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Neck recurrence in papillary thyroid carcinoma

Recidiva cervical no carcinoma papilífero da tireoide

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A B S T R A C T

Introduction: papillary thyroid carcinoma is a tumor with good prognosis. However, some patients treated present neck recurrence. **Objective:** to evaluate the risk factors for neck recurrence. **Methods:** a retrospective study enrolled 89 patients (68 women and 21 men) diagnosed with papillary carcinoma who underwent total thyroidectomy. In 21 patients, neck dissection was performed and 62 patients underwent radioiodinetherapy. Twelve patients relapsed with metastasis in this period with an average of 3.6 years. **Results:** *o*ut of 89 patients, 76.4% were female. Relapse occurred in nine (13.23%) women and three (14.28%) men. The average age of the patients was 44 years in the control group and in patients with relapsed. Eighteen patients (23.37%) in the control group and eight (64.28%) who relapsed had positive lymph nodes at initial diagnosis. The tumor size was significantly larger in the group of patients with cervical recurrence (3.3cm vs. 1.6cm - p=0.008, Student t test), whereas the presence of metastatic lymph nodes at the moment of the first operation was also significant (p=0.004 -Fisher exact test). The tumor size was an independent risk factor for recurrence at the multivariate anaylsis (OR=2.4, IC95%:1.3-4.6 - p=0,007, logistic regression). **Conclusion:** there is an increase in the risk of lymph node recurrence during the follow up of 2.4 folds for each increase of 1cm in the longer nodule diameter.

Keywords: Carcinoma, Papillary. Thyroid Gland. Neck Dissection.

INTRODUCTION

Thyroid cancer is the most common endocrine malignancy, the papillary carcinoma being the most common histologic type, comprising 85-95% of cases. Usually, these are indolent biological behavior tumors, whose 10 year survival rates are greater s 90%[1].

Residual disease after operation in initial stages has been reported between 11% and 30%[2]. Lymph node metastasis occurs in 20% to 50% of patients, and the central compartment of the neck is the most affected site. The lymph nodes typically involved are at levels II, III, IV and VI[3,4].

The importance of regional lymph node disease may have been underestimated in the past, particularly due to the good prognosis of these tumors. The observation of such metastases did not influence the rates of survival, not being considered a risk factor in most proposed systems[2,5]. On the other hand, large scale, population based studies have shown that metastases to regional lymph nodes have relationship with recurrence and mortality[3]. Additionally, the size of the lymph node metastasis in the lateral compartment is a significant risk factor for locoregional recurrence, distant metastasis and shorter survival[6].

Preoperative imaging (ultrasound) and intraoperative findings are important for predicting worse prognoses of papillary carcinoma, such as tumors greater than 4 cm, lymph node metastases larger than 3 cm, and extra thyroidal and extra lymph node

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extension. Male sex and age over 55 years also represent prognostic factors for local recurrence[7,8]. The BRAF mutation was considered a prognostic marker. Present in approximately 45% of cases, this somatic mutation is the most frequently observed genetic alteration in papillary carcinoma patients. Such a mutation is associated with more aggressive tumor behavior, increasing the risk of progression and recurrence[9].

The aim of this study was to evaluate risk factors for lateral regional recurrence in patients previously treated for papillary carcinoma of thyroid.

METHODS

The study was approved by the Ethics in Research Committee of the institution where it was carried out. This is a retrospective study in which we reviewed medical records from the period between 2000 and 2010, with 89 patients (68 women and 21 men) diagnosed with papillary carcinoma and treated at our service. All underwent total thyroidectomy. In addition, 21 patients underwent neck dissection, and 62, radioiodine therapy. Patients were followed up for at least five years, with an average of 8.9 years. There was no locoregional or distant recurrence. Twelve patients had recurrence with cervical metastasis in this period, with an average of 3.6 years of follow-up. Patients were followed for 10 to 20 years.

We recorded age, sex, tumor size, presence of metastasis in the initial diagnosis, neck dissection, radioiodine therapy, and dose performed, and used them to compare the patients who had no recurrence in a period greater than five years (control group) with the group of patients who displayed local relapse, in an attempt to elucidate risk factors for locoregional recurrence.

We organized and described the values obtained by studying each quantitative variable of parametric distribution using the mean and standard deviation. For qualitative ones, we used absolute and relative frequencies. For the comparison between the means of two parametric sample populations, we used the Student's t test. We used the Fisher's exact test to compare categorical variables. We compared the frequency of a phenomenon between groups of qualitative variables using the chi-square test. We used the log-rank test to compare the curves and the Cox regression model in calculating the hazard ratio (HR), with the respective 95% confidence interval (95% CI) in the multivariate analysis. In all analyzes, we used the SPSS® version 17.0 statistical software (SPSS® Inc; Chicago, Ilinois, USA) and in all comparisons we adopted a level of statistical significance of less than 5% ($p \leq 0.05$).

RESULTS

Of the 89 patients with papillary carcinoma included in this study, 68 (76.4%) were female, and 21 (23.6%), male. Relapse occurred in nine (13.23%) women and in three (14.28%) men. The age in the relapse-free group varied between 18 and 78 years. Patients who displayed recurrence had age was between 18 and 70 years. Both groups had a mean age of 44 years.

Regarding the size of the tumor analyzed in the anatomopathological study, in the control group (patients who did not present cervical recurrence), there was a range between 0.2 cm and 5.0 cm, with a mean of 1.61 cm. In the study group (patients with recurrent papillary carcinoma), on its turn, the size of the primary tumor ranged from 0.8 cm to 8.5 cm, with an average of 3.5 cm.

Eighteen patients (23.37%) in the control group and eight (64.28%) of those who evolved with recurrence had compromised lymph nodes in the initial diagnosis.

Fifty-one patients (66.23%) in the control group received radioiodine therapy after surgical resection, with a dose ranging between 90 and 200 cGy, mean of 121.14 cGy. All patients who developed recurrence had received radioiodine therapy as a complementary treatment after total thyroidectomy, with a dose ranging between 81 and 200 cGy, and an average of 158.83 cGy.

Relapses occurred in a maximum period of five years of follow up, with a mean of 3.65 years.

Tumor size was significantly larger in the group of patients who had cervical recurrence (3.3 cm vs. 1.6 cm, $p = 0.008$, Student's t test). We observed the same for the presence of metastatic lymph nodes in the first operation ($p = 0.004$, Fisher's exact test). There

was no association between the presence of regional recurrence and age or dose of adjuvant radioactive iodine. The multivariate analysis indicated tumor size as an independent risk factor for relapse (OR = 2.4, 95% CI: 1.3-4.6, p = 0.007, logistic regression), that is, for every increase of 1 cm in the lesion's largest diameter, there was an increase of approximately 2.4 times in the risk of lymph node recurrence during follow-up.

DISCUSSION

In general, patients with papillary carcinoma have an excellent prognosis, with survival greater than 20 years in more than 90% of cases after tumor resection. However, after total thyroidectomy and ablation of the remaining tissue with radioiodine, approximately 30% of patients with papillary thyroid carcinoma display incomplete response to therapy, usually manifested by locoregional lymph node recurrence and, less commonly, distant metastasis[8-10].

Recurrence does not represent an immediate threat to survival, but it is of great importance for both the surgeon and the patient, especially since a new dissection can increase the risk of complications, such as hypoparathyroidism, lymphatic fistula, and damage to adjacent structures. Therefore, it is important to have well-determined risk factors for recurrence[6,11].

Some of the main risk factors for lymph node recurrence are primary multifocal tumor, large tumors (larger than 4 cm), extrathyroidal invasion, distant metastasis, poorly differentiated papillary carcinoma, patient younger than 20 years old, positive cervical lymph nodes, male sex, and extension of the previous procedure[11,12].

In this study, there was a higher frequency of papillary carcinoma in females (76.40%) than in males (23.59%). Nonetheless, the recurrence was greater among men (28%) than among women (9.09%), in accordance with the literature[11-14]. Tumors of greater aggressiveness were found in male patients, this being an independent prognostic factor[13]. However, in our study, this was not a statistically significant prognostic factors for cervical recurrence.

There was no age difference between the groups; both had, on average, the age of 44, not in accordance with the literature, whose average is about 55 years[11 14]. It is known that elderly patients have tumors with unfavorable characteristics, such as advanced stage, larger size, extrathyroidal invasion, palpable lymph node metastases, greater mitotic activity, nuclear polymorphism, and decreased iodine uptake[15].

Some studies have shown that tumor size larger than 4 cm and male sex are related to a worse prognosis[8]. In addition, even tumors larger than 2 cm are more aggressive than tumors of 2 cm or less, even though they are classified as low-risk tumors[14]. Patients displaying recurrence had tumors greater than 3.5 cm on average, and recurrence free patients had mean tumor size of 1.61 cm, indicating size as a risk factor for lymph node recurrence. Tumors larger than 1.5 cm have a more unfavorable evolution in papillary thyroid carcinoma[16]. In our study, the multivariate analysis point to tumor size as an independent risk factor for recurrence. Additionally, we found that each increase of 1 cm in diameter in the largest lesion axis is related to an increase of 2.4 times the risk of lymph node recurrence. This quantifies the intuitive notion that more advanced primary tumors are more likely to cause lymph node metastases, even if subclinical when the patient is initially evaluated.

Lymph nodes compromised at diagnosis increased recurrence rates, as 64.28% of the patients who developed cervical recurrence had positive lymph nodes at diagnosis. Lymph node metastases are found in up to 70% of cases of papillary thyroid carcinoma, an independent recurrence factor[15-17]. In our study, the univariate analysis indicated that the presence of metastatic lymph nodes at the first procedure increases the likelihood of cervical recurrence, though without significance at the multivariate analysis.

During patients' follow-up, recurrence occurred, on average, after 3.65 years. In a cohort study, 50% of recurrences occurred within three years of the first operation, and 75% within 5 years[18].

CONCLUSION

Upon multivariate analysis, for each 1 cm increase in the tumor's largest diameter, there is an increase of approximately 2.4 times in the risk of lymph node recurrence during follow-up.

RESUMO

Introdução: *o carcinoma papilífero da tireoide é um tumor com bom prognóstico. Entretanto, alguns pacientes tratados evoluem com recidiva cervical*. **Objetivo:** *avaliar os fatores de risco para recidiva cervical.* **Métodos:** *um estudo retrospectivo arrolou 89 pacientes (68 mulheres e 21 homens) diagnosticados com carcinoma papilífero, submetidos à tireoidectomia total. Em 21 pacientes, realizou esvaziamento cervical e, em 62, radioiodoterapia. Doze pacientes apresentaram recorrência linfonodal no período, com media de 3,6 anos.* **Resultados:** *dos 89 pacientes, 76,4% eram mulheres. A falha ocorreu em nove mulheres (13,23%) e três homens (14,28%). A média etária tanto dos pacientes recidivados como do grupo-controle foi de 44 anos. Dezoito pacientes (23,37%) no grupo-controle e oito (64,28%) dentre os que recidivaram tinham linfonodos positivos ao diagnóstico inicial. O tamanho tumoral foi significativamente maior no grupo de pacientes que apresentaram recidiva cervical (3,3 cm vs. 1,6cm - p=0,008, teste t de Student), o mesmo foi observado para a presença de linfonodos metastáticos quando da primeira cirurgia (p=0,004 - teste exato de Fisher). À análise multivariada, o tamanho tumoral foi fator de risco independente de recidiva (OR=2,4, IC95%:1,3-4,6 - p=0,007, regressão logística.* **Conclusão:** *para cada aumento de 1cm no maior diâmetro da lesão, há um aumento de 2,4 vezes no risco de recidiva linfonodal ao longo do acompanhamento*.

Palavras chave: *Glândula Tireoide. Esvaziamento Cervical. Câncer Papilífero da Tireoide.*

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