Impact on Treatment Response of a Highly Selective Radioactive Iodine (RAI) Treatment Strategy in Patients with Differentiated Thyroid Carcinoma (DTC).

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Introduction

- In the treatment of DTC, RAI can be administered for three different purposes[1]:
  - ablation of residual normal thyroid tissue,
  - adjuvant therapy, or
  - treatment of known disease
- In patients with low or intermediate risk DTC who have undergone complete surgery, the subsequent use of RAI treatment is controversial due to the lack of demonstrated benefits, particularly if response to surgery results in excellent or indeterminate response.[2,3].
- Since 2019 we decided to restrict the use of RAI after total thyroidectomy to patients with high-risk of recurrence; or with intermediate-risk of recurrence[4] and either:
  - biochemical incomplete response or
  - indeterminate response and vascular invasion
- Patients with structural incomplete response in the neck were re-operated and RAI decided upon the new response to therapy.
- In low-risk patients, RAI was contemplated only if TG was disproportionally elevated after complete resection.
- The primary objective is to compare outcomes in patients with DTC before and after 2019

Materials and Methods

- This retrospective study was approved by the Institutional Ethics Committee.
- All patients consecutively operated on for DTC between 01/2018 and 12/2021 with available follow-up data were included.
- Staging followed the 8th edition of the American Joint Committee on Cancer (AJCC) for thyroid cancer.[5]
- Risk of recurrence was stratified according to the ATA system into low, intermediate, and high risk.[4]
- Response to therapy was classified into excellent response, indeterminate response, incomplete biochemical response, and incomplete structural response using criteria detailed in:
- The 2015 ATA guidelines for patients treated with RAI.[4]
- The paper by Momesso et al. for patients treated without RAI.[6]
- We analyzed differences between patients operated on before and after 01/2019.
- Differences in TNM, stage, recurrence risk, response to therapy, and recurrence between the two periods were analyzed with chi-square test, with a p-value <0.05 considered statistically significant.
- The mean RAI dose and the mean time to RAI administration (since surgery) were analyzed with the student's t-test.
- Differences in RAI treatment between the two periods were analyzed using ordinal logistic regression after adjusting for risk of recurrence.

References

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Results

- 234 patients were included, median age 55 years, 78% females
- 84% of the cohort had papillary thyroid cancer, 14% had follicular or oncocytic thyroid cancer, and 2% had poorly differentiated thyroid cancer.
- 70 patients were operated on in 2018 (non-selective RAI, first period), and 164 operated on 2019-2021 (selective RAI, second period)
- There were no differences between the cohorts of the two periods in median age (51 vs. 56 years), female sex distribution (84% vs 76%) or histology distribution (papillary thyroid cancer 87% vs 82%).
- Differences in baseline characteristics, treatment and treatment response between periods are shown in Table 1. Patients of the second period had higher rate of lymph node metastases (30% vs 16%, p=0,02)
- The risk of receiving RAI adjusted to the risk of recurrence was 95% lower in the second period.
- There were no differences in treatment response between the two periods.
- The average dose of RAI used did not differ (104 mCi vs 105 mCi); but the mean time from surgery until RAI administration was longer in patients treated during the second period (4 vs 6 months, p=0,026).
- No differences were found in the recurrence rate. There were a total of 5 recurrences, 4 of which occurred in patients who had been treated with RAI (3 had a high risk of recurrence, and 1 had an intermediate risk).

Table 1. Differences in baseline characteristics, treatment and treatment response between periods

	2018	2019-2021	Total	Significance
Stage				
- I/II	69 (99%)	153 (93%)	222 (95%)	P = 0,09
- III/IV	1 (1%)	11 (7%)	12 (5%)	
T				
- T1/2	63 (90%)	140 (85%)	203 (87%)	P = 0,34
- T3/4	7 (10%)	24 (15%)	31 (13%)	
N				
- N0/Nx	59 (84%)	115 (70%)	174 (74%)	P = 0,023
- N1a/b	11 (16%)	49 (30%)	60 (26%)	
M				
- M0/Mx	69 (99%)	158 (96%)	227 (97%)	P = 0,36
- M1	1 (1%)	6 (4%)	7 (3%)	
Risk of recurrence				
- Low	55 (78%)	114 (69%)	169 (72%)	P = 0,054
- Intermediate	11 (16%)	21 (13%)	32 (14%)	
- High	4 (6%)	29 (18%)	33 (14%)	
Rate of treatment with RAI				
- Low risk	19 (34%)	4 (4%)	23 (14%)	0,05 (0,02-0,16)[a]
- Intermediate risk	10 (91%)	5 (24%)	15 (47%)	
- High risk	4 (100%)	27 (93%)	31 (94%)	
Mean dose of RAI	104 mCi ± 39	105mCi±37		P = 0,94
Time from surgery to RAI (mean)	121 days ± 66	184 days ± 144		P = 0,026
Treatment response				
- Excellent	40 (57%)	98 (60%)	138 (59%)	
- Indeterminate	25 (36%)	47 (29%)	72 (31%)	
- Biochemical incomplete	3 (4%)	12 (7%)	15 (6%)	P = 0,61
- Structural incomplete	2 (3%)	7 (4%)	9 (4%)	
Recurrences	2	3	5	P = 0,62

(a): ORa (95% CI). The risk of receiving RAI adjusted for the risk of recurrence was 95% lower in the second period, with patients at intermediate and high risk of recurrence having ORs of 11.4 and 434.3, respectively, compared to those at low risk.

Discussion

- In our study, the risk of receiving RAI adjusted to the risk of recurrence was 95% lower in the second period compared to the first period. However, we found no differences in treatment response and recurrence rate between the two periods.
- Moreover, patients in the second period tended to have more advanced disease at presentation, with a significant increase in lymph node metastases; and a trend towards more advanced stage (stage III/IV in 7% vs 1%, p=0,09); and higher risk of recurrence (high risk in 18% vs 6%, p=0,054).
- Only one recurrence was observed among patients who did not receive RAI. That patient had an intermediate-low risk of recurrence (multifocal papillary microcarcinoma with a 3mm metastatic focus in a central lymph node) treated with hemithyroidectomy. A new focus of papillary microcarcinoma was found in the contralateral lobe during follow-up. After completing thyroidectomy, the patient did not receive RAI and remains in excellent response.
- A study recently published by Dr. Grani et al showed that deferring RAI decision for the first year following surgery in patients with low or lower-intermediate thyroid cancer led to a significant reduction in RAI usage without significant differences in recurrence at 3 years compared to a cohort of patients treated with RAI immediately after surgery.[6] However, contrary to our study, an increase in patients with indeterminate or biochemical incomplete response was observed.
- Previous retrospective studies have shown low rates of recurrence for intermediate-risk tumors with excellent or indeterminate response to surgery not treated with RAI.[2] However, a selection bias could exist, that may have enriched these cohorts with lower-intermediate risk patients.
- In our study, RAI treatment was decided based on response to surgery in all intermediate risk patients. In fact, 7 patients with lateral neck metastases (N1b) with an estimated 20% recurrence rate have not been treated with RAI; and no recurrences have been diagnosed yet after 19 months of follow-up.
- There are several limitations in our study,
  - This is a retrospective study, although all patients consecutively operated were included to minimize the bias.
  - Our follow-up period is short, an it is shorter for patients of the second period, treated selectively with RAI. Thus, longer-term follow-up data is needed to confirm our findings.

Conclusion

- In patients with low/intermediate-risk differentiated thyroid cancer it seems safe to delay RAI treatment decision until response to surgery is established.
- Avoiding RAI in intermediate-risk thyroid caner with excellent and indeterminate response to surgery does not seem to have a significant impact on recurrence rate or response to therapy at last follow-up visit in the short term.
- Longer follow-up data is needed to confirm our findings.

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