Thyroid

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Clinical outcomes of radioactive iodine redifferentiation therapy in previously iodine refractory differentiated thyroid cancers

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Abstract

Objective: Redifferentiation therapy (RDT) can restore radioactive iodine (RAI) uptake in differentiated thyroid cancer (DTC) cells to enable salvage I-131 therapy for previously RAI refractory (RAIR) disease. This study evaluated the clinical outcomes of patients that underwent RDT and identified clinicopathologic characteristics predictive of RAI restoration following RDT.

Methods: This is a retrospective case series of 33 patients with RECIST-progressive metastatic RAIR-DTC who underwent RDT between 2017 and 2022 at the Mayo Clinic Rochester. All patients underwent genomic profiling and received MEK, RET or ALK inhibitors alone or combination BRAF-MEK inhibitors for 4 weeks. At week 3, those with increased RAI avidity in metastatic foci received high dose I-131 therapy. Baseline and clinicopathologic outcomes were comprehensively reviewed.

Results: Of the 33 patients, 57.6% had restored RAI uptake following RDT (Redifferentiated subgroup). 42.1% (8/19) with papillary thyroid cancers (PTC), 100% (4/4) with invasive encapsulated follicular variant PTCs (IEFV-PTC), and 100% (7/7) with follicular thyroid cancers (FTC) redifferentiated. All (11/11) *RAS* mutant tumors redifferentiated compared to 38.9% (7/18) with *BRAF* mutant disease (6 PTC and 1 IEFV-PTC). 76.5% (13/17) of redifferentiated and 66.7% (8/12) of non-redifferentiated patients achieved a best overall RECIST response of stable disease (SD) or non-complete response/non-progressive disease. Both subgroups had a median 12% tumor shrinkage at three weeks on drug(s) alone. The redifferentiated subgroup, following high dose I-131 therapy, achieved an additional median 20% tumor reduction at 6 months after RDT. There were no statistically significant differences between both groups in progression free survival (PFS), time to initiation of systemic therapy and time to any additional therapy. Of the entire cohort, 6.1% (2/33) experienced histologic transformation to anaplastic thyroid cancer and 15.1% (5/33) died, all had redifferentiated following RDT and received I-131 therapy.

Conclusion: RDT has the potential to restore RAI avidity and induce RECIST responses following I-131 therapy in select patients with RAIR-DTC, particularly those with *RAS*-driven 'follicular' phenotypes. In patients with PTC, none of the evaluated clinical outcomes

differed statistically between the redifferentiated and non-redifferentiated subgroups. Further studies are needed to better characterize the long-term survival and/or safety outcomes of high-dose RAI following RDT, particularly whether it could be associated with histologic anaplastic transformation.

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Introduction

Patients with differentiated thyroid cancer (DTC) with persistence, recurrence, or progression of distant disease have a poor prognosis (1-6). With rare exceptions following I-131 therapy, the majority of patients with advanced DTCs have no available curative therapies. Cytotoxic chemotherapy and external radiation therapies have limited efficacy and are associated with significant adverse effects (7-9). Multikinase inhibitors targeting angiogenic growth factor receptors and molecular oncogene targeted therapies have significantly improved progression free survival (PFS) (10-12), but their benefits are limited by significant drug-induced toxicities as well as emergence of tumor resistance (13-15).

In metastatic DTCs, high-dose I^{131} can be associated with complete responses, albeit rarely (16). Most tumor responses following RAI therapy are transient, mixed and/or completely refractory (17-19). Mechanistically, this is due in part to the genomic alterations which induce thyroid oncogenesis as well as inhibit thyroid cancer differentiation leading to impaired expression of the sodium iodine symporter (NIS), decreased follicular iodine uptake, and poor response to I-131 therapy (13,20-21). In 2011, Chakravarty et al, using a mouse model of papillary thyroid cancers (PTC) driven by conditional activation of oncogenic *BRAF* in thyroids, demonstrated that genomic and pharmacologic inhibition of *BRAF*, or downstream *MEK*, led to re-expression of NIS and RAI incorporation in PTCs (22). Subsequently, several pilot clinical trials have demonstrated mixed but promising results with the use of *MAPK* inhibitors to induce redifferentiation and facilitate treatment with I^{131} in patients with advanced DTCs (23).

Redifferentiation therapy (RDT) is a potential salvage therapeutic strategy for patients with advanced DTCs, but with limited efficacy data to date. Currently, much of RDT is off label with outcome data that is limited to small cohorts with marked differences in patient selection and treatment protocols as well as a lack of comparison in clinical outcomes between patients with and without restored RAI avidity following RDT (24). In this study we aimed to characterize clinical patterns of RAI uptake restoration as well as non-RAI restoration in RAIR disease and importantly examine the long-term outcomes of patients re-

treated with high dose I^{131} following RDT. Our goal is to identify the ideal candidates for RDT and assesses the long-term impact and safety of this approach in advanced DTCs.

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Methods:

Design and sample:

This was a retrospective case-series study conducted at the Mayo Clinic, Rochester, MN, USA. The electronic medical records of all patients with DTC that received care between 2018 and 2022 were screened. Adult patients (18 years or older) with progressive metastatic disease over the previous six months (defined by the response evaluation criteria in solid tumors (RECIST) as at least 20% increase in the sum of diameters of target lesions or unequivocal progression of non-target lesions) (25), who were RAIR (lack of any I^{123} uptake on their most recent whole body scan or progression of disease within 6-12 months after I^{131} therapy), and underwent RDT protocol were included in the study (**Supplemental Figure 1**).

All participants underwent genomic profiling and followed a 4-week RDT protocol (**Figure 1**). At week 1, patients were started on *MEK* inhibitor monotherapy for RAS mutant disease, combination *BRAF-MEK* inhibitors for *BRAF* mutant disease, *RET* inhibitor for *RET* fusion, and ALK inhibitor for ALK mutant disease (**Supplemental Table 1**). Two weeks prior to imaging, all patients underwent low iodine diets. At the end of week 3, all patients underwent Thyrogen-stimulated I^{123} whole body scan (WBS) with SPECT/CT. At week 4, those who redifferentiated (any uptake of at least one lesion based on qualitive assessment) were treated with high-dose I^{131} following a previously reported modified dosimetry protocol (26). The latter allows for administration of only 70% of the calculated maximum tolerated activity of RAI and/or a maximum dose of 300 mCi. In some cases, RDT agents were continued beyond the RDT protocol at the discretion of the treating provider.

Baseline characteristics:

In addition to demographic characteristics, a comprehensive description of the clinical, biochemical, and structural disease status at the time of RDT was performed, including staging (following the eight edition of the American joint Committee on Cancer (AJCC)/TNM

staging system)(27), histology, genetic profile, duration of cancer diagnosis, duration of metastatic disease, site and burden of distant metastatic disease, non-stimulated thyroglobulin (tg) levels, prior therapies, and cumulative dose of I^{131}.

Clinical outcomes:

Patients were categorized as redifferentiated if they expressed any RAI uptake following RDT. Patients with no RAI uptake following RDT were deemed non-redifferentiated. Structural responses were defined by RECIST criteria as a) complete response (CR): disappearance of all target lesions or disappearance of all non-target lesions with normalization of tumor marker levels, b) partial response (PR): at least 30% decrease in the sum of diameters of target lesions, c) progressive disease (PD): at least 20% increase in the sum of diameters of target lesions, unequivocal progression of existing non-target lesions or appearance of new non target lesions, d) stable disease: target lesions without CR, PR or PD, or e) non-CR/Non-PD: persistence of non-target lesions without CR or PD (25). A modified objective response definition was used to include those who achieved CR, PR, SD, or non-CR/non-PD following RDT and before initiation of any other treatment. In addition, we assessed overall survival (OS), PFS, variations in tumor burden and non-stimulated thyroglobulin (Tg) levels, additional therapies after RDT, time to initiation of any additional therapy, and time to initiation of systemic therapy.

All variables were evaluated six months before RDT and every six months afterwards for up to the available duration of follow up. All RECIST measurements and comparisons were conducted by the same researcher and the assessment was contrasted with the information available on the radiology reports and clinical documentations. Adverse events were extracted from providers documentation and medication administration records.

Statistical analysis:

Baseline characteristics and clinical outcomes were described separately for the redifferentiated and non-redifferentiated subgroups. Continuous variables were summarized using medians and interquartile ranges (IQR), and categorical variables were described with counts and percentages. For the clinical outcomes, only those who had at least six months of follow up were included in the analysis of RECIST response, PFS, OS, time

to systemic therapy, time to any additional therapy and improvement in tumor size and thyroglobulin levels at six months. Comparisons between both subgroups were established using Fisher exact tests for categorical variables and T tests for continuous variables. Due to the small sample size, multivariate analysis could not be performed. A p-value <0.05 was used as the cutoff for statistical significance.

Given the observed differences in RDT response between different histology subgroups, we further performed a secondary analysis including only patients with papillary thyroid cancer (PTC) histology. In addition, we compared the clinical outcomes between BRAF mutant redifferentiated patients versus RAS mutant redifferentiated patients, and between BRAF mutant redifferentiated versus non-redifferentiated patients.

Ethical considerations:

The study's protocol was reviewed by the Institutional Review Board at Mayo Clinic (19-010708), and the requirement for study specific informed consent was waived. All participants had previously provided the required Minnesota Research Authorization. Participants' information, confidentiality, and integrity were respected throughout the duration of the study.

Results:

Sample and demographic characteristics:

A total of 33 patients who had progressive metastatic RAIR-DTC and underwent RDT were analyzed. Of those, 19 patients (57.6%) redifferentiated and 14 (42.4%) were non-redifferentiated. For the entire cohort, the median age was 65 years (IQR 55-69), there was balanced gender participation (57.6% male versus 42.4% female), and white predominance (94%) (**Table 1**). There were no differences in demographic characteristics between redifferentiated and non-redifferentiated patients. The median follow-up for both subgroups was 24 months.

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Clinical characteristics:

The median durations of cancer diagnosis and metastatic disease at the time of RDT were 8 years (IQR 3-12) and 35 months (20.5-78.2) respectively (**Table 2**). At the time of initial surgical management, most patients were stage II (39.3%) followed by stage I (36.3%). The predominant histology was PTC (69.7%) (**Table 3**), followed by follicular thyroid cancer (FTC; 21.2%), which was reflected genomically by the presence of *BRAF* (54.5%), followed by *RAS* (36.4%), and *TERT* mutations (48.5%). The most common site of distant metastatic disease was the lungs (81.1%) followed by locoregional lymph node involvement (45.4%). The median non stimulated Tg was 103 ng/ml (IQR 16-294). Most patients had received prior I^{131} therapy with a median cumulative dose of 203.5 mci (IQR 150-305.7), 54.5% had prior surgical reintervention, 27.3% had prior localized therapy (such as ethanol ablation), 27.3% had prior radiotherapy, and 24.2% had prior systemic therapy.

Overall, 8 of 19 (42.1%) patients with PTC, 4 of 4 (100%) with invasive encapsulated follicular variant PTC (IEFV-PTC), and 7 of 7 (100%) with FTC redifferentiated following RDT (**Figure 2).** All 11 (100%) RAS mutant tumors (2 classic- PTC, 3 IEFV-PTC, and 6 FTC) and only 7 (38.8%) with *BRAF* mutant tumors (6 PTC, and 1 IEFV-PTC) redifferentiated following RDT. Overall, patients with FTC (p=0.01), *RAS* mutation (p<0.001), non-stimulated Tg of 294 mIU/L or more (p=0.03), largest tumor diameter of 1.7 cm or less (p=0.05) and bone metastases (p=0.007) were likely to redifferentiate following RDT. In contrast, patients with poorly differentiated thyroid cancer (PDTC)(p=0.03), *BRAF* mutation (p=0.01) and locoregional nodal disease at the time of initial surgical management (p<0.001) or at the time of RDT (p=0.001), were less likely to demonstrate restored RAI avidity following RDT.

Clinical outcomes:

All 19 patients that redifferentiated received high dose I^{131} with a median dose of 248 mci (IQR 178.6-291.2) (**Table 4**). Of these patients, 15 (79%) expressed restored I^{123} avidity in lung metastases (including 4 FTC, 12 PTC, 8 *RAS* and 5 *BRAF* mutant disease), and 13 (68.4%) did so in bone metastases (including 5 FTC, 6 PTC, 8 *RAS*, and 3 *BRAF* mutant disease). **Figure 3** characterizes RECIST defined tumor responses and median changes in Tg levels following

RDT. Of the 17 patients that redifferentiated and had at least six months of follow up, 13 (76.5%) had SD or non-CR/non-PD as their best overall RECIST response prior to subsequent treatment (35.2% and 41.2%), 15 (87.2%) achieved objective response, 13 (76.4%) required additional therapy after RDT (including 5 systemic therapy, and 8 radiotherapy). In this group, the median PFS was 18 months, median time to initiation of systemic therapy was 18 months (Participants who were continued on TKI after RDT were excluded from this analysis), and median time to any additional therapy was 24 months (In participants who were continued on TKI after RDT, additional therapy was considered as the need for any additional intervention such as surgery, localized therapy or radiotherapy) (**Figure 4**). The frequency and duration of these outcomes was comparable to that of the non-redifferentiated that did not receive I-131, with no statistically significant differences between both subgroups, even when stratifying the results by BRAF mutation status. Notably, the lack of control group for RAS mutant disease that did not receive RDT limits outcome data for this subpopulation.

Both redifferentiated and non-redifferentiated patients experienced a similar decrease in the median sum of the target lesions' diameters three weeks after treatment with *MAPK* inhibitor(s) (11% versus 12.4%, p=0.7). However, the redifferentiated subgroup developed additional tumor regression at six months following I-131 therapy, while no further improvement was noted in the non-redifferentiated without I-131 therapy (30% versus 13%, p=0.9). Despite this, both subgroups experienced comparable median percentual reduction of non-stimulated Tg levels six months after RDT (60.5 versus 75.7%, p=0.5).

Compared to the *BRAF* mutant non-redifferentiated patients, *BRAF* mutant redifferentiated patients experienced a similar decrease in the median sum of the target lesions' diameters one month after the initiation of the RDT agents (18% versus 10.9%, p=0.28) but with statistically greater decreases at six months (30% versus 12%, p<0.01). Overall, there were no statistically significant differences in median Tg levels nor overall clinical outcomes between these two subgroups on long-term follow up.

Noteworthy, five of the redifferentiated patients were continued on their thyroid kinase inhibitors (TKI) beyond the four weeks of the RDT protocol. Their RECIST responses over the

first six months post RDT was SD for 4 participants and non-CR/non-PD for 1 participant. Likewise, 4 of the non-redifferentiated patients were continued on TKI out of which 2 achieved non-CR/non-PD, 1 SD, and 1 CR at six months from RDT initiation.

Mortality and safety:

The most reported adverse effects were maculopapular rash (42.1% in redifferentiated versus 28.6% in non-redifferentiated, p=0.4) and fatigue (26.3 versus 42.8%, p=0.3) (**Table 5**). Of the entire cohort, 5 (15.1%) patients died. All of these had redifferentiated following RDT and received subsequent high dose I^{131} treatment. 2 of these 5 had experienced non-CR/non-PD or SD following RDT but later experienced histologic transformation to anaplastic thyroid cancer (ATC) (18 and 24 months after RDT) and died within six months. Two initially experienced SD after RDT but died from complications associated with their tumor burden (24 and 30 months after RDT). One progressed despite RAI avidity restoration following RDT (12 months after RDT). Compared to the genetic profile of initial metastatic lesions, in the tall cell subtype PTC that transformed to ATC, genomic interrogations demonstrated an underlying *BRCA2* germline mutation and a newly acquired *PTEN* mutation. In the FTC that transformed to ATC, there were newly identified *TERT, CDKN2A-B, EIF1AX* and *NF2* mutations on subsequent genetic testing. None of these two patients had continued TKI or received any additional therapy after RDT and before anaplastic transformation.

Secondary analysis:

Of the 19 patients with PTC, 4 of 11 (36.4%) with classical PTC (C-PTC), 2 of 4 (50%) with tall cell subtype-PTCs (TCS-PTC), and 2 of 4 (50%) tall cell features-PTCs (TCF-PTC) redifferentiated following RDT. Both (100%) *RAS* mutant tumors (C-PTC) redifferentiated compared to only 6 (33.3%) of the *BRAF* mutant tumors (2 C-PTC, 2 TCS-PTC, and 2 TCF-PTC). The median non-stimulated Tg level was higher in the redifferentiated subgroup (66.5 versus 46 mIU/L, p=0.18). Overall, patients with *RAS* mutation (p=0.08), bone metastasis (p=0.05), prior external radiotherapy (p=0.03), or prior systemic therapy (p<0.01) were more likely to respond to RDT. In contrast, patients with locoregional nodal disease or distant metastasis at the time of initial surgical management (p=0.04 and p=0.05), or with *BRAF* mutant disease (p=0.08) were less likely to restore RAI avidity following RDT.

Regardless of redifferentiation status after RDT, both subgroups had similar outcomes in tumor burden as defined by RECIST criteria. Of the 7 redifferentiated patients who had at least six months of follow up and received a median I^{131} dose of 226.7 mci (IQR 191.8-250.5), 5 (71.4%) had SD or non-CR/non-PD as their best overall RECIST response before initiation of any other treatment (compared to 80% in non-redifferentiated, p=0.6), and 6 (85.7%) achieved objective response (compared to 80% in non-redifferentiated, p=0.7). Redifferentiated patients had a non-statistically significant tendency towards higher median PFS (12 versus 9 months, p=0.5), and time to any additional therapy (18 versus 12 months, p=0.5) as compared to non-redifferentiated patients. The median time to systemic therapy was 12 months for the non-redifferentiated subgroup compared to no additional systemic therapy required in the redifferentiated subgroup (p=0.12). Overall, the mortality incidence was higher in patients that redifferentiated compared to those that did not redifferentiate (50% versus 0%, p=0.01).

Discussion:

Redifferentiation therapy has emerged as a promising strategy for inducing RAI uptake in metastatic DTC to enable therapeutic benefit from I^{131} therapy. Published series with small sample sizes and heterogeneity in patient selection, RDT protocols, and outcome measures, have demonstrated mixed responses in RAI avidity, RECIST responses, PFS, and other clinical outcomes(24). The results of a randomized clinical trial of selumetinib versus placebo followed by I-131 therapy in patients with advanced RAI avid disease (NCT02393690) is expected to be published this year. In the interim, off label RDT in RAI avid and refractory disease is now common in advanced thyroid cancer practices. Our off-label series, which is currently the largest cohort, strengthens previous findings demonstrating a strong phenotype-genotype correlation with clinical outcomes of RDT as well as unexpected durable partial tumor responses to short-term drug therapy alone. Our data also raises important questions about the long-term benefits of RDT, particularly whether this therapy delays the need for systemic therapy with multikinase inhibitors and importantly, whether this therapy may select for and/or induce more aggressive tumor subclonal populations that may eventually progress to anaplastic transformation.

We identified that patients with FTC or IEFV-PTC histologies and *RAS* mutations were more likely to restore RAI avidity following RDT compared to BRAF mutations and/or PTC histologies. *RAS* mutation, high Tg levels, small tumor diameter, bone metastasis, and lack of locoregional nodal disease, all characteristic features of follicular histologies, demonstrated high likelihood of restored RAI avidity following RDT. Similar to Ho et al. and Jaber et al., all *RAS* mutant patients restored RAI avidity with RDT (28-29). This finding is inconsistent with the results from Iravani et al and Leboulleux et al. in which only around 30% of *RAS* mutant patients had restoration of RAI avidity with RDT (30-31). In contrast, only 38% of our *BRAF* mutant patients restored RAI avidity despite the use of combination dabrafenib and trametinib as the RDT agents, and patients with PTC were less likely to restore RAI avidity if they had *BRAF* mutant disease. We hypothesize that these mixed findings may be related to the diversity of disease definitions (i.e., criteria for RAI refractoriness or successful response to RDT), heterogeneity of tumor phenotypes (i.e., PDTC) and genomics (i.e., presence of additional mutations) and/or the predominance of PTC histologies in published series. Additional studies are needed to better understand the discrepancies between the initial *BRAF* mutant animal data by Chakravarty et al. and our human data, indicating that PTCs with *BRAF* mutation are less likely to redifferentiate. This may be due to differences in the tumor microenvironment, host immunity and/or genomic heterogeneity that may impair NIS re-expression.

The discordance between *BRAF* and *RAS* responses to RDT is consistent with TCGA multi genomic profiling of nearly 500 PTCs, together with preclinical data demonstrating attenuated *ERK*-driven negative feedback in *BRAF* driven tumors, resulting in higher *MAPK* output signaling compared to *RAS* driven tumors (32). Despite potent combination *BRAF-MEK* inhibition in *BRAF* mutant PTCs, either incomplete *MAPK* inhibition or alternative signaling pathways likely facilitate resistance to NIS re-expression in most, but not all, advanced *BRAF* mutant PTCs. Conversely, *RAS* driven tumors with lower *MAPK* output relative to *BRAF* driven PTCs have robust reexpression of NIS following *MEK* inhibition; however, tumor heterogeneity results in mixed responses to RAI therapy following RDT. Comprehensive genomic profiling of tumors prior to and following RDT will be important to better understand pathways that may mediate resistance to RDT. For example, advanced

oncocytic thyroid cancers (formerly called Hurthle cell thyroid cancers), well characterized by mitochondrial DNA alterations in the tricarboxylic acid cycle and most often lacking *MAPK* oncogenic drivers, are RAI refractory at baseline, despite high Tg levels (33-34). This suggests that potentially altered mitochondrial metabolism may influence expression of NIS; whether this impacts PTC and FTC, and its reversibility has not been explored.

In our series, 88.2% percent of the patients who responded to RDT experienced RECIST defined SD, non-CR/non-PD, PR, or CR which is consistent with the previously reported series (28-30,35-37). In addition, the median PFS of 18 months, and the median time to additional therapy of 24 months were shorter than those reported by Leboulleux et al. (37). However, in their series, RDT was given as first line therapy for progressive disease, the lesions' size was smaller, and the duration of advanced disease was shorter. This suggests that RDT used earlier in the course of metastatic disease may maximize its potential clinical benefits.

Similar to previous reports (29,35-37), short term therapy with MAPK inhibitors alone appears to have durable tumor control, with 66.7% achieving SD, non-CR/non-PD or some degree of improvement in tumor burden. In our series, both redifferentiated and non-redifferentiated patients experienced a 12% reduction in tumor size three weeks after RDT. In patients that redifferentiated and received subsequent treatment with high dose I^{131}, an additional 20% reduction in tumor size at six months after RDT was seen. Leboulleux et al. also reported that RECIST responses at 6 months were independent of the initial improvement in tumor burden experienced at 1 month (37). Altogether, the evidence suggests that, in patients with restored RAI avidity, retreatment with high dose I^{131} could have added benefit as compared to drug therapy alone. Notably, for follicular phenotypes with *RAS* alterations of which 100% had successful RDT, the lack of 'control' population (for example non-RDT patients) may underestimate the therapeutic benefits of RDT in this particular population.

In general, RDT appeared to be a safe strategy with most patients experiencing only fatigue and maculopapular rash. However, in our series, mortality was higher in the patients that redifferentiated. Two of these patients experienced anaplastic transformation with

evolution of additional genetic alterations likely contributing to their tumor biology and rapidly fatal disease progression. Other adverse events, such as myelodysplastic syndrome with progression to acute leukemia (28) and skin squamous cell carcinomas (35) have been reported following RDT. While the causality between these events and RDT is not clear yet, future clinical trials and pooled data from off label series may better examine the link between adverse events and cumulative I^{131} exposure, transformation to ATC and/or molecular changes following RDT and RAI therapy. These safety concerns need to be weighed against the potential benefits when deciding whether to pursue RDT as a potential strategy in patients with advanced DTCs.

The results of this study should be considered in the context of its limitations. While our series is the largest published so far, it is still relatively small which could lead to underestimation of the statistical significance of our outcomes. Although we used the redifferentiated and non-redifferentiated patients as the comparison subgroups for the statistical analysis, there is marked heterogeneity in histology types and genetic profiles which can influence the individual outcomes of each patient regardless of their response to RDT. Thus, we stratified the results by type of histology and genetic profiles whenever possible and conducted a secondary analysis on PTC patients alone. Future research is needed to examine, in a genotype-phenotype specific manner and with control arms, the effects of RAI therapy following RDT on tumor genomic heterogeneity, time to salvage systemic therapies and overall survival. Given the retrospective design of this study, the severity of adverse events could not be graded. The continuation of TKI beyond the RDT protocol could have overestimated the clinical outcomes in some patients. Missing data may also impact the accuracy of the long-term follow-up findings. Finally, since the agents used for RDT are not FDA approved for this indication, there is a risk of selection bias which could affect the generalization of our findings. Despite these limitations, our results expand the current body of knowledge, do inform current clinical practices, and may guide the design of future randomized prospective studies.

In conclusion, RDT has the potential to restore RAI avidity and induce RECIST responses following I-131 therapy in select patients with RAIR-DTC, particularly those with *RAS* mutations and 'follicular' phenotypes. However, none of the evaluated clinical outcomes differed statistically between those who experienced restored RAI avidity and those who didn't. Importantly however, there was a lack of 'control' arm for RAS mutated disease, all which redifferentiated and received I-131. Responses in this group may underestimate the benefits for RDT for RAS driven disease. RDT agents on their own appeared to have an impact in the burden of disease as evident by improvement in lesion's size and Tg levels during the first six months, regardless of the response to RDT or retreatment with high dose I^{131}. Further prospective, randomized, multicenter studies are needed to facilitate patient selection, evaluate the utility of alternative diagnostics like I-124 PET/CT to predict response to RAI therapy following RDT, and better characterize the long-term efficacy, survival and/or safety outcomes of high-dose I-131 following RDT, particularly whether it could be associated with histologic anaplastic transformation. International collaboration, and standardization of definitions and protocols would facilitate future research and improve the quality of data.

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Figure 1 was created with BioRender.com

Author contributions:

David Toro-Tobon: Conceptualization, methodology, data collection, statistical analysis, manuscript preparation (Initial draft, review, and editing). Mabel Ryder: Conceptualization, methodology and manuscript preparation (Review and editing). John C. Morris, Crystal Hilger, Candy Peskey, and Jolanta Durski: Manuscript preparation (Review and editing).

Disclosures:

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Table 1. Demographic characteristics

Demographic characteristics				
Characteristic	Redifferentiated	Non-redifferentiated	Total sample	P value
Number of participants, n (%)	19 (57.6)	14 (42.4)	33 (100)	-
Age, median in years (IQR)	64 (58-68)	66 (54-68)	65 (55-69)	0.77
Sex, n (%)				
Male	11 (57.9)	8 (57.1)	19 (57.6)	0.96
Female	8 (42.1)	6 (42.9)	14 (42.4)	0.96
Ethnicity, n (%)				
Hispanic or Latino	0 (0)	0 (0)	0 (0)	-
Not Hispanic or Latino	19 (100)	14 (100)	33 (100)	-
Race, n (%)				
Asian	1 (5.3)	0 (0)	1 (3)	0.39
Black or African American	0 (0)	1 (7.1)	1 (3)	0.24
White	18 (94.7)	13 (92.9)	31 (94)	0.82

Redifferentiated: Increased radioactive iodine (RAI) uptake after redifferentiation therapy (RDT)

Non-redifferentiated: No RAI uptake after RDT

Thyroid
Clinical outcomes of radioactive iodine redifferentiation therapy in previously iodine refractory differentiated thyroid cancers (DOI: 10.1089/thy.2023.0456)

Table 2. Baseline clinical characteristics

Baseline Clinical Characteristics				
Characteristic	Redifferentiated (n: 19)	Non-redifferentiated (n: 14)	Total sample (n: 33)	P value
Duration of cancer diagnosis at the time of RDT, median in years (IQR)	8 (4.2-9.7)	9 (1-14)	8 (3-12)	0.64
Duration of metastatic disease at the time of RDT, median in months (IQR)	36 (20.7-78.5)	26.5 (7.5-70.2)	35 (20.5-78.2)	0.54
Site of distant metastatic disease				
Lung	15 (78.9)	12 (85.7)	27 (81.1)	0.62
Bone	10 (52.6)	1 (7.1)	11 (33.3)	0.007
Mediastinal lymph node	1 (5.2)	2 (14.2)	3 (9)	0.37
Locoregional lymph node	5 (26.3)	10 (71.4)	15 (45.4)	0.001
Other	3 (15.7)	3 (21.4)	6 (18.1)	0.67
Largest metastasis diameter, Median in cm (IQR)	1.7 (1.3-2.8)	2.6 (1.6-4)	2.2 (1.6-2.8)	0.05
Prior therapy, n (%)				
Surgical reintervention	8 (42.1)	10 (71.4)	18 (54.5)	0.10
Localized therapy	4 (21.1)	5 (35.7)	9 (27.3)	0.35
Radiotherapy	7 (36.8)	2 (14.3)	9 (27.3)	0.15
Systemic therapy	7[1] (36.8)	1[2] (7.1)	8 (24.2)	0.05
Prior RAIT, n (%)				
Received therapy	18 (94.7)	14 (100)	32 (97)	0.38
Had structural improvement	6 (31.6)	2 (14.3)	8 (24.2)	0.25

Lifetime cumulative RAI dose in mci, median (IQR)	250 (150-300)	200 (125.5-204)	203.5 (150-305.7)	0.10
TSH, median in mIU/mL (IQR)	0.02 (0.01-0.06)	0.05 (0.01-0.1)	0.03 (0.01-0.08)	0.36
FT4, median in ng/dL (IQR)	2 (1.8-2.2)	2.1 (1.7-2.2)	2 (1.8-2.2)	0.90
Non stimulated thyroglobulin, median in ng/mL (IQR)				
Total sample	294 (103-1264)	29 (6-83.7)	103 (16-294)	0.03
PTC subgroup	66.5 (16.2-124.2)	46 (6.4-95.2)	46 (13.5-109)	0.18
IEFV-PTC subgroup	845 (294-1762)	-	-	-
FTC subgroup	342 (148-808)	-	-	-
Redifferentiation agent, n (%)				
Dabrafenib + Trametinib	7 (36.8)	11 (78.7)	18 (54.5)	0.01
Trametinib	12 (63.2)	0 (0)	12 (36.5)	<0.001
Pralsetinib	0 (0)	1 (7.1)	1 (3)	0.24
Alectinib	0 (0)	1 (7.1)	1 (3)	0.24
Selpercatinib	0 (0)	1 (7.1)	1 (3)	0.24

Redifferentiated: Increased radioactive iodine (RAI) uptake after redifferentiation therapy (RDT)

Non-redifferentiated: No RAI uptake after RDT

RAIT: Radioactive iodine therapy

PTC: papillary thyroid cancer

IEFV-PTC: infiltrative encapsulated follicular variant PTC

[1]Pazopanib (1), lenvatinib (6), axitinib (1), sorafenib (1), and dabrafenib (1).

[2]Alectinib (1).

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Table 3. Staging, histology, and genetic characteristics

Staging, histology, and genetic characteristics				
Characteristic	Redifferentiated (n: 19)	Non-redifferentiated (n: 14)	Total sample (n: 33)	P value
TNM classification (AJCC 8th edition)*, n (%)				
T				
2	3 (18.7)	1 (7.6)	4 (13.8)	0.46
3a	6 (37.5)	3 (23.1)	9 (31.0)	0.52
3b	2 (12.5)	3 (23.1)	5 (17.2)	0.39
4a	5 (31.2)	4 (30.8)	9 (31.0)	0.98
4b	0 (0)	2 (15.4.3)	2 (7)	0.09
N				
X	8 (42.1)	3 (21.4)	11 (33.4)	0.21
0a	5 (26.3)	0 (0)	5 (15.1)	0.04
0b	0 (0)	0 (0)	0 (0)	-
1a	4 (21.1)	1 (7.2)	5 (15.1)	0.27
1b	2 (10.5)	10 (71.4)	12 (36.4)	<0.001
M				
0	10 (52.6)	10 (71.4)	20 (60.6)	0.28
1	9 (47.4)	4 (28.6)	13 (39.4)	0.28
Stage*, n (%)				
Less than 55 years old				
I	1 (5.3)	3 (21.5)	4 (12.1)	0.16
II	2 (10.5)	2 (14.3)	4 (12.1)	0.75
55 or more years old				
I	5 (26.3)	3 (21.4)	8 (24.2)	0.74
II	6 (31.6)	3 (21.4)	9 (27.2)	0.53

Thyroid
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Thyroid
Clinical outcomes of radioactive iodine redifferentiation therapy in previously iodine refractory differentiated thyroid cancers (DOI: 10.1089/thy.2023.0456)

III	1 (5.3)	1 (7.1)	2 (6)	0.82
IVa	0 (0)	0 (0)	0 (0)	-
IVb	4 (21)	2 (14.3)	6 (18.1)	0.62
Histology, n (%)				
Papillary thyroid cancer (PTC)	8 (42.1)	11 (78.6)	19 (57.6)	0.03
Classic	4 (21.1)	7 (50.0)	11 (33.4)	0.08
Tall cell subtype	2 (10.6)	2 (14.3)	4 (12.1)	0.75
With tall cell features	2 (10.6)	2 (14.3)	4 (12.1)	0.75
Infiltrative encapsulated follicular variant PTC	4 (21.1)	0 (0)	4 (12.1)	0.07
Follicular thyroid cancer	7 (36.6)	0 (0)	7 (21.2)	0.01
Poorly differentiated thyroid cancer	0 (0)	3 (21.4)	3 (9.1)	0.03
Main mutation(s), n (%)				
BRAF	7 (36.8)	11 (78.6)	18 (54.5)	0.01
RAS	11 (57.9)	0 (0)	12 (36.4)	<0.001
RET	1 (5.3)	2 (14.3)	3 (9.1)	0.38
TERT	8 (42.1)	8 (57.1)	16 (48.5)	0.40
NKX2	4 (21.1)	0 (0)	4 (12.1)	0.07
BRCA2	1 (5.3)	1 (7.1)	2 (6.1)	0.82
CDKN2A	1 (5.3)	1 (7.1)	2 (6.1)	0.82
Alk rearrangement	0 (0)	1 (5.3)	1 (3.0)	0.32
Mutations in pathways and functional groups, n (%)				
P13K/AKT/mTOR pathway	2 (10.5)	2 (14.3)	4 (12.1)	0.75
SWI/SNF complex	3 (15.8)	1 (7.1)	4 (12.1)	0.46
HMTs	2 (10.5)	2 (14.3)	4 (12.1)	0.75
MMR	1 (5.3)	0 (0)	1 (3)	0.39
TMB, median in mut/Mb (IQR)	1.3 (1.1-2.8)	1.6 (0.8-2.6)	1.4 (1-2.7)	0.91
Microsatellite instability, n (%)				
Stable	16 (84.2)	9 (64.3)	25 (75.8)	0.19
High	1 (5.3)	0 (0)	1 (3)	0.39
Unknown	2 (10.5)	5 (35.7)	7 (21.2)	0.08

*At the time of initial surgical management

Redifferentiated: Increased radioactive iodine (RAI) uptake after redifferentiation therapy (RDT)

Non-redifferentiated: No RAI uptake after RDT

PI3K/AKT/mTOR pathway (includes PIK3CA, PTEN, PIK3C2G, PIK3CG, PIK3C3, PIK3R1, PIK3R2, AKT3, TSC1, TSC2, and MTOR)

SWI/SNF chromatin remodeling complex (ARID1A, ARID1B, ARID2, ARID5B, SMARCB1, PBRM1, and ATRX)

HMTs: Mutations of the histone methyltransferases (KMT2A, KMT2C, KMT2D, and SETD2)

MMR: Mismatch excision repair (MSH2, MSH6, and MLH1)

Table 4. Clinical outcomes

Clinical outcomes			
	Redifferentiated (n: 19)	Non-redifferentiated (n: 14)	P
Received RAI after RDT, n (%)	19 (100)	1 (7.1)	<0.001
RAI dose after RDT, median mci (IQR)	248 (178.6 – 291.2)	199.4	-
Region of RAI avidity			
Lung	15 (79)	0 (0)	-
Mediastinal lymph node	3 (15.8)	0 (0)	-
Cervical lymph node	3 (15.8)	0 (0)	-
Bone	13 (68.4)	0 (0)	-
Other	3 (15.8)	0 (0)	-
Best overall RECIST response[1, 2]			
Complete response	0 (0)	1 (8.3)	0.23
Partial response	2 (11.8)	0 (0)	0.22
Stable disease	6 (35.2)	6 (50)	0.43
Progressive disease	2 (11.8)	3 (25)	0.35
Non-CR / non-PD	7 (41.2)	2 (16.7)	0.16
Objective response [1, 2]	15 (87.2)	9 (75)	0.23
Mortality, n (%)	5 (26.3)	0 (0)	0.04
Percentage decrease in sum of TL diameter, median (IQR) [1]			
At 3 weeks from RDT initiation	11 (7.4-18)	12.4 (9.4-18.5)	0.70
At 6 months from RDT initiation	30 (11.1-30)	13 (6.5-18.5)	0.96
Decrease in non-stimulated Tg six months after initiation of RDT agent, median % (IQR) [1]	60.5 (36.8-88)	75.7 (52.3-95.5)	0.51

Thyroid
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New therapies after redifferentiation therapy			
Surgical reintervention	2 (10.5)	2 (14.2)	0.75
Localized therapy	2 (10.5)	1 (7.1)	0.74
Radiotherapy	8 (42)	3 (21.4)	0.22
Systemic therapy	5 (26.3)	1 (7.1)	0.16
Continuation of TKI after completion of re-differentiation protocol, n (%)	5 (26.3)	4 (28.5)	0.89

RDT: redifferentiation therapy

CR: complete response

PD: progressive disease

TL: Target lesion

[1]Two patients were excluded on each subgroup since they had not completed 6 months from RDT

[2] Before initiation of any other treatment

Redifferentiated: Increased radioactive iodine (RAI) uptake after RDT

Non-redifferentiated: No RAI uptake after RDT

RECIST: Response Evaluation Criteria in Solid Tumors

Objective response: CR, partial response, stable disease, or non-CR/non-PD

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Table 5. Safety

Safety			
	Redifferentiated (n: 19)	Non-redifferentiated (n: 14)	P
Histologic transformation to anaplastic cancer, n (%)	2 (10.5)	0 (0)	0.21
Adverse effects			
Maculopapular rash	8 (42.1)	4 (28.6)	0.42
Fatigue	5 (26.3)	6 (42.8)	0.32
Myalgia	1 (5.3)	1 (7.1)	0.82
Nausea	1 (5.3)	3 (21.4)	0.16
Diarrhea	3 (15.8)	2 (14.3)	0.90
Emesis	0 (0)	2 (14.3)	0.09
Increased aminotransferases	2 (10.5)	0 (0)	0.21
Pneumonia	1 (5.3)	1 (7.1)	0.82
Fever	2 (10.5)	1 (7.1)	0.74
Neutropenia	1 (5.3)	1 (7.1)	0.82
Chills/diaphoresis	1 (5.3)	1 (7.1)	0.82
Hyporexia	1 (5.3)	1 (7.1)	0.82
Other	6 (31.6)	6 (42.8)	0.51

Redifferentiated: Increased radioactive iodine (RAI) uptake after redifferentiation therapy (RDT)

Non-redifferentiated: No RAI uptake after RDT

Thyroid
Clinical outcomes of radioactive iodine redifferentiation therapy in previously iodine refractory differentiated thyroid cancers (DOI: 10.1089/thy.2023.0456)

Figure Legends

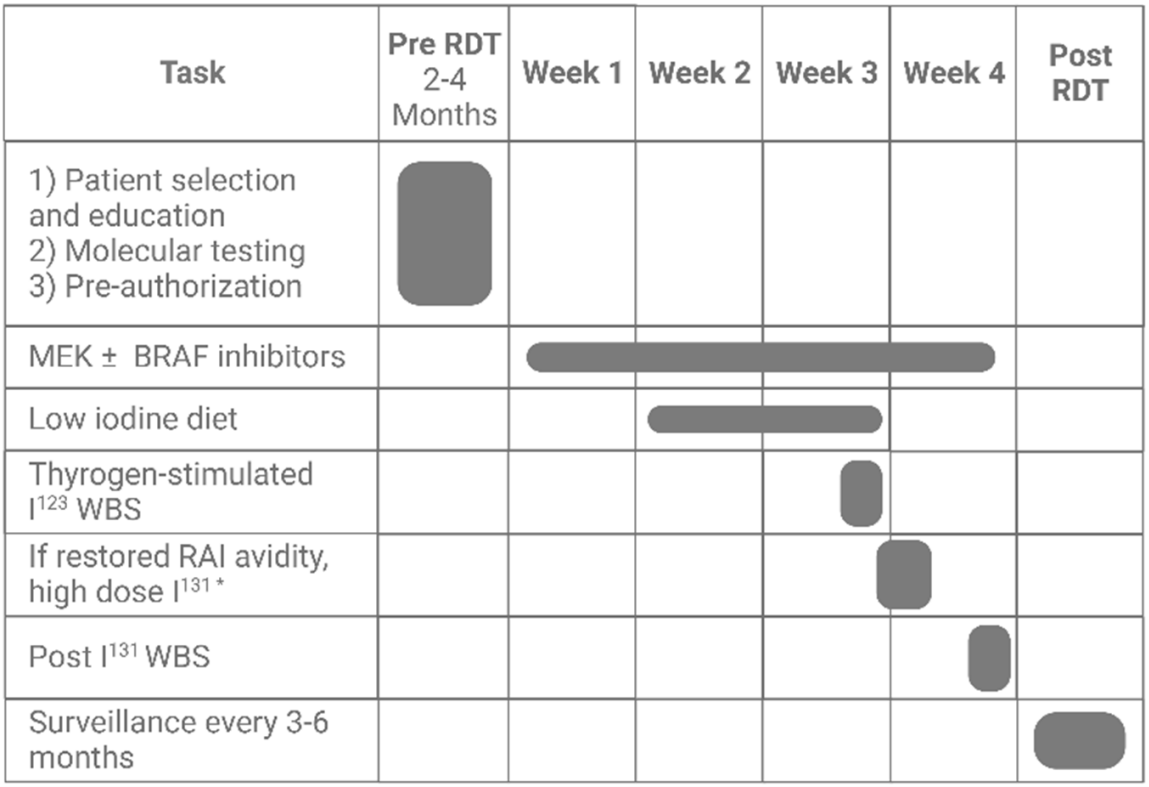

Figure 1. Redifferentiation protocol

*Modified dosimetry protocol

RDT: Redifferentiation therapy; **MEK:** Methyl ethyl ketone; **RAI:** Radioactive iodine; **WBS:** Whole body scan

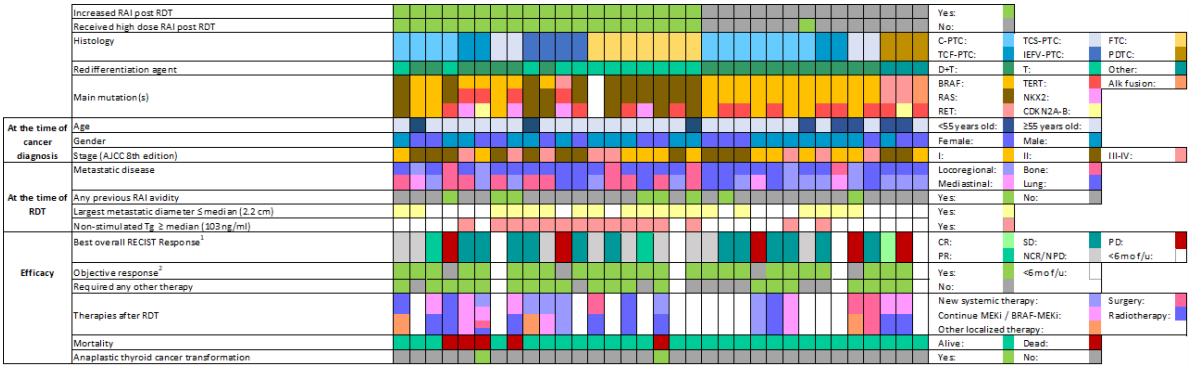

Figure 2. Onco print

RAI: Radioactive iodine; **RDT:** Redifferentiation therapy; **C-PTC:** Classic papillary thyroid cancer; **TCF-PTC:** Tall cell features papillary thyroid cancer; **TCS-PTC:** Tall cell subtype papillary thyroid cancer; **IEFV-PTC:** Invasive encapsulated follicular variant papillary thyroid cancer; **FTC:** Follicular thyroid cancer; **PDTC:** Poorly differentiated thyroid cancer; **D+T:** Dabrafenib and trametinib; **T:** Trametinib; **AJCC:** American Joint Committee on Cancer; **RECIST:** Response Evaluation Criteria in Solid Tumors; **CR:** Complete response; **PR:** Partial response; **SD:** Stable disease; **NCR/NPD:** Non-Complete response/Non-progressive disease; **PD:** Progressive disease; **f/u:** follow up; **MEKi:** Methyl ethyl ketone (MEK) inhibitor

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Thyroid

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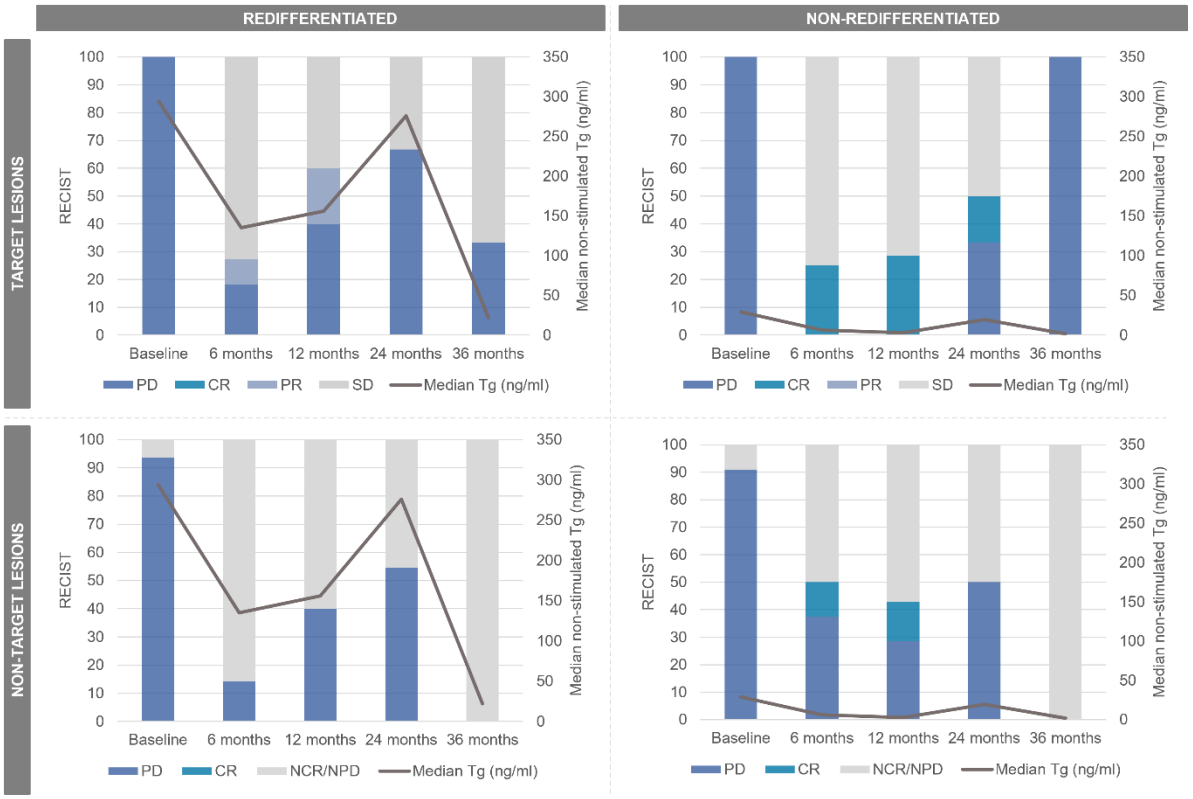

Figure 3. Progression of tumor burden and thyroglobulin levels

[1]Two patients were excluded on each subgroup since they had not completed 6 months from RDT

[2] Before initiation of any other treatment

CR: complete response

PD: progressive disease

PR: partial response

SD: Stable disease

NCR/NPD: non complete response / non progressive disease

Redifferentiated: Increased radioactive iodine (RAI) uptake after RDT

Non-redifferentiated: No RAI uptake after RDT

RECIST: Response Evaluation Criteria in Solid Tumors

Objective response: CR, partial response, stable disease, or non-CR/non-PD

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Clinical outcomes of radioactive iodine redifferentiation therapy in previously iodine refractory differentiated thyroid cancers (DOI: 10.1089/thy.2023.0456)

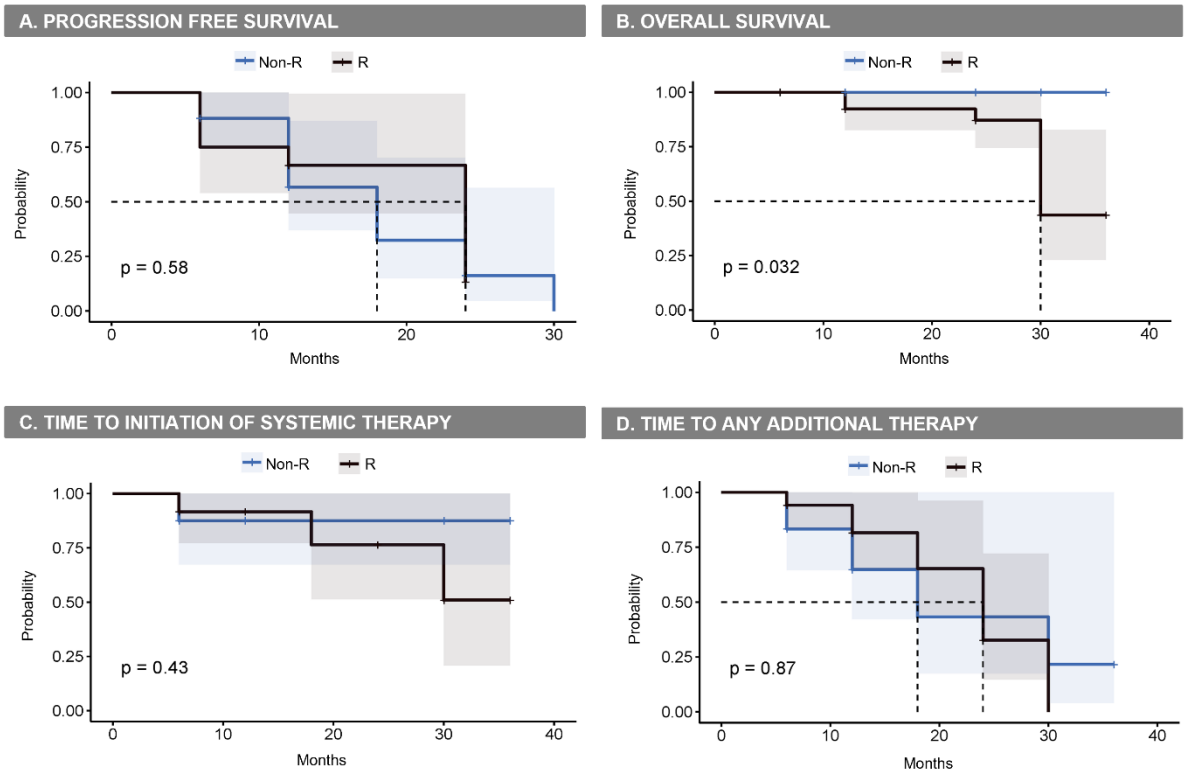

Figure 4. Clinical outcomes

Kaplan Meier curves for: A. Progression free survival, B. Overall survival, C. Time to initiation of systemic therapy, and D. Time to any additional therapy.

* Two patients were excluded on each subgroup since they had not completed 6 months from RDT

R: Redifferentiated (Any radioactive iodine [RAI] uptake after redifferentiation therapy [RDT])

Non-R: Non-redifferentiated (No RAI uptake after RDT)