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EVALUATION OF THE EFFICACY OF UKRAIN IN THE TREATMENT OF BREAST CANCER: CLINICAL AND LABORATORY STUDIES

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Summary: *The aim of this study was to evaluate the efficacy of different doses of Ukrain in the treatment of 75 breast cancer patients. Patients were divided into three groups. Group I (25 patients) and group II (25 patients) were treated with 50 mg and 100 mg Ukrain, respectively, before surgery. The remaining 25 patients served as controls (no Ukrain treatment). Both clinical observations and laboratory parameters indicate that both doses of Ukrain tested had a similar beneficial effect on patient outcome and may be indicated for presurgical treatment of patients with breast cancer.*

Introduction

According to the World Health Organization (WHO) by the year 2000 the number of new cases of breast cancer annualy may reach one million. Unfortunately, current death rates of patients with breast cancer are as high as 30-50%. Reduction of this deadly statistic entails the improvement of timely diagnosis and the development of new, more effective methods of treatment.

Ukrain, a semisynthetic preparation of alkaloids from *Chelidonium majus L.*, may have good clinical prospects. Both the data given in the literature and our studies indicate therapeutic efficacy for Ukrain in patients with breast cancer (1-7).

Previous studies have revealed that Ukrain injected at a dose of 50 mg prior to surgery improves the clinical outcome in patients suffering from breast cancer (3-7). However, the optimal dose of this drug in this pathology remains to be determined. The aim of the present study was to find the optimal dose to be used before surgery in patients with breast cancer.

Methods

Seventy-five randomly selected patients with breast cancer in stages I, II, and III were included in the study. They were divided into three groups,

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Table I *Age of breast cancer patients in the study*

Group of patients	Average age	30-39 years	40-49 years	50-59 years	60-70 years	Total number
Control	54.8	3	5	10	7	25
50 mg Ukrain	53.6	4	4	9	8	25
100 mg Ukrain	55.0	2	6	11	6	25

Table II *Tumor staging and number of patients*

Group of patients	Stage							Total number
	I	IIA		IIB		IIIA		
	T1N0M0	T1N1M0	T2N0M0	T2N1M0	T3N0M0	T1N2M0	T2N2M0	
Control	6	4	6	6	2	1	—	25
50 mg Ukrain	5	5	6	5	1	2	1	25
100 mg Ukrain	6	6	5	4	1	2	1	25

Table III *Types of surgery done in breast cancer patients*

Group of patients	Types of surgery			Total number
	Halsted	Patey	Madden	
Control	2	15	8	25
50 mg Ukrain	2	14	9	25
100 mg Ukrain	1	17	7	25

Table IV *Sonographic and mammographic examination of breast tumors in patients treated with Ukrain*

Group of patients	Sonography Mean tumor size, mm		Mammography Mean tumor size, mm	
	On admission	Prior to surgery	On admission	Prior to surgery
Control	24.7 ± 1.8	24.7 ± 1.8	26.6 ± 3.0	26.6 ± 3.0
50 mg Ukrain	27.8 ± 1.9	31.6 ± 2.4	30.6 ± 2.1	33.2 ± 2.4
100 mg Ukrain	25.8 ± 1.3	28.9 ± 1.6	26.3 ± 2.2	27.5 ± 2.2

Table V *Number of regional lymphatic nodes revealed in breast cancer patients*

Group of patients	Number of lymphatic nodes			Total number
	Axillaris	Subclavicularis	Subscapularis	
Control	7.3 ± 1.1	1.0 ± 0.2	0.3 ± 0.1	8.6 ± 0.4
50 mg Ukrain	14.6 ± 2.4*	5.5 ± 0.9*	0.4 ± 0.1	20.5 ± 2.8*
100 mg Ukrain	14.2 ± 1.9*	5.0 ± 0.7*	0.9 ± 0.3	21.1 ± 2.1*

*$p<0.05$, statistically significant compared with healthy subjects

Table VI *Histopathological characteristics of the removed breast tumors*

Group of patients	Adenocarcinoma			Total number
	G1	G2	G3	
Control	10	9	6	25
50 mg Ukrain	10	10	5	25
100 mg Ukrain	11	9	5	25

Table VII *Characteristics of postoperative complications in breast cancer patients*

Complications	Control		50 mg Ukrain		100 mg Ukrain	
	Abs.	%	Abs.	%	Abs.	%
Prolonged lymphorrhea	2	8	2	8	1	4
Skin necrosis	1	4	1	4	1	4
Suppuration of wound	1	4	—	—	—	—
Pneumonia	1	4	—	—	—	—
Total number of complications	5	20	3	12	2	8

each composed of 25 patients. The first and second groups of patients were treated prior to surgery with Ukrain in a total dose of 50 mg or 100 mg, respectively. The remaining 25 patients, matched clinically to the groups treated with Ukrain, served as controls.

Recruitment of the patients into the groups to be studied was based on the following criteria; age <70 years (Table I), diagnosis of breast cancer confirmed by clinical examination, ultrasonography (USG), mammography (MG), and histology (histological examination of the tumors obtained during surgery) (Table II).

Ukrain was injected i.v. every second day at a dose of 5 mg/per injection in the first group of patients, and in a dose 10 mg per injection in the second group. Both groups were operated on 7-10 days after discontinuation of treatment. The type of surgery performed is presented in Table III.

Patients with breast cancer treated with Ukrain and those from the control group were monitored clinically by USG, MG, and laboratory techniques including biochemistry, hematology, immunology, and endocrinology. Finally, the effect of this drug on a tumor and regional lymph nodes was evaluated by surgeons and material removed during operation was evaluated macro- and microscopically by a pathologist.

Results and discussion

No allergic reactions or side effects have ever been observed after treatment with Ukrain, regardless of the dose studied (8-11). Nevertheless, some patients in study groups treated with the drug noticed slight pain in the tumor area, other patients treated with the larger dose manifested slightly increased temperature of subfebrile value. Slight pain in the tumor area after Ukrain treatment is a phenomenon which has been reported by some investigators and has been suggested to be connected with the therapeutic activity of the drug (8, 10, 12). Clinically, it is worth noting that practically all patients treated with Ukrain prior to surgery reported an improvement in their overall condition, such as improved appetite, disappearance of weakness, and increased confidence in full recov-

Table VIII *Dynamics of hemogram indices in patents with breast cancer on administration of Ukrain*

Parameters	Group examined	On admission	After the course of Ukrain	7-10 days after surgery
Erythrocytes, 10^{12}/l	Healthy	4.4 ± 0.l	–	–
	Control	4.2 ± 0.1	4.2 ± 0.1	3.5 ± 0.1[1,2]
	Ukrain –50	4.2 ± 0.1	4.2 ± 0.1	3.5 ± 0.1[1,2]
	Ukrain –100	4.2 ± 0.1	4.0 ± 0.l	3.6 ± 0.1[2,3]
Hemoglobin, g/l	Healthy	144 ± 6	–	–
	Control	l38 ± 3	138 ± 3	114 ± 4[1,2]
	Ukrain –50	139 ± 4	l40 ± 4	117 ± 5[1,2,3]
	Ukrain –100	142 ± 2	136 ± 3	118 ± 3[1,2,3]
Platelets, 10^9/l	Healthy	244 ± 16	–	–
	Control	218 ± 16	218 ± 16	215 ± 17
	Ukrain - 50	228 ± 12	203 ± 11	227 ± 8
	Ukrain -100	258 ± 18	252 ± 17	258 ± 17
Leukocytes, 10^9/l	Healthy	4.6 ± 0.2	–	–
	Control	5.0 ± 0.4	5.0 ± 0.4	6.0 ± 1.6
	Ukrain - 50	5.1 ± 0.3	4.6 ± 0.3	5.5 ± 0.6
	Ukrain -100	4.4 ± 0.3	5.3 ± 0.4	4.0 ± 0.2[3]
Eosinophils, %	Healthy	1.8 ± 0.3	–	–
	Control	1.1 ± 0.3	1.1 ± 0.3	2.6 ± 1.1
	Ukrain -50	1.2 ± 0.4	1.5 ± 0.6	2.1 ± 0.7
	Ukrain -100	0.9 ± 0.2[1]	1.3 ± 0.4	1.8 ± 0.6
Rod, %	Healthy	l.7 ± 0.2	–	–
	Control	2.0 ± 0.5	2.0 ± 0.5	8.0 ± 2.2[2]
	Ukrain – 50	2.2 ± 0.6	l.0 ± 0.4	3.1 ± 0.7[3]
	Ukrain -100	1.9 ± 0.4	2.4 ± 0.6	3.4 ± 0.8[1]
Filamented, %	Healthy	58.1 ± 1.6	–	–
	Control	61.7 ± l.9	61.7 ± 1.9	68.8 ± 1.2[1]
	Ukrain -50	60.8 ± 2..6	62.7 ± 2.4	61.3 ± 1.8
	Ukrain - 100	68.l ± 2.4[1]	64.8 ± 2.3[1]	61.0 ± 2.8
Basophils, %	Healthy	0.2 ± 0.l	–	–
	Control	0.3 ± 0.2	0.3 ± 0.2	0.4 ± 0.2
	Ukrain -50	0.3 ± 0.2	0.3 ± 0.2	0.3 ± 0.2
	Ukrain -100	0.2 ± 0.1	0.1 ± 0.1	0.3 ± 0.2[2]
Lymphocytes, %	Healthy	34.1 ± 1.4	–	–
	Control	28.5 ± l.7[1]	28.5 ± 1.7[1]	13.6 ± 2.2[1,2]
	Ukrain -50	28.2 ± 2.2[1]	27.3 ± 1.9[1]	25.7 ± 2.2[1]
	Ukrain -100	24.4 ± 2.5[1]	25.4 ± 2.2[1]	27.0 ± 2.7[1]
Monocytes, %	Healthy	4.0 ± 0.5	–	–
	Control	6.4 ± 0.6[1]	6.4 ± 0.6[1]	6.6 ± 0.9[1]
	Ukrain -50	7.3 ± 0.5[1]	5.9 ± 0.5[1]	7.3 ± 0.8[1]
	Ukrain -100	4.7 ± 0.8	6.0 ± 0.6[1]	6.4 ± 0.8[1]
BSR, mm/h	Healthy	6.1 ± 0.5	–	–
	Control	10.7 ± 0.9	10.7 ± 0.9	48.2 ± 6.7[1,2]
	Ukrain -50	10.2 ± 1.2	11.2 ± 2.8	28.6 ± 3.8[1,2,3]
	Ukrain -100	14.1 ± 1.8[1]	17.1 ± 2.0[1]	27.8 ± 3.1[1,2,3]

$p<0.05$ in comparison with 1-healthy patients; 2-indices on admission; 3-indices after the course of Ukrain therapy

Table IX *Some coagulogram parameters in breast cancer patients treated with Ukrain*

Indices	Group examined	On admission	After the course of Ukrain	7-10 days after surgery
Hrothrombin, %	Healthy	0.93 ± 0.02	–	–
	Control	0.95 ± 0.03	0.95 ± 0.03	0.91 ± 0.04
	Ukrain -50	0.92 ± 0.02	0.94 ± 0.02	0.94 ± 0.02
	Ukrain -100	0.95 + 0.02	0.93 ± 0.02	0.86 ± 0.02[2]
Fibrinogen, g/l	Healthy	1.86 ± 0.11	–	–
	Control	2.40 ± 0.17	2.40 ± 0.17	4.61 + 0.39[1,2]
	Ukrain -50	2.33 + 0.21	1.89 ± 0.13	3.02 ± 0.29[1,3]
	Ukrain -100	2.67 + 0.16[1]	2.52 ± 0.23	3.12 + 0.22[1]
Prothrombin time, sec	Healthy	13.7 ± 0.3	–	–
	Control	15.9 ± 0.4[1]	15.9 ± 0.4[1]	13.6 ± 0.2
	Ukrain -50	15.9 ± 0.4[1]	15.8 ± 0.9[1]	15.2 ± 0.8
	Ukrain -100	16.0 ± 0.5[1]	15.6 ± 0.5[1]	15.8 ± 0.6[1]
Fibrinose, sec	Healthy	34.7 ± 1.3	–	–
	Control	42.8 ± 1.9[1]	42.8 ± 1.9[1]	42.6 ± 2.6[1]
	Ukrain -50	41.9 + 2.3[1]	41.2 ± 1.9[1]	44.9 ± 2.4[1]
	Ukrain -100	41.5 ± 2.2	40.9 ± 2.0[1]	43.3 ± 4.6

$p<0.05$ in comparison with 1-healthy patients; 2-indices on admission; 3-indices after the course of Ukrain therapy

ery. The above-described improvement in the behavior of patients after Ukrain treatment is supported by experimental studies (13).

The clinical effects of Ukrain on breast cancer patients are monitored by palpation disclosed tumors hardening and increased definition of contours. By USG, regardless of dose of 50 mg or 100 mg, the tumors showed a slight increase in size and greater contrast in comparison with pretreatment (Table IV). The same changes of breast tumors after Ukrain treatment were observed by MG. As in USG the tumors showed sharper contours and were seen more clearly. In several cases, difficulty in diagnosing breast tumors by MG before treatment was resolved after Ukrain treatment (Table IV). The number of regional lymphatic nodes revealed in breast cancer patients is shown in Table V, while Table VI shows the histopathological characteristics of the removed breast tumors.

These findings indicate that treatment of breast cancer patients with Ukrain prior to surgery has a distinctive beneficial effect both on the tumor directly and on the patient. The beneficial changes reported after Ukrain pretreatment were accompanied by the proliferation of connective tissue, which facilitated the diagnostic procedure of the tumor and the surgery of the breast carcinoma. A lymphoproliferative response of the regional lymph nodes facilitated their detection and removal. These observations are substantiated by the data presented in Table VII. Both clinical observations and laboratory parameters (Tables VIII-XIII) seem to indicate that both doses of Ukrain tested have similar clinical impact on the tumor and the patient and may be suggested for presurgical treatment in patients with breast cancer.

Table X *Biochemical parameters in breast cancer patients treated with Ukrain*

Indices	Groups examined	On admission	After the course of Ukrain	7-10 days after surgery
Total protein, g/l	Healthy	78 ± 1	-	-
	Control	73 ± 2[1]	73 ± 2[1]	72 ± I[1]
	Ukrain -5?	75 ± 2	71 ± 1[1]	66 ± 2[1,2,3]
	Ukrain -100	74 ± 2	76 ± 2	72 ± I1
Urea, mmol/l	Healthy	6.0 ± 0.2	-	-
	Control	6.2 ± 0.7	6.2 ± 0.7	4.8 ± 0.7
	Ukrain -50	6.0 ± 0.6	6.4 ± 0.4	5.6 ± 0.3
	Ukrain -100	6.5 ± 0.6	6.2 ± 0.5	5.9 ± 0.9
Bilirubin, mmol/l	Healthy	13.1 ± 1.2	–	–
	Control	11.1 ± 0.7	11.1 ± 0.7	14.5 ± 2.4
	Ukrain -50	10.0 ± 0.7	10.0 ± 0.5	8.4 ± 0.4[1,2,3]
	Ukrain -100	14.6 ± 1.3	12.4 ± 1.5	10.6 ± 1.22
ALT, mmol/l	Healthy	0.41 ± 0.1[1]	-	-
	Control	0.71 ± 0.26	0.71 ± 0.26	0.59 ± 0.12
	Ukrain -50	0.79 ± 0.36	0.71 ± 0.08[1]	0.57 ± 0.14
	Ukrain -100	0.45 ± 0.09	0.47 ± 0.10	0.51 ± 0.09
AST, mmol/l	Healthy	0.31 ± 0.05	–	–
	Control	0.46 ± 0.09	0.46 ± 0.09	0.52 ± 0.09
	Ukrain -50	0.44 ± 0.12	0.48 ± 0.12	0.42 ± 0.09
	Ukrain -100	0.45 ± 0.09	0.41 ± 0.14	0.38 ± 0.06
K^+, mmol/l	Healthy	3.96 ± 0.13	–	–
	Control	4.29 ± 0.14	4.29 ± 0.14	4.44 ± 0.07[1]
	Ukrain –50	4.39 ± 0.14[1]	4.33 ± 0.07[1]	4.46 ± 0.15[1]
	Ukrain -100	4.15 ± 0.14	4.07 ± 0.16	4.15 ± 0.1[1]
Na^+, mmol/l	Healthy	142 ± 1	–	–
	Control	142 ± 1	142 ± 1	144 ± 1
	Ukrain -50	143 ± 2	144 ± 1	140 ± 1
	Ukrain -100	140 ± 2	142 ± 2	140 ± 1
Cl- mmol/l	Healthy	102 ± 1	–	–
	Control	104 ± 1	104 ± 1	101 ± 1
	Ukrain -50	103 ± 1	107 ± 2[2]	106 ± 1[1]
	Ukrain -100	104 ± 1	106 ± 2	104 ± 1
Glucose, mmol/l	Healthy	4.7 ± 0.1	–	–
	Control	5.2 ± 0.4	5.2 ± 0.4	7.3 ± 1.2
	Ukrain -50	5.1 ± 0.6	5.2 ± 0.4	4.7 ± 0.2
	Ukrain -100	6.0 ± 0.4[1]	6.0 ± 0.5[1]	5.8 ± 0.4[1]

$p<0.05$ in comparison with 1-healthy patients; 2-indices on admission; 3-indices after the course of Ukrain therapy

Table XI *Lymphocyte subsets in patients treated with Ukrain*

Indices	Group examined	On admission	After Ukrain treatment	7-10 days after surgery
Total lymphocytes, %	Healthy	34.4 ± 1.4	–	–
	Control	28.5 ± 1.7[1]	28.5 ± 1.7[1]	13.6 ± 2.2[1,2]
	Ukrain -50	28.2 ± 2.2[1]	27.3 ± 1.9[1]	25.7 ± 2.2[1]
	Ukrain -100	24.4 ± 2.5[1]	25.4 + 2.2[1]	27.0 ± 2.7[1]
T-lymphocytes, %	Healthy	61 ± 2	–	–
	Control	69 ± 5	69 ± 5	56 ± 4[1]
	Ukrain –50	65 ± 3	74 ± 4[1]	61 + 2[3]
	Ukrain –100	69 ± 3	72 ± 2[1]	64 + 2[3]
T-lymphocytes, 10^9/l	Healthy	0.8 ± 0.1	–	–
	Control	1.0 + 0.1	1.0 + 0.1	0.7 + 0.3
	Ukrain –50	0.9 ± 0.1	1.1 ± 0.2	0.8 + 0.2
	Ukrain –100	1.2 + 0.2	1.3 ± 0.2	1.5 + 0.2[1]
Active T-lymphocytes, %	Healthy	34 ± 2	–	–
	Control	43 ± 6	43 ± 6	41 ± 4
	Ukrain -50	50 ± 5[1]	48 ± 5[1]	36 ± 2[2,3]
	Ukrain -100	51 + 41	42 ± 4	56 + 6[1,3]
Active T-lymphocytes, 10^9/l	Healthy	0.4 ± 0.[1]	–	–
	Control	0.6+0.1[1]	0.6 ± 0.1[1]	0.5 + 0.3
	Ukrain -50	0.7 ± 0.1[1]	0.7 ± 0.1[1]	0.5 + 0.1
	Ukrain -100	0.9 ± 0.1[1]	0.9 ± 0.1[1]	1.1 + 0.1[1]
T-suppressors,%	Healthy	7.5 ± 1.6	–	–
	Control	8.0 ± 0.6	8.0 ± 0.6	12.0 + 5.8
	Ukrain -50	9.9 ± 1.1	8.6 + 3.4	6.0 + 2.0
	Ukrain -100	7.7 ± 1.4	9.1 ± 2.6	6.6 + 2.0
T-helpers, %	Healthy	53.0 ± 2.5	–	–
	Control	67.0 + 4.7[1]	67.0 ± 4.7[1]	41.0 + 3.9[1,2]
	Ukrain -50	57.0 ± 3.4	62.0 ± 4.5	55.0 ± 4.3
	Ukrain -100	62.4 ± 3.6[1]	55.8 ± 3.6	66.6 ± 3.3[1,2]
T-suppressors/ T-helpers	Healthy	7.1 ± 1.2	–	–
	Control	8.4 ± 1.4	8.4 ± 1.4	3.4 ± 0.7[1,2]
	Ukrain -50	5.6 ± 1.1	7.2 ± 2.0	9.2 ± 1.5[2]
	Ukrain -100	8.1 ± 0.9	6.1 ± 1.0	10.1 ± 1.3[2,3]

$p<0.05$ in comparison with 1-healthy patients; 2-indices on admission; 3-indices after the Ukrain therapy

Table XII *Indices of immune status of the patients with breast cancer on administration of Ukrain*

Indices	Group examined	On admission	After the course of Ukrain	7-10 days after surgery
IgG, g/l	Healthy	12.5 ± 0.9	–	–
	Control	12.0 ± 1.0	12.0 ± 1.0	11.2 ± 2.0
	Ukrain -50	12.0 ± 1.1	10.0 ± 1.2	10.6 ± 1.0
	Ukrain -100	12.8 ± 0.7	11.7 ± 0.7	11.9 ± 0.8
IgA, g/l	Healthy	1.9 ± 0.3	–	–
	Control	3.5 ± 1.3	3.5 ± 1.3	2.2 ± 0.3
	Ukrain -50	3.8 ± 0.3[1]	2.8 ± 0.4	3.0 ± 0.6
	Ukrain -100	3.5 ± 0.4[1]	3.3 ± 0.3[1]	3.7 ± 0.4[1]
IgM, g/l	Healthy	1.2 ± 0.1	–	–
	Control	0.9 ± 0.2	0.9 ± 0.2	0.8 ± 0.1[1]
	Ukrain -50	1.5 ± 0.1	1..2 ± 0.1	1.3 ± 0.2
	Ukrain -100	1.1 ± 0.1	1.3 ± 0.2	I.0 ± 0.I
Complement titer, %	Healthy	58 ± 4	–	–
	Control	56 ± 2	56 ± 2	70 ± 6
	Ukrain -50	58 ± 5	60 ± 7	54 ± 9
	Ukrain -100	48 ± 6	58 ± 5	49 ± 7
Phagocytic activity of neutrophils, %	Healthy	63 ± 4	–	–
	Control	62 ± 5	62 ± 5	64 ± I
	Ukrain -50	52 ± 7	55 ± 5	58 ± 6
	Ukrain -100	53 ± 3	52 ± 4	57 ± 5

$p<0.05$ in comparison with 1-healthy patients; 2-indices on admission; 3-indices after the course of Ukrain

Table XIII *Dynamics of plasma hormone levels in breast cancer patients*

Hormones and their levels in healthy donors, M ± m	Ukrain 50 mg			Ukrain 100 mg		
	On amission	After the Ukrain course	7-10 days after surgery	On admission	After the Ukrain course	7-10 days after surgery
Cortisol, nmol/l; 490 ± 53	525 ± 87	616 ± 56	529 ± 47	775 ± 102[1]	761 ± 109[1]	611 ± 180
Progesteron, nmol/l; 6.8 ± 3.8	1.1 ± 0.6	0.9 ± 0.1	0.6 ± 0.1[1,2]	1.8 ± 1.0	3.1 ± 2.1	3.8 ± 1.4
Oestradiol, nmol/,0.40 ± 0.10	0.20 ± 0.04	0.30 ± 0.03	0.20 ± 0.05	0.30 ± 0.05	1.01 ± 0,75	1.52 ± 1.08
Prolactin, μmol/l; 314 ± 82	264 ± 104	211 ± 65	751 ± 212[1]	327 ± 108	300 ± 116	656 ± 214
Triiodothyronin, nmol/l; 1.7 ± 0.1	1.5 ± 0.1	1.4 ± 0.2[1]	1.4 ± 0.1[1]	1.5 ± 0.1	1.5 ± 0.2	1.3 ± 0.1
Thyroxine, nmol/l; 105 ± 10	131 ± 15	120 ± 9	103 ± 10	96 ± 8	112 ± 12	105 ± 14

Hormones and their levels in healthy donors, M ± m	Group of patients Control		
	On admission	After the Ukrain course	7-10 days after surgery
Cortisol, nmol/l; 490 ± 53	610 ± 81	610 ± 81	681 ± 85
Progesteron, nmol/l; 6.8 ± 3.8	1.5 ± 0.4	1.5 ± 0.4	2.9 ± 1.9
Oestradiol, nmol/, 0.40 ± 0.10	0.40 ± 0.10	0.40 ± 0.10	0.30 ± 0.10
Prolactin, μmol/l; 314 ± 82	263 ± 73	263 ± 73	716 ± 182[2]
Triiodothyronin, nmol/l; 1.7 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.4 ± 0.21
Thyroxine, nmol/l; 105 ± 10	116 ± 9	116 ± 9	101 ± 7

$p<0.05$ in comparison with 1-indices in healthy patients; 2-indices prior to surgery

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