A systematic review of absorbed doses and response in patients treated with radioiodine for differentiated thyroid cancer.

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Abstract

Background: Treatment of thyroid cancer patients with Na[^{131}I]I is routinely performed with empiric activity levels. Treatment success may be expected to correlate with the absorbed doses delivered to targets (thyroid remnants or metastatic lesions), but no systematic review or meta-analysis of absorbed-dose effect relationships has yet been performed.

Methods: A systematic review and meta-analysis of reports published before 22/08/2025 was performed using PubMed, Web of Science and OVID MEDLINE. Studies were included if they reported the proportion of patients achieving successful outcome as defined in individual publications and the absorbed doses delivered to targets. The study is registered with PROSPERO (CRD42024554956).

Results: 3723 studies were identified of which 18 were eligible for analysis. Number of patients in the included studies ranged from 4 to 509. For patients treated with Na[^{131}I]I for thyroid remnant ablation, the reported success rates ranged from 60 to 100% while lower success rates of 43 to 58% were found for patients with metastatic lesions. Success rates for patients with a thyroid remnant absorbed dose of 300 Gy or more ranged from 78% to 96% while patients with metastatic lesions receiving at least 80 Gy had success rates ranging from 46% to 98%.

Conclusions: While individual studies have demonstrated the importance of absorbed doses from Na[131I]I for differentiated thyroid cancer, no conclusive absorbed dose effect relationship has been established in this review. A lack of standardisation of dosimetry methodologies and follow-up criteria in the studies obscures the relationship. Large-scale observational prospective studies are required to determine the absorbed doses required for successful personalised treatments of thyroid cancer patients with Na[131I]I.

Introduction

The optimal treatment for patients with differentiated thyroid cancer (DTC) remains controversial.[1] Several biomarkers have been proposed to be predictive of clinical outcomes in DTC patients treated with Na[131I]I following thyroidectomy such as post-operative Thyroglobulin (Tg) levels[2-5], the amount of radioiodine administered (in MBq)[6] and the absorbed dose (in Gy) delivered to thyroid remnants or metastatic lesions.[7-14]

The most common approach to the treatment of thyroid cancer with radioiodine is to administer empiric activities. If dosimetry is employed, this is often based on a maximum-tolerated activity (MTA) approach[15,16] where the activity given is based on normal organ toxicity limits such as the absorbed dose to the bone marrow. Klubo-Gwiezdzinska et al[15] reported a higher rate of complete response for the MTA approach when compared to empirical treatment with a similar safety profile.

Treatment optimisation based on thyroid remnant or lesional dosimetry is rarely performed. Studies have provided initial indications that successful thyroid remnant ablation is dependent on the absorbed doses delivered although absorbed dose thresholds were not clear and inconsistent between studies.[7-10] Similarly, absorbed dose thresholds for successful treatments have been reported for the treatment of metastatic lesions.[11-14]

A systematic review of the literature covering studies of absorbed dose response relationships in differentiated thyroid cancer has to our knowledge not yet been performed. A similar systematic review and meta-analysis for patients treated with radioiodine for Grave's disease found a clear absorbed dose-response relationship which could facilitate personalised treatment planning of Grave's disease patients.[17]

The aim of this review was to investigate the evidence for a relationship between radiation dosimetry and treatment outcomes in patients treated with Na[^{131}I]I (radioiodine) for thyroid cancer. The review focussed on the absorbed doses delivered to the thyroid remnant, residual disease and/or metastatic lesions and relationship with clinical outcome of patients.

Methods

Search strategy and selection criteria

A comprehensive systematic review of published studies was performed to evaluate the clinical outcomes of Na[^{131}I]I (radioiodine) therapy for thyroid cancer patients with respect to measurements of the absorbed doses delivered to thyroid remnants, recurrence or metastatic disease. The systematic review was registered on PROSPERO (CRD42024554956).

PubMed, Web of Science and OVID MEDLINE were searched on 28/07/2023 following the principles and checklist provided by PRISMA (preferred reporting items for systematic reviews and meta-analyses).[18] Only English language publications and publications published before 28/07/2023 were included. Two further searches were performed before starting the data extraction on 07/10/2024 and during the peer review on 22/08/2025 to ensure no records have been missed since 28/07/2023. No restrictions on the type of study design were applied.

Databases were searched for the following terms: ("“radioiodine” OR “I131” OR “I-131” OR ‘‘131I’’) AND (‘‘thyroid’’) AND (“cancer”) AND (‘‘dosimetry’’ OR ‘‘absorbed dose’’) NOT (Benign). Study authors were not contacted, and trial registries were not searched.

Only studies that reported the absorbed doses to the thyroid remnant and/or metastatic lesions and outcome (rate of successful treatment as defined in individual studies) at follow-up were included. Studies were included if they reported results for adults diagnosed with thyroid cancer (using any recognised diagnostic criteria) who had undergone a near-total or staged thyroidectomy (hemithyroidectomy followed by completion thyroidectomy) and were treated with Na[^{131}I]I. Studies were excluded if they only reported results for adolescents (under 18 years of age) or if patients had undergone a partial thyroidectomy only.

Studies obtained from the initial search were reviewed by two blinded reviewers (JT, GF) based on title and abstract. After the initial screening, results were collated and discrepancies between the selected studies were resolved as a joint decision by both reviewers and by inclusion of a third reviewer (IM).

The remaining studies were then assessed based on the full text of the publication by all three reviewers (JT, IM and GF). Studies were excluded at this stage if they did not report the absorbed dose to the thyroid remnant or metastatic lesions or the outcome at end of follow-up.

Data analysis

For any included study, the following data were recorded in a Microsoft Excel spreadsheet independently by the three reviewers: Main author, Journal/Edition/Pages, Year of Publication, Title, Type of study, Number of patients in study group(s), Patient cohort (Remnant ablation and/or Metastatic patients, Disease type, Lesion size [ml or g], Lesion location, Pre-treatment Tg [ng/ml], TNM staging, Mean Age [in years], Percentage of patients being male or female, TSH preparation protocol, Follow up period [in months], Absorbed dose to thyroid remnant [in Gy] (if reported), Absorbed dose to metastatic lesions [in Gy] (if reported) or Absorbed dose thresholds [in Gy], Outcome data (Percentage of successful treatment at reported follow-up time), Inclusion of patients with previous Na[^{131}I]I treatments and Details of low iodine diets. Data were recorded for sub-cohorts if publications included results for both remnant and metastatic lesions or if different activities were given to individual sub-cohorts in the study.

In addition, details of the dosimetry methodologies were extracted from all publications, including whether the following items were reported: Traceability of radionuclide calibrators to national standard; Imaging or non-imaging study; Scatter correction type; Attenuation correction type; Dead time correction type; Partial Volume correction type; Number and timing of data points; Fitting procedure to extract time-integrated-activity; Volume determination technique and Absorbed dose algorithm.

Risk of bias was assessed by all three reviewers and disagreement between the three reviewers was resolved by consensus. The majority of studies were case series and the Critical Appraisal Checklist developed by the Joanna Briggs Institute[19] was used to assess the methodological quality of the included studies. For details see Supplementary Material.

Results

A total of 3723 studies were identified for the systematic review of which 697 were excluded due to presentation of duplicate data. A further 2985 studies were excluded for not satisfying the eligibility criteria based on title and abstract. Of the remaining 41 studies, a total of 18[5,7,8,10-14,20-29] full-text articles were deemed eligible for the systematic review following independent analysis (Figure 1). The excluded 23 studies are listed in Supplementary Table 1.

A summary of the study characteristics of the 18 included studies[5,7,8,10-14,20-29] is presented in Table 1. Ten studies[5,7,8,20-22,25,27-29] reported results from a remnant ablation patient cohort, three studies[10,13,14] reported results for a mixture of remnant ablation and metastatic patients and five studies[11,12,23,24,26] considered only patients with metastatic disease. The number of patients included in individual studies ranged from 4 to 509 and from 4 to 124 for remnant ablation and metastatic cohorts, respectively. Table 1 also includes an overview of the different definitions of successful outcome used in the studies.

Dosimetry methodologies for each study are detailed in Table 2. Methodologies for thyroid remnant dosimetry in earlier publications mostly used planar imaging, rectilinear scanners and probe measurements. Later publications have introduced imaging with SPECT or PET/CT. A similar trend is seen for lesional dosimetry with a move from planar or rectilinear imaging to mostly PET/CT in more recent studies. Imaging time points, corrections applied to ensure scans are quantifiable, volume determination techniques and fitting methodologies vary between studies and are often not reported.

The critical appraisal checklist developed by the Joanna Briggs Institute can be found in the Supplementary material. The checklist was extended by one additional question to assess the comparability of methodologies in the present studies. The results of the critical appraisal are summarised in Figure 2. All studies were either classed as having an intermediate or high risk of bias due to the lack of reporting of inclusion criteria in the studies and because treatment methodologies did not match other studies with respect to the dosimetry methodologies used and the assessment of treatment outcome.

Table 3 summarises the administered activities, reported absorbed doses to targets (e.g. thyroid remnants or metastatic lesions) and the percentage of patients with successful treatment, as defined in each study, at final follow-up.

Figure 3 shows the reported success rate as a function of the mean absorbed dose reported for the full patient cohort or sub-cohorts (if reported) in individual studies. Eight[5,7,13,20-22,25,27] studies that report results for remnant ablation cohorts have included both the mean absorbed dose to the thyroid remnant and the percentage of successful treatments. On the other hand, only two metastatic cohorts[12,23] can be included in Figure 3 as the other studies only report success rates above absorbed dose thresholds defined in individual studies. The proportion of patients with successful remnant ablation ranges from 60 to 100% with an apparent plateau around 80%. One study reports a success rate of 100%. Reported success rates for metastatic patient cohorts are lower, ranging from 43% to 45% in Figure 3.

Both for remnant ablation and metastatic patient cohorts, Figure 3 does not appear to show the expected sigmoidal dose-effect relationship between the absorbed dose delivered and the proportion of patients with successful outcome.

In 10[5,7,10-13,20,26,27,29] out of the 18 studies, success rates were reported above absorbed dose thresholds summarised in Table 4. These absorbed dose thresholds were based on criteria defined in the individual studies and can probably not easily be compared. The absorbed dose thresholds for remnant ablation treatments ranged from 49 Gy with a 100% success rate to 4000 Gy with a success rate of 92%. At the absorbed dose threshold of 300 Gy, which was initially proposed by Maxon et al[13], the success rate in different studies varies from 78% to 96%. For metastatic lesions, absorbed dose thresholds between 80 and 650 Gy were reported. At the absorbed dose threshold of 80 Gy, as proposed by Maxon et al[13], the success rate in different studies varies from 46% to 98%. Reported absorbed dose thresholds and the corresponding proportion of patients with successful treatment is presented in Figure 4.

Discussion

The aim of this review was to assess evidence for absorbed dose-response relationships for Na[^{131}I]I treatments of differentiated thyroid cancer. While the review fails to find relationships for either ablation treatments of the thyroid remnant or for therapy administrations for patients with recurrence or metastatic disease, the results of each individual study[5,7,8,10-14,20-29] show that absorbed dose is a predictor of treatment response. Individual studies included in this review show absorbed dose-response relationships, but the data cannot be collated. A confounding factor that may explain this is that the reviewed studies present results from a small number of studies and patients treated over nearly 4 decades. Dosimetry methodologies and tools have evolved as have surgical techniques and clinical management approaches.[1,30]

The risk of bias assessment showed that all studies have an intermediate or high risk of introduction of a bias when collating the results due to differences in dosimetry methodologies, and their respective errors and uncertainties, and outcome assessment. The definition of treatment success and the respective follow-up time in individual studies in the present systematic review vary between studies and even in studies with similar dosimetry methodologies, the outcome criteria vary. There is a lack of consistent or standardised methodology to classify treatment response for metastatic disease and ablation treatments (see Table 1). Imaging assessment of therapy response on an individual lesion level has been used as well as biomarkers, particularly thyroglobulin, which does not give information relating to individual lesions.

In contrast to a previous systematic review of Na[^{131}I]I for the treatment of Graves' disease[17], administered activities in the included studies were not prescribed to achieve a fixed target absorbed dose. In individual studies, a wide range of absorbed doses was delivered to targets (see standard deviations reported in Figure 3). This likely results in the lack of a demonstrable absorbed dose-response relationship in Figure 3.

Four studies[11-13,26] have shown that treatment success rates in patients with metastatic disease are significantly higher if lesions were treated with absorbed doses higher than 80-85 Gy. Nevertheless, this review indicates that reported success rates are not consistent between studies. For example, a value of 80 Gy was proposed by Maxon *et al* as an absorbed dose threshold[13] and has subsequently been utilised by others as a reference for comparison, although this has resulted in varied success rates from 46 to 98%. Jentzen et al[11,12] have demonstrated that success rates may depend on the type/location of lesion, as success rates vary between lesions in bone, lungs or lymph nodes. A further possible confounding factor is variations in radiosensitivity, whether due to genetic differences in the tumours themselves, the microenvironment or other factors such as localised hypoxia. Genomic profiling of the tumour may be used for stratification or sub-cohort analysis in future trials and could potentially predict radiosensitivity and allow for personalised treatment planning. Other factors such as lesion size or histological subtype should also be considered when assessing absorbed dose-response relationships. As shown in Table 1, there are a range of potential confounding biological factors such as lesion size, pre-treatment Tg levels and lesion location that might explain the wide range of response rates observed.

The absorbed dose thresholds reported for thyroid remnant ablations vary from 49 Gy to 4000 Gy and are, therefore, not currently clinical useful. While some of these differences might be due to variations in dosimetry methodologies, as discussed below, there is also a possibility that this may be due to changing practice of surgical management.[30] The studies included here were published from 1983 until 2025.

The reported success rates in the remnant ablation cohorts are in many cases lower than the success rates reported following empiric administration in recent large scale prospective studies such as ESTIMABL2 and HILO of 96%[31] and 98%[32] at 3 years follow-up. A potential reason for this is the change in surgical and clinical management of patients from 1983 to today. Two recent studies by Wierts et al[14] and Szumowski et al[28], published in 2016 and 2021, had reported success rates of 89% and 100%, respectively, in line with the success rates reported in ESTIMABL2 and HILO. As shown in Table 1, the thyroid remnant volumes are likely larger than expected after a modern total thyroidectomy, potentially explaining the lower success rates. In addition, a small number of patients with incomplete thyroidectomy are included in some of the studies which is a limitation of the present work.

As shown in Table 2, a wide range of dosimetry methodologies has been used. Imaging technology has evolved over time from rectilinear scanners to gamma cameras and ^{124}I-PET for metastatic patients. In addition, a range of imaging and non-imaging techniques has been applied for remnant ablation studies. A major contribution to the dosimetry uncertainty is the target volume uncertainty which is a particular issue in remnant ablations but also affects metastatic lesions. The thyroid remnant volume cannot accurately be assessed using PET, SPECT, ultrasound, CT or MRI. Therefore, the absorbed dose delivered to the voxel with maximum uptake was calculated in some studies.[5,7] Furthermore, a part of the thyroid remnant that is rarely removed in thyroid cancer surgery is accessory thyroid tissue such as the pyramidal lobe.[33]

Validation of the accuracy of dosimetry methodologies was not consistently performed for the studies and quantification of the respective errors and uncertainties is not retrospectively possible.

A further limitation is the small number of studies available for both remnant ablation and metastatic patients and the low number of patients included in many of the studies, ranging from 4 to 509 patients. Potential limitations of the present work are the exclusion of non-English studies and search strategy constraints due to the search terms used. In addition, the limited criteria for inclusion and exclusion of studies could have introduced heterogeneity.

A subset of low-risk patients has been shown not to benefit from Na[^{131}I]I ablation of thyroid remnant tissue in the ESTIMABL2[31] and IoN[34] studies. Further work is required to establish the potential benefits for dosimetry in cohorts that still undergo Na[^{131}I]I ablation, where a more tailored approach could potentially lead to patients receiving less Na[^{131}I]I and therefore reducing absorbed doses to normal organs.

Dosimetry driven treatment is likely to be of particular benefit for patients with metastatic disease where total eradication of target cells is observed less frequently compared to complete ablation of normal thyroid remnants. In addition to potentially achieving higher success rates due to treatment personalisation, dosimetry would allow for organs-at-risk to be considered and potentially reduce activities if needed to reduce treatment-related toxicities. Pre-therapy dosimetry using Na[^{123}I]I has been shown to predict absorbed doses delivered after Na[^{131}I]I therapy[35] in metastatic patients and could therefore be used for treatment planning. Pre-therapy dosimetry uncertainties for lesions and healthy tissues would likely be smaller when using Na[^{124}I]I PET pre-therapy dosimetry.

The current review highlights the need for a large-scale multi-centre clinical study to assess the radiation dosimetry with a view to treatment personalisation which will require standardisation of methodologies used. This review emphasises the urgent need for validated dosimetry methodologies and for internationally agreed response assessment criteria.

Conclusions

In this systematic review, no consistent relationship could be demonstrated between absorbed doses and outcomes in the treatment of thyroid cancer using Na[^{131}I]I, due to inconsistent methodologies and a paucity of studies. Nevertheless, individual studies show the potential of radiation dosimetry and the potential for personalised treatment as absorbed dose was found to be a predictor of treatment response in many studies. Comprehensive and standardised data collection will form the basis for future studies, which are required to determine the clinical efficacy and cost-effectiveness of dosimetry-based patient-specific treatment planning.

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Authors' Contributions

JT, IM, KN, KG, JW, GF conceived the design of the systematic review. JT, IM and GF did the abstract and full-text screening. JT, IM and GF did the data extraction. JT performed the data analysis. JT, IM and GF drafted the original article. All authors contributed to the edit and review of the final article.

Author Disclosure Statement

JT, IM, KG and GF have nothing to disclose with respect to the work carried out here. KN and JW have received speaker honoraria from Eisai.

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Figure legends

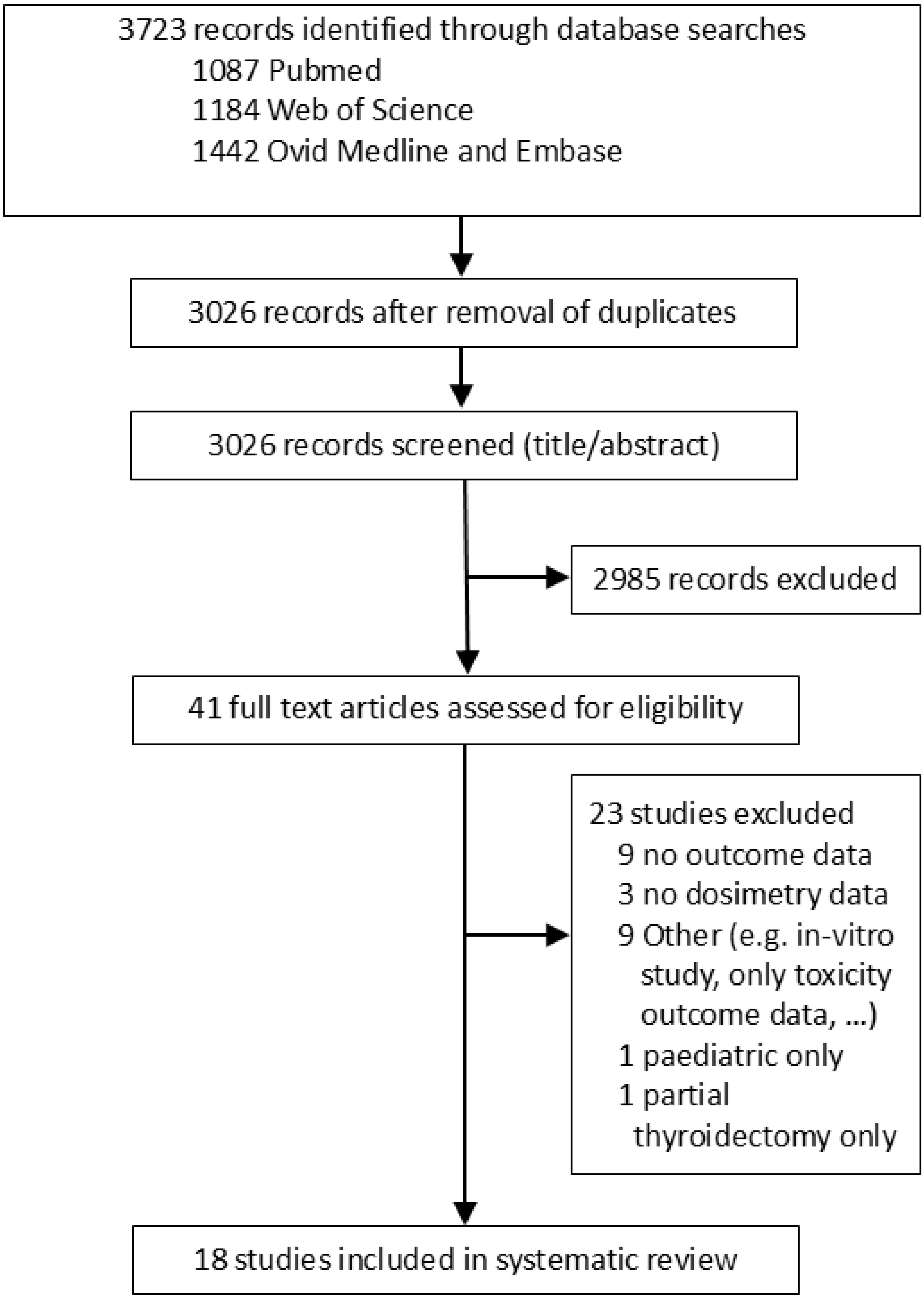

Figure 1: Flowchart for the systematic literature review.

	Question											Risk of bias
	1	2	3	4	5	6	7	8	9	10	11	
Adamczewski, 2007	N	Y	Y	NR	NR	Y	Y	Y	Y	Y	N	High
Bal, 1996	Y	Y	Y	NR	NR	Y	Y	Y	Y	Y	N	Intermediate
Bal, 2004	Y	Y	Y	NR	NR	Y	Y	Y	Y	Y	N	Intermediate
de Keizer, 2003	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Intermediate
Dorn, 2003	N	Y	Y	NR	NR	Y	Y	Y	Y	NR	N	High
Flux, 2010	Y	Y	Y	NR	NR	Y	Y	Y	Y	Y	N	Intermediate
Jentzen, 2014	Y	Y	Y	NR	NR	Y	Y	Y	Y	Y	N	Intermediate
Jentzen, 2015	Y	Y	Y	NR	NR	Y	Y	Y	Y	Y	N	Intermediate
Jentzen, 2016	Y	Y	Y	NR	NR	Y	Y	Y	Y	Y	N	Intermediate
Koral, 1986	N	Y	Y	NR	NR	Y	Y	Y	Y	NR	N	High
Maxon, 1983	Y	Y	Y	NR	NR	N	Y	Y	Y	NR	N	Intermediate
Minguez, 2013	N	Y	Y	NR	NR	Y	Y	Y	Y	Y	N	High
O'Connell, 1993	N	Y	Y	NR	NR	Y	Y	Y	Y	Y	N	High
Plyku, 2022	N	Y	Y	NR	NR	Y	Y	Y	Y	NR	N	High
Samuel, 1994	N	Y	Y	NR	NR	Y	Y	Y	Y	Y	N	High
Szumowski, 2021	N	Y	Y	NR	NR	Y	Y	Y	Y	Y	N	High
Taprogge, 2025	Y	Y	Y	NR	NR	Y	Y	Y	Y	Y	N	Intermediate
Wierts, 2016	N	Y	Y	NR	NR	Y	Y	Y	Y	Y	N	High

Figure 2: Risk of Bias Assessment following the Joanna Briggs Questionnaire (including additional question 11). Details of the questionnaire can be found in the supplementary material

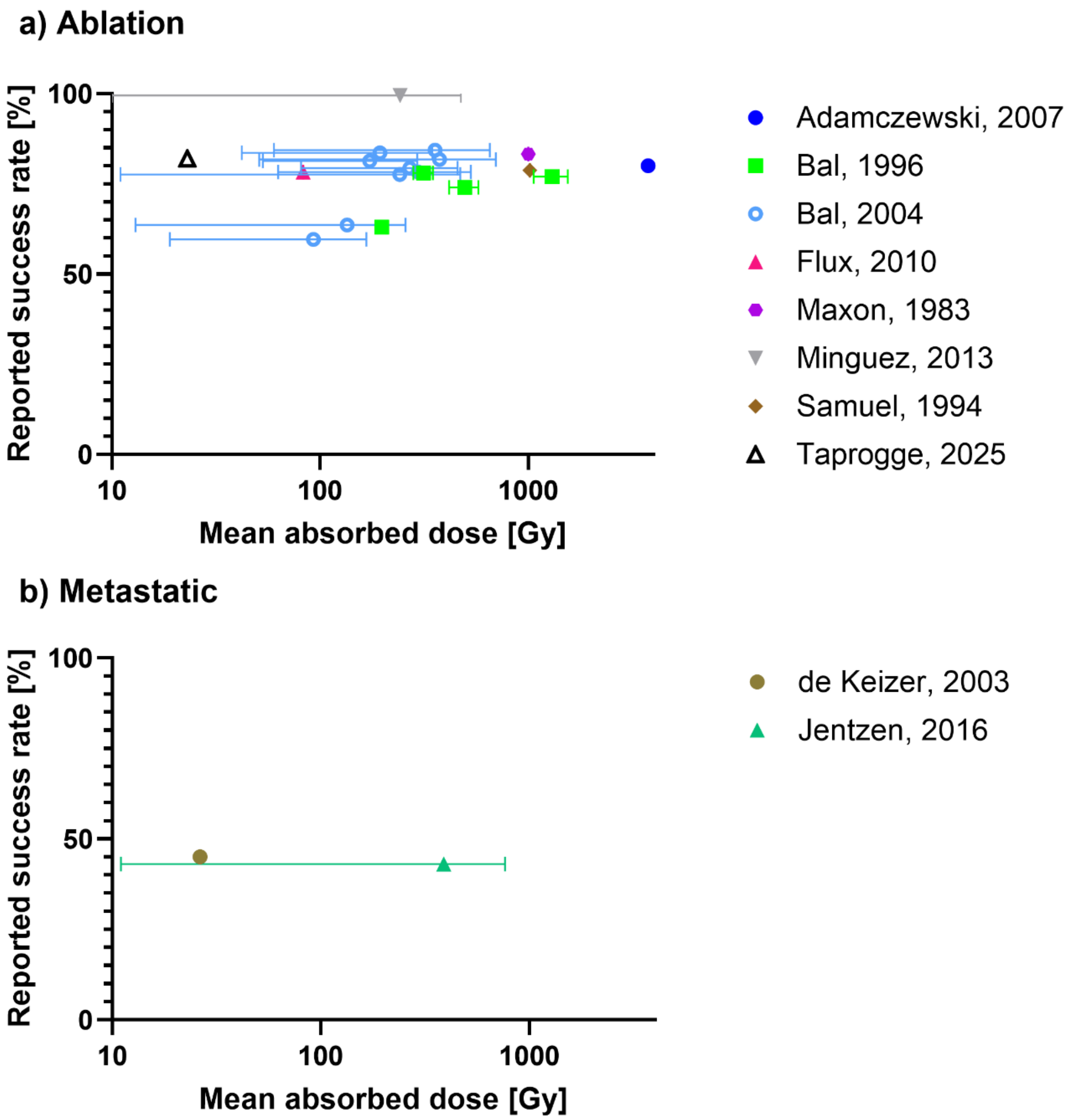

Figure 3: Reported success rate (according to success criteria defined in publication) against the mean (or median if mean not reported) absorbed dose reported for patient cohorts with a) remnant ablation and b) metastatic patients. The standard deviation of the absorbed doses delivered has been added if reported in the studies.

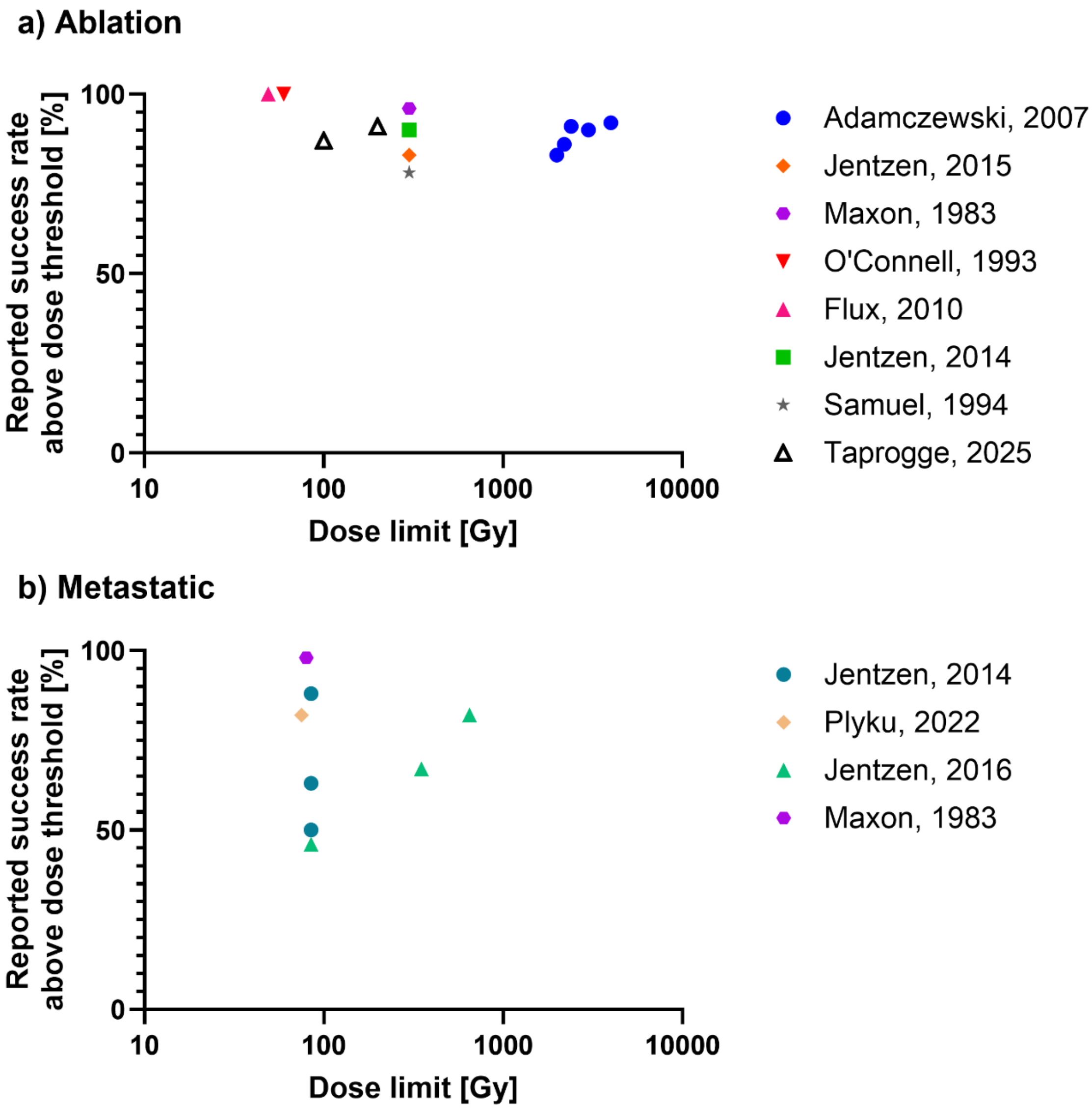

Figure 4: Reported absorbed dose thresholds in publications and corresponding success rate above absorbed dose threshold for patient cohorts with a) remnant ablation and b) metastatic patients.

Table 1: Details of the included studies [5,7,8,10-14,20-29].

Publication (Study country)	***Type of study***	***Patient cohort***	***Target location (Size [ml or g])***	***Number of patients***	***Disease type***	***TNM staging***	***Age (Mean ±SD)***	***Female [%]***	***Preparation***	***Pre-treatment Tg (Mean±SD) [ng/ml]***	***Patients with previous RAI included***	***Low iodine diet***	***Follow up time (Range) [month]***	***Definition of successful outcome***
Adamczewski, 2007 [20] (Poland)	Retrospective	Remnant ablation	TR (Successful: 2.0±1.9 g, Unsuccessful: 3.2±10.6 g)	100	54% PTC, 46% FTC	NR	44.9±13.9	89%	THW	NR	No, remnant ablation only	NR	0-6	Lack of foci of uptake on Na[^{131}I]I scintigraphy and whole-body scan
Bal, 1996 [21] (India)	Prospective[a]	Remnant ablation	TR (NR)	149	58% PTC, 42% FTC	NR	Mean 39 (Range 24-68)	70%	THW	NR	No, remnant ablation only	Yes, no details	6-12	Negative Na[^{131}I]I whole-body scan, neck uptake <0.2% and Tg < 10ng/ml after THW
Bal, 2004 [22] (India)	Prospective[a]	Remnant ablation	TR (NR)	509	81% PTC, 19% FTC	NR	37.5±12.7	73%	THW	NR	No, remnant ablation only	NR	Nominal 6	Negative Na[^{131}I]I whole-body scan, 48-h uptake ≤ 0.2% and Tg ≤ 10 ng/ml
de Keizer, 2003 [23] (Netherlands, Belgium)	Prospective	Metastatic	LN, LU, BO, LR (Range 1-50g)	16	69% PTC, 31% FTC	Yes, details see [23]	Range 41-87	50%	rhTSH	Range <1 - 30000	Yes, previous remnant ablation and therapeutic doses	5 days before, 2 days after RAI	Nominal 3	Change in post-treatment thyroglobulin levels

Dorn, 2003 [24] *(Germany)*	Retrospective	Metastatic	LN, LU, BO, LR (NR)	124	44% PTC, 50% FTC, 6% Hurthle	NR	Mean 59 (Range 4-86)	66%	THW	Range 4.3 - 73600	Yes, multiple treatments.	NR	Data over 15 years, varying follow-up time.	Change in post-treatment thyroglobulin levels
Flux, 2010 [7] *(UK)*	Retrospective	Remnant ablation	TR (NR)	23	74% PTC, 26% FTC	NR	Median 41 (Range 18-70)	65%	THW	NR	No, remnant ablation only	NR	6-8	Undetectable serum Tg following rhTSH in conjunction with a negative neck ultrasound
Jentzen, 2014 [11] *(Germany)*	Retrospective	Metastatic	LN, LU, TR (known volume >0.8 ml)	34	94% PTC, 6% FTC	Yes, details see [11]	36±16	65%	rhTSH or THW	NR	Initial RAI only	4 weeks	3-6	Percentage decrease of Na[^{124}I]I uptake. Response rate defined as ratio of completely responding lesions to total number of lesions.
Jentzen, 2015 [29] *(Germany)*	Retrospective	Remnant ablation	TR (known volume >0.15 ml)	49	86% PTC, 14% FTC	Yes, details see [29]	47±18	55%	NR	NR	No, remnant ablation only	4 weeks prior to ^{124}I PET	4 - 7	Percentage decrease of Na[^{124}I]I uptake. Response rate defined as ratio of completely responding remnants to total number of remnants.

Jentzen, 2016 [12] *(Germany)*	Retrospective	Metastatic	BO (Mean 4.9 ± SD 13.0 ml)	10	50% PTC, 50% FTC	NR	63±13	80%	rhTSH or THW	NR	No	4 weeks prior to ^{124}I PET	4-23	Percentage decrease of Na[^{124}I]I uptake. Response rate defined as ratio of completely responding lesions to total number of lesions.
Koral, 1986 [8] *(United States)*	Prospective	Remnant ablation	TR (Range 0.8 - <4.2 ml)	4	50% PTC, 25% FTC, 25% Mixed	NR	Range 28-47	75%	NR	NR	No, remnant ablation only	NR	8-36	Follow-up scan using pinhole collimator
Maxon, 1983 [13] *(United States)*	Retrospective	Metastatic and Remnant ablation	TR, NE, BO, LU (NR)	50 Remnant ablation 26 Metastatic	74% PTC, 26% FTC	NR	NR	NR	NR	NR	NR	NR	See details in [13]	Diagnostic 131I scan before and after therapy
Minguez, 2013 [25] *(Spain)*	NR	Remnant ablation	TR (Mean 4.1 ± SD 2.1 g	30	77% PTC, 23% FTC	NR	Mean 54 (Range 17-81)	80%	rhTSH	8.6 ± 18.7	No, remnant ablation only	NR	Nominal 12	Successful ablation defined as undetectable serum Tg following rhTSH in conjunction with a negative neck ultrasound.
O'Connell, 1993 [10] *(UK)*	NR	Metastatic and Remnant ablation	TR, NE (TR Range 1.6 – 9.7 g with 5 large remnants Range 9-25 g;	33	70% PTC, 30% FTC	NR	Mean 48 (Range 22-79)	76%	THW	NR	NR	NR	42- 69	Diagnostic 131I or post-therapy scan before and after therapy

			lesions Range 2-6 g)											
Plyku, 2022 [26] *(United States)*	Retrospective	Metastatic	LU, BO, BM (NR)	4	50% PTC, 50% FTC	NR	Range 30-63	NR	rhTSH or THW	NR	NR	NR	NR	Modified RECIST criteria using CT scans
Samuel, 1994 [27] *(India)*	Retrospective	Remnant ablation	TR (Mean 4.1 g Range 1.0 – 14.8 g)	87	60%PTC, 40%FTC	NR	35±9.4	66%	NR	NR	No, remnant ablation only	4 weeks but only salts and drugs	4-6	Diagnostic I-131 scan: Uptake <0.1%, no visual radioiodine uptake and <10ng/ml Tg
Szumowski, 2021 [28] *(Poland)*	Retrospective	Remnant ablation	TR (NR)	57	98% PTC, 2% FTC	Yes, details see [28]	53.9±8.6	80%	rhTSH	2.4±0.8	No, remnant ablation only	1-2 weeks	NR	131I thyroid bed uptake uptake <0.1%; stimulated Tg < 1 ng/ml, negative ultrasound
Taprogge, 2025 [5] *(Germany, UK, France)*	Prospective	Remnant ablation	TR (NR)	103	83% PTC, 15% FTC, 3% Mixed	Yes, details see [5]	47.6±15.5	75%	Mix	Median 1.9 (Range 0.1–148.7)	No, remnant ablation only	NR	9-12	Suppressed Tg < 0.2 ng/mL or TSH-stimulated Tg < 1 ng/mL
Wierts, 2016 [14] *(Germany)*	Retrospective	Metastatic and Remnant ablation	TR, LN, BO, LU (known volume >0.15 ml)	47	NR	NR	Mean 50 (Range 18 – 79)	77%	Mix	NR	Yes	NR	4-64	Functional imaging (124I PET/CT, 131I SPECT/CT, 18F-FDG), anatomic imaging (ultrasonography, MRI), histology, or increased thyroglobulin value

SD = Standard Deviation, RAI = radioiodine, PTC = papillary thyroid carcinoma, FTC =follicular thyroid carcinoma , NR = not reported, THW = thyroid hormone withdrawal, rhTSH = recombinant human thyroid-stimulating hormone, TR = thyroid remnant, BO = bone, LU = lung, LN = lymph node, NE = neck, BM = bone marrow

[a]Prospective randomised controlled trial

Table 2: Dosimetry methodologies used in the publications ordered by year of publication.

Publication	Traceable calibration of dose calibrator?	Imaging/ Non-imaging type	Scatter correction applied?	Attenuation correction applied?	Dead time correction applied?	Partial volume correction applied?	Number and timing of data points	Fitting procedure / fixed half-life? (extrapolation before/ after last time point)	Volume determination technique	Dose formula / Source of S-value
Maxon, 1983[13]	NR	Rectilinear /Gamma camera	NR	Yes, partially	NR	NR	24, 48, 72h	NR	Rectilinear, clinical exam, gamma camera	NR
Koral, 1986[8]	NR	Planar/WB	NR	NR	NR	NR	Up to 9 days	NR	Pinhole orthogonal view	Integration of dose rate
O'Connell, 1993[10]	NR	Rectilinear	NR	NR	NR	NR	~3 scans	NR	Rectilinear	Schlesinger et al. [36]
Samuel, 1994[27]	NR	Rectilinear	Yes	NR	NR	NR	Multiple measurements over 3 days	NR	Elliptical model from rectilinear	modified Marinelli
Bal, 1996[21]	NR	Probe	NR	NR	NR	No	48 h only	T_eff = 5 days	Assumed 7.5 grams	Thomas et al. [37]
Bal, 2004[22]	NR	Planar/WB	NR	NR	NR	NR	NR	T_eff = 5 days	Surgical Notes	Marinelli
de Keizer, 2003[23]	NR	Planar/WB	NR	Yes	NR	No	24, 48, 120, 216 and 336 h	mono-exponential	U/S, chest X-ray or CT using a spherical or ellipsoid model	Schlesinger et al. [36]
Dorn, 2003[24]	NR	Planar/WB	No	No	NR	NR	0h and daily up to 4–5 days	NR	U/S, CT or MRI	MIRD sphere model
Adamczewski, 2007[20]	NR	Probe	NR	NR	NR	NR	24h and additional for 3 to 7 days	NR	U/S ellipsoid	modified Marinelli
Flux, 2010[7]	NR	SPECT	Yes	Yes	Yes	No	24, 48 and 72h (+ 96h	Trapezoidal, uptake at t=0h	N/A	MIRD using voxel with

							in subset)	same as first imaging point, extrapolation using effective half-life		maximum uptake
Minguez, 2013[25]	NR	NR	NR	NR	NR	NR	3 x dose rate, 1 planar/SPECT	NR	NR	MIRDOSE
Jentzen, 2014[11]	NR	PET/CT	Yes	Yes	Yes	Yes	24h + one later than 96h	2 or 3 phases (3rd phase always physical)	PET	Jentzen et al.[38]
Jentzen, 2015[29]	NR	PET/CT	Yes	Yes	Yes	Yes	24h + one later than 96h	Modelled + extrapolation	PET	Jentzen et al.[38]
Jentzen, 2016[12]	NR	PET/CT	Yes	Yes	Yes	Yes	2, 24 and at least 96h	2 or 3 phases (3rd phase always physical)	PET	Jentzen et al.[38]
Wierts, 2016[14]	NR	PET/CT	Yes	Yes	Yes	Yes	24, 96 hours	"Adapted 2 point approach. Jentzen et al. J Nucl Med. 2008;49:1017–1023.	PET	OLINDA spheres
Szumowski, 2021[28]	NR	Planar/WB	NR	NR	NR	NR	6, 24, 48, 72 hrs	NR	US	NR
Plyku, 2022[26]	NR	PET/CT	NR	Yes	NR	Yes	5 scans	NR	CT	Olinda
Taprogge, 2025[5]	Yes	SPECT/CT	Yes	Yes	NR	No	One to six, between 6 and 168 h	Single exponential	N/A	MIRD using voxel with maximum uptake

NR = not reported, N/A = not applicable

Table 3: Summary of reported administered activities, absorbed doses delivered to targets and the percentage of successful treatments as defined in the respective publications. Data are shown for sub-cohorts if reported in the paper (e.g. different administered activities or remnant ablation/metastatic).

Publication	***Patient cohort (Remnant ablation, Metastatic)***	***Number of patients in (sub) cohort***	***Mean Administered activity (SD) [MBq]***	***Mean target absorbed dose (SD) [Gy]***	***Range of target absorbed doses [Gy]***	***Percentage of successful treatment [%]***
Adamczewski, 2007[20]	Remnant ablation	100	NR	3765(NR)	65 to 21660	80%
Bal, 1996[21] (sub cohort 1)	Remnant ablation	27	1110(56)	198(10)	NR	63%
Bal, 1996[21](sub cohort 2)	Remnant ablation	54	1872(200)	314(34)	NR	78%
Bal, 1996[21] (sub cohort 3)	Remnant ablation		3278(518)	496(79)	NR	74%
Bal, 1996[21](sub cohort 4)	Remnant ablation	30	5735(1062)	1302(242)	NR	77%
Bal, 2004[22] (sub cohort 1)	Remnant ablation	47	555(NR)	93(74)	NR	60%
Bal, 2004[22](sub cohort 2)	Remnant ablation	55	740(NR)	135(122)	NR	64%
Bal, 2004[22] (sub cohort 3)	Remnant ablation	70	925(NR)	173(120)	NR	81%
Bal, 2004[22] (sub cohort 4)	Remnant ablation	73	1110(NR)	194(152)	NR	84%
Bal, 2004[22](sub cohort 5)	Remnant ablation	63	1295(NR)	269(188)	NR	79%
Bal, 2004[22](sub cohort 6)	Remnant ablation	60	1480(NR)	296(233)	NR	78%
Bal, 2004[22](sub cohort 7)	Remnant ablation	64	1665(NR)	356(296)	NR	84%
Bal, 2004[22](sub cohort 8)	Remnant ablation	77	1850(NR)	374(323)	NR	82%
Bal, 2004[22](sub cohort 9)	Remnant ablation	509	NR	241(234)	NR	78%

Flux, 2010[7]	Remnant ablation	23	3000(NR)	83(NR)	7 to 570	78%
Jentzen, 2015[29]	Remnant ablation	12	NR	NR	488 to 4781	83%
Koral, 1986[8]	Remnant ablation	4	6244(463)	NR	>24 to >299	100%
Maxon, 1983[13]	Remnant ablation	30	4516(NR)	1000(NR)	52 to 7000	83%
Minguez, 2013[25]	Remnant ablation	30	3700(NR)	242(318)	13 to 181	100%
O'Connell, 1993[10]	Remnant ablation	25	3000(NR)	NR	7 to 3500	60%
Samuel, 1994[27]	Remnant ablation	87	3160(NR)	1018(NR)	59 to 4208	79%
Szumowski, 2021[28]	Remnant ablation	57	3700(NR)	NR	NR	100%
Taprogge, 2025[5]	Remnant ablation	71	1100(NR), 2500(NR) or 3700(NR)	Median 23	<0.1 to 242	82%
Wierts, 2016[14]	Remnant ablation	47	3000(NR)	NR	NR	89%
de Keizer, 2003[23]	Metastatic	16	7400(NR)	26(NR)	1 to 368	45%
Dorn, 2003[24]	Metastatic	124	22100(NR)	NR	100 to >1000	NR
Jentzen, 2014[11]	Metastatic	34	8000(4300)	NR	NR	NR
Jentzen, 2016[12]	Metastatic	10	8000(5000)	388(586)	39 to 3560	43%
Maxon, 1983[13]	Metastatic	19	NR	NR	NR	NR
O'Connell, 1993[10]	Metastatic	7	3000(NR)	NR	NR	NR
Plyku, 2022[26]	Metastatic	4	10120(NR)	NR	NR	58%
Wierts, 2016[14]	Metastatic	47	3000(NR)	NR	NR	69%

SD = Standard Deviation, NR = not reported

Table 4: Reported absorbed dose thresholds and corresponding success rate above the absorbed dose threshold.

Publication	***Patient cohort***	***Absorbed dose limit [Gy]***	***Percentage of successful treatment above absorbed dose limit[%]***
Adamczewski, 2007[20]	Remnant ablation	2000	83
	Remnant ablation	2200	86
	Remnant ablation	2400	91
	Remnant ablation	3000	90
	Remnant ablation	4000	92
Bal, 1996[21]	Remnant ablation	NR	NR
Bal, 2004[22]	Remnant ablation	NR	NR
Flux, 2010[7]	Remnant ablation	49	100
Jentzen, 2014[11]	Remnant ablation	300	90
Jentzen, 2015[29]	Remnant ablation	300	83
Koral, 1986[8]	Remnant ablation	NR	NR
Maxon, 1983[13]	Remnant ablation	300	96
Minguez, 2013[25]	Remnant ablation	NR	NR
O'Connell, 1993[10]	Remnant ablation	60	100
Samuel, 1994[27]	Remnant ablation	300	78
Szumowski, 2021[28]	Remnant ablation	NR	NR
Taprogge, 2025[5]	Remnant ablation	100	87
	Remnant ablation	200	91
Wierts, 2016[14]	Remnant ablation	NR	NR
de Keizer, 2003[23]	Metastatic	NR	NR
Dorn, 2003[24]	Metastatic	NR	NR
Jentzen, 2014[11]	Metastatic (lymph nodes)	85	63
	Metastatic (pulmonary)	85	88
	Metastatic (bone)	85	50
	Metastatic	85	46

Jentzen, 2016[12]	Metastatic	350	67
	Metastatic	650	82
Maxon, 1983[13]	Metastatic	80	98
O'Connell, 1993[10]	Metastatic	NR	NR
Plyku, 2022[26]	Metastatic	75	82

NR = not reported

Supplementary Materials for “A systematic review of absorbed doses and response in patients treated with radioiodine for differentiated thyroid cancer.”

Jan Taprogge, Iain Murray, Kate Newbold, Kate Garcez, Jonathan Wadsley, Glenn D Flux

Joanna Briggs Questionnaire (including additional question 11)

1· Were there clear criteria for inclusion in the case series?

2· Was the condition measured in a standard, reliable way for all participants included in the case series?

3· Were valid methods used for identification of the condition for all participants included in the case series?

4· Did the case series have consecutive inclusion of participants?

5· Did the case series have complete inclusion of participants?

6· Was there clear reporting of the demographics of the participants in the study?

7· Was there clear reporting of clinical information of the participants?

8· Were the outcomes or follow-up results of cases clearly reported?

9· Was there clear reporting of the presenting site(s)/clinic(s) demographic information?

10· Was statistical analysis appropriate?

11· Are treatment methodologies in all sub-groups comparable and match other studies?

Supplementary Table 1: List of excluded reviewed full text articles with reason for exclusion.

Publication	Reason for exclusion
Badam RK, Suram J, Babu DB, et al. Assessment of Salivary Gland Function Using Salivary Scintigraphy in Pre and Post Radioactive Iodine Therapy in Diagnosed Thyroid Carcinoma Patients. J Clin Diagn Res 2016;10(1):Zc60-2, doi:10.7860/jcdr/2016/16091.7121	No therapy outcome data reported.
Bianchi L, Baroli A, Lomuscio G, et al. Dosimetry in the therapy of metastatic differentiated thyroid cancer administering high I-131 activity: the experience of Busto Arsizio Hospital (Italy). Q J Nucl Med Mol Imag 2012;56(6):515-521	
Bushnell DL, Boles MA, Kaufman GE, et al. COMPLICATIONS, SEQUELA AND DOSIMETRY OF I-131 THERAPY FOR THYROID-CARCINOMA. J Nucl Med 1992;33(12):2214-2221	
Freudenberg LS, Fromke C, Petrich T, et al. Thyroid Remnant Dose: I-124-PET/CT Dosimetric Comparison of rhTSH versus Thyroid Hormone Withholding Before Radioiodine Remnant Ablation in Differentiated Thyroid Cancer. Exp Clin Endocrinol Diabet 2010;118(7):393-399, doi:10.1055/s-0029-1225350	
Freudenberg LS, Jentzen W, Gorges R, et al. I-124-PET dosimetry in advanced differentiated thyroid cancer: Therapeutic impact. Nuklearmedizin 2007;46(4):121-128, doi:10.1160/nukmed-0076	
Freudenberg LS, Jentzen W, Marlowe RJ, et al. 124-iodine positron emission tomography/computed tomography dosimetry in pediatric patients with differentiated thyroid cancer. Exp Clin Endocrinol Diabet 2007;115(10):690-693, doi:10.1055/s-2007-985360	
Freudenberg LS, Jentzen W, Petrich T, et al. Lesion dose in differentiated thyroid carcinoma metastases after rhTSH or thyroid hormone withdrawal: 124I PET/CT dosimetric comparisons. Eur J Nucl Med Mol Imaging 2010;37(12):2267-76, doi:10.1007/s00259-010-1565-3	
Freudenberg LS, Jentzen W, Stahl A, et al. Clinical applications of I-124-PET/CT in patients with differentiated thyroid cancer. European Journal of Nuclear Medicine and Molecular Imaging 2011;38(48-56, doi:10.1007/s00259-011-1773-5	
Sun F, Gerrard GE, Roberts JK, et al. Ten Year Experience of Radioiodine Dosimetry: is it Useful in the Management of Metastatic Differentiated Thyroid Cancer? Clin Oncol 2017;29(5):310-315, doi:10.1016/j.clon.2017.01.002	
Benua RS, Cicale NR, Sonenberg M, et al. The relation of radioiodine dosimetry to results and complications in the treatment of metastatic thyroid cancer. Am J Roentgenol Radium Ther Nucl Med 1962;87(171-82)	No dosimetry data reported for lesions or thyroid remnant
Deandreis D, Rubino C, Tala H, et al. Comparison of Empiric Versus Whole-Body/-Blood Clearance Dosimetry Based Approach to Radioactive Iodine Treatment in Patients with Metastases from Differentiated Thyroid Cancer. J Nucl Med 2017;58(5):717-722, doi:10.2967/jnumed.116.179606	
Klubo-Gwiezdzinska J, Van Nostrand D, Atkins F, et al. Efficacy of Dosimetric Versus Empiric Prescribed Activity of I-131 for Therapy of Differentiated Thyroid Cancer. J Clin Endocrinol Metab 2011;96(10):3217-3225, doi:10.1210/jc.2011-0494	
Adamczewski Z, Stasiolek M, Karwowski B, et al. The Effect of Diagnostic Absorbed Doses from 131I on Human Thyrocytes in Vitro. Int J Mol Sci 2015;16(7):14608-14622, doi:10.3390/ijms160714608	Other reasons (e.g. in-vitro study, only toxicity outcome data, …)
Bal C, Kumar A, Tripathi M, et al. High-dose radioiodine treatment for differentiated thyroid carcinoma is not associated with change in female fertility or any genetic risk to the offspring. Int J Radiat Oncol Biol Phys 2005;63(2):449-455, doi:10.1016/j.ijrobp.2005.02.043	
de Keizer B, Hoekstra A, Konijnenberg MW, et al. Bone Marrow Dosimetry and Safety of High ^sup 131^I Activities Given After Recombinant Human Thyroid-Stimulating Hormone to Treat Metastatic Differentiated Thyroid Cancer. The Journal of Nuclear Medicine 2004;45(9):1549-54	

Hammersley PA, Al-Saadi A, Chittenden S, et al. Value of protein-bound radioactive iodine measurements in the management of differentiated thyroid cancer treated with (131)I. Br J Radiol 2001;74(881):429-33, doi:10.1259/bjr.74.881.740429	
Jentzen W, Schneider E, Freudenberg L, et al. Relationship between cumulative radiation dose and salivary gland uptake associated with radioiodine therapy of thyroid cancer. Nucl Med Commun 2006;27(8):669-676, doi:10.1097/00006231-200608000-00009	
Lee SM, Lee JW, Kim SY, et al. Prediction of risk for symptomatic sialadenitis by post-therapeutic dual I-131 scintigraphy in patients with differentiated thyroid cancer. Annals of Nuclear Medicine 2013;27(8):700-709, doi:10.1007/s12149-013-0735-3	
M'Kacher R, Légal JD, Schlumberger M, et al. Sequential biological dosimetry after a single treatment with iodine-131 for differentiated thyroid carcinoma. J Nucl Med 1997;38(3):377-80	
M'Kacher R, Schlumberger M, Legal JD, et al. Biologic dosimetry in thyroid cancer patients after repeated treatments with iodine-131. J Nucl Med 1998;39(5):825-829	
Verburg FA, Lassmann M, Mader U, et al. The absorbed dose to the blood is a better predictor of ablation success than the administered I-131 activity in thyroid cancer patients. European Journal of Nuclear Medicine and Molecular Imaging 2011;38(4):673-680, doi:10.1007/s00259-010-1689-5	
Samuel AM, Rajashekharrao B, Shah DH. Pulmonary metastases in children and adolescents with well-differentiated thyroid cancer. J Nucl Med 1998;39(9):1531-6	Only paediatric and adolescent patients
Bal CS, Kumar A, Pant GS. Radioiodine lobar ablation as an alternative to completion thyroidectomy in patients with differentiated thyroid cancer. Nucl Med Commun 2003;24(2):203-208, doi:10.1097/00006231-200302000-00013	Only partial thyroidectomy