GRHTA
Glob Reg Health Technol Assess 2025; 12: 186-193
ISSN 2283-5733 | DOI: 10.33393/grhta.2025.3531
ORIGINAL RESEARCH ARTICLE

Micro-costing analysis from Italian Guidelines for the management of sporadic primary hyperparathyroidism

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Received: March 14, 2025
Accepted: July 11, 2025
Published online: July 25, 2025

This article includes supplementary material

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ABSTRACT

Introduction: Primary hyperparathyroidism (PHPT) is a common endocrine disorder, primarily caused by single adenomas or multiglandular disease. This study evaluates the economic impact of different PHPT treatment approaches from both the Italian National Health Service and societal perspectives.

Methods: A micro-costing approach was used to estimate the costs of surgical and non-surgical treatments. Data were gathered through a survey among panel members responsible for the Italian PHPT treatment guidelines, ensuring alignment with national clinical practice. The survey examined various cost components, including diagnostic tests, pre-hospitalization assessments, surgery duration, drug use, healthcare professionals involved, disposable materials, and follow-up care requirements.

Results: The total cost for PHPT diagnosis and comorbidity assessment is € 887.96. Parathyroidectomy (PTX) costs € 4,588.00. Non-surgical alternatives, including pharmacological treatment (€ 953.34 annually) and active surveillance (€ 197.42 annually), result in cumulative 30-year costs of € 28,590 and € 5,910, respectively. Since PTX is typically performed at age 55, pharmacological treatment over 30 years incurs an additional € 22,876 per patient compared to surgery.

Conclusions: Despite its higher upfront cost, PTX demonstrated long-term cost efficiency due to the relatively low rates of follow-up complications and the absence of recurring annual costs associated with conservative strategies.

Keywords: Guidelines, Micro-Costing Analysis, Parathyroidectomy, Primary hyperparathyroidism

Introduction

Primary hyperparathyroidism (PHPT) is the third most frequent endocrine disorder and the leading cause of hypercalcemia in outpatient settings (1). An adenoma causes PHPT in 85% of instances, with multiglandular disease being linked to the remainder cases (2). 90–95% of individuals have the primarily sporadic condition (1).

The disease is associated with an annual incidence of 20 cases per 100,000 people and a prevalence in the general population ranging between 0.1%-0.4% (3,4).

The inclusion of serum calcium determination in multichannel automated assays and the increasing diffusion of the screening for osteoporosis resulted in the frequent finding of mild and asymptomatic conditions (3,4).

Two primary clinical presentations of the disease are now recognized:

- *Symptomatic PHPT*, associated with clinically overt complications involving bone and kidney.
- *Asymptomatic PHPT*, diagnosed via routine blood tests without evident clinical symptoms. This category can be further divided into complicated and uncomplicated forms, depending on the presence or absence of subclinical target organ involvement.

Furthermore, the condition of normocalcemic PHPT was recently described but this clinical entity and its management are still matters of debate (5,6).

The diagnosis of PHPT is based on the presence of hypercalcemia alongside inappropriately elevated levels of parathyroid hormone (PTH) (7,8). This requires the exclusion of confounding factors such as pharmacological treatments (7) and familial hypocalciuric hypercalcemia (9).

After a conclusive biochemical diagnosis of PHPT, imaging procedures should be employed for the localization of the affected parathyroid gland(s). Ultrasound scan of the neck and parathyroid scintigraphy are the first-line imaging procedures (10–13).

Parathyroidectomy (PTX) is the only definitive treatment for PHPT (14), offering a cure in 96% of uniglandular cases when performed in high-volume centers (>40 PTX/year) by experienced surgeons (15,16).

Surgical complication rate is low in high-volume centers (1-3%) (17). At present surgical interventions are planned based on pre-operative imaging findings and coupled with the use of intra-operative PTH assay (ioPTH).

While the complication rate is low (1–3%), surgical success is influenced by preoperative imaging and ioPTH, which confirms gland removal by demonstrating a rapid drop in PTH levels (18). Postoperatively, serum calcium and PTH levels are monitored to guide supplementation of calcium and calcitriol and assess surgical outcomes, with long-term relapse rates below 5% over 10 years (19).

Beyond surgical treatment, medical management options for PHPT with different efficacy and mechanisms of action include Cinacalcet, bisphosphonates, and denosumab. Cinacalcet effectively reduces serum calcium levels (20,21), whereas bisphosphonates and denosumab improve bone mineral density (BMD) without affecting calcium or PTH levels (16,22,23).

The benefits of successful PTX have been largely demonstrated at bone (16,24,25), and renal levels (26,27). On the contrary, disease progression is reported in the majority of PHPT patients who are followed-up without surgery (28–31).

Vitamin D deficiency is a recognized risk factor for postoperative complications such as hungry bone syndrome and requires correction when identified (32,33).

Objective

This study aims to evaluate the economic implications of three different management strategies for PHPT: surgical, pharmacological, and observational. The analysis conducted

from both the Italian National Health Service (NHS) and societal perspectives, seeks to estimate the annual economic burden of PHPT and provide actionable recommendations to optimize its management within the Italian healthcare system.

Methods

The economic evaluation was conducted using a micro-costing approach (34–38) for the economic valorization of the alternatives considered, which allows for the identification of cost drivers and enables the estimation of the total cost of each intervention by quantifying individual resource items.

The developed micro-costing framework outlined below was based on standard methods of cost gathering and previous examples of micro-costing (34–38). Micro-costing is a valuation method commonly used in health economics, focusing on evaluating individual services or specific interventions over a period. The primary aim of this approach is to achieve precise measurements of costs and benefits related to the provision of healthcare services (34). It accomplishes this by considering both fixed and variable costs associated with care, considering local prices and the specific institutional setup where the care is delivered. One of the key features of micro-costing is its effort to incorporate all possible costs related to the service, even those that might not be readily observable. For instance, it considers factors such as patient time spent, opportunity costs associated with family members' time, and other unobserved costs (34). To account for these, micro-costing may use shadow prices or employ various interpolation methods. By employing the micro-costing method, researchers and policymakers can obtain a more comprehensive and accurate understanding of the true costs and benefits of healthcare interventions, enabling informed decision-making and resource allocation in the healthcare sector (34). Moreover, micro-costing allows for the assessment of the potential organizational impact and the specific resources involved and allocated.

The micro-costing process involves the realization of the following phases. The first phases is the *Resources' identification,* where the resources necessary for the provision of the therapies under analysis are identified, defining roles and timing of each phase as well as the segments into which the process can be divided, thus allowing the costs to be associated with each operation performed or unit of material used, and allowing the full cost of such sub-activities to be estimated.

The second step of micro-costing analysis is the *Costs' measurement*, involving the identification of cost of each resources identified for the provision of the treatments under analysis. The analysis considered the NHS and societal perspectives. A partial assessment of the social impact of the treatment was included, specifically limited on productivity losses related to the absence of patients and their carers from work.

To determine the cost of these resources, various sources were consulted, including the Tariff of Specialist Outpatient Service (39), AIFA transparency lists (40), and the scientific literature.

For examinations and follow-up visits, the tariffs specified by the Italian Ministry of Health's nomenclature for outpatient specialist care were used as a reference (see Table S1). Additionally, the ex-factory prices of the active ingredients used in the treatments were extracted from the AIFA transparency lists (see Table S2). Inpatient services' costs were estimated through the results obtained in the survey using healthcare professionals' hourly costs extrapolated from Agency for the Negotiating Representation of Public Administrations (ARAN) (41) (see Table S3).

Table S4 reports the acquisition cost of resources required for performing PTX.

In order to valorize the time dedicated by healthcare professionals to the provision of services under analysis and the productivity loss of patients/caregivers, reference was made to the ARAN (41) and the Job Pricing: All About Rewards – Salary Outlook 2019 Report (42) (See Table S5).

The last step is the *Results' valorization*, where the monetary values are attributed to the corresponding cost drivers, allowing the full value of each action carried out and of the supply process to be determined.

Results are expressed in terms of yearly total cost for each management strategy, with a focus on the resource differential between pharmacological and surgical alternatives.

Deterministic analyses were performed to explore the level of uncertainty in the parameters extracted from the survey.

The one-way sensitivity analysis (OWSA) varied each parameter individually between the upper and lower bounds of confidence intervals within pre-specified probabilistic distributions assigned to each parameter. Where the standard error was unavailable to calculate upper and lower confidence intervals, this was assumed to be ±20% of the mean value. A tornado diagram was developed to illustrate the level of uncertainty considering the full cost of the framework at start and of the three strategies based on the upper and lower bounds.

Survey

The analysis used estimates derived from the clinicians' current experience as data sources.

A survey was conducted among the members of the guidelines (GL) panel to reconstruct a scenario consistent with the Italian clinical practice for the treatment of PHPT. The panel, consisting of 10 clinicians from different Italian regions, was composed following the principles of multiprofessionalism and multidisciplinarity The survey was conducted using structured forms, which were completed independently by each panel member. The purpose of this survey was to investigate the parameters involved in the implementation of the therapeutic strategies being assessed.

PTX and alternative pharmacologic treatments – cinacalcet, bisphosphonates, denosumab, and thiazides – were evaluated. As to PTX, the survey investigated the number and type of diagnostic tests and visits provided in the pre-hospitalization phase, the total duration of the operation, the drugs and their average doses used during the operation, the number and types of professionals involved as well as the type and quantity of the employed disposable materials. For each pharmacological approach, the survey

investigated the following aspects: the average dosage, the number and type of diagnostic tests and visits provided for patients' initial assessment, the number and type of yearly diagnostic tests and visits for patients' follow-up. The analysis also investigated the rates of recourse to all available alternatives in the clinical practice to estimate the average weighted cost per patient irrespective of the chosen treatment strategy. As the analysis considered the society perspective, the share of patients who were actively employed and the percentage of those who required a caregiver during and after the procedure was also investigated to obtain an estimate of the productivity losses sustained by patients and caregivers associated with the provision of the treatments under analysis.

These data were obtained through the survey conducted among the clinical panel, who provided estimates based on their clinical experience and patient population. A collective discussion and consensus meeting with the Guidelines (LG) panel was held during the presentation and elaboration of the survey results. The data were then consolidated quantitatively: for each parameter, the mean value and range were used in the cost calculations.

Results

The analysis revealed significant differences in the economic burden and resource consumption associated with the management of PHPT across the approaches investigated.

Diagnosis

This step includes the necessary procedures to establish an accurate diagnosis and evaluate associated conditions, ensuring a robust basis for selecting the most appropriate therapeutic approach. The main complications of PHPT that were considered in this evaluation are bone involvement (with osteoporosis, fractures and brown tumors) and renal involvement (with nephrolithiasis, nephrocalcinosis and chronic kidney disease). The total cost of PHPT diagnostic phase and evaluation of comorbidities/complications is € 887.96 (Table 1) regardless of the subsequent therapeutic strategy.

TABLE 1 - Costs of Framework at start

Procedure	Cost (€)
Procedures for the diagnosis of PHPT	€ 561.15
Procedures for the evaluation of comorbidities and complications	€ 326.81
Framework at start full cost	€ 887.96

Parathyroidectomy

The total cost of PTX amounts to € 4,639.63, including operation expenses, follow-up care, and indirect costs such as productivity losses for the patient and caregiver (Table 2).

TABLE 2 - Parathyroidectomy costs

Parathyroidectomy costs				
	Procedure			**Cost (€)**
Operation	Pre-surgical treatments			€ 258.51
	Procedures before hospitalization			€ 161.95
	Drugs employed during surgery			€ 44.96
	Disposables/devices			€ 206.63
	Procedures during surgery			€ 45.59
	Health professionals			€ 115.20
	Operating room			€ 193.82
	Hospital stay			€ 1329.62
	Sub-total operation			**€ 2356.28**
		Cost (€)	**% of Cases**	**Weighted Cost (€)**
Follow-up	Standard follow-up	€ 395.57	95.02%	€ 375.89
	Follow-up with acute complications	€ 1,546.40	2.54%	€ 32.79
	Follow-up with chronic complications	€ 414.29	2.43%	€ 10.07
	Sub-total follow-up			**€ 418.75**
Indirect costs	Patient	€ 858.21	100%	€ 858.21
	Caregiver	€ 858.21	7.78%	€ 66.80
	Sub-total indirect costs			**€ 925.01**
Parathyroidectomy full cost				**€ 3700.04**
Non-surgical strategies cost				
Pharmacological				
Procedure				Cost (€)
Pharmacological therapy				€ 755.92
Monitoring the patient's clinical condition				€ 197.42
Pharmacological therapy full cost				€ 953.34
Observational strategy				
Procedure				Cost (€)
Monitoring the patient's clinical condition				€ 197.42

In particular, operation costs account for the largest share, representing 63.27% (€ 2,356.28) of the total cost. These include pre-surgical treatments, procedures before hospitalization, drugs and disposables used during surgery, the operating room, and the hospital stay; Follow-up costs represent 11.31% (€ 418.75) of the total and include standard follow-up for the majority of patients (95.02%), as well as follow-up for those with acute (2.54%) or chronic complications (2.43%) during the first years post-surgery; indirect costs contribute 25.00% (€ 925.01) to the total, reflecting productivity losses for patients and caregivers during and after the procedure.

Pharmacological approaches

Regarding the resource consumption associated with the provision of non-surgical therapies, the analysis categorized the drivers related to these strategies into the following major cost classes: Pharmacological therapy and annual follow-up for monitoring the patient's clinical condition.

Regarding the resource consumption associated with pharmacological therapies, Table S19 presents the survey results in terms of average, minimum, and maximum dosages, as well as the percentage of use for each active ingredient. The analysis reveals that the overall utilization rate of pharmacological alternatives is 196.17%, indicating that patients are often prescribed more than one pharmacological therapy simultaneously. Among the therapies, cholecalciferol is associated with the highest utilization rate (81.70%), while cinacalcet accounts for the highest expenditure (mean: € 391.93; range: € 92.31–€ 1,277.11).

The average annual pharmacological expenditure for these therapies, considering the utilization rates of each active ingredient, amounts to € 755.92 (Table 2).

The analysis of non-surgical therapies also examined the annual frequency of specialist visits and diagnostic tests required to monitor the clinical condition of patients with PHPT undergoing pharmacological therapy or only observational strategy. When considering the overall cost of therapeutic strategies as alternatives to PTX, the total reaches € 953.34 per year, encompassing both drugs and follow-ups (Table 2).

For patients following an observational strategy, which primarily involves monitoring the clinical condition without active treatment, the annual cost in the absence of disease complications is € 197.42.

Burden of hyperparathyroidism

Table 3 illustrates the economic burden of PHPT during the first year across three management strategies.

The baseline cost that is common to all approaches includes the procedures for the diagnosis of the disease and its complications and amounts to € 887.96. PTX emerges as the most expensive strategy during the first year, with a cost of € 3,700.04 for surgery, leading to a total first-year expense of € 4,588.00. In contrast, the pharmacological strategy incurs a lower first-year total of € 1,841.30, while the observational approach is the most economical at € 1,085.38.

TABLE 3 - Burden of hyperparathyroidism during the first years for each strategy

	PTX	Pharmacological	Observational
Framework at start full cost		€ 887.96	
PTX	€ 3,700.04	–	–
Pharmacological strategy	–	€ 953.34	–
Observational strategy	–	–	€ 197.42
Total	**€ 4,588.00**	**€ 1,841.30**	**€ 1,085.38**

The analysis also investigated the general recourse rate of the therapies under investigation (Table 4): PTX resulted the strategy associated to the highest recourse (76.11%), while pharmacologic treatments and active surveillance are employed less frequently with similar percentages of 11.44% and 12.44%, respectively.

TABLE 4 - Distribution of patients among alternative treatments for PHPT

Alternative treatments for PHPT	%
Patients undergoing PTX	76.11%
Patients treated only with pharmacologic treatments	11.44%
Patients followed up with active surveillance	12.44%

Considering the annual PHPT incidence of 20 cases per 100,000 individuals, corresponding to approximately 12,000 new annual cases in Italy (60 million population) (3,4) and weighting the total cost of treatments according to each recourse rate, the overall average cost of managing PHPT was estimated equal to € 56.4 million (see Table 5).

TABLE 5 - Annual burden of PHPT

Strategy	N	Annual cost
PTX	9,133	€ 52,185,962.00*
Active surveillance	1,373	€ 1,486,107.70
Pharmacologic treatments	1,494	€ 2,750,902.00
Total	**12,000**	**€ 56,422,971.70**

***** By applying the costs established by the NHS and accounting for the additional cost estimated for the first year for all complementary services, the cost of PTX amounts to € 5,714,00. This is calculated by subtracting the € 2,356 net cost of the procedure (as determined in Table 2) from the € 4,588.00 total cost for the first year and then adding the € 3,482 NHS reimbursement.

A detailed summary of the parameters derived from the survey conducted among members of the GL panel is provided in the Supplementary Materials. Tables S1 to S5 report the input data of analysis.

The calculations outlined in the supplementary material cover all steps involved in extrapolating the total cost of the First diagnosis (Table S6 S7), Surgical Strategies (Table S8S18) and Non-Surgical Treatments (Table S19S20). These calculations include estimates for the number and type of diagnostic tests and visits, the duration of surgical operations, the resources used during surgery (e.g., drugs, doses, materials, and personnel), as well as the average drug dosages and follow-up requirements for pharmacological and observational approaches. Additionally, weighted costs were computed to reflect the rates of recourse to each therapeutic alternative in clinical practice and the Italian annual economic burden of PHPT.

Sensitivity Analysis

The OWSA results are shown in the tornado diagram (Figure 1) for each strategy.

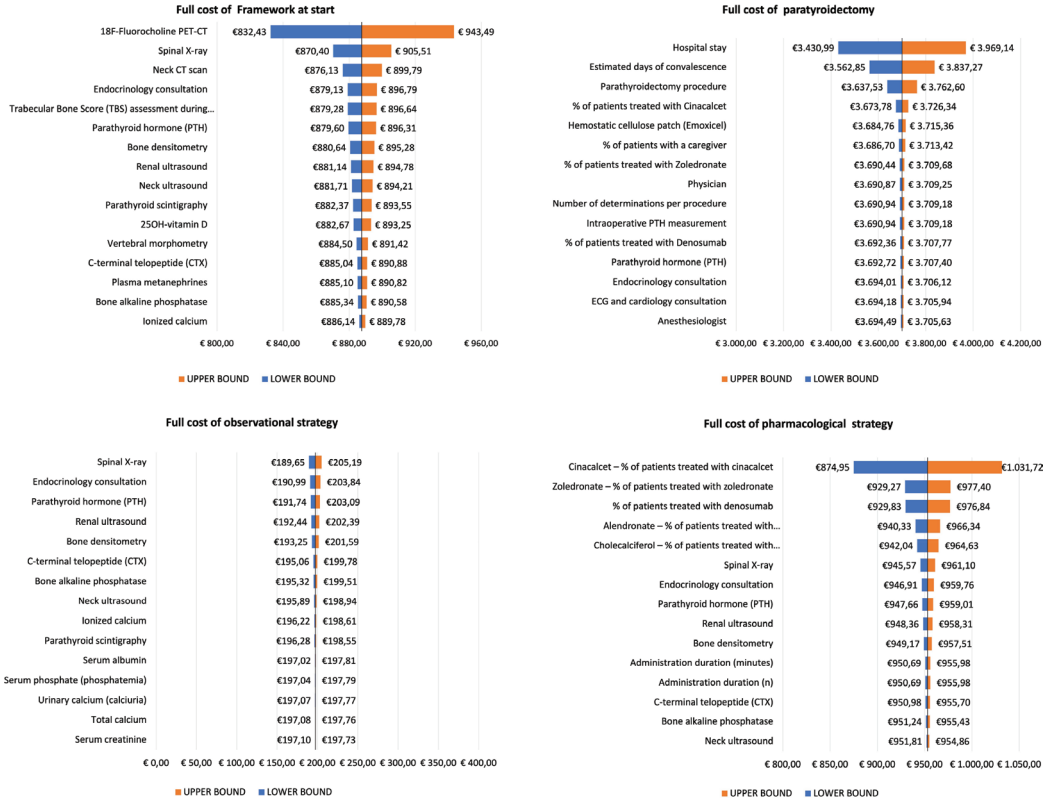

FIGURE 1 - Tornado diagrams.

Each strategy displays a distinct range of uncertainty: PTX exhibits the widest variability, particularly for hospital stay and postoperative recovery, suggesting a high degree of cost sensitivity to clinical and organizational parameters. The pharmacological strategy also shows moderate variability, especially linked to drug choice and treatment duration. In contrast, the observational and framework at start strategies are characterized by narrow uncertainty intervals, indicating more stable and predictable costs.

Discussion

These findings highlight the significant economic burden of PHPT management based on the approaches considered in the analysis. This study provides an analysis of the economic implications associated with various management strategies for PHPT in Italy. By integrating clinical and economic data, the results offer valuable insights into the distribution of patients among therapeutic approaches, the cost drivers of treatment, and the overall economic burden of PHPT management.

PTX emerged as the dominant therapeutic strategy, utilized in 76.11% of cases. This reflects the role of PTX as the gold standard for PHPT treatment, offering a definitive cure in most cases, despite its higher upfront cost (€ 4,588.04 per case).

The annual cost of conservative strategies was estimated at € 197 for active surveillance and € 953 for pharmacologic treatments. However, these annual costs must be multiplied by the follow-up period, which often spans decades. Assuming that surgery is performed at an average age of 55, a conservative estimate of the remaining time horizon is 30 years. (43) Based on an annual cost of €10 for managing chronic complications, the total cost over this period would amount to approximately €300. Combined with the initial cost of PTX (€ 5,714), the total cost for PTX and the management of complications would be approximately € 6,004.

In contrast, the cost of pharmacologic treatments over 30 years is € 28,590, while the cost of active surveillance is significantly lower (€ 5,910). These findings highlight that while pharmacologic treatments are less invasive, their cumulative cost over time far exceeds that of PTX. Importantly, surgical intervention is primarily recommended for patients with complications, making the comparison between PTX and pharmacologic strategies particularly relevant.

The overall economic burden of PHPT management in Italy amounts to € 56,422,971 annually, with surgical interventions accounting for the majority (€ 52,651,745). Although pharmacologic treatments and active surveillance contribute smaller shares, their cumulative costs become significant when considered over the long term.

The increased cost per patient of pharmacologic treatments over 30 years compared to surgical intervention is € 22,876 (delta between pharmacologic treatments cost (€ 28,590) and surgical intervention (€ 5,714), emphasizing the long-term economic efficiency of PTX for eligible patients with complications.

From an efficiency and resource optimization perspective, PTX remains the most competitive strategy for managing

PHPT in patients with symptomatic or complicated disease. The significant cost difference between PTX and pharmacologic treatments reinforces the recommendation of surgical intervention (€ 5,714 per person) as the preferred approach for eligible patients (with symptomatic or complicated disease). Active surveillance, while cost-effective (€ 5,910 over 30 years), is limited to patients with uncomplicated or asymptomatic PHPT, further emphasizing the need for tailored treatment approaches.

In this context, the use of a micro-costing approach proved particularly valuable not only in estimating direct treatment costs, but also in supporting the assessment of the potential organizational impact. It allowed for a more detailed understanding of the specific resources involved, such as personnel time, materials, and facility use, thus informing more effective planning and resource allocation strategies.

In Italy, the reimbursement for the medical activities performed in public health structures is established by regulatory authorities. For PTX (ICD9-CM 06.81 and 06.89) a maximum reimbursement of € 3,482.48 is recognized for ordinary hospitalization, but the costs related to long-term follow-up are not considered. By using the costs applied by the Italian NHS and considering the expected additional costs in the first year for the complementary services, it was possible to establish the total expenditure. The € 2,356 amount calculated for the net cost of the operation should be detracted from the € 4,639,62 total cost for the first year of management. Then, the € 3,482 sum of the NHS reimbursement should be added, bringing the total expense induced by the surgical strategy to € 5,714.

Limitations to a reliable calculation of cost estimates include several factors that introduce variability and uncertainty into the analysis. First, price fluctuations of surgical devices and disposables can significantly affect the overall costs of surgical interventions. Additionally, the risk and associated costs of surgical complications may be higher in real-world settings than reported in studies conducted by specialized centers following good clinical practice guidelines.

Personnel costs for surgical interventions are another area of potential underestimation, as they do not fully account for non-surgical times, including dressing and undressing, patient information and consent procedures, operating room cleaning, and patient monitoring during anesthesia weaning. These additional components may help explain why the DRG tariff is relatively higher compared with the cost for the procedure estimated in this study. Moreover, the analysis assumes that patients following surveillance or pharmacological strategies will adhere to these approaches throughout their lifetime, but drop-out rates could alter long-term costs.

Future price fluctuations of drugs introduce further uncertainty, potentially affecting the cost-effectiveness of pharmacological strategies. The analysis also does not account for the costs or potential savings associated with complications that may be prevented by surgical intervention, such as fractures or nephrolithiasis, with their burden of complications and disability, which could significantly impact the overall economic evaluation.

Finally, indirect costs for patients and caregivers were only considered for surgical strategies, though similar indirect costs are likely associated with other management strategies due to time spent on visits, follow-ups, and hospitalizations for potential complications. Future research should focus on longitudinal studies to validate these findings and explore the cost-effectiveness of emerging therapeutic options, such as new calcimimetics or advanced surgical techniques.

Conclusion

This study highlights the economic and clinical value of PTX as the gold standard for managing PHPT in Italy. While pharmacologic treatments and active surveillance have specific roles in selected patient populations, their cumulative costs over the long term underscore that these strategies do not optimize tresource use relative to surgery for eligible patients. These findings provide actionable insights for policymakers and healthcare providers to optimize resource allocation and improve patient outcomes in PHPT management.

Disclosures

Conflicts of Interest: The authors declare no potential conflict of interest to be disclosed.

Financial support: The present work was developed with no external financial support.

Data Availability Statement: Data sharing not applicable: All data generated or analyzed in this study are included in this published article and available as supplementary material.

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