Radioactive iodine in the treatment of medullary thyroid carcinoma: a controlled multicenter study

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Abstract

Objective: Radioactive iodine (RAI) therapy in medullary thyroid carcinoma (MTC) is applied in some centers, based on the assumption that cross-irradiation from thyroid follicular cells may be beneficial. However, no systematic studies on the effect of RAI treatment in MTC have been performed. The aim of this study was to analyze the effect of RAI treatment on survival in MTC patients.

Design: Retrospective multicenter study in eight University Medical Centers in The Netherlands.

Methods: Two hundred and ninety three MTC patients without distant metastases who had undergone a total thyroidectomy were included between 1980 and 2007. Patients were stratified by clinical appearance, hereditary stage, screening status, and localization. All patients underwent regular surgical treatment with additional RAI treatment in 61 patients. Main outcome measures were disease-free survival (DFS) and disease-specific survival (DSS). Cure was defined as biochemical and radiological absence of disease.

Results: In multivariate analysis, stratification according to clinical appearance (P=0.72), hereditary stage (P=0.96), localization (P=0.69), and screening status (P=0.31) revealed no significant effects of RAI treatment on DFS. Multivariate analysis showed no significant difference in DSS for the two groups stratified according to clinical appearance (P=0.14). Owing to limited number of events, multivariate analysis was not possible for DSS in the other groups of stratification.

Conclusions: Based on the results of the present analysis, we conclude that RAI has no place in the treatment of MTC.

European Journal of Endocrinology 168 779–786

Introduction

Curative treatment of medullary thyroid carcinoma (MTC) consists of a total thyroidectomy and central neck dissection with additional lymph node dissection of lateral compartments when lymph node metastases are proven or suspected (1, 2, 3, 4). In ~75% of patients, MTC is sporadic and in 25% the disease is genetically inherited (either solitary or in the context of MEN2A or MEN2B).

In general, the prognosis is relatively favorable with a 10-year disease-specific survival (DSS) of 75% (5, 6, 7, 8). Besides calcitonin doubling time (9, 10, 11, 12), TNM stage is the most important prognostic factor with 10-year survival rates for stages I, II, III, and IV of 100, 93, 71, and 21% respectively (13).

In contrast to the follicular cell in non-medullary differentiated thyroid carcinoma, parafollicular C-cells do not accumulate iodine. Therefore, radioactive iodine (RAI) therapy is not routinely used in the management of MTC.

The effect of RAI treatment in MTC patients has been investigated in several studies and showed contradictory results. Whereas in some studies no added value was found (13, 14, 15), in one study with MTC patients and in several animal and in vitro studies, a beneficial effect of RAI in MTC (16, 17, 18, 19, 20, 21, 22, 23) was claimed. The effect, if present, is hypothesized to be due to the so-called bystander effect. Follicular cells, remaining in the thyroid bed after total thyroidectomy, may trap a sufficient amount of RAI destroying adjacent non-iodine-trapping cancer cells by the beta emission.
(16, 24). Elimination of remaining C-cells is particularly important in hereditary MTC as every C-cell is capable of malignant degeneration. Consequently, this could be an argument in favor of implementing RAI in the treatment of hereditary MTC. Nevertheless, the before mentioned studies are characterized by methodological limitations such as a small number of patients, limited follow-up duration, and lack of a control group.

The aim of this multicenter study was to analyze the effect of RAI treatment on the DFS and DSS in MTC patients without distant metastases, focusing on hereditary MTC. Given the multifocality and lifelong risk of malignant transformation of C-cells, advantage of RAI treatment would mainly be expected in patients with hereditary MTC. In addition, we hypothesized that if RAI has a beneficial effect, this would be restricted to patients with MTC limited to the thyroid (T1–3N0M0).

Materials and methods

In The Netherlands, MTC patients are generally treated in one of the University Medical Centers (centers). The aforementioned lack of consensus has in the past led to diversity in the application of RAI in the treatment of MTC in The Netherlands. Owing to this diversity, it was possible to assess the impact of RAI on the prognosis of patients with MTC in a retrospective multicenter study.

Patients were identified from hospital administrations and the national database of the Dutch pathology laboratories (PALGA). All patients diagnosed with MTC in one of the eight centers in The Netherlands since 1980 were identified and registered in the national database of the academic collaboration on MTC. The following are registered in this database: data on clinical characteristics; laboratory, histological, and radiological investigations; additional treatment modalities; and follow-up.

In the present analysis, patients diagnosed between 1980 and 2007 were included when MTC was histologically proven, a total thyroidectomy was performed, and clinical data were available for analysis. Patients were excluded if MTC was of medullary-follicular mixed type, follow-up was <6 months, distant metastases were present at presentation or within 6 months after primary surgery, or when primary surgery was not performed with curative intent. Historically, in some centers, RAI was administered according to the insight of the treating physician, some physicians referring all MTC patients for RAI, other physicians only referring hereditary MTC patients.

In order to study the hypothesis that RAI would be most beneficial in hereditary MTC, patients were stratified in hereditary MTC (proven by genetic analysis and/or a family history for MTC, MEN2A, or MEN2B) or sporadic MTC. As it is likely that the prognosis of patients with preclinical MTC or clinically apparent MTC is not comparable, patients were stratified according to this classification. Within the group of patients with clinically apparent MTC, a subanalysis of patients with hereditary MTC was performed.

Clinically apparent MTC was defined according to the American Thyroid Association (ATA) guideline, as a thyroidal node with a fine-needle aspiration or serum calcitonin diagnostic or suspicious for MTC (predominantly sporadic MTC) or a nodule >5 mm on ultrasound at the moment of screening in hereditary MTC. A member from a family with hereditary MTC with a positive genetic or calcitonin screening and a thyroidal node <5 mm on ultrasound was classified as preclinical MTC. Screening was defined as a member from a family with hereditary MTC referred for investigation of the presence of MTC. As we hypothesized that the potential effect of RAI treatment on disease (free) survival is to be expected in patients with MTC localized within the thyroid, patients were also stratified in T1–3N0 (intrathyroidal) MTC or extrathyroidal (T4 and/or N1) (patients with distant metastases at diagnosis or within 6 months after operation were excluded). Besides, to correct for a possible advantage in prognosis, patients with hereditary clinically apparent MTC were stratified according to whether they had been diagnosed by screening or not. Patients were categorized in regular treatment (control group) and additional RAI treatment (RAI group).

TNM staging was classified according to the classification of the International Union Against Cancer (UICC) 6th edition based on pTNM. For the classification of intrathyroidal and extrathyroidal MTC, the 5th edition of the UICC was used because of the more distinct definition of T stage. T stage was determined on the basis of the pathology report; in case of multifocality, the largest MTC localization was used. N stage was based on the pathology report. N0 was defined as the absence of metastases in the dissected lymph nodes from the central compartment (level 6) and, when applicable, the lateral compartment (level 2–5). After primary surgical intervention, basal (non-stimulated) calcitonin was measured frequently during the follow-up. In the presence of biochemical evidence of disease, imaging studies (including: neck ultrasound; CT scan of the neck, thorax, and abdomen; bone scan; or functional imaging (Tc99m, MIBG, somatostatin, 18FDG-PET, or 18F-DOPA—PET-scan) were performed.

Primary outcome variables were disease-free survival (DFS) and disease-specific mortality. The number of patients who underwent a re-intervention was a secondary outcome variable.

Cure was defined as the absence of biochemical and radiological evidence of disease including repeated basal calcitonin levels below the functional detection limit of the used assay (25). Recurrence was defined as biochemical and/or radiological evidence of disease after cure had been established. Biochemical recurrence was defined as calcitonin levels that, after a period of biochemical cure, were repeatedly above the functional detection limit of the assay, after exclusion of other causes of calcitonin elevation.
Death causes were investigated using medical records, death certificates, and autopsy records. The disease-specific mortality was defined when the patient had progressive metastatic or relapsing MTC without other potentially fatal disease and/or when MTC was mentioned as death cause in the death certificate or autopsy file. In all other cases, the patient died due to a non-MTC-specific cause.

Adequacy of the surgical intervention was retrospectively determined according to the most recent ATA guidelines of 2009 (4). In this analysis, a central neck dissection (level VI) was defined adequate, whereas in the pathology report, at least two lymph nodes were described in this compartment.

**Statistical analysis**

Statistical analysis was performed using the Predictive Analytics Software (PASW) Statistics, version 18.0 (Chicago, IL, USA). Categorical data were presented as absolute values and proportions. Quantitative data were presented as the mean ± s.d. in case of a symmetrical distribution or the median (range) for asymmetrical distribution. Differences in patient characteristics were analyzed by (unpaired) t-test, Mann–Whitney U test for non-normally distributed data, or χ²-test (for proportions). Correction for confounding on DSS and DFS was performed using a Cox regression analysis according to the association model (26). In this model, the independent variable was DFS or DSS. The change in regression coefficient (Δβ) of the variable ‘ablation with RAI’ was then used in a multiple regression model. Confounding was considered relevant if the change in regression coefficient was at least 10%. All confounders, together with the primary variable ‘ablation with RAI’, were then used in a multivariable Cox regression analysis to analyze the DFS and DSS. A P value of <0.05 was considered statistically significant. Outcomes are presented with hazard ratios (HRs) with accompanying P values and 95% CI. The following variables were analyzed for possible confounding: age, gender, hereditary stage, center, tumor extension (TNM), localization, adequacy of surgery, and in the group of patients with hereditary clinically apparent MTC also screening status. In addition, pT stage was included as covariable for tumor extension.

**Results**

**Patient characteristics**

In the national database of the academic collaboration on MTC, a total of 490 patients with MTC have been registered since 1980. For the current analysis, 197 patients were excluded (see Fig. 1). Of the included 293 patients, 232 underwent regular surgical treatment (control group) and 61 patients underwent regular surgical treatment with additional RAI treatment (RAI group). The patients in the RAI group were treated in five different centers contributing 2, 4, 10, 22, and 23 patients respectively. Patient characteristics are shown in Table 1.

**Clinically apparent MTC**

MTC was clinically apparent in 230 patients of whom 179 patients underwent regular surgical treatment (control group) and the remaining 51 underwent regular surgical treatment with additional RAI treatment (RAI group). The median follow-up duration of these patients was 116.6 (range 7–372) months. During the follow-up, 21.7% of

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**Figure 1** Study enrollment flow diagram.

**Table 1**

<table>
<thead>
<tr>
<th>RAI</th>
<th>Total</th>
<th>Sporadic</th>
<th>Hereditary</th>
</tr>
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<tbody>
<tr>
<td>Intrathyroidal</td>
<td>51</td>
<td>16</td>
<td>35</td>
</tr>
<tr>
<td>Control</td>
<td>179</td>
<td>104</td>
<td>75</td>
</tr>
<tr>
<td>Intrathyroidal</td>
<td>58</td>
<td>21</td>
<td>37</td>
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</table>

**Table 2**

<table>
<thead>
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<th>RAI</th>
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<tr>
<td>Intrathyroidal</td>
<td>35</td>
<td>26</td>
</tr>
<tr>
<td>Control</td>
<td>75</td>
<td>42</td>
</tr>
<tr>
<td>Intrathyroidal</td>
<td>37</td>
<td>23</td>
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</table>

**Table 3**

<table>
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<tr>
<th>RAI</th>
<th>Total</th>
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<tbody>
<tr>
<td>Intrathyroidal</td>
<td>9</td>
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<tr>
<td>Control</td>
<td>47</td>
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Table 1  Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Clinically apparent MTC</th>
<th>Hereditary clinically apparent</th>
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<tbody>
<tr>
<td></td>
<td>Total (230) RAI (51) Control (179)</td>
<td>P value Total (110) RAI (35) Control (75)</td>
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<tr>
<td>Age (years)</td>
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<td></td>
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<tr>
<td>Mean (range)</td>
<td>40.5 (1.1–77.8) 35.5 (9.1–74.5) 42.0 (1.1–77.8)</td>
<td>31.1 (1.1–67.5) 29.1 (9.1–56.4) 32.1 (1.1–67.5)</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
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<tr>
<td>Female</td>
<td>116 (50.4) 25 (49.0) 91 (50.80)</td>
<td>55 (50.0) 19 (54.3) 36 (48.0)</td>
</tr>
<tr>
<td>Male</td>
<td>114 (49.6) 26 (51.0) 88 (49.2)</td>
<td>55 (50.0) 16 (45.7) 39 (52.0)</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>116.6 (6.8–371.7) 115.9 (15.1–340.6) 116.7 (6.8–371.7)</td>
<td>159.6 (6.7–371.7) 176.5 (30.5–340.6) 157.9 (6.77–371.7)</td>
</tr>
<tr>
<td>Hereditary (%)</td>
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<td></td>
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<tr>
<td>Sporadic</td>
<td>120 (52.2) 16 (31.4) 104 (58.1)</td>
<td>110 (47.8) 35 (68.6) 75 (41.9)</td>
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<tr>
<td>Hereditary</td>
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<tr>
<td>T stagea (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>94 (40.9) 27 (52.9) 67 (37.4)</td>
<td>68 (61.8) 24 (68.5) 44 (56.7)</td>
</tr>
<tr>
<td>T2</td>
<td>57 (24.8) 13 (25.5) 44 (24.6)</td>
<td>23 (20.9) 7 (20.0) 16 (21.3)</td>
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<tr>
<td>T3</td>
<td>46 (20.0) 4 (7.8) 42 (23.5)</td>
<td>11 (10.0) 2 (5.7) 9 (12.0)</td>
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<td>T4a</td>
<td>16 (7.0) 4 (7.8) 12 (6.7)</td>
<td>1 (0.9) 1 (2.9) 0</td>
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<td>T4b</td>
<td>1 (4.3) 0 1 (0.6)</td>
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<tr>
<td>Tx</td>
<td>16 (7.0) 3 (5.9) 13 (7.3)</td>
<td>7 (6.4) 1 (2.9) 6 (8.0)</td>
</tr>
<tr>
<td>N stagea (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>41 (17.8) 13 (25.5) 28 (15.6)</td>
<td>19 (17.3) 8 (22.9) 11 (14.7)</td>
</tr>
<tr>
<td>N1a</td>
<td>27 (11.7) 7 (13.7) 20 (11.2)</td>
<td>17 (15.5) 7 (20.0) 10 (13.3)</td>
</tr>
<tr>
<td>N1b</td>
<td>92 (40.0) 18 (35.3) 74 (41.3)</td>
<td>28 (25.5) 10 (28.6) 18 (24.0)</td>
</tr>
<tr>
<td>Nx</td>
<td>70 (30.4) 13 (25.5) 57 (31.8)</td>
<td>46 (41.8) 10 (28.6) 36 (48.0)</td>
</tr>
<tr>
<td>TNM stagea (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ia</td>
<td>135 (58.7) 37 (72.5) 98 (54.7)</td>
<td>89 (80.9) 31 (88.6) 58 (77.3)</td>
</tr>
<tr>
<td>I</td>
<td>5 (2.2) 1 (2.0) 4 (2.2)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>17 (7.4) 1 (2.0) 16 (8.9)</td>
<td>6 (5.5) 1 (2.9) 5 (6.7)</td>
</tr>
<tr>
<td>Iva</td>
<td>50 (21.7) 10 (19.6) 40 (22.3)</td>
<td>7 (6.4) 3 (8.6) 4 (5.3)</td>
</tr>
<tr>
<td>Ivb</td>
<td>2 (0.9) 0 2 (1.1)</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>21 (9.1) 2 (3.9) 19 (10.6)</td>
<td>8 (7.3) 0 (0) 8 (10.7)</td>
</tr>
<tr>
<td>Localizationb (%)</td>
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<td></td>
</tr>
<tr>
<td>Intrathyroidal</td>
<td>80 (34.8) 22 (43.1) 58 (32.4)</td>
<td>55 (50.0) 18 (51.4) 37 (49.3)</td>
</tr>
<tr>
<td>Extrathyroidal</td>
<td>133 (57.8) 27 (52.9) 106 (59.2)</td>
<td>49 (44.5) 17 (48.6) 32 (42.7)</td>
</tr>
<tr>
<td>Adequate surgeryc (%)</td>
<td>55 (23.9) 15 (29.4) 40 (22.3)</td>
<td>22 (20.0) 8 (22.9) 14 (18.7)</td>
</tr>
<tr>
<td>Screening (%)</td>
<td>68 (61.8) 26 (74.3) 42 (56.0)</td>
<td></td>
</tr>
</tbody>
</table>

aStaging was done according to the 6th edition of the UICC.
bLocalization: the 5th UICC edition was used to classify MTC as intrathyroidal (T1–3N0) or extrathyroidal (T4 or N1). Patients with distant metastases at diagnosis or within 6 months after operation were already excluded.
cAdequate surgery was defined according to the ATA guideline of 2009.

Significant P values are in bold.
patients had a remission and recurrence occurred in 7.4%. In 64.3% of the patients, calcitonin was detectable continuously during the follow-up and consequently could not be formally classified as cured. 6.5% of the patients could not be classified into recurrent or persistent MTC due to missing calcitonin values in the first period after the primary surgical intervention. Twenty-two patients (9.6%) died from MTC, 14 patients died (6.1%) due to other causes, and in eight patients (3.5%) the cause of death was unclear.

There were no significant differences in patient characteristics between the control group and the RAI group (see Table 1) except for hereditary stage and age. In the RAI group, the hereditary type was present in 68.6% compared with 41.9% in the control group \( (P=0.001) \). Mean age of patients in the RAI group was 35.5 years compared with 42.0 years in the control group \( (P=0.02) \).

**Hereditary clinically apparent MTC** One hundred and ten patients had a hereditary clinically apparent MTC, of which 35 were treated with RAI and the remaining patients underwent regular treatment. The median follow-up duration of these patients was 159.6 (range 7–372) months. During the follow-up, 24.5% of patients had a remission and recurrence occurred in 11.8%. In 56.4% of the patients, calcitonin was detectable continuously during the follow-up. Owing to missing calcitonin values in the first period after the primary surgical intervention, 7.3% of the patients could not be classified into recurrent or persistent MTC. Five patients (4.5%) died due to MTC and five patients died (4.5%) due to other causes. There were no significant differences in patient characteristics between the control group and the RAI group (data not shown).

**Disease-free survival**

**Clinically apparent MTC** During the follow-up, remission was obtained in 20.7% of patients in the control group and 25.5% of patients in the RAI group \( (P=0.23) \). Recurrence occurred in 6.1 and 11.8% in the control and RAI groups respectively \( (P=0.23) \). Univariate analysis showed no significant difference in DFS for the two groups \( (HR=0.91 \text{ HR for RAI}; 95\% CI 0.63–1.32; P=0.63; \text{ see Table 2}) \).

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Disease-free survival</th>
<th>Disease-specific survival</th>
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<tbody>
<tr>
<td></td>
<td>HR</td>
<td>P</td>
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<tr>
<td>Clinically apparent disease(^a)</td>
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<tr>
<td>Univariate</td>
<td>0.91</td>
<td>0.63</td>
</tr>
<tr>
<td>Multivariate</td>
<td>1.08</td>
<td>0.72</td>
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<td>Hereditary clinically apparent MTC(^a)</td>
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<tr>
<td>Univariate(^b)</td>
<td>0.80</td>
<td>0.36</td>
</tr>
<tr>
<td>Multivariate(^b)</td>
<td>0.99</td>
<td>0.96</td>
</tr>
<tr>
<td>Intrathyroidal(^b)</td>
<td>0.77</td>
<td>0.48</td>
</tr>
<tr>
<td>Multivariate(^b)</td>
<td>0.80</td>
<td>0.69</td>
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<tr>
<td>Diagnosed by screening(^b)</td>
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<tr>
<td>Univariate(^b)</td>
<td>1.15</td>
<td>0.61</td>
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<tr>
<td>Multivariate(^b)</td>
<td>0.58</td>
<td>0.31</td>
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<tr>
<td>Preclinical(^b)</td>
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<tr>
<td>Univariate(^b)</td>
<td>0.04</td>
<td>0.96</td>
</tr>
<tr>
<td>Multivariate(^b)</td>
<td>–</td>
<td>–</td>
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</table>

\(^a\)Clinically apparent and preclinical disease was defined according to the ATA guideline of 2009.

\(^b\)Owing to the limited amount of events disease-specific survival analysis was not possible.

\(^c\)Localization: the 5th UICC edition was used to classify the MTC as intrathyroidal (T1–3N0) or extrathyroidal (T4 or N1).

\(^d\)Owing to the limited amount of events multivariate disease-free and disease-specific survival analysis was not possible.
The following variables significantly influenced DFS of the included patients: hereditary stage ($\Delta \beta$ 57.8%), i.e. the change in regression coefficient between the model with and without hereditary stage in the Cox regression analysis is % $\Delta \beta$ 57.8%, center ($\Delta \beta$ 128.9%), extrathyroidal localization ($\Delta \beta$ 45.4%), and T stage ($\Delta \beta$ 29.5%).

Inclusion of these confounders in multivariate analysis showed no significant difference in DFS between the two groups (HR = 1.08; 95% CI 0.70–1.67; $P$ = 0.72; see Fig. 2A).

Patients in the RAI group received a mean dosage of 2423 MBq RAI (range 555–7400 MBq). In the Cox regression analysis, the dosage of RAI was not correlated with DFS (data not shown).

**Hereditary clinically apparent MTC** During the follow-up, remission was obtained in 20% of patients in the control group and 34.3% of patients in the RAI group ($P$ = 0.058). Recurrence occurred in 9.3% and 17.1% in the control and RAI groups respectively ($P$ = 0.06). Univariate analysis showed no significant difference in DFS for the two groups (HR = 0.80 HR for RAI; 95% CI 0.49–1.30; $P$ = 0.36; see Table 2). In multivariate analysis (corrected for center, adequacy of surgery, T stage, gender, screening stage, and age), the difference in DFS between the two groups was not significant (HR = 0.99 HR for RAI; 95% CI 0.51–1.91; $P$ = 0.96; see Fig. 2B).

**Subgroup analysis**

**Localization** In patients with hereditary clinically apparent MTC localized within the thyroid, univariate analysis (HR = 0.77 HR for RAI; 95% CI 0.38–1.58; $P$ = 0.48; see Table 2) and multivariate analysis, corrected for center, adequacy of surgery, T stage, gender, screening stage, and age, showed no significant difference in DFS (HR = 0.80; 95% CI 0.26–2.48; $P$ = 0.69; see Fig. 2C).

**Screening status** Within the group of patients with hereditary clinically apparent MTC who were diagnosed with MTC by screening, DFS showed no significant differences between the two groups in univariate analysis (HR = 1.15 HR for RAI; 95% CI 0.67–1.99; $P$ = 0.61; see Table 2) and multivariate analysis (HR = 0.58 HR for RAI; 95% CI 0.20–1.67; $P$ = 0.31; see Fig. 2D), corrected for center, adequacy of surgery, extrathyroidal localization, age, and gender.

**Preclinical MTC** During the follow-up, remission was obtained in 60% of patients in the control group and 100% of patients in the RAI group ($P$ = 0.14). Recurrence occurred in 6.4% in the control group and in none in the RAI group ($P$ = 0.14). Univariate analysis showed no significant difference in DFS for the two groups (HR = 0.04 for RAI; 95% CI 0.00–17.4; $P$ = 0.96). Owing to the limited number of events, multivariate analysis of DFS was not possible.

**Disease-specific survival**

**Clinically apparent MTC** During the follow-up, 20 patients (11.2%) died due to MTC in the control group and two patients (3.9%) died in the RAI group ($P$ = 0.13). Re-operations were undertaken in 55 patients (30.7%) in the control group and in 18 patients (35.3%) in the RAI group ($P$ = 0.54). Univariate analysis showed no significant difference in DSS for the two groups (HR = 0.28; 95% CI 0.07–1.21; $P$ = 0.09; see Table 2). In multivariate analysis, corrected for hereditary stage, extrathyroidal localization, T stage, and adequacy of surgery, DSS for the two groups was not significantly different (HR = 0.30; 95% CI 0.06–1.49; $P$ = 0.14).

**Hereditary clinically apparent MTC** Five patients (6.7%) died due to MTC in the control group and none of the patients died in the RAI group ($P$ = 0.12) during the follow-up. Re-operations were undertaken in 23 patients (30.7%) in the control group and in ten
pre-operation in the control group and none in the RAI
died due to MTC. Two patients (4.2%) underwent a
re-operation in the control group and none in the RAI
group (P=0.53).

Discussion
In the present multicenter study, additional RAI
treatment did not lead to a significant difference in
dFS and DSS in patients with clinically apparent and
preclinical MTC. Neither the stratification according to
hereditary stage nor to tumor localization revealed
significant effects of RAI treatment on the primary and
secondary endpoints. Subgroup analysis of the dosage of
RAI showed no effect on DFS either.

The overall DSS and the proportion of patients
receiving complete remission in our study is consistent
with other studies (27, 28, 29, 30). Compared with the
literature, a high percentage of included patients had
hereditary MTC (47.8% of the patients with clinically
apparent MTC). This is probably due to the fact that
especially hereditary MTC patients are referred to
tertiary centers. In addition, by excluding patients
who had distant metastases or who had primary
surgery without curative intent, particularly patients
with sporadic MTC were excluded.

The absence of significant additional effect of RAI in
the treatment of MTC shown in this study is consistent
with the much smaller studies of Saad et al. (13) and
Nieuwenhuijzen Kruseman et al. (14). Clinical studies on
this topic are scarce and consist mainly of case reports.
The added value of this study is the large number of
patients treated with RAI, availability of a control
group, long follow-up, and verification of the quality of
surgery (see Supplementary Table 1, see section on
supplementary data given at the end of this article).

A limitation of this study is its retrospective character.
However, as the extent of surgery is an important aspect
influencing outcome in MTC (1, 2, 31), we evaluated this
confounding factor in outcome by classifying the
surgical interventions according to the ATA guideline
of 2009. Although allocation of patients to RAI was not
randomized, analysis did not show significant differences
in the other prognostic parameters between the control
and RAI group in general as well as within the hereditary
group (see Table 1). There is no information in the
literature on the level of absorbed beta radiation emanating
from RAI in follicular cells that is likely to
reach and destroy (clusters of) C-cells. The current
dosage of RAI as given in differentiated thyroid
carcinoma was not effective in MTC. Although subgroup
analysis of the dosage of RAI showed no difference in
DSS, we cannot exclude that higher than the current
usual dosage of RAI might be effective in MTC.
Nevertheless, inefficacy of radioiodine ablation might
be due to the short range of beta emission and to the fact
that MTC cells are rather resistant to irradiation.

In conclusion, in this retrospective controlled multi-
center study, we found no significant additional value of
radioiodine in the treatment of MTC, which confirms
the findings of previous studies. Based on the results
of the present analysis, we endorse the current guide-
lines that RAI has no place in the treatment of MTC,
either the hereditary or the sporadic form.

Supplementary data
This is linked to the online version of the paper at http://dx.doi.org/10.1530/EJE-12-0943.

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.

Funding
This research did not receive any specific grant from any funding
agency in the public, commercial or not-for-profit sector.

Acknowledgements
The authors thank Jean-Pierre Sels, Wouter Zandee, Stephan
Hendrks, and Samuel Arends for their help in collecting the data.

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Received 28 October 2012
Revised version received 12 February 2013
Accepted 5 March 2013