A systematic review and meta-analysis of the relationship between the radiation absorbed dose to the thyroid and response in patients treated with radioiodine for Graves' disease

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Running title: Systematic review radioiodine dose Graves' disease

Keywords: Systematic review, meta-analysis, radioiodine, radiation absorbed dose, Graves' disease

Abstract

Background: Patients with Graves' disease are commonly treated with radioiodine. There remains controversy over whether the aim of treatment should be to achieve euthyroidism or hypothyroidism, and whether treatments should be administered with standard levels of radioactivity or personalised according to the radiation absorbed doses delivered to the thyroid. The aim of this review was to investigate whether a relationship exists between radiation absorbed dose and treatment outcome.

Methods: A systematic review and meta-analysis of all reports published before Feb 13, 2020 was performed using PubMed, Web of Science, OVID MEDLINE and Embase. Proportion of patients achieving non-hyperthyroid status was the primary outcome. Secondary outcomes were proportion of patients who were specifically euthyroid or hypothyroid. A random-effects meta-analysis of proportions was performed for primary and secondary outcomes, and the impact of the radiation absorbed dose on treatment outcome was assessed via meta-regression. The study is registered with PROSPERO (CRD42020175010).

Results: 1122 studies were identified of which 15, comprising 2303 Graves' disease patients, were eligible for the meta-analysis. A strong association was found between radiation absorbed dose and non-hyperthyroid and hypothyroid outcomes (OR = 1.11 (95% CI 1.08 – 1.14) and 1.09 (95% CI 1.06 – 1.12) per 10 Gy increase). Higher rates of euthyroid outcome were found for radiation absorbed doses within the range 120 - 180 Gy when compared to outside this range (n = 1172, OR 2.50, 95% CI 1.17 – 5.35, p = 0.018). A maximum euthyroid response of 38% was identified at a radiation absorbed dose of 128 Gy.

Conclusions: The presented radiation absorbed dose-response relationships can facilitate personalised treatment planning for radioiodine treatment of patients with

Graves' disease. Further studies are required to determine how patient-specific covariates can inform personalised treatments.

Introduction

Hyperthyroidism has been widely treated with [^{131}I]NaI (radioiodine) since 1941 (1). However, debate continues as to whether the aim of treatment should be to achieve hypothyroidism or euthyroidism (2-6). Additionally there is a lack of consensus on the optimal strategy to achieve either outcome. The most common approach is based on the administration of standard levels of radioactivity. However a personalised approach based on calculated activities to deliver a specified radiation absorbed dose to the thyroid may deliver a euthyroid outcome where required (3). Recent guidelines from the National Institute for Health and Care Excellence (NICE) highlighted the lack of randomised controlled trials in the use of radioiodine for the treatment of benign thyroid disease (6).

The aim of treatment of hyperthyroidism remains controversial. The American Thyroid Association (4) and the European Thyroid Association (5) recommend a single administration of radioactivity sufficient to render the patient hypothyroid (typically between 370 and 555 MBq). However, the European Association of Nuclear Medicine (EANM) guidelines (3,7) consider hypothyroidism a side effect of the treatment (8,9) which requires life-long thyroid hormone replacement and regular TSH monitoring. An audit of local general practitioners in the UK found that 21% of patients were over-treated with the thyroid replacement drug levothyroxine, while under-treatment was observed in 9% of patients (10). Both outcomes potentially have negative health impacts for patients. A patient survey conducted by the British Thyroid Foundation found that nearly 80% of patients were dissatisfied with their medication (11). The EANM guidelines state that treatment according to disease-specific prescribed radiation doses may achieve a euthyroid state, whereby the patient would not require thyroid hormone replacement (3).

Treatment protocols are currently based on evidence from single centre studies and vary widely. In performing this review, we aimed to consolidate the current literature regarding radiation absorbed doses to the thyroid for radioiodine treatment of hyperthyroidism and to investigate whether a relationship exists between these radiation absorbed doses and treatment outcome.

Material and Methods

Search strategy and selection criteria

A comprehensive systematic review and meta-analysis of published studies was performed to evaluate the clinical outcomes of radioiodine therapy for hyperthyroidism with respect to the radiation absorbed doses to the thyroid. Articles published before Feb 13 2020 were included. No restrictions were applied on language or type of study design. Only studies were included that reported: radiation absorbed dose to the thyroid, follow-up time, and treatment outcomes for adult patients. Only full-text articles published in peer-reviewed journals were assessed. PubMed, Web of Science, OVID MEDLINE, and Embase were searched following the principles and checklist provided by PRISMA (preferred reporting items for systematic reviews and meta-analyses) (12). The databases were searched for the following terms: (“iodine” OR “radioiodine” OR “I131” OR “I-131” OR “131I”) AND (“graves’ disease” OR “hyperthyroidism”) AND (“dosimetry” OR “absorbed dose”). Study authors were not contacted and trial registries were not searched. Details of the protocol for this systematic review were registered on PROSPERO, which can be accessed at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=175010.

Two reviewers (JT, GF) performed the initial search and screened results for duplicates. Two blinded reviewers (JT, GF) screened the remaining studies based on

title and abstract for inclusion. Discrepancies between the selected studies were resolved as a joint decision by the two reviewers. Four reviewers (JT, GF, LP, PG) extracted data independently and collated the results in MS Excel spreadsheets.

Data were extracted on a sub-population level for each treatment arm, corresponding to different radiation doses to the thyroid, where available. Data were extracted for the full study population in cases where data for different treatment arms were not reported.

Data analysis

For each study, the following variables were extracted: number of subjects, disease type, discontinuation of anti-thyroid medication before treatment (yes-all/yes-some/none), presence of ophthalmopathy (yes-all/yes-some/none), follow up period (months), median or mean age (years), proportion of male patients (percentage), median or mean amount of radioactivity (MBq), radiation absorbed dose to the thyroid (Gy), and proportion of patients euthyroid/hypothyroid/hyperthyroid at all follow-up times (percentage). The aim of treatment was recorded as either non-hyperthyroid (encompassing both euthyroid and hypothyroid), specifically euthyroid or specifically hypothyroid. Dosimetry methodology was also extracted.

The main summary measures used were proportions of patients (with 95% CIs) reaching specific endpoints following radioiodine treatment, relative to the size of the treatment arm sub-population. The primary outcome used was proportion of patients who were non-hyperthyroid. Secondary outcomes were proportion of patients who were specifically euthyroid or hypothyroid. These were taken to be mutually exclusive and were individually defined in each study. The proportion of patients with euthyroid outcome was inferred from the difference between the numbers of patients rendered

non-hyperthyroid and hypothyroid, where not explicitly reported. Patients who required further radioiodine treatment were classed as hyperthyroid at follow up.

Two reviewers (JT, LP) assessed risk of bias on a study level using the critical appraisal checklist developed by the Joanna Briggs Institute (13). Studies were classed as having a low, intermediate, or high risk of bias and studies were only included if classed as having low or intermediate risk of bias in the further data synthesis.

The meta-analysis was performed separately for Graves' disease and for any other hyperthyroid conditions. Only the response at last follow-up was included for the meta-analysis. The majority of included studies were uncontrolled and retrospective. Therefore, a random-effects meta-analysis of proportions was performed for: non-hyperthyroid, euthyroid, and hypothyroid outcomes. DerSimonian and Laird method was employed with a logit transformation (14,15). The I^2 test was used to assess heterogeneity between studies. Meta-regression was performed to assess the impact of the extracted variables on the odds of achieving the respective outcomes. For the euthyroid outcome, where a non-monotonic relationship is expected (16), a categorical variable was included to represent whether the radiation absorbed dose was within or outside a particular range. Dose-response relationships were fitted based on a two-parameter log-logistic model (17) using the maximum likelihood principle for the non-hyperthyroid and hypothyroid outcomes. A sensitivity analysis was performed to identify whether results remained significant if only studies classed as having low risk of bias were included.

All statistical analyses were performed using R Statistical Software (version 3.5.2; R Foundation for Statistical Computing, Vienna, Austria) and the add-on package drc (18). The value $p < 0.05$ was considered statistically significant.

Results

A total of 1122 studies were identified for the systematic review of which 419 were excluded due to presentation of duplicate data. A further 668 were excluded for not satisfying the eligibility criteria based on title and abstract. Of the remaining 35 studies, a total of 20 full-text articles (16,19-37) were deemed eligible for the systematic review following independent analysis (Figure 1 (PRISMAWorkflow)). A summary of the study characteristics is presented in Table 1 (Summaries). Thirteen studies reported a patient cohort with Graves' disease, five reported a mixture of hyperthyroid conditions including Graves' disease, one study reported only hyperfunctioning thyroid nodules, and one study considered only patients with toxic nodular goitre.

One study (24), comprising a mixture of hyperthyroid conditions, was excluded from the quantitative synthesis due to a high risk of bias identified from the critical appraisal checklist developed by the Joanna Briggs Institute. The remaining studies were classed as low or intermediate risk of bias (Supplementary Material Table A1). A total of 2328 patients were reported as having Graves' disease, whilst 75, 173, and 57 patients had thyroid nodules, toxic nodular goitre or toxic adenoma, respectively. Only four studies included patients with hyperfunctioning thyroid nodules or toxic nodular goitre, which was insufficient to perform a meta-analysis.

Of the studies reporting outcomes for Graves' disease, the sub-populations, as stratified by radiation absorbed dose, ranged in size from 9 to 284 patients, with a median of 42 patients. The stated aim of treatment varied between studies. In eight studies the aim was to resolve hyperthyroidism by rendering patients either euthyroid or hypothyroid). In four studies the aim was to explicitly induce euthyroidism, in one study to induce hypothyroidism and in five studies the aim was not clearly reported.

A range of dosimetry methodologies (Supplementary Material Table A3) were employed across the studies reporting outcomes for Graves' disease, with the majority (15/18) using a variation of the method proposed by Marinelli (38), which has been adopted into EANM guidelines (3,7). Two studies (27,34) used a method based on the volume-reduction methodology proposed by Traino et al (39) and one used a fixed activity administration with post-therapy dosimetry (26). Seven studies carried out post-therapy verification, whereas eleven based the reported radiation absorbed dose on a pre-therapy tracer study.

One study excluded patients with ophthalmopathy (31), whilst one study adjusted the prescribed radiation absorbed dose based on the presence of ophthalmopathy (34). Only one study reported outcomes separately for patients with ophthalmopathy (32). Less than one third (5/18) of studies included a last follow-up of greater than 12 months. The median last follow-up was 12 months (range 3 – 120 months).

For studies reporting outcomes for Graves' disease a forest plot for the non-hyperthyroid outcome is included in the Supplementary Material (Figure B1). The random-effects meta-analysis for this outcome resulted in an I^2 of 91.1%, suggesting that a pooled estimate of proportion across these studies is of limited use. A strong association was found in meta-regression between the radiation absorbed dose to the thyroid and non-hyperthyroid and hypothyroid outcomes at the last reported follow-up (OR = 1.11 (95% CI 1.08 – 1.14) and 1.09 (95% CI 1.06 – 1.12) per 10 Gy increase in radiation absorbed dose respectively, R^2 = 55.0% and 53.7%, both $p < 0.001$). The absorbed radiation dose response relationships for each outcome are shown in Figure 2 (DoseResponse). Given that, in the majority of studies, the administered radioactivity was calculated to deliver a prescribed radiation absorbed dose to the thyroid, these two variables are not independent (Pearson correlation coefficient r(15) = 0.85,

p<0.001). A graph of administered radioactivities against prescribed radiation absorbed doses is presented in the Supplementary Material (Figure B2). As a result, administered radioactivity was excluded from the univariate analysis. The proportion of patients with non-hyperthyroid and hypothyroid outcomes was seen to plateau with increasing radiation absorbed doses, with limited benefit above 300 Gy. (Figure 2 (DoseResponse)). An association with euthyroid outcome was found for radiation absorbed doses within the range 120 - 180 Gy when compared to outside this range (n = 1172, OR 2.50, 95% CI 1.17 – 5.35, p = 0.018). A maximum euthyroid response of 38% (95% CI 26% – 50%) was identified at a radiation absorbed dose of 128 Gy. Euthyroid, hypothyroid and non-hyperthyroid responses at 150, 200 and 300 Gy are presented in Table 2. All odds ratios calculated in the sensitivity analysis (see Supplementary Material Table A2) agreed with the results in the full analysis to within the stated 95% confidence intervals.

Discussion

The findings of this systematic review and meta-analysis of 15 studies (16,20-22,25-34,37) which reported outcomes of radioiodine treatment for the sub-population of patients with Graves' disease (n=2303), indicate that there is a clear relationship between the radiation absorbed dose delivered to the thyroid and treatment outcome. This offers the potential to treat according to a desired outcome, considering potential risk factors (40,41). While EANM guidelines suggest that dosimetry-based treatment is feasible (3), other professional societies consider such an approach unviable and unproven (2,4,5).

These findings indicate that a radiation absorbed dose to the thyroid of 128 Gy achieves a euthyroid state, without the need for thyroid hormone replacement drugs,

in 38% of patients and resolution of hyperthyroidism in 70% of patients at a median follow-up of 12 months. The remaining 30% of patients would require further treatment to resolve hyperthyroidism. Several studies have shown that unresolved hyperthyroidism is associated with increased risk of cardiovascular mortality (42,43). Therefore, if the clinical priority is resolution of hyperthyroidism, a higher population response rate can be achieved with a higher radiation absorbed dose. However, this will result in more patients becoming hypothyroid. To achieve higher euthyroidism rates than 38%, personalised radiation absorbed dose prescriptions based on patient-specific factors such as the radiation absorbed dose rate (44), sex (8), thyroid volume (45), presenting T4 (8), anti-thyroid medication (46) and duration of the Graves' disease (47) may be required. The exact role of these factors should be further investigated.

The studies in this review show that, while administered radioactivity and radiation absorbed dose are related, different patients required different amounts of radioactivity to deliver a prescribed radiation absorbed dose to the thyroid (see Supplementary Material Figure B2) (16,19-24,27-29,31,33,35-37). Conversely, the administration of empirically determined, standard amounts of radioactivity delivers a wide range of radiation absorbed doses to the thyroid (16,26) which results in varying response rates (Figure 2 (DoseResponse)).

Limitations of the study include the lack of data from randomised control trials (RCT), with only one RCT included (16). Treatment outcomes were not reported at consistent follow-up times across the studies, therefore outcomes at last follow-up were used in our meta-analysis. The median last follow-up at 12 months may not represent the longer term effect of treatment with radioiodine. It has been shown that

incidence of hypothyroidism increases with time following treatment, although this may plateau out (29). However, follow-up time was not found to be significantly associated with outcome in our meta-analysis. Further studies with long-term follow-up are required to determine how long the euthyroid state can be maintained after radioiodine treatment. Dosimetry methodologies vary between studies, which partially explains the observed variation in response rates for a given radiation absorbed dose. Standardisation of dosimetry methodology between centres, which has shown to be feasible (48), would contribute towards reducing this variation in future studies. The lack of available data for other hyperthyroid conditions limited the scope of the meta-analysis to Graves' disease. No patient-specific covariates could be extracted as they were either missing or only reported as population averages. The effect of follow-up time and patient-specific factors such as disease type, thyroid volume or free T4 on treatment outcome should be investigated in future studies.

Conclusions

In this study, a highly significant relationship was demonstrated between radiation absorbed dose and non-hyperthyroid, euthyroid, and hypothyroid outcomes in the treatment of Graves' disease using radioiodine. This could therefore serve as a basis to plan treatment, based on the required outcome. Comprehensive and standardised data collection in future studies would benefit the field. Further studies are required to determine the clinical efficacy and cost effectiveness of dosimetry-based, patient-specific treatment planning and to further investigate the potential role of patient-specific covariates that may be used for stratification.

Author Contribution statement:

GF, FL and JT conceived the design of the systematic review. GF and JT did the abstract and full-text screening, PG, JT and LP did the data extraction, PG performed the data analysis, and GF, PG, JT and LP drafted the original manuscript. All authors contributed to the edit and review of the final manuscript. GF, IM, JG and SH supervised the project until its completion.

Author Disclosure Statement:

JT, PG, LP, JG, IM and GF report grants from Euratom research and training programme 2014-2018 and National Institute for Health Research (NIHR) and funding from National Health Service to the NIHR Biomedical Research Centre at The Royal Marsden and the ICR and NIHR Royal Marsden Clinical Research Facility outside the work of the study. JG reports personal fees and honoraria from The European Association of Nuclear Medicine outside the work of the study.

Funding statement:

NHS funding was provided to the NIHR Biomedical Research Centre at The Royal Marsden and the ICR. The MEDIRAD project has received funding from the Euratom research and training programme 2014-2018 under grant agreement No 755523. The RTTQA group is funded by the National Institute for Health Research (NIHR). We acknowledge infrastructure support from the NIHR Royal Marsden Clinical Research Facility Funding. This report is independent research funded by the National Institute for Health Research (NIHR). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

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507 **Table 1: Characteristics of included studies.**

	# (Disease types)	ATD	FU, months	Age, years	Male sex, %	OP	Prev RAI	Radiation absorbed dose, Gy	Rad Act Admin, MBq	Rates, %		
										HYPO	EU	HYPER
Amato et al (2016, Italy) (19)	69 (GD, TA, TNG)	Yes	47	M 64 (SD 13)	36	NR	NR	M 223 (SD 49)	M 303 (SD 135)	23	72	4
Bajnok et al (1999, Hungary) (20)	76 (GD)	Yes	6	M 49 (SD 12)*	18*	YS	YS	70	M 315 (SD 233)*	20	55	25
Bajnok et al (1999, Hungary) (20)	29 (GD)	Yes	6	M 49 (SD 12)*	18*	YS	YS	M 90 (Rg 80-100)	M 315 (SD 233)*	34	38	28
Bajnok et al (1999, Hungary) (20)	68 (GD)	Yes	12	M 49 (SD 12)*	18*	YS	YS	70	M 315 (SD 233)*	25	51	24
Bajnok et al (1999, Hungary) (20)	25 (GD)	Yes	12	M 49 (SD 12)*	18*	YS	YS	M 90 (Rg 80-100)	M 315 (SD 233)*	44	40	16
Berg et al (1996, Sweden) (21)	191 (GD)	Yes	5	Rg 29 – 70*	18	YS	NR	M 110 (Rg 100 -120)	M 386 (SD 136)	NR	NR	7
Berg et al (1996,	45 (TNG)	Yes	5	Rg 29 – 70*	4	YS	NR	M 110 (Rg 100 -120)	M 461 (SD 115)	NR	NR	7

Sweden) (21)												
Blahd et al (1972, US) (22)	241 (GD)	NR	NR	M 42 (Rg 21 - 78)	100	YS	YS	55	M 206 (SD 110)	NR	NR	45
Bockisch et al (1993, Germany) (23)	14 (TA)	No	12	NR	NR	NR	NR	M 150 (Rg 120 - 180)	Rg 190 – 1100*	7	71	21
Bockisch et al (1993, Germany) (23)	21 (TA, HTN, HN, GD, EuG)	No	12	NR	NR	NR	NR	M 100 (Rg 80 - 120)	Rg 190 – 1100*	5	76	19
Camps et al (1996, Netherlands) (24)	39 (GD)	Yes	12	M 40 (Rg 11 - 80)	22	YS	NR	M 81 (Rg 24 - 163)	M 155 (Rg 54 - 940)	26	48	26
Camps et al (1996, Netherlands) (24)	22 (TNG)	Yes	12	M 67 (Rg 24 - 90)	9	YS	NR	M 160 (Rg 38 - 317)	M 715 (Rg 78 - 1654)	9	59	32
Catargi et al (1999, France) (25)	100 (GD)	NA	72	M 52 (SD 12)	11	NR	No	M 83 (Rg 36 - 232)	NR	41	26	33
Flower et al (1994, UK) (26)	15 (GD)	NR	6	NR	NR	NR	No	M 10 (Rg 0 - 20)	M 75 (SD NR)	0	7	93
Flower et al (1994, UK) (26)	27 (GD)	NR	6	NR	NR	NR	No	M 30 (Rg 20 – 40)	M 75 (SD NR)	0	26	74
Flower et al (1994, UK) (26)	9 (GD)	NR	6	NR	NR	NR	No	M 50 (Rg 40 – 60)	M 75 (SD NR)	11	0	89

Flower et al (1994, UK) (26)	14 (GD)	NR	6	NR	NR	NR	No	M 70 (Rg 60 – 80)	M 75 (SD NR)	14	14	71
Grosso et al (2005, Italy) (27)	32 (GD)	Yes	12	M 61 (SD 13)	24*	YS	NR	M 148 (SD 26)	M 455 (SD 250)	25	59	16
Grosso et al (2005, Italy) (27)	58 (GD)	Yes	12	M 54 (SD 14)	24*	YS	NR	M 295 (SD 52)	M 444 (SD 181)	40	47	14
Howarth et al (2001, Australia) (28)	28 (GD)	Yes	6	M 46 (95 CI 42 - 52)	14*	YS	NR	60	M 154 (95 CI 119 – 190)	7	32	61
Howarth et al (2001, Australia) (28)	29 (GD)	Yes	6	M 42 (95 CI 37 - 45)	14*	YS	NR	90	179 (95 CI 148 - 210)	17	24	59
Hyer et al (2018, UK) (29)	284 (GD)	Yes	18	Md 46 (Rg 18 - 81)*	24*	YS	No	Md 56 (95 CI 55 - 58)	Md 81 (Rg 17 - 1377)	9	44	47
Hyer et al (2018, UK) (29)	284 (GD)	Yes	36	Md 46 (Rg 18 - 82)*	24*	YS	No	Md 56 (95 CI 55 - 58)	Md 81 (Rg 17 - 1377)	13	41	46
Hyer et al (2018, UK) (29)	284 (GD)	Yes	60	Md 46 (Rg 18 - 82)*	24*	YS	No	Md 55 (95 CI 55 -58)	Md 81 (Rg 17 - 1377)	17	38	45
Hyer et al (2018, UK) (29)	284 (GD)	Yes	120	Md 46 (Rg 18 - 82)*	24*	YS	No	Md 56 (95 CI 55 - 58)	Md 81 (Rg 17 - 1377)	21	30	49
Kobe et al (2008, Germany) (30)	30 (GD)	Yes	12	Md 48 (Rg 18 - 80)*	17*	YS	NR	M 190 (SD NR)	NR	NR	NR	7
Kobe et al (2008,	137 (GD)	Yes	12	Md 48 (Rg 18 - 80)*	17*	YS	NR	M 231 (Rg 206 - 255)	NR	NR	NR	4

Germany) (30)												
Kobe et al (2008, Germany) (30)	181 (GD)	Yes	12	Md 48 (Rg 18 - 80)*	17*	YS	NR	M 281 (Rg 256 - 305)	NR	NR	NR	4
Kobe et al (2008, Germany) (30)	128 (GD)	Yes	12	Md 48 (Rg 18 - 80)*	17*	YS	NR	M 331 (Rg 306 - 355)	NR	NR	NR	2
Kobe et al (2008, Germany) (30)	50 (GD)	Yes	12	Md 48 (Rg 18 - 80)*	17*	YS	NR	M 381 (Rg 356 - 405)	NR	NR	NR	2
Orsini et al (2012, Italy) (31)	29 (GD)	Yes	12	M 53 (SD 18)*	29*	No	No	100	NR	NR	NR	52
Orsini et al (2012, Italy) (31)	25 (GD)	Yes	12	M 53 (SD 18)*	29*	No	No	200	NR	NR	NR	36
Orsini et al (2012, Italy) (31)	29 (GD)	Yes	12	M 53 (SD 18)*	29*	No	No	M 407 (SD 23)	M 524 (SD 201)	93	3	3
Oszukowska et al (2010, Poland) (32)	40 (GD, TNG)	Yes	6	M 52 (SD 13)*	15*	No	NR	M 175 (Rg 150 - 200)	NR	20	35	45
Oszukowska et al (2010, Poland) (32)	40 (GD, TNG)	NA	6	M 52 (SD 13)*	15*	No	NR	M 175 (Rg 150 - 200)	NR	18	60	23
Oszukowska et al	40 (GD)	NA	6	M 52 (SD 13)*	15*	Yes	NR	M 300 (Rg 250 - 350)	NR	58	30	13

(2010, Poland) (32)												
Oszukowska et al (2010, Poland) (32)	40 (GD)	NA	6	M 52 (SD 13)*	15*	No	NR	M 300 (Rg 250 - 350)	NR	43	28	30
Peters et al (1995, Germany) (16)	107 (GD)	Yes	6	Md 52 (Rg 31 - 80)	13	YS	YS	Md 119 Gy (Q25 = 90 Gy, Q75 = 154 Gy)	Md 298 (Q25 = 184, Q75 = 555)	23	35	42
Reinhardt et al (2002, Germany) (33)	84 (GD)	YS	16	M 60 (SD 14)	29*	YS	NR	M 177 (SD 49)	M 570 (SD 285)	27	45	27
Reinhardt et al (2002, Germany) (33)	78 (GD)	YS	15	M 58 (SD 15)	29*	YS	NR	M 236 (SD 53)	M 680 (SD 310)	33	44	23
Reinhardt et al (2002, Germany) (33)	62 (GD)	YS	14	M 56 (SD 14)	29*	YS	NR	M 320 (SD 57)	M 940 (SD 480)	68	24	8
Schiavo et al (2011, Italy) (34)	10 (GD)	Yes	36	M 49 (Rg 18 - 83)*	18*	No	NR	M 135 (Rg 120 - 150)	NR	NR	NR	50
Schiavo et al (2011, Italy) (34)	17 (GD)	Yes	36	M 49 (Rg 18 - 83)*	18*	YS	NR	M 175 (Rg 150 - 200)	NR	NR	NR	41
Schiavo et al (2011, Italy) (34)	92 (GD)	Yes	36	M 49 (Rg 18 - 83)*	18*	YS	NR	M 225 (Rg 200 - 250)	NR	NR	NR	13
Schiavo et al (2013, Italy) (36)	75 (HTN)	Yes	30	Md 69 (Rg 31 - 87)	39	No	NR	300 (To Nodule)	Rg 92 - 600	8	91	1

Schiavo et al (2014, Italy) (35)	93 (TNG)	Yes	60	Md 71 (Rg 43 - 84)	30	No	NR	M 275 (Rg 250 - 300)	Md 526 (Rg 156 - 625)	13	69	18
Willemsen et al (1993, Germany) (37)	43 (GD)	Yes	3	NR	16	YS	YS	300	Md 752 (Rg 240 - 3120)	63	23	14
Willemsen et al (1993, Germany) (37)	43 (GD)	Yes	6	NR	16	YS	YS	300	Md 752 (Rg 240 - 3120)	NR	NR	7
Willemsen et al (1993, Germany) (37)	43 (GD)	Yes	12	NR	16	YS	YS	300	Md 752 (Rg 240 - 3120)	NR	NR	0
Willemsen et al (1993, Germany) (37)	43 (GD)	Yes	18	NR	16	YS	YS	300	Md 752 (Rg 240 - 3120)	93	7	0

508

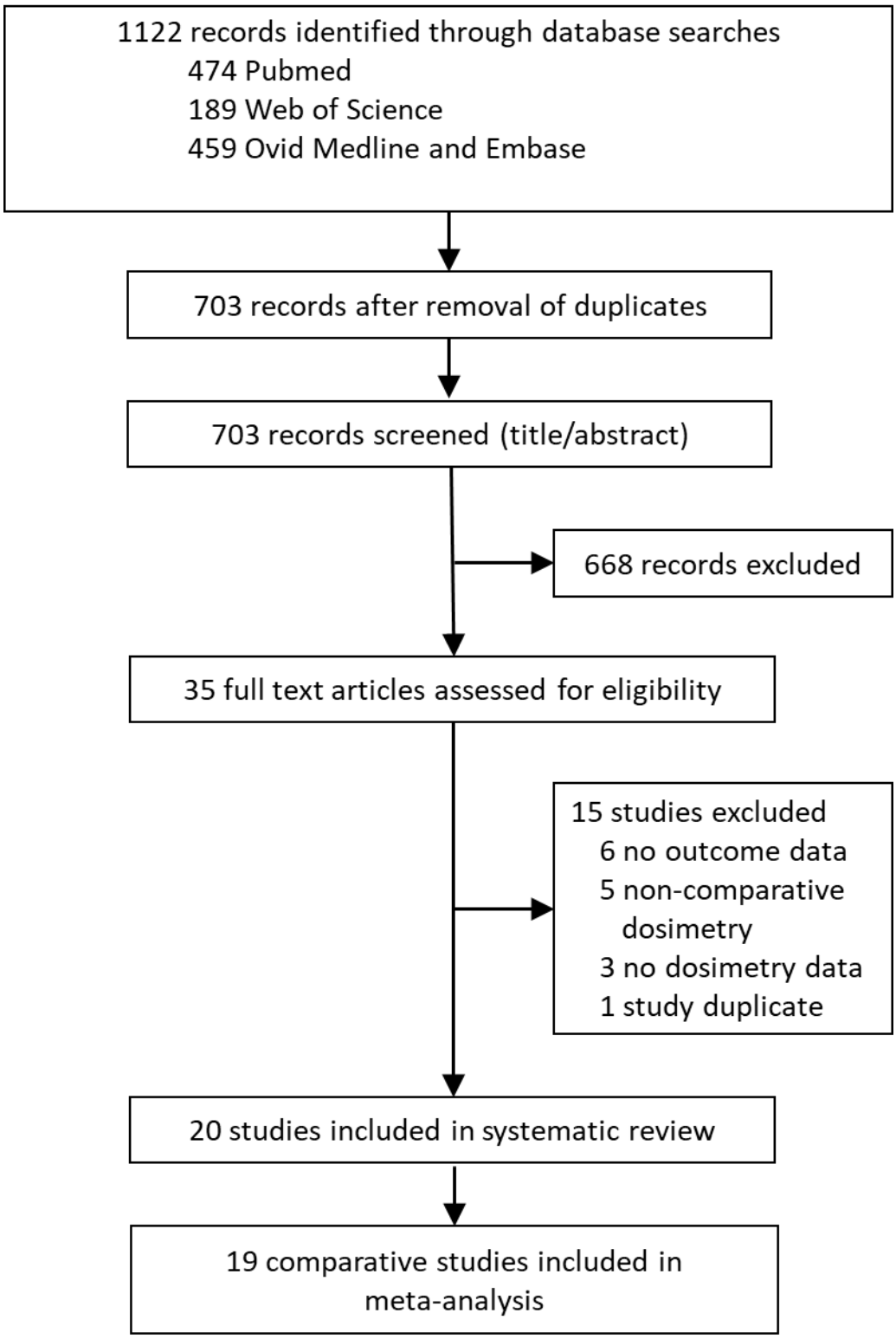
509 Abbreviations used in the table: NR = Not reported in study, NA = Not applicable to study, YS = Yes-
510 Some i.e. only applicable to a fraction of the study population, Yes = Yes-All i.e. applicable to the full
511 study population,, # = number of study subjects, GD = Graves' disease, TA = Toxic adenoma, TNG =
512 Toxic nodular goitre, HN = Homogeneous uptake with No indication of GD, EuG = Euthryoid Goitre,
513 ATD = Use of AntiThyroid drugs during radioiodine administration, FU = Reported Follow Up time, OP
514 = Presence of ophthalmopathy in study population, Prev RAI = Previous RadioActive Iodine
515 administrations, Rad Act Admin = Radioactivity Administered to patients, Hypo = Hypothyroidism
516 outcome at follow up, Eu = Euthyroidism outcome at follow up, Hyper = Hyperthyroidism outcome
517 or further radioiodine treatment at follow up. M = Mean, Md = Median, R = Range, SD = Standard
518 deviation, 95 CI = 95% confidence intervals, Q25= 25^{th} Quartile, Q75 = 75^{th} Quartile.

If results were not reported for the different groups, e.g. for different radiation absorbed dose groups or for patients grouped by disease type, the population result was presented and is indicated by *.

Table 2: Euthyroid, hypothyroid and non-hyperthyroid responses at 150, 200 and 300 Gy.

Radiation absorbed dose to thyroid [Gy]	Euthyroid [%]	Hypothyroid [%]	Non-hyperthyroid [%]
150	38 (95 CI 26 - 50)	36 (95 CI 27 – 46)	74 (95 CI 68 – 81)
200	35 (95 CI 24 – 47)	46 (95 CI 36 – 55)	81 (95 CI 74 – 88)
300	29 (95 CI 16 – 42)	59 (95 CI 48 – 71)	88 (95 CI 82 – 95)

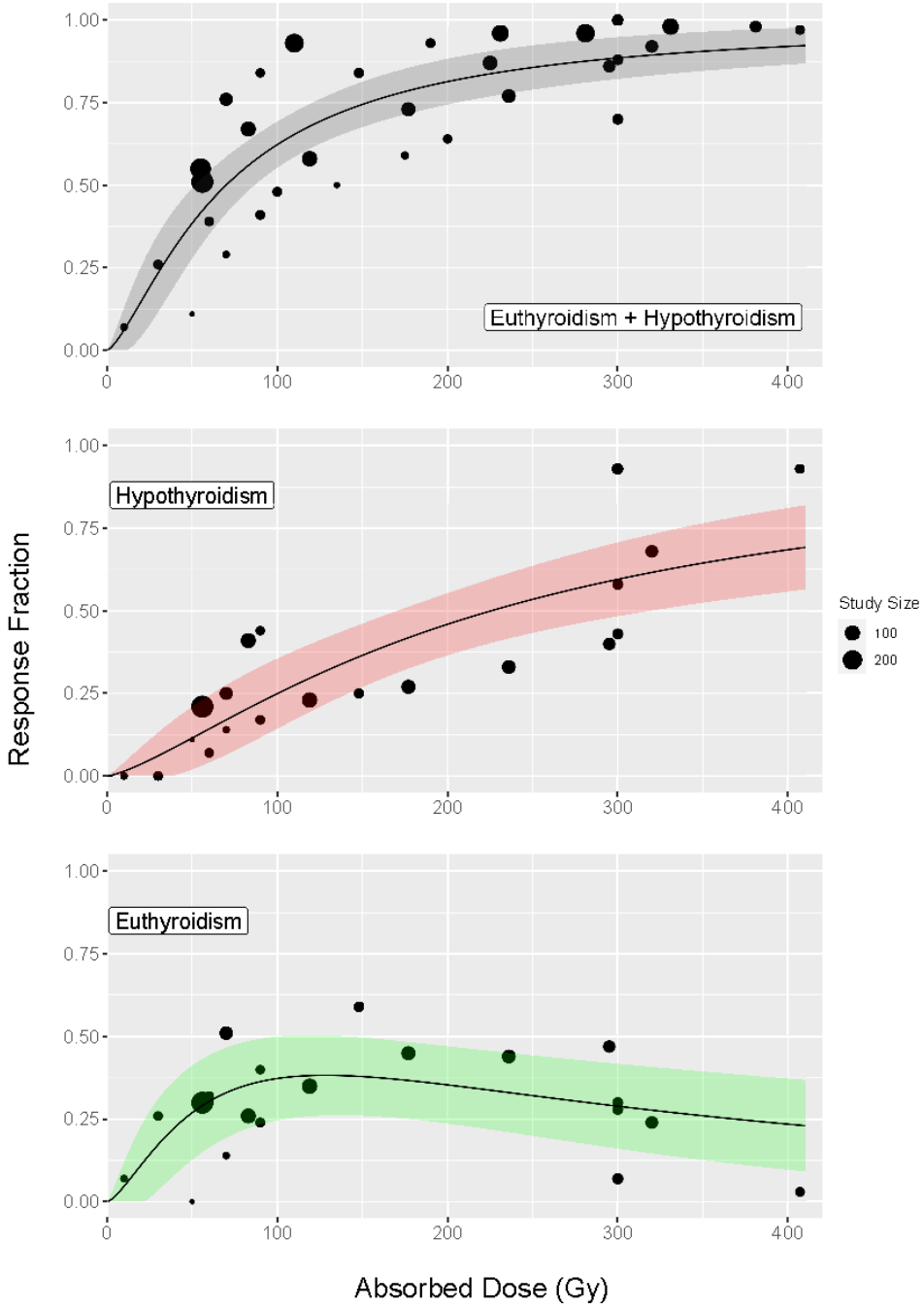
Abbreviation used in the table: 95 CI = 95% confidence intervals.



528

529 **Figure 1:** Flowchart for the systematic literature review.

530



531

532 **Figure 2:** The population fraction achieving non-hyperthyroid, hypothyroid and
533 euthyroid outcomes as a function of radiation absorbed dose at a median follow-up of
534 12 months for patients with Graves' disease. The top figure represents a total of 2303
535 patients while the two bottom figures each represent a total of 1172 patients. The size
536 of each point represents the number of patients in the study. The shaded regions give
537 the 95% confidence interval.