

**SURGICAL TREATMENT OF PRIMARY AND SECONDARY  
HYPERPARATHYROIDISM**

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## Introduction

The parathormon (PTH), secreted by the parathyroid glands, has an important role in the calcium and bone mineral metabolism. The hyperfunction of the parathyroid glands, the primary and the secondary hyperparathyroidism ( HPT ) are rare diseases. However, the incidence of the primary hyperparathyroidism has increased in the past decade. This change is caused by the improvement of the diagnostic methods, such as the routine measurement of the serum Ca and PTH levels.

There are only a few publications about hyperfunctioning parathyroid glands, both in the Hungarian and in the internationale literature. The majority of the articles are about the diagnostic possibilities and the results of the different surgical interventions. Apart from the measurement of the above mentioned topics, we performed long-term follow-up studies after parathyroidectomy. We analysed the improvement of the symptoms of the patients, the alterations of the laboratory parameters and the changes of the bone disorders after the operation. We assessed the changes of the serum PTH levels and the renal osteodystrophy in patients with secondary hyperparathyroidism after kidney transplantation.

By our knowledge, such a long-term follow-up study, with such a large number of patients, has not ever been performed after kidney transplantation yet.

Flow-cytometric DNA analysis is a very rarely used method in the parathyroid pathology. According to the other investigators results, the aneuploid DNA content occurs not only in parathyroid carcinoma, but in in benign, hyperfunctioning parathyroid glands aswell.

In our study we performed complex measurement of primary and secondary hyperparathyroidism. These has not ever been such a study performed yet in Hungary.

## Aims

1. One of my aims was to measure the efficacy of parathyroidectomies from bilateral neck exploration in patients with primary and secondary hyperparathyroidism. During the study biochemical parameters and the symptoms of the patients were assessed.

2. We performed a prospective study to evaluate the efficacy of different preoperative localization techniques in primary hyperparathyroidism. I analysed the sensitivity of Technetium-99m-sestamibi / Technetium-99m-pertechnetate subtraction scintigraphy and the ultrasound for imaging hyperfunctioning parathyroid glands. I measured the sensitivity of subtraction scan and ultrasound for both adenomas and for hyperplastic glands. I compared the sensitivity of scintigraphy and ultrasound for parathyroid glands in loco typico and for ectopic glands.

3. I analysed the nuclear DNA content of hyperfunctioning parathyroid glands after the operation. I measured if it was possible to distinguish adenomas from hyperplasias based on the DNA ploidy status. Furthermore I evaluated the correlation between the DNA ploidy status and gender, age, tumor size, preoperative serum levels of Ca, AP and PTH. To assess the biological behaviour and proliferative potency of parathyroid carcinomas, I measured the DNA content and the proliferative index of tumor cells.

4. I measured the changes in calcium- and bone mineral metabolism after kidney transplantation. I compared the changes in the serum level of Ca, P, Mg, alkaline phosphatase (AP) and PTH in the calcium treated and in the alfacalcidol treated group after transplantation. I measured the presence of secondary hyperparathyroidism after transplantation. I evaluated with bone densitometry that the osteopenia can be prevented by administration of alfacalcidol.

## Patients and Methods

From January 1986 to January 2001, 92 patients with primary HPT underwent parathyroidectomy at the 1<sup>st</sup> Department of Surgery, University of Debrecen. Of the 92 patients 74 were female ( 80 % ) and 18 were male ( 20 % ). Their mean age was 53 years ( range 20 to 77 years ).

Before operation the average of the serum total calcium level was 2.90 mmol/l standard deviation ( SD )  $\pm$  0.35. The mean serum phosphorus concentration was 0.85 mmol/l SD  $\pm$  0.24. The mean serum alkaline phosphatase value was 456 U/l SD: 383. Before January 1994 C-PTH levels were measured, after that i-PTH concentrations were determined. The mean serum level of C-PTH was 169 pmol/l and the i-PTH level was 29.1 pmol/l.

Preoperative localization study was performed in all cases. Neck ultrasound (US) ( 7.5 MHz, Philips SD 800 ) was carried out in 85 patients, Technetium-99m-pertechnetate and Technetium-99m-sestamibi scan was done in 67 cases. CT was performed in 18 and MRI was made in 14 patients.

Our routine operative approach was bilateral neck exploration with identification of all the 4 parathyroid glands. If a solitary adenoma or a double adenoma was diagnosed extirpation was carried out. If diffuse hyperplasia was diagnosed histopathologically by frozen-section examination, then subtotal parathyroidectomy ( 3 1/2 ) was performed.

### *Osteoporosis*

Bone densitometry was performed in 34 cases with primary HPT and showed osteoporosis in all cases. The mean age was 54 years. Of the 34 patients 26 were female ( 77 % ) and 8 were male ( 23 % ). Seventeen patients were in post-menopausa.

Preoperative mean serum calcium level was  $2.77\pm 0.23$  mmol/l, the mean serum phosphorus concentration was  $0.83\pm 0.14$  mmol/l and the mean serum alkaline phosphatase value was  $317\pm 179$  U/l. The mean serum level of i-PTH was  $36.2\pm 23.1$  pmol/l.

Bone densitometry was carried out at the Department of Gynecology, University of Debrecen with a LUNAR DPX-L ( Lunar Corp., Madison, WI, USA) instrument. The bone mineral density (BMD) and Z-score values were measured at the lumbar spine ( L2-4 ).

The laboratory examinations and bone densitometry was performed before parathyroidectomy, in the early post-operative period and yearly after the operation.

Before parathyroidectomy calcitonin treatment was administered in 1 case, alendronate was given to 1 patient and hormone substitution was used in 1 occasion. After parathyroidectomy 4 patients received hormone substitution, calcitonin was administered in 6 cases while 7 patients received alendronate treatment.

The follow-up of the patients ranged from 1 year to 5 years.

#### *DNA analysis*

Using flow cytometry we evaluated nuclear DNA content, DNA index and proliferative index from paraffin-embedded tissues. DNA analysis was performed with the Rabinovitch Multicycle software (Phoenix Flow Systems Inc. San Diego, CA).

The DNA content and the proliferative index (PI) were measured in 29 patients with primary hyperparathyroidism who had undergone parathyroidectomy. 25 patients had parathyroid adenoma and 4 patients had diffuse hyperplasia.

DNA analysis was carried out in 2 cases with parathyroid carcinoma.

### **Secondary hyperparathyroidism**

From January 1987 to December 2000, 48 patients with secondary HPT underwent parathyroidectomy at the 1<sup>st</sup> Department of Surgery, University of Debrecen. Of the 48 patients 21 were male and 27 were female. Their mean age was 45 years.

Previously majority of the patients were treated at 1<sup>st</sup> Department of Internal Medicine, University of Debrecen.

Preoperative mean serum calcium level was  $2.35 \pm 0.28$  mmol/l, the mean serum phosphorus concentration was  $1.97 \pm 0.63$  mmol/l and the mean serum alkaline phosphatase value was  $576 \pm 420$  U/l. The mean serum level of C-PTH was  $1425 \pm 789$  while the i-PTH level was  $87.5 \pm 37.1$  pmol/l.

In patients with secondary HPT subtotal parathyroidectomy ( 3 1/2 ) was performed in most of the cases. When total parathyroidectomy and autotransplantation was carried out the parathyroid tissue was placed into the sternocleidomastoideus muscle. At the reoperation for persistent and recurrent hyperparathyroidism, total parathyroidectomy and autotransplantation was performed ( n:2 ).

### *Kidney transplantation*

From January 1992 to January 1998, 220 kidney transplanted patients from cadaveric donors were enrolled into the study.

The patients were divided into two groups. In Group 1, the recipients ( n: 159 ) received calcium supplements. These patients were transplanted before December 1995. The daily dosage of oral CaCO<sub>3</sub> ranged from 1500 to 3000 mg. In Group 2, the patients ( n: 81 ) received alfacalcidol therapy. These patients were transplanted between December 1995 and January 1998. The daily dosage of alfacalcidol ranged from 0.25 to 2 ug.

There were 31 females (mean age: 39 years ) and 88 males ( man age: 40 years ) in Group 1. There were 33 females ( mean age: 31 years ) and 48 males ( mean age: 40 years ) in Group 2.

After transplantation the immunosuppressive therapy consisted of a combination of Cyclosporin A, methylprednisilone, azathioprine and mycophenolat mofetil.

The serum calcium, phosphorus, Mg, alkaline phosphatase and intact PTH levels were measured before surgery and at 1, 3, 6, 12 and 24 months after transplantation in both groups.

Bone densitometry was performed at the lumbar spine ( L2-4 ) and at the femoral neck region at 3, 6, 12 and 24 months after transplantation.

The follow-up of the patients was 2 years.

Statistical analysis was performed with Student's t test and with Mann Whitney U test. The correlation between variables was assessed by calculating Pearson's correlation coefficient. The mean results and the standard deviation (  $\pm$ SD ) were given. A p value less than 0.05 was considered to be significant.

## Results

Sixty six of the 92 patients with primary HPT had solitary adenoma, and 3 patients out of the 92 had double parathyroid adenoma. In 7 cases the parathyroid glands were found in an ectopic location. Twelve of the 92 patients with primary HPT had diffuse hyperplasia. Five parathyroid glands were ectopic. Histology showed parathyroid cancer in 2 cases.

Six of the 92 patients underwent previous parathyroidectomy. They had persistent hyperparathyroidism. Scintigraphy correctly detected the parathyroid glands in all cases. In one patient the parathyroid adenoma was in the mediastinum and the scan identified it, while the ultrasound was not able to detect it.

Persistent HPT was noted in one patient and recurrent HPT occurred in 4 cases in our series.

The results of preoperative localization methods are presented in Table 1 and 2.

The sensitivity of this subtraction scintigraphy was significantly higher compared to other methods (  $p < 0.05$  ).

In cases of parathyroid adenomas there was a significant difference between the sensitivity of scan and US (  $p = 0.0003$  ). In cases of hyperplastic glands there were no significant differences between the sensitivity of scintigraphy and US (  $p = 0.054$  ).

The sensitivity of scintigraphy and US was significantly higher for adenomas compared to hyperplastic glands (  $p = 0.041$  and  $p = 0.01$  ).

The sensitivity of the employed scintigraphy was 100 % for adenomas in loco typico and it was the same for adenomas in ectopic localizations. The US showed a sensitivity rate of 86 % for adenomas in loco typico and 43 % for adenomas in ectopic localizations (  $p = 0.043$  ). The sensitivity of scan for hyperplastic glands in loco typico was 73 %, and 80 % for ectopic hyperplastic glands. The sensitivity of US was 50 % for hyperplastic glands in

**Table 1 Results of preoperative localizing methods I.**

	total	true-positive	false-positive	false-negative	sensitivity
	n	n	n	%	%
Scan	67	61	2	4	94
US	85	59	5	21	74
CT	18	12	0	6	67
MRI	14	7	0	7	50

**Table 2 Results of preoperative localizing methods II.***Technetium-99m-sestamibi/ Technetium-99m-pertechnetate*

	true-positive	false-positive	false-negative	sensitivity	PPV
	n	n	n	%	%
adenoma	48	1	0	100	98
hyperplasia	13	1	4	76	93
total	61	2	4	94	97

*US*

	true-positive	false-positive	false-negative	sensitivity	PPV
	n	n	n	%	%
adenoma	51	3	12	81	94
hyperplasia	8	2	9	47	80
total	59	5	21	74	92

loco typico and 20 % for ectopic glands. The difference was not significant in both cases ( scan :  $p=0.77$ , UH  $p=0.27$  ).

### *Osteoporosis*

After parathyroidectomy the serum level of calcium significantly decreased within a few days. The serum PTH concentrations decreased into the normal range after operation.

Bone densitometry showed increased BMD values at the lumbar spine compared to the baseline ( Table 3 ). The BMD increased by 8.5% at 1 year, by 12.5 % at 2 years, by 14.1 % at 3 years, by 13.5 % at 4 years and by 11.3 % at 5 years.

The BMD value increased by 0.012, 0.100, 0.228, 0.155 and 0.133  $\text{g/cm}^2$  at 1.,2.,3.,4. and 5 years in those patients who received antiresorptive therapy. The BMD increased by 0.021,0.114, 0.203, 0.119 and 0.112  $\text{g/cm}^2$  at the same period in those patients who did not receive antiresorptive treatment. There was not a significant difference between the two groups.

**Table 3      BMD and T-score values of patients with primary hyperparathyroidism at the lumbar spine**

	BMD ( $\text{g/cm}^2$ )	BMD ( % )	T-score
Before operation	0.787 $\pm$ 0.020	69.0	-2.97 $\pm$ 1.06
1. year ( n:34 )	0.808 $\pm$ 0.082	70.2	-2.75 $\pm$ 1.04
2. year ( n:32 )	0.901 $\pm$ 0.091*	74.4	-2.63 $\pm$ 0.77
3. year ( n:26 )	0.908 $\pm$ 0.119*	75.5	-2.45 $\pm$ 1.02
4. year ( n:11 )	0.906 $\pm$ 0.052*	74.4	-2.49 $\pm$ 0.34
5. years ( n: 6 )	0.882 $\pm$ 0.058*	73.5	-2.74 $\pm$ 0.50

\* Significant deviation compared to the baseline value (  $p < 0,05$  )

*DNA analysis**Benign diseases*

25 glands were histologically classified as parathyroid adenoma, 16 glands were classified as hyperplasia, and 10 glands as normal.

DNA analysis showed that all normal parathyroid glands were diploid. Aneuploid patterns were found in 39 % of all primary hyperparathyroidism. Incidence of aneuploidy was statistically higher in hyperactive glands compared to normal ones (  $p=0.0002$  in adenoma vs. normal,  $p=0.040$  in hyperplasia vs. normal ). There was no statistically significant difference in rate of aneuploidy in adenomas compared to hyperplastic glands ( $p=0.216$ ).

The DNA index ( DI ) ranged from 1.2 to 4.0 in aneuploid cases. Two of the adenomas had near-diploid aneuploid content ( DI :1 - 1.2 ). The DNA content was almost doubled ( DI: 1.8-2.0 ) in 8 specimens. DI for adenomas was higher than for hyperplasias (1.86 vs. 1.45).

The mean S phase fraction was 3.45 % (SD: 1.31) in adenomas and 1.53 % (SD:1.07) in hyperplastic glands (  $p=0.015$  ). Mean PI was 6.48 % (SD:2.26) in adenomas and 2.78 % (SD:0.98) in hyperplastic glands. Our results show that there was a statistically significant difference in PI values between adenomas and hyperplastic glands (  $p=0.006$  ).

The mean S phase fraction was 2.25 % SD:1.74 in diploid cases, and 4.5 % SD: 2.2 in aneuploid cases (  $p= 0.09$  ). Diploid specimens had a mean PI of 4.78 % SD:2.9 and aneuploid glands a mean PI of 7.7 % SD:5.1 (  $p=0.08$  ).

Aneuploid DNA content did not show statistically significant correlation with the following clinicopathological parameters: age (  $r=0.34$ ,  $p=0.05$ ), gender (  $r=0.18$ ,  $p=0.32$ ), preoperative Ca (  $r=-0.07$ ,  $p=0.73$ ), alkaline phosphatase (  $r=0.65$ ,  $p=0.06$ ), i-PTH (  $r=-0.17$ ,  $p=0.54$ ) levels and tumor size (  $r=0.10$ ,  $p=0.58$ ).

The correlation between the PI and DNA ploidy status was  $r=0.20$ . There were negative correlations between PI and age ( $r=-0.19$ ), preoperative Ca ( $r=-0.25$ ), i-PTH ( $r=-0.26$ ) and tumor size ( $r=-0.003$ ) an indicator of the tumorous nature of adenomas.

### *Malignancy*

In one patient the histological examination from the paraffin-embedded specimen revealed parathyroid cancer. Flow cytometric DNA analysis showed aneuploid DNA content. The DNA index was 1.7, the S phase fraction was 1.2 %, and the proliferative index ( PI ) was 1.7 %.

Lymph node dissection was carried out two times and histology revealed metastasis of the parathyroid carcinoma. DNA analysis showed aneuploid tumor cells in both cases. In the first case the DNA index was 1.2. The S phase fraction was 0 %, and the PI was 0.3 %. In the second occasion the DNA index was 1.8, the S phase fraction was 2.4% and the PI was 2.4%.

In 6 months after the third operation the patient died. The patient's survival was 39 months from the initial surgery. Her relapse-free survival was 24 months.

In the other patient histology from paraffin embedded blocks showed parathyroid carcinoma. DNA analysis revealed diploid cancer. The S phase fraction was 1.3 % and the PI was 1.8 %.The patient is alive without evidence of disease. The relapse-free period is 5 years up to now.

### **Secondary hyperparathyroidism**

The mean serum AP level decreased to  $388\pm 184$  U/l, the C-PTH concentration decreased to  $388\pm 148$  pmol/l and the i-PTH level decreased to  $18.7\pm 7.2$  pmol/l after the parathyroidectomy.

Persistent hyperparathyroidism was diagnosed in 5 patients. In these patients 2 parathyroid glands were removed during the primary operation. We performed reoperation in 2 cases because of persistent hyperparathyroidism. At the reoperation for persistent hyperparathyroidism, total parathyroidectomy and autotransplantation was performed. Two patients refused to undergo another operation. One of the 5 patients with persistent hyperparathyroidism died in the early postoperative period.

Recurrent hyperparathyroidism was detected in 2 patients. Subtotal parathyroidectomy was carried out in these cases previously. One of the patients denied to perform another parathyroidectomy. In one case we removed the rest of parathyroid gland and some tissue was autotransplanted.

After parathyroidectomy we observed the decrease of patients' complains. Bone pain decreased in 95 % of the cases and pruritus decreased in 90 % of the patients after parathyroidectomy. Soft tissue calcification showed improvement in 45 % of cases.

#### *Kidney transplantation*

Following kidney transplantation the serum Ca levels values increased and the serum P concentrations decreased in both groups ( Table 4 ).

In Group 1, the decrease in i-PTH level was not significant in the first year. It became significant from the second year after transplantation. In Group 2, the serum i-PTH values significantly decreased during the study period following transplantation. The serum i-PTH level remained within the normal range, in Group 2, after surgery.

Bone densitometric examinations were not performed before transplantation.

Regarding the results, a slightly higher degree of osteopenia could be observed following renal transplantation.

**Table 4** Serum levels of Ca, P, Mg, AP and PTH after kidney transplantation

	Ca (mmol/l)	P (mmol/l)	AP (U/l)	PTH(pmol/l)
<b>Group 1</b>				
Before Tx	2.12 ± 0.31	1.67 ± 0.27	243 ± 136	17.1 ± 9.1
1. month	2.41 ± 0.29*	1.02 ± 0.31*	234 ± 123	
3. month	2.31 ± 0.26*	1.30 ± 0.33*	241 ± 111	
6. month	2.34 ± 0.22*	1.20 ± 0.33*	252 ± 185	9.8 ± 7.4
12. month	2.28 ± 0.21*	1.17 ± 0.34*	260 ± 138	10.4 ± 9.1*
24. month	2.36 ± 0.26*	1.19 ± 0.31*	222 ± 116	9.3 ± 7.8*
<b>Group 2</b>				
Before Tx	2.18 ± 0.25	1.82 ± 0.67	136 ± 66*	17.7 ± 9.4
1. month	2.36 ± 0.26*	1.02 ± 0.40*	155 ± 54	
3. month	2.39 ± 0.22*	1.03 ± 0.34*, <sup>0</sup>	165 ± 71* <sup>0</sup>	
6. month	2.43 ± 0.18*	1.03 ± 0.26*, <sup>0</sup>	191 ± 104* <sup>0</sup>	5.7 ± 3.3* <sup>0</sup>
12. month	2.37 ± 0.19*	0.99 ± 0.23*, <sup>0</sup>	242 ± 146*	6.3 ± 3.8* <sup>0</sup>
24. month	2.43 ± 0.17*	1.10 ± 0.27*	270 ± 127*	7.9 ± 4.8*

Tx= kidney transplantation, mean values ± SD

\* significant deviation compared to the baseline ( p < 0,05 )

<sup>0</sup> significant deviation compared to the Ca treated group ( p < 0,05 )

At 2 years after transplantation the BMD values increased slightly in the calcium group, and decreased in the alfacalcidol group at the lumbar spine compared to the 3 months values. At 2 years the BMD at the femoral neck increased in both group. The observed changes between 3 months and 2 years values were not significant ( Table 5 ).

**Table 5 BMD and Z-score values after kidney transplantation**

**BMD ( g/cm<sup>2</sup> ) values**

	<b>Lumbar spine</b>		<b>Femoral neck</b>	
	<b>Group 1</b>	<b>Group 2</b>	<b>Group 1</b>	<b>Group 2</b>
3. month	0.963 ± 0.242	1.048 ± 0.170	0.932 ± 0.186	0.850 ± 0.154
6. month	0.999 ± 0.146	1.061 ± 0.052	0.860 ± 0.112	0.915 ± 0.071
12 month	1.085 ± 0.210	1.019 ± 0.162	0.856 ± 0.236	0.803 ± 0.132
24 month	1.056 ± 0.182	0.984 ± 0.163	0.910 ± 0.061	0.895 ± 0.112

After transplantation osteonecrosis was diagnosed in 6 patients ( 1 female and 5 males ) in Group 1 , and in 9 recipients ( 5 females and 3 males ) in Group 2. During the first year, osteonecrosis developed in 5 patients in Group 1, and in 7 patients in Group 2. Among them only 2 recipients received steroid bolus therapy because of acute rejection episodes. Bone fracture was diagnosed in 2 transplanted patients during the two year follow-up period. In both cases the fracture developed in the lumbar spine and these patients belonged to Group 2.

## Discussion

Preoperative localization studies identify the abnormal parathyroid glands. However these methods not only give the correct location of parathyroid glands, but might differentiate adenomas from hyperplasias.

In this study we measured the scintigraphic and sonographic findings concerning the localization of the abnormal parathyroid glands. The overall rate of sensitivity was significantly higher with the scan compared to ultrasound. The sensitivities of scintigraphy and US were higher for adenomas than for hyperplastic glands.

Scintigraphy results did not show any major differences concerning the localization of parathyroid glands. This type of scanning was able to detect the ectopic glands with high sensitivity. The sensitivity of US was higher for adenomas in loco typico compared to ectopic adenomas. In patients with ectopic hyperplastic glands there were no significant differences between the sensitivity of US compared to scintigraphy (  $p=0.066$  ).

We used preoperative localization techniques in all cases in spite that we performed bilateral neck exploration in each patient for the identification of the 4 parathyroid glands.

By our opinion the advances of the preoperative localizations are as follows: shorter operative time, improve the success rate in cases of ectopic glands, decrease the possible occurrence of persistent and recurrent hyperparathyroidism.

The high sensitivity rate of this scan may permit more efficient neck dissection and allows surgeons to perform minimally invasive surgery or unilateral neck exploration for parathyroidectomy.

### *Osteoporosis*

The mean levels of calcium and parathyroid hormone rapidly decreased and varied in the normal range after the operation. The mean alkaline phosphatase concentrations also

decreased after surgery, but in most of the cases the difference was not statistically significant. Bone densitometry showed increased bone mineral density at the lumbar spine ( L 2-4 ) after the parathyroidectomy. The increase in the bone mineral density was significant two years after the operation.

There was no significant deviation in the BMD values between the antiresorptive treatment received group compared to the other group after parathyroidectomy. The results suggest that after successful parathyroidectomy the bone mineral density significantly increases, the osteopenia decreases or resolves and it is not necessary to administer antiresorptive therapy.

#### *DNA analysis*

Similarly to other reports, our results show that DNA aneuploidy is not rare in the parathyroid glands of primary hyperparathyroidism. The incidence of DNA aneuploidy in parathyroid adenomas varied from 5 to 45 % . In our study 48 % of 25 adenomas were DNA aneuploid. Four of the sixteen hyperplastic glands were DNA aneuploid. Normal parathyroid glands were diploid.

According to our results DNA aneuploidy did not correlate with age, sex, the preoperative level of Ca, alkaline phosphatase, i-PTH, or the size of the glands.

The values of S phase fraction and PI were very low in normal parathyroid glands. It demonstrates that normal parathyroid glands have low mitotic activity. The S phase fraction and PI values were significantly increased in adenomas compared to hyperplasias. This suggests that adenomas usually have higher proliferative activity than hyperplastic glands.

Some author reported that parathyroid carcinomas are often associated with aneuploid DNA content and high proliferative index. In our cases one patient had aneuploid DNA and one patient had diploid DNA patterns. The S phase fraction and the PI were low in both cases.

However, aneuploid DNA content is not rare in the benign abnormal parathyroid glands. Aneuploid DNA pattern is more common in parathyroid carcinomas than in adenomas, but DNA aneuploidy does not definitively separate malignant from benign lesions of the parathyroid gland.

In our cases the patient with DNA diploid carcinoma had 5-years survival and relapse-free period. Lymph node metastases occurred when the tumor had aneuploid DNA content. Our cases suggest, concerning to other reports, that DNA aneuploidy has a negative influence on survival.

### **Secondary hyperparathyroidism**

In secondary hyperparathyroidism we suggest to perform subtotal parathyroidectomy, because this operation gives almost as good results as total parathyroidectomy with autotransplantation, but the operative time is shorter and the technique is easier.

After subtotal parathyroidectomy the occurrence of hypoparathyroidism was low.

Persistent hyperparathyroidism occurred (n:5) in those cases when inadequate parathyroidectomy was performed. Recurrent hyperparathyroidism was detected in 2 patients. After total parathyroidectomy and autotransplantation persistent or recurrent hyperparathyroidism did not show up.

Some authors reported that pruritus decreased in a few days after parathyroidectomy, and the bone pain decreased within a few weeks after operation. By our results the soft tissue calcifications showed only a moderate improvement and the vessel calcifications did not change. In our cases bone pain decreased in 96 % of the patients and pruritus decreased in 92 % of the cases. Neuropathy showed improvement in 75% of the cases and the metastatic calcification decreased in 45% of the patients.

### *Kidney transplantation*

After successful renal transplantation, the phosphorus excretion increases and the active vitamin D synthesis reverts to normal due to the well functioning graft. For this reason the serum calcium and phosphorus levels quickly normalise following the operation.

The mean serum PTH concentrations decreased in both groups after transplantation. The decrease in PTH levels were more pronounced in the alfacalcidol treated group compared to the calcium treated group. The effect of alfacalcidol on parathyroid glands may have played a role in the significant reduction of the PTH level in Group 2.

Bone densitometric investigations revealed rapid bone loss during the first months after transplantation. In the first 6 months after operation 6-10 % bone loss was reported in kidney transplant recipients. The post-transplant osteopenia and osteonecrosis usually correlates with the pre-existing renal osteodystrophy and with the administered dose of steroids.

The post transplant osteopenia is mainly caused by steroids. For this reason we investigated the role of alfacalcidol in preventing post-transplant osteopenia.

Between 3 months and 2 years after transplantation the BMD values increased at the lumbar spine and decreased at the femoral neck in Group 1. In Group 2, the BMD values increased at the femoral neck and decreased at the lumbar spine, in spite of the fact that this group had a higher decrease of PTH levels during the study. There were no significant differences between the two groups in the BMD values.

Although several studies have showed the positive effects of active D vitamin metabolites in the therapy of osteoporosis, the role of active vitamin D metabolites in the therapy of osteoporosis is still controversial.

Bone densitometry showed moderate osteopenia in patients with long-term renal transplantation in both groups and the alfacalcidol treatment could not prevent the post transplant osteopenia.

## Conclusion

The parathyroidectomy was successful in 99% of the patients with primary hyperparathyroidism. After the operation the serum calcium and PTH levels decreased.

In conclusion, the sensitivity of Technetium-99m-sestambi and Technetium-99m-pertechnetate subtraction scanning was significantly superior compared to other localization methods.

The sensitivity of this subtraction scintigraphy was significantly higher for adenomas than for hyperplastic glands.

The sensitivity of this radionuclide scan was high for parathyroid glands in loco typico and for ectopic glands.

The application of this scintigraphy in combination of bilateral neck exploration can decrease the incidence of persistent or recurrent hyperparathyroidism.

Using this high sensitive Technetium-99m-sestambi and Technetium-99m-pertechnetate subtraction scintigraphy parathyroidectomy can be performed from unilateral neck exploration or minimally invasive surgery.

The serum levels of calcium, AP and PTH significantly decreased after the parathyroidectomy in patients with osteoporosis. After the operation the BMD values significantly increased at the lumbar spine. After successful parathyroidectomy the antiresorptive treatment is not necessary in the most of the cases.

Our results showed that the normal parathyroid glands had diploid DNA content, while aneuploid DNA content is not rare in hyperfunctioning parathyroid glands. The flow cytometric DNA analysis is unable to make a distinction between adenomas and hyperplasias because DNA aneuploidy often occurs in both diseases. In those cases where DNA aneuploidy occurs with high PI in benign parathyroid diseases, close follow-up is required because of their malignant potential.

DNA analysis revealed that both DNA aneuploid and diploid pattern might be present in parathyroid carcinomas. When the carcinoma has aneuploid DNA content the occurrence of lymph node metastases is higher. Our results suggest, in correlation with other authors, that survival decreases when the cancer has aneuploid DNA content.

In secondary hyperparathyroidism the subtotal parathyroidectomy or total parathyroidectomy with autotransplantation cause a rapid decrease of PTH level and the improvement of the clinical symptoms. Persistent hyperparathyroidism occurs in those cases where inadequate parathyroidectomy was performed.

Kidney transplantation improves the calcium- and bone mineral metabolism, but the administered immunosuppressive therapy has a negative influence on this process. Successful kidney transplantation corrects many of the metabolic disturbances. The PTH levels decreased in the calcium and in the alfacalcidol treated group. The decrease of PTH levels were more pronounced in the alfacalcidol treated group. Moderate osteopenia was observed in both groups after the transplantation, despite of the administration of alfacalcidol treatment.