

Original article

Redifferentiation therapy prior to radioiodine in refractory differentiated thyroid cancer: A systematic review and meta-analysis

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Abstract

Background: Radioiodine (RAI)-refractory differentiated thyroid cancer (DTC) has a poor prognosis. Constitutive MAPK activation, frequently driven by BRAF V600E or RAS alterations, suppresses thyroid-specific genes and sodium-iodide symporter expression. Short-course BRAF and/or MEK inhibition before RAI aims to restore iodine avidity.

Methods: We conducted a systematic review and meta-analysis in accordance with PRISMA 2020. PubMed, Embase, CENTRAL, ClinicalTrials.gov, and Google Scholar were searched from inception through March 31, 2025, for prospective studies of short-course BRAF and/or MEK inhibition undertaken with the protocolized intention of restoring RAI

Highlights

- Short-course MAPK inhibition restored detectable radioiodine uptake in an estimated 62.3% of patients, although the therapeutic dosimetric rate was lower when a quantitative threshold was applied.
- Mutation-specific efficacy remains uncertain; the available evidence is insufficient to establish equivalence between

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uptake before therapeutic RAI (PROSPERO: CRD1371813). Random-effects models with REML estimation and logit transformation were used for proportions. Risk of bias was assessed with ROBINS-I and certainty with GRADE.

Results: Five non-randomized single-arm studies (N=72) met the revised eligibility criteria; four studies (n=48) contributed to the primary meta-analysis. The pooled proportion with restored detectable RAI uptake was 62.3% (95% CI 47.8%–74.8%; $I^2=0\%$). When the therapeutic dosimetric threshold reported by Ho et al. was used, the pooled estimate was 57.8% (95% CI 44.0%–71.5%). Excluding Ho et al., it yielded 63.5% (95% CI 45.7%–81.4%). No included study published a hazard ratio for progression-free survival; progression-free and overall survival were therefore synthesized narratively. Adverse-event rates were not pooled because attribution, grading, and exposure duration differed across studies. No treatment-related deaths were reported. Certainty of the evidence was very low for all outcomes.

Conclusions: Short-course MAPK inhibitor-based redifferentiation can restore RAI uptake in selected patients with RAI-refractory DTC, but uptake is a surrogate outcome and does not establish survival benefit. The evidence is insufficient to determine whether efficacy differs by mutation subtype. Controlled, biomarker-stratified trials using standardized imaging and clinically relevant outcomes are needed.

Keywords: Thyroid neoplasms, Cell differentiation, Proto-oncogene proteins B-Raf MAP kinase signaling system, Iodine, Radioisotopes.

BRAF V600E- and RAS-mutated tumors.

- Redifferentiation remains a proof-of-concept, biomarker-guided strategy that requires confirmation in adequately powered controlled trials.

Terapia de rediferenciación previa al yodo radiactivo en el cáncer diferenciado de tiroides refractario: una revisión sistemática y metaanálisis

Resumen

Antecedentes: el cáncer diferenciado de tiroides (CDT) refractario al yodo radiactivo (RAI) tiene un mal pronóstico. La activación constitutiva de MAPK, frecuentemente mediada por alteraciones en BRAF V600E o RAS, reduce la expresión de genes tiroideos y del cotransportador sodio-yoduro. La inhibición breve de BRAF y/o MEK antes del RAI busca restaurar la avidéz por el yodo.

Métodos: se realizó una revisión sistemática y metaanálisis conforme a PRISMA 2020. Se buscaron estudios prospectivos en PubMed, Embase, CENTRAL, ClinicalTrials.gov y Google Scholar desde el inicio hasta el 31 de marzo de 2025. Fueron elegibles los estudios de inhibición breve de BRAF y/o MEK con la intención protocolizada de restaurar la captación antes de RAI terapéutico (PROSPERO: CRD1371813). Se emplearon modelos de efectos aleatorios con REML y transformación logit. El riesgo de sesgo se evaluó con ROBINS-I y la certeza con GRADE.

Resultados: cinco estudios no aleatorizados de un solo brazo (N = 72) cumplieron los criterios revisados; cuatro estudios (n = 48) aportaron al metaanálisis primario. La proporción combinada de restauración de captación detectable fue 62,3 % (IC 95 % 47,8 %–74,8 %; $I^2 = 0\%$). Al utilizar el umbral dosimétrico terapéutico de Ho et al., el estimado fue 57,8 % (IC 95 % 44,0 %–71,5 %); al excluir ese estudio, fue del 63,5 % (IC 95 % 45,7 %–81,4 %). Ningún estudio publicó una razón de riesgos para supervivencia libre de progresión, por lo que esta y la supervivencia global se sintetizaron narrativamente. Las tasas de eventos adversos no se combinaron debido a diferencias en la atribución, la graduación y la duración de la exposición. No se informaron muertes relacionadas con el tratamiento. La certeza de la evidencia fue muy baja para todos los desenlaces.

Destacados

- La inhibición breve de la vía MAPK restauró la captación detectable de radioyodo en una proporción estimada del 62,3 % de los pacientes, aunque la proporción que alcanzó el umbral dosimétrico terapéutico fue menor al aplicar un umbral cuantitativo.
- La eficacia según el subtipo mutacional continúa siendo incierta; la evidencia disponible es insuficiente para establecer equivalencia entre tumores con mutaciones BRAF V600E y RAS.
- La rediferenciación continúa siendo una estrategia de prueba de concepto guiada por biomarcadores que requiere confirmación en ensayos controlados con un tamaño de muestra adecuado.

Conclusiones: la rediferenciación con inhibidores de MAPK puede restaurar la captación de RAI en pacientes seleccionados, pero la captación es un desenlace sustituto y no demuestra beneficio en la supervivencia. La evidencia es insuficiente para definir diferencias según el subtipo mutacional. Se requieren ensayos controlados, estratificados por biomarcadores y con métodos de imagen estandarizados y desenlaces clínicamente relevantes.

Palabras clave: neoplasias tiroideas, diferenciación celular, BRAF, señalización MAPK, radioyodo, revisión sistemática, metaanálisis.

Introduction

Differentiated thyroid cancer (DTC), encompassing papillary and follicular histological types, represents the most common endocrine malignancy worldwide, with an estimated global incidence exceeding 586,000 new cases annually (1). The majority of patients with DTC have an excellent prognosis following surgery and RAI ablation, with five-year survival rates exceeding 98% for localized disease (2). The most important insight gained from molecular studies of differentiated thyroid carcinoma is the concept of 'RAS-like' and 'BRAF p.V600E-like' cancers. RAS-like tumors exhibit characteristic architectural features traditionally associated with follicular thyroid carcinoma. They have colloid-containing follicles and tend to grow as expansile tumors with well-defined borders. They lack the infiltrative growth pattern of most BRAF p.V600E-like papillary thyroid carcinoma. BRAF p.V600E-like thyroid carcinoma refers to papillary thyroid cancers that share molecular and histological features with tumors carrying the BRAF V600E mutation, even if the mutation itself is not directly detected. These cancers typically show aggressive behavior, higher recurrence risk, and distinct signaling pathway activation compared to non-BRAF-driven thyroid tumors (3). However, approximately 5–10% of patients develop distant metastases, and among these, an estimated two-thirds will eventually demonstrate RAI refractoriness, defined by the American Thyroid Association (ATA) as the absence of RAI uptake in metastatic lesions on a diagnostic scan, disease progression within 12 months of RAI treatment despite demonstrable avidity, or cumulative RAI administration exceeding 600 mCi without response (2, 4). Patients meeting these

criteria face a substantially worse prognosis, with a median overall survival of three to five years from the time distant metastases are identified (4–6).

The molecular basis of RAI refractoriness is rooted in the loss of thyroid differentiation, mediated primarily through constitutive activation of the MAPK signaling cascade. BRAF V600E mutations, present in approximately 40–70% of papillary thyroid cancers, and RAS mutations (NRAS, HRAS, KRAS), found in 10–20% of DTC, are the most prevalent genetic drivers of MAPK activation in this disease (7–8). These oncoproteins drive constitutive phosphorylation of MEK1/2 and ERK1/2, resulting in transcriptional repression of thyroid-specific genes, including those encoding NIS (SLC5A5), thyroglobulin, thyroid-stimulating hormone receptor, and thyroid peroxidase (figure 1) (9–10). Reduced NIS membrane expression directly impairs active iodide transport, rendering RAI ineffective (10–11).

The preclinical rationale for pharmacological redifferentiation emerged from observations that MAPK pathway suppression with MEK and BRAF inhibitors restored NIS expression and RAI uptake in murine thyroid cancer models (8). This led to the landmark phase II pilot study by Ho *et al.* in 2013, which demonstrated that the MEK1/2 inhibitor selumetinib increased RAI uptake in 12 of 20 patients with RAI-refractory DTC, resulting in clinically meaningful responses in those who subsequently received RAI (12). These proof-of-concept findings stimulated a series of subsequent studies using other MAPK pathway inhibitors, including the BRAF V600E-selective inhibitor dabrafenib (alone and in combination with the MEK inhibitor trametinib) and vemurafenib (13–17).

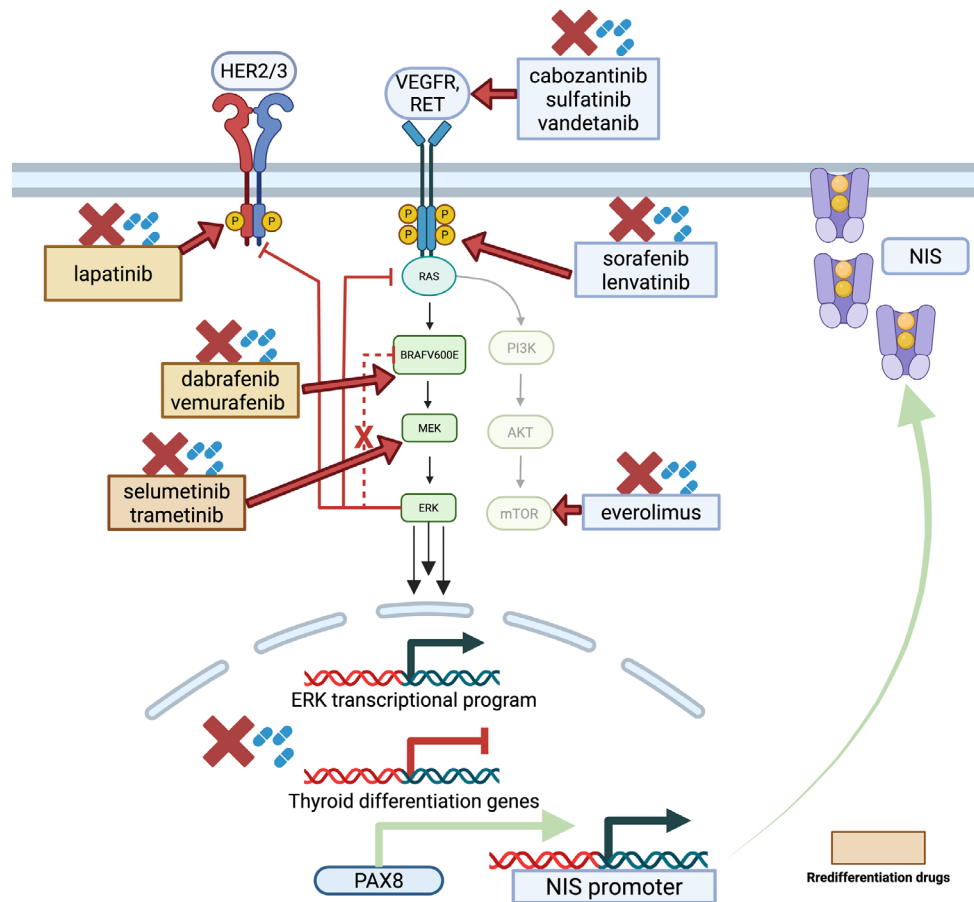


Figure 1. Molecular pathways in thyroid carcinoma and their therapeutic targets

Source: Created by the authors.

Despite this growing body of evidence, no quantitative synthesis has pooled outcomes across these trials. Individual studies are limited by small sample sizes, heterogeneous patient populations and interventions, and variable definitions of RAI restoration. This systematic review and meta-analysis was conducted to quantitatively summarize evidence on the efficacy of redifferentiation therapy prior to RAI in RAI-refractory DTC. The following PICOS framework was used: Population, adults with RAI-refractory DTC harboring BRAF or RAS mutations; intervention, selective BRAF and/or MEK inhibitors prior to RAI; comparator, no comparator (single-arm) or alternative regimen (controlled studies); outcomes, RAI uptake restoration (primary), PFS, OS, safety (including anaplastic transformation); study design, phase I–III clinical trials and prospective cohort studies.

Methodology

Protocol and registration

The protocol for this review was designed in accordance with the recommendations of the Cochrane Handbook (18). This systematic review and meta-analysis were conducted in accordance with the PRISMA 2020 reporting guidelines (19). The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number 1371813). No amendments were made to the prespecified protocol after search initiation.

Eligibility criteria

Studies were included if they: (1) enrolled adult patients (age ≥ 18 years) with histologically

confirmed RAI-refractory DTC (papillary, follicular, Hürthle cell, or poorly differentiated subtypes) using criteria consistent with current ATA definitions; (2) administered at least one BRAF or MEK inhibitor as redifferentiation therapy prior to RAI; (3) reported at least one prespecified outcome; and (4) were available as full-text manuscripts. Studies were excluded if they investigated redifferentiation in the adjuvant (non-refractory) setting, used antiangiogenic multikinase inhibitors as the primary intervention without a redifferentiation component (e.g., sorafenib or lenvatinib as chronic systemic therapy), were single-case reports or editorials, or lacked quantitative outcome data.

Information sources and search strategy

PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, and Google Scholar (grey literature and preprints, n=100 results) were systematically searched from inception through March 31, 2025.

PubMed

(Radioactive iodine therapy OR Radioactivities OR Nuclear Decay OR Decay, Nuclear OR Radioactive Disintegration OR Disintegration, Radioactive OR Disintegrations, Radioactive OR Radioactive Disintegrations OR radioiodine redifferentiation therapy) AND (thyroid cancer OR radioiodine uptake OR radioiodine refractory OR thyroid cancers) Filters: Randomized Controlled Trial.

Embase

'iodine labelling'/exp OR 'iodine labelling' OR (('iodine'/exp OR iodine) AND labelling) OR 'iodine radioisotope'/exp OR 'iodine radioisotope' OR (('iodine'/exp OR iodine) AND ('radioisotope'/exp OR radioisotope)) OR 'iodine radioisotopes'/exp OR 'iodine radioisotopes' OR (('iodine'/exp OR iodine) AND ('radioisotopes'/exp OR radioisotopes)) OR 'iodine, radioactive'/exp OR 'iodine, radioactive' OR (('iodine',/exp OR iodine,) AND radioactive) OR 'radio active iodine'/exp OR 'radio active iodine' OR (('radio'/exp OR radio) AND ('active'/exp OR active) AND ('iodine'/exp OR iodine)) OR 'radio iodide orradio iodine' OR (('radio'/exp OR radio)

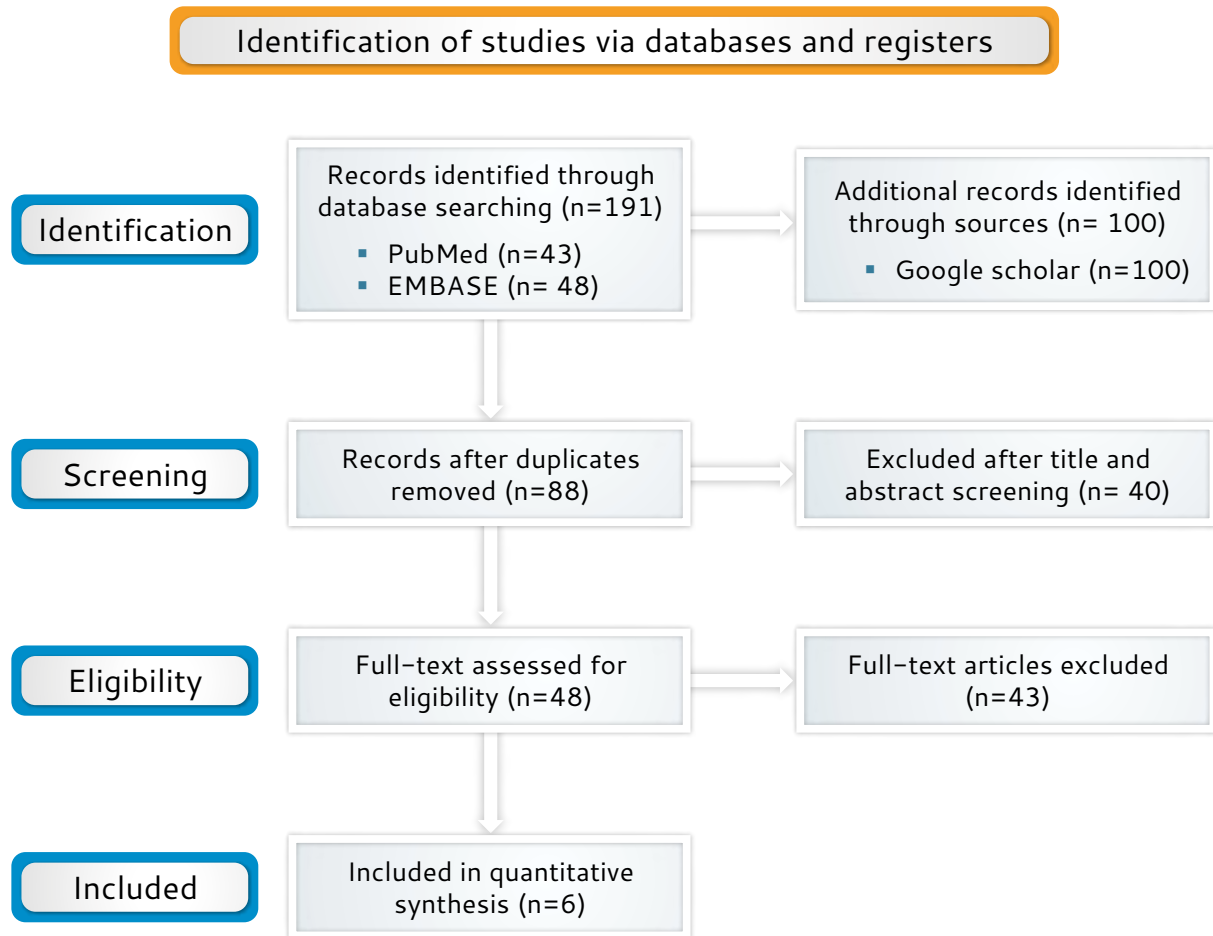
AND ('iodide'/exp OR iodide) AND orradio AND ('iodine'/exp OR iodine)) OR 'radioactive iodide'/exp OR 'radioactive iodide' OR (radioactive AND ('iodide'/exp OR iodide)) OR 'radioiodide'/exp OR radioiodide OR 'radioiodine'/exp OR radioiodine OR 'radioactive iodine'/exp OR 'radioactive iodine' OR (radioactive AND ('iodine'/exp OR iodine)) AND (((((((((((cancer AND in AND the AND thyroid AND gland OR cancer) AND of AND the AND thyroid OR cancer) AND of AND the AND thyroid AND gland OR cancer) AND of AND thyroid OR cancer) AND of AND thyroid AND gland OR cancer,) AND thyroid AND gland OR carcinogenesis) AND in AND the AND thyroid AND gland OR carcinogenesis) AND of AND the AND thyroid OR carcinogenesis) AND of AND thyroid OR carcinomatous) AND thyroid OR malignancies) AND of AND the AND thyroid AND gland OR malignancies) AND of AND thyroid AND gland OR malignancy) AND of AND the AND thyroid AND gland OR malignancy) AND of AND thyroid AND gland OR malignant) AND neoplasm AND of AND the AND thyroid AND gland OR malignant) AND neoplasms AND of AND the AND thyroid AND gland.

Cochrane library

(Radioactive iodine therapy OR Radioactivities OR Nuclear Decay OR Decay, Nuclear OR Radioactive Disintegration OR Disintegration, Radioactive OR Disintegrations, Radioactive OR Radioactive Disintegrations OR radioiodine redifferentiation therapy) AND (thyroid cancer OR radioiodine uptake OR radioiodine refractory OR thyroid cancers).

Study selection and data extraction

Two independent reviewers screened titles and abstracts and retrieved full texts of potentially eligible records. Disagreements were resolved by discussion and consensus. Study selection was documented using a PRISMA 2020 flow diagram (figure 2). Data extraction was performed using a prespecified form capturing the author, year, design, sample size, molecular profile, intervention, RAI dose, outcomes, follow-up, and adverse event data (19).

**Figure 2.** PRISMA flowchart**Source:** Created by the authors.

Quality assessment

Two reviewers independently assessed risk of bias using ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions). The seven domains were biased due to confounding, participant selection, intervention classification, deviations from intended interventions, missing data, outcome measurement, and selection of the reported result. Disagreements were resolved by consensus. Overall judgments were Low, Moderate, Serious, or Critical. RoB 2 was not used because none of the eligible studies was randomized. Certainty of evidence for each outcome was evaluated with GRADE, starting at low certainty for non-randomized evidence and downgrading when warranted for risk of bias, inconsistency,

indirectness, imprecision, or publication bias. The search results were managed in Mendeley v1.19.8 and duplicates were removed. Data were entered into RevMan 5.4 by one reviewer and independently checked by another. No conversion of medians to means was required for the outcomes synthesized in this review (20–21).

The search results were organized using Mendeley v1.19.8 (Mendeley Ltd., Kidlington, United Kingdom), and duplicate records were removed. Three reviewers independently screened all titles and abstracts, assessed the full texts, and extracted data from the relevant studies.

Disagreements were resolved through discussion. The extracted data included study characteristics, methodology, setting, and

participant descriptions. The data were entered into RevMan version 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) by two authors and checked for accuracy. For included studies that reported medians, minimum and maximum values, or first and third quartiles, sample means and standard deviations were calculated according to the method proposed by Wan *et al.* (22).

Statistical analysis

All meta-analyses were performed in R (version 4.4.0) using the meta package (version 8.3.0) and the metafor package (version 4.8.0) (23–24). For the primary outcome, a random-effects model with REML estimation was used; proportions were logit-transformed prior to pooling and back-transformed for presentation. Statistical heterogeneity was quantified using Cochran's Q statistic and the I^2 index (cutoffs: 25% low, 50% moderate, 75% substantial) (25). For PFS, pooled HRs were estimated using random-effects REML. Leave-one-out sensitivity analyses assessed the robustness of pooled estimates. Subgroup analyses by mutation type used a between-group Q-test. Confidence intervals for τ^2 were calculated using the Q-profile method. Publication bias was evaluated by funnel plot; formal Egger's test was not applicable given $k < 10$ (26). For the safety sub-analysis, AE data extracted from included studies were synthesized narratively; proportions of patients with grade ≥ 3 AEs per study are reported as crude proportions from the original publications. Formal pooling of AE rates was not performed due to heterogeneous reporting methods across studies.

Outcomes

The primary outcome was restoration of RAI uptake after short-course MAPK-pathway inhibition. Detectable uptake was defined as new or increased uptake on post-treatment iodine imaging. Because imaging methods were not equivalent, the acquisition method and positivity threshold were extracted for each study. Ho *et al.* (12) used ^{124}I PET/CT lesion dosimetry and applied a therapeutic threshold predicting delivery of at least 2,000 cGy (20 Gy) to one or more lesions; the remaining studies used visual assessment with ^{123}I or ^{131}I scintigraphy/

SPECT-CT. Sensitivity analyses excluded Ho *et al.* and substituted its therapeutic-threshold result (8/20) for its any-increased-uptake result (12/20).

Secondary outcomes were objective tumor response according to the criteria reported by each study, progression-free survival (PFS), overall survival (OS), and safety. PFS was defined as the time from treatment initiation to radiographic progression or death, according to each protocol (27). OS was defined as the time from treatment initiation to death from any cause, censored at the last documented follow-up. Safety outcomes included adverse events, dose modification, discontinuation, treatment-related death, and reported anaplastic transformation. Survival effects were pooled only when a published hazard ratio and variance were available.

Results

Study selection

The database and registry searches identified 191 records: PubMed (n=43), Embase (n=48), and Google Scholar (n=100). After removal of 103 duplicates, 88 unique records underwent title and abstract screening; 40 were excluded, and 48 full-text reports were assessed. Forty-three full-text reports were excluded, leaving five studies for qualitative synthesis. Four studies (n=48) contributed binary data to the primary meta-analysis. Busaidy *et al.* was excluded because dabrafenib with or without trametinib was administered as continuous systemic therapy until progression, and the protocol did not include a redifferentiation phase followed by therapeutic RAI (13).

Study characteristics

The five eligible studies enrolled 72 patients (table 1). All were prospective, non-randomized, single-arm phase I/II studies published from 2013 through 2023. The interventions included selumetinib, dabrafenib, dabrafenib plus trametinib, trametinib, and vemurafenib plus CDX-3379, followed by protocol-directed radioiodine assessment and, when criteria were met, therapeutic RAI. Molecular eligibility and imaging thresholds differed across studies.

Table 1. Characteristics of the included studies

Study	Design	Population	Intervention followed by RAI	Imaging method and positivity criterion	RAI uptake result	N	Country
Ho 2013 (12)	Prospective single-arm pilot	RAI-refractory thyroid cancer; mixed genotypes	Selumetinib, then ^{124}I dosimetry and ^{131}I when threshold met	^{124}I PET/CT; any increased uptake and therapeutic threshold predicting ≥ 20 Gy to a lesion	12/20 any increase; 8/20 therapeutic threshold	20	USA
Rothenberg 2015 (14)	Phase II single-arm	BRAF V600E-mutated metastatic papillary thyroid cancer	Dabrafenib followed by ^{131}I	Diagnostic iodine scan; new uptake by visual assessment	6/10	10	USA
Leboulleux 2023 (15)	Phase II single-arm	Metastatic RAI-refractory BRAF V600E-mutated DTC	Dabrafenib plus trametinib followed by ^{131}I	Protocol iodine imaging; response reported primarily after ^{131}I rather than as a binary uptake denominator	NR for pooled binary uptake	24	France
Leboulleux 2023 RAS cohort (16)	Phase II single-arm	Metastatic RAI-refractory RAS-mutated DTC	Trametinib followed by ^{131}I	Protocol iodine imaging; visually increased uptake sufficient for treatment	8/11	11	France
Tchekmedyan 2022 (17)	Pilot single-arm	BRAF-mutated RAI-refractory DTC	Vemurafenib plus CDX-3379 followed by ^{131}I when warranted	^{124}I PET/CT; increased incorporation warranting therapeutic ^{131}I	4/7 enrolled (4/6 evaluable)	7	USA

NR: Not reported as an extractable binary proportion; RAI: Radioactive iodine.

Note. Busaidy *et al.* (2022) (13) was excluded from the eligible set because it evaluated continuous systemic therapy without a protocolized RAI phase.

Source: Created by the authors.

Risk of bias

ROBINS-I judgments are presented in table 2. Overall risk of bias was judged moderate for Ho *et al.* and both Leboulleux *et al.* studies and serious for Rothenberg *et al.* and Tchekmedyian *et al.* (12, 14–17). Confounding and participant selection were the principal concerns because all studies

lacked random allocation and concurrent controls. Outcome-measurement concerns also arose from non-uniform definitions of restored uptake. These judgments should be interpreted as review-level assessments based on published reports rather than author-provided ROBINS-I adjudications.

Table 2. ROBINS-I risk-of-bias assessment

Study	D1 Confounding	D2 Selection	D3 Classification	D4 Deviations	D5 Missing data	D6 Outcome measurement	D7 Selective reporting	Overall
Ho 2013 (12)	Moderate	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
Rothenberg 2015 (14)	Serious	Serious	Low	Moderate	Moderate	Moderate	Moderate	Serious
Leboulleux 2023 BRAF (15)	Moderate	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
Tchekmedyian 2022 (17)	Serious	Serious	Low	Moderate	Moderate	Moderate	Moderate	Serious
Leboulleux 2023 RAS (16)	Moderate	Moderate	Low	Low	Low	Moderate	Moderate	Moderate

Note. D1–D7 follow ROBINS-I. Judgments were made at the review level from published reports.

Source: Created by the authors.

RAI Uptake restoration: Primary outcome

Four studies provided binary RAI uptake restoration data: Ho 2013 (qualitative: 12/20 = 60.0%; 95% CI 36.1–80.9%; dosimetric threshold: 8/20 = 40.0%), Rothenberg 2015 (6/10 = 60.0%; 95% CI 26.2–87.8%), Tchekmedyian 2022 (4/7

= 57.1%; 95% CI 18.4–90.1%), and Leboulleux 2023 RAS cohort (8/11 = 72.7%; 95% CI 39.0–94.0%). The pooled proportion was 62.3% (95% CI 47.8–74.8%; figure 3). Heterogeneity was minimal ($I^2 = 0\%$, $Q = 0.65$, $df = 3$, $p = 0.89$, $\tau^2 = 0$). Leave-one-out sensitivity analysis demonstrated stability across all omissions (range: 59.5–63.6%; supplementary figure 1).

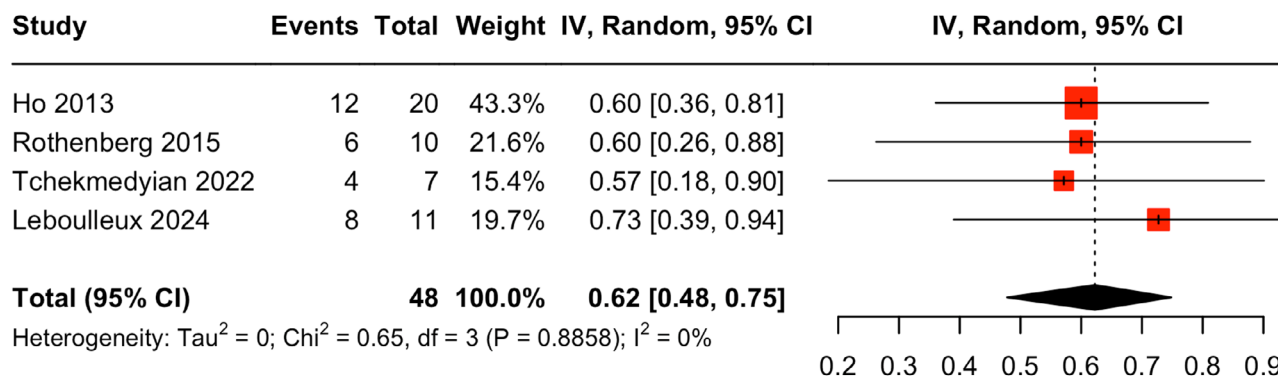


Figure 3. Forest plot: pooled RAI uptake restoration after redifferentiation therapy (random-effects model)

Note. Each square represents the point estimate for an individual study; horizontal lines indicate 95% confidence intervals; square size is proportional to the study weight under the random-effects model. The diamond represents the pooled estimate. Analysis performed using the meta package (version 8.3.0) in R; logit transformation; REML estimator.

Source: Created by the authors.

Progression-free survival

Progression-free survival data were available from four studies in narrative form. Leboulleux 2023 reported Kaplan-Meier (KM)-based PFS rates of 82% at 12 months and 67.5% at 24 months (median not reached). Leboulleux 2024 reported a median PFS of 9.3 months. Rothenberg 2015 reported a median PFS of 11.4 months. Ho 2013 reported a median PFS of 13.0 months in the I-131-treated subgroup. No study published a hazard ratio for PFS; quantitative meta-analysis of this outcome is therefore not possible (15–16).

Overall survival

No study reported a mature OS endpoint. Leboulleux 2023 reported a 24-month OS rate of approximately 72% at a median follow-up of 14 months. Quantitative meta-analysis of OS was not performed (15).

Subgroup analysis by mutation type

Exploratory study-level subgroup estimates were 60.0% for the mixed BRAF/RAS cohort in Ho *et al.* (12), 58.6% across two BRAF V600E studies, and 72.7% in the single RAS-mutated study. The between-group test was not statistically significant

($Q=0.63$; $df=2$; $p=0.73$), but two subgroups contained only one study, and the analysis had very low power. It cannot establish equivalence or absence of effect modification. Within Ho *et al.*, any increased uptake was observed in 5/5 patients with NRAS-mutated tumors and 4/9 with BRAF V600E tumors; all five NRAS-mutated tumors but only one BRAF V600E tumor met the therapeutic dosimetry threshold. These observations are hypothesis-generating only (figure 4).

Sensitivity analysis excluding Ho *et al.* yielded a pooled uptake-restoration estimate of 63.5% ($k=3$, $n=28$; 95% CI 45.7–81.4%). Substituting the therapeutic dosimetry result from Ho *et al.* (8/20) yielded 57.8% ($k=4$, $n=48$; 95% CI 44.0–71.5%). Thus, the main estimate reflects restoration of detectable uptake and should not be interpreted as the proportion necessarily eligible for therapeutically effective RAI.

Safety sub-analysis

Safety findings were synthesized narratively because the studies differed in CTCAE version, attribution rules, denominators, and exposure duration. Ho *et al.* reported that toxic effects attributed to selumetinib were grade 1 or 2; three patients discontinued early because of reversible

ocular events, and no dose reductions were required. The other studies reported regimen-specific adverse events, but the available data were not sufficiently comparable to justify a pooled proportion of grade ≥ 3 AEs. No treatment-related deaths were reported among the five eligible studies. Absence of a reported event must not be interpreted as proof that the event was systematically assessed; therefore, no pooled estimate for anaplastic transformation was calculated (table 3).

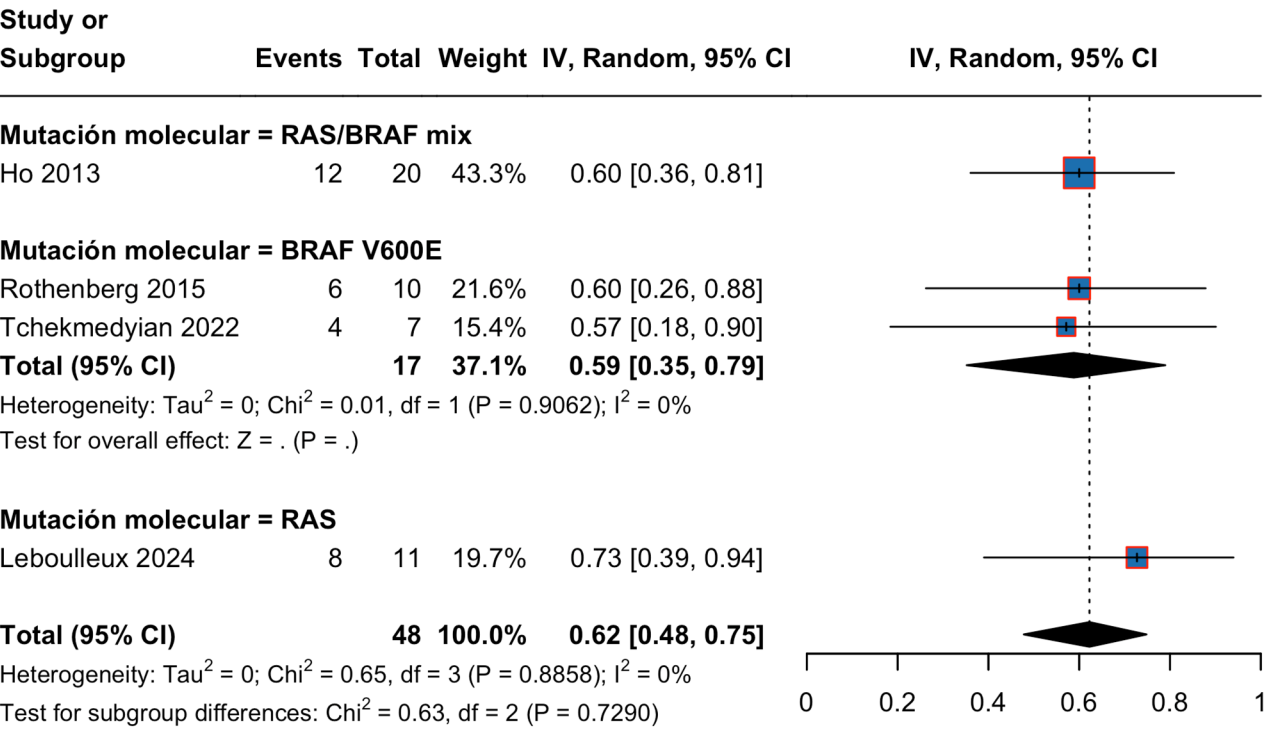


Figure 4. Subgroup analysis of RAI uptake restoration by mutation type (BRAF V600E, RAS, RAS/BRAF mixed)

Note. Between-group Q statistic = 0.63 ($df = 2$, $p = 0.73$). Single-study subgroups (RAS/BRAF mixed, RAS) are presented without τ^2 estimates.

Source: Created by the authors.

Publication bias

The funnel plot for the primary outcome (supplementary figure 2) did not show overt asymmetry on visual inspection. Formal Egger’s regression test was not applicable given $k = 4$ (fewer than 10 studies).

GRADE Evidence summary

GRADE judgments are summarized in supplementary table 1. Certainty was rated very

low for restoration of RAI uptake, PFS, OS, and safety. All bodies of evidence began at low certainty because the eligible studies were non-randomized and were further downgraded for risk of bias and serious or very serious imprecision. Statistical inconsistency was not detected for the primary pooled proportion ($I^2=0\%$); however, clinical and measurement heterogeneity remained important and was considered under indirectness. PFS was not assigned a pooled effect estimate.

Table 3. Safety summary of included studies

Study	N	Published safety information relevant to redifferentiation	Treatment-related deaths	Interpretation
Ho 2013 (12)	20	Toxic effects attributed to selumetinib were grade 1–2; three early discontinuations followed reversible ocular events; no dose reduction was required	0	No grade ≥ 3 toxicity attributed to selumetinib was reported
Rothenberg 2015 (14)	10	Regimen-specific adverse events reported; cross-study grade ≥ 3 denominator not harmonized	0	Narrative synthesis only
Leboulleux 2023 BRAF (15)	24	Adverse events reported under the study protocol; attribution and exposure differ from other studies	0	Narrative synthesis only
Tchekmedyan 2022 (17)	7	No grade 3–4 toxicity related to CDX-3379; vemurafenib-related toxicity reported separately	0	Attribution-specific reporting prevents pooling
Leboulleux 2023 RAS (16)	11	Adverse events reported under the study protocol; small denominator	0	Narrative synthesis only

Note. No pooled adverse-event rate was calculated because definitions, attribution rules, CTCAE versions, denominators, and exposure durations were heterogeneous. NR = not reported.

Source: Created by the authors.

Discussion

Interpretation of the primary outcome

This meta-analysis provides the first pooled quantitative estimate of RAI uptake restoration following MAPK pathway inhibitor-based redifferentiation therapy in RAI-refractory DTC. The pooled rate of 62.3% (95% CI 47.8–74.8%) is clinically meaningful. Without redifferentiation, the natural history of RAI-refractory DTC is characterized by absent or non-progressive RAI uptake; empirical re-treatment with RAI in patients without additional manipulation rarely achieves avidity restoration (4). The absence of significant heterogeneity ($I^2=0\%$) across four contributing

studies lends confidence to the pooled estimate, suggesting comparable efficacy across the spectrum of MAPK-targeting agents included here. It is important to note that RAI uptake restoration is a surrogate rather than a direct measure of OS benefit; not all patients achieving avidity proceed to therapeutically effective RAI dosing, and not all responders achieve durable clinical benefit.

Molecular mechanism

Constitutive MAPK activation through BRAF V600E drives ERK-mediated transcriptional repression of key thyroid differentiation genes including NIS (SLC5A5), thyroglobulin, and thyroid peroxidase (9, 10). Pharmacological blockade of BRAF or MEK attenuates ERK phosphorylation,

allowing partial restoration of PAX8 and TTF-1–driven transcription, with subsequent NIS re-expression at the basolateral membrane and resumption of active iodide transport (10). Dual BRAF/MEK inhibition was designed to prevent paradoxical MAPK reactivation through compensatory RAF dimerization, a phenomenon associated with BRAF monotherapy; however, the Busaidy 2022 RCT found no statistically significant superiority of the combination over dabrafenib monotherapy, suggesting that a ceiling effect or alternative resistance mechanisms may limit incremental benefit (figure 1) (13).

Subgroup analysis: BRAF V600E vs. RAS

The mutation subgroup analysis was exploratory and severely underpowered. A non-significant between-group test does not demonstrate equivalence. The within-study pattern in Ho *et al.* (12) favored NRAS-mutated tumors over BRAF V600E tumors, particularly for the therapeutic dosimetry threshold, but the sample was too small for definitive inference. Treatment selection should therefore be molecularly informed while acknowledging that comparative mutation-specific efficacy remains unproven (13–16).

Progression-free survival

No hazard ratio for PFS was available from an eligible study, precluding quantitative synthesis. Reported Kaplan–Meier estimates and medians cannot be combined as though they were comparative hazard ratios. Descriptive comparisons with historical multikinase-inhibitor trials are vulnerable to confounding by eligibility, disease burden, prior treatment, and endpoint definitions and should not be interpreted as comparative effectiveness evidence (5).

Overall survival

Overall survival reporting was sparse and immature. No study provided an effect estimate suitable for quantitative synthesis. OS was therefore summarized narratively, without drawing an inference regarding benefit attributable to redifferentiation (4).

Risk of bias and evidence quality

All eligible studies were non-randomized and lacked a concurrent untreated or standard-care control. ROBINS-I identified moderate-to-serious concerns, principally related to confounding and selection. These limitations prevent causal attribution of survival outcomes and reduce confidence even in the pooled uptake proportion. GRADE certainty was very low for all outcomes; consequently, the findings support biological plausibility and feasibility, but not strong evidence for a strong clinical recommendation (13).

Comparison with Sorafenib and Lenvatinib

Sorafenib and lenvatinib, the two approved multikinase inhibitors for RAI-refractory DTC, operate through anti-angiogenic and anti-proliferative mechanisms fundamentally distinct from redifferentiation and were therefore excluded from this analysis. The DECISION trial demonstrated a sorafenib-associated median PFS of 10.8 versus 5.8 months with placebo (HR 0.59) (5); the SELECT trial demonstrated a lenvatinib-associated median PFS of 18.3 versus 3.6 months with placebo (HR 0.21) (28). Redifferentiation strategies offer a conceptually distinct advantage: short-course MAPK inhibition to restore RAI avidity, followed by definitive RAI therapy, with the potential for a finite treatment course and more durable responses in patients who achieve sufficient iodide incorporation.

Safety profile and the risk of anaplastic transformation

Short-course MAPK inhibition produced the expected dermatologic, gastrointestinal, febrile, musculoskeletal, and metabolic toxicities. Cross-study pooling was avoided because adverse-event ascertainment, CTCAE versions, attribution, and denominators were not uniform. No treatment-related deaths were reported among the 72 participants, but the sample and follow-up were insufficient to exclude rare harms (5, 28). The zero treatment-related mortality in these short-course redifferentiation protocols provides an important safety benchmark for this population.

The most clinically significant safety concern specific to BRAF/MEK inhibitor-based redifferentiation is the potential for anaplastic transformation, reflecting dedifferentiation of PTC toward anaplastic thyroid carcinoma (ATC). None of the five included studies reported a case of anaplastic transformation. While reassuring, this absence of events cannot exclude a rare risk on the basis of the current evidence base (N=72, median follow-up 12–18 months; upper bound of the 95% CI by Rule of Three: 4.2%).

The biological mechanism of BRAF inhibitor-associated dedifferentiation is grounded in established translational data. Pre-existing subclonal PIK3CA mutations present at low cancer cell fractions in some BRAF V600E-mutant PTCs can achieve clonal dominance under selective BRAF inhibitor pressure through paradoxical PI3K-AKT/mTOR axis activation and CRAF-mediated ERK reactivation. Combined TERT promoter mutations and TP53 loss-of-function represent the “two-hit” molecular substrate for PTC-to-ATC progression, with acquisition of SWI/SNF complex (ARID2, PBRM1) and JAK/STAT (JAK1) alterations further enriching the dedifferentiation-susceptible phenotype. One key series demonstrated that 86% of thyroid tumors that dedifferentiated after BRAF inhibitor therapy harbored these resistance-associated mutations, versus 33% of non-dedifferentiated tumors. In transgenic mouse models combining BRAF V600E expression with p53 loss, progression to ATC occurred with an approximate six-month latency, indicating that sustained selective pressure and additional acquired events are required beyond acute BRAF pathway manipulation alone (29–30).

The critical contextual distinction for redifferentiation is exposure duration. Published cases of anaplastic transformation under BRAF inhibitor therapy involve chronic administration over months to years; redifferentiation protocols use these agents for only 4–6 weeks before RAI, a substantially abbreviated window that likely exerts far less evolutionary selective pressure (29). This mechanistic reasoning provides biological plausibility for the absence of observed transformation in the pooled cohort, though it does not constitute definitive reassurance. None of the

five included studies systematically screened for co-occurring TERT, TP53, or PIK3CA mutations before initiating therapy. Prospective molecular profiling for these high-risk co-mutations, which constitute the pre-existing substrate for anaplastic transformation, should be incorporated into future redifferentiation trial designs to enable risk-stratified analyses and evidence-based patient selection.

The BRAF inhibitor class effect of new primary cutaneous SCC (reported in one patient in Rothenberg [2015]) is consistent with an FDA-labeled class risk. Dermatological surveillance, including baseline and post-treatment skin assessment, should be incorporated into clinical management protocols. For context, the ROAR trial of continuous dabrafenib plus trametinib in BRAF V600E mutant ATC reported grade ≥ 3 AEs in 58% of patients, substantially higher than the 18–29% observed in the redifferentiation cohort, consistent with the shorter exposure window in the short-course approach (31). Finally, the dose modification rate of 36–50% deserves emphasis: in short-course redifferentiation, where the window for achieving adequate MAPK pathway suppression to restore NIS expression is narrow, subtherapeutic drug exposure from dose reductions may directly compromise efficacy. Proactive, algorithm-driven management of pyrexia syndrome and acneiform dermatitis is essential for programmatic delivery.

Clinical implications

The findings support redifferentiation therapy as a biologically rational and clinically feasible approach for patients with RAI-refractory DTC harboring BRAF V600E or RAS mutations. Patient selection should be guided by somatic mutation profiling: BRAF V600E-positive tumors appear to benefit from dual BRAF/MEK inhibition or BRAF monotherapy, while RAS-mutated tumors may respond preferentially to MEK inhibition. The optimal timing of redifferentiation within the treatment sequence, whether before or after first-line multikinase inhibitor therapy, remains undefined. Given the evidence quality limitations, current use of redifferentiation strategies should ideally occur within the framework of prospective clinical trials.

Limitations

This review has major limitations. First, only five studies (N=72) were eligible, and four contributed to the primary analysis, producing substantial imprecision and making formal assessment of small-study effects unreliable. Second, all studies were non-randomized and single-arm, so causal inference for tumor response, PFS, or OS is not possible. Third, imaging methodology and the definition of restored uptake differed: any visually detectable uptake is not equivalent to a quantitative dosimetric threshold predicting therapeutic delivery. The I^2 of 0% does not eliminate this clinical and measurement heterogeneity. Fourth, mutation subgroups were sparse, and no adequately powered interaction analysis was available; equivalence by genotype cannot be concluded. Fifth, no eligible study published an extractable PFS hazard ratio, and OS data were immature. Sixth, safety reporting was heterogeneous and could not be validly pooled. Seventh, the small number of studies precluded reliable evaluation of publication bias. Finally, individual participant data were unavailable.

Future directions

Priority areas for future research include: (1) adequately powered RCTs comparing redifferentiation therapy with standard-of-care TKI therapy or TKI therapy followed by RAI; (2) prospective biomarker-stratified trials exploring mutation-specific responses and predictors of RAI uptake restoration; (3) head-to-head comparisons of different MAPK inhibitor regimens (MEK monotherapy versus BRAF/MEK combination) in molecularly defined subgroups; and (4) studies with longer follow-up (≥ 36 months) to assess mature OS endpoints and the longer-term incidence of anaplastic transformation. The ongoing MERAIODE trial (NCT05276466) represents an important step toward addressing these gaps.

Conclusions

Short-course MAPK-pathway inhibition can restore detectable RAI uptake in selected patients with RAI-refractory DTC; the pooled estimate was approximately 62%, but the therapeutic dosimetric estimate was lower. This outcome is a surrogate,

and the current evidence does not establish a benefit in PFS or OS. Evidence is insufficient to determine whether effects differ between BRAF V600E- and RAS-mutated tumors, and certainty is very low for all outcomes. Redifferentiation should therefore be considered an investigational, biomarker-guided strategy best evaluated in prospective controlled trials with standardized dosimetry, clinically relevant endpoints, and adequate long-term safety follow-up.

Authors' contributions

Carlos Eduardo Jimenez-Canizales: conceptualization, formal analysis, research, methodology, writing (peer review and editing); Rafael Parra Medina: conceptualization, formal analysis, writing (original draft); Cesar Payan: conceptualization, formal analysis, writing (original draft); Carlos Hernan Calderon Franco: conceptualization, formal analysis, research, methodology, writing (peer review and editing); Elio Benevento: conceptualization, formal analysis, writing (original draft); Roberta Modica: conceptualization, formal analysis, writing (original draft); Alfredo Ernesto Romero Rojas: conceptualization, formal analysis, writing (original draft); Mireya Tapiero Garcia: conceptualization, formal analysis, writing (original draft); Juan Felipe Perez Echavarria: conceptualization, formal analysis, writing (original draft).

Ethical statement

This study did not involve animal experiments or the participation of patients or human subjects, nor did it constitute a clinical trial.

Conflicts of interest

The authors declare that they have no conflicts of interest regarding this study.

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Artificial intelligence (AI) disclosure statement

While preparing this paper, the authors used Perplexity Pro to assist with drafting the abstract, highlights, and to check grammar, and DeepL to translate the manuscript. After using these tools or services, the authors reviewed and revised the content as necessary and assume full responsibility for the content of the publication.

Data availability statement

This is a systematic review and meta-analysis. All data supporting the findings of this study are derived from previously published studies, which are cited in full in the reference list. The R analysis code used for statistical synthesis is available from the corresponding author upon reasonable request.

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To our patients, who inspire us to continue exploring new treatment options for their care.

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