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Recurrent and persistence primary hyperparathyroidism occurs more frequently in patients with double adenomas

*Amal Alhefdhi, MD, SB-Surg, ABIS, David F. Schneider, MD, MS, Rebecca Sippel, MD, FACS, and Herbert Chen, MD, FACS**

Section of Endocrine Surgery, Department of Surgery, University of Wisconsin, Madison, Wisconsin

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ABSTRACT

Introduction: The incidence of recurrent primary hyperparathyroidism (PHPT) had been reported to be between 1% and 10%. The purpose of this study was to examine if patients with multigland disease have a different recurrence rate.

Methodology: A retrospective analysis of a prospectively collected database was performed on patients with PHPT who underwent parathyroidectomy at one institution between 2001 and 2013. Patients who underwent initial parathyroidectomy with at least 6 mo of follow-up were included and were divided into three groups according to operative notes: single adenoma (SA), double adenoma (DA), and hyperplasia (HP). An elevated postoperative serum calcium level within 6 mo of surgery was defined as a persistent disease, whereas an elevated calcium after 6 mo was defined as a recurrence.

Results: In total, 1402 patients met inclusion criteria, and the success rate of parathyroidectomy was 98.4%. The mean age was 60 ± 14 y and 78.5% were female. Among them, 1097 patients (78%) had SA, 124 patients (9%) had DA, and 181 patients had HP (13%). The rate of persistent PHPT was higher among patients with DA (4%) *versus* SA (1.3%) and HP (2.2%) ($P = 0.0049$). Moreover, the recurrence rate was higher among patients with DA (7.3%) *versus* SA (1.7%) and HP (4.4%) ($P = 0.0005$) with identical median follow-up time. The median of the follow-up was 11 mo for patients with SA, 12.5 for patients with DA, and 12 for patients with HP ($P = 0.1603$).

Conclusions: Recurrent and persistent PHPT occur more frequently in patients with DA. These data suggest that DA in some cases could represent asymmetric or asynchronous hyperplasia. Therefore, patients with DA may warrant more rigorous intraoperative scrutiny and more vigilant monitoring after parathyroidectomy.

1. Introduction

Primary hyperparathyroidism (PHPT) is a very common clinical endocrine disorder, with 100,000 new cases diagnosed each year in the United States [1]. PHPT is caused by a single adenoma (SA) in around 80%–85% of the cases and multigland disease in the form of double adenoma (DA), four-gland hyperplasia (HP) in around 15%–20% of the cases, or parathyroid

* *Corresponding author*. Section of Endocrine Surgery, Department of Surgery, University of Wisconsin, K3/705 Clinical Science Center, 600 Highland Avenue, Madison, WI 53792. Tel.: +1 608 263 1387; fax: +1 608 252 0912.
E-mail address: chen@surgery.wisc.edu (H. Chen).

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carcinoma in fewer than 1% of cases [1–3]. Although some investigators think that DAs do not exist and instead represent cases of asymmetrical four-gland hyperplasia [4], other investigators recognize DA as a separate clinical entity [5–7]. Although the actuality of parathyroid DAs is still controversial [2,8], it now generally is agreed that DA do exist as a separate clinical entity [5,9]. Different research reported the occurrence of DAs to be around 2%–15% of PHPT patients [4–11].

Parathyroidectomy is the only curative treatment for PHPT [11], with a success rate range from 95% to 98%, if performed by an experienced surgeon [12]. However, the recurrence rate of PHPT had been reported to be between 1% and 10%, and the persistence rate had been reported to be between 2% and 22% [4–11]. Subsequently, a significant number of patients need another surgery. These surgeries can be technically challenging due to the scarring and fibrous tissue from the previous surgery, which obliterates normal tissue planes [13].

The most common reasons for surgical failure at the first exploration are multiglandular disease in the form of DA or four-gland HP and glands in ectopic locations [14]. However, most reports in the literature have been focused on patients with solitary adenomas, and the recurrent and persistence rate in patients with multiglandular disease, especially DAs remains unclear [15,16]. The aim of this study was to examine if patients with multigland disease have a different recurrence rate.

2. Methods

Analysis of a prospective endocrine surgery database was performed on all patients undergoing parathyroidectomy for PHPT from 2001 to 2013 at the University of Wisconsin Hospital. Patients who underwent initial parathyroidectomy with at least 6 months of follow-up were included. Patients were divided into three groups according to the operative notes: SA, DA, and HP, according to the surgeon final diagnosis regardless of the methods used to define the diagnosis.

Demographic data were compared between the three groups. Furthermore, recurrence and persistence rates were calculated and compared between the three groups. An elevated postoperative serum calcium level within 6 mo of surgery was defined as a persistent disease, whereas elevated calcium after 6 mo was defined as a recurrence. A positive family history was defined as a positive history of parathyroid disease among patient first- or second-degree relative.

To ensure there were no other cofactors to explain the high rate of recurrence and persistence rates in DA groups, patient with DA were subdivided into two groups; the cured cases and the noncured cases, which include those who had a persistent disease and those who developed recurrent disease. Those two subgroups were then compared.

Comparisons between groups were evaluated using the Fisher exact test and Student *t*-test, where appropriate. If the data showed a normal distribution, analysis of variance was used; and if the data showed a skewed distribution, Kruskal-Wallis test was used. All statistical calculations were completed using statistical software SAS version 9.2. A *P*-value of ≤ 0.05 was considered to represent statistical significance for all comparisons.

3. Results

In total, 1402 patients meet the inclusion criteria, and the success rate of parathyroidectomy was 98.4%. The mean age was 60 ± 14 y and 78.5% were female. The persistence rate was 23/1402 (1.6%), and the recurrence rate was 36/1402 (2.6%). The median distribution of the recurrence is 8 (7–84) mo. Among them, 1097 patients (78%) had SA, 124 patients (9%) had DA, and 181 patients had HP (13%). There were no differences between the three groups in the form of gender, postoperative calcium level, and follow-up period (Table 1). However, there were statistical significant differences between the three groups regarding the age, preoperative calcium level, and postoperative parathyroid hormone (PTH level).

Patients with HP tend to present in younger age compared with other groups with a mean age of 58 ± 16 y compared with 61 ± 14 in SA and 63 ± 11 in DA ($P = 0.0056$, Table 1). However, patients with SA had a higher preoperative calcium and PTH levels. The means of the preoperative calcium (mg/dL) were 11.1 ± 0.9 in SA, 10.8 ± 0.9 in DA, and 10.7 ± 0.8 in HP ($P < 0.0001$). The means of the preoperative PTH (pg/mL) were

Table 1 – Patients' demographics data.

Category	SA	DA	HP	P value
	$n = 1097$ (78%)	$n = 124$ (9%)	$n = 181$ (13%)	
Gender				0.1087
Male	238 (21.7)	33 (26.6)	30 (16.7)	
Female	859 (78.3)	91 (73.4)	150 (83.3)	
Age (y)*	61 ± 14	63 ± 11	58 ± 16	**0.0056**
Preoperative calcium (mg/dL)*	11.1 ± 0.9	10.8 ± 0.9	10.7 ± 0.8	**<0.0001**
Preoperative PTH (pg/mL)*	127 ± 93	108 ± 59	105 ± 136	**0.0049**
Postoperative calcium (mg/dL)*	9.4 ± 2.3	9.3 ± 0.7	9.2 ± 0.7	0.4412
Postoperative PTH (pg/mL)*	47 ± 31	50 ± 35	38 ± 30	**0.0002**
Follow-up (mo)†	11 (6–132)	12.5 (6–105)	12 (6–106)	0.1603

SA = single adenoma, DA = double adenoma; HP = hyperplasia.
Bold values indicates the statistical significant values.
* Mean ± SD.
† Median (Kruskal-Wallis test).