Drug Resistance Updates 68 (2023) 100939

Contents lists available at ScienceDirect

Drug Resistance Updates

journal homepage: www.elsevier.com/locate/drup

Review

Radioiodine therapy in advanced differentiated thyroid cancer: Resistance and overcoming strategy

Yujia Liu [a,1], Jiafeng Wang [b,1], Xiaoping Hu [a], Zongfu Pan [a,b], Tong Xu [a], Jiajie Xu [b,c], Liehao Jiang [b,c], Ping Huang [a,b], Yiwen Zhang [a,b,*], Minghua Ge [b,c,*]

[a] Center for Clinical Pharmacy, Cancer Center, Department of Pharmacy, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou, Zhejiang, China
[b] Key Laboratory of Endocrine Gland Diseases of Zhejiang Province, China
[c] Otolaryngology & Head and Neck Center, Cancer Center, Department of Head and Neck Surgery, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou, Zhejiang, China

ARTICLE INFO

Keywords:
Advanced differentiated thyroid cancer
Radioiodine (RAI) resistance
Molecular mechanisms
Sodium iodide symporter (NIS)
Tyrosine kinase inhibitors (TKIs)

ABSTRACT

Thyroid cancer is the most prevalent endocrine tumor and its incidence is fast-growing worldwide in recent years. Differentiated thyroid cancer (DTC) is the most common pathological subtype which is typically curable with surgery and Radioactive iodine (RAI) therapy (approximately 85%). Radioactive iodine is the first-line treatment for patients with metastatic Papillary Thyroid Cancer (PTC). However, 60% of patients with aggressive metastasis DTC developed resistance to RAI treatment and had a poor overall prognosis. The molecular mechanisms of RAI resistance include gene mutation and fusion, failure to transport RAI into the DTC cells, and interference with the tumor microenvironment (TME). However, it is unclear whether the above are the main drivers of the inability of patients with DTC to benefit from iodine therapy. With the development of new biological technologies, strategies that bolster RAI function include TKI-targeted therapy, DTC cell redifferentiation, and improved drug delivery via extracellular vesicles (EVs) have emerged. Despite some promising data and early success, overall survival was not prolonged in the majority of patients, and the disease continued to progress. It is still necessary to understand the genetic landscape and signaling pathways leading to iodine resistance and enhance the effectiveness and safety of the RAI sensitization approach. This review will summarize the mechanisms of RAI resistance, predictive biomarkers of RAI resistance, and the current RAI sensitization strategies.

Abbreviations: AD, Absorbed Radiation Dose; AE, Adverse Event; AJ, Adherens Junction; APL, Acute Promyelocytic Leukemia; ATRA, All-Trans Retinoic Acid; Bq, Becquerel; CAF, Cancer-Associated Fibroblasts; CAP, Capsaicin; CREB, cAMP-Responsive Element-Binding Protein; CT, Computed Tomography; DCR, Disease Control Rate; DTC, Differentiated Thyroid Cancer; ECM, Extracellular Matrix; EMA, European Medicines Agency; ER, Endoplasmic Reticulum; EVs, Extracellular Vesicles; FDA, Food and Drug Administration; FTC, Follicular TC; GIST, Gastrointestinal Stromal Tumor; HCC, HÜrthle Cell Carcinoma; HDACIs, HDAC Inhibitors; IR, Insulin Resistance; MKIs, Multiple Kinase Inhibitors; NGS, Next-Generation Sequencing; NIS, Sodium Iodide Symporter; NMPA, National Medical Products Administration; ORR, Objective Response Rate; OS, Overall Survival; PC, Pyruvate Carboxylase; PDGFR, Platelet Derived Growth Factor Receptor; PDTC, Poorly Differentiated Thyroid Carcinoma; PFS, Progression Free Survival; PM, Plasma Membrane; PMAA-AuNPs, Poly (Methacrylic Acid)-Grafted Gold Nanoparticles; PNET, Pancreatic Neuroendocrine Tumor; PR, Partial Response; PSMA, Prostate-Specific Membrane Antigen; RA, Retinoic Acid; RAI, Radioiodine; RAIR-DTC, RAI Refractory Differentiated Thyroid Cancer; rhTSH, Recombinant Human TSH; SH, Sinomenine Hydrochloride; SSRT, Somatostatin Receptors; ST, Salvage Therapy; TC, Thyroid Cancer; TCGA, The Cancer Genome Atlas; THW, Thyroid Hormone Withdrawal; TKIs, Tyrosine Kinase Inhibitors; TKR, TK Transmembrane Receptor; TMB, Tumor Mutational Load; TME, Tumor Microenvironment; TSH, Thyroid Stimulating Hormone; VCP, Valosin Containing Protein; VEGFR, Vascular Endothelial Growth Factor Receptor; WBS, Whole Body Scan.

* Correspondence to: 158 Shangtang Road, Hangzhou 310014, China.
E-mail addresses: zjzyw2003@163.com (Y. Zhang), geminghua@hmc.edu.cn (M. Ge).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.drup.2023.100939
Received 13 December 2022; Received in revised form 16 January 2023; Accepted 4 February 2023
Available online 8 February 2023

1. Introduction

Thyroid cancer (TC) is the most prevalent endocrine cancer (Liu et al., 2022). Although with a low death rate compared to other cancers, published studies reported that the incidence of TC continues to increase in almost every country and region in the world (Deng et al., 2020). The rate of new cases began growing exponentially in 2000 and climbed throughout the years (Davies et al., 2015). The use of sensitive neck ultrasound makes it possible to detect small intrathyroidal tumors, which probably accounts for this rise. By 2030, TC is expected to be one of the most diagnosed cancers, along with breast, prostate, lung and melanoma cancer (Rahib et al., 2014). Female gender, a history of goiter or thyroid nodule, a family history of TC, a low-iodine diet, radiation exposure, and obesity are risk factors for TC (Carling and Udelsman, 2014). DTC, which makes up more than 90% of all diagnosed cases of TC, develops from thyroid follicular cells and is divided into different subcategories, PTC (80%), follicular TC (FTC) (15%) and Hürthle cell carcinoma (HCC).

DTC is typically curable with surgery and RAI therapy in patients with no local progression and no local/distant metastases. However, some DTC tends to invade lymphatic vessels and displays a high incidence of regional lymph node metastasis. There are 1–4% of patients have distant metastasis at first diagnosis and 7–23% have distant metastasis at follow-up (Liu et al., 2022). RAI has been utilized for PTC treatment and functional imaging since the 1940 s (Hertz and Roberts, 1942). RAI includes ^{123}I, ^{131}I and ^{124}I, ^{123}I captures decay emission photons through electrons and allows good imaging quality, but it is expensive and cannot be used for treatment, which limits its clinical use in routine practice (Giovanella et al., 2019). ^{131}I has a physical half-life of 8 days, and a maximum energy of 606 keV emitted from its decaying β particles, β particles can cause multiple ionizations before losing energy and are in charge of the majority of the therapeutic effects. The permeability of electrons in soft tissue is about 1 mm, and their destructive effects are largely confined to thyroid cells. The main clinical applications of ^{124}I are diagnostic imaging and lesion dosimetry (Santhanam et al., 2017). Unfortunately, because of the high cost, ^{124}I is mainly used for research purposes. ^{131}I is cheaper than other radioactive iodine isotopes and is widely available nowadays in TC. RAI is the first-line treatment for patients with unresectable and/or metastatic DTC, however, 30% of these patients do not have iodine uptake at the beginning of RAI therapy; the remaining patients gradually lose response to RAI during treatment. The prognosis of patients with RAIR-DTC is depending on tumor burden and growth rate, but the overall 10-year survival rate is 10%, and median survival is only 3–5 years (Brose et al., 2012; Schlumberger et al., 2014). The most frequent RAI Refractory Thyroid Cancers (RAIR-TCs) are PTC, followed by Poorly Differentiated Thyroid Carcinoma (PDTC) (Leboulleux et al., 2022).

There has been remarkable progress in understanding the molecular mechanisms causing DTC malignant evolution and the transition to RAI resistance over the past few decades. Iodine can accumulate specifically in the thyroid tissue under physiological conditions, which is attributed to Sodium Iodide Symporter (NIS)-mediated iodine uptake located in the basolateral membrane of thyroid cells (Yavuz and Puckett, 2022; Koukkou et al., 2017). The sodium iodide symporter (NIS) is a plasma membrane glycoprotein, a member of solute carrier family 5 A (*slc5a5*) (Aashiq et al., 2019). Thus, sufficient expression, localization and function of NIS are important for RAI treatment (Spitzweg and Morris, 2002). Iodine accumulation in thyroid tissue is also influenced by other thyroid-specific genes and transcription factors such as *tsh*, *tshr* (Rowe et al., 2017), *tg* (Mitchell and Hsu, 2016), *tpo* (Dunn and Dunn, 2001), *pbf* (Read et al., 2011), and *pigu* (Amit et al., 2017), that work together to facilitate RAI accumulation in DTC cells. The gene alterations in DTC include point mutations, gene translocations, chimeric fusion, gene amplifications, and deletions (Fagin and Wells, 2016). MAPK-PI3K-AKT pathways, particularly $braf^{V600E}$ and *ras* mutation are associated with the aberrant silencing and internalization from the basolateral membrane of NIS in DTC cells (Durante et al., 2018; Oh and Ahn, 2021). As shown in Fig. 1, the genetic profile and iodine-transport biological processes inherent in DTC cells seem like not all the mechanisms of resistance to RAI, the crosstalk between DTC cells and TME include cytokines, chemokines, fibroblasts, adipocytes, to escape the RAI cytotoxic should also be taken into account (Ferrari et al., 2020).

Li et al. establish a Radioiodine refractoriness score to evaluate the clinical characteristics of patients with RAI Refractory Differentiated Thyroid Cancer (RAIR-DTC), smoking, tumor type, genetic alterations extra-thyroid extension, number of lymph node metastasis, lymph node metastasis rate and pN stage (N1) were correlated with poor RAI response. However, there was no statistically significant difference in tumor burden, sex, BMI, and TNM stage (Li et al., 2018). Interestingly, other studies presented different results, for example, Jentzen et al. found that absorbed radiation dose (AD) to small lesions was higher than large ones and was more effectively treated by RAI (Jentzen et al., 2014).18 f-Fludeoxyglucose emission tomography computed tomography (18FDG-PET/CT), combined with ^{131}I-whole body scan (WBS), serum TG levels are the most frequently observed in clinics to diagnose the effect of RAI (Chai et al., 2022). However, these evaluations are usually performed after initial RAI therapy. It is still a great challenge to predict the response of metastatic DTC patients to RAI therapy in the early stage. Groundbreaking research from The Cancer Genome Atlas (TCGA) Research Network has analyzed 496 TC samples to identify new oncogenes and new variants of existing genes to characterize aggressive TC (Cancer Genome Atlas Research Network, 2014). The study has pointed out the genetic drivers of PTC which can be divided into two main oncogenic groups: *braf* mutations, and *ras* mutations. *ras*-like tumors are better differentiated, have common follicular histology, and have a better prognosis. *braf*-like PTCs are less differentiated, extremely diverse, and exhibit a high expression of genes downstream of MAPK activation. They found that *braf* mutation exists in several distinct subtypes of TCs and some *braf* mutation is driving TC through different mechanisms, even with some of these subtypes being associated with higher-risk, less differentiated TC that are also resistant to RAI therapy. In addition, analysis of miRNAs expressed In DTC tumor tissues and investigation of circulating miRNAs have been proposed as useful tools for the diagnosis of TC patients (Whiteside, 2017; Wen et al., 2021).

More than 43,000 people die each year from TC worldwide, with an estimated 74,733 deaths by 2040 (Read et al., 2022; Ferlay et al., 2019), indicating that new treatment strategies are urgently needed to address this seemingly unmet treatment need. As a result of more recent targeted therapies, particularly inhibitors of kinase signaling pathways and clinical trials, the treatment pattern of patients with advanced DTC has undergone a significant transformation. it is disappointing that no specific treatment has yet been proven to be a complete response, and no therapy has yet been demonstrated to improve overall survival in any cohort or subset of treated patients in any trial (Pitoia et al., 2022; Fallahi et al., 2022). As previously stated, the ability of DTC to capture ^{131}I is the foundation of RAI therapy. NIS mediates RAI transport and concentrate in DTC cells, from which it emits β particles that disrupt tumor cells (Phillips et al., 2014). Extensive pre-clinical and clinical research has been carried out to improve NIS expression and location, as well as to DTC cell redifferentiation. Therapeutic radioisotopes are typically injected into the tumor via minimally invasive techniques. So the intravenous injection of liposomes, antibodies, or nanoparticles with tumor-targeting ligands as ideal tumor-homing carriers is viable, other than a straight intratumor injection of radioisotopes (Phillips et al., 2014; Bergs et al., 2015). This provides convenience for RAI combination strategies. Additional research is required to overcome resistance and DTC progression.

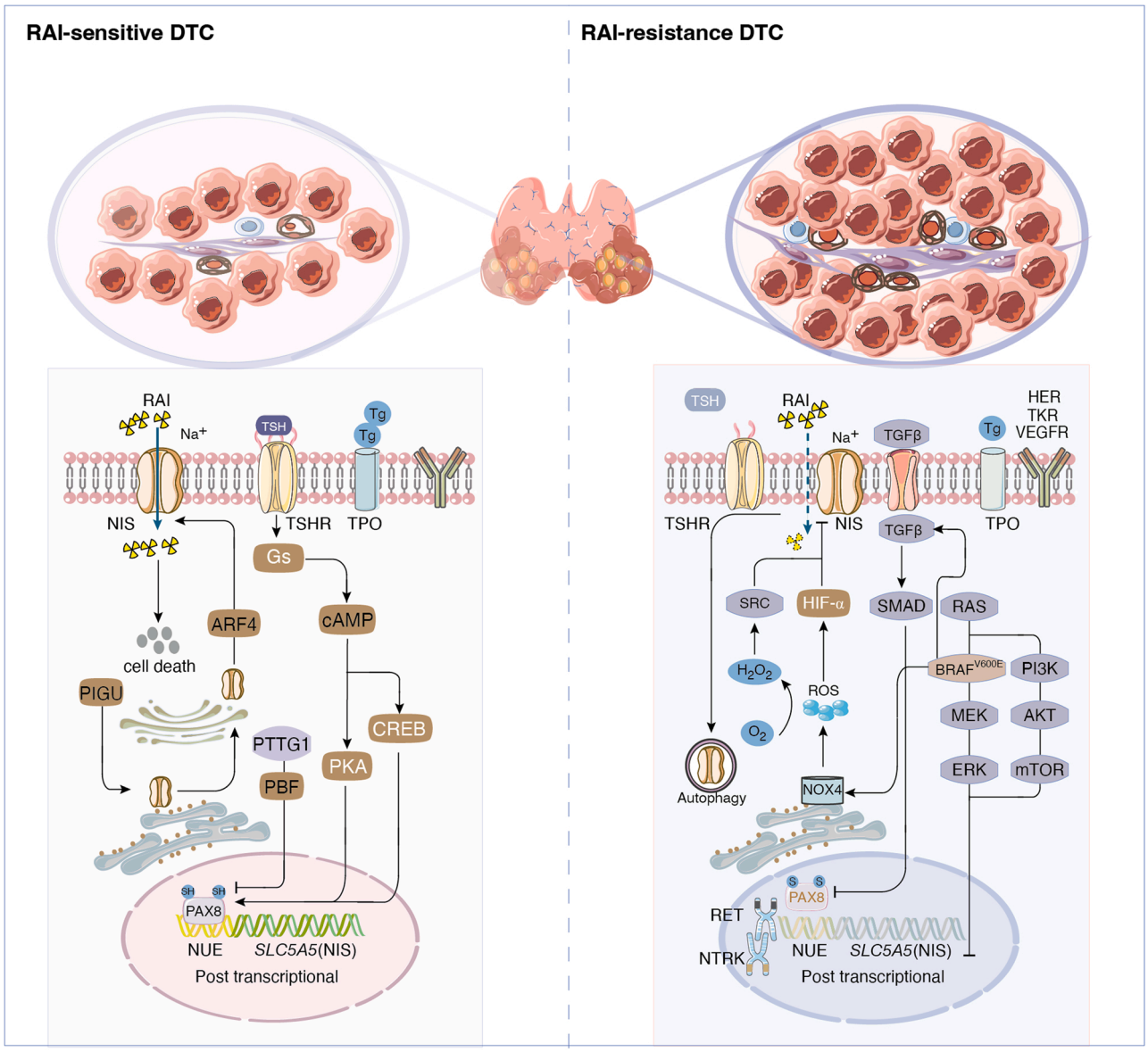

Fig. 1. Graphical representation of the molecular mechanism of RAI resistance in DTC. In RAI-sensitive DTC, RAI is transported from the blood to the DTC cells by NIS which is located on the cell membrane. RAI releases high-energy β particles to kill DTC cells. *slc5a5* transcription is dependent on the TSH/TSHR/cAMP/PKA pathway, and NIS transport to the plasma membrane is regulated by thyroid-specific genes (*tpo, pbf, pigu*) and transcription factors (*ttf1, ttf2,* and *pax8*); In RAIR-DTC, intercellular factors and TME induced RAI refractoriness. Gene mutation and fusion result in aberrant activation of signaling pathways such as RAS-MAPK and PI3K-AKT. The crosstalk between DTC cells and TME contributes to DTC cells escaping from the RAI cytotoxicity. The TGFβ/SMAD signaling pathway in the TME and ROS produced by NOX4 co-regulate the expression of NIS, resulting in RAI refractoriness.

2. Molecular mechanisms causing RAI resistance

2.1. The intracellular driver of RAI resistance

2.1.1. Gene mutations

The loss of radioiodine affinity induced by *braf* mutation is an important reason for the failure of radioiodine therapy and the recurrence of PTC (Brose et al., 2016; Chakravarty et al., 2011). *braf* mutations are associated with the downregulation of iodine metabolism genes in PTC, such as *slc5a5* (Riesco-Eizaguirre et al., 2006), *tpo* (Bastos et al., 2015; Durante et al., 2007), and *tg* (Ge et al., 2020). Restoration of NIS expression in thyroid cells upon inhibition of the BRAF/MEK pathway or silencing $braf^{V600E}$ expression. In addition, $braf^{V600E}$ induces *slc5a5* post-translational modification, which inspires *slc5a5* promoter methylation and inhibits NIS (Choi et al., 2014). Furthermore, $braf^{V600E}$ mutation also exhibited increased GLUT1 expression (Mian et al., 2008), reflecting BRAF-induced reprogramming in glucose metabolism and was associated with suppression of differentiation in TC cells. This may indicate more aggressive metastasis of PTC.

BRAF doesn't always plays a role in DTC by influencing the MAPK pathway. It was also found to inhibit NIS in a MEK-ERK-independent manner by inducing TGFβ secretion. The $braf^{V600E}$ mutation inhibits NIS expression by impairing the binding of PAX8 to the *slc5a5* promoter via TGFβ/SMAD3 signaling (Eloy et al., 2012). *braf* may induce epithelial-mesenchymal transition (EMT) by regulating the Snail/E-cadherin axis to promote DTC progression (Mitchell et al., 2016). *braf* mutations do not correspond with RAI resistance, and although $braf^{V600E}$ is a frequent mutation in DTC, only a small fraction of these is RAI refractory. This suggests that additional molecular events may cooperate with the $braf^{V600E}$ mutation in the loss of RAI affinity.

Telomerase reverse transcriptase (tert) promoter mutations, as a secondary pathogenic event, are encountered in 66% of all TCs and 10%

of PTCs. *tert* promoter mutations are usually associated with an aggressive clinical course, it is more frequent in undifferentiated TCs (29.0%) than in well-differentiated TCs. DTC patients with *tert* promoter-mutated tumors were less to be free of disease at the end of follow-up and were submitted to more radioiodine treatments with higher cumulative activities as well as to a greater number of other treatment modalities (Melo et al., 2014). *tert* promoter mutations are involved in the down-regulation of *slc5a5* mRNA in RAIR-DTC. Mutations in tert seem to decrease NIS protein expression and its location in cell membranes. *slc5a5* mRNA expression has more relationship with DTC aggressiveness and prognostic features than NIS protein expression detected by immunohistochemistry (Tavares et al., 2018).

TSHR is a G-protein coupled receptor that plays an essential role in the regulation of thyroid function. *tshr* inactivating mutations caused overt hypothyroidism, thyroid hypoplasia, and low RAI uptake (Narumi et al., 2011). The *tshr* mutation database (tsh-receptor-mutation-database.org), was established in 1999 and consists of all known *tshr* mutations and their clinical characterizations (Stephenson et al., 2020). *tshr* nonfunctional alleles (truncating mutations) can cause uncompensated TSH resistance, which is associated with molecular defects hampering the adequate transmission of TSH stimulatory signal into thyroid cells (Persani et al., 2010).

2.1.2. Defect in transporting RAI into DTC cells

Under physiological conditions, the thyroid can accumulate iodine specifically, which is attributable to thyroid tissue-specific iodine-transport mechanisms (De La Vieja et al., 2000). NIS, located in the basolateral membrane of the TC cell, utilizes the energy generated by the Na+/K+ ATPase to achieve the uptake of iodine (Cavalieri, 1997). In the apical membrane, iodine is oxidized and bound to TG catalyzed by TPO. *slc5a5* and other related genes and transcription factors work together to prolong the retention of iodine in the thyroid and ensure adequate iodine radiation in the tumor site (Ravera et al., 2017).

NIS is the only transporter responsible for specific cellular iodine uptake, allowing specific targeting of high-energy β particles-emitted by ^{131}I to disrupt the remaining thyroid cells after surgery. Of note, NIS expression is remarkably lower in advanced DTC and has worse iodine affinity than other types of TC (Liu et al., 2019; Peyrottes et al., 2009). Other studies have shown that in some DTC tissues, the NIS protein is present within the cell but not transported to the cell membrane (Dohán et al., 2001), which may explain why it is not biologically active. Therefore, the central mechanism of radioiodine insensitivity is the reduced expression level of NIS and/or its diminished action against the cell membrane.

Thyroid follicular cells express a variety of genes and transcription factors, which together regulate the normal expression and function of NIS. The three transcription factors *ttf1, ttf2*, and the paired box factor *pax8* regulate specific expression of *tg*, *tpo*, and *tshr* on the thyroid gland (Pasca di Magliano et al., 2000). In addition to the transcriptional regulation, *slc5a5* requires fine regulation by other factors. Damage to these genes is strongly associated with a lack of RAI affinity and is usually associated with the $braf^{V600E}$ mutation in TC.

TSH upregulates the expression of NIS and stimulates its transport to the plasma membrane. If the TSH level is increased before RAI treatment, the high level of TSH would significantly increase RAI concentration, not only to promote membrane localization of the NIS but also increase RAI uptake. The transcription of *slc5a5* is induced through the TSH/TSHR/cAMP pathway (Shang et al., 2020). When the TSH binds to the TSHR, the adenylate cyclase is stimulated by the GS protein, which produces cAMP. cAMP then induces *slc5a5* transcription and subsequently stimulates NUE activity by activating multiple signaling pathways. In the absence of TSH stimulation, no RAI uptake was detected after RAI. After TSH stimulation, RAI uptake was detected in 70% of metastatic patients, and serum TG levels were elevated in almost all patients (Berg et al., 2002).

PAX8 is an essential transcription factor from the paired box (PAX) family for thyroid development and differentiation and is a major regulator of *slc5a5* transcription (Taki et al., 2002). PAX8 binds to *slc5a5* upstream enhancer factors in human and rat thyroid cells and induces the expression of NIS protein (Ohno et al., 1999). Redox effects radiation-induced TC imbalance may reduce NIS expression by promoting PAX8 oxidation (Cazarin et al., 2022). This process is regulated by three signaling pathways. First, activation of TGFβ stimulates SMAD3, which inhibits PAX8 binding to NUE. Second, TLR4 stimulation of NFKB affected the binding of PAX8 to NUE. Third, PBF interrupts the interaction between PAX8 and NUE, suppressing *slc5a5* expression. By combining computational prediction of potential targets and mRNA sequencing. miR-146b-5p and miR-146b-3p were identified to be involved in RAI resistant processes. miR-146b-3p binds to the 3′-untranslated region of *pax8*, resulting in impaired protein translation of *slc5a5* and a decrease in iodide uptake (Riesco-Eizaguirre et al., 2015).

One explanation for low membranous NIS expression is poor post-translational modification. PIGU is a subunit of the GPIT complex (Guo et al., 2004), a multi-subunit membrane-bound enzyme, that catalyzes the critical steps of cleaving the signal sequence and attaching the preassembled glycosylphosphatidylinositol (GPI) anchor at the endoplasmic reticulum (ER) (Jiang et al., 2007). PIGU in patients with recurrent DTC was linked to a biochemical response to RAI treatment. PIGU may carry auxiliary functions in the process of GPI lipid anchor attachment, either via direct interaction with NIS or indirectly, by influencing protein transport, positioning, retention, and activity of NIS within the plasmalemma domain (Koumarianou et al., 2022). The expression of PIGU is significantly lower in PTC than in other TCs, PIGU downregulation inhibits NIS glycosylation and trafficking to the cell membrane, resulting in decreased radioiodine uptake. PIGU over-expression in PTC cells resulted in a significant increase in NIS glycosylation and trafficking to the cell membrane, as well as a significant increase in RAI uptake *in vitro* and in vivo (Amit et al., 2017).

Other studies have also found that some genes such as ADP-Ribosylation Factor 4 (ARF4) (Fletcher et al., 2020), and AP-1A/B (Koumarianou et al., 2022), translational or post-translational regulation of NIS expression together with thyroid-specific genes and thyroid-specific transcription factors influence radioactive iodine therapy response. However, iodine uptake efficiency is sometimes not matched to the effect of RAI therapy, as shown in a case report of six patients with $braf^{V600E}$ DTC, two patients had a Partial Response (PR) after treatment with Dabrafenib plus Trametinib, radioactive iodine uptake has not been fully restored. These findings suggest that other mechanisms also affect RAI resistance.

2.1.3. Redox imbalance

Emerging evidence shows that redox imbalance plays a role in thyroid tumorigenesis and dedifferentiation (Kochman et al., 2021). ROS can damage proteins, nucleic acids, lipids, and inorganic molecules, causing reversible or irreversible changes that affect molecule structure and function, influencing physiological and pathophysiological processes of DTC (Jelic et al., 2021). Thyroid cancer tissue has higher ROS levels than normal thyroid tissue (Maier et al., 2006; Wang et al., 2019). The NIS expression and function is regulated by ROS-dependent mechanisms (Cazarin et al., 2022). NADPH oxidases 4 (NOX4) can stabilize HIF1α under hypoxia by increasing ROS, and HIF1α regulates the transport of NIS from the cell membrane to the intracellular compartment by activating β-catenin. *In vivo*, both HIF1α and β-catenin regulate the response of FTC cells to RAI treatment, and NOX4/ HIF1α/β-catenin play a role in iodine handling in DTC cells (Lan et al., 2017).

PAX8 is regulated by the oxidoreductive modification of Cys-45 and Cys-57. In TC cells, redox imbalance may reduce *slc5a5* expression by promoting PAX8 oxidation (Cao et al., 2002). PTTG-PBF has been shown to repress NIS function by decreasing NIS expression and inducing NIS endocytosis from the plasma membrane (Boelaert et al., 2007). Src inhibitor PP1 inhibits PBF phosphorylation, ROS-generating oxidase NOX4-derived H_2O_2 mediated NIS internalization and repression of

iodide uptake by targeting tyrosine kinase Src (Smith et al., 2013). Increased reactive oxygen species production raises thioredoxin reductase mRNA levels and enzyme activity, lowering oxidative stress. Thioredoxin reductase inhibition regulates *slc5a5* at both the gene and activity levels.

2.2. Interference of the TME

2.2.1. Abnormal metabolism

Recent research has suggested that energy metabolism can affect DTC cell function and RAI therapeutic efficacy by influencing TME. Expression of the GLUT1 transporter on the cell membrane was closely related to the pathological grade of TCs. Positive membranous staining was detected predominantly in invasive follicular or metastatic DTC, whereas low or no immunoreactivity could be seen in well-differentiated tumors or normal thyroid tissues (Schönberger et al., 2002). Higher Insulin Resistance (IR) was found in poorly differentiated and anaplastic TCs in contrast to well-differentiated PTC (Kushchayeva et al., 2022). GLUT1 expression is also linked with RAI/glucose uptake in TC with emphasis on PDTC (Grabellus et al., 2012). Glucose metabolism may affect RAI uptake by regulating factors involved in iodine transport. TSH was shown to stimulate the expression of GLUT2 on DTC, leading to increased glucose-stimulated insulin secretion both in vivo and *in vitro* (Lyu et al., 2018). High glucose levels caused an increase in extra- and intracellular H_2O_2 (Santos et al., 2013), then upregulated *duox1* and *nox4*, and reduced *tpo* mRNA levels. In addition, factors related to glucose metabolisms such as EGF, TGFα, FGF, insulin, and IGF-1 can activate the MAPK and PI3K pathways in thyroid cells (Belfiore et al., 1999).

Pyruvate carboxylase (PC) is a key enzyme in gluconeogenesis, *de novo* fatty acid and amino acid synthesis in normal cells, as well as a major anaplerotic reaction enzyme for generating oxaloacetate for the TCA cycle (Liu et al., 2021). A proteomic tandem mass spectrometry analysis of five PTC cells revealed that many metabolism-related proteins, including PC, were upregulated. PC is involved in the tricarboxylic acid cycle replenishment, PC knockdown alters cell proliferative and motility capacities (Strickaert et al., 2019). PC inhibited the expression of iodine metabolism-related genes *tshr*, *slc5a5*, *tpo* and *tg*, and reduced iodine uptake. Furthermore, the PC inhibitor ZY-444 effectively restored the expression of genes related to iodine metabolism and iodine uptake in PTC cells(Liu et al., 2022). PC also invoke RAI avidity by activating the MAPK/ERK pathway in PTC cells. PC produces ATP in process of metabolism, and given that ATP is a phosphate donor for kinases such as MAPK, PC may activate the MAPK/ERK signaling pathway by inducing PTC cell metabolism and increasing ATP ratio (Fransson et al., 2006; Akter et al., 2021). At the same time, MAPK/ERK signaling pathway in TC cells may be blocked by elevated intracellular ROS levels, PC has previously been shown to protect against oxidative stress in tumor cells (Reed et al., 2016). Further studies are needed to determine whether PC affects the MAPK pathway by preventing oxidative stress in PTC cells.

2.2.2. Cancer-associated fibroblasts (CAF)

CAFs have been found in abundance in the DTC TME, while the effect of CAF on RAI resistance, was not commonly reported. Pu et al. used scRNA-seq to examine 158, 577 cells from 11 PTC patients in 2021. They found heterogeneity of stromal cells in PTC and identified two CAF phenotypes, myofibroblastic CAFs and inflammatory subtype, More research is needed to determine whether CAFs, particularly myofibroblastic CAFs, mediate resistance to RAI in PTC (Pu et al., 2021).

Analysis of 8 paired samples of PDTC and PTC revealed the genes deregulation of cell adhesion and intracellular junctions, vimentin was up-regulated and E-cadherin was down-regulated in PDTC. Moreover, SMAD2/TGFβ signal was activated in PDTC. TGFβ-induced SMAD2 phosphorylation, transcriptional activity and induction of EMT through a MAPK-dependent process (Knauf et al., 2011). Expression of TG and NIS is inhibited by TGFB1 treatment in DTC cells (López-Márquez et al., 2022). Suppression of SMAD pathways leads to enhancement of RAI uptake in cancer cells. SMAD2/3 binds to PAX8 and impairs the transactivation of *slc5a5*, which is reversed by SMAD7 expression (Costamagna et al., 2004). The effects of CAFs and the related genes on RAI uptake and resistance in DTC need to be validated.

2.2.3. Tumor infiltrating lymphocytes (TIL)

The understanding of dynamic immune system interaction with the tumor microenvironment has revolutionized the cancer therapy field. The dysfunction of the immune systems involved in the development of TC is increasingly being recognized. The fifth-generation PD-1 inhibitor Penpulimab received its first approval in China for the treatment of Hodgkin's lymphoma in august 2021 (Dhillon, 2021). Peking Union Medical College Hospital is conducting a phase 2 clinical trial about Penpulimab in combination with RAI for DTC (NCT04952493) to assess the efficacy and safety of Penpulimab in combination with RAI in locally advanced/metastatic differentiated TC. Penpulimab may expect to stop the growth of tumor cells and improve RAI uptake.

However, little is known about the influence of the immune microenvironment on RAI therapy. Increased Tregs percentage and decreased B cells ($CD19^+/CD5^+/CD19^+$) percentage in DTC patients were detected after one month of RAI treatment (Jiang et al., 2013). Another study found that the number of $CD4^+$ T cell subsets (Th1, Th2, Th17, and Treg cells) in the TME was all reduced after RAI treatment, suggesting that immunosuppression may be related to RAI therapy (Z.-Y. Shi et al., 2022). Because the immune cell profiles in DTC patients are highly heterogeneous, studies based on large sample sizes are needed to examine the impact of the tumor immune microenvironment on the RAI effect. Another factor hindering research may be that the tumor mutational load (TMB) in PTC is very low compared to other tumor types (Chan et al., 2019), TMB is an important profile of tumor immune features. Because of this low TMB, it is difficult to evaluate the role of tumor immune microenvironment in TC.

2.2.4. Extracellular matrix (ECM)

Cell-cell adhesion may act as a potential candidate stimulus for NIS retention at the plasma membrane (PM). Src recruits and phosphorylates adherens junction (AJ)-associated P120-catenin at the PM, allowing it to recruit RAC1 to the complex (Faria et al., 2021). Disrupting AJ causes a significant decrease in NIS PM abundance without changing its overall levels. AJs between thyroid cells is mainly mediated by E-cadherin (Izaguirre and Casco, 2016). The expression of E-cadherin was significantly associated with susceptibility and clinicopathological characteristics of TC and decreased the aggressiveness of undifferentiated DTC (Calangiu et al., 2014; Izaguirre and Casco, 2016). The loss of E-cadherin in advanced DTC may contribute to the exclusion of NIS PM residence by impairing cell adhesion (Faria et al., 2022).

3. Biomarkers of resistance to RAI

If DTC patients do not respond to ^{131}I therapy, unnecessary RAI therapy should be avoided. Patients should be switched to other more effective therapies as soon as possible. To date, clinical guidelines have recommended the use of 18FDG-PET/CT, in combination with ^{131}I-WBS, CT, and serum TG levels to decide RAI response. Current diagnoses of RAIR-DTC are based on assessment after ^{131}I therapy, in which case the patient may have been exposed to unnecessary RAI and missed the opportunity to receive more effective interventions (targeted therapies). It is a great clinical challenge to explore new effective prognostic factors to predict RAI response.

3.1. Molecular features underlying genes mutation and fusion

Advanced molecular tests have revolutionized the prognosis of RAIR-DTC. PTCs have oncogenes mutations and rearrangements. *braf* and tert mutations are commonly tested in the clinic. These genetic alterations

result in the hyperactivity of the MAPK pathway and PI3K-AKT-mTOR pathway, leading to a loss of sensitivity to RAI therapy and DTC progression.

3.1.1. *braf* ^{V600E} *mutation*

The *braf*^{V600E} point mutation may be related to excessive iodine intake or exposure to the volcanic chemical element (Pellegriti et al., 2009). *braf*^{V600E} results from a gain-of-function transversion mutation in exon 15 (BRAF c 0.1799 T > A). *braf*^{V600E} mutation was first reported in 2002 by H. Davies's group (H. Davies et al., 2002) and is found in nearly 60% of PTC which leads to constitutive activation of BRAF and its downstream targets MEK and ERK (Chung, 2020). Clinically, the presence of *braf*^{V600E} has been linked to larger tumor size, disease recurrence, and death. *braf*^{V600E} mutation was an independent factor correlated with poor outcomes in high risk uncurable disease and death in a 15-year median follow-up study of 102 PTC patients (Jin et al., 2022). Xing et al. (2005) discovered that *braf*^{V600E} mutation may be associated with PTC recurrence (25% vs. 9%) in a multicenter study of 219 PTC patients. This group conducted a multicenter, retrospective study of 1849 patients in 2013, and found that the presence of the *braf*^{V600E} mutation was associated with an increased mortality rate in PTC patients (5.3% vs. 1.1%). A subsequent retrospective multicenter study in 2099 PTC patients from Xing and coworkers demonstrated that *braf*^{V600E} mutation is an independent prognostic value of PTC recurrence (Xing et al., 2015). However, it remains controversial on the independent prognostic value of this mutation in metastasis and RAI refractory (Trovisco et al., 2004; Eloy et al., 2011). A retrospective analysis of 94 patients with metastatic PTC found that positive *braf*^{V600E} mutation affects radioiodine avidity but is not related to the prognosis of metastases of PTC (Huang et al., 2022).

3.1.2. *tert promoter mutations*

TERT is the catalytic subunit of telomerase and is required for telomerase activity (Horn et al., 2013). TERT is upregulated in the vast majority of cancers, including TC. TERT activation occurs in cancer via a variety of mechanisms including promoter mutations, promoter DNA methylation, copy number changes, and *tert* alternative splicing. Two mutations in the *tert* promoter (CHR5:1295228 C > t, termed C228T, and CHR5:1295250 C>T, termed C250T) were first detected in TC in 2013 (Liu et al., 2013). tert promoter mutation was found in approximately 11.7% of PTC and 11.4% of FTC. Several later studies got similar frequency data (Landa et al., 2013; Moon et al., 2017). *tert* mutations are usually associated with older age and advanced stages of the disease (Baloch et al., 2022). When examining the status of *tert* mutation in distant metastatic DTC, there is a correlation between tert mutation and RAI uptake, as well as therapy response ($p < 0.001$). All 15 patients with *tert* mutation were refractory to RAI therapy, the positive predictive rate of follow-up was 100%. But the mechanism underlying it is not clear. Studies also found that tert mutations were more likely to coexist with *braf* mutations ($p = 0.044$) (X. Yang et al., 2017). Recently a Real-World Analysis of 2092 TC Patients was conducted to investigate the frequency of tert promoter mutations. *tert* promoter mutations in PTC were lower than expected, regardless young patients or female patients (Moon et al., 2017).

More than one type of gene mutation may be present in patients with advanced DTC. A comprehensive detection involving all mutations can help predict DTC responses to RAI as well as the likelihood of metastasis. Next-generation sequencing analysis has revealed that many patients with *braf* mutations in PTC have other mutations, such as the *tert* mutation. 30% of patients with DTC metastasis did not exhibit any RAI uptake after adequate TSH stimulation, and the proportion increased to 70% after being screened by *braf*^{V600E} mutation. If both *braf*^{V600E} and *tert* promoter mutations are considered, almost all patients (97%) with both mutations have no RAI uptake. It is suggested that *braf*^{V600E} and *tert* promoter double mutation may be an accurate biomarker to predict patients' response to RAI.

3.1.3. *Rearranged during transfection (ret) fusion*

The membrane TK transmembrane receptor (TK-R) is encoded by RET and functions upstream of MAPK and PI3K-AKT, the most important signaling pathways involved in DTC (Ciampi and Nikiforov, 2007). 85% of abnormal MAPK pathway activation that occurred in PTCs was caused by *ret/ptc* rearrangements (Haroon Al Rasheed and Xu, 2019). *ret* rearrangements are thus important in impaired RAI uptake and metabolism. *ret/ptc1* and *ret/ptc3* are the most common haplotypes of *ret/ptc* rearrangements, accounting for more than 90% of all. Different types of *ret/ptc* are linked to various clinical features: *ret/ptc1* causes benign tumors with typical papillary growth and microcarcinoma; *ret/ptc3* is associated with solid variants of PTC and is more aggressive (Romei et al., 2016). The thyroid cells of children are more vulnerable to ionizing radiation and/or loss of key factors in DNA repair mechanisms, resulting in uncoupled double-strand breaks and translocations with partner genes (Lee et al., 2021). As a result, detecting gene mutations and fusions in children with TC has a greater clinical significance.

In future research, an improved high-throughput pipeline based on next-generation sequencing (NGS) should be used for a more comprehensive analysis of gene expression and DNA binding activity in TC. NGS can identify common and uncommon genomic alterations based on biopsy results and is used to guide treatment via personalized tumor mutation genomics. Next-generation sequencing leads to an improved mechanistic understanding of the mechanism of RAI resistance, as well as facilitates the identification of key target genes to construct an independent predictive risk model of RAI refractory and DTC recurrence.

3.2. *EV-transferred miRNA*

EVs are small lipid bilayer-enclosed vesicles released by cells (Delcorte et al., 2022). EVs constitute complex signals by transporting proteins and nucleic acids and support intercellular and cell-cell communication (Bravo-Miana et al., 2020). EV-miRNAs secreted by tumor cells are now considered important factors in cancer progression, and promising non-invasive markers for disease monitoring (Steenbeek et al., 2018). Several retrospective studies have elucidated the potential of circulating EV-miRNAs as TC biomarkers, but how to conduct in-depth analysis and validation of studies via *in vitro* models is a major issue. EV-transferred miRNAs derived from cultured cell lines have been determined in many studies, EV-miR-146b and miR-222 are over-expressed in PTC cells, compared to normal thyroid cells (Jc et al., 2015). In consistency with the expression of miRNAs measured in plasma as a biomarker for DTC recurrence (Lee et al., 2013).

Due to the histological complexity of TC, EV-miRNAs from tumor tissues are likely to exhibit the origins, properties and effects on the TME, and contribute to predicting response to RAI treatment and DTC recurrence. Recently a few studies examined the properties of tissue-derived EVs. *braf*^{V600E}genetically engineered mouse model of PTC revealed that the dynamic of miRNA deregulation in PTC upon *braf*^{V600E} mutation. The expression of miR-146b-5p, miR-222–5p/3p is increased in the tissues of PTC patients, as compared to benign samples, and has further been associated with the degree of PTC tumor malignancy (Delcorte et al., 2022). PTC released more EVs bearing epithelial and immune cell markers, as compared to the normal thyroid tissue. Maggisano et al. compared the profiles of exosomal miRNAs released by two TC cell lines and non-tumorigenic thyroid cells and explored the network of miRNA-target interaction. Five miRNAs (miR-21–5p, miR-31–5p, miR-221–3p, miR-222–3p, and let-7i–3p) were significantly deregulated in the exosomes of PTC cells, and three of them (miR-31–5p, miR-222–3p, and let-7i–3p) were related with aggressive isotype (Maggisano et al., 2022). A deeper analysis of the functional role of the targets of exosomal miRNAs will provide further information on novel targets of molecular treatments for these neoplasms.

4. Strategy to sensitize RAI treatment

Once patients with DTC are diagnosed as RAI refractory, current treatment guidelines recommend avoiding further RAI treatment. However, given the success of radioactive iodine as an effective and targeted therapy for most DTC, there has been great interest in enhancing or restoring RAI avidity.

4.1. Tyrosine kinase inhibitor (TKI)

In the last several decades, the discovery of signaling pathways and activating mutations has boosted the development of targeted therapies (Fig. 2). There are more than 28 clinical studies examining different TKIs as part of RAI-targeted TC, with or without other treatments. and there are a large number of ongoing clinical studies to identify effective drug regimens for patients with RAIR-DTC. Most of these drugs target multiple receptor classes, including vascular endothelial growth factor receptor (VEGFR), c-KIT, in-transduced receptor and platelet-derived growth factor receptor (PDGFRα/β). The most widely studied and clinically approved single-targeted therapies include anti-angiogenic markers, *braf* mutations, and components of the MAPK pathway (Knauf et al., 2011; Fagin and Wells, 2016). Patients with rapidly progressive and/or symptomatic disease are candidates for TKI, and clinical trials have shown mixed results.

4.1.1. Multiple kinase inhibitors (MKIs)

MKIs are now the first-line treatment for RAIR advanced metastatic DTCs, and although progression-free survival (PFS) improvement, overall survival (OS) benefit is limited. Therefore, there is an interest in developing therapeutic approaches to enhance RAI sensitivity and patient survival.

Sorafenib is an oral TKI of VEGFR, RET, RAF (including $BRAF^{V600E}$), and PDGFRA. In a randomized, double-blind, phase 3 trial, Sorafenib treatment significantly improved PFS compared with placebo (median 10.8 vs. 5.8 months). However, there was no statistically significant difference in OS of locally advanced or metastatic RAIR-DTC. Adverse

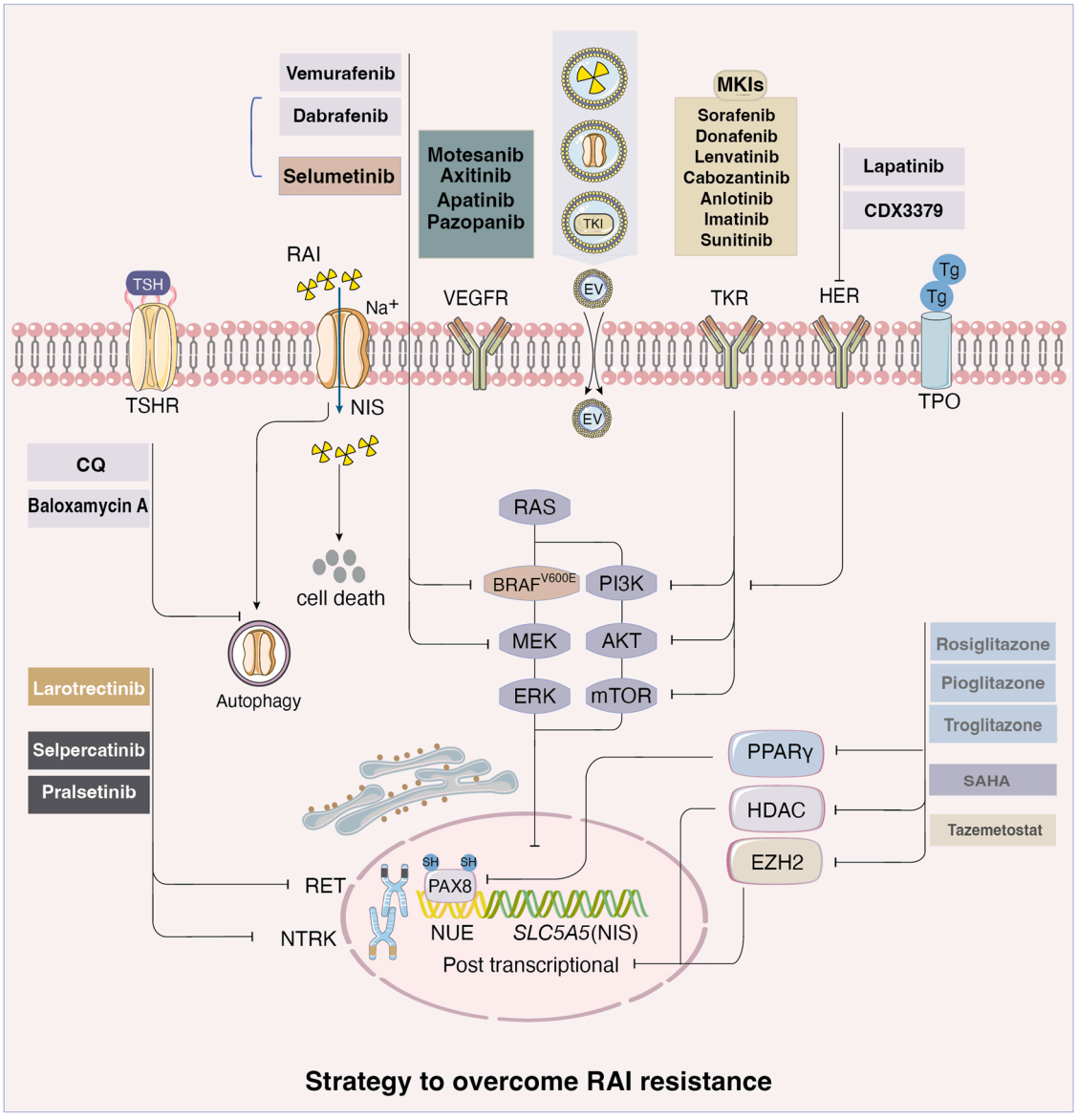

Fig. 2. Strategy to overcome RAI resistance in DTC. In RAI-sensitive DTC, TKIs are effective for RAIR-DTC, including MKIs, such as Lenvatinib, Sorafenib, Cabozantinib and so on. STKIs, such as BRAF inhibitors Dabrafenib and Vemurafenib, MEK inhibitors Trametinib and RET-specific inhibitors, among others. In addition, targeting HER2/3, HDAC, EZH2, and PPARγ can achieve RAIR-DTC cell redifferentiation by inhibiting the expression and localization of NIS. Extracellular vesicles (EVs) contained RAI, NIS, and TKIs could improve drug delivery and could be a promising approach to sensitize RAI therapy.contain

events (AEs) were consistent with the known Sorafenib safety profile. Most AEs were grade 1 or 2. The most common AEs were hand-foot skin reaction (76.3%), diarrhea (68.6%), alopecia (67.1%), and rash/desquamation (50.2%) (Brose et al., 2014). Sorafenib is the first TKI to be approved for use in RAIR-DTC by the Food and Drug Administration (FDA) (11/2013) and European Medicines Agency (EMA) (04/2014). Because of Sorafenib's toxicity, most patients have to stop Sorafenib therapy or have a reduced dose. Low expression of nuclear pAKT was associated with PR to Sorafenib ($p < 0.01$) in advanced DTC (Yarchoan et al., 2016). Baseline and serum TG levels were significantly related to RAI response. The decrease in serum TG was significantly greater in patients who achieved clinical benefit compared with non-responders, Early FDG-PET response could be helpful for the timely identification of nonresponding patients (Marotta et al., 2013). VEGF-A and VEGFR-2 SNPs (AA/CC genotype of the VEGF-A and the AA + AT genotype of the VEGFR-2), which have been demonstrated to correlate with DTC response, were also shown to be associated with a better PFS (Marotta et al., 2017).

In thyroid cells, mTORC1 activity is required for the proliferative effects of TSH, and inhibition of the mTORC1 suppresses the growth of TC cell lines *in vitro*. Temsirolimus is an inhibitor of mTOR. A phase 2 study was conducted to evaluate the efficacy of the combination of Sorafenib with Temsirolimus in patients with TC. When compared to previous data with single-agent, Sorafenib and Temsirolimus appear to be an active combination in RAIR-TC, particularly in patients who received no prior treatment (Sherman et al., 2017). Based on the promising effect of Temsirolimus, a single-arm, multi-institutional phase 2 study of Temsirolimus showed, the median PFS was 12.9 months with a 2-year PFS of 23.6%. Median OS was not reached and 2-year OS was 73.5% (Hanna et al., 2018).

Donafenib, the novel oral MKI in which a trideuteriomethyl group is substituted for a methyl group on the Sorafenib, has therapeutic effects similar to those of Sorafenib (Li et al., 2020). Donafenib was generally well tolerated, the 300-mg arm had a nonsignificant, longer median PFS than the 200-mg arm (14.98 months vs. 9.44 months) ($p = 0.351$). Both Donafenib regimens demonstrated similar efficacy in terms of the Objective Response Rate (ORR) in locally advanced or metastatic RAIR-DTC (Lin et al., 2021). A phase 3 study of Donafenib in patients with RAIR-DTC was successful and results are expected to be published soon.

Lenvatinib is a multi-targeted TKI of VEGFR-1–3, FGFR-1–4, PDGFRα, RET, and KIT, and has been approved by FDA and the EMA for aggressive and advanced PTC. The SELECT trial showed PFS benefit for Lenvatinib for advanced RAIR-DTC patients (Schlumberger et al., 2015). PFS in Real-Life clinical practice in the Netherlands was comparable to previous studies, but inferior to PFS as shown in the SELECT trial ($p = 0.04$) (Aydemirli et al., 2020). Another Real-Life Practice for Lenvatinib in the Treatment of RAIR-TC found similar lower median PFS, and AEs are frequent and should be closely monitored. Dose reductions (59%) or interruption (31%) of Lenvatinib happened for AEs. The most frequent AEs related to treatment were fatigue, hypertension, weight loss, diarrhea, and anorexia (Berdelou et al., 2018). It's worth noting that although more toxicity was seen in older patients, improved PFS with Lenvatinib treatment over placebo was reflected in both age groups. The OS effect was seen in older individuals despite the crossover being permitted after disease progression, suggesting that Lenvatinib should be considered for the treatment of patients with RAIR-DTC of any age (Brose et al., 2017).

In comparison to the phase 3 study samples, the patients who participated in these Real-World analyses tended to have more advanced disease and larger pre-treatment burdens. According to some researchers and panelists, TKI therapy should be started when patients still have a low tumor burden and are in generally excellent health. Younger patients of RAIR-PTC should be treated earlier with TKI therapy because tumor which manifests earlier in life means more aggressive and should be treated sooner (Verburg et al., 2021). Early initiation of Lenvatinib may improve outcomes in high-risk patients with lung metastases of ≥ 1.0 cm, Lenvatinib treatment resulted in longer OS in patients with lung metastases of ≥ 1.0 cm versus placebo (Tahara et al., 2021).

When a standard first-line TKI is not beneficial and the response is not durable, and disease progression or a significant adverse effect occur, salvage therapy (ST) can be an alternative strategy. Lenvatinib was most commonly used for ST, and an OS benefit was analyzed. Although Sorafenib did not show a direct OS benefit, patients who discontinued Sorafenib because of resistance could still benefit from salvage therapy with Lenvatinib, which could prolong median OS (Dacosta Byfield et al., 2019).

TG has been proposed as a potential biomarker to predict the RAI response induced by Lenvatinib. TG decrease was found to have a statistically significant correlation with maximum tumor shrinkage in an open-label, single-arm, phase 2 trial. IL-10 and Ang2 correlated with improved ORR after Lenvatinib therapy (Cabanillas et al., 2015).

Cabozantinib is a TKI that inhibits three important signaling pathways: MET, VEGFR-2, and RET (Yakes et al., 2011). In a phase 1 study of Cabozantinib, five of eight patients with DTC previously treated with a VEGFR-targeted therapy had an objective response to Cabozantinib (Kurzrock et al., 2011). A phase 3 trial of Cabozantinib (COSMIC-311) showed significant improvement in PFS over placebo: median not reached versus 1.9 months (1.8–3.6), objective response in the Cabozantinib group was achieved in 15% vs 0 of 33 in the placebo. Serious treatment-related AEs occurred in 20 (16%) of 125 patients in the Cabozantinib group and 1 (2%) of 62 patients in the placebo group (Brose et al., 2021). Cabozantinib was approved by the FDA for the treatment of adult and pediatric patients older than 12 who suffer from RAIR-DTC (09/2021) (Duke et al., 2022). This is the first approval for patients with RAIR locally advanced or metastatic DTC who have progressed following prior therapy and the first approval in pediatric patients with DTC.

A phase 1 trial has shown that patients respond to Cabozantinib after a previous Sorafenib treatment failure. 62.5% of DTC patients who received Sorafenib as first-line therapy, achieved a PR with Cabozantinib (Silaghi et al., 2022). In an ongoing phase 3 trial (NCT03690388), the efficacy of Cabozantinib in 258 RAIR-DTC patients after prior treatment with a VEGFR inhibitor was also assessed. Tumor genotype may represent a predictor of response to Cabozantinib, as FTC or PTC cases harboring *nras* or *kras* mutations exhibit the largest tumor shrinkage.

Anlotinib is a multi-kinase inhibitor targeting VEGFR, PDGFR, FGFR, and c-KIT. In a randomized, double-blind, multicenter phase 2 trial of Anlotinib in locally advanced or metastatic RAIR-DTC (NCT02586337), the median PFS was 40.54 months in Anlotinib and 8.38 months in placebo. The ORR was 59.21% in Anlotinib, in addition, significant Disease Control Rate (DCR) benefit was observed in Anlotinib treatment (97.37% vs. 78.38%). Serious treatment-related AEs occurred in 15.79% received Anlotinib. The most common AEs were hypertension (84.21%) and hypertriglyceridemia (68.42%) (Chi et al., 2020). Based on its promising efficacy, Anlotinib is currently approved by the China National Medical Products Administration (NMPA) for the indication of RAIR-DTC. The efficacy and safety of Anlotinib promote clinical trials to evaluate the effect of Anlotinib in the neoadjuvant setting for locally advanced TC. Anlotinib showed an ORR of 76.9% (CI 46.2–95.0%) in the setting, and the R0/R1 resection rate is high. The neoadjuvant treatment makes radioactive iodine treatment possible and represents a new option for locally advanced TC (Huang et al., 2021).

Imatinib is the first TKI, received FDA approval for the treatment of leukemia in 2001. Imatinib suppresses tumor growth by blocking PDGFRα (Heinrich et al., 2008). PDGFRα reduces the ability of NIS to transfer RAI into DTC cells (X. Yu et al., 2022). Imatinib may resensitize DTC cells to RAI therapy by activating NIS. There is a phase 1a study of Imatinib (NCT03469011) in trying to bring back RAI sensitivity in patients with advanced TC. Several studies have found that Imatinib does not modulate *slc5a5* mRNA or protein expression, but rather enhances

radioactive iodine uptake by inhibiting the MAPK/ERK signaling pathway (Read et al., 2022).

Sunitinib is an oral MKI that inhibits PDGFR, VEGFR, c-KIT, FMS-related tyrosine kinase 3 (FLT3), and RET. Sunitinib was approved for Imatinib-resistant gastrointestinal stromal tumor (GIST), renal carcinoma, and pancreatic neuroendocrine tumor (PNET) treatment. *In vitro* studies showed that Sunitinib could increase the expression of thyroid-specific genes, *slc5a5*, by targeting MEK/ERK and SAPK/JNK signaling pathways. The combination of forskolin (adenylyl cyclase agonist) with Sunitinib further increases the expression of thyroid-specific genes and the transcription factors that bind the *slc5a5* upstream enhancer NUE in the cells (Fenton et al., 2010). A multicenter phase 2 study of Sunitinib in patients with locally advanced or metastatic DTC showed the primary end-point was reached with an ORR of 22% (95% CI: 10.6–37.6), median PFS and OS were 13.1 and 26.4 months. Side effects were more severe than in previous reports. There were nine unexpected side effects were reported and five induced patient deaths (Ravaud et al., 2017). A decrease in FDG activity in treatment was somewhat predictive of clinical benefit (response or stable disease), and patients with an increase in FDG uptake were more likely to progress (Carr et al., 2010).

4.1.2. Anti-angiogenesis agents targeting VEGFR

Co-administration of antiangiogenic MKIs may improve the efficacy of RAI to eradicate disease, for the reason that they have a dual mechanism that can normalize aberrant vascularization and reduce tumor growth. Anti-angiogenesis agents may contribute to prolonging PFS and OS of RAIR-DTC patients. Vandetanib, Cabozantinib, Sorafenib, and Lenvatinib can also be regarded as antiangiogenic multi-kinase inhibitors, in the following we will discuss VEGFR inhibitors.

Motesanib diphosphate is an oral inhibitor of VEGFR, PDGFR, and KIT. In an open-label, single-group, phase 2 study of progressive DTC (NCT00121628), the ORR was 14%, and the estimate of median PFS was 40 weeks (Sherman et al., 2008). Motesanib diphosphate can induce PR in patients with advanced or metastatic DTC.

Axitinib is a potent and selective second-generation inhibitor of VEGFR, results from a phase 2 study showed that Axitinib is active in all histologic subtypes of metastatic TCs, with an observed ORR of 30%. An additional 38% of patients experienced stable disease for 16 weeks or more by RECIST, and the median PFS was over 18 months which suggests that Axitinib is efficacious (Cohen et al., 2008). A phase 2 trial of Axitinib in patients with advanced TC are as follows: ORR was 38% and 18 (30%) patients had stable disease lasting $\geq$ 16 weeks, responses occurred in all histologic subtypes. With median OS 35 months, the median PFS was 15 months and the median duration of response was 21 months. PK/PD analyses revealed trends toward greater tumor size reduction and response probability with higher Axitinib plasma exposures (Locati et al., 2014). Axitinib appears active and well tolerated in patients with various histologic subtypes of advanced TC, demonstrating durable responses and long OS (Cohen et al., 2014). With a median follow-up of 11.5 months (0–24.3), ORR was 27.7% (DTC: 29.4% and MTC: 23.1%) and median PFS was 8.1 months (95% CI: 4.1–12.2) (DTC: 7.4 months (95% CI: 3.1–11.8) and MTC: 9.4 months (95% CI: 4.8–13.9)). Importantly, quality of life was maintained during treatment with Axitinib and no significant deterioration in symptoms or interference in daily life caused by symptoms was reported. Twelve (25.5%) patients required dose reduction to 3 mg b.i.d. All-grade AEs included asthenia (53.2%), diarrhea (36.2%), hypertension (31.9%) and mucositis (29.8%). Grade 3/4 AEs included anorexia (6.4%), diarrhea (4.3%) and cardiac toxicity (4.3%). What should not be ignored is better outcomes were reported with first-line Axitinib, with an ORR of 53% and a median PFS of 13.6 months compared with 16.7% and 10.6 months as second-line treatment. It means a cross-resistant of antiangiogenic MKI therapy in advanced TC and highlighting the importance of prospective sequential clinical studies (Capdevila et al., 2017).

Apatinib is a small-molecule angiogenesis inhibitor with high selectivity for VEGFR-2. When Apatinib was first used in RAIR-DTC, TG concentration and tumor diameter were significantly decreased (Lin et al., 2017). In the phase 3 randomized clinical trials of 92 RAIR-DTC patients, Apatinib significantly prolonged PFS compared with placebo (22.2 vs 4.5 months). The median OS was not reached for Apatinib (95% CI, 26.25-not reached) and was 29.9 months (95% CI, 18.96-not reached) for the placebo. The confirmed ORR was 54.3% and the DCR was 95.7% in the Apatinib group vs an ORR of 2.2% and DCR of 58.7% in the placebo group. Hypertension was the most common grade 3 or higher-level AE (34.8%), Apatinib showed a manageable safety profile in patients with progressive locally advanced or metastatic RAIR-DTC (Lin et al., 2022). A recent study showed beneficial synergistic and complementary effects when Apatinib is combined with RAI therapy. Four FTC patients developed a PR after Apatinib therapy, with significant reductions in tumor size. After treatment with Apatinib and RAI, tumor size decreased significantly in three patients. Another patient with both FTC and PTC showed progressive disease on Apatinib alone. However, when combined with RAI and Apatinib, tumor size and serum TG levels were decreased. It is suggested that Apatinib promotes RAI therapy. However, because the patient with both FTC and PTC had not been given RAI before, it was not possible to say whether Apatinib promote RAI sensitivity. This study was also limited by the sample size and no control group, follow-up studies are needed to support the effect of Apatinib in iodine therapy (Shi et al., 2022).

Pazopanib is an oral VEGFR inhibitor, in a phase 2 study, Pazopanib induced RECIST PR in a substantial proportion of patients, with an estimated 66% likelihood of having responses longer than 1 year (Bible et al., 2010). Based on these results, a phase 1 study of Pazopanib in combination with escalating doses of RAI in patients with RAIR-DTC was conducted to determine whether Pazopanib is synergistic with RAI. RAI uptake scans were evaluated after therapy and compared to pre-treatment scans. In patients with measurable disease 4/5 (80%) achieved stable disease. Median PFS was 6.7 months. The patients underwent FDG PET/CT before and after the initial Pazopanib treatment to determine the combined impact of Pazopanib on RAI therapy. Despite the possibility of therapeutic efficacy, the combination of Pazopanib and RAI resulted in increased toxicity. There was no convincing evidence that Pazopanib administration improved RAI uptake or retention (Chow et al., 2017).

Hypertension is a frequent AE related to the use of angiogenesis inhibitors, depending on the blocking of VEGF action in normal physiology. Although the incidence of life-threatening liver failure reported with VEGFR TKIs is very low, it is critical for patients receiving VEGFR TKIs to carefully monitor liver function and rule out the possibility of patients with moderate liver injury. Patients treated with either agent should be evaluated at baseline with liver function tests and reassessed periodically during treatment.

4.1.3. Single-target selective inhibitors

MKI has extensive inhibitory activity against many kinases, it leads to more AEs and a large proportion of them are serious. Patients have to adjust the dose or suspend the treatment, seriously affecting life quality. Thus, targeting specific receptors or molecular pathways, and developing highly selective inhibitors, will meet the needs of advanced DTC therapy. Single-target selective inhibitor is a good choice to ensure durable responses without increasing side effects. The key point when using STKI is to screen RAIR-DTC patients for specific gene mutations or fusions.

4.1.3.1. BRAF inhibitor. **Vemurafenib**, a BRAF inhibitor, is approved for the treatment of patients with metastatic *braf*-mutant melanoma. In the phase 2 study of Vemurafenib for advanced TC (n = 51), the PR rate was 38.5% (n = 26) compared to 27.3% (n = 25) in the previous TKI group (Brose et al., 2016). Vemurafenib also demonstrated RAI restoration, 40% of patients with *braf*-mutated RAIR-PTC had a response to RAI (Dunn et al., 2018). However, *braf*-mutant TC is relatively resistant

to Vemurafenib. Targeting autophagy sensitizes *braf*-mutant TC to Vemurafenib, Vemurafenib-induced cell death was amplified by either pharmacological inhibition of autophagy or interfering RNA suppression of crucial autophagy genes, and, in combination with the autophagy inhibitor, hydroxychloroquine led to more dramatic tumor reduction (Wang et al., 2016).

HER2/3 can be activated by MAPK rebound caused by BRAF/MEK inhibitors (Fattore et al., 2013), and HER inhibitor may sensitize $braf^{V600E}$ PTC cells to redifferentiation therapy. A pilot clinical trial involving seven $braf^{V600E}$, RAIR-DTC patients found that the combination of Vemurafenib, and HER3 inhibitor, CDX-3379, could increase the safety and efficacy of RAI absorption. Five patients had increased RAI uptake after treatment, 2 patients achieved PRs after RAI therapy and 2 progressions of disease (Tchekmedyian et al., 2022). Further evaluation of Vemurafenib and CDX-3379 as a combinition therapy in a larger trial is warranted (NCT02456701).

Dabrafenib is a highly selective ATP-competitive inhibitor of BRAF kinase. Antitumor activity was observed in PTC in the phase 1 trial of Dabrafenib to evaluate safety and tolerability in patients (Falchook et al., 2012). Fourteen patients with $braf^{V600E}$-mutant TC were enrolled, 13 (93%) of whom had previously received RAI. Four (29%) patients had PRs, and nine (64%) had at least a 10% decrease. The median PFS was 11.3 months, with only one responder progressing (Falchook et al., 2015). Dabrafenib was well tolerated and produced long-term response in patients with $braf^{V600E}$-mutant DTC. Dabrafenib improves RAI uptake by improving the expression and function of NIS. Dabrafenib can invoke RAI uptake in patients with metastatic $braf^{V600E}$-mutant RAIR-PTC, 60% of patients with $braf^{V600E}$ mutations demonstrated new RAI uptake on WBS after treatment with Dabrafenib. Only two of six patients had PRs and the other four patients had stable disease on standard radiographic restaging at 3 months. Treatment results show that restoration of NIS expression does not guarantee restoration of radiosensitivity (Rothenberg et al., 2015).

4.1.3.2. MEK inhibitor. **Selumetinib** is an oral, small-molecule inhibitor of the MEK1/2. It was the first TKI to demonstrate RAI-sensitive effect in a multicentric prospective non-randomized phase 2 trial. As a result of oncogene activation via signaling pathways, DTC may lose their ability to absorb RAI. Selumetinib can increase RAI avidity in PTC that are resistant to RAI (Ho et al., 2013), however, the addition of Selumetinib to adjuvant RAI failed to increase the CR rate for patients with DTC. In the phase 3, randomized, placebo-controlled trial (ASTRA), compared to RAI alone, Selumetinib plus adjuvant RAI, 18 months after RAI, there was no statistically significant change in the CR rate (Selumetinib, n = 62 [40%]; placebo, n = 30 [38%]; odds ratio, 1.07 [95% CI, 0.61–1.87]). In addition, Selumetinib-related grade 3 AEs were recorded in 25/154 participants (Ho et al., 2022).

MEK alone seems not effective against advanced DTCS with *braf* mutations. After treatment with the MEK inhibitor Selumetinib, only 1 of 9 patients with $braf^{V600E}$ mutations demonstrated improved RAI uptake (Ho et al., 2013). The reason may be owing to the $braf^{V600E}$ mutation, which can restore RAI uptake by activating the MAPK pathway (Chakravarty et al., 2011). Therefore, more effective inhibition of MAPK may improve the efficacy of iodine therapy in patients with $braf^{V600E}$. A phase 2 trial (NCT01723202) with Trametinib (BRAF-wt) or Trametinib plus Dabrafenib (BRAF-mut) treatment had successful restoration of RAI uptake in approximately one-third of patients (Tchekmedyian et al., 2022). This clinical study is the first to demonstrate the successful of BRAF and MEK combination in about one-third of patients in each arm in the RAIR-DTC of BRAF-MUT. A phase 2 combination therapy (NCT03244956) in patients with RAIR-DTC diagnosed with *ras* or $braf^{V600E}$ mutations is currently ongoing, to evaluate the efficacy of MEK (Trametinib) and $braf^{V600E}$ (Dabrafenib) inhibitors RAI response. Other ongoing clinical trials in promoting RAI therapy are shown in Table 1.

In vitro, HER1/2 inhibitor Lapatinib enhanced the effect of Dabrafenib/Selumetinib on iodine- and glucose-handling gene expression, cell membrane location of NIS, RAI uptake and cytotoxic. Combined therapy using HER inhibitor and BRAF/MEK inhibitor presented a more significant redifferentiation effect on PTC cells than BRAF/MEK inhibitor alone (Cheng et al., 2017). A phase 1 trial of HER inhibitors is ongoing, to examine the combined effect of HER inhibitors and Dabrafenib or Selumetinib in $braf^{V600E}$-mutant PTC (NCT01947023).

4.1.3.3. RET Inhibitor. *ret* is a proto-oncogene, and *ret* mutations are the most common cause of MTC. *ret* mutations are found in half of MTC, and 10–20% of PTC (Zhao et al., 2020).

Selpercatinib showed durable efficacy with mainly low-grade toxic effects in patients with previously treated *ret* fusion-positive TC in a phase 1/2 trial. The response percentage was 79% (95% CI, 54–94), and 1-year PFS was 64% (95% CI, 37–82). The most common AEs of grade 3 or higher were hypertension (in 21% of the patients), and 2% of patients discontinued Selpercatinib owing to drug-related AEs (Wirth et al., 2020). Selpercatinib was approved by the FDA and EMA for the treatment of *ret* fusion-positive non-small-cell lung cancer, *ret* fusion-positive TC and *ret*-mutant medullary TC, based on results from the phase 1/2 LIBRETTO-001 trial (Markham, 2020a). Of note, Selpercatinib can enhance RAI uptake in almost all the TC patients of *ret*-rearrangement (Groussin et al., 2021).

Pralsetinib is another RET inhibitor, in a multi-cohort, open-label, registrational, phase 1/2 study (ARROW), Pralsetinib 30–600 mg once or twice daily, then 400 mg once daily, was given to patients with *ret* fusion-positive PTC. In patients with *ret* fusion-positive TC, the ORR was 89%. Hypertension (17%) was the most common treatment-related AE (Vivek Subbiah et al., 2021). Pralsetinib is a new, well-tolerated, and potent once-daily oral treatment option for *ret*-altered TC patients. Pralsetinib was approved for the treatment of *ret* fusion-positive PTC and *ret* mutation-positive MTC (12/2020) (Markham, 2020b).

Patients with $ret^{G810C/S}$ mutations at the solvent front and $ret^{Y806C/N}$ mutation at the hinge initially responded to Selpercatinib and Pralsetinib, but developed resistance after treatment. Selpercatinib and Pralsetinib bind to *ret* in an unusual way that avoids interference from gatekeeper mutations but is vulnerable to non-gatekeeper mutations. These findings suggested the importance of developing next-generation RET TKIs that cover gatekeeper and non-gatekeeper mutations for on-target resistance and deciphering patterns of off-target resistance by alternative mechanisms for combination therapies (V. Subbiah et al., 2021).

4.1.3.4. ntrk1 fusion inhibitor. *ntrk1* was first identified as an oncogene in 1982 (Pulciani et al., 1982). Fusions involving *ntrk1*, *ntrk2*, or *ntrk3* are the most common mechanisms of oncogenic TRK activation (Vaishnavi et al., 2015). *ntrk* fusion can be detected in DTC, *ntrk* fusion inhibitor Larotrectinib inhibited DTC tumor growth and restored radioiodine affinity *in vitro*.

Larotrectinib treatment in patients with *ntrk* fusion-positive cancer was examined, and the response rate to Larotrectinib was 100% in five TC patients (Drilon et al., 2018). A case report shows that Larotrectinib may restore RAI uptake by inhibiting *eml4-ntrk3* signaling pathways. This reactivation of RAI uptake indicates that retreatment with RAI may be considered in patients who are receiving Larotrectinib. But because of the high level of previous radiation exposure, the patient did not receive follow-up RAI treatment (Groussin et al., 2020). Three adult patients with metastatic RAI-resistant *ntrk*-rearranged TC were treated with Larotrectinib. Two patients had RAI reuptake in all or part of their metastatic disease, while the other patient had no RAI reuptake. This means redifferentiation of *ntrk*-rearranged RAIR-TC with Larotrectinib is possible but not universal (Groussin et al., 2022). Waguespack and colleagues combined data from three Larotrectinib phase 1/2 clinical trials (NCT02576431, NCT02122913, and NCT02637687). They found that the ORR in 22 patients with TRK fusion-positive DTC was 86% (95%

Table 1
Summary of clinical trials ongoing to bolster RAI function in DTC.

NCT number	Phase	Status	Title	Sample size	Conditions	Interventions	Target	Primary outcome measures	Secondary outcome measures
NCT02152995	Phase 2	Active, not recruiting	Trametinib in Increasing Tumoral Iodine Incorporation in Patients With Recurrent or Metastatic Thyroid Cancer	34	Metastatic Thyroid Gland Carcinoma, Poorly Differentiated Thyroid Gland Carcinoma Recurrent Thyroid Gland Carcinoma	^{124}I ^{131}I Trametinib	BRAF	Proportion of patients alive following treatment with trametinib and I-124 (Cohort A) Iodine incorporation in thyroid cancer metastases to a predicted lesional absorbed radiation dose equal to or exceeding 2000 cGy with the administration of $\leq$ 300 mCi radioiodine (RAI) (Cohort B) Proportion of patients alive without disease progression (Cohort C)	Adequate increase in iodine corporation (Cohort A) Incidence of toxicity (Cohort A, B,C) ORR (Cohort B) Proportion of patients alive without disease progression (Cohort B, C) Change in thyroglobulin (Cohort A, B, C) Best objective response (Cohort C)
NCT04952493	Phase 2	Recruiting	Anlotinib or Penpulimab in Combination With RAI for DTC	42	Thyroid Cancer	Anlotinib hydrochloride,^{131}I Penpulimab	VEGFR PDGFR FGFR c-Kit	Objective response rate	Disease Control Rate Biochemical Response Rate Progression-free Survival Nuclear medicine functional imaging changes of target lesions
NCT02393690	Phase 2	Active, not recruiting	Iodine I-131 With or Without Selumetinib in Treating Patients With Recurrent or Metastatic Thyroid Cancer	60	Metastatic Thyroid Gland Carcinoma Poorly Differentiated Thyroid Gland Carcinoma Recurrent Thyroid Gland Carcinoma	^{131}I, Selumetinib	MEK	Response at 6 Months	Best Overall Response Progression Free Survival Changes in Serum Thyroglobulin Levels Incidence of Adverse Events
NCT04858867	Phase 2	Not Applicable	Reinducing Radioiodine-sensitivity in Radioiodine-refractory DTC Using Lenvatinib (RESET)	12	Differentiated Thyroid Cancer	rhTSH-stimulated^{124}I Intra-therapeutic^{131}I Lenvatinib	VEGFR-1/2/3 FGFR1 PDGFR cKit Ret	Fraction of RAI-R thyroid cancer patients who are eligible for^{131}I therapy after 6– or 12–week lenvatinib treatment	Extent of RAI uptake at baseline Optimal duration of lenvatinib treatment for maximum redifferentiation to occur Extent of RAI uptake after^{131}I therapy Metabolic treatment response using F-18 FDG PET Unstimulated (TSH suppressed) thyroglobulin levels
NCT03244956	Phase 2	Active, not recruiting	Efficacy of MEK (Trametinib) and BRAFV600E (Dabrafenib) Inhibitors With Radioactive Iodine (RAI) for the	40	Metastatic Radioactive Iodine Refractory Thyroid Cancer Patients With	^{131}I,rhTSH Trametinib Dabrafenib	MEK BRAF	Objective Response Rate (ORR) in metastatic radioactive Iodine Refractory Thyroid Cancer	Not Applicable

(*continued on next page*)

Table 1 (*continued*)

NCT number	Phase	Status	Title	Sample size	Conditions	Interventions	Target	Primary outcome measures	Secondary outcome measures
			Treatment of Refractory Metastatic Differentiated Thyroid Cancer		RAS or BRAF Mutation			patients with RAS or BRAF mutation	
NCT03469011	Phase 1	unknown	A Study to Try to Bring Back Radioiodine Sensitivity in Patients With Advanced Thyroid Cancer	18	Papillary Thyroid Cancer	Imatinib	PDGFRα	Restore iodine uptake	Decrease overall tumor burden
NCT05182931	Phase 2	Recruiting	A Prospective, Multi-Centre Trial of TKI Redifferentiation Therapy in Patients With RAIR Thyroid Cancer (I-FIRST Study) (I-FIRST)	80	Thyroid Cancer	Dabrafenib Trametinib	BRAF MEK	Progression free survival	Overall survival Quantification of treatment related toxicities Quantification of radioiodine uptake
NCT04619316	Phase 2	Recruiting	Enhancing Radioiodine Incorporation Into Radio Iodine Refractory Thyroid Cancers With MAPK Inhibition	20	Metastatic Thyroid Cancer	Trametinib Trametinib Dabrafenib	BRAF MEK	Changes in thyroglobulin levels	The incidence and severity of adverse effects
NCT05507775	Not Applicable	Not yet recruiting	Digoxin for the Reinduction of Radioiodine Uptake in Metastatic or Locally Advanced Non-medullary Thyroid Carcinoma	10	Non-Medullary Thyroid Carcinoma	Digoxin	Not Applicable	Reinduction of radioiodine uptake in target lesion	Beneficial effects of high-dose radioactive iodine treatment after reinduction Safety of digoxin treatment

CI: 64–97) (Waguespack et al., 2022).

Children with progressive RAIR lung metastases harboring the TPR-*ntrk1* fusion oncogene received targeted therapy with Larotrectinib, which reduced tumor size and restored RAI uptake. This study supports further studies of fusion-targeted therapy for RAIR-DTC. This is the first peadiatric study to show that fusion-targeted therapy reactivates RAI uptake and inhibits tumor growth in patients with RAIR-PTC, although sample numbers are not enough (Lee et al., 2021). Future clinical trials and treatment strategies should assess the ability of drugs targeting gene rearrangements to improve antitumor efficacy and restore the RAI effect.

These targeted medicines can stabilize, but not cure advanced DTC, as evidenced by the fact that many patients subsequently developed progressive disease. Patients who should consider enrolling in a therapeutic clinical trial are eligible for such studies. Patient's symptom burden, tumor growth, and potential tolerance for treatment-related adverse effects must be considered when deciding whether to begin TKI therapy. For those patients who are treated with non-investigational therapies, due to the lack of a direct comparison between any treatment regimens, it is difficult to choose an "optimal" medicine as first-line therapy. A professional multidisciplinary team must carefully take into account a variety of tumor-associated and patient-related aspects in the context of optimally managing patients with advanced PTC. Before beginning treatment, preparatory work includes but is not limited to informed consent, safety monitoring and disease reassessment.

4.2. Redifferentiation

TKI treatment can stabilize, but not cure advanced PTC, as evidenced by the fact that many patients subsequently developed progressive disease. In recent decades, increasing attention has been turned to the molecular structure of RAIR-DTCs, the loss of differentiation of thyroid follicular cells is the source of RAI resistance. Therefore, how to redifferentiate DTC cells and facilitate iodine uptake is being investigated. Retinoic acid, the differentiation agent was the first to be treated as a redifferentiation strategy, and it was initially shown to restore RAI sensitivity *in vitro*, but subsequent results and clinical trials were disappointing. Strategies developed regarding NIS-regulated RAI transport and metabolic in DTC are promising.

4.2.1. Traditional differentiation inducers

Retinoic acid (RA) is a bioactive metabolite of vitamin A and plays a key role in cell differentiation during mammalian development (Ott and Lachance, 1979). RA is effective in the differentiation therapy of leukemia cells. It was found that RA could increase the expression of *slc5a5* mRNA in human FTC cells *in vitro*, and in 1998, the clinical trial of RA in the treatment of DTC was carried out, with 50% of RAIR-DTC patients showed radioactive iodine uptake (Simon et al., 1998). Follow-up clinical trials also found that 19/27 (70%) patients with metastatic DTC had RAI uptake after RA treatment, and seven patients eventually achieved PR by ^{123}I or ^{131}I-WBS (Fernández et al., 2009). Subsequent studies have shown disappointing results. The therapeutic effect of RA in TC is less than previously reported, and side effects including a strong "sunburn", cheilitis, mucositis, conjunctivitis and raised transaminases occurred in two-thirds of patients (Grüning et al., 2003). Mata analysis in 2016 found a minority of patients with RAIR-DTC respond to RA treatment (Pak et al., 2018).

All-trans retinoic acid (ATRA) is used in the current treatment of acute promyelocytic leukemia (APL) (Cornic et al., 1994). ATRA had slightly better results, 4/11 patients had an uptake of radioactive iodine and 7/11 patients had responses (Zhang et al., 2007).

Bexarotene is an RXR activator with no significant therapeutic effect

on RAI uptake in patients (Liu et al., 2008). The inconsistency between the increase in iodine uptake and treatment efficacy is speculated to have several reasons. Firstly, it may be related to the molecular characteristics of DTC patients for the reason that genetic and molecular analyses on mutations of *braf*, *ret/ptc*, and *ras* have emerged in recent years. Most clinical trials regarding RA are earlier and do not take into account factors of genetic mutations. In addition, the number of patients was relatively small, the heterogeneity in tumors may have contributed to the difference in outcomes. What's more, RA induces differentiation and growth inhibition of cells through the RARβ receptor without activating *slc5a5* or other thyroid transcription factors. The effect of RA to revert cancer cells to a stable differentiated healthy state has not been duplicated with other cancer types except for leukemia. However, few studies of RA in DTC redifferentiation are ongoing to prove these hypotheses.

4.2.2. Targeting NIS

Numerous pre-clinical and clinical research have attempted to improve NIS expression and function, with a primary focus on redifferentiation drugs that promote the expression of genes specific to thyroid tissues, including *slc5a5*. Read et al. directly screen and identify 1200 FDA-approved medications that can increase radioiodide absorption on a significant pharmacological scale. Carebastine, a second-generation antihistamine, suppressed valosin-containing protein (VCP) to improve RAI uptake, while β2-adrenergic receptor agonist Formoterol and lipid-lowering agents Pravasatin directly increase *slc5a5* mRNA expression (Read et al., 2022).

Curcumin, a natural polyphenol compound, can induce DTC cell differentiation by increasing the expression of thyroid-specific genes. In DTC cells, thyroid-specific transcription factors, *ttf1, ttf2*, and *pax8*, as well as iodine-metabolizing proteins, including TSHR, TPO, and NIS are all increased after treatment with curcumin (Zhang et al., 2021). Curcumin inhibited HDAC activity (Schwertheim et al., 2017) and PI3K-AKT-mTOR signaling pathway. Importantly, curcumin enhanced NIS glycosylation and its membrane transport, significantly improving RAI uptake *in vitro*. It can also reduce TC cell proliferation and induce apoptosis.

Flavonoids have sparked interest in their potential health benefits. Quercetin can reduce TSH-modulated RNA levels of *slc5a5* (Giuliani et al., 2008). It was found that Quercetin could influence thyroid cell growth and function (Gonçalves et al., 2021). Flavonoid and rutin increased radioiodide uptake in DTC cells, resulting in increased NIS expression and decreased radioiodide efflux. Rutin also increases thyroid RAI uptake in rats. In addition, rutin may regulate NIS subcellular distribution, resulting in higher NIS levels at the cell membrane (Gonçalves et al., 2018).

Autophagy is a critical cellular process that protects cells and organisms from stressors. MAPK and PI3K-AKT signaling pathways are the core of the molecular pathogenesis of TC (Xing, 2013). Both the MAPK and PI3K-AKT are closely associated with autophagy (Sui et al., 2014; Jafari et al., 2019). NIS function has been linked to autophagy (Chai et al., 2019). Autophagy can affect iodine uptake in thyroid cells by regulating the stability of NIS protein. HMGB1 protein is up-regulated in TC, and HMGB1 activates AMPK to induce autophagy through a ROS-dependent mechanism, promoting NIS degradation and iodine uptake. HMGB1 is also suggested to be a potential pharmacological target for redifferentiation therapy. Higher plasma membranous NIS concentrations and better clinical outcome are correlated with signs of enhanced autophagy in TC. Well-known inhibitors of autophagy, like Chloroquine and Baloxamycin A, cause significant increases in iodide uptake in thyroid cells (Read et al., 2022), indicating that autophagy is essential to the central processing of NIS. Digitalis-like substances that activate autophagy restored NIS expression and RAI uptake in TC cells (Tesselaar et al., 2017).

However, autophagy is thought to play a dual role in the development and progression of cancer (Kondo et al., 2005), BRAF inhibitor Vemurafenib-induced autophagy-protected TC cells and inhibition of autophagy enhances the antitumor effects of Vemurafenib (Wang et al., 2016). Autophagy was activated by Sorafenib in TC, which was in part due to suppression of the AKT-mTOR pathway. Enhanced autophagy has been reported to promote the radiosensitivity and chemosensitivity of PTC cells. There is a combination effect with autophagy activators and adriamycin or radiation in PTC (Lin et al., 2010). Extensive research needs to be conducted to investigate the complex role of autophagy in TC.

HDAC appears to play a role in regulating the transcription of genes involved in TC. HDAC inhibitors (HDACIs) induce tumor growth arrest, differentiation and apoptosis, and sensitize tumor cells to radiation, increasing radioiodine uptake and radioiodine accumulation within the tumor. In preclinical models, HDACIs represent antitumor activity and the ability to rejuvenate RAI, either as monotherapy or in combination with other anticancer agents (Hou et al., 2010). $braf^{V600E}$ mutation causes impaired NIS expression and radioiodine refractoriness of TC in human TC cells BCPAP, but the mechanism is still unknown. Silencing of the *slc5a5* promoter by $braf^{V600E}$ involves histone deacetylation at critical regulatory regions of the *slc5a5* promoter. $braf^{V600E}$ inhibitor and MEK inhibitor increased histone acetylation of the *slc5a5* promoter, and SAHA, HDAC inhibitor, increased *slc5a5* expression in TC cells (Zhang et al., 2014). Combination therapy targeting major signaling pathways and histone deacetylase are used to restore RAI sensitivity. However, in a clinical trial, the HDAC inhibitor valproic acid failed to show anticancer activity in RAIR-DTC (Nilubol et al., 2017). At present, as far as we know, there are no new clinical trials for HDAC in RAIR-DTC.

EZH2 inhibitor Tazemetostat slightly increased iodine-metabolizing gene expression and promoted radioiodine uptake, irrespective of the BRAF status. Tazemetostat can strengthen BRAF inhibitors Dabrafenib or MEK inhibitor Selumetinib in the differentiation of $braf^{V600E}$-mutant PTC cells through synergistically decreasing global trimethylation of H3K27, which representing a novel differentiation strategy (Fu et al., 2020).

4.2.3. Regulating other thyroid-specific genes

As previously mentioned, thyroid-specific expression of TG, thyroid peroxidase TPO, NIS, and the TSHR is regulated by TTF1, TTF2, and PAX8. RAI therapy can be facilitated by targeting other thyroid-specific genes. RET activation is a common event in PTC, *ret/ptc* expression has been demonstrated to inhibit the transcription of *tg* and *slc5a5*.

PPARγ regulates glucose and lipid metabolism and energy balance. PPARγ was found chromosomal translocated with PAX8 in a subset of TC (Giordano et al., 2018). In an *in vitro* study, PPARγ agonists increased RAI uptake in DTC cells (Fröhlich et al., 2005). Troglitazone significantly increased RAI uptake, the expression of NIS and amount of NIS in the membrane fraction was significantly increased (Park et al., 2005). Studies in some small groups of patients also showed that TZDs increased RAI uptake in some patients. Rosiglitazone also reversed the epithelial-mesenchymal transition and increased the mRNA of *slc5a5*, *tg*, *tshr* and *tpo* (Elola et al., 2011; Aiello et al., 2006). RXR agonists bexarotene potentiated the effects of Rosiglitazone to inhibit cell growth and enhance NIS protein expression (Chen et al., 2020).

But other groups had a different conclusion, there was no difference with or without Rosiglitazone in DTC, although TG was increased in some TC patients (Philips et al., 2004). A phase 2 trial in patients with TG-positive RAIR-DTC showed Rosiglitazone treatment may induce RAI uptake in some patients. But the expression level of the PPARγ was not linked to RAI uptake status (Kebebew et al., 2006). The combination of PPARγ has the potential as a chemotherapeutic strategy for TC. In an open-label, phase 2 trial of oral Rosiglitazone treatment, 25% of 20 patients had a positive radioiodine scan after Rosiglitazone treatment, but Rosiglitazone treatment did not result in clinically significant response on long-term follow-up. Moreover, no patients had responded to Rosiglitazone therapy by anatomic imaging studies (Kebebew et al., 2009). Pioglitazone, another PPARγ inhibitor, had no redifferentiation

effect on 5 progressive DTC patients, and no patient developed a clinically important response associated with the treatment (Rosenbaum-Krumme et al., 2012).

Sinomenine Hydrochloride (SH) promotes TSHR-dependent redifferentiation in PTC (Zhang et al., 2022). Further studies revealed that SH upregulates cAMP and cAMP-Responsive Element-Binding Protein (CREB), activates the TSH/TSHR/cAMP signaling pathway, and ultimately promotes RAI uptake. When cAMP was inhibited, the role of SH in inducing NIS upregulation and increased RAI uptake was blocked due to the inhibition of CREB and PAX8 (Shang et al., 2020). TSH is one of the major regulators of NIS expression in the thyroid. High levels of the TSH are essential for radiation-induced TC of residual tissue during resection, which can promote membrane localization of the NIS and is a critical step in RAI uptake. Studies have found that nevirapine, an antiviral drug, can induce redifferentiation and RAI uptake through the TSHR/cAMP/CREB/PAX8 signaling pathway (Shang et al., 2020). So far, Nevirapine's clinical trials on the RAIR-DTC have not been reported. One case reported a significant increase in RAI uptake in metastatic RAIR-DTC after nevirapine treatment (Modoni et al., 2007). More clinical research is needed to demonstrate the synergy of RAI treatment with Nevirapine.

Capsaicin (CAP) is a transient receptor potential vanilloid type 1 (TRPV1) agonist that is an effective anticancer agent against a variety of cancers (Braga Ferreira et al., 2020). By restoring NIS expression and iodine avidity, CAP treatment may serve as a potential therapeutic strategy for RAIR-DTC, primarily by activating the TRPV1Ca^{2+}/cAMP/PKA/CREB signaling pathway but not the TSH/TSHR/cAMP signal pathway (Xu et al., 2021).

To enhance RAI uptake, TSH stimulation should be administered before, which needs to be completed about a month after thyroid hormone therapy. Current treatment guidelines recommend that TSH are usually set above 30 mU/L and can be achieved by 3 methods: 1, Thyroid hormone withdrawal (THW); 2, giving a period of thyroid hydrochloric acid to avoid deep hypothyroidism side effects (approximately 2–3 weeks before full THW); 3, Recombinant human TSH (rhTSH) stimulation (Sparano et al., 2022). Before the availability of rhTSH, THW was the standard protocol for RAI therapy preparations. However, hypothyroidism resulting from THW reduces patients' life quality (Borget et al., 2015), resulting in short-term impairment of cognitive status and several AEs, including cardiovascular and renal function deterioration (Niri et al., 2020) (Haugen et al., 2016). rhTSH provides a safe and reliable alternative to THW (Haugen et al., 1999). Several studies have proposed the equivalence of rhTSH and THW for resection preparation, it also has the advantage of shortening the duration of hospitalization (Pacini et al., 2003). However, no randomized trials comparing THW-and rhTSH-mediated therapies for distant metastatic disease have been reported. rhTSH has not been approved for patients with metastatic DTC, and, the cost of rhTSH stimulation will cause financial stress for DTC patients (Iravani et al., 2019). Patients with distant metastases are now more likely to receive THW.

Differentiation inducers gave the hope of sensitizing RAI therapy through a redifferentiation strategy, but subsequent clinical studies have been unsatisfactory. Sometimes differentiated DTC cells can be seen, but fail RAI uptake, and sometimes even in the presence of RAI uptake, the DTC disease keeps on progressing. As for NIS, besides expression and membrane localization regulation, NIS is influenced by aberrant miRNA expression and increased oxidative stress. The inherent regulatory diversity significantly increases the complexity of potential therapeutic strategies. In conclusion, there is still a long way to go for the redifferentiation treatment of RAIR-DTC.

4.3. Improved drug delivery via extracellular vesicles (EVs)

Nanomedicine-based approach can be used to reduce the dose of radioiodine required for cancer treatment. Due to their distinct physicochemical characteristics and high X-ray absorption efficiency, metal nanoparticles (NPs), such as those based on platinum or hafnium, are the best radiosensitizers. When combined with a low activity of radioiodine, which by itself appeared to be essentially ineffective against tumor cells, poly (methacrylic acid)-grafted gold nanoparticles (PMAA-AuNPs) could effectively cause a marked tumor cell death, based on the *in vitro* clonogenic assays on melanoma and colorectal cancer cells. Tumor enrichment with PMAA- AuNPs also increased the ability of a systemic RAI treatment to kill cells in vivo (Le Goas et al., 2019). Because of RAI's alleged "cross-fire" effect, some electrons are released when ^{131}I disintegrates and can impact surrounding cells and tissues that are rich in nanoparticles (Hamoudeh et al., 2008). As for advanced PTC, whose insensitivity to RAI is mainly caused by the fact that metastases exhibit substantial spatial non-uniformity (Jentzen et al., 2016), using nanomedicine to sensitize the tissues may achieve more uniform coverage and overcome RAI resistance. Tian et al. created a novel nanomedicine platform by adding ^{131}I to human serum albumin-bound MnO2 (^{131}I-HSA-MnO2) NPs. In the acidic microenvironment, the ^{131}I-HSA-MnO2 NPs will break down into ^{131}I-HSA which is conducive in penetrating tumor tissues due to its excellent permeability and good retention impact (Tian et al., 2017). Additionally, MnO2 can relieve TME hypoxia, increasing the tumor cells' sensitivity to ^{131}I (G. Yang et al., 2017). TME-responsive and TME-modulating nanomedicine may be of great interest to new generations of RAI combination therapies.

Son et al. (2019), Lee et al. (2022) transferred NIS proteins into hepatoma cells Huh7 and isolation of EVs from Huh7 cells. EVs from donor cells contain NIS protein but *slc5a5* mRNA was not detected. Treated with EV-Huh7/NIS in Huh7 cells, NIS protein was significantly elevated and ^{125}I uptake was increased. Pretreatment of EV-Huh7/NIS not only increased the affinity of hepatoma cells to RAI but also enhanced the cytotoxicity of RAI treatment on HUH7 cells by inducing DNA damage. Of note, the increase of RAI uptake peaked at 48 h after EV treatment and then gradually decreased. Therefore, the pretreatment timeline needs to be considered when designing EVs/NIS delivery system.

TKIs are now routinely used in advanced DTC therapy. The low bioavailability of TKI requires high doses, leading to increasing AEs, and patient's financial burden (Sasaki et al., 2020). EV-delivered TKIs can enhance the TKI target effect *in vitro*. EVs were extracted from primary human adipose-derived stem cells, and TKIs were loaded into EVs using sonication (18 cycles; 4 s per cycle). Compared to TKI single treatment, EVs/TKI can increase the iodine-metabolizing protein NIS, TSHR, and PAX8 expression, as well as ^{125}I uptake in TC cells SW1736. In addition, when treated with KCLO4, a NIS inhibitor (Kang et al., 2005), the increased RAI accumulation after EVs/TKI treatment can be completely blocked, demonstrating that EVs/TKI promotes cellular RAI uptake by enhancing NIS function (Rajendran et al., 2021). This was the first study to show that EVs can be used as a TKI vector to restore iodine sensitivity in RAIR-DTC cells. The combination of the EVs drug delivery system and TKI could be a promising approach to sensitize RAI therapy. However, there are some questions which should not be ignored. Firstly, EV function has primarily been studied *in vitro*, cultured cells which spread and grow on plastic dishes are far from cells in vivo (Lucien and Leong, 2019). On the other hand, the large-scale production of EVs must be addressed. Further therapeutic and diagnostic platforms need to be associated with highly advanced, less time-consuming, and high-production yield methods (Saha et al., 2021).

5. Other radiopharmaceuticals for RAIR-DTC

Radiopharmaceuticals for the treatment of RAIR-DTCs have recently piqued the interest of researchers. Despite sufficient RAI uptake in the targeted regions, some DTC patients are resistant to RAI treatment. Astatine (^{211}At) is a halogen element with similar chemical properties to iodine but has a higher linear energy transfer than ^{131}I particles (Watabe et al., 2022). ^{211}At has been considered as a α-emitter for targeted radionuclide therapy. ^{211}At exerts a better therapeutic effect by inducing

DNA double strand breaks, and its ability to inhibit colony formation was more than ten times that of RAI per becquerel (Bq). In addition, in vivo studies also revealed that ^{211}At inhibited tumor growth more than six times that of ^{131}I per Bq (Kaneda-Nakashima et al., 2022). The mechanism of ^{211}At uptake into thyroid cancer cells is mediated by NIS, ascorbic acid could increase the radiochemical purity of astatide and enhance ^{211}At uptake (Watabe et al., 2019). ^{211}At is a short-range α nuclide, allowing for outpatient treatment is possible with ^{211}At therapy (Mease et al., 2022; Watabe et al., 2021), but ^{131}I requires isolated hospitalization in a dedicated radiotherapy room. Weight loss, transient bone marrow suppression and pathological changes were observed in the extended single-dose toxicity study of 50 mBq/kg ^{211}At (Watabe et al., 2021). A phase 1 trial is ongoing to determine the safety, pharmacokinetics of ^{211}At (NCT05275946).

Prostate-Specific Membrane Antigen (PSMA) and Somatostatin Receptors (SSRT) expression were observed in advanced RAIR-DTC, suggesting that targeting these receptors with Ga/Lu could evolve as a novel therapy option. Assadi et al. revealed that promising results of ^{177}Lu-DOTATATE and ^{177}Lu-PSMA therapy in RAIR-DTC patients (Assadi and Ahmadzadehfar, 2019). While earlier studies on ^{177}Lu-DOTATATE revealed heterogeneous response and efficacy, despite good lesional uptake, only one out of five RAIR-DTC patients showed a PR (Roll et al., 2018). The therapeutic efficacy of ^{177}Lu-DOTATATE in RAIR-DTC patients could not be determined, and further clinical trials are recommended (Jois et al., 2014; Chakravarty and Chakraborty, 2021; Maghsoomi et al., 2021). RGD tripeptide sequence targets specificity to integrin $\alpha_v\beta_3$, which plays an important role in angiogenesis and is overexpressed in advanced DTC (Bergh et al., 2005). RAIR-DTC patients reported significant pain relief and clinical benefit after receiving ^{177}Lu-DOTA-RGD2 (Parihar et al., 2018). Though the preliminary clinical study results are promising, randomized clinical trials with a large cohort of patients are required to maximize efficacy (Satapathy and Bal, 2022). Fibroblast activating protein (FAP) is overexpressed and related with $braf^{V600E}$ mutation in RAIR-DTC (Nieminen et al., 2020). The RAIR-DTC patients who participated in the ^{177}Lu-FAPI-46 radionuclide therapy clinical trial (NCT04849247) demonstrated the potential feasibility of ^{177}Lu-FAPI (Fu et al., 2022). Recently, fifteen patients were enrolled in a pilot study of ^{177}Lu-DOTAGA. $(SA.FAPi)_2$ and molecular response evaluation revealed no complete response, but four patients achieved PR and three patients had stable disease. None of the patients had grade 3/4 AEs (Ballal et al., 2022). It is worth noting that ^{177}Lu-DOTAGA. $(SA.FAPi)_2$ is safe and appears to be effective in the treatment of aggressive RAIR-DTC patients who have exhausted all standard treatment options. More research into the pharmacokinetic properties of FAP-targeting vectors may be required.

CT or ultrasound guided ^{125}I seed implantation has received a lot of attention in the field of tumor therapy in recent years (Huang et al., 2016). The first TC patient who received ^{125}I seeds in his tumor bed had no cerebral metastases recur, despite the tumor reappearing in other locations (Parker et al., 1986). ^{125}I seed brachytherapy was used on 15 patients with recurrent DTC, no patients developed locoregional recurrence, and only 3 developed new metastases. There were no significant AEs reported in any patients (Yu et al., 2022). Ultrasound-guided implantation of ^{125}I seed reduced the volume of the nodules from 523 mm^3 to 53 mm^3 ($p < 0.01$) which indicated that ^{125}I seed brachytherapy is feasible for RAIR-DTC (Chen et al., 2021). Furthermore, ^{125}I seed implantation can be performed under local anesthesia with minimal pain and discomfort during hospitalization. CT or ultrasound guidance protects healthy organs from tissue damage (Zhu et al., 2013). However, ^{125}I seed brachytherapy is a difficult procedure, requiring skilled puncture techniques and thorough understanding of radiation dosimetry. For tumors with a huge volume, 3D printed template-guided ^{125}I enabled needles to insert more quickly and accurately, resulting in a better dose distribution (Gao et al., 2021). ^{125}I seed brachytherapy provided a superior therapeutic rate and allowed for curative dose treatment with significant therapeutic enhancement. Additional research is needed to determine the role of ^{125}I seed brachytherapy in RAIR-DTC treatment.

6. Summary and Prospect

Over the past decade, research into the treatment of metastatic DTCs has evolved from an initially empirical administration of non-selective agents based on multi-target therapy. To date, emphasis has been placed on more precise management based on gene mutations and patient clinicopathologic features. Objective response rates observed with MKI in patients with metastatic DTC were about 50%, with a prolonged response duration. The combination effect of selective TKI is better than MKI. However, the rate of complete response remains far from satisfactory, and the OS has not improved. Pausing, stopping, or switching is common during TKI treatment owing to the adverse effects. In addition, rare and severe AEs cannot be predicted due to the short history application of TKI. With the emergence of drug resistance in tumors, once new TKI drugs are available, resistance to TKI will develop, meaning that nearly all patients will develop resistance to TKI sooner or later. Experimental approaches for restoring radioiodine avidity may be a better option for future advanced DTC treatment.

Redifferentiating DTC cells to sensitize RAI therapy has been a hotspot for many years, although have historically yielded disappointing results. Traditional redifferentiation therapy, represented by RA, has had encouraging results in initial preclinical and small-scale clinical trials, but subsequent studies have found little clinical significance. Increased iodine uptake has been observed with many agents, but it is likely to have no iodine response. A retrospective study of 444 patients with TC relapses found that about 30% of PTC patients with normal RAI uptake remained insensitive to RAI treatment (Durante et al., 2006), suggesting that NIS-regulated RAI uptake is not the only factor affecting RAI refractoriness in PTC patients. In conclusion, several questions remain unsolved and high-level research is needed to explore the common molecular mechanism of RAI resistance, to bolster RAI efficiency and diminish cancer recurrence.

Funding

This study was supported by the National Natural Science Foundation of China (82204445, 81872170, 82173855, U20A20382); the National Natural Science Foundation of China-VR (82161138019); the Zhejiang Provincial Natural Science Foundation of China (LYQ20H310001, LY20H310001); Medical and Health Research Program of Zhejiang Province (2022RC008, 2021KY055); the Joint Scientific Research Foundation of Ministry of Health and the Health Bureau of Zhejiang Province (WKJ-ZJ-2115); Zhejiang Provincial Program for the Cultivation of New Heath Talents to Yiwen Zhang and Zongfu Pan; "10000 Talents Plan" of Zhejiang Province to Ping Huang (2020R52029).

CRediT authorship contribution statement

Conceptualization: Yiwen Zhang, Minghua Ge; the first draft of the manuscript was written by Yujia Liu; Jiafeng Wang, Xiaoping Hu, Zongfu Pan, Tong Xu, Jiajie Xu, and Liehao Jiang contributed to the investigation and resources; Ping Huang reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare no competing interest.

References

Aashiq, Mohamed, Silverman, Deborah A., Na'ara, Shorook, Takahashi, Hideaki, Moran, Amit, 2019. Radioiodine-refractory thyroid cancer: molecular basis of redifferentiation therapies, management, and novel therapies. Cancers 11 (9), 1382. https://doi.org/10.3390/cancers11091382.

Aiello, Aurora, Pandini, Giuseppe, Frasca, Francesco, Conte, Enrico, Murabito, Antonella, Sacco, Antonella, Genua, Marco, Vigneri, Riccardo, Belfiore, Antonino, 2006. Peroxisomal proliferator-activated receptor-gamma agonists induce partial reversion of epithelial-mesenchymal transition in anaplastic thyroid cancer cells. Endocrinology 147 (9), 4463–4475 https://doi.org/20200716125809247000.

Akter, Shamima, Sharma, Rakesh Kumar, Sharma, Shilpa, Rastogi, Saumya, Fiebich, Bernd L., Akundi, Ravi Shankar, 2021. Exogenous ATP modulates PGE2 release in macrophages through sustained phosphorylation of CDK9 and P38 MAPK. J. Leukoc. Biol. 110 (4), 663–677. https://doi.org/10.1002/JLB.3A1219-697RR.

Amit, Moran, Na'ara, Shorook, Francis, Demilza, Matanis, Wisam, Zolotov, Sagit, Eisenhaber, Birgit, Eisenhaber, Frank, et al., 2017. Post-translational regulation of radioactive iodine therapy response in papillary thyroid carcinoma. *JNCI: J. Natl. Cancer Inst.* 109 (12): djx092. https://doi.org/10.1093/jnci/djx092.

Assadi, Majid, Ahmadzadehfar, Hojjat, 2019. 177Lu-DOTATATE and 177Lu-prostate-specific membrane antigen therapy in a patient with advanced metastatic radioiodine-refractory differentiated thyroid cancer after failure of tyrosine kinase inhibitors treatment. World J. Nucl. Med. 18 (4), 406–408. https://doi.org/10.4103/wjnm.WJNM_112_18.

Aydemirli, M.D., Kapiteijn, E., Ferrier, K.R.M., Ottevanger, P.B., Links, T.P., van der Horst-Schrivers, A.N.A., Broekman, K.E., Groenwold, R.H.H., Zwaveling, J., 2020. Effectiveness and toxicity of lenvatinib in refractory thyroid cancer: Dutch real-life data. Eur. J. Endocrinol. 182 (2), 131–138. https://doi.org/10.1530/EJE-19-0763.

Ballal, Sanjana, Yadav, Madhav Prasad, Moon, Euy Sung, Roesch, Frank, Kumari, Samta, Agarwal, Shipra, Tripathi, Madhavi, et al., 2022. Novel fibroblast activation protein inhibitor-based targeted theranostics for radioiodine-refractory differentiated thyroid cancer patients: a pilot study. Thyroid.: Off. J. Am. Thyroid. Assoc. 32 (1), 65–77. https://doi.org/10.1089/thy.2021.0412.

Baloch, Zubair, W., Asa, Sylvia L., Barletta, Justine A., Ghossein, Ronald A., Christofer Juhlin, C., Jung, Chan Kwon, LiVolsi, Virginia A., et al., 2022. Overview of the 2022 WHO classification of thyroid neoplasms. Endocr. Pathol. 33 (1), 27–63. https://doi.org/10.1007/s12022-022-09707-3.

Bastos, Uchimura, André, Oler, Gisele, Nozima, Bruno Heidi Nakano, Moysés, Raquel Ajub, Cerutti, Janete Maria, 2015. BRAF V600E and decreased NIS and TPO expression are associated with aggressiveness of a subgroup of papillary thyroid microcarcinoma. Eur. J. Endocrinol. 173 (4), 525–540. https://doi.org/10.1530/EJE-15-0254.

Belfiore, A., Pandini, G., Vella, V., Squatrito, S., Vigneri, R., 1999. Insulin/IGF-I hybrid receptors play a major role in IGF-I signaling in thyroid cancer. Biochimie 81 (4), 403–407. https://doi.org/10.1016/s0300-9084(99)80088-1.

Berdelou, Amandine, Borget, Isabelle, Godbert, Yann, Nguyen, Thierry, Garcia, Marie-Eve, Chougnet, C.écile N., Ferru, Aurélie, et al., 2018. Lenvatinib for the treatment of radioiodine-refractory thyroid cancer in real-life practice. Thyroid.: Off. J. Am. Thyroid. Assoc. 28 (1), 72–78. https://doi.org/10.1089/thy.2017.0205.

Berg, G., Lindstedt, G., Suurküla, M., Jansson, S., 2002. Radioiodine ablation and therapy in differentiated thyroid cancer under stimulation with recombinant human thyroid-stimulating hormone. J. Endocrinol. Investig. 25 (1), 44–52. https://doi.org/10.1007/BF03343960.

Bergh, Joel J., Lin, Hung-Yun, Lansing, Lawrence, Mohamed, Seema N., Davis, Faith B., Mousa, Shaker, Davis, Paul J., 2005. Integrin AlphaVbeta3 contains a cell surface receptor site for thyroid hormone that is linked to activation of mitogen-activated protein kinase and induction of angiogenesis. Endocrinology 146 (7), 2864–2871 https://doi.org/20200716124443420000.

Bergs, Judith W.J., Wacker, Matthias G., Hehlgans, Stephanie, Piiper, Albrecht, Multhoff, Gabriele, Rödel, Claus, Rödel, Franz, 2015. The role of recent nanotechnology in enhancing the efficacy of radiation therapy. Biochim. Et Biophys. Acta 1856 (1), 130–143. https://doi.org/10.1016/j.bbcan.2015.06.008.

Bible, Keith C., Vera, J.Suman, Molina, Julian R., Smallridge, Robert C., Maples, William J., Menefee, Michael E., Rubin, Joseph, et al., 2010. Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a phase 2 consortium study. Lancet Oncol. 11 (10), 962–972. https://doi.org/10.1016/S1470-2045(10)70203-5.

Boelaert, K., Smith, V.E., Stratford, A.L., Kogai, T., Tannahill, L.A., Watkinson, J.C., Eggo, M.C., Franklyn, J.A., McCabe, C.J., 2007. PTTG and PBF repress the human sodium iodide symporter. Oncogene 26 (30), 4344–4356. https://doi.org/10.1038/sj.onc.1210221.

Borget, Isabelle, Julia Bonastre, Bogdan Catargi, Désirée Déandréis, Slimane Zerdoud, Daniela Rusu, Stéphane Bardet, et al., 2015. Quality of life and cost-effectiveness assessment of radioiodine ablation strategies in patients with thyroid cancer: results from the randomized phase III ESTIMABL trial. J. Clin. Oncol.: Off. J. Am. Soc. Clin. Oncol. 33 (26), 2885–2892. https://doi.org/10.1200/JCO.2015.61.6722.

Braga Ferreira, Leonardo Gomes, Faria, Juliana Vieira, Santos, Juliana Pimenta Salles Dos, Faria, Robson Xavier, 2020. Capsaicin: TRPV1-independent mechanisms and novel therapeutic possibilities. Eur. J. Pharmacol. 887 (November), 173356 https://doi.org/10.1016/j.ejphar.2020.173356.

Bravo-Miana, Rocío del Carmen, Vedova, Ana Belén Della, Paul, Ana Lucía De, Remedi, María M.ónica, Guantay, María Laura, Gilardoni, M.ónica Beatriz, Pellizas, Claudia Gabriela, Donadio, Ana Carolina, 2020. Thyroid tumor cells-fibroblasts crosstalk: role of extracellular vesicles. Endocr. Connect. 9 (6), 506–518. https://doi.org/10.1530/EC-20-0113.

Brose, Marcia S., Worden, Francis P., Newbold, Kate L., Guo, Matthew, Arti Hurria, 2017. Effect of age on the efficacy and safety of lenvatinib in radioiodine-refractory differentiated thyroid cancer in the phase III select trial. J. Clin. Oncol.: Off. J. Am. Soc. Clin. Oncol. 35 (23), 2692–2699. https://doi.org/10.1200/JCO.2016.71.6472.

Brose, Marcia S., Nutting, Christopher M., Jarzab, Barbara, Elisei, Rossella, Siena, Salvatore, Bastholt, Lars, Fouchardiere, Christelle de la, et al., 2014. Sorafenib in locally advanced or metastatic, radioactive iodine-refractory, differentiated thyroid cancer: a randomized, double-blind, phase 3 trial. Lancet 384 (9940), 319–328. https://doi.org/10.1016/S0140-6736(14)60421-9.

Brose, Marcia S., Robinson, Bruce, Sherman, Steven I., Krajewska, Jolanta, Lin, Chia-Chi, Vaisman, Fernanda, Hoff, Ana O., et al., 2021. Cabozantinib for radioiodine-refractory differentiated thyroid cancer (COSMIC-311): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 22 (8), 1126–1138. https://doi.org/10.1016/S1470-2045(21)00332-6.

Brose, Marcia S., Cabanillas, Maria E., Cohen, Ezra E.W., Wirth, Lori J., Riehl, Todd, Yue, Huibin, Sherman, Prof Steven I., Sherman, Eric J., 2016. Vemurafenib in patients with BRAFV600E-positive metastatic or unresectable papillary thyroid cancer refractory to radioactive iodine: a non-randomised, multicentre, open-label, phase 2 trial. Lancet Oncol. 17 (9), 1272–1282. https://doi.org/10.1016/S1470-2045(16)30166-8.

Brose, Marcia S., Smit, Johannes, Capdevila, Jaume, Elisei, Rossella, Nutting, Christopher, Pitoia, Fabian, Robinson, Bruce, Schlumberger, Martin, Shong, Young Kee, Takami, Hiroshi, 2012. Regional approaches to the management of patients with advanced, radioactive iodine-refractory differentiated thyroid carcinoma. Expert Rev. Anticancer Ther. 12 (9), 1137–1147. https://doi.org/10.1586/era.12.96.

Cabanillas, Maria E., Schlumberger, Martin, Jarzab, Barbara, Martins, Renato G., Pacini, Furio, Robinson, Bruce, McCaffrey, Judith C., et al., 2015. A phase 2 trial of lenvatinib (E7080) in advanced, progressive, radioiodine-refractory, differentiated thyroid cancer: a clinical outcomes and biomarker assessment. Cancer 121 (16), 2749–2756. https://doi.org/10.1002/cncr.29395.

Calangiu, Cristina Mariana, Simionescu, Cristiana Eugenia, Stepan, Alex Emilian, Cernea, Daniela, Zăvoi, Roxana Eugenia, Mărgăritescu, Claudiu, 2014. The expression of CK19, vimentin and E-cadherin in differentiated thyroid carcinomas. Rom. J. Morphol. Embryol. = Rev. Roum. De. Morphol. Et. Embryol. 55 (3), 919–925.

Cancer Genome Atlas Research Network, 2014. Integrated genomic characterization of papillary thyroid carcinoma. Cell 159 (3), 676–690. https://doi.org/10.1016/j.cell.2014.09.050.

Cao, Xia, Kambe, Fukushi, Ohmori, Sachiko, Seo, Hisao, 2002. Oxidoreductive modification of two cysteine residues in paired domain by Ref-1 regulates DNA-binding activity of pax-8′. Biochem. Biophys. Res. Commun. 297 (2), 288–293. https://doi.org/10.1016/s0006-291x(02)02196-4.

Capdevila, Jaume, Trigo, José Manuel, Aller, Javier, Manzano, José Luís, Adrián, Silvia García, Llopis, Carles Zafón, Reig, Òscar, et al., 2017. Axitinib treatment in advanced rai-resistant differentiated thyroid cancer (DTC) and refractory medullary thyroid cancer (MTC. Eur. J. Endocrinol. 177 (4), 309–317. https://doi.org/10.1530/EJE-17-0243.

Carling, Tobias, Udelsman, Robert, 2014. Thyroid cancer. Annu. Rev. Med. 65, 125–137. https://doi.org/10.1146/annurev-med-061512-105739.

Carr, Laurie L., Mankoff, David A., Goulart, Bernardo H., Eaton, Keith D., Capell, Peter T., Kell, Elizabeth M., Bauman, Julie E., Martins, Renato G., 2010. Phase II study of daily sunitinib in FDG-PET positive, iodine refractory, differentiated thyroid cancer and metastatic medullary carcinoma of thyroid with functional imaging correlation. Clin. Cancer Res.: Off. J. Am. Assoc. Cancer Res. 16 (21), 5260–5268. https://doi.org/10.1158/1078-0432.CCR-10-0994.

Cavalieri, R.R., 1997. Iodine metabolism and thyroid physiology: current concepts. Thyroid.: Off. J. Am. Thyroid. Assoc. 7 (2), 177–181. https://doi.org/10.1089/thy.1997.7.177.

Cazarin, Juliana, Dupuy, Corinne, de Carvalho, Denise Pires, 2022. Redox homeostasis in thyroid cancer: implications in Na+/I- symporter (NIS) regulation. Int. J. Mol. Sci. 23 (11), 6129. https://doi.org/10.3390/ijms23116129.

Chai, Jinyan, Zhang, Ruiguo, Zheng, Wei, Zhang, Guizhi, Jia, Qiang, Tan, Jian, Meng, Zhaowei, Wang, Renfei, 2022. Predictive value of clinical and pathological characteristics for metastatic radioactive iodine-refractory differentiated thyroid carcinoma: a 16-year retrospective study. Front. Endocrinol. 13 (June), 930180 https://doi.org/10.3389/fendo.2022.930180.

Chai, Wenwen, Ye, Fanghua, Zeng, Li, Li, Yanling, Yang, Liangchun, 2019. HMGB1-mediated autophagy regulates sodium/iodide symporter protein degradation in thyroid cancer cells. J. Exp. Clin. Cancer Res.: CR 38 (1), 325. https://doi.org/10.1186/s13046-019-1328-3.

Chakravarty, Debyani, Santos, Elmer, Ryder, Mabel, Knauf, Jeffrey A., Liao, Xiao-Hui, West, Brian L., Bollag, Gideon, et al., 2011. Small-molecule MAPK inhibitors restore radioiodine incorporation in mouse thyroid cancers with conditional BRAF activation\'. J. Clin. Investig. 121 (12), 4700–4711. https://doi.org/10.1172/JCI46382.

Chakravarty, Rubel, Chakraborty, Sudipta, 2021. A review of advances in the last decade on targeted cancer therapy using 177Lu: focusing on 177Lu produced by the direct neutron activation route. Am. J. Nucl. Med. Mol. Imaging 11 (6), 443–475.

Chan, T. A., M. Yarchoan, E. Jaffee, C. Swanton, S. A. Quezada, A. Stenzinger, and S. Peters. 2019. 'Development of Tumor Mutation Burden as an Immunotherapy Biomarker: Utility for the Oncology Clinic'. *Annals of Oncology: Official Journal of the European Society for Medical Oncology* 30 (1): 44–56. https://doi.org/10.1093/annonc/mdy495.

Chen, Jui-Yu, Wang, Jane-Jen, Lee, Hsin-Chen, Chi, Chin-Wen, Lee, Chen-Hsen, Hsu, Yi-Chiung, 2020. Combination of peroxisome proliferator-activated receptor gamma

and retinoid X receptor agonists induces sodium/iodide symporter expression and inhibits cell growth of human thyroid cancer cells. J. Chin. Med. Assoc.: JCMA 83 (10), 923–930. https://doi.org/10.1097/JCMA.0000000000000389.
Chen, Wei, Luo, Yu. Kun, Zhang, Ying, Song, Qing, Tang, Jie, 2021. Ultrasound-guided implantation of radioactive 125I seed in radioiodine refractory differentiated thyroid carcinoma. BMC Cancer 21 (1), 834. https://doi.org/10.1186/s12885-021-08500-5.
Cheng, Lingxiao, Jin, Yuchen, Liu, Min, Ruan, Maomei, Chen, Libo, 2017. HER inhibitor promotes BRAF/MEK inhibitor-induced redifferentiation in papillary thyroid cancer harboring BRAFV600E. Oncotarget 8 (12), 19843–19854. https://doi.org/10.18632/oncotarget.15773.
Chi, Y., Gao, M., Zhang, Y., Shi, F., Cheng, Y., Guo, Z., Ge, M., et al., 2020. 265O anlotinib in locally advanced or metastatic radioiodine-refractory differentiated thyroid carcinoma: a randomized, double-blind, multicenter phase II trial. Ann. Oncol. 31 (November), S1347. https://doi.org/10.1016/j.annonc.2020.10.259.
Choi, Yong Won, Kim, Hyun-Ju, Kim, Young Hwa, Park, So. Hyun, Chwae, Yong Jun, Lee, Jeonghun, Soh, Euy Young, Kim, Jang-Hee, Park, Tae Jun, 2014. B-RafV600E inhibits sodium iodide symporter expression via regulation of DNA methyltransferase 1. Exp. Mol. Med. 46 (11), e120 https://doi.org/10.1038/emm.2014.68.
Chow, Laura Q., Santana-Davila, Rafael, Pantel, Austin, Roth, Mara, Anderson, Leslie N., Failor, Alan, Doot, Robert, Mankoff, David, 2017. A phase I study of pazopanib in combination with escalating doses of 131I in patients with well-differentiated thyroid carcinoma borderline refractory to radioiodine. PLoS One 12 (6), e0178325. https://doi.org/10.1371/journal.pone.0178325.
Chung, Jae Hoon, 2020. BRAF and TERT promoter mutations: clinical application in thyroid cancer. Endocr. J. 67 (6), 577–584. https://doi.org/10.1507/endocrj.EJ20-0063.
Ciampi, Raffaele, Nikiforov, Yuri E., 2007. RET/PTC rearrangements and BRAF mutations in thyroid tumorigenesis. Endocrinology 148 (3), 936–941 https://doi.org/2020071613072630700.
Cohen, E.E.W., Tortorici, M., Kim, S., Ingrosso, A., Pithavala, Y.K., Bycott, P., 2014. A phase II trial of axitinib in patients with various histologic subtypes of advanced thyroid cancer: long-term outcomes and pharmacokinetic/pharmacodynamic analyses. Cancer Chemother. Pharmacol. 74 (6), 1261–1270. https://doi.org/10.1007/s00280-014-2604-8.
Cohen, Ezra E.W., Rosen, Lee S., Vokes, Everett E., Kies, Merrill S., Forastiere, Arlene A., Worden, Francis P., Kane, Madeleine A., et al., 2008. Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: results from a phase II study. J. Clin. Oncol. 26 (29), 4708–4713. https://doi.org/10.1200/JCO.2007.15.9566.
Cornic, M., Delva, L., Castaigne, S., Lefebvre, P., Balitrand, N., Degos, L., Chomienne, C., 1994. In vitro all-trans retinoic acid (ATRA) sensitivity and cellular retinoic acid binding protein (CRABP) levels in relapse leukemic cells after remission induction by ATRA in acute promyelocytic leukemia. Leukemia 8 (6), 914–917.
Costamagna, Eugenia, García, Bibian, Santisteban, Pilar, 2004. The functional interaction between the paired domain transcription factor Pax8 and Smad3 is involved in transforming growth factor-beta repression of the sodium/iodide symporter gene. J. Biol. Chem. 279 (5), 3439–3446. https://doi.org/10.1074/jbc.M307138200.
Dacosta Byfield, Stacey A., Adejoro, Oluwakayode, Copher, Ronda, Chatterjee, Debanjana, Joshi, Prashant R., Worden, Francis P., 2019. Real-world treatment patterns among patients initiating small molecule kinase inhibitor therapies for thyroid cancer in the United States. Adv. Ther. 36 (4), 896–915. https://doi.org/10.1007/s12325-019-0890-6.
Davies, Helen, Bignell, Graham R., Cox, Charles, Stephens, Philip, Edkins, Sarah, Clegg, Sheila, Teague, Jon, et al., 2002. Mutations of the BRAF gene in human cancer. Nature 417 (6892), 949–954. https://doi.org/10.1038/nature00766.
Davies, Louise, Morris, Luc G.T., Haymart, Megan, Chen, Amy Y., Goldenberg, David, Morris, John, Ogilvie, Jennifer B., et al., 2015. AMERICAN association of clinical endocrinologists and american college of endocrinology disease state clinical review: the increasing incidence of thyroid cancer. Endocr. Pract.: Off. J. Am. Coll. Endocrinol. Am. Assoc. Clin. Endocrinol. 21 (6), 686–696. https://doi.org/10.4158/EP14466.DSCR.
De La Vieja, A., Dohan, O., Levy, O., Carrasco, N., 2000. Molecular analysis of the sodium/iodide symporter: impact on thyroid and extrathyroid pathophysiology. Physiol. Rev. 80 (3), 1083–1105. https://doi.org/10.1152/physrev.2000.80.3.1083.
Delcorte, Ophélie, Degosserie, Jonathan, Pierreux, Christophe E., 2022. Role of extracellular vesicles in thyroid physiology and diseases: implications for diagnosis and treatment. Biomedicines 10 (10), 2585. https://doi.org/10.3390/biomedicines10102585.
Delcorte, Ophélie, Spourquet, Catherine, Lemoine, Pascale, Degosserie, Jonathan, Van Der Smissen, Patrick, Dauguet, Nicolas, Loriot, Axelle, et al., 2022. BRAFV600E induction in thyrocytes triggers important changes in the MiRNAs content and the populations of extracellular vesicles released in thyroid tumor microenvironment. Biomedicines 10 (4), 755. https://doi.org/10.3390/biomedicines10040755.
Deng, Yu.Jiao, Li, HongTao, Wang, Meng, Li, Na, Tian, Tian, Wu, Ying, Xu, Peng, et al., 2020. Global burden of thyroid cancer from 1990 to 2017′. JAMA Netw. Open 3 (6), e208759. https://doi.org/10.1001/jamanetworkopen.2020.8759.
Dhillon, Sohita, 2021. Penpulimab: first approval. Drugs 81 (18), 2159–2166. https://doi.org/10.1007/s40265-021-01640-9.
Dohán, O., Baloch, Z., Bánrévi, Z., Livolsi, V., Carrasco, N., 2001. Rapid communication: predominant intracellular overexpression of the Na(+)/I(-) symporter (NIS) in a large sampling of thyroid cancer cases. J. Clin. Endocrinol. Metab. 2697–2700.
Drilon, Alexander, Laetsch, Theodore W., Kummar, Shivaani, DuBois, Steven G., Lassen, Ulrik N., Demetri, George D., Nathenson, Michael, et al., 2018. Efficacy of larotrectinib in TRK fusion–positive cancers in adults and children. New Engl. J. Med. 378 (8), 731–739. https://doi.org/10.1056/NEJMoa1714448.
Duke, Elizabeth S., Barone, Amy K., Chatterjee, Somak, Mishra-Kalyani, Pallavi S., Shen, Yuan-Li, Isikwei, Emasenyie, Zhao, Hong, et al., 2022. FDA approval summary: cabozantinib for differentiated thyroid cancer. Clin. Cancer Res.: Off. J. Am. Assoc. Cancer Res. 28 (19), 4173–4177. https://doi.org/10.1158/1078-0432.CCR-22-0873.
Dunn, J.T., Dunn, A.D., 2001. Update on intrathyroidal iodine metabolism. Thyroid.: Off. J. Am. Thyroid. Assoc. 11 (5), 407–414. https://doi.org/10.1089/105072501300176363.
Dunn, Lara A., Sherman, Eric J., Baxi, Shrujal S., Tchekmedyian, Vatche, Grewal, Ravinder K., Larson, Steven M., Pentlow, Keith S., et al., 2018. Vemurafenib redifferentiation of BRAF mutant, RAI-refractory thyroid cancers. J. Clin. Endocrinol. Metab. 104 (5), 1417–1428 https://doi.org/2019032612192908800.
Durante, C., Haddy, N., Baudin, E., Leboulleux, S., Hartl, D., Travagli, J.P., Caillou, B., et al., 2006. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J. Clin. Endocrinol. Metab. 91 (8), 2892–2899 https://doi.org/2019041114154972900.
Durante, C., Puxeddu, E., Ferretti, E., Morisi, R., Moretti, S., Bruno, R., Barbi, F., et al., 2007. BRAF mutations in papillary thyroid carcinomas inhibit genes involved in iodine metabolism. J. Clin. Endocrinol. Metab. 92 (7), 2840–2843 https://doi.org/2020071613272709900.
Durante, Cosimo, Grani, Giorgio, Lamartina, Livia, Filetti, Sebastiano, Mandel, Susan J., Cooper, David S., 2018. The diagnosis and management of thyroid nodules: a review. JAMA 319 (9), 914–924. https://doi.org/10.1001/jama.2018.0898.
Elola, M., Yoldi, A., Emparanza, J.I., Matteucci, T., Bilbao, I., Goena, M., 2011. Redifferentiation therapy with rosiglitazone in a case of differentiated thyroid cancer with pulmonary metastases and absence of radioiodine uptake. Rev. Esp. De. Med. Nucl. 30 (4), 241–243. https://doi.org/10.1016/j.remn.2010.08.005.
Eloy, C., Santos, J., Cameselle-Teijeiro, J., Soares, P., Sobrinho-Simões, M., 2012. TGF-beta/Smad pathway and BRAF mutation play different roles in circumscribed and infiltrative papillary thyroid carcinoma. Virchows Arch.: Int. J. Pathol. 460 (6), 587–600. https://doi.org/10.1007/s00428-012-1234-y.
Eloy, Catarina, Santos, Joana, Soares, Paula, Sobrinho-Simões, Manuel, 2011. The preeminence of growth pattern and invasiveness and the limited influence of BRAF and RAS mutations in the occurrence of papillary thyroid carcinoma lymph node metastases. Virchows Arch.: Int. J. Pathol. 459 (3), 265–276. https://doi.org/10.1007/s00428-011-1133-7.
Fagin, James A., Wells, Samuel A., 2016. Biologic and clinical perspectives on thyroid cancer. New Engl. J. Med. 375 (11), 1054–1067. https://doi.org/10.1056/NEJMra1501993.
Falchook, G.S., Long, G.V., Kurzrock, R., Kim, K.B., Arkenau, H.T., Brown, M.P., Hamid, O., et al., 2012. RAF inhibitor dabrafenib (GSK2118436) is active in melanoma brain metastases, multiple BRAF genotypes and diverse cancers. Lancet 379 (9829), 1893–1901. https://doi.org/10.1016/S0140-6736(12)60398-5.
Falchook, Gerald S., Millward, Michael, Hong, David, Naing, Aung, Piha-Paul, Sarina, Waguespack, Steven G., Cabanillas, Maria E., et al., 2015. BRAF inhibitor dabrafenib in patients with metastatic BRAF-mutant thyroid cancer. Thyroid.: Off. J. Am. Thyroid. Assoc. 25 (1), 71–77. https://doi.org/10.1089/thy.2014.0123.
Fallahi, Poupak, Ferrari, Silvia Martina, Galdiero, Maria Rosaria, Varricchi, Gilda, Elia, Giusy, Ragusa, Francesca, Paparo, Sabrina Rosaria, Benvenga, Salvatore, Antonelli, Alessandro, 2022. Molecular targets of tyrosine kinase inhibitors in thyroid cancer. Semin. Cancer Biol. 79 (February), 180–196. https://doi.org/10.1016/j.semcancer.2020.11.013.
Faria, M.árcia, Domingues, Rita, Bugalho, Maria João, Silva, Ana Luísa, Matos, Paulo, 2021. Analysis of NIS plasma membrane interactors discloses key regulation by a SRC/RAC1/PAK1/PIP5K/EZRIN pathway with potential implications for radioiodine re-sensitization therapy in thyroid cancer. Cancers 13 (21), 5460. https://doi.org/10.3390/cancers13215460.
Faria, M.árcia, Vareda, José, Miranda, Micaella, Bugalho, Maria João, Silva, Ana Luísa, Matos, Paulo, 2022. Adherens junction integrity is a critical determinant of sodium iodide symporter residency at the plasma membrane of thyroid cells. Cancers 14 (21), 5362. https://doi.org/10.3390/cancers14215362.
Fattore, Luigi, Marra, Emanuele, Pisanu, Maria Elena, Noto, Alessia, Vitis, Claudia de, Belleudi, Francesca, Aurisicchio, Luigi, et al., 2013. Activation of an early feedback survival loop involving phospho-ErbB3 is a general response of melanoma cells to RAF/MEK inhibition and is abrogated by Anti-ErbB3 antibodies. J. Transl. Med. 11 (July), 180. https://doi.org/10.1186/1479-5876-11-180.
Fenton, Mike S., Marion, Kenneth M., Salem, Andrew K., Hogen, Rachel, Naeim, Faramarz, Hershman, Jerome M., 2010. Sunitinib inhibits MEK/ERK and SAPK/JNK pathways and increases sodium/iodide symporter expression in papillary thyroid cancer. Thyroid.: Off. J. Am. Thyroid. Assoc. 20 (9), 965–974. https://doi.org/10.1089/thy.2010.0008.
Fernández, C.A., Puig-Domingo, M., Lomeña, F., Estorch, M., Camacho Martí, V., Bittini, A.L., Marazuela, M., et al., 2009. Effectiveness of retinoic acid treatment for redifferentiation of thyroid cancer in relation to recovery of radioiodine uptake. J. Endocrinol. Investig. 32 (3), 228–233. https://doi.org/10.1007/BF03346457.
Ferrari, Silvia Martina, Fallahi, Poupak, Elia, Giusy, Ragusa, Francesca, Ruffilli, Ilaria, Paparo, Sabrina Rosaria, Antonelli, Alessandro, 2020. Thyroid autoimmune disorders and cancer. Semin. Cancer Biol. 64 (August), 135–146. https://doi.org/10.1016/j.semcancer.2019.05.019.
Fletcher, Alice, Read, Martin L., Thornton, Caitlin E.M., Larner, Dean P., Poole, Vikki L., Brookes, Katie, Nieto, Hannah R., et al., 2020. Targeting novel sodium iodide symporter interactors ADP-ribosylation factor 4 and valosin-containing protein enhances radioiodine uptake. Cancer Res. 80 (1), 102–115. https://doi.org/10.1158/0008-5472.CAN-19-1957.
Fransson, U., Rosengren, A.H., Schuit, F.C., Renström, E., Mulder, H., 2006. Anaplerosis via pyruvate carboxylase is required for the fuel-induced rise in the ATP:ADP ratio in

rat pancreatic islets. Diabetologia 49 (7), 1578–1586. https://doi.org/10.1007/s00125-006-0263-y.
Fröhlich, Eleonore, Machicao, Fausto, Wahl, Richard, 2005. Action of thiazolidinediones on differentiation, proliferation and apoptosis of normal and transformed thyrocytes in culture. Endocr. -Relat. Cancer 12 (2), 291–303. https://doi.org/10.1677/erc.1.00973.
Fu, Hao, Cheng, Lin, Sa, Ri, Jin, Yuchen, Chen, Libo, 2020. Combined tazemetostat and MAPKi enhances differentiation of papillary thyroid cancer cells harbouring BRAFV600E by synergistically decreasing global trimethylation of H3K27. J. Cell. Mol. Med. 24 (6), 3336–3345. https://doi.org/10.1111/jcmm.15007.
Fu, Hao, Huang, Jingxiong, Sun, Long, Wu, Hua, Chen, Haojun, 2022. FAP-targeted radionuclide therapy of advanced radioiodine-refractory differentiated thyroid cancer with multiple cycles of 177 Lu-FAPI-46. Clin. Nucl. Med. 47 (10), 906–907. https://doi.org/10.1097/RLU.0000000000004260.
Gao, Zhen, Zhang, Hongtao, Zhang, Lijuan, Yu, Huimin, Di, Xuemin, Wang, Zeyang, Liu, Zezhou, Sui, Aixia, Wang, Juan, Shi, Gaofeng, 2021. 3D-printed template-guided 125I seed brachytherapy: a salvage approach for locoregional refractory recurrence of papillary thyroid cancer. Eur. Thyroid J. 10 (6), 504–510. https://doi.org/10.1159/000519572.
Ge, Junshang, Wang, Jie, Wang, Hui, Jiang, Xianjie, Liao, Qianjin, Gong, Qian, Mo, Yongzhen, et al., 2020. The BRAF V600E mutation is a predictor of the effect of radioiodine therapy in papillary thyroid cancer. J. Cancer 11 (4), 932–939. https://doi.org/10.7150/jca.33105.
Giordano, Thomas J., Haugen, Bryan R., Sherman, Steven I., Shah, Manisha H., Caoili, Elaine M., Koenig, Ronald J., 2018. Pioglitazone therapy of PAX8-PPARγ fusion protein thyroid carcinoma. J. Clin. Endocrinol. Metab. 103 (4), 1277–1281 https://doi.org/20180626062901.
Giovanella, Luca, Avram, Anca M., Iakovou, Ioannis, Kwak, Jennifer, Lawson, Susan A., Lulaj, Elizabeth, Luster, Markus, et al., 2019. EANM practice guideline/SNMMI procedure standard for RAIU and Thyroid Scintigraphy'. Eur. J. Nucl. Med. Mol. Imaging 46 (12), 2514–2525. https://doi.org/10.1007/s00259-019-04472-8.
Giuliani, Cesidio, Noguchi, Yoshihiko, Harii, Norikazu, Napolitano, Giorgio, Tatone, Dante, Bucci, Ines, Piantelli, Mauro, Monaco, Fabrizio, Kohn, Leonard D., 2008. The flavonoid quercetin regulates growth and gene expression in rat FRTL-5 thyroid cells. Endocrinology 149 (1), 84–92 https://doi.org/20190411221403060900.
Gonçalves, Lima, Carlos Frederico, de Freitas, Mariana Lopes, Fortunato, Rodrigo Soares, Miranda-Alves, Leandro, Carvalho, Denise P., Ferreira, Andrea Claudia Freitas, 2018. Rutin scavenges reactive oxygen species, inactivates 5′-adenosine monophosphate-activated protein kinase, and increases sodium-iodide symporter expression in thyroid PCCL3 cells. Thyroid.: Off. J. Am. Thyroid. Assoc. 28 (2), 265–275. https://doi.org/10.1089/thy.2016.0585.
Gonçalves, Lima, Carlos Frederico, Hecht, Fabio, Cazarin, Juliana, Fortunato, Rodrigo Soares, Vaisman, Mario, de Carvalho, Denise Pires, Ferreira, Andrea Claudia Freitas, 2021. The flavonoid quercetin reduces cell migration and increases NIS and E-cadherin MRNA in the human thyroid cancer cell line BCPAP. Mol. Cell. Endocrinol. 529 (June), 111266 https://doi.org/10.1016/j.mce.2021.111266.
Grabellus, Florian, Nagarajah, James, Bockisch, Andreas, Schmid, Kurt Werner, Sheu, Sien-Yi, 2012. Glucose transporter 1 expression, tumor proliferation, and iodine/glucose uptake in thyroid cancer with emphasis on poorly differentiated thyroid carcinoma. Clin. Nucl. Med. 37 (2), 121–127. https://doi.org/10.1097/RLU.0b013e3182393599.
Groussin, Lionel, Clerc, J.érôme, Huillard, Olivier, 2020. Larotrectinib-enhanced radioactive iodine uptake in advanced thyroid cancer. New Engl. J. Med. 383 (17), 1686–1687. https://doi.org/10.1056/NEJMc2023094.
Groussin, Lionel, Theodon, H.élène, Bessiene, Laura, Bricaire, Leopoldine, Bonnet-Serrano, Fidéline, Cochand-Priollet, B.éatrix, Leroy, Karen, et al., 2022. Redifferentiating effect of larotrectinib in NTRK-Rearranged advanced radioactive-iodine refractory thyroid cancer. Thyroid.: Off. J. Am. Thyroid. Assoc. 32 (5), 594–598. https://doi.org/10.1089/thy.2021.0524.
Groussin, Lionel, Bessiene, Laura, Arrondeau, Jennifer, Garinet, Simon, Cochand-Priollet, B.éatrix, Lupo, Audrey, Zerbit, J.érémie, Clerc, J.érôme, Huillard, Olivier, 2021. Selpercatinib-enhanced radioiodine uptake in RET-rearranged thyroid cancer. Thyroid.: Off. J. Am. Thyroid. Assoc. 31 (10), 1603–1604. https://doi.org/10.1089/thy.2021.0144.
Grüning, Thomas, Tiepolt, Claudia, Zöphel, Klaus, Bredow, Jan, Kropp, Joachim, Franke, Wolf-Gunter, 2003. Retinoic acid for redifferentiation of thyroid cancer–does it hold its promise. Eur. J. Endocrinol. 148 (4), 395–402. https://doi.org/10.1530/eje.0.1480395.
Guo, Zhongmin, Linn, J.ürgen F., Wu, Guojun, Anzick, Sarah L., Eisenberger, Claus F., Halachmi, Sarel, Cohen, Yoram, et al., 2004. CDC91L1 (PIG-U) is a newly discovered oncogene in human bladder cancer. Nat. Med. 10 (4), 374–381. https://doi.org/10.1038/nm1010.
Hamoudeh, Misara, Kamleh, Muhammad Anas, Diab, Roudayna, Fessi, Hatem, 2008. Radionuclides delivery systems for nuclear imaging and radiotherapy of cancer. Adv. Drug Deliv. Rev. 60 (12), 1329–1346. https://doi.org/10.1016/j.addr.2008.04.013.
Hanna, Glenn J., Busaidy, Naifa L., Chau, Nicole G., Wirth, Lori J., Barletta, Justine A., Calles, Antonio, Haddad, Robert I., et al., 2018. Genomic correlates of response to everolimus in aggressive radioiodine-refractory thyroid cancer: a phase II study. Clin. Cancer Res.: Off. J. Am. Assoc. Cancer Res. 24 (7), 1546–1553. https://doi.org/10.1158/1078-0432.CCR-17-2297.
Haroon Al Rasheed, Mohamed Rizwan, Xu, Bin, 2019. Molecular alterations in thyroid carcinoma. Surg. Pathol. Clin. 12 (4), 921–930. https://doi.org/10.1016/j.path.2019.08.002.
Haugen, B.R., Pacini, F., Reiners, C., Schlumberger, M., Ladenson, P.W., Sherman, S.I., Cooper, D.S., et al., 1999. A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. J. Clin. Endocrinol. Metab. 84 (11), 3877–3885 https://doi.org/20200716193220487000.
Haugen, Bryan R., Alexander, Erik K., Bible, Keith C., Doherty, Gerard M., Mandel, Susan J., Nikiforov, Yuri E., Pacini, Furio, et al., 2016. 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the american thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid.: Off. J. Am. Thyroid. Assoc. 26 (1), 1–133. https://doi.org/10.1089/thy.2015.0020.
Heinrich, Michael C., Maki, Robert G., Corless, Christopher L., Antonescu, Cristina R., Harlow, Amy, Griffith, Diana, Town, Ajia, et al., 2008. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. J. Clin. Oncol.: Off. J. Am. Soc. Clin. Oncol. 26 (33), 5352–5359. https://doi.org/10.1200/JCO.2007.15.7461.
Hertz, S., Roberts, A., 1942. Radioactive iodine as an indicator in thyroid physiology. V. the use of radioactive iodine in the differential diagnosis of two types of graves' disease. J. Clin. Investig. 21 (1), 31–32. https://doi.org/10.1172/JCI101276.
Ho, Alan L., Grewal, Ravinder K., Leboeuf, Rebecca, Sherman, Eric J., Pfister, David G., Deandreis, Desiree, Pentlow, Keith S., et al., 2013. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. New Engl. J. Med. 368 (7), 623–632. https://doi.org/10.1056/NEJMoa1209288.
Ho, Alan L., Dedecjus, Marek, Wirth, Lori J., Michael Tuttle, R., Inabnet, William B., Tennvall, Jan, Vaisman, Fernanda, et al., 2022. Selumetinib plus adjuvant radioactive iodine in patients with high-risk differentiated thyroid cancer: a phase III, randomized, placebo-controlled trial (ASTRA. J. Clin. Oncol.: Off. J. Am. Soc. Clin. Oncol. 40 (17), 1870–1878. https://doi.org/10.1200/JCO.21.00714.
Horn, Susanne, Figl, Adina, Sivaramakrishna Rachakonda, P., Fischer, Christine, Sucker, Antje, Gast, Andreas, Kadel, Stephanie, et al., 2013. TERT promoter mutations in familial and sporadic melanoma. Science 339 (6122), 959–961. https://doi.org/10.1126/science.1230062.
Hou, Peng, Bojdani, Ermal, Xing, Mingzhao, 2010. Induction of thyroid gene expression and radioiodine uptake in thyroid cancer cells by targeting major signaling pathways. J. Clin. Endocrinol. Metab. 95 (2), 820–828. https://doi.org/10.1210/jc.2009-1888.
Huang, Hai, Xu, Shaonian, Li, Fusheng, Du, Zhenguang, Wang, Liang, 2016. Clinical application of computed tomography-guided 125I seed interstitial implantation for head and neck cancer patients with unmanageable cervical lymph node metastases. Eur. J. Med. Res. 21 (1), 18. https://doi.org/10.1186/s40001-016-0213-1.
Huang, Nai-Si, Wei, Wen-Jun, Xiang, Jun, Chen, Jia-Ying, Guan, Qing, Lu, Zhong-Wu, Ma, Ben, et al., 2021. The efficacy and safety of anlotinib in neoadjuvant treatment of locally advanced thyroid cancer: a single-arm phase II clinical trial. Thyroid.: Off. J. Am. Thyroid. Assoc. 31 (12), 1808–1813. https://doi.org/10.1089/thy.2021.0307.
Huang, Shuhui, Qi, Mengfang, Tian, Tian, Dai, Hongyuan, Tang, Yuan, Huang, Rui, 2022. Positive BRAFV600E mutation of primary tumor influences radioiodine avidity but not prognosis of papillary thyroid cancer with lung metastases. Front. Endocrinol. 13, 959089 https://doi.org/10.3389/fendo.2022.959089.
Iravani, Amir, Solomon, Benjamin, Pattison, David A., Jackson, Price, Kumar, Aravind Ravi, Kong, Grace, Hofman, Michael S., Akhurst, Tim, Hicks, Rodney J., 2019. Mitogen-activated protein kinase pathway inhibition for redifferentiation of radioiodine refractory differentiated thyroid cancer: an evolving protocol. Thyroid.: Off. J. Am. Thyroid. Assoc. 29 (11), 1634–1645. https://doi.org/10.1089/thy.2019.0143.
Izaguirre, María Fernanda, Casco, Victor Hugo, 2016. E-cadherin roles in animal biology: a perspective on thyroid hormone-influence. Cell Commun. Signal. 14 (1), 27. https://doi.org/10.1186/s12964-016-0150-1.
Jafari, Mahjoobeh, Ghadami, Elham, Dadkhah, Tahereh, Akhavan-Niaki, Haleh, 2019. PI3k/AKT signaling pathway: erythropoiesis and beyond. J. Cell. Physiol. 234 (3), 2373–2385. https://doi.org/10.1002/jcp.27262.
Jc, Lee, Zhao, Jt, Gundara, J., Serpell, J., Bach, La, Sidhu, S., 2015. Papillary thyroid cancer-derived exosomes contain MiRNA-146b and MiRNA-222. J. Surg. Res. 196 (1) https://doi.org/10.1016/j.jss.2015.02.027.
Jelic, Dragan, Marija, Mandic, Aljosa D., Maricic, Slobodan M., Srdjenovic, Branislava U., 2021. Oxidative stress and its role in cancer. J. Cancer Res. Ther. 17 (1), 22–28. https://doi.org/10.4103/jcrt.JCRT_862_16.
Jentzen, Walter, Verschure, Femke, Zon, Annelie van, Kolk, Rudie van de, Wierts, Roel, Schmitz, Jochen, Bockisch, Andreas, Binse, Ina, 2016. 124I PET assessment of response of bone metastases to initial radioiodine treatment of differentiated thyroid cancer. J. Nucl. Med.: Off. Publ. Soc. Nucl. Med. 57 (10), 1499–1504. https://doi.org/10.2967/jnumed.115.170571.
Jentzen, Walter, Hoppenbrouwers, Jan, Leeuwen, Paul van, Velden, Daan van der, Kolk, Rudie van de, Poeppel, Thorsten Dirk, Nagarajah, James, Brandau, Wolfgang, Bockisch, Andreas, Rosenbaum-Krumme, Sandra, 2014. Assessment of lesion response in the initial radioiodine treatment of differentiated thyroid cancer using 124I PET imaging. J. Nucl. Med.: Off. Publ. Soc. Nucl. Med. 55 (11), 1759–1765. https://doi.org/10.2967/jnumed.114.144089.
Jiang, Lei, Zhan, Yanxia, Gu, Yusen, Ye, Yi, Cheng, Yunfeng, Shi, Hongcheng, 2013. Changes of regulatory T and B cells in patients with papillary thyroid carcinoma after 131I radioablation: a preliminary study. BioMed. Res. Int. 2013, 683768 https://doi.org/10.1155/2013/683768.
Jiang, Wei-Wen, Zahurak, Marianna, Zhou, Zeng-Tong, Park, Hannah Lui, Guo, Zhong-Min, Wu, Guo-Jun, Sidransky, David, Trink, Barry, Califano, Joseph A., 2007. Alterations of GPI transamidase subunits in head and neck squamous carcinoma. Mol. Cancer 6 (November), 74. https://doi.org/10.1186/1476-4598-6-74.
Jin, Shuai, Yang, Xing, Zhong, Quliang, Liu, Xiangmei, Zheng, Tao, Zhu, Lingyan, Yang, Jingyuan, 2022. A predictive model for the 10-year overall survival status of patients with distant metastases from differentiated thyroid cancer using XGBoost

algorithm-A population-based analysis. Front. Genet. 13, 896805 https://doi.org/10.3389/fgene.2022.896805.
Jois, Bhargavi, Asopa, Ramesh, Basu, Sandip, 2014. Somatostatin receptor imaging in Non-(131)I-avid metastatic differentiated thyroid carcinoma for determining the feasibility of peptide receptor radionuclide therapy with (177)Lu-DOTATATE: low fraction of patients suitable for peptide receptor radionuclide therapy and evidence of chromogranin a level-positive neuroendocrine differentiation. Clin. Nucl. Med. 39 (6), 505–510. https://doi.org/10.1097/RLU.0000000000000429.
Kaneda-Nakashima, Kazuko, Shirakami, Yoshifumi, Watabe, Tadashi, Ooe, Kazuhiro, Yoshimura, Takashi, Toyoshima, Atsushi, Wang, Yang, Haba, Hiromitsu, Fukase, Koichi, 2022. Effect to therapy of sodium-iodine symporter expression by alpha-ray therapeutic agent via sodium/iodine symporter. Int. J. Mol. Sci. 23 (24), 15509. https://doi.org/10.3390/ijms232415509.
Kang, Joo Hyun, Lee, Dong Soo, Paeng, Jin Chul, Lee, Jae Sung, Kim, Yun Hui, Lee, Yong Jin, Hwang, Do. Won, et al., 2005. Development of a sodium/iodide symporter (NIS)-transgenic mouse for imaging of cardiomyocyte-specific reporter gene expression. J. Nucl. Med.: Off. Publ. Soc. Nucl. Med. 46 (3), 479–483.
Kebebew, Electron, Lindsay, Sheila, Clark, Orlo H., Woeber, Kenneth A., Hawkins, Randall, Greenspan, Francis S., 2009. Results of rosiglitazone therapy in patients with thyroglobulin-positive and radioiodine-negative advanced differentiated thyroid cancer. Thyroid.: Off. J. Am. Thyroid. Assoc. 19 (9), 953–956. https://doi.org/10.1089/thy.2008.0371.
Kebebew, Electron, Peng, Miao, Reiff, Emily, Treseler, Patrick, Woeber, Kenneth A., Clark, Orlo H., Greenspan, Francis S., Lindsay, Sheila, Duh, Quan-Yang, Morita, Eugene, 2006. A phase II trial of rosiglitazone in patients with thyroglobulin-positive and radioiodine-negative differentiated thyroid cancer. discussion 966-967 Surgery 140 (6), 960–966. https://doi.org/10.1016/j.surg.2006.07.038.
Knauf, Jeffrey A., Sartor, Maureen A., Medvedovic, Mario, Lundsmith, Emma, Ryder, Mabel, Salzano, Marcella, Nikiforov, Yuri E., Giordano, Thomas J., Ghossein, Ronald A., Fagin, James A., 2011. Progression of BRAF-induced thyroid cancer is associated with epithelial-mesenchymal transition requiring concomitant MAP kinase and TGFβ signaling. Oncogene 30 (28), 3153–3162. https://doi.org/10.1038/onc.2011.44.
Kochman, Joanna, Jakubczyk, Karolina, Bargiel, Piotr, Janda-Milczarek, Katarzyna, 2021. The influence of oxidative stress on thyroid diseases. Antioxidants 10 (9), 1442. https://doi.org/10.3390/antiox10091442.
Kondo, Yasuko, Kanzawa, Takao, Sawaya, Raymond, Kondo, Seiji, 2005. The role of autophagy in cancer development and response to therapy. Nat. Rev. Cancer 5 (9), 726–734. https://doi.org/10.1038/nrc1692.
Koukkou, Eftychia G., Roupas, Nikolaos D., Markou, Kostas B., 2017. Effect of excess iodine intake on thyroid on human health. Minerva Med. 108 (2), 136–146. https://doi.org/10.23736/S0026-4806.17.04923-0.
Koumarianou, Petrina, Fernández-Méndez, Celia, Fajardo-Delgado, D.ánae, Mielu, Lidia Mirella, Santisteban, Pilar, Vieja, Antonio De. la, 2022. Basolateral sorting of the sodium/iodide symporter is mediated by adaptor protein 1 clathrin adaptor complexes. Thyroid.: Off. J. Am. Thyroid. Assoc. 32 (10), 1259–1270. https://doi.org/10.1089/thy.2022.0163.
Kurzrock, Razelle, Sherman, Steven I., Ball, Douglas W., Forastiere, Arlene A., Cohen, Roger B., Mehra, Ranee, Pfister, David G., et al., 2011. Activity of XL184 (Cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer. J. Clin. Oncol.: Off. J. Am. Soc. Clin. Oncol. 29 (19), 2660–2666. https://doi.org/10.1200/JCO.2010.32.4145.
Kushchayeva, Yevgeniya, Kushchayev, Sergiy, Jensen, Kirk, Brown, Rebecca J., 2022. Impaired glucose metabolism, anti-diabetes medications, and risk of thyroid cancer. Cancers 14 (3), 555. https://doi.org/10.3390/cancers14030555.
Lan, Ling, Basourakos, Spyros, Cui, Dai, Zuo, Xuemei, Deng, Wei, Huo, Lili, Chen, Linghai, et al., 2017. Inhibiting β-catenin expression promotes efficiency of radioiodine treatment in aggressive follicular thyroid cancer cells probably through mediating NIS localization. Oncol. Rep. 37 (1), 426–434. https://doi.org/10.3892/or.2016.5228.
Landa, I.ñigo, Ganly, Ian, Chan, Timothy A., Mitsutake, Norisato, Matsuse, Michiko, Ibrahimpasic, Tihana, Ghossein, Ronald A., Fagin, James A., 2013. Frequent somatic TERT promoter mutations in thyroid cancer: higher prevalence in advanced forms of the disease. J. Clin. Endocrinol. Metab. 98 (9), E1562–E1566 https://doi.org/10.1210/jc.2013-2071.
Le Goas, Marine, Paquet, Marie, Paquirissamy, Aurélie, Guglielmi, Julien, Compin, Cathy, Thariat, Juliette, Vassaux, Georges, et al., 2019. Improving 131I radioiodine therapy by hybrid polymer-grafted gold nanoparticles. Int. J. Nanomed. 14, 7933–7946. https://doi.org/10.2147/IJN.S211496.
Leboulleux, Sophie, Lamartina, Livia, Hadoux, Julien, Baudin, Eric, Schlumberger, Martin, 2022. Emerging drugs for the treatment of radioactive iodine refractory papillary thyroid cancer. Expert Opin. Investig. Drugs 31 (7), 669–679. https://doi.org/10.1080/13543784.2022.2071696.
Lee, James C., Zhao, Jing Ting, Clifton-Bligh, Roderick J., Gill, Anthony, Gundara, Justin S., Ip, Julian C., Glover, Anthony, et al., 2013. MicroRNA-222 and MicroRNA-146b are tissue and circulating biomarkers of recurrent papillary thyroid cancer. Cancer 119 (24), 4358–4365. https://doi.org/10.1002/cncr.28254.
Lee, Jin Hee, Jung, Kyung-Ho, Mina, Kim, Lee, Kyung-Han, 2022. Extracellular vesicles deliver sodium iodide symporter protein and promote cancer cell radioiodine therapy. Sci. Rep. 12 (July), 11190. https://doi.org/10.1038/s41598-022-15524-9.
Lee, Young Ah, Lee, Hyunjung, Im, Sun-Wha, Song, Young Shin, Oh, Do-Youn, Kang, Hyoung Jin, Won, Jae-Kyung, et al., 2021. NTRK and RET fusion–directed therapy in pediatric thyroid cancer yields a tumor response and radioiodine uptake. J. Clin. Investig. 131 (18), e144847 https://doi.org/10.1172/JCI144847.
Li, Genpeng, Lei, Jianyong, Song, Linlin, Jiang, Ke, Wei, Tao, Li, Zhihui, Gong, Rixiang, Zhu, Jingqiang, 2018. Radioiodine refractoriness score: a multivariable prediction model for postoperative radioiodine-refractory differentiated thyroid carcinomas. Cancer Med. 7 (11), 5448–5456. https://doi.org/10.1002/cam4.1794.
Li, Xiaoyu, Qiu, Meng, Wang, ShengJun, Zhu, Hong, Feng, Bi, Zheng, Li, 2020. A phase I dose-escalation, pharmacokinetics and food-effect study of oral donafenib in patients with advanced solid tumours. Cancer Chemother. Pharmacol. 85 (3), 593–604. https://doi.org/10.1007/s00280-020-04031-1.
Lin, Chi-Iou, Whang, Edward E., Donner, David B., Du, Jinyan, Lorch, Jochen, He, Frank, Jiang, Xiaofeng, Price, Brendan D., Moore, Francis D., Ruan, Daniel T., 2010. Autophagy induction with RAD001 enhances chemosensitivity and radiosensitivity through met inhibition in papillary thyroid cancer'. Mol. Cancer Res. 8 (9), 1217–1226. https://doi.org/10.1158/1541-7786.MCR-10-0162.
Lin, Yansong, Wang, Chen, Gao, Wen, Cui, Ruixue, Liang, Jun, 2017. Overwhelming rapid metabolic and structural response to apatinib in radioiodine refractory differentiated thyroid cancer. Oncotarget 8 (26), 42252–42261. https://doi.org/10.18632/oncotarget.15036.
Lin, Yansong, Qin, Shukui, Li, Zhiyong, Yang, Hui, Fu, Wei, Li, Shaohua, Chen, Wenxin, et al., 2022. Apatinib vs placebo in patients with locally advanced or metastatic, radioactive iodine–refractory differentiated thyroid cancer: the reality randomized clinical trial. JAMA Oncol. 8 (2), 242. https://doi.org/10.1001/jamaoncol.2021.6268.
Lin, Yan-Song, Yang, Hui, Ding, Yong, Cheng, Yi-Zhuang, Shi, Feng, Tan, Jian, Deng, Zhi-Yong, et al., 2021. Donafenib in progressive locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer: results of a randomized, multicenter phase II trial. Thyroid 31 (4), 607–615. https://doi.org/10.1089/thy.2020.0235.
Liu, Chang, Zhang, Lu, Liu, Yang, Zhao, Qingqing, Pan, Yu, Zhang, Yifan, 2021. Value of pyruvate carboxylase in thyroid fine-needle aspiration wash-out fluid for predicting papillary thyroid cancer lymph node metastasis. Front. Oncol. 11 (May), 643416 https://doi.org/10.3389/fonc.2021.643416.
Liu, Jierui, Liu, Yanqing, Lin, Yansong, Liang, Jun, 2019. Radioactive iodine-refractory differentiated thyroid cancer and redifferentiation therapy. Endocrinol. Metab. 34 (3), 215. https://doi.org/10.3803/EnM.2019.34.3.215.
Liu, Xiaoli, Bishop, Justin, Shan, Yuan, Pai, Sara, Liu, Dingxie, Murugan, Avaniyapuram Kannan, Sun, Hui, El-Naggar, Adel K., Xing, Mingzhao, 2013. Highly prevalent TERT promoter mutations in aggressive thyroid cancers. Endocr. -Relat. Cancer 20 (4), 603–610. https://doi.org/10.1530/ERC-13-0210.
Liu, Yang, Khan, Suliman, Li, Lin, Ten Hagen, Timo L.M., Falahati, Mojtaba, 2022. Molecular Mechanisms of thyroid cancer: a competing endogenous RNA (CeRNA) point of view. Biomed. Pharmacother. 146 (February), 112251 https://doi.org/10.1016/j.biopha.2021.112251.
Liu, Yang, Liu, Chang, Pan, Yu, Zhou, Jinxin, Ju, Huijun, Zhang, Yifan, 2022. Pyruvate carboxylase promotes malignant transformation of papillary thyroid carcinoma and reduces iodine uptake. Cell Death Discov. 8 (October), 423. https://doi.org/10.1038/s41420-022-01214-y.
Liu, Ying Y., Stokkel, Marcel P., Morreau, Hans A., Pereira, Alberto M., Romijn, Johannes A., Smit, Johannes W.A., 2008. Radioiodine therapy after pretreatment with bexarotene for metastases of differentiated thyroid carcinoma. Clin. Endocrinol. 68 (4), 605–609. https://doi.org/10.1111/j.1365-2265.2007.03096.x.
Locati, Laura D., Licitra, Lisa, Agate, Laura, Ou, Sai-Hong I., Boucher, Andree, Jarzab, Barbara, Qin, Shukui, et al., 2014. Treatment of advanced thyroid cancer with axitinib: phase 2 study with pharmacokinetic/pharmacodynamic and quality-of-life assessments. Cancer 120 (17), 2694–2703. https://doi.org/10.1002/cncr.28766.
López-Márquez, Arístides, Carrasco-López, Carlos, Martínez-Cano, Andrea, Lemoine, Pascale, Pierreux, Christophe E., Santisteban, Pilar, 2022. Sox9 Is involved in the thyroid differentiation program and is regulated by crosstalk between TSH, TGFβ and thyroid transcription factors. Sci. Rep. 12 (1), 2144. https://doi.org/10.1038/s41598-022-06004-1.
Lucien, Fabrice, Leong, Hon S., 2019. The role of extracellular vesicles in cancer microenvironment and metastasis: myths and challenges. Biochem. Soc. Trans. 47 (1), 273–280. https://doi.org/10.1042/BST20180253.
Lyu, Jingya, Imachi, Hitomi, Yoshimoto, Takuo, Fukunaga, Kensaku, Sato, Seisuke, Ibata, Tomohiro, Kobayashi, Toshihiro, et al., 2018. Thyroid stimulating hormone stimulates the expression of glucose transporter 2 via its receptor in pancreatic β cell line, INS-1 cells. Sci. Rep. 8 (January), 1986. https://doi.org/10.1038/s41598-018-20449-3.
Maggisano, Valentina, Capriglione, Francesca, Verrienti, Antonella, Celano, Marilena, Gagliardi, Agnese, Bulotta, Stefania, Sponziello, Marialuisa, et al., 2022. Identification of exosomal microRNAs and their targets in papillary thyroid cancer cells. Biomedicines 10 (5), 961. https://doi.org/10.3390/biomedicines10050961.
Maghsoomi, Zohreh, Emami, Zahra, Malboosbaf, Ramin, Malek, Mojtaba, Khamseh, Mohammad E., 2021. Efficacy and safety of peptide receptor radionuclide therapy in advanced radioiodine-refractory differentiated thyroid cancer and metastatic medullary thyroid cancer: a systematic review. BMC Cancer 21 (1), 579. https://doi.org/10.1186/s12885-021-08257-x.
Maier, J., van Steeg, H., van Oostrom, C., Karger, S., Paschke, R., Krohn, K., 2006. Deoxyribonucleic acid damage and spontaneous mutagenesis in the thyroid gland of rats and mice. Endocrinology 147 (7), 3391–3397. https://doi.org/10.1210/en.2005-1669.
Markham, Anthony, 2020a. Selpercatinib: first approval. Drugs 80 (11), 1119–1124. https://doi.org/10.1007/s40265-020-01343-7.
Markham, Anthony, 2020b. 'Pralsetinib: First Approval'. Drugs 80 (17), 1865–1870. https://doi.org/10.1007/s40265-020-01427-4.
Marotta, Vincenzo, Ramundo, Valeria, Camera, Luigi, Prete, Michela Del, Fonti, Rosa, Esposito, Raffaella, Palmieri, Giovannella, et al., 2013. Sorafenib in advanced iodine-refractory differentiated thyroid cancer: efficacy, safety and exploratory analysis of

role of serum thyroglobulin and FDG-PET. Clin. Endocrinol. 78 (5), 760–767. https://doi.org/10.1111/cen.12057.
Marotta, Vincenzo, Sciammarella, Concetta, Capasso, Mario, Testori, Alessandro, Pivonello, Claudia, Chiofalo, Maria Grazia, Pivonello, Rosario, et al., 2017. Preliminary data of VEGF-A and VEGFR-2 polymorphisms as predictive factors of radiological response and clinical outcome in iodine-refractory differentiated thyroid cancer treated with sorafenib. Endocrine 57 (3), 539–543. https://doi.org/10.1007/s12020-016-1200-6.
Mease, Ronnie C., Kang, Choong Mo, Kumar, Vivek, Banerjee, Sangeeta Ray, Minn, Il, Brummet, Mary, Gabrielson, Kathleen L., et al., 2022. An improved 211At-labeled agent for PSMA-targeted α-therapy. J. Nucl. Med.: Off. Publ. Soc. Nucl. Med. 63 (2), 259–267. https://doi.org/10.2967/jnumed.121.262098.
Melo, Miguel, Rocha, Adriana Gaspar da, Vinagre, João, Batista, Rui, Peixoto, Joana, Tavares, Catarina, Celestino, Ricardo, et al., 2014. TERT promoter mutations are a major indicator of poor outcome in differentiated thyroid carcinomas. J. Clin. Endocrinol. Metab. 99 (5), E754–E765 https://doi.org/2019041113350021900.
Mian, Caterina, Barollo, Susi, Pennelli, Gianmaria, Pavan, Nicodemo, Rugge, Massimo, Pelizzo, Maria Rosa, Mazzarotto, Renzo, et al., 2008. Molecular characteristics in papillary thyroid cancers (PTCs) with No 131I uptake. Clin. Endocrinol. 68 (1), 108–116. https://doi.org/10.1111/j.1365-2265.2007.03008.x.
Mitchell, Brendon, Dhingra, Jagdish K., Mahalingam, Meera, 2016. BRAF and epithelial-mesenchymal transition: lessons from papillary thyroid carcinoma and primary cutaneous melanoma. Adv. Anat. Pathol. 23 (4), 244–271. https://doi.org/10.1097/PAP.0000000000000113.
Mitchell, M.L., Hsu, H.W., 2016. Commentary on the use of thyroglobulin as a biomarker for iodine status in adults. Clin. Endocrinol. 85 (3), 344–346. https://doi.org/10.1111/cen.13109.
Modoni, Sergio, Landriscina, Matteo, Fabiano, Annarita, Fersini, Alberto, Urbano, Nicoletta, Ambrosi, Antonio, Cignarelli, Mauro, 2007. Reinduction of cell differentiation and 131I uptake in a poorly differentiated thyroid tumor in response to the reverse transcriptase (RT) inhibitor nevirapine. Cancer Biother. Radiopharm. 22 (2), 289–295. https://doi.org/10.1089/cbr.2006.316.
Moon, Shinje, Song, Young Shin, Kim, Ye. An, Lim, Jung Ah, Cho, Sun Wook, Moon, Jae Hoon, Hahn, Seokyung, Park, Do. Joon, Joo Park, Young, 2017. Effects of coexistent BRAFV600E and TERT promoter mutations on poor clinical outcomes in papillary thyroid cancer: a meta-analysis. Thyroid.: Off. J. Am. Thyroid. Assoc. 27 (5), 651–660. https://doi.org/10.1089/thy.2016.0350.
Narumi, Satoshi, Nagasaki, Keisuke, Ishii, Tomohiro, Muroya, Koji, Asakura, Yumi, Adachi, Masanori, Hasegawa, Tomonobu, 2011. Nonclassic TSH resistance: TSHR mutation carriers with discrepantly high thyroidal iodine uptake. J. Clin. Endocrinol. Metab. 96 (8), E1340–E1345 https://doi.org/2016092613080000808.
Nieminen, Taina T., Christopher, J.Walker, Olkinuora, Alisa, Genutis, Luke K., O'Malley, Margaret, Wakely, Paul E., LaGuardia, Lisa, et al., 2020. Thyroid carcinomas that occur in familial adenomatous polyposis patients recurrently harbor somatic variants in APC, BRAF, and KTM2D. Thyroid.: Off. J. Am. Thyroid. Assoc. 30 (3), 380–388. https://doi.org/10.1089/thy.2019.0561.
Nilubol, Naris, Merkel, Roxanne, Yang, Lily, Patel, Dhaval, Reynolds, James C., Sadowski, Samira M., Neychev, Vladimir, Kebebew, Electron, 2017. A phase II trial of valproic acid in patients with advanced, radioiodine-resistant thyroid cancers of follicular cell origin. Clin. Endocrinol. 86 (1), 128–133. https://doi.org/10.1111/cen.13154.
Niri, Tetsuro, Horie, Ichiro, Ando, Takao, Kawahara, Hiromi, Ueda, Mayu, Eto, Mami, Sako, Ayaka, et al., 2020. Renal function and plasma renin activity as potential factors causing hyperkalemia in patients with thyroid carcinoma undergoing thyroid hormone withdrawal for radioactive iodine therapy. Endocr. Pract.: Off. J. Am. Coll. Endocrinol. Am. Assoc. Clin. Endocrinol. 26 (2), 197–206. https://doi.org/10.4158/EP-2019-0374.
Oh, Ji. Min, Ahn, Byeong-Cheol, 2021. Molecular mechanisms of radioactive iodine refractoriness in differentiated thyroid cancer: impaired sodium iodide symporter (NIS) expression owing to altered signaling pathway activity and intracellular localization of NIS'. Theranostics 11 (13), 6251–6277. https://doi.org/10.7150/thno.57689.
Ohno, M., Zannini, M., Levy, O., Carrasco, N., di Lauro, R., 1999. The paired-domain transcription factor Pax8 binds to the upstream enhancer of the rat sodium/iodide symporter gene and participates in both thyroid-specific and cyclic-AMP-dependent transcription. Mol. Cell. Biol. 19 (3), 2051–2060. https://doi.org/10.1128/MCB.19.3.2051.
Ott, D.B., Lachance, P.A., 1979. Retinoic acid–a review. Am. J. Clin. Nutr. 32 (12), 2522–2531. https://doi.org/10.1093/ajcn/32.12.2522.
Pacini, F., Molinaro, E., Castagna, M.G., Agate, L., Elisei, R., Ceccarelli, C., Lippi, F., Taddei, D., Grasso, L., Pinchera, A., 2003. Recombinant human thyrotropin-stimulated serum thyroglobulin combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma. J. Clin. Endocrinol. Metab. 88 (8), 3668–3673 https://doi.org/2016092613291900485.
Pak, Kyoungjune, Shin, Seunghyeon, Kim, Seong-Jang, Kim, In-Joo, Chang, Samuel, Koo, Phillip, Kwak, Jennifer, Kim, Jae-Ho, 2018. Response of retinoic acid in patients with radioactive iodine-refractory thyroid cancer: a meta-analysis. Oncol. Res. Treat. 41 (3), 100–104. https://doi.org/10.1159/000484206.
Parihar, Ashwin Singh, Sood, Ashwani, Kumar, Rajender, Bhusari, Priya, Shukla, Jaya, Mittal, Bhagwant Rai, 2018. Novel use of 177Lu-DOTA-RGD2 in treatment of 68Ga-DOTA-RGD2-avid lesions in papillary thyroid cancer with TENIS'. Eur. J. Nucl. Med. Mol. Imaging 45 (10), 1836–1837. https://doi.org/10.1007/s00259-018-4036-x.
Park, Jin-Woo, Zarnegar, Rasa, Kanauchi, Hajime, Wong, Mariwil G., Hyun, William C., Ginzinger, David G., Lobo, Margaret, Cotter, Philip, Duh, Quan-Yang, Clark, Orlo H., 2005. Troglitazone, the peroxisome proliferator-activated receptor-gamma agonist, induces antiproliferation and redifferentiation in human thyroid cancer cell lines. Thyroid.: Off. J. Am. Thyroid. Assoc. 15 (3), 222–231. https://doi.org/10.1089/thy.2005.15.222.
Parker, L.N., Wu, S.Y., Kim, D.D., Kollin, J., Prasasvinichai, S., 1986. Recurrence of papillary thyroid carcinoma presenting as a focal neurologic deficit. Arch. Intern. Med. 146 (10), 1985–1987.
Pasca di Magliano, M., Di Lauro, R., Zannini, M., 2000. 'Pax8 has a key role in thyroid cell differentiation. Proc. Natl. Acad. Sci. USA 97 (24), 13144–13149. https://doi.org/10.1073/pnas.240336397.
Pellegriti, Gabriella, Vathaire, Florent De, Scollo, Claudia, Attard, Marco, Giordano, Carla, Arena, Salvatore, Dardanoni, Gabriella, et al., 2009. Papillary thyroid cancer incidence in the volcanic area of sicily. J. Natl. Cancer Inst. 101 (22), 1575–1583. https://doi.org/10.1093/jnci/djp354.
Persani, Luca, Calebiro, Davide, Cordella, Daniela, Weber, Giovanna, Gelmini, Giulia, Libri, Domenico, de Filippis, Tiziana, Bonomi, Marco, 2010. Genetics and phenomics of hypothyroidism due to TSH resistance. Mol. Cell. Endocrinol. 322 (1–2), 72–82. https://doi.org/10.1016/j.mce.2010.01.008.
Peyrottes, Isabelle, Navarro, Valerie, Ondo-Mendez, Alejandro, Marcellin, Didier, Bellanger, Laurent, Marsault, Robert, Lindenthal, Sabine, Ettore, Francette, Darcourt, Jacques, Pourcher, Thierry, 2009. Immunoanalysis indicates that the sodium iodide symporter is not overexpressed in intracellular compartments in thyroid and breast cancers. Eur. J. Endocrinol. 160 (2), 215–225. https://doi.org/10.1530/EJE-08-0505.
Philips, Jean-Christophe, Petite, Christophe, Willi, Jean-Pierre, Buchegger, Franz, Meier, Christoph A., 2004. Effect of peroxisome proliferator-activated receptor γ agonist, rosiglitazone, on dedifferentiated thyroid cancers. Nucl. Med. Commun. 25 (12), 1183–1186. https://doi.org/10.1097/00006231-200412000-00005.
Phillips, William T., Bao, Ande, Brenner, Andrew J., Goins, Beth A., 2014. Image-guided interventional therapy for cancer with radiotherapeutic nanoparticles. Adv. Drug Deliv. Rev. 76 (September), 39–59. https://doi.org/10.1016/j.addr.2014.07.001.
Pitoia, Fabián, Jerkovich, Fernando, Trimboli, Pierpaolo, Smulever, Anabella, 2022. New approaches for patients with advanced radioiodine-refractory thyroid cancer. World J. Clin. Oncol. 13 (1), 9–27. https://doi.org/10.5306/wjco.v13.i1.9.
Pu, Weilin, Shi, Xiao, Yu, Pengcheng, Zhang, Meiying, Liu, Zhiyan, Tan, Licheng, Han, Peizhen, et al., 2021. Single-cell transcriptomic analysis of the tumor ecosystems underlying initiation and progression of papillary thyroid carcinoma. Nat. Commun. 12 (October), 6058. https://doi.org/10.1038/s41467-021-26343-3.
Pulciani, S., Santos, E., Lauver, A.V., Long, L.K., Aaronson, S.A., Barbacid, M., 1982. Oncogenes in solid human tumours. Nature 300 (5892), 539–542. https://doi.org/10.1038/300539a0.
Rahib, Lola, Smith, Benjamin D., Aizenberg, Rhonda, Rosenzweig, Allison B., Fleshman, Julie M., Matrisian, Lynn M., 2014. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 74 (11), 2913–2921. https://doi.org/10.1158/0008-5472.CAN-14-0155.
Rajendran, Ramya Lakshmi, Paudel, Sanjita, Gangadaran, Prakash, Min Oh, Ji, Oh, Eun Jung, Hong, Chae Moon, Lee, Sangkyu, Chung, Ho. Yun, Lee, Jaetae, Ahn, Byeong-Cheol, 2021. Extracellular vesicles act as nano-transporters of tyrosine kinase inhibitors to revert iodine avidity in thyroid cancer. Pharmaceutics 13 (2), 248. https://doi.org/10.3390/pharmaceutics13020248.
Ravaud, Alain, Fouchardière, Christelle de la, Caron, Philippe, Doussau, Adelaïde, Cao, Christine Do, Asselineau, Julien, Rodien, Patrice, et al., 2017. A multicenter phase II study of sunitinib in patients with locally advanced or metastatic differentiated, anaplastic or medullary thyroid carcinomas: mature data from the THYSU study. Eur. J. Cancer 76 (May), 110–117. https://doi.org/10.1016/j.ejca.2017.01.029.
Ravera, Silvia, Reyna-Neyra, Andrea, Ferrandino, Giuseppe, Mario Amzel, L., Nancy, Carrasco., 2017. The Sodium/Iodide Symporter (NIS): Molecular Physiology and Preclinical and Clinical Applications. Annual Review of Physiology 79 (February):, 261–289. https://doi.org/10.1146/annurev-physiol-022516-034125.
Read, Martin L., Lewy, Greg D., Fong, Jim C.W., Sharma, Neil, Seed, Robert I., Smith, Vicki E., Gentilin, Erica, et al., 2011. Proto-oncogene PBF/PTTG1IP regulates thyroid cell growth and represses radioiodide treatment. Cancer Res. 71 (19), 6153–6164. https://doi.org/10.1158/0008-5472.CAN-11-0720.
Read, Martin L., Brookes, Katie, Thornton, Caitlin E.M., Fletcher, Alice, Nieto, Hannah R., Alshahrani, Mohammed, Khan, Rashida, et al., 2022. Targeting non-canonical pathways as a strategy to modulate the sodium iodide symporter. e7 Cell Chem. Biol. 29 (3), 502–516. https://doi.org/10.1016/j.chembiol.2021.07.016.
Reed, Michelle A.C., Ludwig, Christian, Bunce, Christopher M., Khanim, Farhat L., Günther, Ulrich L., 2016. Malonate as a ROS product is associated with pyruvate carboxylase activity in acute myeloid leukaemia cells. Cancer Metab. 4, 15. https://doi.org/10.1186/s40170-016-0155-7.
Riesco-Eizaguirre, G., Gutiérrez-Martínez, P., García-Cabezas, M.A., Nistal, M., Santisteban, P., 2006. The oncogene BRAF V600E is associated with a high risk of recurrence and less differentiated papillary thyroid carcinoma due to the impairment of Na+/I- targeting to the membrane. Endocr. -Relat. Cancer 13 (1), 257–269. https://doi.org/10.1677/erc.1.01119.
Riesco-Eizaguirre, Garcilaso, Wert-Lamas, León, Perales-Patón, Javier, Sastre-Perona, Ana, Fernández, Lara P., Santisteban, Pilar, 2015. The MiR-146b-3p/PAX8/NIS regulatory circuit modulates the differentiation phenotype and function of thyroid cells during carcinogenesis. Cancer Res. 75 (19), 4119–4130. https://doi.org/10.1158/0008-5472.CAN-14-3547.
Roll, Wolfgang, Riemann, Burkhard, Schäfers, Michael, Stegger, Lars, Vrachimis, Alexis, 2018. 177Lu-DOTATATE therapy in radioiodine-refractory differentiated thyroid cancer: a single center experience. Clin. Nucl. Med. 43 (10), e346–e351. https://doi.org/10.1097/RLU.0000000000002219.

Romei, Cristina, Ciampi, Raffaele, Elisei, Rossella, 2016. A comprehensive overview of the role of the RET proto-oncogene in thyroid carcinoma. Nat. Rev. Endocrinol. 12 (4), 192–202. https://doi.org/10.1038/nrendo.2016.11.

Rosenbaum-Krumme, S.J., Bockisch, A., Nagarajah, J., 2012. Pioglitazone therapy in progressive differentiated thyroid carcinoma. Nukl. Nucl. Med. 51 (4), 111–115. https://doi.org/10.3413/Nukmed-0474-12-01.

Rothenberg, Michael, S., McFadden, David G., Palmer, Edwin L., Daniels, Gilbert H., Wirth, Lori J., 2015. Redifferentiation of iodine-refractory BRAF V600E-mutant metastatic papillary thyroid cancer with dabrafenib. Clin. Cancer Res.: Off. J. Am. Assoc. Cancer Res. 21 (5), 1028–1035. https://doi.org/10.1158/1078-0432.CCR-14-2915.

Rowe, Christopher W., Paul, Jonathan W., Gedye, Craig, Tolosa, Jorge M., Bendinelli, Cino, McGrath, Shaun, Smith, Roger, 2017. Targeting the TSH receptor in thyroid cancer. Endocr. -Relat. Cancer 24 (6), R191–R202. https://doi.org/10.1530/ERC-17-0010.

Saha, Priyanka, Datta, Suchisnigdha, Ghosh, Sukanya, Samanta, Anurima, Ghosh, Paramita, Sinha, Dona, 2021. Bioengineering of extracellular vesicles: exosome-based next-generation therapeutic strategy in cancer. Bioengineering 8 (10), 139. https://doi.org/10.3390/bioengineering8100139.

Santhanam, Prasanna, Taieb, David, Solnes, Lilja, Marashdeh, Wael, Ladenson, Paul W., 2017. Utility of I-124 PET/CT in identifying radioiodine avid lesions in differentiated thyroid cancer: a systematic review and meta-analysis. Clin. Endocrinol. 86 (5), 645–651. https://doi.org/10.1111/cen.13306.

Santos, Maria C.S., Louzada, Ruy A.N., Souza, Elaine C.L., Fortunato, Rodrigo S., Vasconcelos, Andressa L., Souza, Kléber L.A., Castro, João P.S.W., Carvalho, Denise P., Ferreira, Andrea C.F., 2013. Diabetes mellitus increases reactive oxygen species production in the thyroid of male rats. Endocrinology 154 (3), 1361–1372 https://doi.org/2020071612082873800.

Sasaki, Maaya, Aoyama, Tsuyoshi, Sugawara, Mitsuru, Takekuma, Yoh, 2020. Influence of gastrointestinal activity on the absorption of nilotinib. Drug Metab. Pharmacokinet. 35 (1), 102–110. https://doi.org/10.1016/j.dmpk.2019.08.006.

Satapathy, Swayamjeet, Bal, Chandrasekhar, 2022. Theranostic options for radioiodine-refractory differentiated thyroid carcinoma: recent advances, challenges, and road ahead. Front. Endocrinol. 13 (July), 924841 https://doi.org/10.3389/fendo.2022.924841.

Schlumberger, Martin, Brose, Marcia, Elisei, Rosella, Leboulleux, Sophie, Luster, Markus, Pitoia, Fabian, Pacini, Furio, 2014. Definition and management of radioactive iodine-refractory differentiated thyroid cancer. Lancet Diabetes Endocrinol. 2 (5), 356–358. https://doi.org/10.1016/S2213-8587(13)70215-8.

Schlumberger, Martin, Tahara, Makoto, Wirth, Lori J., Robinson, Bruce, Brose, Marcia S., Elisei, Rossella, Habra, Mouhammed Amir, et al., 2015. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. New Engl. J. Med. 372 (7), 621–630. https://doi.org/10.1056/NEJMoa1406470.

Schönberger, Johann, Rüschoff, J., Grimm, Daniela, Marienhagen, J.örg, Rümmele, Petra, Meyringer, Rotraud, Kossmehl, Peter, Hofstaedter, Ferdinand, Eilles, Christoph, 2002. Glucose transporter 1 gene expression is related to thyroid neoplasms with an unfavorable prognosis: an immunohistochemical study. Thyroid.: Off. J. Am. Thyroid. Assoc. 12 (9), 747–754. https://doi.org/10.1089/105072502760339307.

Schwertheim, Suzan, Wein, Frederik, Lennartz, Klaus, Worm, Karl, Schmid, Kurt Werner, Sheu-Grabellus, Sien-Yi, 2017. Curcumin induces G2/M arrest, apoptosis, NF-KB inhibition, and expression of differentiation genes in thyroid carcinoma cells. J. Cancer Res. Clin. Oncol. 143 (7), 1143–1154. https://doi.org/10.1007/s00432-017-2380-z.

Shang, Hongxia, Zhao, Junyu, Yao, Jinming, Wang, Huanjun, Dong, Jianjun, Liao, Lin, 2020. Nevirapine increases sodium/iodide symporter-mediated radioiodide uptake by activation of TSHR/CAMP/CREB/PAX8 signaling pathway in dedifferentiated thyroid cancer. Front. Oncol. 10 (March), 404. https://doi.org/10.3389/fonc.2020.00404.

Sherman, Eric J., Dunn, Lara, Ho, Alan L., Baxi, Shrujal, Ghossein, Ronald A., Fury, Matthew G., Haque, Sofia, et al., 2017. Phase II study evaluating the combination of sorafenib and temsirolimus in the treatment of radioactive iodine-refractory thyroid cancer. Cancer 123 (21), 4114–4121. https://doi.org/10.1002/cncr.30861.

Sherman, Steven I., Wirth, Lori J., Droz, Jean-Pierre, Hofmann, Michael, Bastholt, Lars, Martins, Renato G., Licitra, Lisa, et al., 2008. Motesanib diphosphate in progressive differentiated thyroid cancer. New Engl. J. Med. 359 (1), 31–42. https://doi.org/10.1056/NEJMoa075853.

Shi, Liang, You, Qinqin, Wang, Jun, Wang, Hanjin, Li, Shaohua, Tian, Rui, Yao, Xiaocheng, et al., 2022. Antitumour effects of apatinib in progressive, metastatic differentiated thyroid cancer (DTC. Endocrine 78 (1), 68–76. https://doi.org/10.1007/s12020-022-03113-9.

Shi, Zhi-Yong, Zhang, Sheng-Xiao, Li, Cai-Hong, Fan, Di, Xue, Yan, Cheng, Zhe-Hao, Wu, Li-Xiang, et al., 2022. Differential distribution and prognostic value of CD4+ T cell subsets before and after radioactive iodine therapy in differentiated thyroid cancer with varied curative outcomes. Front. Immunol. 13, 966550 https://doi.org/10.3389/fimmu.2022.966550.

Silaghi, Horatiu, Lozovanu, Vera, Georgescu, Carmen Emanuela, Pop, Cristina, Nasui, Bogdana Adriana, Cătoi, Adriana Florinela, Silaghi, Cristina Alina, 2022. State of the art in the current management and future directions of targeted therapy for differentiated thyroid cancer. Int. J. Mol. Sci. 23 (7), 3470. https://doi.org/10.3390/ijms23073470.

Simon, D., Koehrle, J., Reiners, C., Boerner, A.R., Schmutzler, C., Mainz, K., Goretzki, P. E., Roeher, H.D., 1998. Redifferentiation therapy with retinoids: therapeutic option for advanced follicular and papillary thyroid carcinoma. World J. Surg. 22 (6), 569–574. https://doi.org/10.1007/s002689900436.

Smith, V.E., Sharma, N., Watkins, R.J., Read, M.L., Ryan, G.A., Kwan, P.P., Martin, A., et al., 2013. Manipulation of PBF/PTTG1IP phosphorylation status; a potential new therapeutic strategy for improving radioiodine uptake in thyroid and other tumors. J. Clin. Endocrinol. Metab. 98 (7), 2876–2886 https://doi.org/2019041113251863500.

Son, Seung Hyun, Gangadaran, Prakash, Ahn, Byeong-Cheol, 2019. A novel strategy of transferring NIS protein to cells using extracellular vesicles leads to increase in iodine uptake and cytotoxicity. Int. J. Nanomed. 14, 1779–1787. https://doi.org/10.2147/IJN.S189738.

Sparano, Clotilde, Moog, Sophie, Hadoux, Julien, Dupuy, Corinne, Ghuzlan, Abir Al, Breuskin, Ingrid, Guerlain, Joanne, Hartl, Dana, Baudin, Eric, Lamartina, Livia, 2022. Strategies for radioiodine treatment: what's new. Cancers 14 (15), 3800. https://doi.org/10.3390/cancers14153800.

Spitzweg, Christine, Morris, John C., 2002. The sodium iodide symporter: its pathophysiological and therapeutic implications. Clin. Endocrinol. 57 (5), 559–574. https://doi.org/10.1046/j.1365-2265.2002.01640.x.

Steenbeek, Sander C., Pham, Thang V., de Ligt, Joep, Zomer, Anoek, Knol, Jaco C., Piersma, Sander R., Schelfhorst, Tim, et al., 2018. Cancer cells copy migratory behavior and exchange signaling networks via extracellular vesicles. EMBO J. 37 (15), e98357 https://doi.org/10.15252/embj.201798357.

Stephenson, Alexandra, Lau, Lorraine, Eszlinger, Markus, Paschke, Ralf, 2020. The thyrotropin receptor mutation database update. Thyroid.: Off. J. Am. Thyroid. Assoc. 30 (6), 931–935. https://doi.org/10.1089/thy.2019.0807.

Strickaert, Aurélie, Corbet, Cyril, Spinette, Selim-Alex, Craciun, Ligia, Dom, Geneviève, Andry, Guy, Larsimont, Denis, et al., 2019. Reprogramming of energy metabolism: increased expression and roles of pyruvate carboxylase in papillary thyroid cancer. Thyroid.: Off. J. Am. Thyroid. Assoc. 29 (6), 845–857. https://doi.org/10.1089/thy.2018.0435.

Subbiah, V., Shen, T., Terzyan, S.S., Liu, X., Hu, X., Patel, K.P., Hu, M., et al., 2021. Structural basis of acquired resistance to selpercatinib and pralsetinib mediated by non-gatekeeper RET mutations. Ann. Oncol.: Off. J. Eur. Soc. Med. Oncol. 32 (2), 261–268. https://doi.org/10.1016/j.annonc.2020.10.599.

Subbiah, Vivek, Hu, Mimi I., Wirth, Lori J., Schuler, Martin, Mansfield, Aaron S., Curigliano, Giuseppe, Brose, Marcia S., et al., 2021. Pralsetinib for patients with advanced or metastatic RET-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, phase 1/2 study. Lancet Diabetes Endocrinol. 9 (8), 491–501. https://doi.org/10.1016/S2213-8587(21)00120-0.

Sui, Xinbing, Kong, Na, Ye, Li, Han, Weidong, Zhou, Jichun, Zhang, Qin, He, Chao, Pan, Hongming, 2014. P38 and JNK MAPK pathways control the balance of apoptosis and autophagy in response to chemotherapeutic agents. Cancer Lett. 344 (2), 174–179. https://doi.org/10.1016/j.canlet.2013.11.019.

Tahara, Makoto, Kiyota, Naomi, Hoff, Ana O., Badiu, Corin, Owonikoko, Taofeek K., Dutcus, Corina E., Suzuki, Takuya, Ren, Min, Wirth, Lori J., 2021. Impact of lung metastases on overall survival in the phase 3 select study of lenvatinib in patients with radioiodine-refractory differentiated thyroid cancer. Eur. J. Cancer 147 (April), 51–57. https://doi.org/10.1016/j.ejca.2020.12.032.

Taki, Katsumi, Kogai, Takahiko, Kanamoto, Yoko, Hershman, Jerome M., Brent, Gregory A., 2002. A thyroid-specific far-upstream enhancer in the human sodium/iodide symporter gene requires pax-8 binding and cyclic adenosine 3′,5′-monophosphate response element-like sequence binding proteins for full activity and is differentially regulated in normal and thyroid cancer cells. Mol. Endocrinol. 16 (10), 2266–2282 https://doi.org/2019041122505432600.

Tavares, Catarina, Coelho, Maria João, Eloy, Catarina, Melo, Miguel, Rocha, Adriana Gaspar da, Pestana, Ana, Batista, Rui, et al., 2018. NIS Expression in thyroid tumors, relation with prognosis clinicopathological and molecular features. Endocr. Connect. 7 (1), 78–90. https://doi.org/10.1530/EC-17-0302.

Tchekmedyian, Vatche, Dunn, Lara, Sherman, Eric, Baxi, Shrujal S., Grewal, Ravinder K., Larson, Steven M., Pentlow, Keith S., et al., 2022. Enhancing radioiodine incorporation in BRAF-mutant, radioiodine-refractory thyroid cancers with vemurafenib and the Anti-ErbB3 monoclonal antibody CDX-3379: results of a pilot clinical trial. Thyroid.: Off. J. Am. Thyroid. Assoc. 32 (3), 273–282. https://doi.org/10.1089/thy.2021.0565.

Tesselaar, Marika H., Crezee, Thomas, Swarts, Herman G., Gerrits, Danny, Boerman, Otto C., Koenderink, Jan B., Stunnenberg, Hendrik G., et al., 2017. Digitalis-like compounds facilitate non-medullary thyroid cancer redifferentiation through intracellular Ca2+, FOS, and autophagy-dependent pathways. Mol. Cancer Ther. 16 (1), 169–181. https://doi.org/10.1158/1535-7163.MCT-16-0460.

Tian, Longlong, Chen, Qian, Yi, Xuan, Chen, Jiawen, Liang, Chao, Chao, Yu, Yang, Kai, Liu, Zhuang, 2017. Albumin-templated manganese dioxide nanoparticles for enhanced radioisotope therapy. Small 13 (25), 1700640. https://doi.org/10.1002/smll.201700640.

Trovisco, V.ítor, Castro, Inês Vieira de, Soares, Paula, Máximo, Valdemar, Silva, Paula, Magalhães, João, Abrosimov, Alexander, Guiu, Xavier Matias, Sobrinho-Simões, Manuel, 2004. BRAF mutations are associated with some histological types of papillary thyroid carcinoma. J. Pathol. 202 (2), 247–251. https://doi.org/10.1002/path.1511.

Vaishnavi, Aria, Le, Anh T., Doebele, Robert C., 2015. TRKing down an old oncogene in a new era of targeted therapy. Cancer Discov. 5 (1), 25–34. https://doi.org/10.1158/2159-8290.CD-14-0765.

Verburg, Frederik A., Amthauer, Holger, Binse, Ina, Brink, Ingo, Buck, Andreas, Darr, Andreas, Dierks, Christine, et al., 2021. Questions and controversies in the clinical application of tyrosine kinase inhibitors to treat patients with radioiodine-refractory differentiated thyroid carcinoma: expert perspectives. Horm. Metab. Res. = Horm. - Und Stoffwechs. = Horm. Et. Metab. 53 (3), 149–160. https://doi.org/10.1055/a-1380-4154.

Waguespack, Steven G., Drilon, Alexander, Lin, Jessica J., Brose, Marcia S., McDermott, Ray, Almubarak, Mohammed, Bauman, Jessica, et al., 2022. Efficacy and safety of larotrectinib in patients with TRK fusion-positive thyroid carcinoma. Eur. J. Endocrinol. 186 (6), 631–643. https://doi.org/10.1530/EJE-21-1259.

Wang, Cong, Wang, Zhenglin, Liu, Wei, Ai, Zhilong, 2019. ROS-generating oxidase NOX1 promotes the self-renewal activity of CD133+ thyroid cancer cells through activation of the Akt signaling. Cancer Lett. 447 (April), 154–163. https://doi.org/10.1016/j.canlet.2019.01.028.

Wang, Weibin, Kang, Helen, Zhao, Yinu, Min, Irene, Wyrwas, Brian, Moore, Maureen, Teng, Lisong, Zarnegar, Rasa, Jiang, Xuejun, Fahey, Thomas J., 2016. Targeting autophagy sensitizes BRAF-mutant thyroid cancer to vemurafenib. J. Clin. Endocrinol. Metab. 102 (2), 634–643 https://doi.org/2019041117343321400.

Watabe, Tadashi, Hosono, Makoto, Kinuya, Seigo, Yamada, Takahiro, Yanagida, Sachiko, Namba, Masao, Nakamura, Yoshihide, 2021. Manual on the proper use of sodium astatide ([211At]NaAt) injections in clinical trials for targeted alpha therapy (1st Edition). Ann. Nucl. Med. 35 (7), 753–766. https://doi.org/10.1007/s12149-021-01619-2.

Watabe, Tadashi, Kaneda-Nakashima, Kazuko, Ooe, Kazuhiro, Liu, Yuwei, Kurimoto, Kenta, Murai, Takashi, Shidahara, Yuka, et al., 2021. Extended single-dose toxicity study of [211At]NaAt in mice for the first-in-human clinical trial of targeted alpha therapy for differentiated thyroid cancer. Ann. Nucl. Med. 35 (6), 702–718. https://doi.org/10.1007/s12149-021-01612-9.

Watabe, Tadashi, Liu, Yuwei, Kaneda-Nakashima, Kazuko, Sato, Tatsuhiko, Shirakami, Yoshifumi, Ooe, Kazuhiro, Toyoshima, Atsushi, et al., 2022. Comparison of the therapeutic effects of [211At]NaAt and [131I]NaI in an NIS-expressing thyroid cancer mouse model. Int. J. Mol. Sci. 23 (16), 9434. https://doi.org/10.3390/ijms23169434.

Watabe, Tadashi, Kaneda-Nakashima, Kazuko, Liu, Yuwei, Shirakami, Yoshifumi, Ooe, Kazuhiro, Toyoshima, Atsushi, Shimosegawa, Eku, Fukuda, Mitsuhiro, Shinohara, Atsushi, Hatazawa, Jun, 2019. Enhancement of 211At uptake via the sodium iodide symporter by the addition of ascorbic acid in targeted α-therapy of thyroid cancer. J. Nucl. Med. 60 (9), 1301–1307. https://doi.org/10.2967/jnumed.118.222638.

Wen, Qiuting, Wang, Yulou, Li, Xingjiang, Jin, Xiangguo, Wang, Guimei, 2021. Decreased serum exosomal MiR-29a expression and its clinical significance in papillary thyroid carcinoma. J. Clin. Lab. Anal. 35 (1), e23560 https://doi.org/10.1002/jcla.23560.

Whiteside, Theresa L., 2017. Extracellular vesicles isolation and their biomarker potential: are we ready for testing. Ann. Transl. Med. 5 (3), 54. https://doi.org/10.21037/atm.2017.01.62.

Wirth, Lori J., Sherman, Eric, Robinson, Bruce, Solomon, Benjamin, Kang, Hyunseok, Lorch, Jochen, Worden, Francis, et al., 2020. Efficacy of selpercatinib in RET-altered thyroid cancers. New Engl. J. Med. 383 (9), 825–835. https://doi.org/10.1056/NEJMoa2005651.

Xing, Mingzhao, 2013. Molecular pathogenesis and mechanisms of thyroid cancer. Nat. Rev. Cancer 13 (3), 184–199. https://doi.org/10.1038/nrc3431.

Xing, Mingzhao, Westra, William H., Tufano, Ralph P., Cohen, Yoram, Rosenbaum, Eli, Rhoden, Kerry J., Carson, Kathryn A., et al., 2005. BRAF mutation predicts a poorer clinical prognosis for papillary thyroid cancer. J. Clin. Endocrinol. Metab. 90 (12), 6373–6379 https://doi.org/2020071618330371800.

Xing, Mingzhao, Alzahrani, Ali S., Carson, Kathryn A., Shong, Young Kee, Kim, Tae Yong, Viola, David, Elisei, Rossella, et al., 2015. Association between BRAF V600E mutation and recurrence of papillary thyroid cancer. J. Clin. Oncol.: Off. J. Am. Soc. Clin. Oncol. 33 (1), 42–50. https://doi.org/10.1200/JCO.2014.56.8253.

Xu, Shichen, Cheng, Xian, Wu, Jing, Wang, Yunping, Wang, Xiaowen, Wu, Liying, Yu, Huixin, Bao, Jiandong, Zhang, Li, 2021. Capsaicin restores sodium iodine symporter-mediated radioiodine uptake through bypassing canonical TSH-TSHR pathway in anaplastic thyroid carcinoma cells. J. Mol. Cell Biol. 13 (11), 791–807. https://doi.org/10.1093/jmcb/mjab072.

Yakes, F. Michael, Jason Chen, Jenny Tan, Kyoko Yamaguchi, Yongchang Shi, Peiwen Yu, Fawn Qian, et al. 2011. 'Cabozantinib (XL184), a Novel MET and VEGFR2 Inhibitor, Simultaneously Suppresses Metastasis, Angiogenesis, and Tumor Growth'. *Molecular Cancer Therapeutics* 10 (12): 2298–2308. https://doi.org/10.1158/1535-7163.MCT-11-0264.

Yang, Guangbao, Xu, Ligeng, Chao, Yu, Xu, Jun, Sun, Xiaoqi, Wu, Yifan, Peng, Rui, Liu, Zhuang, 2017. Hollow MnO2 as a tumor-microenvironment-responsive biodegradable nano-platform for combination therapy favoring antitumor immune responses. Nat. Commun. 8 (1), 902. https://doi.org/10.1038/s41467-017-01050-0.

Yang, Xue, Li, Jiao, Li, Xiaoyi, Liang, Zhiyong, Gao, Wen, Liang, Jun, Cheng, Shujun, Lin, Yansong, 2017. TERT promoter mutation predicts radioiodine-refractory character in distant metastatic differentiated thyroid cancer. J. Nucl. Med.: Off. Publ. Soc. Nucl. Med. 58 (2), 258–265. https://doi.org/10.2967/jnumed.116.180240.

Yarchoan, Mark, Ma, Changqing, Troxel, Andrea B., Stopenski, Stephen J., Tang, Waixing, Cohen, Aaron B., Pappas-Paxinos, Marina, et al., 2016. PAKT expression and response to sorafenib in differentiated thyroid cancer. Horm. Cancer 7 (3), 188–195. https://doi.org/10.1007/s12672-016-0253-6.

Yavuz, Sahzene, and Yana Puckett. 2022. 'Iodine-131 Uptake Study'. In StatPearls. Treasure Island (FL): StatPearls Publishing. ⟨http://www.ncbi.nlm.nih.gov/books/NBK559283/⟩.

Yu, Huimin, Zhang, Hongtao, Gao, Zhen, Liu, Xiaoli, Zhang, Lijuan, Di, Xuemin, Wang, Zeyang, et al., 2022. 125I seed brachytherapy for refractory loco-regional recurrence of non-anaplastic thyroid cancer. Front. Oncol. 12, 773708 https://doi.org/10.3389/fonc.2022.773708.

Yu, Xuefei, Zhu, Xuhang, Zhang, Lizhuo, Qin, Jiang-Jiang, Feng, Chunlai, Li, Qinglin, 2022. In silico screening and validation of PDGFRA inhibitors enhancing radioiodine sensitivity in thyroid cancer. Front. Pharmacol. 13, 883581 https://doi.org/10.3389/fphar.2022.883581.

Zhang, Jing, Zhao, Aomei, Jia, Xi, Li, Xinru, Liang, Yiqian, Liu, Yan, Xie, Xin, et al., 2022. Sinomenine hydrochloride promotes TSHR-dependent redifferentiation in papillary thyroid cancer. Int. J. Mol. Sci. 23 (18), 10709. https://doi.org/10.3390/ijms231810709.

Zhang, Li, Xu, Shichen, Cheng, Xian, Wu, Jing, Wang, Xiaowen, Wu, Liying, Yu, Huixin, Bao, Jiandong, 2021. Curcumin enhances the membrane trafficking of the sodium iodide symporter and augments radioiodine uptake in dedifferentiated thyroid cancer cells via suppression of the PI3K-AKT signaling pathway. Food Funct. 12 (18), 8260–8273. https://doi.org/10.1039/d1fo01073e.

Zhang, Yifan, Jia, Shiquan, Liu, Yong, Li, Biao, Wang, Zhaohui, Lu, Hui, Zhu, Chengmo, 2007. A clinical study of all-trans-retinoid-induced differentiation therapy of advanced thyroid cancer. Nucl. Med. Commun. 28 (4), 251–255. https://doi.org/10.1097/MNM.0b013e3280708ebf.

Zhang, Zongjing, Liu, Dingxie, Murugan, Avaniyapuram Kannan, Liu, Zhimin, Xing, Mingzhao, 2014. Histone deacetylation of NIS promoter underlies BRAF V600E-promoted NIS silencing in thyroid cancer. Endocr. -Relat. Cancer 21 (2), 161–173. https://doi.org/10.1530/ERC-13-0399.

Zhao, Zheng, Fu, Tao, Gao, Jiyue, Xu, Yang, Wu, Xue, Chen, Wenjuan, Li, Xuesong, et al., 2020. Identifying novel oncogenic RET mutations and characterising their sensitivity to RET-specific inhibitors. *J. Med. Genet.*, April, jmedgenet- 2019–106546. https://doi.org/10.1136/jmedgenet-2019-106546.

Zhu, Lihong, Jiang, Yuliang, Wang, Junjie, Ran, Weiqiang, Yuan, Huishu, Liu, Chen, Qu, Ang, Yang, Ruijie, 2013. An Investigation of 125I seed permanent implantation for recurrent carcinoma in the head and neck after surgery and external beam radiotherapy. World J. Surg. Oncol. 11 (March), 60. https://doi.org/10.1186/1477-7819-11-60.