Primary tumor diameter is related to the histologic tumor type, extrathyroidal extension, and lymph-node metastases in patients with differentiated thyroid cancer without initial distant metastases

Krämer JA, Schmid KW, Dralle H, Dietlein M, Schicha H, Lerch H, Gerss J, Frankewitsch T, Schober O, Riemann B. Primary tumour size is a prognostic parameter in patients suffering from differentiated thyroid carcinoma with extrathyroidal growth: results of the MSDS trial. Eur J Endocrinol 2010;163:637-44. EJE-10-0116 [pii];10.1530/EJE-10-0116 [doi]

SUMMARY

BACKGROUND

The Multicenter Study Differentiated Thyroid Cancer (MSDS) collective is a well-defined group of patients with thyroid carcinomas with extrathyroidal extension. The aim of this study was to evaluate the relationship of the primary tumor size with clinicopathologic features and the outcome of patients with minimum and extensive extrathyroidal tumor growth. The delineation between low-risk and high-risk tumor size is not well defined, with tumor sizes ranging from 1 cm to 4 cm. Accordingly, it is unclear whether the diameter of the tumor is prognostically relevant for tumors with perithyroidal infiltration (pT3b and pT4a, according to the former 6th edition of the International Union against Cancer tumor–node–metastasis (UICC TNM) classification 2002/2003.

METHODS

The MSDS trial is a prospective, randomized study that was conducted in Germany, Austria, and Switzerland that was performed in order to determine the benefit of adjuvant radiotherapy in patients with differentiated thyroid cancer growth (pT4; UICC 1997) with or without lymph-node metastases and without known distant metastases. The criteria for entry into the study were age from 18 to 70 years at the time of initial surgery, completion of primary surgical therapy with R0 resection (complete removal of all tumor with microscopic examination of margins showing no tumor cells) or R1 resection, (the margins of the resected tumor show tumor cells when viewed microscopically), and Karnofsky index ≥70% (normal activity with effort; some signs or symptoms of disease), without distant metastases at the time of initial radioiodine therapy. Excluded from the study were poorly differentiated (insular) thyroid carcinoma, secondary cancer, and R2-resection (complete resection with residual macroscopic tumor). A reference pathologist reclassified the tumors, if necessary.

Patients who agreed to participate in the study were randomly assigned to two treatment group A (external-beam radiotherapy) or B (no external-beam radiotherapy) at the time of the first ^{131}I scintigraphy 3 to 4 months after initial radioiodine therapy. The MSDS treatment protocol comprised total thyroidectomy with central lymphadenectomy, radioiodine (^{131}I) therapy to ablate the thyroid remnant, and thyrotropin (TSH)-suppressive therapy with levothyroxine suppression of TSH (<0.1 mIU/L). Preparation for remnant ablation was achieved by thyroid hormone withdrawal for 4 weeks followed by standard activities of 3 to 4 GBq (81 to 108 mCi), with a posttherapy whole-body scintigraphy study. If ^{131}I uptake was visible in the thyroid remnant with TSH withdrawal 3 to 4 months after ^{131}I therapy with TSH stimulation, a second treatment of ^{131}I was administered. At the time of each whole-body scan, serum TSH thyroglobulin (Tg), Tg recovery, anti-Tg antibodies (TgAb), blood-cell count, and neck ultrasonography were performed.

For patients in group A, external-beam radiotherapy (EBRT) was initiated after complete elimination of documented cervical ^{131}I uptake in a diagnostic whole-body scan (DxWBS). EBRT included the thyroid bed, with doses of 59.4 Gy after R0 resection and 66.6 Gy after R1 dissection, 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 doses of 50.4 Gy in pN0 and 54.0 Gy in pN1.

^{131}I DxWBS, cervical ultrasonography and serum Tg under endogenous TSH stimulation or recombinant TSH stimulation were performed 3 months and 1 year after the last ^{131}I ablation and thereafter at 2-year intervals. Outpatient follow-up visits were then scheduled at 6-month intervals. As a consequence of a deficit of patient recruitment for EBRT, randomization was closed in 2003 and the trial was continued as a prospective multicenter study.

All patients with thyroid cancer identified before January 2003 were staged according to the 5th edition of the TNM classification. For the purposes of this study, these patients were retrospectively restaged or reclassified according to the 6th edition of the TNM classification, which was used until the end of the study in 2009. A total of 307 patients (94.8%) were assigned to stage pT3b, 17 (5.2%) to stage pT4a, and 137 (4.2.3%) to stage 1 (pT3b-patients <45 years of age, 173 (53.4%) to stage III and 14 (4.3%) to stage IVA, and there were no patients with pT4b tumors. Median follow-up was 6.2 years.

The association between primary tumor size and the following clinicopathologic data were investigated: age, sex, histologic tumor type, and TNM classification; in addition, the correlation between the primary tumor size and event-free and overall survival were assessed. Lastly, the patients were arbitrarily subdivided into three groups according to their primary tumor size, as follows: group 1 (≤1.0 cm, n = 85), group 2 (>1.0 to ≤2 cm, n = 136), and group 3 (>2 cm, n = 103). In the analysis, an event was defined as a local recurrence, metastatic lymph-node recurrence, distant metastases, or death after the achievement of a total clinical tumor-free status.

Remission Was Designated as Follows:

Complete remission was defined as no evidence of disease, comprising negative tumor parameters, serum Tg measurement, DxWBS, and sonographic or radiologic examinations.

Partial remission was defined as a reduction in tumor parameters without reaching complete remission under therapy.

Stable disease was defined as an absence of change in tumor parameters.

Progressive disease was defined as an increase in tumor parameters without a therapeutic response.

Multivariate analysis of prognostic factors was performed using Cox regression. The variables were dichotomized as follows: age <45 vs. ≥45 years, sex, histology (follicular thyroid cancer [FTC] versus papillary thyroid cancer [PTC], tumor diameter ≤2 vs. >2 cm, and TNM classification (6th edition) of pT3b vs. pT4a and pN1 vs. pN0/X.

RESULTS

Distribution of Tumor Size (Figures 1 and 2)

A total of 351 patients were included in the MSDS trial. Complete primary surgical therapy was achieved by one operation in 35% of the patients, by two operations in 59%, and by three operations in 7% of the patients, and systematic lymphadenectomy was performed in 72% of the patients. Patients were treated with a mean cumulative radioiodine activity of 6.5±5.0 GBq (176±135 mCi), and 26 additional patients were treated EBRT.

Initial Follow-up Data (Figures 1 and 2)

Follow-up data were available in 347 of 351 patients (99%). The exact tumor diameter was documented in 324 (92.3%) of the patients, 244 of whom were women and 80 men, with a mean (±SD) age of 47.7±12 years (range, 20.1 to 69.8). A total of 302 patients (93.2%) had PTC, and 22 (6.8%) had FTC. Tumor size was significantly larger in patients with FTC as compared with patients with PTC (3.46 vs. 1.84 cm, P<0.001). In addition, there was a significant difference between tumor size in pT3b and pT4a tumor categories. Patients with minimal extrathyroidal extension (pT3b) had significantly smaller primary tumor diameter as compared with those who had extensive extrathyroidal tumor extension (1.9 vs. 3.0 cm). Patient age was not significantly related to primary tumor size and sex. PT4a tumors were relatively small, with a diameter of at least 1.2 cm. In contrast, patients with initial lymph-node metastases had significantly larger primary tumors as compared with those without lymph-node spread (2.2 vs. 1.8 cm, P<0.001) .

Follow-up During a Median of 6.2 Years

During a median follow-up of 6.2 years, complete remission was achieved by 303 patients (93.5%); 5 (1.5%) had partial remission; 3 (0.9%) had stable disease; and 13 (4%) had progressive disease. After achieving complete remission, 22 patients (6.8%) had a recurrence. The median delay between primary treatment and recurrence in this group was 1.3 years. There were 17 recurrences (77.3%) in patients with PTC and 5 (22.7%) in patients with FTC. Eighteen patients (5.6%) had locoregional tumor recurrence, 7 (2.2%) had recurrence in more than one location, and 11 (3.4%) were found to have distant metastases during follow-up, all of whom had tumors >2 cm (group 3). *(Figure 1)*

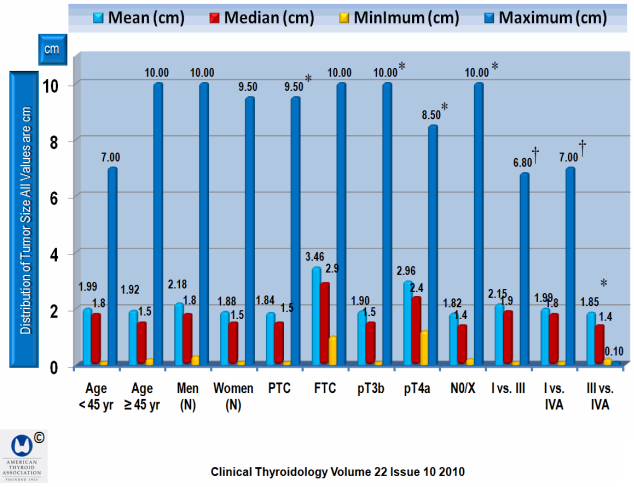

Figure 1. This figure shows the distribution of tumor size of the MSDS patients. The variables were dichotomized as follows: age <45 vs. ≥ 45 years; women vs. men, histology, follicular thyroid carcinoma (FTC) vs. papillary thyroid c (PTC); tumor category PT3b and pT4a; lympnode category, pN1 vs. pN0/X; tumor stages. *P<0.001 comparing PTC and FTC; and pT3b vs. pT4a. †P<0.01 and stages II vs. III, I vs. IVA (P<0.05) and III vs. IVA P<0.01.

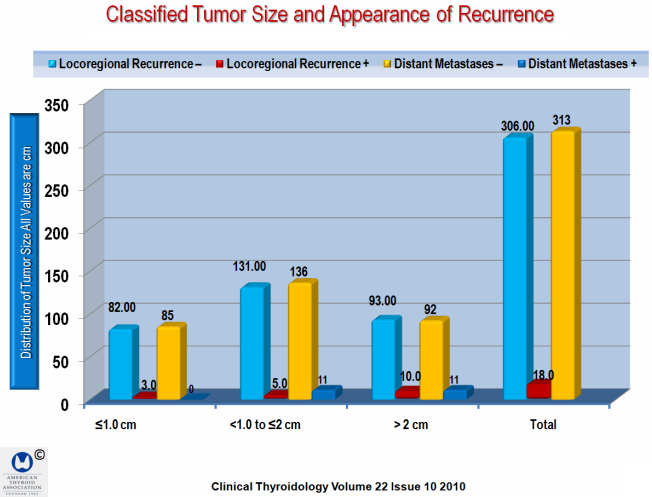

Figure 2. This figure shows the classified tumor size and appearance of recurrence. P<0.01 for locoregional recurrences, and P<0.001 for distant metastases.

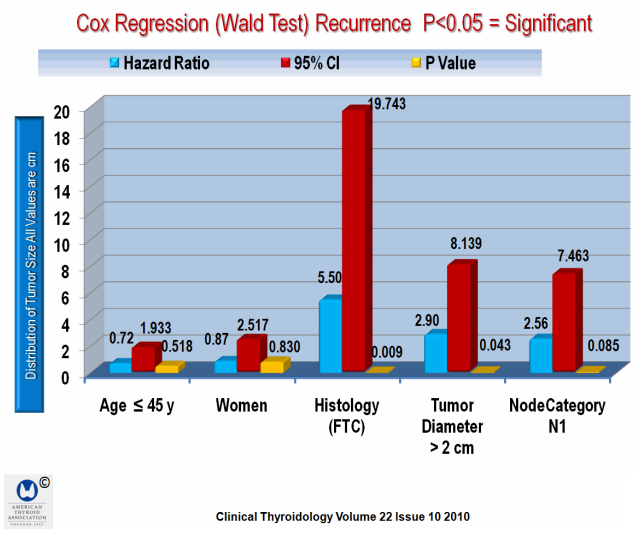

Figure 3. This figure shows the prognostic factors identified by Cox regression, for age, sex, histology (FTC), tumor diameter >2 cm, and tumor category (pT4a) and node category (N1). The P values are shown in the figure.

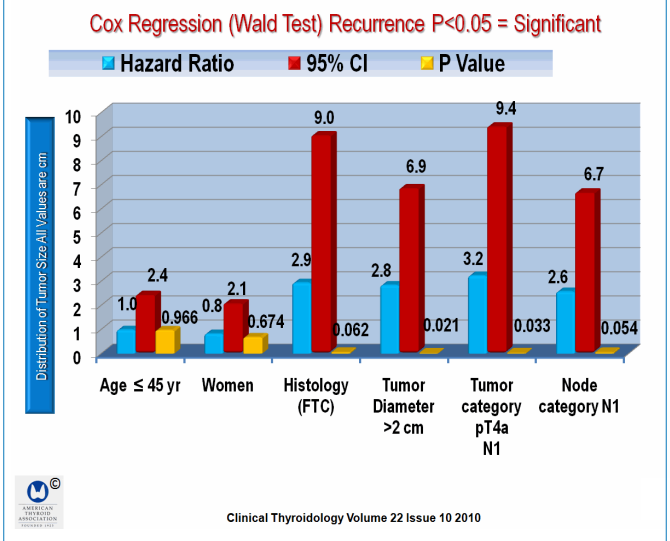

Figure 4. This figure shows the prognostic factors calculated by Cox regression. The hazard ratios and 95% confidence intervals (CIs) are shown in the figure.

Tumor Size and Event-free Survival (Figures 3 and 4)

Event-free survival was significantly correlated with tumor size. Patients with tumors ≤2 cm (groups 1 and 2) had significantly fewer events as compared with patients who had tumors >2 cm (group 3) (P<0.01). As a consequence, a significant threshold tumor diameter of 2 cm was also associated with event-free survival of patients with American Joint Committee on Cancer stage III tumors (P<0.001).

Multivariate analysis showed that a tumor diameter >2 cm and a pT4a category were both independent predictors of event-free survival. However, because of the small number of patients with pT4a tumors, factors associated with recurrences were also studied in the large subgroup of pT3b patients. Still, tumor size remained a significant predictor of tumor recurrence using multivariate analysis. Also, histology was a prognostic factor for event-free survival (P< 0.01) *(Figures 3 and 4)*.

Overall survival in this study cohort was excellent. Only 3 patients (0.9%) had fatal tumor progression, and 1 other patient died in an auto accident. Tumor size was significantly correlated with overall survival (P<0.05) and still was significant if the patient with an auto accident was excluded from the analysis. EBRT had no significant impact on the correlation between primary tumor size and event-free or overall survival. Only one patient treated with EBRT showed a local recurrence and pulmonary metastases.

CONCLUSION

Primary tumor diameter is related to the histologic tumor type, extrathyroidal extension, and lymph-node metastases in patients with differentiated thyroid cancer without initial distant metastases. Whether this holds for patients with distant metastases has not been determined.

COMMENTARY

The MSDS trial represents one of the larger prospective multi institutional cohort studies of high-risk patients with differentiated thyroid cancer. This study was conducted in Germany, Austria, and Switzerland in order to determine the benefit of adjuvant radiotherapy in patients with differentiated thyroid cancer showing extrathyroidal growth (pT4) with or without lymph-node metastases, in which patients who agreed to participate were randomly assigned to either external-beam radiotherapy (EBRT) or no EBRT. In addition, patients were treated with ^{131}I for remnant ablation. On average, patients with lymph-node metastases had significantly larger primary tumors than patients without documented lymph-node spread. The study found that patients with tumors >2 cm (group 3) had significantly higher recurrence rates as compared with those with tumors ≤2 cm. About 5.6% of the patients had locoregional tumor recurrences, and 3.4% presented with distant metastases. The authors point out that <4 cm has been generally accepted as a significant predictor of a high-risk situation, which, according to the authors, should be applied with caution in view of the poorer prognosis with tumors >2 cm if extrathyroidal extension is present. Specifically, the lack of division of pT3 tumors into those with and without extrathyroidal extension in the TNM classification should be reconsidered in view of the present finding in this study. The authors opine that using this large prospective multicenter study database allows for retrospective scientific analysis of a multitude of parameters collected during a follow-up period of up to 9 years.

According to the authors, the MSDS trial represents the largest multiinstitutional study of high-risk patients with differentiated thyroid cancer worldwide, second only to the North American National Thyroid Cancer Treatment Cooperative study (1). Not mentioned is the study by Bilimoria et al. (2) of a U.S. database of 52,173 patients with PTC, in which recurrence rates are shown to be closely related to initial tumor size, beginning with <1 cm, in which 10-year recurrence rates are approximately 5%, increasing incrementally to recurrence rates of approximately 25% with primary tumors >8 cm. In addition, 10-year cancer-specific mortality rates ranged from 2% for tumors <1 cm, which incrementally increased to 19% for tumors >8 mm. This seems to support the hypothesis that PTC outcome is related to the initial tumor size, increasing progressively with increasingly larger tumors. Limiting the cutoff to 2 cm seems to ignore the well-recognized effect of initial primary tumors ranging to over 8 mm in diameter.

While tumor diameter is surely an independent predictor of overall survival and mortality, it seems that increasingly larger tumors have a progressive effect on recurrence, survival, and mortality rates, with or without extrathyroidal extension.

— Ernest L. Mazzaferri, MD, MACP

References

1. Cooper DS, Specker B, Ho M, et al. Thyrotropin suppression and disease progression in patients with differentiated thyroid cancer: results from the National Thyroid Cancer Treatment Cooperative Registry. Thyroid 1998;8:737-44.

2. Bilimoria KY, Bentrem DJ, Ko CY, et al. Extent of surgery affects survival for papillary thyroid cancer. Ann Surg 2007;246:375-84.