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ORIGINAL RESEARCH

In Vivo Characterisation of Parathyroid Lesions by Use of Gamma Probe: Comparison With Ex Vivo Count Method and Frozen Section Results

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OBJECTIVE: In this study we hypothesized that if timing of gamma probe-guided parathyroidectomy were individualized according to an optimal-time-to-surgery technique, in vivo characterization of parathyroid lesions would be possible. We compared our findings with an ex vivo counting method ("20% rule") and frozen section results.

STUDY DESIGN AND SETTINGS: Thirty-five patients who were referred for surgical treatment of hyperparathyroidism were studied. Maximum parathyroid to thyroid sestamibi uptake ratio (UR_{max}) was measured by use of preoperative dynamic scintigraphy. The interval between sestamibi injection and UR_{max} was defined as the optimal time to surgery. On the day of surgery, the patients received the same dose of sestamibi and were taken to the operating room at UR_{max} as determined by preoperative scintigraphy. Intraoperative in vivo gamma probe counts from parathyroid lesions were compared with in vivo contralateral background thyroid counts (in vivo/Bkg) and to ex vivo parathyroid counts relative to postexcision background of the adjacent normal tissue (ex vivo/Bkg).

RESULTS: A total of 70 excised lesions were evaluated. In vivo/Bkg counts obtained from parathyroid adenoma were significantly different from parathyroid hyperplasia ($z = -3.093$, $P = 0.002$) and other lesions ($z = -3.958$, $P = 0.0001$). By receiver operating characteristic curve (ROC) analysis, we found the cutoff value for the in vivo/Bkg counts ratio to be 103% to differentiate parathyroid adenoma from hyperplasia with a sensitivity, specificity, and accuracy of 82.5, 65, and 74.4%, respectively. On the other hand, sensitivity, specificity, and accuracy of the ex vivo/Bkg method to differentiate parathyroid adenoma from hyperplasia with a cutoff value of 34.7 was found to be 70.8%, 60%, and 65.9%, respectively. The difference between the accuracy of these 2 tests was not significant statistically ($P = 0.137$). Sensitivity of frozen section to differentiate parathyroid adenoma and hyperplasia was 76.2% and 33.3%, respectively.

CONCLUSIONS: Patient-specific optimal protocol for timing of sestamibi injection together with in vivo/Bkg method is a useful alternative method in guiding the surgeon to differentiate parathyroid adenoma from parathyroid hyperplasia and other tissues and may help surgeons' decisions during the operation. Combined use of in vivo/Bkg and ex vivo/Bkg methods may give more accurate results than frozen section.

EBM rating: C-4

Preoperative Tc-99m-sestamibi (MIBI) scintigraphy and gamma probe–guided parathyroidectomy have significantly changed the entire approach to parathyroid surgery in patients with primary hyperparathyroidism.[1-4] Reduced operative morbidity, shorter operative time and hospital stay, and increased cost-effectiveness are advantages of this procedure compared with traditional bilateral neck exploration.[5-7] Another major advantage of this procedure is that it allows physicians to evaluate the radioactivity in the excised tissue and distinguish parathyroid adenoma from normal

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parathyroid tissue and other neck structures in order to make appropriate operative decisions. This method, which is also called the "20% rule," was first pioneered by Dr Colleen Murphy and Dr James Norman from the University of Florida (Tampa) and then successfully validated by other investigators.[8-11] The 20% rule claims that any excised tissue containing more than 20% of background radioactivity of the operative basin is a parathyroid adenoma. High background thyroid gland radioactivity is challenging, and in order to apply 20% rule, suspected tissue should be excised first, and then ex vivo radioactivity of the lesion should be measured outside the operative basin. If ex vivo counts are not appropriate, the surgeon should continue dissection and localization of other tissue and again excise it for ex vivo counting. As timing of the operation after MIBI injection is not individualized, activity in the thyroid gland can be significantly high, and the target-to-background activity ratio is variable depending on both the thyroid and the parathyroid washout rates of MIBI. We have previously shown that an optimal lesion-background ratio is essential for the success of gamma probe–guided parathyroidectomy, and this ratio is highly variable among patients.[12] In this study, we hypothesized that if timing of gamma probe–guided parathyroidectomy is individualized according to an optimal-time-to-surgery technique, in vivo characterization of parathyroid lesions can be possible. We compared our findings with the ex vivo counting method (20% rule) and frozen section results.

MATERIALS AND METHODS

Thirty-five patients who were referred for surgical treatment of hyperparathyroidism (26 women, 9 men, mean age 50.7 years) were studied. All patients were recruited at the Hacettepe University Medical Center, Ankara, Turkey, with the prior approval of the institutional review board. All patients had elevated levels of parathyroid hormone (PTH) (mean: 332 pg/mL; range, 75.6-2200 pg/mL; normal range, 10-65 pg/mL). Ultrasonography detected multinodular goiter (including the milimetric nodules) in 15 of them.

Imaging Protocol

The scintigraphy protocol consisted of a dynamic imaging phase and early and delayed static image acquisitions. Dynamic imaging was performed in anterior projection for 30 minutes immediately after intravenous injection of 20 mCi MIBI (1frame/min, 30 frames). Early static images then were obtained (300 kcount/view, anterior and 45° right-and-left anterior oblique neck projections as well as anterior mediastinal images). The preset time needed to achieve sufficient count density for early images was applied for delayed-phase imaging of the same projection of planar images. Clearance from the parathyroid and thyroid glands was measured for 180 minutes and included the 30-minute dynamic imaging. Time-activity curves were generated for thyroid and parathyroid uptake and clearance. Maximum parathyroid-thyroid MIBI uptake ratio (UR_{max}) was measured. The interval between MIBI injection and UR_{max} was defined as the optimal time to surgery, which is the time that the activity retention related to the parathyroid lesion became clearly visible scintigraphically.

Gamma Probe–Guided Parathyroidectomy

On the day of surgery, the patients received the same dose of MIBI and were taken to the operating room at UR_{max} determined by preoperative scintigraphy. Before skin incision, counts over 4 quadrants in the neck as well as over the mediastinum were obtained by use of a gamma probe (Neoprobe 2000, Dublin, OH). A standard collar incision was made, and a bilateral cervical exploration was performed with the gamma probe. All suspected tissues and lesions with high in vivo gamma probe counts relative to contralateral thyroid gland counts were excised. Intraoperative in vivo gamma probe counts from parathyroid lesions were compared with in vivo contralateral background thyroid counts (in vivo/Bkg) and with ex vivo parathyroid counts relative to postexcision background of the adjacent normal tissue (ex vivo/Bkg). Histopathologic confirmation of a successful parathyroidectomy was obtained intraoperatively by frozen section. Exploration of the neck was terminated after a postresection gamma probe survey.

Pathologic Evaluation

Specimens were reviewed with the use of standard hematoxylin and eosin technique. In vivo/Bkg–ex vivo/Bkg ratios and frozen section results were compared with permanent section diagnosis.

Statistical Analysis

The bilateral comparisons were performed with Mann-Whitney test. Results were considered statistically significant when P values < 0.05. Receiver operating characteristic curve (ROC) curve analysis was performed to find cutoff values of each method. Calculations were obtained by use of SPSS for Windows, version 10.0. Significance between in vivo and ex vivo methods was analyzed by means of the MedCalc program.

RESULTS

Histopathology

In the Table patient characteristics are given including the preoperative and postoperative calcium and PTH levels. In total, 70 lesions were examined. Histopathologic examination revealed solitary parathyroid adenoma in 24 lesions, hyperplasia in 20 lesions, and normal parathyroid tissue in 8 lesions. There were 3 ectopic parathyroid adenomas (1 pretracheal, 2 intrathymic). One patient had synchronous papillary thyroid carcinoma and parathyroid adenoma. The histopathologic diagnoses of other excised lesions were as

Table
Patients' histopathology characteristics including the preoperative and postoperative calcium and PTH levels

Patient no.	Histopathology	PTH (pg/mL)	Calcium (mg/mL)	Postoperative PTH	Postoperative calcium	In vivo/Bkg	Ex vivo/Bkg
1	Parathyroid adenoma	118	11.2	60.0	9.2	107	100
2	Parathyroid hyperplasia	2200	11.9	65.0	8.5	92; 123; 137	102; 167; 220
3	Parathyroid adenoma	155	10.5	18.4	9.5	104	89
4	Parathyroid hyperplasia	138	10.4	40.3	9.5	110; 77	20; 12
5	Parathyroid adenoma	193	12	31.8	9.9	115	14
6	Parathyroid adenoma	254	11.2	65.0	10.1	178	78
7	Parathyroid adenoma	117	10.2	53.0	9.8	96	23
8	Parathyroid adenoma	206	12.4	62.0	10.1	87	57
9	Parathyroid adenoma	162	10.2	52.5	8.9	161	32
10	Parathyroid adenoma	169	15	45.0	9.1	158	73
11	Parathyroid adenoma	110	11.9	44.4	10.1	153	44
12	Parathyroid tissue[a]	101	10.2	50.2	10.1	88	9
13	Parathyroid hyperplasia	121	11.1	33.7	8.6	92; 95; 102; 151	66; 61; 32; 16
14	Parathyroid tissue[a]	211	12.7	30.8	9.1	56	8
15	Parathyroid adenoma	244	12.6	49.9	9.4	141	163
16	Parathyroid adenoma	107.9	8.5	44.2	9.2	NA	17
17	Parathyroid hyperplasia	75	11.3	46.7	10.2	91	10
18	Parathyroid adenoma	110	9.5	60.6	9.8	112	49
19	Parathyroid hyperplasia	91.5	10.9	32.1	8.2	128; 112; 88; 78	8; 23; 14; 4
20	Parathyroid adenoma	124.8	9.6	43.1	9.2	145	37
21	Parathyroid adenoma	169.4	12.3	63.2	9.3	94	18
22	Parathyroid hyperplasia	1800	9.4	57	8.6	97; 57; 77; 54	119; 12; 46; 21
23	Parathyroid adenoma	158	9.2	43	9.4	107	58
24	Parathyroid adenoma	103	10.1	53.8	9	156	59
25	Parathyroid adenoma	247	9.1	64	9.4	173	105
26	Parathyroid adenoma	197.2	10.5	31.4	9	128	91
27	Parathyroid adenoma	230.2	10.2	44.4	9.5	78	2
28	Parathyroid adenoma	280.5	8.7	63.5	9.5	136	61
29	Parathyroid adenoma	203.5	10.8	50.3	9.6	143	104
30	Parathyroid adenoma	1303	12.8	64.7	9.7	251	157
31	Parathyroid adenoma	298.2	11.8	27.2	10.2	130	16
32	Parathyroid hyperplasia	1172	14.6	28.3	10.1	172	75
33	Parathyroid tissue[a]	166	10.4	64.3	10.2	105	2
34	Parathyroid adenoma	165	10.1	61.5	10	175	47
35	Parathyroid hyperplasia	122	11.03	53.4	9.1	103	24

PTH, parathyroid hormone; *NA*, not available.
[a]Although histopathologic diagnosis is normal parathyroid tissue, patient's PTH and calcium levels decreased after surgery.

follows: fatty tissue-cyst (2), lymph node (8), thyroid nodule (5), and thymus (2).

Comparison of In Vivo and Ex Vivo Gamma Probe Counts with Frozen Section and Permanent Histopathology; Differentiation of Parathyroid Adenoma from Hyperplasia

The average in vivo/bkg count ratios obtained from parathyroid adenoma and hyperplasia were 136 and 102, respectively. In vivo/Bkg counts obtained from parathyroid adenoma were significantly different from parathyroid hyperplasia ($z = -3.093$, $P = 0.002$) (Fig). By ROC analysis, cutoff value for the in vivo/Bkg count ratio was found to be 103% to differentiate parathyroid adenoma from hyperplasia with a sensitivity, specificity, and accuracy of 82.5%, 65%, and 74.4%, respectively. Nineteen of 24 parathyroid adenomas (79%) were above this cutoff value. In contrast, 7 of 20 (35%) parathyroid hyperplasia counts were above cutoff value (103%).

Average ex vivo/Bkg count ratios obtained from parathyroid adenomas and hyperplasia were 62.4 and 52.7, respectively, and the difference was not statistically significant ($z = -1.355$, $P = 0.175$). On the other hand, sensitivity, specificity, and accuracy of the ex vivo/Bkg method to differentiate parathyroid adenoma from hyperplasia with a cutoff value of 34.7 was found to be 70.8%, 60%, and 65.9%, respectively. The difference in the accuracy of these 2 tests to differentiate parathyroid adenoma from hyperplasia was statistically not significant ($P = 0.137$). The mean hyperplastic lesion volume is 2.3 mL (range, 0.02-10.4 mL), and there is a strong positive correlation between hyperplastic lesion size and ex vivo and in vivo gamma probe counts ($r = 0.698$, $P = 0.019$). Sensitivity of frozen section to differentiate para-

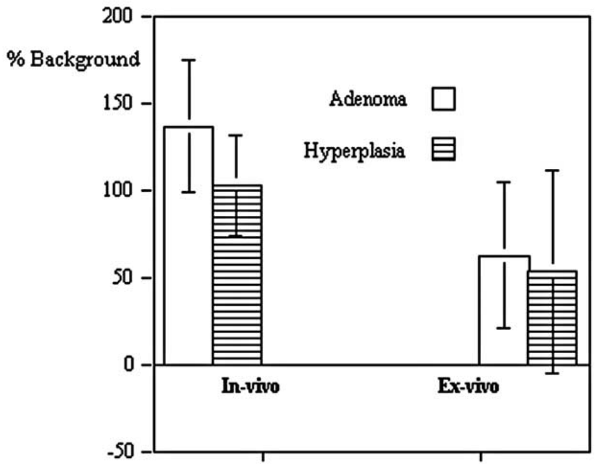

Figure In vivo/Bkg and ex vivo/Bkg counts obtained from parathyroid adenoma and parathyroid hyperplasia (mean ± standard deviation).

thyroid adenoma and hyperplasia was 76.2% and 33.3%, respectively.

Differentiation of Parathyroid Adenoma and Hyperplasia from Other Lesions

The average in vivo/Bkg count ratios obtained from normal parathyroid tissue, fatty tissue-cyst, lymph node, papillary thyroid cancer, thyroid nodule, and thymus were 87, 96, 101, 133, 97, and 105, respectively. Ex vivo/Bkg ratios of the other excised lesions were as follows: normal parathyroid tissue, 6.1; fatty tissue-cyst, 0.17; lymph node, 7.7; papillary thyroid cancer, 106; thyroid nodule, 8.5; and thymus, 0.2 . In vivo/Bkg counts obtained from these excised lesions were significantly different from parathyroid adenoma ($z = -3.958$, $P = 0.0001$) but not from parathyroid hyperplasia. Ex vivo/Bkg ratios of these excised lesions were significantly different from the parathyroid hyperplasia ($z = -4.897$, $P < 0.001$) and parathyroid adenoma ($z = -5.476$, $P < 0.001$). By ROC analysis, the cutoff value for the in vivo/Bkg count ratio was found to be 120% to differentiate parathyroid adenoma and hyperplasia from the other lesions with a sensitivity, specificity, and accuracy of 44.2%, 96%, and 68%, respectively. By ROC analysis, the cutoff value for the ex vivo/Bkg count ratio was found to be 9.5% to differentiate parathyroid adenoma and hyperplasia from the other lesions with a sensitivity, specificity, and accuracy of 93.2%, 86%, and 90%, respectively. Sensitivity, specificity, and accuracy of frozen section to differentiate parathyroid adenoma and hyperplasia from the other lesions were found to be 60.5%, 100%, and 73%, respectively.

DISCUSSION

Until recently, traditional bilateral neck exploration and 4-gland exploration have been accepted as the procedure of choice for parathyroidectomy in many institutions.[13] Surgeons removed enlarged or normal glands based purely on how they looked and waited for the results of frozen section. However, the accuracy of frozen section is not perfect. The main reason for the conflicting reports regarding the precision of frozen section seems to be erroneous frozen section interpretation.[14,15] Failures are most commonly due to the inability to distinguish normal parathyroid tissue from parathyroid adenoma and hyperplasia, the inability to differentiate thyroid nodules from parathyroid tissue, and inadequate sampling by both the surgeon and the pathologist with specimens often interpreted as nondiagnostic.[8] Another important development in the parathyroid surgery of primary hyperparathyroidism has been the quick intraoperative parathyroid hormone assay with a 99% cure rate.[16,17] However, like frozen section, this technique requires waiting for the results for 12-15 minutes, and if the PTH level has not decreased, dissection should continue.

Gamma probe–guided minimally invasive parathyroidectomy is being performed successfully as an alternative to traditional bilateral neck exploration because of its advantages, such as shorter operative time and hospital stay, and increased cost-effectiveness.[18] Another major advantage of gamma probe is its ability to evaluate the radioactivity in the tissue that is removed and to determine whether it is a parathyroid adenoma or normal parathyroid tissue, lymph node, thyroid tissue, or fatty tissue.[8] Murphy and Norman claimed that with this technique, frozen-section analysis and intraoperative measurement of parathyroid hormone are not necessary.[8] Using the 20% rule, Goldstein and coworkers used gamma probe–guided parathyroidectomy without intraoperative parathyroid hormone measurement with an excellent cure rate.[10]

However, because of high thyroid background activity, these tissue radioactivity measurements have to be performed ex vivo after excision of the tissue. In this study, we investigated whether in vivo characterization of parathyroid lesions can be possible if timing of gamma probe–guided parathyroidectomy is individualized according to the optimal-time-to-surgery technique, with a low thyroid background radioactivity.

We found that with the in vivo counting technique, it is possible to differentiate parathyroid adenoma from parathyroid hyperplasia with a slightly better accuracy compared with the ex vivo method. However, the difference in the accuracy of these 2 tests to differentiate parathyroid adenoma from hyperplasia was statistically not significant. Moreover, both in vivo and ex vivo counting methods are able to discriminate parathyroid adenoma and hyperplasia from other tissues. Strong positive correlation between hyperplastic lesion size and ex vivo and in vivo gamma probe counts is in contrast to findings in Murphy and Norman's study.[8] They reported that hyperplastic parathyroid glands will not accumulate more than 18% of background radioactivity whatever their size, and while gathering this information, the surgeon should continue the dissection to find each of the other glands. Our disconsonant finding may result from our study group, in which hyperplastic glands up to 8-10 g existed, and counts from these large glands were as high as 220% (ex vivo) and 186% (in vivo). So the surgeon should be careful because larger hyperplastic glands may behave like a parathyroid adenoma in their total count. We also found that both in vivo and ex vivo counting methods are more accurate than frozen section results. The in vivo method, with a specificity almost equal to that of frozen section, can also be used to confirm that excised tissue is an adenoma. The major advantage of the in vivo counting method over Norman's method is that when a surgeon counts a lesion in vivo and the counts are above 103%, it means that the lesion is more likely to be an adenoma than a hyperplasia and that a focused minimally invasive approach could be done instead of 4-gland exploration. Quick intraoperative PTH assay is very helpful, especially in asymmetric hyperplasia cases, because large hyperplastic glands may give radioactivity counts as high as adenomas. Although the individualization of the best surgical exploration time after MIBI injection is a better approach, it can be difficult to perform in a busy operating room and may cause delays.

CONCLUSIONS

Patient-specific optimal protocol for timing of MIBI injection, together with the in vivo/Bkg method, is useful in guiding the surgeon to differentiate parathyroid adenoma from parathyroid hyperplasia and other tissues that may help surgeons' decisions during the operation. Combined use of in vivo/Bkg and ex vivo/Bkg methods may give more accurate results compared with frozen section.

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