How Should Well Differentiated Thyroid Cancer with Distant Metastatic Disease Be Managed?

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Tanaz Vaghaiwalla and Peter Angelos

Introduction

Well differentiated thyroid cancer (WDTC) typically presents with cancer limited to the thyroid gland with or without spread to regional lymph nodes of the central or lateral neck [1–3]. Patients who present with distant metastatic disease have outcomes that are less favorable and associated with a higher morbidity and mortality [1–5]. Distant metastatic disease can be divided into metastatic pulmonary disease and extra-pulmonary disease, which may include primarily brain and skeletal disease. An aggressive management strategy is recommended by current national and international guidelines which includes locoregional control with surgery and postoperative radioactive iodine (RAI) therapy for [1–3]. Treatment recommendations consist of total thyroidectomy, lymphadenectomy if indicated by presence of disease in the central and/or lateral neck, and subsequent adjuvant treatment with RAI therapy with varying possible dosing regimens. Distant metastases are uncommon but reportedly occurs in 1–23% of patients with well differentiated thyroid cancer [3–5]. Although an uncommon entity, distant metastatic disease is the most frequent cause of cancer related death among these patients. Long term disease specific survival is estimated to be 23–35% in those patients diagnosed with distant metastases secondary to well differentiated thyroid carcinomas [4].

The objective of this chapter was to review the current evidence in managing patients with WDTC with distant metastatic spread and to present our practice experience.

T. Vaghaiwalla (✉) · P. Angelos
Endocrine Surgery Program, Department of Surgery, The University of Chicago Medicine, Chicago, IL, USA
e-mail: Tanaz.Vaghaiwalla@uchospitals.edu

Z. Gooi, N. Agrawal (eds.), *Difficult Decisions in Head and Neck Oncologic Surgery*, Difficult Decisions in Surgery: An Evidence-Based Approach,
https://doi.org/10.1007/978-3-030-15123-2_13

Table 13.1 How should well differentiated thyroid cancer with distant metastatic disease be managed?

Population	Intervention	Comparison	Outcomes
Adults with WDTC and distant metastatic disease	Radioactive iodine treatment Metastasectomy Clinical trials	No radioactive iodine treatment, surgical intervention, or clinical trial interventions	Incidence of distant metastatic disease in WDTC Survival Prognostic factors

Literature Search Strategy

Based on the PICO table (Table 13.1), Pubmed and CENTRAL searches incorporating the terms "differentiated thyroid carcinoma", "papillary", and "follicular" and "distant metastatic disease" were used to review the literature. The bibliography of articles was also reviewed, and papers were reviewed and incorporated when applicable. The search was narrowed to focus on management and outcomes of differentiated thyroid carcinoma with distant metastatic spread in primarily adults. Studies were included if they were published from 1997–2017. The majority of the data on this subject matter arises from retrospective studies and single or multi-institutional studies. Current national and international association guidelines were included. We elected to focus on pulmonary metastases and extra-pulmonary metastases, including skeletal and brain disease.

Result

Pulmonary Metastases

Distant metastatic disease can be divided into metastatic pulmonary and extra-pulmonary disease, which can include primarily skeletal and brain disease. The management of the patient with pulmonary metastases is dependent on several factors which includes the size of the nodules, macronodular or micronodular, and tumor avidity for RAI treatment [1–5]. While many dosing regimens exist, there is no current consensus. According to recent guidelines, the generally recommended dose for both macronodular or micronodular pulmonary metastases ranges from 100–200 mCi when RAI is administered empirically to patients aged <70 years old, and lower range of 100–150 mCi to patients aged ≥70 years old [2]. In order to limit RAI retention, dosimetry estimates may be employed to limit retention to 80 mCi at 48 h and 200 cGy to bone marrow and this recommendation has not changed over the last 10 years [1, 2].

Macronodular pulmonary metastases can be managed with RAI when shown to be iodine avid [1–7]. One study involving 444 patients with well differentiated thyroid cancers treated for distant metastases every 3–9 months with 100 mCi during the first 2 years and then annually until no uptake was visualized on scan.

In patients who achieved negative studies who had lung metastases only, the median cumulative activity given to patients was 220 mCi, ranging from 65 to 700 mCi [7]. The particular treatment regimen is determined by several factors such as age, response to treatment, and any evidence of disease progression between treatment administrations [2, 7]. The response to treatment of macronodular metastases may be demonstrated by following objective clinical variables in order to guide therapy such as thyroglobulin levels or change in lesion size [7]. Remission is less likely with macronodular metastases than with micronodular metastases [2]. RAI therapy is strongly recommended for the treatment of pulmonary micronodular metastases. RAI should be repeated at intervals of approximately 6–12 months while response to treatment and progression of disease is monitored [1–3]. RAI treatment was found to be more effective in younger patients (<40 years of age) and smaller pulmonary metastasis [7].

Pulmonary metastases which do not demonstrate RAI avidity are an entity that remains a therapeutic challenge for clinicians [1, 4–9]. RAI is not recommended as a treatment modality in this disease subgroup, and there are no set guidelines for the management of this disease. Interestingly, a lack of RAI avidity may not be the only predictive factor for disease progression. One retrospective study of 199 patients with follicular cell-derived thyroid cancer with lung metastases demonstrated that there was a strong correlation with overall survival and clinical progression free survival (defined as a 30% increase in longest diameter of the lesion or new lesions), which was shorter not only in RAI refractory disease, but also poorly differentiated cancers, males, older age patients >45 years old, metastases greater than 1 cm, and fluorodeoxyglucose avid lesions [8]. When these factors are taken together, they may identify a subset of patients that benefit from early discussion of other novel treatment modalities. Systemic cytotoxic chemotherapeutic agents, specifically doxorubicin, have been studied as monotherapy or used in combination with another agent. The use of chemotherapeutic options in distant metastatic disease is limited by their toxic profiles and provide little impact on survival or remission [9]. Combination of chemotherapeutic agents does not appear to add significant benefit. Several clinical trials involving anti-angiogenic agents are available for eligible patients with non-RAI avid pulmonary metastases. For patients with symptomatic disease, such as pain or bleeding secondary to pulmonary metastases, resection of metastases, ablative therapies, and external beam radiation may be used [1–4]. In RAI non-avid metastatic lesions, novel therapeutic targets such as kinase inhibitor sorafenib is a potential treatment option. In recent randomized controlled trial phase 3 study, sorafenib demonstrated improved progression free survival of 10.8 months compared to placebo 5.8 months (hazard ration 0.59; 95% CI, 0.45–0.75, $p < 0.0001$), however no overall survival difference was demonstrated [10]. Another potential therapeutic agent is lenvatinib the oral tyrosine kinase inhibitor to several targets including vascular endothelial growth factor rector, platelet derived growth factor, fibroblast growth factor receptor, and RET and KIT proto-oncogenes. In a randomized double-blind phase 3 trial, patients with RAI refractory disease who took lenvatinib

dosage 24 mg/day demonstrated improved progression free survival compared to placebo. Two treatment arms stratified patients by age (median age 56 and 71 years of age) and in both arms there was a statistically significant improvement in progression free survival with lenvatinib of 20.2 months compared to 3.2 months for those who took placebo (HR 0.27; 95% CI, 0.17–0.27; $p < 0.001$) [11].

Pulmonary micronodular metastases should be treated with radioactive iodine (RAI) therapy (quality of evidence moderate; conditional recommendation).

Pulmonary macronodular metastases should be treated with RAI therapy if shown to be RAI (quality of evidence low; conditional recommendation).

Bone Metastases

Extrapulmonary metastases include bone metastases and are associated with a worsened prognosis. Patients with resectable disease who undergo surgery experience improved survival [12]. For patients with symptomatic isolated bone metastasis, surgery is recommended [1–3]. Survival is improved in this patient population. One retrospective study of 245 differentiated thyroid cancer patients with bone metastases evaluated skeletal events, demonstrated the increased morbidity of this disease. The majority of patients presented with a skeletal event, defined as spinal cord compression, pathological fracture, requirement for external beam radiation or surgery, and malignancy related hypercalcemia, at the time of their diagnosis while the remainder presented at a median of 5 months from the time of initial diagnosis [13]. Unresectable disease may be palliated with external beam radiation therapy, RAI, or bisphosphonate infusions. Selective arterial embolization and/or external radiation may also be used; however, these modalities are not associated with improved survival [12]. Iodine-avid lesions should be treated with RAI for improved survival after resecting gross disease. One single institution study evaluating prognostic factors and treatment strategy for patients with bone metastases in 52 of 1398 patients who underwent initial thyroidectomy for WDTC demonstrated a significant 5-year survival advantage in patients who underwent RAI therapy at 59% compared to 23% for those who did not undergo RAI therapy ($p = 0.0028$) [14]. This improved prognosis appeared dependent on the dose of RAI with a cumulative RAI dose ranging from 100 to 600 mCi [14].

RAI is recommended for RAI-avid tumors metastatic to the bone (quality of evidence moderate; conditional recommendation).

Surgical resection is recommended for isolated resectable bone metastases (quality of evidence moderate; conditional recommendation).

Brain Metastases

Brain metastases associated with well differentiated thyroid cancer are rare and estimated to range from 0.5–1% of patients [1–3, 15, 16]. The treatment of brain metastases has few options and there is limited data which arises from retrospective analyses and single institution studies. Surgery is associated with improved survival for both RAI avid and non-avid disease [1]. If surgical resection is not possible, external beam radiation therapy may be employed. RAI therapy is recommended for RAI avid lesions [1, 3]. In one retrospective series of 16 patients with brain metastases treated with local therapies, resection of brain metastases was associated with a longer survival of 20.8 months (n = 13 patients, ranging, 5.2–55.3 months), compared to 2.7 months (n = 3, ranging, 0–6.4 months). Of note while the majority of the patients had either papillary or follicular carcinomas, this series included 3 of 16 patients with medullary thyroid cancer, Hurthle cell, or anaplastic carcinomas [15]. In another single institution study of 25 patients, 16 patients had metastases to the brain, while 9 patients had metastases to the skull. A total of 96% of patients (24 of 25 patients) had extracranial disease at the time of the initial diagnosis of cranial metastases. The factors associated with improved survival were the metastatic site involving only skull ($p < 0.006$), well differentiated histology ($p < 0.001$), and surgical resection ($p < 0.001$) [16].

> Surgical resection is recommended for resectable brain metastases (quality of evidence low; conditional recommendation).

A Personal View of the Data

The approach to treatment of patients with well differentiated thyroid cancer and distant metastatic disease at our institution is in keeping with the current national guidelines. Our institutional practice is to take a multidisciplinary approach to the patient's care. From a surgical standpoint, our practice is to resect all detectable disease, with total thyroidectomy and locoregional lymph node dissection of the central and lateral neck when indicated. Surgical resection of distant metastasis is recommended if the lesion is amenable to resection and when the patient's performance status is amenable for undergoing the procedure. While the recommendations for pulmonary metastases which are RAI avid are stronger and demonstrate an improved survival, particularly in younger patients (<45) with lower metastatic disease burden, there is unfortunately limited data regarding treatment of RAI non-avid metastases. It is in this patient population where significant research is needed in the form of clinical trials targeting cell cycle, angiogenesis, and signaling pathways. Overall, there is a paucity of data on how best to manage these challenging well-differentiated thyroid cancer patients with distant metastases and more data is necessary to make strong recommendations.

References

1. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;11:1167–94.
2. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;1:1–133.
3. Mitchell AL, Gandhi A, Scott-Coombes D, Perros P. Management of thyroid cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130:150–60.
4. Goffredo P, Sosa JA, Roman SA. Differentiated thyroid cancer presenting with distant metastases: a population analysis over two decades. World J Surg. 2013;37:1599–605.
5. Nixon IJ, Whitcher MM, Palmer FL. The impact of distant metastases at presentation on prognosis in patients with differentiated carcinoma of the thyroid gland. Thyroid. 2012;22:884–9.
6. Sampson E, Brierly JD, Le LW, Rotstein L, Tsang RW. Clinical management and outcome of papillary and follicular (differentiated) thyroid cancer presenting with distant metastasis at diagnosis. Cancer. 2007;110:1451–6.
7. Durante C, Haddy E, Leboulleux D, Hartle JP, Travagli B, Caillou M, Ricard JD, Lumbroso F, De Vathaire F, Schlumberger M. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metabol. 2006;91(8):2892–9.
8. Sabra MM, Ghossein R, Tuttle RM. Time course and predictors of structural disease progression in pulmonary metastases arising from follicular cell-derived thyroid cancer. Thyroid. 2016;26(4):518–24.
9. Sherman SI. Cytotoxic chemotherapy for differentiated thyroid carcinoma. Clin Oncol. 2010;22(6):464–8.
10. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, de la Fouchardiere C, Pacini F, Paschke R, Shong YK, Sherman SI, Smit JW, Chung J, Kappeler C, Peña C, Molnár I, Schlumberger MJ, DECISION investigators. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet. 2014;384(9940):319–28.
11. Brose MS, Worden FP, Newbold KL, Guo M, Hurria A. Effect of age on the efficacy and safety of lenvatinib in radioiodine-refractory differentiated thyroid cancer in the Phase III SELECT Trial. J Clin Oncol. 2017;35(23):2692–9.
12. Bernier MO, Leenhardt L, Hoang C, Aurengo A, Mary JY, Menegaux F, Enkaoua E, Turpin G, Chiras J, Saillant G, Hejblum G. Survival and therapeutic modalities in patients with bone metastases of differentiated thyroid carcinomas. J Clin Endocrinol Metabol. 2001;86:1568–73.
13. Farooki A, Leung V, Tala H, Tuttle RM. Skeletal-related events due to bone metastases from differentiated thyroid cancer. J Clin Endocrinol Metab. 2012;97(7):2433–9.
14. Orita Y, Sugitani I, Matsuura M, Ushijima M, Tsukahara K, Fujimoto Y, Kawabata K. Prognostic factors and the therapeutic strategy for patients with bone metastasis from differentiated thyroid carcinoma. Surgery. 2010;147(3):424–31.
15. McWilliams RR, Giannini C, Hay ID, Atkinson JL, Stafford SL, Buckner JC. Management of brain metastases from thyroid carcinoma: a study of 16 pathologically confirmed cases over 25 years. Cancer. 2003;98(2):356–62.
16. Hong YW, Lin JD, Yu MC, Hsu CC, Lin YS. Outcomes and prognostic factors in thyroid cancer patients with cranial metastases: a retrospective cohort study of 4,683 patients. Int J Surg. 2018;55:182–7.