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Unusual metastases from differentiated thyroid carcinoma: analysis of 36 cases

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Abstract

Purpose Metastases of differentiated thyroid cancer (DTC) in sites different from lungs and bone are unusual (UM); their impact in management and prognosis remains unknown. Our aim was to evaluate the prevalence of UM, to describe their characteristics and to analyze their impact in disease outcome and mortality.

Methods We retrospectively reviewed the file records from 8 different centers. Those patients with DTC and UM were included. UM were diagnosed by: (i) biopsy/cytology and/or (ii) radioiodine (RAI) uptake associated to elevated thyroglobulin (Tg) levels and/or c) presence of one or more structural lesion/s with 18-FDG uptake in the PET/CT scan and elevated Tg levels.

Results Thirty-six (0.9%) out of a total of 3982 DTC patients were diagnosed with UM; 75% had papillary histology. The most frequent localization was central nervous system (CNS, 31%). UM were metachronous in 75%, symptomatic in 55.6% and fulfilled RAI-refractoriness criteria in 77.8% of cases. Metastatic lesions in lung/bone and/or locoregional disease were present in 34 cases (94.4%). Diagnosis of UM changed the therapeutic approach in 72.2% of patients. After a median follow up of 13 months, 21 (58.3%) patients died from DTC related causes. In 8 of them CNS progression was the immediate cause of death.

Conclusions Prevalence of UM was low; they were frequently metachronic and RAI-refractory. Although UM were found in patients with widespread disease, their diagnosis usually led to changes in therapy. UM were associated with poor prognosis and high frequency of disease-specific mortality.

Keywords Thyroid carcinoma · Distant metastases · Unusual metastases · Advanced thyroid cancer · Radioiodine refractory

Introduction

Differentiated thyroid carcinoma (DTC) usually has an excellent prognosis, with 10-year disease-specific survival rates over 90% [1]. Adverse prognostic factors related to mortality include: (i) advanced age, (ii) gross extrathyroidal extension, (iii) incomplete surgical resection, (iv) distant metastases, and/or (v) radioiodine refractoriness [2].

When distant metastases are diagnosed, the mean 5-year overall survival generally drops to 50% [3]. Distant metastases are the main cause of disease-specific mortality in patients with DTC [4, 5]. They may be discovered at the moment of DTC diagnosis in 3.4% of patients, and later in the follow-up in other additional 6 to 20% of cases [6, 7]. The most frequently affected distant metastatic sites are lungs and bone. Involvement of other sites is infrequent, and it is mentioned in individual case reports and small series [8, 9]. Data on the optimal management of these unusual metastases from DTC (UM) are scarce, and their influence in morbidity and overall survival remains uncertain.

The present study aims to retrospectively analyze the prevalence of DTC metastases in localizations other from lung and bone, to describe their clinical and pathological features and to evaluate their impact in disease-specific mortality.

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Materials and methods

Data file records from eight hospitals from Argentina were reviewed. Patient's data confidentiality was maintained according to each institution standards.

DTC patients with distant metastases in sites different from lungs and/or bone were included. Pleural metastases were included when they were not related to lung involvement; skin and soft tissue metastases were included when they were not adjacent to bone metastases or primary site tumors. Metastatic lymph nodes in sites other than neck or mediastinum were also included.

Diagnosis of metastases was obtained by: (a) biopsy/cytology, (b) presence of structural lesion with radioiodine (RAI) uptake associated to elevated thyroglobulin (Tg) levels and/or (c) presence of one or more structural lesion/s with 18-FDG uptake in the PET/CT scan and elevated Tg levels. UM were classified as: (i) synchronous when they were found within 6 months of initial diagnosis, and (ii) metachronous when they were diagnosed later in the course of the disease.

All included patients had received a total thyroidectomy and were treated with at least one ablative RAI treatment (≥100 mCi 131-I). Patients were stratified according to AJCC/UICC (8th edition), [10] and risk stratified according to the American Thyroid Association (ATA) 2015 risk of recurrence classification [2] and to the Argentinian Intersocietary Consensus for the management of patients with differentiated thyroid cancer [11].

Patients were treated with RAI until (a) adverse events were noted or, (b) the patient was defined as radioiodine refractory [12].

Other therapeutic modalities, such as external beam radiotherapy (EBRT) and tyrosine kinase inhibitors (TKI) were used according to the criteria of each center.

Statistical analyses were performed using SPSS (version 21: SPSS Inc., Chicago Il). Quantitative variables were expressed as means ± SD; qualitative data were expressed in percentages. Continuous variables were compared using Mann–Whitney and Fisher´s exact test; χ^2 test was used to compare categoric variables. Rates of survival were calculated with the use of the Kaplan-Meier method. A p value <0.05 was considered significant.

Results

Out of a total of 3982 DTC cases, 36 (0.9%) were diagnosed with UM. Clinicopathological characteristics of patients are shown in Table 1.

Forty-five unusual foci of metastatic disease were diagnosed in these 36 patients. In 23 patients (65.7%) diagnosis was confirmed by either cytological or histological analysis of the lesion. Localizations of UM are shown in Fig. 1; the most common site of UM was the brain. Nine patients (25%) had more than one foci of UM. Lung metastases were also present in 27 patients (75%), bone metastases in 16 (44.4%) and 23 patients (63.8%) had evidence of locoregional persistent/recurrent disease. Two patients presented with isolated UM. Both were female PTC patients with synchronous and symptomatic UM. One of them presented with inguinal lymph node metastases. She underwent total thyroidectomy, inguinal lymphadenectomy

Table 1 Characteristics of 36 patients with unusual metastases from differentiated thyroid cancer

	N (%)
Age mean (±SD)	56.7 ± 13.31 years
Older than 55 years	22 (61.1%)
Female/male	21/15 (58.3%/41.6%)
Histology	
Papillary thyroid cancer total	26 (72.2%)
Classic variant	15 (41.6%)
Aggressive variant	7 (19.44%)
Follicular variant	4 (11.11%)
Follicular thyroid cancer	10 (27.77%)
T	
X	3 (8.33%)
1a	1 (2.77%)
1b	4 (11.1%)
2	3 (8.33%)
3	15 (41.66%)
4a	9 (25%)
4b	1 (2.77%)
Tumoral size median (range) cm	4.1 (0.5–15)
N	
X	7 (19.44%)
0	11 (30.55%)
1a	3 (8.33%)
1b	15 (41.66%)
M	
X	3 (8.33%)
0	17 (47.22%)
1	16 (44.44%)
S	
Unknown	5 (13.88%)
I	6 (16.66%)
II	2 (5.55%)
III	2 (5.55%)
IVa	6 (16.66%)
IVb	15 (41.66%)
Argentinian Intersocietary Consensus risk of recurrence	
Unknown	7 (10.3%)
Low	1 (2.77%)
Intermediate	6 (19.44%)
High	22 (61.11%)
American Thyroid Association 2015 risk of recurrence	
Unknown	6 (16.66%)
Intermediate	9 (25%)
High	21 (58.33%)

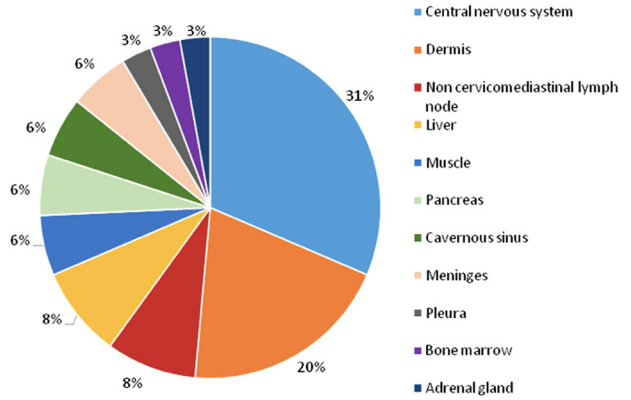

Fig. 1 Location of unusual metastases

and radioiodine treatment. She remains free of disease 10 years after initial diagnosis. The other patient had isolated pleural metastases at diagnosis; she was submitted to total thyroidectomy, pleurodesis, and radioiodine treatment. She died 11 months later due to respiratory insufficiency.

The diagnosis of UM was metachronic in 27 patients (75%). Mean interval from initial diagnosis of DTC to UM detection was 61.7 ± 5 months. In two cases, (one patient with inguinal lymph node metastasis and one with pleural metastasis) the UM was the cause leading to the diagnosis of DTC.

UM were symptomatic in 20 patients (55.6%) and fulfilled the definition criteria for RAI refractory disease in 28 cases (77.8%). In 11 patients (30%) UM were incidentally detected during routine follow-up imaging procedures. 18FDG-PET/CT scan was performed in 15 patients (41.7%); in 11 cases (73.8%) hypermetabolic foci were detected. Mean SUVm value of the lesions was 11.4.

In 26 patients (72.2%), the diagnosis of UM led to changes in treatment strategies. Local treatment for UM, such as surgery, external beam radiotherapy and/or stereotactic radiotherapy was given to 22 patients. By the time the UM was diagnosed, 8 patients were receiving systemic treatment with TKI; in 5 additional patients TKI therapy was administered after the diagnosis. In the remaining 23 patients, TKI were not prescribed due to: (i) pre era of TKI approval (16 cases); (ii) medical comorbidities/poor performance status precluded treatment (3 cases), (iii) refusal of the patient (2 cases) (iv) other (2 cases).

Six patients did not receive specific treatment after the diagnosis of UM was made. In two patients, diagnosis of leptomeningeal metastases was made intra TKI treatment, which was subsequently withdrawn due to disease progression. In these 2 cases, as in the remaining 4 patients (which were diagnosed with metastases to the pancreas and muscle, liver, CNS and bone marrow, respectively) only supportive care was prescribed (due to poor performance status or lack of availability of therapies), and they had a median survival of 8 months (1–48).

The relationship between histological type and site of UM is shown in Fig. 2.

Characteristics of patients with brain metastases ($n = 12$) were compared with patients who had no central nervous system (CNS) involvement. Patients who developed CNS metastases were younger when DTC was diagnosed ($p = 0.035$). CNS metastases were more frequently metachronic (Table 2).

Median follow-up after the diagnosis of UM was 13 months (range 1–25, mean 24.5 ± 34.1). Kaplan–Meier survival curve is shown in Fig. 3. Median overall survival was 24 months (CI: 21.3–26.6). Survival at 12 months was 61.8%; at 36 months dropped to 30%.

At the end of follow-up, 21 patients (58.3%) died of DTC related causes, 12 (33.3%) were alive with persistent structural disease, 2 (5.5%) died of non-DTC related causes and one patient (2.78%) had no evidence of disease. Death related to DTC was more frequent in patients with RAI-refractory disease and in those with symptomatic metastases (Table 3).

Among the 21 patients who died from DTC related causes, in 8 cases (38%) death was attributed to progression of central nervous system metastases. Seven (33.3%) patients died due to respiratory failure, 3 patients (14.3%) because of locoregional progression, 2 patients due to multi-organic failure, and one because of complications of the surgical treatment.

Discussion

Distant metastases are found in less than 10% of DTC patients [13]. The most frequently affected sites are lung and bone [2, 14]. Metastatic disease carries a poor prognosis with 10-year disease-specific mortality rates of 50–60% [15].

Metastatic dissemination to other organs is extremely unusual [9]; consistently with these data, UM were diagnosed in less than 1% of our population. However, under underdiagnosis cannot be excluded, as sites other than lung and bone may not have been systematically evaluated by specific-imaging procedures in all cases.

In the present series, nearly half of the UM were asymptomatic. In 40% of the cases, 18-FDG PET/CT scan detected unsuspected UM, underscoring the usefulness of this procedure to accurately assess the disease extension. Three-quarters of the UM in our series had either cytologic or histologic confirmation. This probably shows the perceived need to rule out other differential diagnosis due to the rarity of UM. Systematic biopsy of newfound metastasis is not routinely recommended in patients with widespread

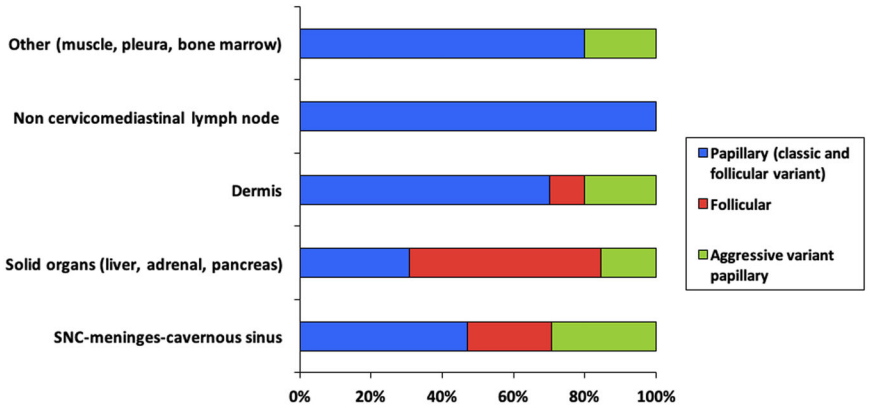

Fig. 2 Histological tumor type according to location of unusual metastases

Table 2 Characteristics of patients with unusual metastases in central nervous system vs. patients with unusual metastases in other sites

	Metastases in CNS ($n = 12$)	Other UM ($n = 24$)	p
Age at diagnosis (years)	49.5 (26–73)[a]	61.5 (42–80)[a]	0.035
Primary tumor diameter (cm)	5 (2.5–15)[a]	3.5 (0.5–5)[a]	ns
Largest diameter of UM (cm)	2 (1–3)[a]	4 (1–25)[a]	ns
Total accumulated activity of I^{131}	600 (100–1300)[a]	400 (130–1100)[a]	ns
Metachronic diagnosis	12 (100%)	15 (62%)	0.014
Time interval since initial DTC diagnosis to UM diagnosis (months)	78 (16–185)[a]	20.5 (3–135)[a]	0.09
Symptoms	8 (66.6%)	12 (50%)	ns
Incidental finding	6 (50%)	5 (21%)	0.07
Death related to DTC	9 (75%)	12 (50%)	0.07
Survival after diagnosis of UM	4 (1–124)[a]	18 (1–125)[a]	0.054

CNS central nervous system, *DTC* differentiated thyroid cancer, *UM* unusual metastases

[a]Data are presented as median and range

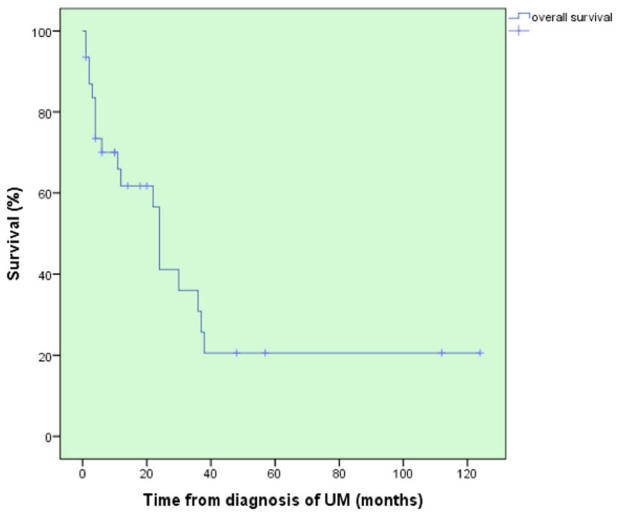

Fig. 3 Kaplan–Meier curve for overall survival in patients with unusual metastases

Table 3 Mortality analysis of differentiated thyroid cancer patients with unusual metastases

	Death related to DTC ($n = 21$)	No ($n = 14$)	p
CNS metastases	9 (42.8%)	2 (14.3%)	0.074
Symptomatic metastases	15 (71.4%)	4 (28.6%)	0.013
Metachronic UM	18 (85.7%)	8 (57%)	0.058
RAI Refractory	18 (100%)[a]	10 (71.4%)	0.015
Gender female/male	14/7	6/8	0.16
Histological type			0.28
Papillary	10 (47.6%)	8 (57.1%)	
Follicular	5 (23.8%)	5 (35.7%)	
Aggressive variant of PTC	6 (28.5%)	1 (7.1%)	
Age, mean (years)	60	63	ns

[a]Data available on 18 patients

disease. However, due to the rarity of UM, cytological or histological confirmation of etiology is desirable in order to exclude other differential diagnosis.

The most frequent histological diagnosis in our series was papillary thyroid cancer (PTC) in 75% of patients. However, since follicular thyroid cancer (FTC) usually accounts for less than 5% of all DTC cases [16], this

histological type is overrepresented in the population of UM. In our population 24% of the cases were FTC; Madani et al. [8], reported an even higher proportion of FTC (39%). These findings are probably related to the higher tendency of FTC to spread through the haematogenous pathway. Moreover, in our population, nearly half of the metastases to solid organs (liver, pancreas, and adrenal gland) were caused by FTCs. Non cervicomediastinal lymph node metastases were in all cases caused by PTC. The mechanisms explaining the selective trophism of different types of DTC for specific tissues remains to be determined. However, improved knowledge of the different metastatic pathways of PTC and FTC might lead to tailoring follow-up strategies according to histological variants in patients with advanced disease.

Most of the patients in our series had widespread disease at the time of detection of UM. However, in 72% of patients, diagnosis of UM led to changes in therapy. Although over 60% of the patients were submitted to local therapies, in 5 cases (13.8%), it was the diagnosis of UM which led to the indication of systemic treatment, thus emphasizing the importance of an accurate diagnosis.

Among UM, the most frequent site is CNS [8, 13], which was involved in one third of our population. Although CNS metastases occur in 0.9–1.5% of DTC patients [17], they can be found in up to 18% of cases when distant metastases are present in other sites. Similarly, autopsy series of DTC patients yielded up to 20% of CNS involvement [18]. These findings led in some cases to recommend systematic CNS imaging in all asymptomatic patients with distant metastatic disease [19, 20]. International and local guidelines do not specifically address this issue [2, 11, 21]. However, due to the improvement in the prognosis of surgically treated CNS metastases, it is likely that patients with widespread disease will benefit from early diagnosis, which allows a directed optimal treatment. Patients with CNS metastases in our series were younger at diagnosis of DTC and frequently had papillary histology. CNS metastases were diagnosed later during the course of the disease, and they tended to be associated to worse survival although this did not reach statistical significance.

Complications of distant metastases represent the main cause of mortality in DTC [4, 5]. Individual prognosis varies according to localization, number and size of the lesions. In addition, outcome is negatively modified according to the histological type (FTC or aggressive variants of PTC), advanced age, lack of significant RAI uptake, and positivity of FDG uptake by the metastatic lesion [13, 14, 21, 22]. These adverse prognostic factors were frequently found in our population.

According to the data reported by Madani et al. [8], most cases of UM (66%) were metachronic; these findings differ from those found by Wang et al. [23] in patients with lung, bone and brain metastases (43%). The proportion of metachronic UM was even higher in our series (75%). Metachronic presentation of metastatic disease was described as an independent predictor of poor prognosis [24]. In a study of 89 DTC patients with distant metastases, those with metachronic disease showed 10-year tumor-related survival rates of 34.8% compared to 66.9%, for those with distant metastases with synchronic presentation. Other studies have shown the same observation [7, 25].

When factors for specific mortality were analyzed, poorer outcomes were observed in patients with RAI refractory disease and in those patients with symptomatic UM. Worse survival in symptomatic UM is probably related to the fact that they were probably diagnosed at a more advanced stage, and fewer treatment modalities might have been feasible.

RAI-refractoriness is an extensively described adverse feature of metastatic disease [12, 14, 26]. It can be found in nearly two thirds of patients with metastases. In our series 78% of cases fulfilled criteria for RAI-refractory disease, and it was a finding significantly associated with poor prognosis. Not only RAI-refractoriness eliminates the possibility for using RAI (the most effective systemic treatment for distant metastases) as a therapy, but also is indicative of less differentiated disease with a worse outcome.

In the present series, median overall survival after UM disease was 24 months, which was shorter than survival reported in patients with lung metastases (48 months) [27] and similar to those with bone metastases (24 months) [28]. Madani et al. [8] in their literature review of 94 cases found a mean overall survival of 60 months; however, this information was available in less than 25% of cases. Mortality in patients with UM is elevated but seems to be highly variable according to the site involved. When CNS metastases were present, disease-specific survival is shorter than a year in untreated patients [17, 19]. Series of other sites of UM are scarce in the literature, but survival longer than 24 months was reported in patients with pancreatic [29], adrenal [30], and skeletal muscle [31]. Survival in patients with liver metastases ranged between 4.75 and 28 months in patients who were not treated and in those who received TKI [32]. As only two cases in our series had isolated UM (without lung, bone or locoregional involvement), no conclusions can be drawn on the specific influence of UM in overall prognosis.

TKI-induced tumor responses seem to differ according to the tissues involved. Bone metastases are less likely to respond after TKI treatment when compared to lung metastases [33, 34]. Studies on the response of UM to TKI are lacking. In our series, less than a third of the patients received treatment with TKI. In most of the cases, however, this was due to the unavailability of these agents at the time of the diagnosis of the UM. Six out of 36 patients (16.6%)

did not received any treatment besides supportive care after the diagnosis of UM. Although prognosis was poor in this group, prolonged survival (4 years) was observed in one patient.

In conclusion, this is, to our knowledge, the largest published series of UM. Despite being an extremely rare finding, their diagnosis frequently led to therapeutic strategies changes. Specific complications of UM led to mortality in over 20% of cases. The most frequently affected site of UM was CNS, hence systemic assessment of extension of disease and systematic imaging of CNS seems recommendable in patients with advanced disease. Closer surveillance of abdominal organs (liver, pancreas, and/or adrenal) is probably suitable for patients with high-risk FTC. Further studies on differential responsiveness of UM to TKI are needed.

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Compliance with ethical standards

Conflict of interest F.P. is medical advisor, speaker, and Steering Committee Bayer and Consultancy/Speaker bureau for Sanofi and Raffo Laboratories. E.F. is medical advisor and speaker for Sanofi and Speaker for Bayer and Raffo Laboratories. I.C. is medical advisor and speaker for Sanofi and Speaker for Bayer and Raffo Laboratories. The remaining authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with animals performed by any of the authors. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments. As this was a retrospective non interventional study, written consent was deemed unnecessary.

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