Definition and management of radioactive iodine-refractory differentiated thyroid cancer

For some patients with metastatic disease from differentiated thyroid cancer, remarkable results can be achieved with eradication of tumour cells through radioactive iodine ($^{131}$I) uptake. However, even after an adequate stimulation by thyroid-stimulating hormone and in the absence of excess iodine, only two thirds of patients with metastases show substantial radioactive iodine uptake, and only 42% of them achieve a cure.\(^1\) Patients who are not responsive to radioactive iodine treatment have a life expectancy of 3–5 years and represent a group for whom there is a clear unmet medical need.\(^1\) Development in this area is hampered by an absence of consensus regarding the definition of radioactive iodine-refractory differentiated thyroid cancer. Therefore, in September, 2012, an expert panel met to propose a working definition and treatment algorithm.

Most patients with radioactive iodine-refractory differentiated thyroid cancer fall into four categories. 1) Patients with metastatic disease that does not take up radioactive iodine at the time of initial treatment. For these patients there is no evidence that treatment with radioactive iodine provides benefit. This group includes patients with structurally evident disease with no radioactive iodine uptake on a diagnostic whole-body scan; in such patients uptake, when present on post-therapy scans, will not be sufficient to induce benefit.\(^2\) 2) Patients whose tumours lose the ability to take up radioactive iodine after previous evidence of uptake. This often occurs in patients with multiple large metastases and is due to the eradication of differentiated cells that take up radioactive iodine but not of poorly differentiated cells that do not take up radioactive iodine. 3) Patients with radioactive iodine uptake retained in some lesions but not in others. This is frequently seen in patients with multiple large metastases, as shown by $^{124}$I studies on PET scan,\(^3\) and by comparing results of fluorodeoxyglucose ($^{18}$F-FDG)-PET or diagnostic CT scans with radioactive iodine whole-body scan. In such patients, progression is likely to occur in metastases without radioactive iodine uptake (in particular when $^{18}$F-FDG uptake is present) and radioactive iodine treatment will not be beneficial.\(^4,5\) 4) Patients with metastatic disease that progresses despite substantial uptake of radioactive iodine. It has been clearly shown that if progression occurs after a course of adequate radioiodine treatment, subsequent radioactive iodine treatment will be ineffective.\(^6\) Tumour response during radioactive iodine treatment is judged on both imaging (CT scan or MRI) and functional methods—ie, radioactive iodine uptake in tumour foci and serum thyroglobulin determination. A similar trend is usually observed with all methods, but there can be some discrepancies, such as a decrease in radioactive iodine uptake and in serum thyroglobulin concentration with progression on imaging, underscoring the need for comprehensive assessment.

Less clear is the situation for patients with visible radioactive iodine uptake in all lesions who are not cured despite several treatment courses, but yet whose disease does not progress according to RECIST criteria.\(^7\) For these patients, the probability of obtaining a cure with further radioactive iodine treatment is low and side-effects might greatly increase, including the risk of secondary cancers and leukaemias.\(^8\) It is controversial as to whether these patients (particularly after receiving more than 600 mCi of radioactive iodine) should be considered as radioactive iodine-refractory, and whether radioactive iodine treatment should be abandoned. The decision to continue radioactive iodine treatment in such patients is generally based on their response to previous treatment courses, persistence of a pronounced level of radioactive iodine uptake during the previous treatment course, low $^{18}$F-FDG uptake in tumour foci, and absence of side-effects. Also in patients with radioactive iodine uptake, the chance to obtain a complete response is reduced when $^{18}$F-FDG uptake in the lesions is high on PET scanning;\(^4,5\) radioactive iodine treatment should however not be withdrawn based only on the presence or intensity of $^{18}$F-FDG uptake.

Finally, there is a subgroup of patients with advanced disease for whom thyroidectomy is not feasible. In these patients, radioactive iodine treatment is usually not administered because radioactive iodine is ineffective when the thyroid gland is still present and radioactive iodine uptake status cannot be assessed. These patients should be managed as iodine-refractory patients.
Once radioactive iodine treatment is terminated, active surveillance should include a $^{18}$F-FDG-PET CT scan or a CT scan of the neck, chest, abdomen, and pelvis with contrast, at an interval that is dictated by the pace of previous disease progression, if known, and of no more than 1 year. The decision to initiate systemic treatment or to enrol in a clinical trial should be based on several parameters, including tumour burden, disease progression, symptoms, or a high risk of local complications. Indeed, patients with multiple lesions greater than 1–2 cm in size, and with progression within less than 12 months, should be considered for systemic treatment. By contrast, patients with few lesions, or lesions less than 1 cm in size, or both, and those with no evidence of progression should be considered for active follow-up. Some patients with large tumour burden and without radioactive iodine uptake and for whom there is no data for progression could be considered for systemic treatment based on uptake of $^{18}$F-FDG on PET scanning or even on primary tumour histology—but only when active surveillance (imaging every 2–3 months) is not feasible, or there is a high risk of complications from disease.

Based on these considerations, we propose a treatment algorithm for management of patients with differentiated thyroid cancer and distant metastases (figure). Patients diagnosed with metastatic differentiated thyroid cancer are managed as appropriate with focal treatment (surgery, external beam radiation, thermoablation), radioactive iodine, or both, based on evidence of radioactive iodine uptake. Once one or more metastatic lesions fail to take up radioactive iodine and continue to grow, these patients are considered refractory and radioactive iodine treatment is abandoned. For such patients, alternative systemic therapy is considered when both the tumour burden is substantial and tumour progression is documented.

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Vaisman F, Tala H, Grewal R, Tuttle RM. In differentiated thyroid cancer, an incomplete structural response to therapy is associated with significantly worse clinical outcomes than only an incomplete thyroglobulin response. Thyroid 2011; 21: 1317–22.


