Change in Practice of Radioactive Iodine Administration in Differentiated Thyroid Cancer: A Single-Centre Experience

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Keywords

Thyroid cancer · Radioactive iodine · Adjuvant therapy · ATA risk stratification

Abstract

Objective: Our study aimed to analyse temporal trends in radioactive iodine (RAI) treatment for thyroid cancer over the past decade; to analyse key factors associated with clinical decisions in RAI dosing; and to confirm lower activities of RAI for low-risk patients were not associated with an increased risk of recurrence. **Methods:** Retrospective analysis of 1,323 patients who received RAI at a quaternary centre in Australia between 2008 and 2018 was performed. Prospectively collected data included age, gender, histology, and American Joint Committee on Cancer stage (7th ed). American Thyroid Association risk was calculated retrospectively. **Results:** The median activities of RAI administered to low-risk patients decreased from 3.85 GBq (104 mCi) in 2008–2016 to 2.0 GBq (54 mCi) in 2017–2018. The principal driver of this change was an increased use of 1 GBq (27 mCi) from 1.3% of prescriptions in 2008–2011 to 18.5% in 2017–2018. In patients assigned as low risk per ATA stratification, lower

activities of 1 GBq or 2 GBq (27 mCi or 54 mCi) were not associated with an increased risk of recurrence. In patients assigned to intermediate- or high-risk categories who received RAI as adjuvant therapy, there was no difference in risk of recurrence between 4 GBq (108 mCi) and 6 GBq (162 mCi). **Conclusions:** Our data demonstrate an evolution of RAI activities consistent with translation of ATA guidelines into clinical practice. Use of lower RAI activities was not associated with an increase in recurrence in low-risk thyroid cancer patients. Our data also suggest lower RAI activities may be as efficacious for adjuvant therapy in intermediate- and high-risk patients.

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Introduction

The incidence of thyroid cancer is increasing worldwide [1]. In Australia, thyroid cancer is increasing more than any other malignancy, with incidence rising from 2.7 to 13 per 100,000 persons between 1982 and 2019 [2, 3]. Over 97% of thyroid cancer is well-differentiated, originating from thyroid follicular cells. Differentiated

thyroid cancer includes papillary, follicular, or Hurthle-cell neoplasms [4]. Radioactive iodine (RAI) is considered following total thyroidectomy for differentiated thyroid cancer for 3 reasons: to ablate remnant thyroid tissue in low-risk patients; prevent recurrent disease in high-risk patients (adjuvant therapy); or to treat residual or metastatic disease [5].

Clinical paradigms have shifted over the past decade towards the use of lower RAI activities. The HiLo and ESTIMABL1 studies showed no difference in biochemical or structural recurrence following 1.1 GBq (29.7 mCi) or 3.7 GBq (100 mCi) for low-risk patients treated with ablative intent in the short term or 5 year follow data [6–9]. In 2015, the American Thyroid Association (ATA guidelines) supported the use of lower activities of RAI therapy by recommending lower activities for low- and intermediate-risk categories [5]. It is well established that patients with metastatic disease have improved survival outcomes with RAI treatment with up to 7.4 GBq (200 mCi) [10, 11]. Conversely, higher RAI activities are associated with increased risks including sialadenitis and secondary malignancy [12].

Adjuvant therapy is defined as treatment of suspected but not confirmed residual disease [13]. Proposed indications for adjuvant therapy include gross extra-thyroidal extension (ETE), lymph node involvement >3 cm and, for follicular thyroid cancers, >4 foci of vascular invasion [14–16]. The ATA guidelines define low- and high-risk categories based on absence or presence of these features, respectively, and also include an intermediate risk group defined by minimal extra-thyroidal extension, and/or venous invasion, and/or lymph node involvement <3 cm, and/or >5 involved lymph nodes [5]. In addition, tumour size >4 cm and/or post-operative thyroglobulin (Tg) >10 ng/L may be associated with increased risk of recurrence, although neither feature has yet been included in ATA guidelines for baseline risk assessment [17–19]. The appropriate RAI activities for adjuvant therapy remains unclear, with activities up to 5.5 GBq (150 mCi) recommended [5]. A paucity of prospective trials and ambiguous definitions of adjuvant therapy have led to inconsistent dosing decisions based on clinical discretion rather than evidence [13].

Our primary aim was to analyse the temporal trends in RAI treatment for thyroid cancer at our institution over the past decade. Our secondary aims were to analyse key factors associated with clinical decisions in RAI dosing; and to confirm lower activities of RAI for low-risk patients were not associated with an increased risk of recurrence. We hypothesized our clinical practice of RAI ad-

ministration had incrementally changed to favour use of lower activities in line with a global shift in clinical paradigms. We also wished to specifically examine whether different RAI choices made by independent clinicians had affected recurrence risk when used in the adjuvant (rather than ablative) setting.

Methodology

All patients aged >18 years who underwent a total or completion thyroidectomy followed by RAI between 2008 and 2018 for differentiated thyroid cancer were identified using the thyroid cancer database at Royal North Shore Hospital, the largest volume thyroid surgery unit in Australia. Three (3) surgeons performed over 85% of all thyroid cancer surgery registered in the database. One hundred and thirty (130) clinicians prescribed RAI over the time period, with 6 clinicians prescribing over 75% of all RAI activity. Our institution had no formal guidelines for the choice of RAI activity in this time frame and dosing decisions were left to the discretion of the clinician prescribing RAI and reviewed by the nuclear medicine specialist. Some clinicians, however, did have the opportunity to present at a fortnightly multidisciplinary team meeting attended by endocrinologists, nuclear medicine physicians, surgeons, pathologists, and radiologists, to aid activity selection. Clinical characteristics extracted included: therapeutic activities, age, gender, histology, tumour size, stimulated Tg, lymph node status, vascular invasion, ETE, presence of metastases and the American Joint Committee on Cancer stage (AJCC 7th ed, 7th ed.; defined by pathological tumour size [pT1–4], central [N1a], and lateral [N1b] lymph node involvement and presence of metastasis [M1]). In addition to these features, ATA thyroid cancer risk categories were retrospectively assigned for each patient (by A.W.) as defined in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000516358). Patients with anaplastic, insular, poorly differentiated, and medullary thyroid cancer were excluded, along with lymphoma of the thyroid gland. RAI activities were categorized into 3 groups: low (<1.3 GBq; 35 mCi), intermediate (1.3–3.74 GBq; 35–101 mCi), and high (≥ 3.75 GBq; 101 mCi). The high-activity group was further divided into H₁ (3.75–5.39 GBq; 101–145.7 mCi) and H₂ (≥ 5.4 GBq; ≥ 145.7 mCi). Recurrence was defined as either surgical intervention or administration of a second activity of RAI. We attempted to examine recurrence as distinct from persistent disease by 2 additional steps: (1) we excluded patients with uptake only in the thyroid bed; (2) we also excluded patients with distant metastasis on baseline imaging or on initial post-treatment iodine uptake scan, as they were frequently administered an additional activity of RAI for persistent disease (Fig. 1). Progression-free survival was defined as the time to recurrence and was censored to death or end of study period. Survival data were obtained from medical records or the Ryerson Index, which is an index to death notices and obituaries appearing in Australian newspapers [20]. Adjuvant therapy was defined when RAI was given for suspected but not confirmed residual disease as per the above criteria. These included intermediate-risk patients with a tumour size >4 cm, microscopic ETE, central (N1a), and lateral (N1b) lymph node involvement or post-operative thyroid-stimulating hormone stimulated Tg between 10

Fig. 1. Study design.

and 30 µg/L; and high-risk patients without structural disease and post-operative thyroid-stimulating hormone stimulated Tg <30 µg/L. The study was approved by the Human Research Ethics Committee at Northern Sydney Local Health District (ETH00360/STE006443).

Statistical Analysis

Descriptive statistics were presented as mean ($\pm$ standard deviation) for normally distributed data; median (interquartile range, [IQR]) for continuous non-normally distributed variables; and frequencies and proportions for categorical variables. One-way ANOVA compared means between the 3 activities groups. Mann-Whitney tests were used to compare medians between 2 groups. χ^2 test was used to compare categorical groups, including histology, gender, ATA risk, and AJCC staging. Linear regression was used to assess changes in RAI activities over time. Univariate and multivariate binomial regression analysis was used to elicit factors associated with dose categories. A multivariate binomial regression analysis of RAI activities categories included gender, age, histology, pathological staging, venous invasion, ETE, and lymph node involvement; distant metastasis was not included in this analysis. Kaplan-Meier curves analyzed progression-free survival (PFS), defined as time to recurrence. A p value of ≤ 0.05 was considered statistically significant. Statistical analyses were conducted using Statistical Package for Social Sciences version 26 (SPSS Inc., Chicago, IL, USA). Figures were created using GraphPad Prism version 8.0.0 for Windows (GraphPad Software, San Diego, CA, USA).

Results

Patient Characteristics

One thousand two hundred and twenty-three (1,323) patients received RAI between 2008 and 2018. One hundred and twenty (120) patients were administered a low activity, 259 received an intermediate activity and 944 received high activities. The median follow-up was 42 months (IQR 15.0–81.3 months). The characteristics of the patients are outlined in Table 1. Between 2008 and 2018, 1,418 patients did not receive RAI following thyroid cancer surgery. Of these patients, 1,023 patients had a total or completion thyroidectomy and 395 underwent a hemi or subtotal thyroidectomy (online suppl. Table 2). The odds of not receiving RAI was 1.2 times more likely in 2017–2018 than 2008–2010 ($p = 0.02$); with the increase in non-RAI treatment driven by an increase in subtotal or hemithyroidectomy over a total thyroidectomy (OR 2.63, 1.86–3.69, $p < 0.001$).

RAI Activities Have Decreased over the Past Decade

Linear regression demonstrated mean RAI activities decreased by 0.135 GBq (3.6 mCi) each year from 2008 ($p < 0.001$). Administered RAI activity was analyzed across 3 retrospective time intervals: 2008–2010, 2011–

Table 1. Baseline characteristics of patients administered an initial dose of radioactive 2008–2018

	Low dose, <i>n</i> = 120	Intermediate dose, <i>n</i> = 259	High dose, <i>n</i> = 944	<i>p</i> value
Dose GBq (median, IQR)	1.03 (1–1.08)	2.07 (2.0–2.58)	4.14 (4.0–4.4)	
Age (mean ± SD)	47.27 (±12.39)	48.47 (±13.61)	51.29 (±15.56)	0.002
Male, <i>n</i> (%)	20 (16.67)	54 (20.8)	270 (28.6)	0.002
Histology, <i>n</i> (%)				
Papillary thyroid cancer	43 (35.8)	75 (30)	332 (35.2)	0.05
Multifocal papillary thyroid cancer	44 (36.7)	128 (49.4)	415 (44)	
Follicular variant thyroid cancer	15 (12.5)	25 (9.7)	63 (6.7)	
FTC	9 (7.5)	23 (8.9)	81 (8.6)	
Hurthle-cell cancer	9 (7.5)	8 (8.9)	53 (5.6)	
Staging (AJCC), <i>n</i> (%)				
1, <i>n</i> = 679	85 (70.8)	174 (67.2)	420 (44.5)	<0.001
2, <i>n</i> = 132	11 (9.2)	33 (12.7)	88 (9.3)	
3, <i>n</i> = 343	20 (16.7)	44 (17)	279 (29.6)	
4A, <i>n</i> = 156	4 (3.3)	4 (1.5)	147 (15.6)	
4C, <i>n</i> = 7		1 (0.4)	6 (0.6)	
NA		2 (0.8)	4 (0.4)	
ATA risk, <i>n</i> (%)				
Low, <i>n</i> = 290	50 (41.6)	98 (37.8)	142 (15)	<0.001
Intermediate, <i>n</i> = 774	58 (48.3)	129 (49.8)	587 (62.1)	
High, <i>n</i> = 182	6 (5)	13 (3.8)	163 (17.2)	
NA	6 (5)	19 (7.3)	52 (5.5)	

FTC, follicular thyroid cancer; ATA, American Thyroid Association; IQR, interquartile range.

2016, and 2017–2018. As shown in Figure 2, the number of high activities decreased from 89% (269/302) of all activities administered in 2008–2010 to 61% (159/259) of doses in 2017–2018. The number of low activities increased from 1.3% of all activities (4/302) in 2008–2010 to 18.5% (48/259) in 2017–2018. The odds of receiving a low activity compared to a high activity were 24 times more likely in 2017–2018 than 2008–2010 ($p < 0.001$).

Data for 1,246 patients were available to permit retrospective stratification of risk according to the modified ATA guidelines: 290 patients were stratified as low risk, 774 as intermediate risk, and 182 as high risk. Of patients stratified as low risk from 2008 to 2018, 17.2% received a low activity, while 49.0% received a high activity. Low-risk patients had a OR of 33.2 (CI 14.8–69.6) to be administered 1 GBq over a higher activity in 2017–2018 ($p < 0.001$). In contrast, intermediate-risk patients had a OR of 0.38 (CI 0.27–0.55, $p < 0.001$) of being administered ≥ 4 GBq activity. There was no statistical difference in the administration of ≥ 4 GBq activity between 2017 and 2018 compared to 2008–2016 for high-risk patients ($p = 0.24$).

Factors Associated with Activity Choice

A multivariate analysis was performed to determine factors associated with activity selection in 214 patients

Fig. 2. Initial RAI dose over 3 time points, 2008–2010, 2011–2016, and 2017–2018. RAI, radioactive iodine.

Table 2. Factors associated with a low and high dose in 2017–2018

	Univariate Analysis		Multivariate Analysis	
	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)
Low dose, <i>n</i> = 259				
Female, <i>n</i> = 152	0.21	1.62 (0.76–3.45)	0.446	1.43 (0.57–3.61)
Age (by 10 years)	0.15	0.86 (0.70–1.06)	0.028	0.73 (0.55–0.97)
Tg	0.49	0.99 (0.99–1.01)	0.865	1.00 (0.998–1.00)
No venous invasion	0.002	2.85 (1.45–5.63)	0.016	2.72 (1.20–6.14)
Lymph node (ref: N1b)				
N0, <i>n</i> = 93	0.008	3.99 (1.44–11.10)	0.003	7.31 (1.94–27.48)
N1a, <i>n</i> = 72	0.16	2.19 (0.73–6.53)	0.136	2.625 (0.739–9.33)
Tumour size (ref: pT3)				
pT1, <i>n</i> = 78	<0.001	4.53 (2.01–10.28)	0.000	7.527 (2.465–22.982)
pT2, <i>n</i> = 52	0.13	2.08 (0.81–5.35)	0.165	2.283 (0.712–7.317)
No ETE, <i>n</i> = 98	0.02	2.20 (1.16–4.20)	0.928	0.961 (0.407–2.268)
High dose, <i>n</i> = 214				
Male, <i>n</i> = 62	0.018	2.04 (1.13–3.70)	0.024	2.45 (1.12–5.34)
Age (by 10 years)	0.16	1.12 (0.96–1.31)	0.007	1.40 (1.10–1.78)
Tg	0.191	1.01 (0.99–1.02)	0.771	1.00 (0.99–1.01)
Venous Invasion, <i>n</i> = 105	<0.001	2.52 (1.50–4.21)	0.016	2.32 (1.17–4.61)
Lymph nodes (ref: N0)				
N1a, <i>n</i> = 72	0.008	2.33 (1.25–4.34)	0.001	3.96 (1.71–9.14)
N1b, <i>n</i> = 49	<0.001	5.17 (2.39–11.17)	0.000	22.81 (6.67–78.05)
Tumour size (ref: pT1)				
pT2, <i>n</i> = 52	0.168	1.57 (0.83–2.99)	0.013	3.35 (1.28–8.72)
pT3, <i>n</i> = 84	<0.001	3.22 (1.76–5.91)	0.001	4.61 (1.89–11.26)
ETE, <i>n</i> = 116	<0.001	2.51 (1.50–4.19)	0.644	1.20 (0.56–2.53)

ETE, extra-thyroidal extension; Tg, thyroglobulin.

treated in most recent years (2017–2018). Thirty (30) of the patients were low-ATA risk, 143 intermediate risk, 31 high risk and 10 were unable to be allocated into an ATA category. As shown in Table 2 factors associated with lower activities included younger age, pT1, absence of venous invasion and absence of lymph node involvement, while factors associated with high activities were male gender, increasing age, pT2, pT3, N1a, and N1b disease.

Recurrence

Seventy-four (74) patients had a recurrence when patients treated for thyroid bed uptake and distant metastasis were excluded from analysis. Median time to recurrence was 14 months (IQR 10–31 months).

In the 1,115 patients included in the recurrence analysis, the initial RAI activities were administered in 2008–2010 for 236 patients, 2011–2016 for 630 patients and 2017–2018 for 249 patients. Of patients who had recurrence, 18 had an initial treatment in 2008–2010, 52 in 2011–2016, and 4 in 2017–2018. Recurrence was 5.06 (CI 1.73–13.96) times more likely to have occurred in patients who received an initial activities in 2008–2010 than pa-

tients treated in 2017–2018 ($p = 0.002$). Similarly, patients who received RAI in 2011–2016 were 5.5 (CI 2.04–14.41) times more likely to have recurred than those whose initial dose was in 2017–2018 ($p < 0.001$).

Analysis of these patients by baseline ATA risk showed recurrence in 3.4% of low-risk patients, 3.7% of intermediate-risk and 16.5% of high-risk patients. There was no statistical difference in the risk of recurrence between the 4 different activity categories (low, intermediate, H1 and H2) in low-risk patients ($p = 0.16$). In intermediate- and high-risk patients, there was no difference in recurrence risk between H1 and H2 activities; $p = 0.07$ and $p = 0.56$, respectively.

Progression-Free Survival

ATA low- and intermediate-risk patients had longer PFS than high-risk patients ($p < 0.001$), but there was no difference in PFS between low- and intermediate-risk patients ($p = 0.58$). No statistically significant difference in PFS was seen between H1 and H2 activities categories for either the intermediate ($p = 0.11$) or high-risk patients ($p = 0.38$).

Fig. 3. PFS using Kaplan-Meier Curve in patients treated with adjuvant therapy in H1 (3.75–5.39 GBq; 101–145.7 mCi) and H2 (≥5.4 GBq; >145.7 mCi) treated patients in intermediate risk (a) and high risk (b). PFS, progression-free survival.

We then restricted our analysis to patients treated with adjuvant RAI, defined in intermediate-risk patients by tumour size >4 cm, microscopic ETE, central (N1a) and lateral (N1b) lymph node involvement, or post-operative Tg between 10 and 30 µg/L; and high-risk patients without structural disease and Tg <30 µg/L (online suppl. Table 3). As shown in Figure 3, there was no significant difference between H1 and H2 activities categories for either intermediate-risk ($p = 0.17$) or high-risk patients ($p = 0.15$).

Discussion

In the current study, we demonstrate RAI activities significantly decreased at our institution over the last decade. Time points associated with the greatest decrease in RAI activities were 2010–2011 and 2016–2017, coinciding with release of 2009 and 2015 ATA guidelines, respectively. Unlike previous studies which have described translation of ATA guidelines into practice, our data also captures clinical and dosing information [21]. The greatest change in RAI selection over time was the use of lower activities for low-risk patients and a reduction in activities >4 GBq (>108 mCi) for intermediate-risk patients. In the 11 year time period, our data demonstrate 14 times increase in the number of low-activity treatments administered. Despite using lower RAI activities, there has been no increased risk of recurrence over median follow-up period of 42 months (IQR 15.0–81.3 months), which is in keeping with long-term follow-up data for low-risk patients in recently published prospective trials and meta-analysis [7, 9, 22].

Our study did not examine outcomes of patients who did not receive RAI, however, our numbers show increased number of patients managed without RAI.

Despite adoption of lower activities of RAI, 36.4% (12/33) of patients classified as low-ATA risk in 2017–2018 received a high-RAI activities (online suppl. Table 4). Of those low-risk patients treated with a high activities, half had multifocal disease. Multifocal disease is not classified as an independent risk factor in the ATA guidelines, so it is interesting our quaternary centre was still influenced by this criterion in recent years.

There are many potential consequences of using lower RAI activities, including reduced side-effects, decreased hospital length of stay, and decreased overall costs [23]. At our institution, patients are admitted for 1 day for a 1 GBq (27 mCi) dose, 2 days for a 2 GBq (54 mCi) dose, and 3 days for a 6 GBq (162 mCi) activities. A 50% reduction was seen in the number of 6 GBq (162 mCi) activities administered over the 11 years, resulting overall in 11% lower hospital bed usage (average length of stay decreasing from 2.14 to 1.9 days).

RAI activity selection is based on multiple clinical and histopathological factors. The 2015 ATA risk stratification proposes general dosing recommendations. However, these guidelines have not been endorsed by all major organizations involved in management of thyroid cancer [24]. We examined patient and disease factors influencing RAI activities selection including factors not currently incorporated in the ATA guidelines. Factors included in the 2015 ATA risk stratification were extra-thyroidal extension and venous invasion, and these were both as-

sociated with the activity selected in recent years. Outside the ATA guidelines, other factors significantly associated with the activities selected in our series were age, gender, tumour size, and central, or lateral LN involvement. Our data, therefore, reflect the Martinique principles, which highlight important factors outside of post-operative status and risk stratification in activity choice [25]. The lack of uniformity in decision-making around RAI therapy results in patients receiving a wide range of RAI activities [26]. An intersocietal working group was formed in 2017 to foster collaboration in the management of patients with DTC and to progress a consensus approach [27].

There is an unequivocal benefit of using higher RAI activities in high-risk patients with known structural persistence/recurrence [28]. In contrast, the optimal activities for adjuvant RAI, to treat suspected but not confirmed residual disease, remains controversial [10, 29–32]. Indeed, a definition for suspected residual disease has yet to be clearly defined [13]. The ATA guidelines currently recommend considering adjuvant RAI in intermediate-risk patients with higher risk features not currently incorporated in ATA risk stratification; in this respect, post-operative, stimulated Tg between 10 and 30 µg/L has been proposed as a marker for the use of adjuvant therapy [5]. In our analysis, using a strict definition of adjuvant therapy which combined higher risk features and raised post-operative Tg, we could not identify a benefit of ~6 GBq (162 mCi, H2) over ~4 GBq (108 mCi, H1) in either intermediate or high-risk patients. Our data questions whether higher activities are required in adjuvant treatment in either intermediate or high-risk patients, which could be addressed by future clinical trials.

Our study, unlike others, assessed clinically significant recurrence, defined as receiving a second RAI activities or further operative management. Our recurrence rates of 3.8, 3.7, and 16.5% for low, intermediate, and high ATA risk groups, respectively, were similar to the structural incomplete response rates of another large study in this area [33].

The key strengths of our study are its size and long follow-up period of 11 years. Although our analyses were retrospective, all data were prospectively entered into our institutional database. Our study has several weakness: it is a single-centre study, our confidence in recurrence rates after lower RAI activities is tempered by temporal changes in RAI dosing, that is, patients treated with lower activities in later years have had shorter follow-up thereby limiting the capture of recurrence data; our use of Tg 10–30 µg/L in the definition of adjuvant therapy for intermediate-risk patients may have missed some intermediate-risk patients with residual disease [18, 34]; and we cannot exclude the possibility some recurrences may have been treated out-

side our institution and, therefore, not captured in our database. We also cannot conclude our results, particularly in regard to low-recurrence rates, may be generalized to community care settings or other countries.

Conclusion

Our data demonstrates an evolution of RAI activity selection consistent with translation of ATA guidelines into local practice. Specifically, low-ATA risk patients now typically receive no >2 GBq (54 mCi) at our institution. The use of lower RAI activities in low-risk patients was not accompanied by any observable increase in recurrence risk. Our analysis could not show any benefit for 6 GBq (162 mCi) over 4 GBq (108 mCi), RAI in intermediate- or high-risk patients treated with adjuvant intent. A randomized control trial is warranted to clarify the optimal RAI activities in the adjuvant setting.

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Statement of Ethics

All patients included in this study have given their informed written consent. This study was completed ethically in accordance with the World Medical Association Declaration of Helsinki and was approved by the Human Research Ethics Committee at Northern Sydney Local Health District (ETH00360/STE006443).

Conflict of Interest Statement

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. No author has competing financial interests.

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Author Contributions

All the authors were responsible for writing, reviewing, and editing the manuscript.

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