

# Effects of High-Dose Radioactive Iodine Treatment On Renal Function In Patients With Differentiated Thyroid Carcinoma: A Retrospective Study

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## Research Article

**Keywords:** blood urea nitrogen, creatinine, differentiated thyroid carcinoma, estimated glomerular filtrate, radioactive iodine, renal function.

**Posted Date:** July 12th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-676477/v1>

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## Abstract

**Aim:** This study aimed to investigate the effects of high-dose radioactive iodine ( $^{131}\text{I}$ ) treatment on the clinical metrics of renal function in patients with differentiated thyroid carcinoma (DTC).

**Patients and methods:** The clinical metrics of renal function were analysed in 850 patients with DTC who received  $^{131}\text{I}$  therapy between January 2012 and December 2019. According to the baseline renal function metrics, the patients were divided into normal renal function group (group A) and abnormal renal function group (group B). Each group was further divided into three subgroups (subgroups 1, 2, and 3) based on the cumulative dose of  $^{131}\text{I}$ . The clinical metrics of renal function including serum creatinine (SCr) levels, blood urea nitrogen (BUN) levels and estimated glomerular filtration rate (eGFR) were measured within 1 month before the initiation of  $^{131}\text{I}$  therapy, 1 year after the last therapy, and 5 years after the initial therapy. The changes in renal function metrics before and after  $^{131}\text{I}$  therapy were compared in each group.

**Result:** In group A (588 patients), no significant difference in the mean levels of SCr and BUN and eGFR was observed in the three subgroups ( $P > 0.05$ ), regardless of gender, before the initial  $^{131}\text{I}$  therapy and 1 year after the last therapy. A total of 8, 3, and 2 patients presented with abnormal renal function after  $^{131}\text{I}$  treatment in subgroups 1, 2, and 3, respectively. No statistically significant difference was observed in the incidence of renal dysfunction among the three subgroups ( $P = 0.287$ ). The mean age of patients with renal dysfunction was significantly greater than that of patients without renal dysfunction after  $^{131}\text{I}$  treatment. In group B, of the 262 patients with abnormal renal function, SCr and BUN levels were elevated in 168 and 155 patients, respectively, and eGFR  $< 60 \text{ mL/min/1.73 m}^2$  was found in 87 patients before the initial  $^{131}\text{I}$  therapy. No significant difference was observed in the parameters among the three subgroups. However, SCr and BUN levels were found to be increased in all subgroups 5 years after the initial  $^{131}\text{I}$  therapy, and they were positively correlated with the cumulative dose of  $^{131}\text{I}$ . The difference was statistically significant ( $P < 0.05$ ). Furthermore, eGFR was found to be decreased in all subgroups after  $^{131}\text{I}$  therapy, and it was negatively correlated with the cumulative dose of  $^{131}\text{I}$ . The difference was statistically significant ( $P < 0.05$ ). A gender bias was not observed in the changing trends of SCr and BUN levels and eGFR.

**Conclusion:** Our findings suggest that the nephrotoxicity of high-dose  $^{131}\text{I}$  therapy, regardless of gender, is very low in patients with DTC with normal renal function; however, high-dose  $^{131}\text{I}$  therapy may exacerbate the loss of renal function in those with renal dysfunction.

## Introduction

The incidence of thyroid cancer is increasing worldwide, and the most common histological subtype of thyroid cancer is papillary carcinoma followed by follicular carcinoma. The carcinomas are collectively referred to as well-differentiated thyroid carcinoma (DTC). The definitive therapy for DTC includes surgical thyroidectomy, with or without adjuvant  $^{131}\text{I}$  therapy depending on histological information and the presence of residual, unresectable, and metastatic disease [1–3].  $^{131}\text{I}$  therapy has been successfully applied for more than 60 years for the management of DTC. Various studies have proven that ablative  $^{131}\text{I}$  therapy significantly reduces the frequency of recurrences and tumour spread in patients with thyroid cancer. In patients with distant metastases, approximately 50% complete responses may be achieved with  $^{131}\text{I}$  treatment.

The well-known possible side effects of high-dose  $^{131}\text{I}$  therapy include radiation thyroiditis, nausea, vomiting, sialadenitis, xerostomia, dental caries, long-term dysphagia, nasolacrimal duct obstruction, increased risk of leukaemia, secondary cancers, and pulmonary fibrosis in advanced stages [3–5]. Considering that  $^{131}\text{I}$  is eliminated from the body mainly by the kidneys, the pathway potentially exposes the associated organs to radiation [6]. Moreover, the sodium/iodide symporter (NIS) protein that accumulates  $^{131}\text{I}$  has been found in the kidneys, primarily in the distal tubular system; it is present at a low concentration in the proximal tubules and is absent in the glomeruli [7]. However, most patients with DTC exhibit a long life expectancy; hence, the use of  $^{131}\text{I}$  therapy has raised concern regarding its potential for developing renal dysfunction. It is critical to comprehensively define the risk of renal impairment caused by  $^{131}\text{I}$  in such patients. To our knowledge, the current literature lacks published data regarding the nephrotoxicity of radioiodine owing to high-dose  $^{131}\text{I}$  treatment. However, with regard to the quality of life, it is important to explore whether relevant nephrotoxicity is caused by  $^{131}\text{I}$  therapy. The aim of this study is to examine whether high-dose  $^{131}\text{I}$  used for the treatment of DTC can result in any change in the metrics of renal function during a relatively long period.

## Patients And Methods

### Patients

We have examined all records of the patients admitted for the treatment of DTC after thyroid hormone withdrawal at the Department of Nuclear Medicine, Tianjin Medical University General Hospital from January 2012 to December 2019. Patients with incomplete data were excluded. A total of 850 patients were enrolled in the study; 326 patients were men and 524 patients were women, both aged between 18 and 72 years

(mean age,  $47.8 \pm 23.4$  years). Of the 850 patients, 716 patients presented with papillary carcinoma and 134 patients presented with follicular carcinoma.

All patients had undergone total or near-total thyroidectomy and received  $^{131}\text{I}$  treatment for the first time. After surgery, 633 patients were treated for the ablation of the thyroid remnant and 217 patients were treated for tumour recurrence and/or metastatic disease.  $^{131}\text{I}$  was administered at a dose of 2.59–7.40 GBq at each time to all patients. If required, subsequent  $^{131}\text{I}$  doses were administered every 6–12 months. The applied accumulated doses ranged from 2.59 to 55.50 GBq with a mean of 13.69 GBq per patient, and the mean number of therapy cycles was  $3.65 \pm 2.84$  (range, 1–7). After the administration of  $^{131}\text{I}$ , the patients were asked to drink more water and urinate more frequently.

## Grouping and follow-up

The  $^{131}\text{I}$  treatment of all patients ended within 4 years, and all patients were followed up for 1–5 years or for at least 1 year after the last treatment. The follow-up (FU) was continued based on clinical examination; neck ultrasonography; hepatorenal function; and blood tests for thyroid hormones, including thyroid-stimulating hormone (TSH) and thyroglobulin (Tg), anti-Tg, and anti-thyroperoxidase antibodies. All renal function parameters were evaluated using an automated analyser (Siemens Viva-ProE). The metrics of renal function, including blood urea nitrogen (BUN; normal range, 3.1–8.0 mmol/L) and serum creatinine (SCr; normal range, 57–97  $\mu\text{mol/L}$ ) levels and estimated glomerular filtration rate (eGFR), were evaluated using the Modification of Diet in Renal Disease (MDRD) equation [8]. The data were systematically recorded in clinical records, and they were collected at least once per year.

SCr and BUN levels and eGFR evaluated within 1 month before the initial  $^{131}\text{I}$  treatment were used as baseline values. The post-therapy SCr and BUN levels and eGFR evaluated 1 year after the last treatment and 5 years after the initial treatment were used as the '1-year FU' and '5-year FU' values, respectively. The development of renal function insufficiency was defined as SCr levels  $> 97 \mu\text{mol/L}$  and/or BUN levels  $> 8.0 \text{ mmol/L}$  (based on the reference standard of the clinical laboratory of Tianjin Medical University General Hospital) and/or eGFR  $< 60 \text{ mL/min/1.73 m}^2$  (based on the chronic kidney disease criteria) [9].

Based on the baseline values, the patients were divided into two groups, namely, normal renal function group (group A) and abnormal renal function group (group B). Group A was defined as patients with baseline SCr levels  $\leq 97 \mu\text{mol/L}$ , BUN levels  $\leq 8.0 \text{ mmol/L}$ , and eGFR  $\geq 60 \text{ mL/min/1.73 m}^2$ , and none of the patients in group A presented with acute or chronic nephropathy or any disease or received any medications that can possibly affect renal function. Whereas those who presented with any disease or received such medications and any of the abnormalities in SCr, BUN and eGFR were included in group B. None of the patients received external irradiation to the abdomen in both the groups.

Based on different cumulative doses of  $^{131}\text{I}$ , the two groups were further divided into three subgroups, namely, subgroup 1, if the cumulative dose was less than 11.1 GBq; subgroup 2, if the cumulative dose was between 11.1 GBq and 18.5 GBq; and subgroup 3, if the cumulative dose was more than 18.5 GBq.

## Statistical analysis

The statistical analysis was performed on SPSS 22.0. The distribution of all parameters was found to be normal. The results were reported as mean  $\pm$  standard deviation (SD). The changes in parameters among the three subgroups were evaluated using repeated measures analysis of variance (ANOVA). The comparison between baseline and follow-up levels of SCr and BUN and eGFR or the comparison of values among the subgroups was analysed using the Student's *t*-test. The chi-squared test was used for comparing the incidence of renal insufficiency among the subgroups after  $^{131}\text{I}$  therapy. Two-tailed *P* values  $< 0.05$  were considered to indicate statistically significant relationships.

## Results

The patients in groups A were subdivided into three groups based on the cumulative dose of  $^{131}\text{I}$ . In group A (588 patients, with 224 male patients and 364 female patients with mean age  $44.6 \pm 28.2$  years), no significant difference was observed in the mean levels of SCr and BUN and eGFR in subgroups 1, 2, and 3, regardless of gender, before the initial  $^{131}\text{I}$  therapy and 1 year after the last therapy. The clinical metrics of renal function are summarised in Table 1. A total of 13 (2.2%) patients developed renal function impairment, which was defined as SCr levels  $> 97 \mu\text{mol/L}$ , BUN levels  $> 8.0 \text{ mmol/L}$ , or eGFR  $< 60 \text{ mL/min/1.73 m}^2$ . A total of 8, 3, and 2 patients presented with abnormal renal function after 1 year of initial  $^{131}\text{I}$  treatment in subgroups 1, 2, and 3, respectively. No statistically significant difference was observed in the incidence of renal dysfunction among the three subgroups (Table 2). In subgroup 3, 4 patients received a cumulative dose of more than 3.7 GBq and none of them presented with abnormal renal function after  $^{131}\text{I}$  therapy. The patients who developed renal impairment were older than those who did not (age,

55.3 ± 13.6 years versus 47.6 ± 18.9 years, respectively;  $P = 0.023$ ), and the difference was statistically significant. In all patients, the absolute increase in SCr and BUN levels was 1.79 µmol/L and 0.10 mmol/L, respectively, and the absolute decrease in eGFR was 2.11 mL/min/1.73 m<sup>2</sup>.

**Table 1** Measurement results of renal metrics of patients with normal renal function before <sup>131</sup>I treatment and 1 year after the last therapy

	n	SCr (µmol/L)		BUN (mmol/L)		eGFR (mL/min/1.73 m <sup>2</sup> )	
		Baseline	Last FU	Baseline	Last FU	Baseline	Last FU
Subgroup 1	445	67.46±15.43	69.48±18.63(p=0.383)	4.54±1.32	4.64±1.27(p=0.752)	106.35±37.18	104.14±36.64(p=0.662)
Male	168	68.62±17.21	70.02±20.45(p=0.754)	4.67±2.04	4.49±1.60(p=0.638)	118.74±41.42	115.82±43.85(p=0.573)
Female	277	66.76±19.35	69.16±16.71(p=0.484)	4.46±1.66	4.73±1.81(p=0.319)	98.84±36.59	97.05±29.68(p=0.824)
Subgroup 2	108	66.79±15.24	67.04±16.40(p=0.499)	4.42±1.28	4.51±1.33(p=0.697)	107.87±38.22	107.29±36.28(p=0.837)
Male	43	68.57±17.26	70.10±15.88(p=0.397)	4.31±1.54	4.48±1.31(p=0.563)	119.82±41.37	116.61±39.83(p=0.496)
Female	65	65.61±15.85	65.01±17.11(p=0.762)	4.49±1.91	4.53±1.84(p=0.954)	99.96±33.59	101.12±25.94(p=0.245)
Subgroup 3	35	66.11±18.26	69.82±15.77(p=0.330)	4.50±1.41	4.64±1.38(p=0.855)	108.43±32.63	103.11±37.39(p=0.255)
Male	13	64.96±16.42	66.43±20.61(p=0.571)	4.65±1.59	4.81±1.91(p=0.564)	126.44±33.51	124.61±42.98(p=0.583)
Female	22	66.79±20.05	71.82±18.77(p=0.243)	4.41±1.88	4.54±2.30(p=0.708)	97.79±28.04	90.41±33.86(p=0.136)

FU: follow-up

**Table 2**  
Patients with abnormal renal function after 1 year of initial <sup>131</sup>I treatment in the three subgroups

	n	Renal function after 1-year FU		χ <sup>2</sup>	P
		Normal	Abnormal		
Subgroup 1	445	437	8	2.499	0.287
Subgroup 2	108	105	3		
Subgroup 3	35	33	2		

In group B, of the 262 patients (102 male patients and 160 female patients; mean age, 55.0 ± 21.3 years) who presented with abnormal renal function before <sup>131</sup>I treatment, SCr and BUN levels were elevated in 168 and 155 patients, respectively, and eGFR < 60 mL/min/1.73 m<sup>2</sup> was found in 87 patients. Before the initial <sup>131</sup>I therapy, there was no significant difference in the three parameters among the three subgroups.

The patients in group B were also subdivided into three subgroups (subgroups 1, 2, and 3) based on the cumulative dose of <sup>131</sup>I. SCr and BUN levels were found to be increased in all subgroups 5 years after the initial <sup>131</sup>I therapy compared with the levels before treatment. The higher the cumulative dose was, the more increase in SCr and BUN levels was observed. The difference was statistically significant. Furthermore, eGFR was found to be decreased in all groups after <sup>131</sup>I treatment, and the greater the cumulative dose was, the more decrease in eGFR was observed. The difference was statistically significant. However, a gender bias was not observed in the changing trends of SCr and BUN levels and eGFR. The results of biochemical parameters are summarised in Table 3–5.

Table 3

Measurement results of SCr levels before and 5 years after initial <sup>131</sup>I treatment of patients with increased SCr levels

	n	SCr (μmol/L)	
		Baseline	Last FU
Subgroup 1	125	112.33 ± 23.50	130.93 ± 31.65(p = 0.012)
Male	57	114.53 ± 26.78	132.12 ± 32.33(p = 0.021)
Female	68	110.49 ± 18.96	129.93 ± 25.75(p = 0.003)
Subgroup 2	24	110.56 ± 25.16	146.48 ± 37.45(p = 0.001) <sup>a</sup>
Male	10	108.55 ± 27.08	143.56 ± 35.87(p = 0.000)
Female	14	112.04 ± 21.48	148.57 ± 29.23(p = 0.004)
Subgroup 3	19	110.41 ± 27.72	160.56 ± 35.92(p = 0.000) <sup>b</sup>
Male	8	111.46 ± 23.75	162.82 ± 40.21(p = 0.000)
Female	11	109.64 ± 24.23	158.91 ± 31.14(p = 0.000)
a, subgroup 2:subgroup 1 (P=0.026); b, subgroup 3:subgroup 2 (P=0.011)			

Table 4

Measurement results of BUN levels before and 5 years after initial <sup>131</sup>I treatment of patients with increased BUN levels

	n	BUN (mmol/L)	
		Baseline	Last FU
Subgroup 1	108	9.19 ± 2.12	11.30 ± 2.32(p = 0.038)
Male	49	9.06 ± 2.70	11.01 ± 3.21(p = 0.032)
Female	59	9.35 ± 2.01	11.54 ± 1.98(p = 0.024)
Subgroup 2	38	9.23 ± 2.06	13.52 ± 2.67(p = 0.013) <sup>a</sup>
Male	15	8.96 ± 3.09	13.82 ± 3.74(p = 0.000)
Female	23	9.41 ± 3.59	13.32 ± 2.61(p = 0.018)
Subgroup 3	9	9.09 ± 2.11	16.44 ± 3.19(p = 0.000) <sup>b</sup>
Male	5	9.25 ± 2.84	16.79 ± 3.27(p = 0.000)
Female	4	8.89 ± 1.77	16.00 ± 2.89(p = 0.000)
a, subgroup 2:subgroup 1 (P=0.031); b, subgroup 3:subgroup 2 (P=0.006)			

Table 5  
Results of eGFR before and 5 years after initial <sup>131</sup>I treatment of patients with decreased eGFR levels

	n	eGFR (mL/min/1.73 m <sup>2</sup> )	
		Baseline	Last FU
Subgroup 1	63	50.50 ± 11.46	42.78 ± 14.54(p = 0.041)
Male	22	55.32 ± 9.74	48.65 ± 15.08(p = 0.033)
Female	41	47.92 ± 12.48	39.63 ± 9.26(p = 0.028)
Subgroup 2	16	49.42 ± 14.07	38.49 ± 13.25(p = 0.014) <sup>a</sup>
Male	5	56.30 ± 15.55	43.72 ± 14.70(p = 0.001)
Female	11	46.30 ± 10.64	36.11 ± 12.03(p = 0.027)
Subgroup 3	8	50.90 ± 17.61	34.86 ± 11.38(p = 0.000) <sup>b</sup>
Male	3	54.83 ± 18.12	38.97 ± 12.78(p = 0.000)
Female	5	48.54 ± 14.53	32.39 ± 11.39(p = 0.000)
a, subgroup 2:subgroup 1 (P=0.037); b, subgroup 3:subgroup 2 (P=0.021)			

## Discussion

We compared the renal function parameters between <sup>131</sup>I pre-therapy and post-therapy patients. It should be emphasized that this is a retrospective study that used a database not specifically designed for this protocol because it is virtually impossible to design a prospective study on the nephrotoxicity of <sup>131</sup>I therapy owing to the long timespan involved. In this retrospective study, we investigated 850 patients treated with <sup>131</sup>I. In 588 patients with normal renal function, our findings revealed a non-statistically significant change in the mean values of renal function parameters (SCr, BUN, and eGFR) after <sup>131</sup>I treatment compared with baseline values, regardless of gender. We did not find an association between radiation exposure and the incidence of renal dysfunction despite the administration of a higher dose of <sup>131</sup>I. However, high-dose <sup>131</sup>I therapy aggravated renal impairment in 262 patients with abnormal renal function. The higher the <sup>131</sup>I cumulative dose was, the greater was the impairment of renal function. A gender bias was not observed in the changing trends of SCr and BUN levels and eGFR.

The kidney is probably most radiosensitive among the abdominal organs [10]. Although the renal tissue is capable of tolerating some radiation depending on the dosage and nuclide types, radiation nephropathy owing to renal irradiation has been recognized as an important complication of external beam radiation therapy (EBRT) or internal radiation therapy such as peptide receptor radionuclide therapy (PRRT). Based on the data derived from patients who have undergone EBRT, it is generally accepted that a dose of 23 Gy to the kidneys, in fractions of approximately 2 Gy, leads to a 5% risk of renal failure in patients within 5 years and that a dose of 28 Gy leads to a 50% risk of renal failure within the same period [11]. In addition, other studies have demonstrated that it is difficult to tolerate ionising radiation of more than 25–30 Gy because the outcome can be hazardous [12, 13]. These data cannot be simply translated to internal irradiation therapy with radionuclides. Unlike external radiation, the dose rate in internal isotope therapy is much lower and of a longer duration than that in EBRT. Radionuclides used in vivo generally deliver a radiation dose over an extended period depending on their physical and biological half-lives [14]. Data from various cancer studies, including studies on neuro-endocrine tumours (NETs) and castrate-resistant prostate cancer, provide some insight into renal damage caused by radio pharmaceuticals. In the largest study group about <sup>90</sup>Y-labelled peptides that included 1106 patients, renal toxicity was found to be 9.2% with a maximum follow-up period of 23 months and 8% with a longer follow-up for approximately 157 months, based on plasma creatinine levels and eGFR evaluated with MDRD formula [15, 16]. In the largest study group of 504 patients about <sup>177</sup>Lu-labelled peptides with a median follow-up of 19 months, serious nephrotoxicity was found to be 0.4% [17]. Anna Yordanova et al [18] suggest that no relevant increase in nephrotoxicity was detected in patients who received a kidney radiation dose > 19 Gy in the follow-up period of the study that used <sup>177</sup>Lu-PSMA (prostate-specific membrane antigen) therapy for patients with castrate-resistant prostate cancer. The results of a study demonstrated that very low doses of <sup>137</sup>Cs with activities of 4000 or 8000 Bq/kg of internal IR (ionizing radiation) not only induced early renal histological injury and acute oxidative stress but also caused DNA damage [19]. As evident from such studies, each radiopharmaceutical exhibit different potential toxicity and side effects owing to its special biodistribution patterns, dosage, nuclide type, and radiation energy. Adequately water-soluble <sup>131</sup>I-labelled radiopharmaceuticals are preferentially excreted through the renal route, with a high renal uptake [20]. Approximately 90% <sup>131</sup>I is excreted in the urine within 48 h of administration [21]. In the <sup>131</sup>I experimental trials, Nihat Yumusak et al [22] demonstrated that cell proliferation and apoptosis began on the seventh day and peaked during the tenth week based on the immunohistochemical analyses of the kidneys. Kolbert et

al [23] provided dose–volume histograms and mean absorbed doses for 14 normal organs; the calculations were performed using a 3D voxel-based method. The mean  $^{131}\text{I}$  dose was approximately 0.10 Gy/GBq in the kidneys. In our study, the patients were usually advised to drink plenty of water to reduce the risk of nephrotoxicity after  $^{131}\text{I}$  therapy. No obvious renal toxicity was observed in patients with normal renal function. A possible explanation is the limited follow-up time in relation to the longer latency period from the time of initial treatment to the development of renal dysfunction. The mean age of 13 patients with renal dysfunction was older greater than that of patients with normal renal function, which in turn raises a speculation regarding radiation damage being more severe in older patients, as is commonly believed for radiation damage [24]. However, a significant radiation dose to the kidneys was observed in patients with pre-therapy for renal insufficiency, despite renoprotection. In patients with abnormal renal function before  $^{131}\text{I}$  therapy, renal function declined after 5 years mainly because of factors such as age, diabetes, high blood pressure, and poor baseline renal function. However, the higher the cumulative dose, the more severe the renal damage, which indicates that high-dose  $^{131}\text{I}$  treatment also leads to the aggravation of renal damage. The excretion of  $^{131}\text{I}$  by the kidneys may be reduced in patients with renal insufficiency [25], which may aggravate further damage of renal function. Vogel K et al [26] stipulated that the biological half-life of  $^{131}\text{I}$  was significantly influenced by eGFR; a decrease in GFR may significantly prolong the half-life of  $^{131}\text{I}$ . Similarly, in some studies, the prescribed activity of  $^{131}\text{I}$  in patients with renal insufficiency is reduced by approximately 30% or 50% to compensate for the prolonged clearance of radioiodine [27–29].

SCr, an amino acid with a molecular mass of 113 D and that is freely filtered by the glomerulus, is the most commonly used metabolite for the assessment of renal function despite several drawbacks. SCr levels are affected by several factors, such as body weight, exercise, diet, tumour burden, sex, and muscle mass, which need to be corrected for the accuracy of assessing renal function [30]. The diagnostic sensitivity of SCr evaluation is considered insufficient for analysing moderate GFR reduction. Therefore, the use of SCr levels as a means to assess the renal function levels alone is not recommended. In some studies, post-therapy SCr levels did not increase proportionately with cumulative radioactivity and renal absorbed doses of the kidneys [31]. To date, GFR has been proposed as the standard that should be used for evaluating radiation-induced renal damage [32]. However, the measured GFR was not a feasible marker in the present study because its measurement requires continuous intravenous (i.v.) infusion of an ideal filtration marker such as inulin and multiple blood or urine collections, which is not practical for clinical routine use [33]. Radiopharmaceuticals for renal function measurements such as  $^{51}\text{Cr}$ -ethylenediaminetetraacetic acid (EDTA) and  $^{99\text{m}}\text{Tc}$ -diethylenetriaminepentaacetic acid (DTPA) are expensive, complicated, and time consuming for the follow-up of large patient groups. Owing to the convenience of SCr evaluation, various equations based on SCr have been introduced for evaluating eGFR levels in order to overcome such limitations. Three formulae are usually recommended, namely, MDRD, Cockcroft–Gault (CG), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations. MDRD seems to be more reliable [34]; hence, we used it to estimate GFR. However, the accuracy of evaluating eGFR using SCr levels remained questionable. During the initial decrease in GFR, the tubular secretion of creatinine enhances, which can alleviate the increase in SCr levels. Until the tubular secretory capacity is saturated, SCr levels may remain normal and eGFR may be overestimated [35, 36].

## Study Limitations

The major limitation of this quality study was the unavailability of control data of patients with thyroid cancer who did not receive  $^{131}\text{I}$  treatment. Another limitation was a relatively short follow-up period for patients with normal renal function before  $^{131}\text{I}$  therapy. Furthermore, the identification of renal dysfunction based on SCr and BUN levels and eGFR instead of measured GFR was another limitation. GFR gradually decreased with age, and age stratification was not performed in this study. In addition, the evidence derived from a retrospective cohort study is typically lower in statistical quality because of various sources of inherent bias such as surveillance bias, which may result in a classification bias.

## Conclusions

In the present study, we found that nephrotoxicity was low in patients with DTC with normal renal function treated with  $^{131}\text{I}$ . Although the cumulative dose was approximately 37 GMq,  $^{131}\text{I}$  did not cause significant nephrotoxicity in the patients. After we subdivided the patients into three subgroups based on the cumulative doses, we failed to demonstrate a statistical difference, and the incidence of renal dysfunction did not achieve a statistically significant level, which was not associated with the cumulative doses. However, our findings revealed an increasing trend in BUN and SCr levels and a decreasing trend in eGFR in patients with renal dysfunction who received  $^{131}\text{I}$  treatment. Moreover, the damage to renal function becomes more severe with an increase in cumulative doses. The present study indicates that close attention should be paid to patients with abnormal renal function before treatment in order to maintain an appropriate balance between therapeutic efficacy and the reduction of nephrotoxicity.

## Declarations

**Funding:** The present study did not receive any funding.

**Conflict of interest:** The authors report no conflict of interest.

**Availability of data and material:** The datasets for the present study were from the Department of Nuclear Medicine, Tianjin Medical University General Hospital.

**Code availability:** Not applicable.

**Authors' contributions:** Liang Yin wrote the manuscript. co-first authors Liang Yin, Yan Wang, Weilong Li and Yangyang Lin contributed equally to the study. Yan Wang, Weilong Li, Yangyang Lin, Zhichun Lin, Qiang Jia, Jian Tan, Xue Li, Qing Guo and Zhaowei Meng revised the manuscript. All authors contributed to manuscript revision, read, approved the submitted version, and agreed to be accountable for all aspects of the research in ensuring the accuracy of this study. All authors have given consent to the publication of this manuscript.

**Ethics approval:** The research reported in this study that involved human participants was in accordance with the ethical standards of the institution and with the principles of the Declaration of Helsinki 1964 and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from the patients for the anonymous use of their clinical, imaging, and histological data.

**Consent for publication:** Not applicable.

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