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Bone Metastasis in Thyroid Cancer: A Literature Review

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Mini Review

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Introduction

Thyroid cancer is the most common endocrine cancer [1]. It is the third most common newly diagnosed cancer in the population aged 20-39 years. The number of cases diagnosed annually is about 4 times that of males in females (5-7 in females and 1-4 in males in 100,000 cases) [2].

About 90% of thyroid cancers are differentiated thyroid cancers. Approximately 85% of follicular cell derived tumors constitute papillary carcinoma and 12% of it constitute follicular carcinoma including conventional and oncocytic (Hurtle cell) carcinomas [3]. Differentiated thyroid cancers develop from thyroid follicular cells. The survival rates of differentiated thyroid cancers are quite high. The 10-year survival rate is reported as 93% for papillary carcinoma and 85% for follicular carcinoma [4]. However, 10-year survival rate of distant metastatic papillary thyroid cancer is reported as 70% [5]. A small group (approximately <3%) of undifferentiated-anaplastic tumors arising from follicular cells, an aggressive tumor with invasive and early metastases, survival expectancy in anaplastic carcinomas is 3-6 months [6-8]. 20-30% of anaplastic cancers have syncrhonous differentiated thyroid cancer with papillary cancer in the majority [9]. Anaplastic thyroid cancer is clinically considered as stage 4 [10]. Medullary thyroid carcinoma originating from parafollicular cells constitutes approximately 1-2% of total thyroid carcinomas. It may be sporadic (about 75%) or hereditary. Hereditary form is associated with multiple endocrine neoplasia type 2A and B (MEN-2A, MEN-2B) and familial medullary thyroid carcinoma. Life expectancy in medullary carcinoma is about 8.6 years [11].

The rate of distant metastasis in differentiated cancers has been reported at 4-23% in various studies [12-16]. The most common site of distant metastasis is the upper mediastinal lymph nodes and lung (%61,5) [17,18]. These are followed by bone (21.2%), hilar lymph nodes, liver and brain [19]. In addition, skin, adrenal gland, kidney, bronchial submucosa, digestive system, and omentum metastasis has been reported [20-24]. Synchronous metastases in the lung and bone have been reported in 15% of cases [25]. The most important prognostic factors for metastatic disease are complete control of local disease and radioactive iodine sensitivity [26]. According to general acceptance in the literature; bone metastasis and distant metastasis resistant to radioactive iodine therapy are independent poor prognostic factors [13,27-29].

Among tumors that metastasize to the bone, thyroid cancers are the third most common [30]. Bone metastasis rate in differentiated thyroid carcinomas has been reported between 2% and 13%. Bone metastasis is especially common in advanced stages of follicular carcinoma [31]. Bone metastasis in follicular cancer is between 7% and 28%, whereas in papillary thyroid cancer this rate is 1.4-7% [32,33]. However, since the number of papillary thyroid cancer patients is higher, some authors argue that the number of papillary thyroid cancer patients will be higher in terms of bone metastasis, and therefore these patients must be carefully screened [34]. Approximately 12% of Hurthle cell carcinomas show vertebral metastases [25].

About 600,000 patients per year are diagnosed with bone metastasis in the USA [35]. Bone is the third most common metastatic site after lung and liver. Bone metastatic disease is more frequent in patients over 40 years of age [36]. Bone metastatic disease consists of five steps: (1) separation from the primary tumor; (2) entry into the lymphatic and / or blood vessels; (3) surviving

and travelling in circulation; (4) reaching the target bone tissue; and (5) living in the new bone environment [37].

Bone metastasis is associated with excess blood flow. However, malignant cells synthesize adhesive molecules that allow for attachment to the bone matrix. It also synthesizes substances that promote angiogenesis and substances that increase bone resorption by activating osteoclasts (IL-1, IL-6, and RANKL) and provide the appropriate environment to replicate in this bone [34]. Metastatic lesions usually cause osteolysis [33].

Bone metastases are frequently seen in the vertebral, pelvis, femur, skull, femur and costa bones [38]. The rate of metastasis to facial bones was 2%, the most frequent was follicular thyroid cancer, and the most frequent metastatic site was reported as mandibula [39-41]. Vertebral metastases are 60-80% thoracic, 15-30% lumbar and <10% cervical25. And infiltrates the corpus of the vertebrate, and often the posterior part [42]. The lesion is often asymptomatic, but it becomes symptomatic when infiltrate the surrounding tissues or pressure the neural structures. The most common symptom is pain, and the other symptoms are fractures, spinal cord edema, and spinal instability [31,33]. Bone metastasis is also the most common cause of cancer-related pain [30].

In various studies, 10-year survival of bone metastatic thyroid cancer cases was reported between 0-34% [16,43-45]. In a study with 444 patients, 20 years of survival in patients with RAI uptake was 33%, while 10 years survival was 3% without RAI uptake [27].

The first option is direct radiography for diagnosis, but may not be visible lesions less than 1 cm. In one study, 8 of 115 patients with bone metastasis had no pathology detected by X-ray [27]. Computed tomography (CT) is valuable in assessing lesion spread. Diagnostic sensivity of CT have been reported between 71% and 100% [33]. Magnetic resonance imaging (MRI) allows evaluation of both bone and bone marrow. MRI is particularly useful in distinguishing compression and tumor infiltration in the spinal cord. In a study of several different types of cancers that metastasize bone, the sensivities of whole body MRI scans were 94% and the diagnostic accuracy was 91% [46].

Bone scintigraphy is often a successful test to distinguish the osteoblastic reaction. Because of bone metastasis of thyroid carcinoma is frequently present with lytic lesions, the false positivity and false negativity rates of the bone scintigraphy is high [47]. 2-Deoxy-2-(18F) fluoro-D-glucose Positron Emission Tomography (FDG-PET) is a useful assay in poorly differentiated metastatic tumors. Especially the FDG-PET with recombinant human TSH (rhTSH) stimulation has been found useful to determine the bone metastases [48]. FDG-PET, Technetium 99 sestamibi (MIBI) and I-131 whole body scanning scintigraphy were compared to determine the location of bone metastasis in 19 patients, and there was no significant difference between these techniques [49]. However, FDG-PET positivity has been associated with very poorly prognosis [50]. A promising method for bone metastasis is I-124-PET-CT, which works by way of sodium iodide uptake and presents a 3-dimensional tumor image. In a study with thyroid cancer cases, the diagnostic values of I-131, I-124, CT and I-124-PET-CT were compared and the diagnostic accuracy rates were 83%, 87%, 56% and 100%, respectively [51]. Consequently, the most accurate approach to bone metastasis is the detailed examination of the region with metastatic focus by MRI or CT if metastatic tumor is detected with one of the whole body screening methods. If spinal cord invasion is suspected, then the whole body MRI will be useful.

Biopsy is not recommended for lesions with I-131 uptake in bone metastatic thyroid cancer. In addition, biopsy from the bone lesion is not required for recurrent disease with previously documented bone metastasis [34]. However, if bone metastasis is the initial focus of recurrent disease, bone biopsy is recommended [52]. In the evaluation of a newly developed bone lesion in a patient with extensive bone metastasis, it is decided according to the clinical indication whether a biopsy is necessary [34].

Treatment options for bone metastatic thyroid cancer include RAI, surgical resection, external radiotherapy, arterial embolization, systemic bisphosphonates or chemotherapy and percutaneous imaging-guided therapies [34,53]. Surgical treatment is considered the first choice in bone metastasis [32]. Complete surgical resection means pathologically clean surgical margins. Palliative surgical resection means that the tumor has been minimized, or the tumor has been found in other organs when the bone tumor has been completely cleared [34]. Surgical indications for bone metastasis can be listed as follows; persistent pain to unresponsive to medical treatment, low radioactive iodine uptake, neural compression or spinal cord involvement [33]. According to the literature, metastasectomy in patients with bone metastasis of 5 or less increases the quality of life and survival time [33,44]. In vertebral metastases, in addition

to surgical approach, RAI and TSH suppression and palliative methods such as laminectomy, embolization and external radiotherapy are recommended [31,54,55]. In cases of cord compression due to follicular carcinoma of the cervical vertebra metastasis, resection of metastatic lesion with total thyroidectomy and additionally RAI, external radiotherapy and TSH suppression are recommended [31,56]. Glucocorticoid treatment is added in the presence of cord pressure [57]. Percutaneous vertebroplasty and kyphoplasty are used as alternative surgical methods to surgical resection in patients with pathologic fractures. In these methods, bone cement inject to the vertebral body, which is bent or broken due to metastasis. Studies have shown that pain and deformity can be reduced in this way [51,58].

As the metastatic tumor increases osteoclastic activity, the use of bisphosphonates that inhibit osteoclasts has been recommended. Studies on IV pamidoranate treatment have provided effective symptomatic treatment with low side effect [59,60]. In a study comparing zoledronic acid and pamidronate treatments, the treatment efficacy was higher in the zoledronic acid group and the rate of complication with skeletal metastasis was significantly lower [61].

Studies have shown that bone metastasis is generally resistant to RAI therapy [16,33,62,63]. The response rate to RAI treatment is approximately 55% [64]. It has been suggested that external radiotherapy can be used following surgical treatment in bone metastasis with RAI therapy resistant [32,65]. However, this treatment provides palliative healing in symptomatic metastases, especially effective for pain [66].

External beam radiation therapy (EBRT) is performed for preserving the functional capacity, especially after surgical treatment of pathologic fractures or in patients with high risk of fractures. Side effects are erythema, skin dryness, mucositis, late hyperpigmentation of the skin and esophageal and tracheal stenosis [34]. In intensity modulated radiation therapy (IMRT), radiation can be delivered more precisely to sites outside the thyroid bed, provides better preservation of the surrounding healthy tissue, and reduced early and late radiation toxicity [67]. This method was observed to have significantly less late radiation-related morbidity compared with EBRT (2% and 22%) [68]. Radiofrequency ablation is also a minimally invasive technique that leads to coagulation necrosis in the targeted tumoral tissue. It has been shown to reduce pain [69,70]. Another treatment method is cryotherapy. In the literature, there is a study of 14 cases treated with cryotherapy without any neurovascular damage or pathologic fractures [71]. Selective embolization of the artery of the tumor was performed in a study, and pain and neurological symptoms are relieved immediately in 59% of patients [72].

SRC (protooncogene SRC) is an oncogene. It is highly expressed in osteoclasts that encode a tyrosine kinase that promotes cellular proliferation and has a crucial importance in the osteoclast cytoskeleton [73,74]. The effects of the SRC inhibitors dasatinib and saracatinib in the treatment of bone metastatic disease are being investigated in various studies [75,76].

Elevated TGF-b production in metastatic bone results in increased tumor cell invasiveness, angiogenesis and immunosuppression at the same time. Thus blocking the TGF-b signaling pathway is also a promising method for the treatment of bone metastatic disease. For this purpose, TGF-b neutralizing antibodies (1D11, Fresolimumab), tyrosine kinase inhibitors (LY2109761, LY2157299), and soluble receptor proteins have been developed and tested in various preclinical studies [77,78]. Denosumab is completely human monoclonal to RANKL and inhibits osteoclast activity [79]. It have been considered to be more effective than zoledronic acid in the prevention or delay of skeletal morbidities in bone metastases of solid tumors [80].

Another treatment option is a micro-RNAs. In an animal study by Ell, et al. [81] it was demonstrated that miR-141 and miR-219 can prevent osteoclast differentiation and bone metastasis. It has been suggested that miR-16 and miR-378 may also be valuable biomarkers for bone metastasis. These findings highlight miRNAs as exciting new strategies for the diagnosis and treatment of cancer skeletal metastasis [81]. Similarly, miR-34a has been found to be effective in inhibiting osteoclast differentiation, bone resorption and skeletal metastasis. A study have shown that in miR-34a overexpressed mice, osteoclast production and bone resorption are decreased and the mice are resistant to bone metastasis of breast cancer and melanoma [82].

In conclusion, early diagnosis and treatment of bone metastasis of thyroid carcinoma can reduced mortality rates. Pain can be a warning symptom of bone metastasis in risky patients. I-131, I-124, FDG-PET CT and I-124-PET CT can be used for whole body scanning in suspected patients and CT, MRI, or X-ray are useful after detection tumor location. Treatment options include curative or palliative surgery or minimally invasive techniques (such

as radiofrequency ablation, cryotherapy, selective arterial embolization) or RAI, EBRT, IMRT, or medication (such as bisphosphonates and human monoclonal antibody).

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