RESEARCH

The effect of radioactive iodine treatment for differentiated thyroid cancer on male gonadal function: a meta-analysis

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Abstract

Purpose: The aim was to investigate the effect of radioactive iodine (RAI) treatment for differentiated thyroid cancer (DTC) on male gonadal function.

Methods: PubMed, Embase, Web of Science, OVID, Scopus, and Wanfang databases were searched up to June 10, 2022, to identify published studies related to RAI and male gonadal function. ReviewManager version 5.4.1 software was used to calculate mean differences (MDs) with 95% CIs.

Results: Initially, 1958 articles were retrieved from the databases, and 6 articles were included in the quantitative analysis. The meta-analysis results showed that follicle-stimulating hormone (FSH) increased when the follow-up duration was ≥12 months after RAI, but the difference was not statistically significant (MD = −2.64, 95% CI = (−5.61, 0.33), P = 0.08). But the results of the subgroup analysis showed that when the follow-up time was ≤6 months, FSH levels were significantly higher after RAI (MD = −7.65, 95% CI = (−13.95, −1.34), P = 0.02). The level of inhibin B was significantly lower at ≥12 months and ≤6 months after RAI (MD = 66.38, 95% CI = (8.39, 124.37), P = 0.02) and (MD = 116.27, 95% CI = (43.56, 188.98), P = 0.002). Additionally, luteinizing hormone (LH) and testosterone have similar results – that is, LH and testosterone levels were higher after RAI, but the difference was not statistically significant (MD = −0.87, 95% CI = (−2.04, 0.30), P = 0.15) and (MD = −1.69, 95% CI = (−7.29, 3.90), P = 0.55).

Conclusions: Male gonadal function may be temporarily impaired within 6 months after RAI but may return to normal levels afterward.

Introduction

Thyroid cancer (TC) is the most common endocrine tumor, and its global incidence is increasing annually; however, the global incidence among females is 10.1 per 100,000, which is three times higher than the incidence among males. TC among male patients tends to be more aggressive at the time of diagnosis and may be associated with a poor prognosis (1, 2). This implies a higher TC risk stratification in men.

Radioactive iodine therapy (RAI or 131I therapy) is the main postoperative treatment for differentiated thyroid carcinoma (DTC). It is primarily used for remnant ablation, and it prevents recurrent disease in intermediate- or high-risk patients or treats residual or metastatic disease (3). Furthermore, RAI can reduce the rate of local recurrence after thyroidecomy or subtotal thyroidecomy in patients with DTC and can significantly improve the 10-year survival rate in patients with DTC. Studies have shown that the 5-year survival rate of patients with papillary thyroid carcinoma (PTC) in DTC can reach 100%, and the...
observed worldwide TC-related mortality has steadily decreased (1), suggesting that they have a good prognosis and still have long survival after treatment. Therefore, it is important to consider whether RAI has an impact on the quality of life of patients.

Previous studies have shown that the use of $^{131}$I is associated with the risk of radiation damage to the body. This damage may affect multiple organs and systems, and it is categorized as early and late adverse reactions. Early adverse reactions mainly include acute salivary gland injury, thyroiditis, gastroenteritis, etc. Late adverse reactions mainly include lung injury and reproductive system injury, leading to a second primary tumor (4, 5).

Compared with elderly patients, young DTC patients (age 15–39) are more likely to receive RAI after surgery, and most of them have fertility needs, so there should be an increased awareness regarding the impact of RAI on the survival of such patients (6). Because receiving RAI may threaten male patients’ testicular function and even affect fertility, it is crucial to understand the impact of RAI on gonadal function in this population.

Although previous domestic and foreign studies focused on this effect and reported the effect of RAI on sex hormones and semen quality parameters in male DTC patients (7, 8, 9, 10, 11, 12, 14), the sample size of single studies is small, and the differences between studies are large. To date, no meta-analysis has examined the effects of RAI treatment on gonadal function in male DTC patients. Therefore, the current meta-analysis aimed to systematically review a number of eligible studies to investigate the effects of RAI on gonadal function in men with DTC.

Materials and methods

Retrieval strategy

The PubMed, Embase, Web of Science, OVID, Scopus, and Wanfang databases were searched from inception to June 2022 to identify published studies related to radioiodine therapy and male gonadal function. To retrieve all the relevant studies, the following descriptors were used to build the search strategies: radioactive iodine therapy, $^{131}$I, iodine 131, RAI, iodine, radioisotope, iodine radioisotope, thyroid cancer, thyroid carcinoma, male, testis, sperm, follicle-stimulating hormone, thyroid neoplasm, gonadotropins, luteinizing hormone, testosterone, among others. The search terms were combined with the Boolean operators AND and OR.

Inclusion and exclusion criteria for the studies

Inclusion criteria: Studies on the effects of RAI on gonadal function in men with DTC were included. These studies provided baseline indicators of gonadal function measures and posttreatment outcome indicators in men before RAI. Study outcomes included the following: (i) any measure of sperm, including sperm concentration, total sperm count, semen volume, sperm viability, or sperm morphology; (ii) any measurement follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, free testosterone, or inhibin B. There were no restrictions on the language, date of publication, or status of the study.

Exclusion criteria: case reports, reviews, and animal studies were excluded. Studies that included non-thyroid cancer patients, such as those with benign thyroid disease, were also excluded. Studies that only assessed semen or reproductive hormone levels after RAI were excluded. Studies in which fertility was the only outcome were excluded. Studies of populations primarily involving men with specific diseases or organic disorders of the reproductive organs, including varicocele, abnormal testicular position, testicular torsion, and a history of severe genital trauma, were excluded.

Study selection and data extraction

Two reviewers independently extracted the relevant data from each study and recorded the information in a standardized form. Disagreements during data extraction were resolved by consensus or by consulting a third investigator. The main extracted data included sex hormones (including FSH, LH, inhibin B, testosterone, etc.) and semen parameters (including sperm concentration, sperm motility, and percentage of normal sperm morphology).

Risk of bias assessment

The authors independently evaluate the methodological quality of the included studies using the Cochrane Collaboration’s risk of bias tool. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the included literature, with scores $\geq 7$ considered reliable and scores $< 7$ considered unreliable.

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Statistical analysis

Meta-analysis was performed by using ReviewManager version 5.4.1 software. For some of the included studies (7), GetData Graph Digitizer was used to extract the data from the graphs. ReviewManager version 5.4.1 software was used to calculate mean differences (MDs) with 95% CIs. Heterogeneity was assessed by the likelihood ratio $I^2$ index. $P < .05$ or $I^2 > 50\%$ suggested heterogeneity. If heterogeneity was observed, a random effects model (REM) was used for the primary meta-analysis to obtain a summary estimate with 95% CIs. Otherwise, a fixed effects model was used. Funnel plots were generated to detect publication bias when more than 10 trials were identified for a particular outcome.

Results

Literature search results

In total, 1958 articles were retrieved after a comprehensive database search. After eliminating duplicate studies, 1571 articles remained for screening. A total of 1536 were excluded based on title and abstract screening, and 29 articles were excluded after full-text assessment. Ultimately, six articles were included in this systematic review and meta-analysis. The study selection process is displayed in Fig. 1.

Meta-analysis results

Effect of RAI on male sex hormones

Among the six studies, five studies examined the effect of RAI on FSH, four studies examined the effect of RAI on LH, three studies examined the effect of RAI on testosterone, and two studies examined the effect of RAI on inhibin B. The $I^2$ test suggested that all sex hormone-related outcome indicators showed large interstudy heterogeneity, so a REM was adopted. Meta-analysis showed that FSH increased at $\geq 12$ months of follow-up after RAI, but the difference was not statistically significant (MD = $-2.64$, 95% CI = $(-5.61, 0.33)$, $P = 0.08$). Similar results were also shown for LH and testosterone; that is, after 1 year of follow-up, LH and testosterone were higher than those before RAI, but the difference was not statistically significant (MD = $-0.87$, 95% CI = $(-2.04, 0.30)$, $P = 0.15$ and MD = $-1.69$, 95% CI = $(-7.29, 3.90)$, $P = 0.55$). In contrast, the two studies that examined inhibin B showed a statistically significant reduction in inhibin B levels 1 year after RAI compared to pretreatment levels (MD = 66.38, 95% CI = $(8.39, 124.37)$, $P = 0.02$) (Fig. 2, 3, 4, and 5).

Effect of RAI on semen-related parameters

Few studies have examined parameters related to semen quality. Three studies examined the effect of RAI on sperm motility, and three studies examined the effect of RAI on inhibin B. The $I^2$ test suggested that all sex hormone-related outcome indicators showed large interstudy heterogeneity, so a REM was adopted. Meta-analysis showed that FSH increased at $\geq 12$ months of follow-up after RAI, but the difference was not statistically significant (MD = $-2.64$, 95% CI = $(-5.61, 0.33)$, $P = 0.08$). Similar results were also shown for LH and testosterone; that is, after 1 year of follow-up, LH and testosterone were higher than those before RAI, but the difference was not statistically significant (MD = $-0.87$, 95% CI = $(-2.04, 0.30)$, $P = 0.15$ and MD = $-1.69$, 95% CI = $(-7.29, 3.90)$, $P = 0.55$). In contrast, the two studies that examined inhibin B showed a statistically significant reduction in inhibin B levels 1 year after RAI compared to pretreatment levels (MD = 66.38, 95% CI = $(8.39, 124.37)$, $P = 0.02$) (Fig. 2, 3, 4, and 5).
of normal sperm morphology, and the follow-up time was significantly different (6 months and 12 months, respectively), which may have an impact on the combined results; therefore, a pooled analysis was not conducted (Fig. 6 and 7).

**Subgroup analysis**

Some studies tested various indicators at different time points. Therefore, REV was used for subgroup analysis, and ≤6 months of each study was extracted, with the follow-up time as the grouping marker. According to the data characteristics, they were divided into two groups: ≤6 months and ≥12 months, and subgroup analysis was conducted. The results showed that when the follow-up time was ≤6 months, posttreatment FSH was significantly higher than that before RAI (MD=−7.65, 95% CI (−13.95, 1.34), P=0.02) (Fig. 2). Moreover, inhibin B was also lower than that before RAI which the difference was statistically significant (MD=116.27, 95% CI=(43.56, 188.98), P=0.002) (Fig. 5). However, posttreatment LH was non significantly higher than that before RAI ≤6 months after RAI (MD=−1.13, 95% CI= (−2.49, 0.24), P=0.11) (Fig. 3).

**Publication bias analysis**

Publication bias was not analysed because of the small number of studies involved in the indicators studied.

**Discussion**

RAI has been widely used postoperatively in DTC patients for remnant ablation and can significantly

### Table 1  Basic characteristics of the included literature.

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Age (years)</th>
<th>Patients (n)</th>
<th>Duration of follow-up (months)</th>
<th>Dosage of RAI</th>
<th>Research indicators</th>
<th>NOS scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maria Wichers, 2000</td>
<td>49 (23–73)</td>
<td>22</td>
<td>0, 3, 6, 12, 18</td>
<td>9.8 ± 0.89 GBq</td>
<td>①②③④</td>
<td>8</td>
</tr>
<tr>
<td>Stephen Hyer, 2002</td>
<td>36 (23–39)</td>
<td>7</td>
<td>0, 12</td>
<td>3 GBq</td>
<td>①</td>
<td>8</td>
</tr>
<tr>
<td>Pedro W S Rosário, 2006</td>
<td>45 ± 9.6</td>
<td>52</td>
<td>0, 6, 12, 18</td>
<td>3.7-5.5GBq</td>
<td>①</td>
<td>8</td>
</tr>
<tr>
<td>Domenico Canale, 2015</td>
<td>30.8 ± 5.4</td>
<td>22</td>
<td>0, 6, 12</td>
<td>−32190 MBq</td>
<td>①</td>
<td>8</td>
</tr>
<tr>
<td>N Bourcigaux, 2018</td>
<td>18–55</td>
<td>24</td>
<td>0, 3, 13</td>
<td>3.7 GBq</td>
<td>①</td>
<td>8</td>
</tr>
<tr>
<td>Peng Liang, 2020</td>
<td>18–40</td>
<td>22</td>
<td>0, 6</td>
<td>5.55 GBq</td>
<td>①</td>
<td>8</td>
</tr>
</tbody>
</table>

① refers to follicle-stimulating hormone (FSH); ② refers to luteinizing hormone (LH); ③ refers to testosterone (T); ④ refers to inhibin B; ⑤ refers to sperm concentration; ⑥ refers to sperm motility; ⑦ refers to morphologically normal forms.

NOS, Newcastle-Ottawa Scale.

**Figure 2**

Meta-analysis forest plot of subgroup analysis of the effect of RAI on follicle-stimulating hormone (FSH) at different follow-up times.
improve the 5-year and 10-year survival rates of DTC patients. RAI leads to unavoidable side effects on patients, including radiation to the gonads. Compared with female patients, male DTC patients may be more affected by this side effect because the germ-generating epithelium in the testis, especially the spermatogonium, is one of the most sensitive tissues to radiation. Low doses of radiation may lead to serious impairment of its function (8, 13). After 131I treatment in male DTC patients, the main sources of RAI's influence on testicular function are iodine protein in blood circulation and 131I in the bladder and intestine. As people have increasingly higher demands on quality of life, especially with regard to fertility, the side effects of RAI on gonadal function should be taken into account.

The results of this meta-analysis showed that RAI had no significant effect on parameters related to sex hormones and sperm quality except for inhibin B when the follow-up time was at least 12 months after RAI treatment, which was consistent with the results of most studies. However, subgroup analysis showed that inhibin B levels were still decreased after RAI treatment when the follow-up time was shortened to 6 months or less. In addition, the level of FSH increased, but RAI did not lead to a significant difference in LH levels. This indicates that the spermatogenic function of patients is impaired to some extent after RAI, but this impairment may be only temporary and can return to normal levels after more than 1 year or more after treatment. This is similar to the study results of Pacini et al. (14); six to twelve months after 131I treatment, some patients showed a temporarily higher than normal value, and the normal level could be recovered in the following months, indicating that 131I treatment for thyroid cancer is associated with temporary impairment of testicular germinal cell function. Importantly, previous studies (15, 16, 17, 18) have shown that inhibin B, along with FSH, are important markers of the competence of...
Sertoli cells and spermatogenesis in a man. Furthermore, Jankowska K showed that reduced inhibin-B concentrations were correlated with sperm count and FSH levels. High levels of FSH and low levels of inhibin B clearly indicate impaired spermatogenic function (19). However, due to few previous studies on inhibin B, different from FSH, the results of this meta-analysis suggest that inhibin-B decreases after RAI treatment, and this conclusion needs to be supported by further research and verification.

Furthermore, since LH acts on Leydig cells and promotes testosterone synthesis through the action of a series of steroid synthases, testicular Leydig cell function can be monitored through testosterone and LH serum levels. That is, when Leydig cells are damaged, testosterone secretion is reduced and the pituitary gland is stimulated to secrete LH through a feedback mechanism. However, studies have shown that the Leydig cells of the testis are more resistant to radiation than the reproductive epithelium and will only be damaged by high doses of therapeutic radiation (12, 20). However, in the results of this study, the differences in changes in LH and testosterone levels before and after RAI treatment were not statistically significant, even in subgroup analysis. This may suggest that the function of Leydig cells is not impaired after RAI, but whether there will be different results when the dose of RAI is increased in patients may require further studies to confirm.

In addition, the results of this meta-analysis showed that regardless of whether the follow-up time was ≥12 months or ≤6 months, the effects of RAI on sperm

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**Figure 5**
Meta-analysis forest plot of subgroup analysis of the effect of RAI on inhibin B at different follow-up times.

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**Figure 6**
Meta-analysis forest plots of subgroup analysis of the effect of RAI on sperm concentration at different follow-up times.
concentration and sperm motility were statistically significant compared with the changes before treatment. In a recent study, Nies et al. (21) conducted a multicenter study on the fertility of male DTC patients with a cumulative dose ≥3.7 GBq and follow-up time ≥2 years after RAI, and the results showed that the long-term semen quality of the patients was normal. The proportion of patients with semen quality parameter scores below the 10th percentile did not differ from that of the general population. Therefore, it is suggested that the administration of RAI will not impair long-term male fertility in DTC patients receiving 100 mCi/3.7 GBq or higher doses. However, Handelsman et al. (22) first described a 32-year-old thyroid cancer patient in 1980 who developed azoospermia within 18 months after three 131I (cumulative dose 12.9 GBq). The semen analysis of a small number of patients by Pacini et al. (14) showed that the number of sperm with normal movement continued to decrease. Canale et al., Rosário et al., Pacini et al., and Handelsman & Turtle (9, 10, 14, 23) reported persistent impairment in elevated FSH or reduced sperm quality at follow-up, particularly in patients receiving higher doses or multiple RAI treatments. Therefore, conflicting findings exist regarding whether RAI has an effect on semen quality; this relationship may be related to the dose of RAI given and the length of follow-up after treatment. Additional long-term prospective studies are needed to verify these effects.

The limitations of this study are as follows: the number of studies collected is small, the research indicators vary among different studies, the number of sample cases is small, most of the research indicators have significant heterogeneity, and the source of heterogeneity is not clear. In addition, due to a lack of data, subgroup analysis of thyroid function status and RAI dose received by patients was not performed in this study, which needs to be included in future prospective studies with larger samples.

In conclusion, increased FSH levels and decreased inhibin-B levels were observed at 6 months after RAI, reflecting the damage to spermatogenesis caused by RAI. However, it returned to normal levels after a follow-up longer than 12 months. This suggests that male gonadal function may be temporarily impaired after RAI but may return to normal levels. However, it is not clear whether there is a dose-dependent effect of RAI on the gonadal function of these patients. Large-sample and high-quality studies are still needed to provide more clinical reference and a theoretical basis for clarifying whether RAI can cause damage to male gonadal function to guide the development of personalized treatment plans for RAI.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.

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