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Can ratio of the biggest tumor diameter to total tumor diameter be a new parameter in the differential diagnosis of agressive and favorable multifocal papillary thyroid microcarcinoma?

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ABSTRACT

Objectives: In this study, we aimed to evaluate the usefulness of a new parameter –ratio of the biggest tumor diameter to total tumor diameter- for the differentiation of agressive and favorable papillary thyroid microcarcinomas (PTMC).
Materials and methods: The diameter of the biggest tumor focus was taken as the primary tumor diameter. Total tumor diameter was calculated as the sum of the maximal diameter of each lesion. Ratio of primary tumor diameter to total tumor diameter was defined as tumor diameter ratio (TDR). Positive and negative predictive value, sensitivity and specificity of TDR to predict capsular invasion, extrathyroidal extension (ETE) and lymph node metastasis (LNM) were determined.
Results: Mean TDR was significantly lower in multifocal PTMC patients with capsular invasion, ETE, lymphovascular invasion and LNM compared to patients without these features. The sensitivities of TDR for the detection of LNM, ETE and capsular invasion were 100%, 100% and 94.2%, respectively. Specificity of TDR was 86.2% for LNM, 88% for ETE and 94.7% for capsular invasion. Best cut off values of TDR that can predict capsular invasion, ETE and LNM in multifocal PTMC were 0.62, 0.57 and 0.56, respectively. Multifocal papillary thyroid carcinoma patients with capsular invasion, ETE and LNM had significantly lower mean TDR when compared to ones without these features.
Conclusion: Decreased TDR was associated with capsular invasion, ETE and LNM in patients with multifocal PTMC and PTC. This new parameter might be particularly helpful for the detection of aggressive behavior in multifocal PTMCs.

Introduction

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer accounting for approximately 85% of all thyroid malignancies [1]. Papillary thyroid microcarcinoma (PTMC) is defined as PTC equal to or less than 1 cm and its incidence has increased by 40% in the last three decades. This increase was mainly attributed to the extensive use of thyroid ultrasonography (US) and US-guided fine-needle aspiration biopsy (FNAB), and more detailed histopathological examination of surgical specimens [2,3]. Despite this significant increase in PTMC incidence, optimal management is still controversial in these patients. Although, PTMC is generally known as an indolent disease with favorable prognosis, aggressive behavior was also reported in some patients in spite of the best available treatment. The risk factors associated with aggressive behavior of PTMC are not well defined. Determination of specific features related with tumoral behavior and prognosis might be helpful to decide clinical management and follow-up in patients with PTMC [3].

Multifocal or bilateral involvement is not rare in PTCs and multifocality is found in as many as 30–40% of all PTMCs [4]. Multifocality was explained by either the coexistence of independent tumoral foci or intrathyroidal metastasis from the primary tumor. Tumors of the latter origin are likely to be aggressive and, accordingly, require aggressive treatment [5]. Molecular pathogenesis, prognostic value, optimal treatment and follow-up of multifocal PTCs remain unclear. Multifocal tumors were associated with

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metastatic disease, recurrence, persistence, higher primary tumor diameter and increased mortality in some previous studies [6–8]. However, several studies did not support the clinical significance of tumoral multifocality and showed that it was not a risk factor for recurrence and metastasis [9,10]. Most of the additional tumoral foci other than the biggest tumor are generally small and detected incidentally [6,11]. The impact of these additional tumors on aggressive behavior is controversial [12]. Evaluation of the biggest tumor size may cause underestimation of tumoral behavior in multifocal carcinomas.

Identifying clinical and pathological features of thyroid cancer that are suggestive of aggressive is important. In this study, we aimed to evaluate the role of the primary tumor diameter to total tumor diameter ratio as a new parameter in predicting tumoral behavior in multifocal PTMCs. We also tried to determine best cut-off values of this parameter that can help to predict aggressive histopathological features.

Materials and methods

We reviewed the database of 2910 patients who underwent total thyroidectomy and diagnosed with PTC or PTMC in our hospital between January 2007 and December 2014. Patients with thyroid lymphoma, anaplastic thyroid carcinoma, medullary thyroid carcinoma, a second malignancy and patients who had history of radiotherapy to the head and neck region were excluded. Patients with unilateral resection and/or incomplete pathological reports were also excluded. PTC that measured 1 cm or less in diameter was classified as PTMC, and PTC measuring greater than 1 cm was labeled as PTC. Age, gender, tumor size, the number of tumor foci, bilaterality, cervical lymph node involvement, extrathyroidal extension (ETE), capsular invasion, radioactive iodine (RAI) therapy and clinical status at the last visit were determined in each patient. Multifocality was defined as 2 or more tumor foci within the thyroid. Bilateral disease was defined when tumoral lesions were detected in both the right and left lobes of the thyroid gland. For multifocal tumors, the one with the biggest diameter was accepted as the primary tumor and the diameter of this focus was taken as the primary tumor diameter. Sum of the maximal diameter of each tumor focus was accepted as total tumor diameter. Consequently, primary tumor diameter was divided by total tumor diameter in each patient and a ratio was obtained which we call tumor diameter ratio (TDR) (primary tumor diameter / total tumor diameter = TDR). Sensitivity, specificity, positive predictive value and negative predictive value of this ratio for the prediction of capsular invasion, ETE and lymph node metastasis (LNM) in multifocal PTMC and PTC were determined. Capsular invasion was defined when thyroid capsule was infiltrated by tumor, but there was no invasion in the surrounding soft tissue and sternothyroid muscle. Invasion of surrounding soft tissue and sternothyroid muscle was defined as ETE.

Neck US and serum thyroglobulin and anti-thyroglobulin antibody (Anti-Tg) measurements were made in the postoperative period with intervals determined according to the clinical status of the patients. Suspicious lymph nodes were evaluated by US guided FNAB and washout Tg levels. The criteria for remission were no clinical or imaging evidence of tumors, serum thyroglobulin levels <2 ng/ml during thyroid-stimulating hormone suppression and stimulation in the absence of Anti-Tg. Patients who never met remission criteria throughout the follow-up periods were assigned to the disease persistence group. Recurrence was defined as a patient who met the remission criteria but then developed evidence of disease in follow-up. The study protocol was approved by the local ethics committee.

Statistical analysis

Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL) was used for statistical analysis. Shapiro-Wilk test was used to check normal distribution of variables. Continuous variables with normal distribution were given as mean ± standard deviation, and continuous variables without normal distribution were given as median (minimum-maximum). Numbers and percentages of categorical variables were presented. Comparison of continuous variables with normal distribution was made by Student *t*-test and comparison of tumoral foci groups was made by ANOVA test. Continuous variables without normal distribution were compared by Mann-Whitney *U* test in two groups and Kruskall Wallis H test in more than 2 groups. Chi-square test and Fisher's exact chi-square test were used to compare categorical variables. In case chi-square conditions are not met, Yates's correction or Monte-Carlo simulation were performed. Independent predictors for LNM were determined by regression models. Diagnostic discrimination of possible risk factors and independent predictors was investigated by ROC curve analysis. Cut-off values were determined by Youden index method. A p value <0.05 and 95% confidence intervals were used to indicate statistical significance.

Results

Clinicopathological features of patients

There were 166 patients with multifocal PTMC and 142 patients with multifocal PTC. Among patients with multifocal PTMC, 29 (17.5%) were male and 137 (82.5%) were female with a mean age of 52.0 ± 11.6 years. The majority (74.1%) of the patients were older than 45. Bilaterality was observed in 91 (54.8%) PTMC patients and 109 (65.7%) patients had 2, 36 (21.7%) had 3 and 21 (12.7%) had 4 or more foci. Mean TDR was 0.67 ± 0.13 and ranged between 0.21 and 0.95. Histopathologically, 52 (31.3%) patients had capsular invasion, 24 (14.5%) had ETE, 14 (8.4%) had LNM and 3 (1.8%) had lymphovascular invasion. Recurrence and persistence were detected in 2 (1.2%) and 3 (1.8%) patients, respectively (Table 1).

Among patients with multifocal PTC, there were 34 (23.9%) male and 108 (76.1%) female patients. Mean age was 48.4 ± 12.1 years and 84 (59.2%) patients were older than 45 years old. Number of tumor foci was 2 in 78 (54.9%), 3 in 30 (21.1%) and 4 or more in 34 (23.9%) patients. Mean TDR was 0.71 ± 0.17 and ranged between 0.24 and 0.98. Tumor was bilateral in 96 (67.6%) of patients with multifocal PTC. Capsular invasion, ETE, LNM and lymphovascular invasion were observed in 64 (45.1%), 33 (23.2%), 25 (17.6%) and 9 (6.3%) patients, respectively. Recurrence was observed in 3 (2.1%) and persistence was observed in 4 (2.8%) patients (Table 1).

Mean age and percentage of patients older than 45 were significantly higher in multifocal PTMC than multifocal PTC patients ($p = 0.009$ and $p = 0.005$, respectively) (Table 1). Bilaterality and percentage of patients with 4 or more tumoral foci were significantly higher in the multifocal PTC ($p = 0.022$ and $p = 0.031$, respectively). Capsular invasion, ETE, LNM and lymphovascular invasion were observed with higher frequencies in multifocal PTC compared to multifocal PTMC group.

Tumor diameter ratio

In patients with multifocal PTMC, there was no significant difference in mean TDR between males and females, and between patients $\leqslant 45$ and >45 years old ($p = 0.696$ and $p = 0.658$,