

Radioactive iodine timing in differentiated thyroid carcinoma: A meta-analysis

Ibrahim Altedlawi Albalawi^{1*}, Hyder Osman Mirghani²

Surgical Oncology, University of Tabuk, Tabuk, Saudi Arabia¹

Department of Internal Medicine, Faculty of Medicine, University of Tabuk, Tabuk, Saudi Arabia²

Corresponding author: 1*



Keywords:

Radioactive iodine, late introduction, early, differentiated thyroid carcinomas

ABSTRACT

Radioactive iodine (RAI) is commonly used postoperatively for differentiated thyroid carcinoma remnant ablation or metastasis. However, literature regarding the time of use lacks. Therefore, this meta-analysis assessed the same. The authors searched PubMed, Cochrane Library, and Google Scholar for references comparing early and late radioactive iodine administration among patients with differentiated thyroid carcinoma. The keywords used were early, late, radioactive iodine, outcomes, disease free survival, response to therapy, survival rates, remnant ablation, differentiated thyroid carcinoma with the Protean "AN" and "OR". Among the 515 titles identified through abstracts and references, 256 articles were eligible, of them ten full texts fulfilled the inclusion and exclusion criteria. Depending on the cut-off period after which RAI therapy is regarded as late we have seven articles with cut-off period= three months and three with a six months period. The studies included 50736 patients and 28418 events, no differences in the outcomes between early and late RAI administration were found when considering either three months or six months as a cut-off. (P-values=0.22 and 0.61 respectively). However, a substantial heterogeneity was observed, I^2 , 75% and 82%, Chi-square, 24.34, and 10.82 respectively, and P-values for heterogeneity, < 0.001 and 0.004 respectively. A sub-analysis showed that our results remained robust even after illuminating the studies with considerable heterogeneity (P-value=0.56, P-value for heterogeneity, 0.49, I^2 =0, Chi-square, 3.41, and mean difference, 4.). Radioactive iodine can be delayed up to six months after surgery paying the time according to the local facilities and the patient's characters.



This work is licensed under a Creative Commons Attribution Non-Commercial 4.0 International License.

1. INTRODUCTION

Differentiated thyroid cancer protocols are evolving to optimize the patient's outcomes. Radioactive iodine (RAI), although an essential component in differentiated thyroid carcinoma (DTC) management. However, the current trends are towards high selectivity to reflect utility depending on risks and benefits [1]. The controversy in DTC management is largely driven by the lack of randomized trials; the available evidence relies on retrospective studies that are prone to selection bias and often-incomplete [2]. The malignancy and

patient's characters further complicate the debate in lobectomy versus total thyroidectomy, neck imaging, and RAI use including timing, dose, and purpose of use [3]. RAI is not without hazards, therefore, the better optimizing the dose and timing is essential [4]. Thus, this meta-analysis aimed to compare early versus late administration of RAI among patients with DTC.

2. Subjects and Methods

2.1 Eligibility Criteria

The authors searched PubMed, Cochrane Library, and Google Scholar for references comparing early and late radioactive iodine administration among patients with differentiated thyroid carcinoma. The period was limited to the first published article up to February 28, 2021. Prospective cohorts, retrospective studies, and case-control studies were included if they compare late and early administration of RAI, case reports and series and studies without a control arm were not included. Studies on human adults were eligible, while studies conducted on children were excluded. The authors were faced with the problem of "early" versus "late" definition, as the definition was not uniform; therefore, the analysis was divided in to two categories depending on the definition of the cut off time [5- 7], [2], [8- 13], table 1, 2. In this meta-analysis, we considered early and late RAI therapy as less than three months and \geq three months respectively. Another category also has a cut-off period of six months. Regarding the stage of differentiated thyroid cancer, we included low/intermediate risk and high-risk malignancies.

2.2 Outcomes Measures

The outcomes included in the present study are, success rate of ablation whole-body scan, response to therapy, and survival. No demarcation was possible between disease free survival and overall survival due to the limited literature.

2.3 Literature Search

The two authors independently searched the PubMed (375), Cochrane Library (40), and Google Scholar (100) for articles published in English without limitation to study period (to the first published article up to February 28, 2021). The keywords used were early, late, radioactive iodine, outcomes, disease free survival, response to therapy, survival rates, remnant ablation, differentiated thyroid carcinoma with the Protean "AN" and "OR". Among the 515 references identified through abstracts and references, 256 articles were eligible, of them ten full texts fulfilled the inclusion and exclusion criteria. Depending on the cut-off period after which RAI therapy is regarded as late we have seven articles with cut-off period= three months and three with a six months period. Figure 1, 2, and table 1.

2.4 Heterogeneity Assessment

We investigated the heterogeneity and found [2], [8] contributed the whole heterogeneity. The studies assessed response to therapy on low/intermediate risk DTC while the rest assessed survival rate. In addition, the later study investigated RAI timing among patients with papillary thyroid carcinoma of more than one cm.

2.5 Statistical Analysis

The RevMan system was used at 95% confidence interval, due to the substantial heterogeneity, the random effect and odd ratio was used. Changing to risk ratio did not improve the results. P-value ≤ 0.05 was considered significant. We conducted two analyses to assess both cut-off of less than three months \geq three months and \geq six months. A sub-analysis was conducted in the first category to test for each study contribution to the heterogeneity.

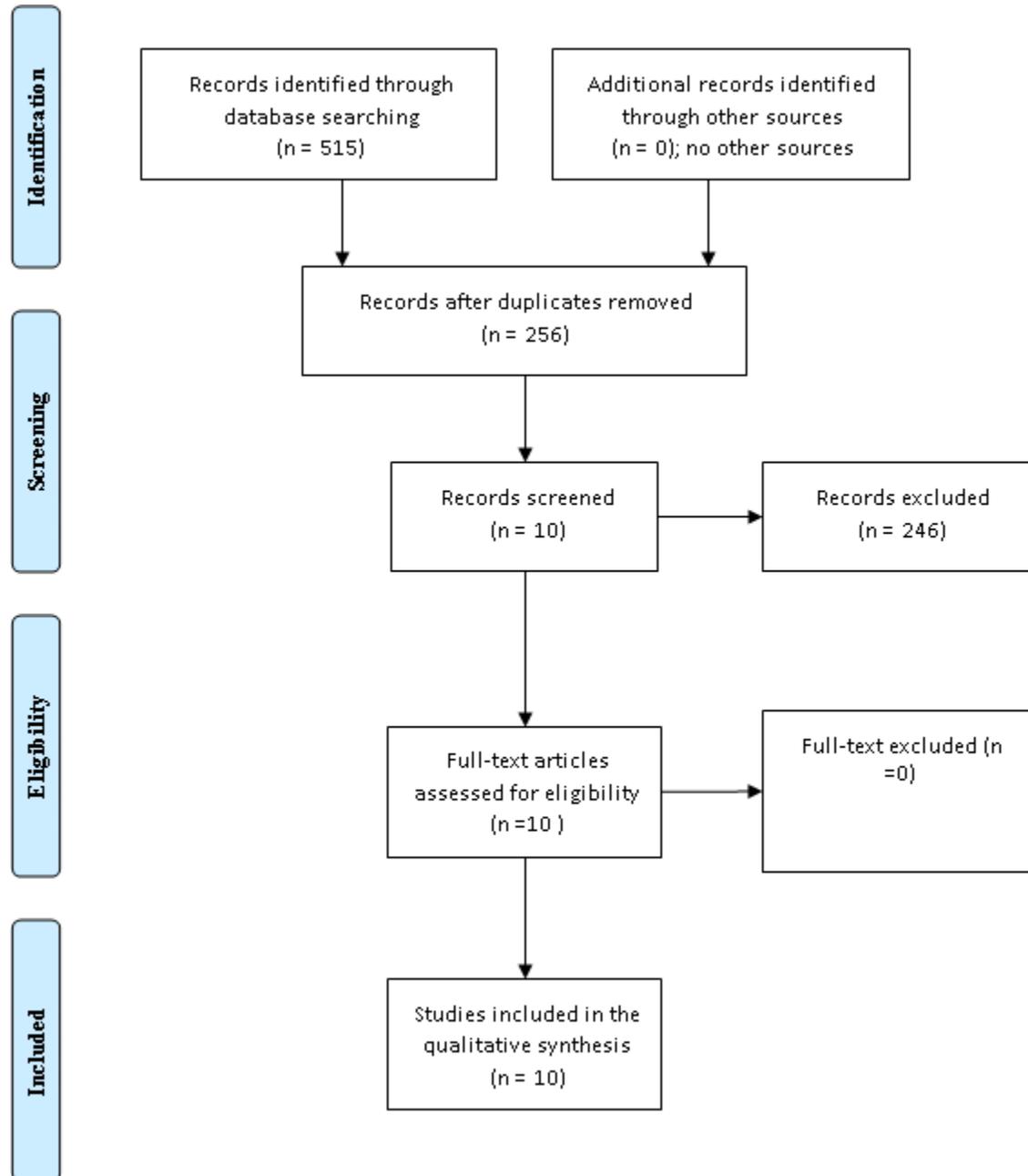


Figure 1. Early Versus Late Radioactive Iodine Therapy Outcomes

3. Results

The present meta-analysis showed no differences between late and early radioactive iodine use among patients with differentiated thyroid carcinoma; ten studies were pooled [2], [5- 13]. Half of the included studies were from Asia, two from the USA, two from Europe, and one from South Americas. The studies included 50736 patients and 28418 events, no differences in the outcomes between early and late RAI administration were found when considering either three months or six months as a cut-off. (P-values=0.22 and 0.61 respectively). However, a substantial heterogeneity was observed, I^2 , 75% and 82%, Chi-square, 24.34, and 10.82 respectively, and P-values for heterogeneity, < 0.001 and 0.004 respectively. A sub-analysis showed that our results remained robust even after illuminating the studies with considerable heterogeneity (P-value=0.56, P-value for heterogeneity, 0.49, $I^2=0$, Chi-square, 3.41, and mean difference, 4.). Figures 2-4.

Table 1. Studies with cut-off Timing of Radioactive Iodine Administration at six months.

Author	Year	Country	Type of study and patient character	Patients and outcome	Result
[5]	2011	Japan	Retrospective, 198 DTC patients with extrathyroidal extension	19/198 vs. 4/198, death assessed	Delaying radioactive iodine is associated with poor outcomes
[6]	2019	Poland	Retrospective/low risk DTC, up to 9 months & 9-24 months	18/323 vs. 16/228, recurrence risk	Late timing predicted poor outcome.
[7]	2016	Brazil	Prospective/different TNM stages DTC	175/ 295 vs. 164/ 250, evidence of thyroid cancer	Equal outcome,

Table 2. Radioactive Iodine Timing and Low/Intermediate Differentiated Thyroid Carcinoma Outcomes (cut-off at three months).

Author	Year	Country	Type of study and patients character	No of patients and outcomes	result
[8]	2020	Korea	Retrospective, /low risk papillary	348/451 vs. 60/75. whole-body scan, response to therapy, and survival	No difference.
[9]	2019	Korea	Retrospective, intermediate/high risk papillary	295/360 vs. 277/360, survival, response to therapy	No significant difference.
[10]	2018	China	Retrospective, low-to intermediate-risk	8/187 vs. 9/48, response to therapy	Delayed therapy associated with poor response
[11]	2016	USA	Retrospective, high-risk, papillary	106/9706 vs. 97/9706, survival	No difference.
[12]	2016	USA	Retrospective, low/intermediate risk	3631/3826 Vs. 22707/23915, survival assessed	No significant difference.
[13]	2014	Greece	Retrospective, low-risk, 4.7 months, median three months	44/50 vs. 52/57, remission assessed	Timing has no effect, urgency not recommended.
[2]	2021	Turkey	Retrospective, low/intermediate DTC	102/151 vs. 286/352, success rate of ablation	Late timing better.

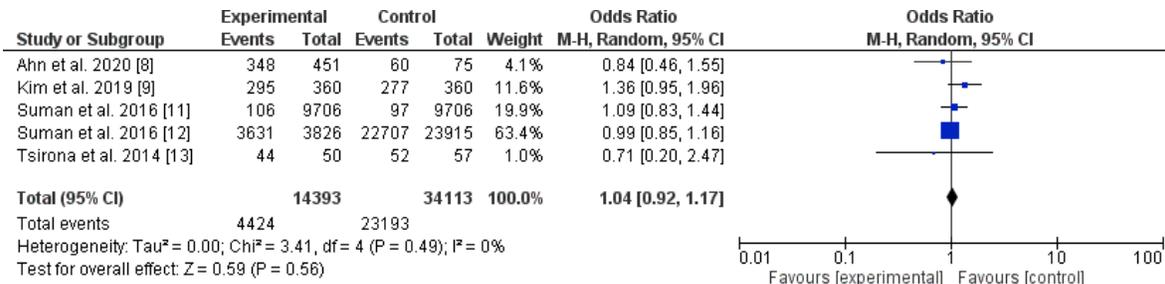


Figure 2. Studies with cut-off Timing of Radioactive Iodine Administration at six months.

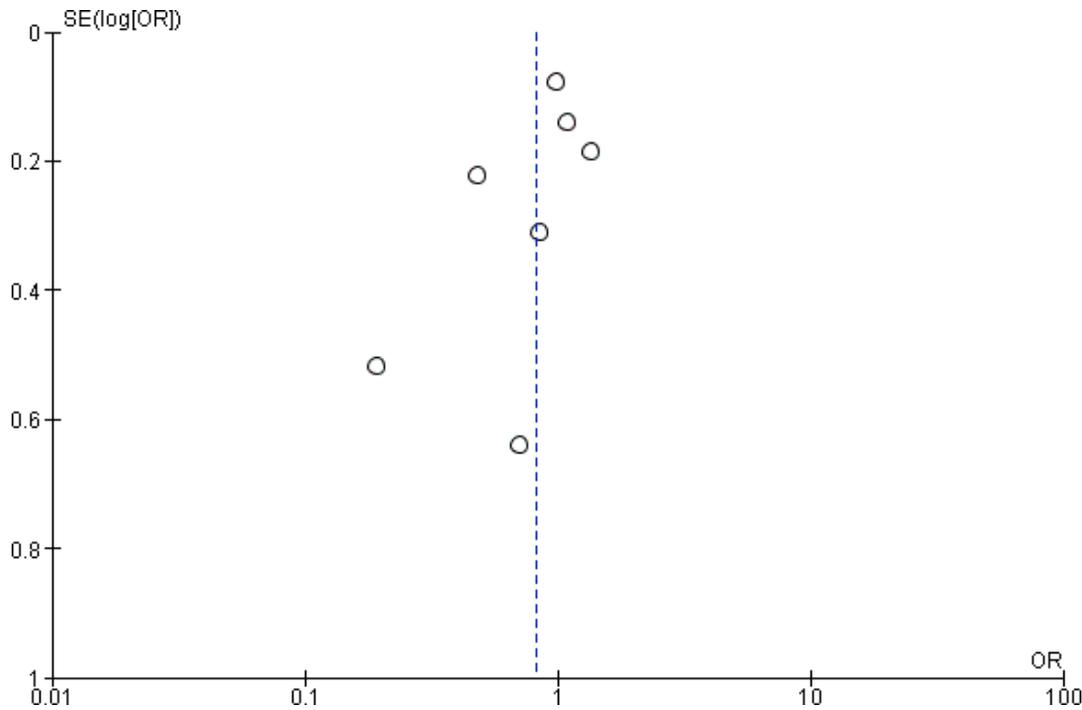
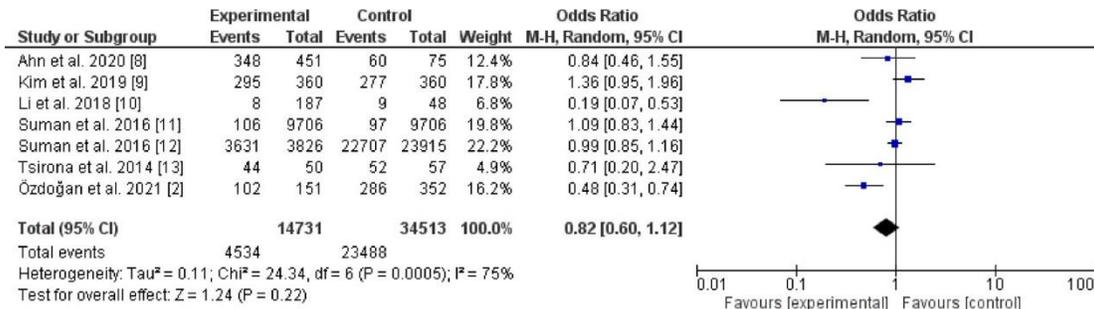


Figure 3. A Comparison between Early and Late Radioactive Iodine in Differentiated Thyroid Carcinoma (Cut-off at Three Months)

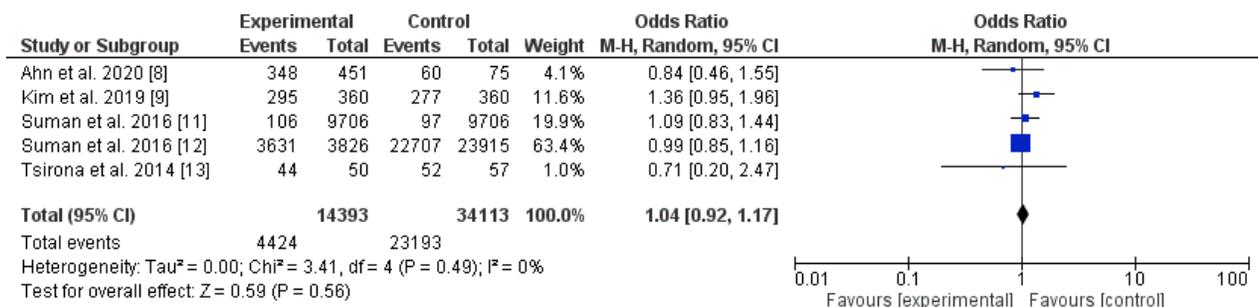


Figure 4. Studies after excluding two study with substantial heterogeneity contribution**4. Discussion**

Thyroid carcinoma is mostly differentiated with five-year survival rate ranging from 90-95% [14], radioactive iodine (RAI) is recommended after total thyroidectomy. However, the dose is controversial [15], [16]. Meta-analyses on the use of RAI are already present, we could not find any similar studies regarding the time of administration. The field of RAI treatment and the management of differentiated thyroid carcinoma (DTC) in general have been discussed controversially due to the lack of randomized trial. A big concern is the emerging DTC resistance to RAI on one side and fearing of RAI unwanted effects in low-risk malignancies. The management of DTC is given in the light of clinicopathological and molecular characteristics [17]. In addition to the above controversy and the emerging less restrictive guidelines, another question of when to administer RAI has been raised [18]. In the current meta-analysis, no significant statistical difference was found between early and late RAI among patient with different risk shades. The results stand robust even after elimination of heterogeneity. The current results imply that urgency in postoperative radioactive iodine may not be needed. The treating physician can schedule RAI according to the availability of care, number of isolation rooms, and socioeconomic character of the patients with no harms. The current results raised the question of the short-term benefits of RAI therapy among patients with differentiated thyroid carcinoma. The current study included patients with different basic characters and risk factors and showed no negative impact on delaying RAI up to six months after surgery; this benefit may give flexibility in scheduling the patients according to the referral opportunities and Hospital facilities including the availability of RAI. Thus, RAI timing may be scheduled according to local care and patients characteristics. A recent study conducted in Brazil showed that the high RAI use during the period from 200-2015 progressively declined (a similarly pattern was observed regarding the activity). The authors also observed inter-institute and regional variations that cannot be explained by the patient's socioeconomic characteristics nor by the referral system [19]. The current results indicated that more actions are needed to improve current guidelines of RAI use among patients with differentiated thyroid carcinoma and incorporating the timing of RAI in the multi-disciplinary care of these patients.

5. Conclusion

A flexible approach in RAI (up to six months after surgery) for patients with DTC may not be harmful to the patients and allow for a better scheduling of the patients according to the local facilities and patients characteristics.

The study limitations were the observational nature of the included studies and the pooling of patients with various basic characters. Randomized controlled trials will solve the issue.

Conflicts of Interest: None to declare

6. Acknowledgment

We would like to acknowledge Mohammed Hyder Osman for formatting the figures of this manuscript.

7. References

- [1] Orosco RK, Hussain T, Noel JE, et al. Radioactive iodine in differentiated thyroid cancer: a national database perspective. *Endocr Relat Cancer*. 2019; (10):795-802. doi: 10.1530/ERC-19-0292.
- [2] Özdoğan Ö, Aksu A, Doğan E, et al. Applying postoperative radioiodine therapy before 3 months seems to decrease ablation success in patients with differentiated thyroid carcinoma. *Ann Nucl Med*. 2021.

doi: 10.1007/s12149-020-01555-7.

- [3] Tuttle RM. Controversial Issues in Thyroid Cancer Management. *J Nucl Med.* 2018;59(8):1187-1194. doi: 10.2967/jnumed.117.192559
- [4] Lin B, Qiang W, Wenqi Z, et al. Clinical response to radioactive iodine therapy for prophylactic central neck dissection is not superior to total thyroidectomy alone in cN0 patients with papillary thyroid cancer. *Nucl Med Commun.* 2017 ;38(12):1036-1040. doi: 10.1097/MNM.0000000000000756.
- [5] Higashi T, Nishii R, Yamada S, et al. Delayed initial radioactive iodine therapy resulted in poor survival in patients with metastatic differentiated thyroid carcinoma: a retrospective statistical analysis of 198 cases. *J Nucl Med.* 2011 May;52(5):683-9. doi: 10.2967/jnumed.110.081059.
- [6] Krajewska J, Jarzab M, Kukulska A, et al. Postoperative Radioiodine Treatment within 9 Months from Diagnosis Significantly Reduces the Risk of Relapse in Low-Risk Differentiated Thyroid Carcinoma. *Nucl Med Mol Imaging.* 2019 ;53(5):320-327. doi: 10.1007/s13139-019-00608-8.
- [7] Scheffel RS, Zanella AB, Dora JM, Maia AL. Timing of Radioactive Iodine Administration Does Not Influence Outcomes in Patients with Differentiated Thyroid Carcinoma. *Thyroid.* 2016; 26(11):1623-1629. doi: 10.1089/thy.2016.0038.
- [8] Ahn J, Jin M, Song E, et al. Clinical Outcomes after Early and Delayed Radioiodine Remnant Ablation in Patients with Low-Risk Papillary Thyroid Carcinoma: Propensity Score Matching Analysis. *Endocrinol Metab (Seoul).* 2020; 35(4):830-837. doi: 10.3803/EnM.2020.747.
- [9] Kim M, Han M, Jeon MJ, et al. Impact of delayed radioiodine therapy in intermediate-/high- risk papillary thyroid carcinoma. *Clin Endocrinol (Oxf).* 2019 Sep;91(3):449-455. doi: 10.1111/cen.14039.
- [10] Suman P, Wang CH, Abadin SS, et al. TIMING OF RADIOACTIVE IODINE THERAPY DOES NOT IMPACT OVERALL SURVIVAL IN HIGH-RISK PAPILLARY THYROID CARCINOMA. *Endocr Pract.* 2016; 22(7):822-31. doi: 10.4158/EP151088.OR.
- [11] Suman P, Wang CH, Moo-Young TA, et al. Timing of Adjuvant Radioactive Iodine Therapy Does Not Affect Overall Survival in Low- and Intermediate-Risk Papillary Thyroid Carcinoma. *Am Surg.* 2016; 82(9):807-14.
- [12] Li H, Zhang YQ, Wang C, et al. Delayed initial radioiodine therapy related to incomplete response in low- to intermediate-risk differentiated thyroid cancer. *Clin Endocrinol (Oxf).* 2018 Apr;88(4):601-606. doi: 10.1111/cen.13551.
- [13] Tsirona S, Vlassopoulou V, Tzanela M, et al. Impact of early vs late postoperative radioiodine remnant ablation on final outcome in patients with low-risk well-differentiated thyroid cancer. *Clin Endocrinol (Oxf).* 2014 Mar;80(3):459-63. doi: 10.1111/cen.12301.
- [14] Vardarli I, Weidemann F, Aboukoura M, et al. Longer-term recurrence rate after low versus high dose radioiodine ablation for differentiated thyroid Cancer in low and intermediate risk patients: a meta-analysis. *BMC Cancer.* 2020; 20 (1):550. doi: 10.1186/s12885-020-07029-3.

- [15] Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016 ;26(1):1-133. doi: 10.1089/thy.2015.0020.
- [16] Perros P, Boelaert K, Colley S, et al; British Thyroid Association. Guidelines for the management of thyroid cancer. *Clin Endocrinol (Oxf)*. 2014 Jul;81 Suppl 1:1-122. doi: 10.1111/cen.12515.
- [17] Luo Y, Jiang H, Xu W, et al. Clinical, Pathological, and Molecular Characteristics Correlating to the Occurrence of Radioiodine Refractory Differentiated Thyroid Carcinoma: A Systematic Review and Meta-Analysis. *Front Oncol*. 2020 Sep 30; 10:549882. doi: 10.3389/fonc.2020.549882
- [18] Fard-Esfahani A, Emami-Ardekani A, Fallahi B, Fard-Esfahani P, Beiki D, Hassanzadeh-Rad A, Eftekhari M. Adverse effects of radioactive iodine-131 treatment for differentiated thyroid carcinoma. *Nucl Med Commun*. 2014 Aug;35(8):808-17. doi: 10.1097/MNM.000000000000132.
- [19] Schwengber WK, Mota LM, Nava CF, Rodrigues JAP, Zanella AB, De Souza Kuchenbecker R, Scheffel RS, Maia AL, Dora JM. Patterns of radioiodine use for differentiated thyroid carcinoma in Brazil: insights and a call for action from a 20-year database. *Arch Endocrinol Metab*. 2020 Oct 21:2359-3997000000302. doi: 10.20945/2359-3997000000302.