Thyroidectomy with or without postoperative radioiodine for patients with low-risk differentiated thyroid cancer in the UK (IoN): a randomised, multicentre, non-inferiority trial

Ujjal Mallick, Kate Newbold*, Matthew Beasley, Kate Garcez, Jonathan Wadsley, Sarah J Johnson, Tim Stephenson, Mark Gaze, Andrew Goodman, Sarah Jefferies, Suganya Sivabalasingham, Nicholas Slevin, David P Wilkinson, Elena Macias-Fernandez, Danielle Power, Tom Roques, Lesley Speed, Christopher Nutting, George Mochloulis, Georgina Gerrard, Charles Candish, Sally Morgan, Devashish Tripathi, Peter Truran, Claire Arthur, Andrzej Wieczorek, Krishnaswamy Madhavan, Jillian Maclean, David Boote, Dae Kim, Abigail Pascoe, Gayani Pitiyage, Sharon Forsyth, Emily Ambrose, Elizabeth Chang, Kate Farnell, Allan Hackshaw**

Lancet 2025; 406: 52–62

Published Online June 18, 2025 https://doi.org/10.1016/S0140-6736(25)00629-4

See Comment page 5

*Contributed equally

Department of Oncology, Freeman Hospital, Newcastle, UK (U Mallick FRCR); Head, Neck and Thyroid Unit, Royal Marsden NHS Foundation Trust, London, UK (K Newbold MD, Prof C Nutting MD); Bristol Cancer Institute, University Hospitals Bristol and Weston Foundation NHS Trust, Bristol, UK (M Beasley FRCR); Department of Clinical Oncology, The Christie NHS Foundation Trust, Manchester, UK (K Garcez MBBCh, Prof N Slevin FRCR, C Arthur MBChB); Department of Oncology, Weston Park Cancer Centre, Sheffield, UK (Prof J Wadsley FRCR); Department of Cellular Pathology, Royal Victoria Infirmary, Newcastle upon Tyne, UK (S J Johnson PhD); Laboratory Medicine, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK (Prof T Stephenson MD); Department of Oncology, University College London Hospitals NHS Foundation Trust, London, UK (Prof M Gaze MD, S Sivabalasingham MD Res); Department of Oncology, Royal Devon and Exeter Hospital, Devon, UK (A Goodman FRCR); Department of Oncology, Addenbrooke's Hospital, Cambridge, UK (S Jefferies FRCR); Department of Radiotherapy and Oncology, James Cook University Hospital, Middlesbrough, UK (D P Wilkinson FRCR); Department of Nuclear

Summary

Background Patients with differentiated thyroid cancer can often be treated with postoperative radioiodine (also called radioiodine ablation) after total thyroidectomy. The IoN trial was designed to assess whether recurrence-free survival was non-inferior after no ablation compared with ablation in patients with low-risk differentiated thyroid cancer.

Methods IoN was a multicentre, non-inferiority, phase 3 randomised trial conducted at 33 UK cancer centres. Eligible patients had complete (R0) resection following total thyroidectomy; stage pT1, pT2, pT3 (according to Tumour, Node, Metastasis staging version 7 [TNM7]), or pT3a (according to TNM8) disease; and N0, Nx, or N1a disease. Participants were randomly assigned (1:1) by minimisation, using a central electronic system, to have either 1·1 GBq ablation or no ablation, following thyroidectomy. Stratification factors were centre, age, T stage, and nodal status. Patients had annual neck ultrasound scans and 6-monthly serum thyroglobulin measurements. The primary endpoint was 5-year recurrence-free survival, defined by the absence of locoregional recurrent or persistent structural disease, distant metastases, or death from thyroid cancer. Non-inferiority was assessed with a margin of 5 percentage points. Per-protocol and intention-to-treat (ITT) analyses were done for the primary endpoint, and safety was analysed in the per-protocol population. The trial is registered with ClinicalTrials.gov (NCT01398085), ISRCTN (ISRCTN80416929), and EUDRACT (2011–000144–21), and is still in active follow-up.

Findings We recruited 504 patients (including 390 [77%] female patients and 114 [23%] male patients) between June 26, 2012 and March 18, 2020 and randomly assigned 251 to receive no ablation and 253 to receive ablation (ITT population). 249 patients in the no ablation group did not have ablation and 231 in the ablation group had ablation (per-protocol population). Median follow-up was 6·8 years (IQR 5·6–8·6) in the no ablation group and 6·6 years (4·8–8·5) in the ablation group; 17 recurrences (eight in the no ablation group and nine in the ablation group; ITT population) occurred during follow-up. 5-year recurrence-free rates were 97·9% (95% CI 96·1–99·7) in the no ablation group versus 96·3% (93·9–98·7) in the ablation group in the ITT analysis, and 97·9% (96·1–99·7) versus 96·9% (94·7–99·1) in the per-protocol analysis. The 5-year absolute risk difference was 0·5 percentage points (95% CI −2·2 to 3·2, $p_{non\text{-}inferiority}$=0·033; ITT analysis), showing that non-inferiority was reached. The observed recurrence rate was higher among patients with pT3 or pT3a tumours (four [9%] of 46 patients overall with pT3 or pT3a tumours *vs* 13 [3%] of 458 with pT1 or pT2 tumours), or N1a tumours (six [13%] of 47 with N1a *vs* 11 [2%] of 457 with N0 or Nx), but they were similar among those who did not receive ablation. Adverse events were similar between the groups, the most common being fatigue (63 [25%] of 249 in the no ablation group *vs* 65 [28%] of 231 in the ablation group), lethargy (34 [14%] *vs* 32 [14%]), and dry mouth (24 [10%] *vs* 21 [9%]), and there were no treatment-related deaths.

Interpretation The IoN trial shows that ablation (or postoperative radioiodine) can be avoided for patients with pT1, pT2, and N0 or Nx tumours with no adverse features. Many patients with low-risk differentiated thyroid cancer worldwide can safely avoid postoperative radioiodine and its related hospitalisation and side-effects, which in turn results in lower health-care costs.

Funding Cancer Research UK.

Introduction

Thyroid cancer is the seventh most common cancer type globally and is ranked 24th in terms of cancer mortality, with 821 000 new cases diagnosed each year and approximately 48 000 annual deaths, as of 2022.[1] The incidence had been rising in both the USA and the UK in

Research in context

Evidence before this study

Standard international practice for patients with well differentiated thyroid cancer has been to administer postoperative radioiodine after a total thyroidectomy (previously called radioiodine ablation, which is the term used throughout this Article). Several observational studies have indicated that selected patients with low-risk differentiated thyroid cancer could avoid ablation. We searched PubMed from Jan 1, 1966, to July 31, 2024 with the search terms "thyroid cancer/carcinoma", "ablation", "thyroidectomy" and "random$" and found only one large randomised trial comparing ablation with no ablation (ESTIMABL2, in France). ESTIMABL2 only included patients with tumours classified as pT1a or pT1b and N0 or Nx and used a composite primary endpoint that included neck ultrasound abnormalities, raised thyroglobulin concentrations, and raised Tg antibody concentrations as events. This trial showed that the event-free rate was similar whether or not patients had ablation. National and international clinical guidelines have been anticipating the IoN trial results.

Added value of this study

The IoN trial provides data on a wider group of patients than ESTIMABL2 (ie, patients with pT2, pT3 [according to Tumour, Node, Metastasis (TNM) staging version 7], or pT3a [according to TNM8] tumours, excluding follicular thyroid cancer larger than 4 cm in diameter), and N1a disease. If patients with pT2 and N0 or Nx tumours do not need ablation, the number of patients who can now avoid this treatment would be double that indicated by ESTIMABL2. IoN also had clinically diagnosed recurrence as the primary endpoint, and long follow-up (more than 5 years) to capture both early and later recurrence events. IoN and ESTIMABL2 are two independent, multicentre, randomised trials that together offer strong and complementary evidence showing that ablation can be safely avoided in patients with low-risk differentiated thyroid cancer (ie, pT1–pT2 tumours with N0 nodal status, and no other adverse features). Due to the small number of patients with pT3, pT3a, or N1a tumours in the IoN trial, subgroup analyses were underpowered for these patients, so care must be taken when applying the results of the trial to all pT3 or N1a tumours. Therefore, a clinical decision was made to not provide a definitive statement on the basis of numerically higher recurrence rates in these patients, even though the rates were not higher among patients who did not have postoperative radioiodine than those who did have ablation. Clinicians can continue with their current practice for these patients.

Implications of all the available evidence

The conclusions of both ESTIMABL2 and IoN suggest that at least 400 000 patients with low-risk differentiated thyroid cancer worldwide could avoid ablation after a total thyroidectomy, based on international estimates of thyroid cancer incidence. Avoiding ablation has clear advantages including no treatment-related adverse events, no need for hospital admission or isolation due to radiation safety restrictions, and no requirement for patients to avoid close contact with children, family, friends, and work colleagues. Other benefits are a substantial cost saving to the health-care provider, reduced radiation exposure to health-care workers, and a positive environmental impact associated with less hospital attendance and reduced manufacture and usage of radioactive iodine.

the past three decades, but it seems to have stabilised.[2,3] Most cases are well differentiated thyroid cancer, which has a high cure rate.[1]

From the 1950s, international clinical practice was to administer an empirical activity of 3·7 GBq radioactive iodine (^{131}I) after a total thyroidectomy, to ablate residual healthy thyroid tissue and possible persistent thyroid cancer. However, many clinical experts were concerned that 3·7 GBq ^{131}I was a higher activity than needed for successful ablation in patients with low-risk differentiated thyroid cancer. In 2012, two large, randomised, non-inferiority trials (HiLo in the UK and ESTIMABL1 in France)[4,5] and their long-term follow-up results[6,7] showed that a lower administered activity of 1·1 GBq was non-inferior to 3·7 GBq. Ablation was a globally used term that has since been overtaken by the non-specific term postoperative radioiodine, which encompasses normal remnant ablation, adjuvant therapy for presumed metastatic disease, and ^{131}I therapy for known metastatic disease; however, we have used the term ablation throughout this Article.

The next step in treatment de-escalation was assessing whether ^{131}I ablation was needed at all in patients with low-risk disease, given that the majority of these patients are effectively treated with total thyroidectomy by a specialist surgeon and thyroid hormone-suppression therapy. The evidence that ablation reduces recurrence rates was based entirely on observational studies with inconsistent results.[8] Therefore, the HiLo and ESTIMABL1 investigators set up IoN and ESTIMABL2[9] to compare ablation with no ablation. In 2022, ESTIMABL2 reported that the 3-year event-free rate was 96% in both trial groups, and concluded that eligible patients can avoid ablation, using a composite primary endpoint of the presence of abnormal foci of radioiodine uptake requiring treatment (in the ablation group only), abnormal findings on neck ultrasound, or elevated concentrations of thyroglobulin or thyroglobulin antibodies (TgAbs).[9]

The 2015 American Thyroid Association guidelines do not recommend ablation if the presurgical tumour is less than 1 cm in diameter and unifocal or multifocal, and if

Medicine, Kent and Canterbury Hospital, Canterbury, UK (E Macias-Fernandez Dr); **Department of Oncology, Imperial College Healthcare NHS Trust, London, UK** (D Power FRCR); **Department of Clinical Oncology, Norfolk and Norwich University Hospital Trust, Norwich, UK** (T Roques FRCR); **Department of Oncology, University Hospitals of Leicester NHS Trust, Leicester, UK** (L Speed MBChB); **Department of Ear, Nose and Throat and Head and Neck Surgery, East and North Herts NHS Trust, Stevenage, UK** (G Mochloulis MD); **Department of Oncology, St James's University Hospital, Leeds, UK** (G Gerrard FRCR); **Department of Oncology, Cheltenham General Hospital, Cheltenham, UK** (C Candish FRCR); **Department of Oncology, Nottingham University Hospitals NHS Trust, Nottingham, UK** (S Morgan FRCR, A Pascoe MBChB); **Department of Oncology, New Cross Hospital, Wolverhampton, UK** (D Tripathi FRCR); **Department of Surgery, Royal Victoria Infirmary, Newcastle upon Tyne, UK** (P Truran MBChB); **Queens Centre for Oncology, Castle Hill Hospital, Cottingham, UK** (A Wieczorek MD); **Department of Oncology, Southend University Hospital, Southend, UK** (K Madhavan FRCR); **Department of Oncology, Velindre Hospital, Cardiff, UK** (J Maclean MD); **Portsmouth Oncology Centre, Queen Alexandra Hospital, Portsmouth, UK** (D Boote FRCP); **St George's University Hospital, London, UK** (Prof D Kim FRCS); **Department of Cellular Pathology, St George's University Hospital, London, UK** (G Pitiyage PhD); **Cancer Research UK & UCL Cancer Trials Centre, UCL Cancer Institute, London, UK** (S Forsyth BSc, E Ambrose MSc, E Chang BA, Prof A Hackshaw MSc); **Butterfly Thyroid Cancer Trust, Newcastle, UK** (K Farnell)

Correspondence to:
Prof Allan Hackshaw, Cancer Research UK & UCL Cancer Trials Centre, UCL Cancer Institute, London W1T 4TJ, UK
a.hackshaw@ucl.ac.uk

thyroid capsule invasion is not present.[10] The 2016 British Thyroid Association guidelines recommend 1·1 GBq ablation for patients with pT1, pT2, or N0 (no evidence of regional nodal involvement) status and complete (R0) resection, with recombinant human thyroid-stimulating hormone (rhTSH, also called thyrotropin alfa) as the preferred method for ablation preparation. UK clinicians also tend not to ablate tumours less than 1 cm in diameter.[11] Both guidelines pre-date the ESTIMABL2 trial. Since the publication of ESTIMABL2, the 2022 European Thyroid Association guidelines and the UK National Institute for Clinical Excellence (NICE) guidelines indicate that ablation could be avoided in patients with the same eligibility as the ESTIMBL2 trial—ie, pT1a or pT1b tumours, N0 or Nx (involvement of regional lymph nodes that cannot be assessed) status, R0 resection, and no clinically significant adverse histological features.[12,13] The European Thyroid Association acknowledge the continuing debate regarding the use of ablation in patients with low-risk differentiated thyroid cancer,[12] and NICE and others wish to see confirmatory evidence from the IoN trial,[13,14] particularly in patients with pT2 tumours.[13]

Here, we report the only other major randomised trial of ^{131}I ablation in low-risk thyroid cancer with long follow-up besides ESTIMABL2 that aimed to show whether ablation is needed.

Methods

Study design and participants

IoN was a national, multicentre, non-inferiority, open-label, randomised controlled trial done in 33 cancer centres across the UK. Patients with well differentiated thyroid cancer who had undergone a total thyroidectomy with R0 tumour resection were approached by their physician to consider the trial soon after diagnosis at their local cancer centre. Specific criteria used to assess low risk for papillary and follicular cancer can be found in appendix 1 (pp 3–7). Eligible patients with papillary thyroid cancer had tumours staged pT1a (all foci ≤1 cm diameter), pT1b (1–2 cm diameter), pT2 (2–4 cm diameter), pT3 (according to Tumour, Node, Metastasis staging version 7 [TNM7]; ie, >4 cm diameter or minimal extrathyroidal extension, or both), or pT3a (according to TNM8; ie, >4 cm diameter), with N0, Nx, or N1a (involvement of lymph nodes close to the thyroid in the neck) nodal status. Patients with follicular cancer that included oncocytic carcinoma (ie, follicular thyroid carcinoma) were eligible if they had minimally invasive disease staged pT1b or pT2 (>1–4 cm diameter), or pT3 (according to TNM7; ie, >4 cm diameter, with minimal extrathyroidal extension). Patients were excluded if they had aggressive features as determined by the pathologist, examples of which included definitely angioinvasive, widely invasive, anaplastic, or poorly differentiated disease. Nodal status (N0 or N1a) was assessed by central compartment neck dissection, but node sampling after intraoperative assessments was also used by surgeons in routine clinical practice.

See Online for appendix 1

The TNM staging system changed during trial recruitment. TNM7 was in use when the trial started (and was used to grade 453 patients) and TNM8 was in use from May 16, 2018 (and was used to grade 51 patients). The main difference between the TNM versions that affects IoN is in terms of defining pT3: in TNM7, pT3 was defined as larger than 4 cm in diameter or having minimal extrathyroidal extension, or both; in TNM8, minimal extrathyroidal extension does not change stage, pT3a is defined as larger than 4 cm in diameter, and pT3b is defined as gross extrathyroidal extension. IoN included papillary thyroid cancers larger than 4 cm in diameter but not follicular thyroid carcinomas more than 4 cm in diameter. Minimal extrathyroidal extension was allowed at the discretion of the local multidisciplinary team. Hereafter, we use pT3 or pT3a to refer to pT3 (assessed with TNM7), or pT3a (assessed with TNM8) with the exclusion of follicular thyroid carcinoma more than 4 cm in diameter. Local pathology assessment was used to reflect routine practice. A central pathology review of histological slides was also done and will be reported separately.

Sex was self-reported by patients with the option of male or female. Data on race and ethnicity were not collected.

The trial adhered to the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable local regulatory requirements and ethics approvals (Research Ethics Committee North-East, reference 11/NE/0228). Patients provided written informed consent before enrolment. The trial was funded by Cancer Research UK with support from the University College London–University College London Hospitals Biomedical Research Centre.

Randomisation and masking

Patients were randomly assigned (1:1) to either receive postoperative radioiodine treatment (ie, ablation) at least 8 weeks after thyroidectomy or not (ie, no ablation). Minimisation with a central computer program was used to generate the random number sequence with the stratification factors of recruiting centre, age group (ie, 17–19 years, 20–45 years, and >45 years), T stage, and nodal status. The physician or research nurse enrolled patients and assigned them to the trial groups, and could have been involved in patient management during follow-up (eg, for clinic and imaging assessments).

Procedures

Patients assigned to have ablation were prepared according to local clinical policy, which was either rhTSH injection into the buttocks on each of the 2 days before ablation or thyroid hormone withdrawal. rhTSH was recommended in the trial protocol. Patients who were prepared using thyroid hormone withdrawal had their

hormone therapy discontinued either 4 weeks before ablation if on thyroxine or 2 weeks before ablation if on tri-iodothyronine. Hormone therapy was then restarted 2 days after ablation. The trial protocol allowed centres to choose an administered ^{131}I activity, but 1·1 GBq was the stated preferred dose.

All patients had a neck ultrasound and stimulated thyroglobulin measurement using either rhTSH or thyroid hormone withdrawal at least 8 weeks after thyroidectomy, and before ablation in the ablation group. 2 months after the initial stimulated thyroglobulin measurement, all patients had a clinical examination and thyroid blood tests, including for thyroglobulin and TgAb concentrations. 6–9 months after the initial thyroglobulin measurement, patients had another stimulated thyroglobulin measurement and neck ultrasound. We used stimulated thyroglobulin in both groups at 8 weeks post-surgery because highly sensitive thyroglobulin assays were unavailable in all UK centres. Additional follow-up of a clinical examination and thyroid blood tests every 6 months and a neck ultrasound every 12 months started 6 months after the 6-month to 9-month assessment and lasted for 5 years. TSH suppression was maintained throughout the trial period to keep TSH concentrations less than 0·1 mIU/L (as per usual UK practice at the time the trial was designed), tri-iodothyronine values within normal range, and to keep the patient clinically euthyroid.

Outcomes

The primary outcome measure was disease-free thyroid cancer survival, defined as no confirmed structural locoregional recurrent or residual disease, distant recurrence, or death from thyroid cancer (patients without an event were censored at the date they were last known to be alive, or date of death if they had died of causes other than thyroid cancer). As no thyroid cancer deaths occurred, the primary endpoint is more accurately described as the recurrence-free rate, used hereafter. Recurrences were diagnosed initially by a neck ultrasound (as the neck is the most common site of recurrence in this group of patients with low-risk disease), and with biopsy, fine needle aspiration cytology, and other forms of imaging (ie, radioiodine scan, CT scan, or MRI scan) when required. Ultrasound criteria for suspicious disease needing more investigation included lymph nodes 10 mm or larger in the smallest diameter; nodes that had increased in size since previous scans with the current size being more than 5 mm or nodes with sonographic appearance of malignancy; or thyroid bed or other soft-tissue abnormalities that had progressively increased in size or appeared malignant on the scan.

Secondary outcome measures included adverse events; health-related quality of life using the European Organisation for Research and Treatment of Cancer QLQ-C30,[15] and duration of avoidance of physical contact after discharge (ablation group only); thyroid cancer deaths; incidence of second primary cancers; abnormal serial ultrasound; biochemical response; delayed ablation in the no ablation group; and cost savings. We used the same definitions of a biochemical event as the ESTIMABL2 trial[9] for comparability. A full list of outcomes is provided in the protocol (appendix 2 p 19).

See Online for appendix 2

Statistical analysis

The 5-year recurrence-free rate among patients who had ablation was taken to be 95%.[7] The sample size was a minimum of 450 patients (for a non-inferiority margin of 6 percentage points, but the target margin to exclude was 5 percentage points) with 80% power and 5% one-sided statistical significance. The analyses in this Article were based on data as of July 18, 2024, to maximise follow-up because of the importance of capturing late recurrences.

The recurrence-free endpoint was analysed using Kaplan–Meier and Cox proportional hazards regression. The between-group difference (and two-sided 90% CI, as per the design) in the recurrence-free rate at 3 years and 5 years of follow-up was estimated by applying the hazard ratio (HR) and its 90% CI to the observed rate in the ablation group, and by using a more contemporary statistical method called regression standardisation that uses modelling to predict the risk of recurrence for each trial group separately, from which an absolute difference can be produced directly from the model.[16,17] Both intention-to-treat (all randomly assigned patients) and per-protocol (excluding patients who did not have the randomised intervention) populations were examined for the primary endpoint (appendix 3). Adverse events and quality of life were analysed in the per-protocol population to reflect what patients actually received. The association between several established risk factors (ie, patient characteristics, pathological features, and post-surgical thyroglobulin concentration) and recurrence was analysed using Cox regression (all randomly assigned patients). We also assessed the sensitivity and specificity of various post-surgical (baseline) unstimulated thyroglobulin cutoff values to predict recurrence. Finally, we estimated the upfront cost savings to the National Health Service (NHS) using trial data on hospital admission for ablation and typical costs of rhTSH drug cost and administration, and hospital stay per day. In England, the NHS cost of ^{131}I ablation is £309 per patient, the cost of rhTSH (given on each of the 2 days before ablation) is £600, and the cost of hospital admission in radiation-protected isolation is £812 per day (Wadsley J, Weston Park Cancer Centre Sheffield, personal communication). The analyses were done using SAS version 15.1. An independent data monitoring committee was in place. The trial is registered with ClinicalTrials.gov (NCT01398085), ISRCTN (ISRCTN80416929), and EUDRACT (2011–000144–21).

See Online for appendix 3

Role of the funding source

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

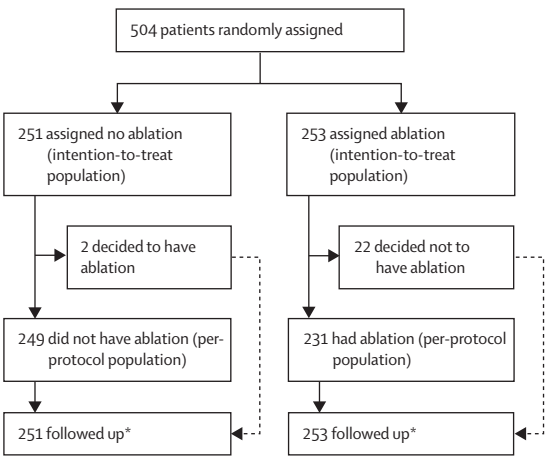

Figure 1: **CONSORT diagram**
Data on the number of patients assessed for eligibility were not collected. *At 5 years of follow-up, five patients in the no ablation group and 12 (5%) of 253 patients in the ablation group were recorded as lost to follow-up, but their data still contributed to the survival analyses.

Results

504 patients were recruited from 33 UK cancer centres between June 26, 2012, and March 18, 2020. 253 patients were randomly assigned to the ablation group and 251 to the no ablation group (figure 1). The only major protocol deviations were patients randomly assigned to one group who had the intervention for the other trial group. The clinical trials centre had oversight of these protocol deviations.

Baseline characteristics were balanced (table 1). 153 (30%) of the 504 patients in the trial were aged 40 years or younger (76 [30%] of 251 in the no ablation group and 77 [30%] of 253 in the ablation group), including 127 (33%) of the 390 female participants and 26 (23%) of the 114 male participants. Of the 504 patients, 235 (47%), 223 (44%), and 46 (9%) had pT1, T2, and T3 or T3a tumours, respectively. 457 (91%) patients had N0 or Nx disease and 47 (9%) had N1a disease.

Of the 251 patients in the no ablation group, two (1%) changed their minds and decided to have ablation. Of the 253 patients in the ablation group, 22 (9%) changed their minds soon after randomisation and decided to not have ablation. Of the other 231 patients in the ablation group, one (<1%) received 3·7 GBq ablation and 230 (>99%) received approximately 1·1 GBq ablation (range 1·02–1·30). Of the 231 patients who received ablation, 189 (82%) were prepared using rhTSH and 42 (18%) were prepared using thyroid hormone withdrawal; the two patients in the no ablation group who had ablation after all were prepared using rhTSH.

The median follow-up was 6·7 years (IQR 5·2–8·5; 6·8 years [5·6–8·6] in the no ablation group and 6·6 years [4·8–8·5] in the ablation group). 388 (77%) of 504 patients had 5 years of follow-up or more, including 202 (80%) of 251 in the no ablation group and 186 (74%) of 253 in the ablation group. 492 (98%) had 3 years of follow-up or more, including 250 (>99%) in the no ablation group and 242 (96%) in the ablation group. At 5 years of follow-up, five (2%) of 251 patients in the no ablation group and 12 (5%) of 253 patients in the ablation group were recorded as lost to follow-up, which is not expected to affect 5-year recurrence rates. At the time of analysis in July, 2024, 17 patients had a recurrence event (eight [47%] in the no ablation group and nine [53%] in the ablation group). 13 (76%; four in the no ablation group and nine in the ablation group) of the 17 recurrences were diagnosed within 3 years, and four (24%; all no ablation group)

	No ablation (N=251)	Ablation (N=253)
Age, years	48 (17–77)	47 (17–80)
Time from thyroidectomy to random assignment, months	2·3 (0·4–5·9)	2·1 (0·6–5·7)
Unstimulated post-surgical thyroglobulin, ng/mL*	0·5 (0·01–14·4)	0·4 (0·01–70·2)
Sex		
Female	191 (76%)	199 (79%)
Male	60 (24%)	54 (21%)
Histology		
Papillary	192 (76%)	204 (81%)
Follicular	52 (21%)	38 (15%)
Oncocytic†	7 (3%)	11 (4%)
Multifocal		
Yes	89 (35%)	97 (38%)
No	162 (65%)	156 (62%)
Stage		
pT1	117 (47%)	118 (47%)
pT2	111 (44%)	112 (44%)
pT3 or pT3a‡	23 (9%)	23 (9%)
Nodal status		
Nx	57 (23%)	57 (23%)
N0§	171 (68%)	172 (68%)
N1a§	23 (9%)	24 (9%)
Stage and nodal status		
pT1 and N0 or Nx	102 (41%)	107 (42%)
pT2 and N0 or Nx	107 (43%)	102 (40%)
pT3 or pT3a and N0 or Nx	19 (8%)	20 (8%)
pT1 and N1a	15 (6%)	11 (4%)
pT2 and N1a	4 (2%)	10 (4%)
pT3 or pT3a and N1a	4 (2%)	3 (1%)
Total thyroidectomy		
One-stage	101 (40%)	107 (42%)
Two-stage	149 (59%)	142 (56%)
Unknown	1 (<1%)	4 (2%)
Central compartment neck dissection	40 (16%)	51 (20%)

Data are median (range) or n (%). TNM=Tumour, Node, Metastasis. *Excluding Tg antibodies. †Hürthle cell. ‡TNM7 for pT3, or TNM8 for pT3a (not follicular thyroid carcinoma >4 cm in diameter). §Assessed using central compartment neck dissection or node sampling.

Table 1: **Baseline characteristics**

occurred between 4 years and 7 years. Of the 17 patients with a recurrence, ten (four in the no ablation group and six in the ablation group) had biopsy or fine-needle aspiration cytology.

Figure 2 shows the Kaplan–Meier curves for recurrence-free survival (the primary endpoint), and table 2 shows the summary results with an expected low recurrence rate. The 5-year recurrence-free rate was similar in both groups: 97·9% (95% CI 96·1–99·7) in the no ablation group versus 96·3% (93·9–98·7) in the ablation group for the intention-to-treat analysis, and 97·9% (95% CI 96·1–99·7) in the no ablation group versus 96·9% (94·7–99·1) in the ablation group for the per-protocol analysis (table 2). The 5-year absolute risk difference in the intention-to-treat population was 0·5 percentage points (90% CI −1·8 to 2·7; 95% CI −2·2 to 3·2) and −0·1 percentage points (90% CI −2·2 to 2·0; 95% CI −2·6 to 2·5) for the per-protocol analysis (table 2). Using the hazard ratio, the p value for non-inferiority was 0·033 for the intention-to-treat population, and 0·093 for the per-protocol analysis (both within the $p_{non\text{-}inferiority}$=0·10 threshold as per the sample size calculation). The point estimates and CIs are within the 5-percentage point non-inferiority margin, so no ablation was non-inferior to ablation.

Among the eight patients with a recurrence in the no ablation group, four (50%) had a recurrence in the thyroid bed, three (38%) had a recurrence that involved lateral cervical lymph nodes, and one (13%) had distant metastatic disease (lung). Of the nine patients in the ablation group, three (33%) had a recurrence in the thyroid bed and six (67%) had a recurrence that involved lateral cervical lymph nodes. The patient who had distant metastatic disease did not have high-risk baseline features (ie, they had papillary carcinoma, pT1 and N0 status, and thyroglobulin and TgAb concentrations that were not raised). This event occurred 82 months after random assignment, and the patient was still alive 30 months after diagnosis with metastatic disease. Recurrences were treated with therapeutic ^{131}I, with or without surgery. In the no ablation group, seven of the eight recurrences had therapeutic ^{131}I and one also had surgery. In the ablation group, eight of the nine recurrences had therapeutic ^{131}I and four also had surgery. Treatment for recurrences were not reported for two patients but should have been at least therapeutic ^{131}I as per standard practice.

17 (7%) of 251 patients in the no ablation group versus 11 (4%) of 253 patients in the ablation group were recorded as having had fine-needle aspiration cytology or biopsy following suspicion of a recurrence, including ten patients who went on to be diagnosed with a recurrence; this difference was not statistically significant (Fisher's exact test p=0·25).

During the trial, eight patients died (four in each group); no deaths were from thyroid cancer. The median age among the patients who died was 64 years

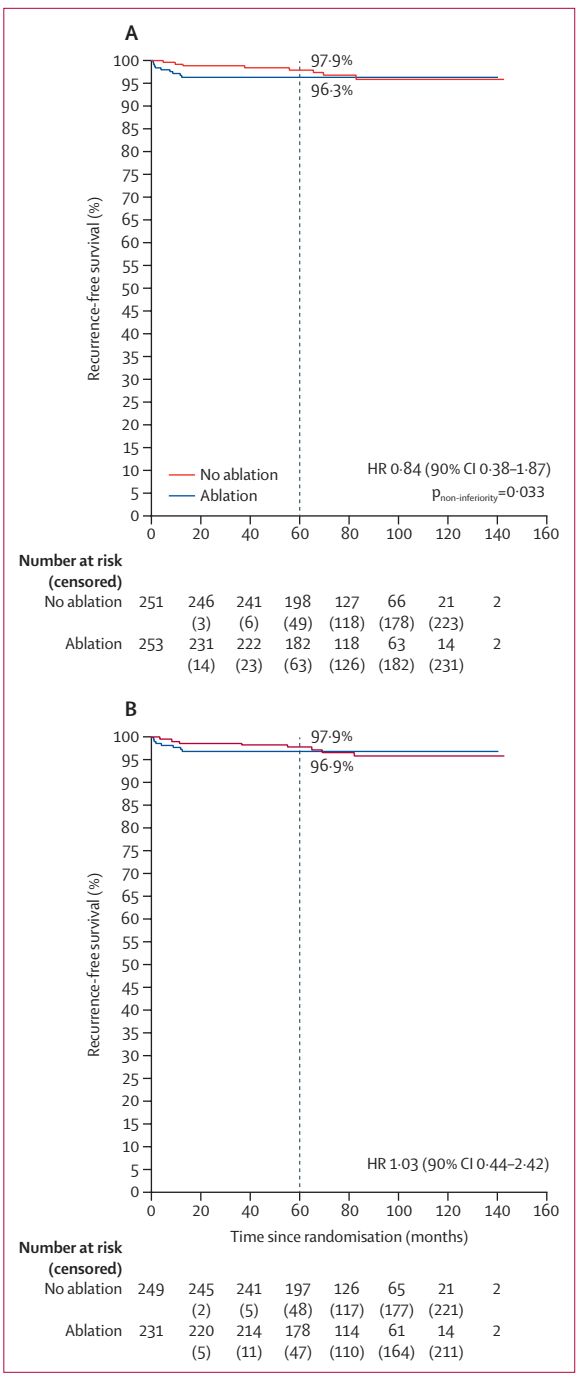

Figure 2: **Recurrence-free survival**
(A) Intention-to-treat analysis using a Cox regression. (B) Per-protocol analysis. 5-year recurrence-free survival (primary endpoint) is shown where the vertical dotted line at 60 months intersects with the survival curve. At 5 years, five patients in the no ablation group and 12 in the ablation group were recorded as lost to follow-up. The apparent difference in the number of censored patients at 20 months (3 *vs* 14) and 40 months (6 *vs* 23) was much smaller with longer follow-up (as of March, 2025) after the main analysis for these patients (2 *vs* 6 at 20 months and 5 *vs* 14 at 40 months). HR=hazard ratio.

	No ablation	Ablation	HR or risk difference
Intention-to-treat analysis			
Number of patients	251	253	..
Number of events	8	9	0·84* (90% CI 0·38 to 1·87)
3-year recurrence-free survival	98·8% (95% CI 97·4–100·0)	96·3% (95% CI 93·9–98·7)	0·4† (90% CI −1·5 to 2·3; 95% CI −1·8 to 2·7)
5-year recurrence-free survival	97·9% (95%CI 96·1–99·7)	96·3% (95% CI 93·9–98·7)	0·5† (90% CI −1·8 to 2·7; 95% CI −2·2 to 3·2)
3-year or 5-year recurrence-free survival	..	..	0·6‡ (90% CI −3·1 to 2·3; 95% CI −4·2 to 2·5)
Per-protocol analysis			
Number of patients	249	231	..
Number of events	8	7	1·03* (90% CI 0·44 to 2·42)
3-year recurrence-free survival	98·8% (95% CI 97·4–100·0)	96·9% (95% CI 94·7–99·1)	−0·1† (90% CI −1·8 to 1·7; 95% CI −2·2 to 2·0)
5-year recurrence-free survival	97·9% (95% CI 96·1–99·7)	96·9% (95% CI 94·7–99·1)	−0·1† (90% CI −2·2 to 2·0; 95% CI −2·6 to 2·5)
3-year or 5-year recurrence-free survival	..	..	−0·1‡ (90% CI −4·2 to 1·7; 95% CI −5·5 to 1·9)

All events were recurrences: no deaths from thyroid cancer occurred. An event is confirmed structural locoregional recurrent or residual disease, or distant recurrence. Units for risk differences are percentage points. HR=hazard ratio. *Unadjusted HR; the HR adjusted for the randomisation stratification factors (age, T stage, and nodal status) was 0·76 (90% CI 0·34–1·70) for the intention-to-treat analysis and 0·95 (0·40–2·25) for the per-protocol analysis. †Risk difference, estimated using regression standardisation.[17] ‡Risk difference, estimated by applying the unadjusted HR and 90% CI to the observed recurrence-free rate in the ablation group.[16] The risk differences are the same at 3 years and 5 years because the rates in the ablation group are the same.

Table 2: **Summary of recurrence-free survival**

(range 40–71). Of the four patients who died in the no ablation group, two died from a new primary cancer (lung or neuroendocrine and multiple myeloma), one died from a myocardial infarction, and one died from liver disease. Of the four patients who died in the ablation group, one had bowel cancer and the other three died from myocardial infarction, limb ischaemia, or an unknown cause. The number and type of second new cancers were similar between the trial groups: 11 (4%) in the no ablation group versus 14 (6%) in the ablation group (appendix 1 p 8). The most common were breast cancer (five cases in the no ablation group *vs* eight cases in the ablation group), basal cell carcinoma (one case *vs* two cases), and multiple myeloma (two cases *vs* one case]).

Appendix 1 (p 9) shows the neck ultrasound findings over time, including potentially malignant or benign lymph nodes. The proportions of patients with abnormal findings were similar between the trial groups. During the 5-year follow-up period during which ultrasound scans were indicated in the trial protocol, 15 (6%) of the 251 patients in the no ablation group versus 11 (4%) of 253 in the ablation group had potentially malignant nodes (Fisher's exact test p=0·43); six of the 15 patients in the no ablation group and two of the 11 patients in the ablation group had a nodal size of 10 mm or larger. 16 of the 17 patients with a recurrence had had abnormal scans, and the remaining patient had metastatic disease found by CT scan. Appendix 1 (p 10) shows the biochemical events during follow-up. The findings were similar between the trial groups. Patients who do not have ablation might show more abnormal ultrasound or thyroglobulin findings that could be indicative of recurrence, so they could be more likely to have cancer investigations than patients who do have ablation, and therefore be disadvantaged by having unnecessary assessments when they do not have recurrence. However, we show that this is not the case (appendix 1 pp 9–10).

The most common adverse events were fatigue, lethargy, and dry mouth, although these and other event types did not substantially differ between the trial groups (table 3; appendix 1 pp 11–12). All-grade fatigue occurred in 63 (25%) of 249 patients in the no ablation group versus 65 (28%) of 231 in the ablation group, lethargy occurred in 34 (14%) versus 32 (14%), and dry mouth in 24 (10%) versus 21 (9%). Fewer adverse events might have been expected in the no ablation group than in the ablation group, but the clinical assessment was done 2 months after the initial stimulated thyroglobulin measurement (and ablation for those who had it). The majority of adverse events are transient, meaning any difference between the trial groups would probably not be seen by this time. Health-related quality of life assessed using the QLQ-C30 was not affected by having ablation or not (appendix 1 p 18). Across 28 quality-of-life domains, the least squares mean differences in quality-of-life score (no ablation *vs* ablation) at 2 months after the initial stimulated thyroglobulin (and ablation for those randomly assigned to have it) ranged from −1·9 (99% CI −6·6 to 2·9), for social functioning, to 2·7 (−2·1 to 7·4), for pain, on a scale of 0 to 100 (all p values >0·14). One quality-of-life feature was the requirement to avoid contact with children. Once discharged from hospital, the 231 patients in the ablation group who received ablation were asked to avoid close and prolonged physical contact with children for a median of 4 days (minimum 0; 10th–90th percentile 1–15 days; IQR 2–9 days)

For the cost analysis, we observed that among the 231 patients who had ablation as randomly assigned,

44 (19%) received it as an outpatient and were discharged on the same day, and 105 (45%), 53 (23%), 24 (10%), and five (2%) spent 1, 2, 3, and 4 days in hospital isolation, respectively. For every 100 patients in the NHS diagnosed with low-risk thyroid cancer (as per our trial eligibility) and with the distribution of hospital admission as observed in the IoN trial, the cost of giving ^{131}I ablation is £213 000, which is the cost saving if all 100 patients did not have ablation. If only patients without pT3, pT3a, or N1a disease (90% of patients with low-risk thyroid cancer) avoid ablation, the cost saving is £193 000 per 100 patients. If those without pT3, pT3a, N1a, or multifocal tumours avoid ablation (54%), the cost saving is £115 000. Finally, if patients without pT3, pT3a, or N1a tumours, or post-surgical thyroglobulin concentrations of 2 ng/mL or higher avoid ablation (80%), the cost saving becomes £171 000.

We explored associations between baseline characteristics known to be risk factors in thyroid cancer and recurrence. However, given that there were only 17 recurrences, these subgroup analyses should be viewed as exploratory, and formal non-inferiority analyses would be underpowered so were not performed. In the per-protocol population, in both treatment groups combined, the crude recurrence rate was highest in patients aged 48 years or younger (12 [5%] of 241) and patients with pT3 or pT3a status (four [9%] of 45), N1a status (six [14%] of 44), or baseline post-surgical thyroglobulin concentrations 2 ng/mL or higher (six [12%] of 50; appendix 1 pp 13–15). The median thyroglobulin concentration, excluding those with TgAbs, was higher among patients with recurrences (2·1 ng/mL [range 0·1–57·6]) than patients without a recurrence (0·4 ng/mL [0·01–70·2]). When we analysed recurrence according to baseline tumour features in each trial group, recurrence rates were not numerically higher in the no ablation group than in the ablation group, for any high-risk feature (ie, pT3, N1a, or multifocal tumours or raised thyroglobulin; appendix 1 p 15). Among all 504 patients (appendix 1 p 14), the observed recurrence rate was higher for those with pT3 or pT3a tumours (four [9%] of 46 patients overall with pT3 or pT3a tumours *vs* 13 [3%] of 458 with pT1 or pT2 tumours), or N1a tumours (six [13%] of 47 with N1a *vs* 11 [2%] 457 with N0 or Nx).

Unstimulated baseline post-surgical thyroglobulin concentration of 2 ng/mL or higher appeared to have the strongest association with the risk of recurrence (HR 12·75 [95% CI 3·67–44·28], p<0·0001), followed by nodal status N1a (HR 2·90 [0·70–11·94], p=0·14) and multifocal tumours (HR 2·32 [0·61–8·83], p=0·22), although the nodal status and multifocal tumour associations were not statistically significant (appendix 1 p 16). We repeated these analyses according to stimulated thyroglobulin concentrations measured at the time of the initial neck ultrasound scan 8 weeks after surgery, and the adjusted HRs were 3·71 (95% CI 1·07–12·93, p=0·039) for thyroglobulin concentration 2 ng/mL or higher and 5·61 (1·63–19·36, p=0·0063) for thyroglobulin concentration 5 ng/mL or higher. A different thyroglobulin threshold to indicate a raised measurement (a marker of recurrence) is expected between patients who had ablation and those who did not, but we used a fixed threshold for our exploratory analysis given the small number of recurrences.

We also attempted to see whether there is a post-surgical (baseline) unstimulated thyroglobulin value that can be used to predict recurrences (appendix 1 p 17). A thyroglobulin threshold of 2 ng/mL or higher identified nine (56%) of 16 recurrences using all thyroglobulin readings and seven (58%) of 12 recurrences excluding samples with TgAbs, with corresponding false-positive rates of 11% (50 of 441) and 13% (44 of 349). These findings are exploratory, as of the 17 recurrences overall, 16 had available thyroglobulin readings and 12 excluded samples with TgAbs; however, they support the general clinical view that thyroglobulin concentrations of 2 ng/mL or higher can be used to identify patients for closer monitoring.

Discussion

Long-term follow-up of the IoN trial shows that ablation is unnecessary in patients with differentiated thyroid cancer, specifically those with pT1 or T2 tumours that are N0 or Nx, as patients who did not receive ablation did not have inferior 5-year recurrence-free rates compared with those who did have ablation.

For any randomised trial, conclusions typically apply to the types of patients who were recruited. For the IoN

	No ablation (N=249)		Ablation (N=231)	
	Grades 1–2	Grade 3	Grades 1–2	Grade 3
Depression	16 (6%)	0	18 (8%)	0
Dizziness	11 (4%)	1 (<1%)	16 (7%)	0
Dry mouth	24 (10%)	0	21 (9%)	0
Dysgeusia	2 (1%)	0	9 (4%)	0
Fatigue	61 (24%)	2 (1%)	65 (28%)	0
Headache	17 (7%)	0	14 (6%)	0
Hoarseness	18 (7%)	0	11 (5%)	0
Hypothyroidism	4 (2%)	0	7 (3%)	0
Lethargy	32 (13%)	2 (1%)	31 (13%)	1 (<1%)
Nausea	8 (3%)	0	13 (6%)	0
Neck pain	7 (3%)	0	9 (4%)	0
Salivary duct inflammation	0	0	3 (1%)	0
Sore throat	8 (3%)	0	11 (5%)	0
Tinnitus	5 (2%)	1 (<1%)	7 (3%)	0
Voice alterations	11 (4%)	0	10 (4%)	0
Any of the above (each patient counted only once)	101 (41%)	4 (2%)	102 (44%)	1 (<1%)

Data are n (%) and based on patients in the per-protocol dataset. Events listed occurred up to 2 months after the initial stimulated thyroglobulin measure in all patients, which corresponds to 2 months post-ablation in patients given ablation. Adverse events not of specific interest (ie, not typically expected with ablation) are in appendix 1 (p 11). Grades are based on the worst Common Terminology Criteria for Adverse Events grade given for each patient and each event type; no grade 4 events occurred in either group.

Table 3: **Adverse events of specific interest (typically expected with ablation)**

study, the non-inferiority conclusion would therefore apply to all disease stages. However, the higher crude recurrence rates seen for pT3 and N1a disease, as expected, lead us to be more cautious about stating that ablation is not required for these particular patients, despite subgroup analyses being underpowered (due to too few patients and events) and the recurrence rates not being numerically higher among patients with pT3 or N1a disease who did not have ablation. This is a clinical, not statistical, decision.

We therefore cannot confidently recommend either for or against ^{131}I ablation at this time for patients with pT3, pT3a, or N1a disease. 1·1 GBq ablation might have been insufficient for these particular patients, as it is typically not considered an adjuvant activity, and the number of recurrences could have therefore been lower had a higher activity been administered. Studies are ongoing to refine the risk of N1 disease and until they are published, clinicians should continue their current practice for treating pT3, pT3a, and N1a disease. Some clinicians will prefer to still offer ablation to these patients, but in some circumstances—for example, if patients with N1a disease have low or undetectable thyroglobulin concentrations and no adverse tumour features—not giving ablation could be considered along with close monitoring.

The conclusions from the ESTIMABL2 trial suggested that only patients with pT1 and N0 or Nx disease could avoid ablation,[9] which would include 107 patients in IoN (among the 231 patients in the ablation group who received ablation). In the IoN trial, 102 patients had pT2 and N0 or Nx disease; therefore, our conclusions indicate that the number of patients who can now avoid ablation is double that of the recommendations from ESTIMABL2.

The main advantages of avoiding ablation include no need for hospital admission or isolation and no treatment-related adverse events, including the risk of a future second malignancy.[18] Furthermore, even when patients are discharged after ablation, they are advised to avoid close contact with children for several days, which is an important issue for patients who have children to care for. Avoiding ablation also results in a substantial cost saving to the health-care provider. Societal benefits among patients are expected (eg, less time off work due to cancer care), as well as a positive environmental impact associated with less hospital attendance and reduced manufacture and use of radioiodine for ablation.[19]

Involvement of a patient with lived experience of differentiated thyroid cancer as a member of the trial management group was a major component of this trial from design through to conduct and interpretation. Several other key strengths of the IoN trial were wider eligibility than ESTIMABL2, recruitment from multiple NHS cancer centres representative of routine practice, the same assessment schedule for all patients, and a clinical primary endpoint of confirmed structural recurrence. A major strength is that 388 (77%) of the 504 patients had at least 5 years of follow-up (median 6·7 years), allowing us to show that recurrence-free rates are high and similar between the trial groups throughout this long period.

One potential limitation of the trial is that the number of recurrences (n=17) could be regarded as low. However, the non-inferiority margin was not exceeded and was statistically significant ($p_{non\text{-}inferiority}$=0·033); therefore, the trial was not underpowered for the primary analysis.

As only seven patients were aged 17–21 years in the IoN trial, our conclusions probably cannot be applied to patients in this young age group, in whom the biological behaviour of thyroid cancer differs from that in older patients. More research is needed to establish whether selected children and teenagers can be safely treated without ^{131}I ablation. Another limitation is that we did not routinely collect molecular data (eg, on *BRAF* and *TERT*) from trial patients. However, a nested study within ESTIMBL2 showed that the frequency of *BRAF* mutations did not differ substantially between patients with and without the primary endpoint (3-year event-free rate), so the presence of such mutations should not be an indication for ^{131}I ablation.[9] During follow-up, TSH suppression was maintained because this was standard UK practice when the trial first began and dynamic risk stratification was not widely implemented. Thyroglobulin testing could therefore have been less accurate than had TSH concentrations been elevated.

Finally, our cost analysis focused on the upfront savings to the NHS, and not patient costs and benefits over the whole care pathway, because these data were not collected. However, ablation does not improve overall survival in these patients with low-risk disease[10] and we found no important difference in quality of life or adverse events, so quality-adjusted life-years or cost per quality-adjusted life-year have little relevance.

IoN and ESTIMABL2 help to resolve the controversy regarding the value of postoperative radioiodine in patients with low-risk disease, for which no evidence from large randomised trials with long follow-up was available.[20–22] Observational studies had mixed findings on whether ablation is necessary.[23–26] ^{131}I ablation[27,28] might be beneficial for intermediate-risk disease as defined by the American Thyroid Association.[10] Ablation is still used worldwide, particularly outside of the USA, although its use has decreased[29] as more patients are offered hemithyroidectomy, which is not followed by ablation.

Three important questions for clinical practice are whether selected patients at low risk should still be offered ^{131}I ablation, as raised previously in the Discussion; how patients in whom ^{131}I ablation is omitted should be followed up, for how long, and by whom (surgeons, endocrinologists, oncologists, or primary care physicians), depending on specific health-care infrastructure and settings; and how TSH suppression should be used.

In our trial, 6-monthly thyroglobulin measurement was feasible and provided patients with reassurance when they did not have ablation. Thyroglobulin could be measured every 6–12 months for 3 years post-surgery, by which time most recurrences are seen. Dynamic risk stratification could also be considered to assess a patient's follow-up and therapeutic options.[30]

Neck ultrasound is routinely performed in some places (but not in other places such as the UK), along with thyroglobulin measurement. Therefore, health-care providers should examine local resources when considering the use and frequency of neck ultrasound. We concur with the ESTIMABL2 investigators that raised postoperative thyroglobulin concentrations could indicate the need for closer follow-up. Building on existing guidance, more data and consensus agreement could be obtained to specify an appropriate frequency of and thresholds for thyroglobulin monitoring, in addition to annual ultrasound as required, in patients who do not have ablation.[31,32]

We acknowledge that TSH suppression is no longer routinely performed after an excellent response following thyroidectomy in patients with low-risk disease. However, TSH suppression could be used alongside frequent follow-up in patients with pT3, pT3a, N1a, and perhaps multifocal tumours for up to 3 years or even 5 years, after which a clinical decision would be made as to whether to continue suppression.

Typical treatment for low-risk differentiated thyroid cancer changed from total thyroidectomy with high-activity ^{131}I ablation to low-dose ablation due to the results of the HiLo and ESTIMABL1 trials,[4,5] and total thyroidectomy alone without ^{131}I ablation in patients defined as having low-risk disease can now be recommended due to the results of the IoN and ESTIMABL2 trials.[9] The next step is to assess whether hemithyroidectomy can replace total thyroidectomy in selected patients. Some organisations already advocate hemithyroidectomy in some circumstances;[10,11,13] however, all evidence to date on hemithyroidectomy comes from observational studies with heterogeneous designs and findings,[33,34] including those reporting higher recurrence rates following hemithyroidectomy. The increasing use of hemithyroidectomy is concerning because patients worry about the risk of recurrence after hemithyroidectomy.[35] Several IoN investigators are conducting a randomised trial of hemithyroidectomy versus total thyroidectomy in patients with low-risk differentiated thyroid cancer (the HoT study, ISRCTN17004671). In the UK, the HiLo, IoN, and HoT trials represent a linked national programme of treatment de-escalation.

A change in UK policy to not offer ablation to all patients with suitably low-risk disease could mean that approximately 2500 patients could safely avoid ^{131}I ablation each year (if 70% of patients newly diagnosed with differentiated thyroid cancer would typically be given ablation).[36] If international policy was similarly changed, at least 400 000 patients could avoid ablation worldwide each year (assuming patients with pT3, pT3a, or N1a tumours still have ^{131}I ablation), acknowledging variation in guidelines between different geographical and health-care settings.

The IoN and ESTIMABL2 trials were designed at a similar time and to be complementary. Therefore, our conclusions and recommendations are based on the combined evidence from these two large, independent, multicentre, national randomised trials. Together, they provide level 1 evidence that convincingly shows that patients with pT1 tumours and no adverse features can avoid ablation (postoperative radioiodine), as this does not affect their risk of recurrence. Furthermore, ESTIMABL2 reported 5-year follow-up data that support their initial conclusion on non-inferiority.[37] IoN now adds to this evidence and indicates that pT2 tumours with no adverse features also do not need ablation. Evidence either for or against the need for ablation in pT3 or pT3a (not including follicular thyroid carcinoma >4 cm) or N1a tumours is insufficient. Guidelines can also outline recommended best-practice monitoring using thyroglobulin measurements and neck ultrasound after expert consensus, specifically in patients who do not have ablation; the IoN trial investigators are planning a position paper for UK practice. Most patients worldwide with low-risk differentiated thyroid cancer can now safely avoid ablation.

Contributors

UM, KN, JW, KF, and AH developed the trial concept. UM, KN, JW, KF, SJJ, TS, KG, MB, GG, and AH developed the trial design and protocol. AH did the statistical analysis. UM, KN, and AH wrote the first draft of the manuscript with input from all authors in the subsequent editing of the manuscript and agreed to be accountable for all aspects of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. AH and UM did the data analysis, had direct access to the data, and can verify the underlying data reported in the manuscript.

Declaration of interests

AP has received honoraria from Esai and the British Medical Ultrasound Society for presenting treatment options for differentiated thyroid cancer. KN has received honoraria from Esai for presenting treatment options for differentiated thyroid cancer. All other authors declare no competing interests.

Data sharing

Requests to have access to deidentified participant data can be made to ctc.ion@ucl.ac.uk. Proposals will be reviewed by members of the IoN Trial Management Group, and if accepted, a data sharing agreement will be put in place. Data would include efficacy, toxicity, and adherence variables that have formed the results in this Article.

Acknowledgments

We are very grateful to all patients and their carers who participated in this trial and the staff across all recruiting centres. We also thank Petros Perros, Simon Pearce, Andy Welch, Nicola Armstrong, Ian Pedley, and Andy James, who helped with trial conduct in Newcastle, and Anna Sawka, Caroline Kelly, and Martin Forster as the Independent Data Monitoring Committee for their valuable contributions and oversight during the trial. Finally, we thank Clive Harmer, who was involved in the initial trial concept and has been supportive of and involved in UK national thyroid cancer trials for many years. The trial was funded by Cancer Research UK, grant numbers CRUK/11/010 and

CTUQQR-Dec22/100009, with additional support from the University College London/University College London Hospitals Biomedical Research Centre.

References

1 Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2024; **74:** 229–63.

2 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019; **69:** 7–34.

3 Cancer Research UK. Thyroid cancer statistics. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/thyroid-cancer#heading-Zero (accessed Nov 27, 2024).

4 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.

5 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.

6 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.

7 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.

8 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.

9 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.

10 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.

11 Mitchell AL, Gandhi A, Scott-Coombes D, Perros P. Management of thyroid cancer: United Kingdom national multidisciplinary guidelines. *J Laryngol Rhinol Otol* 2016; **130:** S150–60.

12 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.

13 National Institute for Health and Care Excellence. Thyroid cancer: assessment and management. Dec 19, 2022. www.nice.org.uk/guidance/ng230 (accessed Nov 27, 2024).

14 Cooper DS. Radioiodine for low-risk thyroid cancer - the swinging pendulum. *N Engl J Med* 2022; **386:** 990–91.

15 Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85:** 365–76.

16 Girling D, Parmar M, Stenning S, Stephens R, Stewart L. Clinical trials in cancer. Oxford University Press, 2003.

17 Sjölander A. Regression standardization with the R package stdReg. *Eur J Epidemiol* 2016; **31:** 563–74.

18 Iyer NG, Morris LG, Tuttle RM, Shaha AR, Ganly I. Rising incidence of second cancers in patients with low-risk (T1N0) thyroid cancer who receive radioactive iodine therapy. *Cancer* 2011; **117:** 4439–46.

19 Nordberg LB, Pohl H, Haavardsholm EA, Lillegraven S, Bretthauer M. Carbon-footprint analyses in RCTs - toward sustainable clinical practice. *N Engl J Med* 2024; **390:** 2234–36.

20 Tuttle RM, Ahuja S, Avram AM, et al. Controversies, consensus, and collaboration in the use of ^{131}I therapy in differentiated thyroid cancer: a joint statement from the American Thyroid Association, the European Association of Nuclear Medicine, the Society of Nuclear Medicine and Molecular Imaging, and the European Thyroid Association. *Thyroid* 2019; **29:** 461–70.

21 Ullmann TM, Papaleontiou M, Sosa JA. Current controversies in low-risk differentiated thyroid cancer: reducing overtreatment in an era of overdiagnosis. *J Clin Endocrinol Metab* 2023; **108:** 271–80.

22 Pacini F. Postsurgical radioiodine ablation in low-risk differentiated thyroid cancer. *Lancet Diabetes Endocrinol* 2022; **10:** 379–81.

23 Satapathy S, Tupalli A, Chandekar KR, Ballal S, Bal C. Radioiodine versus no radioiodine outcomes in low-risk differentiated thyroid cancers: a propensity-score matched analysis. *Clin Endocrinol* 2023; **99:** 483–91.

24 Ilera V, Califano I, Cavallo A, Faure E, Vázquez A, Pitoia F. Is radioiodine ablation with 1.1 GBq (30 mCi) ^{131}I necessary in low-risk thyroid cancer patients? Results from a long-term follow-up prospective study. *Endocrine* 2023; **80:** 606–11.

25 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.

26 Carhill AA, Litofsky DR, Ross DS, et al. Long-term outcomes following therapy in differentiated thyroid carcinoma: NTCTCS Registry analysis 1987–2012. *J Clin Endocrinol Metab* 2015; **100:** 3270–79.

27 van Velsen EFS, Verburg FA. Adjuvant radioiodine for intermediate-risk papillary thyroid cancer-to treat or not to treat. *J Clin Endocrinol Metab* 2023; **108:** e1149–50.

28 Tian T, Qi Z, Huang S, Wang H, Huang R. Radioactive iodine therapy decreases the recurrence of intermediate-risk PTC with low thyroglobulin levels. *J Clin Endocrinol Metab* 2023; **108:** 2033–41.

29 Jacobs D, Breen CT, Pucar D, Holt EH, Judson BL, Mehra S. Changes in population-level and institutional-level prescribing habits of radioiodine therapy for papillary thyroid cancer. *Thyroid* 2021; **31:** 272–79.

30 Tuttle RM, Alzahrani AS. Risk stratification in differentiated thyroid cancer: from detection to final follow-up. *J Clin Endocrinol Metab* 2019; **104:** 4087–100.

31 Sipos JA, Aloi J, Gianoukakis A, et al. Thyroglobulin cutoff values for detecting excellent response to therapy in patients with differentiated thyroid cancer. *J Endocr Soc* 2023; **7:** bvad102.

32 Giovanella L, D'Aurizio F, Algeciras-Schimnich A, et al. Thyroglobulin and thyroglobulin antibody: an updated clinical and laboratory expert consensus. *Eur J Endocrinol* 2023; **189:** R11–27.

33 Chou R, Dana T, Haymart M, et al. Active surveillance versus thyroid surgery for differentiated thyroid cancer: a systematic review. *Thyroid* 2022; **32:** 351–67.

34 Chan S, Karamali K, Kolodziejczyk A, et al. Systematic review of recurrence rate after hemithyroidectomy for low-risk well-differentiated thyroid cancer. *Eur Thyroid J* 2020; **9:** 73–84.

35 Bongers PJ, Greenberg CA, Hsiao R, et al. Differences in long-term quality of life between hemithyroidectomy and total thyroidectomy in patients treated for low-risk differentiated thyroid carcinoma. *Surgery* 2020; **167:** 94–101.

36 Perros P, Mason D, Pearce M, Pearce SHS, Chandler R, Mallick UK. Differentiated thyroid cancer mortality by disease stage in northern England. *Clin Endocrinol* 2020; **93:** 61–66.

37 Leboulleux S, Bournaud C, Chougnet CN, et al. Thyroidectomy without radioiodine in patients with low-risk thyroid cancer: 5 years of follow-up of the prospective randomised ESTIMABL2 trial. *Lancet Diabetes Endocrinol* 2025; **13:** 38–46.