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Real-World Outcomes of Tyrosine Kinase Inhibitors in Radioactive Iodine-Refractory Differentiated Thyroid Cancer: A Cohort Study with Focus on Neoadjuvant Use

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Research Article

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Abstract

Background:

Radioactive iodine-refractory differentiated thyroid cancer (RAIR-DTC) represents a subset of patients with poor prognosis and limited therapeutic options. Tyrosine kinase inhibitors (TKIs), particularly lenvatinib, have demonstrated efficacy in clinical trials; however, real-world data, especially from Latin America, remain limited. Additionally, their role in the neoadjuvant setting is not well established.

Methods:

We conducted a retrospective cohort study including patients with RAIR-DTC treated with TKIs at two high-complexity centers in Colombia between 2014 and 2024. Oncologic response, percentage change in tumor size, and overall survival (OS) were evaluated. Objective response rate (ORR) and disease control rate (DCR) were calculated among evaluable patients. A subgroup analysis was performed in patients treated in the neoadjuvant setting.

Results:

A total of 35 patients were included. Among evaluable patients, the ORR was 40.6%, and the DCR was 81.2%. Median proportion of percentage change in tumor size was 0.25 (IQR: 0.00–0.51). Median overall survival was not reached. In the neoadjuvant subgroup (n = 21), treatment was associated with median proportion of percentage change of 0.29 and enabled surgical resection in a subset of patients, with high rates of complete (R0/R1) resection. Adverse events were reported in 76.5% of patients, with permanent discontinuation in 15.6%.

Conclusions:

In this real-world cohort, TKIs demonstrated meaningful clinical activity in patients with RAIR-DTC, achieving high rates of disease control despite advanced disease. These findings support the effectiveness of lenvatinib in routine practice and suggest a potential role for neoadjuvant therapy to facilitate surgical management in selected patients. Prospective studies are needed to define optimal treatment strategies and patient selection.

Bullet points

- Real-world outcomes of lenvatinib in RAIR-DTC showed an ORR of 40.6% and DCR of 81.2%.
- Median overall survival was not reached in a cohort with predominantly advanced and unresectable disease.

- Neoadjuvant use of TKIs was associated with meaningful tumor reduction and high rates of R0/R1 resection.
- Outcomes were lower than clinical trials but consistent with real-world populations.
- Findings support a role for TKIs beyond palliation, including surgical conversion strategies.

Introduction

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy and represents the ninth most frequently diagnosed cancer worldwide (1, 2). It occurs more commonly in women, with an estimated incidence of 10.3 per 100,000 in females and 3.1 per 100,000 in males (2, 3). Although overall mortality remains low, accounting for approximately 0.4% of cancer-related deaths, and 5-year survival rates approach 98.5%, a subset of patients develops aggressive disease with significantly worse outcomes (2–6).

Despite a generally favorable prognosis, approximately 8–15% of patients with DTC develop aggressive disease characterized by locoregional invasion or distant metastases (7–9). In these cases, conventional treatment strategies—including surgery, thyroid-stimulating hormone (TSH) suppression, and radioactive iodine (RAI)—may be insufficient (10, 11). Radioactive iodine remains a cornerstone of therapy in intermediate- and high-risk disease; however, up to two-thirds of patients may lose the ability to concentrate iodine over time, reflecting tumor dedifferentiation and disease progression (6, 10, 11).

Radioactive iodine-refractory differentiated thyroid cancer (RAIR-DTC) represents a clinically challenging entity within this spectrum. It is defined by the absence of iodine uptake in metastatic lesions, progression despite iodine avidity, or persistent disease after cumulative RAI exposure (9, 12, 13). Patients with RAIR-DTC have a markedly worse prognosis, with a 5-year survival of approximately 66% and less than 10% at 10 years, compared to the excellent outcomes observed in iodine-avid disease (6, 9–12).

Recent consensus efforts have further refined the concept of advanced thyroid cancer, incorporating features such as unresectable disease, bulky or invasive tumors, rapidly progressive disease, and metastatic spread (14). These definitions are clinically relevant, as they guide decisions regarding the initiation of systemic therapy and the use of targeted treatments. In this context, RAIR-DTC represents a key subgroup of advanced disease with limited therapeutic options and a need for improved outcomes.

The introduction of tyrosine kinase inhibitors (TKIs) has significantly changed the therapeutic landscape of RAIR-DTC. These agents, which primarily exert antiangiogenic effects by inhibiting vascular endothelial growth factor receptors and other signaling pathways, have demonstrated clinical benefit in this setting (6, 11, 12, 15–17). Sorafenib and lenvatinib were the first agents approved for this indication, followed by more selective targeted therapies in specific molecular contexts. However, the optimal timing and patient selection for TKI initiation remain unclear, and current clinical practice guidelines differ in their recommendations (4, 7, 12, 13).

Although randomized clinical trials have demonstrated the efficacy of TKIs—most notably lenvatinib, which achieved an objective response rate of 64.8% and a significant improvement in progression-free survival in the SELECT trial (18)—there remains limited evidence of their effectiveness in real-world clinical settings (1, 19, 20). Moreover, data from Latin America are scarce, and existing studies are limited by small sample sizes and heterogeneity, which may reduce their generalizability to specific local populations (1, 19, 20).

An additional emerging area of interest is the use of TKIs in the neoadjuvant setting, particularly in patients with locally advanced or initially unresectable disease. Although preliminary evidence suggests that these agents may facilitate surgical resection and improve operability, data remain limited and largely derived from small series or case reports (25–27).

Given these knowledge gaps, particularly in real-world settings and among underrepresented populations, it is essential to characterize oncologic outcomes associated with TKI therapy in patients with RAIR-DTC. The present study aims to evaluate clinical responses, survival outcomes, and treatment patterns among patients receiving tyrosine kinase inhibitors at two high-complexity centers in Colombia, with a particular focus on real-world effectiveness and the role of neoadjuvant therapy.

Methods

Study design and setting

This was a retrospective, observational cohort study conducted in two high-complexity referral centers in Medellín, Colombia. The study included patients treated between January 2014 and December 2024.

The objective was to evaluate oncologic outcomes in patients with radioactive iodine-refractory differentiated thyroid cancer (RAIR-DTC) treated with tyrosine kinase inhibitors in a real-world clinical setting.

Study population

Adult patients with a diagnosis of differentiated thyroid cancer who met criteria for radioactive iodine-refractory disease and received treatment with the tyrosine kinase inhibitor lenvatinib during the study period were included.

RAIR-DTC was defined according to established clinical criteria, including absence of radioactive iodine uptake in target lesions, disease progression despite radioactive iodine avidity, or persistence of disease after a cumulative radioactive iodine dose, in accordance with international recommendations.

Patients were included if clinical records documenting treatment exposure and follow-up were available. Individuals with missing data for specific outcomes were excluded from the corresponding analyses but were retained in the overall cohort when applicable.

Data collection and variables

Clinical, demographic, and treatment-related data were obtained from institutional medical records. Variables collected included demographic characteristics (age, sex), clinical variables (performance status and comorbidities), tumor characteristics (histological subtype and sites of metastasis), and treatment-related variables (indication for therapy, initial dose, dose modifications, and duration of treatment).

Oncologic response was categorized into four mutually exclusive groups: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), based on radiologic assessments recorded in clinical practice.

Outcomes

The primary outcome was oncologic response, defined as the best overall response during treatment.

Secondary outcomes, assessed according to RECIST 1.1 criteria, included objective response rate (ORR), defined as the proportion of patients achieving CR or PR, and disease control rate (DCR), defined as the proportion achieving CR, PR, or SD. Additional outcomes included percentage change in tumor size (ChangePor) and overall survival (OS).

Overall survival was defined as the time from initiation of tyrosine kinase inhibitor therapy to death from any cause. Patients who were alive at the end of follow-up were censored at the date of last contact.

Subgroup analysis

A predefined subgroup analysis was performed in patients treated in a neoadjuvant setting. This subgroup included patients who received tyrosine kinase inhibitors before surgery with the intention of facilitating resection or reducing tumor burden.

The same outcomes evaluated in the overall cohort were analyzed descriptively in this subgroup.

Statistical analysis

All analyses were descriptive and exploratory. Categorical variables were summarized using absolute frequencies and percentages, while continuous variables were described using mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate.

Oncologic response categories (CR, PR, SD, PD) were treated as mutually exclusive outcomes, and proportions were calculated from the number of evaluable patients for each variable.

The percentage change in tumor size was analyzed as a continuous variable and summarized using mean, SD, median, IQR, and range.

Overall survival was estimated using the Kaplan–Meier method, with corresponding 95% confidence intervals (95% CI). Median survival was reported when reached; otherwise, it was described as not reached. The number of patients at risk over time was included to facilitate the interpretation of survival estimates.

Patients with missing data for follow-up time or vital status were excluded from survival analyses. No imputation of missing data was performed. All analyses were considered exploratory due to the observational design and sample size.

Statistical software

All analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria), version 4.5.2 (2025-10-31 ucrt), using the packages *dplyr*, *readxl*, *survival*, and *survminer*.

Ethical considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was obtained from the institutional ethics committees of all participating centers. Given the retrospective nature of the study and the use of routinely collected clinical data, the requirement for informed consent was waived. Patient confidentiality was maintained throughout the study by anonymizing all data before analysis.

Results

Study population and data completeness

A total of 35 patients with radioactive iodine-refractory differentiated thyroid cancer (RAIR-DTC) treated with tyrosine kinase inhibitors were included in the study. Data completeness for oncologic outcomes was limited: evaluable response data were available in 16 patients (45.7%), while 19 patients (54.3%) had missing information for these variables. A similar proportion of missing data was observed for the percentage change in tumor size, which was available in the same subset of evaluable patients.

For the overall survival analysis, 32 patients were included after excluding 3 individuals with missing follow-up time or vital status. A summary of the main clinical outcomes and survival parameters for the overall cohort is presented in Table 1.

Table 1
Clinical characteristics, oncologic response, and survival outcomes in the overall cohort

Variable	Result
Total patients, n	35
Patients evaluable for response, n (%)	32 (91.4)
Complete response, n (%)	1 (3.1)
Partial response, n (%)	12 (37.5)
Stable disease, n (%)	13 (40.6)
Progressive disease, n (%)	6 (18.8)
Objective response rate (ORR), n (%)	13 (40.6)
Disease control rate (DCR), n (%)	26 (81.2)
Percentage change in tumor size (Changepor)	
Patients with available data, n (%)	28 (80.0)
Median (IQR)	0.25 (0.00–0.51)
Overall survival	
Patients included in OS analysis, n	33
Death events, n (%)	9 (27.3)
Censored patients, n (%)	24 (72.7)
Median overall survival, months (95% CI)	25.7 (18.3–not estimable)

Percentages for oncologic response were calculated based on the number of evaluable patients for each variable. Objective response rate (ORR) was defined as the proportion of patients achieving complete or partial response, while disease control rate (DCR) included patients with complete response, partial response, or stable disease. Median follow-up time was estimated using the reverse Kaplan–Meier method. IQR denotes interquartile range, OS overall survival, and CI confidence interval.

Oncologic response

Among the 32 evaluable patients, the best overall response was predominantly disease control. Complete response was observed in 1 patient (3.1%), partial response in 12 patients (37.5%), and stable disease in 13 patients (40.6%), while 6 patient (18.8%) exhibited progressive disease.

The objective response rate (ORR), defined as the proportion of patients achieving complete or partial response, was 40.6%, whereas the disease control rate (DCR), including stable disease, reached 81.2%. These findings indicate that the majority of evaluable patients achieved at least disease stabilization under treatment.

Percentage change in tumor size

The analysis of the percentage change in tumor size revealed substantial heterogeneity in treatment response. Among the 16 evaluable patients, the median proportion of percentage change was 0.3 (interquartile range [IQR]: 0.19–0.54), with a mean of 32% (standard deviation [SD]: 0.46), and a range from − 1 to 1.

These findings reflect the coexistence of patients with marked tumor shrinkage and others with disease progression. The distribution of individual responses is illustrated in Fig. 4 (waterfall plot), which demonstrates the variability in treatment effect across the cohort.

Overall survival

For the survival analysis, 34 patients were included after excluding two with incomplete data. During follow-up, 9 deaths (26.5%) were recorded, while 25 patients (73.5%) were censored. The median follow-up time, estimated using the reverse Kaplan–Meier method, was 12.9 months (IQR: 4.3–22.1).

Kaplan–Meier analysis demonstrated a progressive decline in overall survival over time. The median overall survival was not reached; although the point estimate was 25.7 months, the confidence interval ranged from 18.3 months to not estimable. However, the precision of survival estimates decreased at later time points due to the limited number of patients at risk. Estimated survival probabilities were approximately 80% at 10 months, 65% at 23 months, and 44% between 26 and 30 months.

The corresponding Kaplan–Meier survival curve, including the number of patients at risk over time, is presented in Fig. 2. The progressive reduction in the number of patients at risk (from 34 at baseline to 20 at 12 months, 4 at 24 months, and 1 at 30 months) should be considered when interpreting long-term survival estimates.

Subgroup analysis: neoadjuvant setting

Oncologic response

A predefined subgroup analysis was performed in patients treated with neoadjuvant intent (n = 21). This subgroup included patients who received tyrosine kinase inhibitors before surgery with the primary intention of facilitating resection or reducing tumor burden. In all cases, neoadjuvant therapy was the intended treatment strategy from the outset. Among these, response evaluation was available in 11 patients (52.4%). A complete response was observed in 1 patient (9.1%), and a partial response in 4 patients (36.4%), resulting in an objective response rate of 45.5%.

Although complete data for all response categories were not available, these findings suggest a meaningful degree of tumor response in the neoadjuvant context. A detailed summary of clinical outcomes in this subgroup is presented in Table 2.

Table 2
Clinical outcomes and survival in patients treated in the neoadjuvant setting

Variable	Result
Patients treated with neoadjuvant therapy, n	21
Patients evaluable for response, n (%)	11 (52.4)
Complete response, n (%)	1 (9.1)
Partial response, n (%)	4 (36.4)
Objective response rate (ORR), n (%)	5 (45.5)
Disease control rate (DCR), n (%)	Not evaluable*
Percentage change in tumor size (Changepor)	
Patients with available data, n (%)	11 (52.4)
Median (IQR)	0.29 (0.19–0.47)
Overall survival	
Patients included in OS analysis, n	20
Death events, n (%)	4 (20.0)
Censored patients, n (%)	16 (80.0)
Median overall survival, months (95% CI)	Not reached

Percentages for oncologic response were calculated based on the number of evaluable patients for each variable. Objective response rate (ORR) was defined as the proportion of patients achieving complete or partial response. Disease control rate (DCR) includes complete response, partial response, and stable disease; however, it was not estimable in this subgroup due to incomplete data on stable disease and progression. Median follow-up time was estimated using the reverse Kaplan–Meier method. IQR denotes interquartile range and OS overall survival.

Percentage change in tumor size

The analysis of tumor size dynamics in the neoadjuvant subgroup showed a median proportion of percentage change of 0.29 (IQR: 0.19–0.47) and a mean of 0.36 (SD: 0.28). All observed values indicated a reduction in lesion size, suggesting a consistent trend toward tumor shrinkage among evaluable patients receiving neoadjuvant therapy.

Surgical outcomes after neoadjuvant therapy

Among patients treated in the neoadjuvant setting, 8 (38.0%) were taken to surgery. Regarding surgical margins, 4 patients (50.0%) achieved an R0 resection, 3 patients (37.5%) had an R1 resection, and 1 patient (%) had an R2 resection.

Overall survival

For survival analysis in the neoadjuvant subgroup, 21 patients were included. During follow-up, 4 deaths were recorded, while 17 patients were censored.

Kaplan–Meier analysis demonstrated a high probability of survival in the early follow-up period, with a gradual decline over time. The median overall survival was not reached, reflecting both the limited number of events and the relatively short follow-up period. Survival probabilities remained above 80% in the early phases and decreased to approximately 55% at 25–30 months.

The survival curve for this subgroup is presented in Fig. 3, illustrating the temporal pattern of survival and the increasing uncertainty in later time points.

Safety and treatment tolerability

Treatment-related adverse events were common in the overall cohort. Among the 35 included patients, 25 (73.5%) experienced at least one adverse event, while 17 (48.5%) developed two or more events, and 8 (23.5%) experienced three or more toxicities.

The median number of adverse events per patient was 1.5 (IQR: 0.25–2.0), with a mean of 1.68 ± 1.59, reflecting a moderate overall toxicity burden.

The most frequently observed adverse event was new-onset hypertension, occurring in 28 of 34 evaluable patients (82.4%; 95% CI: 65.5–93.2). Other common toxicities included weight loss (31.2%), temporary treatment interruption (31.2%), diarrhea (25.0%), asthenia (25.0%), and hand–foot syndrome (21.2%).

Clinically significant treatment modifications were observed in a relevant proportion of patients. Dose reduction was required in 15.6%, and permanent treatment discontinuation occurred in 15.6% of cases.

Severe cardiovascular toxicity appeared uncommon, as no cases of heart failure were documented.

A complete summary of treatment-related adverse events is presented in Table 3.

Table 3
Treatment-related adverse events and treatment modifications

Adverse event	n/N	%	95% CI
New-onset hypertension	28/34	82.4	65.5–93.2
Weight loss	10/32	31.2	16.1–50.0
Temporary interruption	10/32	31.2	16.1–50.0
Diarrhea	8/32	25.0	11.5–43.4
Asthenia	8/32	25.0	11.5–43.4
Hand–foot syndrome	7/32	21.2	9.0–38.9
Dose reduction	5/32	15.6	5.3–32.8
Permanent discontinuation	5/32	15.6	5.3–32.8
Stomatitis	4/32	12.5	3.5–29.0
Alopecia	1/32	3.1	0.1–16.2
Proteinuria	1/32	3.1	0.1–16.2
Heart failure	0/32	0.0	0.0–10.9

Percentages for treatment-related adverse events were calculated based on the number of evaluable patients for each toxicity variable, excluding missing data. Confidence intervals correspond to exact binomial 95% confidence intervals. Dose reduction, temporary interruption, and permanent discontinuation refer to treatment modifications attributable to lenvatinib-related toxicity. IQR denotes interquartile range, and CI confidence interval.

Discussion

In this real-world retrospective cohort of patients with advanced thyroid cancer treated with lenvatinib, the estimated median overall survival was not reached, with an objective response rate (ORR) of 40.6% and a disease control rate (DCR) of 81.2%. Adverse events were reported in 73.5% of patients, with permanent treatment discontinuation in 15.6% of cases.

Compared with pivotal clinical trial data, particularly the SELECT trial, our results show lower response rates and survival. The ORR observed in our cohort (40.6%) was notably lower than the 64.8% reported in SELECT (18). Variations in baseline disease characteristics likely explain these differences. In our cohort, a high proportion of patients presented with locally advanced unresectable disease (77.1%) and systemic progression (11.4%), suggesting a more aggressive disease profile compared to the predominantly metastatic population included in clinical trials. Despite similar distributions of performance status (ECOG 0–1: 91.4% vs. 95%), the higher burden of locally invasive disease in our cohort may have adversely affected both response and survival outcomes.

In comparison with other real-world cohorts, our findings are broadly consistent. Jerkovich et al. (1) reported a median overall survival of 39 months in patients treated with lenvatinib or sorafenib.

However, objective response rates were remarkably similar, with an ORR of 41.7% for first-line lenvatinib, closely aligning with our results. While complete response rates were higher in their cohort (16.7% vs. 3.1%), our study demonstrated higher proportions of partial response and stable disease, suggesting a comparable overall disease control profile. Differences in survival outcomes may again reflect heterogeneity in disease burden and patient selection. Additionally, their reported 12-month progression-free survival of 70% contrasts with our finding that the median PFS was not reached in our responder subgroup. Censoring patterns and follow-up duration may influence this difference.

The role of lenvatinib in the neoadjuvant setting represents a particularly relevant aspect of our study. Our findings support the growing body of evidence suggesting that tyrosine kinase inhibitors may facilitate surgical resection in selected patients with advanced disease. In the Latin American cohort reported by Pitoia et al. (23), the median tumor reduction was 24.5%, closely mirroring the 25% reduction observed in our study. However, although surgery was performed in 55% of patients in their cohort, only 38% of our patients underwent surgery. Notably, our R0/R1 resection rate was substantially higher (87.5% vs. 60%), suggesting that stricter patient selection or differences in surgical strategy may have contributed to improved surgical outcomes. The higher prevalence of metastatic disease in our cohort may have limited surgical eligibility.

Similar findings have been reported in other neoadjuvant series. A Chinese cohort (24) evaluating 17 patients treated with tyrosine kinase inhibitors reported an ORR of 50% and a surgical rate of 62.5%, with R0/R1 resections achieved in 55% of cases. While their surgical rate exceeded that of our cohort, our higher rate of optimal resections may reflect more selective surgical candidacy or differences in baseline disease characteristics, particularly given that the majority of their patients were non-metastatic.

In another series, Russell et al. (25) evaluated a molecularly guided neoadjuvant approach using targeted therapies, including lenvatinib and other agents. They reported greater tumor reduction (37% vs. 25%) and a higher surgical rate (64.7%), with 58.8% achieving R0/R1 resections. These findings suggest that molecular selection and lower metastatic burden may enhance surgical conversion rates. However, despite lower surgical rates in our cohort, resection quality was comparatively higher, reinforcing the importance of appropriate patient selection.

Regarding safety, the toxicity profile observed in our cohort is consistent with previous reports. The relatively high starting dose of lenvatinib (close to 24 mg) likely contributed to both the observed efficacy and the frequency of adverse events. In the cohort described by Hamidi et al. (20), where most patients initiated treatment at lower doses, the ORR was similar; however, treatment discontinuation was more frequent (74.1% vs. 15.6%), primarily due to toxicity. Hypertension rates were comparable between studies (77.8% vs. 82.4%). At the same time, differences in the prevalence of other adverse events—such as fatigue, weight loss, asthenia, and diarrhea—may reflect variations in reporting practices, retrospective data collection, or supportive care strategies. The lower frequency of proteinuria in our

study compared with SELECT (18) and other real-world cohorts (20) may similarly be explained by underreporting or differences in monitoring intensity.

A more detailed safety analysis further supports the manageable toxicity profile of lenvatinib in our cohort. Overall, 73.5% of patients experienced at least one adverse event, and half of the cohort developed two or more toxicities, confirming the substantial treatment-related burden associated with VEGFR-targeted therapy. Hypertension was by far the most frequent adverse event, affecting 82.4% of evaluable patients, which is consistent with the known class effect of antiangiogenic tyrosine kinase inhibitors and aligns closely with rates reported in pivotal and real-world studies. Importantly, despite the high incidence of adverse events, clinically relevant treatment modifications were relatively infrequent, with dose reduction and permanent discontinuation observed in only 15.6% of patients. This finding suggests that, although toxicity was common, it was generally manageable with supportive measures and temporary treatment interruption, allowing most patients to maintain therapy and achieve sustained disease control.

Importantly, our study contributes to the growing evidence supporting the use of tyrosine kinase inhibitors in real-world settings and provides one of the most comprehensive analyses of neoadjuvant use in advanced thyroid cancer. Our findings suggest that, in selected patients, systemic therapy may not only achieve disease control but also enable surgical rescue strategies. Furthermore, the observation that median overall survival was not reached in certain subgroups supports the hypothesis that tumor reduction and disease stabilization may translate into meaningful long-term clinical benefit.

This study has several limitations. Its retrospective design introduces the potential for selection bias and limits control over data completeness and follow-up. The relatively small sample size restricts the robustness of subgroup analyses, which should be interpreted as exploratory. Additionally, heterogeneity in imaging assessment and follow-up intervals may have influenced response evaluation. The absence of comprehensive molecular profiling precludes analysis of genotype–response correlations. Finally, the high rate of censoring highlights the need for longer follow-up to characterize long-term survival outcomes better.

Conclusion

In this real-world cohort of patients with radioactive iodine-refractory differentiated thyroid cancer, treatment with tyrosine kinase inhibitors demonstrated meaningful clinical activity, with high rates of disease control and sustained overall survival despite a population characterized by advanced and often unresectable disease.

Our findings confirm the effectiveness of lenvatinib in routine clinical practice. However, outcomes appear less favorable than those reported in randomized trials, likely reflecting differences in disease burden and patient selection.

Importantly, this study provides additional evidence supporting the role of tyrosine kinase inhibitors in the neoadjuvant setting, where treatment may facilitate surgical resection in selected patients and potentially modify the natural history of the disease.

These results highlight the value of individualized treatment strategies in advanced thyroid cancer and underscore the need for prospective studies to better define optimal patient selection, timing of therapy, and the integration of systemic treatment with surgical approaches.

Declarations

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Conflicts of interest: The authors declare the following conflicts of interest: Carlos E. Builes-Montaño has received consulting and speaking fees from Sanofi, Novo Nordisk, Novartis, Recordati Rare Diseases, Janssen, Chiesi, Abbott, and Boehringer Ingelheim, and is a shareholder of Festina Lente. Alejandro Román-González has received honoraria or institutional support from Amgen, PTC Therapeutics, Sanofi, Novo Nordisk, Ultragenyx, Novartis, Valentech, and Ipsen. All other authors declare no conflicts of interest related to this work.

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Authors' contributions: Alejandro Román-González, Santiago Orozco-Montoya, and Carlos E. Builes-Montaño contributed to the study's conceptualization and methodology. Carlos E. Builes-Montaño was responsible for software development, formal statistical analysis, data curation, and visualization. Guillermo Salazar-Villa, Santiago Orozco-Montoya, and Wilfredo A. Rivera-Martínez conducted the investigation and data collection. Alejandro Román-González provided resources and access to clinical data and contributed to project administration, together with Carlos E. Builes-Montaño.

All authors contributed to the writing of the manuscript, including drafting, critical revision, and editing, approved the final version, and agree to be accountable for all aspects of the work.

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request, in accordance with institutional policies and applicable ethical and legal regulations.

Declaration of Generative AI and AI-assisted technologies in the writing process: Artificial intelligence–assisted tools, including OpenAI and Grammarly, were used to support language editing, clarity, manuscript drafting, and assistance in the development and refinement of statistical scripts. These tools were not used for data generation, data analysis, result interpretation, or clinical decision-making. The authors take full responsibility for the content of the manuscript.

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Figures

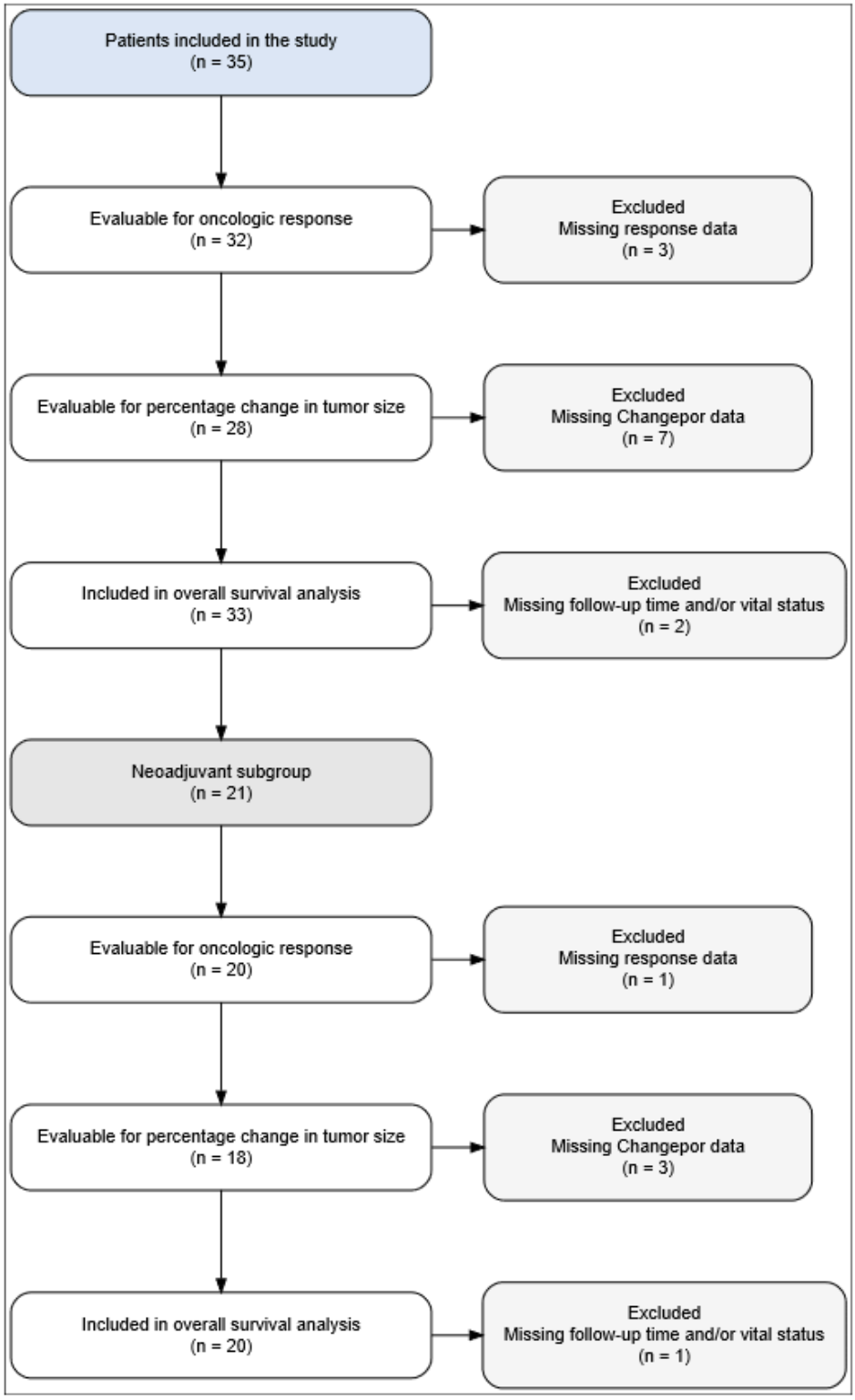

Figure 1

Study flow diagram

CONSORT-style flow diagram illustrating patient inclusion and data availability across analyses. A total of 35 patients with radioactive iodine-refractory differentiated thyroid cancer treated with tyrosine kinase inhibitors were included. The diagram shows the number of patients evaluable for oncologic response,

percentage change in tumor size (Changepor), and overall survival, as well as the corresponding exclusions due to missing data. The flow of patients within the neoadjuvant subgroup is also presented.

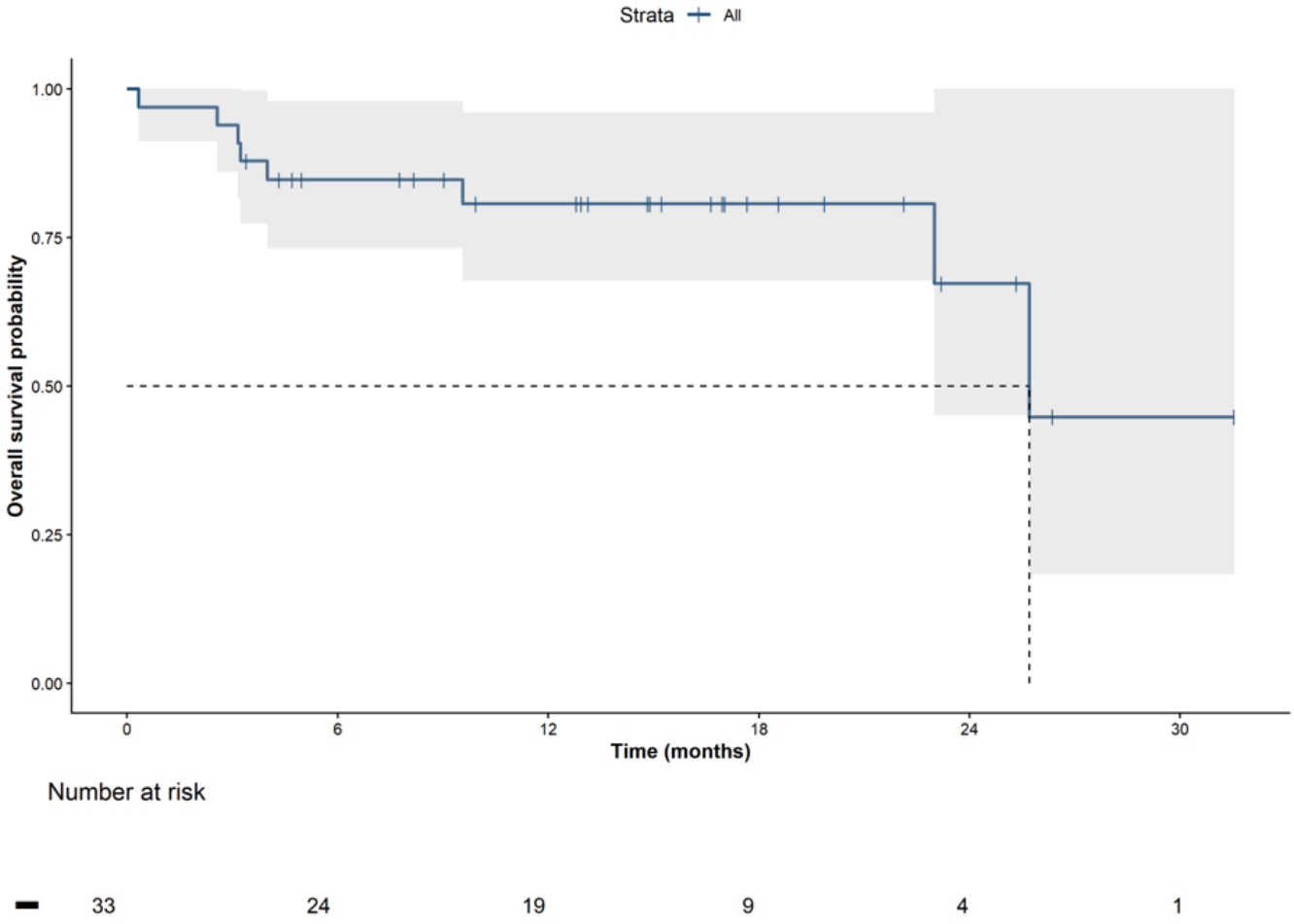

Figure 2

Kaplan–Meier curve for overall survival in the overall cohort

Kaplan–Meier estimates of overall survival in the overall cohort. Overall survival was defined as the time from treatment initiation to death from any cause, with censoring at the last follow-up. The median overall survival was 25.7 months (95% CI: 18.3–not estimable). Tick marks indicate censored observations. The number of patients at risk over time is displayed below the plot.

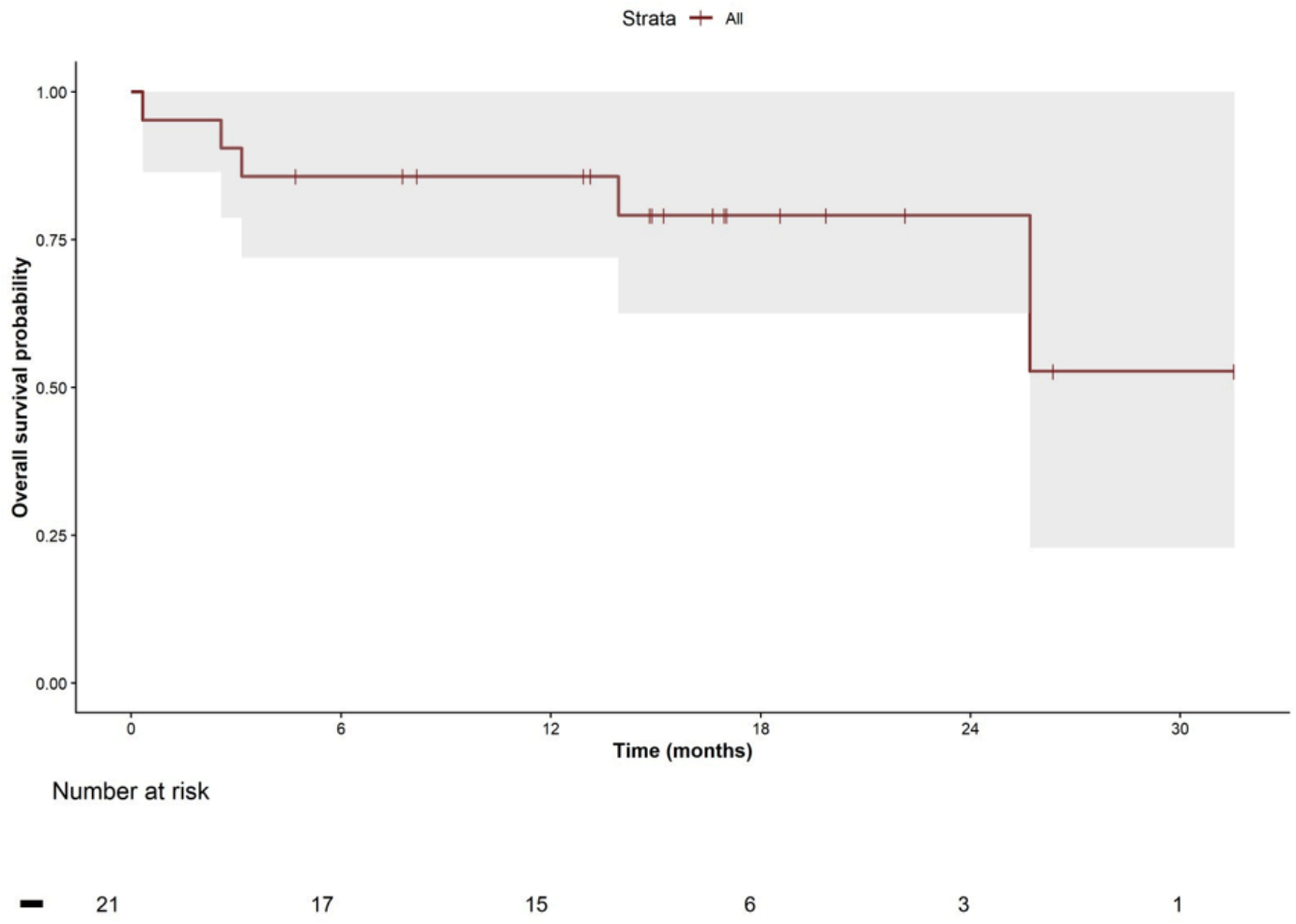

Figure 3

Kaplan–Meier curve for overall survival in the neoadjuvant subgroup

Kaplan–Meier estimates of overall survival among patients treated in the neoadjuvant setting. Overall survival was defined as the time from treatment initiation to death from any cause, with censoring at the last follow-up. The median overall survival was not reached. Tick marks indicate censored observations. The number of patients at risk over time is shown below the curve.

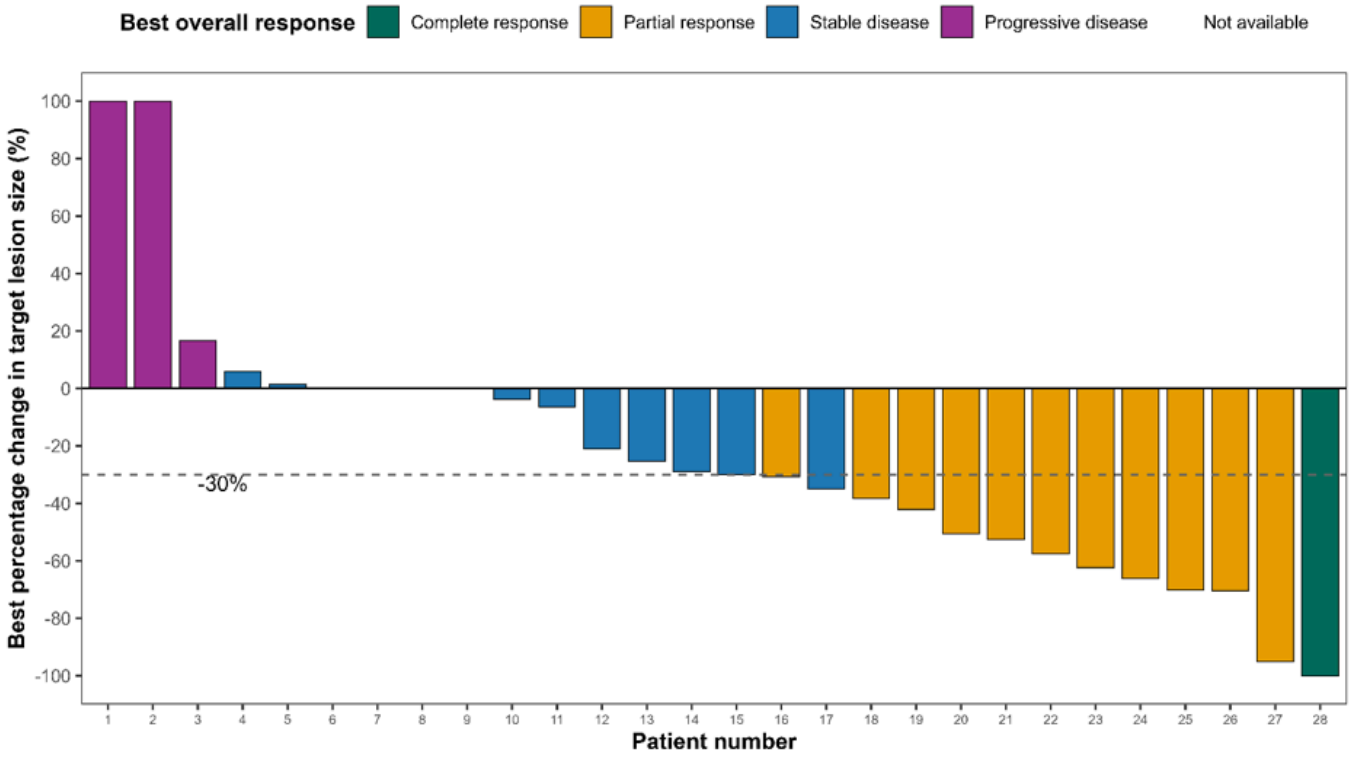

Figure 4

Waterfall plot of percentage change in tumor size

The waterfall plot displays the best percentage change from baseline in tumor burden for each patient with available radiologic assessment data (n = 28). Each bar represents an individual patient and is ordered from the greatest tumor increase to the greatest tumor reduction. Negative values indicate tumor shrinkage, whereas positive values indicate tumor growth. The dashed horizontal line at −30% indicates the conventional RECIST threshold for partial response. Bar colors represent best overall response categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).

Response proportions shown in the figure were calculated only among patients with available percentage-change data and therefore may differ from those reported in Table 1, where percentages were based on all RECIST-evaluable patients (n = 32).