DOI: 10.7860/NJLM/2025/75735.2905

Case Series

Pathology Section

Unanticipated Detection of Subcentimetric Papillary Thyroid Carcinoma: A Series of 10 Cases from a Tertiary Care Hospital of Eastern Odisha, India

PRATIKSHA MISHRA[1], CHANDRAPRAVA MISHRA[2], ITISHREE RANA[3], LITY MOHANTY[4], RUTU RAJESWARI DALEI[5]

ABSTRACT

Papillary Thyroid Carcinoma (PTC) is the most common thyroid malignancy seen among children and adults exposed to ionising radiation. The term "microcarcinoma," previously recognised as a different subtype, has been currently removed from the 5th edition of World Health Organisation (WHO) classification of thyroid tumours in the histomorphological classification, since currently the tumour size is now considered important for assessing aggressiveness. This is a retrospective cross-sectional study carried out in the histopathology section of Department of Pathology at SCB Medical College and Hospital, Cuttack, Odisha, India. The study spanned a total duration of 24 months, from June 2022 to June 2024. All the histopathologically confirmed cases of PTCs based on recent 5th edition of WHO classification of thyroid tumours were collected and analysed. A total of 10 (aged 23 to 54 years) with a mean age of 36.6 years, were studied. The majority of the patients were female, with male to female ratio of 3:7. All 10 cases exhibited tumour sizes less than or equal to 1 cm in diameter. The ratio of left to right lobe involvement was 7:3. Eight cases were diagnosed as the classic subtype, while two other cases were diagnosed as follicular invasive encapsulated type and tall cell subtype of PTC. In present case series, authors observed that it is must to identify all the non neoplastic and neoplastic lesions based on architectural and nuclear features and identify the presence of microfoci measuring less than or equal to 1 cm in diameter, as these subtypes may be aggressive and proper intervention may be required.

Keywords: Lonising radiation, Papillary microcarcinoma, Subcentimetric lesions

INTRODUCTION

Thyroid neoplasms have been broadly categorised into follicular cell derived neoplasms, C-cell-derived neoplasms, mixed varieties, and others, according to the latest 2022 WHO classification of thyroid tumours [1]. The PTC the most common epithelial malignancy, constitutes approximately 80% of all thyroid tumours [2]. The incidence of PTC is on rise due to history of repeated exposures to high-dose ionising radiation during childhood [3]. The PTC is predominantly seen in iodine sufficient regions and in patients with previously diagnosed benign thyroid diseases [2-4]. In the 4th edition of WHO thyroid tumours, papillary thyroid microcarcinoma was considered a different entity [5]. However, current classification states the importance of histomorphological classification rather than the tumour size and hence has removed the term "microcarcinoma." Herein, authors discuss a case series of 10 cases of histopathologically confirmed papillary carcinoma of thyroid of less than or equal to 1 cm in diameter and the removal of the term micropapillary carcinoma from the latest 5th edition of WHO classification of thyroid tumours [6].

CASE SERIES

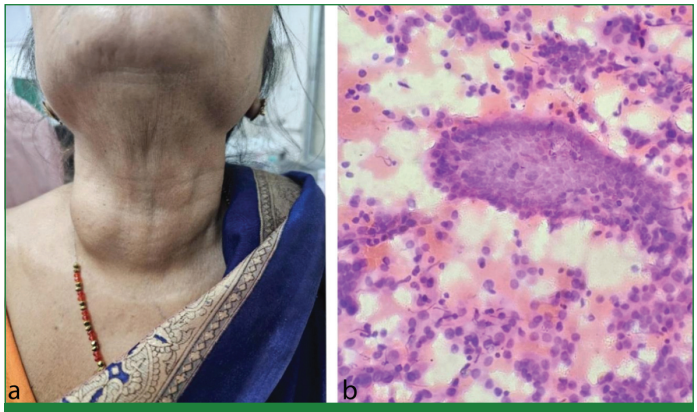
A retrospective cross-sectional study was carried out in the Department of Pathology, SCB Medical College and Hospital, Cuttack, Odisha, India during a period of 24 months (from June 2022 to June 2024). Complete history, detailed clinical examination, and radiological (ultrasonography of neck) details of all PTC cases (a total of 24 cases) were collected and analysed. The thyroidectomy samples received, irrespective of the type, were fixed in 10% neutral buffered formalin overnight grossed adequately. Tissue processing was done using Leica's automated tissue processor or histokinette, following which microsections were stained by Haematoxylin and Eosin (H&E) for Histopathological Examination (HPE).

Inclusion criteria: Cases histopathologically diagnosed as PTC, with macroscopically visible tumour were measuring less than or equal to 1 cm in diameter, were included in the study.

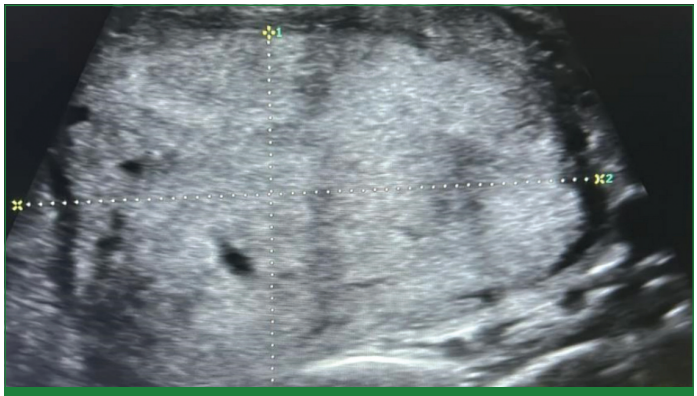
Exclusion criteria: Non neoplastic and other neoplastic lesions of thyroid, apart from PTC, patients lost to follow-up, were excluded from the study.

The mean age of patients was 36.6 years, with age varying from 23 to 54 years. Majority of the patients were females, with male to female ratio of 3:7. All the cases were sent for Fine Needle Aspiration Cytology (FNAC) of thyroid swelling [Table/Fig-1a], along with hormonal assay that showed low free T3 and T4 levels and high TSH levels in seven cases, while the rest were euthyroid. Nine out of 10 cases were diagnosed as benign (The Bethesda System- TBS Category II) in FNAC. However, one case showed an arrangement of thyroid follicular cells in papillary fragments, raising the suspicion of papillary thyroid carcinoma (PTC), and was cytologically diagnosed as a suspicion of malignancy (TBS Category V) [Table/Fig-1b]. Ultrasonography of the neck in all the cases revealed solitary or multiple hypoechoic nodules of subcentimetric size involving the thyroid gland [Table/Fig-2]. Case No. 4 had her previous nodulectomy 15 years prior and presented with an intracranial mass which showed features of metastatic carcinomatous deposits in the intracranial parenchyma. In present setting, the ratio of left lobe to right lobe involvement was 7:3, with case No. 5 involving the isthmus along with the left lobe. Cases No. 5 and 9 showed multifocal involvement, while the others had persistent unifocal involvement of the thyroid gland. Grossly, [Table/Fig-3], thyroid gland showed the presence of solitary or multiple solid greyish-white nodules measuring less than or equal to 1 cm in diameter, with three cases grossly showing areas of haemorrhage. Microscopically classical cases displayed the presence of true papillae, having finger-like projections with fibrovascular core [Table/Fig-4a]. Case No. 1, 3, 6, 8, 9, and 10, in addition to the classic features of PTC, showed

features of Hashimoto thyroiditis with lymphoplasmacytic infiltration [Table/Fig-4a] and single focus showing lymphoid follicle with germinal centre [Table/Fig-4b]. The characteristic nuclear features of PTC was seen in all cases which included nuclear enlargement, nuclear membrane irregularities and chromatin clearing, the typical Orphan Annie nuclei [Table/Fig-4c,d]. Lymphovascular invasion was found in Cases No. 2 and 7, with case No. 7 additionally showing the presence of atypical mitosis (<3/10 HPF). After histological subtyping, eight out of 10 cases were diagnosed as classic subtype, with Case No. 5 diagnosed as invasive follicular encapsulated subtype and Case No. 10 diagnosed as the tall cell subtype of PTC, based on persistence of tall cells (height is three times the width) in more than 30% of the tumour cells [Table/Fig-4e]. Invasive encapsulated follicular variant of papillary carcinoma shows tumour infiltration beyond the capsule [Table/Fig-4f]. All 10 cases of PTC, which were found to have tumour sizes less than or equal to 1 cm in diameter, are listed in [Table/Fig-5]. Authors have followed up on all the cases, although two have been lost to follow-up. Currently, two cases have successfully completed their chemotherapy regimens and are doing well. The remaining cases are still undergoing treatment till the writing this report.

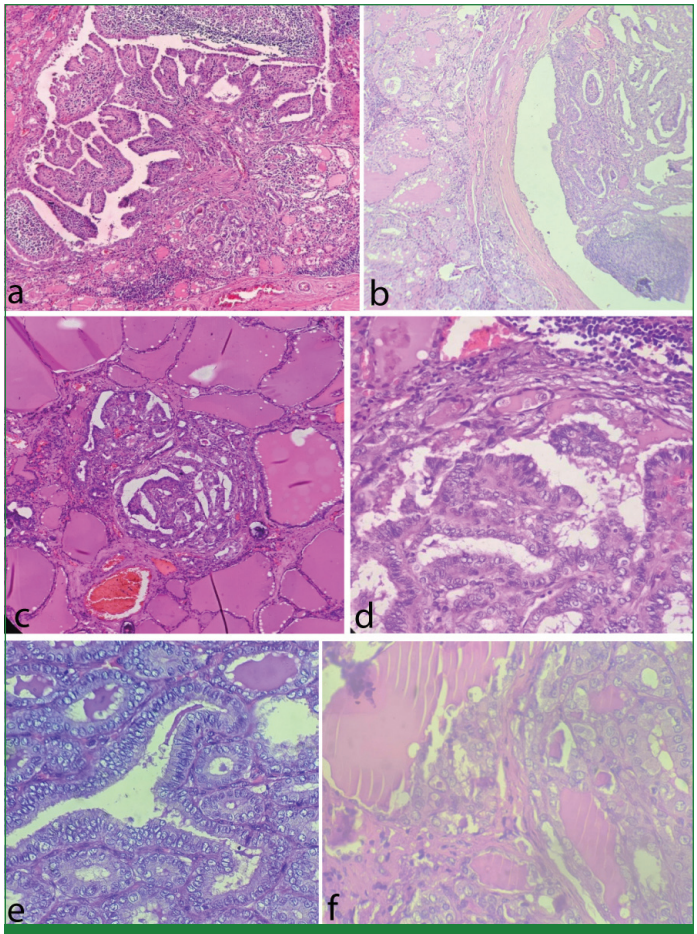


[Table/Fig-1]: a) Case no. 3, 47-year-old female presented with firm non tender multinodular goiter altogether measuring 4×3 cm , more towards right-side. b) Thyroid follicular cells arranged in papillary frond showing distinct anatomical border. Background showing lymphocyte infiltration within the follicular cells (TBS V) (H&E, 400x).



[Table/Fig-2]: Ultrasonography of neck shows presence of solitary subcentimetric hypoechoeic thyroid nodule.

[Table/Fig-3]: Hemithyroidectomy specimen showing multiple small nodules largest measuring 0.6 cm in diameter.



[Table/Fig-4]: a) Photomicrograph shows a small focus of arborising papillae with well with nuclear features of papillary thyroid carcinoma on a background of autoimmune lymphocytic thyroiditis (H&E, 400x). b) Histopathology (HP) shows PTC and a well-defined lymphoid follicle with germinal centre suggesting PTC with associated hashimoto thyroiditis (lower right corner) (H&E, 100x). c) Photomicrograph shows focus of papillae with nuclear features of PTC over extensive areas showing colloid filled thyroid follicles suggesting PTC with colloid goiter (H&E, 400x). d) HPE shows tumour cells having moderate eosinophilic cytoplasm, nuclear enlargement, overlapping, and chromatin clearing with irregular nuclear contour and nuclear grooves in few cells (H&E, 400x). e) HP shows thyroid follicular cells in papillary and follicular pattern having height more than three times the width of tumour cells and nuclear clearing, grooving shows PTC with tall cell change (H&E, 400x). f) HP shows tumour extension into the adjacent thyroid tissue, beyond the well-defined fibrocollagenous capsule suggesting invasive encapsulated follicular variant of papillary carcinoma (H&E, 400x).

DISCUSSION

The PTC is the most common malignant neoplasm in children and adults. With the advanced techniques like thyroid imaging { Ultrasonography (USG) neck and radionuclide scans}, FNAC, and molecular techniques, incidence rates have seen a rapid decline; though it still prevails in the developing countries [7-9]. In present setting, PTC shows a female predominance with male-to-female ratio of 3:7, which is similar to other studies [10]. It is usually diagnosed in third to fifth decades of life, with mean age of approximately 40 years, similar to present study, which shows a mean age range of 36.6 years, although PTC can occur at any age [11]. The PTC may present with a painless thyroid enlargement or may present with metastasis. Multifocality is significantly associated with an increased risk of recurrence in patients with PTC [12,13].

The FNAC plays a key role in guiding clinicians towards diagnosis of PTC. In FNAC, PTC shows tumour cells arranged in monolayered sheets and characteristic papillary fronds. A characteristic feature is presence of an anatomical border, with distinct lining on three sides by cuboidal cells. It presents with a set of distinctive nuclear features, which are more prominent on biopsy. On biopsy, PTC shows delicate papillae-like structures having broad fibrovascular cores. The nuclear features include nuclear overcrowding and enlargement when compared to surrounding normal thyroid follicular epithelial nuclei. Individual tumour cells show powdery chromatin, irregular nuclear borders, nuclear pseudo-inclusions,

Case no.	Age and Gender	Clinical diagnoses	Tumour site	Tumour focality	Tumour size (largest dimension in cm)	Gross findings (cut section)	Necrosis, LVI, PNI	Histopathological diagnosis
1.	30 year and male	Grave's disease	Left lobe	Unifocal	0.6	Greyish white areas with haemorrhage	Not seen	Papillary thyroid carcinoma, classic subtype with autoimmune thyroiditis
2.	42 year and female	Goitre	Right lobe	Unifocal	1	Meaty brown with single homogenous nodule	LVI present	Papillary thyroid carcinoma, classic subtype with colloid goitre
3.	47 year and female	Multi nodular goitre	Left lobe	Unifocal	0.7	Solid, variegated areas of haemorrhage and calcification	Not seen	Papillary thyroid carcinoma, classic subtype with Hashimoto thyroiditis
4.	54 year and female	Follicular carcinoma of thyroid	Left lobe	Unifocal	0.3	Greyish white areas with haemorrhage	Not seen	Papillary thyroid carcinoma, classic subtype with colloid goiter
5.	27 year and female	Papillary thyroid carcinoma	Left lobe and isthmus	Multifocal	0.2	Homogenous whitish nodule	Not identified	Invasive encapsulated follicular variant of papillary carcinoma
6.	23 year and male	Papillary thyroid carcinoma	Left lobe	Unifocal	1	Homogenous, calcified nodule	Not identified	Papillary thyroid carcinoma, classic subtype with Hashimoto thyroiditis
7.	49 year and female	Goitre	Left lobe	Unifocal	0.5	Multiple greyish white nodules	LVI present with mitosis (<3/10 HPF)	Papillary thyroid carcinoma, classic subtype with colloid goitre
8.	38 year and male	Multi nodular goitre	Right lobe	Unifocal	0.8	Firm homogenous nodule	Not seen	Papillary thyroid carcinoma with classic subtype with Hashimoto thyroiditis
9.	33 year and female	Papillary thyroid carcinoma	Right lobe	Multifocal	0.5 and 0.2	Two small firm nodules	Not seen	Papillary thyroid carcinoma, classic subtype with autoimmune thyroiditis
10.	32 year and female	Papillary thyroid carcinoma	Left lobe	Unifocal	0.5	Solid homogenous nodule	Not seen	Papillary thyroid carcinoma, tall cell subtype with autoimmune thyroiditis

[Table/Fig-5]: Clinico-pathological parameters of papillary carcinoma of thyroid of subcentimetres size.
HPF: High power field; PNI: Perineural invasion; LVI: Lymphovascular invasion

grooving, and sometimes prominent nucleoli. There is presence of psammoma bodies and stringy ropy colloid, which are pathognomonic for PTC [14].

The fifth edition of WHO classification of endocrine tumours focusses on the need to histologically subtype the most commonly diagnosed PTC [12]. Subtyping is based on the combination of architectural features (solid, classic, or follicular pattern), cytological features (oncocytic, tall cell, hobnail, and columnar cell), and features of encapsulation (encapsulated, encapsulated follicular, and infiltrative follicular). Previously used criteria for subtyping included the tumour size; however, currently, all the tumours, irrespective of the tumour size, need to be subtyped histopathologically [15]. There are nine subtypes, in contrast to the 15 subtypes in WHO 4th edition.

Classic PTC with a papillary growth and distinct set of nuclear features. The infiltrative follicular variant of PTC shows variably sized follicles filled with deeply stained colloid, infiltrating into the surrounding thyroid parenchyma, often accompanied by sclerosis. The diffuse sclerosing subtype is characterised by diffuse involvement of one or both lobes by dense sclerosis, lymphoplasmacytic infiltrates, and numerous psammoma bodies. Warthin-like PTC shows oncocytic tumour cells lining the cores of the papillae, along with rich lymphoplasmacytic cells. Solid PTC is defined by having ≥50% of solid or trabecular growth. The PTCs with ≥75% oncocytic cells are defined as oncocytic PTC.

Tall-cell PTC presents tumour cells having eosinophilic cytoplasm, where the height of the cells is at-least three times the width, and should represent more than 30% of the tumour cells, represents a characteristic tram track appearance at low power [Table/Fig-4d]. The columnar cell subtype of PTC shows tall columnar cells with pseudostratified, hyperchromatic, oval to elongated nuclei, along with subnuclear vacuoles and cytoplasmic clearing. Hobnail PTC is defined as having ≥30% of the tumour cells exhibiting hobnail features, with variably sized papillae covered by cells with apically placed bulged nuclei.

Authors had a majority of classic PTC cases, totaling eight cases. Papillary microcarcinomas, previously referred to as papillary microtumour, occult, latent, or small papillary carcinomas, are no longer considered distinct variant anymore but are refer to all papillary carcinomas measuring equal to or less than 1 cm in diameter. Some studies have showed that "papillary thyroid microcarcinoma" is a preferable term for all tumours of subcentimeter size, whereas the term "micropapillary carcinoma" should refer to those showing the histological pattern of PTC with a predominance of micropapillary structures that lack fibrovascular cores, according to Basolo F et al., [13].

Subtypes of PTC that show a more aggressive clinical presentation include the tall cell, diffuse sclerosing, the solid, and the follicular subtypes [16]. Hence, it is usually recommended that all the PTC, including subcentimeter carcinomas- whether incidentally found in a thyroid gland removed for other reasons (e.g., multinodular goitre or autoimmune thyroiditis) or discovered clinically or through imaging (palpable, visible nodule)- must undergo subtyping to understand their indolent or aggressive presentation. All the subcentimetric carcinomas must undergo resection and be given radioactive iodine therapy to prevent further recurrence [17].

Although subcentimetric PTCs are no longer recommended to be simply referred to as "papillary thyroid microcarcinoma" without any additional subtype information, they must be histologically subtyped, as small subsets of these lesions have been reported to follow an aggressive clinical course similar to that of their large-sized counterparts [18].

CONCLUSION(S)

The PTC the most prevalent among all the malignant tumours of the thyroid, needs to be subclassified on the basis of proper histomorphological examination. It is of utmost importance to identify all the neoplastic and non neoplastic lesions and adequately examine it thoroughly to identify even a microfocus of malignancy, if present. So, WHO 2022 classification of thyroid tumours has recommended

subtyping all cases of PTC, irrespective of the tumour size, as some of the subtypes may present with worse outcomes. Therefore, it is essential to recognise all the subtypes on histological level and to identify presence of any microfocus during gross examination in order to predict the prognosis and behaviour of the tumour for appropriate management.

REFERENCES

[1] Jung CK, Bychkov A, Kakudo K. Update from the 2022 World Health Organization Classification of thyroid tumors: A standardized diagnostic approach. Endocrinol Metab (Seoul). 2022;37(5):703-18.
[2] Zhu X, Yao J, Tian W. Microarray technology to investigate genes associated with papillary thyroid carcinoma. Mol Med Rep. 2015;11(5):3729-33.
[3] Limaiem F, Rehman A, Mazzoni T. Papillary Thyroid Carcinoma. 2024 Mar 13. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.
[4] Al-Salamah SM, Khalid K, Bismar HA. Incidence of differentiated cancer in nodular goiter. Saudi Med J. 2002;23(8):947-52.
[5] WHO Classification of thyroid tumors, revised 4th edition, 2016 update.
[6] WHO classification of thyroid tumors, 5th edition, 2022 version.
[7] Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26(1):1-133.
[8] Miranda-Filho A, Lortet-Tieulent J, Bray F, Cao B, Franceschi S, Vaccarella, et al. Thyroid cancer incidence trends by histology in 25 countries: a population-based study. Lancet Diabetes Endocrinol. 2021;9(4):225-34.
[9] Roman BR, Morris LG, Davies L. The thyroid cancer epidemic, 2017 perspective. Curr Opin Endocrinol Diabetes Obes. 2017;24(5):332-36.
[10] LiVolsi VA. Papillary thyroid carcinoma: An update. Mod Pathol. 2011;24(Suppl 2):S1-S9.
[11] Kuhn E, Teller L, Piana S, Rosai J, Merino MJ. Different clonal origin of bilateral papillary thyroid carcinoma, with a review of the literature. Endocr Pathol. 2012;23(2):101-07.
[12] Geron Y, Benbassat C, Shteinshneider M, Or K, Markus E, Hirsch D. Multifocality is not an independent prognostic factor in papillary thyroid cancer: a propensity score-matching analysis. Thyroid. 2019;29(4):513-22.
[13] Basolo F, Macerola E, Poma AM, Torregrossa L. The 5th edition of WHO classification of tumors of endocrine organs: Changes in the diagnosis of follicular-derived thyroid carcinoma. Endocrine. 2023;80(3):470-76.
[14] Ali SZ, Baloch ZW, Cochand-Priollet B, Schmitt FC, Vielh P, VanderLaan PA. The 2023 Bethesda System for reporting thyroid cytopathology. Thyroid. 2023;33(9):1039-44.
[15] Bychkov A. Micropapillary thyroid carcinoma versus papillary thyroid microcarcinoma- What's in the name? Am Surg. 2019;85(3):e185-e186.
[16] Christofer Juhlin C, Mete O, Baloch ZW. The 2022 WHO classification of thyroid tumors: novel concepts in nomenclature and grading. Endocr Relat Cancer. 2022;30(2):e220293.
[17] Amado A, Teixeira E, Canberk S, Macedo S, Castro B, Pereira H, et al. Subcentimetric papillary thyroid carcinoma with extensive lymph node and brain metastasis: case report and review of literature. Endocrinol Diabetes Metab Case Rep. 2023;2023(4):23-0025.
[18] Baloch ZW, Solomon AC, LiVolsi VA. Primary mucoepidermoid carcinoma and sclerosing mucoepidermoid carcinoma with eosinophilia of the thyroid gland: a report of nine cases. Mod Pathol. 2000;13(7):802-07.

PARTICULARS OF CONTRIBUTORS:
1. Postgraduate Resident, Department of Pathology, SCB Medical College, Cuttack, Odisha, India.
2. Assistant Professor, Department of Pathology, SCB Medical College, Cuttack, Odisha, India.
3. Assistant Professor, Department of Pathology, SCB Medical College, Cuttack, Odisha, India.
4. Professor, Department of Pathology, SCB Medical College, Cuttack, Odisha, India.
5. Postgraduate Resident, Department of Pathology, SCB Medical College, Cuttack, Odisha, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Chandraprava Mishra,
Assistant Professor, Department of Pathology, SCB Medical College, Cuttack-753001, Odisha, India.
E-mail: chandraprava51@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Sep 28, 2024
- Manual Googling: Nov 29, 2024
- iThenticate Software: Jan 13, 2025 (6%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Sep 27, 2024**
Date of Peer Review: **Oct 26, 2024**
Date of Acceptance: **Jan 14, 2025**
Date of Publishing: **Apr 01, 2025**