Archives of Men's Health. 2026; 10(1): e1

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REVIEW ARTICLE

HER2 Expression in Different Types of Thyroid Neoplasms Assessed by Two Immunohistochemical Scoring Systems: A 3-Year Follow-Up Study in a Referral University Hospital in Tehran, Iran

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Received: November 2025; Accepted: December 2025; Published online: May 2026

Abstract: **Introduction:** Thyroid neoplasms are the most common endocrine malignancy; thus, it is important to introduce diagnostic and predictive factors for them. human epidermal growth factor receptor 2 (HER2), which is overexpressed in some other malignancies such as breast and gastrointestinal (GI) neoplasms, has been proposed as a diagnostic and prognostic factor. In this study, we investigated HER2 expression in different types of thyroid cancer. This study aimed to investigate the expression frequency of the HER2 in thyroid neoplasms, and its relationship with the type, stage, and prognosis of the malignancy.
Material and Methods: We studied 91 patients who were referred to Taleghani Hospital, Tehran, Iran, and underwent thyroidectomy or thyroid lobectomy, in the years 2018 to 2021. Their medical records, hematoxylin and eosin (H&E)-stained slides, and paraffin-embedded blocks were extracted from the hospital pathology archive. The specimens underwent microtomy and were subjected to immunohistochemistry (IHC) for HER2 evaluation. After the interpretation, the data were statistically analyzed.
Results: The only significant relationship was between HER2 expression (when interpreted based on the gastric scoring system) and age (P-value= 0.036). However, there was no significant relationship between HER2 expression and any of the other variables of our study.
Conclusion: Despite HER2 being a prognostic factor in breast and GI neoplasms, our study suggests that HER2 expression has no such role in thyroid neoplasm cases, and is only positive in patients younger than 45 years old with thyroid malignancies (when interpreted based on the gastric scoring system).

Keywords: Thyroid Neoplasm; Immunohistochemistry; HER2 (Human Epidermal Growth Factor Receptor 2); DAKO Scoring Guideline; Gastric Scoring System

Cite this article as: Fahimi M, Mohammadi Maram M, Kamani F, Mohsenifar Z. HER2 Expression in Different Types of Thyroid Neoplasms Assessed by Two Immunohistochemical Scoring Systems: A 3-Year Follow-Up Study in a Referral University Hospital in Tehran, Iran. Archives of Men's Health. 2026; 10(1): e1.

1. Introduction

Thyroid carcinomas are the most common endocrine gland neoplasms, with women at approximately three times more risk of developing these cancers than men. The incidence of thyroid carcinoma has increased in recent years (1-3).
Thyroid cancers are classified into two main groups based on their origin: arising from follicular, or from parafollicular cells. The first group includes papillary (PTC), follicular (FTC), and Hurthle Cell (HCC) thyroid carcinomas and the second one includes medullary thyroid carcinoma (MTC). Furthermore, anaplastic thyroid carcinoma (ATC) is another subtype of thyroid neoplasms that is undifferentiated and its cell type is unknown, but it arises presumably from the follicular cells (4, 5). More than 95% of thyroid neoplasms are derived from follicular cells, whereas less than 3% originate from parafollicular cells. The remaining neoplasms consist mainly of thyroid lymphomas and, rarely, sarcomas. PTC is the most prevalent type of thyroid tumor (more than 70%)

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and is one of the most curable carcinomas. The prevalence of thyroid cancer increases with age (6-8).

Ionizing radiation and exposure to certain environmental endocrine disruptors such as heavy metals, polybrominated diphenyl ethers, and polyaminoamide-epichlorohydrin have been confirmed as risk factors for thyroid neoplasms. At the same time, there are other factors that may increase the risk of developing these malignancies such as past medical history or family history of thyroid diseases or excessive iodine consumption, however, their role is still controversial (1).

Recent advances in molecular biology and investigation of tumorigenic genes have helped us to better understand the pathogenesis of thyroid neoplasms (9). HER2 is a surface cell receptor that belongs to the epidermal growth factor receptor (EGFR) family (10). In some human epithelial malignancies, such as breast, gastric, ovarian, and colorectal cancers, the HER2 gene is commonly overexpressed, which is associated with an unfavorable outcome and the development of tumors with low differentiation phenotypes (11).

Several studies have investigated the HER2 positivity rate in a number of cancers including breast and stomach (12, 13). HER2 expression in thyroid cancer has also been evaluated in some studies. In a 2003 study by Mondi et al. on HER2 expression in thyroid tumors, which was conducted on 36 patients suffering from thyroid neoplasm and 19 with benign thyroid tissue, no significant HER2 overexpression was detected in any of the studied groups. They concluded that HER2 may not have a predictive value for thyroid cancer (9). On the other hand, in the same year, Kremser et al. studied 103 cases of PTC and FTC and followed them up for more than 8 years. Their study showed a significant HER2 overexpression in both subtypes when they had distant metastasis, suggesting a significant correlation between HER2 and the prognosis in terms of predicting metastasis (14).

A study by Freudenberg et al. in 2005, on the prognostic value of HER2 expression in 32 cases of PTC, showed HER2 overexpression in 34% of the cases, and also recurrence or progression of the cancer in 81% of the HER2 positive and 33% of the HER2 negative patients. Their follow-up showed that 27% of the HER2-positive patients had died, while none of the HER2-negative ones were dead. Thus Freudenberg et al. suggested that there is a significant relationship between HER2 expression and the recurrence and progression of the tumor (P-value= 0.02), and also between HER2 and the patients' survival (P-value= 0.03) based on their study results (15).

Ruggeri et al. investigated HER2 expression in 45 cases of FTC and 45 with PTC, using IHC and fluorescent in situ hybridization (FISH) techniques. This study showed no significant correlation between HER2 expression with tumor size and lymph node metastasis. However, the difference between recurrence incidence between HER2 positive and HER2 negative patients was statistically significant (P-value=0.004) (16).

A 2017 cross-sectional study by Rabiee et al. on the expression of HER2 in PTC, which was conducted on 85 patients, showed HER2 expression in 37.6% of the cases. The correlation between HER2 expression and capsular invasion (P-value= 0.000) and between HER2 and tumor size (P-value= 0.000) were significant. However, no significant relationship was found between HER2 expression and lymph node involvement (P-value= 0.649) (17).

In a 2018 cross-sectional study, Kim et al. investigated the HER2 expression using the IHC method in 129 patients with PTC who underwent thyroid surgery. A significant relationship between HER2 expression and both younger age and metastasis to cervical lymph nodes was seen. This study showed no significant correlation between lesion histology, tumor size, extension outside the thyroid gland, and the stage of the tumor (18).

Accordingly, the studies on HER2 expression and its prognostic value in different types of thyroid gland cancers are relatively limited and the published reports are not concordant with each other. Therefore, in this study, we investigated the frequency of HER2 expression in all types of thyroid neoplasms and its relationship with the type and stage of the tumors, as well as the outcome of the patients who underwent thyroidectomy or thyroid lobectomy in Taleghani Hospital from 2018 to 2021.

2. Materials and Methods

2.1. Patients and Samples

From all patients referred to Taleghani Hospital (which is one of the most important academic hospitals in Iran), who underwent thyroidectomy or thyroid lobectomy from 2018 to April 2021, 91 patients entered our study according to the inclusion criteria of having thyroid cancer and the exclusion criteria of patients with any other simultaneous malignancies and patients whose specimens were not available for HER2 evaluation. The patients' medical data including age and sex, and the pathologic characteristics of the tumor, including tumor size, tumor capsular invasion, neurovascular invasion, extranodal spread, and tumor stage were extracted from the patients' medical records. A reevaluation of their H&E-stained slides that were archived in our pathology department was performed in terms of the type of carcinoma and sample characteristics, as well as the adequacy of the specimens for IHC staining, and inappropriate samples were removed. Patients were followed for a 3-year period after diagnosis. Follow-up data were obtained from medical records and, when required, by contacting the patients or their families. Outcomes of interest included disease recurrence and death.

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2.2. Staining Method

After the H&E-stained slides of all the samples were assessed thoroughly, we extracted their paraffin-embedded blocks from our hospital pathology archive for microtomy to undergo IHC staining for HER2 marker from Rabbit anti-human c-erbB2 monoclonal antibody (Clone SP3), which was performed as follows:

- Sections with a thickness of 4 m were prepared on charged slides, and we dried them overnight at a 60°C temperature.
- Then, we deparaffinized and rehydrated the section, and after performing HIER (heat-induced epitope retrieval), we boiled the tissue in 8 pH EDTA buffer for 20 minutes at 95°C. Then we washed them 3 times with distilled water and later cooled them for 20 minutes at room temperature.
- We performed endogenous peroxidase block using peroxidase solution for 10 minutes at room temperature.
- Then we added the primary antibody and incubated them for 10 minutes.
- We used the Master Polymer Plus Detection system (HRP).
- We finally performed counterstaining with hematoxylin and then we fixed the slides.

2.3. Assessment

After the slides were prepared, our pathologists interpreted them. Due to the lack of a specific scoring system for HER2 IHC in thyroid tissue, we used two different scoring systems, and the results were recorded as variables HER2-b and HER2-g. One of these two was the DAKO scoring guideline which is almost always used for breast tissue samples (constituting the data of HER2-b variable), and the other one was the system suggested by Hofmann et al. which is specifically proposed for gastric tumours and is FDA approved (which constituted the HER2-g variable) (19-22).

The DAKO scoring system for the mentioned marker is as follows:

- Score 0 = No or membranous incomplete staining in <10% of tumor cells
- Score 1+ = Faint membranous staining in >10% of tumor cells
- Score 2+ = Weak to moderate complete, basolateral, or lateral membranous staining in >10% of tumor cells
- Score 3+ = Strong complete, basolateral, or lateral membranous staining in >10% of tumor cells
- The scoring system by Hofmann et al. is as follows:
- Score 0 = No membranous staining or staining only in rare cells (less than 5 cohesive cells)
- Score 1+ = Staining is weak or detected in only one part of the membrane of at least 5 cohesive cells
- Score 2+ = Moderate/weak complete or basolateral membranous staining of at least 5 cohesive cells
- Score 3+ = Strong complete or basolateral membranous staining of at least 5 cohesive cells

After the interpretation was done, 2+ and 3+ scores were considered as positive.

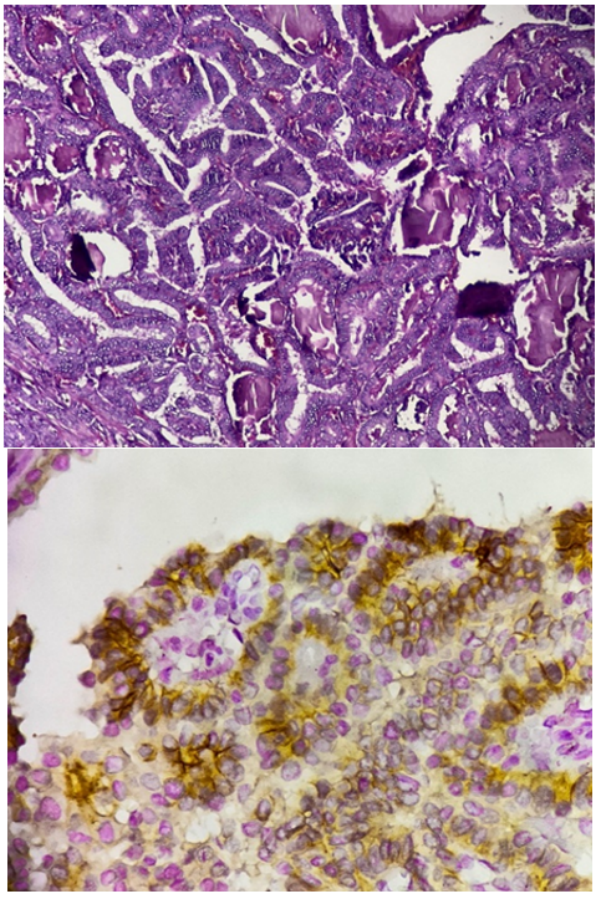

Figure 1: Classical variant of papillary thyroid carcinoma; H&E staining (up) and IHC with 3+ expression (down).

2.4. Statistical Analysis

The data were analyzed by the software SPSS version 26.0. We also used this software for the tables. The Chi-squared and Fisher's exact tests were used to analyze the difference between qualitative variables. To investigate the relationship between HER2 expression (HER2-b and HER2-g) and the age and stage of the tumor, the independent samples t-test was performed. In all the analyses, P-values less than 0.05 were considered significant.

2.5. Ethics Approval and Consent to Participate

The ethical and humane considerations in this study are approved by the research ethics committee of Shahid Beheshti University of Medical Sciences (Code No. IR.SBMU.MSP.REC.1400.140). The consent to participate in the research was not applicable.

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Table 1: Significance of HER2 Expression (HER2-b and HER2-g) in Different Groups of the Variables

		HER2-b		P-value	HER2-g		P-value
		Negative	Positive		Negative	Positive	
Sex	Female	63(91.3%)	6(8.7%)	0.079	52(75.36%)	17(24.64%)	0.141
	Male	17(77.27%)	5(22.73%)		13(59.09%)	9(40.91%)	
Age	≤ 45	41(82%)	9(18%)	0.103	31(62%)	19(38%)	0.036
	≥ 45	39(95.12%)	2(4.88%)		34(82.93%)	7(17.07%)	
Histopathology	ATC	4(100%)	0(0%)	0.86	4(100%)	0(0%)	0.144
	FTC	3(100%)	0(0%)		3(100%)	0(0%)	
	HCC	5(83.33%)	1(16.67%)		5(83.33%)	1(16.67%)	
	MTC	7(100%)	0(0%)		7(100%)	0(0%)	
	PTC	61(85.92%)	10(14.08%)		46(64.79%)	25(35.21%)	
Tumor size	< 2.7 cm	36(87.8%)	5(12.2%)	0.977	31(75.61%)	10(24.39%)	0.424
	> 2.7 cm	44(88%)	6(12%)		34(68%)	16(32%)	
Focality	Multi-focal	31(83.78%)	6(16.22%)	0.317	23(62.16%)	14(37.84%)	0.105
	Uni-focal	49(90.74%)	5(9.26%)		42(77.78%)	12(22.22%)	
Lymph Node Involvement	Negative	13(86.67%)	2(13.33%)	1	9(60%)	6(40%)	0.54
	Positive	20(86.96%)	3(13.04%)		16(69.57%)	7(30.43%)	
Marginal Involvement	Negative	71(86.59%)	11(13.41%)	0.29	57(69.51%)	25(30.49%)	0.44
	Positive	9(100%)	0(0%)		8(88.89%)	1(11.11%)	
Capsular Invasion	Negative	58(86.57%)	9(13.43%)	0.72	48(71.64%)	19(28.36%)	0.94
	Positive	22(91.67%)	2(8.33%)		17(70.83%)	7(29.17%)	
Vascular Invasion	Negative	68(88.31%)	9(11.69%)	0.67	55(71.43%)	22(28.57%)	1
	Positive	12(85.71%)	2(14.29%)		10(71.43%)	4(28.57%)	
Lymphatic Invasion	Negative	70(87.5%)	10(12.5%)	1	58(72.5%)	22(27.5%)	0.723
	Positive	10(90.91%)	1(9.09%)		7(63.64%)	4(36.36%)	
Perineural Invasion	Negative	77(88.51%)	10(11.49%)	0.408	63(72.41%)	24(27.59%)	0.322
	Positive	3(75%)	1(25%)		2(50%)	2(50%)	
Extrathyroidal Extension	Negative	74(88.1%)	10(11.9%)	1	60(71.43%)	24(28.57%)	1
	Positive	6(85.71%)	1(14.29%)		5(71.43%)	2(28.57%)	
Tumor Stage (T)	1	30(88.24%)	4(11.76%)	1	27(79.41%)	7(20.59%)	0.41
	2	22(88%)	3(12%)		17(68%)	8(32%)	
	3	26(86.67%)	4(13.33%)		19(63.33%)	11(36.67%)	
	4	2(100%)	0(0%)		2(100%)	0(0%)	
Tumor Stage (N)	0	13(86.67%)	2(13.33%)	1	9(60%)	6(40%)	0.497
	1	20(86.96%)	3(13.04%)		16(69.57%)	7(30.43%)	
	x	47(88.68%)	6(11.32%)		40(75.47%)	13(24.53%)	
Recurrence	Negative	55(88.71%)	7(11.29%)	0.66	44(70.97%)	18(29.03%)	0.749
	Positive	12(85.71%)	2(14.29%)		9(64.29%)	5(35.71%)	
Survival	Alive	62(88.57%)	8(11.43%)	0.223	50(71.43%)	20(28.57%)	0.195
	Dead	5(71.43%)	2(28.57%)		3(42.86%)	4(57.14%)	
Cause of Death	Lymphoma	1(100%)	0(0%)	0.33	0(0%)	1(100%)	0.4
	Thyroid	4(100%)	0(0%)		3(75%)	1(25%)	
	Unknown	0(0%)	1(100%)		0(0%)	1(100%)	

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3. Results

In this study, we investigated 91 cases of thyroid neoplasm who had undergone thyroidectomy or thyroid lobectomy in Taleghani Hospital, Tehran, Iran from 2018 to April 2021. The youngest and oldest participants were 12 and 69 years old, respectively with the average age being 43.0212.29. The number of our male patients was 22 (24.2%) and 69 (75.8%) were female. Moreover, PTC was the most prevalent histopathology observed (71 cases, 78%) followed by MTC (7.7%), HCC (6.6%), ATC (4.4%), and FTC (3.3%). Among our 91 cases, the marginal involvement was positive in 9 of them (9.9%); Furthermore, there were 54 (59.3%) monofocal and 37 (40.7%) multifocal cases. Capsular, vascular, lymphatic, and perineural invasion, were detected in 24 (26.4%), 14 (15.4%), 11 (12.1%), and 4 (4.4%) of our cases, respectively. Also, lymph node involvement was confirmed in 23 cases (25.3%). The extrathyroidal extension was also confirmed in 7 patients (7.7%). The average size of the tumors was 2.26±3.31 cm. The sizes of the smallest and largest tumors were 2 mm and 12 cm, respectively. Staging of the neoplasms was performed based on the TNM staging system. The tumor stage (T) was T1 in 35 cases (38.5%), T2 in 24 (26.4%), T3 in 30 (33%), and T4 was seen in 2 of our patients (2.2%). In 53 cases (58.2%), the evaluation of regional lymph node invasion was not possible (Nx), while the other ones included 15 cases with N0 (no regional lymph node metastasis) and 23 cases with N1 stage. During the evaluation of HER2 receptor expression, by the DAKO scoring system, 80 cases (87.9%) were confirmed as HER2-b negative and 11 ones (12.1%) as HER2-b positive. Of the 11 HER2-b positive cases, 10 were 2+ and one of them was 3+. Among these 11 HER2-b positive cases, 10 were PTC and one was HCC. From the 80 HER2-b negative cases, 58 were 0, and 23 were 1+. Furthermore, the interpretation according to the gastric scoring system by Hofmann et al. (21), confirmed 26 cases (28.6%) as HER2-g positive and 65 ones (71.4%) as HER2-g negative. The HER2-g positive cases consisted of 7 cases with 3+ and 19 ones with a 2+ score, and these 26 cases included 25 PTC and one HCC. Moreover, 10 of the HER2-g negative cases were 1+ and the remaining 55 were scored as 0.

We were able to contact 76 of our cases (83.5%) to perform the follow-up; 14 of which (18.4%) had undergone recurrence in the first 3 years after the initial diagnosis. PTC was the most common pathology in patients who had undergone recurrence (12 cases; 15.8%). The follow-up also revealed 7 deaths (9.2%) among the 76 patients, 6 of which were due to their thyroid cancer (4 from PTC and 2 from ATC), and one death was due to lymphoma (onset: after thyroid cancer). The 3-year survival of the patients was calculated as 90.8%.

The Chi-squared test and Fisher's exact test were used to analyze the difference between the qualitative variables of our study, which showed no significant difference between HER2 positive and negative cases in relation to any of these variables. Independent samples t-test and Mann-Whitney U test were also used to assess the relationship between HER2 expression and the variables of age and tumor size, which showed no significant difference between HER2 positive and negative cases, except between HER2-g and age, which showed a significant overexpression of HER2 in patients of less than 45 years of age (P-value= 0.036), while the relationship was not significant between HER2-b and age (0.103). Table 1 demonstrates the difference of all of our variables in HER2 positive and negative groups and the p-values calculated. The analysis showed no significant relationship between HER2 (HER2-b or HER2-g) and the type of thyroid carcinoma (P-values= 0.86 and 0.144 respectively), and also none with the stage of cancer (P-values= 1 and 0.41 for T stage and 1 and 0.497 for N stage, respectively). There was no significant relationship between HER2 and any of the characteristics related to the aggressive behavior of the tumor either. The analysis also did not reveal any significant relationship between HER2-b and HER2-g, and the variables of patients' sex (P-values= 0.71 and 0.141), the recurrence (P-values= 0.66 and 0.749), the survival (P-values= 0.223 and 0.195) or the cause of death (P-values= 0.33 and 0.4).

4. Discussion

In this study, we assessed 91 patients who underwent thyroidectomy or thyroid lobectomy in Taleghani Hospital, Tehran, Iran from 2018 to April 2021, to investigate the correlation between HER2 expression and the characteristics of thyroid carcinomas among them. The only significant relationship was found between age and HER2 expression when we interpreted the HER2 IHC-stained slides using the gastric scoring system by Hofmann et al. (P-value= 0.036), while there was not any other significant difference detected between the HER2 positive and negative groups in the investigated variables.

One noteworthy aspect of our study was that we included all subtypes of thyroid neoplasm, unlike most studies in this area. Another novel feature of our work was that we interpreted the results of our HER2 IHC stained slides according to two different scoring guidelines (DAKO and the gastric scoring systems), which also led to a detailed comparison between the results of these two guidelines and their correlation with the different variables of our study.

In the 2003 study by Mondi et al., the thyroid tissue samples of 46 female and 9 male patients, of which 36 had thyroid neoplasm and 19 had benign thyroid tissue were studied. The results showed no significant HER2 overexpression in any of the studied groups, leading to the conclusion that HER2 may not have a predictive value for thyroid cancer (9).

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However, in the study by Kremser et al. on 103 cases of PTC and FTC in the same year, they evaluated the predictive value of HER2 in differentiated neoplasms of the thyroid. They conducted a follow-up for at least 8 years, including the incidence of metastasis in their study sample. The results showed a significant HER2 expression in metastatic PTC and FTC cases, suggesting a significant correlation between HER2 and the prognosis (14). The results of these two studies were not concordant in terms of the prognostic value of HER2 expression. Furthermore, our study results were in agreement with the study by Mondi et al. since our results indicated no significant correlation between HER2 and any of the prognostic variables; however, unlike the study by Kremser et al., our study did not include distant metastasis as one of its variables. Furthermore, we studied all subtypes of thyroid carcinoma, while Kremser et al. studied only PTC and FTC cases, and Mondi et al. studied neoplastic and also benign cases.

In 2005 Freudenberg et al. studied the prognostic value of HER2 expression in PTC cases, of which 34% were HER2 positive. This study showed a significant relationship between HER2 expression and the recurrence of the tumor (P-value= 0.02), and also a statistically significant relationship between HER2 and the patients' survival (P-value= 0.03), therefore suggesting HER2 expression as a prognostic factor in the PTC patients' clinical course (15). However, our study showed no significant relationship between HER2 expression and the two variables of recurrence and survival. The difference in the results of these two studies can be due to the different sample sizes and also the fact that they focused only on PTC, while our sample included the other subtypes as well.

In the 2016 study by Ruggeri et al. on 45 FTC and 45 PTC cases using IHC and FISH techniques, it was demonstrated that in the PTC group, HER2 expression was negative in 12 cases (26.7%), 2+ in 15 patients (33.3%) and in 18 ones (40%) it was 3+. In the FTC group, HER2 expression was negative in 30 patients (66.6%), 2+ in 7 cases (15.5%), and 3+ in 8 ones (17.7%). All 2+ cases were investigated with FISH, which showed that HER2 was positive in 44% of FTCs and 18% of PTCs. The observed difference in HER2 expression between these two types of thyroid neoplasm was statistically significant (P-value = 0.046), although this significance is considered borderline. In this study, there was no significant relationship between HER2 expression and the variables of tumor size and lymph node metastasis at the time of surgery (16). The lack of accordance between the findings of Ruggeri et al. with the results of our study can be due to the higher number of cases of FTC among their sample and the different applied techniques.

In the 2017 study by Rabiee et al. on 85 patients (88.2% female and 11.8% male) suffering from PTC who underwent thyroidectomy, they studied HER2 expression in this subtype of thyroid cancer. The evaluation showed HER2 expression in 37.6% of the cases. The correlations between HER2 expression and the variables of capsular invasion (P-value= 0.000) and tumor size (P-value= 0.000) were significant. However, the relationship between HER2 expression and lymph node involvement was not statistically significant (P-value= 0.649) (17). The incidence of HER2 overexpression in this study was higher than ours. Also, our results were not concordant with the results of the study by Rabiee et al., since our results showed no significant correlation between HER2 and the variables of capsular invasion and tumor size. This lack of accordance can be due to the different study populations in these two studies, since they focused on PTC patients, while our study included PTC, FTC, MTC, ATC, and HCC cases.

Kim et al. observed that HER2 expression was positive in 15.5% of 129 PTC patients and had a significant relationship with age less than 45 years and metastasis to cervical lymph nodes, with p-values of 0.019 and 0.022, respectively. However, they did not observe a significant relationship between HER2 expression with tumor size, extrathyroidal extension, tumor histology, and tumor stage (18). The association of HER2 and younger age is accordant with the findings of our study; however, our study did not show any correlation between HER2 and lymph node involvement by the cancer. Moreover, the significant correlations between HER2 and the two variables of age and lymph node metastasis were contrary to the results of the other studies mentioned above.

Therefore, we concluded that the utilization of IHC for HER2 detection in different types of thyroid neoplasms, might not have a definitive diagnostic or predictive value for pathologists to evaluate the type and severity of these carcinomas and their histologic characteristics, hence their prognosis. Our study also showed that the two scoring systems of HER2 interpretation that we used (DAKO and the gastric system by Hofmann et al.) are probably not significantly different than each other in the interpretation of HER2 staining results in thyroid specimens. However, the patients younger than 45 years old, had an overexpression of the HER2 receptor with a significant difference (P-value= 0.036) when HER2 was interpreted by the gastric scoring system, compared to the other age group, which can be useful in future studies in this area.

5. Conclusion

In this study, there was no significant relationship found between HER2 expression and tumor type, tumor size, or any of the other variables of our study, except between age and HER2 expression, when it was interpreted by the gastric scoring system (by Hofmann et al.). Conducting more extensive studies, with larger sample sizes, and methods based on molecular identification can help to better clarify the role of HER2 expression as a diagnostic and predictive biomarker. Furthermore, we suggest that new studies be designed and

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conducted to introduce new scoring guidelines to interpret HER2 IHC staining results in thyroid samples to enable us to better utilize this marker in the diagnosis and prognosis of the neoplasms of this organ in future cases.

6. Limitations

One of our limitations was the failure to comply with the proportionality between the frequencies of different types of thyroid neoplasm, which creates limitations for some statistical analyses. It is also suggested to use molecular methods to check the expression of HER2 in the target tissue in future studies. On the other hand, the lack of proper distribution between different stages of the neoplasms leads to a decrease in the statistical efficacy of analysis especially in the more severe stages.

7. Appendix

7.1. Acknowledgment

We would like to express our sincere gratitude to all individuals and organizations who contributed to this study but did not meet the criteria for authorship. This includes the Vice-Chancellor's Office for Research, School of Medicine, Shahid Beheshti University of Medical Sciences, for their support.

7.2. Conflict of Interest Statement

The authors declare no conflicts of interest related to the research, authorship, or publication of this article.

7.3. Funding

This study did not receive any external funding.

7.4. Author's contributions

Each author contributed to the manuscript in the following ways:
1. Mahdieh Fahimi: [Data Collection, Statistical Analysis Interpretation, Writing – Original Draft]
2. Mahsa Mohammadi Maram: [Data Collection, Statistical Analysis]
3. Fereshteh Kamani: [Data Collection]
4. Zhaleh Mohsenifar: [Conceptualization, Methodology, Project Administration and Supervision, Writing – Review & Editing] All authors have read and approved the final version of the manuscript.

7.5. Data Availability

The data supporting the study's findings are available and can be provided to others upon reasonable request.

7.6. Abbreviations

HER2: Human epidermal growth factor receptor 2; GI: Gastrointestinal; H&E: Hematoxylin and eosin; IHC: Immunohistochemistry; PTC: Papillary thyroid carcinoma; FTC: Follicular thyroid carcinoma; HCC: Hurthle cell carcinoma; MTC: Medullary thyroid carcinoma; ATC: Anaplastic thyroid carcinoma; FISH: Fluorescent in situ hybridization.

References

1. Yang Y, Bai X, Lu J, Zou R, Ding R, Hua X. Assessment of five typical environmental endocrine disruptors and thyroid cancer risk: a meta-analysis. Front Endocrinol (Lausanne). 2023;14:1283087.
2. Kilfoy BA, Zheng T, Holford TR, Han X, Ward MH, Sjodin A, et al. International patterns and trends in thyroid cancer incidence, 1973-2002. Cancer Causes Control. 2009;20(5):525-31.
3. Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. J Cancer Epidemiol. 2013;2013:965212.
4. Amaral M, Afonso RA, Gaspar MM, Reis CP. Anaplastic thyroid cancer: How far can we go? Excli j. 2020;19:800-12.
5. Hu J, Yuan IJ, Mirshahidi S, Simental A, Lee SC, Yuan X. Thyroid Carcinoma: Phenotypic Features, Underlying Biology and Potential Relevance for Targeting Therapy. Int J Mol Sci. 2021;22(4).
6. Giuffrida D, Scollo C, Pellegriti G, Lavenia G, Iurato MP, Pezzin V, et al. Differentiated thyroid cancer in children and adolescents. J Endocrinol Invest. 2002;25(1):18-24.
7. Kondo T, Ezzat S, Asa SL. Pathogenetic mechanisms in thyroid follicular-cell neoplasia. Nat Rev Cancer. 2006;6(4):292-306.
8. Solomon B, Rischin D. Progress in molecular targeted therapy for thyroid cancer: vandetanib in medullary thyroid cancer. J Clin Oncol. 2012;30(2):119-21.
9. Mondi MM, Rich R, Ituarte P, Wong M, Bergman S, Clark OH, et al. HER2 expression in thyroid tumors. Am Surg. 2003;69(12):1100-3.
10. Rubin I, Yarden Y. The basic biology of HER2. Ann Oncol. 2001;12 Suppl 1:S3-8.
11. Meric-Bernstam F, Johnson AM, Dumbrava EEI, Raghav K, Balaji K, Bhatt M, et al. Advances in HER2-Targeted Therapy: Novel Agents and Opportunities Beyond Breast and Gastric Cancer. Clin Cancer Res. 2019;25(7):2033-41.
12. Zhu Y, Zhu X, Wei X, Tang C, Zhang W. HER2-targeted therapies in gastric cancer. Biochim Biophys Acta Rev Cancer. 2021;1876(1):188549.
13. Sodergren SC, Copson E, White A, Efficace F, Sprangers M, Fitzsimmons D, et al. Systematic Review of the Side Ef-

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fects Associated With Anti-HER2-Targeted Therapies Used in the Treatment of Breast Cancer, on Behalf of the EORTC Quality of Life Group. Target Oncol. 2016;11(3):277-92.
14. Kremser R, Obrist P, Spizzo G, Erler H, Kendler D, Kemmler G, et al. Her2/neu overexpression in differentiated thyroid carcinomas predicts metastatic disease. Virchows Arch. 2003;442(4):322-8.
15. Freudenberg LS, Sheu S, Görges R, Mann K, Bokler S, Frilling A, et al. Prognostic value of c-erbB-2 expression in papillary thyroid carcinoma. Nuklearmedizin. 2005;44(5):179-82, 84.
16. Ruggeri RM, Campennì A, Giuffrè G, Giovanella L, Siracusa M, Simone A, et al. HER2 Analysis in Sporadic Thyroid Cancer of Follicular Cell Origin. Int J Mol Sci. 2016;17(12).
17. Rabiee S, Nadoushan MJ, Rayeni NM, Ansari I. Correlation between human epidermal growth factor receptor 2 oncoprotein expression and some prognostic factors in papillary thyroid carcinoma. Indian J Pathol Microbiol. 2017;60(3):324-7.
18. Kim Y-S, Kim J-S, Kim Y-S. EGFR and HER2 Expression in Papillary Thyroid Carcinoma. Journal of Endocrine Surgery. 2018;18:228.
19. Siraj AK, Beg S, Jehan Z, Prabhakaran S, Al-Sobhi SS, Al-Dawish M, et al. The role of HER2 overexpression in Middle Eastern papillary thyroid cancer. Translational Cancer Research. 2017;6(2):366-73.
20. Abrahao-Machado LF, Scapulatempo-Neto C. HER2 testing in gastric cancer: An update. World J Gastroenterol. 2016;22(19):4619-25.
21. Hofmann M, Stoss O, Shi D, Büttner R, van de Vijver M, Kim W, et al. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. Histopathology. 2008;52(7):797-805.
22. Rüschoff J, Dietel M, Baretton G, Arbogast S, Walch A, Monges G, et al. HER2 diagnostics in gastric cancer-guideline validation and development of standardized immunohistochemical testing. Virchows Arch. 2010;457(3):299-307.

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