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Second Adjuvant Radioiodine Therapy after Reoperation for Locoregionally Persistent or Recurrent Papillary Thyroid Carcinoma

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Abstract

Introduction Differentiated thyroid carcinoma (DTC) has increased incidence. Intermediate- and high-risk patients have lymph node relapse rate ranging from 10 to 50%, and receive multiple reinterventions, increasing the morbidity of the disease. Currently, there are no established guidelines for the use of second radioactive iodine (RAI) therapy after the reintervention for local recurrence.

Materials and Methods This is a retrospective review of the medical records of 1,299 patients treated from January 2016 to July 2019 with DTC. We included 48 patients who received total thyroidectomy, RAI remnant ablation, surgery to remove the locally recurrent/persistent papillary thyroid carcinoma (PTC), and received a second RAI therapy.

Results There were no significant differences between thyroglobulin (Tg) levels before reoperation (Tg0), Tg levels postoperatively (Tg1), and Tg levels after 6 months of second adjuvant RAI therapy (Tg2). However, we evidenced a 69.79% drop in first Tg levels (Tg0: 24.7 vs. Tg1: 7.56, $p = 0.851$) and 44.4% decrease in second Tg levels (Tg1: 7.56 vs. Tg2: 4.20, $p = 0.544$). Also, 77.1% of the patients did not have another documented recurrence. The median relapse-free time was 10.9 months (range: 1.3–58.2 months).

Keywords
- thyroid cancer
- local neoplasm recurrence
- thyroglobulin
- nuclear medicine
- iodine
- reoperation

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Conclusion The results of the study cannot assess that a second RAI treatment after reoperation for locoregionally persistent or recurrent disease have a significant impact on treatment outcomes in intermediate- or high-risk patients with PTC. However, the 77.1% of patients have not presented a second documented recurrence and the median values of Tg and TgAb levels showed a substantial decrease after surgery and second RAI treatment.

Introduction

Differentiated thyroid carcinoma (DTC) represents more than 90% of thyroid carcinomas. In Colombia, 5,304 new cases are diagnostic per year being the sixth cause of cancer.[1] The American Thyroid Association (ATA) 2009 risk stratification of DTC is established by histopathology into three groups: low-risk, intermediate-risk, and high-risk. Iodine ablation is recommended in high-risk or intermediate-risk patients, after total thyroidectomy with or without neck dissection (ND).[2]

Iodine ablation is recommended in high-risk or intermediate-risk patients, after total thyroidectomy with or without ND.[3] Radioiodine remanent ablation (RRA) eradicates the residual thyroid and reduces the risk of recurrence, optimizing the monitoring of thyroid stimulating hormone (TSH), thyroglobulin (Tg), and anti-Tg antibodies (TgAb).[4] Patient response to therapy is classified according to 2015 ATA guidelines.[3] Disease status after primary treatment is categorized as excellent response, biochemical incomplete response, structural incomplete response, or indeterminate response.[2] Also, as described by Tuttle et al in 2008, based on the images and the biochemical levels of the markers, there is a "risk of failure of the primary treatment."[5]

Lymph node recurrence in intermediate- and high-risk groups ranges from 10 to 50%. [3,6] When recurrence is documented by fine-needle aspiration (FNA), it is called an incomplete structural response.[7]

ATA recommends adjuvant therapy for patients with residual or RAI avid disease after surgery for recurrence. [2,3] Hirsch et al[8] and Yim et al[9] reported no clear impact of a second radioactive iodine (RAI) treatment in DTC patients with biochemical incomplete response or structural incomplete response. However, they found that the proportion of patients who were disease free at the last follow-up was twice as high in group that underwent to surgery and second RAI treatment.

Currently, there are no specific guidelines that indicate or recommend a second treatment with iodine in the postoperative period of patients with recurrent or persistent papillary thyroid carcinoma (PTC).

Consequently, we performed a retrospective clinical case series to evaluate the impact of second adjuvant RAI therapy, after reoperation of locoregionally persistent or recurrent PTC, in a tertiary referral cancer center.

Materials and Methods

Study Population

Ethical approval was obtained from the Institutional Review Board (code no.: C41030617–232). A retrospective clinical case series was conducted that included data from health records of 1,299 DTC patients who were discussed at the thyroid institutional meeting (with nuclear medicine, head and neck surgery, endocrinology, radiology, and pathology specialist participation) from January 2016 to July 2019.

We conducted a review of the individual medical records to identify ATA intermediate-risk PTC patients (microscopic invasion of tumor into the perithyroidal soft tissues; RAI-avid metastatic foci in the neck on the first posttreatment whole-body RAI scan; aggressive histology such as tall cell, hobnail variant, columnar cell carcinoma; PTC with vascular invasion; clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension; and multifocal papillary microcarcinoma with ETE) and ATA high-risk PTC patients (postoperative serum Tg suggestive of metastases and pathologic N1 with any metastatic lymph node 3 cm or higher in largest dimension)[2] with PTC over 18-year-old patients and without distant metastases (►**Fig. 1**).

Patients had undergone total thyroidectomy with or without ND in the first surgery, received RRA under thyroid hormone withdrawal RAI activity (range: 30–200 mCi), mean of 116.2 mCi (1.1–7.4 GBq, mean of 4.29 GBq), after documentation with FNA, had neck reoperation, and second adjuvant RAI treatment in tertiary referral cancer center. Based on the data abstraction, 48 patients were included.

The baseline clinical characteristics collected were age at the time of initial diagnosis (≤ 55 or >55 years), initial histopathology (papillary or follicular), PTC aggressive subtype, tumor dimensions, microscopic characteristics, and extrathyroidal extension (T1, T2 or T3, and T4) nodal status at the time of diagnosis (Nx-N0 or N1a-N1b) according to

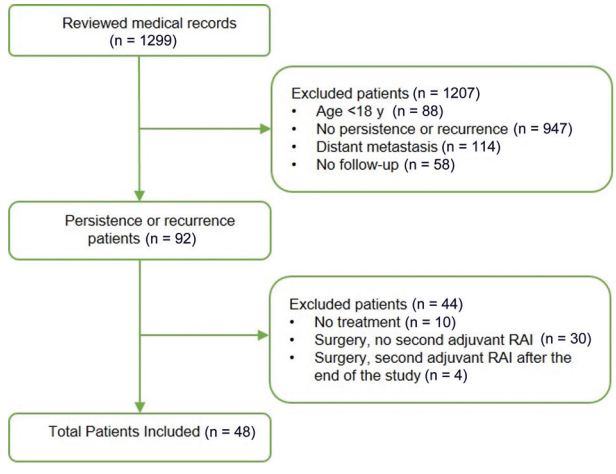

Fig. 1 This algorithm demonstrate how the study patient were selected.

TNM eighth edition[5] and result of I^{131} postablation whole-body scan (WBS).

Patients with surgery or RRA not performed at our institution were included after conducting the histopathology and I^{131} postablation WBS review.

Follow-up consisted of physical examination, monitoring of TSH, Tg, and TgAb, neck ultrasonography, as well as other complementary images (computed tomography [CT] scan, magnetic resonance image, and ^{18}F-fluorodeoxyglucose positron emission tomography [^{18}F-FDG PET]/CT).

Locoregionally persistent disease was defined as that detected within 6 months, following the end of first treatment and locoregionally recurrent disease as defined if it was detected after 6 months from the end of first treatment, this was documented with FNA. Surgery was performed by ND or radio-guided occult lesion location (ROLL) surgery.[10,11]

Review of the second histopathology, included determination of the size and number of resected lymph nodes, size of the metastasis, or soft tissues and verification of extension to adjacent tissues. The second adjuvant radioiodine therapy with RAI activity, range from 100 to 200 mCi, mean of 102.7 mCi (3.7–7.4 GBq, mean of 3.8 GBq), and had postablation WBS; this dose was stablished by our tumor board according to the risk factor of each patient in relation with the 2015 ATA recommended dosage in adjuvant therapy,[3] two patients received a dose of 200 mCi dose for suspected lung metastasis that was ruled out by WBS and CT images.

TSH, Tg levels, and TgAb were assessed between 4 and 8 weeks before reoperation (TSH0, Tg0, and TgAb0), 4 weeks after reoperation (TSH1, Tg1, and TgAb1), and 6 months after second adjuvant RAI treatment (TSH2, Tg2, and TgAb2).

Follow-up

The patients had follow-up of at least for 6 months after second RAI treatment. The response to therapy was classified according to 2015 ATA guidelines.[2] Disease status was categorized as excellent response (no clinical, biochemical, or structural evidence of disease; suppressed Tg level < 0.2 ng/mL), biochemical incomplete response (suppressed Tg level > 1 ng/mL), structural incomplete response (persistent or newly identified locoregional or distant metastases), or indeterminate response (suppressed Tg level of 0.2–1.0 ng/mL and/or nonspecific imaging abnormalities). TSH, Tg levels, and TgAb were assessed between 4 and 8 weeks before reoperation (TSH0, Tg0, and TgAb0), 4 weeks after reoperation (TSH1, Tg1, and TgAb1) and 6 months after second adjuvant RAI treatment (TSH2, Tg2, and TgAb2).

Statistical Analysis

This is a clinical case series. We described the clinical, radiological, and histopathological variables by summary measures that include absolute and relative frequency in the case of qualitative variables and measures of central tendency (mean, medians, standard deviation [SD], ranges, minimum, or maximum) for quantitative variables. The disease-free survival time is described graphically and with time-to-event functions, estimated using the Kaplan–Meier method. Relapse-free survival was defined as the time elapsed in months between the second iodine therapy and FNA diagnostic of relapse at the last follow-up. To stablish difference between the mean values of the biochemical values at the diagnosis of recurrence and after the surgical treatment we performed with paired *t*-test between TSH0, Tg0, and TgAb0 and TSH1, Tg1, and TgAb1. Additionally, to assess the differences between the mean value of the biochemical parameters at the diagnose of recurrence, after the surgical treatment and 6 months after the second RAI treatment, we performed analysis of variance (ANOVA) test using as factor the time of measurement of the laboratory test (TSH0, Tg0, TgAb0, TSH1, Tg1, and TgAb1 and TSH2, Tg2, and TgAb2). Some variables of interest were disaggregated using the Cross Tabulation by SPSS version 19.

This research protocol complied with the guidelines established by the Declaration of Helsinki and the ethical guidelines for biomedical research prepared by the Council of International Organizations of Medical Sciences [CIOMS]) and with the parameters established by national regulations. Additionally, it was approved by the Institutional Research Ethics Committee and was monitored by an independent monitoring team that verified the validity of the information registered in RedCap. The primary source of information was the SAP medical registry, with information on patients with recurrence of DTC who received surgery for the recurrence and second iodine therapy at our institution from June 1, 2016, to July 31, 2019.

Results

Study Population

The clinical case series consist in 48 PTC patients who were treated with total thyroidectomy with or without ND and RRA, neck reoperation for persistent, or recurrent cancer and second adjuvant RAI treatment. The median age at diagnosis of recurrence was 47.03 years (SD = 14.6, range: 21–73) years and 38 (79.2%) of the patients were female. At the time of first surgery, 23 patients (31.2%) had central ND (CND) and CND with lateral ND in 15 patients (31.2%) and no ND in 10 patients (20.8%). Of the patients with only CND, 21 relapsed in the lateral lymph nodes (91.30%). Forty-two patients underwent one-stage surgery, 31 of them in another institution (73.8%).

According to the risk, after the first surgery, we found 28 (58.3%) patients with intermediate risk and 20 (41.7%) patients with high risk. Clinical and histopathological characteristics of the first surgery are described in (►**Table 1**). I^{131} postablation (WBS) demonstrated neck uptake in 44 patients, 34 at the central level, 8 at the lateral and central level, and 2 at the lateral level.

The recurrent/persistent neck disease was treated in 33 (68.7%) patients with ND and in 15 (31.3%) patients by ROLL surgery (►**Table 2**). According to the pathological characteristics of second surgery, the risk was high for 16 patients (33.3%) and intermediate 32 (66.7%). The second adjuvant RAI treatment was 30 mCi (1.1 GBq) for 1 patient, 100 mCi (3.7 GBq) for 45 patients, and 200 mCi (7.4 GBq) for 2 patients. The I^{131} postablation (WBS) showed uptake in

Table 1 Baseline clinical and pathological characteristics of patients at first surgery

Gender	Total ($n = 48$)	Percentage
Male	10	20.8
Female	38	79.2
Thyroidectomy		
One stage	42	87.5
Two stages	6	12.5
Histology (first surgery)		
Tall cells	3	6.3
Classic	31	64.6
Follicular	6	2.1
Size of tumor > 10 mm	42	87.5
True extrathyroidal extension	27	56.3
T status		
T1	13	27
T2	3	6.25
T3	30	62.5
T4	2	4.16
N status		
N0	2	4.16
N1a	22	45.8
N1b	16	33.3
Prognostic stage		
Stage I	31	64.6
Stage II	14	29.2

Table 2 Cross-table pathological characteristics first and second surgery

	First surgery Mean (SD)/ *n* (%)	Second surgery Mean (SD)/ *n* (%)
CND	23 (47.9)	12 (25) ROLL
LND	0	27 (56.25)
CND + LND	15 (31.2)	6 (12.5)
Dissection not performed	10 (20.8)	0
Soft tissue resection	0	3 (6.1)
LN resected	9 (11.2)	22.9 (23.2)
LN affected	5.5 (6.8)	4.36 (5.6)
Size of metastasis (mm)	11.5 (7.3)	12.61 (8.35)
Extranodal extension	19 (39.6)	34 (70.8)
ATA intermediate risk of recurrence	28 (58.3)	32 (66.7)
ATA high risk of recurrence	20 (41.7)	16 (33.3)

Abbreviations: ATA, American Thyroid Association; CND, central neck dissection; LND, lateral neck dissection; LN, lymph node; ROLL, radio-guided occult lesion location; SD, standard deviation.

only 14 (29.2%) patients, 8 in the center of neck, 5 in the lateral neck, and 1 in both.

This dose was stablished by our tumor board according to the risk factor of each patient in relation with the 2015 ATA recommended dosage in adjuvant therapy,[3] two patients received a dose of 200 mCi dose for suspected lung metastasis that was ruled out by WBS and CT images.

This dose was lower in 18 patients when compared with the first dose we found that from the 11 patients that had second recurrence, only 4 had less dose administered.

Follow-up

Patients were followed for a median of 57.6 months after diagnosis of recurrence, with a range of 30 to 196 months (SD = 25.7). The time of first recurrence was 36.39 months (SD = 36.50). We had 77.1% (37 patients) without second documented recurrence, 11 patients had second recurrence which occurred in mean time of 10.9 months (SD = 17.81), 13 patients with biochemical incomplete response which has been stable during the follow-up or in a descending pattern. Also 14 patients with structural incomplete response with lymph nodes less than 10 mm without reinterventions and with stable biochemical parameters that are in strict follow-up.

The risk category changed in 12.5% (six patients) of the total, five from high- to intermediate-risk and one from intermediate to high risk.

Statistical Analysis

The average follow-up from diagnosis of recurrence and last visit for follow-up and closure of the study was 50.65 months (range: 9–145 months), since we had one patient with diagnosis of second recurrence in 2005 and had surgery and second iodine treatment in 2016.

The second recurrence occurred in average of 10.9 months, this is described graphically and with time-to-event functions, estimated using the Kaplan–Meier method, this is considered relapse-free survival time defined as the time elapsed in months between the second iodine therapy and FNA diagnostic of second recurrence at the last follow-up (►**Fig. 2**).

The comparative analysis of the mean values of TSH, Tg, and TgAb (measured within 4 weeks of the diagnosis of recurrence, at 1 month after surgery, and at 6 months after second iodine treatment) demonstrated reduction in the mean values for TSH1 and TSH2 (7.68, SD = 29.2 vs. 1.40, SD = 6.38 with $p = 0.956$) but no statistical difference obtained. Also, the mean values of Tg0 (mean = 24.57, SD = 70.9), Tg1 (mean = 7.56, SD = 32.7), and Tg2 (mean = 4.20, SD = 13.17) were lower after surgery and even lower after second RAI treatment but not statistical difference at the moment of performing paired *t*-test, mean values

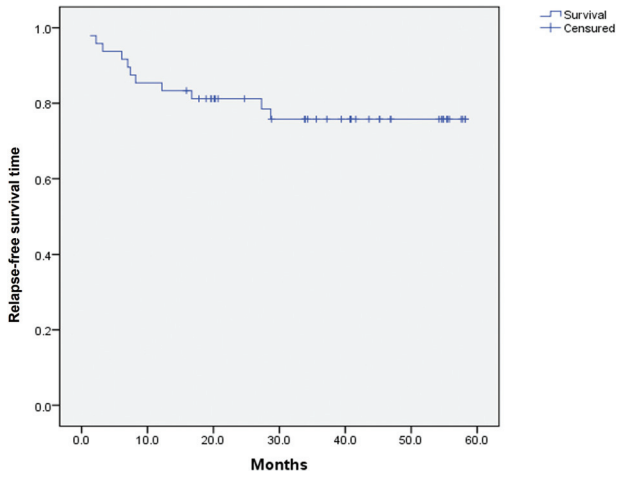

Fig. 2 The median relapse-free time from the second RAI treatment was 10.9 months (range: 1.3–58.2 months). RAI, radioactive iodine.

of Tg0 versus Tg1 (24.57, SD = 70.9 vs. 7.56, SD = 32.7 with $p = 0.851$) and Tg1 versus Tg2 (7.56, SD = 32.7 vs. 4.20, SD = 13.1 with $p = 0.544$) obtained.

For the TgAb analysis, mean values of TgAb0 versus TgAb1 (518.31, SD = 1,842.4 vs. 159.11, SD = 659.19 with $p = 0{,}00$) and mean values of TgAb1 versus TgAb2 (159.11, SD = 659.1 vs. 126.00, SD = 599.8 with $p = 0{,}00$) obtained.

Discussion

The incidence of DTC is increasing in Colombia being prevalent in women,[1] we observed higher recurrence risk in the patients that were primary treated outside from our institution, It is known that patients treated in a noncancer facility could have an increased risk of recurrence related to inadequate initial surgery and poor follow-up after treatment.[12] The ATA classifies these patients as structural incomplete responders,[2,3] this is associated with increased morbidity of local and regional symptoms related to compression of the lymph-node masses and multiple surgical interventions. It has been suggested that RAI treatment for recurrence may be considered in some patients,[13] since its tumoricidal effect on thyroid cancer cells persisting after treatment, second RAI treatment is indicated in distant iodine-avid metastasis,[3,13] but it is an empirical indication in most cases of DTC locoregional recurrence.[14] However, the benefit of RAI treatment after reoperation of persistent/recurrence locoregional disease remains to be demonstrated.[14–16]

We found that surgical extirpation (lateral ND and roll or open resection) of persistent/recurrence PTC is the most favorable treatment for patients with incomplete structural response (mean values Tg0 = 24.57 and Tg1 = 7.56). Roll dissection is a secure technique for supraselective removal of recurrence in thyroid carcinoma.[11,12]

Our patients presented reduction of mean levels of Tg after surgical treatment and after 6 months of second RAI treatment but did not presented statistical difference neither on the TSH or Tg levels. However, the Tg and TgAb levels showed a significant reduction independent of the TSH suppression or the values of the TgAb. This is still a controversial topic, since there are studies that found response to a second RAI treatment in the patients with Tg greater than 1 ng/mL on suppression of TSH as was reported by Piccardo et al,[13] and there are reports as the one presented by Bouvet et al who did not find significant reduction on Tg levels after surgery with adjuvant RAI compared with the group without adjuvant RAI after surgery.[15] As a retrospective clinical case series with a few patients, there was no control on the timing of biochemical analysis in a stricter fashion or could establish Tg levels under TSH suppression, some patients had delayed follow-up from limitations of the health care system or had poor TSH suppression due to factors related to the administration of the medication or malabsorption factors.

The reduction in the Tg levels in our patients is in accordance with reported at the definition of response to RAI therapy in structural disease in the ATA joint statement of 2021 that the response evaluation should include measurements of Tg levels, and if finding a change in the pretreatment to posttreatment levels is reflective to changes in the PTC volume of the tumor[16] which is achieved with the surgical reintervention. Our study cannot assess the cause–effect of each intervention (surgery or RAI) on the structural and biochemical control, since it is a retrospective analysis of one group of patients.

As reported by Hirsch et al[8] and Yim et al,[9] we administered a second adjuvant RAI treatment empirically, so it is unclear whether the good structural response of neck disease was due to this therapy. Schuff et al observed a 50% reduction in Tg levels after reoperation which could improve the effect of the second RAI treatment.[17]

We had 15 patients (31.3%) with excellent response, 13 patients (27.1%) with biochemical incomplete response, 14 patients (29.2%) with structural incomplete response pending FNA, and 6 patients (12.5%) with indeterminate response. This distribution of response to treatment is similar to the "reoperation with RAI" group in the study reported by Hung et al.[18] The patients who presented a second recurrence (22.9%) had characteristic of high-risk of recurrence as no uptake in the second RAI WBS or soft tissue recurrence such as was found by Hirsch et al.[8]

The extent of the second surgery for the recurrence has been indicated in several studies. As reported by Heaton et al,[19] the higher lymph node yield is a determinant factor for lower risk of recurrence, assuring that an optimal extent of dissection is a key factor for less recurrence rates. We had a median of 22.6 lymph nodes resected (range: 0–82), median of 4.36 nodes affected (range: 0–34), and median size of metastasis of 12.6 mm (range: 0.2–36 mm), also 70.8% of the patients had extranodal extension in the removed specimens. This was a recurrent characteristic in the patients with excellent response who were taken to surgery and to a second RAI treatment.

These pathology findings could be into major consideration for prescribing a second iodine therapy in the persistent or recurrent disease after surgery excision.

Limitations

The limitations as a retrospective study of a single group of patients and low sample size that did not allow randomization, also the loss or intermittent follow-up that made difficult the adequate timing for the laboratory analysis.

Conclusion

The results of the study cannot assess that a second RAI treatment after reoperation of locoregionally persistent or recurrent disease have a significant impact on treatment outcomes in intermediate- or high-risk patients with PTC. However, during the follow-up, the 77.1% of our patients have not presented a second documented recurrence and the median values of Tg and TgAb levels showed a substantial decrease after surgery and second RAI treatment.

Conflict of Interest
There are no conflicts of interest to declare.

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