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Evaluation and Therapy of Differentiated Thyroid Cancer:Update

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Ghana- May 2023

- Since the first treatment By Saul Hertz in USA , Nuclear medicine has proved to be very efficient in the treatment of differenciated Thyroid cancer with some differences regards the changing in publications concerning doses, time, etc

- Recently a publication of the SNMMI Procedure Standard/EANM Practice Guideline for Nuclear Medicine Evaluation and Therapy of Differentiated Thyroid Cancer has steblish new and clear indications on these treatments SNMMI Procedure Standard/EANM Practice Guideline for Nuclear Medicine Evaluation and Therapy of Differentiated Thyroid Cancer: Abbreviated Version

Anca M Avram, Luca Giovanella, Bennett Greenspan, Susan A. Lawson, Markus Luster, Douglas Van Nostrand, Justin G. Peacock, Petra Petranović Ovčariček, Edward Silberstein, Mark Tulchinsky, Frederik A. Verburg, Alexis Vrachimis
Journal of Nuclear Medicine Jun 2022, 63 (6) 15N-35N;

The current strategy for DTC management is a risk- stratified approach based on

1- Surgical Histopathology,

3- Molecular markers,

4- Postoperative thyroglobulin (Tg) levels

5-Anatomic/functional imaging studies .

Surgery

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- Total thyroidectomy was traditionally performed in most DTC patients, lobectomy reserved for cytologically indeterminate nodules or patients with unifocal micro- papillary thyroid cancer (PTC) with less than 1cm. Management of low-risk DTC between 2 and 4 cm total thyroidectomy is still largely advised, especially in Europe. Active surveillance is considered on age- related risk of progression, individual surgical risk factors, and patient preference

- Cervical lymph nodal metastases occur in 20%–60% of patients with DTC, When lymph nodal metastases are diagnosed preoperatively, central and/or lateral neck compartment dissection reduces the risk of locoregional recurrence. Prophylactic central neck dissection may improve regional control for invasive tumors (T3–T4), but it is discouraged for low-risk tumors, preoperative neck US generally suffices to plan surgery . MRI or CT without iodine contrastradiologic (contrast agents and iodine-based antiseptics should be avoided for at least 4–6 wk prior to treatment)

- PET/CT with 18F-FDG could be perfomed preoperatively in more aggressive DTC histotypes like poorly differentiated or Hurthle cell carcinoma or anaplastic thyroid cancer

Differentiated Thyroid Cancer: Clinical and Pathologic Characteristics

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Histological subtypes	Morphology	Molecular markers	Pattern of spread	RAI avidity
Papillary thyroid cancer (PTC)	Classical papillae Clear nuclei	BRAF V600E, RET/PTC fus	Lymph nodes	++++
PTC–follicular variant	Follicular structures Clear nuclei	BRAF K601E, RAS, PAX8/PPARγ	Lymph nodes	+++++
PTC–aggressive variants*	Specific cell features and structural changes	BRAF V600E, 1q amp, TERT promoter	Lymph nodes Lung	+++
Follicular thyroid cancer	Capsular invasion (MI) Vascular invasion (WI) Extrathyroidal invasion (WI)	RAS, PAX8/PPARγ, PTEN, TSHR, TERT promoter	Lung Bone	+++++
Hürthle cell thyroid carcinoma	Hürthle cells	RAS, PAX8/PPARγ, PTEN, TSHR, chromosomal loss, mitochondrial DNA mutations, TERT promoter	Lung Bone	++
Poorly differentiated thyroid cancer	Invasion Mitoses >3 Necrosis Convoluted nuclei	RAS, TERT promoter, TP53, PIK3CA, PTEN, CTNNB1, AKT1, EIF1AX, ALK fus	Lymph nodes Lung Bone	+/–
Anaplastic thyroid cancer	Undifferentiated cells with immunohistochemical or ultrastructural features of epithelial origin but of morphological and immunophenotypic markers of thyroid origin	TP53, TERT promoter, PI3K/AKT/mTOR, SWI/SNF subunts, RAS, EIF1AX, BRAF	Local invasion Lung Bone Lymph nodes	–

*Tall, columnar, solid, and hobnail variants.
RAI = radioiodine; MI = minimally invasive; WI = widely invasive; fus = fusion.

Postoperative 131I Therapy

- Considering various parameters, including clinical/pathologic data, laboratory and imaging information

- 1-**Remnant ablation** to eliminate normal thyroid tissue remnant in low-risk patients, thereby ensuring undetectable or minimal serum Tg levels which facilitates follow-up.

- 2- **Adjuvant treatment:** to irradiate suspected but unproven sites of neoplastic cells in low-intermediate– and intermediate risk patients, thereby reducing the risk of disease recurrence

- 3- **Treatment of known disease:** In patients with demonstrated disease

Anna M. Sawka, Kullathorn Thephamongkhol, Melissa Brouwers, Lehana Thabane, George Browman, Hertzel C. Gerstein, A Systematic Review and Metaanalysis of the Effectiveness of Radioactive Iodine Remnant Ablation for Well-Differentiated Thyroid Cancer, *The Journal of Clinical Endocrinology & Metabolism*, Volume 89, Issue 8, 1 August 2004, Pages 3668–3676, https://doi.org/10.1210/jc.2003-031167

Preparation for 131I Therapy

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- Therapy should be scheduled at a minimum of 4 wk after surgery, which allows time for patient preparation and for reaching postoperative Tg plateau levels (Tg t1/2 of 65.2 h) and Tg antithyroglobulin antibodies (TgAb) need to be measured in conjunction with Tg

- Adequate TSH stimulation (TSH 30 mIU/L measured 1–3 d prior to 131I administration) by either thyroid hormone withdrawal (2 ways) or recombinant human TSH stimulation. TSH is used for increasing sodium-iodide symporter (NIS) expression and function in metastatic lesions and residual thyroid tissue),

- For childbearing females (12–50 y old) a negative pregnancy test is required within 72 h of 131I administration or prior to the first rhTSH injection

- Dietary deprivation of stable iodine: It is important for minimizing interference with 131I uptake. Patient compliance with LID can be confirmed by measurement of spot urinary iodine when possible (100 mg/L and optimal 50 mg/L)

Radioiodine Therapy Planning

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- 1-Approach integrating functional imaging information obtained with postoperative preablation Dx radioiodine (123I, 131I, or 124I) scans

- 2- Approach based on clinical–pathologic factors and institutional protocols (i.e., risk-adapted approach).

Preparation*	Day 1	Day 2–3	Day 3–4	Day 5	Day 6–11 (2–7 d post-Rx)
Thyroid hormone management: • Replace T4 with T3 for first 2 wk • Then stop T3 for next 2 wk	Baseline blood tests: • Pregnancy • TSH, Tg, TgAb, F-T4 • CMP • CBC w. Diff	DxWBS: • Review/report scan • Review pathology • Review blood test results • ^{131}I therapy planning	^{131}I therapy administration		PT-WBS scan
Diet management: • Start LID for 2 wk (when T3 is stopped)	Dx RAI adm. (1–2 mCi)	Patient consult: • Explain findings, prognosis • Discuss indications for ^{131}I Rx • Discuss logistics of ^{131}I Rx • Discuss radiation precautions • Discuss management of post-operative hypothyroidism			
			• Patient education for radiation	Patient: • Starts normal	

Sample protocol for ^{131}I theranostics after thyroid hormone withdrawal (THW). *Initial consultation is recommended to discuss preparation protocol with patient and family and explain logistics and expectations of ^{131}I therapy and radiation precautions. RAI = radioiodine; T4 = levothyroxine; T3 = liothyronine; Dx RAI adm. = diagnostic radioiodine activity administration; DxWBS = diagnostic radioiodine whole-body scan; CMP = comprehensive metabolic panel; CBC = complete blood count; RAI Rx = ^{131}I therapy; PT-WBS = posttherapy ^{131}I whole-body scan; rhTSH = recombinant human TSH, Thyrogen®; LID = 2 wk of low-iodine diet; TSH = thyroid-stimulating hormone; F-T4 = free thyroxine; Tg = thyroglobulin.

Management and Integration of Functional Diagnostic Radioiodine Imaging

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- Theragnostic approach to 131I administration involves acquisition of a preoperative Dx radioiodine (123I, 131I, or 124I) scan for planning 131I therapy.

- DxWBS is performed with the intent of identifying and localizing regional and distant disease and for evaluating the capacity of metastatic deposits to concentrate 131I.

- DxWBS may alter management, for ex. providing guidance for additional surgery or altering the prescribed 131I therapy, either by adjusting empiric 131I activity or by performing dosimetry calculations for determining the maximum tolerated therapeutic 131I

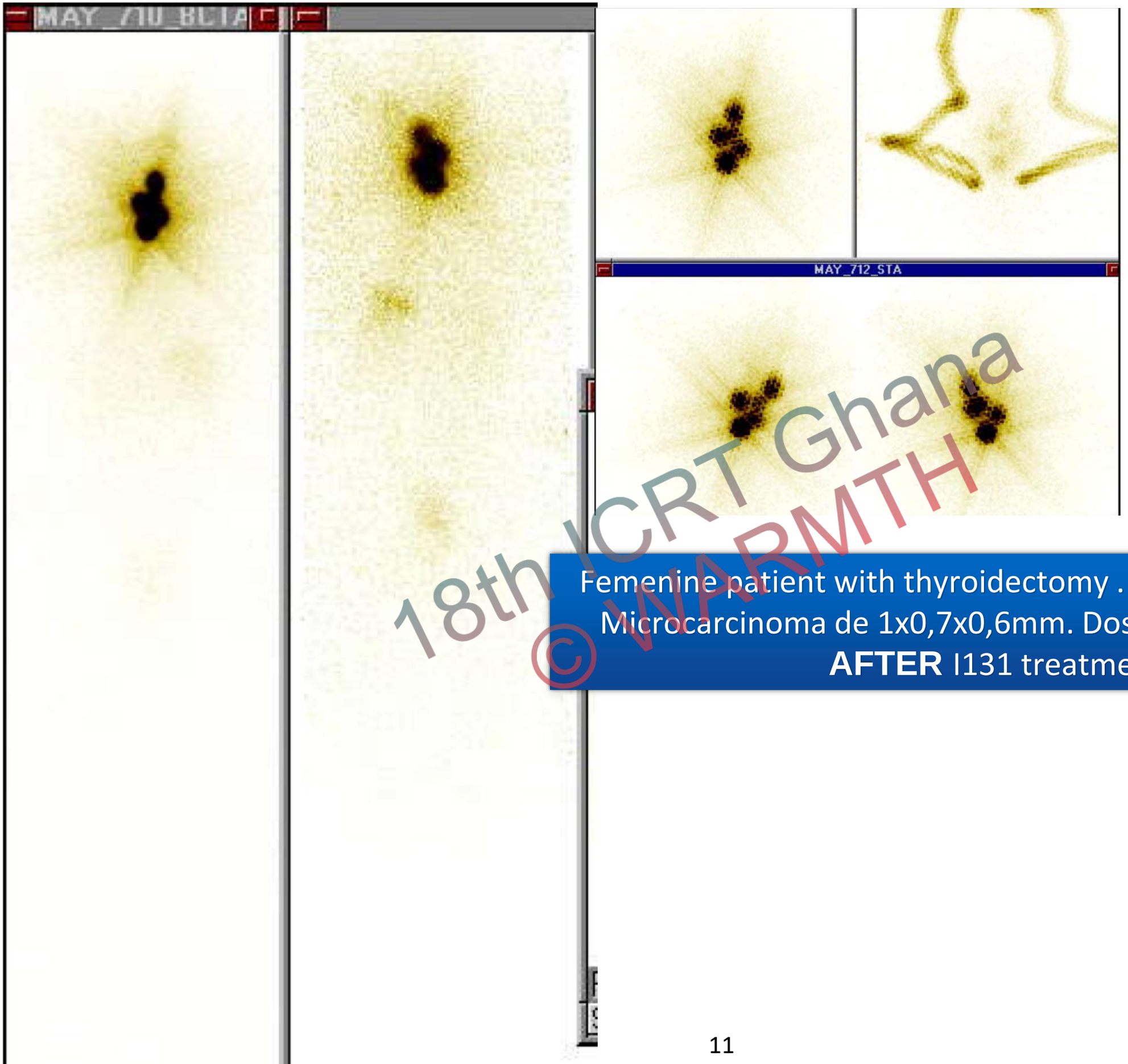
- Also, unnecessary 131I therapy may be avoided if DxWBS finds no evidence of residual thyroid tissue or metastatic disease and the stimulated Tg is ,1 ng/mL in the absence of interfering TgAb

- Additional functional metabolic imaging with 18F-FDG PET/CT when non-iodine–avid metastatic disease is suspected (based on Tg elevation out of proportion to findings on DxWBS)

- DxWBS with or without SPECT/CT may detect metastases in normal-size cervical lymph nodes, may identify pulmonary micrometastases, and may diagnose bone metastases at an early stage diagnosticar mts óseas before anatamic changes

- Dx 123I scans demonstrated their usefulness in thyroid cancer management: preablation 123I WBS provided additional critical information in 25% in low risk patients and in high risk npatients in 50 %

- Depending on the type of patient preparation, Dx radio- iodine (123I or 131I) activities such as 37–74 MBq (1–2 mCi) for THW protocols and 110–148 MBq (3–4 mCi) for rhTSH-stimulation protocols, this is for the competitive inhibition exerted by the iodine content of T4 (levothyroxine) on the uptake of radioiodine or Replacement of levothyroxine with liothyronine (T3) during the preparation



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Femenine patient with thyroidectomy . In left lobule Papilar Microcarcinoma de 1x0,7x0,6mm. Dose 30 mci I131 WBS
AFTER I131 treatment

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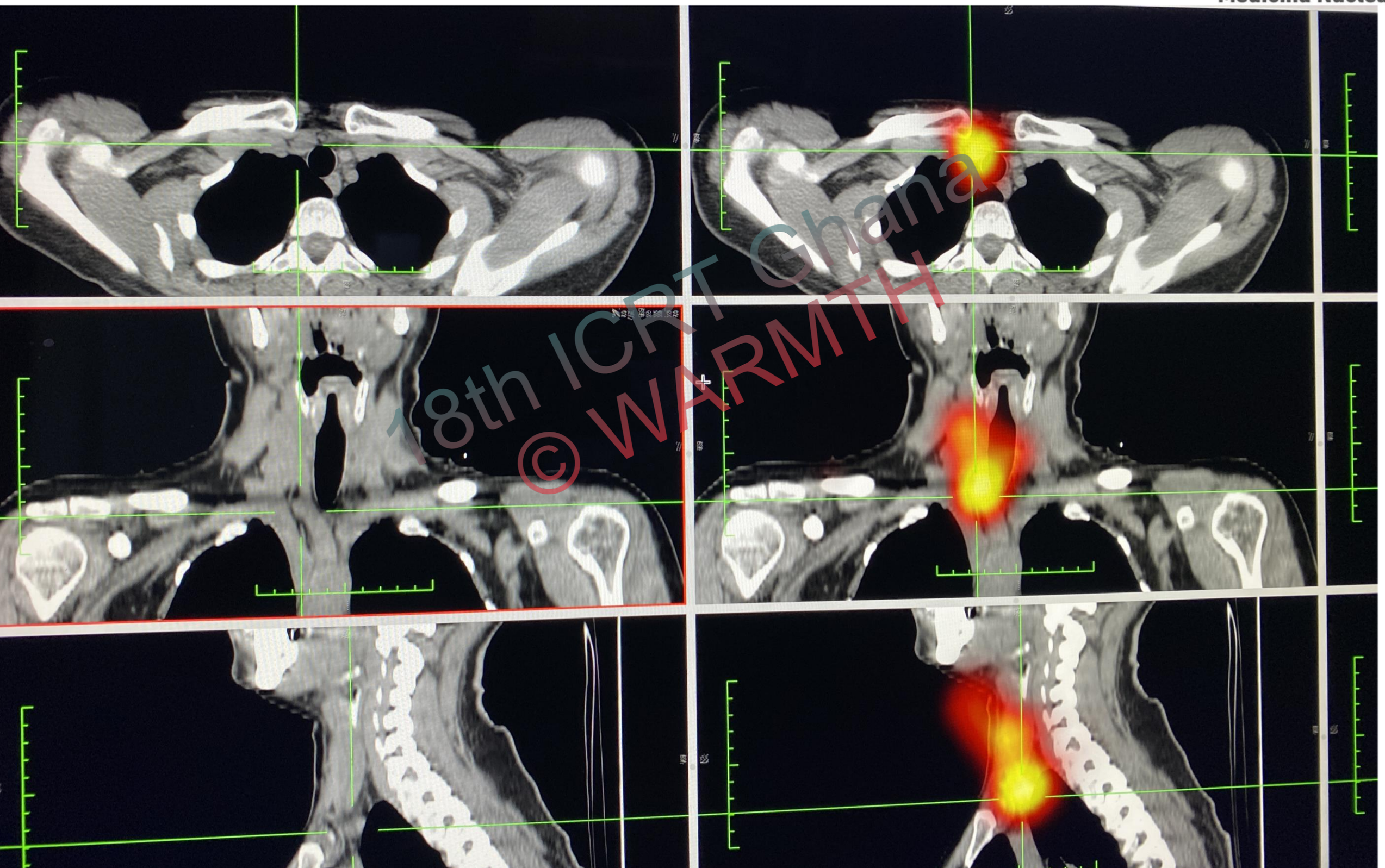

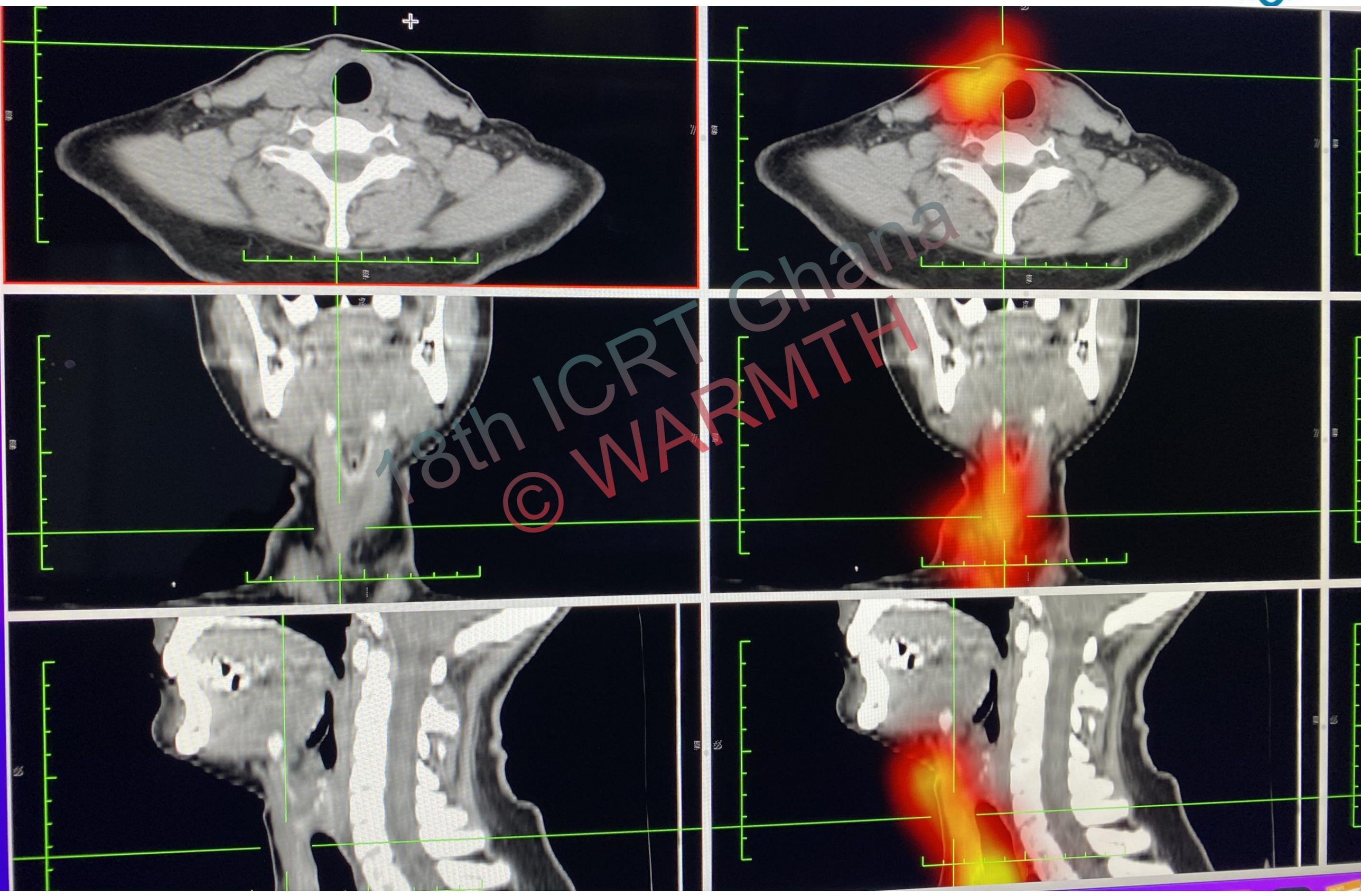

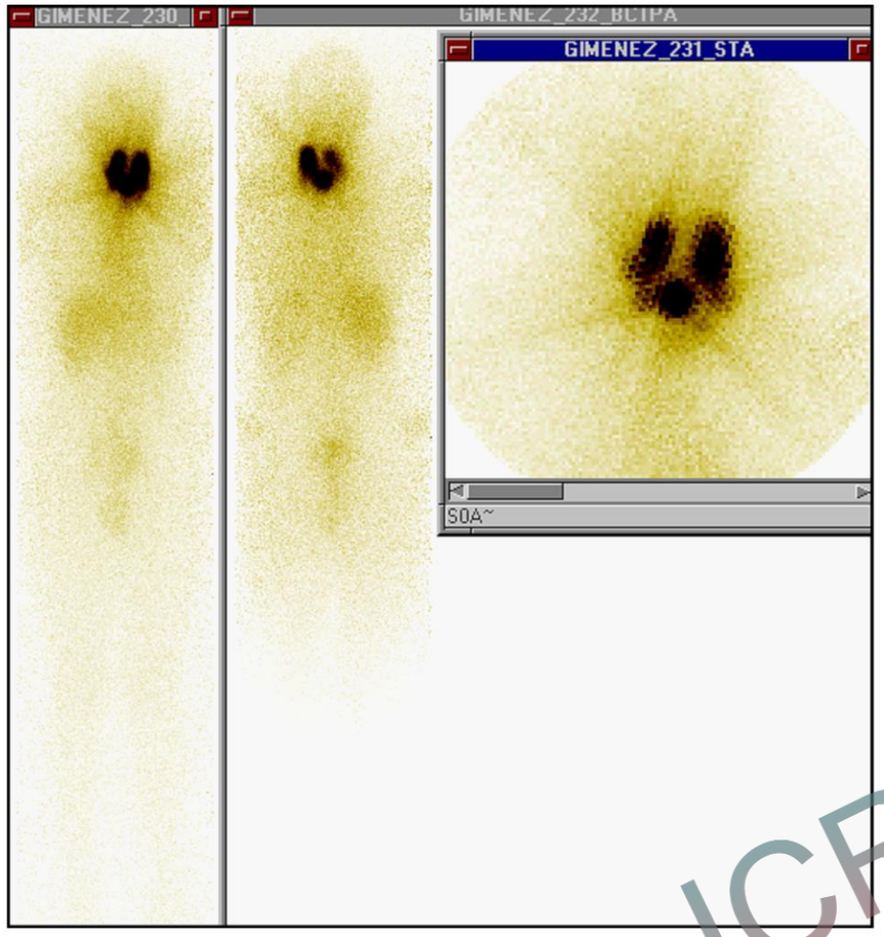

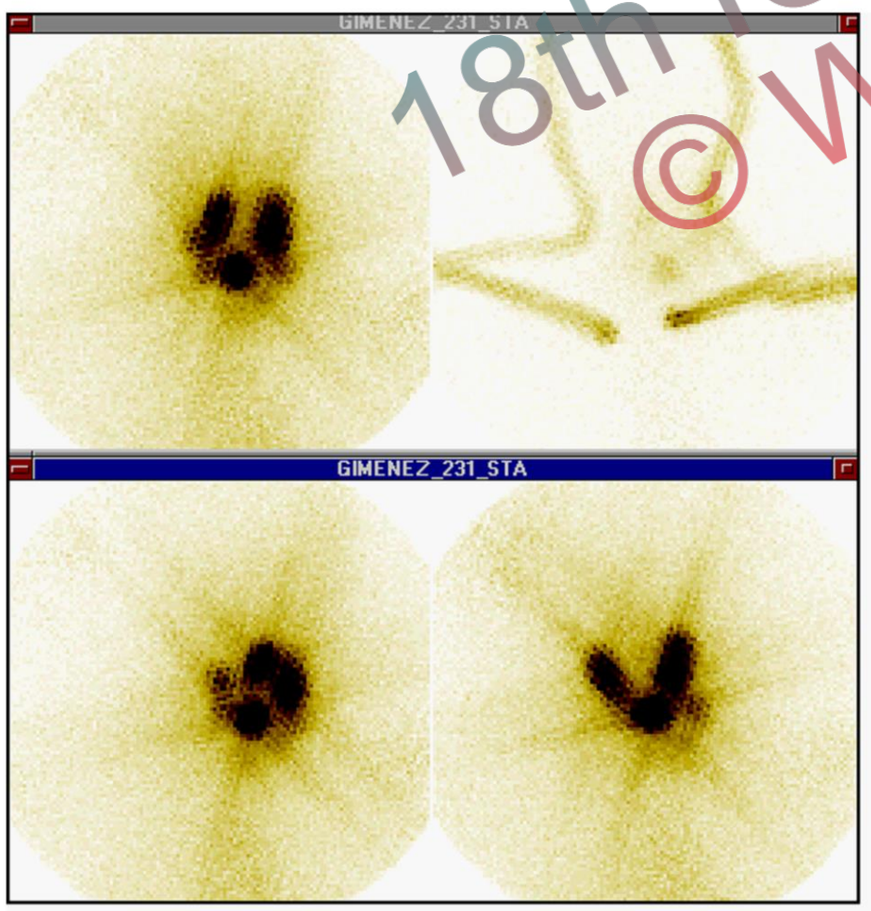

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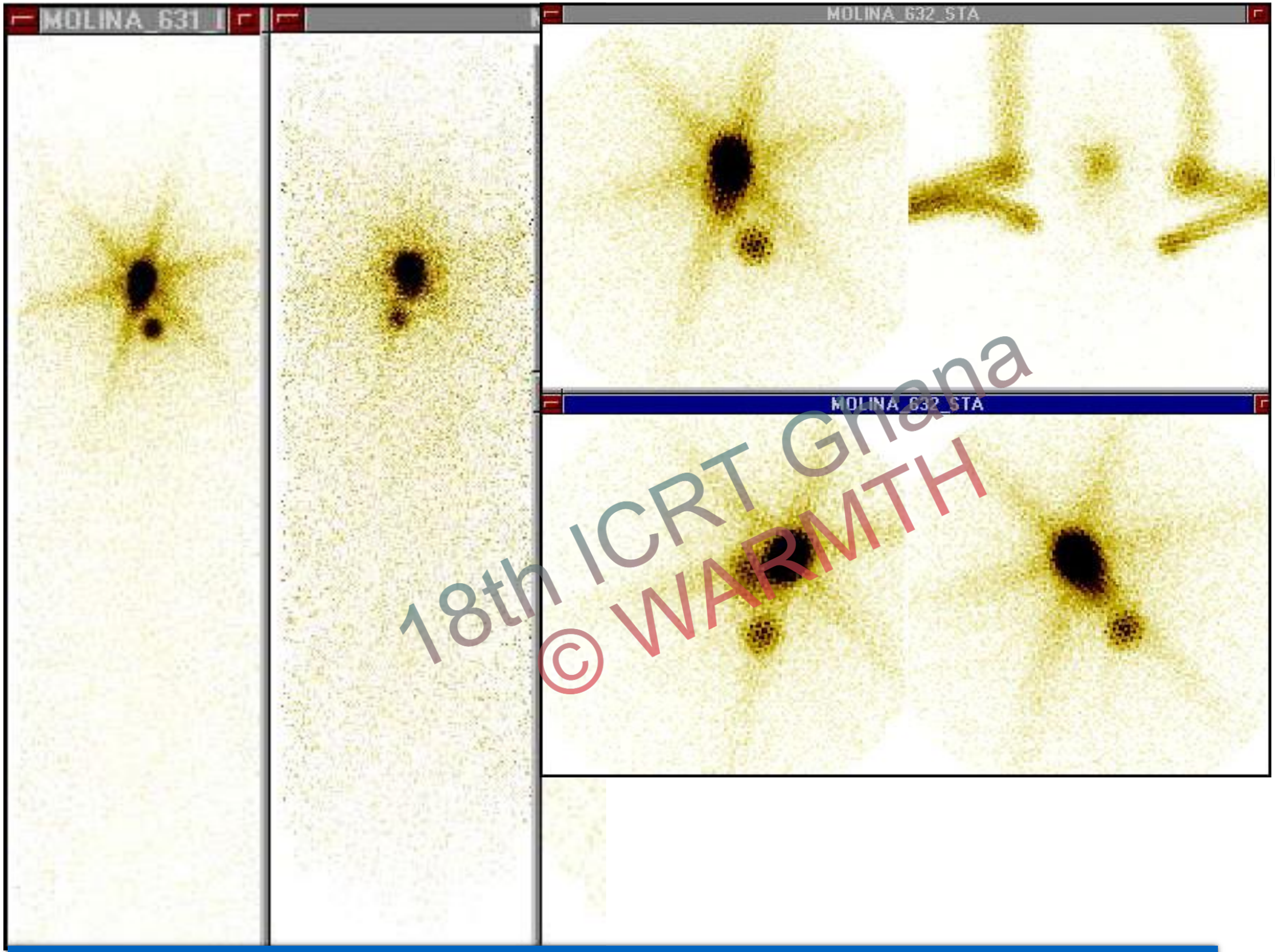
Masculine 15 years old patient with MicroPapillary Thyroid Cancer treated with 30 mci



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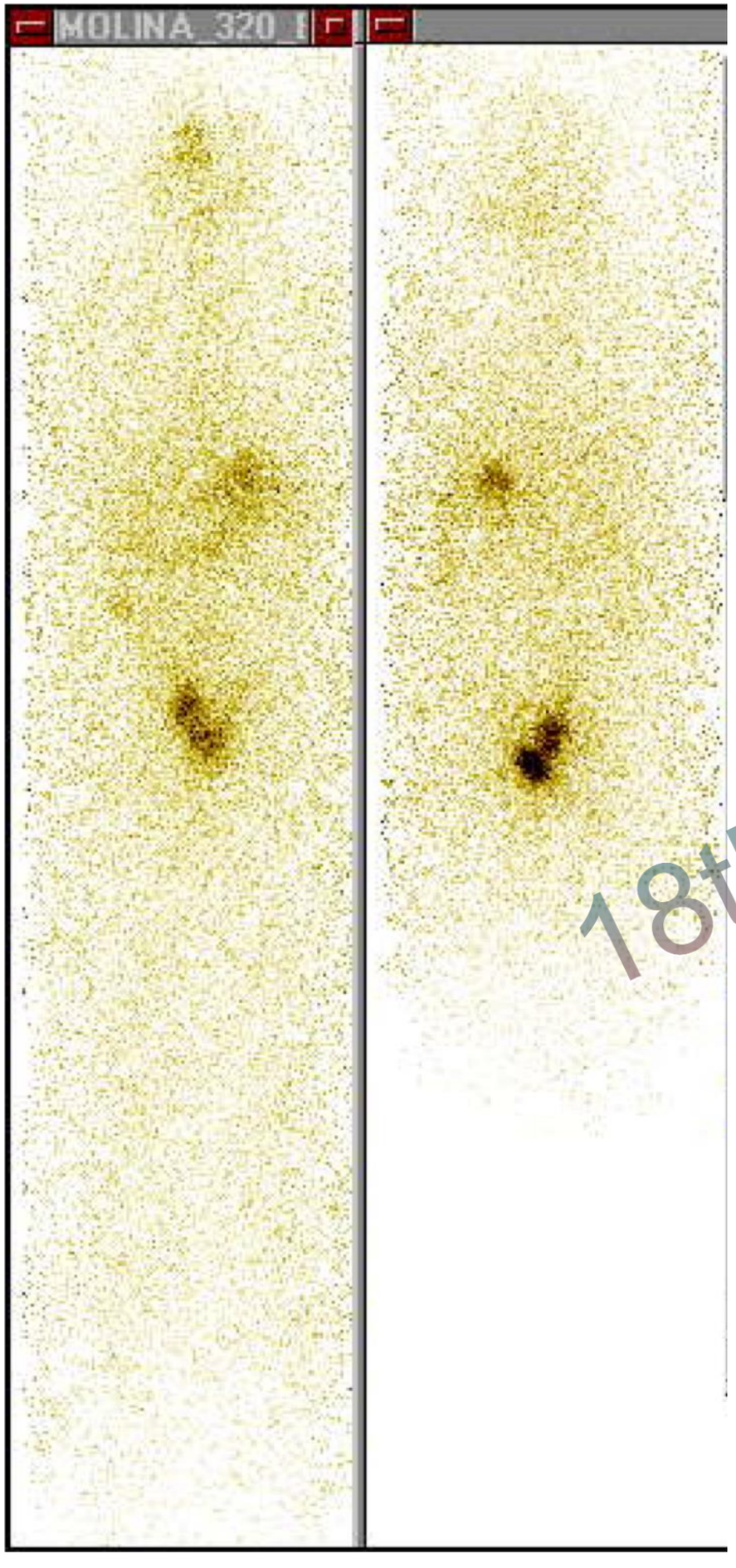
Female patient 40years old post thiyroidectomy: unilateral Papilar carcinoma with multiple focus , the biggest: 1,7x1,5x1 cm and two smaller 0,5cm

Pre surgery US :no adenopatías . Therapy dose 30 mci el 22 nd July 2021



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DWS with 5 mci I131 el 13 May 2022

RESPONSE ASSESSMENT AFTER PRIMARY THERAPY

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- Dynamic risk restratification consists of reassignment of recurrence risk based on response to initial treatment, which is predictive of long-term clinical outcomes

- This is performed during the first 2 y of follow-up after initial therapy (total thyroidectomy followed by 131I therapy) and involves basal and stimulated Tg testing and imaging reevaluation.

- US is a reliable method for detection of locoregional persistent or recurrent DTC (i.e., thyroid bed and cervical lymph nodes) use of US should be limited (particularly in low-risk DTC) and, in the absence of TgAbs, reserved only for patients with unstimulated serum Tg levels ≥1 ng/mL

- US-guided FNA biopsy with Tg determination in the fluid aspirate is used for Dx confirmation of residual disease in suspicious-appearing cervical lymph nodes identified on anatomic imaging.

- In combination with Tg measurement, follow-up DxWBS are helpful for therapy response evaluation and to identify patients with suspected non-iodine–avid metastatic disease (based on elevated basal and/or stimulated Tg and negative WBS), which will prompt further investigation with 18F-FDG PET/CT and/or Dx CT scan for localizing structural persistent disease

TABLE 4

Response to Therapy in DTC Patients: Dynamic Risk Stratification Criteria (Modified from [6])

Excellent response: No clinical, biochemical, or structural evidence of disease: negative imaging and either suppressed Tg <0.2 ng/mL or stimulated Tg <1 ng/mL
Biochemical incomplete response: Abnormal Tg (i.e., suppressed Tg >1 ng/mL or stimulated Tg >10 ng/mL) or rising anti-Tg antibody levels in the absence of localizable disease (i.e., negative imaging)
Structural incomplete response: Persistent or newly identified locoregional or distant metastases (any Tg value)
Indeterminate response: Nonspecific biochemical (i.e., suppressed Tg 0.2–1 ng/mL or stimulated Tg 1–10 ng/mL or stable/declining anti-Tg antibody levels) or structural findings that cannot be confidently classified as either benign or malignant

Tg = thyroglobulin.

THERAPY OF ADVANCED DISEASE

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- Distant metastases develop in about 10% of DTC patients, commonly in lungs and less frequently in bone, brain, liver, and skin

- About two-thirds of patients have radioiodine-avid distant metastases, and >40% of these will achieve remission after 131I treatments ee4d

THERAPY OF ADVANCED DISEASE

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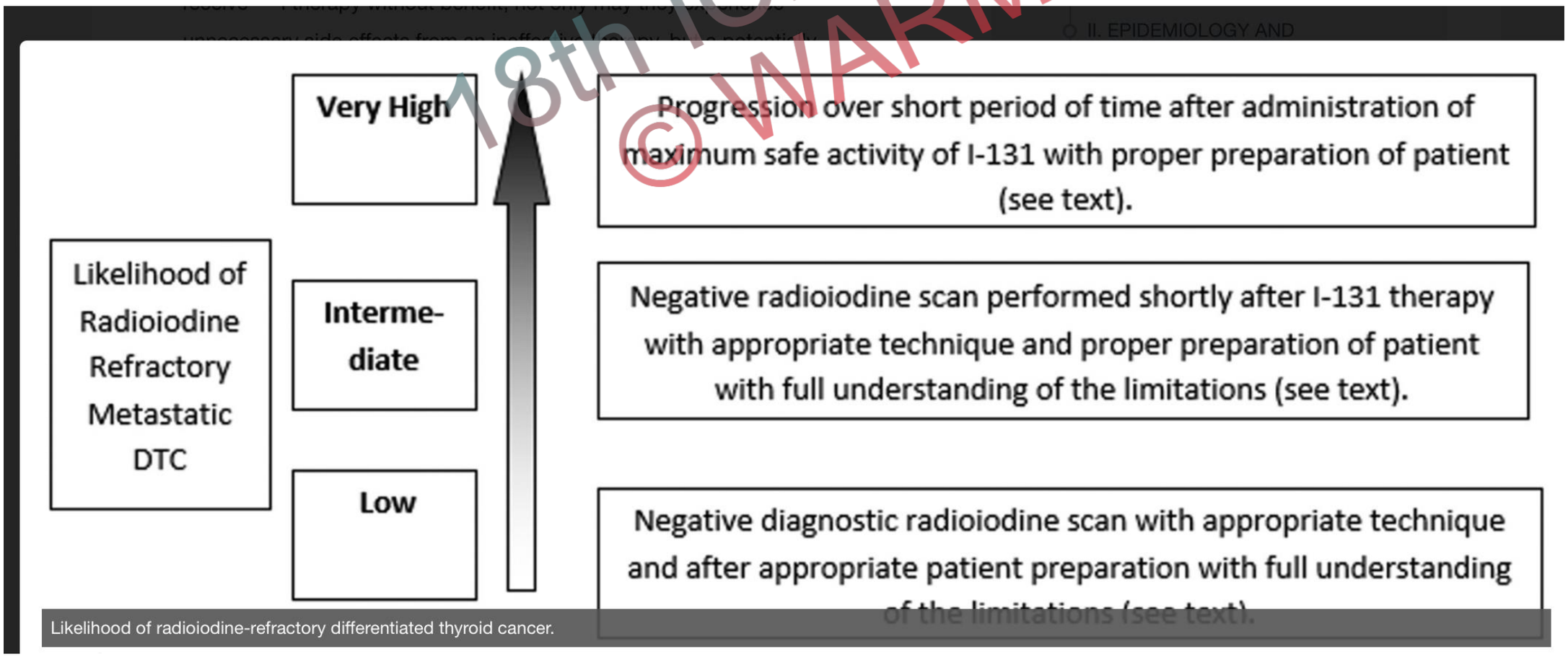
- Distant metastases develop in about 10% of DTC patients, commonly in lungs and less frequently in bone, brain, liver, and skin
- The mainstay of metastatic disease treatment is TSH suppression and repeated courses of 131I treatment as long as the disease remains iodine-avid (>40% of these will achieve remission after 131I
- Classification of a patient as radioiodine refractory is very important and consequential. If one classifies a patient as radioiodine refractory when, in fact, the patient may respond to a 131I therapy, then that patient has lost the potential benefit of an effective 131I therapy in a situation with limited therapeutic options



Likelihood of radioiodine-refractory differentiated thyroid cancer.

Before classifying a patient's DTC as radioiodine refractory:

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- Consider I131 treatment/ Perform radioiodine dosimetry

- Select patients that can receive"resensitizing" or "redifferentiating" agents to determine if radioiodine uptake can be reestablished or increased for a potential 131I therapy

- In the setting of redifferentiation strategy, molecular tumor analysis can direct therapy e.g., BRAFV600E + → dabrafenib [± trametinib, vemurafenib; BRAF– → trametinib])

18F-FDG PET/CT Imaging for Thyroid Cancer

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- Type I : negative 131I/positive FDG and is the most commonly encountered pattern in patients with elevated Tg and negative scintigraphy (46% cases)

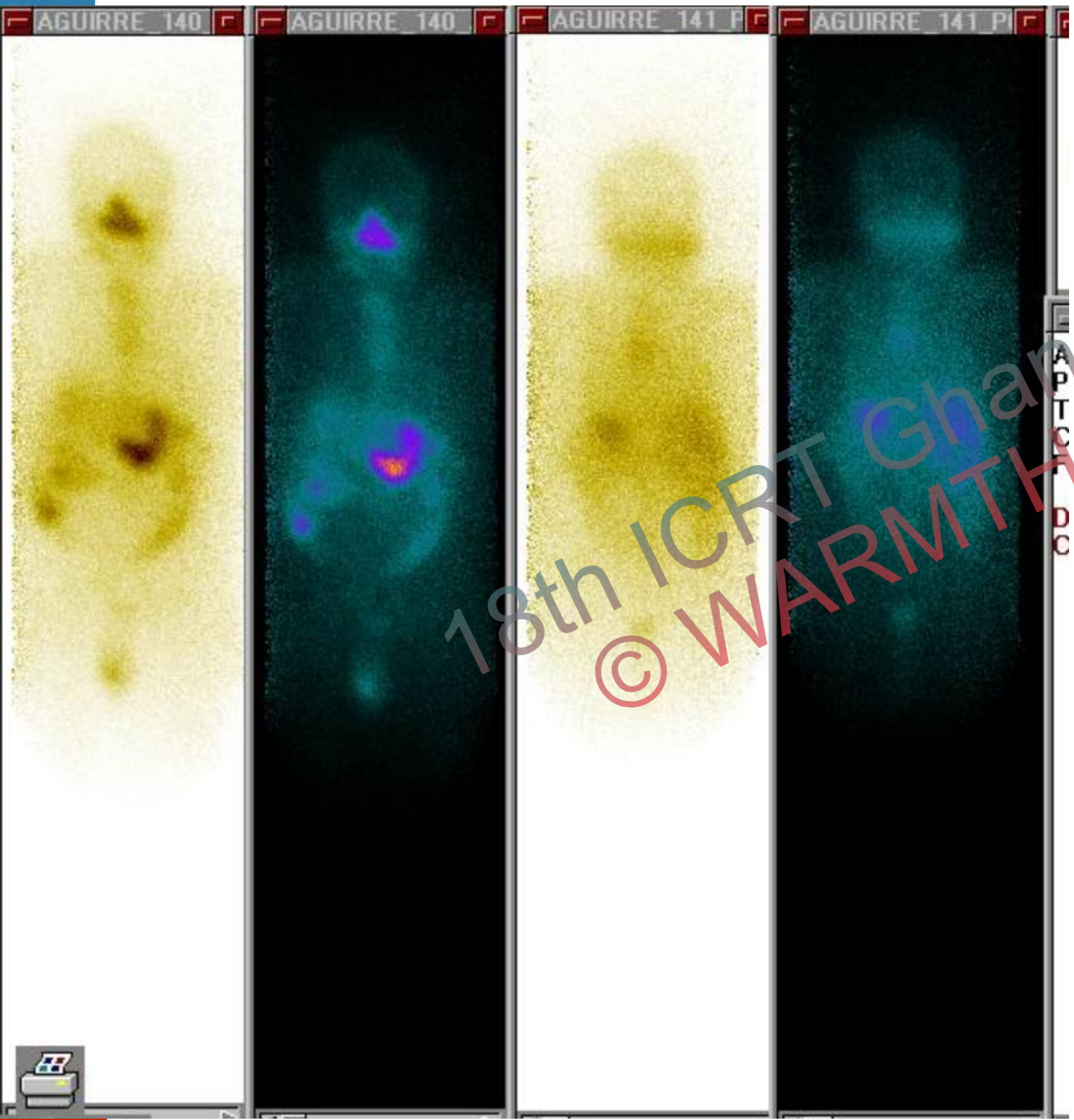
- Type II :positive 131I/negative FDG :therapeutic 131I administration.

- Type III consists of a combination of type I and II patterns recognized in different metastatic lesions within the same patient

- .Type IV positive131I and positive18FDG within the same metastatic lesions.

18F-FDG PET/CT imaging is particularly useful not only for identification and localization of non-iodine–avid metastases but also for predicting the course of disease as aggressive or indolent.

Feine, U., Lietzenmayer, R., Hanke, J. P., Wöhrle, H., & Müller-Schauenburg, W. (1995). 18FDG whole-body PET in differentiated thyroid carcinoma. Flipflop in uptake patterns of 18FDG and 131I. Nuklearmedizin. Nuclear Medicine, 34(4), 127-134.



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Masculine 68 years old Papilar thyroid Carcinoma :
-21/02/21: tiroidectomy with central y lateral neck surgery.Primary tumor de 5x3,5cm . 8 nodes with metástasis.
-21/09/21 resurgery: right cervical, recurrencia and mediastinal with esternotomy . Resection 31 nodes ; 19 positives
-Dic 2021: Treatment with 200mci , WBS post dosis negative

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Lab : TSH :0,04   Tg 4,2. AC anti TG negative

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Management Algorithm for Patients with Elevated Tg and Negative DxWBS (Tg+/Scan–) TENIS syndrome

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- 1-Rule out false-negative DxWBS and false-positive Tg level :screening for a history of recent iodine load, correct diet (low urinary iodine levels),adequate TSH elevation, discard heterophilic antibody interference on Tg measurement, scintigraphy acquisition

- 2-Perform **Dynamic risk restratification**: for low risk for disease recurrence, active surveillance may include: (1) physical exam; (2) Tg, TgAb, and TSH testing; and (3) US of the thyroid bed and neck. However, nonradioiodine imaging is indicated when the patient has an intermediate or higher risk for disease recurrence.

- 3-*Obtain nonradioiodine imaging:* ***Phase1*** (1)neck US; (2) ^{18}F-FDG PET/CT imaging; and/or (3) CT of the neck, chest, abdomen, and pelvis. These studies can be performed sequentially; however, whenever possible, integrated PET/CT imaging is preferable **Phase 2**(1) brain MRI; (2) bone scanning ^{99m}Tc-MDP or ^{18}F-sodium fluoride PET/CT. **(3)**mitochondrial imaging (e.g., ^{99m}Tc- sestamibi, ^{201}Tl, or ^{99m}Tc-tetrofosmin). **Phase 3:** somatostatin receptor (SSR) imaging with radiolabeled somatostatin analogs octreotide and 68Ga-DOTATATE/TOC/NOC.

- 4:-Customize management to the location and number of the metastases: Focally directed therapy needs to be considered for management of unifocal or oligometastatic disease Ex Radiosurgery

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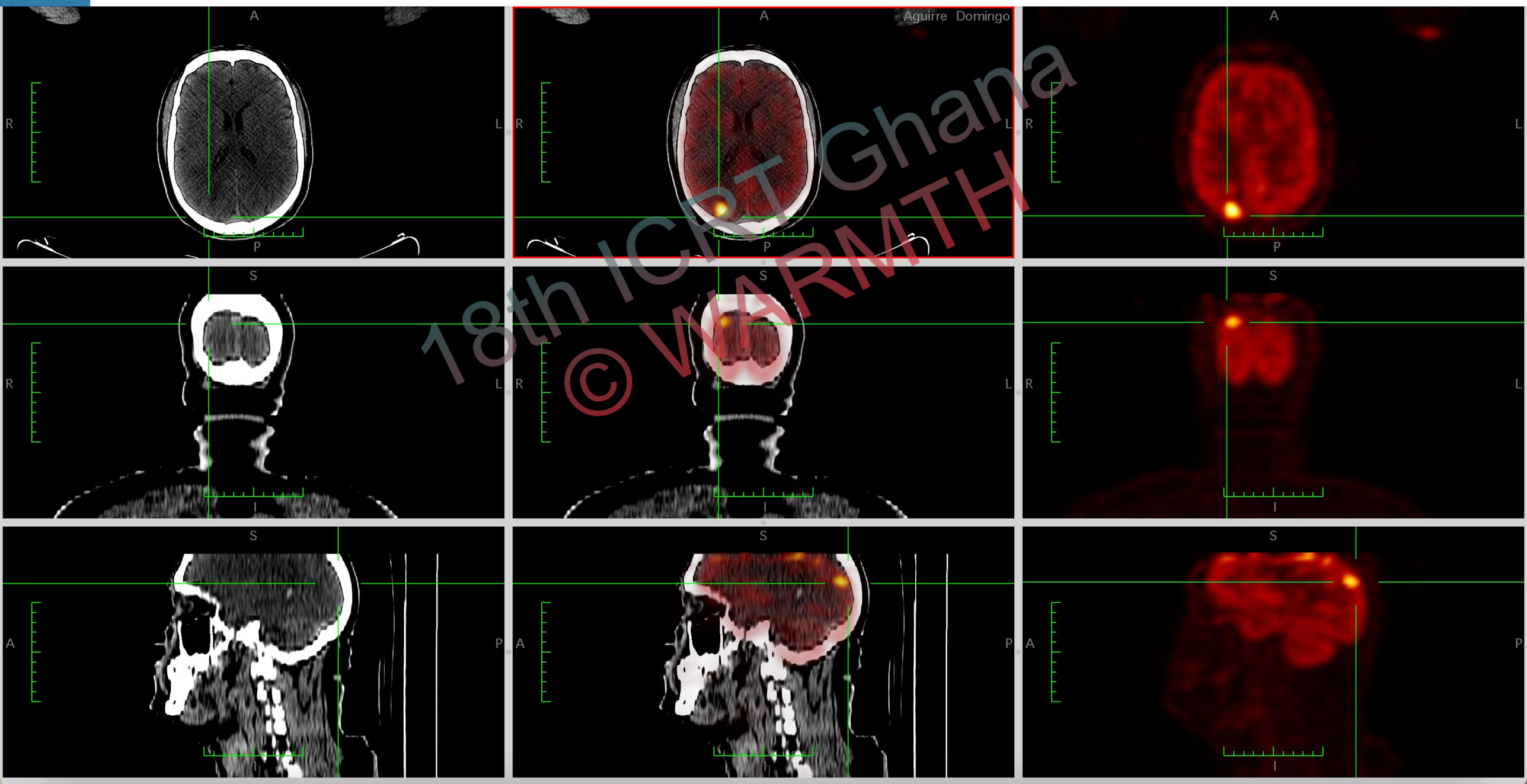

Take home a message

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- DTC is the most common endocrine malignancy, with a rising incidence.

- Treatment should be done through dynamic risk restratification,**:** not only histopathology post surgery, genetic ,Tg but also with **anatomo-functional studies (Diagnostic WBS)**

- Early identification of residual nodal and/or distant metastases is particularly relevant for successful 131I therapy of metastatic disease, because patients who achieve a CR have considerably higher survival rates than patients with structural incomplete responses.

- Integration of Dx radioiodine scintigraphy in the management algorithm of patients with thyroid cancer should be considered **Theragnostic approach**

XXIX CONGRESO ALASBIMN

XXIII CONGRESO AABYMN

BUENOS AIRES 15 al 18 de NOVIEMBRE 2023

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