Impact on Overall Survival of Radioactive Iodine in Low-Risk Differentiated Thyroid Cancer Patients

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Context: American Thyroid Association and European Thyroid Association guidelines cannot recommend for or against radioactive iodine (RAI) ablation after surgery in low-risk differentiated thyroid cancer (DTC) patients.

Objectives: The objective of the study was to assess the survival benefit of RAI for these patients.

Design: We identified 1298 DTC patients at low risk treated between 1975 and 2005. Logistic regressions were used to identify variables associated to RAI and to calculate the propensity score to receive RAI after surgery. We compared overall survival (OS) and disease-free survival (DFS) according to RAI with the log-rank tests and univariate and multivariate Cox analyses. Analyses stratified on propensity score were also performed.

Results: Median follow-up was 10.3 yr. Nine hundred eleven patients received RAI after surgery *vs.* 387 patients without RAI after surgery. Using univariate analysis, 10-yr OS was found to be 95.8% in patients without RAI after surgery *vs.* 94.6% in RAI after surgery ($P = 0.006$), and 10-yr DFS was found to be 93.1% *vs.* 88.7% ($P = 0.001$). All clinical factors except sex were significantly associated with RAI. Using multivariate Cox analyses, RAI was neither significantly nor independently associated with OS ($P = 0.243$) and DFS ($P = 0.2659$). After stratification on propensity score, Cox univariate analyses showed that OS did not differ according to RAI ($P = 0.3524$), with a hazard ratio for RAI of 0.75 (95% confidence interval 0.40–1.38). Similarly, DFS did not differ ($P = 0.48$) with a stratified univariate hazard ratio of 1.11 (95% confidence interval 0.73–1.70).

Conclusion: With a long-term follow-up of 10.3 yr, we failed to prove any survival benefit of RAI after surgery in a large cohort of low-risk DTC patients. **(*J Clin Endocrinol Metab* 97: 1526–1535, 2012)**

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy with a rapidly rising incidence worldwide (1). In France, the increase of incidence is 8.19 and 6.29% per year in women and men, respectively, particularly due to the papillary type with a tumor size of less than 4 cm (2). Recent American and European guidelines (3, 4) recommend radioactive iodine (RAI) ablation when the combination of age, tumor size, lymph node status, and individual histology predicts an intermediate to high risk of recurrence or death from thyroid cancer. However, RAI ablation is not recommended for very low-risk patients with papillary cancer less than 1 cm and

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2011-2512 Received September 8, 2011. Accepted January 23, 2012.
First Published Online February 16, 2012

Abbreviations: ATA, American Thyroid Association; AUC, area under the receiver operating characteristic curve; CI, confidence interval; DFS, disease-free survival; DTC, differentiated thyroid cancer; ETA, European Thyroid Association; M, pathological assessment of the distant metastases; Nx, without lymph node dissection; OS, overall survival; pN, pathological assessment of the regional lymph nodes; pT, pathological assessment of the primary tumor; QoL, quality of life; RAI, radioactive iodine; Tg, thyroglobulin.

confined to the thyroid. When the primary tumor is confined to the thyroid, is between 1 and 4 cm, and lacks other risk factors (worrisome histological subtypes, intrathyroidal vascular invasion, multifocal disease), patients are considered to be at low risk of death or recurrence. For these patients, RAI ablation is still controversial because of conflicting data concerning the benefit of the risk of recurrence (5–9).

To assess the survival benefit of RAI treatment in low-risk patients, we conducted a retrospective multicentric study comparing the clinical outcome of two cohorts of low-risk patients: one group with RAI after surgery and the other group without RAI after surgery.

Patients and Methods

Since 1975, the French thyroid cancer registry in Reims (France) has collected population-based data on all incidentally discovered thyroid cancers diagnosed in the districts of Champagne-Ardennes and Picardie. In Dijon, the more recent hospital-based thyroid cancer registry has collected all medical data for patients with DTC diagnosed in the districts of Bourgogne and Franche-Comté. Patients were referred to this institution for RAI treatment since 1990. We performed a retrospective cohort study considering all patients who were treated for a well-differentiated thyroid cancer between January 1975 and December 2004 at these two institutions.

Among patients with a papillary or follicular thyroid carcinoma, we considered only those at low risk of recurrence and death. Low-risk patients were defined according to the American Thyroid Association (ATA) and European Thyroid Association (ETA) criteria as follows (3, 4): complete tumor resection, multifocal pT (pathological assessment of the primary tumor) 1 less than 1 cm, pT1 greater than 1 cm, pT2, pN0, M0, using American Joint Committee on Cancer/Union for International Cancer Control staging sixth edition (10), corresponding to stage 1 for patients under 45 yr old and stages 1 and 2 for patients over 45 yr old. We also included patients pT1 and pT2 without lymph node dissection (Nx). Patients with unifocal pT1 less than 1 cm (very low risk) and pT4, pT3, pN (pathological assessment of the regional lymph nodes) 1, and M (pathological assessment of the distant metastases) 1 (high risk) or with a histological diagnosis of anaplastic thyroid cancer were excluded from this study.

All low-risk patients were initially treated by surgery, lobectomy, or thyroidectomy. After surgery in Reims, RAI was administered according to prognostic factors (age >45 yr, tumor size >30 mm). In Dijon, all patients were treated with 131I. The RAI ablative treatment was administered 1–3 months after total thyroidectomy when the TSH level was greater than 30 mIU/liter. A posttherapy scan was performed between 3 and 5 d after the dose was initially administered. The mean dose of RAI was 90 mCi (SD 25). Eighty-eight percent of the patients received 100 mCi and 12% of the patients received a lower dose of RAI (20 mCi). All patients were then treated with LT4 therapy to obtain a TSH level suppression.

Follow-up

Patients were followed up with similar protocols at the two institutions, each year for 5 yr after the initial treatment, and then every fifth year. Follow-up examinations included a clinical examination, a serum thyroglobulin (Tg) with Tg antibodies determination (since 1980) and an ultrasonography of the neck (since 1983). For patients treated with RAI, a diagnostic 131-iodine whole-body scan, and a stimulated serum Tg and Tg antibody determination were also performed. In the presence of a significantly elevated level of Tg and/or Tg antibodies, recurrences were searched and documented using various imaging modalities and histological proof when necessary.

Clinical end points

Overall survival (OS) was defined as the time interval from the date of diagnosis to death (all causes). Surviving patients were censored at the last follow-up.

Disease-free survival (DFS) was defined as the time interval from the date of the diagnosis to the date of recurrence (local, distant), second cancer, or death (all causes), whichever occurred first. Surviving patients free of recurrence were censored at the last follow-up.

A recurrence was defined as the reappearance of the disease. Patients were considered to have a recurrent disease if any of the following conditions were met: cytological- or histological-proved lymph nodes or local tumor recurrence, 131-iodine whole-body scan, or other imaging modality highly suspicious for metastatic disease. Biochemical evidence of the persisting disease with a high Tg and/or Tg antibody level was not considered as a relapse without proof of recurrent disease.

Statistical analyses

All analyses were performed with Stata (version11; Stata Corp, College Station, TX) with bilateral α-type one error of 5%.

Continuous variables were described using mean (SD) and median (Min-Max) and compared using the Mann and Whitney test. Categorical variables were described using frequency and percent and compared using χ^2 or the Fisher exact test.

The OS and DFS curves were estimated using Kaplan-Meier estimation and analyzed with the median and rate with a 95% confidence interval (CI). The survival curves were compared using the log-rank test. The median follow-up was estimated using the reverse Kaplan-Meier method.

Univariate and multivariate Cox models were first performed to estimate hazard ratio with a 95% CI and to identify the independent variables associated with survival duration. Internal validation was checked using bootstrapping (1500 replications).

Using the final multivariate model, we computed the Harrell's C statistic for discrimination (a Harrell's C index of 0.5 indicates no predictive discrimination and a Harrell's C index of 1.0 indicates perfect separation of patients).

We then performed a univariate logistic regression to identify which variables were associated with RAI treatment. Based on univariate P value (univariate $P < 0.05$) and clinical relevance, the following variables were considered for logistic multivariate analysis: age (≤45 *vs.* >45 yr old), sex, period of diagnosis (1998 or before *vs.* after 1998), thyroid surgery (lobectomy *vs.* total or near total thyroidectomy), node surgery, histology, and pT. The final multivariate logistic model was used to calculate the probability for each patient to have RAI, which is the propensity score (11–13). We computed the area under the receiver operating

TABLE 1. Patient characteristics according to RAI

	No RAI (n = 387) n (%)	RAI (n = 911) n (%)	*P* value[a]	Total (n = 1298) n (%)
Age (yr)				
≤45	270 (69.8)	324 (35.6)	<0.0001	594 (45.8)
>45	117 (30.2)	587 (64.4)		704 (54.2)
Sex				
Male	54 (14.0)	161 (17.7)	0.099	215 (16.6)
Female	333 (86.1)	750 (82.3)		1083 (83.4)
Period of diagnosis				
≤1998	224 (57.9)	452 (49.6)	0.006	676 (52.1)
>1998	163 (42.1)	459 (50.4)		622 (47.9)
Thyroid surgery				
Lobectomy	237 (61.2)	8 (0.9)	<0.0001	245 (18.9)
Thyroidectomy	147 (38.0)	903 (99.1)		1050 (81.1)
Missing	3 (0.8)	0		3
pN				
pN0	282 (72.9)	429 (47.1)	<0.0001	711 (54.8)
Nx	105 (27.1)	482 (52.9)		587 (45.2)
Histology				
Papillary	240 (62.0)	700 (76.8)	<0.0001	940 (72.4)
Follicular	147 (38.0)	211 (23.2)		358 (27.6)
pT				
pT1 ≤20 mm	262 (67.7)	539 (59.2)	0.004	801 (61.7)
pT2 (20–40) mm	125 (32.3)	372 (40.8)		497 (38.3)
RAI				
No RAI				387 (29.8)
<100 mCi				109 (8.4)
100 mCi				802 (61.8)
District				
Bourgogne	1 (0.2)	221 (24.3)	<0.0001	222 (17.1)
Franche-Comté	0 (0)	25 (2.7)		25 (1.9)
Champagne-Ardenne	289 (74.7)	481 (52.8)		770 (59.3)
Picardie	79 (20.4)	151 (16.6)		230 (17.7)
Other	18 (4.7)	33 (3.6)		51 (3.9)

[a] Mann-Whitney Wilcoxon.

characteristic curve (AUC) to check the discriminate capability of the final multivariate logistic model.

Finally, univariate Cox model stratified on propensity score was performed to estimate RAI hazard ratio with 95% CI, whereas survival curves were produced and adjusted on propensity score to illustrate these results.

Results

We analyzed the data from the 3228 DTC patients treated between 1975 and 2004. According to ATA and ETA criteria, 965 patients (27%) were identified as very low risk, 965 (27%) as high risk, and 1298 (46%) as low risk. The clinical characteristics of the 1298 low-risk patients are found in Table 1. Mean age at diagnosis was 46.6 ± 14 yr (mean ± SD). Female patients represented 83% of the cohort. Seventy-two percent of the patients had a papillary cancer and 28% had a follicular cancer. Eight hundred one tumors were classified as pT1 and 497 as pT2.

Total or near-total thyroidectomy was performed in 81% of the patients. Lymph node dissection was performed in 55% of the cases. Nine hundred eleven patients (70%) received RAI after surgery *vs.* 387 (30%) who did not receive RAI after surgery.

OS and DFS according to RAI

Median follow-up was 10.3 yr (95% CI 9.8–10.7 yr). The OS and DFS curves by Kaplan-Meier estimation were significantly different according to RAI (Fig. 1). The 10-yr OS rates were 94.6% [95% CI (92.55–96.06%)] for patients treated with RAI *vs.* 95.8% [95% CI (92.98–97.53%)] for patients not treated with RAI ($P = 0.006$). The 10-yr DFS rates were 88.7% [95% CI (85.96–90.97%)] for patients treated with RAI and 93.1% [95% CI (89.68–95.47%)] for patients not treated with RAI ($P = 0.0013$). Nineteen recurrences, 61 second cancers, and 105 deaths were recorded. Fifteen recurrences (1.6%) were observed in patients who had RAI and four recurrences (1.0%) were observed in patients who had only surgery. Recurrences consisted of six nodal recurrences; two local recurrences; seven distant metastases (in one patient, a distant metastasis was diagnosed simultaneously with a nodal recurrence) in patients who had RAI;

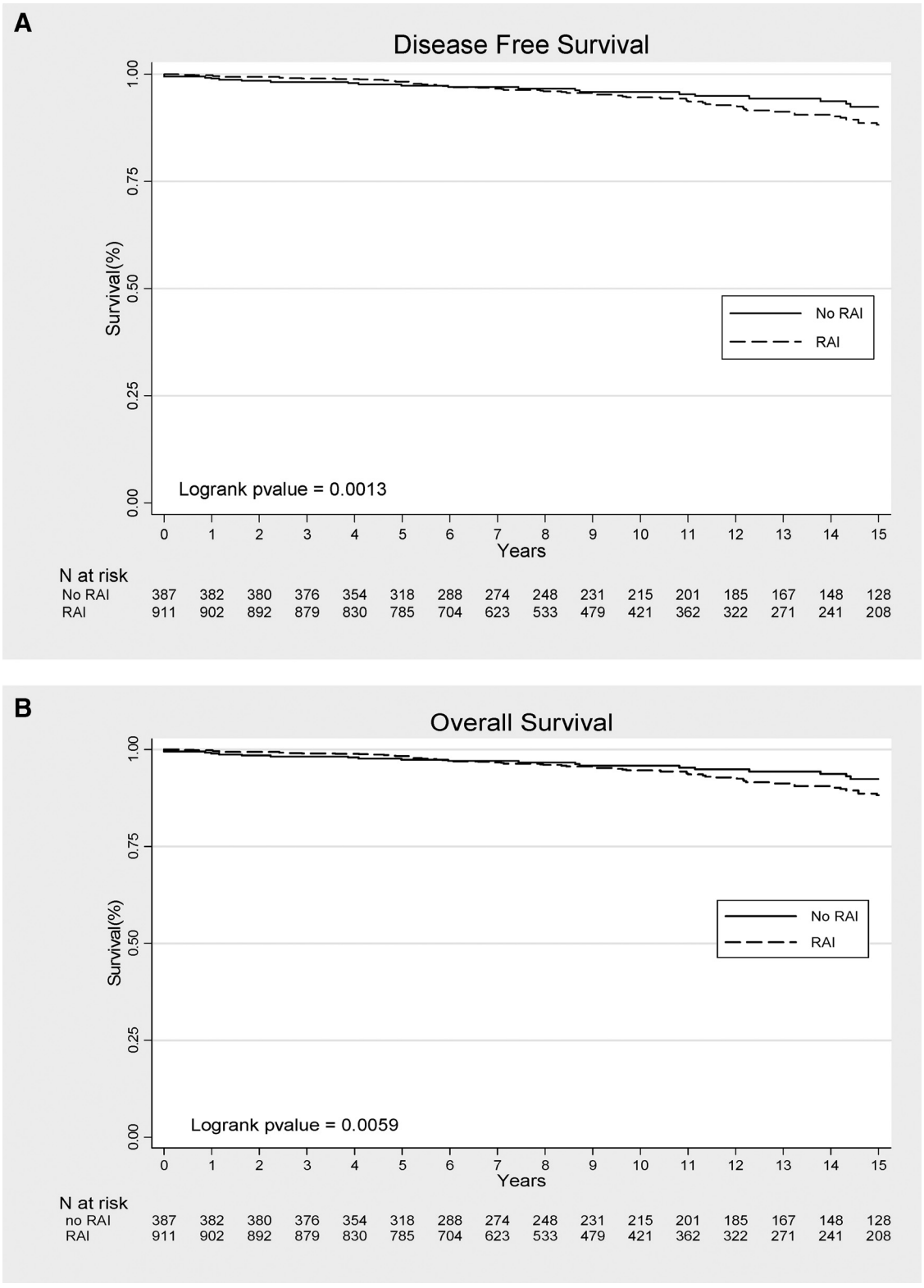

FIG. 1. DFS (A) and OS (B) according to RAI (Kaplan-Meier estimation).

and one nodal recurrence and three distant metastases in patients who had only surgery.

The OS and DFS rates did not differ significantly between patients who had the standard dose of 100 mCi and those who had the lower dose of 20 mCi. We observed no recurrences, and only seven second cancers (including four patients with second cancers followed by a death) and 13 deaths in patients receiving 20 mCi.

Univariate and multivariate Cox analyses showed that the parameters of period of diagnosis, histology, pT, pN,

and districts did not have a significant influence on OS (Table 2) and DFS (Table 3). Based on multivariate Cox analysis, age and sex were the only two independent prognostic factors associated with DFS and OS. If RAI had a significant and deleterious effect on survival in univariate analysis, this effect disappeared after the adjustment was performed on the covariates in the multivariate analysis. All results from multivariate models were confirmed by bootstrapping. The Harrell C Index was 0.77 for OS and 0.70 for DFS.

Predictive factors for RAI treatment

Districts were not a factor because the patients from Bourgogne and Franche-Comté systematically received RAI, whereas in both Champagne-Ardennes and Picardie, the patients received RAI according to their known prognostic factors (Table 1).

As shown with univariate logistic regression (Table 4), the clinical and medical characteristics significantly associated with RAI treatment were: age greater than 45 yr, male gender, a diagnosis before 1998, total and subtotal thyroidectomy, lymph node dissection, papillary histology, and pT2.

Multivariate logistic regression showed that all of these variables, except sex, were independently associated with RAI (Table 4). AUC was equal to 0.87 (95% CI 0.88–0.92). This model was retained to construct the propensity score.

As illustrated in Fig. 2, univariate analyses showed that the OS curves (adjusted on propensity score) did not differ according to RAI (log-rank *P* value stratified on propensity score = 0.3524). Univariate hazard ratio for RAI was equal to 0.75 (95% CI 0.40–1.38).

Similarly, DFS curves (adjusted on propensity score) did not differ according to RAI (log-rank *P* value stratified on propensity score = 0.4800). Univariate hazard ratio for RAI was equal to 1.11 (95% CI 0.73–1.70).

Discussion

In this large cohort of low-risk DTC patients with a long-term follow-up, DFS and OS did not significantly differ

TABLE 2. Univariate and multivariate Cox analyses for OS

	Univariate			Multivariate (n = 1295)			Bootstrapping *P* value
	HR	95% CI	*P* value	HR	95% CI	*P* value	1500 replications
RAI							
No	1						
Yes	1.92	(1.20–3.07)	0.007	0.69	(0.37–1.29)	0.243	0.318
Age (yr)							
≤45	1			1			
>45	7.60	(4.51–12.80)	<0.0001	7.70	(4.45–13.32)	<0.0001	<0.0001
Sex							
Male	1			1			
Female	0.49	(0.31–0.77)	0.002	0.41	(0.26–0.67)	<0.0001	<0.0001
Period of diagnosis							
≤1998	1			1			
>1998	1.07	(0.59–1.93)	0.948	0.88	(0.48–1.61)	0.675	0.697
Thyroid surgery							
Loboisthmectomy	1			1			
Thyroidectomy	2.88	(1.50–5.53)	0.001	1.02	(1.00–1.05)	0.108	0.138
pN							
pN0	1			1			
Nx	1.20	(0.82–1.77)	0.348	0.99	(0.65–1.49)	0.947	0.949
Histology							
Papillary	1			1			
Follicular	1.33	(0.90–1.96)	0.155	1.36	(0.90–2.05)	0.142	0.139
pT							
pT1 ≤20 mm	1			1			
pT2 (20–40) mm	1.34	(0.91–1.96)	0.136	1.31	(0.88–1.95)	0.187	0.192
District							
Bourgogne	1		0.7073	1		0.8250	0.9299
Franche-Comté	1.75	(0.38–8.12)		1.78	(0.38–8.35)		
Champagne-Ardenne	1.12	(0.55–2.27)		1.13	(0.54–2.37)		
Picardie	1.52	(0.69–3.32)		1.40	(0.63–3.11)		
Other	1.21	(0.37–3.96)		1.48	(0.45–4.88)		
				Harrell C Index	0.77		

HR, Hazard ratio.

TABLE 3. Univariate and multivariate Cox analyses for DFS

	Univariate			Multivariate (n = 1295)			
	HR	95% CI	*P* value	HR	95% CI	*P* value	Bootstrapping *P* value 1500 replications
RAI							
No	1						
Yes	1.86	(1.27–2.74)	0.002	0.73	(0.43–1.25)	0.259	0.278
Age (yr)							
≤45	1			1			
>45	5.01	(3.43–7.31)	<0.0001	4.86	(3.26–7.25)	<0.0001	<0.0001
Sex							
Male	1			1			
Female	0.69	(0.46–1.04)	0.078	0.64	(0.42–0.96)	0.033	0.036
Period of diagnosis							
≤1998	1			1			
>1998	1.18	(0.76–1.84)	0.460	0.95	(0.61–1.51)	0.854	0.864
Thyroid surgery							
Loboisthmectomy	1			1			
Thyroidectomy	2.50	(1.51–4.13)	<0.0001	1.68	(0.86–3.31)	0.131	0.146
pN							
pN0	1			1			
Nx	1.31	(0.95–1.79)	0.097	1.17	(0.85–1.64)	0.365	0.365
Histology							
Papillary	1			1			
Follicular	0.97	(0.70–1.35)	0.867	0.73	(0.43–1.25)	0.259	0.942
pT							
pT1 ≤20 mm	1			1			
pT2 (20–40) mm	1.15	(0.84–1.58)	0.382	1.25	(0.37–4.22)	0.722	0.322
District							
Bourgogne	1		0.8129	1		0.957	0.9978
Franche-Comté	1.17	(0.35–3.93)		1.25	(0.37–4.22)		
Champagne-Ardenne	0.84	(0.52–1.38)		0.90	(0.54–1.51)		
Picardie	0.94	(0.53–1.68)		0.92	(0.51–1.67)		
Other	0.57	(0.19–1.68)		0.72	(0.24–2.12)		
				Harrell C Index	0.70		

HR, Hazard ratio.

between patients who received or did not receive RAI after surgery. Our study was specifically focused on these low-risk patients, for whom conflicting data have been previously reported in the literature concerning the potential benefits of RAI ablative therapy. No worldwide consensus has been obtained, resulting in the absence of recommendations for RAI in the American and European guidelines (3, 4). This question remains extremely important because the majority of cases in clinical practice are low-risk patients. In a detailed analysis of peer-reviewed literature, Sacks *et al.* (14) pointed out several deficiencies in the numerous staging systems used to define DTC patients. This has led to various definitions of low-risk patients, making comparisons difficult between institutions.

To define patients at low risk, we used, in this retrospective study, the criteria recently proposed by the ATA and the ETA: all low-risk patients were pT1 or pT2, pN0, or M0. Nx patients were also included. Although pN0 patients are considered only in the low-risk definition of the ATA and ETA, Nx patients represent a significant percentage of low-risk patients treated in institutions, which can exceed 50% (15), 45% of our cohort. They were grouped with the pN0 patients. We verified by the analysis that the OS and DFS curves did not significantly differ between pN0 and Nx patients.

Finally, all patients of the cohort were M0, pN0, or Nx, theoretically minimizing the risk of recurrence and death. This may explain the very low rate of clinical recurrences we observed (1.5%). This recurrence rate is quite similar to the rate of recurrence recently reported by Tuttle *et al.* (16). Applying the ATA definition of low risk to a cohort of 588 DTC patients with a follow-up of 7 yr, recurrent disease was observed in only 1% of low-risk patients. Hay *et al.* at the Mayo Clinic (17) studied a large cohort of 2512 patients with a papillary carcinoma. Two thousand ninety-nine patients presented as low risk (MACIS score <6, where MACIS is the scoring system of the Mayo Clinic: distant Metastases, Age, Completeness of surgery, Invasion of extrathyroidal tissues, and the Size of the thyroid tumor). For the node-negative group (636 patients), the 20-yr tumor recurrence rates were 3.4% after surgery alone and 4.3% after surgery and RAI, respectively. The 10-yr recurrence rates

TABLE 4. Univariate and multivariate logistic regression for RAI

	Univariate			Multivariate (n = 1295)		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age (yr)						
≤45	1			1		
>45	4.2	(3.2–5.4)	<0.0001	3.54	(2.45–5.12)	<0.0001
Sex						
Male	1			1		
Female	0.8	(0.5–1.1)	0.100	0.66	(0.38–1.14)	0.138
Period of diagnosis						
≤1998	1			1		
>1998	1.4	(1.1–1.8)	0.006	0.59	(0.41–0.87)	0.007
Thyroid surgery						
Loboisthmectomy	1			1		
Thyroidectomy	182	(88.1–376.)	<0.0001	176.3	(82.2–378.2)	<0.0001
pN						
Nx	1			1		<0.0001
pN0	3.0	(2.3–3.9)	<0.0001	2.42	(1.66–3.52)	
Histology						
Papillary	1			1		
Follicular	0.5	(0.4–0.6)	<0.0001	0.52	(0.33–0.79)	0.003
pT						
pT1 ≤20 mm	1			1		<0.0001
pT2 (20–40) mm	1.4	(1.1–1.9)	0.004	2.71	(1.77–4.17)	
AUC				0.89	(0.88–0.92)	

OR, Odds ratio.

were not mentioned in this subgroup but should logically be inferior and similar to ours.

The overall survival of the patients was also excellent. The OS rate at 10 yr was 94.5%, meaning that the thyroid specific mortality was lower than 5%. This is consistent with the 1.7% disease-specific mortality rate at 10 yr estimated by Sawka *et al.* (18) in low-risk DTC patients in a detailed review of multiple studies. Such very low recurrence and mortality rates are questionable and reinforce the importance of our study to clarify the real usefulness of RAI.

Looking at DFS and OS, we observed by univariate analysis that RAI did not prolong survival. It was confirmed by multivariate analysis that only two significant parameters, age and sex, were related to survival but not RAI.

For a majority of patients, RAI was not given at random but only after studying the clinical characteristics of the patients. To take into account the specific parameters related to the nonrandom decision of RAI treatment, we used the Propensity Score method. Applied to an observational study, this statistical method aims to balance the clinical covariates and parameters between the groups treated and not treated with RAI and approaches the conditions of a randomized study. After stratification on propensity score, DFS and OS did not significantly differ among patients who received or did not receive RAI. Only two studies examining the usefulness of RAI in DTC patients have used the propensity score analysis. Focusing on 14,545 patients of the Surveillance, Epidemiology and End Results American database, Podnos *et al.* (19) did not find any significant effect of RAI in overall survival after adjustment on propensity score. Contrary to our study, DFS was not studied by Podnos *et al.* They focused their analyses on patients with only papillary histology and on all risk patients (very low, low, and high). Moreover, the number of low-risk patients was not reported and the median follow-up was only 7.9 yr. Jonklaas *et al.* (20) with a prospective cohort of 2936 DTC patients of all stages showed that RAI was beneficial only for stage II, III, and IV patients. A side effect of RAI on OS was observed in stage I patients but was not confirmed by a second analysis (21). Using Propensity Score analysis in stage I patients, DFS at 5 yr did not significantly differ between patients treated and not treated with RAI. This result agrees with ours; it must be noted, however, that the median follow-up was very short in the two analyses, 3 and 5 yr, respectively.

Our study has some limitations. First, given the excellent survival of the low-risk patients, the small number of recorded events did not allow us to study the impact of RAI in each stratum of the propensity score due to statistical power limitations. Second, patients with papillary and follicular carcinomas were combined in our analysis as in the study by Jonklaas *et al.* (20). Diagnostic criteria of DTC have changed during the last 40 yr. Many thyroid carcinomas, considered to be follicular carcinomas in the past,

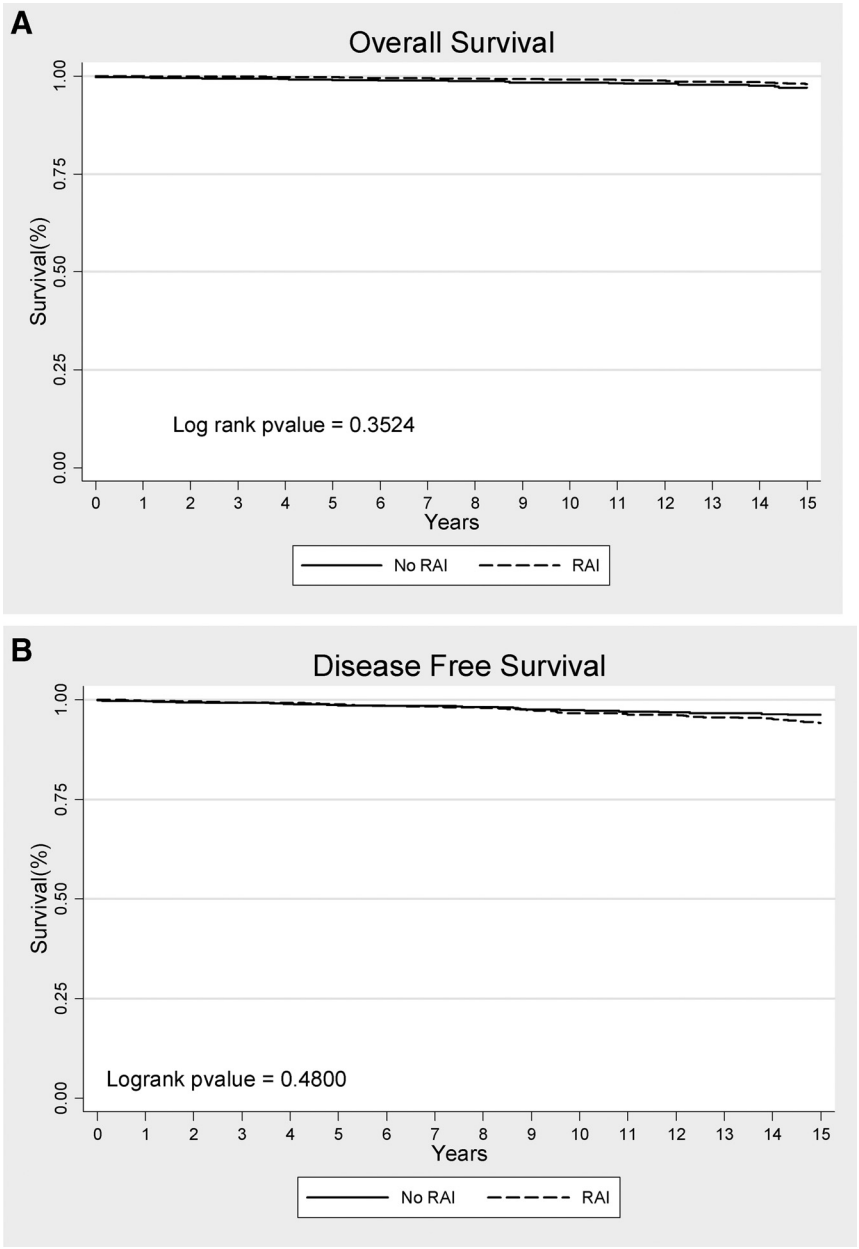

FIG. 2. OS (A) and DFS (B) according to RAI (Kaplan-Meier estimation) adjusted on propensity score. Survival curves were estimated with an adjustment on the propensity score for receiving RAI. Log-rank tests were stratified on the propensity score for receiving RAI.

would be classified today as papillary carcinomas of the follicular variant (22). Moreover, distinguishing the follicular variant of papillary carcinoma from the follicular carcinoma remains problematic for experienced pathologists (23, 24). Although prognosis may differ between papillary thyroid carcinoma and follicular thyroid carcinoma, we observed no significant survival differences in this cohort of low-risk patients. A few patients with more aggressive histological subtypes such as tall cell, oncocytic, columnar, insular, and solid variants, which were not described by pathologists before 1988, may also have been included in this cohort. These patients should have therefore been considered as high risk rather than low risk, even though all of them had received RAI. This fact did not alter our results.

In this study, by inclusion of pT1 greater than 1 cm and pT2 less than 4 cm, we increased the number of patients for whom RAI treatment was associated with no survival benefit, beyond the numbers that would be included in the categories for which the ATA and ETA guidelines recommended no RAI therapy. If confirmed, these results mean that these patients could also be designated as very low risk. Since the early studies of Mazzaferri and Young (25), numerous studies have attempted to demonstrate the role of RAI, broader ranges of patients identified, by various staging methods, as low risk have been studied. The analyses have included cause specific survivals and DFS (17, 19, 20, 26). These patients, whose diseases fall within a broader definition of low risk, appear not to have benefited from RAI therapy. Recently summarizing the most rigorous studies adjusted for prognostic factors, Sawka *et al.* (27) took into account the various definitions of low risk and found no evidence of survival benefit related to RAI, particularly in low-risk patients. Results are mixed regarding the effect of RAI on recurrence, but the majority of studies do not demonstrate a significant reduction of recurrences in low-risk patients. Additionally, by examining medical practice in the last 50 yr, Hay (28) observed an upward trend in using RAI from 1960 to 1990; there was no significant change in either the cause-specific mortality or the outcome during the 5 decades from 1950 to 1999. He concluded that the outcome of these results should raise serious doubts about the efficacy of RAI in patients with low risk.

In conclusion, our study was specifically dedicated to a large cohort of low-risk patients, defined by ATA and ETA criteria, for whom no clear recommendations are known to date. For the ATA, a selected use of RAI is suggested for only some patients who are at higher risk in this subgroup. For the ETA, despite uncertainties as to whether RAI should be administered to all or to specifically selected patients, a probable indication is ultimately retained for all. Our results show insufficient evi-

dence of a beneficial effect of RAI after surgery in low-risk DTC patients. Based on the results of the two different statistical approaches, we demonstrate the absence of a survival benefit related to RAI. Our results reinforce the conclusions of Sawka *et al.* (27) and suggest that low-risk patients should not be overtreated. The rare complications and side effects of RAI should also be considered, and after surgery, RAI treatment should be reserved for only high-risk patients.

These data may have important practical implications because the majority of cases in clinical practice involve low-risk patients. To clarify the clinical benefit of RAI treatment, taking into account the excellent overall survival of these low-risk patients, a randomized controlled study seems to be difficult to perform. A prospective epidemiological study matching patients on the propensity score and also focusing on both recurrences and health-related quality of life (QoL) could be performed to obtain more conclusive data about the clinical benefit of RAI in low-risk patients. In fact, if a treatment has no impact on OS, it may have a clinical benefit or harm for the patients regarding QoL through recurrences. QoL is considered as a clinical outcome *per se* and as the second primary outcome by the Food and Drug Administration when evaluating treatments in oncology (29). When taking into account that few prospective studies have extensively explored this outcome in low-risk patients, we believe that such a study would help definitively address the question of the clinical added value of RAI after surgery in low-risk DTC patients.

Acknowledgments

All authors of this research paper have directly participated in the planning, execution, or analysis of the study. All authors of this paper have read and approved the final version submitted. The contents of this manuscript have not been copyrighted or published previously. The contents of this manuscript are not now under consideration for publication elsewhere. The contents of this manuscript will not be copyrighted, submitted, or published elsewhere while acceptance by the Journal is under consideration. All directly related manuscripts or abstracts, published or unpublished, by one or more authors of this paper have been included with the manuscript submission.

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Disclosure Summary: All authors of this paper have no conflict of interest to disclose.

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