

Radiation exposure from medical imaging in dialyzed patients undergoing renal pre-transplant evaluation

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Abstract

Background and aim Ionizing radiation exposure from medical procedures is rising sharply—the per-capita annual effective dose in the US is 3.0 millisieverts (mSv). Hemodialyzed and kidney transplanted patients receive still higher doses of ionizing radiation due to the presence of multiple comorbidities. The aim of this study was to assess the cumulative effective dose (CED) among dialyzed patients undergoing renal pre-transplant evaluation. **Patients and methods** We evaluated 70 hemodialysis patients between June 2009 and December 2014, aged 46.4 ± 12.0 years. The number and type of radiologic procedures were collected through the Radiology Information System. CED was expressed as total mSv/patient and annual CED (mSv/patient/year).

Results A total of 744 radiologic procedures were performed, accounting for 3869 mSv of ionizing radiation: conventional radiology, computed tomography and nuclear medicine accounted for 78, 14 and 8 % of the procedures, but they represented, respectively, 8, 83 and 9 % of the total CED. The mean (median) annual CED was 35 (7) mSv/patient/year, while total CED was 72 (32) mSv/patient. Thirty-seven patients were active waitlisted and received 47 (10) mSv during the pre-transplant evaluation and 36 (5) mSv during the waiting phase to maintain active

status. Concerning cancer risk, 4 (7 %) patients were classified at low risk (<3 mSv/year), 19 (35 %) at moderate risk (3 to <20 mSv/year), 8 (15 %) at high risk (20 to <50 mSv/year), and 23 (43 %) at very high risk (≥ 50 mSv/year).

Conclusions Our study demonstrated that during renal pre-transplant evaluation, dialyzed patients receive a high dose of ionizing radiation. Considering that transplanted individuals have a high incidence of cancer due to multifactorial etiology, it is mandatory to reduce the ionizing radiation imaging.

Keywords Cumulative effective dose · Hemodialysis · Ionizing radiation exposure · Renal pre-transplant evaluation

Introduction

Medical uses of ionizing radiation have grown rapidly over the past decade and as of 2006 they represent the largest source of exposure in the US population, accounting for 3.0 millisieverts (mSv) compared to an estimated 2.4 mSv from the natural background [1]. In adult or pediatric patients with chronic illnesses the radiation exposure from medical imaging is up to 20 times higher [2, 3] and this is becoming an issue for alarm in public health. The US National Academy of Sciences' National Research Council comprehensively reviewed biological and epidemiological data related to health risks from exposure to ionizing radiation, and published their findings in the Biological Effects of Ionizing Radiation (BEIR)-VII Phase 2 report [4]. The risk estimates were derived from analyses of mortality data based on Japanese atomic bomb survivors, occupationally exposed nuclear workers and individuals

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belonging to patient cohorts exposed to medical diagnostic or therapeutic procedures [5].

Patients with end-stage renal disease (ESRD) on renal replacement therapy (hemodialysis or renal transplantation) receive repeated ionizing radiation imaging procedures for both diagnostic and therapeutic purposes [6–9]. They are also at higher risk of cancer compared to the general population [10–13]. For kidney transplant recipients, the exposure to ionizing radiation during the dialysis pre-transplant evaluation [14] must be added to the exposure occurring in the first period after kidney engrafting. In addition, it is noteworthy that among kidney transplant recipients cancer is the leading cause of death with a functioning graft [15].

The aim of this retrospective study was to quantify the cumulative effective dose (CED) of ionizing radiation received by hemodialysis patients (HDP) undergoing renal pre-transplant evaluation.

Patients and methods

Data sources and study population

We conducted a retrospective study on chronic HDP attending a single university-based dialysis center and screened for renal transplantation between 30 June 2009 and 31 December 2014. According to our Center's guidelines for kidney transplant, patients who were diagnosed with active cancer, severe cardiac vascular lung liver disease or dementia or aged >80 years were excluded. Only patients with a follow-up duration ≥ 12 months were included in the study. Comorbidities were obtained by reviewing medical notes, clinical summaries and patient interviews.

Details of radiological procedures were obtained from the Radiology Information System. For computed tomography (CT) procedures, the number of series, length of coverage for each image of the series, the kV, pitch, average milliamperes, volumetric CT dose index and dose-length product were obtained for each patient from the dose reports in the Picture Archiving and Communication System (PACS) of the Hospital Radiology Department. For the different types of nuclear medicine procedure, the activity of the specific radiopharmaceutical administered to the individual was recorded. Duration of follow-up for each patient was calculated from time of study inception (or date of first hemodialysis session if hemodialysis commenced after the study inception date), to death, kidney transplant or last examination recorded in the PACS.

At the time of the initiation of hemodialysis in our Center, each patient signed an informed consent allowing the use of clinical and anamnestic data in anonymous form for scientific publications.

Radiation dose estimates

Procedures were subdivided into: conventional diagnostic radiology, CT, and nuclear medicine, in accordance with Mettler et al. [16]. To evaluate the radiation exposure for each imaging procedure, we obtained estimates of effective doses administered, assessed in mSv. For common radiology procedures, we relied primarily on data summarized in a recent review or other published sources [16, 17]. Effective doses for CT were estimated using the individual dose reports archived in the PACS and the computational software ImpACT CT Patient Dose Calculator v1.02 (ImpACT, London, UK), which is based on Monte Carlo simulations that use tissue weighting coefficients as specified by the International Commission on Radiological Protection (ICRP) Publication 103 [18]. CT scans were all performed with a 64 row multi-detector CT scanner (Lightspeed VCT, GE, Milwaukee, WI, USA) using both z-axis and angular tube current modulation. For all examinations, CT with and without contrast was counted as two scans; CT with contrast could be counted as having multiple series within the scan to account for multiphase imaging. To estimate the effective dose from nuclear medicine procedures, the dose coefficients from ICRP Publication 80 (ICRP 80, 1998) [19] were used to evaluate the effective dose, starting from the activity of the specific radiopharmaceutical administered [20].

CED was expressed for each patient as the sum over the study period [total CED (mSv)] and as annual CED (mSv per patient-year). Annual CED was defined as low (≤ 3 mSv/year), moderate (>3 to 20 mSv/year), high (>20 to 50 mSv/year) and very high (>50 mSv/year), in accordance with Fazel et al. [21].

Statistical analysis

Data were described as mean and standard deviation (SD) or median and interquartile range (IQR) for non normal distributions. Comparison between groups was performed using the unpaired *t* test and Mann–Whitney *U* test to compare categorical or non-normally distributed continuous variables between two groups, respectively. All statistical analyses were carried out using the software GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA, USA, <http://www.graphpad.com>).

Results

Of 202 patients screened during the study period, 70 HDP met the inclusion criteria and were evaluated for renal transplantation. Of these, 16 did not complete the

evaluation: 6 due to new diagnosis of severe cardiovascular disease, 4 due to new diagnosis of neoplasia, 4 for other causes, and 2 refused to undergo the examinations suggested. The study population therefore consisted of 54 HDP (36 males) who were followed up for 117 patient-years (mean 1.9 ± 1.5 years). Patients' mean age was 46.4 ± 12.0 years, with 23 (43 %) patients younger than 50 years. Overall, 19 (31.5 %) patients were prevalent hemodialysis patients with a mean dialysis vintage of 5.5 ± 5 years, while the remainder initiated dialysis during the study period. Characteristics of patients are summarized in Table 1.

During the study period, 37 (68 %) patients completed the screening and were active waitlisted and 17 (32 %) were undergoing the examinations at the end of the study; 24 (44 %) HDP underwent kidney transplantation. The total number of radiological procedures performed was 744, accounting for 3869 mSv of ionizing radiation. Conventional radiology, CT and nuclear medicine represented 78, 14 and 8 % of these procedures, but they accounted, respectively, for 8, 83 and 9 % of the total CED (Table 2). The mean (median) number of radiological procedures per patient was 14 (10.4). Thirty-three patients (61 %) had at least 1 CT examination during the study period, 34 (63 %) underwent at least 1 nuclear imaging procedure, and 100 % underwent traditional radiological procedures.

The mean (median) annual CED was 35 (7) mSv/patient/year and the mean (median) total CED was 83 (50)

mSv/patient. Thirty-three out of 54 HDP were active wait-listed and received a mean (median) 47 (11) mSv during the evaluation phase and 36 (5) mSv while on the waiting list to maintain their active status. Concerning the cancer risk due to exposure level, 4 (7 %) patients were in the low risk category (<3 mSv/year), 19 (35 %) were at moderate risk (3 to <20 mSv/year), 8 (15 %) were high risk (20 to <50 mSv/year), and 23 (43 %) were in the very high risk category (≥ 50 mSv/year); 7 (14 %) HDP had a total CED >100 mSv. Total CED was higher among patients aged over 50 years or affected by diabetes, ischemic heart disease or previous neoplasia (Table 3). No differences between males and females were found.

Discussion

This study demonstrates that over a 3-year period, a significant fraction of HDP undergoing pre-transplant evaluation receive estimated radiation doses that may put them at increased risk of cancer. The association between the risk of cancer and the level of radiation exposure over time assumes the validity of the linear no-threshold model [22], even if some contend that this model fails to account for the cell's capacity to repair the damage [23]. The assumed risk estimates are ultimately derived from analyses of mortality data based on Japanese atomic bomb survivors [24] who were exposed to intermediate radiation doses (approximately 40 mSv), similar to the typical amount received in two or three CT scans in adults. The atomic bomb data provide strong evidence of an increased cancer mortality risk at equivalent doses greater than 100 mSv, good evidence of an increased cancer risk for doses between 50 and 100 mSv, and reasonable evidence for an increased cancer risk for doses between 10 and 50 mSv [25].

These findings are confirmed by retrospective studies evaluating the relationship between the radiation exposure from CT performed during childhood and the subsequent risk of neoplasia. Pearce et al. [26] found an excess risk of brain tumor and leukemia in about 180,000 adults who received CT (mean dose 50–60 mSv) when they were younger than 22 years. Mathews et al. confirmed an absolute excess incidence of all cancers of 9.38 per 100,000 person-years due to an average effective dose of 4.5 mSv [27]. However, at relatively low doses, there is still uncertainty as to whether there is an association between radiation and disease. The ICRP acknowledges that the dependence of signal transcription at DNA level after irradiation from the dose and the risk of cancer is a field that warrants further studies. The French Academy of Sciences underlines the potential importance of signal transcription and claims the existence of a threshold for cancer risk at low doses [28].

Table 1 Patient characteristics

| Patient characteristics | Total no. of patients = 54 |
|--|----------------------------|
| Mean annual CED (mSv/patient/year), mean \pm SD (median) | 35 \pm 120 (7) |
| Mean total CED (mSv/patient), mean \pm SD (median) | 72 \pm 139 (32) |
| Age, years \pm SD | 46 \pm 12 |
| Males, n (%) | 36 (66.6 %) |
| Diabetes mellitus, n (%) | 11 (20 %) |
| Ischemic heart disease, n (%) | 7 (13 %) |
| Tumor, n (%) | 7 (13 %) |
| Second renal transplant, n (%) | 6 (11 %) |

Table 2 Number of radiological procedures and total CED by procedure type

| Procedure | Examinations n (%) | Total CED mSv (%) |
|-----------------------------------|--------------------|-------------------|
| Overall total | 744 (100 %) | 3869 (100 %) |
| Conventional diagnostic radiology | 581 (78 %) | 280 (9 %) |
| Computed tomography | 103 (14 %) | 3165 (83 %) |
| Nuclear medicine | 60 (8 %) | 301 (8 %) |

Table 3 Patient characteristics and comparison of total CED by presence or not of comorbidity

| Patient characteristics | Total n (%) | Total CED (mSv/pt) (mean ± SD) | | p value |
|-------------------------|----------------|--------------------------------|----------|---------|
| | | Yes | No | |
| Age <50 years | 23 (43 %) | 90 ± 178 | 46 ± 48 | NS |
| Diabetes mellitus | 11 (20 %) | 95 ± 130 | 66 ± 142 | NS |
| Ischemic heart disease | 7 (13 %) | 160 ± 326 | 58 ± 84 | NS |
| Tumor | 7 (13 %) | 46 ± 43 | 75 ± 148 | NS |
| Second renal transplant | 6 (11 %) | 102 ± 145 | 74 ± 98 | NS |

For nephrologists, the association between cancer and chronic kidney disease has long been recognized [12, 13]. The excess mortality from cancer risk begins at a glomerular filtration rate of 55 ml/min/1.73 m² and increases by about 30 % with every 10 ml/min decline in renal function [11]. Patients with ESRD have a fourfold higher risk of cancer compared to the general population: a 1–1.5 fold greater risk on dialysis and a 2.5–5 fold greater risk after kidney transplantation [10, 29]. Excluding non-melanoma skin cancer and cancers that frequently cause ESRD (myeloma, urinary tract tumors), Vajdic et al. [29] found a standardized incidence ratio of cancer of 1.16 among patients with chronic non-end-stage kidney disease, of 1.35 among patients on dialysis, and of 3.27 among patients after kidney transplantation.

The cause of carcinogenesis in ESRD is not completely understood, but several mechanisms are involved, such as drug-induced immunosuppression, oncogenic viral infections, lymphocyte dysregulation and carcinogenesis related to the underlying renal disease (e.g. acquired polycystic kidney disease and renal carcinoma) [12, 13, 31]. In this context, ionizing radiations, which are recognized to induce DNA and RNA damage, could represent an additional mechanism of cancer in dialyzed and transplanted patients.

Renal patients receive higher radiation doses than other chronically ill patients [2], because of the very high prevalence of comorbidities. In an Italian study carried out in over 106 patients with 3 years of follow-up, the mean total and the annual CED was 55.7 and 22.9 mSv, respectively [6]. Patients eligible for renal transplantation received higher doses: mean annual CED 30.5 vs. 18.4 mSv/year. In the study of Kinsella et al. [7], HDP received a median total CED and annual CED of 21.7 and 6.9 mSv/patient in 3.4 years. In another study on kidney transplant patients, the same group [8] found a mean total and annual CED of 15.8 and 0.5 mSv respectively, while the Italian group recorded a mean total and annual CED of 46.1 and 16.3 mSv, respectively [9]. In all these studies the main contribution to the CED was CT, due to the intrinsic characteristics of the imaging procedure. Finally, Brambilla and colleagues [30], on the basis of the estimated organ doses, age and gender, as indicated by the BEIR-VII report [5], calculated the risk of radiation exposure-induced death (REID) from cancer in 159 HDP

followed for 3 years. They found a mean (median) REID of 0.99 (0.45) %, with abdominal organs and lungs constituting the highest risk.

With regard to the HDP patients undergoing renal pre-transplant evaluation, Nguyen and colleagues [14] found a median CED of 28.8 mSv/patient among 172 subjects in 3.7 years; in the 110 HDP with a waitlisted time >1 year, the median annual CED was 12.6 mSv/patient. The risk of higher doses was correlated to the presence of diabetes, older age and black race. The main contributor to the higher doses were the nuclear imaging tests required by the internal protocol of cardiac screening (annual and bi-annual nuclear cardiac stress tests for diabetics and patients aged >50 years, respectively).

In our study, HDP undergoing renal pre-transplant evaluation received a mean total CED of 82 mSv, that could be subdivided into 47 mSv during the evaluation phase and 36 mSv due to monitoring while waiting for the transplant, to maintain the active status. In our Center, apart from the series of investigations carried out for the initial insertion on the waiting list, the continuing suitability of patients is usually assessed every 2 years by means of chest and abdomen X-ray. Patients with diabetes and cardiac ischemic disease or older than 55 years, are requested to undergo a myocardial perfusion scan or nuclear stress test, followed by a coronary angiography when needed. Every additional investigation is performed on the basis of the clinical status. In our study, the main contribution to the CED was CT; comorbidities increased the CED, even if not in a statistically significant manner, perhaps due to their very low prevalence.

In addition, it should be borne in mind that the radiation dose of 82 mSv received during the 3 years before renal transplantation (average waiting time in Italy) must be added to the 46 mSv of the 3 years after transplantation [9] leading to a CED of 120 mSv over a period of about 5–6 years. Although important sources of uncertainties such as the possible reduction in risk for exposure at low doses and dose rates, it cannot be denied that the doses received by these patients put them at an increased risk of cancer, with doses that are higher even than the recommended maximum exposure for occupational purposes (100 mSv every 5 years and maximum 50 mSv per year [18]). As the life expectancy post-transplantation varies

greatly (5–20 years), cancer onset could occur after the first 5 years, which is the time recognized as the latency period from the time of exposure.

In the light of these considerations, nephrologists have the difficult task of balancing the not precisely quantifiable risk of cancer induced by ionizing radiation through imaging against the risk of not obtaining enough information for an effective transplantation and follow-up or of missing a diagnosis and/or subsequent treatment of a specific disease. A reduction in diagnostic/interventional procedures across the board is not desirable; rather, what is necessary and mandatory is to reduce the total CED. Several approaches to achieve this are proposed. First, the number of CT examinations, including repeat investigations, should be reduced and non-ionizing radiation imaging should be performed whenever possible (magnetic resonance, ultrasound procedures). Second, examination protocols and techniques should be optimized to limit the radiation associated with each individual CT scan. Third, when patients undergo repeated imaging over time, the dose level for each patient should be tracked and collected, as recently recommended by the American College of Radiology [31], in order to develop alternative strategies to reduce patient-specific radiation burden.

Our study has several limitations. First, it was conducted in a single center while the pattern of use of radiation-related procedures is highly variable depending both on the available technologies and clinical practice. Moreover, we considered only the total CED registered during the study period on dialysis and as performed at our medical center; this by definition underestimates the radiation exposure. Second, we did not use measures of radiation dose but instead relied on estimates of effective doses; this limitation was partly compensated by a careful recording of the number and location of scans involved in each individual CT, by the use of anthropomorphic phantom and Monte-carlo-based dosimetry calculations and by the estimation of effective dose from nuclear medicine procedures.

In conclusion, dialyzed patients undergoing renal pre-transplant evaluation receive high ionizing radiation doses, linked both to their initial evaluation for inclusion in the waiting list and to the subsequent monitoring necessary to maintain their active status on the waiting list. Considering the young age of patients, the subsequent radiation exposure during the first period post transplantation, and the synergistic effect of immunosuppression drugs, nephrologists should strive to minimize the radiation exposure in order to reduce the risk of cancer in these patients.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval The data of the present study are apart of a bigger study for which the approval of ethics committee of our institution was obtained.

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