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Research Article

Bone metastases from differentiated thyroid carcinoma: experience of the nuclear medicine department at Hassan II University Hospital in Fez

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Abstract

Introduction: *Bone metastases represent one of the main distant dissemination sites of differentiated thyroid carcinoma (DTC) and are associated with a significant reduction in long-term survival. The aim of this study was to analyze the clinical, histopathological, therapeutic, and outcome characteristics of patients with bone metastases managed in our institution.*

Methods: *This retrospective study was conducted over a 12-year period (January 2013 – December 2024). Among 1,608 patients followed for DTC in the Nuclear Medicine Department of Hassan II University Hospital in Fez, 84 patients (5.2%) presented with bone metastases. Medullary and anaplastic carcinomas were excluded. Demographic, histological, radiological, therapeutic, and follow-up data were analyzed.*

Results: *The mean age at diagnosis of bone metastases was 56 years, with a marked female predominance (74%). In nearly one-quarter of cases, bone involvement revealed the underlying thyroid carcinoma. Papillary carcinoma was the predominant histological type. The spine was the most frequently affected anatomical site, and multifocal skeletal involvement was observed in the majority of patients. Lung metastases were the most common associated distant localization. Radioiodine therapy was administered to most patients, often requiring multiple treatment cycles. Additional therapeutic approaches included surgical management of bone lesions, external beam radiotherapy, and, in refractory cases, tyrosine kinase inhibitors. Iodine-refractory disease was observed in more than half of the patients. A favorable outcome was documented in a minority of cases, whereas mortality mainly occurred in advanced stages with extra-skeletal dissemination.*

Conclusion: *Although relatively uncommon, bone metastases in DTC represent a major prognostic factor. Early detection and a multidisciplinary management approach combining different therapeutic modalities are essential to improve survival and preserve quality of life.*

Keywords: *Differentiated thyroid carcinoma – Bone metastases – Radioiodine therapy (Iodine-131) – Iodine refractoriness – Prognostic factors.*

Introduction

Bone is the second most common site of distant metastases in differentiated thyroid carcinoma (DTC), affecting 2 to 13% of patients [1]The diagnosis relies on clinical, biological, and radiological correlation, which is essential for assessing the extent of the lesions. Metabolic radiotherapy with iodine-131 is the first-line treatment, with local interventions and systemic therapies representing second-line options.[2]The clinical course of patients with CDT and bone metastases is highly variable, but overall it remains unfavorable, reducing the 10-year survival rate by approximately 50% and significantly impairing quality of life.[3]

Materials:

This study included patients with bone metastases secondary to differentiated thyroid carcinoma. Undifferentiated and medullary carcinomas were excluded. All patients had previously undergone total thyroidectomy in one or two stages and were treated and followed up at the nuclear medicine department of the Hassan II University Hospital Center in Fez.

Methods

This is a retrospective descriptive study.

Study period:

The study period extends from January 2013 to December 2024, covering a duration of 12 years. During this period, among the 1,608 patients treated for differentiated thyroid carcinoma, 84 presented with secondary bone metastases and were followed up in the nuclear medicine department.

Results

In our series, bone metastases were present in 5.2% of patients with thyroid cancer. The mean age of patients at diagnosis was 56 years, with a range from 25 to 90 years. The study population comprised 62 women (74%) and 22 men (26%), for a male-to-female ratio of 2.82. Bone metastasis was the presenting symptom of thyroid disease in 20 cases (23.8%). In two cases, the disease was revealed by pulmonary metastasis, and in one case by liver metastasis.

The majority of patients (74%) presented with various symptoms related to bone metastases. Bone pain (18%) and radicular or lumbosciatic manifestations (17%) were the most frequent, while severe neurological involvement affected 10% of patients. Bone masses (14%), fractures (6%), and headaches (10%) were less common. Approximately 26% of patients were asymptomatic. Table 1 shows the distribution of clinical

manifestations observed in our series.

Anatomopathologically, follicular carcinoma was identified in 13 cases, while papillary carcinoma was found in 71 cases, including 58 of the classic papillary type and 13 corresponding to papillary follicular subtype. An oncocytic form of papillary thyroid carcinoma was observed in 4 cases, and one case of ovarian teratoma with a degenerated thyroid component was found. Two cases of poorly differentiated thyroid carcinoma (2.3%) and one case of moderately differentiated carcinoma (1.2%) were identified, while all other cases corresponded to well-differentiated carcinomas. Capsular rupture (CR) was observed in 34 cases, representing approximately 40.5% of patients, while vascular emboli (VE) were noted in 30 cases, or 35.7%.

Among the histological variants associated with an unfavorable prognosis, 3 cases of solid variant and 2 cases of insular variant were reported.

In our series, T1-T2 tumors represent approximately 30%, while T3-T4 tumors constitute approximately 54%. The T status remains unspecified (Tx) in 20 patients (approximately 24%). Lymph node status was undetermined in the majority of cases (approximately 74%). Among the patients evaluated, 18 (approximately 21%) presented with regional lymph node metastases, distant metastases were observed in 31 patients (approximately 37%), most often bone metastases, while the metastatic status remained undetermined in 53 patients (approximately 63%).

The detailed TNM classification (Classification of Thyroid Cancers according to the UICC/AJCC 2017 (8th edition)) of patients is presented in Table 2.

Clinical category	**Number of patients**	**Percentage (%)**
Without clinical signs	22	26%
Localized/Diffuse Bone Pain	15	18%
Lumbosciatalgia / radiculalgia / sciatica	14	17%
Severe neurological impairment (paraparesis, paraplegia, tetraplegia, spinal cord compression)	8	10%
Fractures on pathological bone	5	6%
Bone mass/swelling	12	14%
Isolated headaches or headaches associated with a cranial mass	8	10%

Table 1: Clinical profile of metastatic bone involvement in patients of the series

T	Number	Percentage (%)
T1a	2	2.4%
T1b	4	4.8%
T2	19	22.6%
T3a	12	14.3%
T3b	2	2.4%
T3 (subclass not specified)	16	19.0%
T4a	4	4.8%
T4b	1	1.2%
T4 (subclass not specified)	3	3.6%
Tx	20	23.8%
Ovarian teratoma with a thyroid component that has degenerated into papillary carcinoma with vesicular architecture (size unspecified)	1	1.2%

N	Number	Percentage (%)
N0	1	1.2%
N1	18	21.4%
N1a	0	0.0%
N1b	2	2.4%
N2	1	1.2%
Nx	62	73.8%

M	Number	Percentage (%)
M0	0	0%
M1	31	36.9%
Mx	53	63.1%

Table 2: Distribution of cases according to the TNM classification

For biological tumor markers, thyroglobulin levels at the time of diagnosis of bone metastasis ranged from 0.3 ng/mL to 190,900 ng/mL, with mean values of 3,991 ng/mL during hormone withdrawal and 1,139 ng/mL during suppressive hormone therapy. These values are presented in Table 3, according to the patient's status: on suppressive hormone therapy, stopped treatment, or in the withdrawal phase.

Patient condition	Min (ng/mL)	Max (ng/mL)	Average (ng/mL)
In reindeer	0.3	190,900	3,991
Under treatment / suppression	350	2082	1139

Table 3: Thyroglobulin levels according to the patient's condition

In our series, bone metastases predominated in the spine (cervical, thoracic, and lumbar: 63%, 63%, and 74%, respectively), followed by the skull (33%) and pelvis (25%). Long bones (femur 17%, humerus 15%) and other peripheral sites were less frequently involved. The majority of patients (81%) presented with multi-site dissemination, while a single site was observed in 19% of patients, primarily affecting the skull, lumbar spine, or femur.

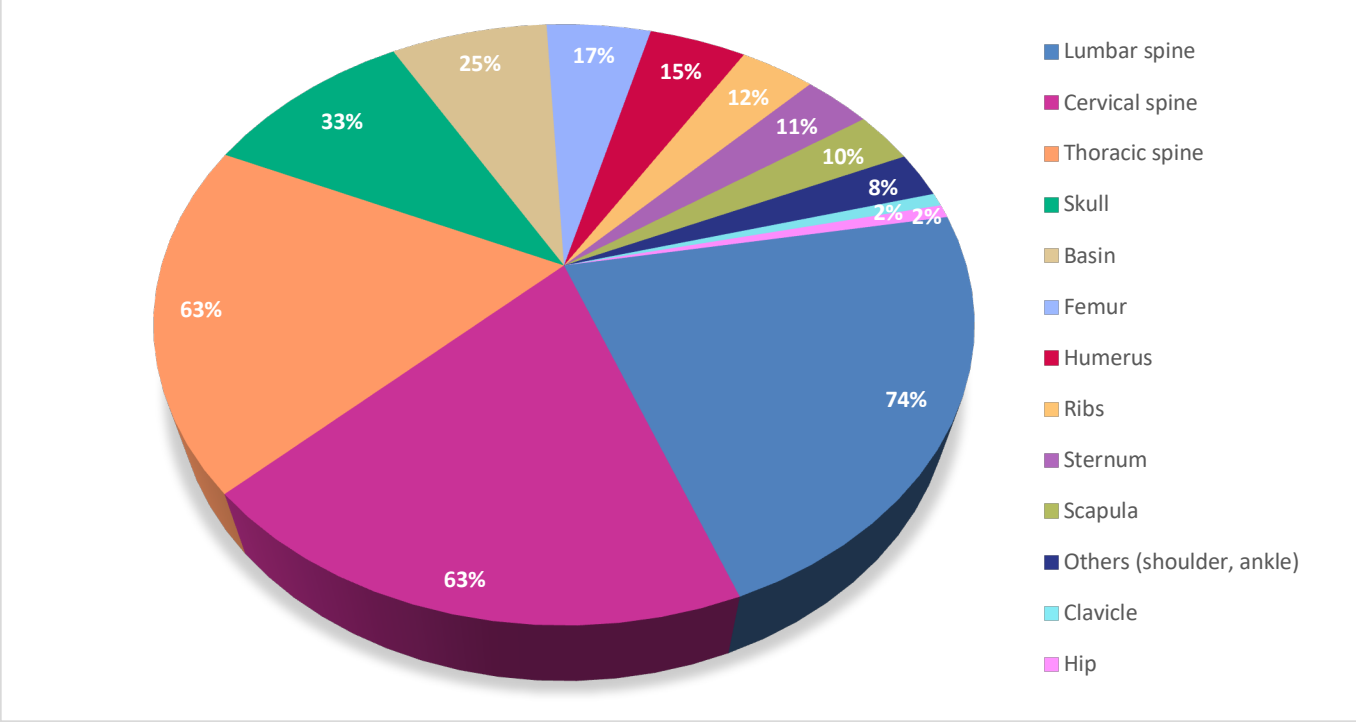


Figure 1: Distribution according to metastatic bone sites

Based on clinical and biological data, particularly thyroglobulin levels, the diagnosis of bone metastases relied primarily on whole-body scans (WBS) post-radioiodine therapy, mainly after the first course of treatment (52% of cases) and in 12% of cases thereafter. Biopsies were performed in 35% of cases, confirming secondary bone involvement. Morphological examinations, such as CT or MRI, enabled diagnosis in 11% of patients, especially in cases of atypical symptoms or locations, while bone scintigraphy was crucial in 6% of cases, generally to assess the extent of bone dissemination.

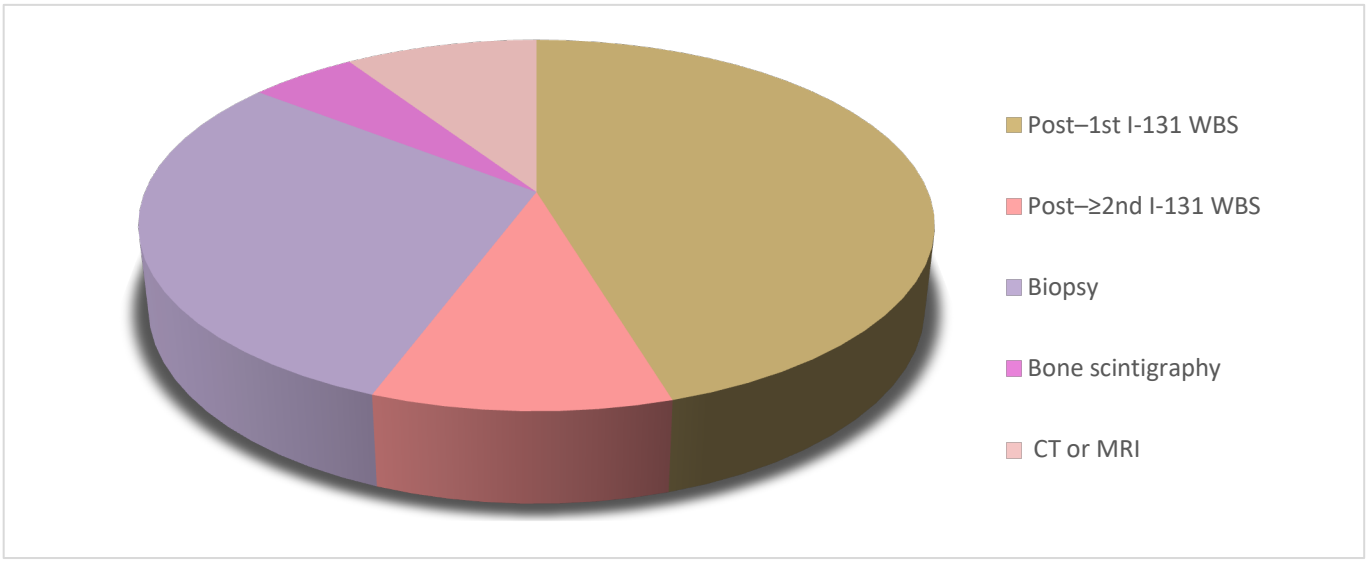


Figure 2: Distribution of diagnostic orientation methods for bone metastases in the series

In our series, CT scans were performed in 66 patients (≈79%) to evaluate bone metastases. They allowed the detection of a wide spectrum of lesions, ranging from subradiological abnormalities initially identified by radionuclide imaging to extensive bone involvement. Among these patients, 42% presented with severe lesions, characterized by expansive bone lysis, cortical involvement, intraspinal extension with spinal cord or nerve root compression, and invasion of adjacent soft tissues. Radiological analysis showed a clear predominance of lytic lesions (72%), while subradiological forms represented 15%, highlighting the major importance of functional and radionuclide imaging for their early detection. Sclerotic and mixed lesions were less common, each representing 5% of cases (Figure 4). Concurrently, 30 patients (≈36%) underwent MRI, primarily in cases of complex locoregional extension or suspected spinal cord compression. Among them, 40% presented with severe lesions, including extensive bone involvement, spinal cord or nerve root compression, and infiltration of adjacent soft tissues and muscles.

Regarding functional imaging, 54 patients (approximately 64%) underwent bone scintigraphy, which detected bone metastases in about 34 patients (approximately 40%). This examination confirmed metastatic spread in many cases and revealed subradiological lesions, although some purely lytic lesions were not detected.

Positron emission tomography with 18F-FDG (FDG-PET), whose primary value remains prognostic, was performed in 4 patients. It identified bone metastases in 3 cases, demonstrated the metabolic activity of the lesions, and revealed additional lesions, including extraosseous ones.

In our series, 34 (approximately 40%) patients underwent histopathological analysis of secondary bone lesions. The examination confirmed the thyroid origin of the metastases in all cases, either by direct biopsy or after surgical excision. In the majority of cases, the immunohistochemical profile of the lesions suggested a well-differentiated follicular thyroid carcinoma.

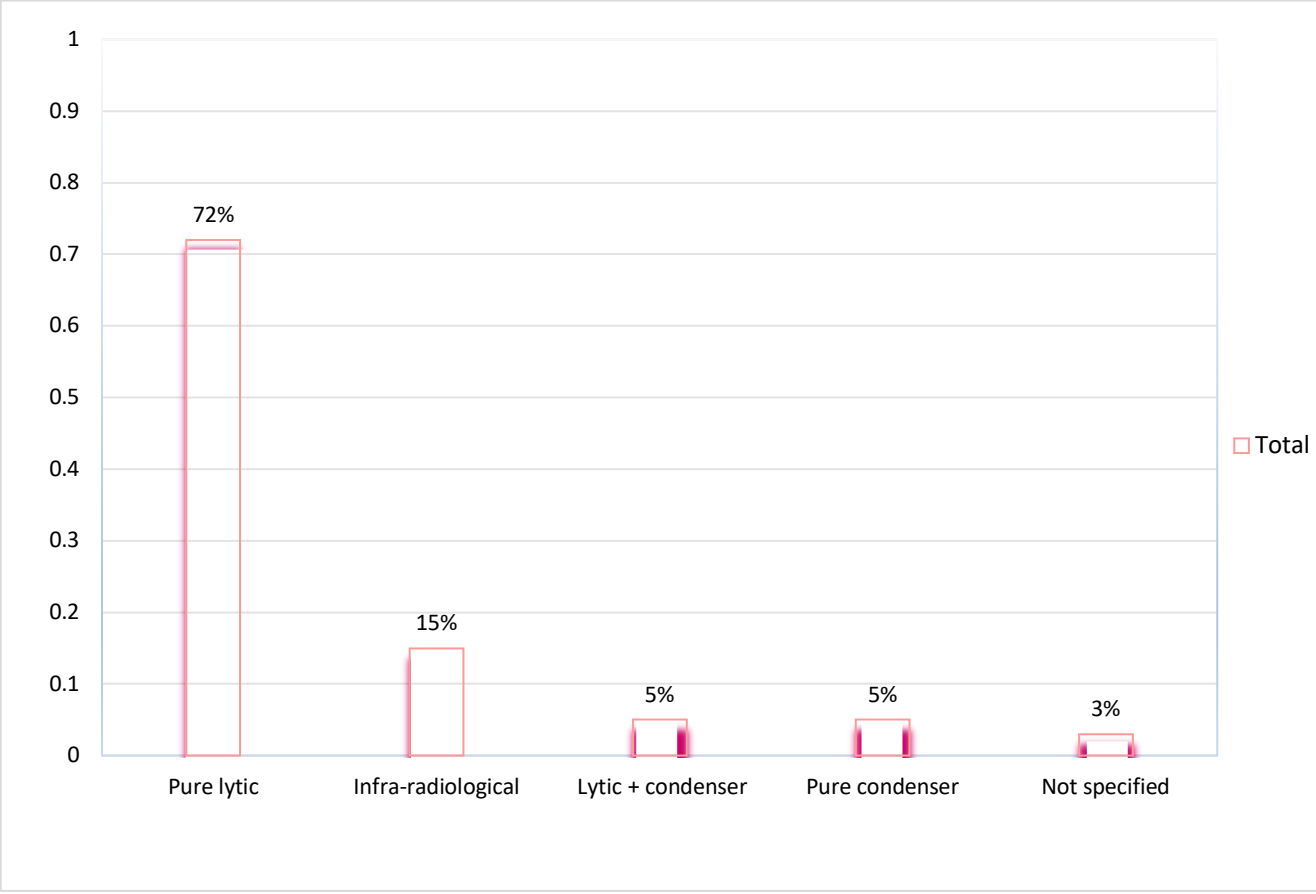


Figure 3: Percentage distribution of radiological patterns of bone metastases in our series

Regarding extra-osseous metastases, 52 patients (≈62%) presented with secondary sites outside the skeleton. Pulmonary involvement was the most frequent, observed in 48 patients (≈57%), followed by lymph node involvement in 16 patients (≈19%). Cerebral metastases were identified in 7 patients (≈8%), hepatic involvement in 3 patients (≈4%), while rarer involvement was noted in the adrenal gland (1 case), muscle (1 case), and mediastinal or subclavian region (2 cases).

In our series, 22 patients (≈26%) underwent targeted surgery for bone metastasis in addition to total

thyroidectomy. Among them, 7% underwent decompressive surgery (laminectomy ± arthrodesis), 8% underwent limb surgery with reconstruction, and 5% underwent simple resection of the bone metastasis.

In our series, 71 patients (84.5%) received radioiodine therapy, of whom 98.5% were treated with a high dose of 3.7 GBq (100 mCi) per cycle, while 13 patients (15.5%) could not receive this treatment, most often due to contraindications such as spinal cord compression, impaired autonomy, or the presence of cerebral lesions. The distribution of the number of cycles reveals some heterogeneity. A short treatment regimen (1–2 courses) was used in 28.5% of patients, while 65.5% received ≥ 4 courses, indicating persistent or progressive lesions. The detailed distribution according to the number of courses is presented in Table 4.

Regarding complementary treatments, 33 patients (≈39%) received radiotherapy, most often for decompressive or palliative purposes, while 18 patients (≈21%) benefited from targeted therapy with tyrosine kinase inhibitors (sorafenib, lenvatinib), generally indicated in refractory or progressive forms.

Number of I-131 treatment cycles	**Patients**	**Percentage (%)**
0 cycles	13	15.5%
1 cycle	7	8.3%
2 cycles	17	20.2%
3 cycles	9	10.7%
4 cycles	17	20.2%
5 cycles	8	9.5%
6 cycles	13	15.5%

Table 4: Distribution of patients according to the number of radioiodine therapy treatments received

The progression patterns observed in our patient cohort showed considerable variability:

- Among the patients studied, 15 cases (18%) experienced a cure, sterilization of the lesions, or a stable course, suggesting a favorable response. The five cured patients (5.9%) were treated solely with radioiodine therapy, with initially subradiological metastases. Histology was dominated by classic papillary carcinomas or follicular variants (73.3%), confirming their generally favorable prognosis.

The majority of patients in this category (46.7%) were at stage T1/T2, while 40% had T3 tumors. Regarding lymph node status, 93% of patients were classified as Nx, 6.7% as N1, and no N0 patients were identified. For metastatic status, 73% were Mx and 26% M1.

More than half of the patients (60%) had no capsular rupture, and 66.7% had no vascular emboli, factors generally associated with a better clinical outcome. Furthermore, the solid variant was found in only one patient, as was the oncocytic variant. The detailed histopathological characteristics of these patients are presented in Table 5.

Finally, 53.3% of patients in this category had metastases associated with bone metastases. Among them, pulmonary metastases were found in all metastatic patients, while only one patient (12.5%) also had lymph node metastases.

Histological type		**Number**	**Percentage (%)**
Classical CPT or vesicular variant		11	73.3
Mixed vesicular + papillary		1	6.7
CVT		1	6.7
Not specified		2	13.3
p-TNM class			
T	***pT1(pT1a/pT1b)/pT2***	7	46.7
	pT3 (pT3a/pT3b)	6	40
	pT4	0	0
	pTx	2	13.3
N	***N0***	0	0
	N1	1	6.7
	Nx	14	93.3
M	***M0***	0	0
	M1	4	26
	Mx	11	73
EC/EV			
EC+		6	40
EC-		9	60
EV+		5	33.3
EV-		10	66.7

Table 5: Histopathological characteristics of patients with a favorable outcome in our series

Forty-five patients (54%) developed iodine-refractory disease, generally after 4 to 5 cycles of radioiodine therapy. The majority of cases corresponded to classic or vesicular forms of papillary carcinoma, representing 64% of patients, while CVT variants accounted for only 4%. Most presented with advanced tumors, with 48.9% T3, 22.2% T2, 15.6% Tx, and 11.1% T4. Lymph node status was mostly unassessed (Nx 82.2%), and M1 was present in 53.3% of patients. Histopathologically, 57.8% showed extracapsular invasion (EC+) and 53.3% vascular emboli (EV+), highlighting an aggressive profile. These characteristics confirm that refractoriness is associated with high TNM stages and a significant risk of metastasis, requiring monitoring and targeted management. Table 6 details the histopathological characteristics of this category.

In the forms with an unfavorable prognosis, there were two oncocytic variants, two insular variants, two solid variants, and two cases of poorly differentiated papillary carcinoma.

In this population, 27 patients (60%) had secondary sites associated with their bone metastases. The most frequently affected sites were the lungs (20 patients, 74%), followed by the lymph nodes (12 patients, 44%) and the brain (5 patients, 18.5%). Less common sites included the liver (2 patients, 7.4%), the adrenal gland (1 patient, 3.7%), the mediastinum (2 patients, 7.4%), the muscles (1 patient, 3.7%), and the supraclavicular region (1 patient, 3.7%). Some patients had multiple metastatic sites simultaneously, illustrating the trend toward multi-organ dissemination in this high-risk population.

Histological type		**Number**	**Percentage (%)**
Classical CPT or vesicular variant		29	64.4
CVT		2	4.4
Mixed vesicular + papillary		0	0
p-TNM class			
T	***pT1(pT1a/pT1b)/pT2***	11	24.4
	pT3 (pT3a/pT3b)	22	48.9
	pT4	5	11.1
	pTx	7	15.6
N	***N0***	1	2.2
	N1	7	15.6
	Nx	37	82.2
M	***M0***	1	2.2
	M1	24	53.3
	Mx	20	44.4

EC/EV		
EC+	26	57.8
EC-	19	42.2
EV+	24	53.3
EV-	21	46.7

Table 6: Histopathological characteristics of refractory patients in our series

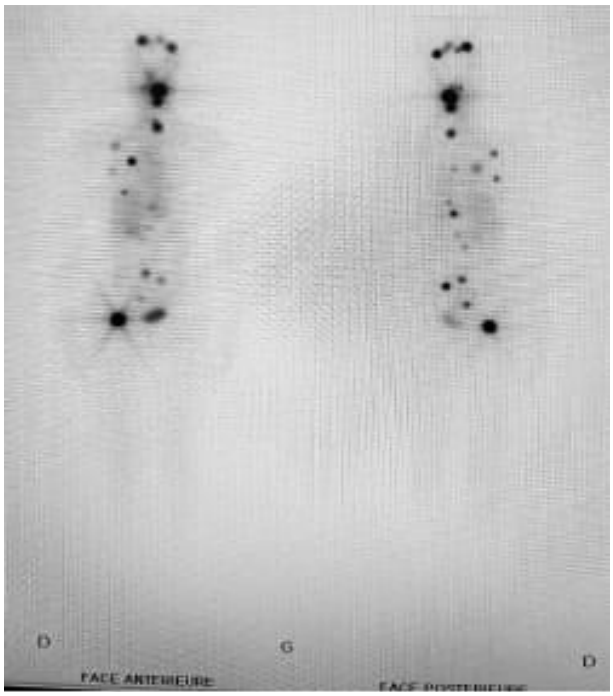
Ten patients (12%) died. The majority had papillary thyroid carcinoma, either classic or follicular, while only one case involved follicular thyroid carcinoma. TNM analysis revealed a predominance of locally advanced tumors, dominated by T4 (40%) and T3 (20%) stages, with indeterminate Tx classifications representing 30% of cases. Lymph node status remained largely undocumented (Nx 70%), although lymph node metastases were observed in 30% of cases. More than half of the patients (60%) had distant metastatic disease (M1), highlighting the severity of the initial presentation. Histopathologically, capsular invasion was reported in only three cases, and vascular emboli were identified in only one patient. Table 7 details the histopathological characteristics observed in this group of patients. Among these patients, 43% (6 cases) presented with multiple extraosseous metastases, most often combining cerebral (found in 5 cases), miliary pulmonary, and lymph node involvement, or hepatic, adrenal, mediastinal, or muscular involvement. Approximately 29% (4 cases) showed more limited metastases, predominantly pulmonary and lymph node involvement. The remaining 28% (4 cases) died without any other identified metastatic sites. In 50% of cases (5 patients), death was attributed to parenchymal brain metastases complicated by herniation and altered consciousness. Two patients (20%) died in the context of a marked deterioration in their general condition. For the other cases, the exact cause of death could not be clearly determined.

Histological type		**Number**	**Percentage (%)**
Classical CPT or vesicular variant		9	90
Mixed vesicular + papillary		0	0
CVT		1	10
p-TNM class			
T	***pT1(pT1a/pT1b)/pT2***	1	10
	pT3 (pT3a/pT3b)	2	20

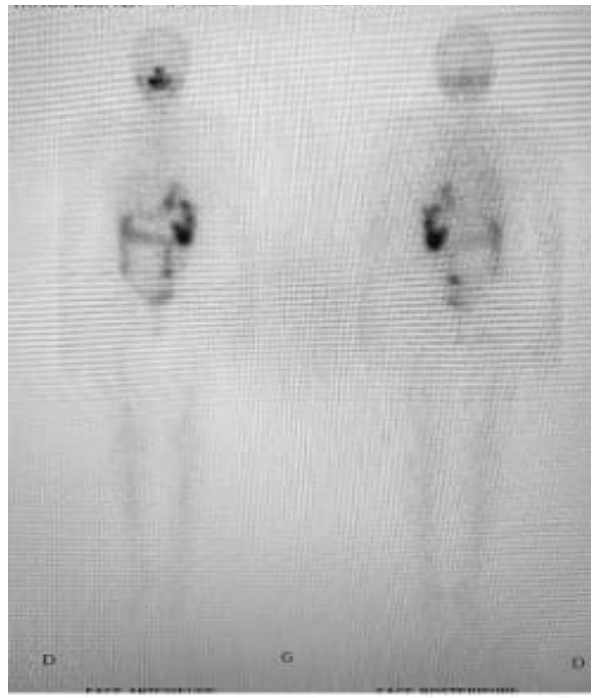
	pT4	4	40
	pTx	3	30
N	***N0***	0	0
	N1/N2	3	30
	Nx	7	70
M	***M0***	0	0
	M1	6	60
	Mx	4	40
EC/EV			
EC+		3	30
EC-/ Not specified		7	70
EV+		1	10
EV-/ Not specified		9	90

Table 7: Histopathological characteristics of deceased patients in our series

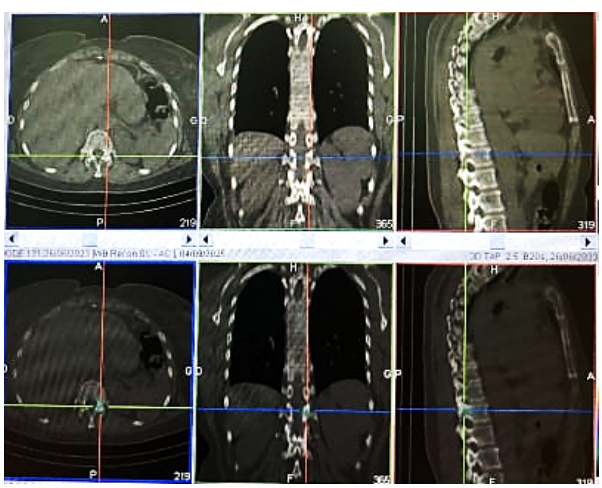
- One patient (1.19%) remains undergoing isotopic treatment, with a third course planned, and their progress remains to be evaluated.
- Thirteen patients (15.4%) were lost to follow-up, making it impossible to document their final outcome.



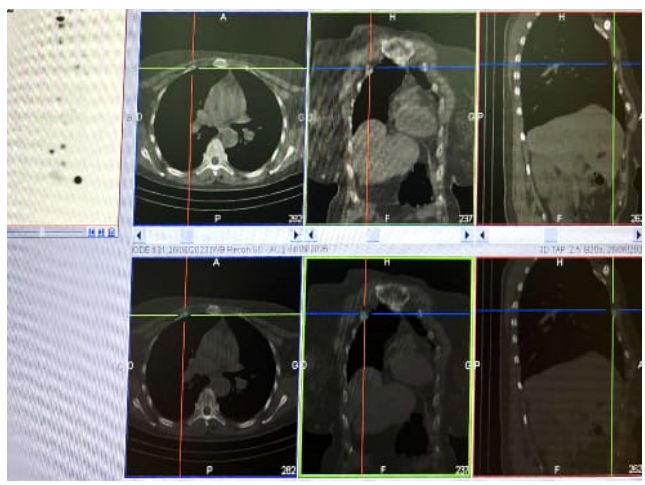
(A): Full body scan after the first treatment



(B): Full body scan after the second treatment

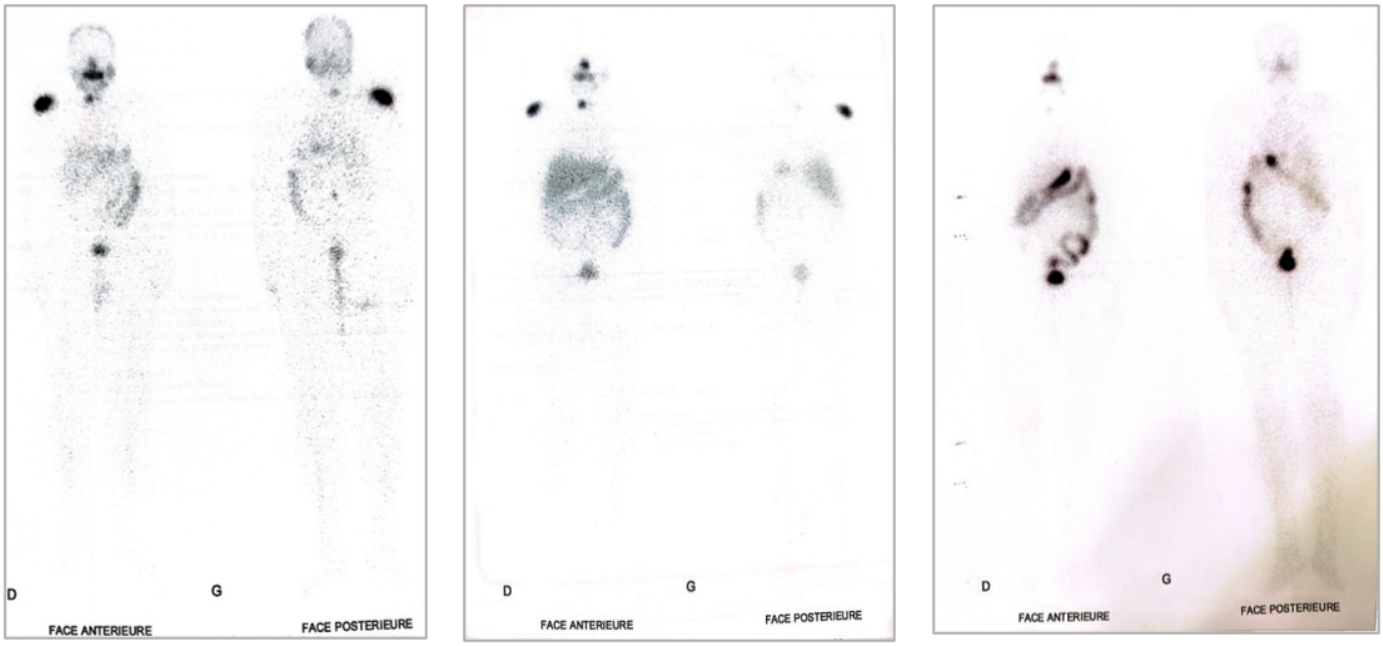


(C)



(D)

Figure 4: A 47-year-old female patient was being treated for papillary thyroid carcinoma, classified as pT3aNxMx, EC+ EV-. She initially received a first course of radioiodine therapy at 3.7 GBq (100 mCi). Post-treatment scintigraphy (Figure A) revealed several foci of iodine uptake located in the skull, vertebral bodies of C2, C3, T2, T7, and T12 (Figure C), the anterior arch of K2 (Figure D), the middle arches of right K4 and K6, the sacrum, and the right femoral head. Most of these foci were not apparent on CT scans, but some corresponded to lytic lesions visible on the localization CT scans (skull, T12, and femoral head). Pulmonary foci of uptake were also identified. The thyroglobulin level during the withdrawal phase before treatment was 12.3 ng/ml. Six months later, the patient was scheduled for a second course of radioiodine therapy. The post-treatment scintigraphy (Figure B) showed complete sterilization of the foci observed during the first course, indicating a favorable therapeutic response to radioiodine therapy.



(A) (B) (C)

Figure 5: A 51-year-old patient, followed for papillary thyroid carcinoma with mixed follicular and papillary components, classified as T3NxM1 (bone metastasis in the right shoulder), initially presented with a painful mass in the right shoulder. He received six cycles of radioiodine therapy, each administered at a dose of 3.7 GBq. Post-treatment follow-up after the first cycle revealed a thyroglobulin level greater than 1000 ng/ml. A whole-body scan (A) showed a cervical iodine-fixing focus corresponding to residual thyroid tissue, as well as a hypermetabolic focus in the right shoulder, correlated on CT scan with an osteolytic lesion of the acromion. During the first five cycles, the biological course was marked by a progressive decrease in the thyroglobulin level, but the iodine-fixing focus in the right shoulder persisted (B). Faced with this local resistance, surgery was performed after the fifth course of treatment, consisting of an excision of the outer third of the right acromial spine. A sixth course of radioiodine therapy completed the treatment. Post-treatment follow-up showed a dramatic decrease in thyroglobulin levels to 0.43 ng/ml, with complete disappearance of the iodine-fixing lesion in the right shoulder on the BCE (C), indicating a complete therapeutic response.

Discussion

Thyroid carcinoma has a high propensity to metastasize to the skeleton compared to other solid tumors. In fact, it is reported as the third most frequent cause of bone metastases after breast and prostate cancer.[4] The average age of onset of bone metastases described in the literature is approximately 60 years.[5] In our series, this age was 56 years, a value comparable to that reported in other studies.[6] There is also a clear female

predominance (74%), consistent with previously published data.[7]Bone metastasis was the presenting symptom in 23.8% of cases, a figure close to that reported by Pittas (28%).[6]

Among the 1,608 thyroid cancer patients followed at our institution during the study period, 84 had bone metastases, representing a frequency of approximately 5.2%. This rate appears slightly higher than that reported by C. Marcocci (3.8%).[8]and CA Proye (4.6%)[9]However, it remains lower than that observed by Anastassios G. Pittas, who found 9% of patients with metastases in his series.[10].

In the literature, several predictive factors for the occurrence of metastases, particularly bone metastases, in thyroid carcinoma have been identified: advanced age, follicular histology, extrathyroidal extension, vascular invasion, tumor size > 4 cm, high thyroglobulin level, poor tumor differentiation, and the presence of certain unfavorable histological variants.[11], [12]The majority of these factors were also found in our population. Although follicular carcinoma is classically described as having a greater tendency than classic papillary carcinoma to metastasize to the bone, the majority of our metastatic patients (84.5%) had papillary carcinoma, a result consistent with other published series.[5], [13].

Metastatic thyroid carcinoma can spread to any bone structure in the body. The most common sites are the spine, skull, and pelvis.[14]In several series, the vertebrae represent the most frequently affected site, an observation that agrees with our results. Furthermore, while the literature reports multiple bone lesions in 50 to 60% of cases[10], [15]They were found in 81% of patients in our cohort, suggesting a more marked dissemination.

In our series, 10% of patients presented with manifestations related to spinal cord compression, a rate close to that reported by Califano et al (11%).[10]Furthermore, the literature indicates that spinal cord compression in the context of bone metastases from thyroid carcinoma can occur in 14 to 50% of cases[10] [16].

The literature reports that combined bone and lung metastases occur in approximately 20% of thyroid carcinoma cases. In our series, this association was more frequent, observed in 48 patients (≈57%). For comparison, CAG Proye found associated metastases in 46% of cases, primarily pulmonary.[9], , whereas in Inés Califano's series, 34.7% of patients presented with associated pulmonary metastases[13]

Due to the complexity of the management, a combined therapeutic approach is generally recommended for patients with bone metastases from thyroid carcinoma.[17]In our series, iodine-131 treatment was administered to 84.5% of patients, surgery was performed in 26%, and external beam radiotherapy, most often for palliative purposes, was offered in 39% of cases. Furthermore, targeted therapies with tyrosine kinase inhibitors were indicated in 21% of refractory or progressive patients.

In our cohort, local surgery for bone metastases was performed in 26% of patients. It primarily played a palliative role (spinal cord decompression, bone stabilization, functional maintenance). Analysis of the results shows clinical/biological stabilization in a few cases, but overall no significant impact on survival, with the

exception of some complete resections of isolated metastases that showed a favorable outcome. However, other reports on the surgical resection of resectable metastases have shown a favorable effect on prognosis.[18].

As reported in the literature, radioactive iodine treatment improves survival in patients with bone metastases from differentiated thyroid carcinoma, particularly when high doses are used.[17]In our series, radioiodine therapy was administered to 84.5% of patients, and the five cured patients (5.9%) received this treatment exclusively, with a median cumulative activity of 200 mCi and initially subradiological metastases. These results highlight the importance of radioiodine therapy in the early stages of metastatic bone disease and confirm previous observations. In advanced stages, combination therapy, including surgery for bone metastases, may be necessary.[19].

The presence of bone metastases is an unfavorable prognostic factor. While the five-year survival rate for differentiated thyroid carcinoma without metastases can exceed 90%, it drops significantly in the presence of bone metastases. According to the literature, factors associated with improved survival include the absence of metastases in organs other than bone during follow-up, the cumulative dose of iodine-131 therapy, and complete surgical resection of bone metastases in patients under 45 years of age.[19], [20].

Conclusion

Bone metastases from differentiated thyroid carcinoma, although relatively rare, represent an unfavorable prognostic factor, associated with a significant decrease in survival and quality of life. Their management relies on a multidisciplinary approach integrating nuclear medicine, surgery, radiotherapy, and systemic therapies, in order to optimize clinical outcomes and improve the prognosis of these patients.

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