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Distant metastases of differentiated thyroid cancer: diagnosis, treatment and outcome

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Abstract

The remarkably good prognosis and long-term survival in differentiated thyroid cancer (DTC) are significantly reduced in patients with distant metastasis (DM). Multi-site metastases are associated with a high mortality rate reaching 92% at 5 years necessitating early diagnosis and treatment. The most common site of metastases are the lungs, followed by the bone, with the former having better prognosis than the latter due to late detection. A number of factors contribute to the development of DM including large and multifocal primary tumour, extrathyroidal extension, aggressive histology and advanced age. In patients with good ^{131}I uptake, ^{131}I therapy appears highly effective and should be offered up to a cumulative activity of 22 GBq. Other measures such as surgery, radiotherapy, arterial embolisation and cementoplasty may be required.

If there is low or no ^{131}I uptake, FDG-PET should be obtained due to its prognostic impact. It may help in selecting patients for other modalities such as cytotoxic chemotherapy and redifferentiation therapy by *13-cis* retinoic acid. The development of tyrosine kinase inhibitors has raised hopes in providing alternative therapy for bone metastasis, especially in older age groups with poorly differentiated tumours with no ^{131}I uptake but good uptake of FDG.

Key words: metastates, differentiated thyroid cancer, diagnosis, treatment

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Although differentiated thyroid cancer (DTC) is usually of good prognosis [1], patients with distant metastases (DM) (4–15%) [2–6] are known to have a markedly reduced survival rate of 50% at 5 yrs, decreasing to 13–33% at 10 yrs [5, 7–12]. However, a recent study by Durante et al. showed a distinction between patients with ^{131}I uptake with persistent imaging abnormalities, who had an overall survival at 10 yrs of 29%, and those who had a negative ^{131}I uptake where survival reached 92% [13]. The 10-year survival was as low as 10% in patients in whom metastases showed no initial ^{131}I uptake. The importance of early diagnosis of functioning DM is thus clearly highlighted. However, the true prognosis for an individual patient with stage IV thyroid cancer is still difficult to assess due to differences in reported outcomes. This is due the heterogeneous analysis of results with regard to timing of development of metastasis, site and extent of disease, age of the patients, histology of the tumour and treatment of the metastatic disease.

Distant metastates are synchronous with the primary diagnosis in 5 to 45 % of patients [6, 11, 12] but could be encountered 5 or 10 years after the initial treatment, thus justifying the prolonged follow-up of thyroid cancer patients [9, 10, 14, 15].

The most common site of metastasis is the lung followed by the bones. Other metastatic areas are less common and involve the mediastinum, brain, liver, skin and so forth. Multi-site disease is associated with a higher rate of mortality that can reach 92% at 5 yrs [7, 12, 16, 17].

Patients with lung metastases have a better outcome compared to other groups [11, 18] whereas bone metastases are usually associated with a poor prognosis [7, 12, 13, 18–26, 28, 29], which might partly be due to the fact that they are rarely detected at an early stage. Among 109 patients with bone metastases described by Bernier et al., only four (4%) had both positive radioiodine uptake and negative standard X-ray examination [19]. Simi-

larly, in the study by Durante et al. [13], radiographs were negative at presentation in only eight (7%) of 115 patients. In our recent series of 16 bone metastases among 921 consecutive thyroid cancer patients [30], we found eight patients (50%) in whom bone metastases were first revealed by ^{131}I scanning, and in whom complementary radiological studies were negative. Six of these patients had a very good response to ^{131}I therapy with ^{131}I uptake and thyroglobulin (Tg) levels becoming undetectable or showing a sharp fall. One patient refused ^{131}I therapy and bone metastases became visible on MRI within one year and the Tg level rose 10-fold.

When it is thought that a patient is at high risk of multiple bone metastases, it may be important to make this diagnosis by conventional imaging before withdrawal of thyroid hormone to avoid dramatic potential complications such as neurological compression at the site of spine metastases that may occur at the time of ^{131}I therapy. These patients may require surgery or cementoplasty before hormone withdrawal and ^{131}I therapy. As patients with DM are usually 10 to 15 years older than non-DM controls [9], the presence of DM should be thus suspected in the case of increasing age, as well as in patients with already known DM where multiple organ involvement is possible, but also increasing primary tumour size, extrathyroidal extension, aggressive histology (poorly differentiated follicular tumours, Hürthle cell tumours [31, 32] and insular tumours [33]). Lastly, male gender [9, 33] and multifocality of the primary tumour [34, 35] have also been described as predisposing factors.

The treatment of DTC with metastasis requires total/near-total thyroidectomy followed by radioiodine therapy, which is the treatment of choice in iodine-avid metastases, and which responds favourably to ^{131}I therapy. This is supported by the literature [3, 13, 26, 36, 37]. However, as already mentioned, bone metastases may require additional therapy such as surgery, radiotherapy and/or alternative treatments by arterial embolisation [38] and cementoplasty in emergencies (vertebral compression, fracture, brain metastasis) or as a first line therapy to reduce the tumour burden or as preparation for ^{131}I therapy. Lastly, treatment with bisphosphonates may delay tumour progression and palliate symptoms.

However, high cumulative activities of radioiodine ($>$ 22 GBq; 600 mCi) are associated with a significantly increased risk of leukaemia (which may differ according to whether ^{131}I is used alone or in combination with external beam radiation therapy) [39] and secondary cancers [39, 40]. For this reason, ^{131}I should be repeated only when benefits are expected. Another potential risk from ^{131}I is pulmonary fibrosis in patients with diffuse pulmonary metastases who receive repeated activities of radioiodine over short intervals of time; pulmonary function should therefore be periodically assessed during ^{131}I therapy, especially in young patients [41]. Therefore, the decision to continue or stop ^{131}I therapy at 22 GBq should depend on the risk associated with metastatic disease and should be taken on an individual basis [14, 15].

^{131}I treatment appears highly effective in younger patients with ^{131}I uptake and with small metastases. In the study of Durante et al [13], the best responses (92% 10-yr survival rate) were observed in patients younger than 40 years old with papillary or follicular well-differentiated subtypes and a limited extent of disease; such patients should be treated until the disappearance of any uptake or until a cumulative activity of 22 GBq is attained. However, in patients who continue to have uptake, the beneficial effects of ^{131}I are difficult to quantify but probably contribute to the reduced 10-yr survival rate that can reach 30% [3, 12, 13, 30, 36]. This is indeed significantly better than the 10-yr survival rate of 10% observed in patients without any detectable uptake, and may be related to different tumour biology and to the beneficial effects of radioiodine therapy [13].

In patients with stable disease over several years with a good quality of life, we recommend that ^{131}I therapy be withheld after 22 GBq and that such patients be monitored with spiral CT scans or MRI and Tg assays, and that further ^{131}I therapy only be given in the event of disease progression [36].

Whenever possible, FDG-PET should be obtained both in patients with non-functioning metastases or those with functioning macrometastases. We believe FDG-PET is an important complementary imaging study in these patients because of its confirmed prognostic impact [42]. It might also help to select candidates for new therapeutic trials in cases of high FDG uptake [43].

Patients with large metastases, poorly differentiated carcinomas and with low or no ^{131}I uptake may be candidates for therapeutic trials with new agents, since the current therapeutic options for such patients are limited [43]. Cytotoxic chemotherapy (especially doxorubicin) has proven to be ineffective in these patients. Redifferentiation therapy by 13-cis retinoic acid (RA) which can induce ^{131}I uptake in about 40% of such patients [44–48] gave great hope in the end of the nineties in patients with loss of differentiation [49], including the loss of radioiodine uptake, but unfortunately the results were controversial [50, 51]. All-trans-retinoic acid (ATRA) has recently been studied [52] and might deserve further investigation. A recent study has demonstrated that histone modification patterns may explain RA-refractoriness in DTC patients and may suggest a potential benefit of combined transcriptional and differentiation therapies [53].

The development of tyrosine kinase inhibitors has recently changed therapeutic strategies in oncology [54], and their role in thyroid cancer management has been underlined in two recent reviews [43, 55]. This new strategy may represent a new hope for such patients, particularly those of older age groups with poorly differentiated tumours who have no or low radioiodine uptake, large metastases, location in bones, rapidly progressive disease and high uptake of FDG. It may also help patients with initial uptake but poor or no response to radioiodine treatment and those with no initial uptake of radioiodine, especially when the disease is progressive. The results of molecular targeted therapies and anti-angiogenic agents, which are being studied in prospective controlled trials, are therefore anticipated with great interest.

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