



# The performance of 4D-CT in the localization of parathyroid adenoma

**Purpose:** The aim of this study was to evaluate the effectiveness of 4D-CT compared to ultrasound in locating the parathyroid adenoma.

**Methods:** 29 patients were included in this study; all had done a 4D-CT but only 26 of them had done an ultrasound. All were surgically operated and the anatomopathological result was considered as the gold-standard to confirm the imaging results.

**Results:** 35 adenomas were explored using 4D-CT, and 32 using ultrasound and 4D-CT. 4D-CT detected 34/35 adenomas (Sensitivity (Se) of 97.1%). Ultrasound detected 12/32 (Se of 37.5% and Positive Predictive Value (PPV) of 92.3%). Stratified by location, the 4D-CT has detected 15/16 eutopic adenomas (Se 93.7%) and 19/19 of ectopic adenomas (Se 100%), and ultrasound has detected 11/15 eutopic adenomas (Se 73.3% and PPV 91.7%) and 1/17 ectopic adenomas (Se 5.9%).

**Conclusion:** 4D-CT is effective in locating the parathyroid adenoma, especially in ectopic locations.

**KEYWORDS:** 4D-CT ■ Ultrasound ■ Parathyroid adenoma ■ Primary hyperparathyroidism

## Introduction

Primary hyperparathyroidism is a frequent disease caused in 89% of cases by a parathyroid adenoma. In 10% of cases, the adenoma is in an ectopic situation due to an aberrant embryological migration of the gland. The evolution of surgical techniques has imposed the need to specify its location preoperatively.

Several imaging modalities have been used, but there is still no universal imaging algorithm; and the choice of imaging modality remains largely dependent on the site and must be based on the expertise and the comfort of surgeons and radiologists.

Practically, ultrasound and scintigraphy are the most frequently used modalities in the first line, despite some limitations due to associated thyroid pathologies for example. The 4D-CT has recently emerged as a precise imaging test which is useful especially in small adenomas, ectopic location, multiple adenomas, and in cases of reintervention [1,2].

Our study then focused on the contribution of 4D-CT in the diagnosis of parathyroid adenoma. We first present the place of 4D-CT compared to other imaging methods, then we present our prospective study which evaluates the effectiveness of 4D-CT in the preoperative detection of parathyroid adenomas, and we compare it to ultrasound.

A parathyroid gland is usually not visible on imaging. The vast majority of individuals have four parathyroid glands, two superior and two inferior, however 2.5 to 13% of individuals have ectopic glands [3].

The superior parathyroids originated from the 4th pharyngeal pouch. The resulting ectopic localizations are found in the retro-pharyngeal or retro-esophageal, and can sometimes extend further down the mediastinum.

The lower parathyroids come from the 3rd pharyngeal pouch with the thymus. The resulting ectopic localizations descend to the anterior mediastinum. A minority presents a stopped descent, and can be found near the carotid space.

Primary hyperparathyroidism is 2 to 4 times more common in women than in men, it often occurs between 50 and 70 years of age.

The etiologies involved include single adenoma (89%), glandular hyperplasia (6%), double adenoma (4%) and parathyroid cancer (1%). Most cases are sporadic [4].

The asymptomatic type remains the most common, circa 85%, however symptomatic patients are at risk for osteoporosis and pathological fractures, nephrolithiasis, pancreatitis, peptic ulcer, renal dysfunction, and cardiovascular diseases [5].

The diagnosis is based on laboratory findings. Definitive treatment is minimally invasive

Samer Abi-Khalil<sup>1,2</sup>,  
 Mohammad Rida<sup>1,2\*</sup>,  
 Elias El-Haddad<sup>1,2</sup>,  
 Lina Menassa  
 Moussa<sup>1,2</sup>, Noel Aoun<sup>1,2</sup>

<sup>1</sup>Medical Imaging Department, Hôtel-Dieu de France Hospital, Alfred-Naccache Avenue, Achrafieh, BP 16-6830, Beirut, Lebanon  
<sup>2</sup>Department of Medicine, Saint Joseph University, Damascus Road, Riad El Solh, BP 11-5076, Beirut, Lebanon  
 \*Author for correspondence  
 mohammad.ryda@gmail.com

parathyroidectomy. This technique represents benefits, namely shorter surgical procedure and hospital stay, local anesthesia, less post-operative pain, and an aesthetic scar [6].

The objective of preoperative imaging is to locate the adenoma in order to guide the surgical procedure, with a success rate of over 95%. The 4D-CT is the most recent imaging modality. 55% of radiologists know this technique and only 10% use it as a first-line [7,8]. 4D stands for “four dimensions”, three of which correspond to the three planes, and the last “D” corresponds to the time which defines the enhancement dynamic. It is made up of 3 phases :

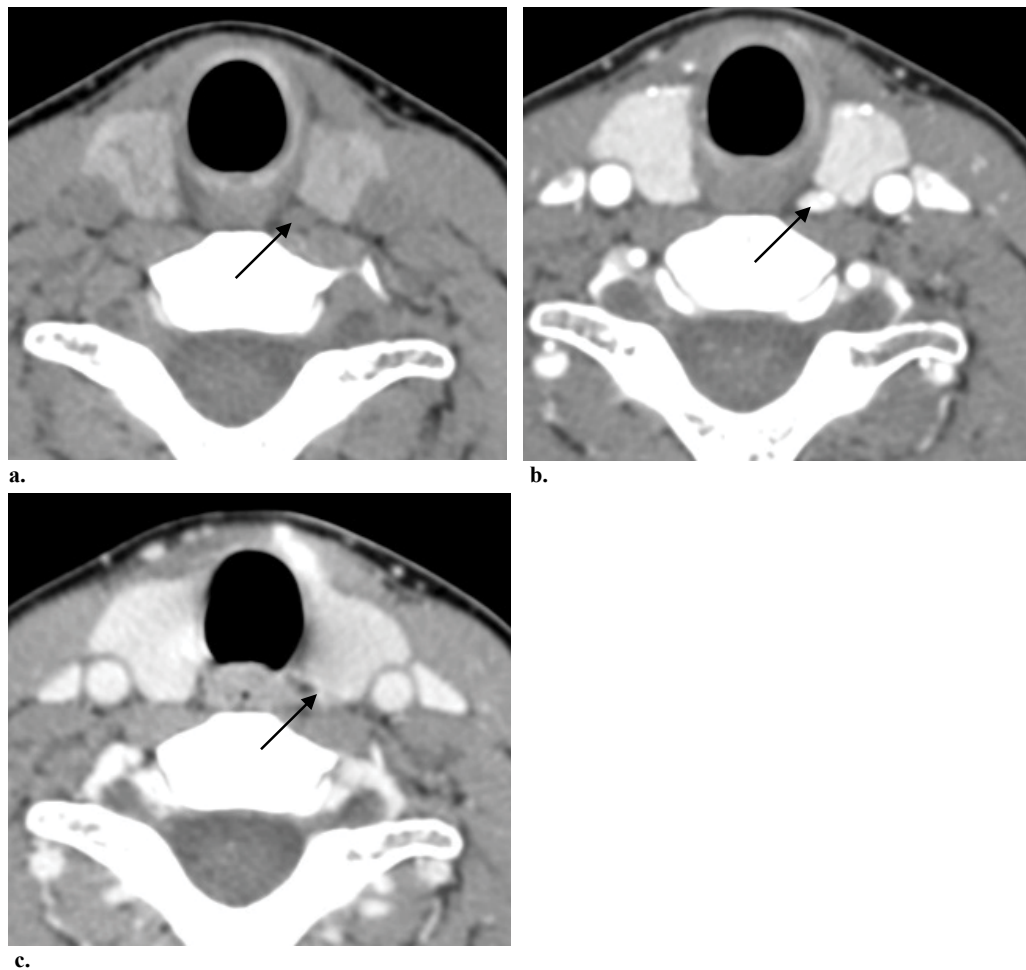
- Nonenhanced phase - IV- : It covers the thyroid from the hyoid bone to the clavicles. Its purpose is to differentiate the adenoma from the thyroid, the latter has a higher density.
- Arterial - IVa and venous delayed - IVv phases : These are performed 30 seconds and 80 seconds respectively after the start of contrast injection, from the angle of the

mandible to the carina in order to include all potential ectopic adenoma locations [9].

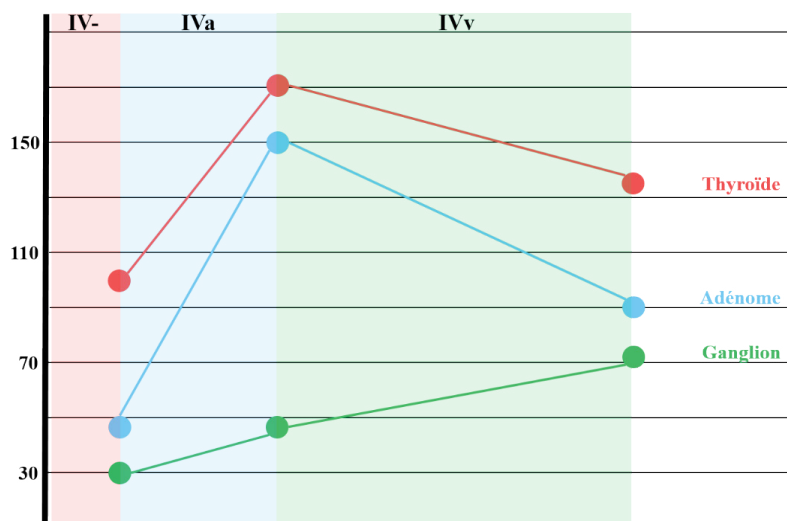
The characteristic 4D-CT appearance of a parathyroid adenoma is a nodule with lower density than the thyroid in IV-, with an enhancement peak in IVa, and a washing out in IVv (Figure 1). This enhancement dynamic allows the differentiation of the thyroid whose enhancement pattern is similar but with a higher density in IV- , and lymph nodes whose enhancement is progressive (Figure 2). A vascular pedicle is seen on 4D-CT in 2/3 of the adenomas [10]. When present, it constitutes the “polar vessel sign” and increases the radiologist’s confidence (Figure 3).

There is no accepted algorithm used for the exploration of parathyroid adenoma. The three main imaging methods used are ultrasound, scintigraphy and the 4D-CT; their sensitivities vary between studies. The choice of imaging is largely based on the choice of the surgeon and the skills and experience of radiologist.

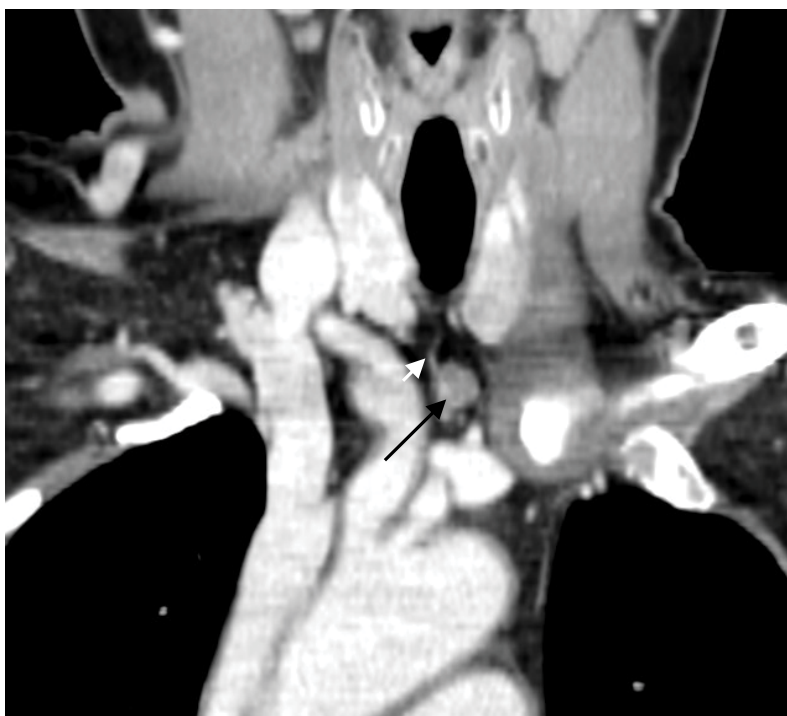
However, 4D-CT is a quick exam and has better



**Figure 1.** a: phase IV-showing the adenoma in lower attenuation than the thyroid; b: phase IVa showing the adenoma in its enhancement peak; c: phase IVv showing partial washing out of the adenoma.



**Figure 2.** Enhancement Dynamic red for thyroid, blue for parathyroid adenoma and green for lymph node.



**Figure 3.** The "polar vessel sign": The adenoma (arrow) with its vascular pedicle (arrowhead).

spatial resolution. It has a higher sensitivity in detecting small and ectopic adenomas (Figure 4), the multigland disease [11-14] and in case of surgical re-intervention in Figure 5 [15,16], and associated thyroid disease (Figure 6). However, this technique has some limitations especially the artefacts associated with the iodinated contrast concentrated in the neck veins which may mask adjacent structures (Figure 7).

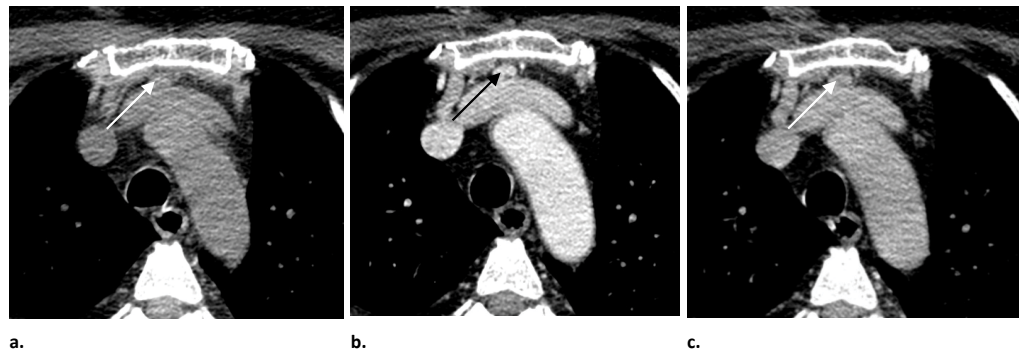
A meta-analysis published the sensitivity and Positive Predictive Value (PPV) of ultrasound, scintigraphy and 4D-CT, which were respectively 76.1% and 93.2% for ultrasound, 78.9% and

90.7% for scintigraphy, and 89.4% and 93.5% for 4D-CT [15].

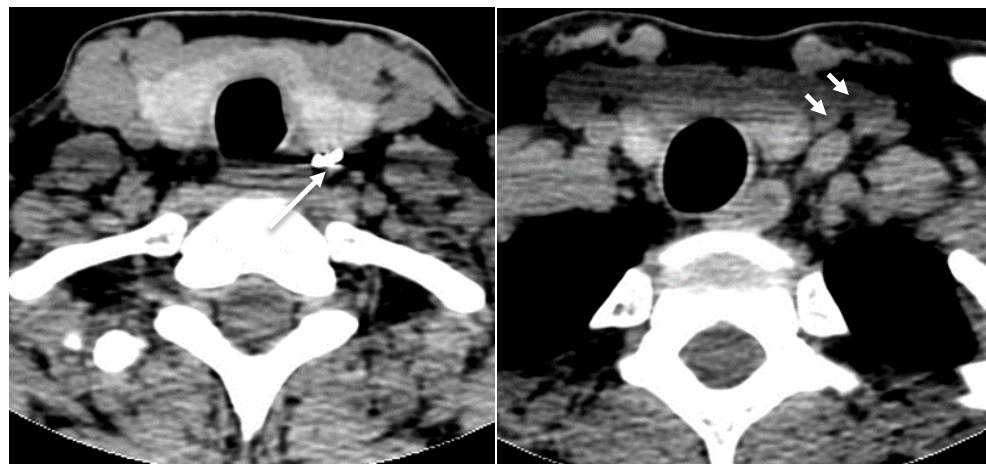
## Materials and Methods

### ■ Recruitment and data collection

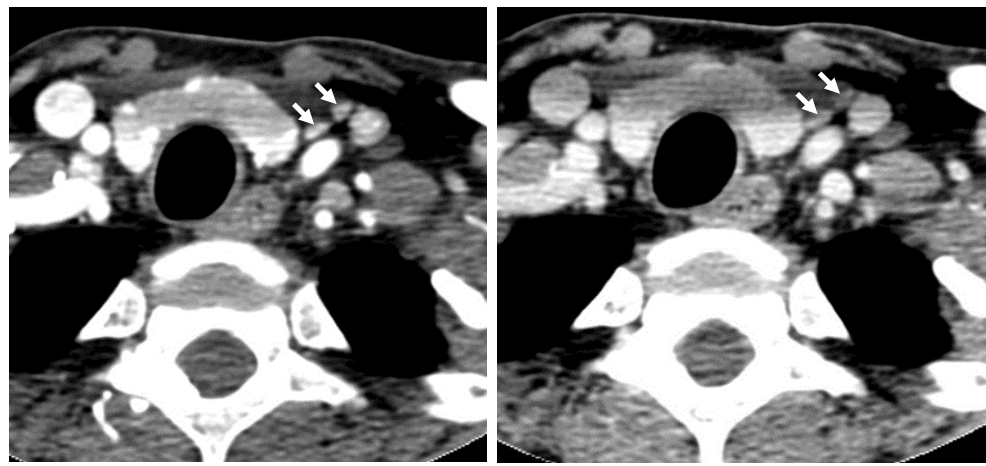
We present a prospective study of all patients referred for a scan for investigations in the context of primary hyperparathyroidism since 1st March 2019 after the agreement of the ethics committee. They all had a CT scan some had an ultrasound already done. The scanners were performed on a GE Light Speed 64-Slice scanner, 4D-CT technique, with an intravenous injection at the



**Figure 4.** Small adenoma at retro-sternal location (arrow) not seen on ultrasound; a: IV-, b: IVa, c: IVv.



**a.** **b.**



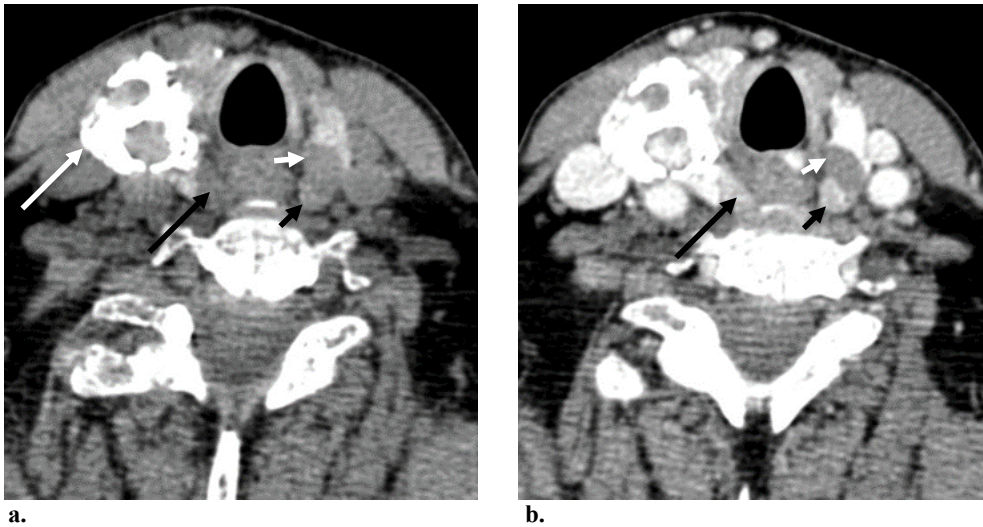
**c.** **d.**

**Figure 5.** a: IV-showing surgical clips (arrow) in a patient with surgical history of left parathyroidectomy; b: IV- ; c: IVa showing 2 adjacent small adenomas (arrowhead); d: IVv showing washing out of both adenomas (arrowhead).

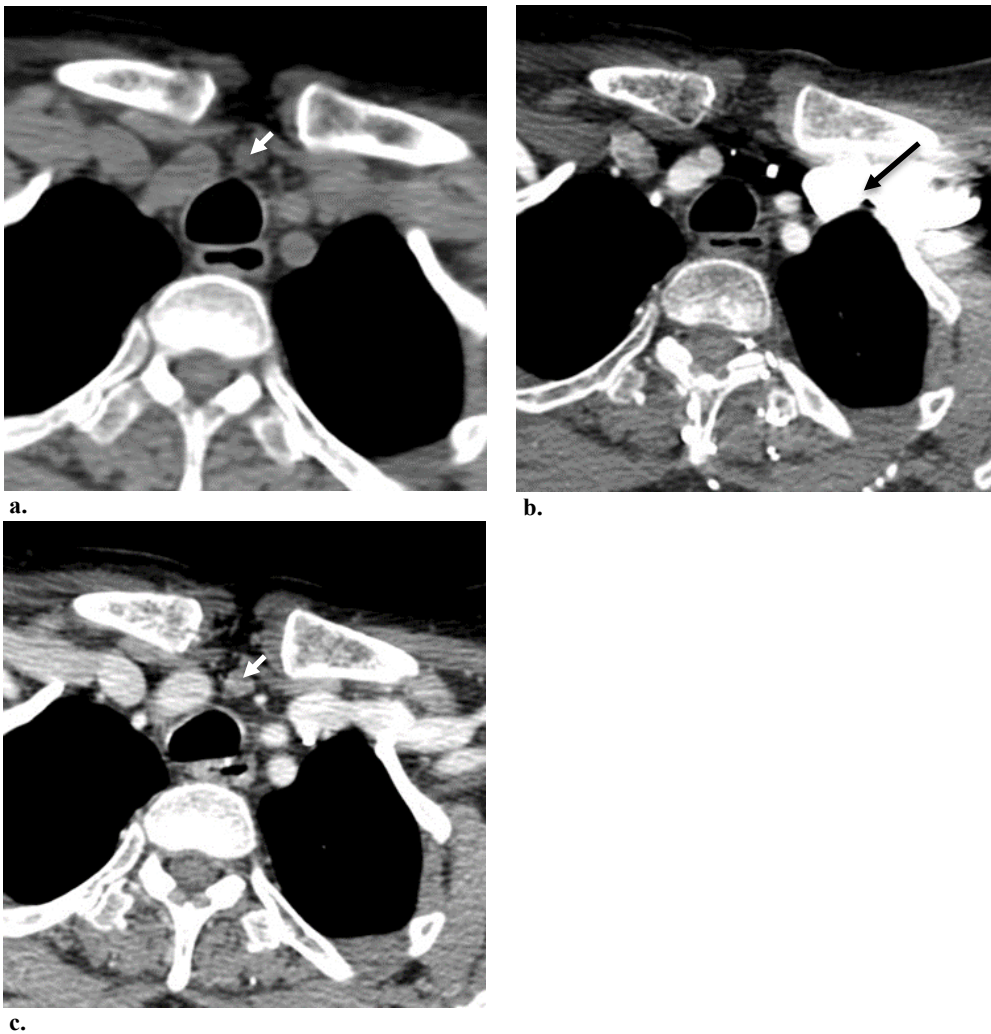
elbow of 80 ml of iodine contrast (Omnipaque 350) in a 20 G intravascular catheter at a rate of 4,5 ml/sec followed by 20 ml of Normal Saline. The ultrasounds were performed on Aixplorer Supersonic, with the Superlinear SL18-5 probe, bandwidth 5 to 18 MHz.

A parathyroid adenoma was defined as a nodule that enhances with an arterial peak and venous washing out, against a gradual progressive enhancement for the lymph nodes. It was clarified that the adenoma has low attenuation compared to thyroid the nonenhanced phase. A "polar vessel sign" was noted if viewed. It was clarified whether the adenoma was eutopic or ectopic.





**Figure 6.** Calcified goiter preventing ultrasound exploration in locating the parathyroid adenoma. The 4D-CT detected 2 latero-esophageal adenomas, one on each side. On the right, it is posteromedial (black arrow) to the calcified thyroid nodule (white arrow). On the left, it is posterior (black arrowhead) to a thyroid cyst (white arrowhead). The two nodules have low attenuation compared to the thyroid stroma in IV- (a), and show a peak enhancement in IVa (b).



**Figure 7.** Ectopic parathyroid adenoma visualized in IV- (arrowhead in a) and in IVv (arrowhead in c), but masked in IVa by hardening artefacts due to accumulation of contrast in the left innominate venous trunk (arrow in b).

All patients were followed for surgery, only operated patients having an anatomopathological result were included.

The anatomopathological result was considered the gold standard to confirm the imaging results.

The data that has been collected are:

- Name, first name
- PIN (patient identification number)
- Age and sex
- Calcemia, phosphoremia, and serum PTH pre and postoperative
- Result of previous imaging
- 4D-CT result
  - Judging Criteria
- a+ : if a parathyroid adenoma was evoked on imaging, the image was noted a+.
- a- : if an image suggestive of parathyroid adenoma and noted a+ on a given imaging did not correspond to an adenoma on another imaging, it was noted a- on the other imaging.
- A- : if an image noted as a+ on at least one imaging did not correspond to a parathyroid adenoma in anatomopathological result , it was noted as A-.
- oEu : an evoked or confirmed adenoma was noted Eu if its location was eutopic.
- oEc : an evoked or confirmed adenoma was noted Ec if its location was ectopic.

The SPSS (Statistical Package for the Social Sciences) software Version 23 was used for statistical analysis. A descriptive analysis concerning the variables studied was carried out: frequencies and percentages were calculated. The rate of false positives, also the Se and the a PPV for the diagnosis of parathyroid adenoma were calculated in the statistical study.

## Results

29 patients were included, 11 men (38%) and 18 women (62%), with an average age of 55 years. All had primary hyperparathyroidism. Of the 29 patients, 6 had 2 adenomas A+ each, and 23 had 1 adenoma A+ each. In sum, 35 parathyroid adenomas were A+, including 16 Eu and 19 Ec (54.3%). An ultrasound was performed in 26 patients, of which 6 patients had 2 adenomas A+ each. A total of 32 parathyroid adenomas A+ were tested on ultrasound. Ultrasound detected 12 adenomas of 32, with

	Anatomopathology			Total	
		A-	A+		
	Ultrasound	a-	0		20
	Ultrasound	a+	1	12	13
Total			1	32	33

**Table 2. Ultrasound Results after stratification according to the location of the adenomas.**

	Location				
	Eu		Ec		
	Anatomopathology				
	A-	A+	A-	A+	
Ultrasound	a-	0	4	0	16
	a+	1	11	0	1

**Table 3. 4D-CT Results.**

	Anatomopathology			Total
		A-	A+	
4D-CT	a-	0	1	1
	a+	0	34	34
Total		0	35	35

**Table 4. 4D-CT Results after stratification according to the location of the adenomas.**

	Location				
	Eu		Ec		
	Anatomopathology				
	A-	A+	A-	A+	
4D-CT	a-	0	1	0	0
	a+	0	15	0	19

an additional 1 false positive, i.e. a Se of 37.5% (95% CI: 21.1 - 56.3%) and a PPV of 92.3% (Table 1).

After stratification according to the location of the adenomas, the ultrasound could detect 11 of 15 eutopic adenomas with a Se of 73.3% (95% CI: 44.9 - 92.2%) and PPV of 91.7%, but only 1 of 17 ectopic adenomas with a Se of 5.9% (95% CI: 0.1 - 28.7%) (Table 2).

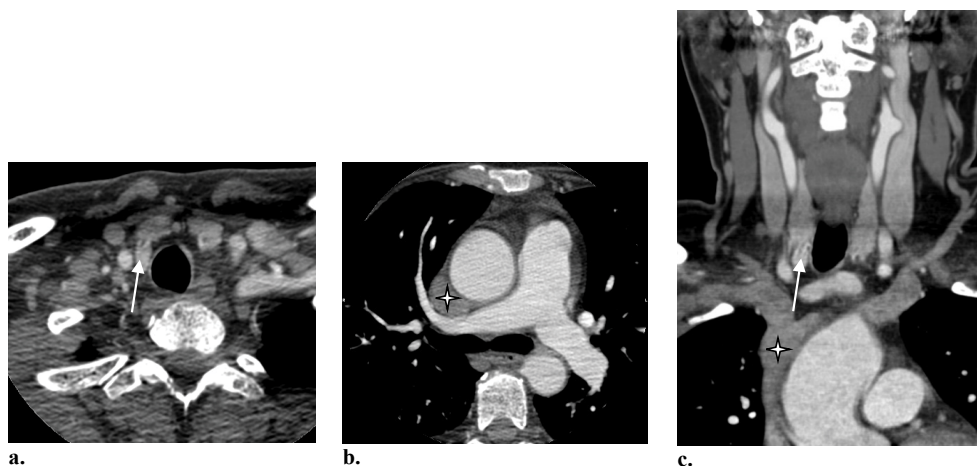
4D-CT detected 34 adenomas of 35 without false positive, i.e. a Se of 97.1% (95% CI: 85.1 - 99.9%) (Table 3).

After stratification according to the location of the adenomas, the 4D-CT was able to detect 19 of 19 ectopic adenomas, and 15 of 16 eutopic adenomas, resulting in a Se of 100% for ectopic adenomas and 93.7% for eutopic adenomas (Table 4).

The average size (measured in the major axis only) of the adenomas detected by 4D-CT was 10.6 mm, with a minimum of 5 mm and a maximum of 26 mm.

## Discussion

Among the imaging modalities used in the localization of parathyroid adenoma, 4D-CT is the most recent technique; it meets the requirements of surgeons in order to reduce post-operative complications such as



**Figure 8.** Parathyroid adenoma appended to the posterior border of the lower pole of the right thyroid lobe (arrow in a and c); no contrast in the superior vena cava (asterisk in b and c).

hypoparathyroidism and post-operative scar. It is particularly useful when the other modalities are negative. Its place will be better defined in the literature as we develop more studies and experience with the technique.

In our series, the injection was performed in the lower limb in a woman with bilateral mastectomy. To ensure a first concentrated passage of contrast product, we injected 100 ml of saline instead of 20 ml, and in order not to miss the optimal moment for arterial acquisition, we used the “smart prep”. There were no artifacts due to the contrast product. Thus, this technique can be adopted to overcome this limitation (Figure.8).

Some institutions omit one of the three acquisitions in order to reduce irradiation [17,18], but the Se of detection decreases in this case to 58% [19], and so an adenoma could be evoked with less confidence. This is especially true for small adenomas.

Thus, the characteristic signs of the adenoma are looked for on the three phases. They are analyzed twice, first each distinctly as a separate sign, then together as a same entity to trace the enhancement dynamic, hence the interest of the 4th “D” in the name of the technique. Therefore, we have opted in our institution to standardize the technique of 4D-CT.

No patient in our series underwent parathyroid standard invasive surgical exploration. In our study, the 4D-CT proved to be of high performance, especially in ectopic locations where its role is essential, with an overall Se of 97.1% which increases to 100% when it is an ectopic location of adenomas. In the literature, Se fluctuated in the first studies on 4D-CT between 73% and 93% [20], it is currently around 96%

and consistent with our numbers. Two points are to be lifted, the first is static; the 4D-CT is very performant, and the second is dynamic; its performance has improved with experience.

We admit that the combination of ultrasound and 4D-CT is beneficial for a better preoperative detection of parathyroid adenomas; 4D-CT being performed as a complement of ultrasound to look for an adenoma not seen on the latter. However, a more targeted function could be attributed to ultrasound if it is the one performed as a complement to confirm a doubtful small adenoma seen on 4D-CT.

Being radiologist dependent, ultrasound has proven to be an easily accessible method of exploration with rapid results. However, with a Se of 37.5%, it is only effective for eutopic adenomas where Se amounts to 73.3% - a value consistent with those in the literature around 76%. This variability between Se is mainly due to the limitation of the radiologist’s field of exploration and the difficult access to mediastinal lesions, hence the need for 4D-CT in case of any clinical or ultrasound doubt. Nevertheless, the probability that a lesion evoked on ultrasound is an adenoma is very high whether it is all adenomas included or only eutopic locations, with respective PPVs of 92.3% and 91.7%, values consistent with the literature. Which go up to 93.2%.

This leads us in practice that a positive diagnostic ultrasound may be sufficient as a preoperative workup.

The limitations of our study include:

- A relative low number of patients, due to the lack of reputation of this technique among endocrinologists and surgeons

- A selection bias since all recruited patients and the examinations are done in the same institution
- An observation bias due to the fact that even if the study is prospective as to the anatomopathological diagnosis of adenoma, among the patients who performed an ultrasound, the majority of them had an established ultrasound result when they presented for 4D-CT.

---

### Conclusion

Of course, our study was carried out in the same institution, and therefore the selection is biased, but this ensured the standardization of the 4D-CT technique and reduced the discrepancy in the interpretations. It has shown that 4D-CT is very efficient in the detection and the localization of parathyroid adenoma preoperatively. Its dominant role is especially in its combination

with ultrasound, especially when the ultrasound fails to find any parathyroid adenoma. Its usefulness has increased with more studies are done, but its first-line place will require more new studies to acquire other relevant findings. We were able to add an essential point to the technique to overcome the artefact due to the contrast product: the injection into the lower limb. In terms of surgical management, the benefits of 4D-CT do not require reinforcement; it has reduced the risk of complications of therapeutic procedures.

---

### Declaration of Conflicting Interests

All authors have no conflict of interest to disclose.

---

### Funding

None.



## References

1. Kuzminski SJ, Sosa JA, Hoang JK. Update in parathyroid imaging. *Magn Reson Imaging Clin N Am.* 26(1): 151-166 (2018).
2. Cham S, Sepahdari AR, Hall KE, et al. Dynamic Parathyroid Computed Tomography (4DCT) Facilitates Reoperative Parathyroidectomy and Enables Cure of Missed Hyperplasia. *Ann Surg Oncol.* 22(11): 3537-42 (2015).
3. Akerstrom G, Malmaeus J, Bergstrom R. Surgical anatomy of human parathyroid glands. *Surgery.* 95(1):14-21(1984)
4. Ruda JM, Hollenbeak CS, Stack Jr. BC. A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. *Otolaryngol Head Neck Surg.* 132(3): 359-372 (2005).
5. Rubin MR, Bilezikian JP, McMahon DJ, et al. The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. *J Clin Endocrinol Metab.* 93(9): 3462-70 (2008).
6. Minisola S, Cipriani C, Pepe J. Parathyroid imaging and successful Parathyroidectomy. *Clin Endocrinol.* 83(5): 671-7 (2015).
7. Udelsman R, Donovan PI. Remedial parathyroid surgery: Changing trends in 130 consecutive cases. *Ann Surg.* 244(3): 471-9 (2006).
8. Hoang JK, Williams K, Gaillard F, et al. Parathyroid 4D-CT: Multi-institutional International Survey of Use and Trends. *Otolaryngol Head Neck Surg.* 155(6): 956-60 (2016).
9. Hoang JK, Sung WK, Bahl M, et al. How to perform parathyroid 4D CT: tips and traps for technique and interpretation. *Radiology.* 270(1): 15-24 (2014).
10. Ghaehri BA, Koslin DB, Wood AH, et al. Preoperative ultrasound is worthwhile for reoperative parathyroid surgery. *Laryngoscope.* 114(12): 2168-71 (2004).
11. Kukar M, Platz TA, Platz TA, et al. The use of modified four-dimensional computed tomography in patients with primary hyperparathyroidism: An argument for the abandonment of routine sestamibi single-positron emission computed tomography (SPECT). *Ann Surg Oncol.* 22(1): 139-45 (2015).
12. Galvin L, Oldan JD, Bahl M, et al. Parathyroid 4D CT and Scintigraphy: What Factors Contribute to Missed Parathyroid Lesions?. *Otolaryngol Head Neck Surg.* 154(5): 847-53(2016).
13. Sepahdari AR, Bahl M, Harari A, et al. Predictors of Multigland Disease in Primary Hyperparathyroidism: A Scoring System with 4D-CT Imaging and Biochemical Markers. *AJNR Am J Neuroradiol.* 36(5): 987-92 (2015).
14. Mortenson MM, Evans DB, Lee JE, et al. Parathyroid exploration in the reoperative neck: improved preoperative localization with 4D-computed tomography. *J Am Coll Surg.* 206(5): 888-95 (2008).
15. Cheung K, Wang TS, Farrokhyar F, et al. A meta-analysis of preoperative localization techniques for patients with primary hyperparathyroidism. *Ann Surg Oncol.* 19(2): 577-83 (2012).
16. Hamidi M, Sullivan M, Hunter G, et al. 4D-CT is Superior to Ultrasound and Sestamibi for Localizing Recurrent Parathyroid Disease. *Ann Surg Oncol.* 25(5): 1403-09 (2018).
17. Kluijfhout WP, Pasternak JD, Beninato T, et al. Diagnostic performance of computed tomography for parathyroid adenoma localization; a systematic review and meta-analysis. *Eur J Radiol.* 88: 117-28 (2017).
18. Noureldine SI, Aygun N, Walden MJ, et al. Multiphase computed tomography for localization of parathyroid disease in patients with primary hyperparathyroidism: How many phases do we really need? *Surgery.* 156(6): 1300-6 (2014).
19. Campbell MJ, Sicuro R, Alseidi A, et al. Two-phase (low-dose) computed tomography is as effective as 4D-CT for identifying enlarged parathyroid glands. *Int J Surg.* 14: 80-4 (2015).
20. Lundstroem AK, Trolle W, Soerensen CH, et al. Preoperative localization of hyperfunctioning parathyroid glands with 4D-CT. *Eur Arch Otorhinolaryngol.* 273(5): 1253-59 (2016).