CLINICAL STUDY

Primary tumour size is a prognostic parameter in patients suffering from differentiated thyroid carcinoma with extrathyroidal growth: results of the MSDS trial

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Abstract

Objective: The Multicentre Study Differentiated Thyroid Cancer (MSDS) collective represents a well-defined group of patients with thyroid carcinomas with extrathyroidal extension. The aim of the present study was to evaluate the relationship of the primary tumour size with clinicopathological features as well as the outcome of patients with minimum and extensive extrathyroidal growth (pT3b- and pT4a-tumours; UICC 2002/2003, 6th ed).

Methods: The tumour diameter was available in 324 out of 351 MSDS patients (244 females, 80 males). Mean age of patients was 47.7 ± 12.0 years (range, 20.1–69.8 years), and the median follow-up was 6.2 years. The relationship between primary tumour size and the following clinicopathological data was investigated: age, gender, histological tumour type (papillary thyroid carcinomas (PTC) versus follicular thyroid carcinomas (FTC)) and UICC/AJCC TNM classification. In addition, the correlation between primary tumour size and event-free and overall survival was assessed.

Results: The FTC of our series were significantly larger than PTC (3.46 vs 1.84 cm; $P < 0.001$). Patients suffering from pT3b-tumours presented with significantly smaller tumour size than those with extensive extrathyroidal growth (pT4a-tumours) (1.9 vs 3.0 cm; $P < 0.01$). All patients with distant metastases suffered from tumours > 2 cm. Furthermore, event-free and overall survival were significantly correlated with increasing tumour size ($P < 0.05$). Using multivariate analysis, a pT4a-category and a tumour diameter > 2 cm remained independent predictors of survival.

Conclusions: In patients suffering from differentiated thyroid carcinoma with extrathyroidal growth (pT3b and pT4a), the tumour size is an independent predictor of event-free and overall survival.

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Introduction

The diameter of the primary tumour has been described as a determinant for outcome in differentiated thyroid cancer. It has been suggested that a larger tumour size is related to other phenomena associated with worse prognosis, such as extrathyroidal growth, multifocality, locoregional and distant metastases (1). Accordingly, primary tumour size has been included in a variety of scoring schemes (AGES, AMES and MACIS) (2–4). However, the delineation between low-risk and high-risk tumour size is unsettled. Mazzaferri & Kloos (5) defined a tumour diameter > 4 cm as a significant predictive factor for a high-risk situation. Machens *et al.* (1) found

a sharply increased risk of distant metastases for primary tumours larger than about 2 cm, whereas Verburg *et al.* (6) reported a threshold tumour size of about 1 cm. The prognostic value of these upper limits in diameters was evaluated mainly for intrathyroidal carcinomas. It remains unclear, whether or not the diameter of the tumour is also prognostically relevant for tumours with perithyroidal infiltration (pT3b and pT4a, former 6th edition of the UICC TNM classification 2002/2003) (7, 8). In the recent 7th edition, the differentiation between pT3a (intrathyroidal tumour > 4 cm) and pT3b (tumour with minimal perithyroidal infiltration) was cancelled (9). But clinically it remains of ongoing interest to have separate data on carcinomas

with minimal perithyroidal infiltration. It was the aim to assess the relationship between the primary tumour size and different clinicopathological data using the well-defined prospective Multicentre Study Differentiated Thyroid Cancer (MSDS) collective with thyroid carcinomas with extrathyroidal growth. The large database allows for retrospective scientific analysis of a multitude of parameters collected over a follow-up time of up to 9 years. In particular, the correlation between primary tumour size and clinical outcome was assessed.

Materials and methods

Patients

Study design The MSDS trial is a prospective, randomised study which was conducted in Germany, Austria and Switzerland. It has been registered at <http://clinicaltrials.gov> (ID NCT00144079) in order to determine the benefit of adjuvant radiotherapy in patients with differentiated thyroid carcinoma showing extrathyroidal growth (pT4; UICC 1997) with or without lymph node metastases and without known distant metastases (M0). Inclusion criteria were age between 18 (incl.) and 70 years (excl.) at the time of initial surgery, completion of primary surgical therapy with R0- or R1-resection, Karnofsky index $\geq 70\%$ and freedom from distant metastases at the time of initial radioiodine therapy (10–12). Exclusion criteria were poorly differentiated (insular) thyroid carcinoma, secondary cancer and R2-resection with macroscopic tumour residues. Cases were seen by a reference pathologist (K W S) and reclassified if necessary.

Patients who agreed to randomisation were randomised into treatment arms A (external beam radiotherapy) or B (no external beam radiotherapy) at the time of the first ^{131}I -scintigraphy 3–4 months after initial radioiodine therapy. The MSDS treatment protocol included total thyroidectomy with central lymphadenectomy, radioiodine therapy to ablate the thyroid remnant and TSH-suppressive therapy with L-thyroxine (TSH <0.1 mU/l) (13, 14). Radioiodine therapy was to be given under endogenous TSH stimulation after 4 weeks' withdrawal of L-thyroxine using standard activities of 3–4 GBq with a post-therapeutic whole body scintigraphy. If scintigraphic ^{131}I uptake by the thyroid remnant was visible 3–4 months after radioiodine therapy under TSH stimulation, a second fraction of radioiodine therapy was to be given. At the time of each whole body scan, TSH, serum thyroglobulin (Tg), Tg recovery, anti-Tg antibodies and blood cell count were required as well as an ultrasound examination of the neck.

For patients in the treatment arm A, radiotherapy was begun after complete elimination of documented cervical ^{131}I uptake in a diagnostic whole body scan (11). Radiotherapy included the thyroid bed with a dose of 59.4 and 66.6 Gy after R0- and R1-resection

respectively and the regional lymph nodes of the neck and upper mediastinum including the posterior cervical chain from the mandible and mastoid process to the tracheal bifurcation with a dose of 50.4 and 54.0 Gy in pN0 and pN1/x diseases respectively. ^{131}I whole body scan, cervical ultrasound and serum Tg under endogenous or exogenous recombinant TSH stimulation were performed 3 months and 1 year after the last ablative radioiodine therapy and thereafter at 2-year intervals. Out-patient follow-up visits were scheduled at half-year intervals (12). Owing to a recruitment deficit for radiotherapy, the randomisation arm was closed in 2003, and the trial was continued as a prospective multicentre study.

All patients diagnosed with differentiated thyroid cancer before January 2003 were staged according to the 5th edition AJCC/UICC TNM staging criteria (15). For the purpose of the present study, these patients were retrospectively restaged or reclassified in accordance to the staging criteria outlined in the 6th edition AJCC/UICC TNM classification (7), used until the end of 2009: 307 (94.8%) patients were assigned to stage pT3b, 17 (5.2%) to stage pT4a (UICC 2002/2003), 137 (42.3%) to AJCC stage I (pT3b-patients <45 years), 173 (53.4%) to stage III, and 14 (4.3%) to stage IVA, but there were no patients with pT4b-tumours. Median follow-up time was 6.2 years. The relationship between primary tumour size and the following clinicopathological data was investigated: age, gender, histological tumour type and UICC/AJCC TNM classification. In addition, the correlation between primary tumour size and event-free and overall survival was assessed. Finally, the patients were subdivided arbitrarily into three groups according to their tumour size group I (≤ 1.0 cm, $n=85$), group II (>1.0 to ≤ 2.0 cm, $n=136$) and group III (>2.0 cm, $n=103$).

Ethical approval was obtained from the joint ethical board of the University of Münster and the locoregional physician's chamber of Westfalen-Lippe. In addition, the votes were collected from the local ethical boards. Informed consent was obtained from patients in accordance with the Declaration of Helsinki.

Statistical analysis

The relationship between primary tumour size on the one hand and classified age ($<45/\geq 45$ years), gender, histology and the UICC/AJCC TNM classification on the other hand was analysed and tested for statistical significance using the Mann–Whitney–Wilcoxon and the Kruskal–Wallis tests. The correlation between classified tumour size and appearance of recurrence was tested for statistical significance using χ^2 -test. Kaplan–Meier analysis and the log-rank test were used to analyse event-free and overall survival curves and to estimate event-free rates. An event was defined as an occurrence of a local recurrence, lymph node recurrence, distant metastasis or death after the achievement of a total, clinical tumour-free status. Complete remission

Table 1 Distribution of tumour size of the MSDS patients. The variables were dichotomised as follows: age: <45 vs ≥45 years; gender: female versus male; histology: follicular thyroid carcinoma (FTC) versus papillary thyroid carcinoma (PTC); T-category: pT3b versus pT4a (6th ed); N-category: pN1 versus pN0/X (6th ed); UICC/AJCC stages: I versus III versus IVA.

	<i>n</i>	Mean (cm)	S.D. (cm)	Median (cm)	Minimum (cm)	Maximum (cm)	Significance <i>P</i> <0.05=significant	
<45 years	137	1.99	1.24	1.80	0.10	7.00	<45 vs ≥45 years	NS ^a
≥45 years	187	1.92	1.53	1.50	0.20	10.00		
Male	80	2.18	1.57	1.80	0.30	10.00	Male versus female	NS ^a
Female	244	1.88	1.36	1.50	0.10	9.50		
PTC	302	1.84	1.26	1.50	0.10	9.50	PTC versus FTC	<i>P</i> <0.001 ^a
FTC	22	3.46	2.34	2.90	1.00	10.00		
pT3b	307	1.90	1.37	1.50	0.10	10.00	pT3b versus pT4a	<i>P</i> <0.01 ^a
pT4a	17	2.96	1.85	2.40	1.20	8.50		
N0/X	194	1.82	1.51	1.40	0.20	10.00	N0/X versus N1	<i>P</i> <0.001 ^a
N1	130	2.15	1.23	1.90	0.10	6.80		
I	137	1.99	1.24	1.80	0.10	7.00	Global:	<i>P</i> <0.01 ^b
							I versus III:	<i>P</i> <0.05 ^a
III	173	1.85	1.49	1.40	0.20	10.00	I versus IVA:	<i>P</i> <0.05 ^a
IVA	14	2.84	1.83	2.20	1.20	8.50	III versus IVA:	<i>P</i> <0.01 ^a

^aTested with Mann–Whitney–Wilcoxon test.

^bTested with Kruskal–Wallis test.

was defined as no evidence of disease, i.e. negative tumour parameters: serum Tg measurement, radioiodine WBS and sonographic/radiological examinations. Partial remission was defined as a reduction in tumour parameters without reaching complete remission under therapy. Stable disease was defined as no change in tumour parameters. Progressive disease was defined as an increase in tumour parameters without therapy response.

Multivariate analysis of reviewed prognostic factors was performed using Cox regression. The variables were dichotomised as follows: age: <45 vs ≥45 years; gender: female versus male, histology: follicular thyroid carcinoma (FTC) versus papillary thyroid carcinoma (PTC); tumour diameter: ≤2 vs >2 cm and UICC/AJCC TNM classification (6th ed): pT3b versus pT4a and pN1 versus pN0/X. Statistical analyses were performed using PASW Statistics 18 for Windows (SPSS Inc., Chicago, IL, USA). A *P* value <0.05 was regarded as significant.

Results

From 2000 to 2004, 351 patients were included in the MSDS trial. Completion of primary surgical therapy was achieved by one operation in 35% of patients, by two operations in 59% and by three operations in 7% of patients. Systematic lymphadenectomy was performed in 72% of patients. Patients received a mean cumulative radioiodine activity of 6.5 ± 5.0 GBq. Additional radiotherapy was performed in 26 patients. The follow-up data of 347 out of 351 MSDS patients were available. The exact tumour diameter was documented in 324 (92.3%; 244 females and 80 males) patients. The mean age of the 324 patients was 47.7 ± 12.0 years (range, 20.1–69.8 years). Histological tumour typing revealed 302 (93.2%) PTC and 22 (6.8%) FTC.

FTC showed a significantly larger tumour size than PTC (3.46 vs 1.84 cm; *P*<0.001). In addition, there was a significant difference between the tumour size in pT3b- and pT4a-categories. Patients suffering from tumours with minimum extrathyroidal extension (pT3b; UICC 2002/2003) presented with a significantly smaller tumour diameter than those with extensive extrathyroidal growth (pT4a; UICC 2002) (1.9 vs 3.0 cm; *P*<0.01; Table 1). There were no significant differences in primary tumour size with respect to age and gender. pT4a-tumours showed a minimum tumour diameter of at least 1.2 cm (Fig. 1). Patients with initial lymph node metastases had significantly larger primary tumours than those without lymphogenic spread

Figure 1 Box–Whisker plot showing the tumour sizes of MSDS patients with pT3b- and pT4a-tumours (6th ed) respectively according to the AJCC/UICC classification 2002/2003. Circles and asterisks denote mild and extreme outliers respectively.

Table 2 Characteristics of patients with recurrent disease or fatal outcome after previously documented complete remission.

Case	Age (years)	Gender	pT-cat.	TD (cm)	Histology, variant	Recurrence	RTx	Outcome
1	23	f	3b	0.10	PTC, conventional type	LN	—	CR
2	41	f	3b	0.90	PTC, conventional type	LN	—	PD
3	24	f	3b	1.00	PTC, conventional type	LN	—	CR
4	48	f	3b	1.10	PTC, tall cell	LN	—	CR
5	41	m	3b	1.30	PTC, conventional type	LN	—	CR
6	49	f	4a	1.80	PTC, conventional type	LN	—	CR
7	58	m	4a	1.80	PTC, follicular	Paratracheal	—	CR
8	31	f	3b	2.00	PTC, conventional type	LN	—	CR
9	51	f	3b	2.30	PTC, conventional type	Lung	—	PD
10	66	f	4a	2.40	PTC, follicular	LN	—	CR
11	62	f	3b	2.50	PTC, conventional type	LN	—	Death
12	29	f	3b	2.50	FTC	Lung	—	Death
13	29	f	3b	2.60	PTC, conventional type	LN, lung	—	PD
14	59	m	3b	2.70	FTC, oncocyctic	Paratracheal, lung	+	PD
15	61	m	3b	3.00	PTC, conventional type	LN, lung	—	PD
16	47	f	3b	3.00	PTC, follicular	—	—	Death (accident)
17	48	m	3b	3.00	FTC	LN, lung	—	PD
18	67	m	4a	3.10	PTC, conventional type	LN, lung	—	PR
19	51	m	4a	3.50	FTC	Lung	—	CR
20	67	m	4a	4.00	PTC, conventional type	Paratracheal	—	PD
21	43	f	3b	4.00	PTC, oncocyctic	Paratracheal, LN, lung	—	PD
22	37	f	3b	4.00	FTC	Mediastinal, lung	—	PD
23	66	m	3b	6.80	PTC, conventional type	Paratracheal, LN, brain	—	Death

f, female; m, male; pT-cat., pT-category (6th ed); TD, primary tumour diameter; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; LN, lymph node; RTx, percutaneous radiotherapy; outcome, status of disease at the end of follow-up; CR, complete remission; PR, partial remission and PD, progressive disease.

(2.2 vs 1.8 cm; $P < 0.001$). During a median follow-up of 6.2 years, 303 (93.5%) patients reached complete remission, and 5 (1.5%) reached partial remission. Three (0.9%) patients had stable disease, and 13 (4.0%) patients suffered from progressive disease.

In 22 (6.8%) patients, recurrences were noted after previously documented complete remission (Table 2). Median delay between primary treatment and diagnosis of recurrence was 1.3 years. Seventeen (77.3%) recurrences occurred in patients with PTC and five (22.7%) occurred in patients with FTC. Eighteen (5.6%) patients had locoregional tumour recurrences. Seven (2.2%) patients showed recurrences in more than one location. Eleven (3.4%) patients presented during follow-up with distant metastases. All of the latter suffered from tumours > 2 cm (group III) (Table 3).

Event-free survival was significantly correlated with tumour size (Fig. 2). Patients with tumours ≤ 2 cm (groups I and II) suffered significantly less events than those with tumours > 2 cm (group III) ($P < 0.01$). In addition, there was a statistically significant difference in the event-free survival between pT3b-patients in groups I and II and those within group III ($P < 0.01$). Accordingly, a significant threshold tumour diameter of 2 cm was also found with respect to the event-free survival of patients with AJCC stage III ($P < 0.001$). Using multivariate analysis, a tumour diameter > 2 cm and a pT4a-category remained independent predictors of event-free survival (Table 4).

Owing to the small number of pT4a-patients, predictive factors of recurrences were also studied in the large subgroup of pT3b-patients. Tumour size remained a significant predictor of tumour recurrence using multivariate analysis. In addition, histology was a prognostic factor for event-free survival ($P < 0.01$; Table 5).

Overall survival of the MSDS patients was excellent. Only three (0.9%) patients showed fatal tumour progress; additionally one patient died from a road accident. Overall survival was significantly correlated with tumour size ($P < 0.05$; Fig. 3). This correlation was still significant if the patient involved in the fatal accident was excluded from the analysis. Percutaneous radiotherapy had no significant impact on the

Table 3 Classified tumour size and appearance of recurrence.

Tumour size	Locoregional recurrences		Distant metastases	
	—	+	—	+
≤ 1.0 cm	82	3	85	0
> 1.0 to ≤ 2.0 cm	131	5	136	0
> 2.0 cm	93	10	92	11
Total	306	18	313	11
	NS ^a		$P < 0.001^a$	

P value < 0.05 was regarded as significant.

^aTested with χ^2 -test.

Figure 2 Event-free survival of the MSDS patients according to tumour size in pT3b- and pT4a-carcinomas (6th ed). Group I (≤ 1.0 cm), group II (> 1.0 to ≤ 2.0 cm) and group III (> 2.0 cm) (I versus II: $P = \text{NS}$; I versus III: $P < 0.05$; II versus III: $P < 0.01$, total: $P < 0.01$).

correlation between primary tumour size and event-free or overall survival. Only one irradiated patient showed a local recurrence and pulmonary metastases (Table 2).

Discussion

The MSDS trial represents the largest multi-institutional cohort of high-risk patients with differentiated thyroid cancer patients worldwide second to the North American National Thyroid Cancer Treatment Cooperative Study (12, 16, 17). Inclusion criteria were PTC and FTC with extrathyroidal extension and without known distant metastases at the time of primary diagnosis. All the patients were treated by thyroidectomy, radioiodine therapy and TSH-suppression. Because of its

Table 4 Multivariate analysis of prognostic factors for event-free survival. Hazard ratio gives the probability of the prognostic factor for an event in comparison to the opposed specification (age: < 45 vs ≥ 45 years; gender: female versus male; histology: follicular thyroid carcinoma (FTC) versus papillary thyroid carcinoma (PTC); tumour size: ≤ 2 vs > 2 cm; T-category: pT3b versus pT4a (6th ed); N-category: pN1 versus pN0/X (6th ed)). 95% confidence interval (CI) represents the 95% CI.

Prognostic factor	Hazard ratio	95% CI	P
Age (≥ 45 years)	0.980	(0.396; 2.425)	0.966
Gender (female)	0.820	(0.325; 2.070)	0.674
Histology (FTC)	2.930	(0.949; 9.046)	0.062
Tumour diameter (> 2 cm)	2.833	(1.172; 6.850)	0.021
T-category (pT4a)	3.230	(1.097; 9.513)	0.033
N-category (N1)	2.565	(0.985; 6.676)	0.054

P values were calculated by the Cox regression (Wald test). P value < 0.05 was regarded as significant.

Table 5 Multivariate analysis of prognostic factors for event-free survival within subgroup pT3b. Hazard ratio gives the probability of the prognostic factor for an event in comparison to the opposed specification (age: < 45 vs ≥ 45 years; gender: female versus male; histology: follicular thyroid carcinoma (FTC) versus papillary thyroid carcinoma (PTC); tumour size: ≤ 2 vs > 2 cm; N-category: pN1 versus pN0/X (6th ed)). 95% confidence interval (CI) represents the 95% CI.

Prognostic factor	Hazard ratio	95% CI	P
Age (≥ 45 years)	0.723	(0.271; 1.933)	0.518
Gender (female)	0.874	(0.304; 2.517)	0.803
Histology (FTC)	5.500	(1.532; 19.743)	0.009
Tumour diameter (> 2 cm)	2.902	(1.035; 8.139)	0.043
N-category (N1)	2.559	(0.878; 7.463)	0.085

P values were calculated by the Cox regression (Wald test). P value < 0.05 was regarded as significant.

highly standardised monitoring system, this database is well suited for retrospective scientific population studies.

It is widely accepted that the size of the primary tumour is of prognostic value in patients with differentiated thyroid cancer (18). In addition, this parameter diameter is correlated with well-known risk factors such as extrathyroidal growth, multifocality and metastasis (1). Whereas the tumour size has been directly integrated in the UICC/AJCC classification for intrathyroidal tumours, this is not the case for extrathyroidal tumours (7). Therefore, it was the aim to assess the impact of the primary tumour size in the large cohort of patients suffering from differentiated thyroid carcinoma with extrathyroidal growth included in the MSDS trial. However, it remains unclear, whether or not the diameter of the tumour is also prognostically relevant for tumours with perithyroidal infiltration (pT3b and pT4a, UICC 2002/2003). There was a uniform distribution of the primary tumour sizes with respect to age (< 45 vs ≥ 45 years) and gender. However, the FTC of this study were significantly larger than PTC. According to the literature, FTC are 6–18 mm larger than their papillary counterparts (19–21) which is in accordance with our data presented. The mean tumour size of the MSDS patients with FTC was 3.5 cm, whereas PTC showed a mean tumour diameter of 1.8 cm. This may be due to a delay in tumour diagnosis because fine needle aspiration cytology does not enable a distinction between follicular carcinoma and follicular adenoma (22). According to the 'linear tumour progression model', FTC develop from follicular adenoma in a sequential progressive manner. The genetic defect ultimately leading to malignancy has to occur in a certain time period before vascular and/or capsular invasion, as the histological hallmarks for the diagnosis of FTC, are fully developed (23). This concept may explain the exceptionally rare occurrence of small FTC in our study. In addition, the higher prevalence of lymph node metastases may lead to an earlier clinical manifestation of PTC compared with follicular carcinomas (1). Whereas the mean

Figure 3 Overall survival of the MSDS patients according to tumour size in pT3b- and pT4a-carcinomas (6th ed). Group I (≤ 1.0 cm), group II (> 1.0 to ≤ 2.0 cm) and group III (> 2.0 cm). (I versus II: $P = \text{NS}$; I versus III: $P = \text{NS}$; II versus III: $P < 0.05$, total: $P < 0.05$).

tumour dimensions in the pT4a-category were significantly larger than those in the pT3b-category, the maximum tumour size was higher in the latter. This may be due to a delayed clinical manifestation of primarily intrathyroidal lesions compared with those with extrathyroidal extension to clinically more apparent structures such as subcutaneous soft tissues, larynx, trachea, oesophagus or recurrent laryngeal nerve (7). It may, however, also be due to a less aggressive tumour biology. To the best of our knowledge, this is the first report on the minimum diameter of 1.2 cm of pT4a-tumours. Interestingly, this figure is above that of thyroid microcarcinomas measuring 1.0 cm or less in diameter (24, 25). Thus, according to our study, thyroid carcinomas measuring ≤ 1 cm seem to show a very small risk of extensive infiltrative growth requiring classification within the pT4a-category (UICC 2002/2003). In case of guideline compatible therapeutic management and follow-up, these patients have survival rates indistinguishable from those of the normal population (26). Interestingly, the whole group of high-risk MSDS patients showed an excellent overall and event-free survival. This may be due to the following reasons. First, the excellent overall and event-free survival in this series of high-risk patients may be due to the standardised diagnostic and therapeutic management in the MSDS trial. Secondly, the MSDS patients benefit from their lifelong medical surveillance in the framework of a clinical study (27). Thereby, other health hazards and potential fatal diseases can be revealed at an earlier stage, making cure possible. Thirdly, strict inclusion and exclusion criteria were applied in the MSDS trial. In particular, the patients with poorly differentiated (insular) thyroid

carcinoma, secondary cancer and R2-resection were excluded.

The initial pN status was also correlated with tumour size. On average, the patients with lymph node metastasis had significantly larger primary tumours than those without documented lymphogenic spread. This finding is in accordance with definitions of a threshold tumour diameter for an increased risk of lymphogenic metastasis. Two studies reported anchoring points of a tumour size-adjusted cumulative risk for nodular metastases at about 0.5–2.0 cm (1, 6).

In the present study, both the overall survival and the event-free survival were significantly correlated with increasing tumour size (Figs 2 and 3). Patients with tumours > 2 cm (group III) showed significantly higher event rates than those with tumours ≤ 2 cm (groups I and II). About 5.6% of the patients had locoregional tumour recurrences, and 3.4% presented with distant metastases. All the patients in the latter group suffered from carcinomas > 2 cm (group III). It is well known that distant metastasis is the single most important determinant for an unfavourable prognosis. Therefore, the early identification of patients prone to the development of distant metastasis is a major challenge. The primary tumour size within the pT3b- and pT4a-groups may be a relevant predictor of distant metastasis. A tumour diameter > 4 cm has been generally accepted as a significant predictor of a high-risk situation (5). This threshold should be applied with caution in view of the poorer prognosis of tumours > 2 cm if extrathyroidal extension is present. In particular, the lack of division of pT3-tumours into those with and without extrathyroidal extension in the current UICC/AJCC TNM classification should be reconsidered in view of the present findings (8, 9).

Conclusion

In patients suffering from differentiated thyroid carcinoma with extrathyroidal growth and without initial distant metastasis, primary tumour size is related to the histological tumour type, degree of extrathyroidal extension and lymph node metastasis. In addition, the tumour diameter is an independent predictor of event-free and overall survival in these patients.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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