

Title: Radioiodine therapy in patient of differentiated thyroid cancer with end-stage renal disease on maintenance hemodialysis: case report with review of literature.

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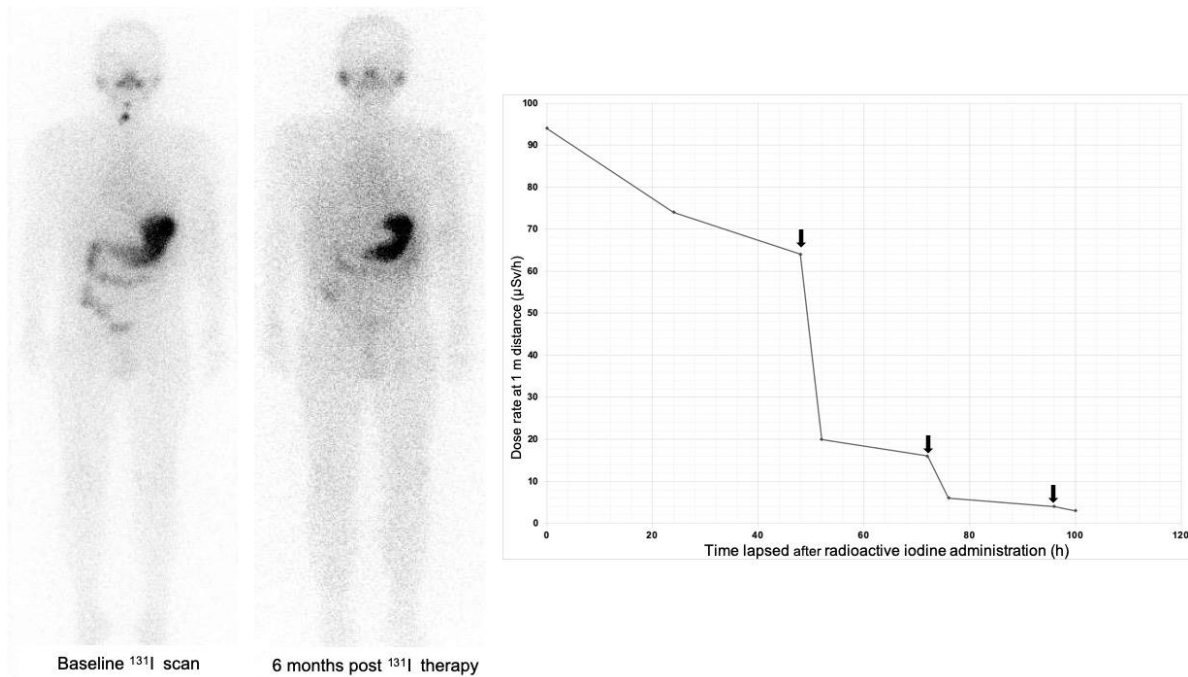
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Running Title: Radioiodine therapy in patient with CKD

Abstract

Surgical resection followed by radioactive-iodine (^{131}I) therapy constitutes a standard treatment for differentiated thyroid cancer (DTC). ^{131}I is normally excreted through kidneys and treatment of patients with end stage renal disease (ESRD) on hemodialysis requires special attention for dosage of ^{131}I , timing of dialysis and radiation safety. We present a case of a post-thyroidectomy patient with ESRD on haemodialysis who required radioactive iodine ablation with review of literature.

Keywords: Radioiodine therapy, ESRD, Thyroid cancer



INTRODUCTION

Thyroid carcinoma is the most common endocrine malignancy and surgical resection followed by radioactive iodine (^{131}I) administration for ablation/therapy is a standard treatment for DTC(1). ^{131}I administered to patient, is absorbed by the thyroidal tissue and majority of the remaining circulating ^{131}I is cleared by kidneys. The clearance of circulating ^{131}I is significantly reduced in patients with chronic kidney disease (CKD) resulting in prolonged effective half-life and potentially resulting in an increased patient's radiation exposure particularly to bone marrow (2). Clearance of ^{131}I in patients with CKD is achieved via dialysis which can be either peritoneal or haemodialysis. But the use of dialysis in a patient administered with ^{131}I poses various questions like dose of ^{131}I , timing of dialysis and radiation safety precautions. Literature on the treatment of DTC with ^{131}I in patients with CKD consists of only a few case reports with no formal guidelines. We present here the review of literature followed by description of our case.

Review of Literature

The incidence of cancers, including DTC in patients suffering from ESRD is relatively higher than in patients with normal renal function. Increasing number of neck ultrasonography for parathyroid imaging, higher prevalence of DTC in patients with high parathyroid levels and higher survival rate of ESRD patients undergoing haemodialysis are few of the postulated reasons (3-5).

CKD causes prolonged excretion of ^{131}I resulting in comparatively higher side effects like sialadenitis, xerostomia and marrow depression (6). Therefore, haemodialysis session needs to be adjusted to ensure maximal thyroidal uptake and minimal extrathyroidal concentration, thereby maximizing the therapeutic effect and minimizing the short- and long-term radiation effects.

DOSE OF ¹³¹I

Two general approaches to determine the dose of ¹³¹I in patients with thyroid cancer are either to give the empiric dose or to perform dosimetry. Individual dosimetry for calculation of maximum tolerable dose of ¹³¹I takes into consideration patient's variables like volume of thyroid remnant, metastases, renal dysfunction, TSH levels and dialysis schedule. But the process is cumbersome and it needs to be made sure that no changes in variables occur between dosimetry and therapy.

The ATA guidelines recommend use of ¹³¹I in patients with intermediate and high-risk DTC with the intent of ablative, adjuvant and treatment of metastatic disease(7). Howard et al. calculated that effective half-life of ¹³¹I in patients on haemodialysis was 4.5 times higher than in patients with normal renal function and reduced the dose of ¹³¹I(8) which was supported by other investigators too (9-11). However, some other investigators recommended increasing the ¹³¹I dose, as they found faster clearance of ¹³¹I in patients of CKD during dialysis sessions and reduced effectiveness of lower dose (12,13).

Another factor important for effective treatment with ¹³¹I is the prior stimulation of thyroid cancer cells with raised levels of thyrotropin (TSH) which can be achieved either via withdrawal of thyroxine supplementation (TW) for 3-4 weeks or by intramuscular injection of recombinant human TSH (rhTSH). Vermandel et al. in their study of 6 DTC patients with ESRD; gave 1 dose of 0.9mg of rhTSH 48 hours before ¹³¹I administration to avoid prolonged and excessive TSH levels instead of giving the standard two doses(10). Both TW and rhTSH are efficient in increasing the TSH levels in ESRD patients and have no major side effects. Unfortunately, data is insufficient to comment on preference of one method over another.

DIALYSIS

Inorganic iodine is cleared via kidneys and in CKD the ^{131}I excretion is further hampered by increased stable iodine levels in the body. The clearance of ^{131}I in hemodialysis is 4-5 times higher than renal clearance(14) which makes planning of the dialysis sessions very crucial so as to allow for ^{131}I to be present in sufficient doses for its therapeutic effect before its removal in hemodialysis. To avoid any emergency need of immediate hemodialysis between the planned timings and to achieve optimum therapeutic effect of ^{131}I , patient should undergo dialysis immediately before the administration of ^{131}I .

Timing of dialysis after administration of ^{131}I differ in various case reports (Table 1). Ideally, post-radioiodine administration, first dialysis should be done after maximum ^{131}I uptake in remnant thyroid tissue/ malignant cells have occurred. Patients on haemodialysis have shown 6% and 10% uptake of ^{131}I in the thyroid remnant at 24 hours and 48 hours respectively(8). Thus, waiting for 48 hours before first dialysis session seems appropriate and a dialysis before 48 hours may lead to undertreatment. However, if the dose is kept same or increased the first dialysis session may be commenced early which in most case reports is within 24 hours after dose administration.

TOXICITY

Vermandel et al. retrospectively calculated the radiation dose to bone marrow in six post-thyroidectomy patients with renal dysfunction, treated with ^{131}I . The mean estimated dose to the bone marrow was 0.992Gy for all the patients with no significant haematological toxicity seen in any of their cases(10). Mello et al. reported fall in haemoglobin levels after second treatment of 100mCi of radioiodine requiring blood transfusion, though the duration at which fall of haemoglobin levels was seen post ^{131}I is not specified (12). Mild sialadenitis and bilateral neck pain below ears has also been reported post ^{131}I treatment(9,15).

RADIATION SAFETY

Haemodialysis can be performed safely after radioiodine administration and should be done with appropriate shielding. In addition to the standard safety precautions that are followed after radioiodine therapy, additional measures were described by other authors like provision of lead aprons to all personnel attending the patient, distance of 2 meters between technicians from the patients or the dialysis technician needs to sit outside the lead shielded room with the door left ajar (16,17). Mello et al. used lead shield between the patient and dialysis technician; each technical staff was changed after spending 2 hours with the patient(12). None of the authors reported any significant exposure to the personnel or contamination of the dialysis machine and room.

Therefore, special precautions should include adequate distance and shielding between patient and technician, providing protective wear to the attending personnel, covering the room with absorbent sheets and disposal of the dialysate directly into the sewer system. More than one technician and nurse may be employed, to reduce the radiation exposure. After 3-4 dialysis in post-radioiodine administration, patient can undergo dialysis in usual manner.

CONTINUOUS AMBULATORY PERITONEAL DIALYSIS (CAPD)

The experience of using of CAPD in such setting is even more limited. In CAPD excretion of iodine is a slow continuous process, at approximately one third the rate of normal renal excretion. Similar to HD dose of ^{131}I is reduced in cases on CAPD(18). Toubert et al. administered 22mCi (814MBq) of ^{131}I instead of the usual 100mCi dose (3700MBq) in a patient of follicular thyroid carcinoma (19). ^{131}I Wang et al. recommended oral administration of ^{131}I after one session of CAPD followed by 3 more courses of CAPD each performed at intervals of 6 hours. The author

even preferred CAPD to HD because of the ease with which contamination of the environment by radiation could be prevented as the collected dialysate can be allowed to decay(20).

CASE REPORT

The patient is a 35-years-old hypertensive man with chronic kidney disease secondary to chronic tubulointerstitial nephritis. He was on alternate day hemodialysis for past one year and presented with left side neck swelling 6 months back. Neck ultrasonography revealed a small 9x7mm hypoechoic nodule with microcalcification in the left lobe of thyroid gland with multiple enlarged left level III and IV cervical lymph nodes. After an inconclusive cytology from the thyroid nodule a biopsy from the left cervical lymph node revealed metastatic papillary carcinoma thyroid. He underwent total thyroidectomy with central and lateral neck dissection within one month. Histopathology revealed a multifocal papillary carcinoma thyroid (maximum tumor dimension ~2.3 cm), with lymphovascular invasion and without extrathyroidal extension. Twenty-six out of the 42 lymph nodes dissected were positive for metastatic disease (T2 N2b Mx) putting him in intermediate risk category according to the American Thyroid Association (ATA)(7).

For preparation the patient was asked to withheld the thyroxine supplementation for 4 weeks. His TSH levels rose to 50 μ IU/mL and stimulated thyroglobulin level was 132 ng/mL with normal anti-thyroglobulin levels. A low dose whole-body 131 I scan done with 1.2mCi (44.4MBq) showed the thyroid bed tracer uptake likely thyroid remnant (Figure 1).

A patient with normal renal function in intermediate risk category would have received a dose of 100mCi (3700MBq) of 131 I for ablation of thyroid remnant and as adjuvant treatment. For our patient after reviewing the literature and discussion in tumor board, the dose of 131 I was reduced

to 50% (50mCi; 1850MBq) to maximize the effect and reduce the radiation exposure to normal tissues.

On the day of therapy, patient underwent dialysis in the morning and received a decided dose 50mCi (1850MBq) of ¹³¹I after 2 hours (Day 0). This was followed by dialysis at 48, 72 and 96 hours. The whole-body radioactivity was measured at stomach level in standing position using an ionization chamber-based gun monitor (ROTEM RAM ION, RotemIndustries, Israel) at a distance of 1metre. The whole-body radioactivity was measured at various time intervals and after each session of dialysis (Supplemental Figure 2). A reduction of whole-body radioactivity by 69% after the first dialysis session. The findings were consistent with literature showing clearance in range of 50-80%(9,16).

A post-therapy whole-body iodine scan done after 5 days showed tracer uptake in the thyroid bed region same as seen in the low-dose diagnostic scan. The patient was discharged after 4 days of radioiodine administration with exposure rate of ~3 µSv/hr measured at stomach level at the distance of 1metre. The patient remained asymptomatic on follow-up with no change after 6 weeks of ¹³¹I therapy from baseline in his white blood cells (5300 vs 5240 cells/ cu.mm) and haemoglobin levels (Hb-8.2g/dL vs 8.4g/dL).

The patient received dialysis at the end of the day when there were no other patients in the room under the supervision of radiation safety officer (RSO) in department of nephrology due to the non-availability of a portable dialysis facility and separate dialysis room with appropriate shielding in our hospital. Care was taken to avoid any blood or fluid spill and contamination. In normal condition, at a time more than 4 patients undergo dialysis in the same room. The floor (near patient bed) was covered with absorbent sheets. During the haemodialysis procedure of 4 hours, technician

was wearing all the necessary protective clothing (shoe covers, gloves, face mask and lead apron). All the personnel attending the patient including the dialysis technician were given pocket dosimeter (RADOS RAD-60S, Israel) for real-time monitoring of exposure rate. The dialyser, blood lines, absorbent sheets and linen generated during the procedure were collected in polythene sheets and stored in radioactive waste storage room of isolated ^{131}I therapy ward for decay. The dialysate drain line was connected to the sewer system. Following the dialysis, the haemodialysis machine was put on rinsing mode to eliminate any ^{131}I contamination, though no contamination was observed in haemodialysis machine checked with GM counter (ROTEM RAM GENE-1, RotemIndustries, Israel). The total dose received by the comforter and dialysis technician was $37\mu\text{Sv}$ and $16\mu\text{Sv}$ respectively far below the permissible levels.

Patient Outcome

Patient showed decline of stimulated serum thyroglobulin level to 5 ng/mL with TSH of 60 μIU /mL after a six-months of follow-up. The low dose ^{131}I scan showed resolution of previous tracer uptake in thyroid bed (Supplemental Figure 3) and patient was followed on suppressive thyroxine doses with target TSH of 0.1-0.5 IU/mL.

Conclusion

Treatment of thyroid cancer with radioiodine therapy in patients with renal dysfunction on maintenance haemodialysis can be performed safely by following radiation safety standardized protocol and with the combined efforts and co-ordination of nuclear medicine physician, nephrologist, radiation safety officer and dialysis team. Literature on the treatment of DTC with ^{131}I in patients with CKD consists of only a few case reports with variable experiences and recommendations. Therefore, more literature and systematic prospective studies are required to formulate standard procedure guidelines.

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Key points:

1. Chronic kidney disease leads to delayed excretion of radioactive iodine and guidelines for dose requirement, timing of dialysis and special radiation safety protocols in patients of CKD requiring radioactive iodine is not available.
2. A multidisciplinary approach involving the endocrinologist, nuclear medicine physician, nephrologist, radiation safety team, and dialysis team is required for management of these cases.
3. 50% of an empiric ^{131}I dose followed by dialysis at 48 hours, 72 hours and 96 hours was followed in our patient of DTC with intermediate risk on maintenance hemodialysis.

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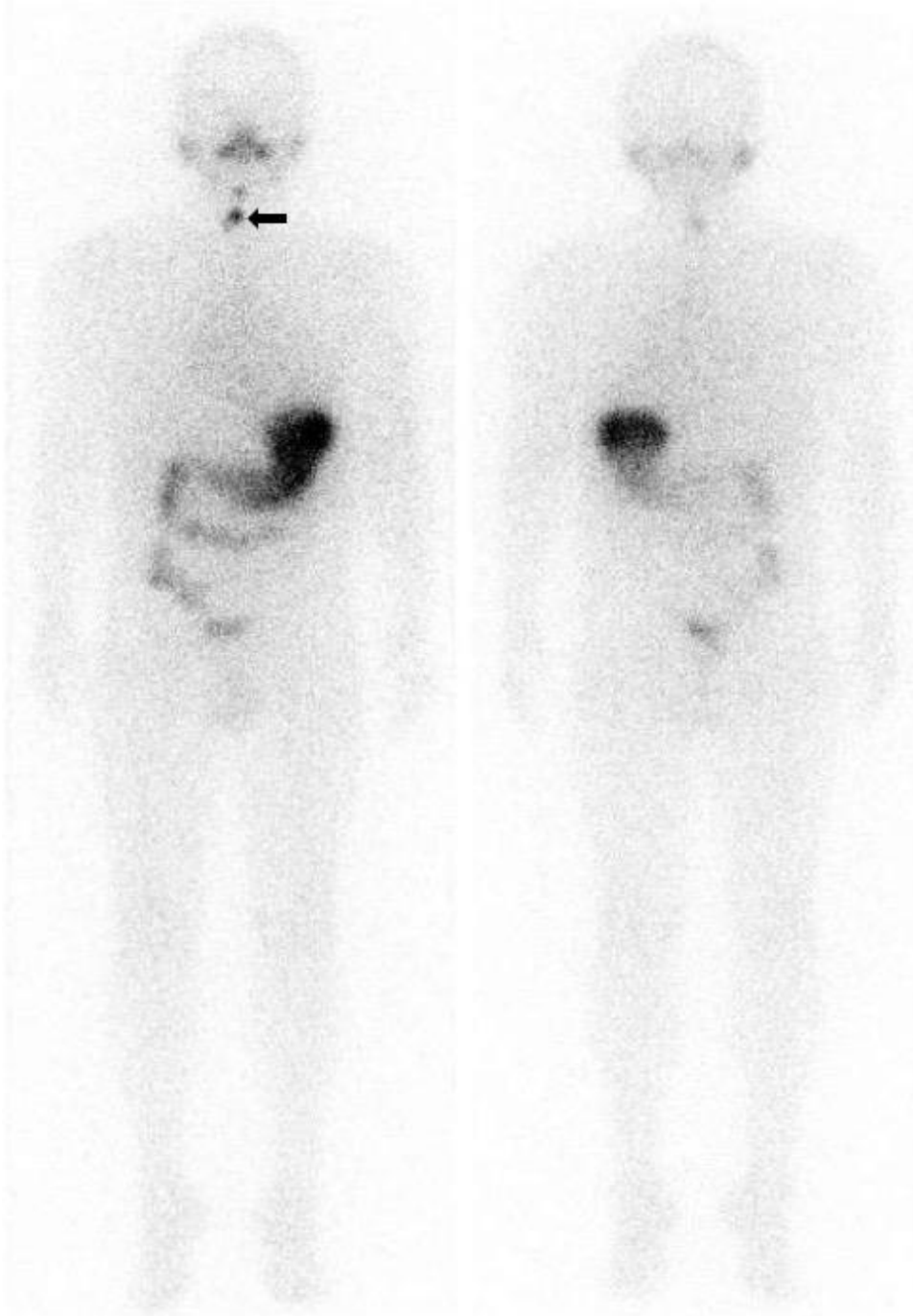
Table 1. Summary of literature on haemodialysis in patients with CKD after radioiodine therapy (n=23)

Authors	Age (yrs)	Cancer	Dose (mCi)	Time of Dialysis	Conclusion of the studies
Vermandel et al. (10)	67	PTC	60	42, 90 hrs	<ul style="list-style-type: none"> ▪ 30% reduction in dose for ablative and adjuvant treatments ▪ For metastatic disease dosimetry should be done ▪ First dialysis 42 hours after dose
	47	PTC	77, 82		
	63	PTC	61		
	63	PTC	50		
	29	PTC	60		
	71	VC	101		
Daumerie et al.(11)	42	PTC	25 in 2 sessions 6 months apart	2, 5, 7 days	<ul style="list-style-type: none"> ▪ Administer 25% of prescribed activity ▪ First dialysis 24 hours after dose
	62	PTC			
	27	PTC			
Jimenez et al.(16)	42	PTC	75	Daily for 5 days	<ul style="list-style-type: none"> ▪ Use dosimetry to determine dose ▪ Dialysis every day for five days
	51	PTC	87		
	34	PTC	120		
Holst et al.(9)	40	PTC	98	2,3,4 days	<ul style="list-style-type: none"> ▪ Use 21-28% of dose ▪ Dialysis at day 2 and 4
Mello et al.(12)	42	PTC	100	41, 98hrs	<ul style="list-style-type: none"> ▪ Use dosimetry to determine dose
Sinsakul et al.(17)	43	PTC	100	20/ 24 hrs	<ul style="list-style-type: none"> ▪ Dialysis 2-24 hours after dose
	56	PTC	157		
Culpepper et al.(14)	56	FTC	129	24, 43, 66 hrs	<ul style="list-style-type: none"> ▪ None
Howard et al. (8)	34	PTC	80	-	<ul style="list-style-type: none"> ▪ Administer 22% of empiric dose ▪ Dialysis 48 hrs after dose

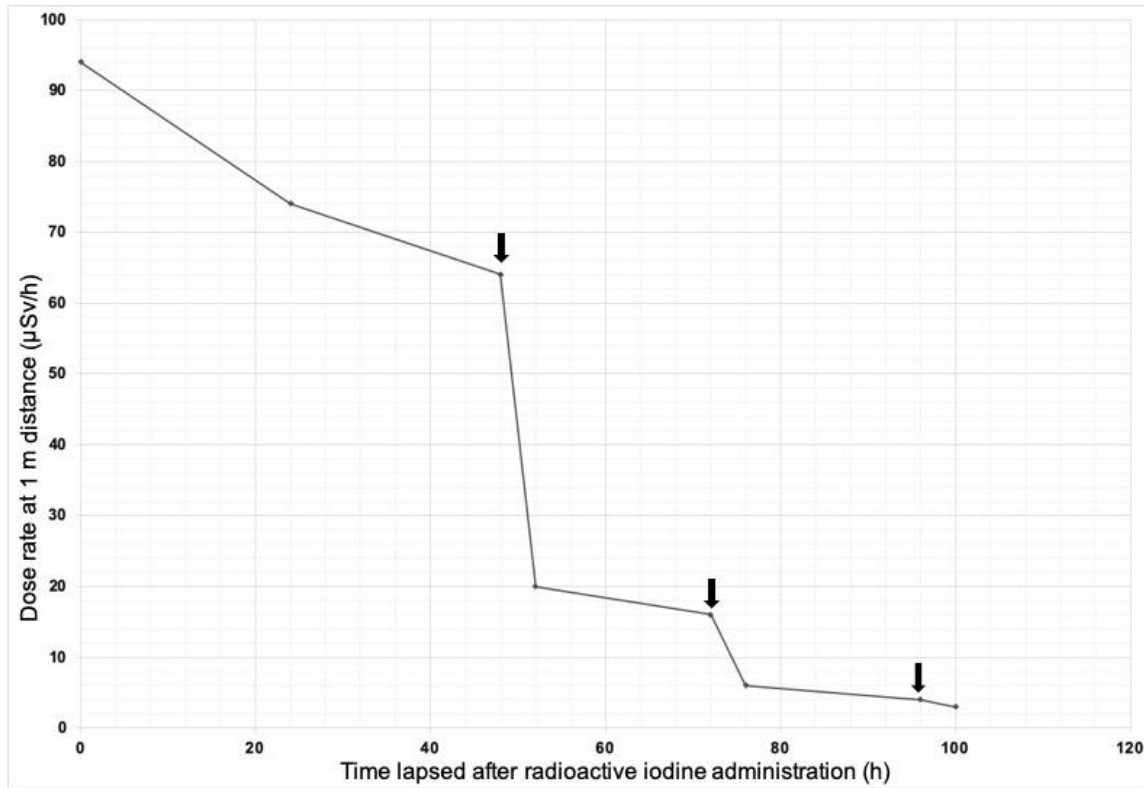
Morrish et al.(13)	36	PTC	50,120,150,250 over 4 year	24- 48 hours	<ul style="list-style-type: none"> ▪ Significantly larger iodine 131 dose required, ▪ First dialysis 48 hrs after dose
Magne at al.(21)	43	PTC	50	1,3,6 days	<ul style="list-style-type: none"> ▪ Increase dose upto 25%
Gallegos-Villalobos et al.(22)	51 52	PTC PTC	100 100	1,2 days	<ul style="list-style-type: none"> ▪ Administer same dose with normal renal function ▪ Two subsequent dialysis daily
Bhat et al.(23)	49	PTC	50	15, 27, 43 hrs	<ul style="list-style-type: none"> ▪ None

Supplemental Figure legends

Supplemental Figure 1. Low dose whole-body radioiodine scan shows focus of tracer uptake in the thyroid region suggestive of thyroid remnant (arrow).



Supplemental Figure 2. Graph showing dose rate at stomach level at a distance of 1 metre from the patient at different time points during the course of treatment (Dialysis done at 48, 72 and 96 hours; arrows).



Supplemental Figure 3. Low dose whole-body radioiodine scan done after six months of radioiodine therapy shows resolution of tracer uptake in the thyroid region.

