm^3), the presence of micrometastases in lymph nodes and lungs that were not detected in the preoperative stage, partial radioresistance of local and distant metastases. In addition, it should be taken into account that an increase in the duration of treatment may be observed in patients with postoperative complications due to the need to correct these complications and reduce the therapeutic activity of radioiodine to prevent laryngeal edema and acute respiratory failure.



1 – group of patients with OC; 2 – group of patients without OC.
Fig. 1. Comparative graphs of TG levels on the background of suppressive therapy in patients with and without OC.



1 – group of patients with OC; 2 – group of patients without OC.
Fig. 3. Dose of thyroxine per 1 kg of body weight in patients with NHT during hormone therapy.

Table I. TG level in patients with thyroid cancer in the long term after radionuclide treatment.

Patient	TG level (ng/ml)	Number of months (after RNT)
H-n	11,9	40
F-a	4,4	20
R-o	2,45	12
O-a	2,1	13
K-a	2,1	12

The third interesting result of using Data Mining technology in relation to the problem of OC was the dose of L-thyroxine in NHT during hormone therapy (Fig. 3).

It was found that in patients with OC the dose of L-thyroxine in NHT was 3.02 (2.3; 4.3) with a total duration of NHT being 13 (9.0; 24.0) months; in patients without OC, the dose of L-thyroxine in NHT was 2.34 (1.9; 2.9) with a total duration of NHT being 9 (4.0; 16.0) months, (Mann-Whitney test, p = 0.0192).

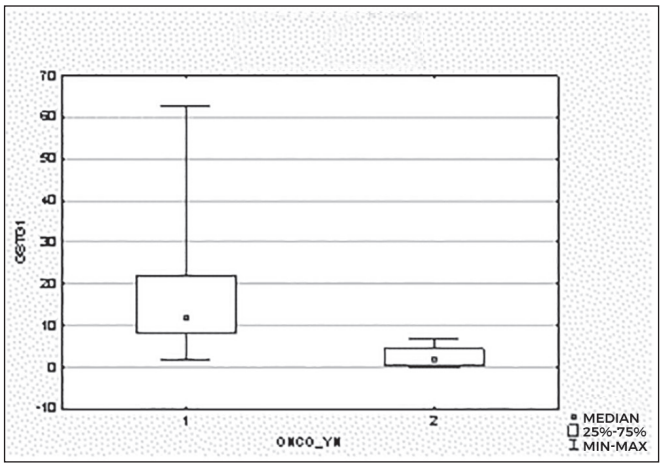
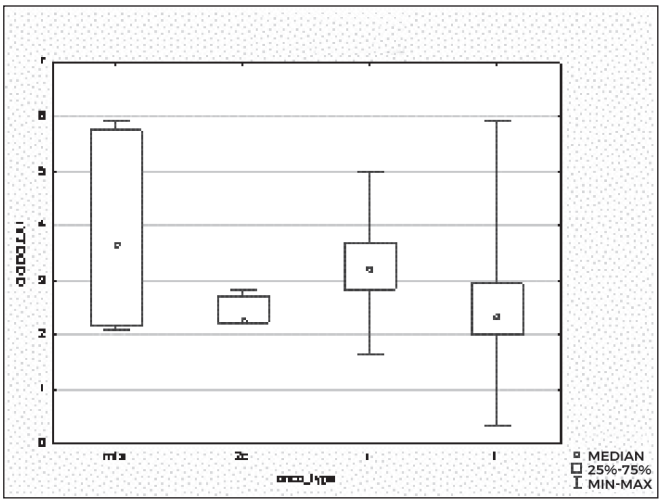


Fig. 2. Comparative graphs of long-term results of treatment (1 – appearance of OC (metastases); 2 – absence of OC).

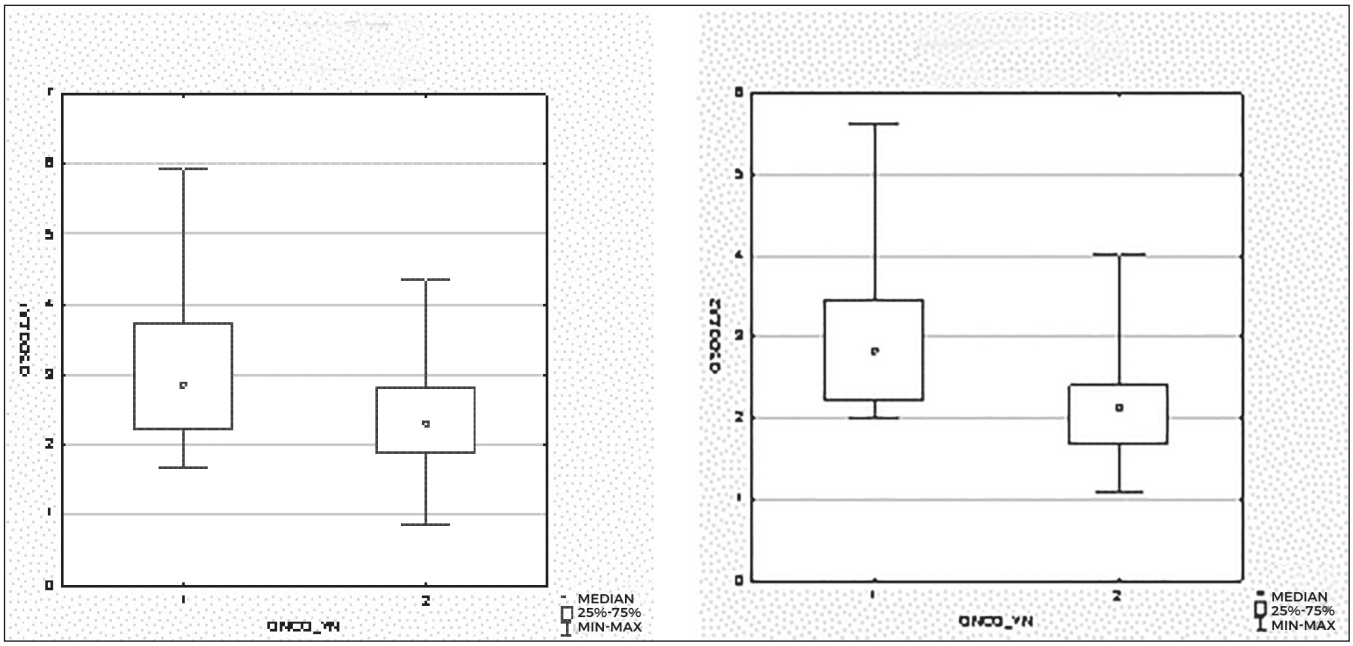


t – group of patients with therapeutic complications (without OC); mts – metastatic lesions of the lymph nodes and / or lungs; 2c – second cancer; r – local recurrences (in the area of the typical location of the thyroid gland).
Fig. 4. Dose of thyroxine per 1 kg of body weight in patients with NHT during hormone therapy

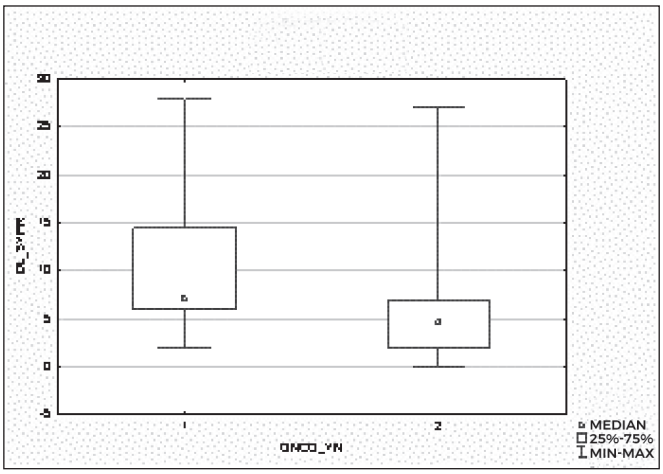
The rate of the L-thyroxine dose in NHT was different not only in groups with and without OC, but also showed markers in the division of effects into groups: without OC, metastases, recurrences, second cancers (median test, p = 0,0034).

From the box graphs of Figure 4, it can be seen that, on the one hand, patients with metastases and recurrences, and, on the other hand, patients with other cancers and patients without OC had similar dose characteristics.

These facts allow us to draw conclusions about the presence of marker signs of the L-thyroxine dose on the background of NHT as well: at a dose of 3.66 (2.2; 5.8) μg / kg there is a risk of distant metastases, and at 3.2 (2.9, 3.7) μg / kg – of local recurrences. Therefore, the presence of NHT at a hormone dose exceeding 2.8 μg / kg should also be an alarming sign of future oncological diseases.



1 – group of patients with OC; 2 – group of patients without OC.
Fig. 5. The dose of thyroxine or levothyroxine sodium per 1 kg of body weight of patients with a suppressive condition at two intervals of observation after treatment.



1 – group of patients with OC; 2 – group of patients without OC.
Fig. 6. Comparative graphs of the total duration of suppressive therapy in patients with OC and without OC.

The fourth non-trivial result of this study was the association of L-thyroxine dose in HRT: a prognostically unfavorable factor for the occurrence of distant OC is the need to increase the dose of thyroid hormone to achieve a suppressive state in patients after special treatment.

The database used in the study contained information of up to three intervals of HRT during hormone therapy. During the analysis, all 3 intervals gave almost identical results: the need to increase the dose of thyroid hormone to a level exceeding 2.8 μg / kg should cause concern about the recurrence of the oncological disease in the future (Fig. 5).

Indeed, as can be seen from the above box graphs, the median values of the suppressive dose of L-thyroxine in patients without oncological complications in the future in the first and second observation intervals are 2.3 μg / kg and 2.1 μg / kg (in the third interval – 2.1 μg / kg), while the corresponding values in patients with oncological complications are 2.9 μg / kg, 2.8 μg / kg and 3.3 μg / kg. At the 1st and 2nd intervals of observation, the dependencies were statistically significant (Mann-Whitney test, p = 0.01 and 0.03, respectively).

The fifth dependence, shown in Figure 6, looks quite paradoxical regarding the characteristics of HRT in terms of appearance of OC: the total duration of therapy in patients with OC is longer than the duration of HRT in patients without OC (7 (6; 14) vs. 4, 5 (2; 7)), p = 0.03, Mann-Whitney test.

In the analyzed sample, no dependence between the duration of HRT and the stage of the process and the age of patients as intervention factors was detected. For further analysis of the detected dependence, HRT duration interval was divided into subbands in accordance with the descriptive statistics of this indicator for patients with and without OC: 1-6 months, 7-14 months, 15 months-22 months, and more than 22 months. The results of data analysis of 42 patients who received a course of HRT (total duration from 1 month to 28 months) after surgery and radionuclide treatment in terms of the presence of OC - duration of treatment and duration of treatment - the presence of OC are shown in Tables II and III.

The results provided in the tables show that it cannot be stated unequivocally that the prolongation of the suppressive state in patients after surgery and radionuclide treatment is a guarantee of the absence of OC in the future. Note that on the background of prolonged duration of HRT patients in the study group showed a tendency to increase the number of distant cardiovascular and gynecological complications, but these dependencies were hypothetical and were not statistically confirmed in the working sample.

Table II. Total HRT duration in patients with thyroid cancer after surgery and radionuclide treatment in terms of the presence of OC – duration of treatment

Group of patients	Duration of suppressive therapy				Total abs.
	1-6 months abs., (%)	7-14 months abs., (%)	15-21 months abs., (%)	more than 22 months abs., (%)	
With OC	4 (33,33)	5 (41,67)	2 (16,67)	1 (8,33)	12
Without OC	22 (73,33)	4 (13,33)	2 (6,67)	2 (6,67)	30
Total	26	9	4	3	42

Table III. Total duration of HRT in patients with thyroid cancer after surgery and radionuclide treatment in terms of duration of treatment – the presence of OC

Duration of suppressive therapy	Presence of OC		
	With OC abs., (%)	Without OC abs., (%)	total abs.
1 -6 months	4 (15,38)	22 (84,62)	26
7-14 months	5 (55,56)	4 (44,44)	9
15 -21 months	2 (50,00)	2 (50,00)	4
more than 22 months	1 (33,33)	2 (66,67)	3
Total	12	30	42

Thus, according to our observations, the specificity of TG as a tumor marker is not an unambiguous issue and the probability of obtaining false-positive results on its basis is quite significant.

The data that the lack of compensation for hypothyroidism is an unfavorable factor in the prognosis of thyroid recurrence are fully confirmed and coincide with the data of other researchers. In addition, it has been shown that violation of the recommended terms for special treatment (surgery and radioiodine therapy) can also be used as a prognostic factor for relapse (patients undergoing special treatment with delays for various reasons need careful attention and more careful examination).

Another interesting fact was that the dose of thyroxine that must be used to achieve suppression can be used as a marker of recurrence of thyroid cancer. It has been shown that the higher the dose, the worse the prognosis regarding the likelihood of future oncological consequences. Taking into consideration the fact that among patients in the observation group the duration of OC ranged from 10 months to 158 months (13 years), a useful practical aspect of post-treatment monitoring is the need for regular monitoring, at least for 13 years with a particularly meticulous attitude to patients receiving or having prescribed a suppressive dose of thyroxine during treatment excessing 2.8 μg / kg.

In addition, we did not find a statistically significant effect on the prevention of remote OC by prolonging the duration of suppressive hormone therapy as a component of thyroid cancer treatment, but there are grounds to believe that prolonged suppression leads to increased cardiovascular and female genital complications..

CONCLUSIONS

Thus, using the new knowledge about the factors predicting the development of cancer complications of the thyroid gland it is possible to:

– increase the accuracy of the prognosis for all stages of thyroid cancer;
– increase the 5 and 10-year survival of patients;
– reduce the average time to detect recurrence of the disease;
– provide less aggressive treatment of recurrence due to its timely detection;
– improve the quality of life of patients by reducing their disability.

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