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Radioguided Parathyroidectomy Effective in Pediatric Patients

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Abstract

Introduction—Radioguided parathyroidectomy (RGP) has been shown to be effective in adult patients with hyperparathyroidism (HPT), but the utility of RGP in pediatric patients has not been systematically examined. It is not known if adult criteria for radioactive counts can accurately detect hyperfunctioning parathyroid glands in pediatric patients. The purpose of our study was to determine the utility of RGP in children with primary hyperparathyroidism.

Materials and Methods—A retrospective review of our prospectively maintained single-institution database for patients who underwent a RGP for primary HPT identified 1694 adult and 19 pediatric patients age 19 years or younger. From the adult population, we selected a control group matched 3 to 1 for gland weight and gender, and compared pre- and post-operative lab values, surgical findings, pathology, and radioguidance values between this and the pediatric group.

Results—Excised glands from pediatric patients were smaller than those in the total adult population (437 ± 60 mg vs. 718 ± 31 mg, p=0.0004). When controlled for gland weight, *ex vivo* counts as a percentage of background were lower in the pediatric group (51 ± 5% vs. 91 ± 11%, p=0.04). However, *ex vivo* radionuclide counts >20% of the background were found in 100% of pediatric patients and 95% of the adult matched control group.

Conclusions—All pediatric patients met the adult detection criteria for parathyroid tissue removal when a RGP was performed, and 100% cure was achieved. We conclude RGP is a useful treatment option for pediatric patients with primary hyperparathyroidism.

Keywords

Minimally invasive parathyroidectomy; Radioguided parathyroidectomy; Primary hyperparathyroidism; Pediatric endocrine surgery; Technetium-99m sestamibi

Introduction

Primary hyperparathyroidism (pHPT) is a disorder caused by the hypersecretion of parathyroid hormone (PTH), usually from a single hyperfunctioning parathyroid gland.(1–3)

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PHPT affects 28 in 100,000 people, with 100,000 new cases each year; however, the diagnosis of pHPT is much rarer in children than in adults.(4–7) Surgical removal of the abnormal parathyroid gland is the only effective cure. This can be accomplished with a radioguided parathyroidectomy (RGP), which uses a gamma probe to detect increased radionuclide counts in hyperfunctioning parathyroid tissue, allowing the surgeon to differentiate between parathyroid adenomas and nonparathyroid tissue.(2, 7–9) This facilitates a minimally invasive approach, which is associated with decreased operative costs, lengths of stay, and postoperative complication rates.(1, 10–12)

Despite the success of RGP in adult patients, conventional teaching suggests that the smaller gland size of children prevents RGP from being definitive in its detection of hyperfunctioning parathyroid glands; however, the utility of RGP in pediatric patients has not been definitively examined.(8) As a result, it is not known if radionuclide counts can accurately detect hyperfunctioning glands in pediatric patients. We undertook this study to determine the efficacy of RGP in children with primary hyperparathyroidism.

Materials and Methods

Patient Selection

We conducted a review of our prospectively collected database of all individuals who underwent a parathyroidectomy for pHPT between January 2001and June 2012 at the University of Wisconsin and the American Family Children's Hospital. Patients were included in the study if their parathyroidectomy involved radioguidance with recorded background and *ex vivo* radionuclide counts of the excised gland(s). Patients with secondary or tertiary hyperparathyroidism were excluded. Individuals age 19 years or younger were categorized as pediatric patients. University of Wisconsin Institutional Review Board approval was obtained for data collection and data analysis. A total of 19 pediatric patients and 1694 adult patients were identified. These groups were compared to each other, examining pre- and post-operative lab values, surgical findings, pathology, and radioguidance values.

Due to the large difference in population sizes, we identified a control group of adult patients matched three to one for gland weight and gender to facilitate a more statistically balanced analysis. This yielded a control group of 57 adult patients that was then compared to the pediatric group of 19 patients in the same areas as above.

Patient Management

Pediatric and adult patients undergo a similar workup, including initial evaluation with history, physical exam, baseline laboratory tests including serum calcium, PTH, and phosphorous levels, and preoperative imaging studies. These imaging studies include a technetium-99m sestamibi scan for all patients and a neck ultrasound for patients based on surgeon preference. All sestamibi scans are reviewed by the operative surgeon to improve adenoma detection rates.(13) All patients then undergo a RGP as previously described(9, 14), regardless of whether preoperative imaging positively localized an adenoma. Briefly, patients are injected with 10–12 mCi of technetium-99m sestamibi between 30 minutes and 2 hours prior to planned incision time. After induction of anesthesia in the operating room, an 11-mm collimated gamma probe (Neoprobe 2000; Ethicon Endo-Surgery Breast Care, Cincinnati, OH) is used to take background counts at the level of the thyroid isthmus through the skin. If preoperative imaging positively localized an adenoma, a minimally invasive parathyroidectomy (MIP) is planned. This is performed through a 2–3 cm midline incision. If both glands on the initial side appear normal and have normal radionuclide counts, the gamma probe can be used to evaluate whether high radionuclide signal is present

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on the contralateral side. The contralateral side is then explored, converting the operation from a unilateral to a bilateral exploration. No extension of the incision is necessary for this conversion. If preoperative localization is negative or inconclusive, a bilateral exploration is planned and is conducted through the same 2–3 cm midline incision.

Once an incision is made, the gamma probe is used to scan for radionuclide counts higher than background to localize abnormal parathyroid glands. *In vivo* counts are recorded as those obtained by scanning an enlarged parathyroid gland *in situ*. *Ex vivo* counts are recorded by scanning the excised parathyroid gland placed on top of the probe and directed away from the patient, and counts are then expressed as a percentage of background. If the *ex vivo* count is >20% of background, the tissue removed is considered to be hyperfunctioning parathyroid tissue based on the "20% rule".(15)

Surgical cure is determined by a serum calcium level <10.2 mg/dL at 6 months postoperatively. Recurrent disease is defined as previously normal postoperative serum calcium levels that then exceed 10.2 mg/dL more than 6 months postoperatively, while persistent disease is defined as serum calcium levels >10.2 mg/dL within 6 months postoperatively. Mean duration of post-surgical follow up was 20 months for both groups (pediatric standard error of the mean (SEM) 4.7 months, range 1–61 months; adult SEM 0.6 months, range 1–120 months).

Data Analysis

Statistical analysis was performed with Microsoft Excel 2007 (Redmond, WA) and R version 2.13.1 (2011-07-08). Data were compared using Student's t-test, χ^2 test, and Fisher's Exact test where appropriate. Data are reported as mean ± SEM unless otherwise indicated. A p-value of <0.05 was considered statistically significant.

Results

Patients and Outcomes

We identified 19 pediatric patients and 1694 adult patients that met inclusion criteria. The average age of the pediatric patients was 16 ± 0.7 years and the adult patients, 61± 0.3 years (Table 1). The percentage of females was statistically similar, 63% in the pediatric and 78% in the adult group. In the pediatric group, the etiology of pHPT was adenoma(s) in 14 (74%) and hyperplasia in 5 (26%); in the adult group, the etiology was adenoma(s) in 1467 (87%), hyperplasia in 222 (13%), and parathyroid adenocarcinoma in 5 (0.3%) (Table 1). The mean preoperative calcium and intact PTH levels in the pediatric patients were statistically higher than in the adult population (Table 1). After RGP, these levels were within normal limits and similar between both groups (Table 1). All of the pediatric patients were cured of hyperparathyroidism (HPT) postoperatively, compared to 96% of the adult population (Table 2). No complications were noted in the pediatric patients; 44/1694 (3%) of the total adult population experienced complications, of which 19 (43%) were transient hypocalcemia or hypoparathyroid levels and 11 (25%) were transient hoarseness.

Radioguidance Data

Patients were injected intravenously with technetium-99m sestamibi prior to operation, at a median of 110 minutes (range 30–960 minutes) in the pediatric group and 60 minutes (range 30–300 minutes) in the adult group. When comparing the total adult group to the pediatric group, the background and *in vivo* counts were statistically similar (Table 2). The raw *ex vivo* counts were also similar, but as a percentage of background they were lower in the pediatric population, though this did not meet statistical significance (Table 2). In the pediatric group, the excised glands of 19 (100%) patients had *ex vivo* counts greater than

20% of background, which was not significantly different from 1635 (97%) in the adult group. Pathological examination showed the excised glands were significantly smaller in the pediatric group, 437 ± 60 mg versus 718 ± 31 mg, p=0.0004 (Table 2).

Matched Control Group Comparison

In order to create a more equal comparison that considered the large difference in population number and the difference in mean gland sizes, a 3:1 adult control group matched for gland weight and gender was identified. These 57 adult patients were compared to the pediatric group, and these data are reported in Table 3. The preoperative serum calcium was still higher in the pediatric group, though preoperative PTH values were statistically similar in the matched comparison. While the etiology of patients' pHPT was not included in the matching criteria, the division between patients with adenomas vs. hyperplasia is statistically similar between the groups (p=0.62). When comparing the radioguidance data, background, *in vivo*, and *ex vivo* counts were statistically similar across both groups. However, *ex vivo* counts as a percentage of background were now significantly lower in the pediatric group, 51 ± 5% versus 91 ± 11%, p=0.04. This did not affect the percentage of patients with excised glands that met the 20% rule; 100% in the pediatric group and 95% in the control group had *ex vivo* counts greater than 20% of background (Table 3). A similar percentage of patients were cured postoperatively, with 100% in the pediatric group and 98% in the adult group meeting criteria for cure.

Discussion

While the utility of radioguidance in parathyroidectomy has been relatively well established in adults, its validity as an operative adjunct has not been well studied in pediatric patients. This study compares 19 pediatric patients who underwent a radioguided parathyroidectomy for pHPT to adults undergoing the same procedure, including a control sample matched for gland weight. We show that, while abnormal parathyroid glands are smaller in pediatric patients, radioguidance was able to accurately detect hyperfunctioning parathyroid tissue in 100% of these patients. This corresponded with an equal cure rates in the pediatric and adult populations.

The utility of radioguided detection of hyperfunctioning parathyroid glands has been demonstrated in multiple studies.(2, 15–17) Technetium-99m sestamibi radioguidance, when used as an adjunct to minimally invasive parathyroidectomy (MIP), has been linked to a reduction in conversion to bilateral exploration, operative time, lengths of stay, and total operative and hospital costs.(1, 10) When initially introduced, the high avidity of hyperfunctioning parathyroid tissue for the technetium-99m sestamibi radionuclide allowed surgeons to accurately identify excised parathyroid tissue as such (and not thyroid, normal parathyroid, adipose, or other) without requiring frozen sections for confirmation.(15) Since the introduction of RGP to the surgeon's armamentarium, it has been shown to be particularly effective in detecting remaining abnormal glands at reoperation for persistent or recurrent disease in adults.(18, 19)

Similarly, radioguidance is useful in identifying ectopic glands, including those not always seen in preoperative imaging studies.(9, 18, 20) This is important to keep in mind when considering the use of this adjunct in pediatric patients, as a large series of 52 pediatric patients with pHPT found that 10% had ectopic glands.(21) Of the 19 pediatric patients in our study, 7 (37%) had ectopic glands identified at operation. Radioguidance was particularly helpful in these patients, as the detection of high radionuclide signals focused the exploration. Of the 7 ectopic glands, 4 were located in the thymus, 1 was undescended and retroesophageal, 1 was within the thyroid capsule, and 1 was in the carotid sheath. While all of these operations were completed through the midline neck incision, radioguidance prevented unnecessary dissection and thereby potential risk to vital structures because the location of the ectopic gland was determined with the gamma probe prior to further dissection when all four glands could not be localized in their normal positions.

RGP was also proven to be equally effective in detecting hyperfunctioning parathyroid tissue in patients whose HPT was due to adenoma(s) or hyperplasia.(9) This had previously been questioned due to a lower sequestration rate of the radionuclide by hyperplastic parathyroid glands,(15, 17) though it was unclear if this was due to gland size or difference in physiology. Of the 5 pediatric patients with hyperplasia in our series, 4/5 (80%) had a family history of parathyroid disorders, and 3 of these patients had undergone testing for multiple endocrine neoplasia type 1 (MEN1) and were positive. Due to the nature of MEN1-related hyperparathyroidism with its high risk of recurrence if parathyroid tissue is left intact, total parathyroidectomy with forearm parathyroid tissue implantation was performed in all patients who had completed or nearly completed puberty. In patients who had not yet completed puberty, a subtotal parathyroidectomy leaving approximately 50 mg of parathyroid tissue *in situ* was performed to avoid the potential growth consequences of the 3–4 weeks hypoparathyroidism that occur after a total parathyroidectomy while the forearm parathyroid graft develops a blood supply and begins to function. Radioguidance was used in these cases to localize all glands more efficiently and minimize dissection, as all glands were detected with signals above baseline *in vivo*.

It is possible that a concern for lack of accurate detection with smaller parathyroid glands has prevented widespread adoption of RGP in pediatric cases. Examination of preoperative localization imaging with technetium-99m sestamibi has indicated that smaller gland size is correlated with higher negative sestamibi scan rates.(22, 23) However, the study of Chen, et al., comparing radioguidance values between parathyroid single adenomas, multiple adenomas, and hyperplastic glands goes at least part way to answer the question of whether lower radionuclide counts are due to physiology or gland size.(9) Specifically, they demonstrated that the mean *ex vivo* counts as percentage of background decreased with increasing numbers of diseased glands, though this trend did not reach statistical significance. In contrast, there was no significant correlation between excised gland weight and *ex vivo* counts as percentage of background. These data support our findings that, while the excised glands are significantly smaller in pediatric patients, the decreased *ex vivo* counts only reach statistical significance when the compared adult group is controlled for gland weight. More important, all of the excised parathyroid glands from pediatric patients met criteria for detection with *ex vivo* counts >20% of background.

Another concern for use of RGP in the pediatric population may be the involved radiation exposure. At our institution, the pediatric patients receive technetium-99m sestamibi doses similar to adults preoperatively to allow for intraoperative parathyroid gland detection. This concern of overexposure may have resulted in the reported long delays in the time between radionuclide injection and operative incision. Two of the 19 pediatric patients had injection times ≥960 minutes before incision. Both patients received their preoperative injection of sestamibi radionuclide, but then their cases were delayed until the following day. Rather than re-inject the patients with radionuclide, the surgeons elected to proceed with the case when there was still detectable radionuclide counts at the thyroid isthmus. This resulted in lower overall counts, but the *ex vivo* counts of the excised adenomas as percent of background were not significantly different from the total population. Efforts to reduce radiation exposure in all patients led to a series of studies with a low-dose technetium-99m sestamibi protocol in adults.(24–26) This protocol uses a single 1 mCi dose of sestamibi radionuclide in the operating room immediately prior to the operation. Initial findings indicated that this protocol effectively identified parathyroid adenomas in a highly selected group of patients, namely those who had a high probability of single adenoma disease (including diagnosis of pHPT, positive sestamibi scan localization, absence of concomitant thyroid disease, and no previous neck radiation). Accordingly, patients with evidence of multi-gland disease or thyroid nodules were excluded. Long term outcomes demonstrate durable cure rates using this protocol.(26) Since pediatric patients with pHPT and no family history of parathyroid disease were shown to uniformly have single adenoma disease in a study by Durkin, et al.,(6) this approach might be appropriate to evaluate in this population in future studies. However, even with the protocol practiced at our institution, the radiation exposure with the current dosage is quite low, equivalent to less than 0.5 rad, or 25% of the exposure dose of one chest x-ray.

This work highlights some differences in the presentation and outcomes of primary hyperparathyroidism between adults and children. The pediatric group had higher preoperative serum calcium and PTH levels than adults, and even when comparisons were matched for gland size, preoperative calcium levels were still higher in the pediatric group (Table 2 and 3). While previous studies of pHPT in children lack a comparison to adult patients, it is common for 89–100% of pediatric patients to present with elevated serum calcium and with evidence of more advanced disease.(6, 21, 27) The reason for this difference has not been definitively explained, but may be due to a combination of delay in diagnosis (as this is a relatively rare disease in children) and factors in metabolic processing and bone turnover in children. Another difference that has been previously highlighted is the rate of complications in pediatric vs. adult endocrine surgery. Interestingly, although previous studies have indicated that children have higher rates of complications with endocrine surgeries than adults,(28) our study involved no complications in the pediatric cohort while showing a 3% complication rate in the adult cohort, which is similar to published adult series.(11) This difference may be due to the small size of the pediatric cohort, as the adult matched control sample also experienced no complications. The mean age of 16 years in the pediatric cohort also places them in the age range of adolescents, who, according to Sosa, et al.'s study, have complication rates most similar to adults.(28) However, it still bears noting that the complication rate in the pediatric group was not higher than in the adult group.

The data presented in this study are subject to the limitations inherent in retrospective reviews, including a lack of precise design for target data and minor changes in practice over time. However, in comparison to many retrospective reviews, our data are collected prospectively at the time of operation, thereby allowing for tracking of long-term follow up data and limiting reviewer bias. Results in this study are arguably more affected by the fact that pediatric parathyroid disease is exceedingly rare, and thus subject groups are limited. In fact, our collection of 19 pediatric patients from a single institution with primary hyperparathyroidism is one of the larger cohorts currently described in the literature.(21, 27) In an attempt to avoid any statistical bias created by comparison of a small sample to a much larger sample, we identified the matched control group of adult patients for definitive comparison.

Despite these limitations, we provide convincing data that RGP is equally effective in the surgical treatment of pediatric patients with pHPT when compared to adults. Intraoperative detection of hyperfunctioning parathyroid tissue was effective and accurate in pediatric patients, with 100% of excised glands meeting the adult criteria of *ex vivo* counts >20% of background and 100% cure rate. We conclude that radioguidance with technetium-99m sestamibi is a valid intraoperative adjunct to parathyroidectomy in the pediatric population.

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Table 1

Patient Demographics and Laboratory Data

	Adult N = 1694	Pediatric N = 19	P-value
Age, yrs (range)	61 ± 0.3 (21–91)	16 ± 0.7 (10–19)	<0.0001
Female (%)	1321 (78%)	12 (63%)	0.21
Preoperative Ca (mg/dL)	11.0 ± 0.0	12.2 ± 0.2	**0.0002**
Preoperative PTH (pg/mL)	124 ± 2	177 ± 43	**0.02**
Postoperative Ca (mg/dL)	9.5 ± 0.1	9.4 ± 0.1	0.58
Postoperative PTH (pg/mL)	47 ± 1	33 ± 7	0.06
Etiology (%)			0.15
Adenoma	1467 (87%)	14 (74%)	
Hyperplasia	222 (13%)	5 (26%)	
Adenocarcinoma	5 (0.3%)	0 (0%)	

Ca=calcium, PTH =parathyroid hormone

Continuous variables are represented as the mean ± standard error of the mean unless otherwise indicated

Table 2

Radioguided Excision Data – Total Population

	Adult N = 1694	Pediatric N = 19	P-value
Gland weight (mg)	718 ± 31	437 ± 60	**0.0004**
Mean background counts	175 ± 3	287 ± 103	0.29
Mean *in vivo* counts	270 ± 4	400 ± 149	0.45
Mean *ex vivo* counts	144 ± 3	180 ± 91	0.70
Mean *ex vivo* counts (% background)	90 ± 3%	51 ± 5%	0.15
Ex vivo counts >20% background (%)	1635 (97%)	19 (100%)	1
Cure (%)	1633 (96%)	19 (100%)	1

Continuous variables are represented as the mean ± standard error of the mean unless otherwise indicated

Table 3

Demographics and Radioguided Excision Data – Control Population

	Adult N = 57	Pediatric N = 19	P-value
Age, yrs (range)	52 ± 2.4 (22–90)	16 ± 0.7 (10–19)	<0.0001
Female (%)	36 (63%)	12 (63%)	1
Preoperative Ca (mg/dL)	10.9 ± 0.1	12.2 ± 0.3	**<0.0001**
Preoperative PTH (pg/mL)	153 ± 21	177 ± 43	0.59
Postoperative Ca (mg/dL)	9.2 ± 0.1	9.4 ± 0.1	0.43
Postoperative PTH (pg/mL)	50 ± 7	33 ± 7	0.22
Etiology (%)			0.62
Adenoma	47 (82%)	14 (74%)	
Hyperplasia	10 (18%)	5 (26%)	
Gland weight (mg)	455 ± 35	437 ± 60	0.80
Mean background counts	197 ± 20	287 ± 103	0.40
Mean *in vivo* counts	176 ± 21	400 ± 149	0.48
Mean *ex vivo* counts	161 ± 20	180 ± 91	0.84
Mean *ex vivo* counts (% background)	91 ± 11%	51 ± 5%	**0.04**
Ex vivo counts >20% background	54 (95%)	19 (100%)	0.57
Cure (%)	56 (98%)	19 (100%)	1

Ca=calcium, PTH=parathyroid hormone

Continuous variables are represented as the mean ± standard error of the mean unless otherwise indicated