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Original Article

Well-differentiated tireoid carcinoma: epidemiological profile, surgical results and oncological response.

Carcinoma bem diferenciado de tireoide: perfil epidemiológico, resultados cirúrgicos e resposta oncológica.

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ABSTRACT

Objective: to know the epidemiological profile of patients undergoing surgery for well-differentiated thyroid carcinoma at the Cassiano Antônio Moraes University Hospital of the Federal University of Espírito Santo, as well as the oncological results and the main postoperative complications. **Methods:** we conducted a cross-sectional, retrospective study of patients with well-differentiated thyroid carcinoma (WDTC) operated from January 2008 to December 2015. **Results:** During the study period, 95 of the 353 patients undergoing surgical treatment of the thyroid gland had WDTC. Papillary carcinoma was the most frequent (91.57%). Total thyroidectomy not associated with cervical emptying was the most frequent surgical procedure (65.26%). Postoperative complications occurred in 6.31% of patients, hematoma being the most frequent. The mean follow-up time was 36.9 months. Relapse occurred in four patients (4.21%), being locoregional in all cases. The prognostic factors analyzed, such as gender, age, tumor size, lymph node involvement, staging, type of surgery, histology and complementary iodine therapy did not show statistical significance. **Conclusion:** papillary carcinoma was the most common thyroid malignant neoplasm, affecting women in the 49-year-old age group more frequently. Loco-regional recurrence occurred in four patients. Hematoma was the most frequent complication.

Keywords: Thyroid Neoplasms. Carcinoma, Papillary. Thyroid Nodule. Carcinoma, Papillary, Follicular. Thyroidectomy.

INTRODUCTION

Well-differentiated thyroid carcinoma (WDTC) is responsible for 90% of malignant thyroid neoplasms. The papillary and follicular subtypes are the most frequent and, in regions with regular iodine intake, represent 80% and 10% of all thyroid carcinomas, respectively[1-3]. Studies show that 85% of patients with WDTC have a good prognosis independent of the therapeutic approach adopted. On the other hand, about 5% of patients will evolve to death, regardless of treatment aggressiveness. Moreover, about 10% of WDTC cases will have their evolution and prognosis directly related to the therapeutic measures received. It is precisely in the latter group that predictive factors are of greater importance in the definition of therapeutic management and survival increase[4].

Thyroid cancer surgery is an important part of a multidisciplinary approach. The operation should be based on recommendations from the literature and the team conducting the case should draw a patient follow-up plan. Iodine therapy is a complementary treatment used adjunctively in WDTC, allowing the elimination of microscopic neoplastic foci[3].

Our objective was to know the epidemiological profile of the patients submitted to WDTC surgical treatment and the oncological results (relapse and death) in the follow-up of patients undergoing treatment in our institution.

METHODS

We analyzed cytopathological and histopathological reports of patients submitted to total or partial thyroidectomy associated or not with cervical emptying at the same surgical time. We selected the cases from the electronic registry file of the Pathology Service of the Cassiano Antônio Moraes University Hospital (HUCAM) of the Federal University of Espírito Santo (UFES) and from analysis of medical records of the Medical and Statistical Archive Service (SAME) of HUCAM/UFES from January 2008 to December 2015. We included patients with malignant neoplasms of the WDTC type (papillary and follicular) submitted to surgical treatment.

We analyzed the medical records regarding the epidemiological distribution, surgical outcome, complications and prognostic factors: gender, age, histological type, tumor size, staging, type of treatment, mean hospitalization time, postoperative complications, complementary iodine therapy, relapse / failure of treatment and

oncological follow-up, inadvertent removal of the parathyroid gland, and mean time between the first consultation with the Head and Neck surgeon and the completion of the surgical treatment.

The Pathology Service of HUCAM began to use the Bethesda classification only in 2011. Thus, the cytopathologic reports from 2011 to 2015 were reclassified using the same system of reports until 2010, namely: unsatisfactory, benign, undetermined or malignant.

Patients who had a cytopathologic report of papillary or follicular carcinoma or Bethesda VI classification were reclassified as malignant cytopathologic outcome. Patients classified as colloid goiter, colloid cyst, Bethesda II classification, hyperplastic nodular goiter and hypercellular follicular proliferation were reclassified as benign cytopathologic outcome. Patients who presented a cytopathologic report of follicular pattern with or without atypical findings were reclassified as undetermined cytopathologic outcome.

We performed a descriptive analysis of the data considering the following variables: age in years, gender, presence of compromised lymph node, presence of parathyroid gland in the surgical specimen, pT staging, pN staging, TNM stage, surgery type, cytopathologic result (FNA), well-differentiated tumor histology, malignant neoplasm of the microcarcinoma type, time of hospitalization, presence and type of postoperative complication, time from diagnosis to surgical treatment in months, postoperative iodine therapy, disease relapse, and death.

The analysis provided an overview of the data central tendency and dispersion through box-plot plots and the estimation of mean, variance, standard deviation and median, and their distribution through the elaboration of tables and other graphs. For univariate logistic regression analysis, we categorized some variables: divided the age in years into two categories (less than 45 years or equal to or greater than 45 years); categorized the type of surgery into three categories (partial thyroidectomy, total thyroidectomy, and total thyroidectomy with cervical emptying); divided the well-differentiated histological types into two categories (papillary carcinoma and follicular carcinoma); evaluated postoperative iodine therapy according to three categories (performed, not indicated, and indicated but not performed).

We performed all statistical calculations and tests on the Statsoft STATISTICA 10 and IBM SPSS 22 software, and considered statistical significance when $p<0.05$.

This work was approved by the Institutional Ethics Committee with the following reference number 38642214.5.0000.5071.

RESULTS

During the study period, 353 patients underwent surgical treatment of the thyroid gland. After applying the inclusion criteria, we selected 99 cases of well-differentiated thyroid carcinoma. Of these, we excluded four due to lack of postoperative follow-up records. Of the 95 patients studied, eight (8.42%) were males and 87 (91.58%), female. The mean age was 50.2 years, with a median of 49 years, ranging from 23 to 81. The age group below 45 years comprised 37.9% of patients, and 45 years or more, 62.1%.

With regard to the histological type, 87 patients (91.6%) had papillary thyroid carcinoma, 23 of them microcarcinomas, ie tumors smaller than 1cm, and eight patients (8.4%) had follicular carcinoma, one of them with Hürthle cell carcinoma, a more aggressive variant of follicular carcinoma.

We were able to obtain the cytopathologic report of the Fine Needle Aspiration (FNA) performed in the preoperative period of 92 patients in the electronic registry of the Pathology Service. With the exception of patients with a diagnosis of malignant neoplasm in FNA, which totaled 50 cases (54.36%), we reclassified all other cytopathologic results (45.64%). In 20 (21.7%) patients the result was benign neoplasia, in 22 (23.9%) it was inconclusive, and in 50 (54.4%), it was positive for well-differentiated carcinoma, as can be observed in figure 1. Of the 20 patients with FNA showing benign neoplasia, nine (45%) had papillary microcarcinoma. Of the 22 patients with inconclusive FNA cytopathology, seven (31.8%) had papillary microcarcinoma.

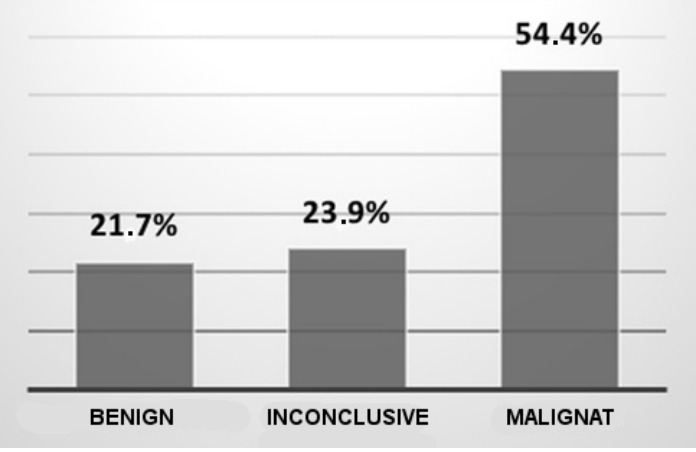

Figure 1. Relative distribution by cytopathologic results of FNA of patients submitted to surgical treatment of WDTC at the HUCAM between 2008 and 2015.

Twelve patients (12.6%) underwent partial thyroidectomy as initial treatment, with diagnosis of microcarcinoma in five, papillary carcinoma, encapsulated variant, in two, and papillary carcinoma, classic variant, in five. Only the patients with microcarcinoma were

not submitted to a new surgical procedure with total thyroidectomy. Sixty-two patients (65.3%) underwent total thyroidectomy and 21 patients (22.1%) underwent total thyroidectomy associated with cervical emptying: eight patients underwent only emptying of the central compartment, ten patients underwent emptying of central compartment associated with unilateral levels II to V, and three patients had central compartment emptying associated with levels II to V bilaterally).

The mean time of hospitalization was 2.24 days, ranging from one to 16. Postoperative complications occurred in six patients, one complication (hematoma, which was submitted to reoperation with drainage and revision of hemostasis), and five clinical complications (one malignant hyperthermia and four atrial fibrillation-type cardiac arrhythmias). None of these patients died or had complications sequelae. The mean length of hospital stay of patients without complications was 1.93 days, and of patients with complications, 6.83 days.

The inadvertent removal of a parathyroid gland occurred in five patients, one undergoing partial thyroidectomy, two undergoing total thyroidectomy, and two undergoing total thyroidectomy associated with some cervical emptying. No patient had more than one parathyroid gland removed inadvertently. None of these patients developed postoperative hypoparathyroidism for more than 30 days.

Tumor T staging was pT1a in 24 patients (23 papillary carcinomas and one follicular carcinoma), pT1b in 16, pT2 in 11, pT3 in 42, and pT4 in two. N staging was pN0 in 75 cases, pN1a in eight, and pN1b in 12. When we applied the staging criteria of the TNM system that uses age groups, we found 67 stage I patients, four stage II patients, 20 stage III patients, and four stage IVA patients (Figure 2).

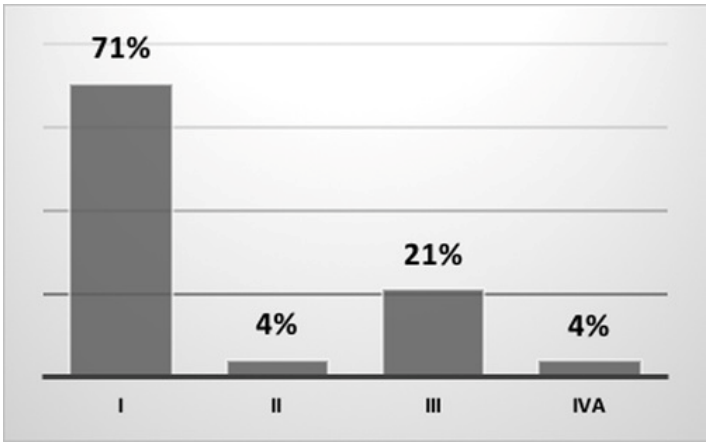

Figure 2. Relative distribution by the TNM staging of patients submitted to surgical treatment of WDTC at the HUCAM between 2008 and 2015.

The mean postoperative follow-up time was 36.9 months, ranging from two to 91. Four patients relapsed. One patient presented lymph node recurrence 14 months after the initial surgery and was submitted to cervical emptying. One individual presented recurrence in the thyroid bed one year after the initial surgery and was submitted to exploratory cervicotomy and emptying. One patient had lymph node recurrence in the mediastinum four months after surgery and underwent anterior-mediastinal emptying. One patient presented recurrence at level V four months later and was submitted to selective cervical emptying at level V. All patients were under regular outpatient follow-up with no evidence of disease (Figure 3).

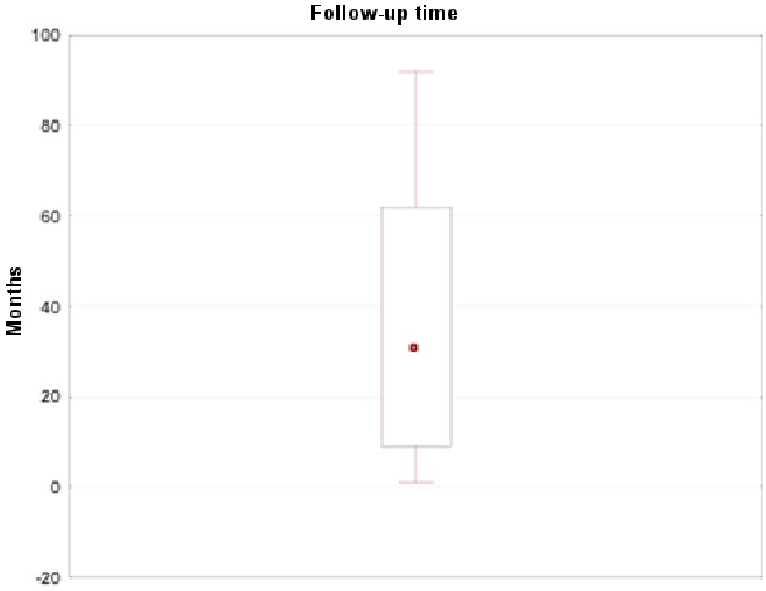

Figure 3. Distribution by follow-up in full months of patients undergoing surgical treatment of WDTC at the HUCAM between 2008 and 2015.

As for the prognostic factors studied, such as gender, age over 45 years, tumor size (pT stage), lymph node involvement (pN stage), disease staging, surgical treatment type, microcarcinoma type tumor, histological type and postoperative iodine therapy, we obtained the results expressed in figure 4.

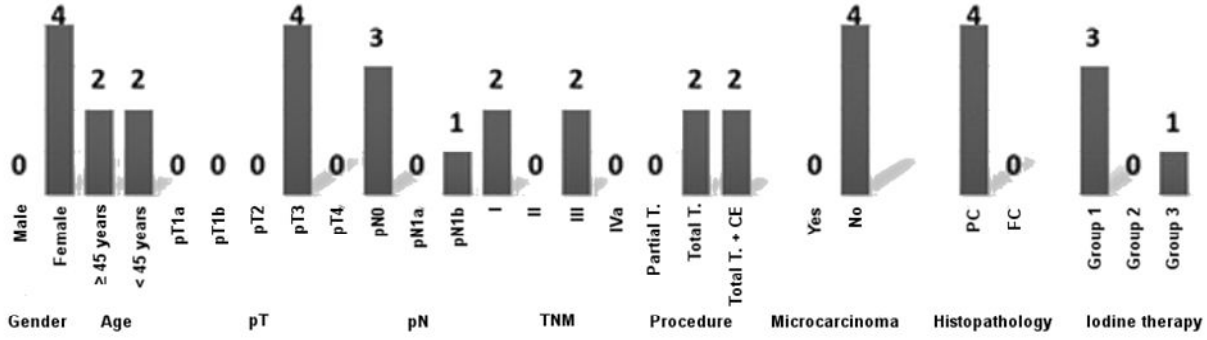

Figure 4. Relapse distribution of patients submitted to surgical treatment for WDTC at the HUCAM between 2008 and 2015 in absolute values. T: Thyroidectomy; CE: Cervical Emptying; PC: Papillary carcinoma; FC: Follicular carcinoma.

Univariate analysis of prognostic factors did not show statistical significance, as shown in table 1.

Table 1. Univariate analysis of prognostic factors for recurrence of well-differentiated thyroid carcinoma.

Prognostic Factor	p value*
Age over 45 years	0.962
pT staging	0.151
pN staging	0.684
TNM staging	0.415
Type of surgery	0.433
Tumor <1 cm	0.424
Histological type	0.575
Iodine therapy	0.619

*Chi-square Test.

DISCUSSION

The well-differentiated thyroid carcinoma is the most frequent endocrine neoplasia and its incidence and prevalence are on the rise. Data from SEER[5] show a growth of new cases of thyroid cancer over the last decades, with an estimated 13.9 new cases per 100,000 inhabitants in 2016, which corresponds to 3.8% of all new cases of cancer in the USA[5,6]. In Brazil, data from INCA estimate an incidence of 5.78 new cases per 100,000 inhabitants[7].

American epidemiological data reveal that the incidence of well-differentiated thyroid carcinoma is about four times higher in women than in men[5]. In our study, the ratio was 10:1. Women tend to have medical appointments more frequently throughout their lives than men. Ultrasonography (USG) routinely ordered by clinicians or gynecologists has increased the diagnosis of thyroid nodules in women, which may explain the increased detection of thyroid cancer in these nodules, especially early tumors. The median age of 49 years approximates the SEER[5] data, which was 51 years. By grouping patients by age, there was a distribution very similar to established epidemiological data[5-7].

The most commonly used test for the diagnosis of thyroid nodules is fine needle aspiration (FNA). The cytology of FNA has a high accuracy in the diagnosis of benign or malignant nodules in the majority of cases. However, up to 10% to 40% of FNA samples are diagnosed as indeterminate for malignancy, often with a diagnosis of malignancy only in histopathology[8]. The diagnostic accuracy of FNA for thyroid nodules may be affected by tumor size, with false negative rates for nodules larger than 3cm to 4 cm reaching up to 30%[9,10]. Positivity for carcinoma in FNA occurred in 54.4% of the patients in our study. The

incidence of tumors smaller than 1cm was elevated, (25.3%) as well as the number of punctures with inconclusive results (23.9%).

The most common histopathological type was papillary carcinoma (91.6%). Data show that about 88% of well-differentiated thyroid tumors are papillary carcinoma, and 12%, follicular carcinoma[8,11,12]. The incidence of microcarcinoma was 25.3%, and studies have shown a distribution of 6% to 28 % of microcarcinomas in well-differentiated tumors. The incidence of microcarcinoma in Japan reaches 28.4% of cases, and in countries like Colombia is about 5.6%. The greater availability of diagnostic exams with higher imaging resolution and the possibility of USG-guided aspiration punctures may explain this higher rate of detection of tumors smaller than 1cm[6,13,14].

The surgical treatment of WDTC remains controversial. Some studies endorsed total thyroidectomy as an initial surgical approach for WDTC greater than 1cm in diameter[15], based on retrospective data suggesting that the bilateral surgical procedure provides a longer patient survival[16], reduces recurrence rates[17,18], allows routine use of complementary iodine therapy and facilitates the detection of recurrent/residual disease during follow-up. However, recent data have shown that in selected patients the clinical response is very similar for partial or total thyroidectomy[19-23]. Japanese studies show that, in low-risk and very low-risk patients, active surveillance without surgical treatment may be a safe initial therapeutic option, thyroidectomy being reserved for patients with signs of disease progression[24].

In Brazil, the standard recommendation for the treatment of well-differentiated thyroid tumors is total thyroidectomy[25]. Partial thyroidectomy may be indicated for unifocal disease less than 1cm (microcarcinoma), without lymph node involvement or capsular extravasation. In our study, 12 patients underwent partial thyroidectomy as initial treatment. Of these, five had microcarcinoma and did not undergo total thyroidectomy. All the other patients were treated with total thyroidectomy, and 21 patients had associated cervical emptying.

We chose to adopt only the pathological staging system according to the AJCC, 7th edition[24], and not the clinical staging, since 21.7% of the patients did not present a cytopathologic examination of malignant neoplasm, but they had the diagnosis of malignant neoplasm after histopathological examination. In addition, the thyroid can often have a bulky nodule and only a small part of this nodule corresponds to tumor volume[9]. AJCC's recent publication on TNM staging, 8th edition, reclassifies WDTC prognostic factors with respect to patient age by increasing the cutoff point from 45 to 55 years.

Lymph node involvement occurred in 21% of patients, which is corroborated by studies showing an incidence of lymph node metastasis in 15 to 30% of patients[26,27], although in some studies it may reach 47.5%[28]. Several studies have shown that the presence of WDTC lymphatic metastasis does not alter overall survival. However, recurrence rates and disease persistence may be higher in patients with lymphatic involvement[4,29,30]. In the presence of metastases in the central compartment, bilateral selective cervical emptying and antero-superior mediastinum should be performed[24,31]. In patients in whom the presence of cervical lymph node at a level outside the central compartment is detected clinically or through imaging, cervical emptying of levels II to V is indicated[24,31].

Complementary iodine therapy is not routinely recommended after thyroidectomy for low risk patients[24], or for those with microcarcinoma undergoing partial or total thyroidectomy. Complementary iodine therapy is indicated for intermediate-risk and high-risk patients 24. In our study, iodine therapy was not indicated in 26.3% of the patients, was performed in 44.2%, and was indicated but had not yet been performed, in 21.1% of the cases. There was no indication of complementary iodotherapy for patients with microcarcinomas without capsular invasion or lymph node involvement, therefore considered as patients of very low risk of disease relapse. In one patient, we did not indicate complementary iodine therapy because the patient had iodine allergy.

The main prognostic factors related to disease recurrence and death were: age greater than 45 years, presence of distant metastasis, extrathyroidal extension, tumor size greater than 4cm, male gender, and follicular histological type[4,15,24,32]. Recurrence of thyroid carcinoma occurred in 4.65% of the patients. However, there was no relation to any of the prognostic factors analyzed. These results certainly reflect the small number of recurrences.

The most frequent postoperative complication was hematoma, occurring in 1.05% of the patients. Studies show that the hemorrhagic complication is the most frequent, occurring in 0.4% to 4% of the cases. The thyroid gland is very vascularized, which increases the occurrence of postoperative hemorrhagic complications[10,33,34].

The inadvertent removal of the parathyroid gland is one of the possible postoperative complications and this may cause hypoparathyroidism, which is present in 1% to 5% of patients undergoing thyroidectomy[35]. Data in the literature reveal an incidence of inadvertent removal of the parathyroid gland, in 6.4% to 16.4%[35]. The incidence of inadvertent removal of the parathyroid gland in our study occurred in five (5.26%) patients.

The extension of the surgical treatment did not influence the withdrawal of the parathyroid gland.

Papillary carcinoma of the thyroid was the most frequent malignant neoplasm, more frequently affecting the female gender in the 49 years age group. Locoregional recurrence occurred in four patients and hematoma was the most frequent complication. Our follow-up time was short, which limits our conclusions about cancer outcomes.

RESUMO

Objetivo: conhecer o perfil epidemiológico dos pacientes submetidos à cirurgia do carcinoma bem diferenciado da tireoide no Hospital Universitário Cassiano Antônio Moraes da Universidade Federal do Espírito Santo, assim como os resultados oncológicos e as principais complicações pós-operatórias. **Métodos:** estudo transversal e retrospectivo de pacientes portadores de carcinoma bem diferenciado da tireoide operados no período de janeiro de 2008 a dezembro de 2015. **Resultados:** no período do estudo, dos 353 pacientes submetidos a tratamento cirúrgico da glândula tireoide, 95 eram portadores de CBDT. O carcinoma papilífero da tireoide foi o mais frequente (91,57%). A tireoidectomia total não associada a esvaziamento cervical foi o procedimento cirúrgico mais frequente (65,26%). As complicações pós-operatórias ocorreram em 6,31% dos pacientes, sendo o hematoma a mais frequente. O tempo médio de seguimento foi de 36,9 meses. A recidiva ocorreu em quatro pacientes (4,21%), sendo locorregional em todos os casos. Os fatores prognósticos analisados, como sexo, idade, tamanho do tumor, acometimento linfonodal, estadiamento, tipo de cirurgia, histologia e iodoterapia complementar não demonstraram significância estatística. **Conclusão:** o carcinoma papilífero da tireoide foi a neoplasia maligna mais frequente, acometendo o sexo feminino na faixa etária dos 49 anos mais frequentemente. A recidiva locorregional ocorreu em quatro pacientes. O hematoma foi a complicação mais frequente.

Descritores: Neoplasias da Glândula Tireoide. Carcinoma Papilar. Nódulo da Glândula Tireoide. Carcinoma Papilar, Variante Folicular. Tireoidectomia.

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