Follicular thyroid carcinoma metastasis to the facial skeleton: a systematic review

Varun V. Varadarajan1, Elizabeth K. Pace2, Vatsal Patel3, Raja Sawhney1, Robert J. Amdur4,5 and Peter T. Dziegielewski1,4*

Abstract

Background: Follicular thyroid carcinoma (FTC) metastasis to the facial skeleton is exceedingly rare. A case of FTC metastasizing to the mandible is presented and a systematic review of the literature describing thyroid metastasis to the facial skeleton is performed.

Case presentation: A 73-year-old female presented with metastatic FTC to the mandible and underwent total thyroidectomy, segmental mandibulectomy, bone impacted fibular free flap reconstruction, and adjuvant radioactive iodine treatment. The PubMed database was searched for literature describing thyroid cancer with facial skeleton metastasis using the key words "thyroid," "cancer," "carcinoma," "metastasis," and "malignancy" with "oral cavity," "maxilla," "mandible," "sinus," "paranasal," and "orbit." Reports that only involved the soft tissues were excluded. Systematic review revealed 59 cases of well-differentiated thyroid cancer with facial skeleton metastasis: 35 mandibular metastases (21 = FTC), 6 maxilla metastases (2 = FTC), 9 orbital metastases (4 = FTC), and 11 paranasal sinus metastases (7 = FTC). Treatment included surgery, RAI, external beam radiotherapy (XRT), or a combination of these modalities. The one, two, and five-year survival rates were 100%, 79%, and 16%, respectively.

Conclusion: Facial skeleton metastasis of FTC is a rare clinical challenge. Optimal treatment appears to include total thyroidectomy and resection of involved structures with or without adjuvant treatment.

Keywords: Follicular thyroid carcinoma, Head and neck surgery, Endocrine surgery, Thyroid neoplasm

Background

Follicular thyroid carcinoma (FTC) is the second most common thyroid carcinoma. It accounts for ~10% of thyroid malignancies, with a higher occurrence in women aged 40–60 years [1]. Follicular thyroid carcinoma is known to disseminate hematogenuously and metastasize in advanced cases. Distant metastases are seen in ~10–15% cases, with bone and lungs as preferred metastatic targets [2]. FTC metastases to the facial skeleton are exceedingly rare and present a treatment challenge.

FTC facial bone metastasis can present in the gnathic bones, the paranasal sinuses, or the orbit. Metastasis to the facial skeleton may be the first clinical sign of an underlying malignancy and clinical presentation varies depending on site of presentation as well as the primary site [3–7]. Oral cavity and maxillofacial region metastasis is uncommon and represent 1–2% of all oral and maxillofacial malignancies [3–5]. Prognoses of such lesions are assumed to be poor; however, there is a paucity of evidence to guide management of these scenarios.

In this report, a case of FTC metastasizing to the mandible is presented and a systematic review of the literature is performed. The purpose is to describe the clinical presentation, treatment, and survival outcomes of thyroid metastasis to the facial skeleton.

Case presentation

A 73-year-old female patient was evaluated at the Head and Neck Surgery Clinic at the University of Florida. Her presenting complaint was numbness and swelling of her left mandible and an intraoral lesion associated with recurrent bleeding episodes. Symptoms were present for several weeks and had initially been presumed to represent an
episode of sialadenitis by an outside provider. Her past medical history was significant for a thyroid nodule and no chronic medical conditions. She had no history of tobacco or alcohol abuse. Physical exam demonstrated a left mandibular lesion approximately 5 cm in size, with fullness of the gingival mucosa overlying the mass. A mucosal punch biopsy was performed and the histology demonstrated a pyogenic granuloma.

Computerized tomography (CT) showed an aggressive mass destroying the mandibular body (Fig. 1) as well as enlarged pulmonary nodules and a lytic bone lesion at T10. Imaging also demonstrated a multinodular thyroid gland with minimal irregularity along the anterior right border. A 4.6 cm nodule was noted in the right thyroid lobe. Fine needle aspiration of the right thyroid mass was interpreted as a follicular lesion of undetermined significance (FLUS). Because the pathology findings were inconsistent with the CT scan, an open biopsy in the OR was performed. A mucosal incision was made over the mass and a biopsy was taken. The lesion was found to be extremely friable and bled significantly requiring ligation of the facial artery. Final pathology demonstrated FTC.

Multidisciplinary tumor board review recommended surgery followed by radioactive iodine and external beam radiotherapy. The patient underwent total thyroidectomy, neck dissection, segmental mandibulectomy, and bone-impacted fibular free flap reconstruction [6]. Intraoperative findings included a 10 cm thyroid mass of the right thyroid lobe that extended beneath the sternum to the innominate vein. A segment of mandible was taken from left angle to right parasympysis, resulting in a defect from right lateral incisor to angle of mandible (Fig. 2). Reconstruction was undertaken via a right bone-impacted fibular free flap with skin paddle in addition to a 2.0 mm mandibular reconstruction bar. Final pathology showed mandibular metastasis of FTC with extension into the tongue and soft tissues of the neck (Fig. 3). Margins were negative. The 4.6 cm thyroid follicular carcinoma appeared to arise from a calcified pre-existing degenerative follicular adenoma. There was evidence of capsular invasion and extensive lymphovascular invasion. The patient underwent post-operative stereotactic body radiation to the T-10 metastatic lesion and 200 mCi of radioactive Iodine-131. She has been disease free for 18 months.

A systematic review of the English literature was performed using PubMed, Medline, Embase, and Scopus databases. Search terms describing FTC presenting as a metastatic lesion in the facial skeleton were compiled and implemented. These terms included: “thyroid,” “cancer,” “thyroid carcinoma,” “thyroid cancer,” “metastasis,” and “malignancy” with “oral cavity,” “maxilla,” “mandible,” “sinus,” “paranasal,” and “orbit.” Papers were gleaned for diagnoses of well-differentiated thyroid cancer, FTC, and metastases to the facial skeleton. Reports of metastasis that only involved the soft tissues were excluded. The reports were organized by subsite: mandible, maxilla, jawbone not otherwise specified, nasal cavity or paranasal sinus, and orbit. Data points obtained from literature review included age, gender, primary oncologic diagnosis, site of metastasis, clinical presentation, treatment modality, survival outcome, and time to follow-up were obtained. Statistical analysis was performed with SPSS 23.0 software package (SPSS Inc., Chicago, IL). Survival was estimated by a Kaplan-Meier analysis to the account for censored data. Survival by treatment was analyzed and compared using the log rank test.

Literature review identified 64 studies reporting 97 cases of thyroid cancer metastasis to the facial skeleton in the English literature. All metastases were present at the time of presentation. 59 case reports specified well-differentiated thyroid cancer as the diagnosis. Table 1 demonstrates details of these cases. 38 case reports did
not specify the diagnosis and were not included [7–18].
The gender distribution was 9 males, 48 females, and 2 cases in which gender was not specified. While the majority of metastases were to the mandible, other craniofacial sites were also found to be involved.

Treatment varied between studies and included: Surgery with or without preoperative embolization and radioactive iodine therapy, external beam radiation (primary or adjuvant treatment), and palliative chemotherapy. 22 patients were treated with surgery as initial treatment with or without postoperative radioactive iodine or external beam radiation. 11 patients were treated with external beam radiation as primary treatment. 14 reports did not specify treatment. 4 patients were treated with palliative care; 2 of these patients received palliative chemotherapy. Cases were grouped into: a surgical arm (those treated with surgery and RAI) and a non-surgical arm. 32 studies reported survival outcome and 27 studies reported time-to-follow up. 24 patients survived treatment and 8 patients expired.

Overall survival for all patients at 2 years was 96% and at 5 years was 59%. Disease specific survival at 2 years was 96% and at 5 years was 72%. Patients treated with surgery and RAI versus those treated by non-surgical means were compared. There was no statistical difference in overall survival ($p = 0.27$) with the surgical group having 2 and 5 year overall survival of 100% and 71%, respectively and those in the non-surgical arm having rates of 92% and 46%.

Disease specific survival for all patients at 2 years was 96% and at 5 years was 72% (Fig. 4). There was a statistically significant difference in disease specific survival (DSS) between patients treated with surgery and RAI versus those treated by non-surgical means ($p = 0.03$). DSS for surgically treated patients at 2 and 5 years was 100% and for non-surgically treated patients was 92% and 46%, respectively.

**Discussion and conclusions**

FTC is the second most common thyroid cancer, following papillary thyroid carcinoma (PTC). 10–15% of FTCs will disseminate hematogenously via angioinvasion. The most common sites of metastases include bone and lungs and less commonly brain, liver, bladder, and skin. Bone metastases can occur in the vertebral bodies followed by the pelvis, femur, skull, and ribs [2, 19]. Treatment often involves high dose radioiodine; however, bony metastases are less likely to concentrate radioiodine, and thus, the efficacy is estimated at 55%. External beam radiation therapy may be used for palliation [2].

Metastasis comprises 1% of all oral-maxillofacial malignancies. Primary sites of tumors metastatic to the facial skeleton are most commonly from the breast and lungs [20]. Thyroid malignancy represents 2% of facial skeleton metastasis [20] and 4.2–6.1% of all jaw metastases [7, 15, 21]. 41% of facial skeleton metastasis from thyroid cancer occurs in the mandible; 59% of these metastases are well-differentiated thyroid cancer. There have been 41 reported cases in the literature of thyroid malignancy with metastasis to the mandible of which 21 reported cases were FTC [4, 9–12, 22–47]. There have been 6 reported cases of metastasis to the maxilla; 2 were FTC [22, 48–52].

The majority of metastatic tumors to the mandible present with facial swelling and an osteolytic lesion. A rapid progression of intraoral or extraoral swelling associated with chin paresthesia and pain is not uncommon [21, 29, 36, 53]. As the tumor invades oral mucosa, a granulation-like mass may form and result in significant bleeding, infection, fractures, and disturbances in swallowing and mastication [32, 40].

Isolated facial skeleton metastasis may be treated with surgical resection, radioactive iodine, external beam radiation or combinations of the three. The patient presented here was treated with a composite resection and...
Table 1 List of reported cases of thyroid cancer metastasis to the facial skeleton

| Author of report | Age, Gender | Primary tumor | Site of presentation | Clinical presentation | Treatment of metastases | Survival | Time to follow-up |
|------------------|-------------|---------------|----------------------|-----------------------|-------------------------|----------|-------------------|
| Agarwal et al. [26] | 45, F | FTC | Mandible | Facial swelling | Resection | Yes | 2 weeks |
| Algahtani et al. [40] | 66, F | FTC | Mandible | Pathologic fracture | Resection | NR | NR |
| Anil et al. [72] | 61, F | FTC | Mandible | Mandibular swelling | NR | NR | NR |
| Bhadage et al. [28] | 40, F | FTC | Mandible | Facial swelling | NR, referred out | NR | NR |
| Bingol et al. [27] | 33, F | PTC | Mandible | Painless mass of mandibular angle | Surgery, RAI | No | 5 years |
| Colella et al. [75] | 50, F | PTC | Mandible | Pain and swelling in RMT | NR | NR | NR |
| Draper et al. [44] | NR, F | FTC | Mandible | Ulcerated oral lesion | XRT, RAI | NR | NR |
| Erdag et al. [23] | 53, F | PTC | Mandible | Right sided facial swelling | Surgery, RAI | Yes | 2.5 years |
| Essakalli et al. [41] | 50, F | PTC | Mandible | Painful swelling of jaw | Resection, RAI | Yes | 2 months |
| Germain et al. [42] | 50, F | PTC | Mandible | Jugular, carotid lymphadenopathy | Resection | Yes | 17 months |
| Ismail et al. [30] | 70, F | FTC | Mandible | Pain, “loose teeth” | NR | NR | NR |
| Kahn and McCord [31] | 82, F | FTC | Mandible | Painful oral swelling | XRT, surgical salvage | No | 18 |
| Kumar RVK et al. [32] | 58, F | FTC | Mandible | Painless facial swelling | Resection, mandible reconstructive bar, second stage thyroidectomy | Yes | 2 years |
| Lavanya et al. [29] | 76, M | FTC | Mandible | Painless mandibular swelling | NR, referred out | NR | NR |
| Liu et al. [33] | 66, M | PTC | Mandible | Cheek mass | Resection, RAI | Yes | 3 years |
| Markitziu et al. [46] | 69, F | PTC | Mandible | Facial swelling | XRT | Yes | 18 months |
| McDaniel et al. [76] | 77, F | FTC | Mandible | Pain, swelling | Resection, parotidectomy, RAI | Yes | 4 years |
| Meyer and Shklar [3] | 51, F | FTC | Mandible | NR | NR | NR | NR |
| Muttagi et al.: 2 cases [34] | NR | PTC | Mandible | NR | Surgery | NR | NR |
| | NR | FTC | Mandible | NR | Surgery | NR | NR |
| Nishikawa et al. [39] | 83, F | PDFTC | Mandible | Painful swelling of jaw and face | None | No | 19 months |
| Osguthorpe and Bratton [35] | 53, M | FTC | Mandible | Slowly enlarging parotid mass | Resection, RAI | Yes | 3 years |
| Ostrosky et al. [25] | 72, M | FTC | Mandible | Painful vascular lesion | Resection, iliac crest graft | NR | NR |
| Pasupula et al. [36] | 40, F | FTC | Mandible | Painful left parotid swelling | Resection | NR | NR |
| Tamiolakis et al. [4] | 69, F | PTC | Mandible | Facial swelling, mucosal ulcerations | Inoperable | NR | NR |
| Tovi et al. [47] | 33, M | FTC | Mandible | Mimicking AVM | RAI | No | 17 days |
| Vazifeh et al. [37] | 58, F | FTC | Mandible | Facial swelling | Resection | NR | NR |
| Vishvshwaraiah et al. [38] | 56, F | FTC | Mandible | Painless facial swelling, face and lip paresthesia | NR, referred out | NR | NR |
| Vural and Hanna [24] | 64, F | FTC | Mandible | Tender, pre-auricular mass | Resection, post op iodine ablation | Yes | 6 weeks |
| Zandi et al. [11] | 64, F | FTC | Mandible | NR | NR | NR | NR |
| | 75, F | FTC | Mandible | NR | NR | NR | NR |
| | 63, F | PTC | Mandible | NR | NR | NR | NR |
| | 44, F | PTC | Mandible | NR | NR | NR | NR |
| | 35, F | PTC | Mandible | NR | NR | NR | NR |
| | 51, F | PTC | Mandible | NR | NR | NR | NR |
radioactive iodine. Her defect was reconstructed with a bone-impacted osteocutaneous fibula free flap. Follow-up CT scanning demonstrated that the neo-mandible retained a dense bone stock from the bone impaction. Free flap reconstruction for metastatic thyroid cancer to the mandible has only been reported once in the literature [42]. The current case is the first report of a bone-impacted fibular free flap used in this scenario.

Metastatic thyroid carcinomas are also reported in the orbit and paranasal sinuses. 9 cases have been described in the bony orbit; 4 of these were FTC [16, 54–61]. Surgical debulking of the metastatic foci may restore vision in cases of sudden onset vision loss; radioiodine treatment has also been documented as treatment for tumors that uptake iodine. External beam radiation can also be an option. There are 17 reported cases of thyroid malignancy

| Antunes et al. [22] | 13, F | FTC | Maxilla | NR | NR | NR | NR |
| Fatahzadeh et al. [48] | 43, F | FTC | Maxilla | Hemorrhagic mass with ulceration and bleeding | | XRT | NR | NR |
| Hefer et al. [52] | 58, M | FTC | Maxilla | Left hard palate pain | | Resection | Yes | 2 years |
| Kumar CS et al. [51] | 31, F | FTC | Maxilla | Painful swelling, mobile teeth | | RAI | Yes | 7 years |
| Nikitakis et al. [49] | 63, M | FTC | Maxilla | Painful swelling of right posterior maxilla | | XRT, palliative chemotherapy | Yes | 2 years |
| Slim et al. [50] | 67, F | FTC | Maxilla, zygoma | Painless malar swelling | | Resection, postoperative iodine ablation | Yes | NR |
| Cinberg et al. [64] | 80, F | FTC | Maxillary sinus | Epistaxis | | RAI | NR | NR |
| Altimay et al. [69] | 68, F | FTC | Nasal Cavity, orbit, skull base | Left eye puffiness, proptosis, vision Loss, facial numbness | | XRT | Yes | 1 month |
| Malhotra et al. [60] | 55, F | FTC | Orbit (Anterolateral orbit) | Proptosis, vision Loss | | Resection, RAI | NR | NR |
| Rocha Filho et al. [57] | 66, F | FTC | Orbit (Frontal bone) | Frontal bone mass | | Palliative chemo | Yes | NR |
| Bernstein-Lipschitz et al. [55] | 56, F | FTC | Orbit (Lacrimal fossa, orbital roof) | Diplopia, ptosis, orbital Pain | | Resection | NR | NR |
| Shyla et al. [54] | 70, F | FTC | Orbit (Posterior orbit extending to ethmoid bone) | Vision loss | | Resection, XRT | Yes | NR |
| Boughattas et al. [56] | 25, F | FTC | Orbit (Supraorbital) | Asymptomatic | | NR | NR | NR |
| Daumerie et al. [58] | 59, F | FTC | Orbit (Supratemporal quadrant) | Left upper eyelid swelling, exophthalmos | | RAI | Yes | 2 months |
| Pagisihan et al. [59] | 49, F | FTC | Orbit (Supraorbital) | Supraorbital mass | | RAI | Yes | 6 months |
| Argibay-Vasquez [77] | 53, F | FTC | Sphenoid | Headache, paresthesia in the right eye region, left monocular diplopia | | RAI, subtotal resection, XRT, RAI | Yes | 3 years |
| Yamasoba et al. [67] | 34, F | FTC | Ethmoid, sphenoid, maxillary, intracranial | Cheek hypoesthesia, hearing Loss | | Embolization, resection | Yes | NR |
| Renner et al. [65] | 61, F | FTC | Sphenoid sinus | Epistaxis, anosmia, visual loss | | RAI, XRT | Yes | 5 months |
| Barrs et al. [63] | 54, F | FTC | Sphenoid sinus, orbit | Visual loss | | RAI, XRT | No | 5 years |
| Altman et al. [68] | 81, M | FTC | Sphenoid, ethmoid, skull base | Headache | | XRT | No | 1 year |
| Freeman et al. [78] | 50, M | FTC | Sphenoid, ethmoid | Facial pain, proptosis of the left globe, left horner’s syndrome | | XRT, RAI | Yes | 1 year |
| Madronio et al. [79] | 53, F | FTC | Sphenoid, ethmoid | Headache, galactorrhea, vision loss | | Surgical debulking | Yes | 13 months |
| Cumberworth et al. [66] | 74, F | FTC | Sphenoid, frontal, ethmoid, and maxillary sinuses | Nasal obstruction | | None | No | 1 week after diagnosis |

*FTC Follicular Thyroid Carcinoma, NR not reported, FTC Papillary Thyroid Carcinoma, RAI Radioactive Iodine Therapy, XRT External Beam Radiation Therapy*
presenting as a paranasal sinus mass (14.1%); 7 of these cases were FTC [8, 13, 14, 17, 18, 62–69]. Two cases presented simultaneously in the paranasal sinus and the bony orbit [63, 69]. Clinical manifestations include epistaxis, nasal obstruction, visual disturbances, and facial or intraoral swelling [70, 71]. The maxillary sinus is the most commonly involved sinus followed by the sphenoid sinus, ethmoid, and frontal sinus [70, 72]. The vertebral venous plexus, which allows retrograde spread of tumor emboli, could explain the etiology of paranasal sinus and orbital metastasis [71, 73]. Craniofacial resection or debulking with or without preoperative vascular embolization can be considered, however, the proximity of the metastatic tumor to the skull base may preclude surgical extirpation [59, 67, 69]. Radioiodine therapy, external beam radiation, chemotherapy, or palliative therapy can be considered in these patients [57, 59, 68, 74].

Survival analysis suggests that surgical resection of involved craniofacial structures with or without adjuvant treatment is the optimal treatment for FTC metastatic to the facial bones. Given the rarity of the condition, the sample size is limited; however, survival analysis demonstrated convincing statistically significant advantages with surgical resection. Treatment plans should be formulated with a multidisciplinary team involving surgical oncology, radiology, pathology, endocrinology, medical oncology, radiation oncology, and possibly palliative care.

In conclusion, facial skeleton metastasis of FTC is a rare clinical challenge. If feasible, surgical-based treatment options offer the best survival outcomes. When mandibular defects are present, reconstruction with a bone impacted fibular free flap may provide a reconstruction with a robust bone stock.

**Abbreviations**

CT: Computerized tomography; FTC: Follicular thyroid carcinoma; NR: Not reported; PTC: Papillary thyroid carcinoma; RAI: Radioactive iodine therapy; XRT: External beam radiation therapy

**Acknowledgements**
The authors have no acknowledgements.

**Funding**
The authors of this study declare no sources of funding for this study.

**Availability of data and materials**
All data generated or analyzed during this study are included in this published article.

**Authors’ contribution**
VV participated in the design of the study, data collection, participated in statistical analysis, and drafted the manuscript. EP participated in data collection, statistical analysis, and in drafting the manuscript. VP participated in data collection, histopathology interpretation, and drafting the manuscript. RS participated in the design of the study and in conceiving the study. RA participated in critically revising the manuscript for important intellectual content. PD conceived and designed the study, performed statistical analysis, and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.
Authors’ information

W is an Otolaryngology –Head and Neck Surgery resident physician at the University of Florida in Gainesville, Florida. EP is a senior medical student at the University of Florida College of Medicine in Gainesville, Florida. VP is a Pathology resident physician at the University of Florida in Gainesville, Florida. RS is an Assistant Professor in the University of Florida Department of Otolaryngology – Division of Facial Plastic Surgery in Gainesville, Florida. RA is a Professor in the University of Florida Department of Radiation Oncology. PD is an Assistant Professor at the University of Florida Department of Otolaryngology and Chief of the Division of Head and Neck Oncologic Surgery in Gainesville, Florida.

Competing interests

The authors of this study manuscript declare that they have no competing interests.

Consent for publication

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images.

Ethics approval and consent to participate

Ethics approval was not necessary for this study and manuscript due to the type of study design (Case Report, Literature Review). All patient data and photographs are de-identified.

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Author details

1Department of Otolaryngology (ENT), University of Florida, Gainesville, FL, USA. 2University of Florida College of Medicine, Gainesville, FL, USA. 3Department of Pathology, University of Florida, Gainesville, FL, USA. 4University of Florida Health Cancer Center, Gainesville, FL, USA. 5Department of Radiology, University of Florida, Gainesville, FL, USA.

Received: 30 November 2016 Accepted: 15 March 2017

Published online: 28 March 2017

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