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Long-term male fertility after treatment with radioactive iodine for differentiated thyroid carcinoma

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Abstract

Context: Whilst radioactive iodine (RAI) is often administered in the treatment for differentiated thyroid carcinoma (DTC), long-term data on male fertility after RAI are scarce.
Objective: To evaluate long-term male fertility after RAI for DTC, and to compare semen quality before and after RAI.
Design, setting, and patients: Multicenter study including males with DTC ≥2 years after their final RAI treatment with a cumulative activity of ≥3.7 GBq.
Main outcome measure(s): Semen analysis, hormonal evaluation, and a fertility-focused questionnaire. Cut-off scores for 'low semen quality' were based on reference values of the general population as defined by the World Health Organization (WHO).
Results: Fifty-one participants had a median age of 40.5 (interquartile range (IQR): 34.0–49.6) years upon evaluation and a median follow-up of 5.8 (IQR: 3.0–9.5) years after their last RAI administration. The median cumulative administered activity of RAI was 7.4 (range: 3.7–23.3) GBq. The proportion of males with a low semen volume, concentration, progressive motility, or total motile sperm count did not differ from the 10th percentile cut-off of a general population (P = 0.500, P = 0.131, P = 0.094, and P = 0.500, respectively). Cryopreserved semen was used by 1 participant of the 20 who had preserved semen.
Conclusions: Participants had a normal long-term semen quality. The proportion of participants with low semen quality parameters scoring below the 10th percentile did not differ from the general population. Cryopreservation of semen of males with DTC is not crucial for conceiving a child after RAI administration but may be considered in individual cases.

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Introduction

For the majority of patients with differentiated thyroid carcinoma (DTC), treatment consists of administration of radioactive iodine (RAI) (1). Although increasing emphasis has been placed on its adverse effects on female fertility (2, 3, 4), little research has been performed regarding the effect of RAI on fertility in males. Knowledge regarding the effect of RAI on male fertility is based on short-term studies, small sample sizes, or a limited evaluation of fertility (i.e. evaluating only blood parameters).

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Damage to testicular cells induced by the β and γ radiation of RAI causes transient subfertility (5, 6, 7, 8, 9, 10, 11). Studies have been performed up to 18 months after RAI treatment and show that administration of RAI causes a decreased semen quality, elevated levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and decreased levels of testosterone (5, 7, 8, 9, 10, 11, 12, 13). However, previous studies have also shown that males treated with RAI for DTC were later able to conceive healthy children (7, 14, 15). Long-term data and studies evaluating semen in larger study groups are scarce.

The short-term impairment of male fertility has been described as dose-dependent (5, 9, 10, 11). Therefore, fertility preservation has been recommended for patients who receive multiple or high-dose treatment because they may be at greater risk for impairment of fertility (1).

The primary aim of this study was to evaluate long-term male fertility after administration of a high cumulative activity of RAI for DTC by evaluating semen quality, serum endocrine markers, and reproductive characteristics. The secondary aim was to compare semen quality before and after treatment with RAI.

Subjects and methods

This multicenter study was initiated by the University Medical Center Groningen (UMCG) in the Netherlands. Its institutional review board approved the protocol on behalf of all participating centers. The study was registered in the Netherlands Trial Register (NL5966). All participants signed written informed consent before participation.

Participants

In local databases, we identified eligible males: aged ≥18 years, diagnosed with DTC from January 2000, at least 2 years after their final RAI treatment, and a cumulative administered activity of RAI ≥100 mCi/3.7 GBq. Participants were excluded if they used testosterone supplementation, chemotherapy, or anabolic steroids; if they had diseases or treatments potentially associated with impairment of semen quality (e.g. vasectomy); if they were currently under treatment (i.e. tyrosine kinase inhibitors, radiotherapy) for progressive DTC; if they had received RAI only after use of recombinant human thyroid-stimulating hormone (rhTSH); or if they were non-compliant with thyroid hormone substitution (i.e. several measurements of TSH >10 mU/L in the year before participation). If a participant had a body temperature >38.5°C in the 3 months before the semen analysis, the semen analysis was postponed. Participants were included from May 2017 to March 2019.

Semen analysis

Participants were asked to abstain from ejaculation for a period of 2–4 days before participation. Semen samples were obtained through masturbation and were produced at the fertility departments of each participating center. Semen analysis took place within 1 h after production, and analyses were performed according to the laboratory manual of the World Health Organization (WHO), with additional guidelines provided by Björndahl *et al.* and Barratt *et al.* (16, 17, 18). Semen samples were evaluated for pH, viscosity (scored as thin liquid, moderately viscous, or very viscous), volume (in mL), concentration of spermatozoa (per mL), motility (percentage of rapid progressive forward, slow progressive forward, non-progressive, and immotile sperm cells), round cells (per mL), and morphology (percentage of sperm cells with normal morphology). Motility was assessed at 37°C (using a warmed microscope stage), except for one center where motility was assessed at room temperature for logistic reasons. Assessment of the percentage of sperm of cells with a normal morphology was performed centrally in the UMCG according to Tygerberg criteria (19) and using Papanicolaou staining.

Blood sampling and hormonal measurements

Blood was drawn from participants before noon, and samples were stored in a −80°C environment. FSH, LH, total and free testosterone, albumin, sex hormone-binding globulin, TSH, and free thyroxine (FT4) were measured centrally in the UMCG. Assay characteristics are shown in Supplementary Table 1 (see section on supplementary materials given at the end of this article) and reference ranges of the assays are reported in the relevant tables.

Questionnaire

Each participant was asked to complete a questionnaire regarding general health (medical history, use of drugs, intoxications, height, and weight), reproductive health, and reproductive characteristics (conceived pregnancies and outcomes, fertility treatment, and fertility preservation).

Medical records and results of other semen analysis

Medical records were evaluated for diagnostic, treatment, and follow-up characteristics, and information regarding semen cryopreservation (if performed).

Study definitions

Date of diagnosis was defined as the first histological confirmation of DTC. Age upon evaluation was defined as age upon semen analysis. Follow-up was defined as time from diagnosis and last RAI administration to semen analysis. The eighth edition of the American Joint Committee on Cancer (AJCC) tumor node metastasis scoring system was used (20). Total sperm count (TSC) was defined as the product of the concentration and volume of the ejaculate. Total motile sperm count (TMSC) was defined as the product of the volume, concentration, and percentage of progressive spermatozoa of the ejaculate, divided by 100%. If no spermatozoa were present in the ejaculate, this was defined as azoospermia. Oligozoospermia was defined as a semen concentration below 15 million/mL, severe oligozoospermia was defined as a semen concentration below 1 million/mL. Asthenozoospermia was noted if the percentage of progressive motile spermatozoa was below 32.

Normal semen quality has a wide range, and only having low semen quality has clinical consequences. We determined cut-off values for having low semen quality based on the reference values of a general population for semen characteristics, provided by the WHO (21). 'Low semen quality' meant a score below the 10th percentile. If this percentage doubled (i.e. 20%), we considered it to be a clinically relevant finding.

Statistical analysis

Variables were described using median and interquartile range (IQR), unless stated otherwise. In case of protocol violations, these observations were excluded from analysis. Binomial tests evaluated whether the proportion of participants having low semen quality (parameters) significantly differed from the 10% in a general population (21). The Clopper–Pearson binomial proportion 95% CI was used to show estimated proportions. We also evaluated whether the results changed when we performed binominal tests based on the 5th or 25th percentiles.

Using Mann–Whitney U tests, age upon evaluation, BMI, follow-up period since the last RAI administration, and the cumulative activity of RAI were compared between the groups that scored below or above the 10th percentile and between participants who did or did not conceive children. We evaluated whether the proportion of participants scoring below cut-off values differed depending on whether they had undergone single or multiple administrations of RAI; for this we used chi-square tests or Fisher's exact tests (if >20% of the cells had an expected count <5).

The Wilcoxon signed-rank test tested the difference between the median TMSC upon semen cryopreservation and during follow-up. For this analysis, we evaluated only participants who cryopreserved semen before their first administration of RAI. If semen was preserved multiple times before RAI, we calculated the median TMSC.

A P value ≤0.05 was considered statistically significant. For statistical analyses, IBM SPSS Statistics version 23.0.0.3 for Windows (IBM) and Microsoft Excel Professional Plus 2016 were used.

Results

Participants

We identified 236 males who met the inclusion criteria (Fig. 1). Seventy-one males met exclusion criteria (vasectomy (n = 25), comorbidity (n = 24), other reason (n = 22)). Of the 165 eligible males, 51 (30.9%) completed their participation.

All 51 participants had the Dutch nationality. The median age of participants upon evaluation was 40.5 (IQR 34.0–49.6) years, with a median age at diagnosis of 33.7 (IQR 26.9–39.8) years. Participants had a median BMI of 26.8 (IQR 24.0–29.4) kg/m^2. BMI was unknown in two participants. At the moment of evaluation, 1 participant (2.0%) was an active smoker, 13 (25.5%) participants had previously smoked, and 32 (62.7%) had never smoked. The smoking status of five participants was unknown. Four participants reported having had an orchidopexy due to cryptorchidism. One participant reported having used anabolic steroids; his latest use had been 3 years before evaluation. One participant had been treated with testosterone during puberty to decrease his final height; he participated in the study at the age of 36. The participants with cryptorchidism, a history of anabolic steroid use, and testosterone treatment did not have abnormal semen quality upon study participation.

Treatment and pathology characteristics

Treatment characteristics of the participants are shown in Supplementary Table 2. All participants were treated

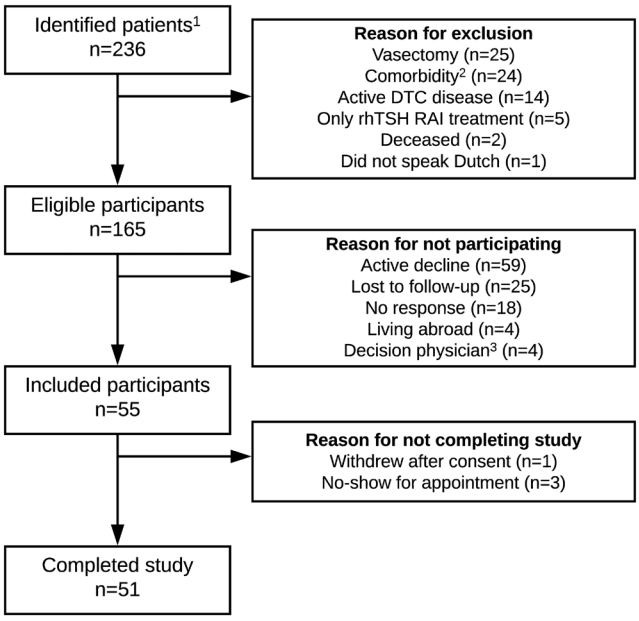

Figure 1

Flowchart of inclusion. [1]All identified males aged 18–60 years old, diagnosed with differentiated thyroid carcinoma, treated with a cumulative activity of radioactive iodine ≥100 mCi/3.7 GBq, and at least 2 years after their last treatment with radioactive iodine. [2]Comorbidities: malignancy or current or previous treatment with drugs impairing fertility (*n* = 16), erectile dysfunction (*n* = 3), psychiatric disorder interfering with ability to participate (*n* = 2), spinal cord injury/paraplegia (*n* = 1), treatment with testosterone (*n* = 1), and mentally disabled (*n* = 1). [3]Decision physician: vulnerable patient (*n* = 3) and non-compliant to therapy (*n* = 1). DTC, differentiated thyroid carcinoma; rhTSH, recombinant human thyrotropin; RAI, radioactive iodine.

with a total thyroidectomy, 32 of whom (62.7%) had an initial lymph node dissection. Most participants received one administration of RAI (*n* = 26, 51.0%). Seventeen participants (33.3%) received two RAI administrations, four participants (7.8%) received three RAI administrations, and four participants (7.8%) were treated with four RAI administrations. The median cumulative activity of RAI was 7.4 (IQR: 5.6–11.1; range: 3.7–23.3) GBq. Twenty out of 51 patients received a cumulative activity of RAI of 11.1 GBq or more. Median follow-up since the last RAI administration was 5.8 (IQR: 3.0–9.5) years.

Papillary thyroid carcinoma was the most common histology type (*n* = 49, 96.1%). One participant (2.0%) had follicular thyroid carcinoma and one (2.0%) was diagnosed with Hürthle cell carcinoma. T2 and T3a/T3b were the most common tumor stages (39.2 and 35.3%, respectively). Thirty participants (58.8%) had metastases of DTC to the regional lymph nodes, and three (5.9%) had lung metastases (Supplementary Table 3).

Semen analysis

The median abstinence period was 4 (IQR: 3–6) days. Semen analysis took place within 1 h after ejaculation for 46 (90.2%) participants. Semen samples were analyzed between 1 and 2 h in four participants. Time to analysis can affect the motility of spermatozoa, but the progressive motility percentages did not significantly differ between semen samples analyzed within 1 h and samples analyzed between 1 and 2 h (P = 0.447). Time to analysis was unknown in one participant.

Semen characteristics of the participants are shown in Supplementary Table 4. The median TSC and TMSC of the participants was 192 and 116 million, respectively. For the general population, as defined by the WHO, these numbers are 196 and 117 million, respectively (21). None of the participants had azoospermia. Eight participants (15.7%) had oligozoospermia, of whom one (2.0%) had severe oligozoospermia. Lastly, asthenozoospermia was noted in eight participants (15.7%).

The proportion of participants scoring below the 10th percentile cut-off point for TMSC was 10.0% (*n* = 4 out of 40 participants with evaluable TMSC). This percentage was lower than the 20% that we defined as clinically relevant. A binomial test showed that this proportion did not significantly differ from the 10% in the general population (P = 0.500) (21). The proportions of participants scoring below the 10th percentile cut-off point for volume, concentration, and progressive motile spermatozoa were 9.8, 15.7, and 17.5%, respectively (see Table 1). The binomial test showed that these proportions did not differ significantly from the 10% in a general population (P = 0.500, P = 0.131, and P = 0.094, respectively) (21).

When cut-off points for volume, concentration, progressive motility, TSC, and TMSC were based on the 5th or 25th percentile of the general population, the proportion of males with low concentration (11.8 and 37.3%, respectively) and low progressive motility (15.0 and 37.5% respectively) was statistically significantly higher in the studied participants. However, the proportion of participants with low volume, low TSC, or low TMSC did not differ from the general population for the 5th percentile, nor for the 25th percentile. Since the TSC and TMSC reflect a combined result of volume, concentration, and motility, the mutual compensation between the latter

Table 1 Semen characteristics of 51 participants treated with radioactive iodine for differentiated thyroid carcinoma compared to the 10th percentile of reference values based on a general population.[1]

10th percentile cut-off points	Participants, *n* (%)	*P*-value	95% CI of estimated proportion
Volume (mL)		0.500[2]	
≥1.6 mL	46 (90.2)		
<1.6 mL	5 (9.8)		(3.3–21.4%)
Concentration (×10^6)		0.131[2]	
≥17	43 (84.3)		
<17	8 (15.7)		(7.0–28.6%)
Progressive motility[3] (%)		0.094[2]	
≥ 39%	33 (82.5)		
< 39%	7 (17.5)		(7.3–32.8%)
Total sperm count (×10^6)		0.426[2]	
≥27.2	45 (88.2)		
<27.2	6 (11.8)		(4.4–23.9%)
Total motile sperm count[3, 4] (×10^6)		0.500[2]	
≥10.6	36 (90.0)		
<10.6	4 (10.0)		(2.8–23.7%)

[1]Cut-off points were based on the 10th percentile of a general population, as described by Cooper TG *et al.*, Human Reproduction update, 2010. 16(3): p. 231–245, reference (21). [2]Binomial tests with the hypothesized proportion of 0.1. Clopper–Pearson binomial proportion CIs are shown. [3]*n* = 40; it was not possible to perform motility evaluations at a temperature of 37°C in one center, we excluded these cases from analysis (*n* = 11). [4]Total motile sperm count is defined as the product of the cut-off values of the 10th percentile as defined by Cooper *et al.* for concentration, and percentage of progressive spermatozoa of ejaculate, divided by 100%.

parameters resulted in an overall normal outcome for TSC and TMSC (Supplementary Table 5).

Evaluation of serum hormone levels

Hormonal evaluation was performed in 48 participants (Table 2). The median values of FSH, LH, total testosterone, free testosterone, and TSH were within reference values of the corresponding assays, except for the median value of total testosterone for participants aged 50 years or older (9.7 nmol/L, reference range: 10.90–30.79 nmol/L). The median FT4 of 23.3 pmol/L was outside the reference range of 11.0–19.5 pmol/L.

Characteristics associated with male fertility

The participants scoring above the 10th percentile cut-off value for volume had a higher median BMI than those scoring lower than the cut-off value (27.1 vs 22.2 kg/m^2, P = 0.009). Participants who conceived children had a higher median age upon evaluation than participants who never conceived children (44.7 vs 33.6 years, P = 0.005). Other associations between participant or treatment characteristics and semen characteristics were not statistically significant. Semen quality parameters did not differ between participants who received a single administration or multiple administrations of RAI (see Supplementary Table 6).

Reproductive characteristics

Of 51 participants, 50 completed the questionnaire. Thirty of these 50 participants (60.0%) reported having achieved a pregnancy. Three of the 50 participants (6.0%) reported

Table 2 Hormonal evaluation of participants treated with radioactive iodine for differentiated thyroid carcinoma.

Hormone	Participants, *n* = 48[1]		Reference range
	Median (IQR)	Range	
Follicle-stimulating hormone (U/L)	3.7 (2.9–5.9)	1.5–23.5	1.5–12.4
Luteinizing hormone (U/L)	4.9 (4.0–6.8)	2.6–11.9	1.7–8.6
Total testosterone (nmol/L)	13.6 (9.8–16.7)	6.3–28.2	n.a.
<50 years old[2]	14.7 (10.6–17.1)	6.9–28.2	11.37–34.32
≥50 years old[3]	9.7 (9.3–15.0)	6.3–24.8	10.90–30.79
Free testosterone (nmol/L)	0.3 (0.2–0.4)	0.2–0.6	0.3–0.64
Thyroid-stimulating hormone (mU/L)	0.5 (0.1–1.6)	<0.1–7.7	0.5–4.0
Free thyroxine (pmol/L)	23.3 (21.4–25.6)	18.3–32.4	11.0–19.5

[1]Forty-eight of 51 participants had a serum sample drawn. [2]*n* = 37. [3]*n* = 11.
n.a., not applicable.

having an unfulfilled desire to have (more) children, two due to the lack of a partner, and one due to a miscarriage. Nine of the 50 participants (18.0%) reported that their desire to have children had changed because of their diagnosis and treatment of DTC.

Six of the 50 participants (12.0%) had previously visited a fertility clinic or physician for not being able to conceive naturally; three of them underwent fertility treatment (*in vitro* fertilization and intracytoplasmic sperm injection (n = 1), intra uterine insemination (n = 1), and unknown (n = 1)). Three never had a fertility treatment.

An overview of conceived pregnancies and pregnancy outcomes before and after RAI administrations is shown in Supplementary Fig. 1. The live birth rates before and after RAI administration were 82.5 and 78.9%. None of the participants reported having fathered children with congenital malformations or major health problems.

Semen cryopreservation and longitudinal evaluation of semen quality

Semen cryopreservation was performed in 20/50 participants (40%). For one participant, it was unknown whether semen cryopreservation was performed. Participants had a median age of 32.4 (IQR: 23.6–33.8, range: 16.6–50.1) years upon semen cryopreservation.

One participant (5.0%) reported having used his cryopreserved semen. Seventeen participants (85.0%) did not use their cryopreserved semen and two (10%) did not report their usage.

For the second aim of the study, we compared semen quality before and after RAI. We evaluated only the 15/20 participants in whom semen cryopreservation took place before their first administration of RAI. For these 15 participants, the median TMSC significantly increased from 66.9 (IQR: 17.1–115.1) million upon semen cryopreservation to 121.2 (IQR: 48.4–204.6) million (P = 0.036) upon follow-up after a median follow-up period of 4.1 (IQR: 3.1–6.4) years. Based on available TSH values, 10/15 participants were hypothyroid at the moment of semen cryopreservation, 3/15 were euthyroid, and for the remaining 2/15 TSH levels were not available at the time of semen cryopreservation. The median TMSC of the 10 participants who were hypothyroid at preservation was 21.4 million upon semen cryopreservation. At the moment of their current evaluation, median TMSC was 115.9 million. For the three patients who were euthyroid at preservation, median TMSC was 106.3 million at semen cryopreservation and 108.6 at current evaluation.

We asked participants whether they found it important to be offered the possibility of semen preservation; 58% reported finding this very important, 18% found it fairly important, 18% was neutral, and 4% found it not important at all. One participant did not answer this question.

Discussion

The current study assessed long-term male fertility after treatment with a high administered activity of RAI for DTC evaluating semen quality, hormone levels, and reproductive characteristics. The median semen quality of the participants was similar to the median semen quality of the general population, as defined by the WHO (21). No statistically or clinically relevant differences in semen quality were seen between the participants and the general population based on the 10th percentile (21). Some participants treated with RAI for DTC had long-term poor semen quality, depicted by the higher number of participants with low semen motility and concentration for the 5th and 10th percentile. However, the clinical consequences of this finding are limited since the TSC and the TMSC never differed between the two populations for all cut-off values, indicating compensation between the combined semen parameters. Thereby, we found no detrimental effects on reproductive characteristics and the evaluation of LH, FSH, total testosterone, and free testosterone did not show relevant abnormalities.

Evaluated after a median of 6 years after their final treatment with RAI, the normal male fertility in the majority of current survivors seems to confirm the prospect of recovery of parameters of male fertility over time, as also indicated by other studies. Previous studies reported transient damage of male fertility up to a maximum of 18 months after RAI (5, 8, 9, 10, 11, 12, 13). Some reported normalization of parameters; others found a persistent disturbance upon 12 or 18 months of follow-up, especially in patients treated with higher or multiple administrations of RAI (5, 11), suggesting a dose-dependent effect (5, 9, 10, 11). However, a dose-dependent effect was not confirmed in the current long-term study nor in a previous short-term study on male fertility after DTC (13). In the current study, the long-term follow-up period apparently allowed for continued spermatogenesis in most participants with subsequent normal findings (22). Therefore, a possible transient dose-dependent effect could not be identified.

By defining various cut-off values for low semen quality, we were able to detect subtle disturbances in semen quality of males treated with DTC as there were more

participants with poor semen motility and concentration in the lower range. No predictors for poor semen quality were identified. No relation between BMI and semen volume has previously been described (23).

A low usage rate of the cryopreserved semen, as in our study, was previously described in males treated for other cancer types (24). Possible explanations for this current low usage rate may be that males have conceived naturally or indicate a change in the wish to conceive children. Considering the age of the participants, future use of cryopreserved semen can, however, not be ruled out.

The reported reproductive characteristics did not show major abnormalities in the 12% of participants who sought medical assistance for not being able to conceive. This number is comparable to other couples in the Netherlands (25). Thereby, live birth rate before and after RAI administration did not differ.

There is no firm evidence indicating that fertility preservation is necessary for fathering a child after treatment with RAI for DTC. However, semen cryopreservation can be performed as a precaution, considering the more frequent occurrence of low semen quality in some males. Another reason to perform semen cryopreservation may be that the patient in question has a desire to have children soon after RAI treatment. One additional argument to continue semen preservation may be the slight (but significant) elevation of numerical chromosomal aberrations in spermatozoa after RAI administration (8). Theoretically, this can affect offspring, but current and previous results show no proof of health defects in children fathered by patients treated with RAI (7, 15).

Our data indicate that the impairment in semen quality caused by hypothyroidism seems probably more relevant than long-term impairment of semen quality caused by RAI. Upon semen cryopreservation, hypothyroid participants had a lower TMSC than euthyroid patients. Due to the small number of patients, extrapolation of this finding is not feasible. However, if semen is cryopreserved, a euthyroid state of the patient would provide semen of optimal quality (26).

Strengths and limitations

This is the first study to evaluate a broad range of aspects of long-term male fertility after a high-activity RAI administration. A limitation of this study was the lack of control group. However, the reference ranges used to compare results are currently used in daily practice. By defining several cut-off values for our analysis, we avoided basing our results on an arbitrary cut-off point. The sample size was limited by the number of laboratories able to perform semen analyses according to our protocol. Due to the retrospective nature of this study, we were not able to retrieve semen at a euthyroidal state for the majority of the males who cryopreserved their semen. The relatively high percentage of eligible participants who actively declined participation or were lost to follow-up might be explained by the personal extent of the study and the fact that we only included patients with a follow-up period of at least 2 years and patients were in follow-up with their general practitioner. However, a selection bias could not be excluded. We only included participants who were endogenously TSH stimulated before RAI administration, as was the standard of care in the Netherlands up to 2015. Only 5 out of 236 patients were excluded based on this criterion. We therefore do not expect this created a selection bias.

Conclusion

In conclusion, administration of RAI for DTC does not impair long-term male fertility of the patients treated with 100 mCi/3.7 GBq or more. Based on current results, we believe that semen cryopreservation does not need to be routinely advised for males receiving RAI for DTC. However, cryopreservation of semen before administration of RAI for DTC can be discussed as a precaution in individual cases.

Supplementary materials

The supplementary data referred to in this article is available at https://doi.org/10.6084/m9.figshare.13415156.v3.

Declaration of interest

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

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Author contribution statement

Conception or design of the work: M N, E G J M A, J G M B, A N A H S, A E P C, and T P L; data collection: M N, E G J M A, E F S V, A C M K, E P M C, R T N M, R P P, and T P L; data analysis and interpretation: M N, E G J M A, J G M B, A C M K, A E P C, and T P L; drafting the article: M N, E G J M A, A E P C, and T P L; critical revision of the article: E F S V, J G M B, A C M K, E P M C, R T N M,

R P P, and A N A H S; Final approval of the version to be published: all authors. A E P C and T P L: Shared last authors.

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