Introduction

Differentiated thyroid cancer (DTC) is the most common form of thyroid malignancy, with an increasing incidence across the globe. This kind of cancer is derived from the follicular cells, including papillary thyroid carcinoma, follicular thyroid carcinoma, and their variants. These are the most common types of thyroid cancer, accounting for 90-95% of all cases. They are generally slow-growing cancers and have an excellent overall prognosis, with overall 20-year survival rate greater than 90% with standard therapy. However, a subset of patients with DTC presents a more aggressive disease and develops recurrent or metastatic disease that is refractory to radioactive iodine(I-131) therapy. The 10-year survival rates of this radioactive iodine refractory (RAI-R) patients decline to approximately 15-20%.

Treatment strategy of DTC

Current standard treatment for patients with DTC generally involves total or near-total thyroidectomy followed by I-131 treatment, if indicated, and life-long thyroid hormone therapy. I-131 is often administered postoperatively to ablate remaining thyroid tissue, eliminate any suspected micrometastases, and decrease risk of disease recurrence. In some cases, external beam radiation therapy may be used as the adjunct treatment for bone or brain metastases. For most patients with DTC, these treatments are highly effective. Patients with persistent disease after the first I-131 treatment may need repeated doses of I-131. However, multiple repeated doses of I-131 may not guarantee disease remission. Patients receiving a high cumulative dose of I-131 expose a higher risk of I-131 complications, such as sialadenitis, xerostomia, impaired gonadal function, nasolacrimal duct obstruction, and radiation-induced secondary cancers and leukemia. Balancing between benefits and risks of I-131 is therefore crucial upon variable clinical courses of each particular patient. About 25-35% of patients with locally advanced or metastatic disease finally becomes RAI-R. Identification of RAI-R status in patients with DTC indicates that I-131 has no further role and helps guide other treatment strategy, including thyroid hormone therapy, direct local treatment, and systemic targeted therapy.
Basic concept of RAI-R disease

It is often difficult to determine whether metastatic thyroid cancer is likely to be responsive to I-131 treatment because significant therapeutic benefit is sometimes detected even in patients with poorly differentiated cancer, Hurthle cell carcinoma, widely metastatic follicular carcinoma, or patients with large tumor burden. A variety of factors are associated with suboptimal RAI avidity in metastatic thyroid cancer lesions. Ideally, a direct measurement of RAI dose achieved within each metastatic lesion in every patient would allow clinicians to confidently determine whether RAI is likely tumoricidal. RAI can be expected to be effective if the lesional dose exceeds 8,000 cGy. However, lesional dosimetry is not practical and may not be available in several centers. Therefore, indirect methods have been opted to determine whether RAI treatment is likely to be effective for individual patient. These methods include 1) negative post-therapy whole body scan (following a properly performed administration of ≥ 30 mCi with either thyroid hormone withdrawal or recombinant human TSH), 2) negative diagnostic RAI scan in the setting of structurally identifiable disease, 3) markedly positive F-18 FDG PET imaging, and 4) cumulative I-131 administered activities ≥ 600 mCi. In addition, response to I-131 is more likely to be poor in older patients (age > 40 years) and in patients with poorly differentiated tumors or large tumor burden.

Clinical diagnosis of RAI-R patients with DTC

Although diagnostic criteria of patients with RAI-R are not universally established, some have proposed the definition of RAI-R patients, mainly based on imaging and clinical information. Among these, the definition proposed by the American Thyroid Association (ATA) is probably the most widely used. According to the 2015 ATA guidelines, RAI-R DTC is classified in patients with appropriate TSH stimulation and iodine preparation as having any one of the following four criteria: 1) the malignant or metastatic tissue does not ever concentrate RAI as evident by no RAI uptake outside thyroid bed at the first post-therapy whole body scan, 2) the tumor tissue loses the ability to concentrate RAI after previous evidence of RAI-avid disease, 3) RAI is concentrated in some lesions but not in others; and 4) metastatic disease progresses despite significant concentration of RAI. Once RAI-R is diagnosed, I-131 treatment should not be further given.

Definition of RAI-R thyroid cancer

In patients treated with I-131, treatment efficacy is assessed by functioning parameters (serum thyroglobulin level or I-131 uptake on post-therapy whole body scan) and also anatomical imaging with CT scan or MRI. Favorable responses are characterized by parallel decreases in tumor volume on
anatomical imaging, I-131 uptake, and serum thyroglobulin levels. In contrast, a decrease in I-131 uptake without a decrease in tumor volume signifies the destruction of differentiated thyroid cancer cell with high uptake and the persistence of poorly differentiated foci that will progress. These patients should be considered as being refractory to RAI. These patients usually fall into six categories. It should be noted that the first four categories are in line with the ATA definition of RAI-R thyroid cancer.

Category 1. Patients with metastatic disease that does not take up I-131 at the time of initial treatment. There is evidence that I-131 treatment does not provide any benefit. This group includes patients with structural evidence of disease with no I-131 uptake on diagnostic whole body scan, because in such patients I-131 uptake, even when present on post-therapy scan, will not be sufficient to induce clinical benefits.

Category 2. Patients whose tumors lose the ability to take up I-131 after previous evidence of uptake. This is due to the eradication by I-131 treatment of differentiated cells that are able to take up I-131 but not of poorly differentiated cells that do not take up I-131. Progression is likely to occur in these poorly differentiated cells.

Category 3. Patients with I-131 uptake retained in some lesions but not in others. This is frequently seen in patients with multiple large metastases. In these patients, progression is likely to occur in metastases without I-131 uptake and in particular when FDG uptake is present.

Category 4. Patients with metastatic disease that progresses despite significant uptake of I-131. It has been shown that if progression occurs following a course of adequate I-131 treatment, subsequent I-131 treatment will be ineffective.

Category 5. Patients with persistent visible I-131 uptake in all residual lesions who are not cured despite several treatment courses but whose the disease does not progress according to the RECIST criteria. The probability of cure with further I-131 treatment is low, whereas the complications of I-131 are significantly increased. This kind of patients, particularly who received more than 600 mCi of I-131, should be regarded as RAI-R, because further I-131 treatment can hardly induce disease remission. However, decision to continue I-131 treatment may be considered based on response to previous treatment, persistence of significant level of I-131 uptake on the previous post-therapy whole body scan, low FDG uptake in tumor foci, or degree of patients’ acceptable range of I-131 side effects.
Category 6. Patients with advanced disease for whom thyroidectomy is not feasible. In these cases, I-131 treatment is usually not recommended because it is likely ineffective when thyroid gland is still present. In addition, I-131 avidity status of any possible metastatic lesions cannot be assessed. These patients may be managed as RAI-R cases.

Summary

RAI-R thyroid cancer is not a rare condition and it has significantly adverse clinical outcomes for DTC patients. Diagnosis of RAI-R is mainly based on clinical and imaging information and definitions of RAI-R have been proposed. It is crucial to diagnose this condition before consideration of further appropriate treatment strategy.