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碩士論文

Graduate Institute of Clinical Medicine
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Master's Thesis

原發性副甲狀腺功能亢進的術前偵測和定位

Preoperative Detection and Localization in Primary Hyperparathyroidism

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將此研究獻給每位在生命當中幫助過我的人，所有愛我以及我愛的人
以及每一位照顧過的病人

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中文摘要

背景

副甲狀腺切除術是治療原發性副甲狀腺功能亢進症的首選方法。原發性副甲狀腺功能亢進症可以通過手術很好地治療。術前定位影像學研究對於副甲狀腺切除術至關重要，包括識別副甲狀腺、微創手術、降低風險和併發症（如損傷附近結構如喉返神經或意外切除正常甲狀腺組織）等好處。超音波（Ultrasonography）和 99mTechnetium-sestamibi (Tc-99m MIBI) SPECT/CT 在術前影像調查中常規使用，但它們在確定副甲狀腺不同位置的價值尚不清楚。儘管雙側頸部探查手術傳統上是手術的標準方法，但準確的術前定位病變的副甲狀腺至關重要。然而，對於影像不一致時的最佳定位方法尚無共識。

方法

本回顧性研究納入在 2004 年至 2023 年間在單一醫療中心接受副甲狀腺切除術的副甲狀腺功能亢進症患者。記錄了術前定位副甲狀腺瘤的超音波和 Tc-99m MIBI SPECT/CT 檢查。計算了每種方法的敏感性和陽性預測值。

結果

本回顧性研究共納入 331 名患者。超音波的敏感性為 77.3%，陽性預測值為 94.31%。MIBI 掃描的敏感性為 89.61%，陽性預測值為 94.07%。根據結果，MIBI 掃描的敏感性比超音波更高，而兩者的陽性預測值則非常接近。新的術前定位方法包含正子斷層造影，4D 電腦斷層和術中副甲狀腺賀爾蒙靜脈取樣，能提供臨床上更多選擇。

結論

超音波結合 Tc-99m MIBI SPECT/CT 在原發性副甲狀腺功能亢進患者術前定位副甲狀腺瘤方面具有很大的臨床價值。對於影像不一致的病例，Tc-99m MIBI SPECT/CT 顯示出更高的可靠性。此外，我們提出了一個流程表包含近來開發的影像偵測方法以及術中副甲狀腺賀爾蒙靜脈取樣。影像學的選擇應透過個別患者的臨床資料進行量身定制，並考慮了輻射暴露、成本以及手術醫師對該方法的可操作性等因素，並謹慎選擇新的方法。

關鍵詞

原發性副甲狀腺功能亢進症，副甲狀腺手術，術前定位

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英文摘要

Background

Parathyroidectomy is the definite treatment for primary hyperparathyroidism (pHPT). pHPT is well treatable surgically. Preoperative localization imaging studies are crucial for parathyroidectomy, including the benefit as identification of parathyroid glands, minimally invasive surgery, reduced risk and complications such as damage to nearby structures like the recurrent laryngeal nerve or accidental removal of normal thyroid tissue. Ultrasonography (US) and technetium-99m-sestamibi-single photon emission computed tomography/computed tomography (MIBI SPECT/CT) are used routinely in pre-operative image surveys, but it is unclear how valuable they are in determining parathyroid glands' distinct locations. However, when image discordancy, there is no consensus on the optimal modality for localization.

Method

Retrospectively reviewed who had pHPT and underwent parathyroidectomy in National Taiwan University Hospital, 2004-2023. Preoperative localization between US and MIBI SPECT/CT for parathyroid nodules were recorded. The sensitivity and positive predictive value of each imaging method were determined. New preoperative localization modalities, including PET/CT, 4D CT, and intraoperative parathyroid venous sampling, offer more clinical options.

Result

331 patients were enrolled in this retrospective study. US sensitivity is 77.3% and the positive predictive value is 94.31%. MIBI SPECT/CT sensitivity is 89.61%, and the positive predictive value is 94.07%. According to the results, the MIBI SPECT/CT has a higher sensitivity compared to ultrasound, while the positive predictive value of both is remarkably close.

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Conclusion

US combined with MIBI SPECT/CT achieved highly valuable for preoperative localization of parathyroid nodules in patients with pHPT. For discordancy cases, MIBI SPECT/CT showed more reliability. Furthermore, we proposed an algorithm containing recently developed detections method for pHPT, tailored to each patient's clinical profile, considering factors such as radiation exposure, cost, and the surgeon's accessibility.

Key word

primary hyperparathyroidism, parathyroidectomy, preoperative localization

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Chapter 1 Introduction

Primary hyperparathyroidism (PHPT) is a common clinical problem, and the only definitive treatment is surgery. Parathyroidectomy is recommended for all patients with symptoms related to primary hyperparathyroidism. Additionally, it should be considered for most asymptomatic patients. [1] Notably, parathyroidectomy has been found to be more cost-effective than observation or pharmacologic therapy. [2] Pre-operative localization for focused lesion was the important role.

Epidemiology of Primary Hyperparathyroidism

In well-equipped healthcare systems where serum calcium levels are routinely assessed, patients with primary hyperparathyroidism usually exhibit mild-to-moderate hypercalcemia. Additionally, their parathyroid hormone (PTH) levels are either no suppressed or elevated. These PTH levels are typically measured using an immunoassay that primarily detects intact hormone forms. [3]

It is evident that the incidence rates and prevalence of pHPT are rising in countries outside North America and Europe. This increase is attributed to more frequent serum calcium measurements, which have also led to a shift in patient presentation from symptomatic to asymptomatic disease. Consequently, a global rise in the incidence rates and prevalence of pHPT is expected.[4]

In Asia, the prevalence of pHPT among middle-aged and elderly Chinese (n = 2451) was reported to be 0.204%.[5] A single-center retrospective study conducted (2013-2016) estimated the occurrence of PHPT to be 0.4% in patients hospitalized for urolithiasis in Korea.[6]

In Taiwan, one single-center experience showed 28 patients of the 4,359 asymptomatic adults (0.64%) were found to have hypercalcemia; 4 patient (nearly 0.1%) were diagnosed with pHPT. [7]

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Etiology of Primary Hyperparathyroidism

Primary hyperparathyroidism (pHPT) is often a sporadic condition, with 85-90% of cases due to a solitary adenoma. Less frequently, pHPT results from multiglandular involvement, which can include hyperplasia of all four parathyroid glands or multiple adenomas, accounting for 5-10% of cases. Rarely, pHPT is caused by parathyroid carcinoma, which occurs in less than 1% of cases. Multiglandular involvement may present asynchronously, potentially leading to confusion with a single adenoma if only one abnormal gland found during the intra-operative condition. Over time, another remnant parathyroid adenomas may become clinically evident. In rare cases, pHPT may result from ectopic secretion of parathyroid hormone by a non-parathyroid lesion.

The exact reason of pHPT remains unclear for most patients, though some cases have been associated with a history of long-term lithium therapy, external neck irradiation incident during youth, or exposure to nuclear event in adulthood. pHPT can result from genetic endocrine syndromes, including multiple endocrine neoplasia types 1 (MEN1) and 2A (MEN2A), MEN4 (a condition resembling MEN1 but lacking MEN1 gene mutations), neonatal severe hyperparathyroidism, hereditary, familial isolated hyperparathyroidism, familial hypocalciuric hypercalcemia (FHH), and hyperparathyroidism-jaw tumor syndrome. [8] Identifying hereditary cases can be difficult when there is no family history, in which case a newly germline mutation must be examined.[9]

The development of sporadic parathyroid adenomas is well known linked to the overexpression of cyclin D1. Cyclin D1 is located on chromosome 11q13. Pericentromeric inversion leads to rearrangement of tumor specific DNA between CCND1 and PTH, resulting in the transcriptional cascade activation and cyclin D1 overexpression. This genetic abnormality found in approximately 8% of sporadic

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parathyroid adenomas, while elevated CCND1 over expression has been reported in 20-40% of cases. Additionally, biallelic inactivating mutations of the MEN1 gene have been observed in about 15-35% of sporadic parathyroid adenomas. Cyclin D1 is essential in regulating cell cycle progression, with its role in promoting proliferation through the phosphorylation of retinoblastoma protein (RB). [10-12]

In small percentage of parathyroid adenomas, additional genetic abnormalities have been identified, including mutations in CDKN1B, CDC73, and AIP(aryl hydrocarbon receptor interacting protein).[13] [14] CTNNB1mutations which encodes β-catenin involving phosphorylation of serine and threonine has been reported, though findings have been contradictory. [15] About 30 proteins involved in different pathways such as response to biotic stimulation, cell organization, and signal transduction. These performances are differentially between parathyroid adenomas and normal parathyroid glands. Among these proteins, 14-3-3ζ/δ may play a significant role in the development of parathyroid adenomas.[16]

Primary Hyperparathyroidism Surgical Indications and Outcomes of Intervention

Parathyroid surgery is recommended for all symptomatic patients unless medical reasons contraindicate it. For asymptomatic individuals, the focus is on identifying those at higher risk of disease-related complications. Surgery is advised for individuals with calcium levels more than 1 mg/dL (0.25 mmol/L) above the upper limit of normal. Additionally, surgical intervention is recommended if there are signs of skeletal involvement, such as a T-score of ≤ –2.5 on a DXA scan or the presence of a morphometric vertebral fracture detected by X-ray or VFA. Although a T-score in the osteoporotic range may be due to factors other than PHPT, studies have shown significant improvements in bone mineral density (BMD) after successful parathyroidectomy, even when other factors contribute to reduced bone mass. This

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supports using bone density as a criterion for surgery. Renal involvement, indicated by a creatinine clearance of <60 mL/min, imaging evidence of nephrolithiasis or nephrocalcinosis, or hypercalciuria (>250 mg/day in women or >300 mg/day in men), also warrants surgical intervention.[17-19]

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Chapter 2 Method

Screening operation record treated for pHPT at one single medical center from 2004 to 2023, total patient number is 361. Exclusion criteria included recurrent primary hyperparathyroidism in 7 patients, previous neck surgery history in 15 patients, multiglandular disease in 5 patients, and multiple endocrine neoplasia (MEN) in 3 patients. After reviewing histology data, normal parathyroid in 4 patients, no parathyroid tissue in 2 patients, parathyroid carcinoma in 1 patient were also excluded. A total of 331 patients were enrolled in this retrospective study who had pHPT and underwent parathyroidectomy in one single medical center, 2004-2023. All the patients received preoperative localization method as US and MIBI SPECT/CT. And divided into groups as both detection of parathyroid nodule, discordancy of two image study and no detection of parathyroid nodule as Figure 1. US and Tc-99m MIBI SPECT/CT examinations for preoperative localization of parathyroid nodules were recorded. The algorithm of patient selection as Figure 2, the sensitivity and the positive predictive value of each modality were calculated.

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Chapter 3 Result

Of 331 patients, with 60.58 ± 13.79 years mean age, 104 male(31%) and 227 female(69%), preoperative calcium level (mmol/L ± SD)is 2.81 ± 0.27, albumin level(g/dL ± SD) 4.41 ± 0.48, preoperative PTH (pg/mL ± SD) is 283.07 ± 386.38, parathyroid adenoma weight(gram ± SD) showed 1.16 ± 0.13 (Tabel. 1) Calcium level (mmol/L ± SD) in preoperative showed 2.81 ± 0.27, and decreased level in postoperative day1(2.41 ± 0.22) and 6 month(2.35 ± 0.15). PTH (pg/mL ± SD) in preoperative level showed 283.07 ± 386.38, decreased level in postoperative day1 (22.59 ± 38.34), 6 month(63.39 ± 58.66). (Table. 2)

Although the postoperative calcium levels decreased not significantly compared to the PTH levels, this was expected as we administered calcium gluconate on the postoperative day to prevent hypocalcemia.

The US sensitivity is 77.3% and the positive predictive value is 94.31%. MIBI SPECT/CT sensitivity is 89.61%, and the positive predictive value is 94.07%. From the results, the MIBI SPECT/CT has a higher sensitivity compared to ultrasound, while the positive predictive value of both is very close. (Table. 3) When there was discordancy in the imaging studies, 85 patients were affected, accounting for 25.9% of all patients in this study. MIBI SPECT/CT had higher prediction rate as 74.1% in pre-operation localization. (Table. 4)

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Chapter 4 Discussion

The traditional surgical approach involves the surgeon examining both sides of the neck, identifying the diseased parathyroid glands, and removing them. In recent decades, advanced techniques for parathyroid localization have emerged. However, there is no consensus on the optimal localization procedure or imaging protocol. Clinical approaches vary based on local expertise and institutional practices.

Due to its widespread availability, neck US is often the initial imaging modality used. A retrospective analysis of 63 patients showed that the sensitivity and positive predictive value (PPV) of neck ultrasound were significantly higher when performed after 99mTc-sestamibi SPECT/CT (90.9% and 100%, respectively) compared to when it was performed first (56.6% and 72.2%, respectively; $P < 0.05$). However, the performance of MIBI SPECT/CT was not enhanced by prior knowledge of neck US results. These findings, if validated in a prospective study, could have important practical implications. [20]

Currently, US and MIBI SPECT/CT are widely accepted for preoperative localization in most cases. However, precise localization can be challenging, particularly in patients with multiglandular disease, ectopic glands, recurrent disease, and normocalcemic primary hyperparathyroidism. Our research indicates that Tc-99m MIBI SPECT/CT provides better accuracy for localizing parathyroid adenomas compared to sonography. Additionally, new modalities for preoperative localization, such as positron emission tomography/computed tomography (PET/CT) and parathyroid venous sampling, have shown improvements in sensitivity and accuracy.

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Ultrasonography (US)

Ultrasound is a widely used in initial practice for preoperative localization in pHPT due to its easily accessibility, accuracy, non-radiated, and cost-effectiveness. The superficial position of parathyroid glands in the central of neck region allows for the high-frequency linear probe. Color Doppler can improve the detection of abnormal parathyroid lesions. [21]

A typical parathyroid adenoma appears as a well-defined margin, bean shape, homogenous texture, anechoic to hypoechoic echogenicity lesion relative to thyroid tissue. Adenomas are often more vascular than lymph nodes and thyroid nodules. Color Doppler can find a distinct vessel feeding at one pole and encircling the gland's peripheral vascularity.[22, 23] Unlike lymph nodes, which have an echogenic fatty hilum and a central blood supply, adenomas can be distinguished by these characteristics. Additional features include asymmetrically increased vascularity in the thyroid gland on the side of the lesion and within the hyperechoic capsule. Color Doppler imaging increases the sensitivity of ultrasound in detecting these differences. Larger adenomas may present as multi-lobulated, occasionally cystic, or, in rare cases, calcification noted. Normal parathyroid glands are usually not visible due to their small size.[24]

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Ultrasound offers several key advantages: it does not involve ionizing radiation, is non-invasive, and is more affordable than other imaging modalities. It is also faster than the more time-consuming MIBI scans and are portable, making bedside and in-office imaging possible. However, US is less sensitive in detecting ectopic glands or multiglandular disease (MGD).[25]

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^{99}mTc-sestamibi scintigraphy (MIBI scan)

Since 1989, Coakley et al first mentioned detecting parathyroid lesions as radiotracer method. [26] 99mTc-sestamibi used lipophilic cationic radiotracer whose uptake on plasma and mitochondrial membrane. With rich in oxyphil cells, adenomatous and hyperplastic parathyroid tissues, avidly absorb 99mTc-sestamibi, resulting in slow washout.

Carpentier et al.[27] reported that a higher oxyphil content (>25%) was linked to increased late technetium uptake. However, Thompson et al. [28]found no significant correlation between MIBI scan results and oxyphil content in 14 false-negative specimens. Nicholas et al [29]showed glands with high oxyphil content consistently showed true-positive results, while those with fewer oxyphils had false-negative results. Parathyroid specimens with more than 25% oxyphil content were more likely to yield positive MIBI scan results. Abnormal parathyroid tissue retained a higher mean dose per gram of the injected substance compared to normal thyroid and parathyroid tissues. Immunohistochemistry showed that abnormal parathyroid tissue has lower levels of p-glycoprotein expression.[30]

To enhance sensitivity and gather more anatomical details, a protocol combining 99mTc-sestamibi with SPECT/CT was developed. [31] Not only anatomical details but also enables differentiation of parathyroid lesions from other sources of 99mTc-sestamibi uptake, such as thyroid nodules and cervical lymph nodes.[32] Additionally, the detection rate of 99mTc-sestamibi may be reduced in cases with low PTH levels or normocalcemic pHPT[33]. Despite these limitations, it remains the first-line imaging modality

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New Preoperative and Intraoperative Localization modality

PET/CT

PET/CT is used as a second-line diagnostic tool when conventional scintigraphy is negative or inconsistent with ultrasound results of the neck. Patients receive 100 MBq of ^{18}F-fluorocholine (a radioactive isotope of fluorine labeled choline) intravenously after fasting for 6 hours. PET/CT imaging is then conducted on the neck and upper mediastinum, extending to the level of the aortic arch, at 5 and 60 minutes post-injection. The procedure involves low-dose CT (25 mAs, 120 kV) followed by PET imaging. [34] ^{18}F-fluorocholine is actively taken up by cells with high choline metabolism. It provides high-resolution images due to its longer half-life (about 110 minutes), making it suitable for clinical use in detecting prostate cancer and parathyroid tumors.

^{18}F-fluorocholine PET/CT outperformed conventional scintigraphy methods, whether used alone or in combination. The sensitivity for PET/CT was about 90%, compared to 39%–56% for conventional imaging methods. In subgroup analysis, PET/CT proved particularly valuable for identifying multiple hyperfunctioning parathyroid glands, with a sensitivity of 88%, while conventional imaging methods were significantly less effective, with sensitivities ranging from 22% to 34%.[34] Other radiotracer such as ^{11}C choline (shorter half-life, about 20 minutes) and ^{11}C methionine (shorter half-life, about 20 minutes; incorporated into proteins, so tumors with high protein synthesis rates) were also under studied. One paper showed ^{11}C choline PET/CT has proven to be more effective than ^{11}C methionine PET/CT and 4D-CT in localizing parathyroid adenomas, accurately identifying 85% of adenomas. [35]

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4D CT

The 4D is fourth dimension refers to the time component, as this technique captures a sequence of images over time, which helps in visualizing the dynamics of contrast enhancement. Involves capturing multiple phases of contrast enhancement, including non-contrast phase which provides baseline information before contrast is administered. Arterial phase acquired 25-30 seconds after contrast injection, highlighting vascular structures. Venous or delayed phase obtained 60-80 seconds after contrast injection, which shows the enhancement of parathyroid glands and helps distinguish them from surrounding tissues. [36, 37]

In a retrospective study of redo parathyroidectomy, 4D CT scans showed an 87% concordance rate with intra-operative findings. This indicates that 4D CT is highly effective in identifying parathyroid pathology in re-operative cases and can serve as a valuable pre-operative tool for guiding surgical management.[38]

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Parathyroid venous sampling

By comparing the PTH levels from different venous sites, the surgeon can identify the region with the highest hormone concentration, which likely corresponds to the hyperfunctioning gland. PTH has a very short half-life, typically around 2 to 5 minutes, which allows surgeons to quickly determine whether the hyperfunctioning parathyroid tissue has been successfully removed by measuring PTH levels before and after excision.[39]

Since1991, the algorithm of intraoperative parathyroid hormone (IOPTH) monitoring was announced in Miami University, 10-minute post excision IOPTH level that decreased 50% from baseline and is normal or near normal is highly successful, this is so called Miami criterion. [40]

Other than intraoperative status, in pre-operative status could predict the diseases side. At the University of Wisconsin in 2007, 168 patients underwent bilateral internal jugular (BIJ) PTH sampling. [41] In the operating room, after the induction of general anesthesia and prior to the surgical incision, internal jugular venous blood was drawn percutaneously from both the left and right sides using a 23- to 25-gauge needle and a 3 mL syringe. BIJ PTH levels were considered lateralizing if there was a difference of more than 5% between the samples taken from the right and left internal jugular veins.

In summary, this article presents a proposed algorithm for managing pHPT patients. During the preoperative stage, the first-line imaging methods are US and MIBI SPECT/CT. For second-line imaging, options include 18F-fluorocholine, 11C-choline, 11C-methionine PET/CT, or 4D-CT. In the intraoperative stage, intraoperative parathyroid hormone (IOPTH) monitoring serves as a third tool, with the Miami criteria requiring a 50% decrease from baseline within 10 minutes. If

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parathyroid adenomas are still not identified, bilateral exploration is necessary. (Figure 3)

Limitation

This is a retrospective study and in one single medical center may confined the result. The accuracy of the new imaging techniques remains a subject of debate.

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Chapter 5 Conclusions

US combined with MIBI SPECT/CT achieved highly valuable for preoperative localization of parathyroid nodules in patients with pHPT. For discordancy cases, MIBI SPECT/CT showed more reliability. Otherwise, we proposed an algorithm containing recently developed detection method for pHPT, tailored to each patient's clinical profile, considering factors such as radiation exposure, cost, and the surgeon's accessibility.

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Chapter 6 Figure and Table

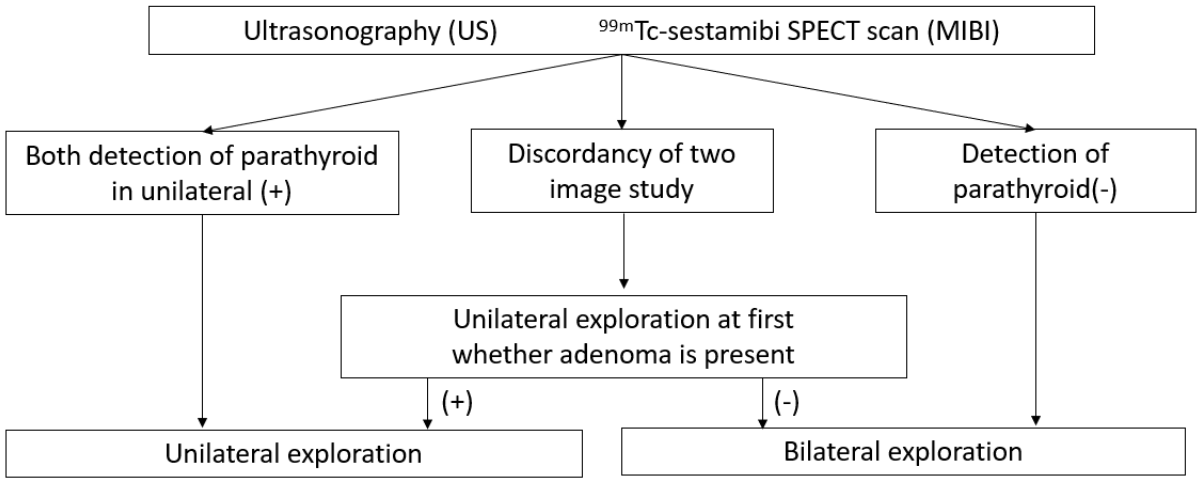

Figure 1.
Current surgical planning for the management of primary hyperparathyroidism, all patient received ultrasonography and MIBI scan; when both detections showed in unilateral side, unilateral exploration was done; when discordancy of these two image study, unilateral exploration at first, if parathyroid adenoma is presented then only unilateral exploration, otherwise, bilateral exploration was performed; when non detection of thyroid in both image, bilateral exploration was performed

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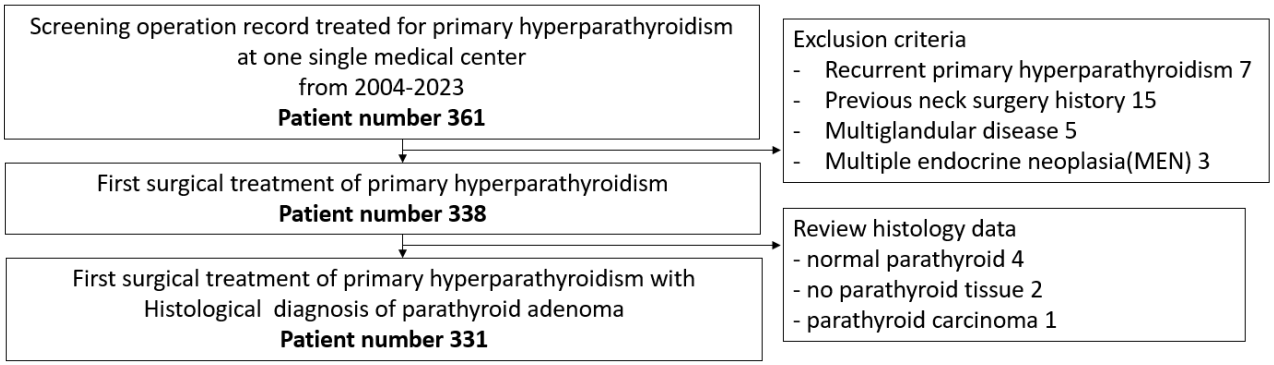

Figure 2.
Flowchart of the patient accrual of primary hyperparathyroidism(pPTH) received operation from 2004 to 2023 in one single medical center, after exclusion of recurrent primary hyperparathyroidism, previous neck surgery history, multiglandular disease, multiple endocrine neoplasia(MEN); and review histological diagnosis which confirmed parathyroid adenoma were included in this study

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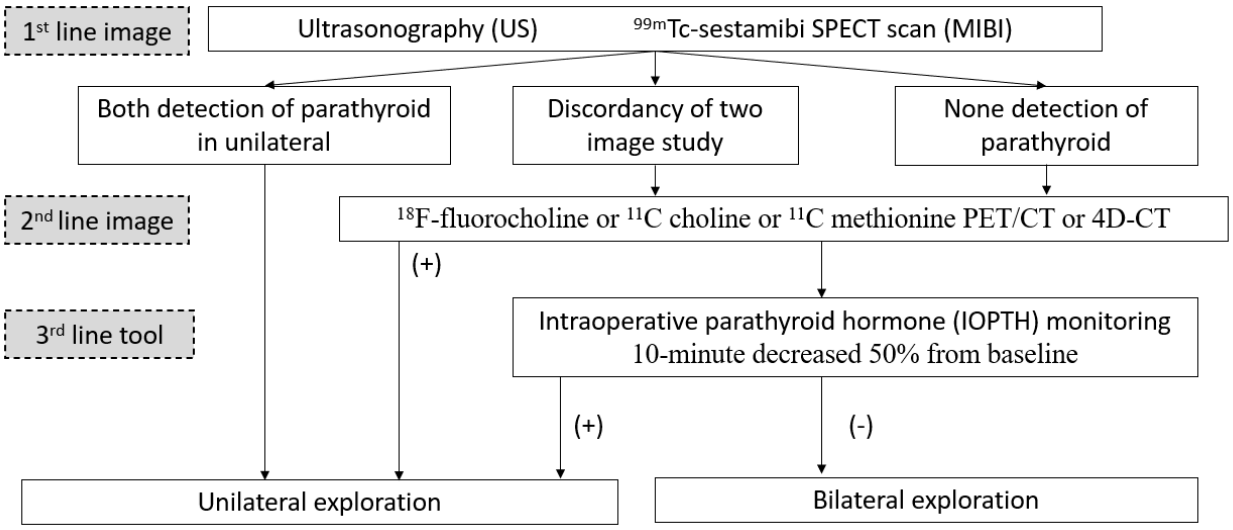

Figure 3.
Proposed algorithm of preoperative detection image as and localization in primary hyperparathyroidism. In the intraoperative stage, intraoperative parathyroid hormone (IOPTH) monitoring serves as a third tool; if parathyroid adenomas are still not identified, bilateral exploration is necessary

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Table. 1 Demographics of Patients

Demographics	n = 331
Age in years (mean ± SD)	60.58 ± 13.79
Sex Male(%) : Female(%)	104(31%): 227(69%)
Pre-op Calcium level (mmol/L ± SD)	2.81 ± 0.27
Albumin (g/dl ± SD)	4.41 ± 0.48
Pre-op PTH (pg/ml ± SD)	283.07 ± 386.38
Parathyroid adenoma weight (gram ± SD)	1.16 ± 0.13

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Table. 2 Ca/PTH level after operation	
Calcium level (mmol/L)	
Pre – op (± SD)	2.81 ± 0.27
1day Post –op (± SD)	2.41 ± 0.22
6month Post –op (± SD)	2.35 ± 0.15
PTH (pg/ml)	
Pre – op (± SD)	283.07 ± 386.38
1day Post –op (± SD)	22.59 ± 38.34
6month Post –op (± SD)	63.39 ± 58.66

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Table. 3 Image method to localize parathyroid adenoma in primary hyperparathyroidism

Image method	Sensitivity	Positive Predictive Value
Ultrasonography	77.33	94.31
Tc-99m MIBI SPECT/CT	89.61	94.07

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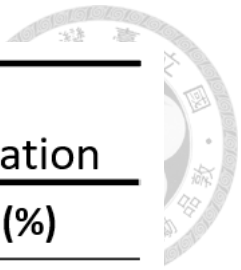

Table. 4 Discordance in image study correct prediction in pre-operation localization

Image study	n = 85 (%)
Ultrasonography	22 (25.9)
Tc-99m MIBI SPECT/CT	63 (74.1)

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