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Iodine or Not for Low-risk Differentiated Thyroid Cancer: How Should We Implement the Findings into UK Practice? An Expert Consensus Opinion

K. Newbold [*], N. Armstrong [†], M. Beasley [‡], K. Farnell [§], K. Garcez [¶], F. Hassan [||], S. Iqbal [†], V. Paleri [*], N. Reed [**], M. Strachan [††], J. Wadsley [‡‡], A. Hackshaw [§§], U. Mallick [†]

[*] *The Royal Marsden NHS Foundation Trust, London, UK*
[†] *Department of Oncology, Freeman Hospital, Newcastle, UK*
[‡] *Bristol Haematology & Oncology Centre, University Hospitals Bristol, Bristol, UK*
[§] *Butterfly Thyroid Cancer Trust, Newcastle, UK*
[¶] *Department of Clinical Oncology, The Christie Hospital, Manchester, UK*
[||] *Department of Nuclear Medicine, Guys and St Thomas' NHS Foundation Trust, London, UK*
[**] *The Beatson Oncology Centre, Glasgow, UK*
[††] *Department of Endocrinology, Western General Hospital, Edinburgh, UK*
[‡‡] *Department of Oncology, Weston Park Cancer Centre, Sheffield, UK*
[§§] *Department of Oncology, University College London Hospitals, London, UK*

Abstract

Aims: To develop a national consensus on how to implement findings of recent practice changing Iodine or Not (IoN) trial.
Materials and Methods: A multidisciplinary group of UK clinicians specialising in the management of thyroid cancer was convened to discuss the impact of the IoN trial on the management of early stage, low risk differentiated thyroid cancer in the UK. Virtual meetings were held to discuss the trial data and to develop a position statement on how to implement the findings ahead of changes in national guidelines.
Results: A position statement providing recommendations for the managemnet of early stage, low risk differentiated thyroid cancer based on the group consensus opinion and interpretation of the IoN trial data was defined.
Conclusion: The Iodine or Not (IoN) trial was a UK multicentre prospective randomised controlled trial that investigated the role of radioiodine ablation in early stage, low-risk differentiated thyroid cancer. The findings showed non-inferiority of omitting radioiodine in terms of recurrence-free survival. This provides level 1 evidence to support sparing many patients with low-risk thyroid cancer treatment with radioiodine and the possible associated treatment-related adverse events. Ahead of changes in national and international guidelines this multidisciplinary group of specialists involved in the management of thyroid cancer proposes a position statement on how to implement these findings into UK practice.

Key words: Cancer; consensus; IoN; radioiodine; thyroid

Introduction

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy. According to the latest Cancer Research UK data [1], there are around 3,900 new thyroid cancer cases in the UK every year. Since the early 1990s, thyroid cancer incidence rates in females have almost tripled (184%), and rates in males have increased by more

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Author for correspondence: K. Newbold, Thyroid Unit, The Royal Marsden NHS Foundation Trust, 203 Fulham Road, London, SW3 6JJ. UK.
E-mail addresses: kate.newbold@rmh.nhs.uk (K. Newbold), nicola.armstrong4@nhs.net (N. Armstrong), matthew.beasley@uhbw.nhs.uk (M. Beasley), butterfly1357@btinternet.com (K. Farnell), kate.garcez@nhs.net (K. Garcez), fahim-ul.hassan@gstt.nhs.uk (F. Hassan), shahid.iqbal@nhs.net (S. Iqbal), vinidh.paleri@rmh.nhs.uk (V. Paleri), nick.reed@nhs.scot (N. Reed), mark.strachan@nhs.scot (M. Strachan), Jonathan.wadsley1@nhs.net (J. Wadsley), a.hackshaw@ucl.ac.uk (A. Hackshaw), u.mallick@btinternet.com (U. Mallick).

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than two-and-a-half times (173%) (2016-2018) [1]. The majority are low-risk, early-stage cancers. Incidence rates for thyroid cancer are projected to continue to rise, by 74% in the UK between 2014 and 2035, to 11 cases per 100,000 people by 2035 [1]. Despite this steep rise in incidence, mortality rates from thyroid cancer remain stable in the UK with around 410 thyroid cancer deaths every year [1].

It can be inferred, therefore, that there are increasing numbers of patients who have been, and will be, successfully treated for thyroid cancer in the UK. Whilst cure is the primary goal of treatment, minimising treatment-induced morbidity for patients is also critically important, particularly in this population of patients who will have a normal life expectancy.

Historically, the standard approach to the treatment of early-stage thyroid cancer has been primarily surgical, with removal of the thyroid, (total thyroidectomy, TT), and involved lymph nodes. Radioiodine (RAI) is administered in the adjuvant setting to ablate normal thyroid remnant together with any remaining thyroid cancer. Finally, thyroxine replacement is dosed to supraphysiological levels in order to suppress the levels of thyroid stimulating hormone (TSH) to minimise the stimulation of growth of any persistent DTC cells through TSH receptors.

The management of thyroid cancer has therefore been a one-size-fits-all model with TT, RAI ablation, and long-term TSH suppression. The risk with this approach is that although outcomes in terms of survival and disease control are excellent, many patients receive more treatment than they need to achieve cure and hence are exposed unnecessarily to treatment-induced adverse events, some of which are long-term.

A good quality evidence base for the management of thyroid cancer has lagged behind that of more common cancers. This may be due to several factors. Thyroid cancer remains an uncommon cancer, therefore, requiring multicentre, often multinational, participation in trials to achieve adequate accrual and meaningful results. In addition, historically, it has been managed by a variety of specialities including endocrinology, nuclear medicine, oncology, endocrine, and ear, nose, and throat surgery, with little cross-speciality standardisation or collection of data.

It has been well recognised that the treatment approach is overly intensive for the majority of low-risk, good prognosis thyroid cancers. The UK set out to investigate the de-escalation of treatment in this cohort of patients with DTC. A stepwise approach was adopted.

Reducing Administered Activity of RAI for Ablation

The first step was to address the question of whether the activity of RAI administered for successful ablation could be safely reduced. The HiLo trial [2] was the seminal phase III clinical trial of higher versus lower activity of radioiodine, with or without recombinant human thyroid stimulating hormone (rhTSH) for thyroid remnant ablation. It was the first ever national, multicentre, prospective thyroid cancer trial in the UK and proved that the lower activity (1.1 GBq) with rhTSH or thyroxine withdrawal is non-inferior to the previous standard higher activity (3.7 GBq) in the treatment of low-to intermediate-risk DTC. This was confirmed by a similarly designed trial in France (Essai Stimulation Ablation, ESTIMABL) published concurrently [3]. These studies also proved that the lower activity resulted in reduced hospital isolation for the patient, reduced treatment-induced adverse events together with health economic benefits without affecting recurrence rates [2–4]. Practice, in the UK and internationally, changed as a result of these two trials.

Avoidance of RAI Ablation

The logical next step was to investigate the possibility of omitting RAI in a highly selected cohort of patients with low-risk DTC. Building on and working with the collaborative network of UK centres involved in the HiLo trial, the Iodine or Not (IoN) trial was conceived [5]. This was a randomised non-inferiority phase II/III multicentre UK trial in 570 patients with low-risk DTC. The inclusion criteria were more permissive than the low-risk groupings suggested by the American Thyroid Association (ATA) Guidelines [6] and included T3 (intrathyroidal, T3 TNM7 or T3a TNM8), N1a disease and minimally invasive follicular cancers with capsular invasion only up to stage T2 [7]. The main objective was to determine whether 5-year disease-free survival was no worse in the patients who did not have radioiodine ablation, compared with those who did receive it. The trial compared TT and TSH suppression therapy (TSHST) with TT, TSHST, and RAI ablation. An initial phase II feasibility study confirmed patient recruitment was adequate and the trial proceeded to a phase III study. A recurrence-free rate of 95% at 5 years with RAI ablation was assumed. The primary outcome measure was radiological structural locoregional recurrence or residual disease confirmed by tissue diagnosis on biopsy.

Careful consideration was given to the definition of 'low-risk' DTC based on available risk stratification criteria at the time of trial design [7]. Eligible patients were those with completely resected (R0) disease following total thyroidectomy and included the following: papillary thyroid cancer with non-aggressive histological features, stages pT1b (1-2 cm), pT2 (2-4 cm), pT3 intrathyroidal only, multifocal microcarcinoma and pN0, pN1a, and pNX; follicular thyroid and oncocytic (Hurthle as was at the time of protocol development and trial opening) cell cancer (minimally invasive with capsular invasion only) stages pT1b (1–2 cm) or pT2 (2–4 cm) [7].

Following TT, a baseline ultrasound (US) was carried out to ensure no residual macroscopic disease at least 2 months after surgery as well as a baseline thyroglobulin (Tg) on levothyroxine. Patients were then randomised to receive RAI (1.1 GBq) or not. Between 6 and 9 months later, both groups had a neck US and stimulated Tg. Patients were followed up for 5 years within the trial. Thyroglobulin was measured every 6 months on levothyroxine. Neck US was carried out every 6 months in the first year and then annually [7].

Five hundred four patients were recruited from 33 centres across the UK [7]. Two hundred fifty-one individuals were randomised to no RAI ablation and 253 to receive RAI

ablation. The 5-year event-free rates were 97.9% (ablation) vs 96.3% (no ablation). The 5-year absolute risk difference was 0.5 percentage points (95% CI, -2.2 to 3.2), showing that non-inferiority was achieved. During follow-up, there were no material differences in adverse events, quality of life, abnormal US scans, or thyroglobulin responses. There were higher recurrence rates in pT3/T3a or N1a tumours, or patients with post TT thyroglobulin, on levothyroxine, ≥2ng/mL, but this was regardless of whether they received ablation or not. Multifocality did not reach statistical significance for a risk factor for recurrence [7].

The only other randomised controlled trial assessing the omission of RAI in low-risk DTC was the ESTIMABL2 trial [8]. This was a similar design to IoN, prospectively randomising 730 patients with T1a(m), T1b, and node-negative DTC with no adverse features to RAI 1.1GBq or no RAI. The primary endpoint in this trial was the occurrence of events that included the presence of abnormal foci of radioiodine uptake on whole-body scanning that required subsequent treatment (in the radioiodine group only), abnormal findings on neck US, or elevated levels of thyroglobulin or thyroglobulin antibodies. At 3 years post randomisation, the percentage of patients without an event was 95.6% (95% CI, 93.0 to 97.5) in the no radioiodine group and 95.9% (95% CI, 93.3 to 97.7) in the radioiodine group, a difference of −0.3 percentage points (two-sided 90% CI, −2.7 to 2.2), a result that met the non-inferiority criteria. The non-inferiority between the two trial arms has been confirmed in an update at 5 years follow-up post randomisation [9].

Reduction in Extent of Surgery

The third step in treatment de-escalation is the reduction of the extent of initial surgery to less than a total thyroidectomy. This is currently being investigated within the third UK prospective randomised controlled trial, the HoT trial, hemithyroidectomy or total thyroidectomy (ISRCTN17004671). This trial is still actively recruiting.

Consensus Opinion

In this statement, we consider how to translate the IoN trial results into daily clinical practice in the UK. It was a pragmatic trial design [6], taking into consideration the variations in practice that were revealed in a survey of the management of a selection of cases for RAI ablation by clinical oncologists who treat thyroid cancer in the UK, Table 1 [personal communication Dr Shahid Iqbal]. This variability in UK practice has highlighted the need to form a consensus on the management of early thyroid cancer.

The NICE guidelines published in December 2022 [10] accepted the data from the ESTIMABL2 trial to recommend omitting RAI ablation in patients with T1 thyroid cancers with no adverse features and notably recommended a trial investigating the role of RAI ablation in T2 tumours.

For T1 N0 disease completely excised with no adverse features, both the IoN and ESTIMABL 2 trials provide us with high-quality evidence to be confident to recommend the omission of RAI ablation in these patients. The IoN trial extends this level 1 evidence to include T2 N0 disease with no adverse features, so we advise also including this subgroup in the recommendation to safely avoid RAI ablation. This is applicable to a significant proportion of patients in the UK (44% of those in the IoN trial); so worldwide, substantial numbers of patients can be spared from unnecessary RAI.

The IoN trial included patients with pT3 (TNM7)/T3a (TNM8) and those with N1a disease. The numbers in both these subgroups; however, were small, 45 and 44, respectively, and, therefore, how we manage patients with these stages of DTC requires further consideration. As an expert group of clinicians managing thyroid cancer in the UK, we do not feel that the IoN data are sufficient to recommend omission of RAI ablation in all patients with disease that falls within these subgroups. Examining the results in more detail, we see that recurrence rates were higher in both subgroups but numerically equivalent whether RAI was given or not [7]. An exploratory endpoint in the IoN trial examined the predictive value of postoperative serum thyroglobulin levels for risk of recurrence. The results suggest that patients with a postoperative Tg≥2 ng/mL may be at more at risk of recurrence [7]. We believe that patients with pT3 (TNM7)/T3a (TNM8) and those with N1a disease still need an individualised discussion within a multidisciplinary team when deciding whether a recommendation for RAI should be made. Postoperative Tg levels may play a part in these discussions.

It is also important to note the adverse features within the exclusion criteria of the IoN trial including positive resection margins, adverse histopathological subtypes such as tall cell, columnar cell, and diffuse sclerosing variants, widely invasive or poorly differentiated disease, more than four foci of vascular invasion in follicular thyroid carcinoma, lateral neck node involvement (N1b), and distant metastatic disease (M1). The following consensus statements do not apply to cases with any of these adverse features.

Consensus:

pT1 N0/Nx*

- RAI ablation not recommended.
  Concurs with: NCCN 2025, NICE 2022, ETA 2022, ESMO 2019, ATA 2015

pT2 N0/Nx*

- RAI ablation not recommended.
  Concurs with: NCCN 2025, ATA 2015; Differs from: NICE 2022 ‘Offer’ RAI; ETA 2022 consider RAI; ESMO 2019 not defined

pT1-2 and N1a

- Consider RAI ablation on an individual basis with Multidisciplinary Team (MDT) discussion.
  Concurs with: NCCN 2025, ETA 2022, ATA 2015; Differs from: NICE 2022 ‘Offer’ RAI; ESMO 2019 consider RAI

Table 1
A survey of the UK practice of choice of radioactive iodine therapy in differentiated thyroid cancer, post total thyroidectomy (respondent clinical oncologists: 21)

Case	Case description	No RAI (no.respondents)	1.1GBq (no.respondents)	3.7GBq (no.respondents)	5.5GBq (no.respondents)
1	32 yo F, PTC, 20% tall cell component. No vascular invasion. pT2 (m) pNx R0	1	13	7	0
2	70 yo M, 17.0 mm PTC, minimal ETE & microscopic invasion into strap muscles. Possible LVI. 2 central neck & 2 perithyroidal LNs negative. pT3b pN0 R0	0	10	11	0
3	56 yo F, angioinvasive oncocytic carcinoma (28 mm) with capsular & vascular invasion, intrathyroidal & completely excised. Mitotic activity 3/10 HPF & 'small-cell' areas. 6/10 LNs +ve from level 4. pT2 pN1b R0	1	1	19	0
4	24 yo F, follicular variant of PTC capsular invasion, no vascular invasion (44 mm), intrathyroidal & completely excised. pT3a NX R0.	3	16	2	0
5	59 yo M, PTC with extensive tall cell subtype. 19/35 LN +ve, 10 with ENE, pT4a (m) pN1b R1	0	0	18	3
6	44 yo F multifocal PTC, largest 12 mm, with 2 more smaller foci 4 and 1.1 mm. No LVI. 2/19 positive LNs. No ENE. pT1(m) pN1a R0.	3	14	4	0
7	28 yo F, 9mm classical PTC with no LVI. Tumour intrathyroidal & completely excised. One small normal peri-isthmic LN negative. pT1a pN0 R0. (Benchmark case)	21	0	0	0
8	61 yo M, widely invasive FTC (45mm), extensive LVI. Microscopic ETE into surrounding adipose tissue & skeletal muscle. pT3b Nx R1.	0	1	18	2

Abbreviations: ENE, extranodal extension; ETE, extra thyroidal extension; F, female; FTC, follicular thyroid carcinoma; LN, lymph nodes; LVI, lymphovascular invasion; M, male; PTC, papillary thyroid carcinoma; RAI, radioactive iodine; yo, year old.

pT3/T3a and N0/Nx

- Consider RAI ablation on an individual basis with MDT discussion.
  Concurs with: NCCN 2025, ETA 2022, ATA 2015; Differs from: NICE 2022 'Offer' RAI; ESMO 2019 'Consider' RAI

pT3/T3a and N1a

- Consider RAI ablation on an individual basis with MDT discussion.
  Concurs with: NCCN 2025, ETA 2022, ATA 2015; Differs from: NICE 2022 'Offer' RAI; ESMO 2019 'Consider' RAI

*If no adverse features present
NICE [11]; ETA [12]; ESMO [13]; ATA [7]; NCCN [14]

Follow-up of Patients Who Have Not Undergone RAI Ablation

Omitting RAI ablation necessitates a review of how we follow-up patients with early-stage DTC. Those who have had a TT (single or two-stage procedure) may have residual normal thyroid remnant and, therefore, interpretation of serum Tg levels may be less clear cut than in those patients who have had remnant ablation. The dynamic risk stratification (DRS) [15] that has become part of routine follow-up at 9 to 12 months post ablation has been reviewed, readjusted, and validated in patients who have had thyroidectomy alone [16]. In this retrospective study of 507 patients from two large centres, recurrent or persistent structural evident disease was observed in 0% of the 326 patients with excellent response to therapy (defined as non-stimulated Tg following TT $<$ 0.2 ng/mL and following lobectomy $<$30 ng/mL, undetectable Tg antibodies [TgAb], and negative imaging); 2 out of 152 (1.3%) of patients with indeterminate response (non-stimulated Tg for TT 0.2-5 ng/mL, stable or declining TgAb, and/or nonspecific imaging findings); 6 out of 19 (31.6%) of the patients with biochemical incomplete response (non-stimulated Tg for TT $>$ 5 ng/mL and for lobectomy $>$30 ng/mL and/or increasing Tg with similar TSH levels and/or increasing TgAb and negative imaging); 10 out of 10 (100%) patients with structural incomplete response ($P < .0001$) [16] This provides some reassurance that those patients with risk of disease recurrence can be reliably predicted based on response to treatment as assessed by serum Tg and

imaging, even when no RAI ablation has been given. These data and that presented by Durante *et al.* [17] suggest that if US shows no structural disease and Tg on a sensitive assay is undetectable at DRS, there is no need for surveillance ultrasound. A prospective study examining the sensitivity of the Elecsys Tg II assay provided further data supporting the excellent negative predictive value and acceptable positive predictive value of Tg, with values for sensitivity and specificity comparable between RAI-treated and non-RAI-treated groups [18]. A rise in Tg from an undetectable nadir will be sufficiently sensitive to detect an early recurrence.

In the IoN trial, both arms had baseline US post surgery to exclude macroscopic residue (disease). Only two cases in the IoN trial [8] and just 2.3% of patients in the HiLo trial [2] had a large remnant (multiple foci or one large focus) on the basis of pre-ablation scanning. This likely reflects the centralisation of thyroid surgery to high volume units in the UK and specifically in the centres participating in these two trials. This, however, cannot be safely assumed in real-world practice and, therefore, the relatively cost-efficient (compared to RAI ablation) utilisation of neck US post surgery would seem a reasonable safety net where omission of RAI ablation is considered.

Dynamic risk stratification should be undertaken at 9 to 12 months. If US does not show structural disease, Tg is <0.2 ng/mL and no Tg Ab, we would recommend 6 to 12 monthly Tg with US on demand for rising Tg for the first 3 years (it should be noted that 13/17 recurrences in IoN occurred within 3 years of randomisation [7]). TSH suppression could also be reduced, aiming for a target TSH of 0.3–2.0 mIU/L. Thereafter, Tg should be assessed annually and discharge considered at 5 years.

Consensus:

- **Post surgery**
  Patients who have had total thyroidectomy but who do not undergo RAI ablation consider baseline neck US around 3 to 6 months post surgery to exclude macroscopic residual disease.
  Concurs with: NCCN 2025 US 6–12 months; NICE 2022 US 6–12 months; ATA 2015 timing of US not specified; Differs from: ESMO 2019: US 6–18 months; ETA 2022 not discussed
- **Follow-up during 12 months post surgery**
  Follow-up of patients who have had total thyroidectomy, but not undergone RAI ablation, should include 3 to 6 monthly serum Tg in the first year post surgery.
  Concurs with: NCCN 2025 Tg and TgAb 6–12 weeks; Differs from: NICE 2022 does not specify timings of serum Tg; ESMO 2019 serum Tg at 6–18 months; ATA 2015 serum Tg every 6–12 months; ETA 2022 not discussed
- **Dynamic risk stratification**
  DRS should be carried out at 9 to 12 months using neck US and non-stimulated serum Tg*.
  Concurs with: NICE 2022; ESMO 2019; ATA 2015; Differs from: NCCN 2025 DRS not specified, annual Tg and TgAb and US as clinically indicated; ETA 2022 not discussed
- **Ongoing follow-up**
  Excellent responders at DRS should then have annual serum Tg (with neck US if rising Tg) and consider discharge at 5 years.
  Concurs with: NCCN 2025 except discharge not discussed. NICE 2022 annual Tg and US if clinically indicated with discharge considered between 2 and 5 years; Differs from: ESMO 2019 12–24 monthly; ATA 2015 not specified; ETA 2022 not discussed
- **Discharge at 5 years**
  At discharge, all cases should have Tg <0.2ng/mL* with no Tg antibodies and neck US negative for persistent or recurrent disease.
  Concurs with: NICE 2022; Differs from: NCCN 2025 not discussed; ETA 2022 not discussed; ESMO 2019 not specified; ATA 2015 not specified

*This assumes sensitive thyroglobulin assay available. If this is not the case, consider stimulated thyroglobulin <1ng/mL

NICE [11]; ETA [12]; ESMO [13]; ATA [7]; NCCN [14]

TSH Suppression in Patients Who Have Not Undergone RAI Ablation

In the IoN trial, all patients had TSH suppression to <0.1 for 5 years of follow-up [7]. When IoN was designed, this was the prevalent practice in the UK prior to the adoption of DRS and relaxation of TSH suppression following an excellent response in low-risk patients. The level or duration of TSH suppression, if any, in patients in the ESTIMABL2 trial was not specified [8,9]. Current UK practice is to follow recommendations based on DRS outcome and to relax TSH suppression from <0.1mIU/L after the first year post initial treatment if excellent response has been achieved. Indeed, a large population-based retrospective cohort study of 26,336 patients with low-risk DTC concluded that there was no difference in clinically significant recurrence in those with low-risk DTC maintained with a TSH of 0.5 to 2 mIU/L compared with 2 to 4 mIU/L [19]. Our consensus opinion is to relax TSH suppression (to 0.3-2.0mIU/L) according to DRS in patients with T1-T2 N0, who have undergone TT but no RAI ablation. The extent and duration of TSH suppression may be a factor to be considered by the MDT as an additional precaution in those patients with a higher risk of recurrence— T3/T3a, N1a, post TT baseline Tg > 2, multifocal disease, and in whom an MDT decision is to omit RAI ablation.

Consensus:

- **TSH suppression**
  Consider TSH suppression to <0.1mIU/L in patients who have had total thyroidectomy but not undergone RAI ablation following surgery until DRS at 9 to 12 months.

Differs from: NCCN 2025 no TSH suppression if no evidence of structural or biochemical persistent disease, persistent Tg (level not defined) TSH 0.1-0.5; NICE: no TSH suppression where ablation omitted*; ESMO 2019 not defined; ATA 2015 TSH 0.1-0.5; ETA 2022 not discussed

- **TSH suppression post DRS**
  TSH levels should be adjusted according to response assessed at 9-12 month DRS [15].
  Differs from: NCCN 2025 no TSH suppression if no evidence of structural or biochemical persistent disease, persistent Tg (level not defined) TSH 0.1-0.5.
  Concurs with: NICE 2022; ATA 2015; ETA 2022 not discussed; ESMO 2019 not discussed

*referred to pT1 tumours only
NICE [11]; ETA [12]; ESMO [13]; ATA [7]; NCCN 2025 [14]

Conclusion

Building on the seminal HiLo trial, the IoN trial has provided a further huge step forward in the evidence base surrounding the role of RAI in the management of low-risk DTC. This will inform clinical decision-making that will lead to a significant number of patients avoiding RAI and the consequent reduction in treatment-induced morbidity, impact on quality of life, environmental radiation exposure, and burden on our health service.

The IoN trial provides evidence to change practice in early-stage, low-risk DTC and this necessitates adaptation of follow-up of this cohort of patients. This group of UK thyroid cancer specialists has considered and developed a consensus statement on how to interpret and integrate the IoN trial results into the management of low-risk DTC in the UK, filling the gap before national and international guidelines are reviewed and updated.

We are grateful to our patients and clinical colleagues for continuing to support these UK trials and thereby providing the thyroid cancer community with valuable data to inform and improve the management of DTC.

Author Contribution

1 K. Newbold contributed as guarantor of integrity of the entire study.

2 K. Newbold, A. Hackshaw, and U. Mallick contributed to study concepts and design.

3 K. Newbold contributed to literature research.

4 Contribution to clinical studies; experimental studies/data analysis and statistical analysis is not applicable.

5 K. Newbold, N. Armstrong, M. Beasley, K. Farnell, K. Garcez, F. Hassan, S. Iqbal, V. Paleri, N. Reed, M. Strachan, J. Wadsley, A. Hackshaw, and U. Mallick contributed to manuscript preparation.

6 K. Newbold, N. Armstrong, M. Beasley, K. Farnell, K. Garcez, F. Hassan, S. Iqbal, V. Paleri, N. Reed, M. Strachan, J. Wadsley, A. Hackshaw, and U. Mallick contributed to manuscript editing.

Conflict of interest

The authors declare no conflict of interest.

References

[1] Cancer Research UK. Cancer statistics reports for the UK, https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/thyroid-cancer.

[2] Mallick U, Harmer C, Yap B, Wadsley J, Clarke S, Moss L, *et al.* Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. *N Engl J Med* 2012;366:1674–1685.

[3] Schlumberger M, Catargi B, Borget I, Deandreis D, Zerdoud S, Bridji B, *et al.* Strategies of radioiodine ablation in patients with low-risk thyroid cancer. *N Engl J Med* 2012;366:1663–1673.

[4] Borget I, Bonastre J, Catargi B, Déandréis D, Zerdoud S, Rusu D, *et al.* Quality of life and cost-effectiveness assessment of radioiodine ablation strategies in patients with thyroid cancer: results from the randomized phase III ESTIMABL trial. *J Clin Oncol* 2015;33:2885–2892.

[5] Dehbi HM, 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 Jan;7:44–51.

[6] Mallick U, Harmer C, Hackshaw A, Moss L, IoN Trial Management Group. Iodine or Not (IoN) for low-risk differentiated thyroid cancer: the next UK National Cancer Research Network randomised trial following HiLo. *Clin Oncol (R Coll Radiol)* 2012 Apr;24(3):159–161.

[7] Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, *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* Jan 2016;26(1):1–133.

[8] Mallick U, Newbold K, Beasley M, Garcez K, Wadsley J, Johnson S, *et al.* Thyroidectomy with or without radioiodine ablation for low risk differentiated thyroid cancer patients: a UK randomised multicentre noninferiority trial (IoN). *Lancet* 2025;406:52–62.

[9] Leboulleux S, Bournaud C, Chougnet CN, Zerdoud S, Al Ghuzlan A, Catargi B, *et al.* Thyroidectomy without Radioiodine in Patients with Low-Risk Thyroid Cancer. *N Engl J Med* 2022;386(10):923–932.

[10] Leboulleux S, Bournaud C, Chougnet CN, Lamartina L, Zerdoud S, Do Cao C, *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* 2024;2.

[11] Thyroid cancer: assessment and management, https://www.nice.org.uk/guidance/ng230.

[12] Pacini e 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] Filetti S, Durante C, Hartl D, Leboulleux S, Locati LD, Newbold K, *et al*, ESMO Guidelines Committee. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol* 2019;30:1856–1883.
[14] www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf.
[15] Tuttle RM, Alzahrani AS. Risk Stratification in Differentiated Thyroid Cancer: From Detection to Final Follow-Up. *J Clin Endocrinol Metab* 2019;104(9):4087–4100.
[16] Momesso DP, Vaisman F, Yang SP, Bulzico DA, Corbo R, Vaisman M, *et al*. Dynamic Risk Stratification in Patients with Differentiated Thyroid Cancer Treated Without Radioactive Iodine. *J Clin Endocrinol Metab* 2016;101(7):2692–2700.
[17] Durante C, Montesano T, Attard M, Torlontano M, Monzani F, Costante G, on behalf of the PTC Study Group. 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(8):2748–2753. https://doi.org/10.1210/jc.2012-1123.
[18] Sipos J, Aloi J, Gianoukakis A, Lee L, Klopper J, Kung J, *et al*. Thyroglobulin Cutoff Values for Detecting Excellent Response to Therapy in Patients With Differentiated Thyroid Cancer. *J Endocr Soc* 2023;7(9):bvad102.
[19] Qiang JK, Sutradhar R, Everett K, Eskander A, Lega IC, Zahedi A, *et al*. Association Between Serum Thyrotropin and cancer Recurrence in Differentiated Thyroid Cancer: A population -Based Retrospective Cohort Study. *Thyroid* 2025 Feb; 35(2):208–215. https://doi.org/10.1089/thy.2024.0330.