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Permalink

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Journal

Annals of Surgical Oncology, 22(4)

ISSN

1068-9265

Authors

Elfenbein, Dawn M
Weber, Sara
Schneider, David F
[et al.](#)

Publication Date

2015-04-01

DOI

10.1245/s10434-014-4080-0

Peer reviewed



Published in final edited form as:

Ann Surg Oncol. 2015 April ; 22(4): 1191–1195. doi:10.1245/s10434-014-4080-0.

CaPTHUS Scoring Model in Primary Hyperparathyroidism: Can it Eliminate the need for ioPTH?

Dawn M. Eifenbein, MD, MPH, Sara Weber, BD, David F. Schneider, MD, MS, Rebecca S. Sippel, MD, and Herbert Chen, MD

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

Abstract

Background—The CaPTHUS model was reported to have a positive predictive value (PPV) of 100% to correctly predict single-gland disease in patients with primary hyperparathyroidism, thus obviating the need for ioPTH. We sought to apply the CaPTHUS scoring model in our patient population, and also its utility in predicting long-term biochemical cure.

Methods—Retrospective review of all parathyroidectomies for primary hyperparathyroidism performed at our university hospital from 2003–2012. We routinely perform ioPTH testing. Biochemical cure was defined as a normal calcium level at 6 months.

Results—1421 patients met inclusion criteria: 78% of patients had a single adenoma at the time of surgery, 98% of patients had a normal serum calcium at 1 week postoperatively, and 96% of patients had a normal serum calcium level 6 months postoperatively. Using the previously described CaPTHUS scoring model, 307 (22.5%) patients had a score 3, with a PPV of 91% for single adenoma. A CaPTHUS score 3 had a PPV of 98% for biochemical cure at 1 week as well as at 6 months.

Conclusions—In our population where ioPTH is used routinely to guide use of bilateral exploration, patients with a pre-operative CaPTHUS score 3 had good long-term biochemical cure rates. However, the model only predicted adenoma in 91% of cases. If MIP without ioPTH had been done for these patients, the cure rate would have dropped from 98% to an unacceptable 89%. Even in these patients with high CaPTHUS scores, multigland disease is present in almost 10% and ioPTH is necessary.

Primary hyperparathyroidism is a common disease of the endocrine system and is becoming more prevalent in the United States. (1, 2) It is classically characterized by high levels of both serum calcium and parathyroid hormone (PTH). The most common underlying pathology causing primary hyperparathyroidism is a single parathyroid adenoma, but involvement of more than one gland either in the form of multiple adenomas or four-gland hyperplasia occurs not infrequently. There has been much interest and research over the last 15 years dedicated to distinguishing patients with a single adenoma from those with multi-gland disease, thus selecting patients who could undergo a focused, “minimally invasive” parathyroidectomy instead of the classic four gland exploration. The adjuncts involved in

this focused approach include preoperative imaging techniques to localize enlarged parathyroid glands prior to making an incision, and the use of intraoperative PTH (ioPTH) monitoring to determine when all hyperfunctioning parathyroid tissue is removed, thus telling a surgeon when to conclude the operation.(3)

Several scoring criteria have been proposed to help surgeons determine which patients are highly likely to have a single adenoma. One such model includes 4 variables collected in the preoperative period: calcium level, PTH level, sestamibi scan, and ultrasound (Table 1). High scores on the CaPTHUS model predicted with 100% confidence the patients who were found to have a single adenoma at the time of surgery for the cohort of patients studied, and all of these patients had normal calcium levels at their first follow up visit.(4) The authors suggested that since this model was able to predict single adenoma patients with 100% accuracy, the focused removal of that one gland would be curative and measuring ioPTH levels would be of no added value.

Since the publication of the CaPTHUS scoring criteria in 2006, there has been increased recognition of milder forms of primary hyperparathyroidism: normal calcium levels with inappropriately elevated PTH, or elevated calcium levels that do not appropriately suppress PTH. Recent literature has reported that normalization of calcium and PTH with surgical parathyroidectomy confers benefits even in mild forms of the disease. (5) Mild primary hyperparathyroidism is more often associated with multigland disease and negative localization studies. (6)

Given the changing presentation of patients with primary hyperparathyroidism, as well as the increasing pressures to control costs in the operating room, we sought to apply the CaPTHUS scoring model in our patient population and to test its validity in a real patient population in predicting adenoma, thus obviating the need to monitor ioPTH in patients with high scores. Secondly, since the original CaPTHUS scoring model reported short term follow up labs of serum calcium and PTH levels at the patients' first postoperative visit 2–3 weeks after surgery,(4) we sought to extend follow up of patients and evaluate the utility of the model in predicting longer-term biochemical cure.

Methods

A retrospective review of our prospectively collected database of consecutive parathyroidectomies for patients with primary hyperparathyroidism was performed. This database consists of patients who underwent initial parathyroidectomy with ioPTH monitoring at our institution, and 10 years of data from 2003–2012 was queried. Patients with previous parathyroidectomy or any patient with less than 6 months of follow up during this time period were excluded. Patients with preoperative imaging studies (either sestamibi, ultrasound or both) that suggested a single adenoma were generally managed with a focused, unilateral approach with ioPTH levels dictating the extent of further exploration and resection. PTH levels were drawn at 5, 10 and 15 minutes for all patients, and a 50% drop from baseline indicated cure and the operation was generally concluded. When the 5 minute level was higher than baseline, a fourth PTH level was drawn at 20 minutes and the new higher level was used as the new baseline for cure criteria.

For purposes of calculating CaPTHUS score, patients were given 1 point for each of the 5 factors in the model (Table 1). All patients had data for calcium and PTH levels and received 1 point for levels high enough to meet criteria based on the scoring model. Most patients underwent sestamibi scans, and those patients received 1 point if the scan was positive and 0 points if the scan was negative. Patients received 0 points if a sestamibi scan was not performed. Fewer patients underwent ultrasound localization. Similar to sestamibi, if the ultrasound was positive, patients received 1 point, but received 0 points if the ultrasound is negative or if it was not performed. In the original publication of the scoring criteria, nearly all patients underwent both imaging modalities. We sought to test this scoring model in a real patient population, not an idealized study sample. Therefore, we felt it was prudent to include all patients whether they underwent both imaging modalities or not. It is still possible to achieve a high score of 3 on the CaPTHUS scoring model on the basis of high PTH and high Ca and a single positive study, so we included all patients regardless of the type and number of preoperative imaging studies that they underwent.

The diagnosis of single adenoma or multi-gland disease was made by the surgeon at the time of the operation and is coded as such in our database. Serum calcium and PTH levels were evaluated at 1–2 weeks postoperatively and again at 6 months for all patients in this cohort. Normal serum calcium (<10.2mg/dL) at the 6 month time point defined durable operative cure for this study.

Statistical analysis was performed using Stata v.11 (Stata Corporation, College Station, TX). All variables were categorical for this study (Calcium and PTH were categorized based on whether they met criteria based on the scoring model), and chi-square analysis was performed. Multivariate logistic regression models were used to parse out which components of the scoring model were most useful in predicting long-term cure. This study was reviewed and approved by the institutional review board at the University of Wisconsin, informed consent was waived for patients, and all data was stored on secure, HIPAA-compliant servers within the health system.

Results

Between 2003 and 2013, 1421 patients met inclusion criteria. 78% of patients had a single adenoma resected, and 35% of patients underwent bilateral exploration at the discretion of the surgeon, either because of a bilateral exploration was planned, patient had negative localization studies, or because ioPTH failed to fall by 50%. At their first postoperative visit, 98% of patients had normal serum calcium levels, and 96% had normal calcium levels at 6 months and were defined as cured for the purposes of this study.

The median CaPTHUS score of this sample was 1, with just 22.5% of patients having a score 3. Figure 1 shows the number of patients with multigland disease, single adenoma, and then the total number of patients in each score category from 0 to 5. Table 2 shows how many patients in our sample met each of the five factors for the scoring model. A positive sestamibi scan was the criteria met by the highest number of patients and a serum calcium 12mg/dL was present in less than 10% of patients, illustrating the milder disease presentation in this patient population. The percentage of patients who had a single adenoma

increased with CaPTHUS score, with only 55% of patients with a score of 0 having a single adenoma and 100% of patients with a score of 5 (Figure 2).

Figure 3 shows the distribution of operative approach by CaPTHUS score. Although patients with high CaPTH scores were more likely to undergo focused exploration, bilateral exploration was performed in around 20% of patients with scores ≥ 3 .

Around one-third of our sample (534 patients) underwent both sestamibi and ultrasound prior to surgery. A subset analysis of these patients was performed as they represent patients who fulfilled all four components of the scoring system and represent a sample that more closely mirrors the original publication. 48% of patients who underwent dual imaging had CaPTHUS scores of ≥ 3 , compared to only 22.5% of the entire cohort ($p < 0.05$). Despite higher scores that should predict higher rates of single adenoma, 38% of patients in this dual imaging subset underwent bilateral exploration, and the cure rate was 96%, neither of which are statistically different than the overall cohort.

A logistic regression model was created to determine which components of the CaPTHUS scoring model are independently most predictive of long-term cure. A positive sestamibi scan was the only factor that independently was associated with cure (OR = 2.5, 95% Confidence Interval 1.3, 4.7), but for the other four factors in the scoring model, the combination of having multiple positive criteria is more predictive as none were independently associated with cure. Of the patients with a score ≥ 3 , the positive predictive value of the scoring model for a single adenoma is only 91%, compared to 100% in the original study describing the model. The positive predictive value for single adenoma of the subset of patients who underwent dual imaging is also only 91%. In the current sample, where ioPTH was routinely used, the positive predictive value of the CaPTHUS model for biochemical cure at 6 months was 98%. However, if ioPTH were eliminated in the surgery for these patients with scores ≥ 3 , 28 patients with multigland disease would have been missed, and the cure rate for these patients would have dropped to 89%. Even in these patients with high calcium, high PTH, and/or strongly positive imaging studies, multigland disease was present in almost 1 in 10 patients.

Discussion

Parathyroidectomy clearly confers cost savings and improved quality of life over medical treatment of primary hyperparathyroidism, (7, 8) which is being recognized at increasingly earlier and milder stages of the disease. Both traditional four gland exploration and targeted parathyroidectomy with peri-operative adjuncts such as ioPTH are acceptable surgical approaches with similar cure rates. (9) Medical technology continues to advance, imaging techniques are getting more refined every year, and patients as consumers want their surgeon to use the latest and most innovative new techniques, even when medical evidence does not necessarily support one technique over another. (10) In the pursuit of mastering a perfect technique to perform a reliably successful targeted parathyroidectomy, surgeons have proposed numerous algorithms of various imaging studies and peri-operative adjuncts. (11, 12) Because ioPTH monitoring can be time-consuming, is not universally available, and

can be challenging to interpret in some settings, some authors have proposed eliminating its use in select cases where the risk of multigland disease is low.

Our study found that multigland disease was present in a significant portion of patients with high levels of calcium and PTH, and strongly positive imaging studies. The elimination of ioPTH in these patients would have resulted in an unacceptably low cure rate. In the original publication done almost 10 years ago, this same group of patients had a single adenoma 100% of the time, and all had normal calcium at their first follow-up visit. (4) The reasons for this difference may be that the patient population has shifted over the past 10 years, and we are seeing a different mix of patients, disease states, and surgeon preferences in workup schemas. The percentage of patients in the current study with CaPTHUS scores ≥ 3 was only 22% compared to the original publication's 35%, and this probably reflects both shift towards milder forms of disease, as well as our deliberate inclusion of all patients regardless of whether they underwent pre-operative imaging tests. The original study cohort was a selected group where almost every patient underwent both ultrasound and sestamibi, whereas we looked at a consecutive sample of patients where imaging was not used in every patient and often only one of the two studies was performed preoperatively. Although we acknowledge that including all patients will make the model less accurate, we feel that testing in this way has more widespread applicability to surgeons in practice who seek to apply the model to their patient population. Furthermore, when we analyzed the subset of patients who underwent both imaging studies, our conclusion remained the same as for the entire cohort, indicating that doing both imaging studies did not necessarily help a surgeon identify the presence of a single adenoma.

Our secondary goal was to test this model's long term ability to predict long-term cure, not just operative finding of a single adenoma and 1–2 week normalization of calcium. We routinely use ioPTH, and with that routine use, the long term predictability for cure was good at 98%. The authors of the original study suggested that when patients score high on the model, routine use of ioPTH could be eliminated. Several other authors have come to similar conclusions. (13–15) We did not find evidence to support this however, finding that elimination of ioPTH would have led to the premature conclusion of almost 10% of operations in patients with CaPTHUS ≥ 3 . A very small portion of our sample (5%, or 62 patients of the 1421) had CaPTHUS scores of 4 or 5, and only 1 patient in that small subset of patients had multigland disease. It may be that using a higher cutoff of 4 may make elimination of ioPTH possible, but this needs to be further validated and may not be all that clinically relevant given the very small number of patients who meet this cutoff.

In the original study, because lab values were drawn one week postoperatively, it is unknown whether these patients all remained normocalcemic in the long-term. Our data presented here suggests that at least some patients with high CaPTHUS scores may still have some degree of multigland disease. Almost 20% of patients in our cohort that had high CaPTHUS scores underwent four-gland exploration, which was often guided by ioPTH. Although the rate of four-gland exploration is lower in patients with high CaPTHUS scores, it is nowhere near zero, and the model should not be considered alone in the absence of adjuncts to guide the operation. Monitoring ioPTH in patients with multigland disease or

imaging studies that are equivocal or discordant is helpful in guiding the extent of operation. (16, 17)

Our study found that the CaPTHUS scoring model predicts single adenoma in 91% of patients, which is much less than the 100% positive predictive value reported in the original manuscript. This study is limited in its retrospective design and the lack of standardization in preoperative workup. This was done intentionally, however, because our aim was to test this model in a real-world patient population. Models must be developed in highly selected patients where all data is intentionally and carefully collected, but then they should be tested in a more heterogeneous population that more closely mirrors what is seen in a given practice order to verify its widespread applicability. (18)

In summary, preoperative biochemical testing and imaging may be used to help distinguish between single adenoma and multigland disease in primary hyperparathyroidism, but the presence of 3 or more factors on the CaPTHUS scoring model does not predict adenoma with 100% accuracy. Routine use of ioPTH along with the information gained from the CaPTHUS scoring model results in 98% cure rate at six months in patients with a score 3, but elimination of ioPTH is not recommended as it would result in lower long-term cure rates.

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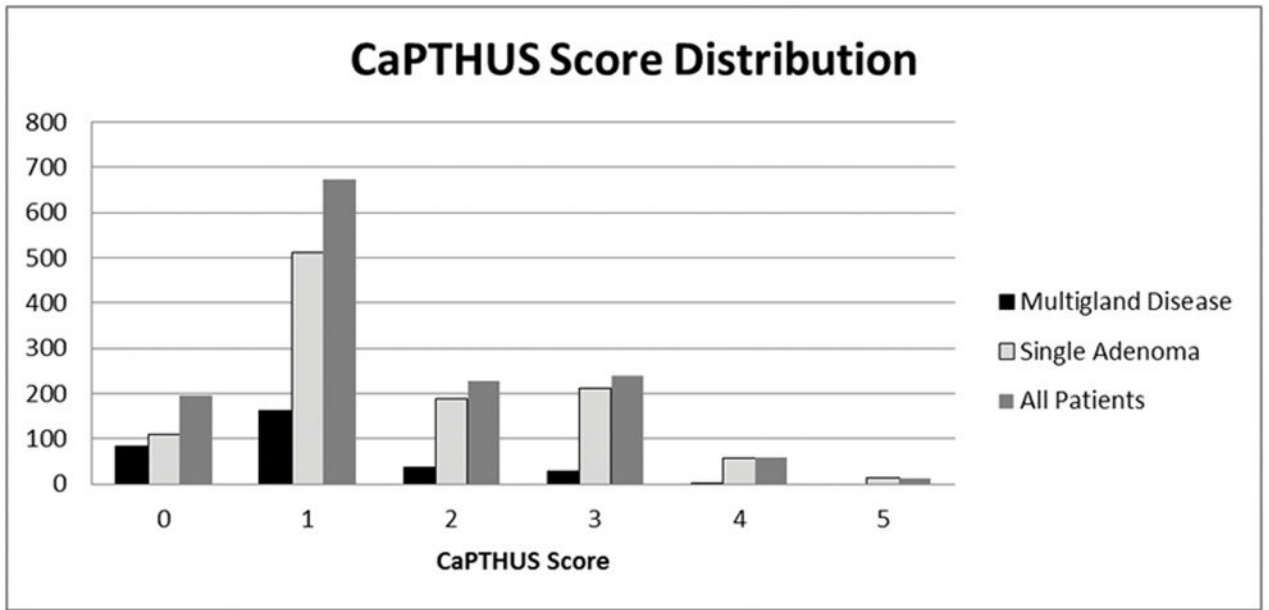


Figure 1.

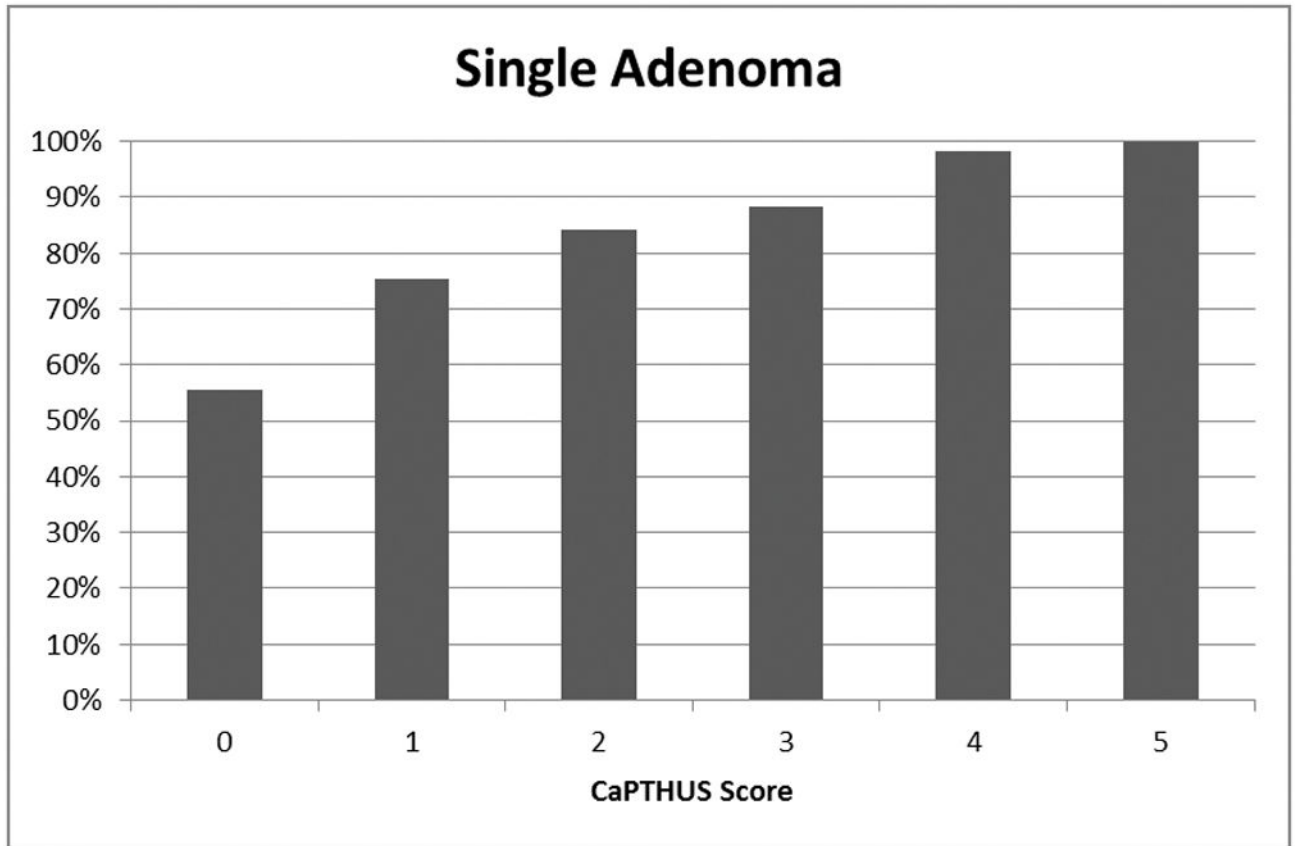


Figure 2.

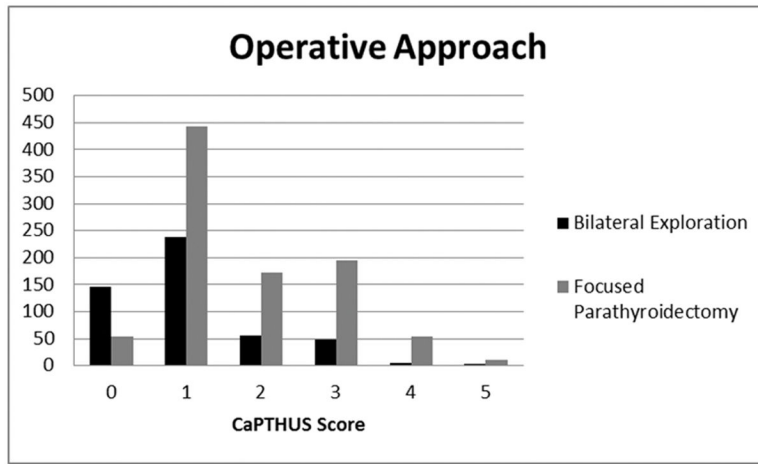


Figure 3.

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Table 1

CaPTHUS scoring model

Predictive Factor	Points
Pre-operative total serum Ca level ≥ 3 mmol/L or ≥ 12 mg/dL	1
Intact PTH level ≥ 2 times upper limit of normal PTH levels	1
Sestamibi scan results positive for 1 enlarged parathyroid gland	1
Neck ultrasound results positive for 1 enlarged thyroid gland	1
Concordant sestamibi and neck ultrasound study results (identifying 1 enlarged gland on the same side of the neck)	1
Total	0–5

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Table 2

Percentage of patients in the study sample who were assigned a point for each factor of the CaPTHUS scoring model

Predictive Factor	Percentage of sample who fulfilled criteria
Sestamibi scan results positive for 1 enlarged parathyroid gland	74%
Neck ultrasound results positive for 1 enlarged thyroid gland	28.5%
Intact PTH level 2 times upper limit of normal PTH levels	22.6%
Concordant sestamibi and neck ultrasound study results (identifying 1 enlarged gland on the same side of the neck)	18.2%
Pre-operative total serum Ca level 3mmol/L or 12 mg/dL	9.2%

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