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Original Research

Early Dynamic Risk Stratification Decreases Rate of Ablative and Adjuvant Radioiodine Use in ATA Low and Intermediate Risk Papillary Thyroid Cancer Patients

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Abstract

Objectives: In differentiated thyroid cancer (DTC), radioiodine (RAI) therapy is most frequently employed for remnant ablation or as adjuvant therapy for the remaining disease. The application of RAI to patients classified as intermediate risk (InR) is still a matter of debate. The aim of this study is to analyze the effect of early postoperative risk assessment on RAI use on papillary thyroid cancer patients who are classified as low risk (LoR) or InR.

Methods: This is a single-center, prospective registry study. One-hundred-eighty-six patients operated between January 2012 and August 2021 and categorized as LoR or InR were included in this study. All patients had total thyroidectomy and central lymph node dissection by the same endocrine surgeon. An early dynamic risk assessment (EDRA) consisting of neck ultrasonography, serum thyroglobulin (Tg) and anti-Tg levels was performed 6 weeks after surgery. Most of the patients were either followed up without RAI or received ablative low activity (30–50 mCi) RAI based on predetermined criteria.

Results: Median follow-up was 63 months. Sixty-six (61%) patients in the LoR group and 43 (56%) patients in the InR group did not receive RAI treatment. Thirty-eight (35%) and 22 (29%) patients in LoR and InR groups received ablative (30–50 mCi) RAI therapy, respectively. In LoR group 5 (4.6%) patients and in InR group 12 (16%) patients received 100 mCi or more RAI activity. Only one patient in the InR group recurred during follow-up. No statistically significant difference regarding local recurrence was found between patients who didn't receive RAI or were treated with RAI within both LoR (p=0.152) and InR (p=0.272) groups.

Conclusion: There is consensus for LoR patients about omitting RAI therapy after surgery. Indications for RAI treatment in InR DTC are still under debate. RAI use based on EDRA seems to be a better option than decisions solely made on histopathological risk factors and decreases adjuvant high-activity RAI use without increasing recurrence risk.

Keywords: ATA risk stratification, papillary thyroid cancer, radioiodine therapy

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Differentiated thyroid cancer (DTC) encompasses papillary and follicular histology and has a favorable prognosis when treated with a multimodal approach. About 80–85% of all thyroid cancers are papillary thyroid carcinomas (PTC).[1] Surgery is the mainstay of treatment, followed by radioiodine (RAI) therapy in indicated cases. Prognosis in PTC cases shows a close correlation with the presence of extracapsular invasion, vascular invasion, larger tumor size, distant metastasis, the existence of BRAF mutation, and successful surgery.[2,3]

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RAI use in DTC aims for ablation of remnant thyroid tissue, destruction of subclinical tumor deposits (adjuvant treatment), or treatment of known metastatic foci. The decision to administer RAI is made considering patient and disease characteristics, risk stratification for recurrence, choice and capabilities of medical facilities, and patients' informed preference. It is logical to do risk stratification before RAI therapy decision. Basically, the appropriate usage of adjuvant therapy is still a debate in most of the intermediate-risk (InR) DTC patients.[4] However, the selection of low-activity (30 mCi) is recommended and found equally effective for ablative purposes as high activity (100 mCi).[5]

Currently, RAI decisions are made depending mostly on histopathologic risk factors alone. American Thyroid Association (ATA) guidelines classified DTCs into low, intermediate, and high-risk groups (Table 1) for recurrence in 2009. They added further modifications to consider in their 2015 guideline.[6] Although RAI is not routinely recommended to ATA low-risk (LoR) patients and strongly recommended to ATA high-risk patients; it is still one of the hottest topics of debate whether to administer RAI to patients classified as InR group. Existing data imply that the true benefit of RAI therapy may exist for patients with unfavorable cancer histology, high volume nodal disease, lymph node disease beyond the central compartment, and older age. However, there is a lack of data investigating RAI effectiveness by risk category.[6]

Another challenging problem in PTC treatment is performing central lymph node dissection (CLND) in every case. It has been shown that multicentricity, lymphovascular invasion (LVI), and tumor stage are independent risk factors for determining the possibility of central lymph node metastasis.[7] We have reported 38% lymph node metastases in central lymph nodes in pT1N0 patients previously.[8] The impact of CLND on the prognosis of PTC is unclear.[9] In some retrospective studies,[10-13] despite not being linked to overall survival (OS), central lymph node metastasis has been found to increase the likelihood of locoregional recurrence. Another advantage of CLND is that it provides information for the use of adjuvant RAI.[14-17] CLND has the potential to reduce post-treatment thyroglobulin (Tg) levels and consequently the necessity for RAI therapy.[18-24]

The purpose of this study is to analyze the role and effect of RAI treatment in PTC patients who are classified as ATA LoR or InR.

Table 1. ATA risk stratification system with proposed modifications

ATA low risk	● Papillary thyroid cancer (with all of the following): ○ No local or distant metastases. ○ All macroscopic tumor has been resected. ○ No tumor invasion of loco-regional tissues or structures. ○ The tumor does not have aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma). ○ If I^{131} is given, there are no RAI-avid metastatic foci outside the thyroid bed on the first post treatment whole-body RAI scan. ○ No vascular invasion. ○ Clinical N0 or ≤5 pathologic N1 micrometastasis (<0.2 cm in largest dimension)[a]. ● Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer ● Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion[a] ● Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including BRAFV600E mutated (if known)[a]
ATA intermediate risk	● Microscopic invasion of tumor into the perithyroidal soft tissues ● RAI-avid metastatic foci in the neck on the first post treatment whole-body RAI scan ● Aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) ● Papillary thyroid cancer with vascular invasion ● Clinical N1 or >5 pathologic N1with all involved lymph nodes <3 cm in largest dimension[a] ● Multifocal papillary microcarcinoma with ETE and $BRAF^{V600E}$ mutated (if known)[a]
ATA high risk	● Macroscopic invasion of tumor into the perithyroidal soft tissues (gross ETE) ● Incomplete tumor resection ● Distant metastases ● Postoperative serum thyroglobulin suggestive of distant metastases ● Pathologic N1 with any metastatic lymph node ≥3 cm in largest dimension[a] ● Follicular thyroid cancer with extensive vascular invasion (>4 foci)[a]

[a]Proposed modifications; ETE: Extrathyroidal extension; RAI: Radioiodine; ATA: American thyroid association.

Methods

This is a single-center, prospective registry study. Approval for this study was obtained from Ankara Guven Hospital's local scientific research and ethics committee with the date of May 24th, 2021 and registry number 210524-1262. One-hundred-eighty-six PTC patients who were operated by a single endocrine surgeon between January 2012 and August 2021 were enrolled. Patients who had total thyroidectomy (TT) and CLND that are classified as ATA LoR or InR were included. However, patients with follicular thyroid carcinoma and patients with PTC who also had lateral neck compartment lymph node dissection were excluded from this analysis despite the fact that they may be in the InR group. Overall, 186 patients with complete follow-up data were analyzed. This study was conducted in accordance with the ethical principles stated in the "declaration of Helsinki" adopted by the World Medical Association.[25]

All patients had undergone an early dynamic risk assessment (EDRA) at postoperative 6th week with neck ultrasonography (US) and stimulated or unstimulated Tg and anti-Tg (Anti-Tg) levels. For both risk groups, RAI ablation was performed if Anti-Tg levels were positive and did not decline during follow-up, regardless of findings in the US. In patients with normal Anti-Tg levels at 6th week; Tg levels were taken into consideration for RAI treatment planning. Patients were followed up without RAI treatment if non-stimulated serum Tg level was below 0.2 ng/mL and US examination was normal. However, patients received an ablative dose (30–50 mCi) of RAI when serum Tg levels are between 0.2 ng/mL and 1 ng/mL. Patients that have structural disease or inappropriately high levels of Tg (Tg >1 ng/mL) received adjuvant RAI therapy. Neck US, serum Tg, and Anti-Tg measurements were conducted at 6 month intervals in all patients, and response to initial therapy was graded as good, biochemical incomplete, structural incomplete, or indeterminate.

Data Collection and Statistical Analysis

Patient records were anonymized and collected in Microsoft Excel (Microsoft, Redmond, Washington, United States) and analyzed using R statistical language release 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria). Response to treatment in both groups was compared using Fisher's exact test. Differences between LoR and InR groups regarding epidemiologic parameters, pathologic findings, test results, and treatments received were analyzed using Mann-Whitney U test, Pearson's Chi-squared test, and Fisher's exact test where appropriate.

Results

Among 186 patients included in this study, 109 and 77 were classified as ATA LoR and InR, respectively. The mean age of the patients included in this study was 40; the InR group was younger than the LoR group (p>0.001). Regarding male-to-female ratios within each group, the groups were not significantly different (p=0.091). Demographic features of the patients, central lymph node positivity, and treatment response are all presented in Table 2.

The median follow-up time was 63 months (LoR=66 months, InR=60 months). All patients had TT with therapeutic or prophylactic CLND. In both groups, a median of 8 lymph nodes (7 in LoR group and 10 in InR group) were dissected from the central neck compartment. Central lymph node metastasis was observed in 64 (83%) and LVIwas observed in 45 (58%) patients in the InR group.

In LoR group, 66 (61%) patients and in InR group, 43 (56%) patients did not receive RAI treatment. Number of patients receiving ablative RAI therapy (30–50 mCi) in LoR and InR groups were 38 (35%) and 22 (29%), respectively. In LoR group 5 (4.6%) patients and in InR group 12 (16%) patients received 100 mCi or more RAI activity.

At a median of 60 months follow-up, excellent response to treatment was observed in 105 (96%) patients of LoR and 68 (88%) of InR group (p<0.05). Four patients (4%) in LoR and 8 patients (10%) in InR groups had biochemically incomplete responses to treatment (p<0.05). One patient in the InR group developed a lateral cervical lymph node metastasis at the 63rd month of follow-up. Thus, 1 (1.3%) patient in the InR group had a structural incomplete response to treatment.

When comparing patients who underwent RAI therapy and those who were followed up expectantly, there was no statistically significant difference in response to treatment in both LoR (p=0.152) (Table 3) and InR (p=0.272) (Table 4) groups.

Discussion

ATA management Guideline does not recommend RAI therapy to LoR patients and recommends selective use of RAI to InR risk group.[6] Lamartina et al.[26] revealed conflicting results in a recently published systematic review on the effect of RAI therapy on recurrence, stating in particular that 11 non-randomized trials implied a benefit while 13 studies did not demonstrate a meaningful advantage. According to multivariate adjusted studies from the SEER database, aggressive PTC histology has been associated with better OS when postsurgical RAI therapy is used.[27,28] Considerations in RAI decision-making include the comparatively favor-

Table 2. Demographics and descriptive statistics of patients enrolled in this study

	ATA risk group			p[2]
	Overall, n=186[1]	Low risk, n=109[1]	Intermediate risk, n=77[1]	
Age	39 (±9)	42 (±8)	35 (±9)	>0.001
Sex				0.091
Female	153 (82%)	94 (86%)	59 (77%)	
Male	33 (18%)	15 (14%)	18 (23%)	
Follow-up (months)	63 (±29)	66 (±30)	60 (±28)	0.263
Central lymph node metastasis				<0.001
No	121 (65%)	108 (99%)	13 (17%)	
Yes	65 (35%)	1 (0.9%)	64 (83%)	
Positive lymph nodes	0 (±2)	0 (±0.1)	2 (±2.6)	<0.001
Total lymph nodes	8 (±5.1)	7 (±4.1)	10 (±5.4)	0.004
Lymphovascular invasion				<0.001
No	141 (76%)	109 (100%)	32 (42%)	
Yes	45 (24%)	0 (0%)	45 (58%)	
RAI				0.521
Not applied	109 (59%)	66 (61%)	43 (56%)	
Applied	77 (41%)	43 (39%)	34 (44%)	
RAI dosage				0.035
None	109 (59%)	66 (61%)	43 (56%)	
30–50 mCi	60 (32%)	38 (35%)	22 (29%)	
100 mCi and above	17 (9.1%)	5 (4.6%)	12 (16%)	
Local recurrence				0.414
No	185 (99%)	109 (96%)	76 (99%)	
Yes	1 (0.5%)	0 (0%)	1 (1.3%)	
Response to treatment				0.048
Excellent	173 (93%)	105 (96%)	68 (88%)	
Biochemical incomplete	12 (6.5%)	4 (3.7%)	8 (10%)	
Structural incomplete	1 (0.5%)	0 (0%)	1 (1.3%)	

[1]Median (±SD); n (%); [2]Mann-Whitney U test; Pearson's Chi-squared test; Fisher's exact test; ATA: American thyroid association.

Table 3. Comparison of response to treatment of patients in ATA low risk group who either received RAI or followed-up expectantly. No statistically significant difference was observed between groups (p=0.152)

	Response to treatment				
	Excellent	Biochemical incomplete	Structural incomplete	Total cases	p[1]
RAI					
No	62	4	0	66	0.152
Yes	43	0	0	43	
Total cases	105	4	0	109	

[1]Fisher's exact test; RAI: Radioiodine; ATA: American thyroid association.

able overall prognosis of this group and the uncertainty of RAI therapeutic effectiveness for this subgroup. It is unclear whether adjuvant RAI treatment is useful in enhancing long-term outcomes for patients with thyroid cancer who have only microscopic central lymph node metastasis in the absence of any other negative traits. The 2009 ATA risk stratification framework classifies all DTC patients with central compartment nodal metastases as InR. However, according to recent studies the risk of structural recurrence varies from 4% if a patient has <5 metastatic lymph nodes to 19% if over five lymph nodes have been affected. The risk even increases further to 27% if any of the metastatic

Table 4. Comparison of response to treatment of patients in ATA intermediate risk group who either received RAI or followed-up expectantly. No statistically significant difference was observed between groups (p=0.272)

	Response to treatment				
	Excellent	Biochemical incomplete	Structural incomplete	Total cases	p[1]
RAI					
No	37	6	0	43	0.272
Yes	31	2	1	34	
Total cases	68	8	1	77	

[1]Fisher's exact test; RAI: Radioiodine; ATA: American thyroid association.

lymph nodes is >3 cm in size.[29,30] Because of the diversity within the ATA InR category, it is challenging to predict recurrence rates using just ATA risk stratification parameters.

RAI treatment is beneficial only if there is residual thyroid tissue or metastatic disease. This status cannot be assessed based on histopathological findings. If RAI decision is based on ATA risk stratification criteria and histopathologic findings alone, more than necessary RAI decisions may be made. The decision to give RAI needs to be based on the postoperative disease status of each patient individually. The most suitable tools for this purpose are neck US, serum Tg levels and Anti-Tg levels. Postoperative Tg levels are assumed to drop to a minimum by week 4 in almost all patients.[31] In our study, we performed EDRA at postoperative week 6 to evaluate postoperative disease status in each patient. Some patients classified as ATA InR who were negative for Anti-Tg and had Tg levels <0.2 ng/mL and a normal neck US were placed on an expectant follow-up protocol. Some patients who were initially classified as ATA LoR demonstrated Tg levels >1 ng/mL, and despite having a normal US, they are elected for RAI treatment. All patients with non-declining Anti-Tg levels received RAI treatment. This approach allowed us to choose patients who may be candidates for RAI ablation and adjuvant therapy and define patients who might be followed up without further treatment.

Our patient group differs from many other studies because it includes patients with routine CLND. It has been argued that routine CLND might lead to more RAI use by exposing a substantial amount of clinically insignificant metastasis in central lymph nodes and converting cN0 patients to pN1. However, cNx and CN0 lymph node status could only be objectively categorized with routine CLND. Moreover, routine CLND removes potentially metastatic lymph nodes effectively and decreases postoperative serum Tg levels and hence decreases RAI use. Nonstimulated postoperative Tg levels of 1 ng/mL are associated with excellent clinical outcomes and a presumably acceptable recurrence rate of <1% in patients who are classified as ATA LoR and InR and who did not undergo RAI remnant ablation.[32] Increasing the risk of postoperative complications by performing routine CLND might be an understandable concern. However, it has been shown that performing CLND in addition to TT does not increase the risk of permanent injury to neither parathyroid glands nor recurrent laryngeal nerves.[33]

Postoperative serum Tg measurements will probably find their value as a useful tool for distinguishing who may benefit from RAI ablation from those who had been cured by surgery, as indicated in the ATA 2015 recommendation. RAI ablation may improve follow-up for patients with detectable Tg levels and normal neck US. However, a postoperative Tg value of 1 ng/mL does not mean RAI therapy will have no benefit in a high-risk patient and is thus unlikely to affect the choice to continue with RAI treatment.[6] Consequently, we believe that assuming all cN0 cases are free of central lymph node metastasis without performing a CLND is a cause for underestimating disease status and furthermore influences the evaluation of postoperative serum Tg levels negatively.

This study has several limitations. It is based on data obtained from one endocrine surgeon's patients who were followed up and evaluated by one nuclear medicine specialist. Furthermore, it is a prospective registry study by design. Thus, data are neither blinded nor randomized. Follow up time also is less than optimal for this risk group who have a reasonably favorable prognosis. Our conclusions might be more grounded if our study groups were larger and more heterogenous and our follow-up period was 10 years.

Conclusion

We believe that, in patients with DTC, RAI therapy decisions should not be based only on histopathological features alone. We also believe that the presence of central lymph node metastasis alone should not prompt RAI therapy without EDRA. Our findings are in harmony with these statements.

For ATA LoR group and Anti-Tg negative patients, RAI is not indicated if Tg levels are below 0.2 ng/mL and neck US is normal.

For patients classified as ATA InR, an EDRA consisting of serum Tg and Anti-Tg levels and a neck US could help to define patients who may be candidates for follow-up without adjuvant or ablative RAI therapy safely. If US or Tg results are suggestive for residual tissue or metastatic disease, then ablative or adjuvant doses of RAI might be applied as recommended.

Follow-up results that will be obtained at 10 years would provide more data that would facilitate decision-making and the utility of using EDRA before proceeding with RAI therapy.

Disclosures

Ethics Committee Approval: Approval for this study was obtained from Ankara Guven Hospital's local scientific research and ethics committee with the date of May 24th, 2021 and registry number 210524-1262.

Peer-review: Externally peer-reviewed.

Conflict of Interest: There are no conflicts of interests regarding the authors of this study and any third-parties.

Informed consent: Consent was taken from all enrolled patients regarding their participation and their data being used after anonymization in this prospective registry study.

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