

Cumulative ionizing radiation exposure in patients with end stage kidney disease: a 6-year retrospective analysis

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Abstract

Objective: To quantify cumulative exposure to ionizing radiation in patients with end stage kidney disease (ESKD). To investigate factors which may be independently associated with risk of high cumulative effective dose (CED).

Materials and methods: The study had local institutional review board ethical approval. We conducted a retrospective study of 394 period prevalent ESKD patients attending a single tertiary referral centre between 2004 and 2009. Patient demographics were obtained from case records. Details of radiological investigations were obtained from the institutional radiology computerized database. CED was calculated using standard procedure specific radiation levels. High exposure was defined as CED > 50 mSv, an exposure which has been reported to increase cancer mortality by 5%. Data were compared using Pearson χ^2 and Mann–Whitney *U* test or Kruskal–Wallis tests.

Results: 394 patients were followed for a median of 4 years (1518 patient years follow-up). Of these 63% were male. Seventeen percent of patients had a CED of > 50 mSv. Computed tomography (CT) accounted for 9% of total radiological studies/procedures while contributing 61.4% of total study dose. Median cumulative dose and median dose per patient year were significantly higher in the hemodialysis (HD) group (15.13 and 5.79 mSv, respectively) compared to the post-transplant group (2.9 and 0.52 mSv, respectively) ($P < 0.001$).

Conclusion: ESKD patients are at risk of cumulative exposure to significant levels of diagnostic radiation. The majority of this exposure is imparted as a result of CT examinations to patients in the HD group.

Key words: Radiation—Computed tomography—End stage renal disease—Hemodialysis—Cumulative effective dose

Long-term exposure to low level ionizing radiation is accepted to be associated with an increased incidence of malignancy [1, 2]. The magnitude of the attributable risk is however less definitive [3]. Ionizing radiation has recently been officially categorized as a carcinogen by the World Health Organisation International Agency for Research on Cancer and radiation from medical imaging currently represents the single largest source of exposure to radiation for the general public [4]. While the diagnostic and therapeutic benefits of medical imaging are unquestionable, trends exhibit a very rapid rise in the use of ionizing radiation in the past decade [5]. In particular, computed tomography (CT) scanning has exhibited a recent exponential increase in use and thus radiation doses imparted from this modality have increased in parallel [6].

Attention has turned to concerns regarding the potential harmful effects of ionizing radiation from diagnostic imaging [7]. Particular focus has been placed on patients with chronic disease for whom the ongoing use of imaging is necessary and increasingly frequent [8]. Patients with end stage kidney disease (ESKD), both on hemodialysis (HD) and post-renal transplant, are exposed to a wide range of diagnostic and therapeutic radiologic procedures, in many cases from an early age. Many of these procedures impart fractionated though nevertheless cumulative doses of ionizing radiation.

Maintenance renal replacement therapy is in itself also associated with an increased risk of malignancy, the etiology of which is unclear [9]. Cancer risks from

radiation are potentially multiplicative of the background cancer risks [1, 10]. Thus, in this particular patient cohort, the overall projected risk may be attendantly higher. Virtually no data has, however, been published to date on the cumulative radiation exposure which this population accrues over time and its potential health consequences.

The aim of this study was to examine the use of diagnostic imaging in patients receiving renal replacement therapy in a single university-based tertiary referral center. We aim to: (1) quantify exposure through estimation of cumulative effective dose (CED); (2) investigate trends in exposure by imaging modality; (3) identify patient groups at risk for high exposure; and (4) identify actions which may be taken to monitor or reduce radiation dose from medical imaging in this cohort.

Materials and methods

Study population

The study protocol was approved by the Institutional Clinical Research Ethics Committee. We conducted a retrospective study of period prevalent maintenance renal replacement therapy patients attending a single university-based dialysis center over a 6-year period, from 2004 to 2010. This report confirms and extends our preliminary observations in 100 patients [11]. We included those patients on HD and those with functioning renal transplants. Data was collected from a total of 426 patients. We excluded those who attended for less than 6 months during the study period to avoid overestimating average patient dose per year ($n = 32$). This particular subset of patients tended to be more acutely unwell (22 of these patients died) and in consequence required more imaging studies over a short period than those for whom follow-up was more long term. The remaining 394 patients are included in our analysis. We censored patients at time of death, time of transplant (for HD patients), and time of transplant failure. At study conclusion, 306 patients remained under active follow-up, 88 patients had deceased.

Patient details and diagnostic imaging

As our center is the sole regional provider of dialysis services, all patients attended this center exclusively for provision of all aspects of care. The centralized provision of services, including radiology, allowed for complete, accurate, and reliable collection of details of the vast majority of radiological procedures performed over the study period. These details were retrieved from the local computerized Patient Archiving and Communications System (PACS) and via a central computerized patient registration system (Keogh Radiology Information Systems, version 2.7). Clinical details were obtained by review of patients' medical notes. The clinically attributed

cause of ESKD was obtained from the institutional ESKD registry.

CT examinations were performed using either single slice CT (Siemens Somatom, Siemens Medical Solutions, Erlangen, Germany), four-section multi-detector row CT (Toshiba Aquilion, Toshiba Medical Systems, Zoetermeer, The Netherlands) or sixty-four-section multi-detector row CT (Lightspeed, General Electric Medical Systems, Waukesha, Wisconsin). Vascular interventional procedures such as HD catheter placement, central and peripheral arteriography, and fistulogram and fistuloplasty were performed by a number of staff interventional radiologists, fellows, and residents.

All studies performed for both diagnostic and therapeutic procedures were included to ensure an accurate estimate of total cumulative dose. Studies performed and recorded which imparted no ionizing radiation were excluded from calculations regarding dose.

Dose estimation

The overall detrimental biologic effect of a radiation exposure was quantified using the cumulative effective dose in millisieverts (mSv) [12]. The calculation of actual absorbed ionizing radiation dose to a living human is extremely complex. It is based on direct radiation measurements, weighting factors developed using mathematical representations of the human body and by applying tissue weighting factors [13]. Thus, the term dose estimate is used rather than dose. It is important to understand that dose absorbed may vary by as much as 5%–10% depending on individual patients and manner of image acquisition [14]. The calculation, however, allows for useful population-level comparisons across different types of radiation exposure [7, 12].

We calculated CED retrospectively of all imaging studies and interventional radiology procedures using average procedure specific reference effective doses for diagnostic imaging studies published by the United Kingdom National Radiation Protection Board (NRPB), 2002 [13] (Table 1).

For those procedures not referenced in the NRPB report, we used recent published effective doses from international literature [5]. In our study, high CED was

Table 1. Radiation doses for common imaging studies (13)

Imaging study	Effective dose of radiation (mSv)
Chest X-ray	0.02
Plain film abdomen	0.7
C Spine X-ray	0.07
HD catheter placement	0.48
Nephrostomy	3.4
Coronary angiography	6.6
CT brain	2
CT thorax	8
CT abdomen	10
CT pelvis	10

defined as exposure in excess of 50 mSv (effective dose equivalent of 2500 chest X-rays). Data from the most comprehensive epidemiologic studies supporting the carcinogenic effect of radiation is that of the atomic bomb survivors in Japan. The data from this study show an approximate 5% increased risk of cancer at estimated dose exposures in excess of 50 mSv [15].

In order to assess the effect of renal replacement therapy on CED, we examined the relationship between renal replacement modality at start of study and exposure to > 50 mSv radiation. We also assessed the factors associated with higher radiation exposure by comparing clinical and demographic characteristics, including age, in groups exposed to high and low levels of radiation. As CT was considered to most likely be the greatest contributor to radiation exposure, we more closely examined the factors associated with CED, which was attributable to CT examinations.

Statistical analysis

Data were described using mean and standard deviation (SD) or for non parametric distributions using median and intra-quartile range (IQR). Comparison between

groups was performed using Pearson's χ^2 for categorical variables and Mann–Whitney U test, or Kruskal–Wallis test for non-normally distributed continuous variables with two or more than two groups, respectively.

Data compilation and statistical analyses were performed using Microsoft Access 2007 (Microsoft Corporation, Washington, USA) and Statistical Package for the Social Sciences (SPSS) version 16.0 software (IBM, Chicago, Illinois, USA) using a two-sided type 1 error rate of 0.05.

Results

Patient demographics and cumulative doses

The 394 patients were followed for a median (IQR) of 4.0 years (1.7–6.0) and a total of 1518 patient years of follow-up. 36% were male and 17% were diabetic. The commonest cause of ESKD was glomerulonephritis (32.5%). Mean (SD) age at study entry was 53 (16.8) years. At the end of study follow-up, 88 patients had deceased. Modality of renal replacement therapy at commencement of study was HD ($n = 244$ patients) and functioning transplants ($n = 150$ patients) (Table 2).

Ninety-seven percent of the population had at least one radiological study performed during the course of follow-up. A total of 7311 radiographic examinations were performed. Overall, this was equivalent to one study performed every 75 days. Patients on HD had, on average, one study every 45 days whereas patients in the transplant group had one study every 185 days. These studies exposed the population to a cumulative total of 10548 mSv of radiation (Table 3).

Imaging modality contributors to patient dose

The proportion of radiation from each different modality is shown in Fig. 1. Plain radiographs account for 62% of the total number of studies while accounting for only 6% of total cumulative radiation exposure. Conversely, CT accounted for only 9% of total number of studies while contributing 61.4% of total radiation exposure. In total, 878 dialysis access-related procedures were performed comprising 12% of total number of studies and accounting for 7.4% of total dose. Forty-nine percent had at least one CT study performed. CT accounted for

Table 2. Associations between patient factors and high CED exposures (> 50 mSv)

Patient characteristic	Total	CED < 50 mSv	CED > 50 mSv	<i>P</i>
<i>N</i>	394	325	69	
Transplant patients	150	138	12	<0.001
HD patients	244	187	57	<0.001
<i>Cause of ESKD (%)</i>				
Diabetes	10.9	10.5	13.0	
Glomerulonephritis	32.5	32.3	33.3	
Congenital/reflux	19.3	20.9	11.6	
Hereditary nephropathy	12.9	11.7	18.8	0.121
RVD/hypertension	5.3	6.2	1.5	
Uncertain etiology	13.7	12.6	18.8	
Miscellaneous	5.3	5.8	2.9	
<i>Comorbidities over follow-up (%)</i>				
Coronary artery disease	27.6	22.8	50.7	0.001
Heart failure	10.2	9.5	13.0	0.381
Cerebrovascular disease	9.1	8.0	14.5	0.089
Diabetes	17.3	16.6	20.3	0.463
Pulmonary disease	8.9	6.8	18.8	0.001
Peripheral vascular disease	10.2	8	20.3	0.002
Non-skin malignancy	6.9	5.2	14.5	0.006

Table 3. Associations between modality of renal replacement therapy and CEDs

	Total	HD	Transplant	<i>P</i>
No. of patients	394	244	150	
Male (%)	249 (63.2)	157 (64.3)	92 (61.3)	NS (χ^2)
Mean (SD) age study entry (years)	52.7 (16.8)	57.0 (17.5)	45.7 (13.0)	<0.001 (<i>t</i> test)
Median (IQR) duration of follow-up (years)	4.0 (1.7–6.0)	2.3 (1.3–4.3)	6 (–)	<0.001 (Mann–Whitney <i>U</i>)
Number of radiological procedures	7311	5679	1632	<0.001 (Mann–Whitney <i>U</i>)
Total cumulative dose (mSv)	10548.32	8171.35	2376.97	<0.001 (Mann–Whitney <i>U</i>)
Median (IQR) cumulative dose (mSv)	9.17 (1.0–33.2)	15.13 (2.0–47.32)	2.9 (0.35–21.9)	<0.001 (Mann–Whitney <i>U</i>)
Median (IQR) dose per patient year (mSv)	2.99 (0.3–11.7)	5.79 (1.2–20.1)	0.52 (0.06–4.47)	<0.001 (Mann–Whitney <i>U</i>)

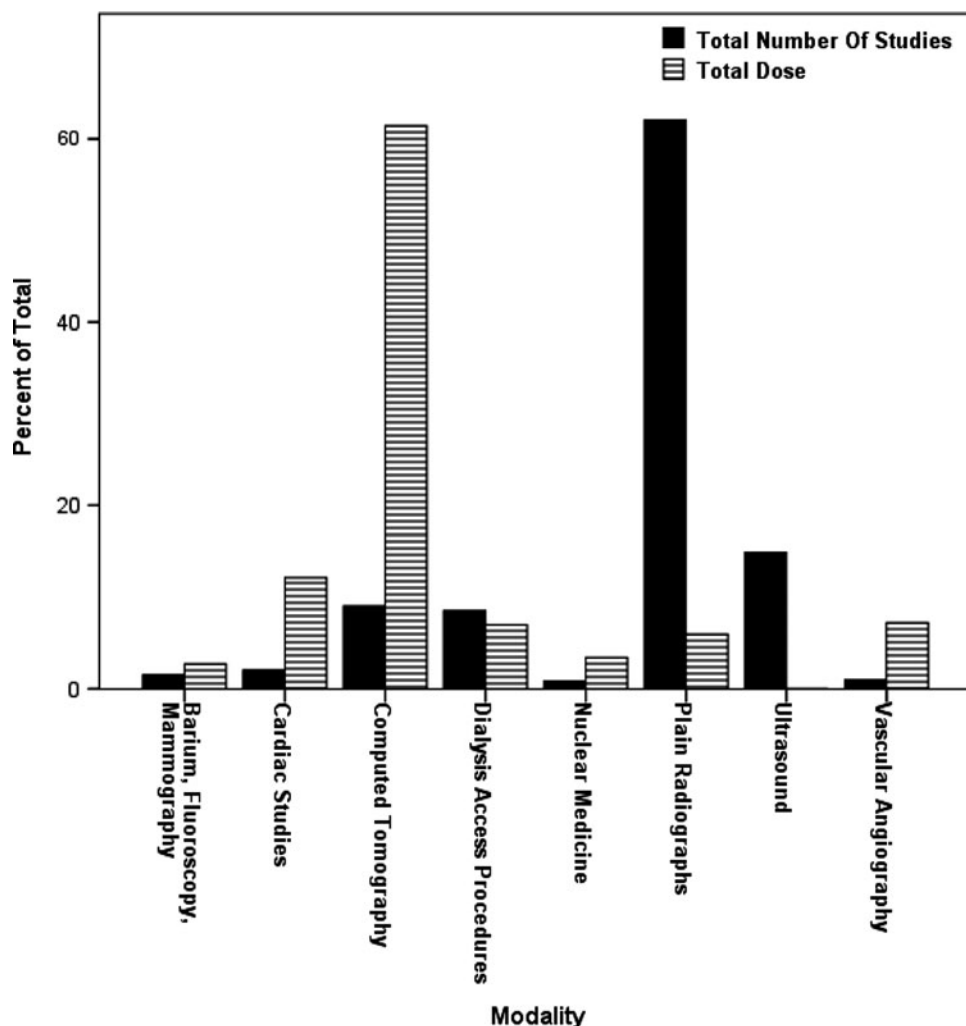


Fig. 1. Modality contributions to total study numbers compared to contribution to total radiation dose. The very large contribution of CT examinations to total dose relative to study number is noted, as is the relatively small contribution to total dose from plain radiographs, relative to the larger number performed.

5.9% of annual total number of studies in the first year of the study while accounting for 9.5% of annual total number of studies in the final year of the study 2009. Of note, however CT accounted for 52% of total annual radiation exposure in the first year of the study while accounting for 68% of total annual radiation exposure in the final year of the study.

The proportion of radiation from CT studies of different types is illustrated in Fig. 2. CT abdomen/pelvis accounted for 44% of total radiation dose from CT while accounting for 21% of total number of CT Studies. CT brain accounted for 6% of total radiation dose from CT while accounting for 27% of the total number of CT studies.

Patients at risk of high exposure (CED > 50 mSv)

Seventeen percent of patients had a CED of > 50 mSv. The median (IQR) total cumulative dose (mSv) per patient was 9.17 (1.0–33.2). Significantly more HD patients

than transplant patients had cumulative exposure > 50 mSv, (23.4% vs. 8%), $P < 0.001$, Pearson's χ^2 . Median cumulative dose and median dose per patient year was significantly higher in the HD group compared to the transplant group (Table 2). There was no significant difference in cumulative radiation dose between males and females.

There were significantly different CEDs between age groups. Median total CED in the overall study population and in the HD group was significantly higher in the 54–66-year old group, $P < 0.001$, Kruskal–Wallis; however, in the transplant group, patients in the over 66-year old group received the highest median CED of radiation (Table 4).

Cause of ESKD was not significantly associated with a total CED of > 50 mSv. Regarding patient co-morbidities recorded at the end of study period, only coronary artery disease, pulmonary disease, peripheral vascular disease, and non-skin malignancy were significantly associated with a median CED of > 50 mSv (Table 2).

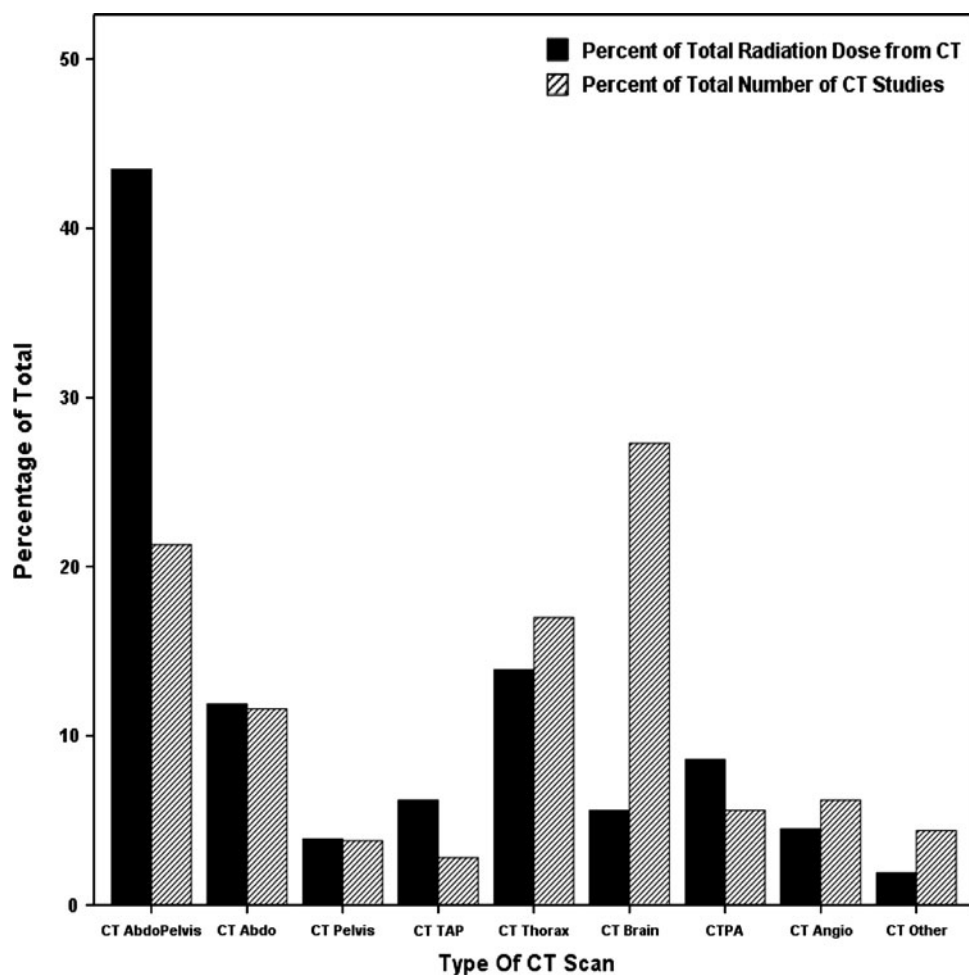


Fig. 2. Contribution of individual CT studies to CED from CT as a single modality and to total CT study number. CT abdomen/pelvis provided the largest percentage total of dose from CT (44%) while providing only 21% of total study CT number. CT brain was the most frequently performed CT study (27% of total CT study numbers) while accounting for only 6% of total study dose from CT.

Table 4. Median (IQR) cumulative dose by quartile of age (years)

Quartile of age (years)	Total (n = 394)	HD (n = 244)	Transplant (n = 150)
< 39	1.5 (0.3–16.0)	2.8 (0.4–21.8)	1.0 (0.4–4.3)
39–53	6.7 (0.8–28.5)	13.1 (1.1–54.3)	4.5 (0.9–20.1)
54–66	20.5 (2.0–70.4)	30.5 (3.3–84.7)	3.3 (0.03–27.9)
> 66	18.4 (3.3–38.4)	19.5 (3.4–41.9)	10.2 (2.7–34.1)
P ANOVA	<0.001	<0.001	<0.05

HD as an independent risk factor for high exposure

In order to determine the effect of renal replacement modality on CED, we examined the relationship between modality at the start of study and exposure to > 50 mSv radiation. On univariate logistic regression analysis, patients on HD had significantly increased crude odds ratio (OR) of cumulative exposure > 50 mSv (OR 3.5, 95% CI 1.8–6.8) compared with the transplant group (Table 5, model 1). Following simultaneous adjustment for age at start of study and duration of follow-up, this relationship remained significant with an adjusted OR of 8.3 (95% CI 3.7–18.5). Following further sequential adjustment for cause of ESKD (model 3, Table 5) and

Table 5. Crude and adjusted OR for the association of renal replacement modality (HD vs. transplant) with estimated total cumulative effective radiation dose (CED) > 50 mSv

	OR	95% Confidence interval	P value
Model 1	3.5	1.8–6.8	<0.001
Model 2	8.3	3.7–18.5	<0.001
Model 3	8.6	3.7–19.7	<0.001
Model 4	9.2	3.8–22.6	<0.001

Model 1: unadjusted, Model 2: adjusted for age at start of study and duration of follow-up, Model 3: adjusted for age at start of study, duration of follow-up and cause of ESKD as shown in Table 2, Model 4: adjusted for age at start of study, duration of follow-up ESKD, and co-morbidities over follow-up as shown in Table 2

co-morbidities at end of study as shown in Table 2 (model 4, Table 5), HD remained significantly and independently associated with CED > 50 mSv with a fully adjusted OR of 9.2 (95% CI 3.8–22.6).

As CT accounted for the majority of radiation exposure, we also examined factors associated with a cumulative effective radiation dose purely from CT. Similar to the factors associated with total exposure > 50 mSv, on univariate analysis patients on HD had a significantly increased crude OR of cumulative exposure

Table 6. Crude and adjusted OR for the association of renal replacement modality (HD vs. transplant) with estimated CT derived cumulative effective radiation dose (CED) > 50 mSv

	OR	95% Confidence interval	P value
Model A	4.7	1.9–11.4	<0.001
Model B	9.6	3.5–26.5	<0.001
Model C	10.6	3.8–30.0	<0.001
Model D	9.5	3.3–27.7	<0.001

Model A: unadjusted, Model B: adjusted for age at start of study and duration of follow-up, Model C: adjusted for age at start of study, duration of follow-up and cause of ESKD as shown in Table 2, Model D: adjusted for age at start of study, duration of follow-up ESKD, and co-morbidities over follow-up as shown in Table 2

from CT > 50 mSv, of 4.7 (95% CI 1.9–11.4) compared with the transplant group (model A, Table 6). Using similar models as described previously, HD remained significantly associated with CT exposure > 50 mSv despite simultaneous and sequential adjustment for age, duration of follow-up (model B, Table 6) cause of ESKD (model C, Table 6) and co-morbidities described in Table 2 (model D, Table 6).

Discussion

We show that over a short period of follow-up, maintenance renal replacement therapy patients are exposed to substantial doses of ionizing radiation. The potential health consequences of this exposure are of concern and this may represent an under-appreciated long-term risk factor for malignancy within this population.

It is estimated that 0.5% of cancer deaths in the US are currently attributable to diagnostic radiation [16]. There is no lower threshold below which the stochastic effects of radiation, and thus risks of cancer do not occur. In occupational settings, radiation exposure dose recording is mandated where exposure to medical personnel may exceed recommended thresholds. For patients, however, no standard upper threshold dose is imposed. The need for medical imaging is often fundamental to and unavoidable in both diagnosis and treatment. In recognition of this, the As Low As Reasonably Achievable (ALARA) principle is applied [17]. The application of ALARA becomes especially important in patient groups, where repeated radiation exposures are necessary over time with a resultant risk of high cumulative radiation exposure. Awareness of the extent of radiation exposure should thus be one element considered in the therapeutic and diagnostic decision-making process.

Urgent consideration should be given to the development of protocols to monitor the CED of patients, particularly in identifiable groups where exposure levels may become high, as in our cohort and in many chronic diseases [8].

Strategies to prospectively monitor cumulative dose may include recommendations such as: the creation of

dose registries; the mandatory recording of dose within the examination images or report; recording of dose within the patient's medical record; mandatory standards for technical staff; and mandatory accreditation of imaging facilities.

The significantly increased exposure demonstrated in the HD population, relative to the transplant population, was noted. Highest exposure in the HD group was also delivered to a younger population than in the transplant group. This was in keeping with the relative age profile of the entire cohort. In the context of increased life expectancy this data indicates that potential lifetime exposure may thus be higher. Ten-year survival of post renal transplant patients is now quoted at 86%. This cohort of patients exhibits a high background incidence of malignancy, quoted at as much as 11% following transplant. While, longer survival follow-up and chronic immunosuppression are likely contributors, here, the exact etiology is unknown [9, 18]. Many studies investigate the increased frequency of malignancy post-transplant; however, none to our knowledge, have included cumulative radiation dose as a consideration of cause. Exposure to high levels of radiation in these patients may represent a potential contributory factor in development of malignancy.

We found CT to be the largest single modality contributor of radiation dose. The disproportionate contribution of CT to radiation dose relative to its contribution to the overall number of studies was noted. The increase in the annual frequency of CT examinations from initiation to completion of the study also suggests a trend for increased use of this modality. This reflects reported worldwide trends where over the past 10 years CT has more than doubled its contribution to overall dose from ionizing medical radiation [5]. CT is now responsible for more than 40% of total dose to the population from medical X-rays [3, 13]. Dose in CT is seen to be primarily dependent on number of examinations performed [19]. Thus, it is critical that the radiologist and the clinician must work together to justify each individual study. In patients at risk for high cumulative exposures, CT should be avoided when an Ultrasound or MRI offers comparable or more information.

Radiation exposure from CT examinations has been shown to vary up to tenfold in clinical practice depending on user parameters [3]. In cases where no viable alternative to CT is possible, substantial dose reduction can be achieved without compromise to diagnostic efficacy. Appropriate selection of parameters such as tube current, peak kilovoltage, beam pitch, scan volume, and duration of scanning helps to optimize the radiation dose to the patient [20]. The scan should be limited to the region of interest, as when other scan parameters are kept constant the radiation dose is directly proportional to the scan volume. Appropriate patient shielding and protection should be used. Dose reductions of 25%–50%

are broadly possible with such methods, especially with newer generation technology [20]. Examples of CT technology that has been developed for radiation dose optimization include automatic tube current modulation and more recently, iterative reconstruction techniques. Low-dose protocols can be developed specifically for individual clinical indications without compromising diagnostic image quality [20]. The development of low-dose protocols should thus be an immediate priority of all imaging centers.

Our study was limited by its retrospective design and by the fact that it was performed in a single center. In reality, the cumulative radiation dose will vary between institutions with inevitable local differences in clinical practices. In particular, different radiation exposures from one center to another can result from varying CT protocols and available hardware. Differences will also occur from heavily operator-dependent vascular access procedures and in centers with a high proportion of arterio-venous grafts where aggressive approaches to assisted patency exist. The actual effective doses associated with different imaging studies and interventional procedures, could not be recorded retrospectively. Thus, we applied the detailed estimated effective dose references supplied by the NRPB were applicable and for other studies not included in the NRPB report we used various published estimated doses from the literature. In our study, we capture only the radiation exposure during the study period, when patients were undergoing renal replacement therapy. As a result, we omit radiation exposures from pre- and post-study illness and thus inevitably underestimate total lifetime exposure.

In conclusion, this study confirms that patients on HD and post-renal transplant are at risk of significant cumulative radiation exposures as a result of diagnostic and interventional radiology procedures often at a young age, the majority of which is imparted via CT examinations to patients in the HD group.

The potential health consequences of this require urgent further investigation. Strategies to monitor CED in these patients should be developed. Protocols to minimize exposure should be developed by specialist centers. These low-dose protocols can significantly reduce dose imparted without detrimental effect on diagnostic outcomes of clinically necessary examinations.

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