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Clinicopathological Characteristic of Radioactive Iodine-Refractory Differentiated Thyroid Carcinoma at Dr. Hasan Sadikin Hospital 2016-2021

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ABSTRACT

Background
Initial therapy for differentiated thyroid carcinoma (DTC) is thyroidectomy with or without cervical lymph node dissection. Furthermore, radioactive iodine (RAI) is given to patients by considering risk stratification and other patient factors. Although most cases of DTC have a good prognosis after standard therapeutic approaches, the risks of local recurrence and distant metastases can be as high as 20% and 10%. Among these patients, two-thirds showed RAI-refractory. This is concerning because 10-year survival rate is less than 10%. This study aimed to analyze the clinicopathological characteristics of RAI-refractory DTC.

Methods
This is a case-control study. Data was collected from the Department of Nuclear Medicine and Molecular Theranostics and Department of Anatomical Pathology, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin Hospital, Bandung period 1 January 2016-31 December 2021.

Results
Clinicopathological factors associated with RAI-refractory DTC are age, sex, aggressive histologic subtype, LVI (lymphovascular invasion), m-ETE (microscopic extrathyroid extension), TNM (tumor, nodal, metastasis) stage, and ENE (extranodal extension), with p-value <0.05. Meanwhile, there was no significant difference in the histologic type between RAI-refractory and non-RAI-refractory groups.

Conclusion
In the pathology report, it is necessary to include prognostically relevant tumor histopathological characteristics. In addition to histologic type, histologic subtype, and tumor size, other features such as presence and extent of capsular invasion, LVI, microscopic and macroscopic ETE, ENE, and number and size of metastatic lymph nodes, have been shown to provide additional prognostic information and are required in standard pathology reports for DTC.

Keywords: Clinicopathology, differentiated thyroid carcinoma, radioactive iodine-refractory

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INTRODUCTION

Thyroid cancer is responsible for 586,000 cases worldwide, ranked 9th for incidence in 2020. Death rates from the disease are much lower, with 0.5 per 100,000 in women and 0.3 per 100,000 in men and estimated 44,000 deaths in both.[1] In Indonesia, the prevalence of thyroid cancer in the last 5 years has been recorded at 38,650 cases for all ages and genders, and in 2020 it ranks 12th for all types of cancer with a total of 13,114 cases and 2,224 deaths.[2]

Thyroid carcinoma derivate from follicular cells in the thyroid gland, which secrete iodine-containing thyroid hormones.[3] Differentiated thyroid carcinoma group consists of papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), Hurthle (oncocytic) cell carcinoma (OCA), and poorly differentiated thyroid carcinoma (PDTC).[4-7] Differentiated thyroid carcinoma accounts for approximately 90% of all thyroid cancers and overall has an excellent 10-year disease-specific survival of approximately 95%.[8]

Initial therapy for differentiated thyroid carcinoma is thyroidectomy with or without central or lateral compartment of cervical lymph node dissection. Furthermore, radioactive iodine (RAI) is given to patients with a medium to high-risk stratification and other patient factors.[8] Radioactive iodine therapy (^{131}I) is indicated for the management of hyper-functioning thyroid disease and thyroid carcinoma. This therapy is classified as a radioactive nuclear medicine and was first synthesized in 1941, then the Food and Drug Administration (FDA) approved it in 1971 for therapeutic use. This therapy causes permanent damage to thyroid tissue by emitting two types of radiation, gamma and beta rays.[9] The effect of gamma radiation is more useful for diagnostic purposes, while the effect of beta radiation is therapeutic. Ionization and excitation of cells under the influence of radiation lead to lethal or non-lethal effects. Cell death is usually caused by improperly repaired double-stranded deoxyribonucleic acid (DNA) damage or not repaired at all. Due to changes in the DNA chain, while the cell tries to activate mitosis, this will result in cell death. Many healthy cells and radiation-induced malignant cells will undergo apoptosis.[10] The effect of RAI depends on the uptake of iodine from thyroid tissue and is not effective in patients who have hyperfunctioning disease without iodine uptake. RAI therapy can be given as adjunctive therapy after surgery in patients with thyroid carcinoma and can be given four to six weeks postoperative.[9] Radioactive iodine therapy has some potential side effects, which are classified as early and late complications. Early complications include gastrointestinal symptoms, sialadenitis/xerostomia, bone marrow suppression, gonadal damage, dry eyes, and nasolacrimal duct obstruction. Late complications include secondary cancer, pulmonary fibrosis, permanent bone marrow suppression, and genetic effects.[11]

Although most cases of differentiated thyroid carcinoma have a good prognosis after standard therapeutic approaches, including surgery, selective RAI therapy, and thyroid-stimulating hormone (TSH) suppressive therapy, the risks of local recurrence and distant metastases can be as high as 20% and 10%. Among these patients, two-thirds showed loss of iodine uptake ability early in therapy or gradually due to dysfunction, and even loss of sodium (Na)-iodide symporter (NIS) expression in the basement membrane, indicating an altered differential state known as RAI-refractory. Radioactive iodine-refractory based on the 2015 ATA management guidelines for adult patients differentiated thyroid carcinoma structurally evident is classified in patients with appropriate TSH stimulation and iodine preparation in four basic ways: (i) the malignant/metastatic tissue does not ever concentrate RAI (no uptake outside the thyroid bed at the first therapeutic WBS), (ii) the tumor tissue loses the ability to concentrate RAI after previous evidence of RAI-avid disease (in the absence of stable iodine contamination), (iii) RAI is concentrated in some lesions but not in others, and (iv) metastatic disease progresses despite significant concentration of RAI.[5] This is a cause for concern because the 10-year survival rate is less than 10%.[4] It is still a challenge for clinicians to know the possibility of RAI-refractory occurring early to adjust further therapy individually and avoid unwanted side effects of therapy.[12]

Based on the description above, this study aimed to analyze the clinicopathological characteristics associated with RAI-refractory differentiated thyroid carcinoma.

METHOD

This research is an analytic observational study with a case-control design. Case-control research is an observational analytic epidemiological study that examines the relationship between effects (disease or health conditions) and risk factors. In case-

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control, the value that will appear in OR or odds ratio, this is the strength of cause-and-effect relationship.

The subjects of this study were differentiated thyroid carcinoma patients who had undergone total thyroidectomy with or without cervical lymph node dissection, had been diagnosed histopathologically as differentiated thyroid carcinoma in Department of Anatomic Pathology, and a whole body scan (WBS) was performed with Radioactive iodine (RAI) in Department of Nuclear Medicine and Molecular Theranostic, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin Hospital period 1 January 2016-31 December 2021.

For the case criteria, it has been declared RAI-refractory based on the 2015 ATA management guidelines for adult patients with differentiated thyroid carcinoma. While for the control criteria, non-RAI-refractory, is a condition of excellent response after RAI therapy which is characterized by negative imaging of the tumor mass, undetectable (thyroglobulin) Tg antibodies, and Tg <0.2 ng/ml.[5] The inclusion criteria in this study were complete clinical data in medical records such as: age, sex, medical history, history of RAI therapy, and presence of paraffin block with the above criteria. The data that has been obtained is 34 cases of RAI-refractory and 34 cases of non-RAI-refractory differentiated thyroid carcinoma. Furthermore, data were obtained from patient medical records, paraffin block reviews, and Hematoxylin and eosin staining (H&E) slides reviews.

The data obtained are recorded in a special form and then processed through the SPSS program version 24.0 for Windows. For numerical data, p-value is tested by unpaired t-test if the data is normally distributed, with alternative Mann-Whitney test if the data is not normally distributed. For categorical data, p-value is calculated based on the Chi-Square test with alternative Kolmogorov Smirnov and Fisher's Exact tests if the Chi-Square conditions are not fulfilled. The difference is considered significant if the p-value<0.05.

RESULT

The clinicopathological characteristics of this study are summarized in table 1. The mean age at initial diagnosis was 48 years old, with the youngest being 17 years old and the oldest being 76 years old. The number of women compared to men is 62% vs 38%. From a total of 70 samples, the most common histologic type found was PTC which was diagnosed in 56 samples (80%).

For histologic types, because The World Health Organization (WHO) classification of tumors is updated regularly, we use the newest edition (5th edition) of the classification of thyroid tumors that was released in March 2022. For aggressive histologic subtypes, classic and follicular subtype PTCs were less aggressive, and were classified as the low-risk histologic group, while the others were categorized as the high-risk histologic group: tall cell PTC, diffuse sclerosing PTC, hobnail PTC, FTC (including OCA), and PDTC.[13] Meanwhile, there are additions Differentiated high-grade thyroid carcinoma (DHGTC) and PDTC are classified under the tumor type “follicular-derived carcinomas, high-grade” in the new 2022 WHO classification. The new subtype DHGTC requires the presence of ≥5 mitoses per 2 mm2 and/or tumor necrosis. PTC, FTC, and OCA showing high-grade histologic features (mitotic count and tumor necrosis) are now classified as DHGTC.[14] The TNM staging system is based on the American Joint Committee on Cancer/Tumor-Node-Metastatic Staging System for Differentiated and Anaplastic Thyroid Cancer (Eighth Edition) 2017.[15] Lymphovascular invasion (LVI) is defined as tumor cell invasion of blood vessels within or more of the tumor capsule, with intravascular tumor cells attached to the wall and protruding into the lumen, covered by endothelium, or surrounded by fibrin in a fashion similar to that of an ordinary thrombus.[16,17] Microscopic extrathyroidal extension (m-ETE) was determined histologically using microscopic evaluation.[18] Extranodal extension (ENE) is defined histologically as tumor cells that extend beyond the lymph node capsule and into the perinodal fibroadipose tissue either microscopically or grossly.[19]

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Table 1. Clinicopathological characteristics of differentiated thyroid carcinoma.

Variable	Group		OR (CI 95%)	p-value
	RAI-*refractory* N=34	Non-RAI-refractory N=34		
Age			-	0.011*
Mean±Std	52.8 ± 14.5	43.6±14.6		
Median	54.5	43		
Range (min-max)	18-76	17-70		
Age Group			4.667	0.005*
≥55 years old	17 (50%)	6 (17.6%)	(1.540; 14.143)	
<55 years old	17 (50%)	28 (82.4%)		
Sex			4.643	0.012*
Man	13 (38.2%)	4 (11.8%)	(1.328; 16.233)	
Woman	21 (61.8%)	30 (88.2%)		
Histologic type			-	0.665
PTC	24 (70.6%)	24 (70.6%)		
FTC	1 (2.9%)	3 (8.8%)		
IEFVPTC	2 (5.9%)	6 (17.6%)		
Follicular-derived carcinomas, high-grade	7 (20.6%)	1 (2.9)		
Aggressive histologic subtype			5.921	0.003*
Yes	15 (44.1%)	4 (11.8%)	(1.707-20.536)	
No	19 (55.9%)	30 (88.2%)		
Tumor			92.8	0.0001**
T3-T4	29 (85.3%)	2 (5.9%)	(16.699; 15.705)	
T1-T2	5 (14.7%)	32 (94.1%)		
Nodal			12.127	0.0001**
N1	23 (67.6%)	5 (14.7%)	(3.688; 39.878)	
N0	11 (32.4%)	29 (85.3%)		
Metastasis				0,005*
M1	8 (22,2%)	0 (0%)	∞	
M0	28 (77,8%)	34 (100%)		
Stage			∞	0.025*
III-IV	6 (17.6%)	0 (0%)		
I-II	28 (82.4%)	34 (100%)		
LVI			28.704	0.0001*
Yes	31 (91.2%)	9 (26.5%)	(7.016; 117.435)	
No	3 (8.8%)	25 (73.5%)		
m-ETE			56.250	0.0001*
Yes	30 (88.2%)	4 (11.8%)	(12.864-45.971)	
No	4 (11.8%)	30 (88.2%)		
ENE			-	0.0001*
Yes	22 (64.7%)	2 (5.9%)		
No	1 (2.9%)	3 (8.8%)		
Not Available	11 (32.4%)	29 (85.3%)		

Abbreviations: RAI: radioactive iodine; OR: odds ratio; CI: confidence interval; PTC: papillary thyroid carcinoma; FTC: follicular thyroid carcinoma; IEFVPTC: Invasive encapsulated follicular variant of papillary thyroid carcinoma; LVI: lymphovascular invasion; m-ETE: microscopic extrathyroidal extension; ENE: extranodal extension

Table 1 shows that the average age in the RAI-refractory group is 52.8 years old and the average age in the non-RAI-refractory group is 43.6 years old. The results for the age, age group, and sex variables were statistically significant, that there were differences in the proportions between the RAI-refractory group and non-RAI-refractory group. The odds ratio that is the probability of patients in the age group ≥55 years old of being RAI-refractory is 4.667 times compared to patients in the age group <55 years old, with a confidence index of 1.393; 12.519. The odds ratio that is the probability of a man being RAI-refractory is 4.643 times compared to a woman, with a confidence index of 1.328; 16.233.

The analysis data in the pathological characteristics table 1 was tested using the Chi-Square for aggressive histologic subtype, tumor, nodal, LVI, and m-ETE variables. Alternative Fisher's Exact test for metastatic and stage variable and Kolmogorov Smirnov test for histologic type and ENE variables. The results for aggressive histologic subtype, LVI, m-ETE, tumor, nodal, metastasis, stage, and ENE variables were statistically significant, that there were differences in the proportions between the RAI-refractory group and non-RAI-refractory group. Meanwhile, there was no significant difference for histologic type variables. The odds ratio that is the probability of a patient with aggressive histologic subtype,

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LVI, m-ETE, and for T3-T4 is 5.921, 28.704, 56.250, 92.8, 12.127, respectively.

In this study, we found aggressive histological subtypes consisting of tall cell PTC, FTC, DHGTC, and PDTC. There is a difference in the definition of tall cell PTC between WHO 2017 and the current WHO classification of thyroid tumors, where in the latest edition tall cell PTC is composed of cells whose height is at least three times their width and show abundant eosinophilic cytoplasm with a prominent cell membrane, an exuberant and tightly-knitted growth pattern of elongated follicles giving rise to a so-called "tram-track" appearance. Tall cells should represent at least 30% or more of the PTC cells to make the diagnosis of tall cell PTC.[20]

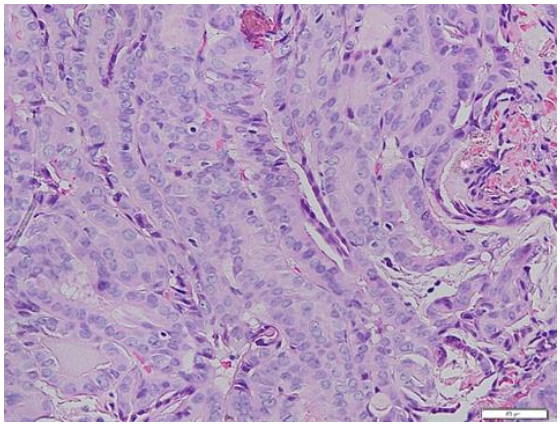

Figure 1. Histopathological feature of tall cell PTC cells whose height is at least three times their width, "tram-track" appearance. (H&E, 200 times).

Based on prognostic risk classification, the intermediate risk of follicular cell-derived carcinomas of the thyroid gland is differentiated high-grade thyroid carcinoma (PTC, FTC, OCA) and poorly differentiated thyroid carcinoma.[21] Differentiated high-grade thyroid carcinoma (DHGTC) are not poorly differentiated histologically but all have increased mitotic counts and/or tumor necrosis. The mitotic count must by definition be ≥ 5 mitoses per 2 mm^2 after evaluation of the most mitotically active areas ("hot spot" mitotic counting). Tumour necrosis is defined by karyorrhectic nuclear debris or ghost contours of dead tumor cells. Poorly differentiated thyroid carcinoma (PDTC) diagnosis is based on Turin consensus criteria: (i) presence of a solid/trabecular/insular pattern of growth; (ii) absence of conventional nuclear features of papillary carcinoma; (iii) presence of at least one of the following: convoluted nuclei, mitotic count ≥ 3 per 2 mm^2, tumor necrosis.[22]

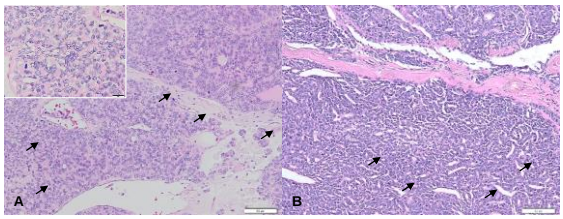

Figure 2. Histopathological feature of follicular-derived carcinomas, high-grade (A) Differentiated high-grade thyroid carcinoma with ≥5 mitoses per 2 mm^2 (black arrows) (H&E, 100 times). (B) Poorly differentiated thyroid carcinoma with solid/trabecular pattern, absence of conventional nuclear features of PTC, and mitotic count ≥3 per 2 mm^2 (black arrows) (H&E, 100 times).

DISCUSSION

The sample comes from data that has been declared RAI-refractory or non-RAI-refractory for the period 1 January 2016-31 December 2021 at the Department of Nuclear Medicine and Molecular Theranostic, Faculty of Medicine, Padjadjaran University/Dr. Hasan Sadikin Hospital, Bandung. Samples were from post-total thyroidectomy patients with or without cervical lymph node dissection that had been diagnosed histopathologically as differentiated thyroid carcinoma (PCT, FTC, OCA, DHGTC, PDTC), had whole body scan (WBS), and had received RAI therapy but structurally with the appropriate TSH stimulus and iodine preparations are declared as RAI-refractory. Radioactive iodine-refractory according to the American Thyroid Association (ATA) 2015 is a condition in which malignant/metastatic tissue never concentrates RAI (no uptake outside the thyroid bed at the first WBS diagnosis or therapy, tumor tissue loses the ability to concentrate RAI after previous evidence of tumor is RAI-avid (in the absence of stable iodine contamination), RAI assesses some lesions but not others, or metastatic disease develops despite significant RAI concentrations. While non-RAI-refractory is a condition of excellent response after RAI therapy which is characterized by negative imaging of tumor masses, undetectable Tg antibodies, and Tg <0.2 ng/ml.[5] Data obtained over the last 6 years were 34 RAI-refractory cases and 34 non-RAI-refractory cases.

Based on the clinical characteristics of this study, the mean age for the RAI-refractory group was 52 years old and the non-RAI-refractory group was 43 years old. For

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numerical data on the age variable, an unpaired t-test was carried out and the results showed that there was a statistically significant between the age variable and the RAI-refractory condition. So, it can be concluded that the group aged ≥55 years old increases the risk of RAI-refractory. This is in line with the research of Liu et al and Chai et al which found that increasing age significantly increases the risk of RAI-refractory. The age group that increases the incidence of RAI-refractory in Liu et al and Chai et al study is ≥48 years old and >40 years old, whereas in Liu et al study, ages ≥48 years old were included in the Scoring System for Predicting RAI-refractory Differentiated Thyroid Carcinoma.[23,24] This is consistent with the general model of multi-step progression from well-differentiated to poorly differentiated to undifferentiated carcinoma, the genetic change encompassing early and late events. The most frequent late changes were mutations in *TP53* and *TERT* promoter.[22] However, in a meta-analysis study by Luo et al, there was no significant difference in age between the RAI-refractory and non-RAI-refractory groups.[13] Other clinical characteristics examined in this study were gender. In Chi-Square test, there was a statistically significant difference between gender and RAI-refractory condition. So, it can be concluded that male increases the risk of RAI-refractory. This is based on generally male patients having a worse prognosis than females in differentiated thyroid carcinoma.[13] However, the results were different in the studies of Liu et al, Chai et al, and a meta-analysis study by Luo et al where there were no significant differences in gender between the RAI-refractory and non-RAI-refractory groups.[13,23,24] Meta-analytic studies based on individual participant-level appear to be able to provide more reliable estimates of risk than meta-analytic studies based on data.

Pathological characteristics in this study, including histologic type, aggressive histologic subtype, TNM stage, LVI, m-ETE and ENE were tested using the Chi-Square, and the results showed that there was a statistically significant between aggressive histologic subtypes, TNM stage, LVI, m-ETE and ENE with RAI-refractory condition, but not for histologic type. This is in line with the research of Liu et al, Meng et al, and Li G et al In Liu et al study obtained histologic type was not a statistically significant factor, although there was a relatively low proportion of aggressive subtypes in their study.[23] In Meng et al study, although the distribution of histologic types between the two groups was not different, other clinicopathological characteristics such as primary tumor diameter, multifocality, lymph node involvement, and clinical stage were significantly different by univariate analysis (all P <0.01).[25] In the study by Li G et al, using univariate analysis, there were 12 factors that significantly increased the risk of RAI-refractory, including: age at diagnosis ≥55 years old; BMI ≥24 kg/m^2; smoking; primary tumor size >10 mm; primary tumor size >20 mm; tumor type; ETE; lymph node metastasis number; lymph node metastasis rate; pT classification; pN stage; and pTNM stage (all P < 0.05).[26] A meta-analysis study conducted by Luo et al, found high-risk histologic subtypes including tall cell PTC, diffuse sclerosing, hobnail, FTC (including OCA), and PDTC were predictors of RAI-refractory (OR: 1.94, 95% CI: 1.15; 3.27, p=0.01). In addition, it was found that ETE had a positive relationship with the development of RAI-refractory (p<0.01, OR: 2.28, 95% CI:1.43; 3.64). However, ETE is associated with other factors such as histologic subtype, location of the primary lesion, and time at diagnosis. For example, the probability of ETE tumors is higher in the isthmus than in the lobes of the thyroid gland because of their anatomic position. Thus ETE may be a risk factor, but it needs to be combined with other factors when making clinical decisions and strategies, and further research is urgently needed.[13]

CONCLUSION

Clinicopathological characteristics (age, sex, aggressive histologic subtype, TNM stage, LVI, m-ETE, and ENE) are associated with differentiated RAI-refractory thyroid carcinoma. In the pathology report, it is necessary to include prognostically relevant tumor histopathological characteristics. In addition to histologic type, histologic subtype, and tumor size, other features such as presence and extent of capsular invasion, LVI, microscopic and macroscopic ETE, ENE, and number and size of metastatic lymph nodes, have been shown to provide additional prognostic information and are required in standard pathology report for differentiated thyroid carcinoma, and in preliminary risk stratification published by organizations such as the American Thyroid Association (ATA), the National Comprehensive Cancer Network (NCCN) and the American Joint Committee for Cancer (AJCC) staging manual, to guide

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management and determine the need for RAI ablation therapy.

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