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Some Approaches to Treatment of Patients with Thyroid Nodular Diseases in the Semipalatinsk Region of Kazakhstan

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ABSTRACT

It was determined by experts that in the region adjacent to the Semipalatinsk Nuclear Test Site thyroid nodular prevalence was significantly associated with radiation dose from nuclear weapons testing. The medical rehabilitation of patients is of special practical and scientific importance in this region. Some patients have contraindications for surgery and radioiodine or refuse them for various reasons. Percutaneous intranodular injection therapy by "Paoscle" (PIITP) was used for treatment of patients with benign thyroid nodular diseases. The study group included a total of 107 patients (mainly "pretoxic" and "compensated" nodules). Seventy-four patients received PIITP on an out-patient basis. Seventy-two of them were women and 2 men, mean age, 52.9 ± 1.3 years; range 26 to 77 years. Thyroid ultrasound examination, fine-needle aspiration biopsy, thyroid function tests and cytopathology were performed in all patients to evaluate the effectiveness of treatment. The nodule volume reduction rate for patients with thyroid adenomas was 56 % on average and 60.2 % in the case of colloid nodules. The reduction rate of thyroid adenomas with necrotic and cystic degeneration was higher and reached 72 %. The suggested method is indicated for cases of benign nodular thyroid diseases (cysts, adenomas, adenomas with necrotic and cystic degeneration, colloid nodules, polynodular goiter). We did not reveal any complications or thyroid test abnormalities after the treatment. A tendency to normalization of the blood serum thyroglobulin level and antibodies to thyroglobulin was documented. Analysis of the treatment results revealed that this approach is effective, inexpensive, safe, well tolerated and can be used on an outpatient basis.

Key words: *Fallout Exposure, Late effects, Radiation-induced neoplasm, Therapeutic approaches*

For the last decade there has been an increase in the number of patients with nodular diseases of the thyroid gland, consisting of 6–8 % of the adult population in the world. This problem is actually seen in ecologically unfavorable regions, especially in regions, which have experienced had a high surface radiation and where the risk of the diseases and cancer transformation of the nodule is very high. Frequency of malignant nodules varies up to 20 %, and it is usually influenced by the geographical peculiarities of the region, pathomorphological criteria of the malignant process, ecology and other factors[10]. It requires the development of adequate diagnostic and treatment techniques for nodular disease of the thyroid gland[2,6,9,12]. Regions in the Northeastern part of Kazakhstan were contaminated with high levels of radioactive fallout from atomic bomb tests at the Semipalatinsk Nuclear Test Site (SNTS), especially during the period of above-ground testing (1949–1962). The total yield of atmospheric tests was nearly 6.6 Mt. Former Soviet Union counterparts to the US Nevada Test Site. The total yield of atmospheric tests was nearly 1.0 Mt. It was determined by experts that in the region adjacent to the SNTS thyroid nodule prevalence was significantly associated with both external and internal radiation dose: excess relative risk per Gy (ERR/Gy) was estimated at 0.7 for gamma rays and 0.4 for internal doses (mainly from ^{131}I)[8,13,17,18].

The medical rehabilitation of patients with thyroid nodular diseases is of special practical and scientific interest in the Semipalatinsk region of Kazakhstan. The critical issue is to define not only

the question but also the desired outcomes from any therapeutic choice and then prospectively to test the efficacy and benefit of the intervention. Herein lies the problem. Desired outcomes for benign hypofunctioning thyroid nodules have not been rigorously defined. Physicians and patients may have varying and sometimes different goals for desired outcomes, ranging from prevention of malignant transformation to reduction in nodule size, prevention of additional growth, prevention of new nodules elsewhere in the thyroid, prevention or relief of symptoms caused by the thyroid nodule, or cosmetic relief. Each of these outcomes may have merit, but none should be accepted without challenge[1,4,11]. Surgery, radioiodine, and thyroxin therapy are still the main treatment modalities for thyroid nodular diseases. The choice among these modalities of treatment mainly depends on the age of the patient, the size, morphology of the nodule, and the risk for surgery. Complications of these treatment modalities and cost-effectiveness are well known. Some, especially immunocompromised, patients in the Semipalatinsk region have contraindications for surgery and radioiodine or refuse these modalities for various reasons. Patients really need non-invasive, inexpensive, effective and rapid treatment modalities. In consideration of the relatively non-fatal behavior of differentiated thyroid cancer in the Semipalatinsk region of Kazakhstan, some non-invasive treatment modalities should be developed and rigorously tested in terms of their effectiveness and long-term outcomes for treatment of exposed patients with thyroid nodular diseases. In the past decade several studies have evaluated and proposed percutaneous intranodular ethanol injection therapy (PIEIT) as a treatment for thyroid nodular diseases. It helps to avoid invasive surgical operation as well as the development of some postoperative complications[1,3,4,11]. Constant improvement and perfection of diagnostic abilities, accumulation of new data on molecular research and some features of the clinical development of different thyroid diseases have renewed interest in this disease and showed the necessity of revising the strategy and methods of treatment. Currently ultrasound-guided PIEIT as an alternative treatment is receiving much attention. At the same time, some side-effects of PIEIT have been described: local or radiating pain, a transient local burning sensation, mild-transient dysphonia, local hematoma, and short-lasting fever. As a rule these complications are described on the first stage of ethanol application and were always self-limiting. Nevertheless, we need a treatment method which can allow us to avoid the described side effects. The problem of treating large benign thyroid nodules with a solid structure, the development of criteria for the effectiveness of PIEIT, and estimation of long-term results especially regarding thyroid function require further detailed research.

In this study we report our experience of using percutaneous intranodular injection therapy by "Paoscle" (PIITP) in a group of patients from the Semipalatinsk region of Kazakhstan with benign thyroid nodular diseases. This was attempted to improve the results of treatment for patients having contraindications or refusing standard treatment modalities, and to study the indications, contraindications and effectiveness of this method.

MATERIALS AND METHODS

In our study we used a sclerosing agent "Paoscle" for treatment of benign thyroid nodular diseases. The main acting ingredient of "Paoscle" is 5 % phenol. Testing of its sclerosing effect in comparison with other sclerosing agents revealed that "Paoscle" has the least toxic effect and the greatest effectiveness in influencing the tissue and significantly stimulates collagen production. "Paoscle" has been applied for sclerotherapy to treat hemorrhoid bleedings as well as the sclerosing of vessels in cases of open prostatectomy in urology and in proctology to prevent children from having rectal prolapse[5,7,15,16]. Thus, clinical and experimental research shows the advisability of the wider application of "Paoscle" in clinical practice. The study group included a total of 107 patients with thyroid nodular diseases (mainly "pretoxic" and "compensated" nodules). 74 patients with different benign thyroid nodular diseases received percutaneous intranodular injection therapy by "Paoscle" (PIITP) on an out-patient basis. Seventy-two of them were women and 2 men, mean age, 52.9 ± 1.3 years, range 26 to 77 years. We also have experience (the results published in Kazakhstan) in the treatment of 138 patients with thyroid nodular disease by PIEIT[19,20]. In the case of PIEIT, sterile 96 % ethanol is injected through a 23-gauge spinal needle, without anesthesia. We selected from this previous study 18 cases of thyroid adenoma with a very high resistance to ethanol therapy, the volume of which equaled ≥ 10 cm^3, and 15 cases with thyroid cysts that had undergone sclerosing therapy by means of 96 % ethanol injection to compare the results of treatment with those of our study group[19,20]. Thyroid ultrasound examination, fine-needle aspiration biopsy, thyroid function tests and cytopathology were performed in all patients before the treatment session and 1, 3, 6, 12 months afterwards. A special 23 gauge needle made by Terumo®, Belgium, was used for aspiration biopsy and the injection of solutions into the nodule. We prefer to use the 'free hand' method. We found 2 cases of thyroid cancer (follicular carcinoma) and they underwent surgery. Those patients were excluded from our study. Sonographically measured thyroid volume was investigated in all subjects. Thyroid

volume was estimated using real-time sonography with a Hitachi machine EUB-405, using a 7.5 MHz linear array transducer. Longitudinal and transverse scans were performed allowing the measurement of the thickness, the width and the length of each lobe. The volume was estimated by multiplication of thickness, width and length, using a standard geometric formula: volume of a prolate ellipsoid - $V = \pi/6 \times D1 \times D2 \times D3$; ($\pi/6$ = 0.524). The volume of the whole thyroid gland was calculated as the sum of each lobe. Thyroid volume was expressed as mL. The volume of the isthmus was not included. The volume of a nodule was calculated on the basis of an analogous formula. Thyroid function tests: Serum samples were available from 36 patients. Serum free thyroxine (Free T_4) (reference range 1.8–2.9 ng/dl), serum thyrotropin [thyroid-stimulating hormone (TSH)] (reference range: 0.35–3.73 μIU/ml), serum triiodothyronine [(T_3), (reference range 2.2–4.1 pg/ml)], serum thyroglobulin (Tg) (reference range < 30 ng/ml), Anti-thyroid antibodies (TPOAb and TgAb) were assayed. Reference ranges (TgAb < 0.4 U/ml, TPOAb < 0.3U/ml). The research was carried out using as the testing system Eicken RIA kits, Tokyo, Japan, as well as luminescent immune analysis by the use of Centaur TSH II, Centaur FT_3, Centaur FT_4 reagents produced by Bayer Medical.

Statistical methods: The data were analyzed by Student's t test of paired and unpaired data. Indicated P values were significant or not significant by both the nonparametric and parametric statistical methods employed. All P values are the result of two-tailed tests.

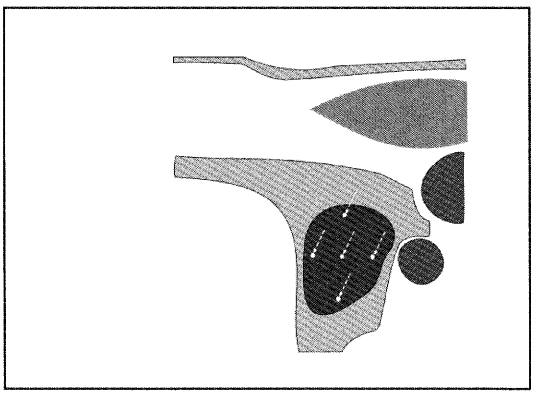

Fig. 1. The scheme of "Paoscle" injection into a thyroid nodule (PIITP)

To investigate the effectiveness of this method, taking into account the morphological structure of nodules, we divided the patients of our study group into 5 groups. The first group represented 33 patients with a diagnosis of thyroid adenoma. The second group comprised 9 patients with a diagnosis of thyroid adenoma with necrotic degeneration. The third group included 14 patients with a diagnosis of thyroid colloid goiter. The fourth group represented 11 patients with a diagnosis of thyroid adenoma with cystic degeneration. The fifth group consisted of 7 patients with thyroid cysts. In accordance with our clinical experience, ultrasound examination results, the morphological features and volume size of thyroid nodules in the Semipalatinsk region of Kazakhstan and to facilitate evaluation of treatment results and long-term outcomes, we grouped all nodular thyroid diseases by their volume size at diagnosis (Table 1). The whole sclerosing process was conducted under ultrasonographic control and it could be controlled on the display. Fig. 1 shows the scheme of "Paoscle" injection into a thyroid nodule. Patient follow-up was performed 1, 3, 6 and 12 months after the treatment session, using clinical and ultrasound examinations and thyroid function tests. Side effects were not observed. Sometimes patients with large solid nodules noted transient local pain during injection, possibly because of a transient increase of local pressure in the subsequent thyroid lobe. It can be avoided and "Paoscle" injection should not be rapid. All patients showed good tolerance toward the treatment.

RESULTS

Ultrasound examination revealed that thyroid gland volume among women varied from 5.7 cm^3 to 57.1 cm^3; mean: 18.1 ± 1.2 cm^3. Thyroid nodule volume range 0.5 to 29.0 cm^3; mean 5.5 ± 0.8 cm^3. Thyroid gland volume was 30.3 cm^3 and 25.9 cm^3 in two men, and thyroid nodule volume was 11.7 cm^3 and 3.1 cm^3 respectively. Cytopathology detected coexisting lymphocytic thyroiditis in 22 patients (29.7 %) of the study group. Thyroid function test measurement revealed significantly elevated levels of serum Tg among 75 % of examined

Table 1. Frequency of "Poascle" injection sessions depending on the nodule volume

Group	Volume of nodule (cm^3)	Frequency of "Paoscle" injections
1. Micro-nodule	Up to 0.5	Observation
2. Small nodule	0.6–2.5	Single injection
3. Middle-sized nodule	2.6–5.0	Double injection with an interval of 24 hours
4. Big nodule	5.1–8.0	Double injection with an interval of 72 hours
5. Gigantic nodule	≥ 8.1	Triple injection with an interval of 48 and 72 hours

patients (n = 27), TPOAb -30.6% (n = 11), and TgAb- 30.6 % (n = 11). TSH level was elevated in 8.3 % of patients (n = 3). A significantly low TSH level was detected in 16.7 % (n = 6). T_3 and FT_4 levels were in the reference range of these tests.

The nodule volume reduction rate after PIITP was slow and lasted about 6–12 months. In Fig. 2 the diagram shows the thyroid nodule volume reduction rate depending on morphological type after treatment. Reduction of a nodule began 1 month after the treatment started and reached a maximum 6 or 12 months later. Then the process of reduction proceeded very slowly. Indeed, it takes time to evaluate long-term outcomes of the treatment. Analysis of the results of treatment revealed that the nodule volume reduction rate in cases of thyroid adenomas and colloid nodules was less intensive than that of adenomas with necrotic and cystic degeneration. For patients with thyroid adenomas the nodule volume reduction rate was 50.2 ± 9.0 % on average ($p < 0.01$ in comparison with pretreatment rate) six months after treatment and for patients with colloid nodules, thyroid adenomas with cystic degeneration and thyroid adenomas with necrotic degeneration it was 53.4 ± 7.2 %, 66.4 ± 5.7 % and 64.1 ± 15.0 % respectively ($p < 0.01$ in comparison with pretreatment rate). There was a more intensive tendency in the reduction rate for thyroid adenomas with necrotic and cystic degeneration compared to thyroid adenomas and thyroid colloid nodules, but it was not statistically significant. For example, as we mentioned, the nodule volume reduction rate for thyroid adenomas with cystic degeneration was 66.4 ± 5.7 % versus 50.2 ± 9.0 % for thyroid adenomas ($p < 0.2$). The nodule volume reduction rate for thyroid adenomas after 12 months of observation equaled 56.0 ± 9.0 % on average ($p < 0.01$ in comparison with pretreatment rate). The dynamic of the nodule volume reduction rate for thyroid colloid nodules showed the same intensiveness as the reduction rate for thyroid adenomas. One year later it was 60.2 ± 7.2 % on average ($p < 0.01$ in comparison with pretreatment rate). The nodule volume reduction rate of adenomas with necrotic degeneration and cystic degeneration was more intensive and equaled 72 % on average ($p < 0.01$ in comparison with pretreatment rate). There was a more noticeable tendency in the reduction rate after 12 months of observation compared to the reduction rate of thyroid adenomas and thyroid colloid nodules, but again it was statistically not significant. The nodule reduction volume was 72.2 ± 15.0 % for thyroid adenomas with necrotic degeneration versus 56.0 ± 9.0 % for thyroid adenomas ($p < 0.5$). It was 72.3 ± 5.7 % for thyroid adenomas with cystic degeneration versus 56.0 ± 9.0 for thyroid adenomas ($p < 0.2$). Possibly more cases are needed in each study group to verify this tendency.

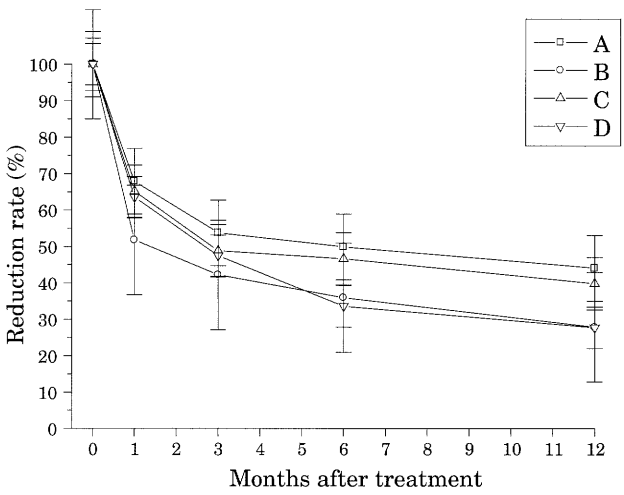

Fig. 2. Thyroid nodule volume reduction rate, depending on morphological type, after conducted treatment. (mean ± SD).
0: Before treatment, 1: 1 month after treatment, 3: 3 months after treatment, 6: 6 months after treatment, 12: 12 months after treatment.
A: thyroid adenoma, B: thyroid adenoma with necrotic degeneration, C: thyroid colloid nodules, D: thyroid adenoma with cystic degeneration.

The following case can be described as a clinical example (Figs. 3, 4 and 4.1). The patient T., 1930 date of birth, had been referred to the outpatient clinic of the Semipalatinsk State Medical Academy on November 9th, 2000, with complaints of an unpleasant feeling when swallowing, a feeling of pressure and short breath. On physical examination of the patient no visible changes on the front surface of the neck were found. There was a tumor-like formation in the left lobe that could be felt with palpation. Thyroid ultrasonography showed that the volume of the right lobe was 24.3 cm^3, the left lobe was 6.1 cm^3, the structure of the gland was uneven, and the echogenity was moderately lowered. Almost the whole left lobe was invaded by a nodule of an uneven structure and a volume of 11.6 cm^3. Fine-needle aspiration biopsy was conducted. Conclusion: thyroid adenoma with cystic degeneration (Fig. 3). The patient refused a surgical operation. PIITP was suggested. The patient agreed and gave his written consent. At the beginning of the procedure under ultrasonographic control the cystic cavities of the nodule were aspirated, then a triple course of 'Paoscle' injections was conducted with a dose of 3.5 ml at a time. Ultrasonography 3 months after treatment (Part 2 of Fig. 4 and 4.1) detected that the nodule volume had decreased to 3.0 cm^3 (that equaled 74.3 %). 6 months later (part 3) the nodule volume had decreased to 1.6 cm^3 (86.2 %) and 12 months later (part 4) the nodule volume equaled 0.86 cm^3 (92.6 %). Aspiration of the cystic cavity, being a part of the nodule structure, is a necessary procedure that should be performed in the treatment of

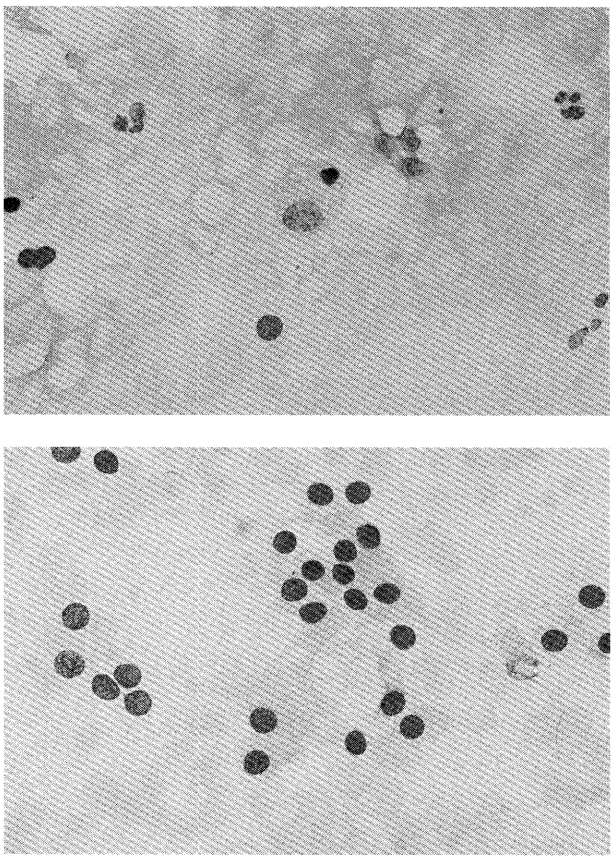

Fig. 3. Thyroid adenoma with cystic degeneration, × 40 Papanicolau staining

adenomas with cystic degeneration. On the basis of our experience we concluded that the nodule volume reduction rate for adenomas with necrotic and cystic degeneration is higher than that for adenomas and colloid nodules.

Thyroid function tests were determined before the treatment and 1, 3, 6 months later after the completion of treatment (Table 2). As we mentioned earlier, a significant increase in the serum thyroglobulin level was detected in 75% of examined patients. Before treatment, serum Tg level was 454.3 + 80.6 ng/ml, TPOAb-10.5 ± 4.5 U/ml, TgAb-6.5 ± 5.5 U/ml. It indicates thyroid tissue alteration and the prevalence of the autoimmune component. At the same time, before the treatment serum T_3 and FT_4 levels of the patients were in the reference range. After treatment, no significant change regarding serum T_3, FT_4 and TSH level was observed. Serum thyroglobulin and autoantibody levels decreased significantly. Six months after treatment, the serum Tg level was 91.2 ± 39.0 ng/ml, TgAb-2.3 ± 0.3 U/ml. Possibly, this indicates a thyroid function normalization tendency. At the same time, neither clinical nor laboratory methods revealed significant disturbances of thyroid function among patients who had undergone the treatment.

To determine the comparative effectiveness of the treatment modalities for benign thyroid nodular diseases by different methods, we analyzed 18

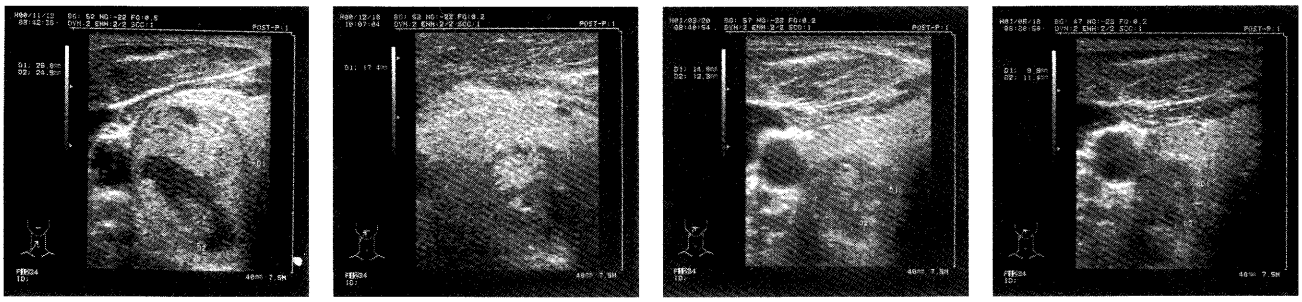

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Fig. 4. Ultrasound examination pictures of patient T (2 parameters).
Part 1: Before treatment, Part 2: 3 months after treatment,
Part 3: 6 months after treatment, Part 4: 12 months after treatment

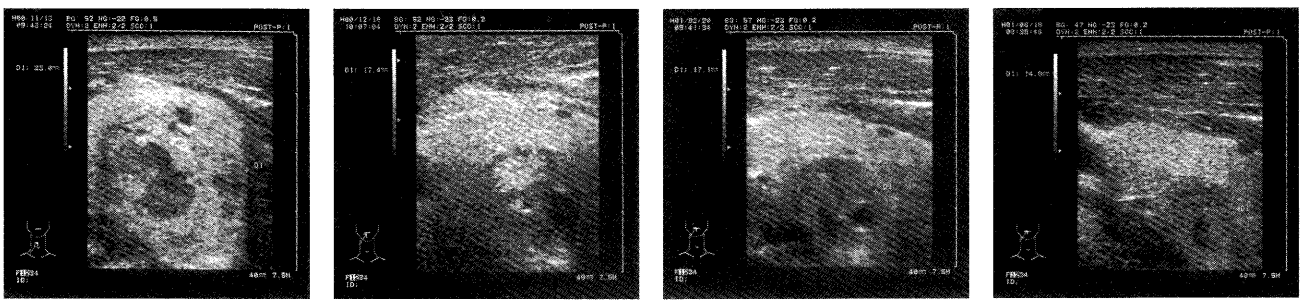

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Fig. 4.1. Ultrasound examination pictures of patient T (1 parameter).
Part 1: Before treatment, Part 2: 3 months after treatment.
Part 3: 6 months after treatment, Part 4: 12 months after treatment.

Table 2. Dynamic of thyroid tests in patients, who have received PIITP

Time-interval	TSH (μU/ml)	T3 (pg/ml)	FT4 (ng/ml)	Tg (ng/ml)	TPOAb (U/ml)	TgAb (U/ml)
Normal range	0.35–3.73	2.20–4.10	1.80–2.90	< 30.0	< 0.3	< 0.4
Before treatment	1.03 ± 0.30	3.39 ± 0.31	1.68 ± 0.17	454.3 ± 80.6	10.5 ± 4.5	6.5 ± 5.5
1 month after treatment	1.54 ± 0.30	3.31 ± 0.13	1.40 ± 0.10	251.3 ± 65.9	10.5 ± 4.4	8.0 ± 5.5
3 months after treatment	1.48 ± 0.30	3.24 ± 0.15	1.50 ± 0.10	308.1 ± 70.1	13.3 ± 4.2	9.0 ± 5.4
6 months after ± treatment	1.10 ± 0.10	2.29 ± 0.20	1.64 ± 0.02	91.2 ± 39.0*	10.2 ± 2.5	2.3 ± 0.3

Values are expressed as mean ± S.D. *p < 0.05 versus before treatment.
TSH: thyroid-stimulating hormone; T3: triiodothyronine; FT4: free thyroxine; Tg: thyroglobulin; TPOAb: anti-TPO antibody; TgAb: anti-thyroglobulin antibody.

Table 3. Comparative characteristics of treatment modalities with the application of PIEIT and PIITP

Ethanol	Paoscle
Intensive pain during injection with irradiation into lower jaw and ears	No
Transient disphonia	No
Fever elevation	No
Reduction rate for thyroid adenomas with the volume of ≥ 10 cm^3 on the 12th month of observation equals 40.0 %	Reduction rate for thyroid adenomas with the volume of ≥ 10 cm^3 on the 12th month of observation equals 56 %
Number of treatment sessions reached 5–6	Number of treatment session in case: Small nodules-single injection Middle-sized and big nodules-double injection Gigantic nodules-triple injection

cases of thyroid adenomas with a volume of ≥ 10 cm^3 which underwent PIEIT. The results of analysis showed that the nodule volume reduction rate equaled 40 % on average 12 months after treatment. PIITP for treating adenomas of the same volume showed a more intensive reduction of the nodules. The nodule volume reduction rate on the 12th month after treatment equaled 56 % on average. Thus, PIITP is a more effective method for the treatment of adenomas with a volume ≥ 10 cm^3 than the application of PIEIT (Table 3). We can thus see that PIITP has certain advantages in comparison with PIEIT for the treatment of benign thyroid nodular diseases.

In addition, PIITP was used for treatment of 7 patients with thyroid cysts. Total cure was observed in all cases. Based on our experience a single injection of "Paoscle" equal to 1/3 of the initial volume of a cyst is adequate for the treatment of thyroid cysts. It should be noted that preliminary aspiration of the liquid of the thyroid cyst is an essential procedure. From our experience PIEIT is very effective for treatment of thyroid cysts as well, but at least three treatment sessions is usually necessary for patients. Clinical implementation of PIITP allowed a decrease in the number of treatment sessions. It is one of the medical and economic advantages of this treatment method. The following case can be described as a clinical example (Fig. 5). The patient M., 1975 date of birth, was referred to the outpatient clinic of the Semipalatinsk State Medical Academy on February 25th, 2001 with a complaint of a transient unpleasant feeling when swallowing. Ultrasound examination revealed that the volume of the right thyroid gland lobe was 5.0 cm^3, the left lobe volume equaled 3.7 cm^3. The structure of the gland was even. In the right thyroid lobe a cystic nodule was detected with a volume of 1.7 cm^3. The patient refused a surgical operation. PIITP was suggested and the patient agreed. The thyroid cyst was punctured and 1.5 ml of cystic liquid aspirated. Fine-needle aspiration biopsy was performed. Conclusion of cytopathology: thyroid cyst without any atypical cells. After aspiration of the cystic cavity 0.6 ml of "Paoscle" was injected into the cystic cavity under ultrasound control. Control examination after 1 month showed no cystic cavity. Examination of the patient 12 months later showed no signs of cystic relapse and no complaints (part 2 of Fig. 5). On the basis of our experience and currently available literature[5,7,15,16,20], we attempted to formulate the main indications and contra-indications for PIITP.

Indications:
- thyroid cysts [of any volume];
- toxic thyroid adenoma;
- adenoma with necrotic and cystic degeneration;
- colloid nodules;
- polynodular goiter [if compression is absent].

Possible contra-indications:
- diffusive toxic goiter
- thyroid malignant tumors
- increasing compression of the neck organs by a

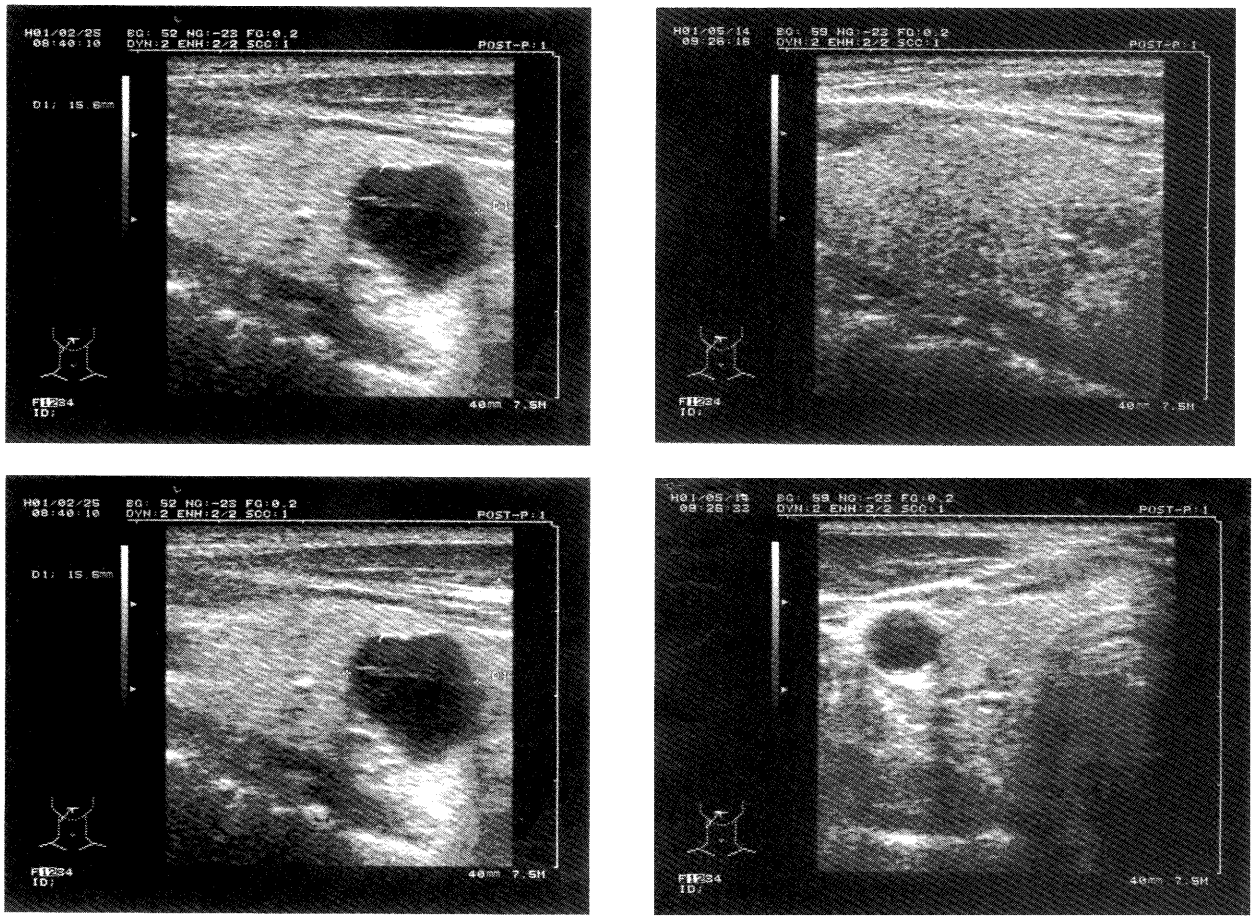

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Fig. 5. Ultrasound examination pictures of patient M. Thyroid cyst of the right lobe.
1: Before treatment, 2: 12 months after treatment.

nodule.

In the case of malignant thyroid tumors we recommended and performed thyroid surgery. The suggested method is indicated in cases of benign nodular thyroid diseases (cysts, adenomas, adenomas with necrotic and cystic degeneration, colloid nodules, polynodular goiter). We did not reveal any complications or thyroid test abnormalities after treatment. The tendency to normalization of the blood serum thyroglobulin level and antibodies to thyroglobulin was documented. Analysis of treatment results has revealed that this approach is effective, inexpensive, safe, well tolerated and can be used on an outpatient basis.

DISCUSSION

It has long been recognized that thyroid nodules and thyroid cancer can be induced after radiation exposure, especially during childhood[14]. In August, 1998, a binational team of Kazakh and American specialists conducted an epidemiological study of thyroid disease prevalence in the population in regions adjacent to the Semipalatinsk Nuclear Test Site. The study revealed an apparently strong association between fallout exposure and thyroid disease prevalence in the Semipalatinsk region of Kazakhstan. The population suffering from thyroid nodular diseases really need effective and inexpensive treatment modalities. Treatment of thyroid nodular diseases is dictated either by the excessive functioning of the thyroid, causing thyrotoxicosis, or by its size, causing compression of the neighboring structures or cosmetic disturbances. Treatment may also be conducted to prevent the occurrence of thyrotoxicosis or evolution of a non-toxic or toxic nodule, and to prevent further growth of the nodules or malignant transformation. Surgery, radioiodine, and thyroxin therapy are still the main treatment modalities for thyroid nodular disease. The complications of these treatment modalities and their cost-effectiveness are well known. Some, especially immunocompromised, patients in the Semipalatinsk region have contraindications for surgery and radioiodine or refuse these modalities for various reasons. In the past, percutaneous intranodular ethanol injection therapy (PIEIT) was introduced as an alternative to surgery or radioiodine[1,3,6,11,19,20]. Several transient side-effects were described. The long-term results of PIEIT need to be properly evaluated. At the same time it was documented that PIEIT is a simple and useful therapy and may be performed in patients of any age and particularly in patients

with significant surgical risk. In our study 74 patients with different benign thyroid nodular diseases received percutaneous intranodular injection therapy by "Paoscle" (PIITP) on an outpatient basis. Analysis of the comparative effectiveness of the treatment modalities for benign thyroid nodular diseases by different methods revealed that PIITP is a more effective method in particular cases than PIEIT and can be implemented in daily clinical practice. We did not find any side effects related to PIITP in comparison with the implementation of PIEIT.

During the realization of the Kazakh-American scientific project we followed the algorithm of thyroid disease screening suggested by American scientists from the National Cancer Institute of the USA. But analysis of field work results and research material as well as our own experience in the treatment of nodular thyroid diseases allowed us to make some recommendations in the screening algorithm and treatment of nodular thyroid diseases. Evaluation of ultrasonographic pictures should be done in four phases: preliminary evaluation at the stage of diagnostics and preparation for the treatment procedure, control examination during treatment procedure, conclusive examination at the end of the manipulation, monitoring at 3, 6, 12 months after treatment. Taking into account the fact that part of the Semipalatinsk region is an endemic zone for thyroid pathology, we think that to make an adequate estimation it is necessary to take into consideration the volume of the thyroid gland and the nodule, because the volume of the gland decreases with the reduction of the nodule. Atrophic thyroiditis is often to be met in the Semipalatinsk region of Kazakhstan. Different nodular thyroid diseases and thyroiditis were found among the people of the Semipalatinsk region depending on the place of residence and its distance from the nuclear test site. There were cases of thyroiditis accompanied by atrophy of the thyroid tissue as well as by hypertrophy. Congenital absence of one thyroid lobe was found in one case. The sizes of the gland and the nodules were estimated on the basis of two parameters during our field work, but later we recommended three parameters and the obligatory measurement of thyroid gland volume and nodule volume. From this proposal if the volume of a nodule is ≤ 0.5 cm^3 we recommend just observation and ultrasonography once per year. If the volume of the nodule is more than 0.5 cm^3, the fine-needle aspiration biopsy of the nodule should be conducted. During our field work the TSH hormone level was determined by using a DELFIA® Neonatal hTSH kit. This kit is intended for the quantitative determination of thyrotropin in blood specimens dried on filter paper. It should be noted that TSH hormone level assessment by using DELFIA® Neonatal hTSH kit during our field work was easy to do, but was not found to be as informative and diagnostically valuable as other TSH assessment tests and did not allow us to characterize TSH/FT4 discordances. Assessment of the main thyroid function tests [serum free thyroxin (Free T_4)], serum thyrotropin [thyroid-stimulating hormone (TSH)], serum triiodothyronine (T_3), serum thyroglobulin (Tg), Antithyroid antibodies (TPOAb and TgAb)] is a more valuable approach to diagnosis and treatment of thyroid nodular disease. Indeed, this approach is more expensive and time-consuming, but in the cases of ecologically unfavorable regions and radiation exposure only this approach allows the clarification of the real influence of different factors and the selection an adequate strategy of treatment. It also allows an increase in the quality of diagnostic and therapeutical measures. Our study revealed that PIITP is effective, inexpensive, well tolerated and can be used in clinical practice. More detailed follow-up study and further treatment of patients is now under way to clarify the long-term outcomes of treatment and its effectiveness.

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