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Genetic Alterations in MAPK/PI3K Pathways and Their Impact on Radioiodine Therapy in Differentiated Thyroid Cancer

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Differentiated thyroid cancer (DTC), primarily papillary (PTC) and follicular (FTC) subtypes, usually follows a favorable course after total or near-total thyroidectomy combined with radioactive iodine (RAI, I-131) ablation. Nevertheless, 10–15% of patients experience recurrence, distant metastases, or progression to radioiodine-refractory thyroid cancer (RAIR-TC), which represents the major cause of disease-specific mortality in DTC [1]. Such variability in treatment response strongly suggests that underlying molecular factors play a decisive role. Among these, genetic alterations in oncogenic pathways, particularly MAPK (Ras → Raf → MEK → ERK) and PI3K (PI3K → AKT → mTOR), are critical determinants of cell differentiation, invasive behavior, and iodide uptake [1]. Understanding these alterations provides a rational framework for predicting RAI failure and guiding individualized therapeutic strategies.
The BRAF V600E mutation is the most common genetic alteration in PTC, with prevalence ranging from 30% to 80% depending on population [2]. Numerous studies have demonstrated its association with aggressive features such as extrathyroidal extension, cervical lymph node metastasis, and increased recurrence risk [3]. Importantly, BRAF V600E has been linked to reduced expression of thyroid-specific genes including the sodium-iodide symporter (NIS), thyroglobulin (Tg), and thyroid peroxidase (TPO), thereby impairing iodine uptake [4]. Clinically, serum thyroglobulin levels following I-131 treatment are significantly higher in BRAF-mutant patients compared with wild-type, reflecting diminished ablation efficacy [4]. In metastatic settings, BRAF V600E positivity in the primary tumor has been correlated with reduced iodine avidity of lung metastases [5]. A separate study demonstrated that absorbed doses of I-131 were markedly lower in BRAF-mutant cases (5.4 Gy/MBq) compared with wild-type tumors (20 Gy/MBq, $p = 0.02$) [6]. Nevertheless, some reports suggest that BRAF status alone may not consistently predict RAI sensitivity, highlighting the influence of additional molecular events [7].
Mutations in the TERT promoter (most frequently C228T and C250T) are established molecular markers of adverse outcome in thyroid cancer, being associated with recurrence, distant metastasis, and disease-specific mortality [8]. Their clinical significance is particularly striking when coexisting with BRAF V600E. This "genetic duet" predicts a profound loss of iodine avidity: in recurrent PTC, iodine uptake was absent in 97.4% of tumors harboring both BRAF and TERT promoter mutations, compared with 70.3% of BRAF-only tumors and 30.2% of wild-type [9]. Long-term survival analyses further confirm the prognostic strength of this combination, with 10-year disease-specific survival dropping from 99.4% in double-negative patients to 82.6% in those with dual mutations [10]. Meta-analyses also demonstrate that the coexistence of TERT and BRAF or RAS mutations significantly worsens prognosis beyond the effect of either mutation alone [11]. These findings highlight the clinical necessity of combined genetic profiling rather than reliance on single markers.
Mechanistically, BRAF V600E promotes histone deacetylation at the NIS promoter (SLC5A5), thereby silencing NIS transcription and directly impairing iodide transport; this repression can be reversed with histone deacetylase inhibitors or targeted blockade of the MAPK pathway [12]. In addition, BRAF V600E enhances non-homologous end joining (NHEJ) DNA repair, conferring resistance to radiation therapy—an effect that can be mitigated with BRAF inhibitors [13]. Clinically, redifferentiation therapies targeting MAPK signaling have shown promise in restoring RAI sensitivity. Dabrafenib and vemurafenib, selective BRAF inhibitors, have re-established iodine uptake in BRAF-mutant RAIR-TC, enabling renewed I-131 efficacy in several patients [14]. Similarly, selumetinib, a MEK inhibitor, enhanced iodine uptake in a phase II trial, leading to therapeutic responses in advanced DTC [15]. Notably, dual inhibition of BRAF and MEK

appears more effective in re-inducing NIS expression than monotherapy, suggesting that combination regimens may maximize clinical benefit [15].

The accumulated evidence underscores that genetic alterations in the MAPK and PI3K pathways serve as crucial biomarkers for prognosis and therapeutic guidance in DTC. Specifically, dual BRAF/TERT mutations identify patients at highest risk of recurrence, metastasis, and RAI refractoriness, warranting intensified monitoring and early consideration of systemic therapies or clinical trial enrollment. In addition to BRAF and TERT, alterations in RAS, PIK3CA, and PTEN also shape tumor biology and influence therapeutic resistance, further emphasizing the need for comprehensive molecular profiling. While most data are derived from Western and East Asian populations, molecular epidemiology in Vietnam and other Southeast Asian countries remains sparse. Establishing such datasets will be essential for refining patient-specific management and integrating precision oncology into routine thyroid cancer care. Ultimately, bridging molecular genetics with clinical practice offers the potential to optimize the use of RAI, overcome resistance, and improve long-term survival in differentiated thyroid cancer.

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