Thyroidectomy without radioiodine in patients with low-risk thyroid cancer: 5 years of follow-up of the prospective randomised ESTIMABL2 trial

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See **Comment** page 5

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Summary

Background ESTIMABL2, a multicentre randomised phase 3 trial in patients with low-risk differentiated thyroid cancer (ie, pT1am or pT1b, N0 [no evidence of regional nodal involvement] or Nx [involvement of regional lymph nodes that cannot be assessed in the absence of neck dissection]), showed the non-inferiority of a follow-up strategy without radioactive iodine (^{131}I) administration compared with a postoperative ^{131}I administration at 3 years post-randomisation. Here, we report a pre-specified analysis after 5 years of follow-up.

Methods Patients treated with total thyroidectomy with or without prophylactic neck lymph node dissection, without postoperative suspicious findings on neck ultrasonography, were randomly assigned to the no-radioiodine group or to the radioiodine group (1·1 GBq-30 mCi after recombinant human thyrotropin-stimulating hormone). Follow-up consisted of annual thyroglobulin and thyroglobulin antibody determinations during levothyroxine treatment and neck ultrasonography in odd-numbered years. An event was defined as abnormal foci of ^{131}I uptake on the post-treatment whole-body-scan requiring subsequent treatment, abnormal neck ultrasonography, elevated thyroglobulin levels, increasing titres or appearance of thyroglobulin antibody (using the same laboratory assay), or a combination of these definitions. Non-inferiority of the proportion of patients without an event in one group compared with the other at 5 years after randomisation was shown if this proportion and its CI did not differ by more than –5%. This study was registered on ClinicalTrials.gov (NCT01837745) and is completed.

Findings Of the 776 patients (n=642 [82·7%] female and n=134 [17·3%] male, median age 52·9 years [IQR 42·6–63·1]) enrolled, 698 were evaluable at 5 years. The proportions of patients without events were 93·2% in the no-radioiodine group and 94·8% in the radioiodine group, for a difference of –1·6% (90% CI –4·5 to 1·4). Events consisted of structural or functional abnormalities (n=11) and biological abnormalities (n=31).

Interpretation The non-inferiority of a follow-up strategy compared with postoperative ^{131}I administration in low risk differentiated thyroid cancer was confirmed at 5 years. There is no loss of opportunity in following these patients without postoperative ablation.

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Introduction

Radioactive iodine (^{131}I) has been used in the treatment of thyroid cancer for decades. The first successful treatment of a patient with metastatic thyroid cancer with ^{131}I was reported in 1946.[1] ^{131}I is administered after total thyroidectomy to destroy normal thyroid remnants (ablation) and to treat suspected (adjuvant) or proven persistent disease with the goal of improving recurrence-free and overall survival. In the 1990s, a large retrospective study including more than 900 patients with a long median follow-up of 15·7 years found an improvement in survival and recurrence-free survival in patients with thyroid cancer larger than 15 mm or metastatic lymph nodes in the absence of known distant metastases when radioactive iodine was given.[2] At that time, ^{131}I was widely administered to most, if not all, patients with follicular cell-derived thyroid cancer. Currently, however, most patients have a low-risk follicular-cell derived thyroid cancer with stage I disease with a risk of thyroid cancer-related death of less than 2% and a risk of recurrence of less than 5%.[3] Among these patients with low-risk thyroid cancer, there is a broad consensus to avoid ^{131}I administration in the case of intrathyroidal unifocal microcarcinoma (≤10 mm in diameter), but in the other low-risk thyroid cancer, the modalities and use of radioiodine remain controversial.[4–6]

Research in context

Evidence before this study

On June 1, 2024, we searched PubMed using the following terms: "low-risk", "thyroid cancer", "prospective", "randomized trial", "radioiodine", without language or date restrictions. In patients with low-risk follicular cell-derived thyroid cancer, a randomised trial showed that a follow-up without postoperative radioactive iodine (^{131}I) administration was not inferior to a low-activity (1·1 GBq [30 mCi]) of ^{131}I, administered to euthyroid patients after injections of recombinant human thyroid-stimulating hormone in terms of functional, structural, or biological events during a 3 year-follow-up. Longer-term follow-up was needed to ensure detection of late recurrences.

Added value of this study

After a 5-year follow-up, among 698 patients evaluable at 5 years, the proportions of patients without events were 93·2% in the no radioiodine group and 94·8% in the radioiodine group, for a difference of –1·6% (90% CI –4·5 to 1·4). Events consisted of structural or functional abnormalities (n=11: five in the radioiodine group and six in the no radioiodine group) and biological abnormalities (n=31; 13 in the radioiodine group and 18 in the no radioiodine group). After randomisation and initial treatment (radioiodine or not), 11 patients in each group underwent a subsequent treatment (surgery with ^{131}I). We also found that a postoperative serum thyroglobulin level of >1ng/mL measured under thyroid hormone treatment, an age between 55 and 60 years, a follicular histology, and a larger tumour size were prognostic for an event.

Implications of all the available evidence

Our study confirms that in patients with low-risk thyroid cancer there is no need for systematic postoperative ablation.

A meta-analysis concluded that the benefit of ^{131}I in patients with stage I (which includes patients at low risk of recurrence but also some at intermediate or even at high risk of recurrence) was inconsistent.[7] Moreover, another review of retrospective studies in patients with thyroid cancer with a low risk of recurrence did not show a benefit of ^{131}I.[8]

Two large, randomised trials have shown that postoperative administration of a low activity (1·1 GBq) ^{131}I after administration of recombinant human thyrotropin-stimulating hormone is non-inferior to a high activity (3·7 GBq) ^{131}I after thyroid hormone treatment withdrawal in terms of ablation success rate and 5-year recurrence rate in patients with follicular cell-derived thyroid cancer with low to intermediate risk of recurrence.[9–12] These two trials allowed a de-escalation in the ^{131}I activity administered in these patients with low-risk differentiated thyroid cancer. Although retrospective studies have shown no benefit of radioactive administration in low risk differentiated thyroid cancer, postoperative ^{131}I is still prescribed or recommended in differentiated thyroid cancer for tumours greater than 10 mm by some experts.[13,14]

We recently published an open-label, investigator-initiated, phase 3 randomised trial (ESTIMABL2) showing that in patients with thyroid cancer with a low risk of recurrence undergoing thyroidectomy, a follow-up strategy without postoperative radioiodine administration was not inferior to an ablation strategy with 1·1 GBq (30 mCi) radioiodine with respect to the occurrence of functional, structural, and biological events after the first 3 years from randomisation.[15] In fact, the rate of patients without an event was 95·6% in the no radioiodine group and 95·9% in the radioiodine group (a difference of –0·3%; 90% CI –2·7 to 2·2). Most recurrences of thyroid cancer occur within the first 5 years, so a follow-up of 3 years might be too short given the indolent nature of most low-risk and intermediate-risk thyroid cancer.[11,16–18] Therefore, the benefit of post-operative ^{131}I still remains controversial for some clinicians, especially in the field of nuclear medicine.[19]

Here, we aim to present the pre-specified secondary endpoint of the ESTIMABL2 trial, which was to assess non-inferiority in the percentage of patients free of events after 5 years following randomisation.

Methods

Study design and participants

Details of the study design and protocol have been published previously[15] (appendix p 2). The study was an open-label, randomised phase 3 trial conducted across 35 centres of the French Endocan-TuThyRef network. From May 2013, to March 2017, patients treated with total thyroidectomy with or without prophylactic neck lymph node dissection, without postoperative suspicious findings on neck ultrasonography were randomly assigned to receive postoperative radioiodine (radioiodine group) or no postoperative radioiodine (non-radioiodine group). The primary objective was to assess the non-inferiority of the non-radioiodine group compared with the radioiodine group in terms of the percentage of patients without a functional, structural, or biological event after the 3 years following randomisation. The randomisation process was done centrally at the biostatistics service of Gustave Roussy using the TenAlea website (created by the Netherlands Cancer Institute, Amsterdam) by investigators or duly authorised people with a random block method (block size of four patients). Randomisation was stratified by study centre and lymph node status (ie, N0 [no evidence of regional nodal involvement] or Nx [involvement of regional lymph nodes that cannot be assessed in the absence of neck dissection]). A secondary objective was to compare the percentage of patients without an event after 5 years following randomisation.

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See Online for appendix

The main inclusion criteria were: treatment with total thyroidectomy with or without prophylactic neck lymph node dissection and no postoperative suspicious findings on neck ultrasonography, aged 18 years or older, differentiated thyroid cancer (ie, papillary, follicular, or oncocytic) with multifocal pT1a tumours (diameter of each lesion ≤1 cm and sum of the longest diameters of the lesions ≤2 cm) or pT1b tumours (>1 cm and ≤2 cm), an N0 or Nx lymph node status, and the absence of extra-thyroidal extension. Patients with aggressive histological subtypes (tall cell, clear cell, columnar cell, and diffuse sclerosing variants of papillary thyroid cancer that are poorly differentiated) based on local diagnosis were excluded. A full list of inclusion and exclusion criteria are available in the appendix (p 4). The study was conducted in accordance with the protocol approved by the ethics committee and national authorities and in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Procedures and outcomes

Patients randomly assigned to the radioiodine group received 1·1 GBq (30 mCi) ^{131}I under thyroid hormone treatment, 24 h after the second intramuscular injection of recombinant human thyrotropin (Thyrogen, Sanofi, Paris, France) given at a dose of 0·9 mg on 2 consecutive days. Whole-body scanning and single-photon emission CT of the neck were performed 2 to 5 days after radioiodine administration. Follow-up of patients in the radioiodine group consisted of measurement of thyroglobulin under recombinant human thyrotropin-stimulating hormone stimulation with measurement of thyroglobulin antibodies and neck ultrasonography at 10 months after randomisation (appendix p 2). Thereafter, follow-up consisted of measurement of thyroglobulin under thyroid hormone treatment and of thyroglobulin antibody every year, and a neck ultrasonography every other year. Follow-up for patients in the no radioiodine group consisted of measurements of thyroglobulin while on thyroid hormone treatment and of thyroglobulin antibodies every year, and a neck ultrasonography every other year. Diagnostic radioiodine scanning was not performed during follow-up, because it is not considered a standard of care for thyroid cancer surveillance in France and most European countries.

An event was a composite criterion of functional, structural, or biological events. A functional event was defined by the presence of foci of ^{131}I uptake outside the thyroid bed on the post-therapeutic whole-body scan with subsequent treatment including the administration of another therapeutic activity of ^{131}I or surgery. A structural event was defined as the presence of a suspicious lymph node on neck ultrasonography with abnormal cytology findings, a thyroglobulin level of more than 10 ng/mL in the aspirate fluid, an abnormal mass in the thyroid bed with abnormal cytology findings, or a combination of these factors. A biological event was defined as an elevated thyroglobulin level, or the occurrence of an elevated thyroglobulin antibody titre above the upper limit of the normal range or an increase in the thyroglobulin antibody titre by more than 50% in two determinations performed 6 months apart, using the same laboratory assay. The threshold for an elevated serum thyroglobulin for patients in the radioiodine group was a thyroglobulin level greater than 1 ng/mL and less than 5 ng/mL on thyroid hormone treatment in two measurements performed 6 months apart or a thyroglobulin level greater than 5 ng/mL. The threshold for an elevated serum thyroglobulin for patients in the no radioiodine group was a thyroglobulin level greater than 2 ng/mL and less than 5 ng/mL on thyroid hormone treatment on two measurements performed 6 months apart or a thyroglobulin level greater than 5 ng/mL. For the present analysis, for patients with two consecutive events, only the first one was considered.

For the assessment of the appearance of elevated thyroglobulin and for the appearance and increase of serum thyroglobulin and thyroglobulin antibody levels, determinations had to be performed using the same laboratory assay. In contrast to the 3-year evaluation, only local serum thyroglobulin and thyroglobulin antibody determinations were performed at the 5-year follow-up.

A central review was performed for functional events, but only for patients in the radioiodine group. Otherwise, for the two treatment groups, assessment of structural events required confirmation by cytology or elevated thyroglobulin levels in the liquid fluid, and biological events used predefined abnormal thresholds, with investigators not necessarily masked to treatment group.

Statistical analyses

Descriptive quantitative data were expressed as means (SD) or median (IQR), depending on the distribution, whereas qualitative data were expressed as absolute number, percentage, and 95% CIs (calculated using the Wilson score method).

For the main outcome, we calculated the difference in the observed percentages of patients without an event and those with an event and its 90% two-sided exact CI (the lower limit of the latter being equal to the lower limit of upper one-sided 95% CI). The results are presented without and with adjustment on stratification variables. For the calculation of the 90% CI of the difference of two proportions, the exact method based on a score statistic was used.[20] Non-inferiority is declared if the lower limit for the two-sided 90% CI for the proportion of patients without an event in the no radioiodine group minus that in the radioiodine group is more than –5%. Because the rate of adverse events related to radioiodine ablation is very low, we chose a low non-inferiority margin of –5% with the goal of encouraging a change in clinical practice if non-inferiority was shown.

The primary analysis was performed on all evaluable patients in the per-protocol population, ie, patients whose treatment and follow-up were consistent with the study protocol. A sensitivity analysis was performed in the intention-to-treat population (ie, 776 randomly assigned patients) reporting the results in event-free survival at 5 years using a time-to-event analysis and its two-sided 90% CI. Prognostic factors associated with the risk of event were searched using a Poisson approach with a generalised estimating equation estimation to assess the relative risk (RR) and its 95% CI.

A post-hoc analysis was performed to compare between the two groups the percentage of excellent responses according to the American Thyroid Association risk classification, published in 2016 after the start of ESTIMABL2 trial.[4] SAS software (version 9.4) was used for statistical analyses. The study was registered at ClinicalTrials.gov (NCT01837745).

	Radioiodine group (n=389)	No radioiodine group (n=387)
Age, years	52·2 (42·3–62·7)	52·9 (42·7–63·9)
Sex		
Female	319 (82·0%)	323 (83·5%)
Male	70 (18·0%)	64 (16·5%)
Days from thyroidectomy to randomisation	92·1 (23·2)	91·2 (23·6)
Histology		
Papillary	372 (95·6%)	372 (96·1%)
Follicular	13 (3·3%)	11 (2·8%)
Oncocytic	4 (1·0%)	4 (1·0%)
Largest tumour size, mm	13 (11–15)	14 (11–17)
pTNM stage		
pT1amN0	26 (6·7%)	23 (5·9%)
pT1amNx	56 (14·4%)	42 (10·9%)
pT1bN0	143 (36·8%)	148 (38·2%)
pT1bNx	164 (42·2%)	174 (45·0%)
Multifocality	178 (45·8%)	156 (40·3%)
Neck dissection performed	171 (44·0%)	171 (44·2%)
Type of neck dissection performed		
Central only	69 (17·7%)	77 (19·9%)
Central and lateral	74 (19·0%)	65 (16·8%)
Lateral only	26 (6·7%)	27 (7·0%)
Unknown	2 (0·5%)	2 (0·5%)
Thyroglobulin levels at randomisation in the 597 patients without thyroglobulin antibodies	N=304	N=293
Median (IQR)	0·26 (0·10–0·59)	0·20 (0·10–0·40)
<0·2 ng/mL	94 (30·9%)	104 (35·5%)
0·2–1·0 ng/mL	161 (53·0%)	155 (52·9%)
>1·0 ng/mL	32 (10·5%)	18 (6·1%)
Missing value	17 (5·6%)	16 (5·5%)

Data are n (%), mean (SD), or median (IQR).

Table 1: **Characteristics of the patients at randomisation**

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From May 2013, to March 2017, 776 patients (642 [82·7%] were female and 134 (17·3%) were male, with a median age of 52·9 years [IQR 42·6–63·1]) were randomly assigned (table 1, figure 1). The tumour histology was predominantly papillary (n=744, 95·9%) and the pTNM stage was mainly pT1b N0 and Nx (n=629, 81·1%). One patient randomly assigned to the no radioiodine group did not meet the inclusion criteria due to the presence of suspicious lymph nodes. 730 patients (94·1%) were evaluable at 3-year post-randomisation and 698 (89·9%) were evaluable at 5-year post-randomisation (figure 1).

The number of patients without an event after 5 years was 330 (93·2%) of 354 (95% CI 90·1 to 95·4) in the no radioiodine group and 326 (94·8%) of 344 (91·9 to 96·7) in the radioiodine group, for a unadjusted difference of –1·6% (90% CI –4·5 to 1·4), indicating that the no post-operative radioiodine strategy remains non-inferior to routine radioiodine administration (table 2, figure 2;

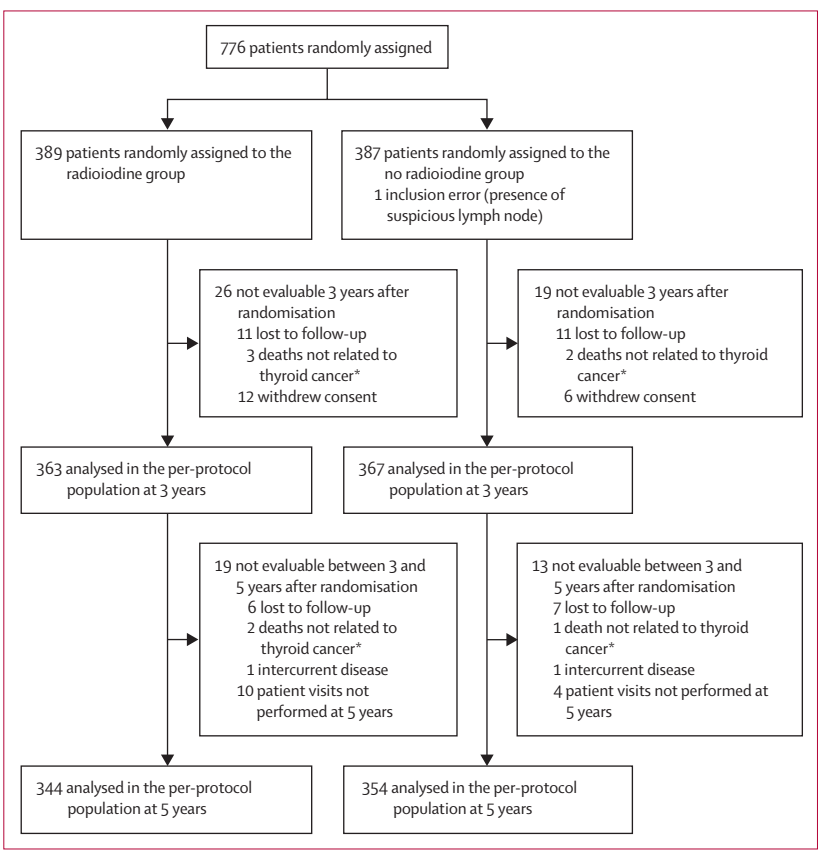

Figure 1: **Trial profile**

*Causes of death in the iodine group: pulmonary embolism (n=1), sarcomatoid lung cancer (n=1), aneurysm rupture (n=1), pancreatic cancer (n=1), and heart failure (n=1). Causes of death in the no iodine group: heart failure (n=1), peritoneal cancer (n=1), and lymphoma-related adverse event (n=1).

	Radioiodine group (n=344)	No radioiodine group (n=354)
Number of patients without an event during the 5 years, n (%); 95% CI*	326 (94·8%); 91·9 to 96·7	330 (93·2%); 90·1 to 95·4
Difference in the percentage of patients without an event at 5 years (90% CI), in the no-radioiodine group compared with the radioiodine group	NA	−1·6% (−4·5 to 1·4);† −1·3% (−3·9 to 0·01)‡
Number of patients with at least one event during the 5 years, n (%); 95% CI	18 (5·2%); 3·3 to 8·1	24 (6·8%); 4·6 to 9·9
Type of events		
Foci of radioactive iodine uptake outside the thyroid bed needing further treatment	3	NA
Abnormal neck ultrasonography with abnormal cytology or elevated thyroglobulin in the liquid fluid		
Abnormal lymph node	2§	4¶
Abnormal thyroid mass	0	2‖
Biological events		
Thyroglobulin after recombinant human thyrotropin-stimulating hormone >5 ng/mL (radioiodine group)	3	NA
Thyroglobulin after recombinant human thyrotropin-stimulating hormone >1 ng/mL and ≤5 ng/mL on two consecutive measurements (radioiodine group)	6	NA
Thyroglobulin level on thyroid hormone treatment >5 ng/mL (both groups)	0	4
Thyroglobulin level on thyroid hormone treatment >1 ng/mL and ≤ 5 ng/mL on two consecutive measurements (radioiodine group)	0	NA
Thyroglobulin level on thyroid hormone treatment >2 ng/mL and ≤5 ng/mL on two consecutive measurements (no radioiodine group)	NA	6
Appearance of thyroglobulin antibodies	3	6
Increase of thyroglobulin antibody titre over time	1	2

NA=not applicable. *CI of the proportion is estimated using the Wilson score method. †CI of the difference of the two proportions is estimated using an exact method based on a score statistic. ‡Adjusted estimate of the difference of two proportions is estimated using a generalised linear model using a binomial distribution and identity link. The adjustment variables are N status (N0 or Nx) and study centre (grouped into three categories regarding the number of patients recruited in the trial: small centre [<20 patients included], intermediate centre (20 to 30 patients included), or large centre (>30 patients included). The 90% CI is obtained via the sandwich variance estimator. §Thyroglobulin or thyroid hormone treatment level of 0·2 ng/mL and <0·1 ng/mL when recurrence was diagnosed. ¶Thyroglobulin or thyroid hormone treatment level of 0·1 ng/mL, 0·7 ng/mL, 2·5 ng/mL and 3·0 ng/mL when recurrence was diagnosed. ‖Thyroglobulin or thyroid hormone treatment level of 0·1 ng/mL and 0·2 ng/mL when recurrence was diagnosed.

Table 2: **Number and type of events occurring during the 5 years following randomisation**

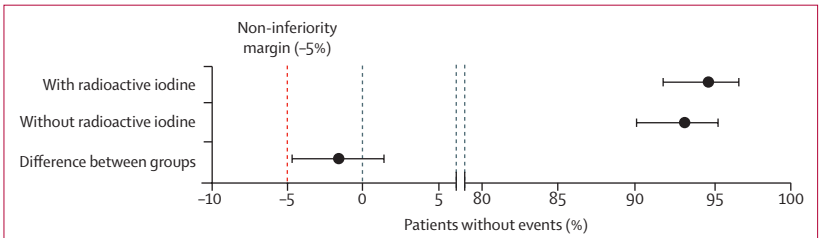

Figure 2: **Proportion of patients without events during the 5 years after randomisation**
Circles represent the percentage of patients without an event during the 5 years after randomisation for each group, with error-bars representing their 95% CIs, estimated using the Wilson score method. The last line on the left represents the unadjusted difference of percentages of patients without an event between groups, and its 90% two-sided exact CI, and the non-inferiority margin (ΔL=−5%) defined in the protocol.

appendix p 3). Similar results were obtained both after adjustment and in the intention-to-treat population in terms of 5-years event-free survival (table 2, appendix p 5). Of note, characteristics of the patients not included in the per-protocol analysis did not differ to those included in the per-protocol population (appendix p 6). Events occurred in 24 (6·8%) of 354 patients (95% CI 4·6 to 9·9) in the no radioiodine group and in 18 (5·2%) of 344 patients (3·3 to 8·1) in the iodine group (table 2).

Compared with the analysis at 3 years, there were eight patients with new events in the no radioiodine group and three patients with new events in the radioiodine group (figure 3). Events consisted of structural or functional abnormalities in 11 patients and biological abnormalities in the remaining 31 patients (table 2, figure 3). Structural or functional events included abnormal ^{131}I uptake leading to further treatment in three patients (in the radioiodine group), lymph node metastasis in six patients (two in the radioiodine group and four in the no radioiodine group), and thyroid bed mass recurrence in two patients (in the no radioiodine group). Treatment of patients with abnormal iodine uptake consisted of ^{131}I administration in three patients. Treatment of patients with lymph node metastases consisted of surgery in two patients, ^{131}I administration in two patients, and both surgery and ^{131}I administration in the two patients. Treatment of patients with thyroid bed recurrence consisted of surgery and ^{131}I administration in one patient and follow-up only in one patient.

Thyroglobulin levels under levothyroxine treatment measured at the time of diagnosis of structural recurrence ranged from 0·1 to 3·0 ng/mL in patients in the no radioiodine group and were between <0·1 and 0·2 ng/mL in patients in the radioiodine group. No patients had elevated thyroglobulin antibody (table 2).

Among biological events, elevated thyroglobulin levels (between 1 and 5 ng/mL, between 2 and 5 ng/mL, or >5 ng/mL) were the most frequent events (n=19), followed by the appearance of thyroglobulin antibodies (n=9), and finally increases in thyroglobulin antibody titres (n=3; table 2). Compared with the analysis at the 3-year follow-up, there were three new structural events at the 5 year-follow up (recurrence in the thyroid bed in two patients and in a metastatic lymph node in one patient, all in the no radioiodine group). Overall, the number of subsequent treatments (surgery, ^{131}I administration, or both) was 11 in the no radioiodine group and 11 in the radioiodine group, while the remaining patients with an event were followed up (seven patients in the no radioiodine group and 13 patients in the radioiodine group).

Of the 19 patients with elevated thyroglobulin levels, ten underwent further treatment, mostly in the patients with the highest thyroglobulin levels. Among the nine patients who did not receive any treatment, two of five patients in the no radioiodine group had a spontaneous decrease in thyroglobulin levels and normalisation of thyroglobulin levels (<2 ng/mL), and the four patients in the radioiodine group had a spontaneous decrease in thyroglobulin levels and

normalisation of thyroglobulin levels (<1 ng/mL; appendix p 7). There was a total of eight deaths, none of which were related to thyroid cancer.

On multivariable univariate analysis in patients without thyroglobulin antibodies, prognostic factors associated with a significantly higher risk of events were an elevated postoperative thyroglobulin level under thyroid hormone treatment (with thresholds of >1 ng/mL), age (especially for patients aged 55–60 years *vs* those aged <55 years), larger tumour size, and follicular and oncocytic histology (appendix p 8). Non-significant results were observed for ages greater than 60 years, gender, pN status (ie, N0 or Nx), or multifocality. The event rate was 4·0% (n=19) in the 481 patients with a postoperative thyroglobulin level measured under thyroid hormone treatment of 1 ng/mL or less versus 23·9% (n=11) in the 46 patients with a thyroglobulin level of more than 1 ng/mL (RR=6·31, 95% CI 2·83–14·05; appendix p 8). Among patients with postoperative thyroglobulin levels greater than 1 ng/mL without thyroglobulin antibodies measured under levothyroxine treatment at inclusion, events occurred in patients from both groups (appendix p 9). There was one structural or functional event in the no radioiodine group and one in the radioiodine group and six biological events in the no radioiodine group and three in the iodine group (appendix p 9). Among patients without thyroglobulin antibodies, events occurred in 19 (4·0%) of the 481 patients with postoperative thyroglobulin levels of 1 ng/mL or less, in 14 (3·5%) of the 404 patients with postoperative thyroglobulin levels of 0·5 ng/mL or less and in nine (3·2%) of the 277 patients with postoperative thyroglobulin levels of 0·2 ng/mL or less without thyroglobulin antibodies. In all cases, events occurred in both treatment groups (appendix p 9).

Using local thyroglobulin determination, the proportion of patients with an excellent response according to the 2015 American Thyroid Association treatment response definition was higher in the no radioiodine group (295 [83·3%] of 354 patients) than in the radioiodine group (260 [75·6%] of 344 patients), and the proportion of patients with an indeterminate response was higher in the radioiodine group (68 [19·8%]) than in the no radioiodine group (26 [7·3%]; appendix p 10). However, there was no difference in the proportions of patients with structural disease (three [0·9%] in the no radioiodine group and 0 in the radioiodine).

Discussion

After 5-years of follow-up, we found that a follow-up strategy without a postoperative radioiodine administration is not inferior to a postoperative administration of 1·1 GBq ^{131}I after recombinant human thyrotropin-stimulating hormone, with an event rate including functional, structural, and biological events of 6·0%. If only structural events are considered, the rate is even lower at 1·1%, and if functional events from the radioiodine group plus structural events from both groups are considered, the rate of event is 1·6%.

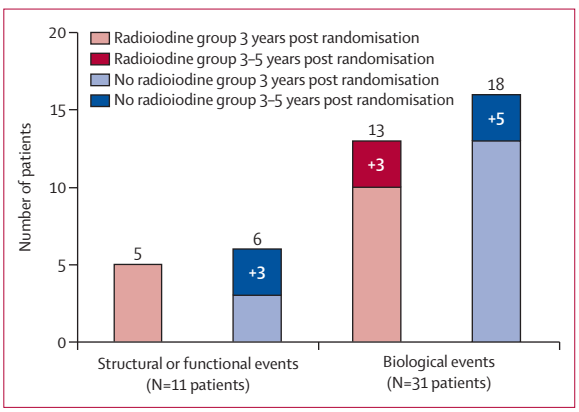

Figure 3: **Structural or functional and biological events occurring during the 5 years of follow-up**

In the literature, the majority of follicular cell-derived thyroid cancer recurrences are consistently reported as being detected within the first 5 years of follow-up.[21,22] Late recurrences can occur though and the patients from the present study are scheduled for further follow-up. As expected, we observed eight functional or structural events within the first 3 years and three additional structural events during the subsequent 2 years. Similarly, we observed 25 biological events in 23 patients within the first 3 years, and another eight patients had a biological event during the subsequent 2 years. Overall, biological events were more frequent, accounting for 74% of all events. Among the biological events, increases in thyroglobulin levels (61%) were more frequently observed than the appearance or the increase of thyroglobulin antibody titres (31%). Of note, given the high rates of discordance between thyroglobulin and thyroglobulin antibody results from one laboratory assay to another one, clinicians should interpret any thyroglobulin modification or appearance of thyroglobulin antibodies with caution regarding the method used.[23,24] The de novo detection of thyroglobulin antibodies is not always associated with recurrence, whereas the trend of thyroglobulin antibodies usually is.[25,26] In the present study we only considered thyroglobulin antibody appearance or increase if generated from the same laboratory assay and confirmed by two consecutive blood tests performed 6 months apart.

The definition of an event including functional or structural events and biological events is the subject of discussion. However, functional or structural events occurred in similar numbers in both groups. Biological events are more difficult to clearly define as recurrent disease. One reason to administer ^{131}I is to destroy thyroid remnants to facilitate follow-up. We show in the present study that in the absence of ^{131}I there are no more biological events during the first 5 years of follow-up, that thyroglobulin levels can be reliably interpreted, and that elevation of thyroglobulin antibodies is less

frequent than thyroglobulin elevation. The absence of central thyroglobulin and thyroglobulin antibody determination might have introduced biases but has the advantage of reflecting a real-life assessment. However, the threshold for a thyroglobulin level to be considered as significantly elevated is different whether patients are treated with postoperative ^{131}I or not. The threshold of 2 ng/mL was chosen in the present study in 2012, based on data that were available at that time on the thyroglobulin levels of patients followed after total thyroidectomy in the absence of postoperative ^{131}I administration.[27,28] In fact, this value is similar to the value derived from a systematic review of the literature.[29] This difference in the threshold used explains the difference in the excellent response and the indeterminate response rates according to the American Thyroid Association post-treatment classification.[4] The main result of the present study is that the rate of incomplete structural response is low and similar in both groups. Thyroglobulin levels at the time of structural disease detection was low (<1 ng/mL) in most patients, which is usually associated to small recurrences with a very good prognosis. Furthermore, the number of subsequent treatments (ie, ^{131}I or surgery) were similar in both groups. Of note, in an observational study comparing patients submitted to ^{131}I ablation or not, the rate of biological events (ie, biochemical incomplete or indeterminate response) was higher in patients who did not receive ^{131}I compared with those who did, but the difference tended to decrease over time.[30] We did not take into account the trend of thyroglobulin that could occur during follow-up with a spontaneous decrease of thyroglobulin levels after surgery or after surgery and radioiodine in the absence of any recurrence.[28,31] We only included fixed thresholds of thyroglobulin levels to define biological recurrence and requested two thyroglobulin measurements 6 months apart in case of thyroglobulin values less than 5ng/mL. Elevation of thyroglobulin levels, in 19 patients (nine in the radioiodine group and ten in the no radioiodine group), was followed by subsequent treatment in ten patients, and among the untreated patients, six (67%) of nine had spontaneous normalisation of serum thyroglobulin levels. This emphasises the fact that when thyroglobulin levels are slightly elevated, there is no emergency to administer empiric activities of radioiodine.[28,31]

Events can occur in patients with low postoperative thyroglobulin levels and even in patients with postoperative thyroglobulin levels less than 0·2 ng/mL, a threshold used for the definition of excellent response for patients treated with ^{131}I. We confirm that a postoperative thyroglobulin level greater than 1 ng/mL is associated with a higher risk of events. This finding was expected because elevated thyroglobulin levels were included in the definition of an event, similar to the inclusion of thyroglobulin levels in the treatment response classification. Most of the patients that we treated with ^{131}I were already cured after surgery, but this has been the standard of care for decades. If we consider the postoperative thyroglobulin level as a parameter to decide for radioiodine administration, which seems reasonable, the number of patients to be treated will decrease drastically.[32] Since a thyroglobulin level greater than 1 ng/mL was found to be a prognostic factor for an event in the present study, but the threshold of 2 ng/mL was chosen to monitor the patients without ^{131}I and to define an event, a cutoff of 2 ng/mL could be used as a threshold to give ^{131}I to these patients. Persistent disease or uncomplete surgery could then be the reason for ^{131}I. However, proof that the outcome of these patients will be improved by the ^{131}I is still needed with prospective studies. In fact, in the present study, among patients with postoperative thyroglobulin levels greater than 1 ng/mL, events occurred both in patients with and without postoperative iodine administration.

Other prognostic factors included age, with a higher risk of an event in patients aged 55–60 years (compared with those aged <55 years), tumour size, with a higher risk of an event in patients with large tumours (compared with small tumours), and histology, with a higher risk of an event in patients with follicular cancers (compared with papillary thyroid cancer). Older age and tumour size are known to be prognostic factors in thyroid cancer. The present multivariate analysis looking at size in a continuous manner showed that size has a prognostic role in the occurrence of events, which is consistent with the literature. Finally, due to the small number of oncocytic cancers, these were included with the follicular cancers, but none of them reported an event. Of note, the pN status was not prognostic for an event, with patients with pNx being treated with total thyroidectomy only and patients with pN0 being treated with total thyroidectomy and neck dissection.

Although per-protocol analysis is considered the primary analysis for a non-inferiority trial compared with an intention-to-treat analysis because of its conservatism, some limitations need to be highlighted even if non-inferiority was observed for both per-protocol and intention-to-treat populations in the present trial. Patients excluded from the per-protocol analysis could have led to selection bias in the per-protocol estimates. These patients (n=78) represented 10% of the intention-to-treat population (n=45 in the experimental group and n=33 in the control group), but patients included or not in the per-protocol population had similar initial characteristics (appendix p 6).

Furthermore, as the definition of an event at 5 years is a composite criterion and differs between groups (eg, functional events are included in the control group but not in the experimental group), a possible measurement bias might exist. Its effect is expected to be low, though, since there were only three functional events observed in the control group. Finally, selection bias due to missing outcomes (missingness) should be discussed.

Missingness is related to the possible effect of missing data on the conclusion. In the present study, 32 patients (4·4% of the cohort; n=19 from the control group and n=13 from the experimental group) had no outcome measurement at 5 years. In most cases, this was due to loss of follow-up before 5 years or due to the absence of the 5-year visit (N=27 patients: n=16 in the control group and n=11 in the experimental group), which occurred in both groups and are not related to the outcome defined by the occurrence of an event or not. Whatever the true value of the outcome (having an event or not) at 5 years should be, the missingness in the outcome data does not depend on its true value.

The conclusions of this study can only apply to patients similar to those included in the study. All patients had total thyroidectomy and even if surgeries were not performed in tertiary centres, one should recognise that many patients were well operated on with thyroglobulin levels being less than 0·2 ng/mL in one third of the patients. Furthermore, not all patients with low-risk thyroid cancer were included in ESTIMABL2, but, all low-risk thyroid cancers have a risk of recurrence of less than 5%, so the impact of postoperative ^{131}I administration might be difficult to show. Instead, some patients with an intermediate risk of recurrence were enrolled in ESTIMABL2 trial: the inclusion criteria were defined in 2012, before the 2015 American Thyroid Association risk level definition, and some patients at an intermediate risk of vascular invasion or extra-thyroid extension were enrolled.[4] The presence of thyroid cancer with vascular invasion and extra thyroid extension was shown in the nested case analysis that was performed, in which among the 90 patients with a central pathology review, 23% had vascular invasion and 15% had minimal extra-thyroid extension.[15] However, reclassifying all patients as being at low or intermediate risk was not possible. We did this in the nested case–control analysis at 3 years of follow-up only for those patients who had a central pathology review.

Notably, our results are consistent with the results of the randomised phase 3 trial, IoN, in which 500 patients with low to intermediate risk differentiated thyroid cancer were randomly assigned to follow-up without postoperative ^{131}I administration or to postoperative administration of ^{131}I (ie, 30 mCi after recombinant human thyrotropin-stimulating hormone). Surveillance appeared to be non-inferior to ^{131}I administration with a 3-year recurrence-free rate of 98·4% in the absence of ^{131}I and 96·2% in the radioiodine group.[33] Only structural events were considered in the IoN study.

In conclusion, the non-inferiority of a follow-up strategy compared with the postoperative administration of ^{131}I in low-risk thyroid cancer already reported at 3 years was confirmed at 5 years. There is no loss of opportunity in following these patients without postoperative ablation.

Contributors

SL, IB, and MS conceived the study and contributed to the study design and protocol development. IB drafted the statistical analysis plan. IB and SL accessed and verified the underlying data reported in the manuscript. IB did the statistical analyses. SL wrote the first draft of the manuscript. All authors made substantive comments thereon and approved the final version for submission. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

LL declares consultancy fees from EISAI, IPSEN, and Eli Lilly. SL declares consultancy fees from EISAI, Eli Lilly, and Bayer. All other authors declare no competing interests.

Data sharing

Anonymised data can be requested after publication from the corresponding author to be shared subject to the approval of all institutional review boards.

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References

1 Seidlin SM, Marinelli LD, Oshry E. Radioactive iodine therapy; effect on functioning metastases of adenocarcinoma of the thyroid. *J Am Med Assoc* 1946; **132:** 838–47.
2 Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med* 1994; **97:** 418–28.
3 Tuttle RM, Haugen B, Perrier ND. Updated American Joint Committee on cancer/tumor-node-metastasis staging system for differentiated and anaplastic thyroid cancer (eighth edition): what changed and why? *Thyroid* 2017; **27:** 751–56.
4 Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 2016; **26:** 1–133.
5 Pacini F, Fuhrer D, Elisei R, et al. 2022 ETA Consensus Statement: what are the indications for post-surgical radioiodine therapy in differentiated thyroid cancer? *Eur Thyroid J* 2022; **11:** e210046.
6 Gulec SA, Ahuja S, Avram AM, et al. A joint statement from the American Thyroid Association, the European Association of Nuclear Medicine, the European Thyroid Association, the Society of Nuclear Medicine and Molecular Imaging on current diagnostic and theranostic approaches in the management of thyroid cancer. *Thyroid* 2021; **31:** 1009–19.
7 Sawka AM, Brierley JD, Tsang RW, et al. An updated systematic review and commentary examining the effectiveness of radioactive iodine remnant ablation in well-differentiated thyroid cancer. *Endocrinol Metab Clin North Am* 2008; **37:** 457–80.
8 Lamartina L, Durante C, Filetti S, Cooper DS. Low-risk differentiated thyroid cancer and radioiodine remnant ablation: a systematic review of the literature. *J Clin Endocrinol Metab* 2015; **100:** 1748–61.
9 Schlumberger M, Catargi B, Borget I, et al. Strategies of radioiodine ablation in patients with low-risk thyroid cancer. *N Engl J Med* 2012; **366:** 1663–73.
10 Schlumberger M, Leboulleux S, Catargi B, et al. Outcome after ablation in patients with low-risk thyroid cancer (ESTIMABL1): 5-year follow-up results of a randomised, phase 3, equivalence trial. *Lancet Diabetes Endocrinol* 2018; **6:** 618–26.
11 Mallick U, Harmer C, Yap B, et al. Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. *N Engl J Med* 2012; **366:** 1674–85.
12 Dehbi H-M, Mallick U, Wadsley J, Newbold K, Harmer C, Hackshaw A. Recurrence after low-dose radioiodine ablation and recombinant human thyroid-stimulating hormone for differentiated thyroid cancer (HiLo): long-term results of an open-label, non-inferiority randomised controlled trial. *Lancet Diabetes Endocrinol* 2019; **7:** 44–51.
13 Verburg FA, Flux G, Giovanella L, van Nostrand D, Muylle K, Luster M. Differentiated thyroid cancer patients potentially benefitting from postoperative I-131 therapy: a review of the literature of the past decade. *Eur J Nucl Med Mol Imaging* 2020; **47:** 78–83.

14 Pasqual E, Sosa JA, Chen Y, Schonfeld SJ, Berrington de Gonzalez A, Kitahara CM. Trends in the management of localized papillary thyroid carcinoma in the United States (2000–2018). *Thyroid* 2022; **32:** 397–410.

15 Leboulleux S, Bournaud C, Chougnet CN, et al. Thyroidectomy without radioiodine in patients with low-risk thyroid cancer. *N Engl J Med* 2022; **386:** 923–32.

16 Yip L, Nikiforova MN, Yoo JY, et al. Tumor genotype determines phenotype and disease-related outcomes in thyroid cancer: a study of 1510 patients. *Ann Surg* 2015; **262:** 519–25, discussion 524–25.

17 Doerfler WD, Morariu E, Carty SE, Nikiforova M, Nikiforov YE, Yip L. Disease-related outcomes in patients with thyroid cancer on long term follow-up: analysis of 1487 patients. *J Endocr Soc* 2023; **7** (suppl 1)**:** bvad114.2061.

18 Brassard M, Borget I, Edet-Sanson A, et al. Long-term follow-up of patients with papillary and follicular thyroid cancer: a prospective study on 715 patients. *J Clin Endocrinol Metab* 2011; **96:** 1352–59.

19 Tuncel M, Vrachimis A, Campenni A, et al. To give or not to give? A critical appraisal of a clinical trial on radioiodine treatment. *Eur J Nucl Med Mol Imaging* 2022; **49:** 3316–19.

20 Chan IS, Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. *Biometrics* 1999; **55:** 1202–09.

21 Durante C, Montesano T, Torlontano M, et al. Papillary thyroid cancer: time course of recurrences during postsurgery surveillance. *J Clin Endocrinol Metab* 2013; **98:** 636–42.

22 Hay ID, Kaggal S, Iniguez-Ariza NM, Reinalda MS, Wiseman GA, Thompson GB. Inability of radioiodine remnant ablation to improve postoperative outcome in adult patients with low-risk papillary thyroid carcinoma. *Mayo Clin Proc* 2021; **96:** 1727–45.

23 Schlumberger M, Hitzel A, Toubert ME, et al. Comparison of seven serum thyroglobulin assays in the follow-up of papillary and follicular thyroid cancer patients. *J Clin Endocrinol Metab* 2007; **92:** 2487–95.

24 van Kinschot CMJ, Peeters RP, van den Berg SAA, et al. Thyroglobulin and thyroglobulin antibodies: assay-dependent management consequences in patients with differentiated thyroid carcinoma. *Clin Chem Lab Med* 2022; **60:** 756–65.

25 Yin N, Sherman SI, Pak Y, et al. The *de novo* detection of anti-thyroglobulin antibodies and differentiated thyroid cancer recurrence. *Thyroid* 2020; **30:** 1490–95.

26 Kim WG, Yoon JH, Kim WB, et al. Change of serum antithyroglobulin antibody levels is useful for prediction of clinical recurrence in thyroglobulin-negative patients with differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 2008; **93:** 4683–89.

27 Nascimento C, Borget I, Troalen F, et al. Ultrasensitive serum thyroglobulin measurement is useful for the follow-up of patients treated with total thyroidectomy without radioactive iodine ablation. *Eur J Endocrinol* 2013; **169:** 689–93.

28 Durante C, Montesano T, Attard M, et al. Long-term surveillance of papillary thyroid cancer patients who do not undergo postoperative radioiodine remnant ablation: is there a role for serum thyroglobulin measurement? *J Clin Endocrinol Metab* 2012; **97:** 2748–53.

29 Chou R, Dana T, Brent GA, et al. Serum thyroglobulin measurement following surgery without radioactive iodine for differentiated thyroid cancer: a systematic review. *Thyroid* 2022; **32:** 613–39.

30 Grani G, Lamartina L, Alfò M, et al. Selective use of radioactive iodine therapy for papillary thyroid cancers with low or lower-intermediate recurrence risk. *J Clin Endocrinol Metab* 2021; **106:** e1717–27.

31 Baudin E, Do Cao C, Cailleux AF, Leboulleux S, Travagli JP, Schlumberger M. Positive predictive value of serum thyroglobulin levels, measured during the first year of follow-up after thyroid hormone withdrawal, in thyroid cancer patients. *J Clin Endocrinol Metab* 2003; **88:** 1107–11.

32 Giovanella L, Milan L, Roll W, et al. Postoperative thyroglobulin as a yard-stick for radioiodine therapy: decision tree analysis in a European multicenter series of 1317 patients with differentiated thyroid cancer. *Eur J Nucl Med Mol Imaging* 2023; **50:** 2767–74.

33 Hackshaw A, Newbold K, Beasley M, et al. 2212MO Major secondary outcomes in the multicentre noninferiority randomised trial IoN: is ablative radioiodine necessary for low-risk differentiated thyroid cancer patients? *Ann Oncol* 2023; **34:** S1142.