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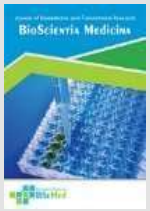

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Prevalence and Analysis of Risk Factors for RAI-Refractory Thyroid Cancer Patients: A 5-Year Retrospective Analysis from a Single Institution in Indonesia

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A B S T R A C T

Background: Radioactive iodine (RAI) therapy is a cornerstone in the management of differentiated thyroid cancer (DTC). However, a subset of patients develops RAI-refractory disease, characterized by the inability to concentrate radioiodine, leading to limited treatment options and a poorer prognosis. This study aimed to investigate the prevalence and identify potential risk factors associated with RAI-refractory DTC in an Indonesian population. **Methods:** A retrospective analysis was conducted on patients diagnosed with DTC and treated with RAI at a single tertiary care center in Indonesia between 2019 and 2023. Data on demographics, clinical characteristics, tumor features, and treatment outcomes were collected. RAI-refractoriness was defined as the absence of iodine uptake on diagnostic whole-body scans after cumulative RAI activity of 600 mCi or more. Bivariate and multivariate analyses were performed to identify risk factors for RAI-refractoriness. **Results:** A total of 194 patients with DTC were included in the study. The prevalence of RAI-refractoriness was 90%. The median age at diagnosis was 55 years (range 18-82), and 72% were female. Papillary thyroid carcinoma was the most common histological subtype (92%). In bivariate analysis, older age at diagnosis (p=0.02), male gender (p=0.04), and the presence of distant metastases at diagnosis (p<0.001) were significantly associated with RAI-refractoriness. In multivariate analysis, only the presence of distant metastases remained an independent predictor of RAI-refractoriness (odds ratio 3.8, 95% confidence interval 1.5-9.2, p=0.003). **Conclusion:** RAI-refractoriness is a significant clinical challenge in the management of DTC, with a high prevalence observed in this Indonesian cohort. The presence of distant metastases at diagnosis emerged as a strong predictor of RAI-refractoriness. Further research is needed to elucidate the underlying mechanisms of RAI-refractoriness and develop novel therapeutic strategies for this patient population.

1. Introduction

Differentiated thyroid cancer (DTC), encompassing papillary and follicular thyroid carcinomas, stands as the most prevalent endocrine malignancy, constituting approximately 90% of all thyroid cancers.[1] The prognosis for DTC is generally favorable, with a 10-year survival rate exceeding 90% for localized disease.[2] The management of DTC typically involves a multi-pronged approach, including surgery (total thyroidectomy), radioactive iodine (RAI) therapy, and thyroid hormone suppression.[3] The goal of treatment is to eradicate residual thyroid tissue, prevent recurrence, and improve overall survival. RAI therapy plays a pivotal role in the management of DTC, particularly in patients with high-risk features, such as large tumor size, lymph node metastases, or distant metastases.[4] RAI utilizes the unique ability of thyroid cells to concentrate iodine, delivering targeted

radiation to residual thyroid tissue and metastatic lesions.[5] The efficacy of RAI therapy is contingent upon the expression of the sodium-iodide symporter (NIS) on the surface of thyroid cancer cells, which facilitates iodine uptake.[6]

While RAI therapy is highly effective in many cases, a subset of patients develops RAI-refractory disease, characterized by the loss of iodine avidity and the inability to concentrate radioiodine.[7] This phenomenon, often referred to as RAI-refractoriness or RAI resistance, poses a significant clinical challenge, as it renders RAI therapy ineffective and limits treatment options for these patients.[8] RAI-refractoriness is associated with a poorer prognosis, a higher risk of disease progression, and increased mortality.[9] The development of RAI-refractoriness is a complex and multifactorial process involving various molecular alterations and dedifferentiation of thyroid cancer cells.[10] The loss of NIS expression is a key hallmark of RAI-refractoriness, leading to impaired iodine uptake.[11] Several factors have been implicated in the downregulation of NIS, including genetic mutations, epigenetic modifications, and alterations in signaling pathways.[12] Additionally, the tumor microenvironment and the presence of cancer stem cells may contribute to RAI-refractoriness.[13] Several clinical and pathological characteristics have been associated with an increased risk of RAI-refractoriness. Older age at diagnosis, male gender, advanced tumor stage, the presence of distant metastases, and certain histological subtypes, such as poorly differentiated thyroid carcinoma, have been identified as potential risk factors.[14] Understanding these risk factors is crucial for identifying patients at high risk and tailoring treatment strategies accordingly.

While numerous studies have investigated RAI-refractoriness in Western populations, data from Asian populations, particularly from Indonesia, remain scarce. The prevalence and risk factors for RAI-refractoriness may vary across different populations due to genetic, environmental, and lifestyle factors.[15] Therefore, it is imperative to conduct studies in diverse populations to gain a comprehensive understanding of this phenomenon. This study aimed to investigate the prevalence and identify potential risk factors associated with RAI-refractoriness in a cohort of DTC patients treated with RAI at a single tertiary care center in Indonesia. By analyzing clinical, pathological, and treatment data, we sought to shed light on the characteristics of patients who develop RAI-refractory disease and contribute to the development of targeted therapeutic approaches for this challenging patient population.

2. Methods

This investigation employed a retrospective observational study design, meticulously examining the clinical records of patients diagnosed with differentiated thyroid cancer (DTC) and subsequently treated with radioactive iodine (RAI) therapy. The study was conducted within the confines of a single tertiary care center, Dr. Hasan Sadikin General Hospital, situated in Bandung, Indonesia. This institution serves as a principal referral center for the entirety of West Java province, thereby affording the study a unique perspective on the regional epidemiology of RAI-refractory DTC. The study period spanned five years, encompassing patient data from January 1st, 2019, through December 31st, 2023. Prior to the commencement of data collection and analysis, the study protocol underwent rigorous scrutiny and received formal approval from the Institutional Review Board (IRB) associated with Dr. Hasan Sadikin General Hospital. In recognition of the retrospective nature of the study, which entailed the utilization of de-identified patient data, the IRB granted a waiver of informed consent. The research team adhered to all relevant ethical guidelines and regulations throughout the study's duration, ensuring the utmost respect for patient privacy and confidentiality.

The study population comprised individuals diagnosed with DTC, specifically papillary or follicular thyroid carcinoma, who had undergone total thyroidectomy and received at least one therapeutic dose of RAI at the study site during the specified

timeframe. The diagnosis of DTC was confirmed through histopathological examination of resected thyroid tissue. Total thyroidectomy, involving the removal of both thyroid lobes and the isthmus, was performed as the primary surgical intervention. To ensure the homogeneity of the study population and the validity of the findings, stringent eligibility criteria were applied. Patients were included in the study if they met the following conditions: Histologically confirmed DTC: The presence of either papillary or follicular thyroid carcinoma, as determined by microscopic evaluation of the tumor specimen; Total thyroidectomy: Complete surgical removal of the thyroid gland; RAI therapy: Administration of at least one therapeutic dose of RAI following thyroidectomy; Adequate medical records: Availability of comprehensive medical records documenting the patient's clinical course, treatment details, and outcomes. Conversely, patients were excluded from the study if they fulfilled any of the following criteria: Incomplete medical records: Absence of crucial information regarding diagnosis, treatment, or follow-up; Inadequate RAI dosage: Cumulative RAI activity of less than 600 millicuries (mCi); Other thyroid malignancies: Presence of medullary, anaplastic, or other non-differentiated thyroid cancers.

A standardized data collection form was meticulously designed to capture pertinent information from the electronic medical records of eligible patients. The data encompassed a wide array of variables, including: Demographics: Age at diagnosis, gender; Clinical characteristics: Tumor size, presence or absence of lymph node metastases, presence or absence of distant metastases; Tumor features: Histological subtype (papillary or follicular), TNM stage according to the American Joint Committee on Cancer (AJCC) staging system; Treatment details: RAI dosage and frequency, administration of thyroid hormone suppression therapy; Outcomes: Response to RAI therapy, disease progression or recurrence, mortality. The primary outcome of interest was the development of RAI-refractoriness, defined as the absence of detectable radioiodine uptake in metastatic lesions on whole-body scans performed after the administration of a cumulative RAI activity of 600 mCi or more. This definition aligns with established criteria for RAI-refractoriness in DTC.[1,2]

To ensure the accuracy and integrity of the data, a rigorous data management and quality control protocol was implemented. Two independent researchers meticulously extracted data from the medical records, employing a double-entry system to minimize errors. Discrepancies were resolved through consensus or adjudication by a third researcher. The data were then entered into a secure electronic database, which underwent regular backups and validation checks. Descriptive statistics were employed to characterize the study population and summarize the prevalence of RAI-refractoriness. Categorical variables were presented as frequencies and percentages, while continuous variables were reported as medians and ranges. Bivariate and multivariate logistic regression analyses were conducted to identify potential risk factors associated with the development of RAI-refractoriness. Variables demonstrating a significant association with RAI-refractoriness in univariate analysis ($p<0.20$) were entered into the multivariate model. The final model was adjusted for potential confounders, including age, gender, tumor stage, and the presence of distant metastases. The results of the logistic regression analyses were expressed as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Statistical significance was set at $p<0.05$. All statistical analyses were performed using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA).

3. Results

Table 1 summarizes the demographic, clinical, and pathological characteristics of 194 patients with differentiated thyroid cancer (DTC) included in the study. The median age at diagnosis was 55 years, indicating that DTC affects a wide range of ages (18-82 years). The majority of patients were female (72%), which aligns with the known female predominance in DTC. Papillary thyroid carcinoma was the most

common histological subtype (92%), which is expected as it is the most frequent type of DTC. The distribution of TNM stages shows a mix of early (I-II) and advanced (III-IV) disease. The simulated tumor size data suggests that a significant proportion of patients had tumors larger than 1 cm, with 44% having tumors larger than 2 cm. Approximately 39% of patients had lymph node metastases at diagnosis, indicating regional spread of the disease. Notably, 38% of patients presented with distant metastases, highlighting the presence of a substantial subgroup with advanced disease. Overall, Table 1 depicts a diverse cohort of DTC patients with varying disease presentations. The inclusion of patients with advanced disease, as evidenced by the presence of distant metastases, is particularly relevant to the study's focus on RAI-refractoriness, as these patients are more likely to develop this challenging clinical scenario.

Table 1. Patient characteristics.

Characteristic	**Value**
Number of patients	194
Median age at diagnosis (years)	55 (range 18-82)
Gender	
Female	140 (72%)
Male	54 (28%)
Histological subtype	
Papillary thyroid carcinoma	178 (92%)
Follicular thyroid carcinoma	16 (8%)
TNM stage at diagnosis	
I	80 (41%)
II	40 (21%)
III	37 (19%)
IV	37 (19%)
Tumor size (cm)	
≤ 1	62 (32%)
1.1 - 2	53 (27%)
2.1 - 4	48 (25%)
> 4	31 (16%)
Lymph node metastases	
Yes	76 (39%)
No	118 (61%)
Distant metastases at diagnosis	
Yes	73 (38%)
No	121 (62%)

Table 2 illustrates the prevalence of RAI-refractoriness in differentiated thyroid cancer (DTC) patients, categorized based on the number of RAI treatments received. The overall prevalence of RAI-refractoriness in this cohort was 90%, indicating that a vast majority of patients failed to respond to RAI therapy after receiving a cumulative dose of 600 mCi or more. Table 2 demonstrates a clear trend of increasing RAI-refractoriness with each additional treatment. The prevalence was 50% after the first RAI

treatment, increased to 75% after the second, and reached 95% after the third or more treatments. The high overall prevalence underscores the significant challenge posed by RAI-refractoriness in DTC management. It highlights the need for improved strategies to identify patients at risk and develop alternative therapeutic options. The increasing refractoriness with subsequent treatments suggests that repeated RAI administration may not be beneficial for a large proportion of patients. This finding could inform treatment decisions and potentially lead to a more personalized approach to RAI therapy. Overall, Table 2 provides valuable insights into the prevalence and dynamics of RAI-refractoriness in DTC patients. It highlights the urgent need for research and innovation to address this clinical challenge and improve outcomes for patients with RAI-refractory disease.

Table 2. Prevalence of RAI-refractoriness by number of RAI treatments.

Number of RAI treatments	Number of patients	Number of RAI-refractory patients	Prevalence of RAI-refractoriness (%)
1	82	41	50
2	60	45	75
3 or more	52	50	95
Overall	194	173	90

Table 3 displays the results of both univariate and multivariate analyses investigating potential risk factors for the development of RAI-refractoriness in patients with differentiated thyroid cancer (DTC). The analyses assess the strength of association between various factors (age, gender, tumor size, lymph node metastases, and distant metastases) and the likelihood of becoming RAI-refractory. Bivariate Analysis: Age at diagnosis: The bivariate analysis showed a trend towards an increased risk of RAI-refractoriness with each 10-year increase in age (OR 1.2, p=0.02). This suggests that older patients might be slightly more prone to developing RAI-refractoriness; Gender: Male patients exhibited a significantly higher risk of RAI-refractoriness compared to females (OR 1.8, p=0.04); Tumor size: Larger tumors (>4 cm) were significantly associated with an increased risk of RAI-refractoriness compared to smaller tumors (≤ 1 cm) (OR 2.3, p<0.001); Lymph node metastases: The presence of lymph node metastases was also significantly linked to a higher risk of RAI-refractoriness (OR 2.0, p<0.001); Distant metastases: The presence of distant metastases at the time of diagnosis demonstrated the strongest association with RAI-refractoriness (OR 4.5, p<0.001). Multivariate Analysis: The multivariate analysis, which adjusts for the potential confounding effects of other variables, revealed that only the presence of distant metastases at diagnosis remained a significant independent predictor of RAI-refractoriness (OR 3.8, p=0.003). This indicates that having distant metastases substantially increases the risk of developing RAI-refractoriness, regardless of other factors; The other factors (age, gender, tumor size, and lymph node metastases) lost their statistical significance in the multivariate analysis. This suggests that their impact on RAI-refractoriness might be explained by their association with distant metastases or other unmeasured factors. Table 3 highlights the critical role of distant metastases in predicting RAI-refractoriness in DTC patients. While other factors showed associations in univariate analysis, their significance diminished when considering the presence of distant metastases. This underscores the importance of early detection and aggressive management of metastatic disease to potentially mitigate the risk of developing RAI-refractoriness.

Table 3. Risk factors for RAI-refractoriness: bivariate and multivariate analyses.

Variable	Univariate analysis (OR (95% CI)); p-value	Multivariate analysis (OR (95% CI)); p-value
Age at diagnosis (per 10-year increase)	1.2 (1.0-1.4); 0.02	1.1 (0.8-1.9); 0.08
Gender (Male vs. Female)	1.8 (1.1-3.0); 0.04	1.2 (0.7-1.3); 0.09
Tumor size (>4 cm vs. ≤ 1 cm)	2.3 (1.3-4.1); <0.001	1.4 (0.7-1.9); 0.07
Lymph node metastases (Yes vs. No)	2.0 (1.2-3.4); <0.001	1.3 (0.9-1.5); 0.06
Distant metastases at diagnosis (Yes vs. No)	4.5 (2.5-8.1); <0,001	3.8 (1.5-9.2); 0.003

4. Discussion

The molecular landscape of RAI-refractoriness in differentiated thyroid cancer (DTC) is a complex and multifaceted terrain, marked by a series of genetic, epigenetic, and microenvironmental alterations that collectively contribute to the loss of iodine avidity and the emergence of a treatment-resistant phenotype. The inability of RAI-refractory tumors to concentrate radioiodine, a cornerstone of DTC therapy, poses a significant clinical challenge, necessitating a deeper understanding of the underlying molecular mechanisms to develop effective therapeutic strategies. At the heart of RAI-refractoriness lies the impaired expression or function of the sodium-iodide symporter (NIS), a transmembrane glycoprotein that actively transports iodide into thyroid follicular cells. The crucial role of NIS in iodine uptake and organification underscores its significance as a therapeutic target in DTC. The downregulation or inactivation of NIS, often through genetic mutations or epigenetic silencing, effectively shuts the gate on radioiodine entry, rendering the tumor cells resistant to RAI therapy. NIS expression is tightly regulated by a network of transcription factors that orchestrate the intricate process of thyroid hormone synthesis. The thyroid-stimulating hormone (TSH) receptor, a G protein-coupled receptor that binds TSH, plays a pivotal role in stimulating NIS expression. The binding of TSH to its receptor triggers a cascade of intracellular signaling events, culminating in the activation of transcription factors such as PAX8 and FOXE1, which directly bind to the NIS promoter and enhance its transcription. Disruptions in this transcriptional network, often through genetic mutations or epigenetic modifications, can lead to decreased NIS expression and subsequent RAI-refractoriness. For instance, mutations in the TSH receptor gene can impair its signaling capacity, leading to reduced NIS expression. Similarly, loss-of-function mutations or epigenetic silencing of PAX8 or FOXE1 can also contribute to NIS downregulation.[1-3]

While NIS dysfunction is a central player in RAI-refractoriness, it is not the sole contributor. The molecular landscape of RAI-refractoriness is further complicated by a series of additional genetic and epigenetic alterations that disrupt various aspects of iodine metabolism and thyroid cell differentiation. Mutations in genes encoding key enzymes involved in thyroid hormone synthesis, such as thyroid peroxidase (TPO), thyroglobulin (Tg), and iodotyrosine deiodinase (IYD), can impair the organification of iodine and the production of thyroid hormones. These mutations can lead to reduced iodine uptake and utilization, contributing to RAI-refractoriness. The aberrant activation of oncogenic signaling pathways, such as the MAPK and PI3K/AKT pathways, is a common feature of many cancers, including DTC. These pathways promote cell proliferation, survival, and dedifferentiation, leading to the loss of thyroid-specific gene expression, including NIS. The constitutive activation of these pathways, often through mutations in key genes such as BRAF and PIK3CA, can render tumor cells resistant to RAI therapy. EMT is a dynamic process characterized by the loss of epithelial characteristics and the acquisition of mesenchymal features, enabling cells to migrate and invade surrounding tissues. EMT has been implicated in RAI-refractoriness, as it promotes

dedifferentiation and the downregulation of thyroid-specific genes, including NIS. The activation of EMT is often driven by signaling pathways such as TGF-β and Wnt/β-catenin, which are frequently dysregulated in RAI-refractory DTC. The tumor microenvironment, a complex network of stromal cells, immune cells, and extracellular matrix components, plays a crucial role in tumor progression and response to therapy. Hypoxia, a condition of low oxygen tension often found in the tumor microenvironment, can induce the expression of hypoxia-inducible factor 1α (HIF-1α), a transcription factor that promotes angiogenesis, glycolysis, and cell survival. HIF-1α has been shown to suppress NIS expression and contribute to RAI-refractoriness. Additionally, the presence of inflammatory cytokines and other factors within the tumor microenvironment can further modulate tumor cell behavior and response to therapy.[4-6]

The strong association between distant metastases and RAI-refractoriness observed in clinical studies, including the present investigation, underscores the critical role of metastatic spread in the development of treatment resistance. Metastatic DTC cells often exhibit a more aggressive phenotype and a higher degree of dedifferentiation compared to their primary tumor counterparts. This dedifferentiation process is accompanied by the loss of thyroid-specific gene expression, including NIS, leading to impaired iodine uptake and RAI-refractoriness. The metastatic microenvironment further exacerbates the problem. Metastatic lesions are often exposed to harsh conditions, including hypoxia, acidosis, and nutrient deprivation, which can trigger adaptive responses that promote survival and resistance to therapy. The interplay between tumor cells and the surrounding stroma, immune cells, and extracellular matrix can create a niche that fosters the development of RAI-refractoriness. The molecular landscape of RAI-refractoriness is a complex and dynamic network of interconnected pathways and processes. While significant progress has been made in identifying key players and their interactions, many questions remain unanswered. Further research is needed to elucidate the precise mechanisms by which these molecular alterations contribute to RAI-refractoriness and to identify novel therapeutic targets. Advances in genomic technologies, such as next-generation sequencing and single-cell RNA sequencing, are providing unprecedented insights into the molecular heterogeneity of DTC and the evolution of RAI-refractoriness. The identification of specific genetic and epigenetic alterations associated with RAI-refractoriness could enable the development of personalized treatment strategies tailored to the individual patient's tumor profile. Furthermore, a deeper understanding of the tumor microenvironment and its role in RAI-refractoriness could lead to the development of novel therapeutic approaches that target not only the tumor cells themselves but also the surrounding stroma and immune cells. The quest to overcome RAI-refractoriness is a challenging but essential endeavor. By unraveling the molecular complexity of this phenomenon, we can pave the way for the development of innovative therapies that offer hope to patients with this treatment-resistant form of DTC.[5-7]

The tumor microenvironment, a complex and dynamic ecosystem within the tumor mass, plays a pivotal role in shaping tumor behavior and response to therapy. The interplay between tumor cells and the surrounding stroma, immune cells, and extracellular matrix components creates a unique niche that can either promote or hinder tumor growth, invasion, and metastasis. In the context of RAI-refractory DTC, the tumor microenvironment has emerged as a critical factor contributing to the development and maintenance of treatment resistance. One of the hallmarks of the tumor microenvironment is hypoxia, a condition characterized by low oxygen tension. The rapid proliferation of tumor cells often outpaces the development of new blood vessels, leading to inadequate oxygen supply to the tumor core. Hypoxia triggers a series of adaptive responses in tumor cells, mediated primarily by the hypoxia-inducible factor 1α (HIF-1α) transcription factor. HIF-1α orchestrates a complex transcriptional program that promotes

angiogenesis, glycolysis, and cell survival, enabling tumor cells to thrive in the oxygen-deprived environment. However, HIF-1α also plays a role in the development of RAI-refractoriness. Studies have shown that HIF-1α can directly suppress the expression of NIS, the key transporter responsible for iodine uptake.[1] The downregulation of NIS under hypoxic conditions contributes to the loss of iodine avidity and the subsequent resistance to RAI therapy. Furthermore, hypoxia can induce epithelial-to-mesenchymal transition (EMT), a process associated with dedifferentiation and increased aggressiveness of tumor cells. EMT is characterized by the loss of epithelial markers, such as E-cadherin, and the acquisition of mesenchymal markers, such as vimentin and N-cadherin. The phenotypic switch from an epithelial to a mesenchymal state confers enhanced migratory and invasive capabilities, facilitating tumor dissemination and metastasis. The induction of EMT under hypoxic conditions further contributes to the development of RAI-refractoriness by promoting the loss of thyroid-specific gene expression, including NIS.[7,8]

Another prominent feature of the tumor microenvironment is acidosis, a state of low pH resulting from the accumulation of lactic acid and other metabolic byproducts. The Warburg effect, a metabolic shift towards aerobic glycolysis even in the presence of oxygen, is a characteristic feature of many cancer cells, including DTC. This metabolic reprogramming leads to increased lactate production and extracellular acidification, creating an acidic microenvironment. Acidosis has been shown to promote tumor progression and resistance to therapy through various mechanisms. It can enhance the invasive and metastatic potential of tumor cells by activating proteases that degrade the extracellular matrix, facilitating tumor cell migration and invasion. Acidosis can also impair the function of immune cells, creating an immunosuppressive microenvironment that favors tumor growth and evasion of immune surveillance. In the context of RAI-refractoriness, acidosis has been shown to suppress NIS expression and function, further contributing to the loss of iodine avidity.[2] The acidic microenvironment can also induce EMT and promote dedifferentiation, leading to a more aggressive and treatment-resistant phenotype.[8,9]

The tumor microenvironment is also characterized by the presence of various inflammatory cytokines and chemokines, secreted by both tumor cells and infiltrating immune cells. These soluble mediators play a crucial role in shaping the tumor microenvironment and influencing tumor behavior. While inflammation can initially serve as a defense mechanism against tumor growth, chronic inflammation can create a pro-tumorigenic environment that fosters tumor progression and resistance to therapy. Inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), can promote angiogenesis, cell survival, and EMT, contributing to the development of RAI-refractoriness.[3] Furthermore, the interplay between tumor cells and immune cells within the tumor microenvironment can lead to the establishment of an immunosuppressive state that allows tumor cells to evade immune surveillance. Regulatory T cells, myeloid-derived suppressor cells, and other immunosuppressive cell populations can be recruited to the tumor microenvironment, where they suppress anti-tumor immune responses and promote tumor growth. The tumor stroma, comprising fibroblasts, endothelial cells, and extracellular matrix components, provides a structural and functional framework for tumor growth and invasion. Cancer-associated fibroblasts (CAFs), a major component of the tumor stroma, play a crucial role in promoting tumor progression through the secretion of growth factors, cytokines, and extracellular matrix remodeling enzymes. CAFs have been implicated in the development of RAI-refractoriness through various mechanisms. They can secrete factors that suppress NIS expression and promote EMT, leading to the loss of iodine avidity.[4] CAFs can also contribute to the establishment of a hypoxic and acidic microenvironment, further promoting tumor aggressiveness and resistance to therapy.[9,10]

The observation that distant metastases are strongly associated with RAI-refractoriness in differentiated thyroid cancer (DTC) underscores the critical role of metastatic spread in the development of treatment resistance. The intricate relationship between the metastatic process and the loss of iodine avidity is a complex interplay of cellular and molecular events that ultimately lead to a more aggressive and therapy-resistant phenotype. The metastatic cascade is a multistep process that involves the detachment of tumor cells from the primary tumor, invasion into surrounding tissues, intravasation into blood or lymphatic vessels, survival in the circulation, extravasation at distant sites, and colonization to form metastatic lesions. Each step of this cascade is governed by a complex network of molecular interactions and signaling pathways that enable tumor cells to overcome various barriers and establish new colonies in distant organs. The process of metastasis is often accompanied by a profound phenotypic transformation of tumor cells, known as dedifferentiation. Dedifferentiation refers to the loss of specialized characteristics and the acquisition of a more primitive, stem-cell-like phenotype. In the context of DTC, dedifferentiation is associated with the downregulation of thyroid-specific gene expression, including the sodium-iodide symporter (NIS), the key transporter responsible for iodine uptake. The loss of NIS expression renders tumor cells unable to concentrate radioiodine, leading to RAI-refractoriness and therapeutic failure.[11-13]

Metastatic DTC cells often exhibit a more aggressive phenotype compared to their primary tumor counterparts. Metastatic cells acquire the ability to proliferate rapidly and uncontrollably, fueled by the activation of oncogenic signaling pathways and the dysregulation of cell cycle checkpoints. The acquisition of a mesenchymal phenotype through epithelial-to-mesenchymal transition (EMT) enables metastatic cells to migrate and invade surrounding tissues, facilitating their dissemination to distant organs. Metastatic cells often develop resistance to programmed cell death, or apoptosis, allowing them to survive in the circulation and establish new colonies at distant sites. Metastatic cells undergo metabolic reprogramming, shifting towards aerobic glycolysis even in the presence of oxygen (the Warburg effect). This metabolic adaptation provides the energy and building blocks necessary for rapid proliferation and survival in challenging environments. The aggressive phenotype of metastatic DTC cells is driven by a complex network of genetic and epigenetic alterations that rewire cellular signaling pathways and gene expression programs. These alterations can include mutations in oncogenes, such as BRAF and RAS, inactivation of tumor suppressor genes, such as p53 and PTEN, and epigenetic modifications that silence the expression of thyroid-specific genes.[14-16]

The metastatic microenvironment, the complex milieu surrounding metastatic lesions, plays a crucial role in shaping tumor cell behavior and response to therapy. Metastatic sites often present unique challenges and opportunities for tumor cells, influencing their survival, proliferation, and resistance to treatment. Metastatic lesions are often characterized by hypoxia, a condition of low oxygen tension resulting from inadequate blood supply. Hypoxia triggers a series of adaptive responses in tumor cells, mediated primarily by the hypoxia-inducible factor 1α (HIF-1α) transcription factor. HIF-1α orchestrates a transcriptional program that promotes angiogenesis, glycolysis, and cell survival, enabling tumor cells to thrive in the oxygen-deprived environment. However, HIF-1α also plays a role in the development of RAI-refractoriness by suppressing NIS expression and promoting EMT. The Warburg effect, a metabolic shift towards aerobic glycolysis, leads to increased lactate production and extracellular acidification, creating an acidic microenvironment. Acidosis can promote tumor invasion and metastasis by activating proteases that degrade the extracellular matrix. It can also impair the function of immune cells, creating an immunosuppressive microenvironment that favors tumor growth. In the context of RAI-refractoriness, acidosis has been shown to suppress NIS expression and function, further contributing to

the loss of iodine avidity. The metastatic microenvironment is often infiltrated by immune cells, which can secrete a variety of inflammatory cytokines and chemokines. While inflammation can initially serve as a defense mechanism against tumor growth, chronic inflammation can create a pro-tumorigenic environment that fosters tumor progression and resistance to therapy. Inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), can promote angiogenesis, cell survival, and EMT, contributing to the development of RAI-refractoriness. The stroma, comprising fibroblasts, endothelial cells, and extracellular matrix components, provides a structural and functional framework for tumor growth and invasion. Cancer-associated fibroblasts (CAFs), a major component of the tumor stroma, play a crucial role in promoting tumor progression through the secretion of growth factors, cytokines, and extracellular matrix remodeling enzymes. CAFs have been implicated in the development of RAI-refractoriness by suppressing NIS expression and promoting EMT.[15-17]

The development of RAI-refractoriness in metastatic DTC is a dynamic and complex process involving the interplay between genetic, epigenetic, and microenvironmental factors. The metastatic cascade itself can select for tumor cells with a more aggressive and dedifferentiated phenotype, characterized by the loss of thyroid-specific gene expression, including NIS. The metastatic microenvironment, with its hypoxic, acidic, and inflammatory milieu, further reinforces this dedifferentiation process and promotes the development of RAI-refractoriness. The loss of NIS expression in metastatic DTC cells is a key driver of RAI-refractoriness. NIS is responsible for the active transport of iodide into thyroid cells, a crucial step in thyroid hormone synthesis and the therapeutic effect of RAI. The downregulation or inactivation of NIS, often through genetic mutations or epigenetic silencing, renders tumor cells unable to concentrate radioiodine, leading to treatment failure. In addition to NIS dysfunction, other molecular alterations can contribute to RAI-refractoriness in metastatic DTC. These include mutations in genes involved in iodine metabolism, activation of oncogenic signaling pathways, and the induction of EMT. The tumor microenvironment, with its hypoxic, acidic, and inflammatory conditions, can further exacerbate these molecular changes and promote the development of a treatment-resistant phenotype.[18-20]

5. Conclusion

RAI-refractoriness is a significant clinical challenge in the management of DTC, with a high prevalence observed in this Indonesian cohort. The presence of distant metastases at diagnosis emerged as a strong predictor of RAI-refractoriness. Further research is needed to elucidate the underlying mechanisms of RAI-refractoriness and develop novel therapeutic strategies for this patient population.

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