Outcomes of Low-Risk Differentiated Thyroid Cancer (DTC) without Radioactive Iodine (RAI) Ablation Therapy Post-Thyroidectomy: An Experience from a Tertiary Centre in Karachi

Nazish Fatima[1], Zareen Kiran[1], Javaid Iqbal[2], Akhtar Ali Baloch[1], SM Salman Habib[1] and Akhtar Ahmed[2]

[1]*National Institute of Diabetes and Endocrinology, Dow International Medical College, Dow University of Health Sciences, Karachi, Pakistan*

[2]*Department of Nuclear Medicine, Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN) Hospital, Karachi, Pakistan*

ABSTRACT

Objective: To assess the outcomes of low-risk differentiated thyroid cancer (DTC) with tumour size 1 to 4 cm post-thyroidectomy in patients who never received radioactive iodine (RAI) ablation and to compare the outcomes with those who received RAI therapy.

Study Design: Observational study.

Place and Duration of the Study: Department of Nuclear Medicine, Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN) Hospital, Karachi, Pakistan, from January 2016 to December 2020.

Methodology: A total of 130 consecutive patients of low-risk DTC of both genders aged between 18-75 years were identified who underwent thyroidectomy. Patients were classified as either being treated or not treated with RAI, based on RAI data post-thyroidectomy. Patients were followed up for two to five years depending on their date of diagnosis from 2016 to 2020, using thyroglobulin (Tg), anti-thyroglobulin (anti-Tg), and thyrotropin (TSH) levels and ultrasound neck. Association between patients who received RAI and who did not receive RAI was determined and a p-value <0.05 was considered as statistical significance.

Results: Patients had mean age of 34.5 ± 10.4 years with majority of females (75.4%). Majority of the patients (94.6%) had total thyroidectomy with no neck dissection (83.1%). RAI therapy was conducted among 70.8% participants, of which, 56.9% participants received a dose of 100 mci. Most of the patients had positive outcomes as there was no recurrence among 96.2% participants. There was a significant difference in RAI therapy with total thyroidectomy as compared to subtotal, RAI dose, tumour stage, neck dissection, and lymph node involvement (p ≤0.001).

Conclusion: After complete tumour resection, a highly selected group of patients with low-risk local disease have shown low rate of recurrence when managed without RAI. Interestingly, the disease recurrence was also only seen in patients who received RAI therapy in comparison to those who did not receive RAI therapy.

Key Words: *Outcomes, Differentiated thyroid cancer, Radioactive iodine, Ablation therapy, Post-surgery.*

How to cite this article: Fatima N, Kiran Z, Iqbal J, Baloch AA, Habib SS, Ahmed A. Outcomes of Low-Risk Differentiated Thyroid Cancer (DTC) without Radioactive Iodine (RAI) Ablation Therapy Post-Thyroidectomy: An Experience from a Tertiary Centre in Karachi. *J Coll Physicians Surg Pak* 2024; **34(08)**:968-973.

INTRODUCTION

Thyroid malignancies are the most common endocrine neoplasms, and 90% of them are comprised of differentiated thyroid cancers (DTC). It could be papillary or follicular in histology, which arises from thyroid follicular cells.[1]

Correspondence to: Dr. Nazish Fatima, National Institute of Diabetes and Endocrinology, Dow International Medical College, Dow University of Health Sciences, Karachi, Pakistan
E-mail: nazzishfatima@gmail.com

Received: June 19, 2023; Revised: December 14, 2023; Accepted: July 01, 2024
DOI: https://doi.org/10.29271/jcpsp.2024.08.968

Long-term survival of most patients with DTC is excellent, whereas a significant number of patients might have recurrence or persistent disease, and some eventually die because of thyroid malignancy.[2]

The low-risk DTC is defined as tumours <4cm in size, without lymphadenopathy, and extrathyroidal or local invasion.[3] The outcomes in patients with low-risk DTC have not shown much improvement after RAI ablation therapy, and there is no comparable survival benefit. Hence, the American Thyroid Association (ATA) guidelines do not encourage routine use of RAI ablation therapy in patients with low-risk DTC.[4]

A review of different studies has shown needless use of RAI ablation therapy, irrespective of tumour size, specifically for low-risk DTC who are harbouring Stage I and II tumours without distant metastases, and most of these patients are over-

treated.[5-7] Several studies have proved that post-thyroidectomy RAI ablation therapy does not affect the end result of low-risk DTC without distant metastases, as they already have an overall excellent outcome.[5] Besides, there are grave consequences of RAI ablation therapy with increased risk of infertility and second primary malignancies (SPMs).[8]

In accordance with previous research, the calculated risk for SPMs after RAI is 27%, which might increase with increased doses of RAI.[9] In females, there are chances of temporary secondary amenorrhea, oligomenorrhea, and early menopause after RAI therapy.[8] The unwanted use of RAI ablation therapy also increases the healthcare costs related to thyroid cancer treatment.[6] Due to uncertain results of RAI administration, previous studies have wide variation regarding the risk and benefits of RAI ablation.[7,10] With the rising prevalence of low-risk DTC, it is better to consider and analyse the outcomes of this low-risk category for future practices in terms of RAI ablation therapy.[11]

In patients with microcarcinoma, there is lack of evidence in support of the benefits of RAI therapy.[4] However, studies also described a reduction in tumour recurrence and decreased mortality following RAI ablation for tumours larger than 1cm but less than 2cm.[12] Thus, this study aimed to analyse the outcomes of low-risk DTC with tumour size between 1 and 4 cm in the patients who never received RAI ablation and to compare the outcomes with those who received RAI therapy.

METHODOLOGY

It was an observational retrospective chart review of patients with DTC enrolled from January 2016 to December 2020, at the Karachi Institute of Radiotherapy and Nuclear Medicine, (KIRAN) Hospital. Following the approval from Institutional Review Board, 130 consecutive patients out of 441 were identified and recruited for the study.

Patients of both genders, aged 18-75 years, who were not diagnosed with any other comorbidity and categorised with low-risk DTC with either papillary or follicular thyroid carcinoma, were included in the study. They had no aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma), no local or distant metastases, and no tumour invasion of loco-regional tissues or structures, and no vascular invasion, with all macroscopic tumour completely resected. If 131-iodine was given, there were no RAI-avid metastatic foci outside the thyroid bed on the first post-treatment whole-body RAI scan. Further features include; clinical N0 or <5 pathologic N1 micrometastases (<0.2cm in largest dimension), intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion, and no or minimal (<4 foci) vascular invasion with tumour size between 1 and 4 cm (Stage T1b - T2).[4] However, patients with tumour size >4 cm (T3 and T4), with local or distant metastases, and patients with missing data were excluded.

As per ATA-defined structural and biochemical responses, the study outcomes were defined. Excellent response was no structural disease recurrence defined as both clinical absence of local lymph nodes or palpable thyroid tissue and absence of abnormal lymph nodes or thyroid tissue, in addition to no biochemical disease with suppressed serum thyroglobulin (Tg) <0.2 ng/mL or thyroid stimulating hormone (TSH)-stimulated (Tg) <1 ng/mL.[13] Biochemical incomplete response was serum Tg >1ng/mL or rising anti-thyroglobulin (anti-Tg) antibody levels in the absence of localisable disease, negative imaging, and suppressed Tg >1ng/mL or TSH-stimulated Tg >10ng/mL or rising anti-Tg antibody levels. Structural incomplete response was persistent or newly identified loco-regional or distant metastases and structural or functional evidence of disease with any Tg level with or without anti-Tg antibodies.[13] Indeterminate response was non-specific biochemical or structural findings which could not be classified as either benign or malignant.[13]

Sample size was calculated using Open Epi, version 3, open-source calculator. Keeping 97% confidence interval (CI) and recurrence-free survival of 92% in pT1/T2 N0, as reported in a previous study, and margin of error as 5%, the current study sample size was calculated to be 139 patients.[3]

Out of 441 patients, the data of 130 patients who underwent thyroidectomy and fulfilled the inclusion criteria were collected through medical chart reviews, retrospectively for age, gender, and ethnicity. Any history of comorbid illness such as diabetes, hypertension, cardiovascular disease, or malignancy was noted for exclusion criteria. Moreover, pathologic data were also reviewed in detail and staged according to the tumour, node, and metastasis (TNM) staging system, eighth edition American Joint Committee on Cancer (AJCC) / TNM classification for differentiated thyroid carcinoma.[14]

Patients were followed up with similar protocol. On follow-up examination, TSH (off-thyroxin / stimulated), Tg, Anti-Tg, and ultrasound were included post-thyroidectomy. The first follow-up was at 6 months and then each year, for 5 years, after the initial treatment. A highly selected group of patients with pT1b-2 tumours without ultrasonography evidence of suspicious lymph nodes and favourable histopathology features were managed with observation without RAI and with careful monitoring of thyroglobulin levels and regular ultrasound out of all 130 patients. For patients treated with RAI, a diagnostic 131-iodine whole-body scan, and a stimulated serum Tg and Tg antibody determination were also performed if there was rising Tg or anti-Tg (suppressed / on-thyroxin) at follow-up visit. In the presence of a significantly elevated level of Tg and / or Tg antibodies, recurrences were searched and documented using various imaging modalities and histological proof when necessary.

Patients were classified as either being treated or not treated with RAI based on RAI data from the KIRAN and ATA RAI guidelines.

Patients were followed up for almost 2 to 5 years, depending on their date of diagnosis from 2016 to 2020. Long follow-up corresponds to the recurrence rates and treatment strategies among the patients to be included in this study. However, this study does not report the recurrence data of those patients who had less follow-up years, specifically those diagnosed from 2019 onwards.

Data were entered and analysed in SPSS version 24. Mean and standard deviation were calculated for numerical variables such as age, duration of disease, and postoperative baseline parameters and their association was confirmed through Shapiro-Wilk's test. Frequencies and percentages were calculated for categorical variables such as gender, tumour size, and involvement of lymph nodes and their association were analysed through Chi-square and Fisher's exact test. Odds ratio with 95% CI was calculated to compare the patients who received RAI and those who did not receive RAI. A p-value <0.05 was considered for statistical significance.

RESULTS

Out of 441 patients, total 130 patients' data were included in terms of RAI received and RAI not received in this study. Patients' characteristics of the follow-up parameters of DTC are detailed in Table I.

Majority of the participants were females (75.4%). Most of the patients had total thyroidectomy (94.6%) with no neck dissection (83.1%) as per the records. Patients had a mean tumour size of 1.91 (0.69) cm. Lymph nodes were not available in 83.1% participants. Additionally, most of the patients had T2NxMx tumour stage (66.2%). RAI therapy was conducted among 70.8% participants, of which, 59.2% participants received a dose of 30-100 mci. It was found that there was a significant difference of RAI therapy with total thyroidectomy as compared to subtotal (p = 0.012), decreased RAI dose (p = 0.0001), lower tumour stage (p = 0.006), no neck dissection (p = 0.003), and no lymph node involvement (p = 0.018, Table II). Moreover, RAI therapy had strong positive odds ratio or significant difference with gender and neck dissection among the patients.

Additionally, disease recurrence rate was not significantly associated with the RAI therapy (p = 0.342), further odds ratio of 0.69 determined the negative association; that is the patients who did not receive RAI therapy had less chance for recurrence of DTC (Table III).

Table I: Description of the participants as per the retrospective chart review (n = 130).

Description	Mean ± SD	RAI therapy	
		RAI received (n = 92)	RAI not received (n = 38)
Mean age (years)	34.57 ± 10.42	35.61 ± 11.16	32.05 ± 7.91
Mean follow-up duration (years)	3.09 ± 1.27	2.90 ± 1.27	3.55 ± 1.17
Tumour Size (cm)	1.91 ± 0.69	1.96 ± 0.69	1.79 ± 0.70
Mean TGB (ng/ml) (post-thyroidectomy)	29.25 ± 100.5	38.68 ± 118.39	6.42 ± 7.23
Mean anti-Tg (IU/mL) (post-thyroidectomy) (Reference ranges of Anti-Tg <40 IU/ml)	73.47 ± 235.5	79.26 ± 253.66	59.45 ± 186.94
Mean TSH (IU/mL) (post-thyroidectomy)	65.83 ± 36.72	72.59 ± 29.09	49.47 ± 47.34

Applied Shapiro-Wilk's test.

Table II: Frequency distribution of individuals who received / not received RAI therapy.

Frequency distribution		RAI therapy		Odds ratio*	p-value
		RAI received (n = 92)	RAI not received (n = 38)		
Gender	Male	25 (27.2%)	7 (18.4%)	1.652	0.292
	Female	67 (72.8%)	31 (81.6%)		
Thyroidectomy	Total	90 (97.8%)	33 (86.8%)	6.818	0.012
	Subtotal	2 (2.2%)	5 (13.2%)		
Neck Dissection	Yes	21 (22.8%)	1 (2.6%)	10.944	0.003
	No	71 (77.2%)	37 (97.4%)		
Tumour size	1 cm - 2 cm	76 (82.6%)	34 (89.5%)	0.559	0.324
	2 cm - 4 cm	16 (17.4%)	4 (10.5%)		
Lymph node	N/A	71 (77.2%)	37 (97.4%)	N/A	0.018
	Negative	10 (10.9%)	1 (2.6%)		
	Positive	11 (12.0%)	0 (0.0%)		
Tumour stage	T1bN1aMx	1 (1.1%)	0 (0.0%)	N/A	0.006
	T1bN1Mx	1 (1.1%)	0 (0.0%)		
	T1bN1Mx	2 (2.2%)	0 (0.0%)		
	T1bNoMx	2 (2.2%)	0 (0.0%)		
	T1bNxMx	8 (8.7%)	15 (39.5%)		
	T2N1aMx	2 (2.2%)	0 (0.0%)		
	T2N1bMx	4 (4.3%)	0 (0.0%)		
	T2NoMx	8 (8.7%)	1 (2.6%)		
	T2NxMx	64 (69.6%)	22 (57.9%)		
RAI dose (n = 92)	30 – 100 mci	77 (83.7%)	0 (0.0%)	N/A	0.0001
	>100 mci	15 (16.3%)	0 (0.0%)		

**Applied Chi-square and Fisher's exact test.*

Table III: Comparison of RAI therapy with outcomes.

Variables	RAI therapy		Odds ratio	p-value
	RAI received (n = 92)	RAI not received (n = 38)		
Disease outcome			0.69	0.342
Expired	1 (1.1%)	0 (0.0%)		
No recurrence	87 (94.6%)	38 (100.0%)		
Recurrence	4 (4.3%)	0 (0.0%)		

**Applied Chi-square test.*

Nevertheless, it was found that all four individuals who had recurrence were females, had total thyroidectomy, had advanced tumour stage with tumour size between 1.5 and 4 cm, and also received RAI ablation therapy of doses 100 mci and 150 mci initially. Second dose of RAI was given in 2nd-3rd year of follow-up after recurrence. Thus, it was observed that patients who received RAI were found to be at higher risk of disease recurrence, specifically those with advanced stages of tumour, increased ages, and female gender in particular.

DISCUSSION

The prognosis of DTC has become excellent in recent years through the evolution of better treatment options and increasing use of RAI therapy for the ablation of remnant thyroid tissues postoperatively.[5,15,16] However, the evidence of selective use of RAI ablation therapy is still in controversy.[17] Therefore, this particular study was conducted with an aim to assess and compare the outcomes of low-risk DTC with tumour size 1 to 4 cm post-thyroidectomy in patients who never received RAI ablation and those who received RAI therapy. Many studies have demonstrated the significant effect of RAI therapy in the survival of high-risk group patients, while some other studies showed no significant differences in overall outcomes.[12,15,16,18-20]

Additionally, studies regarding the recurrence rates are variably reported where some studies showed improved outcomes[21] while others did not.[15,20,22] Similarly, this study also showed that RAI ablation therapy significantly improved outcomes in less advanced stages of tumour. The disease recurrence rate was less but occurred only in individuals who received RAI ablation and had advanced stage of tumour at initial therapy. Another study conducted to assess the survival benefits among the low-risk DTC patients found non-significant difference between disease-free survival and overall survival among patients who received RAI in comparison to those who did not receive RAI.[21]

Nevertheless, it has been stated in international guidelines that RAI therapy should be considered for tumours above 1 cm and that are metastasised outside the thyroid gland.[23,24] Thus, most patients included in this study had tumour sizes above 1 cm, with or without extrathyroidal extension. Following the international guidelines, the majority of patients received RAI therapy. It has also been established in the literature that detectable Tg levels could be found in patients who did not receive RAI therapy, possibly coming from the remnant thyroid gland tissue. In these circumstances, disease-free survival could be attained by following stable levels of Tg over time. In this study, patients with tumour stage T2 received RAI therapy because of the high risk of recurrence with increasing size of tumour, whereas patients with tumour stage T1 without any high-risk features of recurrence in histopathology and low Tg level post-thyroidectomy did not receive RAI therapy. This was considered due to the underlying risk of malignancies, acute and sub-acute side effects and unclear effects of RAI on the DTC outcomes, as reported in a study by Sacks *et al*.[25]

This study had some limitations. It was based on the retrospective study design where patient and physician-related selection biases could occur. Moreover, the outcomes of the patients are reported for both papillary as well as follicular thyroid carcinomas. Finally, due to the low sample size, the generalisability of the results could not be attained and comparison of RAI could not be reported. However, this study included data from a single cancer referral institute which is managed with a uniform histopathological, baseline, postoperative, and follow-up reporting system. This study reinforces the results of Sawka *et al.* and suggests that low-risk patients should not be overtreated. The rare complications and side effects of RAI should also be considered, and after surgery, RAI treatment should be reserved only for high-risk patients.[19] For further validation of this study's results, a prospective cohort study should be performed to obtain more conclusive data about the clinical benefits of RAI in low-risk patients and to observe the effects of RAI ablation therapy on the patients' outcome in the long-term, in addition to longer follow-up duration to assess the significance of RAI on the survival rates and recurrence of disease among the patients.

CONCLUSION

This study concluded that following complete tumour resection, with total thyroidectomy, highly selected group of patients with low risk local disease have low rates of recurrence when managed without RAI. Interestingly, the disease recurrence was also only seen in patients who received RAI ablation therapy as compared to those who did not receive the RAI therapy. Moreover, it could be predicted that patients who received RAI were found to be at higher risk of disease recurrence as compared to those who did not receive RAI therapy, specifically because of advanced stage of tumour at the initial stage of therapy.

ETHICAL APPROVAL:
The study was conducted after obtaining approval from the Review Board of the Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN) Hospital.

PATIENTS' CONSENT:
Written informed consent was obtained from the participants.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
NF, ZK, JI, SH: Study conception and design.
NF, ZK, KS, SH: Data collection.
NF, ZK, AAB, SH, AA: Analysis and interpretation of results.
NF, ZK, JI, AAB, SH, AA: Manuscript preparation.
All authors approved the final version of the manuscript to be published.

REFERENCES

1. Davies L, Welch HG. Current thyroid cancer trends in the United States. *JAMA Otolaryngol Head Neck Surg* 2014; **140(4)**:317-22. doi: 10.1001/jamaoto.2014.1.
2. Carhill AA, Litofsky DR, Ross DS, Jonklaas J, Cooper DS, Brierley JD, *et al*. Long-term outcomes following therapy in differentiated thyroid carcinoma: NTCTCS registry analysis 1987-2012. *J Clin Endocrinol Metab* 2015; **100(9)**:3270-9. doi: 10.1210/JC.2015-1346.
3. Nixon IJ, Ganly I, Patel SG, Palmer FL, Di Lorenzo MM, Grewal RK, *et al*. The results of selective use of radioactive iodine on survival and on recurrence in the management of papillary thyroid cancer, based on memorial sloan-kettering cancer center risk group stratification. *Thyroid* 2013; **23(6)**:683-94. doi: 10.1089/thy.2012.0307.
4. Haugen BR, Sawka AM, Alexander EK, Bible KC, Caturegli P, Doherty GM, *et al*. American thyroid association guidelines on the management of thyroid nodules and differentiated thyroid cancer task force review and recommendation on the proposed renaming of encapsulated follicular variant papillary thyroid carcinoma without invasion to noninvasive follicular thyroid neoplasm with papillary-like nuclear features. *Thyroid* 2017; **27(4)**: 481-3. doi: 10.1089/thy.2016.0628.
5. Yer 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(19)**:4439-46. doi: 10.1002/ cncr.26070.
6. Haymart MR, Banerjee M, Stewart AK, Koenig RJ, Birkmeyer JD, Griggs JJ. Use of radioactive iodine for thyroid cancer. *JAMA* 2011; **306(7)**:721-8. doi: 10.1001/jama.2011.1139.
7. Schuessler KM, Banerjee M, Yang D, Stewart AK, Doherty GM, Haymart MR. Surgeon training and use of radioactive iodine in stage I thyroid cancer patients. *Ann Surg Oncol* 2013; **20(3)**:733-8. doi: 10.1245/s10434-012-2745-0.
8. Sawka AM, Lakra DC, Lea J, Alshehri B, Tsang RW, Brierley JD, *et al*. A systematic review examining the effects of therapeutic radioactive iodine on ovarian function and future pregnancy in female thyroid cancer survivors. *Clin Endocrinol (Oxf)* 2008; **69(3)**:479-90. doi: 10.1111/j.1365-2265.2008.03222.x.
9. Hebestreit H, Biko J, Drozd V, Demidchik Y, Burkhardt A, Trusen A, *et al*. Pulmonary fibrosis in youth treated with radioiodine for juvenile thyroid cancer and lung metastases after Chernobyl. *Eur J Nucl Med Mol Imaging* 2011; **38(9)**:1683-90. doi: 10.1007/s00259-011-1841-x.
10. Papaleontiou M, Banerjee M, Yang D, Sisson JC, Koenig RJ, Haymart MR. Factors that influence radioactive iodine use for thyroid cancer. *Thyroid* 2013; **23(2)**:219-24. doi: 10.1089/thy.2012.0380.
11. James BC, Mitchell JM, Jeon HD, Vasilottos N, Grogan RH, Aschebrook-Kilfoy B. An update in international trends in incidence rates of thyroid cancer, 1973-2007. *Cancer Causes Control* 2018; **29(4-5)**:465-73. doi: 10.1007/s10552-018-1023-2.
12. Mazzaferri EL. Thyroid remnant 131I ablation for papillary and follicular thyroid carcinoma. *Thyroid* 1997; **7(2)**: 265-71. doi: 10.1089/thy.1997.7.265.
13. Vaisman F, Momesso D, Bulzico DA, Pessoa CH, Dias F, Corbo R, *et al*. Spontaneous remission in thyroid cancer patients after biochemical incomplete response to initial therapy. *Clin Endocrinol (Oxf)* 2012; **77(1)**:132-8. doi: 10.1111/j.1365-2265.2012.04342.x.
14. Tuttle RM, Morris LF, Haugen BR, Shah JP, Sosa JA, Rohren E, *et al*. Thyroid–differentiated and anaplastic carcinoma. *AJCC Cancer Staging Manual* 2016; 881-98.
15. Barney BM, Hitchcock YJ, Sharma P, Shrieve DC, Tward JD. Overall and cause-specific survival for patients undergoing lobectomy, near-total, or total thyroidectomy for differentiated thyroid cancer. *Head Neck* 2011; **33(5)**:645-9. doi: 10.1002/hed.21504.
16. Jonklaas J, Sarlis NJ, Litofsky D, Ain KB, Bigos ST, Brierley JD, *et al*. Outcomes of patients with differentiated thyroid carcinoma following initial therapy. *Thyroid* 2006; **16(12)**:1229-42. doi: 10.1089/thy.2006.16.1229.
17. Sawka AM, Brierley JD, Tsang RW, Thabane L, Rotstein L, Gafni A, *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(2)**:457-80, x. doi: 10.1016/j.ecl.2008.02.007.
18. Jung TS, Kim TY, Kim KW, Oh YL, Park DJ, Cho BY, *et al*. Clinical features and prognostic factors for survival in patients with poorly differentiated thyroid carcinoma and compari-son to the patients with the aggressive variants of papillary thyroid carcinoma. *Endocr J* 2007; **54(2)**:265-74. doi: 10.1507/endocrj.k06-166.
19. Hay ID, Hutchinson ME, Gonzalez-Losada T, McIver B, Reinalda ME, Grant CS, *et al*. Papillary thyroid microcarcinoma: A study of 900 cases observed in a 60-year period. *Surgery* 2008; **144(6)**:980-7. doi: 10.1016/j.surg.2008.08.035.
20. Ross DS, Litofsky D, Ain KB, Bigos T, Brierley JD, Cooper DS, *et al*. Recurrence after treatment of micropapillary thyroid cancer. *Thyroid* 2009; **19(10)**:1043-8. doi: 10.1089/thy.2008.0407.

21. Schvartz C, Bonnetain F, Dabakuyo S, Gauthier M, Cueff A, Fieffe S, *et al*. Impact on overall survival of radioactive iodine in low-risk differentiated thyroid cancer patients. *J Clin Endocrinol Metab* 2012; **97(5)**:1526-35. doi: 10.1210/jc.2011-2512.
22. Patel SS, Goldfarb M. Well-differentiated thyroid carcinoma: The role of post-operative radioactive iodine administration. *J Surg Oncol* 2013; **107(6)**:665-72. doi: 10.1002/jso.23295.
23. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, *et al*. Revised American thyroid association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009; **19(11)**:1167-214. doi: 10.1089/thy.2009.0110.
24. 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(6)**:787-803. doi: 10.1530/eje.1.02158.
25. Sacks W, Wong RM, Bresee C, Braunstein GD. Use of evidence-based guidelines reduces radioactive iodine treatment in patients with low-risk differentiated thyroid cancer. *Thyroid* 2015; **25(4)**:377-85. doi: 10.1089/thy.2014.0298.