



Review article

Bone metastases in thyroid cancer

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ABSTRACT

Whereas preemptive screening for the presence of lymph node and lung metastases is standard-of-care in thyroid cancer patients, bone metastases are less well studied and are often neglected in thyroid cancer patient surveillance. Bone metastases in thyroid cancer are, however, independently associated with poor/worse prognosis with a median overall survival from detection of only 4 years despite an otherwise excellent prognosis for the vast majority of thyroid cancer patients. In this review we summarize the state of current knowledge as pertinent to bony metastatic disease in thyroid cancer, including clinical implications, impacts on patient function and quality of life, pathogenesis, and therapeutic opportunities, proposing approaches to patient care accordingly. In particular, bone metastasis pathogenesis appears to reflect cooperatively between cancer and the bone micro-environment creating a “vicious cycle” of bone destruction rather than due exclusively to tumor invasion into bone. Additionally, bone metastases are more frequent in follicular and medullary thyroid cancers, requiring closer bone surveillance in patients with these histologies. Emerging data also suggest that treatments such as multikinase inhibitors (MKIs) can be less effective in controlling bone, as opposed to other (e.g. lung), metastases in thyroid cancers, making special attention to bone critical even in the setting of active MKI therapy. Although locoregional therapies including surgery, radiotherapy and ablation play important roles in palliation, anti-resorptive agents including bisphosphonates and denosumab appear individually to delay and/or lessen skeletal morbidity and complications, with dosing frequency of every 3 months appearing optimal; their early application should therefore be strongly considered.

1. Introduction

1.1. Overview

Osseous metastases (OMs) occur in only ~4% of all thyroid cancer (TC) patients and are consequently poorly studied but nevertheless associated with considerably heightened morbidity and mortality [1-3]. Although 10-year overall survival (OS) in metastatic TC is ~40% [1], soberingly, 70% of TC patients with OMs have historically died within 4 years of discovery [4]. Recent data remain limited, with 5 and 10-year OS from initial OM diagnosis of 61% and 27%, respectively, in patients with differentiated thyroid cancer (DTC) [5], with poorly differentiated thyroid cancer (PDTC), having worse 10-year OS of only 15% [6]. OMs represent thereby a major clinical problem and the focus of this review.

1.2. Prevalence/Incidence

OMs are observed in all TC histologies, occurring in 2–15% of pooled differentiated TC (DTC) patient series [2,3,7-13]; this literature is summarized in Table 1. Importantly, OMs are at least twice more frequent in follicular (FTC, 7–28%) than in papillary DTC patients (PTC, 1.4–7%) [3,11], and occur also at similarly higher (16–19%) frequency in medullary thyroid cancer (MTC) patients [3,14], stressing the importance of looking for OMs especially diligently in FTC and MTC patients.

Reports of OM frequencies in the literature, however, vary widely (Table 1), likely attributable to biases among many reports that enrich or alter OM frequency in the reports. For example, among OMs in 202 TC patients pooling 37 from a single center and 165 from the literature [15], vertebral OM prevalence by histotype was overall reported very high: 63% FTC, 28% PTC, 5% MTC, 3% HCC (Hürthle cell carcinoma) and 1% for ATC (anaplastic thyroid cancer). Alternatively, a recent

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Table 1
Osseous metastases (OMs) in thyroid cancers (TCs) – major published studies.

Study	OMs/Sample Size/%	Histology	Number of OMs reported/ % of all TC OMs	Prevalence by histology	Number of SREs (%)	Clinical data	Mortality/survival data	Notes
[4] Consecutive Referral Mayo Clinic USA	44/1142 (3.9%)	PTC FTC	15 (34%) 14 (32%)	2% of PTCs 12% of FTCs	Not described	Solitary OMs in 13 (30%) Multiple OMs in 31 (70%)	70% of TC patients with OMs, died < 4 years of detection. At last FU, 42/44 (95%) with OMs had died from TC	
[10] Consecutive referral Univ. of Pisa, Italy	30/780 (3.8%)	PTC	4 (13%)	0.7% of PTCs	Fracture 23%, Surgery 47%	Bone pain initial symptom in 36.7%, Multiple OMs in 11 (37%)	Mean survival 7.1 years; survival at 5 and 10 years - 65% and 18%	
[12] consecutive surgeries CHUP, Lille, France	28/600 (4%)	PTC FTC	2 (7%) 26 (93%)	0.9% of PTCs 7% of FTCs	EBRT, 64%; Surgery in 25%	OMs at Diagnosis, 54%; Multiple OMs, 75%	75% died of TC	RAI cures only 7% of pts with OMs.
[13] Consecutive referral, Institut Gustave- Roussy, France	180/2200 (8%)	DTC	Not reported by histology	Not reported	EBRT + RAI, 64%; EBRT only, 12%; Surgery, 39%	33% with single OM	21% 10-yr survival	
[8] Taipei, Taiwan	39/907 (4.3%)	PTC FTC	11 (28%) 28 (72%)		Not described	Multiple OMs, 80%	65% 5 year survival	
[9] CGMH Linkou, Taiwan	62/1197 (5%)	PTC FTC	20 (32%) 42 (68%)	2% of PTCs 21% of FTCs	Not evaluated	Surgery and EBRT to spine OMs associated with better prognosis	At 6.6 years, 24% of PTC patients with OMs had died. At 7 years, 36% of FTCs with OMs had died	
[2] MSKCC New York 1960–1998 USA	146/1636 (9%) Data at right for subset of 83:	PTC FTC HCC MTC ATC MTC ATC MTC Lymphoma Other	19 (23%) 17 (21%) 9 (11%) 6 (7%) 10 (12%) 6 (7%) 3 (4%) 13 (16%)	Not reported	EBRT, 75%; surgery, 26%; Fracture 27%; Cord comp., 14%	Multiple OMs in 53%; OMs at diagnosis in 47%	10yr-survival from the time of diagnosis of TC was 35% and from diagnosis of OM was 13%	
[7] Hopital Pitie- Salpêtrière, Paris, France	109/1977 (5.5%)	PTC FTC	19 (17%) 77 (71%)	Not reported	Surgery, 77%; EBRT, 36%; Fracture, 13%; cord comp., 34%	Multiple OM in 52% The detection of OM as revealing symptom of TC, was associated with improved survival	84% died; alive at 5, 10, and 20 years: 41, 15, and 7%; median survival 3.9 years (mean, 5.6 years)	Only: bone metastases, total RAI dosage, OM resection correlated with improved survival in patients <45 years old.
[16] Retrospective, MSKCC, New York USA	245 DTCs with OMs [145 from Pitas et al., 143 new]	PTC FVPTC FTC HCC	46 (19%) 25 (10%) 84 (34%) 31 (13%)	Not reported	78% had ≥ 1 SREs, median 5 months from OM Diagnosis	OM symptomatic in 67%; EBRT, 46%; 65% developed 2nd SRE, median 10.7 months after 1st	67% died; mortality higher in patients with OMs who developed SREs vs. those who did not (P < 0.0001).	
[15] Retrospective study Medstar, Washington DC, USA	202 TCs with vertebral OMs (VOMs, 37 single site, 165 literature)	PTC FTC HCC MTC ATC	54 (28%) 120 (63%) 6 (3%) 9 (5%) 2 (1%)	Not reported	Cord 45%, radicular 12%, pain 28%; surg. 67%; RT 25%	Multiple 51%, PTC vertebral OMs asymptomatic 38%	Not reported	RAI avid: -FTC 66%, -PTC 43%
[3] Retrospective longitudinal population-based SEER-Medicare, USA	2457/30,063 (8.2%) (either OMs or SREs) 1173/30,063 (3.9%) OMs	PTC FTC HCC MTC ATC	1703 (69%) 370 (15%) 148 (6%) 142 (6%) 94 (4%)	6.9% of PTCs 15% of FTCs 11% of HCC 16.4% of MTC 13.4% of ATC	5.5% SREs, Pathologic Fracture 4%; myelopathy 0.9%, Surgery or EBRT 1%	Patients with FTC and MTC were more likely to develop OM (OR, 2.25; 95% CI, 1.85–2.74 and OR, 2.16; 95% CI, 1.60–2.86)	OMs associated with greater risk of overall and disease-specific mortality [HR, 2.14; 95% CI, 1.94–2.36 and HR, 1.59; 95% CI, 1.48 - 1.71; P <0.001]	Data appear impaired—as more patients were reported to have SREs than OMs, and fractures appear under-reported as treated.

= Bone event (either OMs or SREs)

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Table 1 (continued)

Study	OMs/Sample Size/%	Histology	Number of OMs reported/ % of all TC OMs	Prevalence by histology	Number of SREs (%)	Clinical data	Mortality/survival data	Notes
[74] Retrospective multicenter study (11 centers) Italy	143 DTCs with OMs	PTC FVPTC FTC HCC PDTC*	35 (24.5%) 32 (22.4%) 48 (33.6%) 13 (9.1%) 15 (10.5%)	Not reported	37.1% SREs (excluding surgery and EBRT); 24.5% fracture, 7% hypercalcemia, 11.9% cord compression	Multiple OMs in 66.4%	27.3% of patients died during the study period; overall mortality was significantly associated with development of SREs and localization of OM to the hip. Overall mortality was lower in patients who received RAI.	SRE-free survival was significantly shorter with metachronous OMs, those involving cervical spine, and those without RAI uptake.
[6] Portugal	86 DTC with OMs	PTC FTC PDTC	41 (47.7%) 34 (39.5%) 11 (12.8%)	Not reported	76.7% at least 1 SRE, of these 53% > 1 SREs; 66.3% EBRT, 26.7% surgery, 25.7% cord compression, 24.2%	Multiple OMs in 59.3%	Five and 10 year OS were, respectively, 58 and 55% for PTC, 63 and 50% for FTC, and 61 and 15% for PDTC (P = 0.415 and P = 0.336, respectively).	Not consistent with other studies as the presence of SREs was not associated with significant increase in mortality at 5 and 10 years.
[33] Israel	64 DTC with OMs	PTC FVPTC FTC PDTC**	13 (20.3%) 13 (20.3%) (32.8%) (26.6%)	Not reported, but of 2268 patients with DTC in registry, 64 (2.8%) met inclusion criteria	Not described	OMs were synchronous in 50%. Distant metastases at DTC diagnosis in 43 (67.2%): 18 bone-only, 10 lung-only and 14 both.	Overall, 54.7% of patients died, 71.4% of DTC. The mean time to death after DTC detection was 9.6 years ± 7.4 years.	Younger age and non-spinal OMs were independent predictors of improved survival.
[5] Retrospective study Medstar, Washington DC, USA	77 DTC with OMs and at least one dose of RAI	PTC FVPTC FTC	18 (23.3%) 17 (22%) 42 (54.5%)	Not reported	31% surgery, 47% EBRT	OMs synchronous with DTC 29 (56%), signs/symptoms of OMs 32 (42%), single OM at dx of OM 26 (45%)	The 5 and 10-year OS after OM diagnosis was 61% and 27%, respectively.	Age at initial diagnosis of DTC, and RAI within 6 months of thyroidectomy, were independent prognostic factors for survival.

Abbreviations: SRE, skeletal related events; DTC, differentiated thyroid cancer; PTC, papillary thyroid cancer; FVPTC, follicular variant papillary thyroid cancer; EBRT, external beam radiotherapy; RAI, radioactive iodine; FTC WD, follicular thyroid cancer well-differentiated, FTC LD, follicular thyroid cancer less-differentiated; SEER, Surveillance Epidemiology and End Results; HR, hazard ratio; Comp, compression; FU, follow up; SREs, skeletal related events.

* Aggressive histology DTC (e.g., presence of tall cell, columnar cell, or hobnail variants of PTC) or PDTC.

** PDTC/intermediately differentiated carcinoma.

population-based study [3] differed; bone metastases and/or skeletal related events developed in 7–15% of DTC (15% FTC, 11% HCC, 7% PTC), 16.4% of MTC and in 13.4% of ATC patients. In consecutive TC patients receiving primary treatment during a 25-year period (1946–1970) at the Mayo Clinic, 9% developed pulmonary, and 3.9% skeletal, metastases [4], with risk of OMs highest (12–17%) among Hürthle cell (HCC) and FTC DTC histologies. Among 44 patients with OMs, the majority, 31 (70%), were multicentric. Mean time from the diagnosis to first OM was shortest in ATC (mean, 0.5 years), and longest in HCC (mean, 8 years); 70% died within 4 years of OM discovery, indicating correlation with poor prognosis.

In a later Memorial Sloan Kettering Cancer Center (MSKCC) series of 146 patients [2], OMs were present upon TC diagnosis in 47%, multiple at diagnosis of first OM in half, likely reflecting enrichment due to referral of poor prognosis patients with extensive disease. In this MSKCC cohort, 27% of patients with OMs suffered pathological fracture, and 14% developed spinal cord compression. 10-year OS from time of TC diagnosis in this group was 35%, and from initial OM was 13%. By univariate analysis, radioiodine uptake by OMs, absence of non-osseous metastases, and treatment with radioiodine were factors associated with favorable OS; the former two factors remaining significant upon multivariate analysis. A review of published data clearly indicates risk of over reporting of OMs due to referral bias in non-population-based studies.

1.3. Clinic impacts/skeletal-related events (SREs)

In a study of 245 patients with DTC and OMs [16], 78% (192/245) presented with, or developed, ≥ 1 skeletal-related event (SRE) after initial detection of OMs. Median time from identification of OMs to first SRE was ~ 5 months, excluding 97 with first SRE at the time of initial OM detection. After initial SRE, 65% (125/192) sustained a second SRE, a median of 10.7 months later. SREs were often multiple; 39% (74/192) sustained ≥ 3 discrete SREs.

Alternatively, a population based study [3] reported OMs and/or SREs among 7.9% of DTC patients per our analysis of their presented data. This lower prevalence appears to reflect absence of referral bias otherwise enriching OM prevalence at referral cancer centers [16]. This population study also reported increased SREs in tall/cell variant PTC (11.9% vs. 6.8% classic PTC, 6.9% follicular variant PTC and 6.3% diffuse sclerosing PTC) and in insular/trabecular FTC (22% vs. 6.8% minimally invasive FTC, 16% classic FTC). Patients > 65 years of age were also found more often to develop OMs and SREs than those ≤ 50 years of age [OR 1.87 with 95% CI 1.45–2.45 and OR 2.4 CI 1.96–2.97]. Older age and male gender were also associated with greater mortality. Patients with FTC and MTC were more likely to develop bone metastases [OR 2.25 95% CI 1.85–2.74 and OR 2.16 CI 1.60–2.86, respectively] or SREs [OR 1.40 95% CI 1.15–1.68 and OR 1.62 CI 1.23–2.11, respectively]. Moreover, OMs were independently correlated with higher risk of overall mortality [HR 2.14 95% CI 1.94–2.36] and with disease-specific mortality [HR 1.59 95% CI 1.48–1.71]. Clearly, analysis of the presented outcome data indicate that OMs represent a major threat to patients with advanced TCs with need for improved and early detection, therapeutics, and preventative approaches.

2. Biology and pathogenesis of bone metastases

Metastases, including OMs, arise from a multistep process involving loss of cell-to-cell adhesion, invasion, and dissemination through the blood and/or lymphatics, and deposition in receptive end organs/tissues (depicted in Fig. 1). Numerous processes have been implicated in fostering metastasis, including epithelial mesenchymal plasticity, cancer stem cells, noncoding RNAs, cytokines, and receptor tyrosine kinase (RTK) pathways [17].

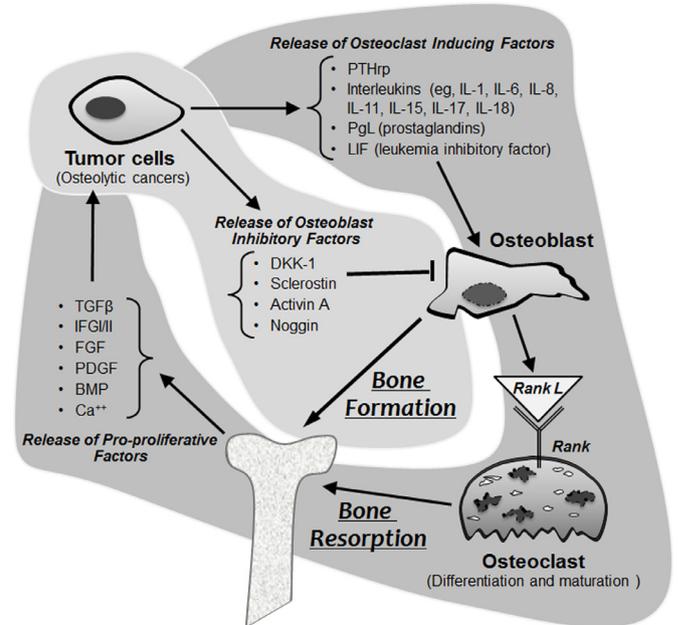


Fig. 1. Cellular compartments and their effects on bone on osseous metastases.

2.1. Epithelial to mesenchymal transition (EMT)

EMT serves essential roles in embryology and in the differentiation of multiple tissues and organs [18] and also contributes to tissue repair. Alternatively, EMT can be disruptive and coopted to cause organ fibrosis and promote cancer progression, convey migratory and invasive properties, induce stem cell-like properties, attenuate apoptosis and senescence, and contribute to immunosuppression to allow tumor evasion of the immune system [19,20].

2.2. Tumor microenvironment

The tumor microenvironment (TM), and not exclusively cancer cells per se, is also intimately involved in metastasis formation via genetic and epigenetic alterations that affect the ability of cancer cells to form viable metastases. Cancers “activate” tumor stroma to release factors, including hepatocyte growth factor (HGF), tumor necrosis factor (TNF)- α , Notch, Hedgehog, transforming growth factor- β (TGF- β), Wingless/int (Wnts), and platelet derived growth factor (PDGF) [18] promoting tumor sustenance, progression and EMT. Hypoxia and inflammation in the TM also induce EMT and metastasis [17,21].

Focal adhesion kinase (FAK), a non-receptor protein kinase implicated in integrin-mediated signaling, oncogenic transformation, and invasion [22,23] is moreover highly expressed in aggressive TCs, functioning as a scaffold for protein-protein interactions and also as a kinase capable of phosphorylating multiple substrates. However, FAK expression also plays a dominant role in regulating TC independent of its kinase functions [24]. cDNA expression in primary, compared to metastatic, FTC has also shown differential gene alterations associated with cell cycle regulation, apoptosis, DNA damage response, angiogenesis, cell adhesion and mobility, invasion, and immune response - emphasizing the importance of TM in metastasis [25].

2.3. Osteoclasts, osteoblasts and bone metastases

Bone itself is also sometimes specifically permissive of metastasis, but effects of tumor on bone are variable. Bone microenvironment contains stroma as well as osteoclasts and osteoblasts that can be coopted or “reprogrammed” by metastatic tumor cells to promote OMs. OMs are broadly defined as lytic, sclerotic, or mixed; many DTC

metastases are predominantly osteolytic.

Integrin $\alpha\beta3$ elaboration by tumor accelerates development of osteolytic lesions, presumably through increased adhesion and bone invasion [26]. Solid tumor cells and multiple myeloma coopt osteoclast and osteoblast functions, triggering cytokine release from bone matrix to disrupt physiological bone remodeling. Marrow-resident tumor cells also secrete factors including parathyroid hormone-related peptide [PTHrp], interleukins [IL-6, IL-8, IL-11, IL-15, IL-18], prostaglandins, and leukemia inhibitory factor (LIF) to activate osteoblast RANKL release to promote lytic lesions. Many cancers also secrete activin A, dickkopf-1, sclerostin, and/or noggin, that alternately inhibit osteoblast differentiation and activity, impairing repair of lytic lesions [27-29].

2.4. The “vicious cycle” of osteolytic bone metastases (Fig. 1)

Bone is unique, in that it is a large repository of immobilized growth factors [TGF β , IGF-I/II, FGF, PDGF, bone morphogenetic protein (BMP)], and calcium. Perhaps unexpectedly, osteolysis is triggered principally by tumor-stimulated osteoclast differentiation and activation - rather than by replacement of bone by tumor per se [30]. Tumor-associated macrophages and metastatic cancer cells often overexpress osteoclast-inducing factors to prompt bone resorption/osteolysis, this osteolysis in turn, leads to the release of active matrix-embedded cytokines/growth factors, like TGF β and IGFs [31,32], thereby promoting tumor growth in bone in a “vicious cycle” (Fig. 1).

Primary and metastatic tumors are frequently heterogeneous [17], with metastases often clonally distinct from their primary tumors and sometimes better suited to preferential adhesion and metastasis formation at specific anatomical sites. The ability of tumor cells to recruit blood supply is critical to the development of macrometastases; >80% of DTC OMs are located in the axial skeleton red marrow - where blood flow is highest, with vertebrae (29–47%), pelvis (22–38%), ribs (17–22%), and femur (11%) representing the most common sites of metastases [2,33]. Bone also contains niches wherein vascular sinusoids lacking basement membranes are permissive of invasion [23,34]. Moreover, cancer subclonal cells that exchange biological information with bone are best able to establish OMs [11,35] via disrupting a normally tightly regulated process called “coupling” linking bone resorption to bone formation [30].

3. Genomic and signaling milieu in advanced thyroid cancer involving bone

3.1. Discovery of pathogenic and “driver” mutations in thyroid cancer

The first evidence to conclusively link genomic alterations to TC came with the appreciation that MTC occurs in a heritable form linked to gain-of-function (activating) germ line mutations in *RET* (REarranged during Transfection). *RET* is a transmembrane receptor protein kinase, signaling through downstream pathways including the mitogen activated protein kinase (MAPK) cascade involving RAS/RAF/MEK/ERK. Activated/mutated *RET* thus drives pro-proliferative signaling and is thought to represent the dominant MTC driver in the majority of patients, realizing that mutated *HRAS* alternatively drives a minority of MTCs. Because *RET* requires ATP as a substrate to phosphorylate and thus activate downstream proteins, the hypothesis arose that *RET* activity might be blocked by small molecule ATP decoys that block downstream signal transduction. Two multi- and *RET*-kinase inhibitors (vandetanib and cabozantinib) are now approved for treatment of advanced MTC, two additional ATP mimics are approved in DTC (sorafenib and lenvatinib) and a combination therapy (dabrafenib plus trametinib) is presently approved for *BRAFV600E* mutated ATC based on limited data [36,37], with additional and more selective *RET* inhibitors now in clinical trial in MTC.

Several key somatic mutations associated with the development and progression of DTC have now been identified, termed “driver

mutations” leading to constitutive activation of either of two seminal signaling pathways in TC: the mitogen activated protein kinase (MAPK: also known as RAS/RAF/MEK/ERK signaling transduction cascade) or/and the phosphatidylinositol 3-kinase/v-AKT murine thymoma viral oncogene homolog 1/mammalian target of rapamycin (PI3K/AKT/mTOR) [38,39] pathway. Tumor initiation is believed to be the consequence of activation of various growth factors or proto-oncogenes like *RET* or *RAS* [39]. Angiogenesis, in part due to increased expression of VEGF in TC, is typical in advanced disease [40-42].

The best characterized mutation in DTC occurs in PTC and involves *BRAF*, in particular *BRAF V600E*, that occurs in 45–59% of PTCs [43], especially in classic and tall cell variant PTC. However, only 10–15% of these tumors evolve into a more aggressive phenotype. Cancer Genome Atlas (TCGA) Project [43] results demonstrated a significant heterogeneity in gene expression pattern among tumors with *BRAF V600E* mutations, identifying at least 4 distinct molecular subgroups among *BRAF*-mutant tumors, indicating that they are heterogeneous despite a common driver mutation. The second most frequently identified DTC driver was *RAS*, which leads to constitutive activation of both MAPK and PI3K/AKT pathways, found mutated in 40–50% of FTC [38].

Of consideration is that the relatively low overall frequency of somatic mutations in PTC compared to most other cancers may contribute to its generally more indolent clinical behavior [43]. TCGA data identified candidate driver mutations in 96% of assessed PTCs, reporting new driver mutations in PTC (e.g. *EIF1AX*) or novel alterations of known drivers (e.g. of *RET*, *BRAF* and *ALK*). TCGA defined individual genes (*CHEK2*, *ATM*, and *TERT*) - and sets of functionally related genes - with alterations or expression patterns defining clinically relevant PTC subclasses. *TERT* promoter mutations (the gene encoding telomerase reverse transcriptase: *TERT 228C>T*), in particular, defined a subset of more aggressive, less differentiated PTCs.

As expected, among TCGA-assessed PTCs, the two most-common drivers were *BRAF V600E* and *RAS*; these seemed largely mutually exclusive, allowing the development of a “*BRAF V600E*-*RAS* score” (BRS). Likewise, a measure of thyroid cell differentiation, termed the “Thyroid Differentiation Score” (TDS), was developed through analysis of clustered thyroid-related gene expression profiles [44]. TCGA further described meta-clusters of *BRAFV600E*-like PTCs (BVL-PTCs) and *RAS*-like PTCs (RL-PTCs). The BVL-PTCs signal preferentially through MAPK, while RL-PTCs signal through both MAPK and PI3K. The RL-PTCs were highly differentiated follicular tumors, occurring in younger patients with lower risk of recurrence. However, BVL-PTCs were less-differentiated tall cell and classical type histological variants with greater ERK pathway activation than RL-PTCs. One of the pathological subgroups of BVL-PTCS comprised >70% of the tall cell variant tumors, which were typically *BRAFV600E*-mutated, had lower BRS and TDS values, and were associated with more advanced stage, high-risk disease.

3.2. Chromosomal rearrangements

The 2 most common chromosomal rearrangements described in TC are *RET*/PTC (papillary TC) and *PAX8*/*PPAR γ* (paired box 8-peroxisome proliferator activated receptor). *RET*/PTC rearrangement results in constitutive activation of the MAPK and PI3K/AKT pathways. Clonal *RET*/PTC rearrangements occur in 10–20% of PTCs and are more commonly found in patients with a history of neck radiation treatment. The *PAX8*/*PPAR γ* rearrangement inhibits the tumor suppressor *PPAR γ* and activates genes responsive to *PAX8*, occurring in 30–35% of FTCs.

4. Clinical evaluation and diagnosis of OMS

OMS are often initially occult. Pain, resulting from mechanical damage from mass effect, or due to release of cytokines triggering periosteal irritation and stimulating pain receptors, is the most common OM presentation [45,46]. After pain, fracture is responsible for

presentation, with the least common clinical presentations now hypercalcemia or spinal cord compression [46]. Skeletal-related events (SRE) constitute a standardized composite endpoint encompassing: (1) spinal cord compression, (2) pathological fracture, (3) requirement for external beam irradiation or surgery to control pain or prevent impending fracture, and/or (4) hypercalcemia of malignancy (rare).

4.1. Laboratory evaluation

Complete blood count; serum calcium/phosphorus, albumin, total alkaline phosphatase, parathyroid hormone (PTH), and markers of bone turnover (serum bone alkaline phosphatase and beta-CTX-telopeptide) constitute key laboratory studies that have potential to provide insights related to the extent of compromise of baseline bone health and related to the extent of active bone destruction ongoing in response to metastatic bony disease. Biomarkers of bone remodeling can also be assessed, but seldom are [30]. In particular, peptides released by osteoblasts/bone formation (including osteocalcin [OC], bone alkaline phosphatase [BAP], or procollagen type 1 aminoterminal propeptide [P1NP]), or by osteoclasts/bone resorption (including urinary hydroxyproline, or β -isomerized carboxyterminal crosslinking telopeptide of type I collagen[β -CTX]) are the primary surrogate means of biochemical assessment of bone remodeling. In clinical practice, however, wherein the primary focus of care is usually on palliation of OMs, these marker are not typically drivers of care or actionable in-and-of themselves and are thus not often assessed.

4.2. Imaging

Imaging is critical to assessing the extent of OMs and to defining optimal treatment, both locoregional and systemic (Table 2). Plain films are most useful in assessing structural bone integrity, risk of fracture, and need for surgery; >50% trabecular bone destruction may be required for lesions to be evident on X-ray, however [46]. More sensitive, are CT (71–100%) [11], and MR (94%) - with 91% accuracy in screening for OMs at 2-mm lesion size [47] and also in defining soft tissue extent and neural compromise [48]. MR T1 images are particularly useful (metastatic lesions typically produce decreased T1 signal due to replacement of fat with water-containing tumor, and correspondingly increased T2 marrow signal) in locations including spine and pelvis, where both insufficiency fractures and metastatic disease commonly occur [49,50]. Corresponding gadolinium uptake and T1-weighted images with fat presaturation render OMs more obvious [51].

Bone scan (with ^{99m}technetium-labeled diphosphonates such as methylene diphosphonate [MDP]) detects osteoblastic reaction to bone damage; since TC OMs are primarily osteolytic, bone scans are relatively insensitive [52]. SPECT (single-photon tomography) can improve OM detection sensitivity and specificity [53,54]. ¹³¹I or ¹²³I whole-body scans (WBS) can alternatively be helpful among RAI-avid thyroid tumors [11,55,56], with ¹²⁴I-PET more sensitive than ¹³¹I-WBS [11]. A small study showed 56, 87 and 100% OM detection for CT, ¹²⁴I-PET, and combined ¹²⁴I-PET/CT imaging, respectively [57]. Alternatively, ¹⁸F-DG-PET is readily available and especially helpful in defining bone involvement in RAI non-avid disease. Although rhTSH stimulation might improve OM detection [58], it remains of uncertain incremental clinical benefit and is not favored.

An important question that is unfortunately not meaningfully addressed in the literature is that of how to most productively integrate the use of various imaging modalities in the clinical evaluations of patients with OMs. It has been our experience that, once OMs are suspected clinically, metabolic imaging using FDG-PET is a very useful screening approach to identify thyroid cancer OMs in the cases of differentiated and anaplastic thyroid cancers; alternatively, gallium dotatate PET imaging may be more helpful in screening for OMs in medullary thyroid cancer. Lesions identified via these screening approaches should trigger further targeted imaging. In the case of

Table 2
Approaches to imaging osseous metastases (OMs).

Imaging modality	Strengths	Shortcomings	OM detection sensitivity	References
Plane Films (X-rays)	Assessment of structural integrity/surgical necessity Readily available, good at detecting structural bone disease	Low sensitivity	44–50%	[46]
CT (Computerized Tomography)	Assessment of neurological invasion and soft tissue extent Assesses metabolism, supplements anatomical imaging	Intermediate sensitivity	71–100%	[11]
MR (Magnetic Resonance)	Improves detection rate when added to bone scan Useful in RAI-avid disease	Higher cost, can affect implantable electronics, longer residence time in scanner, requires general anesthesia in severely claustrophobic patients Relatively Insensitive	94%	[47]
Bone Scan planar scintigraphy	Useful in RAI-avid disease, improved sensitivity over RAI WBS	Useless in RAI non-avid disease; not commonly available	78%	[52]
Bone SPECT (single-photon emission CT)	Most useful in RAI-insensitive disease, in which case sensitivity is very high	Higher cost than planar scintigraphy bone scan Useless in RAI non-avid disease	90.5%	[53]
^{123/131} I RAI (Radioactive Iodine) Whole Body Scan (WBS)			75%	[55]
¹²⁴ I PET/CT			(83% lesion detectability)	[57]
¹⁸ F-DG-PET (Positron Emission Tomography)/CT			87% lesion detectability	[57]
			73–92% NSCLC, 95% breast cancer	[115,116]
				[117]

Abbreviations: OM, osseous metastases; CT, computed tomography; MR, magnetic resonance; SPECT single-photon emission computed tomography; RAI, radioactive iodine; PET, positron emission tomography; NSCLC, non-small cell lung cancer.

identified long bone metastases, plain films are required to best assess structural integrity of bone. Alternatively, in the case of spine metastases, MR imaging is required to in parallel assess the extent of neural compromise so as to adequately inform surgical decision making.

4.3. Selective proactive surveillance and early detection of OMS

Because OMs represent a major problem, contributor to morbidity, and a poor prognostic correlate in thyroid cancers, it is our view that there is a strong rationale to undertake proactive surveillance for OMs in high risk and metastatic thyroid cancers – especially in follicular, Hurthle cell, medullary, and also in all anaplastic thyroid cancers. This said, there is little motivation alternatively to screen for OMs in most PTCs that involve only the thyroid gland or/and neck lymph nodes and in most patient with follicular, Hurthle cell, and medullary thyroid cancers that are resected with expectation of curative intention. We thus propose selective, not universal, screening for OMs based upon thyroid cancer histology, disease extent, risk factors and also cancer behavior.

Firstly, it is critical to aggressively assess symptoms that might reflect bony metastatic disease—this is a given, and does not reflect screening but simply good clinical care. Secondly, patients with prior OMs are at greater risk of additional OMs, and they constitute a particular high risk group that should be proactively and regularly screened for OMs. Thirdly, patients with metastatic and/or high risk follicular, Hurthle cell, and medullary thyroid cancers represent also higher risk patients wherein unexpected changes in tumor markers and/or unpredictable cancer behavior should trigger institution of proactive OM screening.

There are nuisances in terms of how best to screen for OMs that vary depending upon clinical situation. Metabolic/functional imaging can be a very helpful as a rule, as it can image the entire skeleton at once, and has high sensitivity. In follicular cell derived thyroid cancers deemed worthy of proactive OM screening, the first question is whether they might have iodine avid disease; if so, diagnostic RAI imaging can be very helpful; if not, FDG PET is superior for Om screening. In medullary thyroid cancer, gallium dotatate PET is sometimes (or even often) more sensitive than FDG PET in detection OMs and should be alternatively considered if available. In anaplastic thyroid cancer, FDG PET is a suitable screening approach. The key is to be aware of, and prominently consider, OMs in metastatic high risk patient contexts.

5. Treatment of OMS

Treatments can be broadly classified as: symptomatically palliative, disease-modifying, or structurally preservative/restorative – with considerable potential for overlap. Therapeutic options include: pain management/symptom control (symptomatically palliative); systemic therapy (e.g. radioactive iodine, kinase inhibitors, antiresorptive agents; disease-modifying); and regional approaches including: radiotherapy, directed (thermal) ablation, and/or surgery (structurally preservative/restorative), best applied and coordinated by experienced multispecialty teams.

5.1. Pain management - systemic and regional analgesic therapies

The four key medicinal therapeutic approaches to the management of structural pain are: pure systemic analgesics (e.g. acetaminophen, opioids), systemic anti-inflammatory agents (e.g. nonsteroidal anti-inflammatory agents like ibuprofen, glucocorticoids like dexamethasone), agents targeting neuropathic pain (e.g. gabapentin, pregabalin), and regional analgesic approaches (e.g. regional injections or blocks, pain infusion pumps). Broadly construed, palliation of symptoms arising from OMs is now commonly within the purview of the specialty of Palliative Care, yet all providers need familiarity with available approaches as expeditious symptom palliation is central to the care of any

patient.

Pure systemic analgesics include non-narcotic agents such as acetaminophen and oral narcotics (tramadol, codeine derivatives, and morphine derivatives – all of which have long and shorter acting preparations). Our initial approach is to optimize use of non-opioid approaches and to rely upon shorter acting agents up to the point wherein sleep is compromised by pain—in which case longer active preparations become a requirement. Importantly, when other approach to treating pain effectively exist (e.g. focal radiation therapy, ablation, surgery), these should be pursued aggressively in parallel with pharmacological approaches. The goal is to attain robust pain control and to minimize chronic narcotic usage to the extent possible and humane.

There are important reasons to consider shorter acting opioids in preference to sustained release preparations if pain is generally absent at rest and is not disrupting sleep. In particular, if there is no pain to be treated at rest and no disruption of sleep, during those times opioids are potentially adding side effects (e.g. constipation, neurocognitive effects, nausea) without providing counterbalancing benefits, making the rationale for use of sustained release preparations unclear. Thus we favor titrating long acting opioid preparations to allow for fitful sleep, relying upon fast acting/immediate release preparations to treat and preemptively treat activity related pain.

Systemic anti-inflammatory agents include non-steroidal anti-inflammatory agents (e.g. ibuprofen, naproxen) which can relieve pain and also inflammation - and corticosteroids (e.g. dexamethasone, prednisone); these agents can sometimes relieve pain more effectively and/or in a complementary fashion when used in conjunction with opioids. When acute structural compromise such as spinal cord compression is to be palliated, corticosteroids are imperative to minimize neural compromise from inflammation itself, until such time as more definitive structural palliation can be undertaken.

Systemic agents targeting neuropathic pain include newer agents including pregabalin and gabapentin, as well as historical agents such as amitriptyline, which may also assist with sedation and sleep.

Regional analgesia can be accomplished either by local infusion of analgesics, for example by intrathecal infusion of narcotics, or using ablative “nerve block” procedures, such as celiac plexus block.

5.2. Adaptive approaches – physical and occupational medicine

Debility even in the absence of pain from OMs also requires palliation, often best addressed via physical and occupational medicine specialists. Restoration of function through rehabilitation should also be sought whenever possible, else adaptive approaches used, such as braces (in foot drop, for example) or adaptive equipment used to best advantage.

5.3. Structure preservation/restoration

Locoregional/focal bone metastasis treatment strategies targeting preservation or remediation of structural damage from bone metastases include surgery, radiotherapy, embolization, and thermal ablation (e.g., radiofrequency ablation, RFA; or cryoablation); these approaches are best applied in the setting of focally painful or threatening bone metastatic lesions and ineffective systemic therapies (Table 3). Anti-resorptive therapies (e.g. zoledronic acid, denosumab), however, should be strongly considered in parallel.

Surgery: Primary surgical indications include structural instability, fracture and/or pain refractory to other therapeutic approaches. Prophylactic fixation for impending pathologic fracture is usually considered if there is >50% cortical loss in long bones [59]. En bloc resection may optimize local tumor control, and radical surgical removal of OMs in DTC has also been associated with improved survival [60]. Curative OM resection is rare; therefore, radiotherapy is best also administered postoperatively. In spinal cord compression due to cancer, decompressive surgery plus postoperative radiotherapy appears

Table 3
Locoregional therapeutic approaches to osseous metastases (OMs).

Modalities	Technique	Strengths	Weaknesses	References
Surgery	Prophylactic fixation <i>En bloc</i> resection (usually for solitary OM) De-compression surgery	For impending pathologic fracture Radical removal and improved survival Rapid treatment of Spinal Cord compression syndrome	<ul style="list-style-type: none"> • Curative OM resection is rare • Usually requires postoperative radiotherapy 	[59] [60] [61]
External Beam Radiation Therapy (EBRT)	<ul style="list-style-type: none"> • Single fraction: 8 Gy • Multiple fraction: 30 Gy in 10 treatments 	<ul style="list-style-type: none"> • Complete or partial pain relief • Single and multiple fraction regimens equal pain relief • Can at times be done in 1 fraction • > 80% tumor control rate • Can at times be done in 1 fraction. • Minimizes damage to adjacent unaffected tissues via better sculpting of field compared to EBRT 	<ul style="list-style-type: none"> • Risks of adjacent tissue and neurological damage upon re-irradiation • Side effects such as myelopathy or vertebral fractures can occur 	[70] [71] [118,119] [120] [121]
Stereotactic radiosurgery: Stereotactic Body Radiation Therapy (SBRT), CyberKnife	<ul style="list-style-type: none"> • Non-invasive and painless • No anesthesia needed • High energy photon radiation produced by linear accelerator: <ul style="list-style-type: none"> ◦ Single fraction 8 Gy ◦ Multiple fraction to 30 Gy in (2–5) fractions • Requires a collimator “helmet” surrounding patient’s head • Targets only brain or cervical spine Single treatment of high dose radiation. Fixed-array of Cobalt-60 sources 	<ul style="list-style-type: none"> • Can be used in selected cases of prior EBRT • Gamma units have a superior mechanical precision compared to linear accelerator units • Can use for skull, as well as for brain, metastases. 	<ul style="list-style-type: none"> • Gamma Knife require rigid fixation of the head to a reference frame, and this can be uncomfortable • Usually used for brain metastases; cannot treat OMs outside of cranium and upper cervical spine • Not available in most centers • Cost 	[122]
Stereotactic radiation: Proton Beam Radiotherapy “Charged particle radiosurgery”	<ul style="list-style-type: none"> • Uses heavy charged particles such as protons 	<ul style="list-style-type: none"> • Newest type of stereotactic radiosurgery • Higher radiation doses while sparing surrounding healthy tissue • Best control of penetration depth compared to photon or gamma radiation • Can deliver high-quality Planning Target Volume (PTV) that surround the spinal cord • Less invasive than surgery • Can be highly effective 	<ul style="list-style-type: none"> • Under general anesthesia • Pain, transient neurologic deficits or vertebral fracture can result 	[123]
Thermal Ablation	<ul style="list-style-type: none"> • RFA exposure to > 50–60 °C • Cryoablation exposure to – 40 °C 	<ul style="list-style-type: none"> • Can be used preoperatively to embolize hypervascular bone metastases to reduce intraoperative bleeding 	<ul style="list-style-type: none"> • Under general anesthesia • Pain, transient neurologic deficits or vertebral fracture can result 	[65-68]
Arterial Embolization	<ul style="list-style-type: none"> • Vertebral body embolization usually performed using right common femoral artery approach • Embolization should be performed only if a secure catheter position is attainable and spinal arteries are not visualized during spinal angiography • Conscious sedation • Particle embolization • Common choice 150 to 250 µm diameter particles of polyvinyl alcohol 	<ul style="list-style-type: none"> • Alternative approach • Palliation of unresectable lesions • Pain and growth control • Can be used preoperatively to embolize hypervascular bone metastases to reduce intraoperative bleeding 	<ul style="list-style-type: none"> • Rapid but transient relief of symptoms • Cervical metastases obtain blood supply from the vertebral arteries and embolization carries risk of ischemic stroke in the posterior circulation of the brain 	[62-64,124]

Abbreviations: Gy, Gray.

superior to treatment with radiotherapy alone [61].

In patients with pain but without neurological damage or spinal instability, less invasive techniques such as percutaneous vertebroplasty and kyphoplasty may be considered. Percutaneous vertebral augmentation with or without polymethylmethacrylate (PMMA) has also been used after vertebral compression fracture.

5.4. Arterial embolization

Arterial embolization may palliate pain and growth of OMs, particularly in large unresectable lesions [62,63], but is uncommonly applied due to the high success of alternative approaches. Selective embolization of 41 skeletal lesions among 16 DTC patients with symptomatic OMs [64] was deemed successful in 24 lesions (59%); tumor control lasted 6.5 vs. 15 months for embolization alone compared to RAI or irradiation ($P = 0.0146$). Arterial embolization can also be used as a prodrome to surgery, wherein tumor vascularity is reduced with potential to lessen bleeding complications.

5.5. Ablative techniques

Imaging-guided ablative techniques are less invasive than surgery and can be highly effective [65,66], accomplished via exposure to increased (>50 – 60 °C, radiofrequency ablation, RFA) or decreased (-40 °C, cryoablation) temperatures using thermal probes inserted under general anesthesia. Bone defects developing consequent to thermal ablation can be reinforced by percutaneous PMMA cement (“cementoplasty”); however, such approaches are palliative, mainly used to alleviate pain [65].

RFA and cryoablation require highly specialized teams and technologies [11], but has “salvage” potential even after progression despite prior radiotherapy, and among patients not candidates for surgery. RFA is more commonly used in treating liver metastases; cryoablation is preferable in ablating OMs, as it is associated with lessened immediate post-procedural pain compared with RFA and avoids electrical conduction, thus allowing treatments despite presence of metallic surgical or electrical cardiac devices such as pacemakers or defibrillators; ablation of large tumor volumes using multiple cryoprobes is feasible [67].

Specific experience with ablative therapies in TC is limited, so most data are from treating OMs from other solid tumors. In a study of cryoablation of sternal metastases that [68] included one patient with TC; 12 patients underwent 15 sternal cryoablation procedures for pain palliation and local tumor control. The TC patient enjoyed complete resolution of pain with short follow up (1.9 months). Another single institution retrospective DTC study among 25 patients undergoing 49 procedures [cementoplasty (77.5%), cryoablation (14.3%) or radiofrequency ablation (8.2%)] [67] with 4.6 year median follow-up reported complete local remission rates of 71.6%, 66.8% and 60.1% at 1, 2 and 3 years, respectively. Another study of which 16% of patients had TC [69] showed favorable prognostic factors by multivariate analyses to be: oligometastatic ($P = 0.02$), metachronous ($P = 0.004$) or small-size ($P = 0.001$) disease; absence of cortical destruction ($P = 0.01$); or absence of neurological invasion ($P = 0.002$). Toxicity from thermal ablation is low, but local pain or transient neurological deficits or vertebral fracture arise in 5–6%.

5.6. External beam radiation therapy (EBRT) and stereotactic body radiotherapy (SBRT)

EBRT to bone is indicated when pain, risk for fracture, and/or neurological complications are present or predicted and is standard of care when surgery is not indicated [70]. Non-RAI-avid DTC OMs often respond to EBRT with complete or partial pain relief (~80%, lasting >6 months in 50% of cases) [11,71].

SBRT, or similar proprietary technologies such as “Cyberknife[®]”,

allow the delivery of more focused/concentrated radiotherapy compared to EBRT, potentially lessening collateral damage to adjacent structures. SBRT is especially useful in re-irradiating previously EBRT-treated lesions and in treating liver and lung metastases, wherein preservation of adjacent normal tissue is critical. SBRT delivers a maximum of 30 Gy administered in 1–5 fractions, but a lower single dose of 12.5–15 Gy may achieve similar results. Prominent SBRT side effects, especially with treatment of large-volume OMs, however, can include myelopathy or late vertebral fractures. Newer approaches using alternatives to photons - such as protons or other “heavy particles” - can also be very helpful in retreating previously irradiated areas and those close to critical adjacent structures, but is not widely available and is less well studied.

5.7. Systemic therapies - radioactive iodine (DTC only)

RAI targets only RAI-avid disease, and is thus ineffective in RAI-insensitive DTC; RAI is moreover ineffective in MTC and ATC. Factors causing low RAI efficacy (29–35%) [10,11,72] in DTC include: large skeletal burden and high dose requirements for effective treatment of OMs. One study of 394 individuals with lung and/or OMs showed that, although two-thirds of patients had ^{131}I uptake in their metastases, only 46% achieved a complete response to therapy [13]. Prognostic factors for complete response in OMs to RAI were: younger age, ^{131}I uptake in metastases, and smaller extent of skeletal disease. Long-term survival in this cohort was 33% at 15 years; multivariate analysis demonstrated younger age, early metastasis detection, well-differentiated TC, RAI-avid metastases, small skeletal extent of disease, and year of discovery of metastases to be favorable factors with regard to OS. Among the 46% of patients who achieved complete RAI response, 15-year survival was 89% vs. 8% among those who did not. Better prognosis in patients with solitary OMs, or alternatively among those who underwent bone surgery before RAI, has also been observed [73], suggesting benefit of RAI in a subset of DTC patients with OMs. In an Italian multicenter study of 143 patients with DTC-related OMs, overall mortality was found lower in association with RAI therapy (HR 0.10; $P = 0.02$) [74]. However, the time frame of RAI administration seems to have importance, with patients receiving RAI within 6 months of thyroidectomy having better outcomes. It is also important to aim for a multimodal approach; median OS for OM DTC patients is of 3.9 years vs 7.7 years for those treated with RAI alone vs those treated with RAI plus combination therapies, respectively [5].

5.8. Re-differentiation agents in DTC: RAI “resensitization” therapy (DTC only)

Re-differentiation of TCs may allow for reconstituted effective RAI therapy. Selumetinib, a MAPK kinase [MEK1 and MEK2] inhibitor, increased uptake of iodine-124 in 12 of 20 patients (4 of 9 patients with *BRAF* mutations, and 5 of 5 patients with *NRAS* mutations) [75]. Eight of the 12 reached the dosimetry threshold for RAI, including all 5 with *NRAS* mutations. Of 8 treated with radioiodine, 5 had confirmed partial responses and 3 had stable disease, while all patients enjoyed decreased thyroglobulin levels (mean reduction, 89%). Striking increases in selumetinib-induced iodine-124 uptake were also observed in OMs, suggesting potential benefit even in this context.

Another candidate therapeutic strategy involves mutation -guided “personalized” targeted therapy. Because aggressive TC develops when multiple signaling pathways are involved and new mutations are acquired, characterizing which genetic alterations and pathways are involved in a specific patient may reveal additional patient-specific therapeutic options that may be in flux [38].

5.9. Systemic approaches other than RAI (cytotoxics)

The majority of therapeutic emphasis in the context of bone

metastases in thyroid cancer has been placed on treating established and threatening lesions, as opposed to prevention and preemptive approaches. Moreover, emphasis has been on focal therapies, as opposed to systemic therapies in this setting. However, emerging data support efficacy also of systemic approaches to treating OMs in thyroid cancer with systemic approaches; we review available data below and place it into clinical context.

For many years doxorubicin was the only FDA-approved chemotherapy for advanced TCs; low efficacy [11] associated with significant toxicities [76,77] limit use. Durable responses are uncommon [39]. Among 49 non-anaplastic patients treated over 10-years with 5 successive chemotherapeutic protocols containing doxorubicin [78] only 2 objective responses were noted (3%). Nonetheless, cytotoxic chemotherapy might occasionally have a role in selected patients unresponsive to RAI and to the newer kinase inhibitors therapies [66,79], but its roles in treating OMs in thyroid cancer remain unknown.

5.10. Radiopharmaceuticals other than RAI for bone metastatic disease

Radioisotopes emitting beta particles [e.g. strontium-89 (⁸⁹Sr), samarium-153 (¹⁵³Sa)] that home to bone may also palliate bone pain from OMs in a variety of cancers, typically requiring 1–4 weeks for symptom palliation, and yet are uncommonly utilized. These agents target healthy as well as diseased bone, and can damage hematopoietic reserve, and have therefore traditionally been applied primarily for pain palliation in the setting of end-stage disease, especially in prostate cancer. Duration of pain palliation can be >18 months, reducing analgesic use 40–95% [80], but when used alone may not convey OS benefit [46], perhaps because it is used so late in disease course.

Radionuclides with high linear energy transfer α -particles like Radium-223 (²²³Ra) have enhanced radiobiological potency compared to β -emitting radionuclides [81]. Advantages of α -emitters include delivery of high-energy radiation over a much shorter distance than β -emitting ¹⁵³Sm or ⁸⁹Sr. ²²³Ra is FDA-approved for the treatment of castration-resistant prostate cancer with symptomatic OMs, but is being investigated in a phase II clinical trial in TC (NCT02390934) at the Gustave-Roussy Institute in France. These agents are presently best otherwise reserved for persistent or recurrent multifocal bone pain after EBRT and/or other forms of local therapy.

5.11. Bone microenvironment-targeted treatments

The concept that locally increased bone resorption and decreased bone formation are critical for OM progression (Fig. 1) suggests that, if osteolysis might be disrupted, bone lesions might be stabilize *even without direct cancer targeting*. The clinical rationale for the development of specific inhibitors of bone resorption has arisen from an understanding that the bone microenvironment itself helps facilitate OM growth (Fig. 1).

At present, two classes of antiresorptive agents are available for use in thyroid cancer OMs, realizing that most data relate to other solid tumor OMs. Bisphosphonates represent one of the two classes, and bind preferentially to hydroxyapatite crystals in bone at sites of active metabolism, reaching very high local concentrations. Bisphosphonates are slowly released from bone matrix during bone resorption, and are internalized by osteoclasts within bone resorption lacunae, leading to osteoclast apoptosis, in turn reducing osteoclast-mediated bone resorption including that stimulated by OMs.

Nitrogen-containing bisphosphonates (zoledronic acid, pamidronate, ibandronate) also inhibit farnesyl diphosphate synthase, an enzyme in the mevalonate pathway, thereby attenuating prenylation of small GTPase signaling proteins in osteoclasts as required for normal cellular function. Inhibition of farnesyl diphosphate synthase seems to account for *in vitro* antitumor effects, and for activation of T-cells resulting in release of tumor necrosis factor- α , a feature of the acute-phase response sometimes seen after bisphosphonate treatment in

humans. Non-nitrogen-containing bisphosphonates such as clodronate do not inhibit farnesyl diphosphate synthase or protein prenylation, but instead trigger formation of cytotoxic metabolites in osteoclasts that can lead to osteoclast dysfunction [82].

In vitro and *in vivo* studies indicate that nitrogen-containing bisphosphonates induce apoptosis of osteoclasts and tumor cells alike [83]. In TC cell lines, clodronate inhibits cell growth of endocytic macrophages, osteoclasts, and cancer cells in a dosage-dependent manner [84]. Concentrations required for these effects *in vitro*, however, are much higher than those used in clinical practice, so relevance to observed clinical effects remains uncertain [11]. In postmenopausal breast cancer, early zoledronic acid use seems to produce improved cancer-specific and all-cause mortality [85]. A recent meta-analysis showed that adjuvant bisphosphonate use reduces the rate of breast cancer recurrence in the bone and improve breast cancer survival in women who were postmenopausal when treatment was started, indicating that decrease in bone recurrence was the likely driver of disease free survival [86].

Alternatively, denosumab is a humanized monoclonal antibody [directed against receptor-activator of nuclear factor-kappa B (RANKL)] that has potent activity blocking bone resorption when administered subcutaneously, with good results in treating OMs in a variety of solid tumors. Unlike bisphosphonates, wherein dosage-reduction is required in patients with renal dysfunction, denosumab has no renal liability – but comes at greater cost than bisphosphonates. Zoledronic acid and denosumab are approved for treatment of OMs based upon delayed time to first SRE and decrease SRE incidence across multiple cancers, but is not specifically approved for TC OMs [87–93] (Supplemental Table 1). Randomized controlled trials have been performed to evaluate bone-directed therapies for treatment of bone metastasis (Supplemental Table 1), but not yet in TC. On this basis, antiresorptive agents are the standard of care for treatment and prevention of OMs in solid tumors and myeloma.

Very few studies specifically evaluate antiresorptive therapy in advanced TC (Table 4). In an early study [94], 10 TC patients with painful osteolytic bone metastases receiving pamidronate monthly experienced decreased bone pain, improved quality of life, and partial radiographic responses. Another study [95] evaluated 50 patients with DTC OMs; 22 received zoledronic acid (ZA) and 28 did not; SREs occurred at lower frequency in ZA-treated patients (3/22, 14% vs. 14/28, 50%; $P = 0.007$) also associated with delayed onset of SREs ($P = 0.04$) - but two ZA-treated patients (9%) developed jaw osteonecrosis. The same group [96] later studied 19 ZA-treated patients compared to 16 historical controls. Eight patients (42%) experienced one SRE during an observation period [EBRT, $n = 4$ (21%); surgery, $n = 3$ (16%); metastatic spinal cord compression, $n = 1$ (5%)], but none receiving ZA experienced bone fracture or hypercalcemia, with fewer ($P = 0.017$) and later onset ($P = 0.042$) of spinal cord compression also noted, suggesting benefit specifically in TC OMs. In a recent retrospective multicenter study in a “real life setting”, of 143 DTC–OMs patients, 32 (22.4%) received antiresorptive therapies (31 zoledronic acid and 1 denosumab) and in most cases these drugs were started after the development of a SRE. The limited number of patients treated with ZA precluded the evaluation of the potential effect of ZA in preventing SRE in clinical practice [74].

The situation in MTC has also been preliminarily examined. In a study [14] of OMs among 188 MTC patients, 45/180 (25%) were found to have OMs within 3 months of MTC diagnosis. The numbers of OMs were as follows: > 10 (65%), 6–10 (12%), 2–5 (16%), and 1 (6%). Spine was most commonly affected (92%), followed by pelvis (69%) and ribs (53%); 48% experienced ≥ 1 SREs (60% had 1 and 40% had ≥ 2 SREs), most commonly requiring radiotherapy (67/90; 74%) or developing pathological fracture (21/90; 23%). The first SRE most often affected spine (58%), followed by pelvis (17%) and extremities (11%). Patients with > 10 OMs were more likely to experience later SREs (odds ratio [OR] = 2.4; $P = 0.007$), but no difference in 5-year OS after MTC

Table 4
Antiresorptive therapy in thyroid cancer (TC) patients with osseous metastases (OMs) – published studies.

Study	Sample size/ %	Histology	Number of OMs	Therapy administered	Number of SREs (%)	Clinical data	Mortality/survival data	Notes
[94] Prospective trial Napoli, Italy	10 TC patients with painful OMs	PTC	2 (20%)	Pamidronate (90 mg IV monthly, 12 months)	Not Assessed	Decrease bone pain ($p < 0.005$); performance status improved ($p < 0.05$)	> 50% decrease in OM lesion in 2/ 10; 5/10 achieved OM stabilization.	Small study population
[95] Retrospective study Cancer Institute Hospital, Tokyo, Japan	50 patients with OM from DTC	MTC	2 (20%)	Group A: sham (n = 28); Group B: zoledronic acid (n = 22)	SREs: 50% Gp A; 14% Gp B (P = 0.007)	Multiple OMs in 28 (56%); Two Group B patients developed ONJ	27 (54%) died of the disease.	Zoledronic acid associated with delayed SREs (P = 0.04).
[96] Prospective, single arm; Cancer Institute Hospital, Tokyo, Japan	19 patients with OM from DTC	FTC	24 (48%) [GrpA 11; GrpB 13]	Zoledronic acid, 4 mg IV monthly	SREs 42%; EBRT 21%; Surgery, 15%	Multiple OMs 47% No responses; stable disease, 53%	32% died of TC.	No correlations between changes in bone metabolic markers and SRE development.
[141] Retrospective study M MDACC, Houston, Texas USA	188 MTCs with OM of 1008 MTC (19%)	MTC	Not reported	84/177 (47%) received: Zoledronic acid IV (n = 64), or Pamidronate IV (n = 16) or Denosumab IV (n = 12)	≥ 1 SRE in 48%; EBRT 74%, Fracture 23%, Surgery 13%, HCM 7%, Cord comp 3%	Only 6% had single OM lesion 168 (89%) had non-OM distant metastases.	At 1.6 year (0–23.2) Median follow-up 59%, dead No difference in mortality was seen between patients with and without antiresorptive agents.	Out of 120 patients with germline mutation <i>RET</i> testing, 25% were positive.
Mazziotti et al. 2018 Retrospective multicenter study (11 centers) Italy	143 DTCs with OMs	PTC	35 (24.5%)	32 (24%) received anti- resorptives: 31 zoledronic acid, 1 denosumab	At the start of treatment, 24 of 32 (75%) receiving zoledronic acid or denosumab had ≥ 1 SRE.	Patients treated with ARs had less frequently PTC and > frequently aggressive histotypes, > frequent metachronous OMs, and > frequent pathological fractures.	27.3% of patients died during the study period; antiresorptives had no significant effect over OS (P = 0.36).	Use of ARs was not included in the SRE-free survival analysis, since in most cases the drugs were started after SRE development.
[6] Portugal	86 DTC with OMs	FTC	41 (47.7%)	17 (19.8%) received bisphosphonates: pamidronate acid in 9, zoledronic acid in 5 and clodronic acid in 3	76.7% at least 1 SRE	The presence of SRE was not significantly associated with therapy with bisphosphonates (P = 0.454).	At the end of the study, 50 (58.1%) had died.	Only a small number of patients received bisphosphonates.
[5] Retrospective study Medstar, Washington DC, USA	77 DTC with OMs and at least one dose of RAI	PTC	18 (23.3%)	Bisphosphonate 30 (39%), denosumab 22 (29%)	31% surgery, 47% EBRT	OMs synchronous with DTC 29 (56%), signs/symptoms of OMs 32 (42%), single OM at dx of OM 26 (45%).	In the total cohort, patients who received denosumab had longer median OS than those who did not (7.7 vs 5.2 years; P = 0.03). Those who received bisphosphonates seemed to have slightly improved survival (7.8 vs. 6.0 years; P = 0.31).	In the RAI plus combination group, individual analysis showed no significant improvement in median OS with antiresorptives.

Abbreviations: SRE, skeletal related events; OM, osseous metastases; DTC, differentiated thyroid cancer; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; MTC, medullary thyroid cancer; Grp, group; Mo, month, EBRT, external beam radiotherapy; HCM, hypercalcemia of malignancy; Comp, compression.

* Aggressive histology DTC (e.g., presence of tall cell, columnar cell, or hobnail variants of PTC) or PDTC.; ARs, antiresorptives.

diagnosis was observed between patients with (31%) or without (23%) SREs ($P = 0.11$). In all, 84 of 177 (47%) received antiresorptive agents, 13 receiving multiple agents; median duration of antiresorptive treatment was 3.9 months (0–117) with median total doses of 2 (1–64). ARs were given to patients with more lesions ($P = 0.006$) and more involved sites ($P = 0.026$). In a published abstract [97], fewer patients receiving antiresorptive therapy developed SREs compared with controls (25% vs 42%, $P = 0.026$), suggesting benefit, with the effect remaining significant after adjusting for age, gender, and distant non-bone metastases ($P = 0.047$). In addition, fewer antiresorptive therapy patients developed subsequent OMs (59% vs 84%, $P = 0.005$), suggesting also a chemopreventive role.

The ATA 2015 DTC guidelines [66] recommend that bisphosphonate or denosumab therapy be considered in patients with diffuse and/or symptomatic OMs from RAI-refractory DTC, either alone or concomitantly with other systemic therapies. Adequate renal function is recommended before bisphosphonate therapy, with serum calcium and 25-hydroxyvitamin D levels assessed before bisphosphonate or denosumab therapy. Dental evaluation was also recommended before use of either agent. The ATA MTC guidelines [98], due in part to limited data regarding OMs in MTC, provided only one recommendation regarding use of antiresorptive agents (denosumab or bisphosphonate), suggesting limiting their use to patients with painful OMs.

Importantly, care must be taken when using anti-resorptives in the setting of patients with hypocalcemia such as that due to post-surgical hypoparathyroidism; if administered, antiresorptive agents should be used cautiously and only after correction of hypocalcemia and close monitoring after administration. Of note also is that patients should be monitored for the development of additional antiresorptive related adverse events. The prevalence of atypical subtrochanteric femoral fractures in the setting of OMs treated with IV bisphosphonates appears to be low, but noteworthy [99]. Osteonecrosis of the jaw (ONJ) can occur in the setting of OM treatment with anti-resorptives, and dentoalveolar trauma seems key in its development, with denosumab likely associated with an earlier occurrence of ONJ when compared to zoledronic acid and pamidronate [100]. Preemptive dental evaluation plays an important role in the prevention of ONJ, and reduced frequency of administration of antiresorptive agents to every 3 months may also be helpful—with available evidence indicating similar efficacy and lessened toxicities in response to every three month, as opposed to monthly, dosing in several types of solid tumors.

5.12. Other non-bisphosphonate non-RANK ligand-directed candidate treatments for bone metastases

Investigation of the biology of OMs has identified additional molecular targets of potential relevance to OM pathogenesis, including TGF- β and PTHrP [27]. Moreover, cathepsin K inhibitors (e.g., odanacatib) decrease bone resorption while simultaneously maintaining bone formation, but odanacatib development has been recently stopped due to increased risk of stroke. Src inhibitors (e.g., dasatinib, saracatinib, bosutinib) may also palliate OMs, as Src is activated in response to RANKL/RANK interactions in osteoclasts. mTOR acts both upstream and downstream of AKT, at a key junction in the PI3Kinase pathway. Drugs targeting mTORC1, such as the rapamycin analogues (rapalogs) everolimus and temsirolimus, are under current investigation. Interestingly, RANKL promotes osteoclast survival by signaling through mTORC1, whereas rapamycin induces osteoclast apoptosis and suppresses *in vitro* bone resorption.

Other attractive emerging therapeutic targets include Endothelin-1 (ET-1), as ET-1 seems to play a role in the formation of osteosclerotic lesions; Activin-A, which in OMs is produced by tumor cells, and stimulates bone degradation, inhibits osteoblast differentiation, and stimulates osteoclast differentiation; Wnt, which drives osteoblastogenesis (bone formation), is normally inhibited by specific antagonists such as dickkopf-1 (DKK-1), sclerostin, and frizzled-related proteins, resulting

in reduction of new bone formation; tumor cells (breast, prostate, lung, myeloma) that metastasize to bone are capable of producing these antagonists of bone formation, consequently blocking these antagonists represent a potential therapeutic target [27,101].

Although the imbalance between bone formation and bone resorption in osteolytic cancers is mainly due to increased bone resorption mediated by osteoclasts, decrease in bone formation may also be occurring in patients with OMs. Hence, agents that counteract inhibition of osteoblast activity may also be of therapeutic relevance in treating OMs, and is an area for future investigation.

5.13. Kinase inhibitor (MKI) therapy

Many MKIs have been specifically investigated as therapeutics in advanced DTC and MTC, including sorafenib, lenvatinib, sunitinib, axitinib, pazopanib, motesanib, vandetanib and cabozantinib—but not specifically in the context of OMs. Vandetanib and cabozantinib were approved for treatment of MTC (medullary TC) in 2011 and 2012 respectively [102–104]. More recently, sorafenib and lenvatinib were approved in advanced iodine-refractory DTC (November 2013 and February 2015, respectively) [105,106], and dabrafenib combined with trametinib was approved in ATC. With the exception of a small, recently completed, International Thyroid Oncology Group (ITOG) trial of the effects of cabozantinib on OMs in DTC [107], MKIs, however, have not been specifically studied with respect to effect on OMs, albeit some studies have examined OM outcomes.

In the DECISION trial [105], at baseline 57 in the sorafenib group and 56 in the placebo group had OMs. Sorafenib was associated with a 5-month improvement in median progression-free survival (PFS); in the SELECT trial, lenvatinib alternatively showed a median PFS 14.7 months longer than placebo [106]. Both drugs were associated with frequent side effects, most managed by dose reduction or interruption, plus standard clinical interventions. In both trials, if progression was seen in the placebo group, patients were allowed to switch to the active treatment arm, which may be one of the reasons neither trial achieved a statistically significant prolongation of OS. Lenvatinib was associated with frequent adverse events, with 75% of treated patients suffering \geq grade 3 toxicities; frequent adverse events remain a challenging limitation of all MKIs. Patient selection is thus critically important, with providers astute in patient selection to assure favorable risk/benefit profiles.

Emerging data, however, appear to indicate that MKIs have constrained efficacy in treating OMs [102]. A single center study [108] indicated that different responses of metastases involving different tissues may occur during MKI treatment within a single patient, with OMs more MKI refractory. In the SELECT trial [106], progression of existing OMs occurred in 9 of 38 in the lenvatinib group (23.7%), and in 23 of 39 in the placebo group (59%), however, indicating that lenvatinib likely incompletely restrains OMs, but yet has some benefit.

Given the oncogenic roles of mutations in the serine kinase BRAF, tyrosine kinase (TK) RET and RAS, selective BRAF inhibitors (vemurafenib, dabrafenib) and mTOR inhibitors (everolimus, temsirolimus) are under investigation in DTC, as are inhibitors of ALK, EGFR, MET and MEK. No trial of these agents, however, is examining bone-specific disease-modifying activity; more specific study of effect on TC OMs is clearly nonetheless needed.

6. Assessing response to therapy in OMS

A variety of imaging approaches are available to assess bone lesions, with the utilities of these approaches varying depending upon intended purpose(s). On plain films, a positive response to treatment may be visible in the form of lesional sclerosis in the absence of expanding lytic component. If a bone scan is used, a “flare phenomenon” can occur [11], with increased uptake seen initially due to healing bone that can instead be confused with disease progression. Therefore, increased bone

metabolic activity on bone scan or PET imaging should be interpreted with caution. Importantly, RECIST [109] (Response Evaluation Criteria in Solid Tumors) does not include criteria specific to the evaluation of OMs. However, the WHO (World Health Organization) and the International Union Against Cancer (UICC) have suggested criteria for response in bone [110–112]. UICC criteria are based on anatomical assessment of bone lesions on plain radiography, in some ways analogous to the RECIST approach at other disease sites. A “Revised Criteria Proposed for Assessment of Bone Response” [110] added to the UICC and WHO criteria CT and MRI findings, and incorporated changes in bone sclerosis and/or metabolic activity. These revised criteria of Hamak et al. [110] regarding bone imaging in metastatic breast cancer, may also be relevant to the TC population.

In a practical sense, serial assessment of bone lesions is primarily intended to assure non-progression, as healing can be very slow, and difficult to assess anatomically. Metabolic responses, however, can be assessed using FDG-PET, gallium DOTATATE-PET/CT or OctreoScan, but may be confounded by the occurrence of “flare phenomenon”, also sometimes called “pseudo-progression” [113], prompting need for care in using metabolic imaging, albeit often useful.

7. Conclusions

The presence of OMs in advanced TC conveys worse prognosis [3,114], high morbidity, therapeutic challenges, and difficulties in assessing OM response to applied therapies. As the risk of OM development is increased in MTC, FTC and HCC, proactive surveillance of patients with these TC histologies is especially important. In this regard, RAI imaging (iodine avid follicular cell derived thyroid cancers only), FDG-PET, or gallium dotatate-PET, are preferable imaging approaches with regard to detecting OMs. Although kinase inhibitors have proven clinical activity in DTC and MTC, MKI effects in controlling OMs appear attenuated relative to effects at other metastatic sites. Early use of antiresorptive palliative therapy (e.g. zoledronic acid, denosumab) is thus favored based upon analogy to data from other cancers and limited data specific to TCs – and also given that advanced DTC patients are usually treated with TSH-suppressive doses of levothyroxine with consequently heightened risk for bone loss. Providers should therefore have a low threshold for institution of antiresorptive therapy to supplement other therapeutic approaches, with data general supporting similar efficacy and lessened toxicities with every three monthly, versus monthly, dosing. Still, much work is needed to develop more effective systemic therapeutic approaches to preventing and managing OMs.

Literature acquisition methods

This narrative review was performed based upon literature data obtained from PubMed interrogations using the search terms: “bone metastasis”, “bone metastases”, “thyroid cancer”, “bisphosphonate”, “treatment”, “denosumab”, “cancer” “randomized controlled trials”, “tyrosine kinase inhibitors”.

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Nicole M. Iñiguez-Ariza: Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Keith C. Bible:** Methodology, Data curation, Formal analysis, Supervision, Writing - original draft, Writing - review & editing. **Bart L. Clarke:** Conceptualization, Methodology, Data curation, Formal analysis, Supervision.

Declaration of Competing Interest

All authors state that they have no conflicts of interest.

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Supplementary materials

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