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ORIGINAL ARTICLE

Distinguishing synchronous from metachronous manifestation of distant metastases: a prognostic feature in differentiated thyroid carcinoma

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Abstract
Aim Distant metastasis has a negative impact on survival in differentiated thyroid carcinoma (DTC). The timing of this manifestation, however, is of unknown prognostic relevance. The aim of this retrospective study was to investigate the potential significance of discriminating synchronous versus metachronous distant metastases (SDM vs. MDM) for the outcome of patients with DTC.
Methods We retrospectively analyzed a consecutive cohort of $n = 89$ patients with distant metastases of DTC (43 with follicular, 46 with papillary DTC histology; mean age 52.6 ± 17.7 years) undergoing radioiodine treatment at our institution. All patients were treated with the same protocol consisting of ablative radioiodine therapy (RIT, 3.7 GBq) and one post-ablation treatment after 3 months (3.7–11.1 GBq). Further cycles of RIT were administered for recurrent, progressive or newly developed metastatic disease. We distinguished 2 types of distant metastases according to the time of manifestation: SDM (within ≤12 months after DTC diagnosis) and MDM (occurring >12 months after diagnosis). Tumor-related survival was analyzed using the Kaplan–Meier method. Uni- and multivariate analyses including the Cox proportional hazards model were performed with a significance level of $p < 0.05$.
Results The mean follow-up period was 13.8 ± 1.2 years. SDM were present in 49 (55.1 %), MDM in 40 (44.9 %) patients. MDM were associated with shorter tumor-related survival ($p = 0.002$). 5-year and 10-year survival rates were 68.5 % and 34.8 % for MDM, and 84.3 % and 66.9 % for SDM, respectively. Within both age subgroups of <45 and ≥45 years, SDM were also linked with longer survival. No effect on tumor-related survival was found for the covariables sex, lymph node metastases and histologic type.
Conclusion Distinguishing synchronous from metachronous manifestation of distant metastases may add an important prognostic feature to risk stratification in DTC, as proven metachronous appearance is associated with impaired survival.

Keywords Differentiated thyroid cancer · Radioiodine therapy · Risk stratification · Distant metastases

Introduction

Differentiated thyroid cancer (DTC) accounts for more than 90 % of all thyroid cancers and is characterized by an indolent course of disease [1]. Standard treatment for DTC consists of total thyroidectomy followed by radioiodine (^{131}I) ablation therapy (RIT) of remnant tissue [2–5]. The overall prognosis of DTC is excellent, with a 10-year disease-specific survival rate exceeding 85 % [6, 7]. Distant metastatic involvement along with advancing age, aggressive histological features, and inability to concentrate ^{131}I are the main factors for impaired survival [8–11]. Synchronous distant metastases

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(SDM) are present at the time of initial thyroid cancer diagnosis in 1–3 % of patients and metachronous distant metastases (MDM) occur in 7–23 % patients particularly within the first years after the initial treatment [11]. The prognostic significance of the temporal onset of distant metastases in DTC is, to date, unclear. The purpose of this retrospective study was to investigate this issue, the prognostic difference of SDM versus MDM regarding the outcome of patients with DTC.

Material and methods

Eighty nine patients (32 males and 57 females, mean age 52.6 ± 17.7 years) with histologically confirmed DTC and distant metastasis receiving RIT according to the same protocol previously used in our institute between 1979 and 2009 were retrospectively analyzed [12, 13]. The cut-off date was chosen to allow a sufficient follow-up duration. To facilitate comparative analysis, only patients treated with the same empirical treatment protocol based on previous national guidelines [14–16] were included: All patients underwent surgical thyroidectomy, ablative RIT with an activity of 3.7 GBq (100 mCi) 4–5 weeks after thyroidectomy, and subsequent RIT 3 months after ablative therapy. No thyroid hormone replacement was initiated before ablative RIT with sufficient endogenous thyroid-stimulating hormone (TSH) stimulation (TSH >30 mU/l) required for treatment. Patients were instructed to avoid significant stable iodine exposure, and the semi-quantitative urine test prior to RIT excluded iodine excess (>150 μg/g creatinine) in all patients. A post-ablation whole body scan (WBS) was performed 5–7 days after the administration of ^{131}I. Based on the results of WBS, post-ablative RIT was performed with 3.7–7.4 GBq if no distant metastases were present and with 11.1 GBq for patients with synchronous metastatic involvement.

After the completion of RIT, hormone replacement with Levothyroxine in doses achieving TSH suppression was started. Measurement of serum thyroglobulin levels after endogenous or exogenous TSH stimulation along with diagnostic radioiodine scanning was used for surveillance during the follow-up [3, 5]. Further cycles of RIT were administered for recurrent, progressive, or newly developed metastatic disease using the same activities as for post-ablative RIT. Patients with potentially interfering elevated Tg-specific auto-antibodies in the serum were not included in the study.

Patients were retrospectively divided into two groups based on the temporal onset of metastatic disease: SDM were defined as the metastases present at initial diagnosis or treatment of DTC (i.e. within 12 months from initial diagnosis) and MDM as appearance of metastases later than 12 months after initial diagnosis. Survival analysis was performed with the Kaplan–Meier method. Tumor-related survival (TRS) was assessed from the onset of distant metastases, and death from DTC was considered as an event. Survival outcomes were stratified by various variables and compared using the log-rank test with a significance level set at $p < 0.05$. Multivariate analysis using with the Cox proportional hazards model was performed for significant factors in univariate analysis. The software package SPSS 20 was used for statistical analysis.

Results

Forty six patients (51.7 %) had papillary and 43 patients (48.3 %) follicular histology of thyroid cancer. Lymph node involvement was observed in 51 patients (57.3 %). Metastatic sites were as follows: 40 pulmonary; 22 bone; 1 brain; 17 pulmonary and bone; 2 pulmonary and brain; 4 bone and brain; 2 pulmonary, bone and brain; 1 pulmonary, bone and liver. 49 patients (55.1 %) had SDM and 40 patients (44.9 %) developed MDM during the follow up. The mean time interval between initial diagnosis and onset of metastatic disease in patients with MDM was 5.7 ± 0.8 years. The SDM and MDM groups were well balanced regarding the variables of sex, age, lymph node involvement and histologic type of DTC (Table 1).

The mean follow-up period was 13.8 ± 1.2 years. 37 patients died during the follow-up, of which 30 were DTC-

Table 1 Patients' characteristics and proportions within the SDM and MDM groups

Characteristics	SDM	MDM	*p*
All patients	49	40	
Age			
<45 y	13 (26.5)	5 (12.5)	0.119
≥45 y	36 (73.5)	35 (87.5)	
Sex			
Male	16 (32.7)	16 (40)	
Female	33 (67.3)	24 (60)	
Histology			
Papillary	26 (53.1)	20 (50)	0.470
Follicular	23 (46.9)	20 (50)	
T-Staging			
T1	2 (4.3)	1 (2.7)	0.573
T2	11 (23.9)	10 (27)	
T3	7 (15.2)	9 (21.6)	
T4	26 (56.5)	18 (48.6)	
Tx	3 (6.1)	2 (5.0)	
Presence of LNM			
Yes	20 (40.8)	18 (45)	0.428
No	29 (59)	22 (55)	

Abbreviations: *SDM* synchronous distant metastases, *MDM* metachronous distant metastases, *LNM* lymph node metastases

related deaths. The median tumor-related survival (TRS) from the diagnosis of metastatic disease was 11 years (95%CI, 5.4–16.6) for the entire cohort. On univariate analysis, patients with MDM had shorter survival from the onset of distant metastases (median TRS 8 years, 95%CI 5.7–10.2) compared to patients with SDM (median TRS not reached, $p = 0.002$). Five-year and 10-year survival rates were 84.3 ± 5.5 % and 66.9 ± 8.8 % for patients with SDM, and 68.5 ± 8.5 % and 34.8 ± 11.3 % for patients with MDM, respectively. Figure 1 shows the Kaplan–Meier curves of the patients stratified by SDM and MDM onset.

Advanced age at diagnosis of distant metastasis was the other significant risk factor of impaired survival in our analysis. Patients with age ≥45 years had shorter tumor-related survival (median TRS 8.7 years, 95 % CI 6.5–11) than patients of age <45 years (median TRS not reached, $p = 0.002$; Fig. 2). In both age subgroups, temporal onset of distant metastatic disease (synchronous vs. metachronous) was of prognostic relevance and MDM was associated with shorter TRS in both subgroups (Fig. 3). Lymph node involvement ($p = 0.965$), sex ($p = 0.430$), histologic type ($p = 0.326$), and the presence of pulmonary metastases ($n = 62$ with pulmonary, $n = 27$ with only extra-pulmonary distant metastases) had no impact on disease-related outcome in our cohort ($p = 0.895$, Table 2). On multivariate analysis, both patient age ≥45 y (HR 10.0; 95 % CI, 1.3–75.0; $p = 0.024$) and metachronous onset of distant metastases (HR 2.6; 95 % CI, 1.2–5.4; $p = 0.014$) remained as independent negative predictors for tumor-related survival. Table 2 summarizes the results of univariate and multivariate analyses regarding the endpoint of TRS.

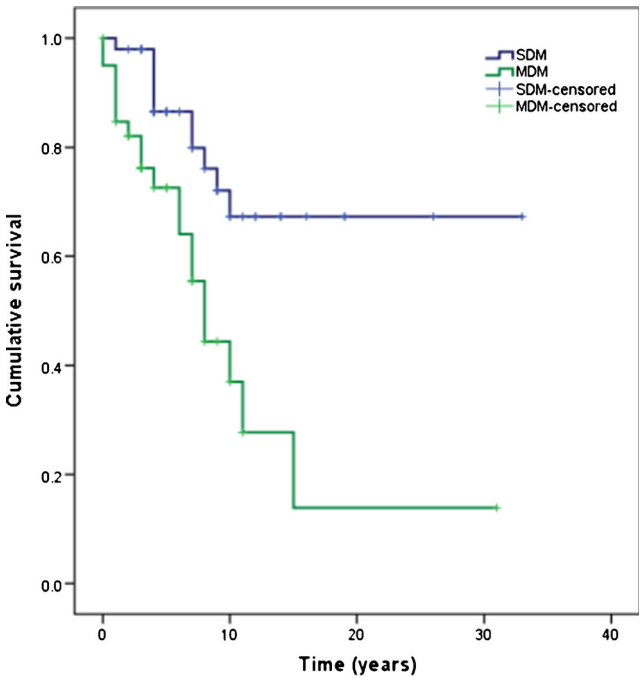

Fig. 1 Tumor-related survival (TRS) stratified by the SDM versus MDM appearance of distant metastases. Survival was significantly worse in patients with MDM development of distant metastases (median TRS 8 years [95 % CI 5.7–10.2]) compared to those with SDM distant metastatic disease (median TRS not reached), $p = 0.002$

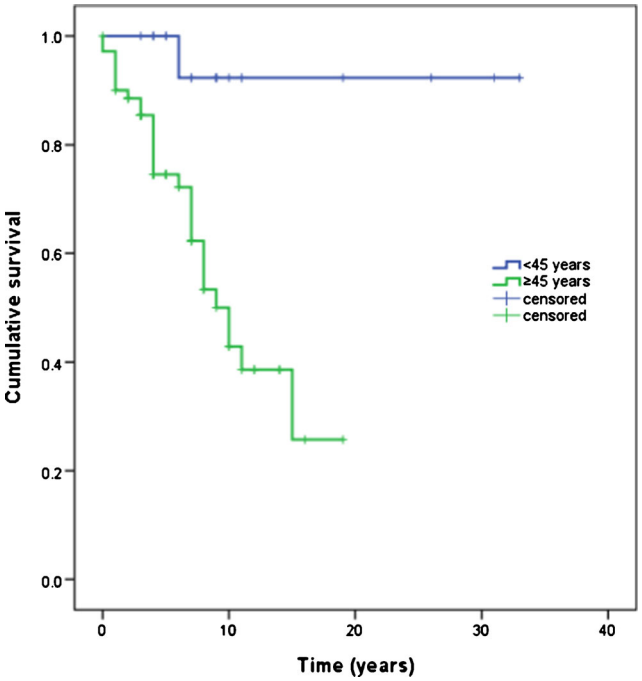

Fig. 2 Tumor related survival (TRS) stratified by age. Patients with ≥45 years of age at the time of diagnosis of metastatic disease had a significantly shorter survival (median TRS: 8.7 years [95 % CI: 6.5–11]) than patients <45 years (median TRS not reached), $p = 0.002$

Discussion

This retrospective study on 89 patients with metastatic differentiated thyroid carcinoma undergoing "high-dose" RIT according to the same treatment protocol demonstrates the prognostic difference of synchronous and metachronous distant metastases. Presence of distant metastases (DM) is a well-established factor for poor prognosis in DTC [10, 17, 18] but there is few data regarding the prognostic relevance of its time of onset. In our study, patients with SDM had a better prognosis compared to patients developing MDM.

Few studies have reported higher 10-year disease-specific survival rates in patients with DM, but with no significant difference [19, 20]. In contrast to this, we observed a favorable TRS in patients presenting with initial distant metastatic DTC (median TRS not reached during the follow-up period of 13.8 ± 1.2 years) compared to patients who develop metachronous metastases during later follow-up (median TRS 8 years, 95 % CI 5.7–10.2; $p = 0.002$; Fig. 1). This finding is in accordance with a recent report suggesting metachronous bone metastases as a risk factor for impaired outcome in patients with DTC, employing only univariate analysis [21]. In our study, metachronous onset of distant metastases proved to be a

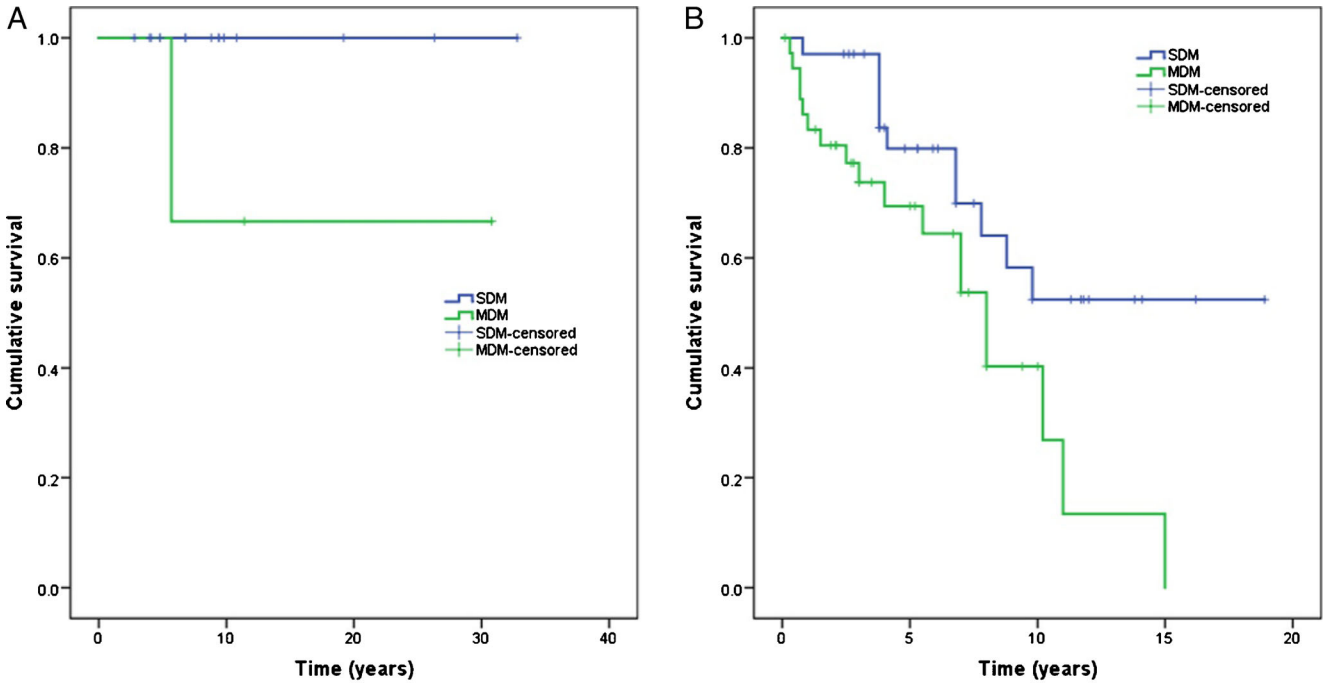

Fig. 3 Significant prognostic difference of SDM and MDM in **a** patients <45 years (10-year TRS: 100 % vs. 65.7 ± 27.3 %; $p = 0.063$) and **b** ≥45 years of age (10 year TRS: 52.4 ± 11.2 % vs. 26.7 ± 13.2; $p = 0.022$)

negative independent predictor of outcome also on multivariate analysis (Table 2).

Advanced age is a predictive factor for recurrence and mortality in DTC and various staging systems have incorporated age with a cut-off of 45 y for risk stratification and management allocation of patients (UICC, AJCC, NTCTCS, ATA) [2, 22–25]. Applying the same cut-off, age was the only factor among the baseline patient characteristics that showed a significant contribution to survival in our cohort. Interestingly, MDM was associated with impaired survival in patients of

Table 2 Uni- and multivariate analyses of potential factors contributing to tumor-related survival (TRS)

Variable	TRS (y)	95%CI	Univariate analyses *p*	Multivariate analysis HR (95 % CI)	*p*
Onset of DM					
Synchronous	NR	NR	0.002	3.1 (1.3–5.8)	0.014
Metachronous	8	5.7–10.2			
Age					
<45 y	NR	NR	0.002	10.0 (1.3–75.0)	0.024
≥45 y	8.7	6.5–11			
Sex					
Male	10.2	5–15.5	0.430		
Female	15	7.4–23			
Presence of LNM					
Yes	11	NA	0.965		
No	15	7.1–22.8			
Metastatic site					
Pulmonary metastasis	15	4.8–25.3	0.895		
No pulmonary metastasis	11	7.1–14.9			
Histology					
Papillary	15	8.1–21.9	0.383		
Follicular	8	NA			

Abbreviations: *HR* hazard ratio, *NR* not reached, *NA* not applicable, *DM* distant metastases, *LNM* lymph node metastases

both age groups. Therefore, time of metastatic manifestation may complement age for prognostic stratification of patients with distant metastatic DTC.

Not surprisingly, the presence of lymph node metastases was of no prognostic significance in our cohort with distant metastases. Similarly, other prognostic parameters in unselected DTC cohorts such as papillary vs. follicular histology type may have little influence in the presence of distant metastases, as in our cohort analysis [19, 26].

Limitations

There are obvious limitations of this study associated with the retrospective nature of the analysis. Firstly, the used treatment protocol covering 30 years of RIT inevitably differs from the current international guidelines advocating the administration of lower activities (i.e. 1–3.7 GBq) especially in the absence of metastatic disease [2, 27]. However, confining the cohort to patients treated with the same empirical protocol, albeit dated, excludes the treatment protocol as a contributing factor to different survival outcomes of the two groups (i.e. with SDM vs. MDM). The low number of events in the subgroup analysis of patients aged <45 years may weaken the strength of conclusions in this particular patient subset. Furthermore, the heterogeneity of metastatic sites in our cohort hampered the comparative analysis of the prognostic impact of each site. The preliminary finding of the prognostic impact of the onset of metastases has to be confirmed by larger analyses before applying it into clinical practice and decision-making.

Conclusions

Distinction between synchronous and metachronous manifestation of distant metastases may add an important prognostic feature to risk stratification of DTC. The metachronous onset seems to constitute an independent negative predictor for the diagnosis of distant metastases. This insight may impact future patient management if confirmed by larger studies.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This article does not contain any studies with animals.

Informed consent For this type of study, formal consent is not required.

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