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Original Research

Outcomes and prognostic factors in thyroid cancer patients with cranial metastases: A retrospective cohort study of 4,683 patients

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ABSTRACT

Background: Cranial metastasis of thyroid cancer is rare. The aim of this study was to analyse the clinical characteristics, treatments and outcomes of thyroid cancer patients with cranial metastasis and to identify the associated prognostic factors.

Materials and methods: Between January 1977 and August 2017, a total of 4683 patients were histologically confirmed to have thyroid cancer. Among them, 25 patients (0.53%) were identified as having cranial metastases, and their medical records were reviewed. The Kaplan-Meier method with a log-rank test was performed with cancer-specific survival as the main outcome. Cox regression analysis was used to examine the potential prognostic factors influencing patient survival.

Results: Of the 25 patients, 21 were female, and 4 were male. The median age at the time of diagnosis of cranial metastasis was 63 years. Sixteen patients had metastases to the brain, and nine patients had metastases involving the skull only. Papillary carcinoma and follicular carcinoma accounted for 84.0% of cases. Twenty-four cases (96.0%) had extracranial metastases at the time of diagnosis of cranial metastases. Twenty patients received surgery, and 4 patients received palliative radiotherapy. One patient received supportive care only. The median cancer-specific survival after the diagnosis of cranial metastases was 27 months. According to the Kaplan-Meier test, 3 factors had a significant impact on survival, the metastatic site, histological types and surgical resection. According to the Cox regression analysis, skull metastases (HR: 0.274, 95% CI: 0.083–0.904, p = 0.033) and surgical resection (HR: 0.134, 95% CI: 0.019–0.929, p = 0.042) were identified as independent prognostic factors for a better outcome.

Conclusions: Surgical resection is the mainstay therapy for thyroid cancer patients with cranial metastasis. Cranial metastases involving the skull only are associated with a better outcome.

1. Introduction

Thyroid cancer (TC) is a common malignancy of the endocrine system. Papillary and follicular carcinoma, collectively termed well-differentiated thyroid carcinoma (WDTC), comprise approximately 85%–90% of all TC and usually have a favourable prognosis following appropriate treatment [1,2]. However, distant metastasis from TC is reported in approximately 3–20% of cases at initial presentation or during subsequent follow-up [3,4]. Distant metastases from TC most frequently appear in the lung and bone [3,4]. Brain metastasis originating from TC is rare, occurring in approximately 1% of all TC cases [5]. Skull metastasis from TC is also rare, with an incidence of approximately 2.5% [6]. According to previous reports, metastasis to either the brain or skull is a poor prognostic factor associated with short survival in patients with TC [5,6]. Because of the rarity of cranial metastases from TC, their management is discussed in only a few retrospective studies or case reports. Moreover, no study has compared the clinical characteristics and outcomes of patients with brain metastasis or skull metastasis from TC. The present study is a review of our experience with TC with cranial metastasis over the past 40 years in a tertiary referral medical centre. We analysed the clinical characteristics and histology of TC with cranial metastases and the patient treatments and outcomes. Furthermore, we aimed to evaluate the prognostic factors affecting cancer-specific survival in TC patients with cranial metastases.

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2. Materials and methods

2.1. Study design

The prospectively maintained institutional database at XXX Hospital, XX branch, was retrospectively searched for patients with TC. This retrospective cohort study was conducted in accordance with the STROCSS Statement guidelines [7]. Between January 1977 and August 2017, a total of 4683 patients were diagnosed with histologically proven TC either by fine needle aspiration biopsy or by surgical specimen analysis, including 3918 with papillary carcinoma (PTC), 433 with follicular carcinoma (FTC), 62 with Hurthle cell carcinoma, 87 with medullary carcinoma, 135 with anaplastic carcinoma, and 48 with poorly differentiated carcinoma. Among the 4683 patients, 29 were recorded to have cranial metastases to either the brain or skull; however, 4 patients were excluded because of synchronous malignancies or insufficient clinical data. For the remaining 25 cases, all cranial metastases were identified by computerized tomography (CT) or magnetic resonance imaging (MRI). Based on CT or MRI, patients were categorized into two groups: Group A included 16 patients (64.0%) with metastases involving the brain parenchyma (cerebrum in 14 cases and cerebellum in 2 cases). In this group, 3 cases had metastases to both the brain and skull diagnosed simultaneously. Group B included 9 patients with metastases involving only the skull bone. The thyroid origin of cranial metastases was histologically confirmed for 21 patients after biopsy or resection of cranial metastases. Medical records were reviewed, and the following data were reported: patient sex and age (at initial diagnosis and at cranial metastasis diagnosis), pathology, treatment modalities of the primary TC and cranial metastases, patient outcomes and coexistence of other distant metastases. All pathology specimens were reviewed and classified according to the World Health Organization (WHO) criteria [8]. The American Joint Committee on Cancer-tumour node metastasis (AJCC-TNM) criteria, 7th Edition, was used for staging in this study [9].

2.2. Statistical analyses

Statistical Packages for Social Sciences (SPSS) version 22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. The primary outcome was cancer-specific survival, and survival time was measured from the date of the diagnosis of cranial metastasis to death or the last follow-up. The last doctor's visit was August 31, 2017. Nominal variables were analysed using Pearson's chi-square test or Fisher's exact test if the value observed was < 5, and continuous variables were analysed using the Mann-Whitney *U* test. The Kaplan-Meier method was used to calculate the survival rate. Survival curves for various subgroups of patients and treatments were compared using a two-sided log-rank test. A Cox regression analysis was used to examine the potential prognostic factors influencing cancer-specific patient survival, which was interpreted by hazard ratios (HRs) with 95% confidence intervals (CIs). A p-value < 0.05 was considered significant.

3. Results

3.1. Patient characteristics and pathology of the primary thyroid cancer

The incidence of TC metastasizing to the brain and skull was 0.34% (16/4683) and 0.19% (9/4683), respectively. Together, the overall incidence of cranial metastases was 0.53%. Demographic characteristics for this cohort of patients are presented in Table 1. Cranial metastasis of thyroid origin was the first pathological diagnosis in 9 patients (36.0%) following cranial surgery. The other 16 patients (64.0%) were diagnosed with cranial metastasis after thyroidectomy, and the mean interval between initial diagnosis and cranial metastasis was 6.3 ± 5.3 years (range 0.1–18.0 years). The mean interval between initial diagnosis and brain and skull metastasis was 5.5 ± 5.8 and 7.8 ± 4.3 years, respectively ($p = 0.267$).

Twenty-four cases (96.0%) had extracranial metastases at the time of diagnosis of cranial metastases. The incidence of metastasis according to location was as follows: 80.0% in the lung, 76.0% in bone, 4.0% in the liver and 4.0% in soft tissue.

Based on histological type, the incidence of cranial metastases was 4.1% (2/48) in poorly differentiated carcinoma, 2.0% (9/433) in FTC, 1.1% (1/87) in medullary carcinoma, 0.7% (1/135) in anaplastic carcinoma and 0.3% (11/3918) in PTC. We further categorized Hurthle cell carcinoma into WDTC. The incidence of cranial metastasis was 0.5% (21/4413) in WDTC, which was lower than the incidence of 1.5% (4/270) in non-WDTC ($p = 0.052$). Regarding sex distribution, the ratio of WDTC to non-WDTC cases was higher in female patients than in male patients (19/2 vs. 2/2, respectively).

Extrathyroidal extension was identified in 10 cases (40.0%), including 5 cases with minimal extension to the strap muscle or perithyroid soft tissue and 5 cases with advanced extension beyond the strap muscle. Eight (32.0%) of the 25 cases were proven to have cervical lymph node metastases at the time of initial treatment.

3.2. Radioactive iodine therapy

Except for patients diagnosed with anaplastic carcinoma ($n = 1$) and medullary carcinoma ($n = 1$), the other 23 patients received radioactive iodine (^{131}I) for either remnant ablation after initial thyroidectomy or adjuvant therapy for persistent cervical disease or distant metastases. A post-therapeutic whole-body scan (WBS) was performed one week after the administration of ^{131}I. Only 1 of 23 cases (4.3%) had ^{131}I-avid lesions on the skull on the WBS, and a CT scan revealed skull metastasis to the parietal bone.

3.3. Clinical presentations of cranial metastases

On clinical presentation of cranial metastases, 16 patients with brain metastases presented with neurological symptoms, including headache, nausea, vomiting, motor or sensory deficits, conscious disturbance, or seizure. Nine patients with skull metastases presented with palpable skull tumours without neurological symptoms.

3.4. Treatment for cranial metastases

One patient with skull metastasis refused further treatment, and only supportive care was provided. Twenty patients underwent surgical resection of 1 or more accessible metastatic lesions (single lesion in 15 cases, two lesions in 5 cases). The histopathology of cranial metastases matched the primary TC in all operated cases. Among the 20 patients receiving surgery, 12 underwent postoperative adjuvant radiotherapy. During follow-up, 3 patients with skull metastases had recurrences at the skull and underwent another operation, and 1 case with brain metastasis had recurrence, but no further surgical intervention was performed due to rapid progression and deteriorated general performance. Four patients (one with PTC, one with poorly differentiated carcinoma, one with anaplastic carcinoma and one with medullary carcinoma) with multiple metastases in bilateral cerebral lobes underwent palliative whole-brain radiotherapy alone.

Sorafenib (Nexavar®), a tyrosine kinase inhibitor (TKI), was approved by the Taiwan Food and Drug Administration in 2017 for targeted therapy of advanced radioiodine-refractory TC. Therefore, we did not have experience with TKIs in the treatment of cranial metastases from TC during this study period.

3.5. Comparison of clinical characteristics between patients with brain and skull metastases

Although none of the differences in variables between Groups A and B were statistically significant (Table 1), several differences in clinical