

Editorial

Redifferentiation in radioiodine-refractory thyroid cancer: Is restoring iodine uptake enough?

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Radioiodine (RAI) refractoriness represents a major turning point in the natural history of differentiated thyroid cancer (DTC). Loss of iodine avidity may reflect suppression of the molecular machinery responsible for iodine transport and metabolism, frequently driven by constitutive activation of the MAPK pathway. Pharmacologic inhibition of this pathway has therefore generated considerable interest as a strategy to restore thyroid differentiation and potentially re-enable treatment with RAI. The systematic review and meta-analysis published in this issue offers a useful opportunity to reconsider what redifferentiation has actually achieved so far and what remains uncertain (1). In the present meta-analysis, short-term MAPK inhibition restored detectable RAI uptake in 62.3% of patients, although the proportion decreased when a more stringent therapeutic dosimetric threshold was applied (1). Across prospective studies, depending on the molecular context, treatment regimen, imaging methodology, and definition of successful redifferentiation, restoration of iodine uptake has ranged from approximately 60% to more than 90% (2–4). In the MERAIODE trial, diagnostic

RAI uptake was restored in 65% of patients, whereas abnormal uptake was observed in 95% of post-treatment scans, following dabrafenib plus trametinib (3).

However, restoring iodine uptake and restoring RAI sensitivity are not necessarily equivalent. This distinction is probably the central question surrounding redifferentiation today. Structural responses are consistently less frequent than restoration of iodine avidity. In prospective studies, objective responses after subsequent RAI therapy have been variable and generally less frequent than restoration of iodine uptake (2–4). In MERAIODE, the 6-month partial response rate was 38% in *BRAFV600E*-mutated tumors and 20% in the RAS-mutated cohort (3–4).

It remains uncertain whether this strategy changes the long-term natural history of RAI-refractory DTC. As emphasized by the current systematic review, none of the eligible studies provided a hazard ratio allowing for a quantitative assessment of progression-free survival, while overall survival data remain immature (1). The available studies are small, predominantly single-

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arm phase I/II trials, and therefore cannot determine whether the observed disease control results from MAPK inhibition itself, subsequent RAI administration, or their combination. For now, restored uptake should therefore be viewed as a surrogate endpoint, not as proof of long-term clinical benefit. The molecular basis of redifferentiation is also likely to be more complex than the presence or absence of a specific driver mutation. McGoron, Gulec and colleagues recently showed substantial heterogeneity in the expression of genes involved in iodine metabolism among DTCs, including tumors sharing the same oncogenic driver (5). *BRAF* V600E-driven tumors exhibited greater suppression of the RAI theranostic transcriptome than *RAS*-driven tumors, but considerable variability existed within both molecular groups. These observations support the concept that genotype alone may be insufficient to predict which tumors can be functionally redifferentiated. Future approaches incorporating molecular and functional differentiation profiles may eventually help us better select patients than mutation status alone. Our own recent experience also reflects this variability. Among four patients with metastatic *BRAF* V600E-mutated papillary thyroid carcinoma treated with a short, 30-day course of dabrafenib, three recovered RAI uptake, whereas structural or biochemical benefit was observed in only two (6).

Redifferentiation may not be restricted to *BRAF*- or *RAS*-driven tumors. Selective inhibition of oncogenic fusions has produced similar observations. Larotrectinib restored RAI uptake in patients with NTRK-rearranged RAI-refractory thyroid cancer (7), while cases harboring NTRK or RET fusions have shown restoration of iodine avidity after treatment with larotrectinib or selpercatinib (8). More recently, durable structural and biochemical responses following selpercatinib-induced redifferentiation and subsequent RAI therapy have also been reported in *RET* fusion-positive disease (9). Although the evidence remains limited and is based largely on small series and case reports, prospective studies are now evaluating fusion-directed redifferentiation strategies, including selpercatinib followed by RAI in *RET* fusion-positive DTC (10).

The real challenge in redifferentiation is to identify in whom this restored uptake will translate into meaningful and durable clinical benefit. We also need to define when in the course of RAI-refractory DTC it should be considered, how restored uptake should be quantified, and whether adequate tumor dosimetry is ultimately achieved. Redifferentiation has opened a therapeutic window in RAI-refractory DTC; whether it changes outcomes is the question prospective trials now need to answer.

Ethical statement

The author declares that this manuscript does not raise any ethical issues.

Conflicts of interest

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Use of artificial intelligence

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