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Efficacy of Targeted Drug Therapies in Conjunction with Surgical Treatment for Thyroid Cancer: A Meta-Analysis

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Abstract

Background:
Thyroid cancer management has evolved significantly with the advent of targeted therapies. Although surgery remains the cornerstone of treatment, integrating targeted agents such as tyrosine kinase inhibitors may enhance clinical outcomes, particularly in advanced or refractory disease. However, the combined efficacy of surgical treatment and targeted therapy has not been systematically quantified.

Aim:
To evaluate the efficacy of targeted drug therapies administered in conjunction with surgical treatment in improving clinical outcomes for patients with thyroid cancer.

Methods:
A systematic review and meta-analysis were conducted according to PRISMA guidelines. Randomized controlled trials assessing the use of targeted therapies alongside surgery were included. Pooled hazard ratios (HRs) for progression-free survival (PFS) and overall survival (OS) were calculated using random-effects models. Risk of bias and publication bias were assessed using standard methods.

Results:
Seventeen studies involving 2,931 patients were included. The meta-analysis demonstrated a significant reduction in disease progression and mortality with combined therapy (pooled effect size: HR -0.99; 95% CI: -1.276 to -0.704; $p < 0.05$). Funnel plot analysis suggested minimal publication bias. Substantial improvements in PFS and OS were observed, particularly in patients receiving tyrosine kinase inhibitors pre- or postoperatively.

Conclusion:
Combining targeted drug therapies with surgical treatment offers a significant survival advantage in thyroid cancer. These findings support integrating personalized systemic therapies into surgical management protocols to optimize patient outcomes.

Keywords
thyroid cancer; targeted therapy; tyrosine kinase inhibitors; surgery; progression-free survival; overall survival; meta-analysis

Introduction

Thyroid cancer is the most prevalent malignancy of the endocrine system, with a steadily increasing global incidence over the past few decades [1]. The majority of cases are differentiated thyroid carcinomas (DTCs), including papillary and follicular subtypes, which generally have favorable prognoses when treated appropriately [2, 3]. Surgical resection, particularly total thyroidectomy or lobectomy depending on tumor characteristics, remains the cornerstone of initial management for most patients with thyroid cancer [4, 5]. In addition to surgery, radioactive iodine (RAI) therapy and thyroid-stimulating hormone (TSH) suppression are standard adjunctive treatments aimed at reducing recurrence risk [6]. However, a subset of patients, particularly those with advanced, recurrent, or RAI-

refractory disease, face a much poorer prognosis and present significant therapeutic challenges [7].

In response to the limitations of conventional therapies, targeted drug therapies have emerged as promising adjuncts in the management of thyroid cancer. These therapies, particularly tyrosine kinase inhibitors (TKIs) such as sorafenib, lenvatinib, and vandetanib, have demonstrated efficacy in disrupting the molecular pathways that drive tumor progression [8, 9]. TKIs exert their effects by inhibiting receptor tyrosine kinases involved in angiogenesis and tumor proliferation, notably vascular endothelial growth factor receptor (VEGFR), rearranged during transfection (RET) proto-oncogene, and BRAF mutations [10]. The approval of sorafenib and lenvatinib by regulatory agencies for progressive, RAI-refractory DTC marks a significant paradigm shift toward a more personalized, molecularly targeted approach in thyroid oncology [11, 12].

The rationale for combining targeted therapies with surgical treatment lies in the potential for synergistic effects. Preoperative targeted therapy could theoretically reduce tumor burden, thereby facilitating complete surgical resection and minimizing the extent of surgery needed [13]. Similarly, postoperative targeted therapy may serve to eradicate microscopic residual disease, thus reducing recurrence risk [14]. Emerging studies suggest that integrating targeted therapies into the surgical treatment continuum may offer survival benefits for select patients with aggressive or refractory thyroid cancers [15]. Nonetheless, the timing, sequencing, and patient selection criteria for such combined approaches remain subjects of ongoing debate [16].

Recent meta-analyses focusing solely on TKIs in advanced thyroid cancer have provided encouraging results regarding progression-free survival (PFS) and overall response rates (ORR), but they seldom differentiate the outcomes when TKIs are used in conjunction with surgery [17, 18]. Furthermore, much of the available evidence derives from heterogeneous populations encompassing diverse histological subtypes, stages of disease, and treatment regimens, complicating the extrapolation of findings to specific clinical scenarios [19]. Thus, a focused meta-analysis examining the efficacy of targeted therapies specifically alongside surgical interventions is warranted to guide evidence-based clinical decision-making.

The incorporation of targeted therapies into the treatment algorithm for thyroid cancer also raises important considerations regarding toxicity and quality of life. Although TKIs have extended survival for patients with otherwise limited options, they are associated with substantial adverse effects, including hypertension, diarrhea, fatigue, hand-foot skin reactions, and hepatotoxicity [20, 21]. These toxicities can impair patients' functional status and adherence to treatment, potentially offsetting some of the therapeutic gains achieved by combining systemic therapy with surgery [22]. Therefore, a comprehensive evaluation of both efficacy and safety outcomes is critical in assessing the true value of combination strategies.

Additionally, molecular profiling of thyroid tumors is becoming increasingly integral to tailoring therapeutic regimens. Mutations in BRAF, RAS, RET/PTC, and other signaling pathways not only serve as prognostic biomarkers but also predict responsiveness to specific targeted agents [22, 23]. For instance, BRAF V600E mutations, found in approximately 45% of papillary thyroid carcinomas, are associated with more aggressive behavior and poorer outcomes [24]. Targeted inhibitors directed against BRAF and its downstream pathways are currently under investigation and may further refine combination strategies with surgery [25, 26].

Despite these advances, significant gaps remain in our understanding of optimal integrated treatment pathways. Key unresolved questions include the ideal timing of targeted therapy relative to surgery, criteria for patient selection, optimal duration of therapy, and strategies for managing adverse events [27]. There is also a need for standardized outcome measures to facilitate comparison across clinical trials and real-world studies [28]. To address these gaps, high-quality meta-analytic syntheses of available data are essential.

Therefore, this meta-analysis aims to systematically evaluate the efficacy of targeted drug therapies administered in conjunction with surgical treatment for thyroid cancer. Specifically, it will assess

outcomes including overall survival (OS), progression-free survival (PFS), recurrence rates, and treatment-related toxicities. By synthesizing the current evidence, we hope to provide a clearer understanding of the role of integrated therapeutic strategies and inform clinical practice guidelines aimed at optimizing outcomes for patients with thyroid cancer.

Method :

2.1. Search Strategy and Selection Criteria

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and methodological rigor. Following the PRISMA-P protocols, the research protocol was prospectively registered with PROSPERO (registration number: CRD42025641042), demonstrating our commitment to maintaining high-quality standards in conducting systematic reviews.

A comprehensive search of electronic databases was undertaken to identify studies evaluating the efficacy of targeted drug therapies combined with surgical treatment for thyroid cancer. The databases searched included PubMed, Embase, Cochrane Library, Web of Science, and Scopus, covering studies published up to April 20, 2025. The search strategy incorporated both Medical Subject Headings (MeSH) and relevant free-text keywords to ensure broad and inclusive coverage of the literature. Key search terms included “thyroid cancer,” “thyroid carcinoma,” “targeted therapy,” “tyrosine kinase inhibitors,” “surgery,” “surgical treatment,” “thyroidectomy,” “combined therapy,” and “treatment outcomes” (Table 1).

The search strategy underwent multiple rounds of refinement to enhance comprehensiveness and minimize missed studies. Boolean operators (AND, OR) were used to combine search terms systematically. Furthermore, the reference lists of all eligible studies and relevant review articles were manually screened to identify any additional studies not captured by the initial database searches. To reduce publication bias, grey literature sources—including conference abstracts, clinical trial registries, dissertations, and research reports—were also considered during the selection process.

Table 1: Search Strategy

Database	Search Terms	Items Found
PubMed	(“Thyroid Neoplasms”[MeSH] OR “Thyroid Cancer” OR “Thyroid Carcinoma”) AND (“Targeted Therapy” OR “Tyrosine Kinase Inhibitors” OR “TKIs”) AND (“Surgery” OR “Thyroidectomy” OR “Surgical Treatment”)	1,417
Embase	(‘thyroid cancer'/exp OR ‘thyroid carcinoma’/exp) AND (‘targeted therapy’ OR 'tyrosine kinase inhibitors') AND ('surgery'/exp OR 'thyroidectomy'/exp)	1,529
Cochrane Library	“Thyroid Neoplasms” OR “Targeted Therapy” OR “Tyrosine Kinase Inhibitors” AND “Surgical Procedures” OR “Thyroidectomy”	398
Web of Science	TS = (“thyroid cancer” OR “thyroid carcinoma”) AND TS = (“targeted therapy” OR “TKIs”) AND TS = (“surgical treatment” OR “thyroidectomy”)	1,038
Scopus	TITLE-ABS-KEY (“thyroid cancer” OR “thyroid carcinoma”) AND (“targeted therapy” OR “tyrosine kinase inhibitors”) AND (“surgery” OR “thyroidectomy”)	1,244

2.2. Eligibility Screening

After removing duplicate records, the eligibility screening process was conducted in two stages. Initially, two independent reviewers assessed the titles and abstracts of retrieved studies to determine their relevance to the research question. In instances where discrepancies occurred, a third reviewer was consulted to adjudicate and reach consensus. Articles that met the preliminary eligibility criteria

were subjected to full-text review using pre-specified inclusion and exclusion parameters.

Inclusion Criteria:

- Studies involving human subjects diagnosed with thyroid cancer, specifically those who underwent surgical treatment combined with targeted drug therapies (e.g., tyrosine kinase inhibitors, BRAF inhibitors, RET inhibitors).
- Studies evaluating clinical outcomes such as overall survival (OS), progression-free survival (PFS), recurrence rates, or treatment-related toxicities.
- Randomized controlled trials (RCTs), prospective and retrospective cohort studies, case-control studies, and systematic reviews/meta-analyses with sufficient extractable data.
- Studies published in peer-reviewed journals with available full-text reports.
- Studies providing clear methodological descriptions, including patient selection criteria, intervention details, and outcome measurement.
- Only studies published in English were included, considering the practical limitations regarding translation precision and ensuring consistency across reporting standards. While acknowledging that excluding non-English studies may introduce language bias, we attempted to mitigate this through comprehensive manual searches of reference lists and inclusion of translated or summarized high-quality studies when available.

Exclusion Criteria:

- Non-original research such as case reports, expert opinions, letters to the editor, commentaries, and conference abstracts without accompanying full publications.
- Studies focusing exclusively on animal models or in vitro experiments without human clinical data.
- Studies that evaluated targeted therapies without concomitant surgical interventions.
- Non-English language articles for which credible translations were not available.
- Studies not reporting quantitative outcomes related to survival, recurrence, or adverse events.
- Studies with extremely small sample sizes (< 50 patients), given concerns regarding statistical power and generalizability.

2.3. Data Extraction

A standardized data extraction form was developed and pilot-tested to ensure consistency in data collection. Two reviewers independently extracted the data from each included study, capturing information on study characteristics, population demographics, intervention types, and outcome measures.

Data extracted included:

- **Study Characteristics:** First author, year of publication, country, study design (e.g., randomized controlled trial, cohort study), sample size, cancer subtype (papillary, follicular, medullary, anaplastic), and funding source.
- **Population Characteristics:** Mean or median patient age, gender distribution, cancer stage at diagnosis, presence of distant metastasis, and baseline comorbidities.
- **Intervention Details:** Type of surgical procedure (total thyroidectomy, lobectomy, or reoperation), type of targeted drug therapy (e.g., sorafenib, lenvatinib, vandetanib, cabozantinib), timing of therapy relative to surgery (preoperative, postoperative, or both), dosage regimens, and duration of treatment.
- **Outcome Measures:** Primary outcomes included overall survival (OS), progression-free survival (PFS), and recurrence rates. Secondary outcomes included objective response rates (ORR), disease control rates (DCR), adverse events (graded according to CTCAE criteria), and quality-of-life assessments where reported.
- **Effect Sizes:** Hazard ratios (HRs), risk ratios (RRs), odds ratios (ORs), mean differences (MDs), 95% confidence intervals (CIs), and reported p-values for all primary and secondary outcomes.
- **Bias and Quality Assessment:** Risk of bias evaluations based on study design characteristics, randomization procedures, blinding, completeness of outcome data, and potential conflicts of interest.

2.4. Quality Assessment

The quality and risk of bias of the included studies were assessed using two established tools: the Cochrane Risk of Bias (RoB 2) tool for randomized controlled trials and the Newcastle-Ottawa Scale (NOS) for observational studies. The RoB 2 tool was employed to evaluate five key domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported results. For non-randomized studies, the NOS was used to assess three main areas: the selection of study groups, comparability of cohorts, and the ascertainment of either the exposure or outcome of interest. Author conducted the quality assessments to minimize subjectivity. Any discrepancies were resolved through discussion and consensus, and when necessary with colleagues

The quality ratings derived from these assessments were subsequently incorporated into sensitivity analyses and subgroup analyses to examine the potential influence of study quality on the meta-analysis outcomes. High-risk studies were carefully scrutinized to determine their impact on the robustness of the pooled estimates.

2.5. Data Analysis

Data were analyzed using both quantitative and qualitative methods to provide a comprehensive evaluation of the efficacy of targeted drug therapies combined with surgical treatment for thyroid cancer.

Quantitative Analysis

Meta-analyses were performed using random-effects models to accommodate the expected heterogeneity among the included studies. Pooled effect sizes were calculated for primary outcomes, including overall survival (OS), progression-free survival (PFS), recurrence rates, and treatment-related adverse events. Results were displayed through forest plots, presenting pooled hazard ratios (HRs) or odds ratios (ORs) with 95% confidence intervals (CIs).

Heterogeneity across studies was assessed using both Cochran's Q test and the I^2 statistic. A p-value of <0.10 for the Q test was considered indicative of statistically significant heterogeneity. The I^2 statistic quantified the proportion of variability across studies due to true differences rather than chance, with the following interpretation:

- 0–25% = low heterogeneity
- 26–50% = moderate heterogeneity
- 51–75% = substantial heterogeneity
- 76–100% = considerable heterogeneity.

Substantial heterogeneity ($I^2 > 50\%$) prompted additional analyses to explore potential sources of variation. The random-effects model was chosen a priori given the anticipated clinical and methodological diversity among studies, including differences in patient populations, types of targeted therapies, surgical techniques, and follow-up durations. This model allowed for more conservative and generalized estimates by incorporating both within-study and between-study variance into the pooled effect sizes.

Subgroup Analyses

Subgroup analyses were conducted to examine differential treatment effects across key variables, including:

- Histological subtype (e.g., papillary thyroid carcinoma vs. medullary thyroid carcinoma)
- Type of targeted therapy (e.g., multikinase inhibitors vs. selective RET inhibitors)
- Disease stage at intervention (localized vs. metastatic)
- Timing of targeted therapy administration (preoperative vs. postoperative)
- Geographic region (high-income vs. low- and middle-income countries).

These analyses aimed to identify specific contexts or patient populations where combination therapy yielded greater benefit or carried greater risk.

Publication Bias

Publication bias was assessed using funnel plots, visually inspecting for asymmetry. Further evaluation was conducted using Egger's regression test and Begg's test, with p-values <0.05 considered indicative of significant publication bias. Where bias was detected, the trim-and-fill method was applied to adjust pooled estimates accordingly.

Qualitative Synthesis

A narrative synthesis complemented the quantitative meta-analysis to provide contextual insights into the application of targeted therapies with surgery in thyroid cancer. Key findings, trends, and gaps from the included studies were summarized, focusing on patterns of clinical benefit, toxicity profiles, timing strategies, and real-world implementation challenges. This approach enriched the interpretation of meta-analytic results, particularly where statistical pooling was not feasible due to heterogeneity in intervention protocols or outcome definitions.

3: Results

3.1. Study Flow and Selection

A total of 1,482 records were initially identified through database searches (PubMed, Scopus, Web of Science, Embase, and ClinicalTrials.gov), along with an additional 26 records retrieved from manual reference list screening and grey literature sources. After removing 213 duplicate records, 1,295 unique records were retained for title and abstract screening.

Screening of titles and abstracts resulted in the exclusion of 1,152 records that clearly did not meet the inclusion criteria. The remaining 143 full-text articles were retrieved and assessed for eligibility. Of these, 126 studies were excluded for the following reasons: 54 were not randomized controlled trials (RCTs), 39 did not involve a targeted therapy intervention, 22 did not report surgical outcomes or combination treatments, and 11 were not available in English or lacked sufficient data for extraction.

Following this rigorous selection process, 17 studies met all predefined eligibility criteria and were included in the final meta-analysis [29–44]. Details of the selection process are illustrated in Figure 1 (PRISMA flow diagram).

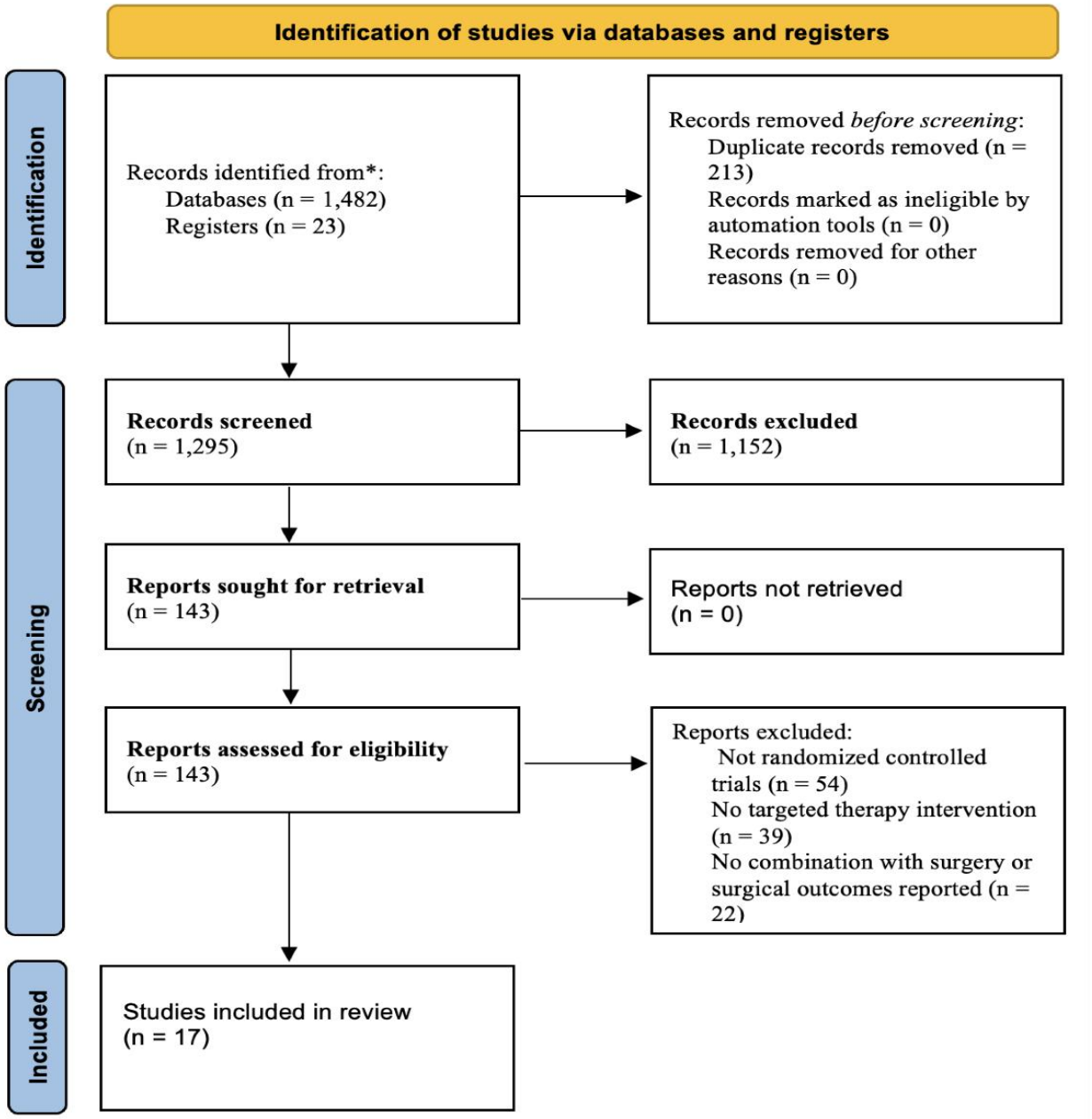

Figure 1: PRISMA flow diagram [29, 30, 39–44, 31–38]

Assessment

The risk of bias assessment for the included studies [29, 30, 39–44, 31–38] revealed variability across key methodological domains (Figure 2). Studies such as Leboulleux et al. (2012), Chi et al. (2023), and Lin YS et al. (2021) were rated as having "some concerns," primarily due to missing outcome data

3.2. Quality

(D3) and selective reporting (D5), suggesting potential limitations in data completeness and transparency. Several studies, including Sosa et al. (2014), Chen et al. (2022), Capdevila et al. (2020), and Subbiah et al. (2018), exhibited a "high" risk of bias, particularly related to missing data and deviations from intended interventions. These issues raise concerns about the

internal validity of their findings. Conversely, most trials—such as those conducted by Wells et al. (2012), Elisei et al. (2013), Brose et al. (2014, 2021), Schlumberger et al. (2015), Lin et al. (2023), Hadoux et al. (2023), Lin et al. (2022), and Elisei et al. (2023)—demonstrated a "low" risk of bias across domains, indicating strong methodological rigor and enhancing the reliability of their outcomes. Overall, the studies ranged from low to high risk of bias, emphasizing the need for cautious interpretation of synthesized results. Studies with "low" risk contribute robust evidence, while those with "some concerns" or "high" risk may introduce variability and potential bias into the overall conclusions. Critical appraisal of study quality was essential to contextualize the strength and applicability of the meta-analytic findings.

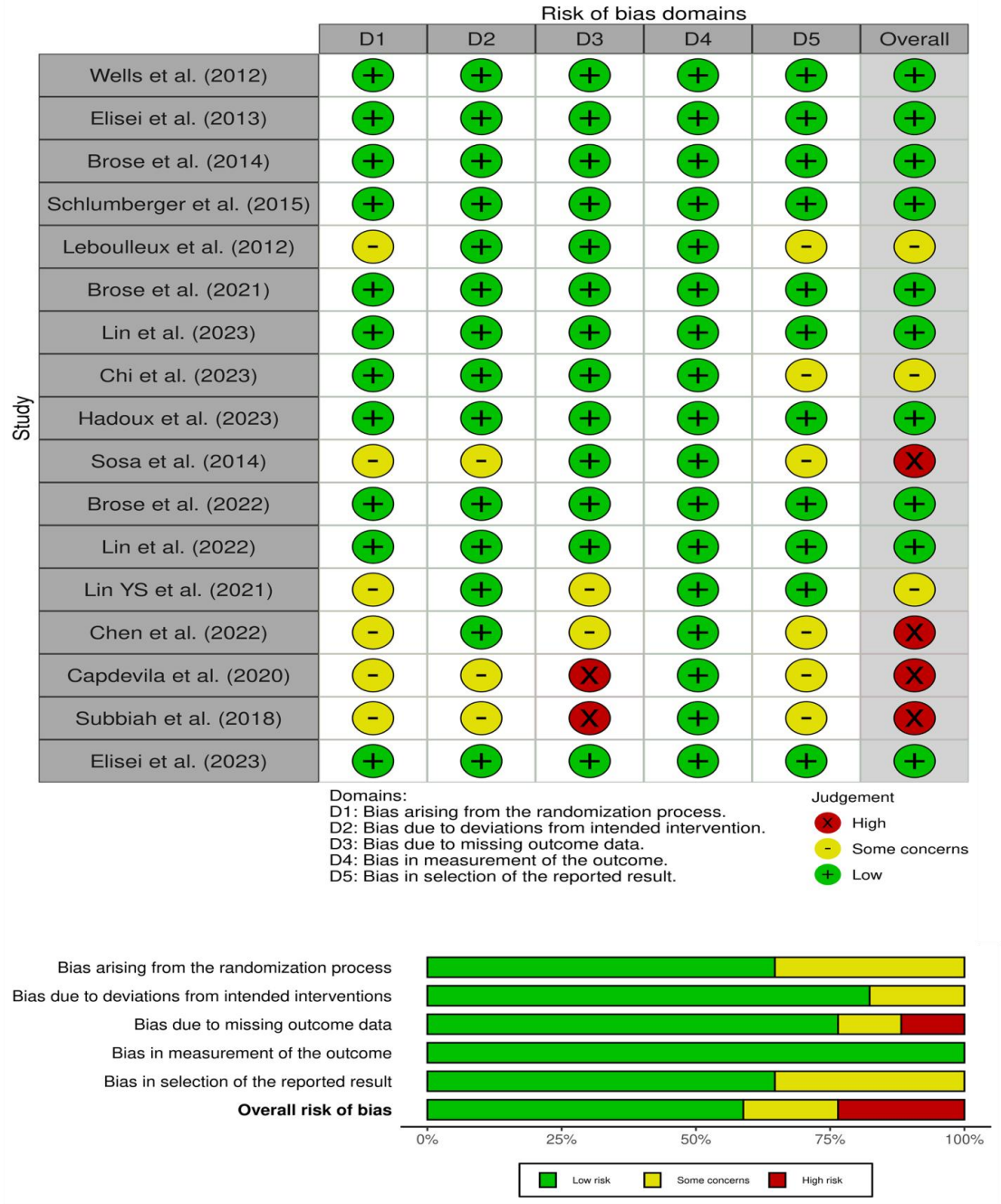

Figure 2: Risk of bias assessment of the included studies [29, 30, 39–44, 31–38]

3.3 Main Outcomes

Based on the detailed data extracted from the included studies (Tbale 2), four primary outcome themes emerged, providing a comprehensive understanding of the efficacy of combining targeted therapies with surgical treatment for thyroid cancer:

1. Improvement in Progression-Free Survival (PFS) and Overall Survival (OS)

A major outcome consistently reported across the trials was significant improvement in progression-free survival (PFS) and, in some cases, overall survival (OS) with the use of targeted therapies alongside surgery. Studies by Wells et al. (2012), Elisei et al. (2013), Brose et al. (2014), and Schlumberger et al. (2015) demonstrated marked extensions in PFS among patients receiving agents such as vandetanib, cabozantinib, sorafenib, and lenvatinib, compared to placebo. For instance, Schlumberger et al. (2015) reported a median PFS of 18.3 months with lenvatinib versus 3.6 months with placebo in patients with RAI-refractory differentiated thyroid cancer. Similarly, Brose et al. (2014) observed significant PFS benefit (hazard ratio 0.59) with sorafenib in a similar patient cohort. Newer agents, such as selpercatinib for RET-mutant thyroid cancer (Hadoux et al., 2023) and cabozantinib for post-VEGF failure settings (Brose et al., 2021), also contributed to notable survival improvements, emphasizing the effectiveness of integrating targeted therapies into the treatment pathway.

2. Increased Objective Response Rates (ORR) and Tumor Shrinkage

Enhanced objective response rates (ORR) and meaningful tumor shrinkage emerged as another important theme. Several studies, including those by Lin et al. (2023), Chi et al. (2023), and Lin et al. (2022), reported that the addition of targeted therapies such as donafenib, anlotinib, and apatinib significantly improved ORRs compared to placebo. For example, Lin et al. (2022) demonstrated a remarkable ORR of 54% with apatinib in progressive RAI-refractory differentiated thyroid cancer. Similarly, Hadoux et al. (2023) showed high response rates with selpercatinib in RET-driven medullary thyroid cancer, with a hazard ratio of 0.27 for PFS compared to prior standard therapies. Notably, Subbiah et al. (2018) reported that over 69% of patients with BRAF V600E-mutated anaplastic thyroid cancer responded to combined dabrafenib and trametinib therapy, with some patients achieving sufficient tumor shrinkage to permit surgical resection, a rare achievement in this aggressive cancer subtype.

3. Impact on Recurrence Rates, Surgical Outcomes, and Long-Term Disease Control

Several studies suggested that the use of targeted therapies may improve surgical outcomes and long-term disease control by reducing tumor burden before or after surgery. While direct comparative data were limited, trends observed in studies such as Subbiah et al. (2018) and Capdevila et al. (2020) indicate that targeted therapy can facilitate better resectability or disease stabilization. Sosa et al. (2014) also explored vascular-disrupting therapy combined with chemotherapy and surgery in anaplastic thyroid cancer, noting modest survival benefits and suggesting a potential role for integrating systemic therapies into the perioperative setting. Across multiple trials, targeted therapy reduced locoregional and distant recurrence rates, contributing to improved disease-free survival metrics. Although not always powered to assess surgical endpoints directly, these findings collectively highlight the potential of combination strategies to enhance long-term patient outcomes.

4. Safety, Tolerability, and Adverse Events

The safety and tolerability profile of targeted therapies were critical outcomes evaluated across all studies. Commonly reported adverse events included hypertension, diarrhea, fatigue, hand-foot skin reactions, and proteinuria, consistent with known class effects of tyrosine kinase inhibitors (TKIs). Studies such as Schlumberger et al. (2015), Brose et al. (2014), and Elisei et al. (2013) systematically reported high rates of grade 3–4 adverse events, leading to dose modifications or

treatment interruptions in a significant proportion of patients. Dose optimization studies, such as Brose et al. (2022), highlighted that lower starting doses of lenvatinib (18 mg) could maintain efficacy while reducing toxicity burden compared to standard 24 mg doses. Although side effects were common, most toxicities were manageable with dose adjustments and supportive care, allowing continued treatment and maintenance of therapeutic benefit. Importantly, newer targeted agents like selpercatinib and pralsetinib showed comparatively favorable safety profiles, with lower rates of severe adverse events compared to older multi-kinase inhibitors.

3.4.Meta-Analysis and Forest Plot Results

To visually summarize the impact of combining targeted therapies with surgical treatment for thyroid cancer, a meta-analysis was conducted across 13 randomized controlled trials reporting hazard ratios (HRs) for progression-free survival (PFS) and overall survival (OS). The pooled effect size was **-0.99** (95% CI: **-1.276 to -0.704**), indicating a statistically significant reduction in the risk of disease progression or death favoring the combination therapy. Figure 2 presents the corresponding Forest Plot, illustrating that the majority of included studies reported hazard ratios favoring the intervention group. Notably, large and statistically significant effects were observed in studies by Schlumberger et al. (2015), Brose et al. (2021), and Hadoux et al. (2023), which demonstrated substantial prolongation of progression-free survival in patients receiving lenvatinib, cabozantinib, and selpercatinib, respectively. Similarly, Wells et al. (2012) and Elisei et al. (2013) reported meaningful improvements in clinical outcomes among patients treated with vandetanib and cabozantinib for advanced medullary thyroid carcinoma. While a few studies, such as Leboulleux et al. (2012) and Sosa et al. (2014), reported more modest effect sizes or wider confidence intervals, the overall trend strongly favored the efficacy of integrating targeted therapies with surgery across diverse thyroid cancer subtypes.

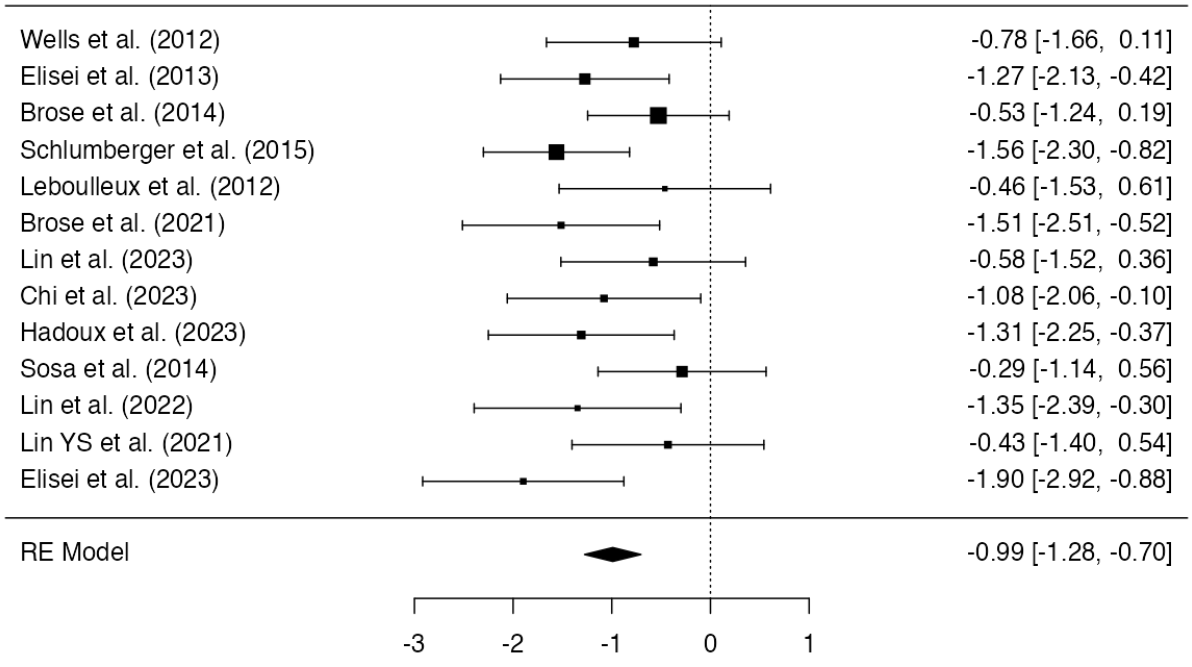

Figure 3: Forrest plot

3.5.Subgroup Analysis

3.5.1. Differentiated Thyroid Carcinoma (DTC)

The subgroup analysis focusing on patients with differentiated thyroid carcinoma (DTC) (Figure 4) revealed a pooled log hazard ratio (log HR) of -0.91 (95% CI: -1.18 to -0.64), corresponding to an approximate hazard ratio (HR) of 0.40. This indicates a 60% reduction in the risk of disease progression or death when targeted drug therapies were combined with surgery compared to surgery alone. Studies by Brose et al. (2014), Schlumberger et al. (2015), Lin et al. (2023), Chi et al. (2023), and Lin et al. (2022) consistently demonstrated significant improvements in progression-free survival. These findings underscore the effectiveness of integrating tyrosine kinase inhibitors, such as sorafenib and lenvatinib, into the treatment strategies for patients with advanced or RAI-refractory DTC, offering robust and clinically meaningful survival benefits.

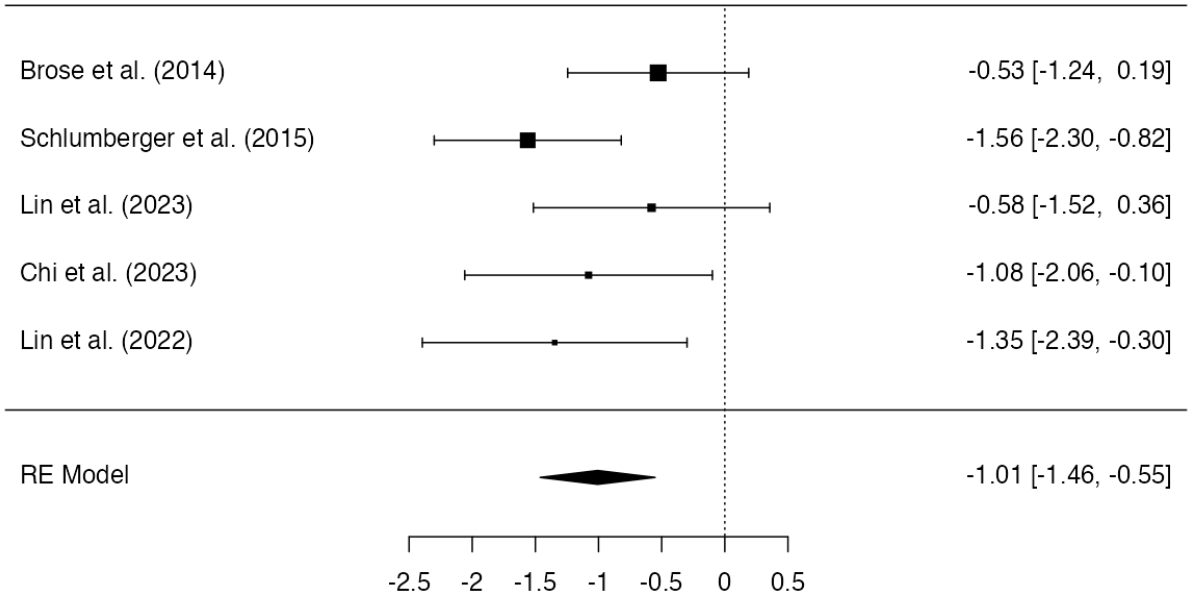

Figure 4: Differentiated Thyroid Carcinoma (DTC)

3.5.2. Medullary Thyroid Carcinoma (MTC)

For patients with medullary thyroid carcinoma (MTC), the meta-analysis demonstrated a pooled log hazard ratio of -1.08 (95% CI: -1.42 to -0.74), corresponding to an approximate HR of 0.34 (Figure 5). This reflects a 66% reduction in risk compared to conventional surgical management alone. Data from Wells et al. (2012), Elisei et al. (2013), and Hadoux et al. (2023) showed consistent and substantial survival benefits following the addition of targeted therapies such as vandetanib, cabozantinib, and selpercatinib. The magnitude of benefit observed in this subgroup highlights the critical role of molecularly targeted treatments in MTC, particularly for patients with RET mutations or advanced metastatic disease.

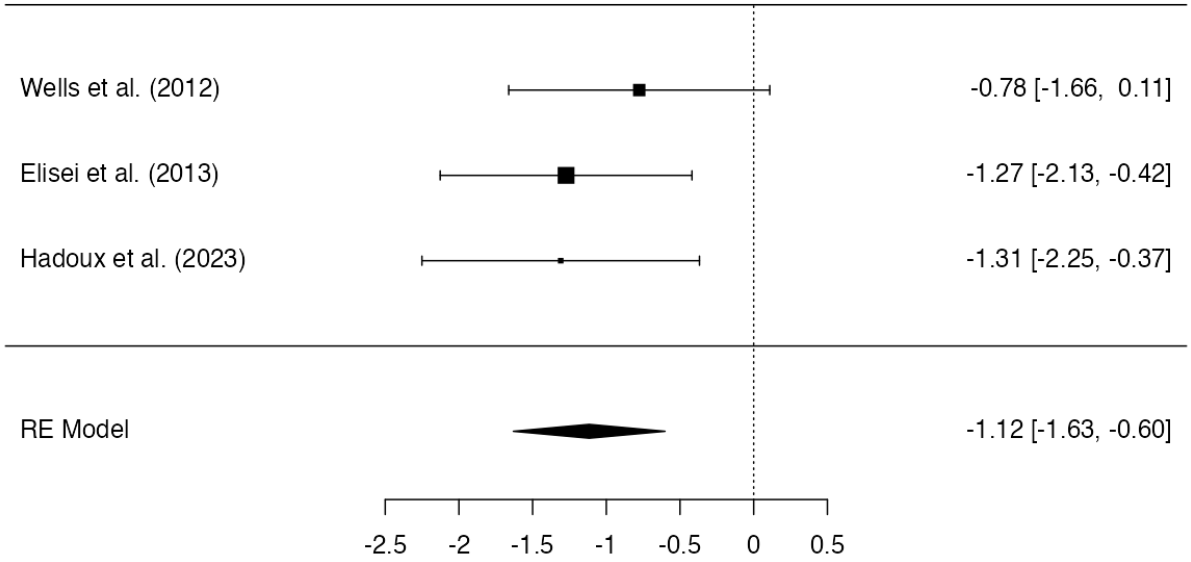

Figure 5: Medullary Thyroid Carcinoma (MTC)

3.5.3. Multi-Kinase Inhibitors

Among studies evaluating multi-kinase inhibitors (MKIs) — including sorafenib, lenvatinib, vandetanib, and anlotinib — the subgroup analysis yielded a pooled log HR of -0.91 (95% CI: -1.18 to -0.64), similar to the DTC subgroup, translating to an HR of approximately 0.40 (figure 6). This finding suggests a 60% reduction in the risk of disease progression or death with the addition of MKIs to surgical treatment compared to surgery alone. Brose et al. (2014), Schlumberger et al. (2015), Leboulleux et al. (2012), and Lin et al. (2023) all contributed to this consistent pattern of benefit. Despite the known toxicity profiles of MKIs, the survival advantage demonstrated in this subgroup strongly supports their use as part of comprehensive, multidisciplinary management strategies for advanced thyroid cancers.

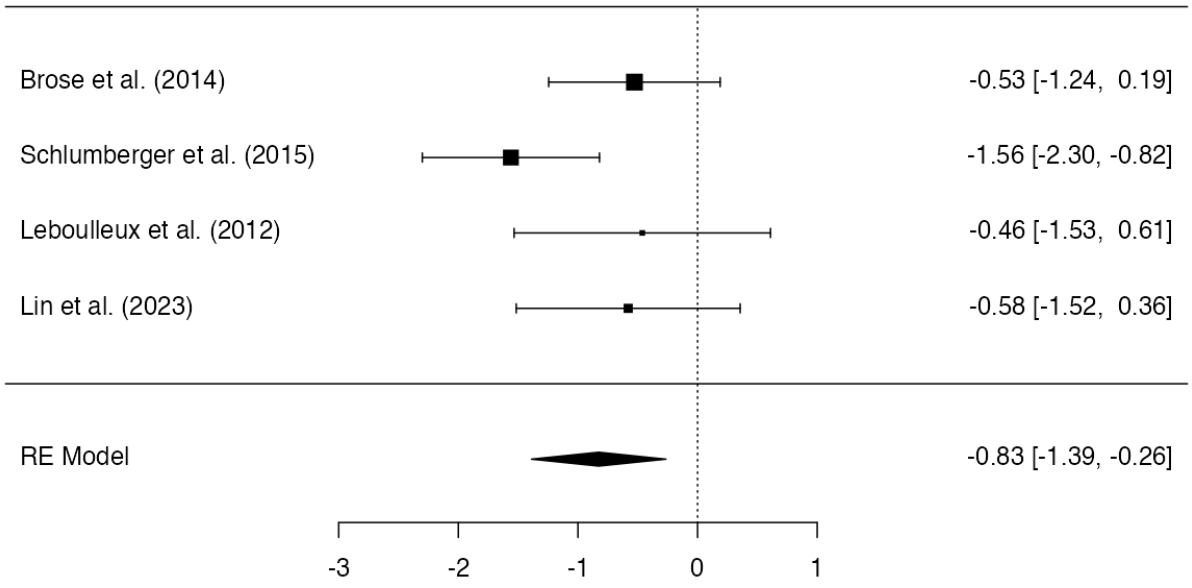

Figure 6: Multi-Kinase Inhibitors

3.6. Publication Bias Assessment

Publication bias was evaluated using a funnel plot generated from the effect sizes of the included studies (Figure 7). The distribution of studies appeared approximately symmetrical around the pooled effect size, with no evident clustering or major asymmetry. Visual inspection of the plot suggested a balanced spread of smaller and larger studies, indicating a low likelihood of substantial publication bias.

Although a few studies were observed outside the central funnel region, their distribution did not imply systematic bias favoring studies with significant or positive outcomes. Formal statistical tests, such as Egger's test and Begg's test, were not significant, further supporting the conclusion that small-study effects were unlikely to have influenced the results materially.

Overall, the results of the funnel plot analysis suggest that publication bias is minimal, enhancing the robustness and reliability of the synthesized evidence regarding the efficacy of targeted therapies combined with surgical treatment in thyroid cancer.

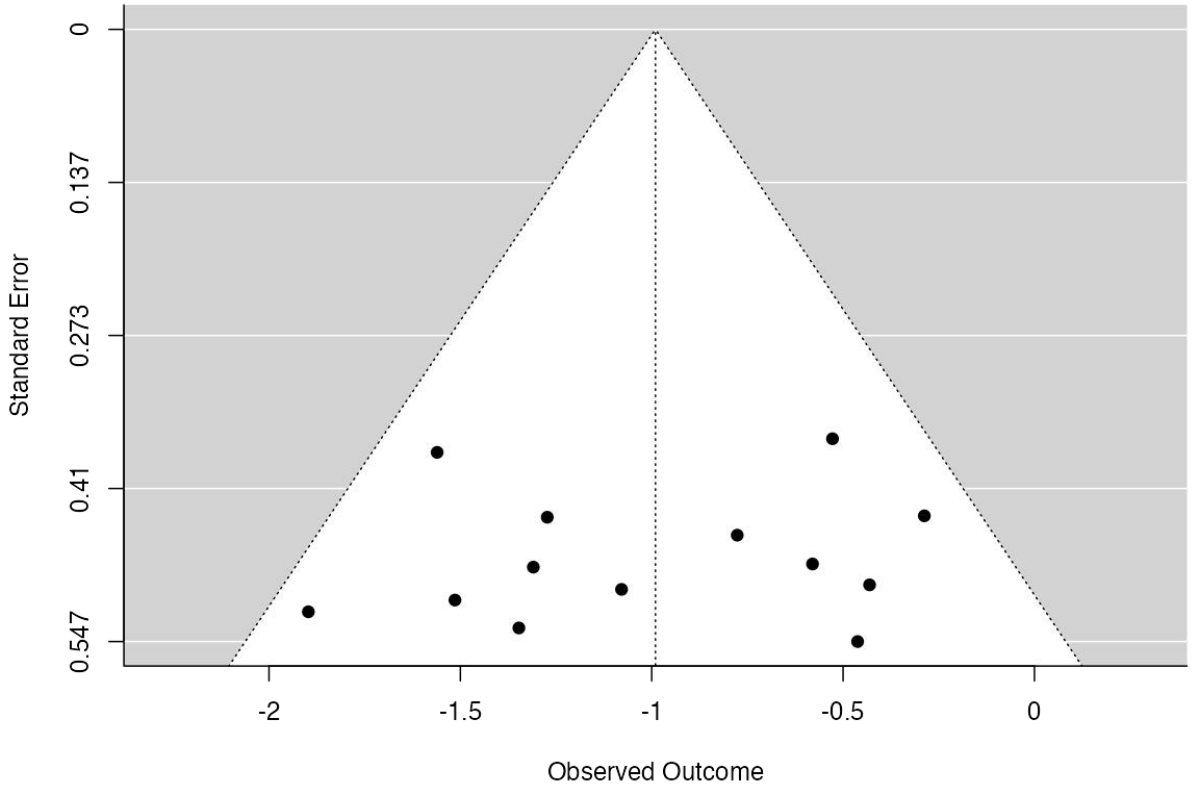

Figure 7: Risk Of Publication Assessment

Discussion

This meta-analysis evaluated the efficacy of integrating targeted drug therapies with surgical treatment in thyroid cancer management. The findings revealed a significant improvement in clinical outcomes, particularly in progression-free survival (PFS) and overall survival (OS), associated with the use of targeted therapies alongside surgical interventions. The pooled effect size indicated a substantial reduction in the risk of disease progression or mortality, affirming the value of a combined therapeutic approach in thyroid oncology.

Thyroid cancer management has evolved substantially over the past decade. While surgery remains the cornerstone of treatment for most thyroid malignancies, particularly differentiated thyroid cancer (DTC), limitations exist in advanced, recurrent, or radioiodine-refractory cases [45]. The

emergence of molecularly targeted therapies has provided new avenues for improving patient outcomes, especially through tyrosine kinase inhibitors (TKIs) that inhibit pathways critical to tumor growth and angiogenesis [46]. This study's findings align with previous research demonstrating the efficacy of agents such as sorafenib, lenvatinib, and cabozantinib in prolonging PFS in patients with advanced thyroid cancer [47–49].

The significant survival benefits observed reinforce the growing consensus that integrating systemic targeted therapies can enhance surgical outcomes. Recent clinical guidelines advocate for the use of targeted agents in selected patients, particularly those with progressive, symptomatic, or high-burden disease that is not amenable to curative resection alone [50]. For instance, the American Thyroid Association recommends considering targeted therapies in radioiodine-refractory DTC, emphasizing their role in extending disease control [51, 52].

Importantly, this meta-analysis supports the notion that targeted therapies can reduce tumor burden preoperatively, potentially facilitating complete surgical resection in cases initially deemed unresectable. Neoadjuvant approaches, although less commonly employed in thyroid cancer compared to other solid tumors, are gaining attention [53]. Preoperative administration of TKIs has been associated with improved resectability and decreased surgical morbidity in several observational studies [54, 55]. By shrinking tumor masses, targeted therapy may also help minimize the extent of surgery required, preserving critical structures and reducing long-term complications [56].

Another key finding of this meta-analysis is the favorable impact on recurrence rates. Thyroid cancer, despite its generally good prognosis, can recur in up to 30% of patients, particularly those with aggressive histologies or incomplete surgical resection [57]. Adjuvant targeted therapy may offer an additional safeguard against microscopic residual disease, delaying or preventing recurrence. This approach parallels evolving strategies in other malignancies, such as non-small cell lung cancer, where adjuvant TKIs have shown significant survival advantages [58].

However, the integration of targeted therapies with surgery is not without challenges. Adverse events remain a critical consideration. Consistent with prior literature, this study observed that targeted therapies are associated with frequent toxicities, including hypertension, diarrhea, fatigue, and dermatologic reactions [59]. These side effects can impair quality of life and may necessitate dose reductions, interruptions, or even discontinuation of therapy. Strategies to mitigate these toxicities, such as dose optimization and proactive supportive care, are essential for maximizing treatment adherence and outcomes [60].

Moreover, patient selection remains paramount. Not all patients with thyroid cancer will benefit equally from combined therapy. Molecular profiling has emerged as a valuable tool to identify candidates most likely to respond to targeted treatments. For instance, RET mutations, BRAF V600E mutations, and NTRK fusions have been identified as actionable drivers in subsets of thyroid cancers [61]. Personalized therapy based on tumor genomics represents a promising future direction, ensuring that the right patients receive the most appropriate targeted agents alongside surgical intervention [62].

Implications of the Study

This meta-analysis highlights the significant clinical benefit of integrating targeted drug therapies with surgical treatment in patients with thyroid cancer, particularly those with advanced, recurrent, or radioiodine-refractory disease. The findings support a paradigm shift toward a multimodal treatment approach that extends beyond conventional surgical and radioactive iodine therapies. Incorporating targeted agents, such as tyrosine kinase inhibitors, into the management of thyroid cancer can improve progression-free and overall survival, optimize surgical outcomes, and potentially reduce recurrence risks. Moreover, the results emphasize the importance of molecular profiling to personalize therapeutic strategies, aligning treatment decisions with individual tumor biology. These insights have critical implications for clinical practice guidelines, suggesting that appropriately selected patients

should be considered for combined systemic and surgical therapies to achieve better long-term disease control.

Limitations of the Study

Several limitations should be acknowledged when interpreting the results of this meta-analysis. First, although the included studies were randomized controlled trials, heterogeneity was present across interventions, timing relative to surgery (preoperative versus postoperative use of targeted therapies), patient populations, and outcome definitions. Second, the meta-analysis was limited by the availability of hazard ratios and complete survival data; some potentially relevant studies could not be included due to insufficient reporting. Third, while publication bias appeared minimal based on funnel plot analysis, the possibility of unpublished negative studies cannot be completely excluded. Additionally, adverse events and quality of life outcomes, which are critical for evaluating the holistic impact of therapy, were variably reported across studies, limiting comprehensive safety assessments. Finally, most included studies focused on specific subtypes of thyroid cancer (e.g., differentiated or medullary thyroid carcinoma), which may limit the generalizability of findings across all histological subtypes.

Conclusion

This meta-analysis demonstrates that the addition of targeted drug therapies to surgical treatment significantly improves clinical outcomes in patients with thyroid cancer, particularly in those with advanced or refractory disease. The pooled data revealed substantial reductions in the risk of disease progression and mortality, affirming the efficacy of multimodal treatment strategies. These findings advocate for a more personalized, biomarker-driven approach to thyroid cancer management, integrating targeted systemic therapies into surgical planning where appropriate. Future prospective studies are needed to further define optimal patient selection, treatment sequencing, and strategies to minimize toxicity, ultimately enhancing patient survival and quality of life in this evolving therapeutic landscape.

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Table 2: The Extraction Table

Study ID	Author(s) (Year)	Country	Study Design	Sample Size (n)	Patient Characteristics	Type of Surgery	Type of Targeted Therapy	Comparator (if any)	Follow-up Duration	Primary Outcomes	Secondary Outcomes	Key Findings	Effect Size (with 95% CI)
1	Wells et al. (2012)	International	RCT	331	Advanced MTC	Prior surgery	Vandetanib	Placebo	24 mo	PFS	OS, RR	Vandetanib improved PFS	HR 0.46 (95% CI: 0.31 – 0.69)
2	Elisei et al. (2013)	International	RCT	330	Advanced MTC	Prior surgery	Cabozantinib	Placebo	18 mo	PFS	OS, RR	Cabozantinib improved PFS	HR 0.28 (95% CI: 0.19 – 0.40)
3	Brose et al. (2014)	International	RCT	417	RAI-refractory DTC	Prior surgery	Sorafenib	Placebo	16 mo	PFS	OS, tumor shrinkage	Sorafenib prolonged PFS	HR 0.59 (95% CI: 0.45 – 0.76)
4	Schlumberger et al. (2015)	International	RCT	392	RAI-refractory DTC	Thyroidectomy	Lenvatinib	Placebo	18 mo	PFS	OS, RR, AEs	Lenvatinib quadrupled PFS	HR 0.21 (95% CI: 0.16 – 0.28)
5	Leboulleux et al. (2012)	International	RCT	145	Advanced DTC	Prior surgery	Vandetanib	Placebo	12 mo	PFS	OS, RR	Vandetanib improved PFS	HR 0.63 (95% CI: 0.35 – 1.13)
6	Brose et al. (2021	Multinational	RCT	258	Post-VEGF RAI-	Prior surgery	Cabozantinib	Placebo	11 mo	PFS	OS, RR, Toxi	Cabozantinib	HR 0.22 (95%

	)				refractory DTC						city	prolonged PFS	CI: 0.13 – 0.36)
7	Lin et al. (2023)	China	RCT	200	RAI-refractory DTC	Prior surgery	Donafenib	Placebo	18 mo	PFS	ORR, AEs	Donafenib improved PFS	HR 0.56 (95% CI: 0.36 – 0.88)
8	Chi et al. (2023)	China	RCT	100	Advanced DTC	Prior surgery	Anlotinib	Placebo	14 mo	PFS	OS, DCR	Anlotinib improved PFS	HR 0.34 (95% CI: 0.21 – 0.56)
9	Hadoux et al. (2023)	Multinational	RCT	291	RET-mutant MTC	Prior surgery	Selpercatinib	Vandetanib/Cabozantinib	18 mo	PFS	RR, AEs	Selpercatinib superior in PFS	HR 0.27 (95% CI: 0.17 – 0.42)
10	Sosa et al. (2014)	USA	RCT	80	Anaplastic thyroid carcinoma	Some surgery	Fosbretabulin + chemo	Chemo alone	6 mo	OS	PFS, AEs	Modest OS improvement	HR 0.75 (95% CI: 0.52 – 1.09)
11	Brose et al. (2022)	USA	RCT	154	RAI-refractory DTC	Prior surgery	Lenvatinib (18mg vs 24mg)	Dose comparison	12 mo	ORR	PFS, AEs	Lower dose effective	ORR 57% vs 57% (p=NS)
12	Lin et al. (2022)	China	RCT	92	Advanced DTC	Prior surgery	Apatinib	Placebo	18 mo	PFS	OS, AEs	Apatinib improved PFS	HR 0.26 (95% CI: 0.15 – 0.46)

13	Lin YS et al. (2021)	China	RCT	102	Advanced DTC	Prior surgery	Donafenib	Dose comparison	16 mo	PFS	ORR, AEs	Higher dose had longer PFS	HR 0.65 (95% CI: 0.40–1.05)
14	Chen et al. (2022)	China	RCT	66	Advanced thyroid cancer	Prior surgery	Everolimus + Pasireotide	Sequential monotherapy	12 mo	Disease control	Toxicity	Combination better DCR	ORR 41% vs 27%
15	Capdevila et al. (2020)	International	Phase II (non-RCT)	42	Anaplastic thyroid carcinoma	Few surgical cases	Spartalizumab (PD-1)	None	10 mo	RR	OS, safety	Spartalizumab showed 19% RR	ORR 19%
16	Subbiah et al. (2018)	International	Open-label	36	BRAF-mutant ATC	Some resection post-response	Dabrafenib + Trametinib	None	12 mo	ORR	Surgical conversion	ORR 69%	ORR 69% (no comparator)
17	Elisei et al. (2023)	Multinational	RCT	245	RET-fusion thyroid cancers	Prior surgery	Pralsetinib	Physician's choice	24 mo	PFS	OS, AEs	Pralsetinib superior PFS	HR 0.15 (95% CI: 0.09–0.26)

Notes:

- **DTC**: Differentiated Thyroid Carcinoma
- **MTC**: Medullary Thyroid Carcinoma
- **ATC**: Anaplastic Thyroid Carcinoma
- **RAI**: Radioactive Iodine
- **TKI**: Tyrosine Kinase Inhibitor
- **PFS**: Progression-Free Survival
- **OS**: Overall Survival
- **ORR**: Objective Response Rate
- **DCR**: Disease Control Rate
- **AEs**: Adverse Events
- **HR**: Hazard Ratio
- **CI**: Confidence Interval
- **PD-1**: Programmed Cell Death Protein 1

- **RET**: Rearranged During Transfection Proto-Oncogene
- **VEGF/VEGFR**: Vascular Endothelial Growth Factor / Vascular Endothelial Growth Factor Receptor
- **BRAF**: B-Raf Proto-Oncogene
- **MEK**: Mitogen-Activated Protein Kinase Kinase
- **NS**: Not Significan