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Evaluation of HER2 cell surface protein expression in differentiated thyroid cancers and its relationship with tumor size and stage

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ABSTRACT

Background and Aims: We aimed to evaluate the expression of HER2 marker in differentiated thyroid cancers and its correlation with tumor size and stage.

Materials and Methods: This is a cross-sectional study that was performed at Tehran Shohada-E-Tajrish hospital from 2015 to 2019. Patients with differentiated thyroid cancer were enrolled in the study. Patients' baseline characteristics and tumor properties were recorded. Expression of tumor marker testing was conducted with IHC. Analysis was performed with SPSS version 20.

Results: Fifty cases of thyroid cancer with a mean age of 46.6 years (78% females) were evaluated. 86% of cases were PTC, 10% FTC, and 4% hurthle cell carcinoma. HER2 positivity rate was 34% totally. HER2 positivity in FTC and PTC patients was 40% and 34.9%, respectively. 84% of patients had a sporadic tumor. HER2 positivity rate in sporadic tumors was 28.6% and 62.5% in familial cases (p=0.063). HER2 status did not association with clinicopathologic factors, significantly.

Conclusion: With the findings of our study, HER2 can't be considered a prognostic factor associated with clinicopathologic parameters.

INTRODUCTION

Thyroid cancer is the greatest prevalent endocrine system cancer. Medullary, anaplastic, and differentiated including papillary, follicular, and hurtle are the three major histologic forms.[1-3] Ionizing radiation exposures and a few rare familial syndromes are among the few known risk factors for thyroid cancer. Thyroid cancer is more common in women, according to epidemiological findings.[4, 5] The fact that thyroid cancer is more common in women during their menstrual years indicates that estrogen and progesterone may play important roles in thyroid cancer pathogenesis. Thyroid cancer risk was found to be lower in women after menopause. [6, 7] Several human epithelial tumors, including breast, ovarian, gastric, and colorectal cancers, have the human epidermal growth factor receptor 2 (HER2) gene enhanced and the protein overexpressed. [8-10] Overexpression and amplification of HER2 have been related to a poor outcome and a poorly differentiated phenotype in these tumors. [8, 11] The HER2 is of special interest in tumor biology since it is both a powerful predictive factor in a variety of tumor types and a very useful therapeutic target in breast and stomach cancer. There isn't enough evidence to determine that HER2 has an effect in thyroid cancer. In some studies it was observed that in involving thyroid patients, reported HER2 overexpression rates range from 0% to 79.5 percent. [12-16] In the recent literature, there is very little general agreement on this marker's possible prognostic and therapeutic importance in thyroid cancer. [17, 18] Due to there is a low consensus about the effect of HER2 on thyroid cancer and its relationship with size and stage of tumors, in this study, we aimed to investigate the expression of HER2 surface protein in differentiated thyroid cancer and evaluation of its relationship with stage and size of tumors.

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MATERIALS and METHODS

This study was approved by ethical committee of medical university of Shahid Beheshti and it took ethical code from this committee (IR.SBMU.MSP.REC.1398.870). In this descriptive cross-sectional study, patients who were referred to Shohada-e-Tajrish Hospital (Tehran-Iran) for thyroid cancer surgery from 2015 to 2018 with thyroid cancers, were studied. All patients in this duration were studied. The inclusion criterion was having differentiated thyroid cancer and exclusion criteria were patients with other concomitant malignancies, patients who did not consent to study, patients whose samples were not available for HER2 testing, and undifferentiated cancers in pathology. Five hundred and fifty-eight patients were evaluated and finally, 50 patients were enrolled in the study according to inclusion and exclusion criteria.

Written informed consent was obtained from all patients to participate in the study and no costs were imposed on patients. Patient's data including age, sex, and family history were asked from them. Tumor characteristics including pathology type, tumor size, tumor invasion status were determined by preoperative and postoperative pathological examination and evaluation of surface protein expression. HER2 tumor cells were analyzed by IHC. All histopathologic specimens were studied by a specific expert pathologist during the study.

Follow-ups of patients (one week, six months, and one year after surgery) were performed over time, and recovery status, recurrence, or mortality was recorded. Whole-exon mutation data were extracted from the Thyroid Cancer Genomic Data Analysis Center (GDAC) for genetic analysis. HER2-related information was obtained from this center and their mutations were assessed in patient samples.

Statistical analysis

SPSS software version 20 was used for data analysis. Absolute and relative abundance of markers was reported in the subgroups. In non-parametric data, the Mann-Whitney U test was used to compare patients age and tumor size between groups and used Chi-square test to compare difference between percent's in each categorical factors. Statistically significant limit (p-value) was considered lower than 0.05.

RESULTS

In this study, 50 differentiated thyroid cancers were studied with a mean age of 46.60 ± 13.96 years. Thirty-nine patients were female (78%) and 11 (22%) were male. Histologically, 5 cases (10%) had follicular thyroid carcinoma, 2 cases (4%) had hurthle cell cancer and 43 cases (86%) had papillary thyroid carcinoma. The HER2 marker was negative in 33 cases (66%) and overexpressed in 17 cases (34%). In terms of family distribution pattern, 42 cases (84%) had a sporadic pattern and 8 cases (16%) had cancer with a familial distribution pattern. The mean of the largest tumor diameters in this study was 2.32 ± 2.33 cm. In terms of staging, 35 patients (70%) had stage I and 15 patients (30%) stage II. In terms of tumor invasion depth (T), 33 cases (66%) were T1, 11 cases (22%) were T2, and 6 cases (12%) were T3. In terms of lymph node involvement, 39 patients (78%) did not have lymph node involvement and 11 patients (22%) had lymph node involvement.

The patient's gender composition was measured by HER-2 status. In females, 25 patients (64.1%) were negative and 14 patients (35.9%) were positive for HER2. Among males, 8 cases (72.7%) were negative and 3 cases (27.3%) were positive for HER2 ($p = 0.594$ -based on chi square.) The age of patients in the HER2 positive group was 45.88 ± 16.73 years and in the HER-2 negative group was 47.06 ± 12.57 years ($p = 0.780$). There was no statistically significant difference between HER2 positive and negative groups in the terms of age and sex.

In follicular thyroid carcinoma cases, 3 patients were HER2 negative (60%) and 2 patients were HER2 positive (40%). In Hurthle cell cases, 2 patients (100%) were HER2 negative. In PTC cases, 28 patients (65.1%) were HER2 negative and 15 patients (34.9%) were HER2 positive ($p = 0.570$ -based on chi square).

Between sporadic cases, 30 patients (71.4%) were HER2 negative and 12 patients (28.6%) were HER2 positive and in familial cases, 3 patients (37.3%) were HER2 negative and 5 patients (62.5%) were HER2 positive ($p = 0.063$-based on chi square).

The mean tumor size in the HER2 positive group was 2.63 ± 2.49 cm and in the HER2 negative group was 2.16 ± 2.26 cm ($p = 0.509$). In terms of disease stage, in stage-1 cases, 23 patients (65.7%) were HER2 negative and 12 patients (34.3%) were HER2 positive. In stage-2, 10 patients (66.7%) were HER2 negative and 5 patients (33.3%) were HER2 positive ($p = 0.948$-based on chi square).

In T1 cases, 24 patients (72.7%) were HER2 negative and 9 patients (27.3%) were HER2 positive. In T2 cases, 5 patients (45.5%) were HER2 negative and 6 patients (54.5%) were HER2 positive. In T3 cases, 4 patients (66.7%) were HER2 negative and 2 patients (33.3%) were HER2 positive ($p = 0.255$-based on chi square). In cases with N0, 27 patients (69.2%) were HER2 negative and 12 patients (30.8%) were HER2 positive. In N1 cases, 6 patients (54.5%) were HER2 negative and 5 patients (45.5%) were HER2 positive ($p = 0.364$-based on chi square).

In the following, we have analyzed the parameters based on the histological type of cancer and due to the very small number of Hurthle cases, we excluded them from the analysis.

The gender compositions were: in follicular cases, 4 patients were female (80%) and 1 was male (20%) and in the PTC cases, 33 patients (76.7%) were female and 10 patients (23.3%) were male ($p = 0.735$-based on chi square). The patient's age in the follicular group was 45.20 ±12.93 years and in the PTC group was 47.11 ±14.43 years ($p = 0.778$-based on Mann-Whitney U-test). In the follicular group, all cases (100%) were sporadic, and in the PTC group, 36 cases were sporadic (83.7%) and 7 cases (16.3%) were familial

(p = 0.262- based on chi square). Tumor size in the follicular group was 5.70 ± 3.09 cm and in the PTC group was 1.89 ± 1.95 cm (p <0.001- based on Mann-Whitney U-test).

In terms of disease stage, in the follicular group, 2 patients (40%) were in stage 1 and 3 patients (60%) were in stage 2. In PTC cases, 31 patients (72.1%) were in stage 1 and 12 patients (27.9%) were in stage 2 (p = 0.213- based on chi square).

In terms of tumor invasion depth, in the follicular group, 3 cases (60%) were T2 and 2 cases (40%) were T3. In the PTC group, 32 cases (74.4%) were in T1 stage, 7 patients (16.3%) were in T2 stage and 4 patients (9.3%) were in T3 stage (p = 0.016- based on chi square).

In terms of lymph node involvement in the follicular group, N0 in 4 patients (80%) and N1 in 1 patient (20%) were seen. In the case of PTC, 33 patients (76.7%) were N0 and 10 patients (23.3%) were N1 (p = 0.735- based on chi square).

The status of the parameters was analyzed based on the sporadic/familial distribution of the tumors. Among females, 32 cases (82.1%) were sporadic and 7 cases (17.9%) were familial and in the males, 10 cases (90.9%) were sporadic and 1 case (9.1%) was familial (p = 0.479- based on chi square). the mean patient's age was 45.61± 13.70 years in sporadic cases and 52.12 ± 14.98 years in familial cases (p = 0.231). Tumor size in sporadic cases was 2.17 ± 2.38 cm and in familial cases was 3.15 ± 1.94 cm (p = 0.281). About staging, in sporadic cases, tumor stages were stage 1 in 30 cases (71.4%) and stage 2 in 12 cases (28.6%) and in familial cases, in 5 cases (62.5%) were in the stage 1 and 3 cases (37.5%) were in the stage 2 (p = 0.614- based on chi square). About the depth of tumor invasion in sporadic cases, 31 cases were (73.8%) T1, 7 cases (16.7%) were T2 and in 4 cases (9.5%) were T3 and in familial cases, 2 cases (25%) were T1, 4 cases (50%) were T2 and 2 cases (25%) were T3 (p = 0.028- based on chi square).

In sporadic cases, 33 cases (78.6%) were N0 and 9 cases (21.4%) were N1 and in familial cases, 6 cases (75%) were N0 and 2 cases (25%) were N1 (p = 0.823- based on chi square).

There was no mortality in all patients during the study.

DISCUSSION

In the current study that was performed on 50 patients with thyroid cancers including PTC, FTC, and hurthle cell, 78% were female and 22% were male. About subtypes of carcinomas, FTC in 10%, hurthle cell in 4%, and PTC in 86% was seen. HER2 was negative in 33 cases (66%) and overexpressed in 17 cases (34%), overall. In the Ruggeri et al study, it was found HER2 overexpression was discovered in 20/45 (44%) FTC and 8/45 (18%) PTC, and it had a significant difference. We found that HER2 was positive in 40% of cases with FTC. In PTC cases, HER2 was positive in 34.9% of cases. Our findings were similar to Ruggeri et al study, approximately. In fact, about the relationship between FTC and HER2, these findings were similar but about HER2 relationship with PTC, there was a contrast between these two studies. This difference may be coming from the understudy population because, in the present study, 50 patients were studied but in the Ruggeri et al study, it was 90 patients.[19]

In the Dai et al study, it was demonstrated that there was a significant correlation between HER2 and PTC. In fact, there was a positive correlation between HER2 and PTC, and overexpression of HER2 can increase the risk of PTC occurrence. In the present study, we observed HER2 positive cells were seen in about 35% of patients with PTC. We saw HER2 had more correlation with FTC. In the Dai et al study HER2 relationship with FTC did not assess. About the relationship between PTC andHER2, it seems these studies are similar. [20]

In the Wei et al study, it was concluded that HER2 is a potential biomarker for anaplastic thyroid cancer. In the current study, we found that HER2 could be found in PTC and MTC but we didn't evaluate this relation with anaplastic thyroid cancer.[21]

In the Kavanagh et al study it was found that HER2 was associated with poorly differentiated tumors, tumor invasion, and disease relapse. In the current study, although we observed invasion mount of HER2 positive carcinomas were not statistically significant and HER2 negative carcinomas had a higher amount of invasion than HER2 positive, HER2 positive carcinomas had considerable rates of invasion, and some studies should be performed in the future. Also, in the present study, 34.3% of HER2 positive carcinomas were stage1, 33.3% of them were in stage2 and all of them didn't have a statistically significant difference. In fact, HER2 did not correlate with types of differentiation. These studies are different in findings . [22]

In the Zhang et al study, it was found that there was a significant relationship between differentiated thyroid carcinomas size and mortality, especially about PTC. Higher tumor size had a higher hazard ratio for mortality. In the current study, we saw there was no relation between mortality rate and size of tumors and follicular type had higher size than PTC. These findings are very different. One of the reasons for this difference could be the difference in follow-up duration in the two studies. In the current study, all patients were followed up for one year but in the Zhang et al study, it was about 2 years. This could be the cause of mortality in Zhang et al study. Also, in the Zhang et al study, all patients were in stage4 for differentiated carcinomas and it could be another reason for the difference. In the current study, FTCs had a higher size than PTCs and it was another difference between these studies. [23]

In our study, the sporadic or familial distribution of thyroid cancer in HER2 positive patients in 28.6% of cases, and in 62.5% of cases it was familial, but this difference was not significant. A study by Caria et al found a significant relationship of HER2 with familial type in PTC. These findings in these two studies were different. Also, these studies were different in terms of method of study because our study was performed on all differentiated thyroid cancer but Caria et al

study was performed on PTC. [24] In the Jiwang et al study it was mentioned that there was a significant relationship between T and N stage between the familial and sporadic PTC. These findings were approximately similar to our results because in the current study we found that higher sporadic pattern in PTC but this difference was not statistically significant [25].

CONCLUSION

There is no significant difference between age, sex, type on differentiated thyroid cancer, sporadic/familial type, TMN scoring with HER2 positivity or negativity. Also, between PTC and FTC there were no statistically significant differences in sex, age, familial/sporadic type, staging, and lymph node involvement. But there were significant differences between FTC and PTC in terms of size and depth of tumor invasion of the tumor. Overall, there was a significant difference between the depth of tumor invasion in the sporadic and familial types of tumors.

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