



High-dose radioactive iodine therapy is associated with decreased risk of recurrence in high-risk papillary thyroid cancer[☆]



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ABSTRACT

Objectives: We aimed to determine the effect of adjuvant radioactive iodine dose on recurrence rate in high-risk papillary thyroid cancer.

Methods: More than 1,500 patients treated for papillary thyroid cancer at high-volume centers in France and the United States from 2004–2014 were reviewed. Patients considered at high risk for recurrence per the 2015 American Thyroid Association guidelines were analyzed and grouped by initial radioactive iodine dose: intermediate (median 100 mCi) or high dose (median 150 mCi). Propensity score matching was performed to control for baseline characteristics.

Results: In a propensity-matched cohort of 66 patient pairs, there were equivalent rates of gross extrathyroidal extension (71% vs 71%, $P=1.00$), positive margins (55% vs 55%, $P=1.00$), lymph node metastases ≥ 3 cm (9% vs 9%, $P=1.00$), extranodal extension (32% vs 33%, $P=.85$), and distant metastases (2% vs 5%, $P=.31$). Over a median follow-up of 4.5 years (interquartile ratio 2.0–7.5 years), the intermediate-dose radioactive iodine group had a significantly higher rate of recurrence than patients in the high-dose radioactive iodine group: 24 out of 66 (36%) vs 13 out of 66 (20%), $P=.03$.

Conclusion: High-dose radioactive iodine is associated with lower recurrence rate compared with intermediate-dose radioactive iodine for patients with American Thyroid Association high-risk papillary thyroid cancer.

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Introduction

Radioactive iodine (RAI; ¹³¹I) is an effective therapy for well-differentiated thyroid cancers, such as papillary thyroid cancer (PTC), that demonstrate iodine uptake.¹ Given the dose-dependent side effects associated with administration of RAI, which range from xerostomia and salivary gland dysfunction to secondary malignancy, recent efforts have focused on optimal dose determination and attempts to identify patients who will benefit from therapy.^{2,3}

In contrast to historical patterns of RAI usage in which virtually all patients with PTC received treatment, multiple retrospec-

tive studies have suggested that a subset of low-risk patients with localized disease and nonaggressive histologic characteristics have no recurrence or survival benefit from postoperative RAI administration.^{4,5} In addition, 2 recent randomized trials for patients with intermediate-risk tumors without metastases had equivalent rates of ablation between low dose (30 mCi) and intermediate dose (100 mCi) RAI^{6,7}; this dose reduction is reflected in the 2015 American Thyroid Association (ATA) guidelines. However, although RAI does have an established benefit in recurrence and overall survival for patients with gross extrathyroidal extension (ETE) and distant metastases, the potential for dose reduction in adjuvant and treatment-dose RAI therapy has not been well elucidated in this group.^{4,8}

We aimed to identify the benefit of high-dose RAI (≥ 150 mCi) versus intermediate-dose RAI (100 mCi) in these high-risk patients. To address this question, we reviewed a sequential cohort of more than 1,500 patients with differentiated thyroid cancer from high-volume medical centers in France and the United States and

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selected only patients with ATA 2015 high-risk characteristics. Pursuant to respective national guidelines, almost all patients in the French cohort were treated with a lower initial dose of RAI than patients in the American cohort. Patient outcomes were compared using propensity score matching to control for baseline characteristics and used to evaluate the impact of RAI dose on tumor recurrence in high-risk patients.

Methods

Patient selection

All patients undergoing treatment for PTC at 2 high-volume centers in France and an unaffiliated high-volume center in the United States between 2004 and 2014 were retrospectively reviewed. Patients from all centers underwent post hoc stratification using the 2015 ATA guidelines, and only high-risk patients were included for analysis. Patients were considered high risk if they had any of the following characteristics: gross ETE (defined on gross pathologic analysis or identified by the surgeon at the time of operation), positive pathologic margins, distant metastases, lymph node metastases greater than 3 cm, or extranodal extension with at least 3 lymph nodes involved. Classical papillary thyroid cancer, follicular variant PTC, and tall cell variant PTC were included. There were no follicular carcinomas in this cohort. Poorly differentiated and anaplastic lesions and lesions of nonthyroidal origin were excluded, as were patients younger than age 18 years, those who did not receive RAI, and those with incomplete records of RAI administration. The primary endpoint was a composite metric of locoregional and distant recurrence.

Surgical approach

Before radioactive iodine administration, all patients underwent total thyroidectomy by a general surgeon trained in endocrine surgery with at least 5 years of experience. Both hospital systems provide high-volume, specialized care in endocrine surgery. Patients underwent preoperative workup at the discretion of the clinical team, consisting of baseline ultrasound imaging of the thyroid and cervical lymph nodes, fine needle biopsy, and baseline thyroid hormone levels. Central neck dissection (evaluation of level VI lymph nodes) was performed either prophylactically or because of the presence of suspicious lymph nodes on clinical examination or imaging; lateral neck dissection (evaluation of level II–IV lymph nodes) was performed only in the presence of suspicious lymph nodes in the lateral compartments on preoperative workup.

Radioactive iodine therapy and follow-up

After thyroidectomy, patients were given adjuvant RAI therapy at the discretion of the treating clinicians. In the United States, patients were routinely prepared with a low-iodine diet and either levothyroxine withdrawal or recombinant thyroid-stimulating hormone administration. In France, patients underwent levothyroxine withdrawal alone. Dosimetry was not routinely used in either country. With the exception of 2 patients, all French patients received an initial RAI dose of 100 mCi. RAI dosing in the American cohort ranged from 50 mCi to more than 400 mCi. For analysis, patients were grouped into intermediate-dose RAI (median 100 mCi, interquartile range [IQR] 100–100 mCi) versus high-dose RAI (median 150 mCi, IQR 149–158 mCi). Only the initial postoperative dose of RAI was considered for the primary analysis. After treatment, patients were followed every 6 to 12 months with ultrasound surveillance and serum thyroglobulin levels, with additional imaging obtained as clinically indicated. Time to follow-up was defined as the interval between the date of surgery and the date of

last surveillance imaging or bloodwork. Recurrence was defined as the development of structural disease on imaging and thereafter confirmed on histologic examination or by an elevation in serologic thyroglobulin level after a period of clearance. Local recurrence was defined as regrowth of malignant tissue in the thyroid bed that was not contained within lymph nodes.

Statistical analysis

Statistical analysis was performed using Stata 13.1 (Stata Corporation, College Station, TX). Propensity score estimation with 1:1 nearest neighbor matching was performed to control for baseline characteristics; patients were matched on presence of high-risk features, time to follow-up, histologic subtype, and presence of microscopic ETE. Categorical variables were compared using a χ^2 test. Student's *t* test was used to compare the means of parametric variables and Wilcoxon rank sum was used to compare nonparametric continuous variables. Adjusted logistic regression was used to identify risk factors for recurrence in the full cohort. This study was approved by the Institutional Review Boards at the respective institutions, and informed consent was obtained.

Results

Unmatched patient characteristics

More than 1,500 patients undergoing treatment for PTC were reviewed; 183 were classified as high risk by the ATA 2015 criteria (US cohort, $n = 106$; French cohort, $n = 77$) and were included for analysis. Patients were stratified into intermediate-dose RAI ($n = 117$) and high-dose RAI ($n = 66$). A total of 97% of French patients received an intermediate initial dose of RAI versus 36% of American patients ($P < .001$). In the unmatched cohort, baseline characteristics were dissimilar between groups, with more patients in the high-dose group having gross ETE (47/66, 71% vs 32/117, 27%; $P < .001$) and more patients in the intermediate-dose group having positive margins (97/117, 83% vs 36/66, 55%; $P < .001$) and microscopic ETE (76/117, 65% vs 16/66, 24%; $P < .001$).

Matched patient characteristics

To control for baseline characteristics, patients were propensity matched (C statistic 0.764) to create 66 matched pairs with reduction of bias between groups (Fig. 1). After matching, there were no differences in high-risk characteristics. There remained a greater percentage of female patients receiving intermediate-dose RAI (62/66, 94% vs 41/66, 62%; $P < .001$); patients were otherwise well matched between treatment groups (Table 1). All patients had undergone total thyroidectomy before receiving RAI, and 87% underwent central neck dissection with a median of 13 lymph nodes harvested (IQR 6–34, $P = .14$ between groups). In the intermediate-dose group, 29 out of 66 (44%) underwent lateral neck dissection at the initial operation vs 18 out of 66 (27%) in the high-dose group ($P = .05$). There was no difference in the number of patients with pathologic lymph node metastases in the central compartment (28/66, 44% in the intermediate-dose group vs 33 out of 66 (50%) in the high-dose group, $P = .38$) or the number of patients with pathologic lateral neck metastases (24/66, 38% vs 18/66, 27%, $P = .26$). BRAF V600E mutation status was only available for 19 patients and was therefore not included in the matched cohort.

Four patients with distant metastases at the time of presentation were included for analysis. One patient with a bony metastasis to the clavicle underwent clavicular resection at the time of thyroidectomy followed by 200 mCi of RAI in divided doses with

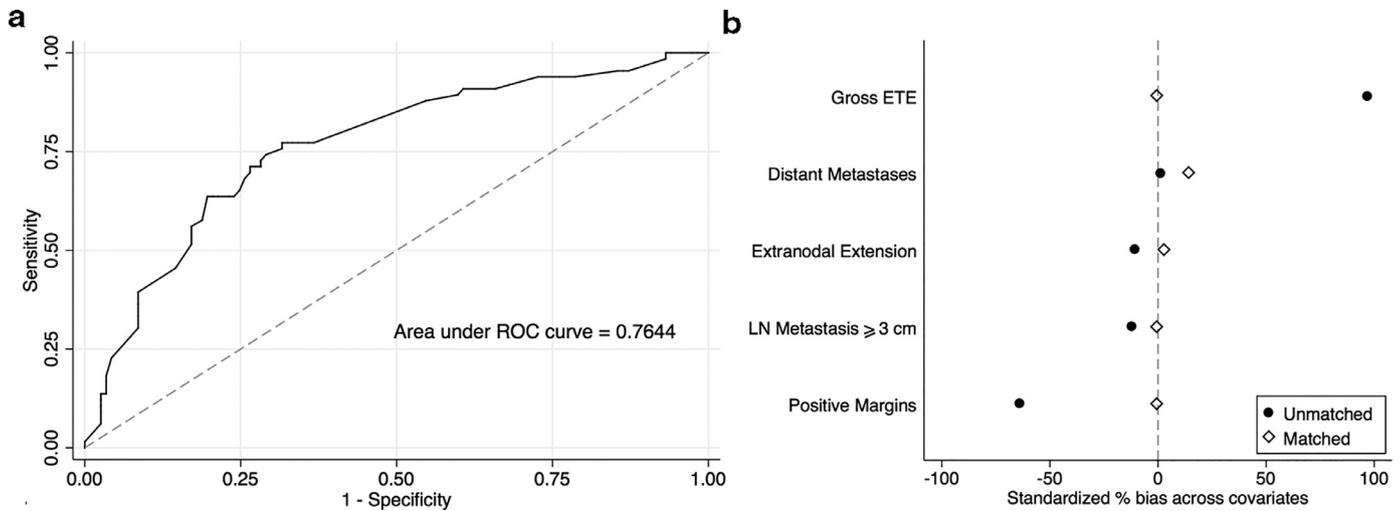


Fig. 1. Evaluation of propensity matching. (A) Receiver operating characteristic (ROC) curve. (B) Standardized bias of high-risk covariates before and after matching. *ETE*, extrathyroidal extension; *LN*, lymph node.

Table 1

Baseline patient and tumor characteristics in unmatched and matched cohorts.

	Unmatched			Matched		
	Intermediate dose (n = 117)	High dose (n = 66)	P	Intermediate dose (n = 66)	High dose (n = 66)	P
Age (y)	47 ± 15	47 ± 14	.89	51 ± 16	47 ± 14	.10
Female sex	93 (79%)	41 (62%)	.01	62 (94%)	41 (62%)	<.001
Country of origin			<.001			<.001
France	75 (64%)	2 (3%)		24 (36%)	2 (3%)	
United States	42 (36%)	64 (97%)		42 (64%)	64 (97%)	
Histology			.93			.92
Classical PTC	69 (59%)	37 (56%)		40 (61%)	37 (56%)	
Follicular variant PTC	22 (19%)	13 (20%)		8 (12%)	13 (20%)	
Tall cell variant PTC	26 (22%)	16 (24%)		18 (27%)	16 (24%)	
Nodule size (cm)	2.3 ± 1.9	2.4 ± 1.8	.76	2.6 ± 2.1	2.4 ± 1.8	.69
Multifocal	63 (54%)	28 (42%)	.14	18 (27%)	28 (42%)	.07
No. of lymph nodes, median (IQR)						
No. of LN positive	3 (1–9)	4 (1–10.5)	.37	3 (2–8)	4 (1–10.5)	.08
No. of LN harvested	14 (7–35)	11 (5–26.5)	.21	24 (9–40)	11 (5–26.5)	.14
Central neck dissection	93 (82%)	57 (86%)	.41	54 (87%)	57 (86%)	.90
Positive level VI lymph nodes	36 (31%)	33 (50%)	.001	28 (44%)	33 (50%)	.46
Lateral neck dissection	53 (46%)	18 (27%)	.01	29 (44%)	18 (27%)	.05
Positive level II–IV lymph nodes	40 (34%)	18 (27%)	.33	24 (38%)	18 (27%)	.26
Lymphovascular invasion	53 (45%)	26 (39%)	.44	30 (45%)	26 (39%)	.49
Microscopic ETE	76 (65%)	16 (24%)	<.001	23 (35%)	16 (24%)	.18
BRAF V600E mutation	1/4 (25%)	10/15 (67%)	.13	—	—	—
High-risk features						
Gross ETE	32 (27%)	47 (71%)	<.001	47 (71%)	47 (71%)	1.00
Incomplete tumor resection	97 (83%)	36 (55%)	<.001	36 (55%)	36 (55%)	1.00
LN metastasis ≥ 3 cm	15 (13%)	6 (9%)	.45	6 (9%)	6 (9%)	1.00
Extranodal extension	45 (38%)	22 (33%)	.49	21 (32%)	22 (33%)	.85
Distant metastases at diagnosis	5 (4%)	3 (5%)	.93	1 (2%)	3 (5%)	.31

LN, lymph node.

no recurrence of disease. The remaining 3 patients had disease recurrence as follows: a patient who underwent metastasectomy for a pulmonary metastasis and received 150 mCi of RAI after thyroidectomy who had disease recurrence in the lung after 5 years and underwent repeat metastasectomy; a patient with bony metastases treated with 150 mCi RAI who had disease recurrence with disseminated hepatic disease after 6 years; and a patient with diffuse lung metastases who was treated with 293 mCi with suppression of disease for 2 years until the development of recurrent pulmonary and diffuse abdominal disease.

Recurrence and follow-up

Over a median follow-up of 4.5 years (IQR 2.0–7.5 years, $P = .79$ between groups), matched patients in the intermediate-dose RAI

group had a significantly higher rate of recurrence than patients in the high-dose RAI group: 24 out of 66 (36%) vs 13 out of 66 (20%), $P = .03$ (Fig. 2). Time to recurrence was shorter in the intermediate-dose group than the high-dose group, median 0.8 years (IQR 0.4–4.0 years) vs median 2.5 years (IQR 1.3–6.1 years), $P = .03$. The most common site of recurrence in both groups was the cervical lymph nodes; the rate of lymph node metastases (20/66, 30% vs 8/66, 12%; $P = .01$) and local recurrence (11/66, 17% vs 3/66, 5%; $P = .02$) were both higher in the intermediate-dose group (Fig. 3). There was no difference in incidence of recurrence in the form of distant metastases between groups (9/66, 14% vs 5/66, 8%; $P = .26$). On multivariate analysis, the only independent predictor of recurrence was extranodal extension (odds ratio [OR] 3.5, 95% confidence interval [CI] 1.4–8.4; $P = .006$) (Table 2).

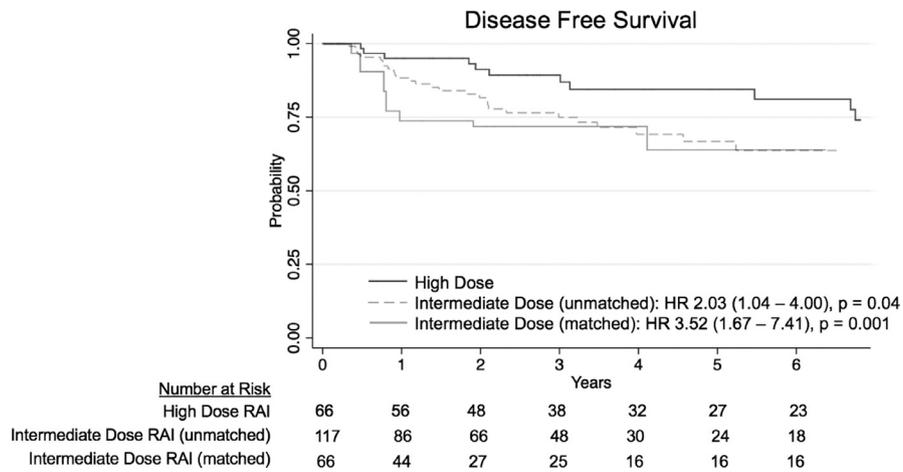


Fig. 2. Kaplan-Meier distributions of disease-free survival in high-dose, intermediate-dose (unmatched), and intermediate-dose (matched) groups. HR, hazard ratio; RAI, radioactive iodine.

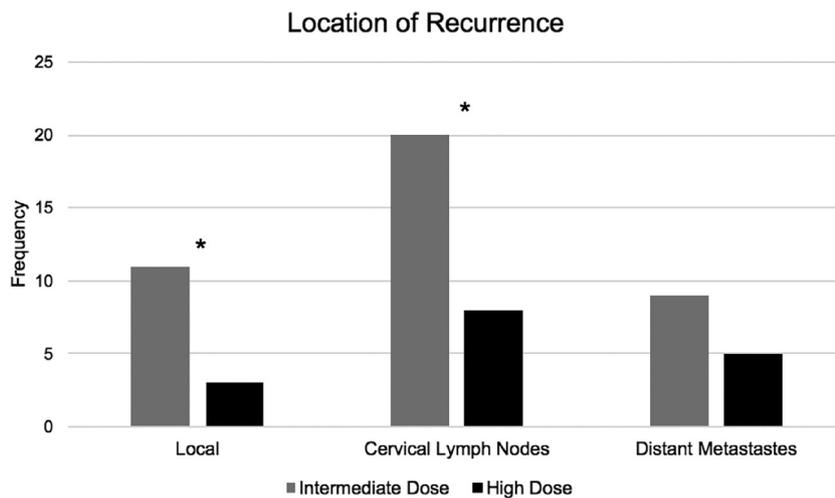


Fig. 3. Location of recurrence in matched cohort. *P < .05.

Table 2

Multivariate analysis of baseline tumor and patient characteristics as risk factors for recurrence.

	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Age > 45	0.9 (0.4–1.8)	.73	1.0 (0.5–2.4)	.91
Male sex	1.7 (0.8–3.5)	.17	1.2 (0.5–2.9)	.75
Country of origin				
United States	1	—	1	—
France	2.4 (1.2–4.7)	.02	1.7 (0.6–4.5)	.29
Histology				
Classical PTC	1	—	1	—
Follicular variant PTC	1.4 (0.6–3.2)	.48	1.3 (0.5–3.7)	.62
Tall cell variant PTC	0.9 (0.4–2.2)	.87	1.3 (0.5–3.5)	.61
High-risk features				
Gross ETE	0.9 (0.5–1.9)	.84	1.4 (0.6–3.6)	.45
Incomplete tumor resection	1.1 (0.5–2.4)	.77	1.2 (0.5–3.1)	.73
LN metastasis ≥ 3 cm	2.8 (1.1–7.3)	.03	1.2 (0.4–3.8)	.78
Extranodal extension	4.2 (2.1–8.7)	<.01	3.4 (1.4–8.4)	.01
Distant metastases at diagnosis	3.5 (0.8–14.6)	.09	4.4 (0.5–35.7)	.17

LN, lymph nodes.

There was one death in a patient 7.5 years after resection. This patient presented with distant metastases and received an initial dose of 150 mCi followed by an additional 600 mCi in divided doses for extensive disease that progressed to undifferentiated histologic stage.

Additional treatment and treatment of recurrence

Eight patients in the unmatched intermediate group and 2 patients in the matched intermediate-dose group received additional doses of RAI totaling between 100 to 200 mCi each because of per-

sistence of disease. Of patients who did have recurrence, those in the intermediate-dose group were more likely to be treated with additional doses of RAI with or without re-resection (17/24, 71% vs 3/13, 23%; $P = .005$). After all treatments, the median cumulative dose of RAI treatment was higher in the high-dose group (150 mCi, IQR 149–200 mCi) versus the intermediate-dose group (100 mCi, IQR 100–102 mCi), $P < .001$.

Final disease status was known for 31/37 (84%) patients after undergoing treatment for recurrence. At time of last follow-up, 15/31 (48%) had successful treatment of recurrence with no evidence of disease, 11/31 (35%) had stable disease, and 5/31 (16%) had progressive disease.

Adverse events

Adverse events from RAI occurred in 5 out of 63 patients (8%) in the high dose group and 0 out of 40 patients in the intermediate-dose group for whom data were available ($P = .07$). Parotiditis occurred in 2 patients, one of whom required surgical drainage of a secondary infection (250 mCi and 156 mCi, respectively). Two patients developed lacrimal gland stenosis requiring stenting (150 mCi, 446 mCi), and 1 patient had massive swelling of the salivary glands and temporary ageusia (150 mCi). An additional patient who received 293 mCi of RAI underwent planned hemodialysis after therapy because of preexisting chronic renal insufficiency. No patients were known to develop RAI-associated malignancy.

Discussion

In this study we evaluated the risk of disease recurrence in a propensity-matched cohort of patients with ATA 2015 high-risk differentiated thyroid cancer from 2 high-volume institutions with differing treatment algorithms. We found that for patients with gross extrathyroidal extension, positive margins, lymph node metastasis greater than 3 cm, extranodal extension, or distant metastases, a higher initial dose of radioactive iodine was associated with decreased locoregional recurrence.

Radioactive iodine administration for patients with high-risk differentiated thyroid cancer varies by institution, and there is no international consensus in expert guidelines. The ATA 2015 guidelines state that doses “up to 150 mCi are generally recommended” and that it is “uncertain whether... [doses] >150 mCi in this setting will reduce structural disease recurrence for T3 and N1 disease.”¹ Meanwhile, consensus guidelines of the French Societies of Nuclear Medicine, Endocrinology, Pathology, Biology, Endocrine Surgery, and Head and Neck Surgery in 2017 recommend administration of high-activity (ie, at least 100 mCi) RAI for high-risk patients; both sets of guidelines suggest repeated administration for patients without complete tumor response.⁹ These recommendations are reflective of a body of a literature that indicates a benefit of radioactive iodine in patients with advanced or metastatic PTC but has not yet defined the optimal dose for treatment.^{5,8,10}

Few studies have specifically addressed RAI dosing for high-risk patients. A European database study that included 434 patients with T3–T4 tumors without distant metastases found that higher initial dose of RAI (>81 mCi) resulted in higher complete response to therapy, lower cumulative dose of RAI, and lower recurrence and improved overall survival rates compared with RAI < 54 mCi.¹¹ Doses higher than 81 mCi were not specifically considered in this study, and no survival benefit to the higher dose was found when patients with distant metastases were considered. An additional single-institution retrospective review of 181 patients with N1b disease also found that doses of RAI as high as 150 to 260 mCi were associated with an improved initial response to therapy in patients older than 45 years.¹² In a nuclear

medicine study in which dosimetry was used to ensure protection of vulnerable tissue such as bone marrow, doses as high as 1,000 mCi were required for successful ablation of metastases.¹³ These findings, as well as those in the present study, suggest that therapeutic iodine administration for residual or metastatic disease may require higher dose RAI.

Even with optimal surgical and ablative therapy, the risk of recurrence is high in differentiated thyroid cancer with certain risk factors—up to 68% in some series and as high as 36% in the present analysis.¹⁴ In our cohort, extranodal extension was the only independent risk factor for recurrence. Other risk factors for recurrence include genetic mutations in BRAF V600E and TERT C228T; however, testing for these mutations is not yet routine in most centers, and this information was not available for the majority of the patients included here.^{15,16} Finally, initial response to treatment as a marker of response to radioactive iodine therapy has been found to be a strong predictor of eventual disease recurrence.¹⁴

In the present study, patients in the intermediate-dose group were more likely to be treated with additional iodine therapy at the time of recurrence, whereas patients receiving initial high-dose therapy were more likely to undergo repeat resection alone; this difference is due to institutional practice patterns between the 2 countries included in this study. Importantly, at time of last follow-up, there was no difference in the number of patients with undetectable disease, stable disease, or progressive disease after treated recurrence. Although this study was not powered to elucidate optimal treatment algorithms for recurrence, these findings suggest that multiple treatment algorithms for recurrence may be successful.

Adverse events can be limiting in the administration of high-dose RAI. In our population we had an 8% rate of complications from RAI in the high-dose group. Although patients with complications from RAI did require procedural intervention (such as lacrimal stenting), all patients had eventual resolution of their symptoms and no patients were known to develop RAI-related secondary malignancy. Regardless, the risk for developing hematologic and solid organ malignancies after ¹³¹I treatment is well known,^{17,18} and these risks must be balanced with the benefit of high-dose RAI.

As a retrospective study with inherent selection bias and potential for missing information, the largest limitation of this study is the potential for unmeasured confounders between these international populations. Although every attempt was made to present complete data with adjustment for confounders with the statistical design of propensity score matching, there is a potential for unmeasured differences in treatment technique or genetic differences between the populations that may influence the difference in recurrence rate found here. Unfortunately, primarily because of the timing of the study period, data were not available on mutational status for most tumors. In addition, the fact that RAI dosing was not controlled and was at the discretion of individual physicians means that intragroup variability in dose limits the ability to determine the specific dose that is best to treat high-risk disease. Finally, despite the use of propensity matching to control for baseline characteristics, the high-dose group contained a higher proportion of male patients, which is a known risk factor for recurrence¹⁹; however, this bias is in the opposite direction of our findings. Similarly, although there was no difference in the number of lymph node metastases to the lateral neck between groups, there were more patients in the intermediate-dose group who underwent lateral neck dissection, which must also be considered as a potential source of bias.

In conclusion, we found that RAI dose > 150 mCi was associated with a decreased recurrence rate in a propensity-matched cohort of patients with differentiated thyroid cancer with high-risk features. A prospective, randomized study is indicated.

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Discussion

Dr Tracy Wang (Milwaukee, WI): Very nicely presented. My 2 questions for you are if you can define recurrence—whether it's biochemical or structural—and related to that, the protocols for follow-up differed between the 2 institutions. Did you do withdrawal for scans routinely or did some use Thyrogen instead?

Dr Katherine D. Gray: The routines for our follow-up were very similar between the 2 countries. All patients underwent both biochemical testing including thyroglobulin levels as well as ultrasound every 6 to 12 months and then followed yearly. Recurrence was defined fairly rigorously. It was defined as the development of new structural disease seen on imaging. At times this was prompted first by a rise in thyroglobulin, but all of these recurrences were confirmed to have a structural component with identifiable disease.

With regards to RAI treatment, there actually were a couple of slight differences in the way that the patients were prepared. In the US, patients were prepared with a low-iodine diet as well as hormone withdrawal or recombinant TSH. The French patients were prepared using hormone withdrawal alone without recommending a low-iodine diet.

Dr Tracy Wang (Milwaukee, WI): Do you know the number of patients who had Thyrogen and whether there might have been differences in recurrence based on that?

Dr Katherine D. Gray: Unfortunately, we weren't able to capture that, but it's a great question.

Dr Ashok R. Shaha (New York, NY): Excellent study. You put in a lot of effort trying to analyze the philosophy of RAI postoperatively, and the analysis you have done is excellent.

A couple of questions: Was there any dosimetry done to decide the dose? Or was it just lump sum philosophy of the institution or the nuclear medicine department?

The second question I have is whether you have any data on re-treatment with RAI? For patients that recur, there was a time when we used to give RAI every 6 months if the scans were negative.

And the last question is, if you are using 150 mCi and telling me that the results are good and the complication rate is minimal, why not give 250 mCi? Thank you.

Dr Katherine D. Gray: Thank you very much for those questions. Dosimetry was not routinely used in either cohort. However, it was selectively employed for a few patients. The most significant example that I can recall was a patient that was treated with 450 millicuries of RAI in the US cohort who had underlying renal failure. Dosimetry was used to ensure tolerance of such a high dose.

Dr Ashok R. Shaha (New York, NY): And the last one, retreatment.

Dr Katherine D. Gray: We did look at how recurrences were treated. There were 37. What we found was that the French treat recurrences differently than the US does. The French tended to treat patients with additional doses of RAI at the time of identification of recurrence, plus or minus additional surgery. Whereas the US took the opposite approach and we tended to treat people with surgery alone and not with RAI.



The numbers are small. I did do a subanalysis to evaluate that and there was no difference. Of the patients that recurred that were treated in these 2 different manners, there was no difference on final follow-up of disease status. But the numbers are small, so it's a little hard to talk about that.

In terms of increasing RAI dose, it's known that there is a relationship between RAI therapy and the development of side effects. So I think that's where a prospective study would really be valuable, to identify what that optimal dose is. We all recognize that if you treat with 500 or 1,000 mCi, you are going to cause harm to the patient. So we want to make sure that we are treating with an appropriate dose that's eliminating the risk of recurrence but is also safe.

Dr Ashok R. Shaha (New York, NY): Is there an optimal dose in relation to sialadenitis?

Dr Katherine D. Gray: I think that there is the potential for salivary glandular side effects with even very low doses. I don't think that's something that we can predict.

Dr Scott Wilhelm (Cleveland, OH): Obviously your major area of recurrence was in cervical lymph node beds. Was the recurrence back in the bed where they had previous extranodal extension? Was it in the same bed? Was it on the opposite side? And for your patients that were high-risk for other reasons—people who had extra thyroidal extension of the primary tumor itself but then went on to develop nodal disease—were there differences in those groups?

Dr Katherine D. Gray: It's a great question and it would be valuable to have that information. At this point, the numbers got so small that we didn't do any sort of analysis like that, but that would be interesting to look at.

Dr Fiemu Nwariaku (Dallas, TX): My question is similar to Dr Shaha's. Was there a difference in the pattern of treatment? So, for instance, if people got 30 millicuries four times over the period versus 150 one time, was there a difference in their recurrence rate?

And then the 5-year endpoint is a little short. I'm sure many of these patients are still alive. Is there a way you can go back and look at the total amount of RAI that they received, particularly when you start thinking about secondary cancers in the long term?

Dr Katherine D. Gray: We did look at cumulative dosing. The median cumulative dose in the high-dose group was significantly higher than those patients who got retreated, even accounting for those French patients who got additional doses of RAI for recurrence. The numbers were something like 200 mCi in the US group and about 130 mCi in the French group. So there's still a discrepancy in patients that were treated with high-dose RAI initially. In terms of initial dosing, we analyzed this in an intention-to-treat manner. In terms of selecting patients per group, we used only the very first RAI dose that they received.

No one got 30 mCi four times. Everybody in the French group (in the intermediate-dose group) got an initial dose of 100 mCi. There were a couple of patients that had biochemical persistence and had an additional dose of 100 mCi in the French cohort, but we considered the initial dose for this analysis.

Dr Roger Tabah (Montreal, Canada): Was there any attempt to stratify RAI dosage on the basis of stimulated thyroglobulin?

Dr Katherine D. Gray: No, we did not look at that.