Estimated radiation risk of cancer from medical imaging in haemodialysis patients

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Abstract

Background. In recent years the widespread use of medical procedures increased the cumulative effective doses of ionizing radiation. Although many haemodialysis patients undergo multiple examinations with high radiation exposure, no data are available characterizing their attendant potential risks of cancer.

Methods. The radiation exposures were obtained from a retrospective study of 159 consecutive haemodialysis patients with a follow-up duration ≥1 year. Effective dose and organ dose were estimated on an individual basis. Radiation risk was expressed as risk of exposure-induced death (REID) (%).

Results. The 159 patients (101 males) were followed for a median of 2.7 years (mean 3.0 years). A total of 486 patient-years were available for follow-up. The mean age at study entry was 65.3 years. The mean cumulative organ doses were 103, 102, 100, 99, 77 and 58 mSv for kidneys, lung, stomach, liver, colon and bone marrow, respectively. On average, computed tomography, nuclear medicine and interventional radiology accounted for 90, 4.5 and 5.5% of organ doses, respectively. The average REID was 0.99% (i.e. odds 1 in 100) and the median REID was 0.45%. At univariate analysis, increasing age and presence of diabetes were independent predictors of lower REID, whilst patients eligible for kidney transplantation were exposed to a significantly higher REID. At multivariate analysis, younger age was an independent predictor of higher REID.

Conclusions. The excess cancer risk-attributable radiation exposure in haemodialysis patients is not negligible. Particular attention should be paid to younger patients and to patients who will undergo kidney transplantation.

Keywords: cancer risk, haemodialysis, radiation dosimetry

Introduction

Advances in medical imaging have been associated with increased ionizing radiation (IR) exposure, especially for adult or paediatric patients with chronic illnesses [1, 2].

Haemodialysis patients usually require repeated exposure to IR due to their multiple comorbid conditions and to dialysis access-related procedures. The cumulative exposure to IR is high in haemodialysis patients with a mean annual cumulative effective dose (CED) >7-fold the background radiation of ~3 mSv/year [3]. Exposures >50–100 mSv of CED accrued in 3–4 years are common in this study cohort, occurring in almost one-third of subjects [4].

Three single centres form Ireland, Italy and the USA reported IR exposure in patients on haemodialysis [3–5]. The results suggested that some patients on haemodialysis might have a sufficiently high IR exposure due to radiological procedures to explain part of the increased risk of cancer. This must also be interpreted in the light of the increased incidence of cancer of unclear aetiology in haemodialysis patients [6].

Effective dose (ED) was used in those studies to provide a single dose value associated with a sequence of examinations. ED is age and sex averaged, and, although it can be used to enable comparison of relative detriment between procedures that utilize ionizing radiation, it should not be used to
determine individual risk. For risk estimation, the organ dose is the preferred quantity. It is possible to estimate the cancer risks associated with the radiation exposure from any given IR scan by estimating the organ doses involved an applying organ specific cancer incidence or mortality data that were summarized in the Biological Effects of Ionizing Radiation (BEIR) VII report [7].

The aims of this retrospective, observational study were to quantify the CED of ionizing radiation in haemodialysis patients, to calculate the cumulated radiation dose to relevant organs and to assess radiation risks on an individual basis.

**MATERIALS AND METHODS**

**Data sources and study population**

We conducted a retrospective study of period prevalent maintenance haemodialysis patients attending a single university-based dialysis centre between 30 June 2007 and 31 December 2011. We excluded patients who were diagnosed with cancer before or during the study period, under the assumption that they were unlikely to be related to further scan-related cancers. Only patients with a follow-up duration ≥1 year were included in the study. Comorbidities were obtained by reviewing medical notes, clinical summaries and patient interviews.

Details of radiological procedures performed on patients in the cohort during the study period were obtained from the Radiology Information System. For CT procedures the number of series, the length of coverage per each of the series, the kV, pitch, average mAs, volumetric CT dose index and dose-length product were obtained in each patient and in each anatomical region by the dose reports in the Picture Archiving and Communication System of the Hospital Radiology Department. For the different types of nuclear medicine procedures the individual administered activity of a specific radiopharmaceutical was recorded. For interventional radiology procedures the dose area product was recorded.

Duration of follow-up for each patient within the study period was calculated from time of study inception or date of first haemodialysis (if haemodialysis commenced after the study inception date), to death, kidney transplant or last recorded IR examination recorded in the Picture Archiving and Communication System, to ensure a conservative estimate of the length of the follow-up.

The study was approved by the Institutional Ethics Committee.

**Estimates of radiation doses**

For conventional diagnostic radiology procedures, we relied on dose estimates summarized in a recent review [8].

Main determinants of radiation dose from fluoroscopy including patient habitus, operator techniques and procedural complexity, the x-ray system and selected setting were all taken into consideration in the patient-specific dose calculations.

For interventional radiology procedures radiation doses were measured by the dose area product in Gy cm² using inbuilt ionization chambers. A backscatter factor of 1.38 was used to convert the dose in air to a dose in tissue [9]. Imaging was assumed to be posteroanterior: the distance between the anode and the patient was taken as 40 cm. The effective dose and the organ doses were derived using the PCXMC 1.5 software (STUK, Radiation and Nuclear Safety Authority, Helsinki, Finland).

CT scans were performed using a 64 row scanner (Lightspeed VCT, GE, Milwaukee, WI, USA) or a 16 row scanner (Brilliance; Philips, Eindhoven, the Netherlands) equipped with both z-axis and angular tube current modulation. The tube current f values recorded after extracting the information from the DICOM header of the stored images. These values were multiplied by the rotation time to obtain the mAs values. No iterative reconstruction software was available on the CT scanners during the study period.

Effective doses and organ doses for CT were estimated using the individual dose reports and the computational software ImPACT CT PATIENT DOSE CALCULATOR v1.02 (ImPACT, London, UK) which uses tissue weighing coefficients, as specified by the International Commission on Radiological Protection publication 103 [10]. The calculation procedure was modified to consider the actual distribution of organ dose consequent to the tube current modulation, as previously described [11]. The accuracy of the volumetric CT dose index provided by the equipment user interface was verified by comparison with values measured during the routine quality controls, finding a maximum difference of 5%. CT was counted as having multiple series within the scan to account for multiphase imaging [12].

Procedural frequencies and CED of radiation were calculated for the study population over the study period. CED is expressed for each patient as a summation over the study period [total CED (mSv)] and as annual CED (mSv per patient year). We classified population-based rates of effective doses for the study populations according to the following annual CED categories [13]: low-moderate (<20 mSv/year), high (>20 to 50 mSv/year) and very high (>50 mSv/year).

**Estimates of radiation risk**

The cancer risk resulting from the exposure to ionizing radiation was estimated using the BEIR VII model and the PCXMC 1.5 software.

Briefly, the BEIR VII committee has derived risk models for cancer mortality. The models take into account the cancer site, sex, age at the exposure and attained age. Risks models have been developed for leukaemia, solid cancers in some organs and for all solid cancers combined. The cancer risks are non-zero only after a latency period (5 years for solid cancer and 2 years for leukaemia): these values are used in the PCXMC software as a default.

In PCXMC lifetime risks are expressed in terms of risk of exposure-induced death (REID). For practical purposes, at typical dose levels encountered in X-ray diagnostics, REID and Lifetime attributable risks can be interpreted to present the excess radiation-induced cancer risk and their numerical values are close enough to be interpreted identical considering the uncertainties involved in the models.
Statistical analysis

Data were described using mean and standard deviation or median and intra-quartile range (IQR) for non-normal distributions. Univariate analysis was performed by using Mann–Whitney U-test for non-normally distributed continuous variables. A multiple linear regression model was created using analysis of covariance to assess the independent impact of continuous and nominal variables resulted significant predictors at univariate analysis.

Statistical analyses was performed using the software STATISTICA 6.0 (StatSoft, Inc., Tulsa, OK, USA) using a two-sided type I error rate of 0.05.

RESULTS

Forty-one patients out of 200 eligible patients were excluded from the analysis since they already had a diagnosis of cancer at the start of the study (27 patients) or were diagnosed with cancer during the follow-up period (14 patients). The cancer sites in these patients were as follows: eight lungs, six colon, six urinary tract and prostate, five kidney, five uterus and ovaries, four haematopoietic system, four thyroid and three other sites. The remaining 159 patients (101 males) were followed for a median of 2.7 years (mean 3.0 years). During the study period, 53 patients (33.3%) died of non-oncologic causes (Table 1), while 13 (8.1%) underwent kidney transplantation. In these cases the data were censored at the date of death or of transplantation. A total of 486 patient-years were available for follow-up. The mean ± SD age at study entry was 65.3 ± 15.9 years.

Among the subjects, 28 (18%) were in the 18–50 years of age group, 58 (36%) were in the 50–70 years of age group and 73 (46%) were older than 70 years. In all, 41% of the subjects were prevalent with a median (intra-quartile range IQR) dialysis period of 4.3 (1.6–8.6) years, and the remainder 59% initiated dialysis during the study period.

The median total CED was 35.9 (IQR = 8.9–98.7) and the mean was 84.2 ± 140.6 mSv. The median annual CED was 12.1 (IQR = 3.6–29.9) and the mean was 28.1 ± 44.0 mSv. Among the subjects, 61.6% were in the low-moderate (<20 mSv per year), 22.6% were in the high (20 to <50 mSv per year) and 15.7% in the very high (≥50 mSv per year) radiation dose groups; 75% of patients had a total CED <100 mSv, 15% were in the 100 to <200 mSv group, and the remaining 10% had a total CED ≥200 mSv.

The total number of radiological procedures related to dialysis-related procedures and follow-up in the study period for all patients was 2163 and the median (IQR) number of radiological procedures was 4.0 (2.1–6.9) per patient-year. The proportion of total radiation exposure attributable to different types of investigations is shown in Table 1.

The contribution of conventional diagnostic radiology was not taken into consideration for organ dose estimation and risk assessment purposes, since insufficient information was present in the databases regarding the characteristic of each exposure in order to allow reliable estimates of individual organ doses. Accordingly, organ dose and risk estimation were not performed on the subsample of 29 patients that only had conventional diagnostic X-ray examinations. In these cases, both organ doses and risks were arbitrarily set to zero in order to err on the side of underestimating exposure. Figure 1 represents the cumulated doses to relevant organs in 159 patients due to CT, nuclear medicine and interventional radiology procedures. The mean cumulative organ doses were 103, 102, 100, 99, 77 and 58 mSv for kidneys, lung, stomach, liver, colon and bone marrow, respectively. On average, CT contributed to ~90% to organ doses with a maximum of 97.4% for breast doses in females and a minimum of 81.2% for lung. Nuclear medicine contributed on average to 4.8% of organ dose with a maximum of 10% for bladder and colon. Interventional radiology contributed on average to ~5.8% of organ doses with a maximum of 18% for lung.

The average REID was 0.99% (i.e. odds 1 in 100), the median (IQR) REID was 0.45% (0.02–1.71) and the maximum REID was 4.46%. The REID (%) for various types of cancers due to IR examinations is reported in Figure 2. The contribution of each radiological procedure for various types of cancer is reported in Figure 3.

By univariate analysis, the average REID was significantly correlated with patient’s age at study entry (r = −0.31; P < 0.001). The transplant waiting list status was associated with a significantly higher REID (P = 0.003). Average REID was significantly lower in the presence diabetes mellitus (P = 0.05) (Table 2). The results of the multivariate analysis are shown in Table 3. Younger age was the only independent and significant predictor of higher (P = 0.045).

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number of examinations N (%)</th>
<th>Annual CED (mSv per patient-year) mean ± SD</th>
<th>Total CED mSv (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall total</td>
<td>2163 (100%)</td>
<td>28.1 ± 44</td>
<td>13393 (100%)</td>
</tr>
<tr>
<td>Conventional diagnostic radiology</td>
<td>1555 (71.9%)</td>
<td>1.9 ± 1.5</td>
<td>855.3 (6.2%)</td>
</tr>
<tr>
<td>Computed Tomography</td>
<td>344 (15.9%)</td>
<td>23.1 ± 42.5</td>
<td>11054 (82.5%)</td>
</tr>
<tr>
<td>Nuclear Medicine</td>
<td>130 (6.0%)</td>
<td>1.2 ± 2.2</td>
<td>504 (3.8%)</td>
</tr>
<tr>
<td>Interventional</td>
<td>134 (6.2%)</td>
<td>2.0 ± 4.4</td>
<td>1000 (7.5%)</td>
</tr>
</tbody>
</table>

CED, cumulative effective radiation dose; SD, standard deviation.

DISCUSSION

Radiation is one of the most extensively studied carcinogens. The BEIR VII report summarized the results from studies of the Japanese atomic bomb survivors, from nuclear workers and patients receiving multiple diagnostic X-rays. There is direct evidence that radiation dose of the magnitude of 50–100 mSv can cause cancer and that the magnitude of the risk at these doses is largely consistent with the risks at higher doses. Estimates of potential cancer risk from radiation are currently based on a linear no-threshold model, which, while unproven, is the model best supported by currently available epidemiological data [14].
The long-term risk due to the use of medical radiation should always be incorporated in the risk-benefit assessment of diagnostic and therapeutic imaging. Nonetheless, this assessment is difficult as the risk of radiation inducing carcinogenesis might be controversial in this very special group of patients with multiple complicating comorbidities and severe competing and confounding risks for death and cancer (including viruses and immunosuppression from uraemia, prior treatment of renal disease and subsequent treatment for transplantation). On the other hand, although of an unclear aetiology, the overall incidence of cancer is reported to be higher in patients with end-stage kidney disease than in the general population [6].

Doses of radiation from medical imaging procedures including fluoroscopy, CT and NM procedures can be substantial in certain groups of patients for whom the likelihood of repetitive studies is high. A recent systematic review pointed to patients with end-stage kidney disease as the most exposed to IR, among chronic or recurrent patients [1]. Given their retrospective design, the majority of the studies included in this review were obliged to use standardized procedure-specific mean effective radiation doses to calculate individual CED, instead of patient-specific dose information. This, by definition, produces inaccurate estimates. Moreover, ED were used in these studies to give a single dose value associated with a sequence of examinations. It should be kept in mind that the application of the nominal coefficient of risk ($\sim 5\% \, Sv^{-1}$) averaged over several populations and all ages and provided by the international commission on radiological protection [10] to calculate this risk is in principle inappropriate. For risk estimation the organ dose is the preferred quantity.

To our knowledge this is the first study aimed at estimating risks in haemodialysis patients using an individual estimation of organ doses.

When looking at organ doses, our data show that the CT is by far the major contributor accounting on average for $>90\%$ of IR exposure, whilst NM and IR procedures contributed for $\sim 5\%$ each. Among the 344 CT procedures, 136 (39.5\%) were performed to diagnose a specific disease, 139 (40.4\%) were performed to monitor a previously diagnosed disease and 69 (20.1\%) were performed in patients on the waiting list for kidney transplantation, due to clinical indications.

In the patients on the waiting list for kidney transplantation, apart from the series of investigations for the first insertion, the suitability continuity is assessed every 2 years by means of chest and abdomen X-ray examinations. In addition, patients with diabetes and with known ischaemic heart disease are assessed with a myocardial perfusion scan, every 2 years, followed by a coronary angiography when needed.

The contribution of each imaging modality is differentiated when looking at the doses for a single organ or tissue. NM

**Figure 1:** Cumulated doses to relevant organs due to computed tomography, nuclear medicine and interventional radiology procedures in haemodialysis patients.

**Figure 2:** Risk of exposure-induced death REID (%) for various cancers types due to medical imaging procedures in haemodialysis patients.
provided the maximum contribution (10%) in colon and bladder, since the preferred pathway of excretion of most radionuclides is by urine voiding or through the faeces. IR provided the higher contribution in lungs (18%) that are the most exposed organ during cardiac procedures, such as coronary angiography or percutaneous transluminal angioplasty. The contribution of each radiological procedure to the risk of various types of cancer is in close relation with the estimated organ doses.

Our data show that the radiation risk associated to medical imaging for haemodialysis patient is not negligible, amounting to a median REID of 0.45%. Notwithstanding the advanced age of patients in the cohorts examined (average of 65 years), it must be underlined that the REID already takes into account the patient’s age, differently from risk projections based on the nominal coefficient of risk multiplied for the ED, which are averaged over all ages. Our current estimates are for IR scans obtained from 2007 to 2011 and, since cancer risks remain elevated for many decades after radiation exposure, these projected radiation-related cancers would be spread out over many decades in the future.

Nonetheless, there are a number of uncertainties and assumptions involved in these risk projections. A method to quantify the uncertainties in the risk models, including statistical uncertainties in risk parameters, has been proposed by Berrington de Gonzales et al. [15]. Among them, three are of particular relevance in the context of this study. If the radiation-related solid cancer latency is assumed of 10 years, instead of 5 years as in our calculation, we would have a maximum change of −4% in the risk estimations. If we assume an all-cause mortality rate of 50% higher than the general population, we would have a maximum change of −20% in the risk estimation. Conversely, a possible source of underestimation is that risk models were not available for some cancer sites because the number of cases in the Japanese atomic bomb survivors study was small. The inclusion of cancer sites without detailed risk models (i.e. kidney) would have led to an increase of +20% in the risk estimation.

As expected, the risks are higher for younger patients since they have a greater life-span and the potential malignancy risk from radiation exposures is a long-term stochastic concern that can occur decades from exposure. These risk projections are consistent with the results of an epidemiological study in a large cohort of end-stage renal disease patients treated by dialysis, in which a higher risk of cancer (with a standardized incidence ratio of 3.68) was observed in patients younger than 35 years, with the risk gradually decreasing with increasing age [16].

Reliable quantification of the risk by cancer site in haemodialysis patients is based on only few studies. Previous Japanese [17, 18] and US [19] studies evidenced an increased incidence of cancer of the colon, kidney, uterus and breast than in the general population. Buccianti et al. [20] found a significant increased risks of liver, kidney, thyroid cancer, lymphoma and multiple myeloma in a small population of uraemic patients in the region of Lombardy, Italy (that is similar to our sample). Two major studies examined site-specific cancer risk associated with dialysis [6, 16]. The largest of the two [16] assembled a cohort of 831804 patients who received dialysis during the period 1980–94 in the USA, Europe, Australia or New Zealand. Cancers most strongly associated with dialysis included tumours of the kidney (with a relative risk ranging from 3 to 10), thyroid (with a relative risk ranging from 2 to 9), bladder, stomach, liver, lung and cervix (with a relative risk ranging from 1.5 to 2).

The pattern of site-specific projected cancer risks from medical imaging derived from our study presents some overlap with the site-specific cancer risk associated with dialysis and obtained from epidemiological studies. However, we
should keep in mind that our projected radiation-related cancers would be spread out over many decades in the future and assume that the use of imaging with IR remains at the current level or increases. Conversely, the radiation attributable risk at present is likely to be lower, as current cancers would be related to the medical use of radiation in the past decades, when level of use was lower. Thus, the comparison of observed site-specific cancer risk associated with dialysis in the past and projected cancer risks due to the use of IR imaging should be interpreted with caution.

Patients without diabetes mellitus and patients eligible for kidney transplantation are exposed to a significantly higher risk at univariate analysis. The fact that both variables did not result as significant predictors of REID in multivariable analysis can be explained when considering that patients without diabetes and patients eligible for kidney transplantation are, on average, younger than the remaining patients, so that their independent contribution to the REID, once age has been already entered in the multivariable model, is diminished.

There are limitations in the present study that must be acknowledged. First and most important this is a single centre study. There is sufficient variability in practice involving the use of IR procedures between different centres to suggest that our results are not necessarily generalizable. Secondly, the risk estimation was not performed in a subsample of 29 patients for whom the only source of IR exposure was through conventional diagnostic radiology. Although we do not have data at hand to allow an individual risk estimation in these patients, we decided to arbitrarily set to zero these risks to err on the side of underestimating risks. Finally, although performed on an individual basis, organ dose estimations are subjected to some uncertainties due to the retrospective nature of the study.

**CONCLUSIONS**

The excess cancer risk attributable to IR exposure is not negligible. This should be of concern for nephrologists since patients on haemodialysis are living longer and have a number of concomitant risks factor for future cancer including immunosuppression for those who will eventually undergo kidney transplantation. The potential risks of tests using IR must be weighted up against the potential benefits of these tests and the risk of missing an important diagnosis if imaging is not performed because of concerns about radiation exposure. Particular attention should be paid to younger patients who have an increased risk. For haemodialysis patients, tracking of the cumulative radiation dose should be part of the patient’s record so that careful considerations of further exposure can be properly documented during the course of treatment.

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**CONFLICT OF INTEREST STATEMENT**

The results presented in this paper have not been published previously in whole or part, except in abstract format.

**REFERENCES**

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ORIGINAL ARTICLE

Glomerular hypertrophy in subjects with low nephron number: contributions of sex, body size and race

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ABSTRACT

Background. We have shown that low nephron number (N_glon) is a strong determinant of individual glomerular volume (IGV) in male Americans. However, whether the same pattern is present in female Americans remains unclear. The contributions of body surface area (BSA) and race to IGV in the context of N_glon also require further evaluation.

Methods. Kidneys without overt renal disease were collected at autopsy in Mississippi, USA. The extremes of female N_glon were used to define high and low N_glon for both sexes. N_glon and IGV were estimated by design-based stereology. A total of 24 African and Caucasian American females (n = 12 per race; 6 per N_glon extreme) were included. These subjects were subsequently matched to 24 comparable males by age and N_glon and to 18 additional males by age, N_glon and BSA.

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