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REVIEW ARTICLE

Outcomes of Radioactive Iodine Versus Surgery for the Treatment of Graves' Disease: a Systematic Review and Meta-analysis

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Abstract

Graves' disease (GD) is a systemic autoimmune disorder mainly affecting the thyroid gland. During GD management, the principal target is to control the hyperthyroid state. There have been three rather similarly effective modalities: medical therapy with antithyroid drugs (ATD), radioactive iodine (RAI), or surgical excision of the thyroid tissue (thyroidectomy). Defining the relative risks and benefits of each of the two potential definitive treatment options (RAI or thyroidectomy) is crucial for creating evidence-based therapy algorithms. This systematic review and meta-analysis aimed to compare the outcomes of these two treatment options. This is a systematic review and meta-analysis that analyzed the studies comparing RAI and thyroidectomy to treat GD. Studies were obtained by searching on Scopus, the Cochrane Central Register of Controlled Trials, and PubMed central database. The surgically treated group showed significantly lower failure rates, non-significantly lower cardiovascular morbidities, non-significantly higher complication rates, and significantly lower mortality rates. The RAI-related complications were mostly the development or worsening of Graves' ophthalmopathy. This review and meta-analysis comparing surgery and radioactive iodine for the treatment of Grave's disease from 16 well-conducted trials has shown that although surgery viz., total thyroidectomy was less frequently utilized for the treatment of Grave's disease, it controlled the symptoms with greater success and without any worsening of Grave's ophthalmopathy.

Keywords Graves' disease · Surgical treatment · Radioactive iodine · Failure · Complications

Introduction

Graves' disease (GD) is a systemic autoimmune disorder mainly affecting the thyroid gland. It is the most prevalent cause of hyperthyroidism and has been reported to affect about 1–1.5% of the world population [1]. Graves' disease affects people of all ages, but notably middle-aged women [2].

Graves' disease develops as a result of thyroid-stimulating immunoglobulin (TSI) impact on the thyroid-stimulating hormone receptors (TSHR), leading to excessive secretion of thyroxin and loss of pituitary feedback control on the thyroid gland [3]. Thyroid-stimulating immunoglobulins also contribute to Graves' orbitopathy (GO) development through their effect on retro-orbital tissue thyrotropin receptors [2]. Although GD is primarily predisposed by genetic causes, environmental causes, including smoking, vitamin D deficiency, and iodine excess, contribute to the occurrence of the disease [4].

During GD management, the principal target is to control the hyperthyroid state by normalization of the thyroid

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hormone concentration. The presence of GO and/or a goiter (enlarged nodular thyroid gland) will influence the choice of therapy [2]. There have been three rather similarly effective modalities: medical therapy with antithyroid drugs (ATD) that inhibit the thyroid hormone production, radioactive iodine (RAI) for induction of thyroid tissue shrinkage, or surgical excision of the thyroid tissue (thyroidectomy) [5].

The choice of either treatment approach is an issue of wide debate. While thyroidectomy or ATD is the favorable choice in Europe, RAI is the preferred modality in the USA [6–10]. Indeed, the current guidelines have assumed surgical management as an equivalent therapy choice to RAI, with a comparable long-term outcome regarding the quality of life [8, 11, 12]. Moreover, some studies have recently shown that thyroidectomy is the definitive treatment of choice [13–15].

Radioactive iodine is indicated in patients with persistent thyrotoxicosis despite a course of ATD for 1–1.5 years, patients with recurrent or relapsed hyperthyroidism, those who are not candidates for ATDs, and those who prefer this modality. It is contraindicated in pregnant and lactating women, in cases of GO, nodular goiter, or suspected thyroid malignancy [8, 16–18].

Thyroidectomy is indicated in patients with persistent, recurrent, or relapsed thyrotoxicosis after completing the ATDs course, those with goiter, suspected thyroid malignancy, active GO, and pregnant females during the second trimester [8, 17–20]. Defining the relative risks and benefits of each of the two potential definitive treatment options (RAI or thyroidectomy) is crucial for creating evidence-based therapy algorithms. This systematic review and meta-analysis aimed to compare the outcomes of these two treatment options.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed when conducting this study [20].

Selection Strategy and Criteria

The following electronic resources were searched for the required articles: the Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and the PubMed central database.

Two independent researchers (the first and second authors) conducted the search using the following keywords: Graves' disease, primary hyperthyroidism, radioactive iodine, operative treatment, and surgery. Only original works published in English were included in the search. The acquired articles were screened, and then they underwent an eligibility check.

Inclusion Criteria

Original data comparing the outcomes of surgery and RAI for the treatment of adult patients with Graves' disease were eligible for the study.

Exclusion Criteria

Reviews, commentaries, and letters to the editor were excluded. Studies that did not compare operative treatment and RAI in terms of clinical outcome, efficacy, and safety; studies that did not discriminate cases of Graves' disease from other causes of hyperthyroidism; and those involving pediatric patients were also excluded.

Data Extraction, Collection, and Analysis

The included articles were assessed, and the data related to the search was extracted and analyzed. The included studies were evaluated for the bias encountered using the "Cochrane Collaboration tool for assessing the risk of bias."

Summary Measures

The primary outcomes were the difference between the two operations in the perioperative data, the postoperative complications, and the rate of recurrence. The secondary outcomes were the difference in the quality of life (QoL) and the satisfaction rate.

Statistical Analysis

The collected data were tabulated and analyzed. Using the Review Manager Software (RevMan version 5.4, the Cochrane Collaboration, London, United Kingdom), the meta-analysis tests and bias evaluation were carried out. The categorical data were expressed as risk ratios and 95% confidence intervals (CIs), and the numerical data were compared with the differences in means of the effects between the two groups. The I2 statistic's indication of data heterogeneity led to the use of random or fixed-effect models for the analysis.

Results

Initially, researching the electronic resources yielded 2151 records. The remaining records after adjusting for the duplications were 382. After checking the articles' titles and abstracts, an additional 311 articles were excluded. Reading the full texts of the remaining 71 articles resulted in the exclusion of 59 articles. Research in the references of the remaining included articles yielded an additional 4 studies. Finally, sixteen articles were eligible for this analysis [12, 21–35], of which only one was a randomized controlled trial (RCT) [23], two were prospective studies [22, 25], and the remaining thirteen were retrospective [12, 21, 24, 26–35]. The review flow chart is shown in Fig. 1.

The publications included in this analysis covered around four decades of research and were published between 1980 and 2022. Patients with Graves' disease who were scheduled for surgery or RAI made up the study population. The included studies' sample sizes ranged from 13 [25] to 1844 [31], with a total population of 8395. Of those, 2010 (23.9%) patients were treated surgically, and 6385 (76.1%) were treated with RAI. The patients were followed for anything between 6.8 and 94 months (Tables 1 and 2).

In terms of the study outcomes, these focused mostly on the difference between groups in the relapse/

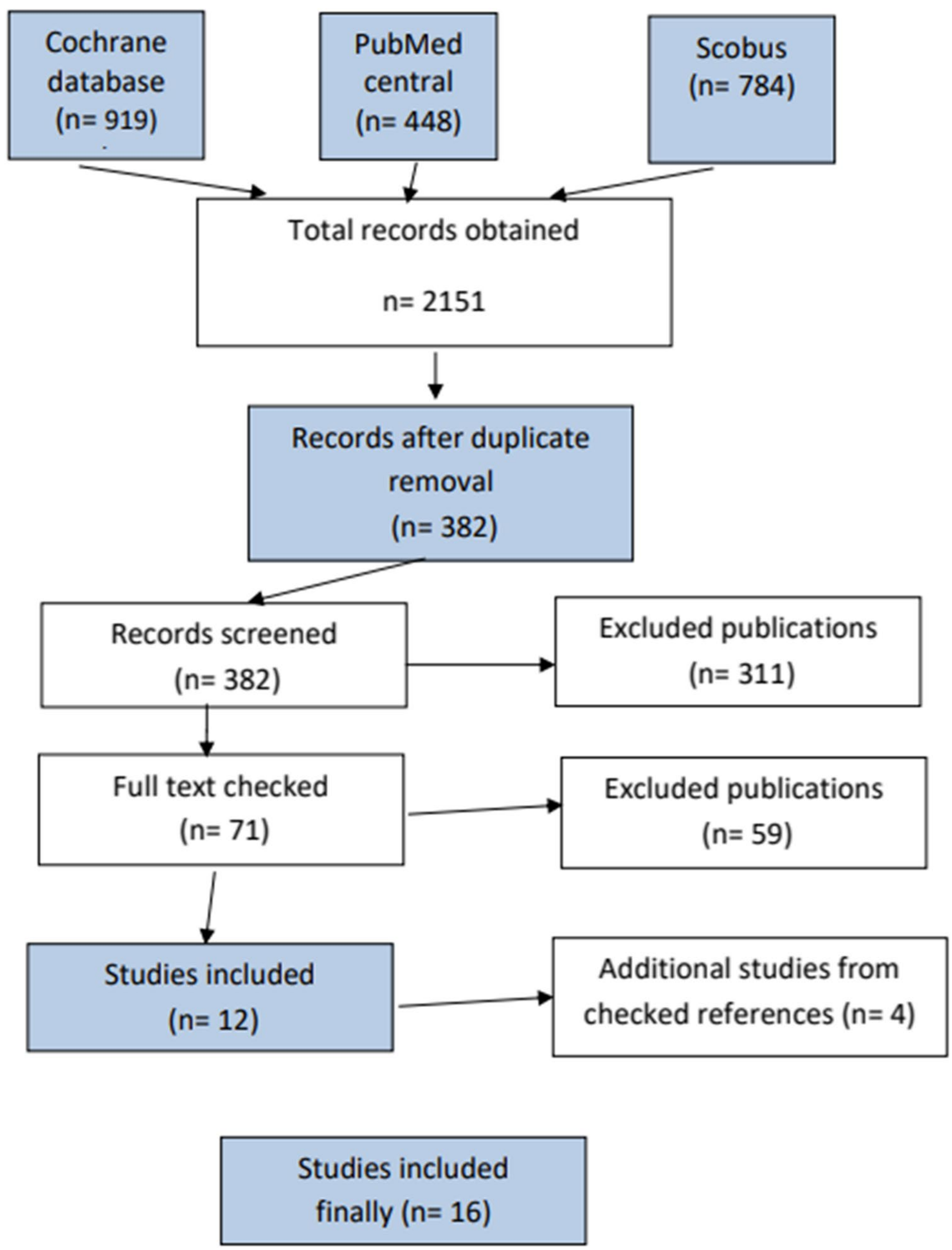

Fig. 1 PRISMA study selection flow chart

Table 1 Sociodemographic characteristics of the studies' population

Study	Design	Place	Study population (S/R)	Age (S/R)	Female % (S/R)	Surgery type	RAI mean dose	Mean follow-up period (S/R)	Prevalence of GO (S/R)
Sugrue et al. (1980)	RS	Ireland	266/43	NR	NR	Subtotal	7.45	60	NR
Berglund et al. (1991)	PS	Sweden	23/5	NR	NR	Subtotal	NR	17/36	NR
Törring et al. (1996)	RCT	Sweden	37/41	NR	84.4/87.8	Subtotal	6.8	42/6.8	NR
Leary et al. (1999)	RS	Ireland	5/38	NR	NR	Subtotal	7.5	40/75	NR
Abraham-Nordling et al. (2005)	RS	Sweden	34/34	33–55	NR	NR	NR	3	29.4/38.2
Tütüncü et al. (2006)	PS	Turkey	6/7	NR	NR	NR	NR	3.3 ± 1.8/6.4 ± 2.6	NR
Kautbally et al. (2012)	RS	Belgium	40/40	38.8 (14.1)/43.2 (16.0)	87.5/82.5	Total	8.3	40	17.5/10
Wu et al. (2017)	RS	USA	85/268	33.1 (15.3)/39.1 (15.3)	83.5/72.5	Total	12.9	NR	29.7/29.6
Sundaresh et al. (2017)	RS	USA	35/664	NR	78.9/76.1	NR	NR	4.3 (3.1)/3.8 (3)	NR
Törring et al. (2019)	RS	Sweden	233/395	35 (29- 46)/54 (45–63)	85/79	NR	NR	NR	NR
Brito et al. (2020)	RS	USA	295/1549	49.4 (13.4)/49.2 (14.1)	88.5/78.4	Total and subtotal	NR	4.5 (2.1)/ 4.7 (2.3)	9.5/5.9
Gibson et al. (2020)	RS	USA	110/54	43.1 (14.8)/45.7 (16.2)	75/70	Total	18.4	3.9 (3.4)/4.0 (2.4)	30/19
Kim et al. (2021)	RS	South Korea	106/968	39 (14)/41 (13)	86/69	Total and subtotal	NR	5.5 ± 3.3/7.2 ± 4.4	44,811
Liu et al. (2021)	RS	China	327/1247	46.88 (1.59)/44.99 (0.67)	72.96/72.93	NR	NR	94/82	NR
Thewjitch-aroen et al. (2021)	RS	Thailand	26/277	36.3 (12.0)	82%	Total and subtotal	15		NR
Liu et al. (2022)	RS	China	395/755	42.34 (13.13)/47.94 (15.34)	81/68.2	NR	NR	79	1.6/4.231

persistency of hyperthyroidism and post-treatment complications. The baseline demographic parameters of the patients were generally comparable in the two groups.

The meta-analysis of 13 studies [12, 21–28, 31–34] that evaluated the post-treatment failure (persistence or relapse) demonstrated higher failure recurrence rates in patients treated with RAI compared to those treated surgically (12.7% vs. 3.1%) with a statistically significant difference ($p = 0.03$) (Fig. 2).

Postoperative complication rates were described in 8 studies [23, 25–28, 30, 31, 34]. Higher rates were noted in the surgically treated group, with

Table 2 Treatment-related complications

	Surgically treated patients ($n = 643$)	RAI-treated patients ($n = 2897$)
Total cases with complication, n (%)	160 (2.5%)	215 (7.4%)
Type of complications: n (%)	• Transient hypocalcemia: 115 (18.1%) • Permanent hypocalcemia: 6 (0.95%) • Hemorrhage, seroma, infection, vocal cord paralysis,dysphonia, and thyrotoxicosis: 39 (6.15%)	• Development or worsening of GO: 174(6%) • Radiation thyroiditis: 21 (0.72%) • Thyrotoxicosis: 14 (0.48%) • Acute hyperthyroid crisis, permanent elevation of TSI, dysphagia, tachycardia, and sialadenitis: 6 (0.21%)

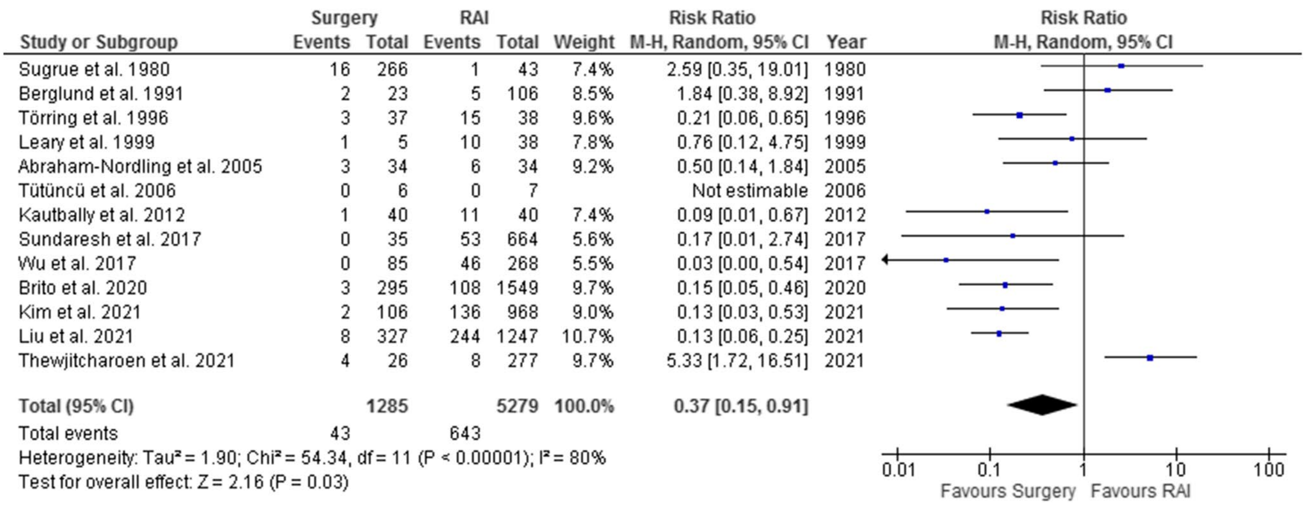

Fig. 2 Forest plot for the treatment failure

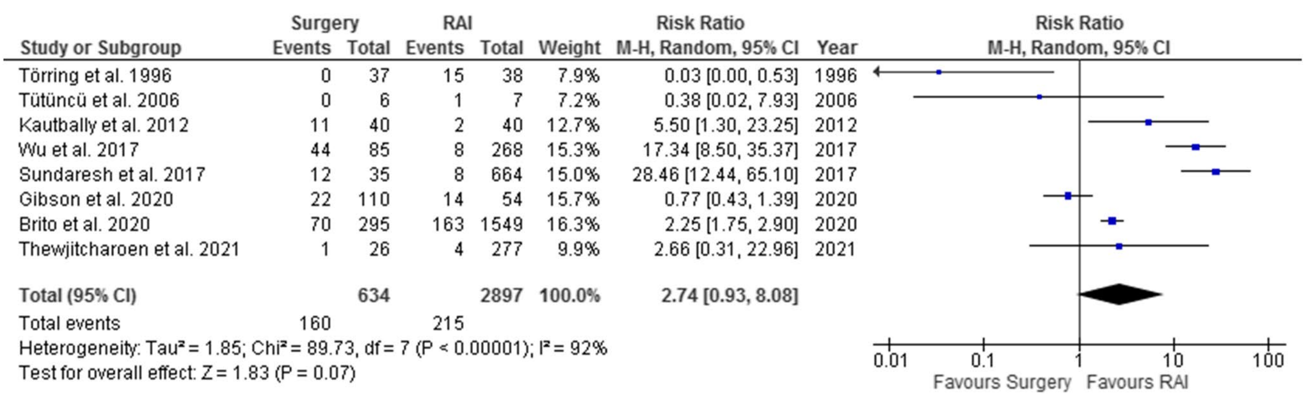

Fig. 3 Forest plot for the prevalence of post-treatment complications

non-statistically significant differences ($p = 0.07$) (Fig. 3). Most of the surgery-related complications were transient and easily controlled, while the majority of complications in the RAI group were developing or worsening orbitopathy (80.5%). Cardiovascular complications were non-significantly higher in the RAI group [12, 30, 32, 35] without statistical significance ($p = 0.1$) (Fig. 4).

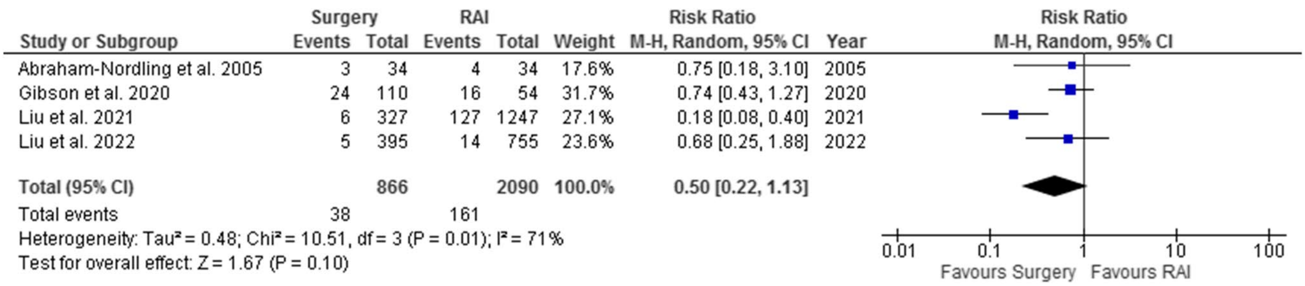

Fig. 4 Forest plot for the prevalence of post-treatment cardiovascular morbidity

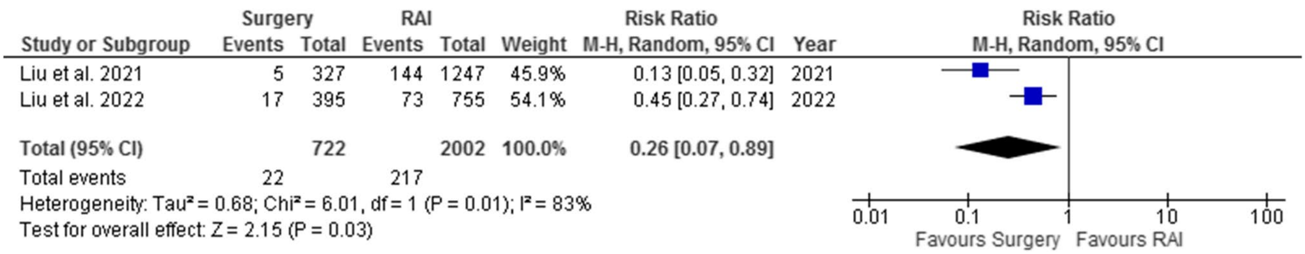

Fig. 5 Forest plot for the prevalence of all-cause mortality

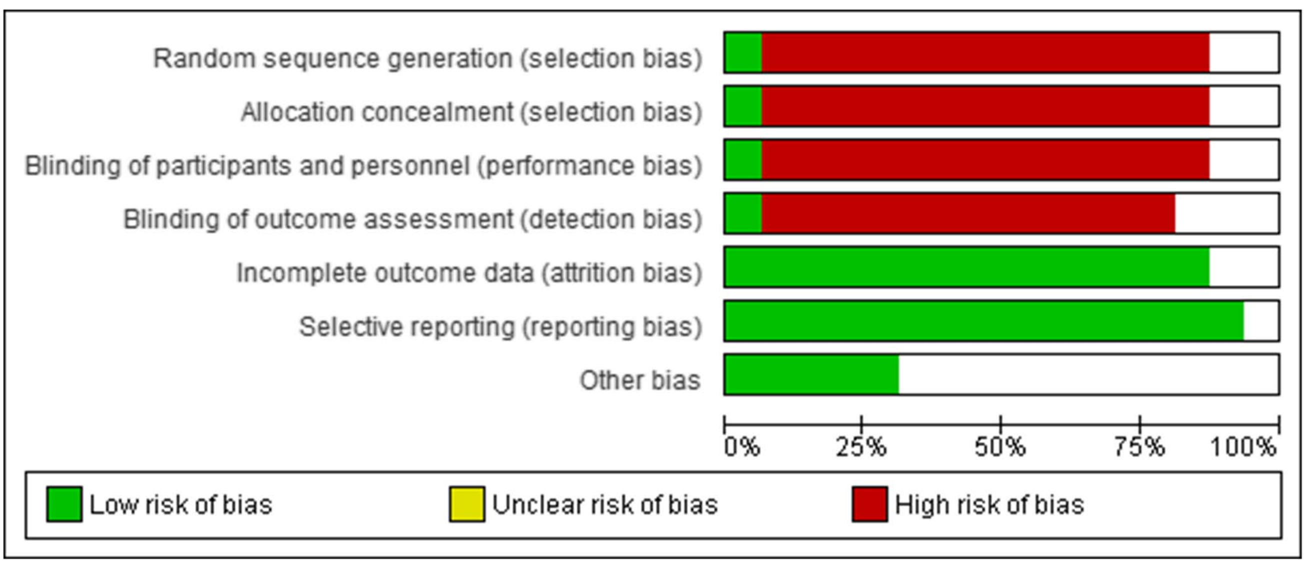

Fig. 6 Risk of bias summary

Only 2 studies mentioned the rates of mortality [32, 34]. Their analysis revealed statistically higher RAI-associated mortality (10.8 *vs.* 3.05, $p = 0.03$) (Fig. 5). The long-term QoL outcome was investigated in two studies [12, 29]. Both concluded that patients undergoing treatment for Graves' hyperthyroidism had worse QoL in comparison with the general population. One of them stated that the type of treatment for GD, whether medical, surgical or by RAI, has little effect on the long-term QoL [12], while the other established that patients treated with RAI had worsened long-term thyroid-specific and general QoL [29].

Risks of Bias

The figure displays the review authors' critical evaluation of the studies' potential for bias and presents their conclusions as percentages across all included studies for each risk of bias item. The primary bias in the included studies was a result of selection and performance bias, which was built into the study design (Fig. 6).

Discussion

Worldwide, GD is the most frequent cause of adult-onset persistent hyperthyroidism. Treatment of Graves' disease is influenced by institutional-based practices, surgical considerations, and the dominance of endocrinologists or nuclear physicians. Moreover, referral for surgical intervention is likely affected by the financial, cultural, and preferences of the physician or the patient.

Thus, a proper decision should be based on dedicated knowledge of the benefits and risks of each choice. Only one systematic review could be found comparing the treatment options for Graves' disease [36]. This was published in 2013, since when some original research studies have been published addressing this topic. Hence, we conducted this analysis in an attempt to provide a summary of the latest available evidence investigating the pros and cons of each treatment option for GD. More specifically, management by thyroidectomy and RAI, being the definitive treatment for GD, was compared in this analysis.

This study demonstrated that surgical treatment overall had a better outcome, with a significantly lower failure rate. These findings are congruent with the previously reported data [36, 37]. Although the surgical option was associated with more frequent complications, most of these complications were transient. Moreover, surgery was associated with statistically less mortality. Despite being drawn from the analysis of two studies only, the significantly higher RAI-related mortality must not be overlooked.

The majority of the RAI-related complications in this analysis were the de novo development or worsening of Grave's ophthalmopathy. This is in line with the meta-analysis conducted by Li et al. [38] which concluded that RAI treatment resulted in a higher risk of the occurrence or worsening of GO. This may be explained by the abrupt elevation of TSH receptor antibodies during the first 6 months after treatment with RAI [39].

RAI was associated with a significantly higher long-term incidence of cardiovascular morbidity. Radiation has been shown to accelerate atherosclerosis and induce reactive oxygen species formation, which is crucial in the development and worsening of cardiovascular disease [40]. Adopting RAI as favored management has emerged following its initial introduction in the 1900s due to the surgery-associated high complication rates and costs at that time. Nevertheless, currently, the pendulum is likely turning back to the re-consideration of operative treatment for GD. It has been assumed that RAI may lead to higher malignancy rates [41].

The thyroidectomy option is advantageous by treating GD immediately and definitively with avoidance of the risks related to the long-term administration of ATD or RAI. However, thyroidectomy is the least preferred choice for hyperthyroidism treatment [42–45]. This is attributed to concerns regarding the potential postoperative complications, such as recurrent laryngeal nerve (RLN) injury, hypoparathyroidism, as well as permanent hypothyroidism, and neck scarring.

Advances in operative procedures, including the remote-access thyroidectomy and intraoperative monitoring of the RLN, together with the present awareness of the RAI-associated risks, raise the need to shed light on thyroidectomy as the main definite treatment for GD, by considering RAI only for cases where patients with GD are contraindicated to surgery.

This study is strengthened by summing up evidence driven by studies comparing the two treatment options in a large cohort over about 4 decades, extending until the year 2022. The work is limited by that most of the included studies were retrospective analyses. The study is also limited by not addressing the effect of the number of RAI doses or the extent of thyroidectomy on the outcome. However, we think that this is beyond the scope of this study.

Conclusion

This review and meta-analysis comparing surgery and radioactive iodine for the treatment of Grave's disease from 16 well-conducted trials has shown that although surgery viz. total thyroidectomy was less frequently utilized for the treatment of Grave's disease, it controlled the symptoms with greater success and without any worsening of Grave's ophthalmopathy.

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Declarations

Conflict of Interest The authors declare no competing interests.

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