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Original Research Article

Characteristic of risk factor of thyroid cancer related metastatic bone disease at Sanglah General Hospital Denpasar between January 2013 to March 2019

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ABSTRACT

Background: Metastatic bone disease (MBD) causes a massive morbidity, pain, and disability for the sufferers. Thyroid carcinoma, which is the most common endocrine cancer worldwide, also contributes to the increased rate of MBD, as 60% of patients with thyroid carcinoma experience bone metastasis. An urgency to further analyze the risk factors of bone metastasis in thyroid cancer is necessary in order to prevent and treat this unwanted occurrence earlier and better.
Methods: A descriptive retrospective study was conducted using patients's medical record data obtained from Sanglah General Hospital between January 2013 until March 2019. The variables obtained were sex, age, diagnosis, management, and fracture site.
Results: There were 15 patients involved in this study, presenting with pathological fracture due to MBD from thyroid cancer. Ten patients were female (66.7%) and 5 were male (33.3%). According to the age group, 2 patients (13.3%) were <40 years old, 5 patients (33.3%) were >60 years old, while the majority of 8 patients (53.4%) were 40-60 years old. From the pathological result, 9 patients had follicular neoplasm (60%) and 5 patients had papillary neoplasm (33%). The most common site of metastasis was humerus in 7 patients (47%), while the other sites were femur, pelvic, and tibia.
Conclusions: According to this series, there are several risk factors related to MBD from thyroid carcinoma, including female gender, the age of 40-60 years old, and follicular type neoplasm. A further study with bigger amount of sample is needed to improve the result.

Keywords: Bone metastasis, Epidemiology, Thyroid cancer

INTRODUCTION

Thyroid cancer is the ninth most common cancer in Indonesia and the most common endocrine cancer found in the world. It is also the third most common newly diagnosed cancer in the population aged 20-39 years.[1,2] Thyroid cancer accounts for roughly 1% of all new malignant disease, about 0.5% of cancers in men and 1.5% in women. The 10-year survival rate of thyroid cancer was reported as 93% for papillary carcinoma, 85% for follicular carcinoma, and 70% for distant metastatic papillary thyroid cancer.[3] Bone is the third most frequent site of metastasis, after lung and liver.[3] In thyroid cancer, the relative incidence of metastatic bone disease (MBD) is approximately 60%. MBD are a major cause for morbidity, characterized by severe pain, impaired mobility, pathologic fractures, spinal cord compression, bone marrow aplasia and hypercalcemia.[1,3,4] An urgency to further analyze the risk factors of bone metastasis in thyroid cancer is necessary in order to prevent and treat

this unwanted occurrence earlier and better. The objectives of this study were to determine the association of thyroid tumor molecular subtypes onsite of metastatic disease and incidence of metastatic bone disease. The determinant factors included sex, age, pathological results, and region of metastasis.

METHODS

Authors conducted a descriptive retrospective study to the patients with thyroid cancer-related metastatic bone disease in Sanglah General Hospital.

Inclusion criteria

- All patients with metastatic bone disease caused by thyroid cancer in Sanglah General Hospital between January 2013 until March 2019.

Exclusion criteria

- Patients with incomplete data in medical records and patients with doubtful diagnosis of thyroid cancer.

Authors studied total of 15 patients with thyroid cancer related metastatic bone disease and the secondary data was obtained from the patients's medical records. The determinants factors obtained from the medical records were sex, age, pathological results, and region of metastasis. The data was collected and tabulated, then the descriptive analysis was performed by frequency and percentage table.

RESULTS

The results showed that in total of 15 patients with thyroid cancer-related MBD. There was five male and ten female patients so most of the patients were female (10 patients, 66.7%). There were two patients with age below 40 years old, eight patients with age between 40-60 years old, and five patients with age more than 60 years old so most of the patients were in age group of 40-60 years old. The histopathological result most common found in this study was follicular neoplasm (9 patients, 60%), followed by papillary neoplasm (5 patients, 33%). One patient didn't have the result for histopathologic examination because there was no data from the medical record. For the metastatic region, the most common site of bone metastasis in this series was humerus (7 patients, 47%) followed by femur (five patients/ 33%), pelvic region (two patients, 13%), and tibia (one patients, 7%) consecutively. The determinant factors of the patients can be seen in (Table 1).

Table 1: The determinant factors of the patients.

Variables		Frequency	Percentages
Sex	Male	5	33,3%
	Female	10	66,7%
Age (years old)	<40	2	13,3%
	40-60	8	53,4%
	>60	5	33,3%
Histopathological Results	Follicular neoplasm	9	60%
	Papillary neoplasm	5	33%
	No result	1	7%
Region	Humerus	7	47%
	Femur	5	33%
	Pelvic region	2	13%
	Tibia	1	7%

DISCUSSION

In this studies, from total of 15 patients with thyroid cancer-related MBD, most of the patients were female (10 patients, 66,7%). This result supported a research by Liu et al, and Goktas, stating that bone metastasis in thyroid carcinoma affected females more than males.[5,6] However, a study by Tickoostated that female is more commonly affected in Papillary Neoplasm, but not Follicular Neoplasm.[7] In this series, the most prevalent age group was age group of 40-60 years old. This result is consistent with a study by Liu et al, stating that the most common age group affected by bone metastasis from thyroid carcinoma is 40-60 years old.[5] However, a study by Tickoo resulted in slightly different mean age for Follicular Neoplasm (64.4 years old), while Papillary Neoplasm's was 58.4 years old, supporting the result of this study.[7]

The incidence patterns of each histologic type of thyroid cancer is different according to demographic and tumor characteristics.[8] Among women, papillary thyroid cancer rates were highest among Asians and lowest among blacks. However, follicular cancer rates did not vary substantially by

ethnicity whilst medullary cancer rates were highest among Hispanics and whites and anaplastic rates were highest among Hispanics. Among men, both papillary and follicular thyroid cancer rates were highest among whites, medullary cancer rates were highest among Hispanics and anaplastic rates were highest among Asians. Racial/ethnic-specific rates did not vary notably across registries. In contrast to age-specific rates of papillary thyroid cancer that peaked in midlife (age 50), especially pronounced among women, rates for follicular, medullary, and anaplastic types continued to rise across virtually the entire age range, especially for anaplastic carcinomas. Female-to-male incidence rate ratios among whites decreased with age most steeply for the follicular type and least steeply for the medullary type.[1-3]

Pathological analysis is one of the routine tests that we do for the patients with MBD in Sanglah General Hospital. The purpose of the test is to investigate whether the neoplasms were primary or not. According to the results, the histopathological result most common found in this series was follicular neoplasm (9 patients, 60%), followed by papillary neoplasm (5 patients, 33%). This finding is different from a study by Liu et al, proving that Papillary Neoplasm was the most commonly found type of thyroid carcinoma, contrary to this finding of mostly follicular neoplasms.[5] A study by Goktas also found Papillary Neoplasm more common than Follicular Neoplasm, supporting Liu's.[6]

There are several different types of thyroid cancer, which are classified based on how similar they look to normal thyroid cells under a microscope and by the type of cell from which they develop. Those types include differentiated type such as papillary carcinoma, follicular carcinoma, Hürthle cell carcinoma or oxyphil cell carcinoma, medullary thyroid carcinoma, and undifferentiated type such as anaplastic carcinoma. About 90% of thyroid cancers are differentiated thyroid cancers and papillary carcinoma is the most common type of thyroid cancer, accounting for approximately 80% of all cases of thyroid cancer.[1,2,4] For the metastatic region, the most common site of bone metastasis in this series was humerus (7 patients, 47%) followed by femur, pelvic region, and tibia consecutively. Regarding the region of bone metastasis, the study stated that the most common site of metastasis was facial bones, particularly mandibles. The other common sites of metastasis were vertebrae, which are often asymptomatic, or if symptomatic, presents with pain, fracture, or instability.[6] While the most frequent site of bone metastasis according to a study by Gibiezaite was spine, followed by pelvis, ribs, femur, and skull. Humerus comprised 10% of overall bone metastasis.[9] These studies are contrary to this study that concluded humerus as the most common site of bone metastases in thyroid carcinoma.

The pathophysiology of MBD is quite complex. For bone metastases to occur, there must be several interactions between the malignant cell and the skeleton. First, the cancer cell must lose its cell to cell interactions and its cell-matrix cohesion. The adhesion of cells to their neighbors helps regulate major cellular processes including motility, growth, differentiation, and survival. The malignant potential of a cell is characterized by significant modifications in its cytoskeleton structure, decreased cellular adhesion, and aberrant adhesion-mediated signalling. The disruption of physiologic cell to cell adhesion in malignant cells may contribute to their improved ability to migrate and proliferate, leading to invasion and metastasis. After the loss of cell–cell interactions, the cancer cell must gain motility and take on the ability to invade other tissue. Eventually, the cell must navigate the vascular or lymphatic system and exit that environment so that it can take residence in a new, distant site. Once in its new site, the malignant cell must expand and multiply in number for it to become an established location for metastasis.[10] When the cells from the primary tumour are shed into circulation, the now called circulating tumour cells (CTCs) instructs homing of haematopoietic stem cells (HSCs). Disseminated tumour cells occupy niches within bone and niche cells interact with tumour cells via integrin and chemokine axes, such as α4β1-vascular cell adhesion molecule-1 (VCAM-1) and CXCL12-CXCR4. In some cases, tumor cells escape from dormancy, resulting in metastatic progression, formation of a secondary tumour in bone. The pathogenesis of bone metastasis is explained in (Figure 1).[11]

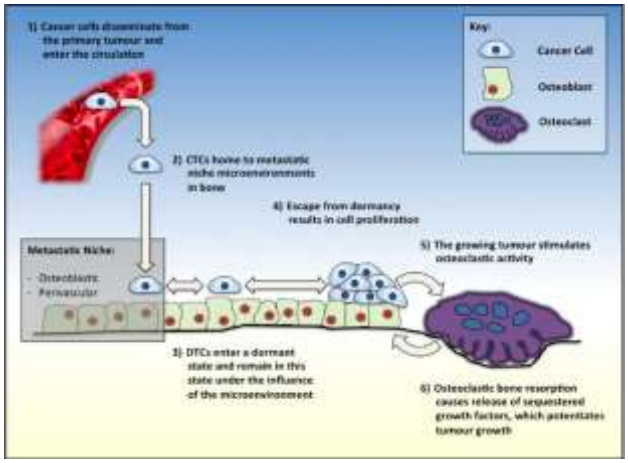

Figure 1: Pathogenesis of Bone Metastasis.[11]

Thyroid cancer most frequently causes lytic lesions when it metastasizes to bone. The osteolytic process is ultimately driven by the receptor activator of the RANK/RANK-L/OPG pathway in which increase the recruitment and maturation of osteoclasts.[10] Besides that, there are also activation of many mediators that increase the formation of osteoclasts through the RANK system such as IL-6 (interleukin-6), prostaglandin E2 (PGE2), tumor necrosis factor (TNF), macrophage colony-stimulating factor (M-CSF), and parathyroid hormone-related peptide (PTH-rP). Osteoclasts release transforming growth factor-b (TGF-b), insulin-like growth factors (IGFs), fibroblast growth factors (FGFs), platelet-derived growth factor (PDGF), and bone

morphogenetic proteins (BMPs), causing bone resorption, as well as the production of growth factors that increase tumor growth. Osteoprotegerin also plays a role. (Figure 2) explains the cycle of bone metastasis in thyroid carcinoma.[12,13]

Distant metastasis may be the initial presentation of the disease or it may occur after initial treatment for cancer. The incidence of distant metastases at the time of initial presentation in differentiated thyroid cancer is approximately 4%.[6] The incidence of distant metastasis after total thyroidectomy for thyroid cancer is between 7% and 23%, while for patients presenting initially with distant metastasis, it is approximately 1-9%.[7] The most common site of distant metastasis is the upper mediastinal lymph nodes and lung (61.5%). These are followed by bone (21.2%), hilar lymph nodes, liver and brain. In addition, skin, adrenal gland, kidney, bronchial submucosa, digestive system, and omentum metastasis has been reported.[14] Patient with bone metastasis had a significantly poorer ten-year overall survival rate than those with pulmonary metastasis.[15] Some studies suggest that poor outcome in bone metastasis may be due to lack of effectiveness of radioactive iodine therapy.[16,17]

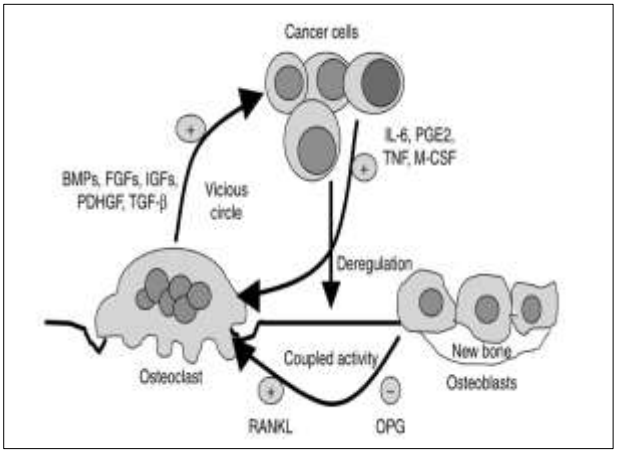

Figure 2: The cycle of bone metastasis in thyroid carcinoma.[13]

CONCLUSION

According to this series, there are several risk factors related to MBD from thyroid carcinoma, including female gender, the age of 40-60 years old, and follicular type neoplasm. The determinant factors included sex, age, pathological results, and region of metastasis. Because the pathophysiology of MBD in thyroid cancer is very complex, there may be another determinant factors contributing in occurrence of MBD in patients with thyroid cancer. A further study with bigger amount of sample is needed to improve the result.

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