Journal of Medical Case Reports and Reviews
Received 5 Nov 2021 | Revised 10 Nov 2021 | Accepted 16 Jan 2022 | Published Online 2 Feb 2022

DOI: https://doi.org/10.52845/JMCRR/2022/5-2-1
JMCRR 5 (02), 1068–1078 (2022)

ISSN (O) 2589-8655 | (P) 2589-8647 IF:2.964

Article Type
Research Article

Contents of Calcium, Chlorine, Iodine, Potassium, Magnesium, Manganese, and Sodium in Thyroid Malignant Nodules and ThyroidTissue Adjacent to Nodules

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Abstract

Objectives and Backgrounds: Thyroid malignant nodules (TMNs) are the most common endocrine cancer and the fifth most frequently occurring type of malignancies. The etiology and pathogenesis of TMNs must be considered as multifactorial. The present study was performed to clarify the role of some chemical elements (ChEs) in the etiology of these thyroid disorders.

Methods and patients: Thyroid tissue levels of calcium (Ca), chlorine (Cl), iodine (I), potassium (K), magnesium (Mg), manganese (Mn), and sodium (Na) were prospectively evaluated in malignant tumor and tissue adjacent to tumor of 41 patients with TMNs. Measurements were performed using non-destructive instrumental neutron activation analysis with high resolution spectrometry of short-lived radionuclides. Tissue samples were divided into two portions. One was used for morphological study while the other was intended for ChEs analysis. Results of the study were additionally compared with previously ob-tained data for the same ChEs in "normal" thyroid tissue.

Results: It was observed that in malignant tissue the mass fraction of Cl, K, Mg, and Na were approximately 2.3, 1.6, 1.6, and 1.3 times, respectively, higher whereas mass fraction of I was 25.6 times lower than in the normal thyroid. In a general sense K, Mg, Mn, and Na contents found in the "normal" and "adjacent" groups of thyroid tissue samples were very similar. However, in the "adjacent" group mean mass fractions of Cl and I were 1.57 and 1.73 times, respectively, higher, while mean value of Ca content almost 2 times lower than in the "normal" group. In malignant tumor Ca, Cl, and K contents were approximately 2.8, 1.4, and 1.7 times, respectively, higher, while I content 43.5 times lower than in "adjacent" group of tissue samples.were very similar. However, in the "adjacent" group mean mass fractions of Cl and I were 1.57 and 1.73 times, respectively, higher, while mean value of Ca content almost 2 times lower than in the "normal" group. In malignant tumor Ca, Cl, and K contents were approximately 2.8, 1.4, and 1.7 times, respectively, higher, while I content 43.5 times lower than in "adjacent" group of tissue samples.

Conclusions: From results obtained, it was possible to conclude that the common characteristics of TMNs in comparison with "normal" thyroid and visually "intact" thyroid tissue adjacent to malignant tumors were elevated levels of Cl and K, as well as drastically reduced level of I. It was supposed that elevated levels of Cl and K, as well as drastically reduced level of I in cancerous tissue could possibly be explored for differential diagnosis of benign and malignant thyroid nodules.

Keywords: Chemical elements, Neutron activation analysis, Thyroid, Thyroid malignant nodules

1 | INTRODUCTION

Thyroid malignant nodules (TMNs) are the most common endocrine cancer and the fifth most frequently occurring type of malignancies (1) . (2) The incidence of TMNs has increased worldwide over the past four decades. TMNs are divided into three main histological types: differentiated (papillary and follicular thyroid cancer), undifferentiated (poorly differentiated and anaplastic thyroid cancer, and medullary thyroid cancer, arising from C cells of thyroid (3) . For over 20th century, there was the dominant opinion that TMNs is the simple consequence of iodine deficiency (4) . However, it was found that TMNs is a frequent disease even in those countries and regions where the population is never exposed to iodine shortage. Moreover, it was shown that iodine excess has severe consequences on human health and associated with the presence of TMNs (5–8) . It was also demonstrated that besides the iodine deficiency and excess many other dietary, environmental, and occupational factors are associated with the TMNs incidence (9–11) . Among these factors a disturbance of evolutionary stable input of many chemical elements (ChEs) in human body after industrial revolution plays a significant role in etiology of TMNs (12) .

Besides iodine, many other ChEs have also essential physiological functions (13) . Essential or toxic (goitrogenic, mutagenic, carcinogenic) properties of ChEs depend on tissue-specific need or tolerance, respectively (13) .Excessive accumulation or an imbalance of the ChEs may disturb the cell functions and may result in cellular proliferation, degeneration, death, benign or malignant transformation (13–15) .

In our previous studies the complex of in vivo and in vitro nuclear analytical and related methods was developed and used for the investigation of iodine and other ChEs contents in the normal and pathological thyroid (16–22) . Iodine level in the normal thyroid was investigated in relation to age, gender and some non-thyroidal diseases (23, 24) . After that, variations of many ChEs content with age in the thyroid of males and females were studied and age- and gender-dependence of some ChEs was observed (25–41) . Furthermore, a significant difference between some ChEs contents in colloid goiter, thyroiditis, and thyroid adenoma in comparison with normal thyroid was demonstrated (42–46) .

To date, the etiology and pathogenesis of TMNs must be considered as multifactorial. The present study was performed to find out differences in ChEs contents between the group of cancerous tissues and tissue adjacent to tumor, as well as to clarify the role of some ChEs in the etiology of TMNs. Having this in mind, the aim of this exploratory study was to examine differences in the content of calcium (Ca), chlorine (Cl), iodine (I), potassium (K), magnesium (Mg), manganese (Mn), and sodium (Na) in nodular and adjacent to nodules tissues of thyroids with TMNs using a non-destructive instrumental neutron activation analysis with high resolution spectrometry of short-lived radionuclides (INAA-SLR), and to compare the levels of these ChEs in two groups (tumor and adjacent to tumor tissues) of the cohort of TMNs samples. Moreover, for understanding a possible role of ChEs in etiology and pathogenesis of TMNs results of the study were compared with previously obtained data for the same ChEs in “normal” thyroid tissue (42–46) .

Patients and method

All patients with TMNs (n=41, mean age MSD was 4615 years, range 16-75) were hospitalized in the Head and Neck Department of the Medical Radiological Research Centre (MRRC), Obninsk.. Thick-needle puncture biopsy of suspicious nodules of the thyroid was performed for every patient, to permit morphological study of thyroid tissue at these sites and to estimate their trace element contents. In all cases the diagnosis has been confirmed by clinical and morphological results obtained during studies of biopsy and resected materials. Histological conclusions for malignant tumors were: 25 papillary adenocarcinomas, 8 follicular adenocarcinomas, 7 solid carcinomas, and 1 reticulosarcoma. Tissue samples of tumor and visually intact tissue adjacent to tumor were taken from resected materials.

Supplementary information The online version of this article (https://doi.org/xx.xxx/xxx.xx) contains supplementary material, which is available to authorized users.

"Normal" thyroids for the control group samples were removed at necropsy from 105 deceased (mean age 4421 years, range 2-87), who had died suddenly. The majority of deaths were due to trauma. A histological examination in the control group was used to control the age norm conformity, as well as to confirm the absence of micro-nodules and latent cancer.

All studies were approved by the Ethical Committees of MRRC. All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments, or with comparable ethical standards. Informed consent was obtained from all individual participants included in the study

All tissue samples obtained from tumors and visually intact tissue adjacent to tumors were divided into two portions using a titanium scalpel to prevent contamination by ChEs of stainless steel (47) . One was used for morphological study while the other was intended for ChEs analysis. After the samples intended for ChEs analysis were weighed, they were freeze-dried and homogenized (48) . The pounded samples weighing about 10 mg (for biopsy) and 100 mg (for resected materials) were used for ChEs measurement by INAA-SLR.

To determine contents of the ChE by comparison with a known standard, biological synthetic standards (BSS) prepared from phenol-formaldehyde resins were used (49) . In addition to BSS, aliquots of commercial, chemically pure compounds were also used as standards. Ten sub-samples of certified reference material (CRM) of the International Atomic Energy Agency (IAEA) IAEA H-4 (animal muscle) weighing about 100 mg were treated and analyzed in the same conditions as thyroid samples to estimate the precision and accuracy of results.

The content of Ca, Cl, I, K, Mg, Mn, and Na were determined by INAA-SLR using a horizontal channel equipped with the pneumatic rabbit system of the WWR-c research nuclear reactor (Branch of Karpov Institute, Obninsk). Details of used nuclear reactions, radionuclides, gamma-energies, spectrometric unit, sample preparation, and the quality control of results were presented in our earlier publications concerning the INAA-SLR of ChEs contents in human thyroid, scalp hair, and prostate (27, 28, 50) . (51) (52)

A dedicated computer program for INAA-SLR mode optimization was used (53) . All thyroid samples for ChEs analysis were prepared in duplicate, and mean values of ChEs contents were used in final calculation. Using Microsoft Office Excel software, a summary of the statistics, including, arithmetic mean, standard deviation, standard error of mean, minimum and maximum values, median, percentiles with 0.025 and 0.975 levels was calculated for ChEs contents in malignant and adjacent to tumor tissue of thyroids with TMNs. Data for "normal" thyroid were taken from our previous publications (42–46) . The difference in the results between three groups of samples ("normal", "tumor", and "adjacent") was evaluated by the parametric Student's t-test and non-parametric Wilcoxon-Mann-Whitney U-test.

2 | RESULTS

Table 1 presents certain statistical parameters (arithmetic mean, standard deviation, standard error of mean, minimal and maximal values, median, percentiles with 0.025 and 0.975 levels) of theCa, Cl, I, K, Mg, Mn, and Na mass fraction in "normal", "tumor", and "adjacent" groups of thyroid tissue samples.

The ratios of means and the comparison of mean values of Ca, Cl, I, K, Mg, Mn, and Na mass fractions in pairs of sample groups such as "normal" and "tumor", "normal" and "adjacent", and also "adjacent" and "tumor" are presented in Table 2, 3, and 4, respectively.

3 | DISCUSSION

As was shown before (27, 28, 50–52) good agreement of the Ca, Cl, I, K, Mg, Mn, and Na contents in CRM IAEA H-4 samples analyzed by INAA-SLR with the certified data of this CRM indicates acceptable accuracy of the results obtained in the study of thyroid tissue samples presented in Tables 1–4.

From Table 2, it is observed that in malignant tissue the mass fraction of Cl, K, Mg, and Na are approximately 2.3, 1.6, 1.6, and 1.3 times, respectively, higher whereas mass fraction of I is 25.6 times lower than in the normal thyroid. Thus, if we accept the ChEs contents in thyroid glands of the "normal" group as a norm, we have to conclude that with a malignant transformation the Cl, I, K, Mg, and Na contents in thyroid tissue significantly changed. In a general sense K, Mg, Mn, and Na contents found in the "normal" and "adjacent" groups of thyroid tissue samples were very similar (Table 3). However, in the "adjacent" group mean mass fractions of Cl and I were 1.57 and 1.73 times, respectively, higher, while mean value of Ca content was 2 times lower than in the "normal" group. Significant changes of tumor ChEs contents in comparison with thyroid tissue adjacent to tumor were found for Ca (increase), Cl (increase), I (decrease), and K (increase). In malignant tumor Ca, Cl, and K contents were approximately 2.8, 1.4, and 1.7 times, respectively, higher, while I content 43.5 times lower than in "adjacent" group of tissue samples (Table 4). Thus, from results obtained, it was possible to conclude that the common characteristics of TMNs in comparison with "normal" thyroid and visually "intact" thyroid tissue adjacent to malignant tumors were elevated levels of Cl and K, as well as drastically reduced level of I (Tables 2 and 4). (54) (55) (56) (57) (58)

Characteristically, elevated or reduced levels of ChEs observed in thyroid nodules are discussed in terms of their potential role in the initiation and promotion of these thyroid lesions. In other words, using the low or high levels of the ChEs in affected thyroid tissues researchers try to determine the role of the deficiency or excess of each ChE in the etiology and pathogenesis of thyroid diseases. In our opinion, abnormal levels of many ChEs in TMNs could be and cause, and also effect of thyroid tissue transformation. From the results of such kind studies, it is not always possible to decide whether the measured decrease or increase in ChEs level in pathologically altered tissue is the reason for alterations or vice versa. According to our opinion, investigation of ChEs contents in thyroid tissue adjacent to malignant nodules and comparison obtained results with ChEs levels typical of "normal" thyroid gland may give additional useful information on the topic because these data show conditions of tissue in which TMNs were originated and developed.

Chlorine and sodium: Cl and Na are ubiquitous, extracellular electrolytes essential to more than one metabolic pathway. In the body, Cl and Na mostly present as sodium chloride. Therefore, as usual, there is a correlation between Na and Cl contents in tissues and fluids of human body. Because Cl is halogen like I, in the thyroid gland the biological behavior of chloride has to be similar to the biological behavior of iodide. The main source of natural Cl for human body is salt in food and chlorinated drinking water. Environment (air, water and food) polluted by artificial nonorganic Cl-contained compounds, for example such as sodium chlorate ($NaClO_3$), and organic Cl-contained compounds, for example such as polychlorinated biphenyls (PCBs) and dioxin, is other source. There is a clear association between using chlorinated drinking water, levels $NaClO_3$, PCBs and dioxin in environment and thyroid disorders, including cancer [54-58}. Thus, on the one hand, the accumulated data suggest that Cl level in thyroid tissue might be responsible for TMNs development. However, on the other hand, it is well known that Cl and Na mass fractions in human tissue samples depend mainly on the extracellular water volume (59) . Tumors and adjacent to tumors thyroid tissues can be more vascularized than normal thyroid. Because blood is extracellular liquid, it is possible to speculate that more intensive vascularization could be the reason for elevated levels of Cl and Na in TMNs and adjacent tissue. If that is the case, the equilibrium between Cl and Na increases has to be, however, in comparison with "normal" thyroid the change of Cl level in tumors and adjacent tissue is significantly

TABLE 1: Some statistical parameters of, Ca, Cl, I, K, Mg, Mn, and Na mass fraction (mg/kg, dry mass basis) in normal thyroid and thyroid cancer (tumor and ``intact'' thyroid tissue adjacent to tumor)

Tissue	Element	Mean	SD	SEM	Min	Max	Median	P 0.025	P 0.975
Normal	Ca	1692	1022	109	414	6230	1451	460	3805
thyroid	Cl	3400	1452	174	1030	6000	3470	1244	5869
	I	1841	1027	107	114	5061	1695	230	4232
	K	6071	2773	306	1740	14300	5477	2541	13285
	Mg	285	139	16.5	66.0	930	271	81.6	541
	Mn	1.35	0.58	0.07	0.510	4.18	1.32	0.537	2.23
	Na	6702	1764	178	3050	13453	6690	3855	10709
Cancer	Ca	2398	2368	558	452	8309	1302	467	7428
(tumor)	Cl	7699	2900	703	4214	14761	7216	4240	13619
	I	71.8	62.0	10	2.00	261	62.1	2.93	192
	K	9655	4444	970	1660	19255	8746	3181	19035
	Mg	450	232	51	122	1033	408	126	931
	Mn	1.90	1.41	0.32	0.100	5.79	1.59	0.100	5.37
	Na	8556	2959	646	4083	17284	7264	4704	14543
Cancer	Ca	862	560	140	81.0	1909	672	149	1822
(adjacent	Cl	5339	22512	581	2526	11767	4922	2595	10201
tissue)	I	3183	1673	301	563	8240	2982	853	7766
	K	5717	2525	652	2097	12681	5429	2466	10953
	Mg	339	407	105	15.0	1412	199	15.0	1287
	Mn	1.72	1.63	0.41	0.410	6.78	1.15	0.429	5.54
	Na	7671	2597	649	3865	14373	7434	4169	13009

M – arithmetic mean, SD – standard deviation, SEM – standard error of mean, Min – minimum value, Max – maximum value, P 0.025 – percentile with 0.025 level, P 0.975 – percentile with 0.975 level.

TABLE 2: Differences between mean values (M±SEM) of Ca, Cl, I, K, Mg, Mn, and Na mass fraction (mg/kg, dry mass basis) in normal thyroid and thyroid cancer (tumor)

	Thyroid tissue				Ratio
	Normal thyroid	Cancer (tumor)	Student's t-test p£	U-test p	Tumor/Normal
Ca	1692±109	2398±558	0.243	>0.05	1.42
Cl	3400±174	7699±703	**0.000013**	≤**0.01**	2.26
I	1841±107	71.8±10.0	**0.00000000001**	≤**0.01**	0.039
K	6071±306	9655±970	**0.0017**	≤**0.01**	1.59
Mg	285±17	450±51	**0.0047**	≤**0.01**	1.58
Mn	1.35±0.07	1.90±0.32	0.107	>0.05	1.41
Na	6702±1785	8556±646	**0.011**	≤**0.01**	1.28

M – arithmetic mean, SEM – standard error of mean, Statistically significant values are in bold.

higher than change of Na level. Thus, it is possible to assume that an excessive accumulation of Cl in thyroid tissue is involved in TMNs etiology. Overall, the elevated levels of Cl in thyroid tissue could possibly be explored as risk factor of TMNs.

Iodine: Nowadays it was well established that iodine deficiency or excess has severe consequences on human health and associated with the presence of TMNs (4–8, 60–63) . In present study elevated level of I in thyroid tissue adjacent to malignant tumor and drastically reduced I mass fraction in cancerous tissue was found in comparison with “normal” thyroid.

Compared to other soft tissues, the human thyroid gland has higher levels of I, because this element plays an important role in its normal functions, through the production of thyroid hormones (thy-

TABLE3: 3. Differences between mean values (M±SEM) of Ca, Cl, I, K, Mg, Mn, and Na mass fraction (mg/kg, dry mass basis) in normal thyroid and ``intact'' thyroid tissue adjacent to tumor

	Thyroid tissue				Ratio
	Normal thyroid	Cancer (adjacent)	Student's t-test p£	U-test p	Adjacent/Normal
Ca	1692±109	862±140	**0.000028**	**≤0.01**	0.51
Cl	3400±174	5339±581	**0.0054**	**≤0.01**	1.57
I	1841±107	3183±301	**0.00015**	**≤0.01**	1.73
K	6071±306	5717±652	0.629	>0.05	0.94
Mg	285±17	339±105	0.617	>0.05	1.19
Mn	1.35±0.07	1.72±0.41	0.391	>0.05	1.27
Na	6702±1785	7671±649	0.168	>0.05	1.14

M – arithmetic mean, SEM – standard error of mean, Statistically significant values are in bold.

TABLE 4: Differences between mean values (M±SEM) of Ca, Cl, I, K, Mg, Mn, and Na mass fraction (mg/kg, dry mass basis) in thyroid cancer and ``intact'' thyroid tissue adjacent to tumor

	Thyroid tissue				Ratio
	Cancer (adjacent)	Cancer (tumor)	Student's t-test p	U-test p	Adjacent/Tumor
Ca	862±140	2398±558	**0.015**	**≤0.01**	2.78
Cl	5339±581	7699±703	**0.015**	**≤0.01**	1.44
I	3183±301	71.8±10.0	**0.00000000001**	**≤0.01**	0.023
K	5717±652	9655±970	**0.0019**	**≤0.01**	1.69
Mg	339±105	450±51	0.351	>0.05	1.33
Mn	1.72±0.41	1.90±0.32	0.107	>0.05	1.10
Na	7671±649	8556±646	0.340	>0.05	1.12

M – arithmetic mean, SEM – standard error of mean, Statistically significant values are in bold.

roxin and triiodothyronine) which are essential for cellular oxidation, growth, reproduction, and the activity of the central and autonomic nervous system. As was shown in present study, malignant transformation is accompanied by a significant loss of tissue-specific functional features, which leads to a drastically reduction in I content associated with functional characteristics of the human thyroid tissue. Because the malignant part of gland stopped to produce thyroid hormones, the rest "intact" part of thyroid tries to compensate thyroid hormones deficiency and work more intensive than usual. The intensive work may explain elevated level of I in thyroid tissue adjacent to malignant tumor.

Drastically reduced level of I content in cancerous tissue could possibly be explored for differential diagnosis of benign and malignant thyroid nodules, because, as was found in our ealier studies, thyroid benign trasformation (goiter, thyroiditis, and adenoma) is accompanied by a little loss of I accumulation [42-46].

Potassium: An uncontrollable cell proliferation characterize the malignant tumors. Therefore, morphological structures of TMNs differ from the structure of normal thyroid parenchyma. Because K is mainly an intracellular electrolyte, an elevated level of K content in cancerous tissue in comparison with "normal" and "adjacent" tissue might reflect increase of ratio "mass of transformed thyroid cell – mass of follicular colloid" in the malignant tumors. Nevertheless, the accumulation of K in neoplastic thyroids could possibly be explored for diagnosis of TMNs.

Magnesium: Mg is abundant in the human body. This element is essential for the functions of more than 300 enzymes (e.g. alkaline phosphatases, ATPases, phosphokinases, the oxidative phosphorylation pathway). It plays a crucial role in many cell functions such as energy metabolism, protein and DNA syntheses, and cytoskeleton activation. Moreover, Mg plays a central role in determining the clinical picture associated with thyroid disease (64) . Experimental data have shown that high doses of magnesium increase the activity of the thyroid gland (65)

. Magnesium deficiency can influence bioavailability and tissue distribution of selenium which then appears diminished (66) . From these data, one can conclude that Mg is involved in the thyroid function. If so, significant reduction in Mg content cam be associate with TMNs, because malignant transformation is accompanied by a loss of thyroid-specific functional features. However, it is well known that malignant tumors have an usually higher Mg levels than do normal tissues (67–73) , possibly caused by the ”retention” of Mg by the tumor (74) , as a result of the high Mg requirement of growing cells. In addition, cultured proliferating cells have long been known to contain more magnesium than quiescent cells, and experimental conditions that decreased magnesium availability affected cell proliferation rate (75) . Thus, the elevated levels of Mg in neoplastic thyroids could possibly be explored for diagnosis of TMNs.

Limitations: This study has several limitations. Firstly, analytical techniques employed in this study measure only seven ChEs (Ca, Cl, I, K, Mg, Mn, and Na) mass fractions. Future studies should be directed toward using other analytical methods which will extend the list of ChE investigated in “normal” thyroid and in pathologically altered tissue. Secondly, the sample size of TMNs group was relatively small and prevented investigations of ChEs contents in this group using differentials like gender, histological types of TMNs, tumor functional activity, stage of disease, and dietary habits of patients with TMNs. Lastly, generalization of our results may be limited to Russian population. Despite these limitations, this study provides evidence on many ChEs level alteration in malignant tumor and adjacent to tumor tissue and shows the necessity to continue ChEs research of TMNs.

4 | CONCLUSION

In this work, ChEs analysis was carried out in the tissue samples of TMNs using INAA-SLR. It was shown that INAA-SLR is an adequate analytical tool for the non-destructive determination of Ca, Cl, I, K, Mg, Mn, and Na content in the tissue samples of human thyroid in norm and pathology, including needle-biopsy specimens. It was observed that in malignant tissue the mass fraction of Cl, K, Mg, and Na were approximately 2.3, 1.6, 1.6, and 1.3 times, respectively, higher whereas mass fraction of I was 25.6 times lower than in the normal thyroid. In a general sense K, Mg, Mn, and Na contents found in the “normal” and “adjacent” groups of thyroid tissue samples were very similar. However, in the “adjacent” group mean mass fractions of Cl and I were 1.57 and 1.73 times, respectively, higher, while mean value of Ca content almost 2 times lower than in the “normal” group. In malignant tumor Ca, Cl, and K contents were approximately 2.8, 1.4, and 1.7 times, respectively, higher, while I content 43.5 times lower than in “adjacent” group of tissue samples. Thus, from results obtained, it was possible to conclude that the common characteristics of TMNs in comparison with “normal” thyroid and visually “intact” thyroid tissue adjacent to malignant tumors were elevated levels of Cl and K, as well as drastically reduced level of I. It was supposed that elevated levels of Cl and K, as well as drastically reduced level of I in cancerous tissue could possibly be explored for differential diagnosis of benign and malignant thyroid nodules.

ACKNOWLEDGEMENTS

The author is extremely grateful to Profs. B.M. Vtyurin and V.S. Medvedev, Medical Radiological Research Center, Obninsk, as well as to Dr. Yu. Choporov, former Head of the Forensic Medicine Department of City Hospital, Obninsk, for supplying thyroid samples.

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How to cite this article: Zaichick V. Contents Of Calcium, Chlorine, Iodine, Potassium, Magnesium, Manganese, and Sodium in Thyroid Malignant Nodules and ThyroidTissue Adjacent to Nodules . Journal of Medical Case Reports and Reviews. 2022;5(1):1061−1071. https://doi.org/10.52845/JMCRR/2022/5-1-3