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Review Article

Metastasis of Differentiated Thyroid Carcinoma: A Descriptive Study of 75 Patients

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Abstract

Introduction: Differentiated Thyroid Carcinoma (DTC) is the most common endocrine malignancy, and is generally of favorable prognosis. However, this latter is significantly worse when initial distant metastasis is present. The aim of our study is to describe the clinical, paraclinical, and therapeutic aspects of metastatic carcinomas in patients followed-up at the Endocrinology Department of the CHU Ibn Rochd in Casablanca, Morocco.

Methods: This is a retrospective descriptive study of patients diagnosed with metastatic differentiated thyroid cancers and followed in the endocrinology service at the university hospital of Ibn Rochd in Casablanca over a 34 years period (1986- 2020). The variables studied were age, histological type and features, TNM stage, and metastasis localizations. Data analysis was performed using SPSS 22.0 software.

Results: We included 75 patients in our study. The mean age at diagnosis was 46.4 years ± 14.2 years. The sex ratio M / F: 0.1. Metastases were revelatory of DTC in 19 cases. Fifty-seven patients had lymph node metastasis, 17 patients had bone metastasis and 15 patients had lung metastasis. The most frequent histological types were classical papillary carcinoma (47%), papillary carcinoma with vesicular differentiation (21%), then vesicular carcinoma (11%). Regarding the histological characteristics, capsular effraction was found in 35% of cases,

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vascular emboli in 18% and multifocality in 23% of cases. Analysis of the variables studied showed that gender was not a predictive factor for the appearance of a certain type of metastasis. However, patients older than 55 were significantly more likely to develop lung metastases (p=0.01). Concerning histological features, the existence of vascular emboli was significantly associated with the apparition of lymph node and bone metastases (p=0.01) as well as lung metastases, although not significantly (p=0.1). The mortality rate in our sample was relatively low at 8%.

Conclusion: Patients with vascular emboli were more likely to develop lymph nodes and bone metastases, and patients older than 55 were more likely to develop lung metastases. Even if metastases occur, prognosis is generally favorable for DTCs compared to other types of thyroid cancers.

Keywords

Differentiated Thyroid Carcinoma; Metastases; Lymph Nodes

Introduction

Differentiated Thyroid Cancers (DTC) account for 95% of all thyroid cancers and are generally effectively treated by surgery, radioactive iodine, and thyroid hormone therapy [1]. However, about 10% of DTCs spread or recidivate within 5 to 7 years after diagnosis.

Clinical manifestations of DTC metastasis are related to the metastatic site. After lymph nodes, bones and lungs are the most common metastatic sites. Follow-up should identify severe forms, detect recurrences early, and treat them appropriately.

In recent years, new diagnostic tools have been developed, such as Fluorodeoxyglucose Positron Emission Tomography (FDG PET-CT) [2]. The range of therapeutic tools is currently expanding with notably the development of high-performance locoregional treatments and targeted therapies such as tyrosine kinase inhibitors [1].

The aim of our work is to describe the clinical, paraclinical, and therapeutic aspects of metastatic carcinomas in patients followed-up at the Endocrinology Department of the CHU Ibn Rochd in Casablanca, Morocco.

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Methods

Over a period of 34 years from January 1986 to March 2020, 767 patients were diagnosed with thyroid carcinoma and followed-up at our service. We included in our study patients with confirmed DTC metastasis revealed either by imaging modalities or a histological and immunohistochemical confirmation. We excluded from our study all patients with a non or poorly differentiated thyroid carcinoma or medullary carcinoma.

The studies variables were: age, gender, history, initial treatment, pathology, histologic variant, capsular invasion, vascular emboli, TNM stage, multifocality, time of diagnosis of metastasis, radiology, treatment, monitoring, and progression.

The statistical analyses were performed using Microsoft Excel 2019 and IBM SPSS Statistics version 22.0. Quantitative variables were described by means and standard deviations. Qualitative variables were described by counts and percentages. A p-value of ≤ 0.05 was considered as statistically significant. In order to find the factors associated with the different metastases' localizations, a linear regression analysis was performed.

Results

We included 75 patients in our study. Their characteristics are shown in Table 1. The mean age of our patients was 46 ± 14.38 years ranging from 10 to 85 years, with a female predominance. Only 7 patients had prior cancers: 2 cases of breast cancer, 1 case of cavum cancer and 4 cases of familial papillary carcinoma. Bioassays conducted revealed functional metastases with hyperthyroidism in only two cases, one of which was sternal.

Metastases predominated at the lymph node with 57 cases. Seventeen patients had bone metastases and 15 had pulmonary metastases. Retro-orbital, skin, laryngeal, or parathyroid metastases were found in 4 patients.

Initial total thyroidectomy was indicated for every patient but couldn't be performed in two, one due to tumor adhesion and pulmonary morbidity, and the other due to the patient's death prior to surgery. Node dissection was performed in 36 patients (48%): central and lateral lymph node dissection in 21 patients and only central in 15 patients. Only 19% of our patients were surgically treated for their metastases. The performed surgeries were: total removal of the bone tumor in 12 patients, and tumor resection for the retro-orbital, cutaneous, and parathyroid metastasis. The anatomopathological study of the surgical specimens and biopsies was carried out for all surgically-treated patients. This confirmed the thyroid origin of the metastases.

Iodine-131 therapy was indicated for each patient except two whom thyroid carcinoma was not operable. At the time of data collection, 77% of patients had received iodine-131. It was performed immediately after surgery or after thyroid hormone withdrawal (at least 6 weeks).

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The average time between surgery and therapy was 19 months. Seventeen patients (23%) had benefited from 2 or more courses of treatment with an average cumulative dose of 260 mCi. Radiotherapy of metastatic sites was performed for 12 patients (16%), 5 of whom had iodo-refractory metastases, and 1 case of non-operable adherent thyroid carcinoma (Table 2).

Targeted therapy was indicated in 2 patients with sorafenib-type chemotherapy at a dose of 400 mg/d. The first patient was refractory to radioiodine therapy and the second patient had an inoperable thyroid carcinoma with pulmonary metastases.

Hormone therapy was systematically prescribed for all our patients and was started post-operatively, or after radioiodine therapy if done immediately after surgery. L-Thyroxine was used at a suppressive dose (starting with 2 ug/kg/day). The efficacy of hormone therapy was controlled after 6 weeks by measuring TSH (<0.1mIU/L).

Our patients benefited from quarterly monitoring for the first few years, then annually for life. Thyroglobulin levels after total thyroidectomy were greater than 1 ng/ml in all our patients, with a maximum of 16,000 ng/ml. After radioiodine therapy, thyroglobulin was undetectable in 62 patients (83%).

Age (mean (SD))	46 (14.38)
< 55 years old (n(%))	45 (60)
⩾ 55 years old (n(%))	30 (40)
Women (n(%))	68 (90)
History of neoplasia (n(%))	7 (9.3)
Reason for consultation (n(%)	
Goiter (n(%))	38 (50.6)
Nodule (n(%))	11 (14.6)
Lymphadenopathy (n(%))	4 (5.3)
Distant metastasis (n(%))	15 (20)
Unknown (n(%))	7 (9.3)
Histological type (n(%))	

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Papillary carcinoma	35 (46.6)
Papillary microcarcinoma	9 (12)
Follicular variant of papillary thyroid carcinoma	16 (21.3)
Insular variant of papillary thyroid carcinoma	3 (4)
Oncocytic variant of papillary thyroid carcinoma	1 (1,3)
Follicular thyroid carcinoma	8 (10.6)
Insular Carcinoma	3 (4)
Histological features (n(%))	
Capsular invasion	26 (34.6)
Vascular emboli	13 (17.33)
Lymphocytic thyroiditis	2 (2.6)
Multifocality	17 (22.6)
TNM stage (n(%))	
T1	19 (25)
T2	18 (24)
T3	11 (15)
T4	8 (11)
Unknown	19 (25)
Metastasis (n(%))	
Lymph node	57 (76)
Bone	17 (22.6)
Lung	15 (20)

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Other	4 (5.3)
Evolution (n(%))	
Complete remission (n(%))	50 (66.6)
Incomplete remission (n(%))	12 (16)
Death (n(%))	6 (8)

Table 1: Population characteristics (n=75).

Total Thyroidectomy (n(%))	73 (97.3)
Neck dissection (n(%))	36 (48)
Radioiodine therapy (n(%))	58 (77)
⩾ 2 courses	17 (23)
Average delay between surgery and radioiodine therapy (months)	19
Postoperative complications (n(%))	
Transient hypoparathyroidism	10 (13.3)
Definitive hypoparathyroidism	6 (8)
Recurrent paralysis	3 (4)
Radiotherapy of metastatic sites (n(%))	12 (16)
Targeted therapy (n(%))	2 (2.7)

Table 2: Treatment received by our patients.

Evolution

Our patients were followed-up for 34 years. Complete remission was observed in 50 cases (67%). Criteria for remission were defined by an undetectable thyroglobulin level and a

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morphological or functional exploration that does not detect any anomaly. Twelve of our patients (16%) were not yet in remission with no progression of metastatic lesions, and decreaed kinetics of thyroglobulin levels. Six cases of death were noted (8%) due to the metastatic disease progression.

Prognostic Factors

Patients under 55 had fewer vascular emboli than older patients, but this was not significant (p=0.06). Multifocality was more common in men, but was not significant (p=0.1).

The results of the linear regression analysis are shown in Table 3. Gender type was not a predictive factor for the appearance of a certain type of metastasis. However, patients older than 55 were significantly more likely to develop lung metastases (p=0.01). Concerning histological features, we have found that the existence of vascular emboli was significantly associated with the apparition of lymph node and bone metastases (p=0.01) as well as lung metastases, although not significantly (p=0.1).

The majority of patients with vesicular carcinoma (78%) were in complete remission. In contrast, only 48% of those with papillary carcinoma were in remission. The pejorative histological features objectified were: capsular invasion in 34% of cases (p=0.5), vascular emboli in 16% (p=0.03), and multifocality in 23% (p=0.33). In the group that had undergone lymph node dissection, we obtained complete remission in 75% of cases (p=0.2).

	Patients with Lymph node metastases (n=57)		**Patients with Bone metastases (n=17)**		**Patients with Lung metastases (n=15)**	
	n(%)	**p value**	**n(%)**	**p value**	**n(%)**	**p value**
Females	53(93)	0.318	15(88.2)	0.971	13(86.7)	0.348
Age at diagnosis > 55 years	17(31.5)	0.959	13(76.5)	0.467	10(66.7)	0.01
Histological features						
Capsular effraction	21(36.8)	0.237	5(29.4)	0.446	6(40)	1
Vascular emboli	8(14)	0.01	5(29.4)	0.01	5(33.3)	0.105
Multifocality	16(28.1)	0.213	2(11.8)	0.616	3(20)	0.667

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Histological type						
Insular carcinoma	1(1.8)	0.013	2(11.8)	0.03	1(6.7)	1
Follicular variant of papillary thyroid carcinoma	14(24.6)	0.027	4(23.5)	0.341	4(26.7)	1
Papillary carcinoma	31(57.4)	0.013	3(17.6)	0.046	8(53.3)	0.923
Insular variant of papillary thyroid carcinoma	0(0)	0.999	1(5.9)	1	0(0)	0.999
Oncocytic variant of papillary thyroid carcinoma	1(1.8)	1	0(0)	1	0(0)	1
Follicular thyroid carcinoma	1(1.8)	0.59	7(41.2)	0.184	2(13.3)	1
Papillary microcarcinoma	9(16.7)	0.999	0(0)	0.999	0(0)	0.999

Table 3: Correlation between metastases' localizations and histological characteristics.

Discussion

Between 1% and 4% of patients with DTC have distant metastases at diagnosis while 7 to 23% will develop metastases during follow-up [3]. This is in contrast to our study where 20% of patients had distant metastases at diagnosis. Even though imaging technologies have developed and are more readily available in Morocco, late diagnosis remains a major issue.

In our study, 90% of the patients affected with metastatic DTCs were females. Consistent with the literature, thyroid carcinomas and the appearance of metastases generally affect women more often than men. This could be tied to estrogen imbalances as a risk factor, but further studies are needed [3-5].

According to the literature, the average age at diagnosis of thyroid carcinoma is between 45 and 60 [3,4]. In Morocco, in the study by Ben Rais et al, the median age is 42.5 years for papillary carcinoma and 48 years for vesicular carcinoma [6]. In our study, the median age of diagnosis was 46 years.

The preferred locations of metastases are, in decreasing order of frequency: lungs, bones, mediastinal lymph node metastases, then brain, liver, kidney, and finally skin in the same level as eye, myocardium, spleen, adrenal gland, pancreas, muscles, mammary gland, and subcutaneous cellular tissue [7]. Concerning our patients, lymph node metastases were the most

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frequent with a 76% occurrence rate, then bone metastases (23%), lung metastases (20%) and finally other sites (5.3%). Multifocal metastases were present in 19% of our patients. Bone metastases are more frequently found in older patients [8]. This is in accordance to our study where 66.7% of patients with lung metastases were older than 55 (p=0.01).

Studies have shown that vascular emboli increases the metastatic potential of DTCs [9,10]. Indeed, the presence of vascular emboli was significantly correlated with the appearance of metastases in lymph nodes and bones.

Papillary carcinomas spread lymphatically, which explains why patients with papillary carcinomas in our study were more likely to develop lymph node metastases (p=0.013). In contrast, vesicular carcinomas spread hematogenously.

Radioiodine therapy is the main treatment for pulmonary metastases. Treatment consists of administering 100 to 200 mCi of iodine-131, or 100-150 mCi if >70 years of age. This treatment can be repeated several times with a free interval of 6 to 12 months. The maximum cumulative dose should take into account the risk of pulmonary fibrosis (in children) and the hematologic risks for doses greater than 600 mCi [11]. For bone metastases, radioactive iodine is rarely curative and may require another therapeutic modality. However, it increases the survival rate [12]. In our study, the cumulative dose varied from patient to patient, ranging from 100 mCi to 700 mCi. Cures were spaced 4 to 6 months apart. The highest dose was administered in a combination of disseminated pulmonary metastases with muscle metastases.

Radiotherapy plays an important role in bone metastases, as it can complement surgery in case of incomplete resection or be used alone for pain relief or as a palliative treatment. In our study, radiotherapy of metastatic sites was performed in 12 patients (15%) with poor carcinogenic improvement, yet it provided significant palliative care.

The mortality rate in our sample was relatively low at 8%. Even if metastases occur, prognosis is generally favorable for DTCs compared to other types of thyroid cancers.

Even though our study is retrospective with a relatively low sample rate of 75 patients, analyzing the factors associated with each metastatic localization yielded significant results. Concerning long term patient follow-up, further data is needed in order to calculate prognostic factors.

Conclusion

Differentiated thyroid cancers management requires multidisciplinary skills in surgery, pathology, nuclear medicine and endocrinology. Approximately 10% of patients with DTC will have locally advanced disease. Remote metastasis is the leading cause of death with overall mortality rates of 65% at 5 and 10 years [1]. In Morocco, late diagnosis of DTC is a major issue

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that needs to be addressed with appropriate measures. Over the last decade, progress has been made in the treatment of DTC. Surgery, hormone-blocking therapy and radioiodine therapy remain the most effective modalities for patients at high risk of recurrence or mortality.

Conflict of Interest

The author declares no conflicts of interest.

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