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Original Research

The Relationship of Negative Imaging Result and Surgical Success Rate in Primary Hyperparathyroidism

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Abstract

Objectives: In present, the effect of pre-operative negative imaging results on surgical outcomes of primary hyperparathyroidism (pHPT) is still controversial. In this study, we aimed to evaluate the effect of pre-operative imaging on surgical outcomes.

Methods: The data of pHPT patients who were operated between 2009 and 2018 were evaluated retrospectively. Patients were divided three groups according to scintigraphy and/or ultrasonography results: Group 1; both imaging positive, Group 2; single imaging positive, and Group 3; patients in whom both imaging modalities are negative. Pre-operative biochemical characteristics, parathyroid pathologies, diameter and volume of the pathological gland, surgery rates, persistence, and recurrent disease rates of the groups were compared.

Results: Of 311 patients (258F, 53M) with a mean follow-up period of 24.7±18 months and a mean age of 54.1±12.9 years; 161 were in Group 1, 111 were in Group 2, and 39 were in Group 3. The diameter of pathological gland (2.1±0.8, 1.6±0.9, 1.5±0.7 cm; p<0.001; in Group 1,2,3 respectively) and the volume of pathological gland (2±3.2, 1.4±2.9, 1.1±2.2 cm^3; p<0.001; in Group 1,2,3, respectively) in Group 1; the rate of multi gland disease (5.7%, 11%, 21%; p=0.024; in Group 1, 2, 3, respectively) in Group 3 were significantly higher. In the 1, 2, 3 group; bilateral exploration rates were 93.2%, 48.6%, and 5.1%, and focused surgery or unilateral exploration rates were 6.8%, 51.4%, and 94.9%, respectively, with a significant difference (p<0.001). After the first surgery, the cure rate was 91.3%, 93.7%, and 89.7%, and the persistent patient rate was 7.5%, 3.6%, and 10.3% in Groups 1,2,3, respectively, and there was no significant difference. At the end of the follow-up period after secondary intervention applied in persistent and recurrent patients, the overall cure rate was 97.4%, 96.4%, and 97.4%, persistent disease rate 1.3%, 1.8%, and 2.6%, recurrent disease rate 1.3%, 1.8%, and 0%, respectively.

Conclusion: In imaging-negative patients with pHPT, the possibility of multi gland disease and smaller pathological glands should be considered at the time of surgery. Surgery in imaging-negative patients can be performed with a similar and acceptable cure rate to imaging-positive patients.

Keywords: Parathyroid surgery, preoperative imaging, primary hyperparathyroidism

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Primary hyperparathyroidism (pHPT) is the most common cause of hypercalcemia and the only curative treatment is surgery.[1]

In the last quarter of the last century, ultrasonography (USG) and scintigraphy started to be used in parathyroid imaging, and with the development of technology, these methods

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not only developed, but also new imaging methods were defined.[2] The cause of the disease in pHPT is single gland disease in 80–85% of the cases, and it is possible to detect most of the pathological glands with pre-operative imaging methods.[2,3]

Bilateral neck exploration (BNE) is still the gold standard treatment for pHPT. Although BNE can be performed without imaging methods, pre-operative imaging methods are gaining more and more importance. In the present, the use of parathyroid imaging methods has become routine in patients with pHPT with surgical indication.[4,5] Pathological gland cannot be localized with non-invasive methods in nearly 10–20% of pHPT patients.[6]

The success rate of pHPT surgery is above 95% with experienced surgeons and this result is independent from pre-operative localization methods and surgical technique.[7] Although pre-operative imaging has no place in diagnosing, confirming or excluding pHPT, in determining whether there is a surgical indication or not, 90% of endocrinologists have one or more imaging modalities performed before referring the patient to the surgeon.[8,9] In 79% of endocrinologists, the feasibility of minimally invasive parathyroidectomy increases the number of patients referred for surgery.[9] Negative scintigraphy result decreases the rate of referring patient to surgeon and delays the referring for 25 months.[10]

The effect of negative imaging results on surgical outcomes is still unclear. Although some studies have reported that negative scintigraphy and USG results are factors that increase the risk of persistent disease, other studies have reported that not localizing the pathological gland is not associated with a decrease in surgical cure rate.[11-13]

USG and scintigraphic methods are the most commonly used methods in the first imaging before the primary intervention, and these two imaging methods are routinely combined in many centers.[14,15] Pre-operative USG and scintigraphy are routinely used in primary cases in our center, too. In this study, we aimed to evaluate the effect of imaging negativity on surgical success.

Methods

The data of patients who were operated by a single and same surgeon between 2009 and 2018 were evaluated retrospectively. The study was approved by the local ethics committee (Date: March 02, 2021 Number: 3168). Patients with pre- and post-operative data and at least 6 months of follow-up were included in the study. Patients who did not have follow-up, operated for persistent pHPT after the first operation, and patients operated for secondary and tertiary hyperparathyroidism were excluded from the study.

During this period, pre-operative USG and sestamibi scintigraphy methods were routinely performed to the patients. If both images were negative, surgical treatment was recommended to the patient without further imaging. Scintigraphic and ultrasound results of the patients were evaluated according to whether they were positive on the right or left side or ectopic. If both imaging (USG and scintigraphy) results of patients were positive and concordant on the same side, it was defined as two positive imaging; if single imaging result was positive or 2 imaging results were positive but discordant, it was defined as single imaging positive; if both imaging results were negative, it was defined as negative imaging. According to these definitions, patients were divided into three groups. Group 1; both imaging positive, Group 2; single imaging positive, and Group 3; patients in whom both imaging modalities are negative.

Focused surgery (FP) or unilateral neck exploration (UNE) was performed without intraoperative parathyroid hormone (ioPTH) measurement in patients with two positive images. FP with ioPTH or UNE without ioPTH were performed in single imaging positive patients. If the enlarged gland and the other parathyroid gland on the same side were normal in UNE, the operation was terminated. Surgical method was converted to BNE in patients with discordant intraoperative findings with the pre-operative imaging results which underwent FP or UNE patients or when there was no sufficient PTH decrease in patients who underwent FP or UNE with ioPTH. BNE was performed in patients with two imaging negative.

FP and UNE were usually performed with a lateral 2.5–3 cm open incision made from the anterior border of the sternocleidomastoid muscle. Rarely, UNE was performed by entering the midline with a Kocher incision. BNE was performed midline with a standard Kocher incision. Both neck sides were explored. Intraoperatively, normal localization areas of the parathyroids and possible ectopic localization areas for parathyroids that cannot be found in the normal localization were explored. Enlarged parathyroid or parathyroids were removed. When necessary, parathyroid was confirmed by frozen examination. Normal parathyroids were preserved. If four parathyroids were enlarged, subtotal parathyroidectomy was performed. Biopsy was taken from the tip of the normal parathyroid in some patients with suspected asymmetric hyperplasia. Frozen examination was performed when the excised lesion was suspicious for parathyroid. Enlarged parathyroid was confirmed by frozen or paraffin section examination.

Parathyroid adenoma was assumed to be an ellipsoid shape and was calculated from the adenoma dimensions (cm) in the pathology reports with the formula

(cm^3)=π/6xR1XR2XR3. Surgical cure was defined as achieving normocalcemia at 6 months postoperatively.[8]

Patients in whom hypercalcemia persisted after the first operation or in whom hypercalcemia emerged within 6 months were defined as persistent. Surgical cure was achieved by applying secondary interventions with the contribution of imaging methods in some of the patients who persisted after the first operation. The final evaluation cure rate defines the cure rate based on the patients' last evaluated long-term results.

Pre-operative biochemical characteristics of the groups, parathyroid pathologies, diameter and volume of the pathological gland, type of surgery performed, additional thyroidectomy, persistent, and recurrent disease rates were compared.

Statistical Analysis

IBM SPSS Statistics for Windows V25 (IBM Corp., Armonk, NY) program was used for all statistical analyses. Descriptive statistics; numbers; and percentages were calculated for categorical variables, mean, standard deviation, minimum, and maximum were calculated for numerical variables.

Pearson Chi-square and Fisher exact test were used to compare categorically independent groups. Non-parametric comparisons were made with Mann–Whitney U test. P<0.05 was considered significant. According to Bonferroni Corection (0.05/3=0.017), p<0.017 was considered significant in the comparison of two groups between three groups.

Results

Of 311 patients (257 F, 53 M), with 24.7±18 months mean follow-up and 54.1±12.9 years mean age, 161 patients were located in Group 1, 111 in Group 2, and 39 in Group 3. The mean age of groups was significantly different (p=0.001) (Table 1). In the pairwise comparison of the groups, the mean age of Group 2 was significantly higher than group 1 (p<0.001). There were no other significant differences in other comparisons. Pre-operative PTH levels were higher in Group 1, and the difference was significant between groups (p<0.001) (Table 1). In pair-wise comparison, PTH levels of Group 1 and 2 were higher than group 3 (p<0.001, p=0.011, respectively). In between the groups, pre-operative P and 25(OH)vitD3 levels were higher in Group 3, and the difference between the groups was significant (p=0.017, p=0.024, respectively) (Table 1). Only Group 1 was significantly lower than Group 3 in pair-wise comparisons for both (p=0.012, p=0.007, respectively).

There was a significant difference according to the performed surgery type in between groups (p<0.001). FP or UNE was applied in 93.2% of patients in Group 1, while BNE was applied in 94.9% of patients in Group 3. In Group 2, 48.6% of the patients had FP or UNE and 51.4% had BNE (Table 2). There was a significant difference in pair-wise comparisons of all three groups (p<0.001 for all).

The maximum diameter and volume of the pathological gland were also significantly different between the groups (p<0.001 for both). In the pair-wise comparison of the

Table 1. Comparison of the characteristics of the groups

	Group 1 (n=161)	Group 2 (n=111)	Group 3 (n=39)	p
Age	51.6±12.9 (17–80)	57.9±12.3 (27–85)	53.6±12.4 (29–88)	<0.001
Gender				
Male	135 (83.9%)	93 (83.8%)	30 (76.9%)	0.563
Female	26 (16.1%)	18 (16.2%)	9 (23.1%)	
Pre-operative PTH (pg/mL) (mean±SD) (min-max)	375.7±375.7 (53–3308)	226.7±235.3 (65–1411)	206.8±415 (39–2610)	<0.001
Pre-operative Ca (mg/dL) (mean±SD) (min-max)	11.4±1 (9.3–17)	11.1±0.7 (8.6–12.9)	11.1±0.8 (8.6–12.7)	0.193
Pre-operative Mg mg/dL) (mean±SD) (min-max)	2±0.9 (1–2.7)	2±0.2 (1.0–2.5)	2±0.2 (1.2–2.4)	0.835
Pre-operative P (mg/dL) (mean±SD) (min-max)	2.6±0.6 (1.1–5.4)	2.7±0.5 (1.6–4.1)	2.8±0.5 (1.6–4.2)	0.017
Pre-operative ALP (U/L) (mean±SD) (min-max)	139.2±226 (46–2555)	99.4±63.4 (26–456)	100.6±36.9 (45–239)	0.090
Pre-operative Creatinine (mg/dL) (mean±SD) (min-max)	0.8±0.3 (0.4–2.2)	0.8±0.3 (0.4–2)	0.7±0.2 (0.5–1.5)	0.199
Pre-operative 25 (OH) Vitamin D3 ng/ml (mean±SD) (min-max)	16.6±11.4 (3–59.7)	20.7±16.5 (3–84)	22.8±14.7 (6.3–61.7)	0.024

PTH: Parathyroid hormone; Ca: Calcium; P: Phosphorus; Mg: Magnesium; ALP: Alkaline phosphatase; SD: Standard Deviation; Min: Minimum; Max: Maximum.

groups, parathyroid diameter and volume were significantly larger in Group 1 than both Group 2 (p<0.001 for both) and Group 3 (p<0.001 for both), respectively. There was no significant difference between Group 2 and 3 in terms of diameter and volume.

The difference between the groups in terms of pathological outcome was significant (p=0.024). Single gland disease rates were 94.3%, 89%, and 79% and multi gland disease rates were 5.7%, 11%, and 20.9% in Group 1, 2, 3, respectively. According to pair-wise comparisons, there was a significant difference in between Group 1 and 3 (p=0.003) while there were no significant differences in other comparisons.

The follow-up time of study was 24.1±18.1 months and there was a significant difference in groups according to the follow-up times (p=0.004) (Table 2). In pair-wise comparisons, follow-up time in Group 2 was significantly higher than in Group 1 and Group 3 (p=0.003, p=0.015, respectively). There was no significant difference in terms of follow-up times of Groups 1 and 3.

After the first surgery, the cure rate was 91.3%, 93.7%, and 89.7%, and the persistent patient rate was 7.5%, 3.6%, and 10.3% in Groups 1,2,3, respectively, and there was no significant difference. At the end of the follow-up period after secondary intervention applied in persistent and recurrent patients; the overall cure rate was detected 97.4%, 96.4%, and 97.4%, persistent disease rate was detected 1.3%, 1.8%, and 2.6% and recurrent disease rate was detected 1.3%, 1.8%, and 0%, respectively.

There was no difference between the groups in terms of gender, Ca, Mg, ALP, and creatinine (Table 1).

Discussion

In present, pre-operative imaging methods are routinely used in pHPT patients and the combination of USG and scintigraphy is the most commonly used modality in clinical practice.[14,15] Despite all the technological and radiological developments, pathological parathyroid glands can be localized in 80–90% of patients with pHPT by pre-operative imaging methods.[2] However, in some patients, no pathological gland or glands can be detected. Many factors related to pre-operative negative imaging results have been evaluated in the literature.

In our center, a combination of pre-operative USG and scintigraphy is routinely applied in primary cases, and we evaluated the results of these patients. According to our results, both imaging were negative in 39 (12.5%) patients, similar to the literature rates. However, in some series which one or more imaging is applied, the negativity rate can reach 28–38%.[11,12]

In this study, there was no significant difference detected in groups according to the gender while the age was signifi-

Table 2. Comparison of the characteristics of patients with pHPT who underwent FP or UNE (group 1) and BNE (group 2)

	Group 1 (n=161)	Group 2 (n=111)	Group 3 (n=39)	p
Surgery Type				
FP or UNE	150 (93.2%)	54 (48.6%)	2 (5.1%)	<0.001
BNE	11 (6.8%)	57 (51.4%)	37 (94.9%)	
Additional Thyroidectomy	19 (11.8%)	35 (31.5%)	10 (25.6%)	<0.001
Maximum diameter of excised parathyroid gland (cm)	2.1±0.8 (0.9-5)	1.6±0.9 (0.7-5)	1.5±0.7 (0.6-4)	<0.001
Volume of the excised parathyroid gland (cm^3)	2±3.2 (0.03-24)	1.4±2.9 (0.05-20.9)	1.1±2.2 (0.04-9.4)	<0.001
Pathology result				
Single adenoma	150 (94.3%)	97 (89%)	30 (79%)	0.024
Double adenoma	7 (4.4%)	8 (7.3%)	4 (10.5%)	
Hyperplasia	2 (1.3%)	4 (3.7%)	4 (10.5%)	
Follow-up duration (months)	22.4±17.8 (6-97)	27.7±18.5 (6-120)	20.7±16.6 (2.5-120)	0.004
Cure rates in first operation				
Cured	147 (91.3%)	104 (93.7%)	35 (89.7%)	0.894
Persistant	12 (7.5%)	4 (3.6%)	4 (10.3%)	
Recurrent	2 (1.2%)	3 82.7%)	0	
Cure rates at the last evaluation				
Cured	157 (97.4%)	107 (96.4%)	38 (97.4%)	0.894
Persistent	2 (1.3%)	2 (1.8%)	1 (2.6%)	
Recurrent	2 (1.3%)	2 (1.8%)	0	

FP: Focused parathyroidectomy; UNE: Unilateral neck exploration; BNE: Bilateral neck exploration.

cantly different in between groups. There was no significant difference in age between the imaging negative group and the other groups. The difference between Groups 1 and 2 is significant, and this result may be related to the distribution of the study group. In the literature, no significant difference was found in terms of age in scintigraphy negative/ positive or localized/non-localized patients.[11,12,16]

When the biochemical results were evaluated according to the imaging positivity; the pre-operative PTH level was found to be significantly higher in both Group 1 and 2 compared to Group 3 (p<0.001, p=0.011, respectively) (Table 1). In addition, pre-operative P and 25(OH)vitD3 levels were significantly higher in Group 3 compared to other groups (p=0.017, p=0.024; respectively). In pair-wise comparison, the difference was significant in between Group 3 and 1 (p=0.012, p=0.007; respectively). Pre-operative Ca levels were similar between the groups. These statistically significant differences may not have clinical significance. The data in the literature are not compatible with each other.

Scott-Coombes et al.[16] found that both pre-operative Ca and PTH levels were lower in two imaging negative patients than in at least single imaging positive patientsWachtel et al.[12] found lower PTH and Ca levels in pre-operative non-localized cases compared to localized cases in pair-wise comparisons, and determined Ca level as an independent risk factor for non-localization in multivariance analysis. However, in this study, Ca and PTH levels were found to be similar between localized and non-localized groups in the matched cohort group.

Similar to our results, Vuong et al. found that although PTH levels were higher in preoperative localized patients in pHPT compared to non-localized patients, Ca levels were similar. On the other hand, Dy et al.[17] found Ca (10.9 vs. 11.0 mg/mL, p=0.02, respectively) and P (2.9 vs. 3.1 mg/dl, p<0.001) levels lower in the MIBI scintigraphy negative group compared to the positive group but also PTH and 25OHvitD3 levels were similar.

In this study, the diameter and volume of the removed pathological parathyroid glands were significantly different between the groups (p<0.001 for both). In the pair-wise comparison, both diameter and volume were significantly larger in Group 1 patients than in the single imaging positive group (p<0.001 for both) and the imaging negative group (p<0.001 for both). Both imaging negatives are associated with smaller adenoma size.[12]

In some studies, a positive correlation was detected between adenoma volume with PTH and Ca.[18,19]

Filser et al. determined a negative correlation in between adenoma volume and P; however, in the study of Bindlish et al., there was not any correlation.[18,19]

In the present study, small adenoma volume and diameter and low PTH level in imaging-negative patients could be explained by positive correlation and high P level by negative correlation.

The incidence of multi gland disease is higher in imaging negative patients.[11,12,16,20] The rate of multi gland disease in the etiology of pHPT is between 7 and 33% in the literature.[21]

In our study, multi gland disease rate was 5.7% in two imaging positive group, 11% in single imaging positive group, 21% in negative imaging group, and difference was significant in between groups (p=0.024). In pair-wise comparison, the rate of multi gland disease was significantly higher in two positive imaging group compared to negative imaging group (p=0.003). The fact that the rate of multi gland disease is higher especially in imaging negative patients has been revealed in many studies in the literature. In other comparable studies in the literature, the rate of multi-gland disease in patients with negative imaging is similar to or higher than our study and reported between 22 and 38%.[11-13,16,17,22]

The effect of pre-operative imaging in the success rate of parathyroidectomy surgery is still debatable in the literature and the surgical success rate is reported 82–97%.[10-13,16,17]

In this study, the surgical cure rate, at first surgical intervention, was similar in negative imaging group to single and two positive imaging groups (89.7%, 91.3%, 93.7%; p=0.094; respectively). The cause of persistent disease in all three groups at the first operation was usually multi gland disease. With the interventions applied to persistent patients, surgical cure rates of 97.4%, 96.4%, and 97.4% were achieved in the three groups, in a follow-up period of 24.1+18.1 months, although the follow-up periods were different for each group. According to our results, negative imaging does not reduce the early and late cure rates.

The success rate in patients with negative imaging at the first operation is acceptable. However, the first surgery success rate may be lower than expected in two imaging positive patients. The reason for this may be related to not using ioPTH in these patients. In another recent study, we demonstrated that the surgical cure rate of minimally invasive parathyroidectomy could be increased from 93.3% to 97.6% with the contribution of ioPTH in patients with pHPT who were two imaging positive and compatible. The most important reason for surgical failure in this study was the failure of two imaging to detect multi gland disease.[23]

Multi gland disease remains an important problem in preoperative imaging. USG, scintigraphy, or a combination of the these methods are not reliable in predicting multi gland disease.[24] In a study using routine ioPTH, the surgical cure rate at the first operation in imaging positive and negative patients was higher in the imaging positive group (96.8% vs. 92.7%, respectively, p<0.05). In this study, similar to our results, the surgical cure rate with the second operation in the negative imaging group increased to 96%, similar to the imaging positive group.[16]

Vuong et al.[11] reported that high cure rates as comparable with localized patients without increased surgical morbidity in non-localized patients can be achieved in pHPT patients, who are non-localized with USG and scintigraphy although the necessity of BNE and the rate of multi gland disease is higher. Wachtel et al.,[12] although the rate of negative exploration (2.5% vs. 0.9%, respectively, p=0.003) was higher in non-localized patients than localized patients; found similar intraoperative success (93.9% vs. 95.6%, p=0.073) and 6-month cure rates (96.2% vs 97.7%, respectively, p=0.291) according to the intraoperative PTH criteria. They concluded that pre-operative localization of pathological glands in pHPT did not reduce the surgical cure rate. In addition that, in another study, it is reported; negative exploration rate could be alarmingly increased above 10% in first surgery in patients with negative USG and scintigraphy and the risk of persistent disease could be increased to 18%, also the surgical cure rate could be 82%.[13]

Elaraj et al.[25] reported that the surgical cure rate was lower in patients with negative scintigraphy in pHPT than in patients with positive scintigraphy (89% vs. 97% p=0.008, respectively) and emphasized that negative scintigraphy was associated with multi gland disease and low cure rate.

Similarly, in the other study, the surgical cure rate was found to be lower in patients with negative scintigraphy than in patients with positive scintigraphy (90.4% vs. 97.5%, respectively; p=0.001). In this study, the cure rate was 89% in both USG and scintigraphy negative patients. The authors emphasized that the cure rate is acceptably low in patients with negative imaging and this should be taken into account in the surgical decision.[17]

In present, minimal invasive parathyroidectomy has become the standard treatment for selected patients with positive imaging in the treatment of pHPT.[4] BNE, which is still the gold standard, is required in the surgical treatment of the majority of imaging-negative pHPT patients.[8]

In this study, the types of surgical interventions were significantly different between the groups (p<0.001), FP or UNE was performed in 93.2% in the two imaging positive group and 94.9% BNE in the imaging negative group at the first surgery, and these rates are consistent with the current standard approach in the literature. In single imaging positive patients, 48.6% FP or UNE and 51.4% BNE were performed. In addition, the rates of additional thyroidectomy in Groups 1, 2, 3 were 11.8%, 31.5% and 25.6%, respectively, and the difference was significant (p<0.001). In the pairwise comparison, the rate of additional thyroidectomy was significantly higher in single imaging positive patients (Group 2) than in two imaging positive patients (p<0.001). This may have been an additional factor that increased the rate of BNE in Group 2.

FP or UNE can be performed with the help of ioPTH in single imaging positive or imaging inconsistent patients.[24,26] In the evidence-based literature, BNE is recommended as the standard approach in imaging-negative patients.[21,24,27] However, it has been revealed in the literature that 18–46% of imaging-negative patients can be operated with UNE with ioPTH measurement.[11,16,17,28] In addition, considering the risk of multi gland disease, long-term follow-up of these patients for recurrent pHPT is recommended.[16]

The main limitation of this study is that it is retrospective. However, it is not possible to conduct a prospective, randomized, and controlled trial in which patients were randomized to localized or non-localized. We think that this study will contribute to the literature on the factors affecting negative imaging and its effect on surgical cure.

Conclusion

It should be taken into account that the possibility of multi gland disease and smaller pathological glands may be higher during surgery in imaging negative patients with pHPT. Surgery in imaging negative patients can be performed with a similar and acceptable cure rate to imaging positive patients.

Disclosures

Ethics Committee Approval: The study was approved by the local ethics committee (Date: March 02, 2021 Number: 3168).

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Conflict of Interest: None declared.

Authorship Contributions: Concept – M.U., N.A., M.T.U.; Design – M.U., T.A.S., M.K.; Supervision – N.A., T.A.S., M.K.; Data collection &/or processing – M.K., O.C., T.A.S.; Analysis and/or interpretation – M.U., N.A., M.T.U.; Literature search – M.T.U., T.A.S., O.C.; Writing – M.K., O.C., N.A.; Critical review – M.U., M.K., M.T.U.

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