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ORIGINAL ARTICLE

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Efficacy of posttreatment radioiodine scanning in patients with differentiated thyroid cancer

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Abstract

Background: Differentiated thyroid cancers often require radioiodine treatment followed by posttreatment scan. We aimed in this study to assess the utility of the posttreatment radioiodine scan in this population.

Methods: An analysis of patients who received radioiodine treatment at Rambam Campus, during 2006-2013. Scans showing remnant normal thyroid tissue were considered as normal. Positive uptake was defined as uptake in the lateral neck or distant sites.

Results: A total of 455 patients were analyzed, 68% had T1-T2 and 28% had positive lymph nodes. Positive uptake in the lateral neck was recorded in 52 (11.4%) and in distant sites in 41 (9%) patients. Tracheal invasion, esophageal invasion, nerve invasion, and N1b classification were associated with a positive scan ($P < .05$). A positive radioactive iodine scan was not related to poor prognosis.

Conclusions: Posttreatment scans are positive in only 20% of patients. Locally invasive tumor and positive nodes are associated with positive scans.

KEYWORDS

cancer, papillary carcinoma, radioiodine treatment, thyroid, whole-body scan

1 | INTRODUCTION

Differentiated thyroid cancer (DTC), which includes papillary and follicular cancers, accounts for the vast majority of thyroid cancers.[1] Papillary thyroid carcinoma (PTC) is the most common type of DTC and comprises about 80%-85% of all follicular cell-derived thyroid cancers.[2-6] Patients with DTC have excellent prognosis, with a 10-year overall survival (OS) of over 90%.[7,8]

Treatment of DTC is mainly surgical and includes thyroidectomy with or without neck dissection, depending on regional spread.[2,9] Following surgical treatment, patients are classified with low, intermediate, or high-risk disease, according to American Thyroid Association Management (ATA) guidelines.[10] Low-risk disease is limited to the thyroid without regional or distant metastasis, and without adverse pathological variant. Intermediate and high risk disease may have an adverse pathological variant, extrathyroidal invasion to the muscle or adjacent tissue, lymph node involvement, or distant metastases.[10] Treatment with radioactive iodine I_{131} (RAI) is recommended for patients with a residual disease or risk of recurrence.[10] Routine performance of posttreatment whole-body scanning after RAI administration is acceptable for evaluation of regional and distant disease.[11] However, the sensitivity of posttreatment scans is limited by tumor size and iodine avidity, and its clinical utility is not well defined.[11] Furthermore, the cost effectiveness of posttreatment RAI scanning is not well established and risk stratification of patients has not been studied.[12]

The objective of the present study was to assess the utility of the posttreatment RAI scan in patients with DTC, and to stratify the risk factors that predict a positive scan.

2 | METHODS

In this work, we retrospectively analyzed all patients with DTC who received RAI treatment at Rambam Health Care Campus, which is both a primary health care facility and a referral center, during the years 2006-2013. The study was approved by the local institutional review board committee (RMB-0238). All patients underwent total thyroidectomy with or without neck dissection prior to the RAI treatment. The decision to perform neck dissection was considered exclusively in patients with clinically positive cervical lymph nodes (>1 cm), confirmed as metastatic by fine-needle aspiration.[10]

Only patients with papillary carcinoma and follicular carcinoma were included in the analysis. All admission charts were screened and data including demographics, medical history, staging, pathological characteristics, treatment, serum Tg levels, survival, and follow-up were extracted. Patients lacking follow-up and survival data were excluded from the analysis.

The ablative dose (30-200 mCi) was administered during hypothyroidism (TSH > 25 mIU/L), obtained after thyroxin withdrawal or after administration of Thyrogen (thyrotropin alfa for injection, two doses of 0.9 mg IM injection 24 hours prior to RAI administration). This is a retrospective study, and the determination of RAI dose evolved over the study period. In the earlier period of the study (before 2012), dose ranged between 30 and 150 mCi according to the I_{131} uptake scan (0.5 mCi) prior to the RAI ablation.[13] Later, when new data on RAI treatment were published, RAI dose was determined according to risk stratification: patients with low risk received 30 mCi, patients with intermediate risk received 30-100 mCi, and patients with high risk received 100-200 mCi.[14]

Posttreatment scanning was performed 5-7 days after administration of I_{131}. All patients underwent whole-body anterior and posterior planar images, with or without single photon emission CT/low-dose CT (SPECT/CT). SPECT/CT was added for patients whose planar findings were inconclusive, using a dual-head gamma camera with high-energy parallel-hole collimators (Either VG, Infinia Hawkeye-1 or Discovery 670, all cameras were from GE Healthcare, Milwaukee, Wisconsin). All scans were interpreted by two experienced nuclear medicine physicians. The reports were retrospectively reviewed, and the results were classified as normal (no uptake or physiological uptake in the thyroid bed) or positive (uptake in the lateral neck, lungs, or skeleton, or other distant metastasis).

The follow-up protocol changed during the study period. Before 2012, all patients had thyroid function tests, Thyroglobulin (Tg) level, and neck ultrasonography every 6 months. Whole-body scan with 0.5 mCi I_{131} was performed and Tg serum measured 1 year after RAI ablation, during Levothyroxine withdrawal. Chest CT was performed if there was high risk of distant metastases. After 2012, we modified the follow-up protocol according to the European Society for Medical Oncology clinical practice guidelines: serum Tg was measured 3 months after surgery and then every 6-12 months under Levothyroxine therapy along with neck ultrasonography.[15]

Five-year OS, disease-specific survival (DSS), disease-free survival (DFS), and distant metastasis rates were calculated using the Kaplan-Meier method as described elsewhere.[16] Differences in survival rates were assessed by the log-rank test. OS was measured from the date of RAI treatment to the date of death or the last follow-up. DSS for patients who died from causes other than DTC was established as the time of death. DFS was defined as the time in months from RAI treatment to the date of recurrence—biochemical or structural.

The variables that showed prognostic potential in univariate analysis were included in the multivariate analyses with the Cox proportional hazards regression model.[16] All analyses were performed on JMP 10 software (SAS Institute Inc, Cary, North Carolina) and confirmed by an independent statistician on an IBM SPSS Statistics package (IBM Corporation, Armonk, New York). All *P* values were two-sided, and a *P* value of less than .05 was adopted as the threshold for significance.

3 | RESULTS

The cohort comprised 485 patients who received RAI treatment at our institution followed by a posttreatment radioiodine scan. Of them, 30 patients were excluded from the analysis due to missing data. The final cohort consisted of 455 patients; their demographic and tumor characteristics, and treatment modalities are summarized in Table 1. The patients' ages ranged from 19 to 90 years (mean 47 ± 15); 320 (70%) were female. The mean follow-up time was 62 months. The histological subtypes were classical PTC in 351 patients (77%), a follicular variant of PTC in 45 (9.8%), a tall cell variant in 18 patients (3.9%), and Hürthle cell or follicular carcinoma in 31 (6.8%) patients. The primary tumor classification was T1-2 in 304 (67%) and T3-4 in 107 (24%) (Table 1). Regional lymph node metastases were present in 128 patients (28%).

After surgery, all the patients received RAI ablation therapy followed by posttreatment radioiodine scans. A normal scan was defined as a scan with no uptake or with physiological uptake in the thyroid bed; whereas positive uptake was defined as uptake in the lateral neck, lungs, or skeleton, or other distant metastasis.

Normal scans were documented in 362 (80%) patients: negative uptake in 35 (7.6%) patients, and physiological uptake in the thyroid bed in 327 (72%). Positive uptake in the lateral neck was recorded in 52 (11%) and in distant sites in 41 (9%) patients (Table 2). Among patients with uptake in

TABLE 1 Demographic and clinical characteristics of the patients

Variable		No. of patients	%
Median age, y (range)	47 (19-90)	455	100
Sex	Male	135	29.7
	Female	320	70.3
T classification (n = 411)	T1	212	51.5
	T2	92	22.3
	T3	96	23.3
	T4	11	2.6
N classification (n = 414)	N−	286	69
	N+	128	30.9
Tumor histology	PTC	351	77
	FCV/TCV	63	13.8
	FTC	21	4.6
	HC	10	2.1
	Mixed	10	2.1
Surgical margins (n = 431)	Positive	187	43.3
	Negative	244	56.6
Median follow-up (mo)	62.5	455	100

Abbreviations: FCV, follicular cell variant; FTC, follicular thyroid carcinoma; HC, Hurthle cell; PTC, papillary thyroid carcinoma; TCV, tall-cell variant.

TABLE 2 Sites of positive radioactive iodine I_{131} scans

Site (n = 455)		No. of patients	%
Thyroid bed		327	71.8
Lateral neck		52	11.4
Distant sites		41	9
	Lungs	20	48.7
	Skeleton	5	12
	Lungs and skeleton	5	12
	Mediastinum	3	7.3
	Lungs and mediastinum	2	4.8
	Liver	2	4.8
	Skeleton and mediastinum	1	2.4
	Other	3	7.3
Negative uptake		35	7.6

distant sites, 27 (66%) were in the lung and 6 (15%) in the mediastinum (Table 2).

We evaluated the following variables as possible clinicopathological factors that could predict a positive postoperative RAI scan: sex, age, tumor size, T classification, N classification, margin status, capsular invasion, lymphovascular invasion, muscle invasion, tracheal invasion, esophageal invasion, and perineural invasion. Tracheal invasion, esophageal invasion, nerve invasion, and N1b classification were found to be associated with positive RAI scans (Table 3). Overall, patients who were at high risk, according to the 2015 ATA guidelines, had a significant probability for a positive RAI scan ($P < .001$).

During the follow-up period, 16 patients died (OS rate 96%). The 5-year and 10-year OS rates were 97.5% and 96%, respectively. The 5-year and 10-year DSS rates were 99.1% and 98.8%, respectively. The 5-year OS was 97% in the normal scan group and 91% in the positive scan group (Figure 1). Of the 362 patients in the normal RAI scan group, 56 (15.4%) developed recurrent disease. In contrast, in the positive RAI scan group, 20 of 93 (21.5%) developed recurrence. Kaplan-Meier analysis showed that a pathological RAI scan was not associated with OS, DSS, or DFS. Due to the low mortality rate, OS rates did not differ significantly between patients with uptake in the lateral neck (93.5%) and those with uptake in distant sites (88.6%), $P = .37$.

We evaluated the correlation between RAI scans and post RAI serum Tg levels. We found positive Tg levels (serum levels >0.9 ng/mL) in 39% of patients with positive scans compared to 13% in patients with negative scans ($P < .001$).

In addition to the above, we assessed if patients with positive scans received further treatment. Of those with lateral neck uptake, four underwent neck dissection, two of whom were followed with a second dose of RAI treatment. Six patients received a second dose of RAI without additional surgery. Of the patients with uptake in distant sites, 22 received a second dose of RAI. Additional treatments given to this group were surgical resection (n = 1), radiotherapy (n = 4), and surafinib (n = 1).

In total, 30 (33%) patients with positive scans received a second dose of RAI compared to 55 (15.3%) patients with normal scans ($P < .001$).

4 | DISCUSSION

Treatment of DTC entails surgery, whereas RAI therapy is directed toward ablation or treatment of residual disease, distant spread, or extrathyroidal extension.[10] Following RAI ablation, patients routinely undergo radioiodine scans, aka posttreatment scans. This scanning is aimed to identify unknown regional and distant metastases. In the current study, we analyzed the records of 455 patients, of whom 52 (11.4%) had positive uptake in the posttreatment scan in the lateral neck and 41 (9%) in distant sites. We identified predictors of positive scans and examined correlations of the scan results with the prognosis of these patients.

Donahue et al compared pretreatment to posttreatment RAI scans of 19% new pathological uptake sites that were revealed in the posttreatment scan.[17] This resulted in upstaging of the disease in 10% of the patients. Consequently, the authors recommended performing posttreatment scans for all patients who undergo RAI treatment. At our

TABLE 3 Prognostic factors for positive posttreatment scans

Variable		Positive scan	Normal scan	*P* value
Age, y		47.9 ± 17.5	46.4 ± 15.2	.44
Sex	Female	61 (66%)	259 (72%)	.31
Multifocal tumors		61 (67%)	213 (60%)	.23
Tumor size >2 cm		40 (47.1%)	149 (42.6%)	.47
Tumor size >4 cm		17 (20%)	43 (12%)	.08
T classification	T1	33 (44.6%)	178 (53.5%)	.19
	T2	18 (24.3%)	73 (21.9%)	.65
	T3	19 (25.7%)	76 (22.8%)	.65
	T4	4 (5.4%)	6 (1.8%)	.08
Margin status	Negative	48 (57%)	196 (57%)	1
	Positive	37 (43%)	150 (43%)	
Tumor invasion to-	Capsule	24 (26%)	89 (25%)	.41
	Lymphatics	12 (13%)	34 (9%)	.68
	Vessels	8 (9%)	18 (5%)	.32
	Muscles	6 (7%)	14 (4%)	.41
	Trachea/esophagus	4 (4.3%)	1 (0.3%)	.007
	Nerve	5 (5%)	1 (0.3%)	.002
N classification (n = 413)	Positive	34 (44.7%)	91 (27%)	.004
	N1a	24	63	.51
	N1b	10	28	.01
	Negative	42 (55.2%)	246 (72.9%)	.002
ATA risk group[a]	Low risk	4 (4%)	74 (61%)	<.001
	Intermediate risk	40 (44%)	40 (28%)	.16
	High risk	47 (52%)	30 (21%)	<.001

Note: Data are presented as mean ± SD of number (%).
Abbreviations: ATA, American Thyroid Association; WBS, whole-body scan.
[a]According to the 2015 guidelines of the American Thyroid Association.

institution, pretreatment RAI scanning is not routine when the operation is performed by one of our head and neck surgeons. This is to avoid a stunning effect.[18]

Other studies also showed that posttreatment radioiodine scans can reveal new findings that were not detectable by other diagnostic modalities prior to the RAI treatment.[19-22] About 10% of the findings in the RAI scan were reported to have impact on clinical management.[23] In the current study, we aimed to define the utility of posttreatment RAI scans and the cost effectiveness of this modality.

Of the 455 patients who had posttreatment RAI scans in the current study, only 20% had positive findings that were suggestive of regional or distant metastases. The prognostic factors that were related to having a positive scan were: locally invasive disease (neural invasion, invasion to the esophagus, or trachea) and N1b pathological classification. In a smaller study of 63 patients with positive RAI scans, only multifocality and tumor size >2 cm were associated with positive scans.[12] Sherman et al analyzed data of 93 patients and found that posttreatment scans were likely to reveal clinically new information only among young patients (<45 years old) who had previously received RAI therapy.[24] In contrast, several earlier studies did not detect statistically significant prognostic factors associated with positive RAI scans.[19,20,25] Although we were able to identify risk factors that predict the probability of a positive scan, the false negative rate of this model is 11% (patients who had positive posttreatment scans but without any adverse features). This subset of patients can be monitored by serum Tg levels for follow-up according to the ATA guidelines.[10]

We do not routinely perform serum thyroglobulin measurements before and after scans at our institution, rather only as a follow-up to the RAI treatment. However, a study by Liu et al showed that patients with intermediate-risk PTC and pretreatment Tg levels less than 1 ng/mL have very low likelihood of a positive pathologic posttreatment scan (3.3%), and hence posttreatment scan might be omitted in this subpopulation of patients.[26]

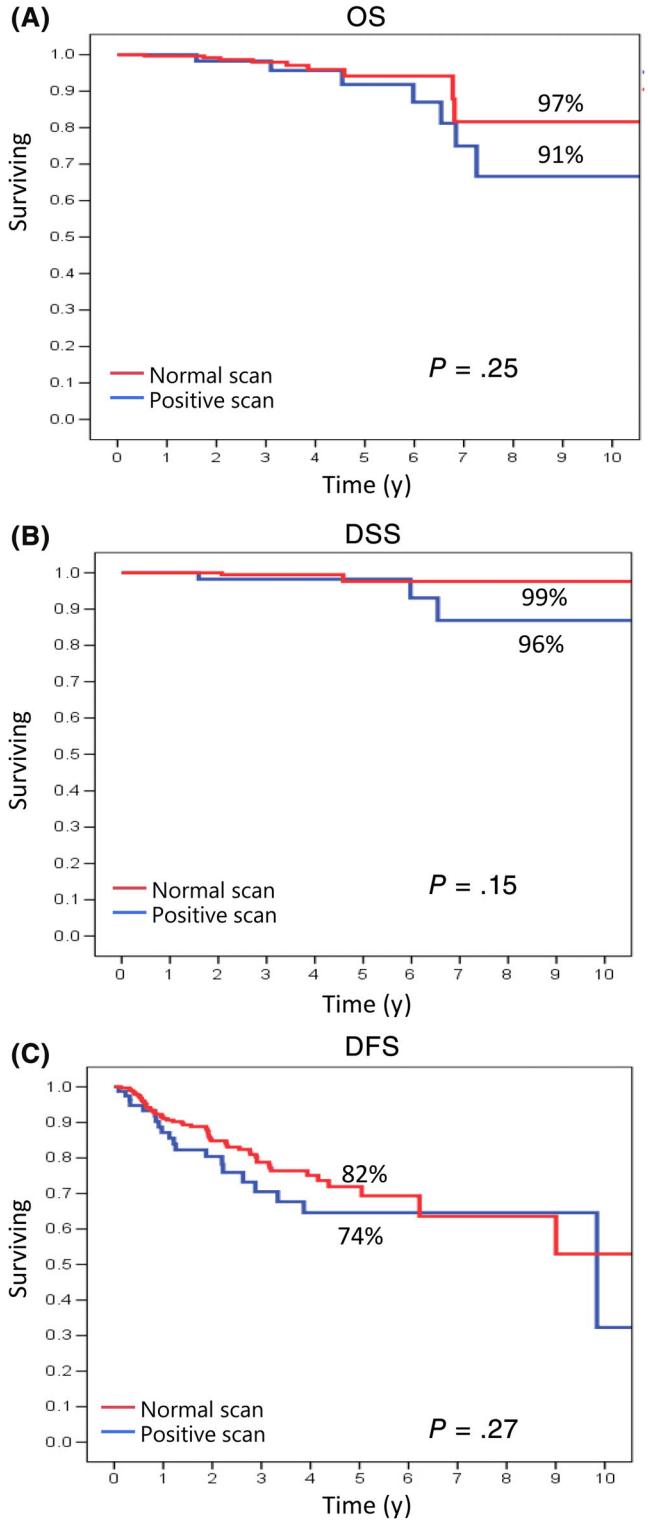

FIGURE 1 Kaplan-Meier survival analysis according to iodine scan results. A, Overall survival (OS); B, disease-specific survival (DSS); and C, disease-free survival (DFS). Normal scan (red) vs positive scan (blue) [Color figure can be viewed at wileyonlinelibrary.com]

In the current study, we found that posttreatment scans could have been avoided for the majority of patients who received RAI therapy. Although positive postoperative RAI scans were not associated with poor outcome, they yielded clinically important information in patients with local tumor invasion and in those with positive nodal disease. Most of these patients received a second dose of RAI treatment or underwent a neck dissection for neck metastasis, which could explain the comparable outcome measures. In recent years, strict guidelines have emerged regarding risk stratification of patients with DTC and the benefit of RAI treatment. Focusing on posttreatment scans, our results support minimizing the utility of RAI scans to patients who are at intermediate to high risk.

We attempted to estimate the costs that could be saved by proper risk stratification of the whole-body scan. According to the Surveillance, Epidemiology, and End Results program of the National Cancer Institute, the estimated number of new cases of thyroid cancer in 2017, in the United States, was 56 870. The incidence of regional spread to the lymph nodes was 27% and the rate of distant metastases was 4%. According to the National Cancer Database, about 70% of patients with DTC received RAI treatment, which translates to 39 809 patients per year.[27] Based on these numbers, we estimate that approximately 27 500 radioactive scans can be avoided if only high-risk patients are scanned (12 341 patients overall).

The retrospective design of this work precluded controlling for confounding variables, including measurements of serum thyroglobulin, which are not performed routinely following surgery and prior to RAI treatment, despite this being a powerful predictor of disease status.

Our results suggest that posttreatment whole-body RAI scans may have value in the follow-up of patients classified as intermediate and high risk according to the ATA guidelines, mainly, those with local tumor invasion, lateral lymph node metastases, and distant metastases. More information is required to evaluate the utility of RAI scans for the majority of DTC patients, who are in the low-risk category.

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