ORIGINAL ARTICLE

Ablation with Low-Dose Radioiodine and Thyrotropin Alfa in Thyroid Cancer

Ujjal Mallick, F.R.C.R., Clive Harmer, F.R.C.P., Beng Yap, F.R.C.P., Jonathan Wadsley, F.R.C.R., Susan Clarke, F.R.C.P., Laura Moss, F.R.C.P., Alice Nicol, Ph.D., Penelope M. Clark, F.R.C.Path., Kate Farnell, R.C.N., Ralph McCready, D.Sc., James Smellie, M.D., Jayne A. Franklyn, F.Med.Sci., Rhys John, F.R.C.Path., Christopher M. Nutting, M.D., Kate Newbold, F.R.C.R., Catherine Lemon, F.R.C.R., Georgina Gerrard, F.R.C.R., Abdel Abdel-Hamid, F.R.C.R., John Hardman, F.R.C.R., Elena Macias, M.D., Tom Roques, F.R.C.R., Stephen Whitaker, M.D., Rengarajan Vijayan, F.R.C.R., Pablo Alvarez, M.Sc., Sandy Beare, Ph.D., Sharon Forsyth, B.Sc., Latha Kadalayil, Ph.D., and Allan Hackshaw, M.Sc.

ABSTRACT

BACKGROUND

It is not known whether low-dose radioiodine (1.1 GBq [30 mCi]) is as effective as high-dose radioiodine (3.7 GBq [100 mCi]) for treating patients with differentiated thyroid cancer or whether the effects of radioiodine (especially at a low dose) are influenced by using either recombinant human thyrotropin (thyrotropin alfa) or thyroid hormone withdrawal.

METHODS

At 29 centers in the United Kingdom, we conducted a randomized noninferiority trial comparing low-dose and high-dose radioiodine, each in combination with either thyrotropin alfa or thyroid hormone withdrawal before ablation. Patients (age range, 16 to 80 years) had tumor stage T1 to T3, with possible spread to nearby lymph nodes but without metastasis. End points were the rate of success of ablation at 6 to 9 months, adverse events, quality of life, and length of hospital stay.

RESULTS

A total of 438 patients underwent randomization; data could be analyzed for 421. Ablation success rates were 85.0% in the group receiving low-dose radioiodine versus 88.9% in the group receiving the high dose and 87.1% in the thyrotropin alfa group versus 86.7% in the group undergoing thyroid hormone withdrawal. All 95% confidence intervals for the differences were within ±10 percentage points, indicating noninferiority. Similar results were found for low-dose radioiodine plus thyrotropin alfa (84.3%) versus high-dose radioiodine plus thyroid hormone withdrawal (87.6%) or high-dose radioiodine plus thyrotropin alfa (90.2%). More patients in the high-dose group than in the low-dose group were hospitalized for at least 3 days (36.3% vs. 13.0%, P<0.001). The proportions of patients with adverse events were 21% in the low-dose group versus 33% in the high-dose group (P=0.007) and 23% in the thyrotropin alfa group versus 30% in the group undergoing thyroid hormone withdrawal (P=0.11).

CONCLUSIONS

Low-dose radioiodine plus thyrotropin alfa was as effective as high-dose radioiodine, with a lower rate of adverse events. (Funded by Cancer Research UK; ClinicalTrials.gov number, NCT00415233.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Mallick at the Northern Centre for Cancer Care, Freeman Hospital, Level 4, Freeman Rd., Newcastle upon Tyne, NE7 7DN United Kingdom, or at ujjal.mallick@nuth.nhs.uk.

N Engl J Med 2012;366:1674-85.

Thyroid cancer is the most frequently occurring endocrine cancer, with more than 2100 new cases each year in the United Kingdom and more than 48,000 in the United States.[1,2] Most cases are differentiated thyroid cancer, which is associated with a high 10-year survival rate (90 to 95%).[3]

Many patients with differentiated thyroid cancer undergo radioiodine ablation to remove residual normal thyroid tissue after surgery. Some nonrandomized studies have suggested that radioiodine ablation reduces rates of death and recurrence.[4-7] However, there is uncertainty over the dose (administered activity) of radioiodine required for effective ablation. A systematic review of randomized and observational studies (many small) was inconclusive as to whether low-dose radioiodine (1.1 GBq [30 mCi]) was associated with rates of ablation success that were similar to or lower than rates with high-dose radioiodine (3.7 GBq [100 mCi]).[8] In the United Kingdom, 2007 guidelines recommend the use of high-dose radioiodine.[9] Guidelines of the U.S. National Comprehensive Cancer Network (2010), the American Thyroid Association (2009), and a European consensus report (2006) indicate that clinicians can choose between the low dose and the high dose; the authors could not stipulate which to use without reliable evidence from large randomized studies.[10-12]

The use of a reduced dose of radioiodine has important advantages. Patients, many of whom are women with children, would spend less time in hospital isolation and have fewer side effects, especially a reduced risk of a second primary cancer caused by exposure to radioactive substances.[13,14] Lower-dose radiation also reduces financial costs incurred by the health service provider and reduces exposure to radioactive iodine in the environment.

Another important issue is that patients must undergo temporary thyroid hormone withdrawal 2 to 4 weeks before ablation. During this time, hypothyroidism develops in many patients, which reduces their quality of life and ability to function at home and work.

Thyroid hormone withdrawal can be avoided with the use of recombinant human thyrotropin (thyrotropin alfa). However, there is uncertainty over whether the use of thyrotropin alfa reduces rates of ablation success, especially with low-dose radioiodine.[8]

In this randomized, noninferiority, factorial study, called the HiLo trial, we aimed to determine whether low-dose radioiodine could be used instead of high-dose radioiodine and whether patients could receive thyrotropin alfa before ablation instead of thyroid hormone withdrawal.

METHODS

STUDY DESIGN

From January 2007 through July 2010, we conducted the study in 29 centers in the United Kingdom National Cancer Research Network. Approval was obtained from the national research ethics panel. All patients provided written informed consent to participate in the study. The study protocol is available with the full text of this article at NEJM.org.

PATIENTS

Eligibility criteria were an age of 16 to 80 years, a performance status of 0 to 2 (with 0 indicating normal function, 1 indicating that the patient is restricted in strenuous activity but ambulatory, and 2 indicating that the patient is capable of self-care but is unable to work), histological confirmation of differentiated thyroid cancer (including Hürthle-cell carcinoma) requiring radioiodine ablation[9,11]; tumor stage T1 to T3 with the possibility of lymph-node involvement but no distant metastasis and no microscopical residual disease (i.e., N0, NX, N1, and M0 in the tumor—node—metastasis [TNM sixth] staging system), and one- or two-stage total thyroidectomy, with or without central lymph-node dissection.

Exclusion criteria were the presence of aggressive malignant variants, including tall-cell, insular, poorly differentiated, and diffuse sclerosing thyroid cancer; anaplastic or medullary carcinoma; pregnancy; severe coexisting conditions; previous cancer with limited life expectancy; previous iodine-131 or iodine-123 preablation scanning; and previous treatment for thyroid cancer except surgery.

RANDOMIZATION AND STUDY TREATMENT

Patients were randomly assigned to one of four study groups: low-dose or high-dose radioiodine, each combined with thyrotropin alfa (Thyrogen, Genzyme) or thyroid hormone withdrawal. Randomization was performed centrally, with stratification according to center, tumor stage, and nod-

al stage. All patients were instructed to follow a low-iodine diet for 3 weeks before ablation.

Radioiodine ablation was recommended 1 to 6 months after surgery. Thyrotropin alfa was administered on each of the 2 days before ablation by intramuscular injection (0.9 mg). Among the patients undergoing thyroid hormone withdrawal, thyroxine (average dose, 200 μg per day) was discontinued 4 weeks before ablation in 11 patients, and triiodothyronine (average dose, 60 μg per day) was discontinued for 2 weeks in 204 patients; data were missing for 4 patients. Thyrotropin levels were similar in the thyroxine and triiodothyronine groups (median, 80.5 mU and 61.5 mU per liter, respectively; P=0.56).

Radioactive iodine-131 was administered at a dose of 1.1 GBq or 3.7 GBq, depending on the study group. Patients remained in hospital isolation until an assessment of radiation risk and clinical conditions permitted discharge.

ASSESSMENTS

Patients underwent physical examination and biochemical evaluation before surgery or ablation. A central review of a representative paraffin tumor block confirmed the histologic diagnosis.

On the day of ablation, preablation radionuclide scanning with 80 MBq technetium-99m pertechnetate given intravenously was performed to assess remnant size, and the results were subsequently reviewed centrally. The use of technetium-99m, instead of iodine-131 or iodine-123, prevents stunning (i.e., a lower uptake of radioiodine by thyroid cells during the subsequent ablation dose, which can reduce ablation success rates, particularly with lower doses, such as 1.1 GBq); imaging was performed 20 minutes later.[15] Also, thyrotropin was measured in the group undergoing thyroid hormone withdrawal to check that the level exceeded an empirical 30 mU per liter, a prespecified cutoff

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Thyrotropin Alfa		Thyroid Hormone Withdrawal	
	Low-Dose Radioiodine (N=110)	High-Dose Radioiodine (N=109)	Low-Dose Radioiodine (N=110)	High-Dose Radioiodine (N=109)
Age — yr				
Median	44	44	45	43
Range	20–82	21–76	17–73	18–77
Sex — no. (%)				
Male	33 (30)	17 (16)	30 (27)	31 (28)
Female	77 (70)	92 (84)	79 (72)	78 (72)
Not reported	0	0	1 (1)	0
Tumor stage — no. (%)				
T1	32 (29)	31 (28)	33 (30)	32 (29)
T2	52 (47)	53 (49)	53 (48)†	51 (47)
T3	25 (23)	25 (23)	24 (22)	26 (24)
Not reported	1 (1)	0	0	0
Nodal stage — no. (%)				
N0	66 (60)	62 (57)	66 (60)	63 (58)
N1	17 (15)	18 (17)	17 (15)	17 (16)
NX	27 (25)	29 (27)	27 (25)	29 (27)
Previous thyroid surgery — no. (%)				
Near-total thyroidectomy	2 (2)	0	0	1 (1)
Total thyroidectomy	46 (42)	34 (31)	31 (28)	49 (45)
Completion thyroidectomy	62 (56)	72 (66)	75 (68)	58 (53)
Not reported	0	3 (3)	4 (4)	1 (1)

Table 1. (Continued.)

Characteristic	Thyrotropin Alfa		Thyroid Hormone Withdrawal	
	Low-Dose Radioiodine (N=110)	High-Dose Radioiodine (N=109)	Low-Dose Radioiodine (N=110)	High-Dose Radioiodine (N=109)
Time from surgery to ablation — days				
Median	83	85	87	90
Range	29–532	15–317	32–369	28–354
Thyrotropin level on the day of ablation‡				
Median — mU/liter	100	100	68	68
No. of patients with <25 mU/liter	2	2	2	2
Thyroglobulin level on the day of ablation§				
Median — ng/ml	2.3	1.6	3.8	1.5
No. of patients with <2.0 ng/ml	25	30	23	33

* A low dose of radioiodine was defined as 1.1 GBq, and a high dose was defined as 3.7 GBq. There were no significant differences between the groups at baseline, except for thyrotropin levels, as indicated.
† In one patient, the tumor stage was later revised to T4.
‡ P<0.001 for the comparison among the four groups. Patients with a thyrotropin level of less than 25 mU per liter were included in the intention-to-treat analysis but were excluded from the sensitivity analysis. The protocol stated that only patients with a thyrotropin level of more than 30 mU per liter would be eligible for ablation, but those who had a level of more than 25 mU per liter were included in the analysis to account for assay imprecision.
§ This category includes only patients who were negative for thyroglobulin antibody. A total of 111 patients with a thyroglobulin level of less than 2.0 ng per milliliter were included in the sensitivity analysis, in which ablation success was based only on the diagnostic scan at 6 to 9 months. Each center used its own commercial thyroglobulin assay, with the lower limit of sensitivity ranging from less than 0.2 μg per liter to 5 ng per milliliter. P=0.16 for the between-group difference in median thyroglobulin levels. After ablation, 70 of the 111 patients had neck uptake on an iodine-131 scan, 22 (in whom iodine-131 scanning was not performed or the results were not available) had positive results on a technetium-99m scan, 12 had no uptake on the iodine-131 scan but had a positive technetium-99m scan, 2 had no uptake on the iodine-131 scan or the technetium-99m scan, and 5 had missing data.

value that was required for ablation (though patients with a thyrotropin level of more than 25 mU per liter were included in the analysis to allow for assay imprecision). In the thyrotropin alfa group, blood was obtained approximately 24 hours after the second injection.

Whole-body iodine-131 scanning was performed 3 to 7 days after ablation with the use of a gamma camera with high-energy collimators. Diagnostic whole-body scanning was performed 6 to 9 months after ablation with the use of iodine-131 (140 to 185 MBq). Uptake of iodine-131 in the thyroid bed was measured 48 hours after administration. Patients were instructed to start a low-iodine diet 3 weeks before the diagnostic scan and were given an intramuscular injection of 0.9 mg of thyrotropin alfa on days 1 and 2 before the scan. (A total of 140 patients had undergone thyroid hormone withdrawal before Genzyme began its participation in June 2009.) An iodine-131 capsule was administered on day 3, and the scanning and stimulated thyroglobulin testing were performed on day 5.

Serum samples were taken on the day of the diagnostic scanning. Thyroglobulin and thyroglobulin antibody were measured by immunometric assay (Tg-pluS, BRAHMS [analytical sensitivity, 0.08 ng per milliliter, functional sensitivity, 0.2 ng per milliliter]; and Tg-Ab, Roche) at a central laboratory; thyroglobulin was measured by radioimmunoassay at another central laboratory. Discordant results of immunometric assay and radioimmunoassay among patients who were positive for thyroglobulin antibody (>46 kU per liter) on the immunometric assay suggested assay interference, indicating that the thyroglobulin levels could be unreliable.[16]

The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) was used to evaluate patients' quality of life,[17] with surveys completed at the time of consent, on the day of ablation before radioiodine administration, and 3 months after ablation. On the day of ablation, patients also completed a questionnaire about thyroid cancer–specific symptoms and economic indicators, covering the previous 4 weeks. (The questionnaire is

provided in the Supplementary Appendix, available at NEJM.org.)

STUDY END POINTS

The primary end point was the success rate for ablation, which was defined as both a negative scan (<0.1% uptake on the basis of the region-of-interest method drawn over the thyroid bed) and a thyroglobulin level of less than 2.0 ng per milliliter at 6 to 9 months.[18,19] One of these criteria was used if the other was not available. The thyroglobulin level on immunometric assay was used if patients were antibody-negative (331 patients) or if they were antibody-positive and the results of immunometric assay and radioimmunoassay were concordant (13 patients) — in other words, if the level on immunometric assay was less than 2.0 ng per milliliter and the level on radioimmunoassay was less than 5.0 ng per milliliter. Only the scan result was considered for ablation success or failure for 94 patients: 22 patients who were antibody-positive with discordant thyroglobulin measurements, 4 patients with an unknown antibody status, and 68 patients for whom a serum sample was unavailable.

Sensitivity analysis was performed for patients whose thyroglobulin level on the day of ablation (on the basis of local assays) was less than 2.0 ng per milliliter in the absence of thyroglobulin antibodies (i.e., only the scan at 6 to 9 months was used to determine ablation success or failure). All but two of these patients had neck uptake on the technetium-99m scan or postablation iodine-131 scan.

Secondary end points were the number of days of hospitalization; adverse events during ablation and 3 months after ablation, according to the Common Terminology Criteria for Adverse Events, version 3.0[20]; tumor recurrence; quality of life; and socioeconomic factors.

STUDY OVERSIGHT

In 2009, Genzyme began providing the thyrotropin alfa that was used in the study but had no other involvement. The data were gathered by the Cancer Research UK and University College London Cancer Trials Centre (UCL Cancer Institute). All the authors vouch for the completeness and accuracy of the data and were responsible for trial coordination. All authors were involved in the writing of the manuscript and the decision to submit it for publication.

STATISTICAL ANALYSIS

The sample size was based on the difference in rates of ablation success between patients receiving low-dose radioiodine and those receiving high-dose radioiodine or between those receiving thyrotropin alfa and those undergoing thyroid hormone withdrawal. We assumed an ablation success rate of 80% for the high dose of radioiodine (or thyroid hormone withdrawal) and a maximum allowable difference of 10 percentage points (i.e., low-dose radioiodine or thyrotropin alfa should not have a success rate of less than 70%); independent peer reviewers agreed on the difference. We determined that an enrollment of 421 patients with nonmissing data would provide a power of 82%, with a one-sided P value of 0.05.

The differences between the two success rates are provided for each of the two main comparisons: low-dose versus high-dose radioiodine and thyrotropin alfa versus thyroid hormone withdrawal. Two additional comparisons reflected clinical practice: low-dose radioiodine plus thyrotropin alfa versus high-dose radioiodine plus thyroid hormone withdrawal and low-dose radioiodine plus thyrotropin alfa versus high-dose radioiodine plus thyrotropin alfa. Sensitivity analyses were performed to allow for 17 patients who did not undergo assessment at 6 to 9 months.

RESULTS

PATIENTS

Data on enrollment and outcomes are provided in Figure 1 in the Supplementary Appendix. The patients' characteristics were well balanced at baseline (Table 1). Of the 438 patients, 23% had stage T3 tumors, and 16% had lymph-node involvement; 17% had T1 tumors without lymph-node involvement, 5% had T1 tumors with lymph-node involvement, and 7% had T1 tumors with nodal involvement that could not be assessed; for patients with T2 tumors, the proportions were 30%, 5%, and 12%, respectively.

HOSPITAL ISOLATION

Patients receiving low-dose radioiodine spent less time in hospital isolation than did those receiving high-dose radioiodine, with 39.6% versus 7.1% requiring only 1 day in hospital isolation and 13.0% versus 36.3% requiring 3 days or more (P<0.001 for both comparisons) (Fig. 1). Table 1 in the Supplementary Appendix shows the distribution of

hospital stay in each of the four trial groups. The proportion of patients who spent 3 days or more in hospital isolation was lower in the group given thyrotropin alfa than in the group that underwent thyroid hormone withdrawal, regardless of the radioiodine dose.

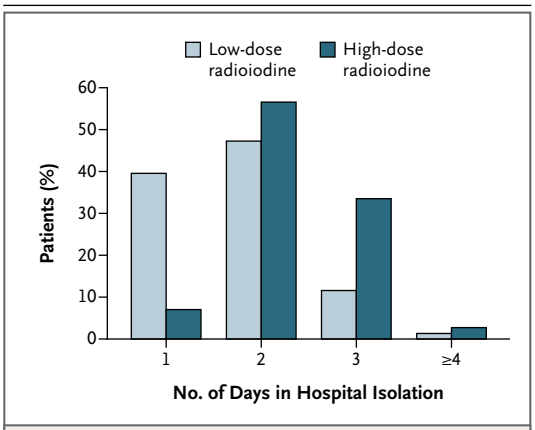

Figure 1. Days of Hospital Isolation, According to Radioiodine Dose.

Shown are the proportions of patients receiving low-dose radioiodine (1.1 GBq) or high-dose radioiodine (3.7 GBq) who spent 1 to 4 or more days in hospital isolation after ablation (P<0.001 by the chi-square test).

ABLATION SUCCESS

Only 2.3% of patients had a large remnant (multiple foci or one large focus) on the basis of preablation scanning, and the thyroglobulin level on the day of ablation was not strongly correlated with the outcome. For every increase of 0.5 ng per milliliter in the thyroglobulin level, the odds ratio for ablation failure was 1.02 among all patients (1.09 in the group receiving low-dose radioiodine plus thyrotropin alfa).

Ablation was successful in 182 of 214 patients (85.0%) in the group receiving low-dose radioiodine versus 184 of 207 patients (88.9%) in the group receiving the high dose (Table 2). The difference in the success rate for this comparison was –2.7 percentage points on the basis of scanning results alone and –3.8 percentage points on the basis of both scanning results and thyroglobulin level. The 95% confidence intervals were within the allowable difference of ±10 percentage points, so the success rate with low-dose radioiodine was considered to be noninferior to that with high-dose radioiodine.

The success rates were also similar in the comparison of thyrotropin alfa and thyroid hormone withdrawal, with successful ablation in 183 of 210 patients (87.1%) in the thyrotropin alfa group versus 183 of 211 patients (86.7%) in the group undergoing thyroid hormone withdrawal. The difference in the success rate for this comparison was 0.4 percentage points, and the 95% confidence interval was within ±10 percentage points.

Results for low-dose radioiodine plus thyrotropin alfa, as compared with either high-dose radioiodine plus thyrotropin alfa or high-dose radioiodine plus thyroid hormone withdrawal, were consistent with the main comparisons (with wider confidence intervals because of smaller sample sizes). There was no evidence of an interaction between radioiodine dose and method of preparation (thyrotropin alfa or thyroid hormone withdrawal) on success rates (P=0.51).

Table 2 in the Supplementary Appendix shows sensitivity analyses for patients for whom neither scanning results nor thyroglobulin levels were available. None of the rounded 95% confidence intervals had lower limits that exceeded –10 percentage points (i.e., all limits were consistent with noninferiority).

The treatment effects for patients with stage T3 tumors or lymph-node involvement were consistent with those for all patients (Table 3 in the Supplementary Appendix). The wider confidence intervals among results for these patients reflect smaller sample sizes. The difference in success rate with low-dose radioiodine versus high-dose radioiodine was –0.7 percentage points for patients with stage T3 tumors and 4.9 percentage points for those with lymph-node involvement. Logistic-regression analyses indicated that success rates did not differ significantly between the low dose and the high dose on the basis of either tumor stage (P=0.71 for interaction) or nodal stage (P=0.27 for interaction) (Table 4 in the Supplementary Appendix).

RETREATMENT AND RECURRENCE

A total of 21 patients (9.5%) receiving low-dose radioiodine were given a subsequent second dose, as compared with 9 patients (4.1%) receiving high-dose radioiodine (P=0.02). Among the 21 patients in the low-dose group, the second radioiodine doses were 1.1 GBq in 1 patient, 3 to 4 GBq in 8 patients, and more than 4 GBq in 12 patients. Among the 9 patients in the high-dose group, all second doses were more than 4 GBq. The second

Table 2. Ablation Success Rates at 6 to 9 Months, According to Four Comparisons of Radioiodine Doses and Methods of Preparation.*

Variable	Comparison 1		Comparison 2	
	Low-Dose Radioiodine	High-Dose Radioiodine	Thyrotropin Alfa	Thyroid Hormone Withdrawal
Ablation success based on diagnostic scan alone — no./total no. (%)	198/214 (92.5)	197/207 (95.2)	197/210 (93.8)	198/211 (93.8)
Risk difference (95% CI) — percentage points	–2.7 (–7.2 to 1.9)		–0.03 (–4.6 to 4.6)	
P value	0.26		0.99	
Ablation success based on thyroglobulin alone — no./total no. (%)	159/186 (85.5)	153/173 (88.4)	162/185 (87.6)	150/174 (86.2)
Risk difference (95% CI) — percentage points	–2.9 (–9.9 to 4.0)		1.4 (–5.6 to 8.3)	
P value	0.41		0.70	
Ablation success based on both diagnostic scan and thyroglobulin — no./total no. (%)	182/214 (85.0)	184/207 (88.9)	183/210 (87.1)	183/211 (86.7)
Risk difference (95% CI) — percentage points†	–3.8 (–10.2 to 2.6)		0.4 (–6.0 to 6.8)	
P value	0.24		0.90	
Risk difference on sensitivity analyses‡	–4.9 (–11.2 to 1.4)		0.4 (–6.0 to 6.8)	

* Patients were excluded from each comparison if they had neither diagnostic scanning nor thyroglobulin testing. Ablation success rates on the basis of both diagnostic scanning and thyroglobulin testing were similar between patients who were prepared for the diagnostic scan at 6 to 9 months with the use of thyrotropin alfa or thyroid hormone withdrawal plus either low-dose radioiodine (86.1% vs. 81.3%, P=0.37) or high-dose radioiodine (88.2% vs. 89.2%, P=0.89). CI denotes confidence interval.

† When patients with T3 or T2N1 disease were excluded from the analysis, the risk differences were –6.2% for comparison 1, +0.2% for comparison 2, –6.2% for comparison 3, and –7.6% for comparison 4.

‡ The sensitivity analyses excluded 8 patients who had a thyrotropin level of less than 25 mU per liter at the time of ablation, and only the diagnostic scan was used for 111 patients who were negative for thyroglobulin antibody and had a thyroglobulin level of less than 2.0 ng per milliliter on the day of ablation.

radioiodine dose was given mainly because clinicians were concerned about an initially positive scan or an increase in the thyroglobulin level at 6 to 9 months in patients receiving low-dose radioiodine, even though such results have been shown to normalize spontaneously over time.[21,22] After a median follow-up of 13 months (with ≥24 months of follow-up in 21% of patients), six recurrences were detected (three in each radioiodine-dose group) according to a combination of results on ultrasonography, fine-needle aspiration, and computed tomography.

ADVERSE EVENTS

During ablation and up to 1 week after the procedure, no patient had an adverse event with a severity grade of more than 2 (Tables 5 and 6 in the Supplementary Appendix). The proportion of patients who had any adverse event was 21% among those receiving low-dose radioiodine versus 33% among those receiving high-dose radioiodine (P=0.007), with rates of neck pain (7% vs. 17%) and nausea (4% vs. 13%) favoring the low-dose group. Rates of adverse events were similar in the thyrotropin alfa group and the group undergoing thyroid hormone withdrawal, though there was a trend favoring the thyrotropin alfa group (23% vs. 30%, P=0.11). Three months after ablation, the rates of adverse events were 27% in the low-dose group versus 24% in the high-dose group (P=0.55) and 27% in the thyrotropin alfa group versus 24% in the group undergoing thyroid hormone withdrawal (P=0.34).

Six patients had a serious adverse event with one in the low-dose group (a spinal fracture) and five in the high-dose group (vomiting of blood, chest pain [in two patients], pelvic pain, and acute renal failure). None of the events were deemed by the clinician in charge of the patient's care to be causally related to the trial interventions on the basis of clinical assessment. The rate of adverse events was lower for patients receiving low-dose radioiodine plus thyrotropin alfa (16%) than for those receiving either high-dose radioiodine plus thyroid hormone withdrawal (35%, P=0.001) or high-dose radioiodine

Comparison 3		Comparison 4	
Low-Dose Radioiodine plus Thyrotropin Alfa	High-Dose Radioiodine plus Thyroid Hormone Withdrawal	Low-Dose Radioiodine plus Thyrotropin Alfa	High-Dose Radioiodine plus Thyrotropin Alfa
100/108 (92.6)	100/105 (95.2)	100/108 (92.6)	97/102 (95.1)
–2.6 (–9.0 to 3.7)		–2.5 (–9.0 to 4.0)	
0.42		0.45	
81/96 (84.4)	72/84 (85.7)	81/96 (84.4)	81/89 (91.0)
–1.3 (–11.8 to 9.1)		–6.6 (–16.0 to 2.8)	
0.80		0.17	
91/108 (84.3)	92/105 (87.6)	91/108 (84.3)	92/102 (90.2)
–3.3 (–12.7 to 6.0)		–5.9 (–14.9 to 3.0)	
0.48		0.20	
–4.4 (–13.5 to 4.6)		–6.1 (–14.9 to 2.7)	

plus thyrotropin alfa (30%, P=0.01) (Table 7 in the Supplementary Appendix).

QUALITY OF LIFE AND ECONOMIC INDICATORS

There were no significant differences in quality-of-life scores on the SF-36 between patients receiving low-dose radioiodine and those receiving high-dose radioiodine (Tables 8 and 9 in the Supplementary Appendix). Before ablation, there were clear benefits among patients receiving thyrotropin alfa, as compared with those undergoing thyroid hormone withdrawal — namely, in physical and social functioning, role limitations, and energy or fatigue (P<0.001 for most comparisons). Similar differences were observed when the low-dose group receiving thyrotropin alfa was compared with the high-dose group undergoing thyroid hormone withdrawal. These effects were large: 30 to 40 units in favor of thyrotropin alfa with respect to combined categories of physical functioning and 38 to 40 units for combined categories of psychological functioning. No differences were seen 3 months after ablation for any comparison.

The thyroid cancer–specific survey showed that fewer patients receiving thyrotropin alfa than those undergoing thyroid hormone withdrawal had symptoms associated with hypothyroidism (P<0.001 for most comparisons) (Table 3). The proportion of patients with three or more symptoms was higher among those undergoing thyroid hormone withdrawal than among those receiving thyrotropin alfa (51.1% vs. 29.7%). Fewer patients who were receiving thyrotropin alfa had difficulty performing usual household activities or taking care of their children than did those who were undergoing thyroid hormone withdrawal; among patients who were employed, fewer who were receiving thyrotropin alfa had difficulty concentrating at work (9.4% vs. 22.1%, P=0.004) (Table 3, and Table 10 in the Supplementary Appendix).

On the basis of data in Figure 1 and an assigned cost of £443 ($704) per patient per day in hospital isolation (National Health Service tariff and itemized costs from Freeman Hospital), the estimated total costs for hospital stays for all 438 patients were £169,000 ($268,677) for those receiving low-dose radioiodine and £222,000 ($352,936) for those receiving high-dose radioiodine, for a relative reduction of 24% in the low-dose group. Among patients receiving low-dose radioiodine, the mean cost per patient was £1,356 ($2,156) among those receiving thyrotropin alfa and £776 ($1,234) among those undergoing thyroid hormone withdrawal; among patients receiving high-dose radioiodine, the mean cost was £1,582 ($2,515) among those receiving thyrotropin alfa and £1,056 ($1,679) among those undergoing thyroid hormone withdrawal, on the basis of the costs of thyrotropin alfa (£583 [$927] per patient) and the hospital stay. Cost estimates depend on the duration and costs of the hospital stay and the cost of

Table 3. Symptoms Reported by Patients during the 4 Weeks before Ablation.*

Symptom	Thyrotropin Alfa (N=219)	Thyroid Hormone Withdrawal (N=219)	Risk Difference (99% CI)†	P Value
	percent		*percentage points*	
Anxiety	15.1	18.3	−3.2 (−12.4 to 6.0)	0.37
Changes in menstrual cycle	4.1	5.5	−1.4 (−6.6 to 3.9)	0.50
Constipation	6.9	15.1	−8.2 (−15.8 to −0.6)	0.006
Depression	9.6	12.8	−3.2 (−10.9 to 5.7)	0.29
Increased sensitivity to cold temperatures	15.1	23.7	−8.6 (−18.3 to 1.0)	0.02
Difficulty concentrating	18.3	36.5	−18.2 (−29.0 to −7.5)	<0.001
Dry skin	14.2	20.1	−5.9 (−15.2 to 3.3)	0.10
Fatigue	29.7	48.9	−19.2 (−31.0 to −7.4)	<0.001
Hoarseness	11.0	18.3	−7.3 (−15.9 to 1.3)	0.03
Mood swings	14.6	16.9	−2.3 (−11.2 to 6.7)	0.51
Puffy face and hands	4.1	21.9	−17.8 (−25.8 to −9.8)	<0.001
Reduced sexual activity	19.6	21.0	−1.4 (−11.3 to 8.5)	0.72
Sleep disturbance	19.2	40.2	−21.0 (−31.9 to −10.1)	<0.001
Weight gain	12.8	23.7	−10.9 (−20.3 to −1.5)	0.003
No. of symptoms‡				
1	15.5	9.1	6.4 (0.3 to 12.5)	0.04
2	8.7	11.4	−2.7 (−8.4 to 2.9)	0.34
≥3	29.7	51.1	−21.4 (−30.4 to −12.5)	<0.001
Difficulty in performing usual activities at home	13.2	19.2	−6.0 (−15.0 to 3.1)	0.09
Difficulty in taking care of children at home§	8.1	14.5	−6.4 (−19.3 to 6.4)	0.19
Difficulty in performing usual activities at work¶	9.4	22.1	−12.7 (−23.9 to −15.6)	0.004

* Symptoms were reported in a questionnaire that was specific for thyroid cancer, which was completed on the day of ablation. Data shown are for patients who described their symptoms as either "moderate" or "a lot."

† A negative difference indicates that patients receiving thyrotropin alfa had better scores for symptoms or quality of life than did those undergoing thyroid hormone withdrawal. To allow for multiple comparisons, 99% confidence intervals were used.

‡ After consultation with their clinician, patients who underwent thyroid hormone withdrawal may have expected to have symptoms of hypothyroidism, which may have influenced the overall number of symptoms reported.

§ The percentages in this category are based on responses from 87 patients in the thyrotropin alfa group and 76 patients in the group undergoing thyroid hormone withdrawal.

¶ The percentages in this category are based on responses from 139 patients in the thyrotropin alfa group and 136 patients in the group undergoing thyroid hormone withdrawal.

thyrotropin alfa in a particular region; for example, in the United States, the list price for thyrotropin alfa is approximately $2,000, but for uninsured patients (approximately 16% or more of all patients), the direct charge could be greater.

The patient survey, which included questions about current employment, revealed that 44.6% of patients receiving thyrotropin alfa versus 28.7% of those undergoing thyroid hormone withdrawal continued to work without taking time off during the 4 weeks before ablation (P<0.001). The median number of days absent from work was 1 among patients receiving thyrotropin alfa versus 5 among those undergoing thyroid hormone withdrawal (P=0.17).

DISCUSSION

Our study answers two central questions involving radioiodine ablation of thyroid remnants after

surgery for differentiated thyroid cancer: namely, that the efficacy of low-dose radioiodine is similar to that of high-dose radioiodine, and that the efficacy of low-dose radioiodine ablation is not compromised by the use of thyrotropin alfa instead of thyroid hormone withdrawal. Previous small studies had conflicting results on both counts.[8,23]

Ablation success rates were similar for low-dose and high-dose radioiodine with either thyrotropin alfa or thyroid hormone withdrawal, including in subgroups of patients with T3 stage tumors and lymph-node involvement. We confirmed that patients receiving low-dose radioiodine and thyrotropin alfa had fewer early side effects, reported having a significantly better quality of life, and spent less time in hospital isolation than those receiving the high dose with either thyrotropin alfa or thyroid hormone withdrawal.[19,24] Outpatient ablation has been proposed for low-dose radioiodine.[24-26] This would reduce costs further, and the renal clearance of iodine-131 is faster with thyrotropin alfa than with thyroid hormone withdrawal. A combination of low-dose radioiodine and thyrotropin alfa would pose fewer radiation-protection issues, and the lower radiation exposure is likely to reduce the risk of late second cancers, satisfying the principle of exposure that is "as low as reasonably achievable" (referred to as ALARA).[19,23,24] As with other curable cancers (e.g., childhood cancers and lymphomas), it is important to reduce the risk of a radiation-induced second cancer, which might be less curable than the primary thyroid cancer.

The incidence of thyroid cancer is increasing worldwide (213,000 new cases in 2008),[27] including an increase by a factor of 2.6 in the United States from 1973 through 2006.[28,29] Unlike most other cancers, thyroid cancer affects young adults. Our findings have potential implications for improvements in treatment by making therapies safer, more cost-effective, and more convenient.

Our findings relate to ablation success at 6 to 9 months and do not address future recurrences. Long-term follow-up will be required to examine recurrence rates, which have previously been reported to be low in studies involving patients receiving low-dose radioiodine.[30,31]

Our study has several key strengths. We included T3 and lymph-node–positive tumors, and we avoided design limitations of previous studies as follows: histopathological findings were reviewed by central independent evaluators, only specialist surgeons were involved to reduce variation in the extent of surgery, and preablation scanning was performed with technetium-99m to assess remnant size by central review. Thyroglobulin levels were measured in two central laboratories by means of immunometric assay with thyroglobulin-antibody levels in one laboratory and by radioimmunoassay in the other. Furthermore, we assessed thyroid-specific symptoms and economic indicators on the basis of a fixed timeline (6 to 9 months) after ablation, using a specific definition of ablation success on the basis of both stimulated thyroglobulin testing and diagnostic scanning, and we collected tumor blocks for translational research.

We recommend surgery by specialist surgeons because in such cases a smaller thyroid remnant is generally found, as confirmed by the low percentage of patients (2.3%) with large remnants in our study and by consequently decreased levels of stimulated thyroglobulin at ablation. In our study, increased thyroglobulin levels were not strongly associated with ablation failure, as has been reported previously.[32]

Radionuclide scans were used for assessing ablation success, as reported previously.[19] Obtaining standardized results from high-resolution ultrasonography among all participating centers is difficult, since such findings are operator-dependent. Also, whether ultrasonography is superior to radionuclide scanning in assessing ablation success remains controversial.[33] We did not measure urinary iodide levels because patients followed a strict 3-week low-iodine diet, and the body iodine content does not affect the ablation outcome in such patients.[34]

A similar trial in France (ClinicalTrials.gov number, NCT00435851), involving 753 patients, had findings similar to those of our study regarding low and high doses of radioiodine and thyrotropin alfa and thyroid hormone withdrawal.[35] In that study, the design was similar to ours but patients with stage T3 tumors or stage T2 tumors with lymph-node involvement were excluded. Further differences are associated with the above-mentioned design strengths of our study. The results of a recent randomized, single-center trial involving 160 patients and comparing low-dose radioiodine with the high dose, with both groups undergoing thyroid hormone withdrawal, were similar to our findings.[36] Long-term

results of a randomized study involving 309 patients that compared radioiodine doses of 1.1, 2.2, and 3.7 GBq, with all patients undergoing thyroxine withdrawal, showed a similar rate of local relapse at 5 years, although more patients in the group receiving 1.1 GBq required a second radioiodine treatment.[37] In a trial involving 291 patients, 89 were randomly assigned to thyroxine withdrawal, 133 were assigned to triiodothyronine withdrawal, and 69 were assigned to receive thyrotropin alfa before receiving low-dose radioiodine; ablation success rates were similar in the three groups.[38] Nonrandomized studies of low-dose radioiodine and thyrotropin alfa had similar findings.[39]

Our study shows that for patients meeting our inclusion criteria, low-dose radioiodine plus thyrotropin alfa is an effective and convenient treatment with reduced radiation exposure, providing benefits to both patients and health care providers. Radioiodine use is increasing in the United States, with concern over who should receive it, particularly among patients with low-risk tumors.[40] Therefore, reducing the radiation exposure is a major step forward. The question about whether radioiodine ablation can be safely avoided in low-risk patients is currently being addressed in a randomized trial in the United Kingdom (NCT01398085).[41]

Supported by grants from Cancer Research UK (C18243/A5802) and University College London and the University College London Hospital Comprehensive Biomedical Research Centre.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank all the patients who participated in the study; the members of the thyroid multidisciplinary teams at the study sites (surgeons, endocrinologists, oncologists, nurses, pathologists, radiologists, nuclear medicine clinicians, biochemists, and other collaborators); the research nurses and trials unit staff from all recruiting centers; Reshma Bhat, Milena Toncheva, and Dhanesh Patel for data management and trial coordination; and pathologists Sarah Johnson, Tim Stephenson, and Ken Maclennan for performing the central reviews.

APPENDIX

The authors' affiliations (all in the United Kingdom) are as follows: Freeman Hospital, Newcastle (U.M.); Christie National Health Service (NHS) Foundation Trust, Manchester (B.Y.); Weston Park Hospital, Sheffield (J.W.); Velindre Cancer Center (L.M.) and University Hospital of Wales (R.J.) — both in Cardiff; Southern General Hospital, Glasgow (A.N.); University Hospitals Birmingham NHS Foundation Trust (P.M.C.) and the Department of Medicine, University of Birmingham Edgbaston (J.A.F.) — both in Birmingham; Butterfly Cancer Trust UK, Rowlands Gill (K.F.); Brighton and Sussex University Hospital, Brighton (R.M.); Guy's and St. Thomas' Hospital (S.C.), Chelsea and Westminster Hospital (J.S.), and University College London (S.B., S.F., P.A., L.K., A.H.) — all in London; Institute of Cancer Research (C.M.N.), and Royal Marsden Hospital (C.H., K.N.) — both in Sutton; Mount Vernon Hospital, Northwood (C.L.); Cookridge Hospital, Leeds (G.G.); Castle Hill Hospital, Cottingham (A.A.-H.); James Cook University Hospital, Middlesborough (J.H.); East Kent Hospitals University NHS Foundation Trust, Canterbury (E.M.); Norfolk and Norwich University Hospital, Norwich (T.R.); Royal Surrey County Hospital, Guildford (S.W.); and Royal Derby Hospitals, Derby (R.V.).

REFERENCES

1. Cancer Research UK. Thyroid cancer statistics — UK (http://info.cancerresearchuk.org/cancerstats/types/thyroid).
2. National Cancer Institute. Thyroid cancer (http://www.cancer.gov/cancertopics/types/thyroid).
3. Sawka AM, Thephamongkhol K, Brouwers M, Thabane L, Browman G, Gerstein HC. Clinical review 170: a systematic review and metaanalysis of the effectiveness of radioactive iodine remnant ablation for well-differentiated thyroid cancer. J Clin Endocrinol Metab 2004;89:3668-76.
4. 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.
5. Mazzaferri EL, Kloos RT. Current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 2001;86:1447-63.
6. Pacini F, Schlumberger M, Harmer C, et al. Post-surgical use of radioiodine (^{131}I) in patients with papillary and follicular thyroid cancer and the issue of remnant ablation: a consensus report. Eur J Endocrinol 2005;153:651-9.
7. Verburg FA, de Keizer B, Lips CJM, Zelissen PMJ, de Klerk JMH. Prognostic significance of successful ablation with radioiodine of differentiated thyroid cancer patients. Eur J Endocrinol 2005;152:33-7.
8. Hackshaw A, Harmer C, Mallick U, Haq M, Franklyn JA. ^{131}I activity for remnant ablation in patients with differentiated thyroid cancer: a systematic review. J Clin Endocrinol Metab 2007;92:28-38.
9. British Thyroid Association. Guidelines for the management of thyroid cancer: second edition. London: Royal College of Physicians, 2007 (http://www.british-thyroid-association.org/news/Docs/Thyroid_cancer_guidelines_2007.pdf).
10. Tuttle RM, Ball DW, Byrd D, et al. Thyroid carcinoma. J Natl Compr Canc Netw 2010;8:1228-74.
11. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214. [Erratum, Thyroid 2010;20:674-5.]
12. Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006;154:787-803. [Erratum, Eur J Endocrinol 2006;155:385.]
13. Rubino C, de Vathaire F, Dottorini ME, et al. Second primary malignancies in thyroid cancer patients. Br J Cancer 2003;89:1638-44.
14. 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.
15. Giovanella L, Suriano S, Ricci R, Ceriani L, Anton Verburg F. Postsurgical thyroid remnant estimation by (^{99}m) Tc-pertechnetate scintigraphy predicts radioiodine ablation effectiveness in patients with differentiated thyroid carcinoma. Head Neck 2011;33:552-6.
16. Spencer CA, Takeuchi M, Kazarosyan M, et al. Serum thyroglobulin autoantibod-

ies: prevalence, influence on serum thyroglobulin measurement and prognostic significance in patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab 1998;83:1121-7.
17. QualityMetric. SF-36v2 health survey (http://www.qualitymetric.com/WhatWeDo/GenericHealthSurveys/SF36v2HealthSurvey/tabid/185/Default.aspx).
18. Mazzaferri EL, Robbins RJ, Spencer CA, et al. A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. J Clin Endocrinol Metab 2003;88:1433-41.
19. Pacini F, Ladenson PW, Schlumberger M, et al. Radioiodine ablation of thyroid remnants after preparation with recombinant human thyrotropin in differentiated thyroid carcinoma: results of an international, randomized, controlled study. J Clin Endocrinol Metab 2006;91:926-32.
20. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (http://www.acrin.org/Portals/0/Protocols/common/resources/CTCAEv3.pdf).
21. Lim DJ, O JH, Kim MH, et al. Clinical significance of observation without repeated radioiodine therapy in differentiated thyroid carcinoma patients with positive surveillance whole-body scans and negative thyroglobulin. Korean J Intern Med 2010;25:408-14.
22. Pacini F, Agate L, Elisei R, et al. Outcome of differentiated thyroid cancer with detectable serum Tg and negative diagnostic (131I)I whole body scan: comparison of patients treated with high (131)I activities versus untreated patients. J Clin Endocrinol Metab 2001;86:4092-7.
23. Barbaro D, Verburg FA, Luster M, Reiners C, Rubello D. ALARA in rhTSH-stimulated post-surgical thyroid remnant ablation: what is the lowest reasonably achievable activity? Eur J Nucl Med Mol Imaging 2010;37:1251-4.
24. Molinaro E, Viola D, Passannanti P, et al. Recombinant human TSH (rhTSH) in 2009: new perspectives in diagnosis and therapy. Q J Nucl Med Mol Imaging 2009; 53:490-502.
25. Kloos RT. Survey of radioiodine therapy safety practices highlights the need for user-friendly recommendations. Thyroid 2011;21:97-9.
26. Willegaignon J, Sapienza M, Ono C, et al. Outpatient radioiodine therapy for thyroid cancer: a safe nuclear medicine procedure. Clin Nucl Med 2011;36:440-5.
27. Globocan 2008. Most frequent cancers: men (http://globocan.iarc.fr/factsheets/populations/factsheet.asp?uno=900).
28. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 2006;295:2164-7.
29. Cramer JD, Fu P, Harth KC, Margevicius S, Wilhelm SM. Analysis of the rising incidence of thyroid cancer using the Surveillance, Epidemiology and End Results national cancer data registry. Surgery 2010; 148:1147-52.
30. Brassard M, Borget I, Edet-Sanson A, et al. Long-term follow-up of patients with papillary and follicular thyroid cancer: a prospective study on 715 patients. J Clin Endocrinol Metab 2011;96:1352-9.
31. Powell C, Welsh L, Haq M, et al. Excellent long-term outcome following 1.1 GBq radioiodine remnant ablation for differentiated thyroid cancer. Presented at the European Thyroid Association 35th Annual Meeting, Krakow, Poland, September 10–14, 2011:P126. abstract.
32. Tamilia M, Al-Kahtani N, Rochon L, et al. Serum thyroglobulin predicts thyroid remnant ablation failure with 30 mCi iodine-131 treatment in patients with papillary thyroid carcinoma. Nucl Med Commun 2011;32:212-20.
33. Salvatori M, Perotti G, Giovanella L, Dottorini ME. Can an undetectable value of TG and a negative neck ultrasound study be considered reliable methods to assess the completeness of thyroid ablation? Eur J Nucl Med Mol Imaging 2010; 37:1039-40.
34. Tala Jury HP, Castagna MG, Fioravanti C, Cipri C, Brianzoni E, Pacini F. Lack of association between urinary iodine excretion and successful thyroid ablation in thyroid cancer patients. J Clin Endocrinol Metab 2010;95:230-7.
35. Catargi B, Borget I, Deandreis D, et al. Comparison of four strategies of radioiodine ablation in patients with thyroid cancer with low-risk of recurrence: the randomized, prospective ESTIMABL study. Presented at the 14th International Thyroid Congress, Paris, September 11–16, 2010. abstract.
36. Mäenpää HO, Heikkonen J, Vaalavirta L, Tenhunen M, Joensuu H. Low vs. high radioiodine activity to ablate the thyroid after thyroidectomy for cancer: a randomized study. PLoS One 2008;3(4):e1885.
37. Kukulska A, Krajewska J, Gawkowska-Suwińska M, et al. Radioiodine thyroid remnant ablation in patients with differentiated thyroid carcinoma (DTC): prospective comparison of long-term outcomes of treatment with 30, 60, and 100 mCi. Thyroid Res 2010;3:9.
38. Lee J, Yun MJ, Nam KH, Chung WY, Soh EY, Park CS. Quality of life and effectiveness comparisons of thyroxine withdrawal, triiodothyronine withdrawal, and recombinant thyroid-stimulating hormone administration for low-dose radioiodine remnant ablation of differentiated thyroid carcinoma. Thyroid 2010;20:173-9.
39. Rosario PW, Xavier AC. Recombinant human thyroid stimulating hormone in thyroid remnant ablation with 1.1 GBq 131Iodine in low-risk patients. Am J Clin Oncol 2012;35:101-4.
40. Haymart MR, Banerjee M, Stewart AK, Koenig RJ, Birkmeyer JD, Griggs JJ. Use of radioactive iodine for thyroid cancer. JAMA 2011;306:721-8.
41. Mallick U, Harmer C, Hackshaw A, Moss L. 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;24:159-61.