

Bone Metastases in Thyroid Carcinoma: A Retrospective Analysis

Tiroid Kanserinde Kemik Metastazı: Retrospektif Bir Analiz

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ABSTRACT Objective: In this study, we aimed to evaluate the outcome of metastatic bone disease in patients with differentiated thyroid carcinoma (DTC), retrospectively. **Material and Methods:** During a 13 year period, five hundred ninety six patients with DTC were treated and monitored at Ankara University, Medical Faculty, Department of Nuclear Medicine. Twenty three patients (15 females 65.2%, 8 males 34.8%; age range 26-74) with bone metastases were included in this study. 9/23 patients had papillary, 14/23 patients had follicular thyroid carcinoma. A total of 3.7- 53.65 GBq (100-1450 mCi) I-131 was given to each patient. The follow-up period was from 6 to 132 months. I-131 whole-body scan (WBS), Tc-^{99m} MDP whole-body bone scan (WBBS), the determination of thyroglobulin (Tg) level and/or computed tomography (CT) scan were carried out in the assessment of the diagnosis and follow-up of patients with bone metastases. **Results:** The frequency of bone metastases were found 3.9 % (23/596) in our analysis. Classification was performed according to the time of diagnosis of bone metastases. In group1, 19 patients were diagnosed as thyroid carcinoma from primary bone metastases with histopathological examination, and in Group 2 in 4 patients with DTC, bone metastases were diagnosed in the follow-up period. Patients were followed 6-132 months after the therapy for bone metastases and in the final examination 42.1% patients had progressive disease (PD), 26.3% patients had partial response (PR) and 31.6% patients had stable disease (SD) in Group 1. 75% patients had PD and 25% patient had SD in Group 2. All patients had Tg levels higher than 10 ng.ml⁻¹ in both groups (mean Tg values 19168 ng.ml⁻¹ and 3144 ng.ml⁻¹ for groups, respectively). **Conclusions:** The prognosis of patients with metastases at the follow-up was worse than patients with metastases at the initial diagnosis or at the ablation therapy. Tg is an important parameter and the prevalence of the other organ metastases is high in DTC patients with bone metastases.

Key Words: Thyroid neoplasms, bone and bones, neoplasm metastases

ÖZET Amaç: Bu çalışmanın amacı diferansiye tiroid kanserli (DTK) hastalarda metastatik kemik hastalığının sonuçlarını değerlendirmektir. **Gereç ve Yöntemler:** 13 yıllık dönemde, DTK'li 596 hasta Ankara Üniversitesi Tıp Fakültesi Nükleer Tıp Anabilim Dalı'nda tedavi ve takip edildi. Bu hastalardan kemik metastazı olan 23 hasta (15 kadın %65.2, 8 erkek %34.8; yaş aralığı 26-74 yıl) çalışmaya dahil edildi. 9/23 hasta papiller, 14/23 hasta folliküler tiroid karsinomaydı. Her hastaya toplamda 3.7- 53.65 GBq (100-1450 mCi) I-131 verildi. Takip periyodu 6-132 aydı. Kemik metastazlı hastaların tanı ve takibinde I-131 tüm vücut tarama (TVT), Tc-^{99m} MDP tüm vücut kemik sintigrafisi (TVKS), Tiroglobulin (Tg) düzeyi ve/veya bilgisayarlı tomografi (BT) kullanıldı. **Bulgular:** Hasta grubumuzda kemik metastazı sıklığı %3.9 (23/596) bulundu. Hastalar kemik metastazının saptandığı döneme göre iki gruba ayrıldı. Grup 1; primer kemik metastazından histopatolojik değerlendirme ile tiroid kanseri tanısı alan 19 hasta ve Grup 2 tipte kemik metastazı saptanan tiroid kanserli 4 hastadan oluşmaktaydı. Hastalar tedavi sonrası 6-132 ay takip edildi. Grup 1'den %42.1 hastada progresif hastalık (PH), %26.3 hastada kısmi yanıt (KY) ve %31.6 hastada stabil hastalık (SH) izlenirken, grup 2'de %75 hastada PH ve %25 hastada SH gözlemlendi. Her iki gruptaki tüm hastalar için Tg değeri 10 ng.ml⁻¹'den yüksekti (gruplar için ort. Tg değeri sırasıyla 19168 ng.ml⁻¹ ve 3144 ng.ml⁻¹). **Sonuç:** Takipte kemik metastazı saptanan hastaların prognozu tanı anında veya ablasyon tedavisi sırasında kemik metastazı saptanan hastaların prognozundan daha kötüdür. Kemik metastazı bulunan DTK'da diğer organ metastazlarının sıklığı da yüksektir ve Tg bu hastaların takibinde önemli bir parametredir.

Anahtar Kelimeler: Tiroid tümörleri, kemik ve kemikler, tümör metastazı

Distant metastases develop in 7-23% of patients with differentiated thyroid carcinoma (DTC) whereas only 1-3% of patients with thyroid carcinoma have distant metastases at the time of initial diagnosis.¹⁻⁴ Bone is the second most frequent distant localisation of metastases resulting from DTC (2-13%).⁵ Radioiodine therapy is generally performed for bone metastases of DTC.⁶ In addition to radioiodine therapy, surgery and/or radiation therapy could be used. Prognosis of bone metastases is poor in spite of multimodality therapy regimes. The number of the bone metastases and the uptake of radioiodine are one of the prognostic factors associated with improved survival.^{1,2,7} The prognosis of patients with bone metastases at the initial diagnosis was reported to be better than patients with bone metastases after treatment.⁶ The reports have showed that surgery of distant metastases had a favourable effect on prognosis and quality of life and complete bone metastases surgery improved survival in patients younger than 45 years.^{8,9} Thyroglobulin (Tg) level could be used as a prognostic factor and a follow up marker of the progressive disease but there is no international consensus regarding the preferred Tg threshold value for disease progression.

The aim of this study was to evaluate outcome of metastatic bone disease in our DTC group, retrospectively.

MATERIALS AND METHODS

STUDY POPULATION

During a 13-year period (1994 through 2007), 596 patients with DTC were treated and monitored at Ankara University. Bone metastases were found in 23 patients (3.9%) at diagnosis and follow-up. According to histopathologic findings, 9 patients were diagnosed as papillary and 14 patients as follicular carcinoma. 15 of the patients were females (female/male= 1.9:1). The age at the time of diagnosis of thyroid carcinoma ranged between 26 and 74 years (mean age 54.9 ± 10.9 years). Patients were divided to two groups according to the time of diagnosis of bone metastases.

In Group 1, 19 patients diagnosed as thyroid carcinoma from primary bone metastases with histopathological examination, included 5 male and 14 female. Histopathological examination revealed papillary carcinoma in 6/19 patients, follicular carcinoma in 13/19 patients. The mean and range of ages were 56.9 ± 11.1 and 26-74 years. The follow-up period was 6-132 months.

In Group 2, 4 patients with bone metastases diagnosed in the follow-up period, included 3 male, 1 female. Histopathological examination revealed papillary carcinoma in 3/4 patients, follicular carcinoma in 1/4 patients. The mean and range of ages were 45.5 ± 9.4 and 36-59 years. Bone metastases were observed in average 6.5 years after the thyroid carcinoma diagnosis and mean age was 52 ± 10.1 at the time of diagnosis of bone metastases. The follow-up period was 6-24 months.

LABORATORY TESTS

Serum Tg measurements for each patient were performed using a commercial immunoradiometric assay (IMMULITE Systems, Thyroglobulin kit, EURO/DPC Ltd; normal range was 1.6-59.9 ng.ml⁻¹, functional sensitivity was 0.5 ng.ml⁻¹).

SURGICAL TREATMENT OF THE PRIMARY TUMOR

Thyroid surgery was performed in all 23 patients. Three patients had initial thyroid surgery as near or subtotal thyroidectomy, 36-156 months prior to the diagnosis of thyroid carcinoma. After diagnosis of thyroid carcinoma, two patients with initial thyroid surgery underwent second operation for completion thyroidectomy. In the rest of patients, total thyroidectomy and near-total thyroidectomy were performed in 18 and 2 patients, respectively. Lymph node dissection was performed in 5 patients and lymph node involvement was present in 4 patients. Tumor stages pT1, pT2, pT3, pT4 and pTx were diagnosed in 3, 4, 5, 5 and 6 patients, respectively.

SURGERY OF BONE METASTASES

In 5 patients, bone metastases were surgically removed. Three of these 5 patients had additional extraskeletal distant metastases whereas 2 patients had

metastases restricted to the bones. 4 patients with solitary and 1 patient with two metastatic foci were operated. Laminectomy in three patients, rib resection in one patient, sternum and iliac wing resection in one patient were performed.

EXTERNAL BEAM RADIOTHERAPY

In 7 patients, external beam radiation therapy to the metastatic areas was performed additional to radioiodine treatment and surgery.

RADIOIODINE ABLATION AND THERAPY

The patients were informed about the different therapeutic strategies and the need for more than one course of radioiodine treatment to eliminate thyroid remnants. All of the patients had radioiodine ablation therapy for residual thyroid tissue. Four weeks before I-131 therapy, L-thyroxine replacement therapy was withdrawn and low iodine diet protocols were applied. Thyroid-stimulating hormone (TSH) levels increased to at least 30 ng/ml, except six patients. In these 6 patients, recombinant TSH were applied. A total of 3.7-53.65 GBq (100-1450 mCi) I-131 was given to each patient. In the presence of persistent functioning bone metastases, radioiodine therapy was repeated periodically (at least 6 months after the therapy). None of these 23 patients underwent I-131 whole-body scan (WBS) before the first therapy dose of radioiodine. After primary treatment, all patients received L-thyroxine in suppressive doses.

Post treatment I-131 WBS and spot images were obtained in anterior and posterior projections. It was performed on the sixth post-treatment day using a large field-view dual head gamma camera equipped with a high energy (peak energy centred on 360 keV with a 20% energy window) parallel hole collimator (GE Millenium MG).

PROTOCOL FOR ROUTINE FOLLOW UP

Suppressive hormone therapy (L-thyroxine) was started 48-72 h after radioiodine therapy. Diagnostic I-131 WBS (DWBS) and Tg levels were obtained after the first treatment for the first follow-up in 6 months. We determined the feasible cut-off Tg level as 10 ng.ml⁻¹ for prediction of development of the progressive disease according to our published

study. Thyroid hormone withdrawal and low iodine diet protocols were applied for 4 weeks. The DWBS was performed with a 185 MBq (5mCi) dose of I-131. DWBS and spot images were acquired in anterior and posterior projections at the 24 and 72h (early and late images) using a large field-view dual head gamma camera equipped with a high energy parallel hole collimator (GE Millenium MG). Patients with normal DWBS were evaluated with periodic follow-up, at first once a year and then every 2 or 3 years within a 11-year period. However, Tg levels of all patients were obtained every 6 months. Suppressive hormone therapy was resumed after each I-131 WBS. Patients were evaluated regarding positive bone uptake on the DWBS.

RESULTS

Bone metastases were detected in 23/596 patients with I-131 WBS and/or radiological examination. Classification was performed according to the detection time of bone metastases. In group 1, 19 patients diagnosed as thyroid carcinoma from primary bone metastases with histological examination or postablative WBS showed bone metastases that confirmed radiological and/or histopathological examination. In Group 2 in 4 patients with DTC, bone metastases were diagnosed in the follow-up period. Detailed characteristics of all 23 patients are summarized in Table 1.

At the initial examination, in Group 1; 6/19 (31.6%) patients had multiple (>3) skeletal metastatic foci. 13/19 (68.4%) patients had only bone metastases, and 6/19 (31.6%) patients had additional distant metastases (1 brain, 5 lungs). All patients had Tg levels higher than 10 ng.ml⁻¹ (mean Tg values 18737). Stage IV disease was observed in 16/19 (84.2%) patients. External radiation therapy and/or surgery of bone metastases were performed in 9/19 (47.4%) patients. In Group 2; 2/4 patients (50%) had multiple skeletal metastatic foci. There is no other distant metastases except bone. All patients had Tg levels higher than 10 ng.ml⁻¹ (mean Tg values 824). Stage I disease in three patients and Stage III disease in one patient were observed, respectively.

Patients were followed from 6 to 132 months (mean follow-up period 19 months). According to

TABLE 1: Detailed characteristics of 23 patients with bone metastases from differentiated thyroid carcinoma.

| | Group 1 Number or value | Group 2 Number or value | Total Characteristics |
|--|----------------------------|----------------------------|-----------------------|
| Gender | | | |
| Male | 5 | 3 | 8 |
| Female | 14 | 1 | 15 |
| Age at diagnosis of thyroid cancer (years) | 56.9±11.1 | 45.5±9.4 | |
| Age at diagnosis of metastases (years) | 56.9±11.1 | 52±10.1 | |
| Histology | | | |
| Papillary | 6 | 3 | 9 |
| Follicular | 13 | 1 | 14 |
| Primary tumor stage | | | |
| pT1 | 2 | 1 | 3 |
| pT2 | 4 | - | 4 |
| pT3 | 5 | - | 5 |
| pT4 | 3 | 2 | 5 |
| pTx | 5 | 1 | 6 |
| Surgery | | | |
| BTT | 15 | 3 | 18 |
| BNNT | 2 | - | 2 |
| Previous surgery | 2 | 1 | 3 |
| Lymph node dissection | 3 | 2 | 5 |
| Metastatic lymph node | 2 | 2 | 4 |

the final examination, patients were evaluated in three categories: 1) Stable disease (SD), the number of metastases and Tg level did not change. 2) Partial response (PR), decrease of number of metastases and/or Tg level. 3) Progressive disease (PD), increase of number of metastases and/or Tg level.

In Group 1; 7/19 (36.8%) patients had multiple metastatic foci. 9/19 (47.4%) patients had additional distant metastases, 3 of them was newly diagnosed metastases (3 lung). 8/19 patients had PD (42.1%), 5/19 patients had PR (26.3%), 6/19 patients had SD (31.6%). All patients had Tg levels higher than 10 ng/ml⁻¹ (mean Tg values 19168). Three patients with PD died.

In Group 2; 3/4 (75%) patients had multiple metastatic foci. 3/4 (75%) patients had additional distant metastases (3 lung, 1 brain, 1 lymph node). 3/4 (75%) patients had PD and 1/4 (25%) patient had SD. All patients had Tg levels higher than 10 ng.ml⁻¹ (mean Tg values 3144). Two patients with PD died.

Detailed follow-up of all 23 patients are summarized in Table 2 and 3.

DISCUSSION

The frequency of bone metastases has been reported in 4-13% of patients with DTC.^{3,7,9-11} In our patient population, this ratio was 3.9%. While the ratio of bone metastases at the initial diagnosis was reported as 54-68%,^{7,12} we showed bone metastases at the initial diagnosis in 82.6% of patients (19/23). These ratios are higher than the literature. This result can be explained with delayed diagnosis. Different diagnostic tools were recommended for diagnosis of bone metastasis from DTCs. Because slowly growing bone metastases are often difficult to view on bone scintigraphy, MRI of the spine and pelvis should be considered.¹³ Standardized imaging could be repeated every 6-12 months and progression rate is assessed using RECIST in the absence of treatment.¹⁴

Patients with bone metastases must be followed by multidisciplinary and therapeutic work

TABLE 2: Staging of patients at diagnosis.

| No | Group | Age | Sex | Pathology | TNM | Stage |
|----|-------|-----|-----|-----------|---------|-----------|
| 1 | 1 | 67 | M | TPC | T4mN1M1 | IV |
| 2 | 1 | 57 | F | TPC | T3mNOM1 | Stage IV |
| 3 | 1 | 57 | M | TFC | T3NOM1 | Stage IV |
| 4 | 1 | 50 | F | TFC | T2NOM1 | Stage IV |
| 5 | 1 | 61 | F | TFC | T2mNOM1 | Stage IV |
| 6 | 1 | 70 | F | TFC | T2NOM1 | Stage IV |
| 7 | 1 | 44 | M | TPC | T4mN1M1 | Stage II |
| 8 | 1 | 57 | F | TFC | TxNOM1 | Stage IV |
| 9 | 1 | 63 | F | TFC | T3NOM1 | Stage IV |
| 10 | 1 | 57 | F | TFC | TxNOM1 | Stage IV |
| 11 | 1 | 56 | F | TPC | T2mNxM1 | Stage IV |
| 12 | 1 | 74 | M | TFC | T1NOM1 | Stage IV |
| 13 | 1 | 56 | F | TFC | TxNxM1 | Stage IV |
| 14 | 1 | 62 | F | TFC | TxNxM1 | Stage IV |
| 15 | 1 | 64 | F | TFC | T3NxM1 | Stage IV |
| 16 | 1 | 68 | M | TFC | TxNxM1 | Stage IV |
| 17 | 1 | 43 | F | TPC | T1NOM1 | Stage II |
| 18 | 1 | 26 | F | TFC | T4NxM0 | Stage I |
| 19 | 1 | 50 | F | TPC | T3N1M1 | Stage IV |
| 20 | 2 | 44 | F | TPC | TxNxM0 | Stage I |
| 21 | 2 | 65 | M | TPC | T4NOM0 | Stage III |
| 22 | 2 | 44 | M | TFC | T4N1M0 | Stage I |
| 23 | 2 | 55 | M | TPC | T1mN1M0 | Stage I |

up owing to their prognosis. The therapeutic regime is still controversial. Although the role of radionuclide therapy is not well defined, it is still widely used. Schlumberger et al.¹ reported that radioiodine might be effective on the metastasis at the initial diagnosis. In our study, at the initial diagnosis, 19 patients had bone metastases and 5 of them had (26.3%) PR and 6 of them had (31.6%) SD.

According to the published studies, the number of metastases and uptake of radioiodine were important for prognosis.^{1,3,7} In Group 1, the number of metastatic foci increased from 31.6% to 36.8% and PD was seen in 42.1% and the number of metastatic foci increased from 50% to 75% and PD was seen in 75% in Group 2.

Surgery is a useful treatment approach especially in limited number of metastases. Niederle et al.⁸ showed that the prognosis improved with surgery.

In addition to these results, Bernier et al.⁹ reported better prognosis with surgery in patients younger than 45 years. Mishra et al.¹⁵ showed that surgical resection of the distant metastases allowed more effective radioiodine therapy. Durante et al.¹⁶ reported that other treatment modalities such as radiotherapy can be used in patients without no I-131 uptake or response to radioactive iodine. In a study published by Ito et al., the authors reported that patients who underwent locally curative surgery having distant metastases showing RAI uptake and who underwent thyroid stimulation hormone suppression therapy showed a better cause specific survival rates than those who underwent only palliative surgery, having distant metastases without RAI uptake, and who did not undergo TSH suppression therapy. But the difference between these groups' cause specific survival rate had not been found statistically significant. They had recommended locally curative surgery, RAI therapy, and TSH suppression therapy for M1 patients when conditions permit.¹⁷ Orita et al. recommended that radioactive iodine therapy combined with resection of bone metastasis is the most potent therapy of bone metastasis of DTC. Also they noticed that bone metastasis is a strong sign of poor prognosis. So early detection and administration of appropriate therapy using radioactive iodine are likely to improve the survival rate of patients with bone metastasis with DTC.¹⁸ In our study, 10 patients were treated by surgery and/or radiotherapy additional to radioiodine treatment. 4/10 had SD and 6/10 had progression. The stable disease was observed in patients with <3 metastatic foci.

The diagnosis time, the number of metastatic focus are important prognostic factors for bone metastases. The prognosis of patients with metastases at the follow-up was worse than patients with metastasis at the initial diagnosis or the ablation therapy.^{16,19} In our patient group, we found the ratio of bone metastases at the initial diagnosis or at the ablation therapy was higher (82.6%) and their prognosis was better than the patients with bone metastases in follow-up period. The ratio of PR in patient with initial diagnosis was 5/19 (26.3%) and the ratio of SD was 6/19 (31.6%). We didn't obser-

TABLE 3: Bone and other metastases, Tg levels, therapy management and therapy response at baseline and follow-up.

| | no of bone met. at baseline | no of bone met. at follow up | other met. at baseline | other met. at follow up | Tg levels at baseline | Tg levels at follow up | RhT | S | RAI (mCi) | Response | Survey |
|----|--------------------------------|---------------------------------|---------------------------|----------------------------|--------------------------|---------------------------|----------|----------|-----------|----------|--------|
| 1 | 1 | >3 | No | lung | 300 | 3292 | | | 350 | PD | |
| 2 | >3 | >3 | lung | lung | 68 | 350 | positive | | 100 | PD | ex |
| 3 | >3 | >3 | lung | lung | 228 | 572 | positive | positive | 1050 | PD | ex |
| 4 | 1 | 1 | | | 6814 | 789 | positive | positive | 425 | PR | |
| 5 | 1 | 1 | | | 18725 | 17000 | | | 150 | SD | |
| 6 | 1 | 1 | | | 5000 | 4800 | | | 200 | SD | |
| 7 | >3 | >3 | lung | lung | 12670 | 34742 | positive | | 550 | PD | ex |
| 8 | 2 | >3 | | | 248 | 530 | positive | | 1100 | PD | |
| 9 | >3 | >3 | | lung | 300 | 1458 | positive | | 1200 | PD | |
| 10 | >3 | 2 | | | 2163 | 500 | | | 550 | PR | |
| 11 | >3 | >3 | brain | brain | 184627 | 178226 | positive | | 350 | SD | |
| 12 | 1 | 1 | | | 2544 | 346 | | | 350 | PR | |
| 13 | 1 | 1 | | lung | 180 | 358 | | positive | 1300 | PD | |
| 14 | 1 | 1 | | | 110621 | 115420 | | | 550 | SD | |
| 15 | 1 | 1 | lung | lung | 3420 | 3920 | | | 125 | SD | |
| 16 | 1 | 1 | | | 4239 | 278 | | | 1300 | PR | |
| 17 | 1 | 1 | | | 3000 | 1389 | | positive | 450 | PR | |
| 18 | 1 | 1 | | | 815 | 75 | | | 325 | SD | |
| 19 | 3 | 3 | lung | lung | 55 | 150 | | | 200 | PD | |
| 20 | 1 | >3 | | bone, lung | 103 | 5915 | | positive | 1200 | PD | ex |
| 21 | 1 | 1 | | bone | 93 | 84 | | | 300 | SD | |
| 22 | >3 | >3 | | bone, lung, lymphnode | 2800 | 5980 | | | 800 | PD | |
| 23 | >3 | >3 | | bone, lung, brain | 300 | 600 | | | 1000 | PD | ex |

RhT: Radiotherapy, S: Surgery, PD: Progressive Disease, PR: Partial Response, SD: Stable Disease

ve any PR in group with bone metastases diagnosed in the follow-up period and the ratio of PD was 75%.

The multiple organ metastases were also an important factor for prognosis of these patients. 7/23 patients had pulmonary and 1/23 had brain metastases in addition to bone. 3 patients had multiple organ metastases at the diagnosis and 2 of them died during the follow-up period.

Some researchers have reported different Tg threshold values in the range 2-30 ng.ml⁻¹ 20,21 but we determined the feasible cut-off Tg level as 10 ng.ml⁻¹ in our published study.²²

The limitation of this study is that PET/CT could not be performed. Recently, we are performing anti Tg measurements in all patients and PET/CT in case of suspicion.

In summary, bone is the second most common distant metastases of DTC. The prognosis of patients with metastases at the follow-up was worse than patients with at the initial diagnosis or at the ablation therapy. The diagnosis time, the number of foci and the Tg level were important prognostic factors for these patients. The ratio of bone metastases at the diagnosis was higher than in the follow-up period.

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