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Comparison of the two treatment methods in primary hyperparathyroidism due to solitary parathyroid adenoma, Ultrasound-guided percutaneous alcohol ablation vs. parathyroidectomy: a randomized controlled trial

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Abstract

Background Primary hyperparathyroidism (pHPT) is the third most common endocrine system disorder. Parathyroidectomy (PTx) is the gold standard of care in symptomatic patients. Patients who are not surgical candidates may benefit from percutaneous ethanol ablation, which is a minimally invasive procedure. This study aims to evaluate the effectiveness and safety of PTx vs. PEA.

Method A single-centered randomized, not-blinded parallel clinical trial in consecutive patients with pHPT treated with percutaneous alcohol ablation (PEA) between January 2020 and November 2021. Patients with a confirmed solitary parathyroid adenoma and a biochemically verified pHPT were randomly enrolled in the PTx or PEA groups. Complications and lab data were evaluated 24 h, 2 weeks, 3 months, and 6 months following interventions. Effectiveness was defined as complete response (normal calcium and PTH), partial response (reduced but not normalized PTH with normal serum calcium), or disease persistence (elevated calcium and PTH). SPSS 22.0 was used for statistical analysis.

Result The final sample comprised 68 patients in each group which 113 of whom were female (83.0%). Complete response was observed in 91.1% ($n=62$) of the PEA group and 98.5% ($n=67$) of the PTx group. According to repeated-measures analysis, Calcium, PTH, Phosphorus, and Alkaline phosphatase fell significantly and continuously in each intervention group, except for the persistent patients. According to ROC analysis, a cutoff of > 425.5 mm3 for the adenoma volume and > 13.5 mm for its largest diameter showed a sensitivity = 75% and specificity = 69% for partial

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response in the PEA group (AUC = 0.81 and 0.84, respectively). PTx group experienced statistically significant higher pain according to the Visual Analogue Scale (VAS score) ($p < 0.001$).

Conclusion PTH, serum-adjusted Calcium, and adenoma size and volume were all significantly reduced by PTx and PEA, with no significant difference between them. PEA is an effective alternative to PTx, particularly in adenomas with a volume of less than 425.5 mm3 and a maximum diameter of 13.5 mm.

Trial registration number IRCT20210204050241N1 (04/26/2021).

Keywords Parathyroidectomy, Primary hyperparathyroidism, Ablation techniques, Parathyroid adenoma

Introduction

Primary hyperparathyroidism (pHPT) ranks as the third most prevalent condition of the endocrine system [1]. In about 80–85% of cases, pHPT is caused by a single adenoma [2]. Asymptomatically elevated serum calcium levels are frequently the initial indicator of this condition. Women are three times as likely as males to be affected by pHPT [3].

According to the National Institutes of Health (NIH), Parathyroidectomy (PTx) is the only permanently effective treatment for patients with pHPT [4]. Parathyroid surgery, performed by skilled endocrine surgeons, is a secure technique with a complication rate of approximately 1%. However, this rate increases to 4–10% in the elderly population [5]. Nevertheless, certain complications are linked to this procedure, such as infection, hematoma, skin tethering, keloid formation, and nerve injury, and in the case of reoperation, the complications risk increased to 27–54% [6–8]. The mortality rate is roughly 0% in patients without comorbidity [9] and about 1% in the geriatric population, primarily attributable to comorbidities and not surgical operations [10]. The most common complication of PTx is transient hypocalcemia in 15–30% of patients [9]. The risk of recurrent laryngeal nerve damage (RLN) is less than 1%, however, it rises to 9% in case of reoperation [11].

Ultrasound-guided percutaneous ethanol ablation (PEA) [12, 13] shows a promising response rate in certain case studies, serving as a potential alternative to PTx [14, 15]. However, there is a lack of data on the long-term effects of PEA, as well as a lack of high-quality studies, such as randomized control trials, to compare the effects of PEA and PTx in pHPT patients with parathyroid adenoma. This study aims to assess and compare the effectiveness and complications of PEA and PTx in pHPT patients with parathyroid adenoma.

Methods and materials

Trial design

The study was carried out as a single-centered randomized, not-blinded parallel clinical trial in a hospital and an interventional radiology center of Isfahan University of Medical Sciences between January 2020 and November 2021. This trial was accepted by the ethics committee of the Isfahan University of Medical Sciences, with the ethical code: IR.MUI.MED.REC.1399.049. and registration in the clinical trials databases with the IRCT20210204050241N1 code. All methods in this study were carried out according to the ethical requirements of institutional and national research committees and the Helsinki Declarations of 1964 and their subsequent amendments. Written informed permission was obtained from all participants before enrollment. We used the CONSORT checklist when writing our report [16].

Participants and eligibility criteria

220 patients with biochemically verified pHPT or normocalcemic pHPT with surgical indication and unequivocal localization of a solitary parathyroid adenoma confirmed by ultrasound, sestamibi scan, and fine-needle aspiration with PTH washout who wish to participate in the study were assessed for inclusion. Patients with suspect MEN2 or MEN1 syndrome (based on history, physical examination, family history, laboratory tests, and genetic evaluations for RET proto-oncogene), suspect to malignancy (based on the size of adenoma), secondary or tertiary hyperparathyroidism, vitamin D deficiency (< 30 ng/mL), hypercalciuria and glomerular filtration rate (GFR) < 60 ml/min/1.72 m2 were excluded from this study.

According to the Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism [17] in 2014 the diagnosis of normocalcemic pHPT was based on persistently high serum PTH levels in the setting of persistently normal serum total and ionized calcium levels, measured at least three times consecutively throughout 3 to 6 months after secondary causes of increased serum PTH were excluded [18].

During registration, a checklist of demographic factors such as age, gender, body mass index (BMI), history of renal stones, laboratory data Calcium adjusted with albumin (Corrected calcium (mg/dL) = (0.8 [4.0– patient's albumin (g/dL)]) + total calcium (mg/dL)), Phosphorus, PTH, 25-hydroxy vitamin D, Alkaline phosphatase (Alk-p), Cr, eGFR, and adenoma features (location, greatest diameter, and volume) were collected.

Surgical intervention

One surgical team conducted all of the PTx procedures. Following the administration of general anesthesia, the skin was prepared using standard methods. A conventional transverse incision was made on the neck. The thyroid tissue was revealed and retracted after dissecting through the strap muscles. We targeted the culprit corner based on previous reports. The adenoma was excised after a thorough examination for any pathological tissue. The integrity of all thyroid tissue and other parathyroid glands, as well as their associated blood vessels, was preserved. Once enough hemostasis is achieved, the anatomical layers are sequentially sutured.

Radiological intervention

A single proficient interventional radiologist performed all of the PEA procedures. The PEA group underwent comprehensive neck color Doppler ultrasonography to assess the number, dimensions, volume (calculated using the formula $\pi/6 \times a \times b \times c$, where a, b, and c represent the diameters of the adenoma in three dimensions), location, and vascularity index of the adenomas [19]. Under local anesthetic, after preparation and draping, hydrodissection of the surrounding tissue was conducted by injecting distilled water under ultrasound guidance. The adenoma was successfully removed from the trachea, esophagus, and recurrent laryngeal nerve. Afterward, a solution of sterile ethanol with a purity of 99.5% was injected into the adenoma at a rate that was comparable to 85% of the calculated volume of the adenoma. The injection was done gradually until the adenoma no longer had blood vessels, as confirmed by a color Doppler scan. The intervention was considered technically successful when no blood flow was observed with color Doppler mode, and the adenoma became echogenic. The procedure stopped immediately and was modified to a better approach if any leakage occurred [20].

Follow-ups

In follow-ups after both interventions, patients were asked for any complications such as pain (using a Visual Analogue Scale (VAS) with a 10-point Likert scale), irritation (i.e., discomfort in the neck), voice change (in comparison to their experience before intervention), rebleeding, infection, dysphasia, and recurrence in 24 h, 2 weeks, 3 months, and 6 months. To track changes, Ca, PTH, P, and Alk-p levels were repeated 24 h, 2 weeks, 3 months, and 6 months after the intervention. All blood and urine samples were evaluated in the same laboratory by the same team using the same techniques and kits. In patients with PHPT, the criteria for a complete response were defined as serum PTH and calcium levels reduced to within normal ranges at the last follow-up. The criteria for a partial response were as follows: reduced serum PTH levels that remained above the upper limit of normal (> 65 pg/mL) or serum calcium levels that remained above the upper limit of normal (> 10.5 mg/dL) after treatment. The criteria for persistent disease were as follows: serum PTH or calcium levels after treatment that were unchanged or above baseline levels measured before treatment (In cases with possible recurrence, we used Doppler ultrasonography to evaluate each parathyroid gland's shape, size, and vascularity and compare them to the pre-intervention reports and sestamibi scan to localize the hot point with the highest radiotracer uptake.

Sample size

Based on our PEA experience published before [20], and a mean success rate of 51% for PEA of patients with pHPA in the literature, considering $\alpha = 0.05$ and $\beta = 0.2$, $p = 50\%$, $d = 0.1$, and 20% missing cases during follow-up, a total of 70 patients for each was calculated to be sufficient.

Randomization

Patients were randomly assigned to either the PTx or the PEA groups using a non-stratified block randomization method (1:1) To maintain an equitable randomization ratio. Our professional analysts used the Random Allocation Software to establish the list and group of patients. He was unaware of the selection process and the pre-and postoperative evaluations. The block size was equal and set to 4, and the allocation code was put on sequential. Then, each code was written on a non-transparent envelope, and a piece of paper with the words "PTx" or "PEA" written on it was placed inside. The envelopes were numbered in accordance with the software's list. The analyst employs the designated envelope as the patients enrolled in the trial sequentially. The mechanism of randomization and block size was not revealed to the lead investigator and other physicians involved in the research until the trial was completed.

Statistical analysis

The IBM SPSS software (version 22.0) was used for statistical analysis. The numerical variables are reported as mean and standard deviation. The categorical variables are reported as numbers and percentages. The Kolmogorov–Smirnov normality test was used to examine if variables are normally distributed. Missing data (six patients) due to unavoidable causes were managed by intentiontotreat analysis (ITT). ITT analysis includes every patient who is randomized according to randomized treatment assignment. Chi-square was used to compare the categorical variables and Fisher's exact test was used when the numbers were lower than 10. The independent t-test and its equivalent nonparametric test were used to compare each variable between the overall results

in the PEA and PTx groups. The repeated measure was used to compare a numerical variable within a single group between different evaluation times. ANOVA with LSD and Tukey *posthoc* was used to compare a numerical variable between different groups in a single evaluation time. Logistic regression with potential variables was used to find out important factors that could predict recurrence or response to PEA. ROC analysis was used to determine a cutoff for potential variables that impact recurrence after PEA. The AUC and its upper and lower limits for significant factors in ROC analysis are reported accordingly. The p-value < 0.05 was considered statistically significant.

Results

A total of 220 patients were assessed for eligibility, and finally, 68 patients were enrolled in each treatment group. All of the included and randomized patients completed the study, and their data was entered into the analysis (Fig. 1). The demographic data and baseline characteristics are presented in Table 1.

Based on the response to the intervention mentioned in the method section, the PEA group was divided into three groups. 91.1% ($n = 62$) of patients showed complete response until the 6-month follow-up. 5.8% ($n = 4$) of the patients showed partial response. Finally, 2.9% ($n = 2$) of the patients did not respond to the PEA and categorized as disease persistence. The six patients, consisting of four in the partial response group and two in the disease persistence group, had surgery after six and one month of follow-up, respectively. They were effectively treated by the same surgical team. These individuals experienced surgical challenges related to dissection and tissue adhesions as a result of prior PEA.

In the PTx group, only one patient (1.4%) didn't experience a decline in PTH and underwent PTx again and was treated successfully. Patients' baseline evaluations are listed in Table 1. In both groups, the female gender was the most prevalent.

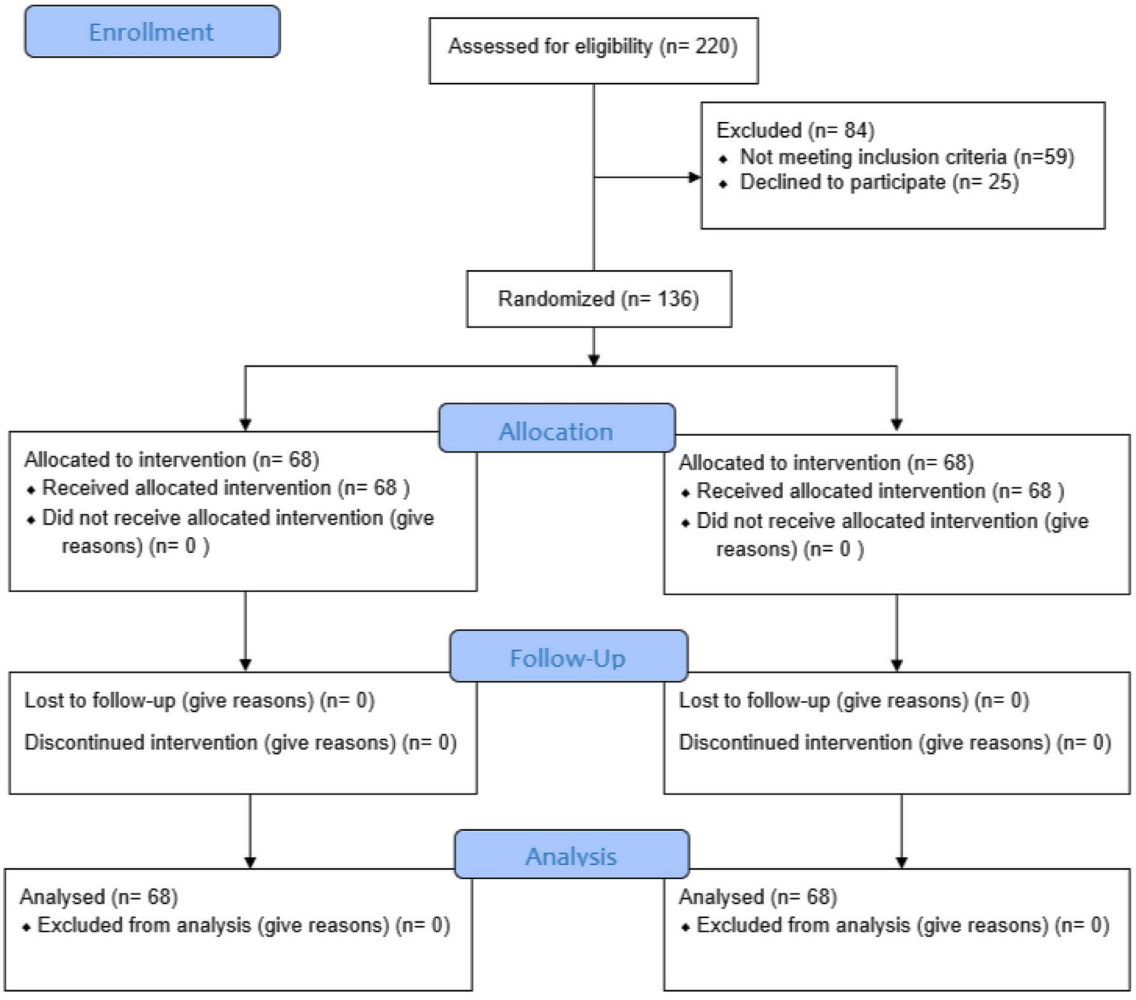

Fig. 1 CONSORT 2010 flow diagram

Table 1 Patient's demographics lab data and adenoma characteristics at the beginning of the study

			PEA (*n* = 68)				PTx (*n* = 68)†
			Overall (*n* = 68)	Complete response (*n* = 62)	Partial response (*n* = 4)	Disease persistence (*n* = 2)	
Demographic	Female sex, n (%)		58 (85.2%)	53 (85.4%)	3 (75%)	2 (100%)	55 (80.8%)
	Age (years)		56.2 ± 10.4	56.4 ± 10.3	49.5 ± 12.0	62.0 ± 5.6	52.7 ± 11.0
	BMI		27.6 ± 5.7	27.5 ± 5.9	26.1 ± 2.7	32.5 ± 0.7	27.5 ± 5.7
Lab	Serum-adjusted Ca (mg/dL) Reference range [8.6–10.2 mg/dL]		10.5 ± 0.8	10.5 ± 0.8	10.4 ± 0.61	10.2 ± 0.07	10.5 ± 1.1
	Normocalcemic HP, n (%)		33 (48.5%)	29 (46.7%)	2 (50%)	2 (100%)	33 (48.5%)
	Phosphorus Reference range [3.0–4.5 mg/dL]		2.6 ± 0.4	2.6 ± 0.4	3.0 ± 0.5	2.4 ± 0.4	2.6 ± 0.4
	PTH (pg/mL) Reference range [10–65 pg/mL]		146.4 ± 62.9	144.4 ± 60.6	137.2 ± 88.9	225.5 ± 68.5	149.1 ± 50.1
	25-hydroxy vitamin D (ng/mL) Reference range [30–60 ng/mL]		36.2 ± 13.6	36.7 ± 13.8	24.6 ± 4.1	44.9 ± 10.0	32.8 ± 11.3
	Alkaline phosphatase (IU/L) Reference range [30–120 U/L]		221.6 ± 61.8	220.0 ± 60.0	201.2 ± 45.8	310.0 ± 113.1	219.7 ± 63.4
Adenoma characteristics	Adenoma localization by ultrasound	Upper right, n (%)	13 (19.1%)				10 (14.7%)
		Lower right, n (%)	19 (27.9%)				16 (23.5%)
		Upper left, n (%)	12 (17.6%)				11 (16.1%)
		Lower left, n (%)	24 (35.2%)				31 (45.5%)
	Maximum adenoma diameter (mm)		12.4 ± 3.8	11.9 ± 3.5	17.9 ± 4.9	15.3 ± 0.42*	13.7 ± 3.8
	Volume (mm^3)		398.3 ± 351.6	347.8 ± 287.4	739.5 ± 556.3	1282.8 ± 360.2**	502.5 ± 285.8

* and ** ANOVA between alcohol ablation subgroups with p-values of 0.004 and < 0.001, respectively

† Independent t-test or Chi-square between Surgery and Alcohol ablation (overall) was used for comparison and none of the p-values was statistically significant

48.5% (*n* = 66) of the total number of patients had normocalcemic pHPT. The volume of the adenoma and its largest diameter differed significantly between the three PEA groups. According to the posthoc, the complete response had a lower adenoma volume, but the largest diameter was the only difference between the responder and recurrence groups. Table 2 shows the post-intervention surveillance lab findings.

According to repeated-measures analysis, Ca, PTH, Ph, and Alk-P fell considerably and continuously in each intervention group, except for the persistent patients. Ca and Alk-P in the 3 months and 6 months and PTH in all four evaluations showed a significant difference between the three groups in response to PEA. The ANOVA posthoc analysis revealed that the persistent group contained all of the significant observations. In each evaluation, there was no significant difference in lab results between the two intervention groups. However, the PTx group had a significantly higher P in 6mo and Alk-p in 24 h and 2w compared to the PEA at the same time.

No reportable factor was found in the logistic regression analysis for predicting the status of response to the PEA. However, according to the ROC analysis (Fig. 2), a cutoff of > 425.5 mm^3 for the adenoma volume and > 13.5 mm for its largest diameter showed a sensitivity = 75% and specificity = 69% for recurrence in the alcohol ablation group (AUC = 0.81 and 0.84, respectively).

In terms of complications, the PTx group had a significantly higher VAS score than the PEA group ($p < 0.001$). Irritation and voice change were seen more in the PEA group and dysphagia was higher in the PTx group but they weren't statistically significant. Neither intervention group experienced rebleeding or infection. Data on post-operation complications are presented in Table 3.

Discussion

The current study found that PEA and PTx considerably reduced PTH, serum-adjusted Ca, and adenoma size and volume, with no significant difference between them, and based on 6 months of follow-up, alcohol ablation worked well for adenomas of volumes less than 425 ml. To the best of our knowledge, this is the first randomized controlled trial evaluating the efficacy of PEA versus PTx in individuals with pHPT.

According to Iglesias and colleagues [21], an expert surgeon can achieve 95–98% success rates with PTx. Even

Table 2 Parathyroid panel findings in follow-up evaluations after each intervention

Characteristics	Group		Follow up				P*
			24 h	2 weeks	3 months	6 months	
Serum-adjusted Ca (mg/dL) Reference range [8.6–10.2 mg/dL]	PEA	Overall ($n=68$)	9.3 ± 0.4	9.4 ± 0.4	9.0 ± 0.2	8.8 ± 0.3	< 0.001
		Complete response ($n=62$)	9.3 ± 0.4	9.3 ± 0.4	9.0 ± 0.2	8.8 ± 0.2	< 0.001
		Partial response ($n=4$)	9.1 ± 0.26	9.4 ± 0.13	9.1 ± 0.1	8.8 ± 0.1	< 0.001
		Disease persistence ($n=2$)	10.0 ± 0.07	9.8 ± 0.07	9.7 ± 0.07	10.3 ± 0.07	-
		P†	0.04	0.36	0.002	< 0.001	-
	PTx ($n=68$)		9.2 ± 0.4	9.4 ± 0.5	8.9 ± 0.3	8.7 ± 0.4	< 0.001
	P‡		0.23	0.56	0.08	0.25	-
PTH (pg/mL) Reference range [10–65 pg/mL]	PEA	Overall ($n=68$)	54.2 ± 14.2	44.0 ± 13.9	38.2 ± 13.9	31.3 ± 15.8	< 0.001
		Complete response ($n=62$)	52.0 ± 7.3	42.4 ± 9.7	35.0 ± 8.9	27.1 ± 8.4	< 0.001
		Partial response ($n=4$)	55.7 ± 5.0	40.5 ± 1.0	61.2 ± 1.8	73.5 ± 7.1	< 0.001
		Disease persistence ($n=2$)	121.5 ± 30.4	101.5 ± 23.3	89.5 ± 13.4	77.0 ± 2.82	0.08
		P†	< 0.001	< 0.001	< 0.001	< 0.001	-
	PTx ($n=68$)		53.6 ± 9.7	45.7 ± 12.1	38.3 ± 12.0	29.9 ± 12.6	< 0.001
	P‡		0.75	0.45	0.95	0.565	-
Phosphorus Reference range [3.0–4.5 mg/dL]	PEA	Overall ($n=68$)	3.3 ± 0.4	3.4 ± 0.4	3.3 ± 0.2	3.5 ± 0.3	< 0.001
		Complete response ($n=62$)	3.3 ± 0.4	3.4 ± 0.3	3.3 ± 0.2	3.5 ± 0.3	< 0.001
		Partial response ($n=4$)	3.2 ± 0.5	3.7 ± 0.6	3.3 ± 0.2	3.5 ± 0.3	< 0.001
		Disease persistence ($n=2$)	3.0 ± 0.0	3.1 ± 0.07	3.0 ± 0.07	3.0 ± 0.0	-
		P†	0.50	0.2	0.36	0.12	-
	PTx ($n=68$)		3.3 ± 0.4	3.4 ± 0.3	3.4 ± 0.5	3.8 ± 0.4	< 0.001
	P‡		0.79	0.93	0.06	< 0.001	-
Alkaline phosphatase (U/L) Reference range [30–120 U/L]	PEA	Overall ($n=68$)	222.1 ± 101.8	183.4 ± 103.7	157.9 ± 30.1	143.3 ± 33.0	< 0.001
		Complete response ($n=62$)	224.8 ± 104.4	183.2 ± 107.0	156.3 ± 23.8	139.6 ± 20.4	< 0.001
		Partial response ($n=4$)	166.2 ± 72.0	158.2 ± 67.6	135.7 ± 43.0	129.0 ± 38.9	0.012
		Disease persistence ($n=2$)	249.5 ± 9.1	239.5 ± 2.1	254.0 ± 5.6	287.0 ± 8.4	0.006
		P†	0.50	0.67	< 0.001	< 0.001	-
	PTx ($n=68$)		284.7 ± 105.1	272.0 ± 100.1	161.5 ± 12.9	145.9 ± 17.3	< 0.001
	P‡		0.001	< 0.001	0.37	0.57	-

PEA: percutaneous ethanol ablation, PTH: parathyroid hormone, PTx: parathyroidectomy

* Repeated measure for postoperative assessments in one group between different timing

† ANOVA was used for these p-values

‡ Independent t-test was used for these p-values

though PTx has a high success rate, it can cause complications like infection, hematoma, keloid formation, pain, and neck swelling [22, 23]. According to Harman et al. [24], PEA is the most appropriate treatment option if a patient's preferences, medical conditions, partial ablation, and surgical challenges are taken into account.

According to the American Association of Endocrine Surgeons Guidelines, PTx is more cost-effective than pharmacological therapy or monitoring in case of patients experiencing symptoms (strong recommendation; high-quality evidence) or when the serum calcium level is more than 1 mg/dL above normal (strong recommendation; low-quality evidence), irrespective of the presence or absence of objective symptoms [4].

During the fourth international workshop on the management of asymptomatic pHPT in 2014 [25], experts recommended that patients with Normocalcemic pHPT should undergo annual serum Ca and PTH tests, as well as DXA scans every 1–2 years. This monitoring should continue until the condition progresses to hypercalcemic pHPT or until there is a deterioration in bone mineral density (BMD), the occurrence of fractures, or nephrocalcinosis. In these latter cases, surgery is indicated. As stated by Bilezikian et al. [26], it is crucial to exclude secondary hyperparathyroidism causes, such as insufficient levels of vitamin D, which is the most prevalent explanation. According to a meta-analysis published in 2021, PTx did not outperform active surveillance in terms of quality of life, nephrolithiasis, or fracture risk in mild asymptomatic pHPT patients [27].

Several studies have been carried out to determine the efficacy of PEA in the treatment of pHPT. Vergès et al. [28] reported a 65.4% cure rate in a retrospective examination of 31 patients who had undergone PEA in 2000 and were followed up for five years. In 2015, Alherabi et al. [14] described a case of a single parathyroid adenoma with many comorbidities who were at high risk for anesthesia and received PEA with a significant response on

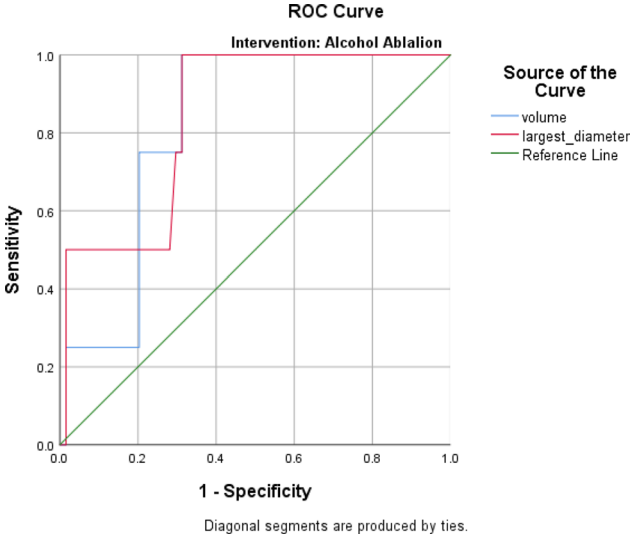

Fig. 2 ROC curve analysis to establish a cutoff criterion for the recurrence of hyperparathyroidism following alcohol ablation, based on the volume and maximum diameter of the adenoma. A threshold of > 425.5 mm^3 for adenoma volume and > 13.5 mm for its greatest diameter demonstrated a sensitivity of 75% and specificity of 69% for recurrence in the alcohol ablation group (AUC = 0.81 and 0.84, respectively)

Table 3 Post-operative complications after each intervention

Complication	PTx ($n=68$)	PEA ($n=68$)	*P* value*
Pain on VAS score (mean ± SD)	2.5 ± 1.0	0.7 ± 0.8	< 0.001
Irritation N (%)	4 (5.8%)	9 (13.2%)	0.243
Voice change N (%)	3 (4.4%)	5 (7.3%)	0.718
Dysphagia N (%)	3 (4.4%)	1 (1.5%)	0.619
Rebleeding N (%)	0	0	-
Infection N (%)	0	0	-

* Independent t-test

clinical symptoms and lab tests. This case report emphasizes PEA as an alternative treatment, especially for patients with many comorbidities or high-risk patients.

Radiofrequency ablation (RFA) is another option for pHPT tretment, with a recent meta-analysis showing a 91.2% success rate at the 6-month follow-up [29]. The overall incidence of complications was 3.0%, and there were no major complications. The overall rate of problems was 3.0%, with no significant issues. Temporary dysphonia was the most prevalent adverse consequence, whereas inadequate ablation and undiscovered multiglandular disease were the main causes of failure [29].

Within the PEA group, we observed that four patients in the partial response category and two in the disease persistence category did not exhibit a positive response to treatment. Consequently, surgical intervention became necessary, and the dissection process posed challenges due to scar tissue. This underscores the necessity for improved classifications to accurately categorize individuals into PTx or PEA groups. Based on our data, adenomas that are larger than 13.5 mm and have a volume of 425.5 mm^3 are recommended to perform PTx in order to prevent the need for additional procedures and to minimize surgical challenges.

This study, like many others, has limitations. First, one patient in the PTx group failed to be treated in the first operation and was successfully treated with a second surgery perhaps if we had intra-operative PTH monitoring we could avoid this according to Govind et al. [30]. Second, our study covered both pHPT and Normocalcemic pHPT patients, and we highly advise future studies to include Normocalcemic pHPT or pHPT with a longer follow-up period. Third, we employed corrected calcium levels as described in the fourth international workshop on the management of asymptomatic pHPT [25], which may result in some patients with primary hyperparathyroidism being incorrectly categorised as normocalcemic if free ionised calcium is not recorded. We will address this issue during our forthcoming trials.

Conclusion

According to the findings of this study, PTx and PEA both significantly reduced PTH, serum-adjusted Ca, and adenoma size and volume, with no significant difference between them. PEA is a suitable alternative to PTx, especially in patients with adenoma max diameter 11.9 ± 3.5 mm who are not surgical candidates or have multiple comorbidities that make surgery a high-risk procedure. To ensure the long-term efficacy and safety of PEA, additional research with a more extended follow-up period is needed.

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Author contributions

ME and BT contributed to the study design, while AF, AP, and MM aided in interpretation, drafting, and analysis, and BI supervised trial running. All authors read and approved the final manuscript.

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Data availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This trial was accepted by the ethics committee of the Isfahan University of Medical Sciences, with the ethical code: IR.MUI.MED.1400.003 and registration in the clinical trials databases with the IRCT20210204050241N1 code. Written informed consent was obtained from all participants before enrollment.

Consent for publication

Not Applicable.

Competing interests
The authors declare no competing interests.

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