Outcome of Bone Metastases in 47 Patients with Differentiated Thyroid Cancer

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ABSTRACT

Distant metastasis is an infrequent event in patients with differentiated thyroid cancer (DTC) and it occurs approximately in 10 % of cases. Bone is the second metastatic site in patients with DTC. The aim of this multicentre retrospective study has been to describe the diagnosis and treatment of bone metastases (BMs) in patients followed up at ten different hospitals in Argentina. Diagnosis of BM was made when: a) BM was confirmed by biopsy, b) a structural bone lesion was found following $^{131}$I uptake associated with elevated levels of serum thyroglobulin (Tg) or c) a structural bone lesion was demonstrated by $^{18}$FDG uptake on PET/CT, also associated with high levels of serum Tg. Demographical, clinical, pathological and outcome data were obtained from hospital charts. We included 47 patients: 55 % were women, with a median age of 55 years old. Histology of DTC was as follows: 55 % had papillary thyroid cancer, 32 % had follicular thyroid cancer and 13 % had other variants. Diagnosis of BM was synchronous in 47 % of patients (at the same time as DTC diagnosis) and metachronous in 53 %, occurring within a mean period of 72 months after initial diagnosis. In 64 % of patients, BM was symptomatic: pain was referred in 70% of these cases. In 68 % of cases, there were multiple sites of BM, with the spine being the most frequent localization (36 %). In 68 % of patients, other distant metastases were observed, mainly in the lungs. Stimulated Tg levels were known in 38 patients at diagnosis: $>100$ ng/ml in 87 % and $<100$ng/ml in 13 %. Serum calcium levels were normal in all subjects in whom they were measured (n=41). In 9 (29 %) of the 31 patients studied, serum bone turnover markers were elevated. At least one modality of treatment was prescribed in 96 % of patients with BM. Radioiodine was indicated in 78 % of cases, bisphosphonates were prescribed in 64 % of patients, while surgery was performed in 53 %. In 55 % of cases, external beam radiotherapy was also indicated and 23 % of individuals received other therapeutic approaches. Median follow-up was 24 months (range 1-228 months). The survival rate at the end of follow-up was 41 %. One patient (3 %) was considered to have no evidence of disease, 28 patients (59 %) died as a consequence of the DTC. The cause of death was known in 27 cases and it was related to BM in only 8 patients (30 %). In conclusion, BM was mainly observed in patients >45 years old, with similar gender distribution. Papillary thyroid cancer was the most frequent histological variant found. BMs were multiple and had mainly an axial skeletal localization, causing high morbidity in most patients. Although bone turnover markers were elevated in one third of cases, none of the patients presented with hypercalcemia. Multiple modalities of treatment were used in the majority of cases, which indicates the importance of a multidisciplinary approach. Finally, although BM was associated with incurable disease, mortality was mainly related to the spread of DTC to other sites, and not specifically to BM. Rev Argent Endocrinol Metab 51:51-58, 2014

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Key words: Bone metastases, thyroid cancer
INTRODUCTION

Differentiated thyroid cancer (DTC) accounts for over 90% of all thyroid tumors and includes papillary and follicular types. The incidence of this disease is rising rapidly worldwide, especially in women (1,2). Long-term survival is excellent and it usually achieves 80-90% (3).

However, about 10% of patients may experience distant metastases, which reduces 10-year survival to 40% (3). The most common metastases are lung metastasis (approximately 50% of cases), 25 to 30% occur in bone (BM), 20% occur in both organs and 10% in other sites (4-6). About one-third of patients with distant metastasis may become refractory to radioiodine therapy. This subset of patients has a poor prognosis, with a 10-year survival of 10% (4,7,8).

BM frequently cause significant morbidity, causing pathological fracture, spinal cord compression and impaired quality of life in 78% of patients (9). Management of BM is complex and requires a multidisciplinary approach by a team that should include endocrinologists, nuclear medicine physicians, orthopedists, surgeons, radiation therapists and oncologists (10).

Given the low frequency of BM observed at each individual site, at the Thyroid Department of the Argentine Society of Endocrinology and Metabolism, we decided to perform a joint review of cases of this disease to evaluate epidemiological data, form of presentation, therapies offered and progress.

PATIENTS AND METHODS

We retrospectively reviewed the databases of patients followed up at 10 sites in Argentina (Hospitals: Alemán, Clínicas, Chucurruca, Durand, Italiano, Fernández, Milstein, Ramos Mejía and Roffo in the Autonomous City of Buenos Aires, and Hospital Presidente Perón in Formosa). We included patients with DTC and presence of BM diagnosed by one or more of the following methods: a) biopsy of the lesion, b) bone structural lesion with uptake following 131I administration, associated with elevated levels of serum thyroglobulin (Tg) or c) a structural bone lesion demonstrated by 18 fluor-deoxy-glucose (FDG) uptake on PET/CT, also associated with high levels of serum Tg.

The following data were collected: age at the time of diagnosis of DTC, gender, histology, staging according to TNM (UICC-AJCC-7th edition)(11), risk staging according to the American Thyroid Association (ATA)(12) and Latin American Thyroid Society (LATS) (13), stimulated thyroglobulin (Tg) levels and thyroglobulin antibodies (TgAb) at the time of diagnosis of BM.

The following clinical and pathological characteristics of BM were considered: symptoms attributed to metastatic lesion, number and localization of sites, uptake following administration of a therapeutic dose of radioiodine, form of diagnosis and presence of locoregional disease or lesions at other non-skeletal sites.

BM was classified as synchronous when detected within six months of DTC diagnosis and metachronous when found after follow-up.

Data from calcium-phosphorous metabolism were obtained (blood calcium, bone formation and resorption markers).

Follow-up was performed by thyroglobulin measurement under hormone therapy and/or measurement of stimulated thyroglobulin, with imaging performed as appropriate depending on the location of lesions, at variable times according to progress and treatment.

Measurement of Tg and TgAb was performed at the various sites using ultrasensitive methods.
The BM treatments considered included surgical therapy, cumulative dose of radiiodine following diagnosis of BM, external radiotherapy, use of bisphosphonates, among other therapies.

The follow-up time was evaluated as time to death or last contact, and final status was defined as alive with and without persistent disease and dead due to causes related or unrelated to underlying disease.

Death was considered to be due to BM when related to BM complications or treatment.

Data were analyzed by descriptive and analytical statistics using SPSS 20.0 for Windows.

RESULTS

Data were obtained from 47 patients treated at 10 healthcare centers. In 32 cases (68%) diagnosis was confirmed by biopsy of BM. The patient’s characteristics are shown in Table 1.

The most common histology was papillary carcinoma (n = 26.55%), followed by follicular carcinoma (n = 15.32%).

Considering patients with a diagnosis of papillary carcinoma, the classical variant was the most frequent (n = 15.58%), followed by the follicular variant (n = 7.27%), tall cell variant (n = 3, 11%) and oncocytic variant (n = 1.4%).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>55</td>
</tr>
<tr>
<td>Range &gt;45 years</td>
<td>15-84</td>
</tr>
<tr>
<td>&gt;45 years</td>
<td>38 (81%)</td>
</tr>
<tr>
<td>Female gender</td>
<td>26 (55%)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td>26 (55%)</td>
</tr>
<tr>
<td>Follicular carcinoma</td>
<td>15 (32%)</td>
</tr>
<tr>
<td>Hürthle cell carcinoma</td>
<td>3 (6.5%)</td>
</tr>
<tr>
<td>Poorly differentiated carcinoma</td>
<td>3 (6.5%)</td>
</tr>
<tr>
<td>Stage (AJCC/UICC 7°)</td>
<td></td>
</tr>
<tr>
<td>x</td>
<td>4 (8.5%)</td>
</tr>
<tr>
<td>I</td>
<td>5 (10.6%)</td>
</tr>
<tr>
<td>II</td>
<td>5 (10.6%)</td>
</tr>
<tr>
<td>III</td>
<td>5 (10.6%)</td>
</tr>
<tr>
<td>IV</td>
<td>28 (59.5%)</td>
</tr>
<tr>
<td>ATA risk (n=42)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>12 (28.5%)</td>
</tr>
<tr>
<td>High</td>
<td>30 (71.5%)</td>
</tr>
<tr>
<td>LATS (n=42)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>7 (17%)</td>
</tr>
<tr>
<td>High</td>
<td>35 (83%)</td>
</tr>
</tbody>
</table>
The time of diagnosis of BM was known in 46 cases. BM was synchronous in 22 patients (47%) and metachronous in all remaining 24 cases, detected on average at 72 months (range 7-240) after initial diagnosis.

BM were symptomatic in 30 cases (64%). The most common symptom was pain (n = 21), followed by fracture (n = 3), tumor (n = 3) and neurological symptoms (n = 3) (Figure 1).

The characteristics of BM are shown in Table 2.

In 16 cases (34%), locoregional relapse was confirmed, while in 33 patients (68%) metastases were found in other sites, mainly the lungs (30 cases, 90%).

BM's were multiple in 32 cases (68%), with 114 sites being detected. The most common location was the spine (35 metastatic sites, 36%), followed by rib/clavicle, pelvis and limbs (Figure 2).

Data of stimulated Tg were obtained at the time of diagnosis of BM in 41 patients (87%); in three of them TgAb were positive, being excluded from the review. Tg levels were below 100 ng/ml in five cases, 100 to 1000 ng/ml in 17 and above 1000 ng/ml in the remaining 16.

Blood calcium levels were measured in 41 patients, being normal in all cases. Bone remodeling markers were measured in 31 patients, being elevated in 9 (29%).

BM's were treated in 46 patients (Figure 3); in 43 cases at least two therapeutic modalities were used. Thirty-seven (78%) patients received $^{131}$I after diagnosis of BM, with the median dose being 200 mCi (range 100-1500).

Intravenous bisphosphonates were used in 31 cases. Pamidronate was the most commonly used (19 cases, 61%).
Twenty-five patients were operated on; resection of metastatic lesion was performed in 13 cases (52%) and other types of surgeries were performed in the remaining patients. Nine patients (36%) underwent more than one surgery.

In 26 cases, external radiotherapy was delivered. In 11 patients, other therapeutic modalities were implemented (thyrosine kinase inhibitors, embolization, radiofrequency ablation, thalidomide, alcoholization, doxorubicin).

The median follow-up after diagnosis of BM was 24 months (range 1-228). Twenty-eight patients (59%) died, eighteen (38%) survived with persistent disease and one patient (3%) lived free of disease. The cause of death was not known in 27 cases, being related to BM in 8 (30%) (Figure 4).

**TABLE 2.** Characteristics of bone metastases in 47 patients with thyroid cancer

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iodine uptake</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>28 (60%)</td>
</tr>
<tr>
<td>Absent</td>
<td>19 (40%)</td>
</tr>
<tr>
<td>Number of BM</td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>15 (32%)</td>
</tr>
<tr>
<td>Two</td>
<td>8 (17%)</td>
</tr>
<tr>
<td>Three</td>
<td>10 (21%)</td>
</tr>
<tr>
<td>Four</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>More than four</td>
<td>9 (19%)</td>
</tr>
<tr>
<td>Extent of disease (n=37)</td>
<td></td>
</tr>
<tr>
<td>Isolated BM</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>BM and locoregional relapse</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>BM and other distant metastases</td>
<td>17 (46%)</td>
</tr>
<tr>
<td>BM, locoregional relapse and other metastases</td>
<td>12 (32%)</td>
</tr>
</tbody>
</table>

BM: bone metastasis

![Figure 2](image-url). Location of bone metastases in 47 patients with thyroid cancer.

Referencias de la figura: Vertebras: vertebrae
Figure 3. Therapeutic modalities used in 47 patients with thyroid cancer and bone metastases.

**Referencias de la figura:**
Radioyodo: radioiodine
Bibosfonatos: bisphosphonates
Cirugía: surgery
Radioterapia: radiotherapy
Tratamiento: treatment

Figure 4. Follow-up to end of study in 47 patients with DTC and BM

**Referencias de la figura:**
Vivos con enfermedad: alive with disease
Sin evidencia de enfermedad: no evidence of disease
Fallecidos: dead
Fallecidos por enfermedad: dead due to disease

**DISCUSSION**

BMs are the second most frequent distant metastases of DTC. Durante et al.\(^{(4)}\) demonstrated that 44% of patients with distant metastases have BMs, which impair the quality of life and are associated with a reduced survival\(^{(8,14)}\).
DTC is usually 2 to 3 times more common in women than in men. In our series, the ratio was even, similarly to findings reported by Farooki et al(9) and Qiu et al(15).

In agreement with other publications(5,9,15-18), over 80% of our patients were older than 45 at the time of diagnosis, with a median age of 55 years old.

The histological type that most frequently causes BM is follicular carcinoma (7-28% vs. 1.4-7% found in patients with papillary carcinoma). In total numbers, we have found a larger number of patients with papillary carcinoma and BM, similarly to data reported by Do et al(16) and Orita et al(17). In our study, the percentage of patients with bone metastasis in relation to the total number of patients evaluated at each site was not considered; therefore, we cannot provide data about the prevalence of bone metastasis in relation to histological type. Although it is not known which percentage of TDCs are follicular carcinomas in our country, the incidence is likely to be similar to that reported in other series (4-7%) (19), (Hospital de Clínicas [FP, data not published] and Instituto Roffo [IC, data not published], with the proportion of BM being higher in follicular carcinoma.

More than half the patients had stage IV carcinoma at the time of diagnosis; 70-80% belonged to the high-risk of recurrence category according to the ATA and LATs(12,13) classifications, respectively. These findings show, in consistency with the literature, that BMs occurred in most cases in patients with multiple factors of poor prognosis.

More than 80% of bone metastases from all tumors are located in axial skeleton red marrow where blood flow is high (vertebrae, ribs, pelvis and femoral bone) (20). The location of BM in our series was similar to that reported by other authors, with vertebral involvement being the most prevalent (36%). Sixty-eight percent of patients also developed metastases in other sites, the most common being the lung in 90% of cases, similarly to findings reported by other authors(4,5,18).

In 53% of this series, the diagnosis of metastatic disease was metachronous, similarly to data reported by Schlumberger et al(5) and Farooki et al(9). However, this situation may vary, as shown by Bernier et al(18). The metachronous diagnosis of bone metastasis may be influenced by various factors, namely, availability of appropriate imaging technology to evaluate the extent of disease at the time of diagnosis and suspicion of these locations to perform a systematic screening.

The most common manifestations of bone metastases of DTC include pain, fractures, and spinal cord compression associated with lesions in the axial skeleton. In agreement with other publications(9), the most common symptom in our population was pain in 70% of cases, which served as an alert to the site of metastasis. Pain is often progressive and usually resistant to non-opioid analgesics. In 12% of cases, bone lesions were asymptomatic, detected on whole-body radioiodine scans or other imaging methods.

There is a correlation between Tg levels and disease volume. As in most cases of BM, tumor load is elevated, Tg levels are usually higher than those found in patients with presence of disease in other sites. Robbins et al(21) reported that the median stimulated Tg in patients with BM was 416 ng/ml. In our series, 87% of patients had Tg levels above 100 ng/ml. However, levels below 100 ng/ml do not rule out the presence of BM, as observed in 13% of our patients.

Hypercalcemia is infrequent in BM of DTC; Farooki et al(9) reported hypercalcemia in 3% of the patients from their series. In all 41 patients of our series who had blood calcium measurements performed, results were normal. Markers of bone resorption were increased in 29% of cases.

As regards the therapeutic options, surgery is recommended in cases of solitary BM, where surgical resection has a curative intent. Clearly, this situation is unusual in patients with advanced disease. The indication for surgery may have palliative
purposes, in cases of resolution of pathological fractures or in the event of lesions with risk of fracture or imminent neurological involvement, or intractable pain. In our series, 53% of patients were surgically treated.

Radioiodine therapy is rarely curative for patients with BM. This occurred in one case of this series. Similarly, Durante et al. reported that remission, in patients with BM treated with radioiodine therapy occurred only in 7% of cases, while Sabra et al. did not find remission in a series of patients with structural metastases treated with multiple doses of radioiodine.

External radiotherapy was used in 55% to manage symptoms, similarly to reports in other series.

Treatment with bone resorption inhibitors has been shown to decrease the morbidity associated to skeletal-related events in patients with bone metastases from multiple solid tumors. First-line options include intravenous bisphosphonates administered on a monthly basis (pamidronate 90 mg or zoledronate 4 mg). Zoledronic acid has been shown to reduce the rate of skeletal-related events when compared to patients who did not receive antiresorptive therapy. In our series, pamidronate was the most commonly used (61%) in patients treated with bone resorption inhibitors. This may be due to the lower cost and easy availability of this drug in hospitals.

Recently, denosumab 120 mg administered subcutaneously on a monthly basis in patients with BM from various solid tumors proved to be more effective than zoledronic acid, but no data are available on BM from DTC.

As regards systemic therapies, conventional chemotherapy did not show any benefits, therefore its use is not recommended. Tyrosine kinase inhibitors may be a therapeutic option in patients with radioiodine-refractory disease, progressive and/or symptomatic disease. However, there is evidence on the lower effectiveness in BM compared to other sites of metastasis; in addition, toxicity secondary to the use of these drugs is significant.

It is important to highlight that TSH suppression with levothyroxine, in spite of the cardiovascular risks it implies for this elderly population, has demonstrated to be useful and should be considered as part of the therapeutic options.

The follow-up time was 1 to 228 months (median 24 months) and final survival was 41% on completion of the last contact. Twenty-eight patients (59%) died. The cause of death was known in 27 of these patients and could be attributed to BM or BM complications in 8 (30%) and to other causes in 19 (70%). Our findings are concordant with those published by Kitamura et al., who reported that the main cause of mortality in DTC was respiratory failure.

In conclusion, our population of 47 patient were of an advanced age, with a similar gender-based distribution, and with papillary carcinoma being the most frequent variant in total numbers. Bone metastases were multiple, predominantly axial and with significant morbidity. The population showed high mortality, mainly related to the spread of the disease and not to the BM itself.

Even if the endocrinologist should be responsible for the management of these patients, we think that a multidisciplinary approach is needed. Furthermore, patients should be involved in treatment decision-making, and the treating physician should be responsible for offering the best treatment option for the patient’s situation.

It should be noted that, despite the poor prognosis of BM compared to DTC in general, long-term survival is not rare in these patients. Therefore, the patient’s quality of life should be a priority, and the objective should be to reduce morbidity secondary to skeletal-related events. Treatment should be tailored to the extent and location of
disease, complications, co-morbidities, socioeconomic context and potential responses to treatment.

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