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Published in:
European Journal of Radiology

DOI:
10.1016/j.ejrad.2020.108898

Publication date:
2020

European Journal of Radiology 125 (2020) 108898

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Which patients are prone to undergo disproportionate recurrent CT imaging and should we worry?

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ARTICLE INFO

Keywords:
Computed tomography
Kidney failure
Medical oncology
Radiation exposure
Second cancer

ABSTRACT

Purpose: To identify the spectrum of patients who undergo disproportionate recurrent computed tomography (CT) imaging, and to explore the cumulative effects of radiation exposure and intravenously injected contrast agents in these patients.

Methods: This retrospective study investigated all patients who had undergone 40 or more CT scans at a tertiary care center between 2007–2017.

Results: Fifty-six patients who had undergone a median of 47 (range: 40–92) CT scans were included. The main reason for CT scanning in all patients was oncological, and 55 patients (98.2 %) had metastatic disease. Twenty-six patients (45.6) had received chemotherapy, 35 (62.5 %) radiation therapy, 38 (67.9 %) targeted therapy, 12 (21.4 %) liver tumor microwave ablation, 44 (78.6 %) major surgery, and 34 (60.7 %) had participated in a therapeutic trial. Mean cumulative effective dose was 187.4 mSv (range: 120.7–278.4 mSv). Median estimated radiation-induced lifetime attributable risk (LAR) of cancer incidence was 1.0 % (range: 0.20–2.36 %). Mean estimated radiation-induced LAR of cancer mortality was 0.68 % (range: 0.18–1.37 %). Mean cumulative volume of intravenously injected iomeprol was 2339 mL (range: 540 – 3605 mL). Three patients (5.4 %) had developed severely decreased kidney function (estimated glomerular filtration rate between 15 and 29 mL/min per 1.73 m^2 for at least 3 months).

Conclusion: Patients with metastatic disease who experience a relatively long survival may be prone to undergo disproportionate recurrent CT imaging. The non-negligible CT radiation-induced cancer risk and mortality should be taken into account in these patients, while the effect of cumulatively administered CT contrast agents on kidney function requires further investigation.

1. Introduction

Computed tomography (CT) has revolutionized the practice of medicine. It benefits many patients by providing faster and more accurate diagnostic information in a less invasive manner than in the pre-CT era. However, a disadvantage of CT is the use of ionizing radiation, which may cause second cancers [1]. Furthermore, the frequent concomitant use of iodinated contrast agents for CT may amplify radiation-induced DNA damage [2], cause acute kidney injury [3], and induce allergic reactions [4]. Therefore, unnecessary CT examinations should be avoided.

The number of CT examinations has increased considerably in the Western world over the years [5,6]. Causes for this trend are multifactorial, and include improvements in CT technology, widespread availability of CT, patient and physician-generated demand, defensive medical practices, and medical uncertainty [5]. Importantly, some patients undergo repeated CT examinations. For example, a study at a tertiary care center in the United States reported that a cohort of 31,462 adult patients who underwent CT in 2007, had undergone 190,712 CT examinations over the prior 22 years [7]. Thirty-three percent of these 31,462 patients underwent more than five CT examinations, 5% underwent more than 22 examinations, and 1% underwent more than 38 examinations over their 22-year study period [7].

The high rates of repeated imaging may be considered worrisome given the cumulative potential side effects of CT scanning in these patients. There concerns have been reaffirmed by several recent studies

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https://doi.org/10.1016/j.ejrad.2020.108898
Received 22 November 2019; Received in revised form 8 January 2020; Accepted 11 February 2020

[8–10]. Further studies are necessary to gain insight into which patient groups are particularly prone to undergo disproportionate recurrent CT imaging, and on the associated cumulative radiation burden and amount of intravenously injected iodinated contrast agents. Such data may increase awareness among radiologists and referring clinicians, and may potentially prevent unnecessary repeated CT examinations in such patients in the future.

The purpose of this study was therefore to identify the spectrum of patients who undergo disproportionate recurrent CT imaging, and to explore the cumulative effects of radiation exposure and intravenously injected contrast agents in these patients.

2. Materials and methods

2.1. Study design

This retrospective study was approved by the local institutional review board (IRB number: 201900012) and the requirement for informed consent was waived. The database of the University Medical Center Groningen, which is a tertiary care center that provides primary and specialty care to approximately 2.2 million people in the north-east of the Netherlands, was searched for all patients who underwent at least one CT scan within a 10-year period (November 2007 to November 2017). Patients were included in this study if they had undergone disproportionate recurrent CT imaging, which was arbitrarily defined as 40 or more CT scans within this 10-year period. Importantly, whether or not these CT scans were clinically useful, was outside the topic of this study. CT scans performed for both diagnostic and interventional purposes (e.g. biopsy, hookwire and drainage catheter placement, and radiofrequency ablation) were included. CT scans of different body regions were counted separately, even when concurrently performed (e.g. a CT scan of neck-chest-abdomen performed in one session was counted as three different CT scans), in line with previous research [7].

2.2. Patient characteristics and follow-up

Medical records were reviewed to determine patients' age, gender, indication for CT scanning, and participation in any therapeutic trial during the 10-year period in which the CT scans were performed. In patients with cancer, type of cancer(s), presence of metastatic disease, use of chemotherapy, radiation therapy, targeted therapy (including monoclonal antibodies and tyrosine kinase inhibitors), or any other type of anticancer therapy, and (history of) major surgery (i.e. surgery requiring opening of a body cavity, organ removal, or alteration of normal anatomy) were also determined. In addition, in all patients reported contrast agent-induced allergic reactions were reviewed, and estimated glomerular filtration rates (eGFRs) were extracted before the first CT scan (i.e. baseline) and after the last CT scan were performed in the predefined 10-year period. Medical records were also reviewed to determine overall survival calculated from the moment of first CT scan.

2.3. CT scanning

All CT scans were performed using single-source 16- to 64-detector row and dual-source 64–96 row CT systems (Sensation and Somatom series, Siemens Healthineers, Erlangen, Germany). All contrast-enhanced CT scans were performed after intravenous injection of 350 mg/mL iomeprol (Iomeron 350, Bracco Imaging, Milan, Italy), which is a nonionic, monomeric iodinated contrast medium, with 90 mL for brain scans, 75 mL for neck scans, 55 mL for chest scans, and 100 mL for abdomen scans in adult patients. Contrast agent administration was done using a power injector. When different body regions were concurrently imaged, the injected contrast volume equaled the highest dose of one of the individual body regions that was in the scan volume (e.g. a contrast-enhanced CT-scan of neck-chest-abdomen performed in one session would require 100 mL of 350 mg/mL iomeprol). Tube voltage values ranged between 80 and 140 kV (adjusted according to age, body weight, and body region) and automatic dose modulation was applied.

Table 1
Average effective doses for the most commonly used CT protocols in adults at our institution, which were relevant for this study.

CT protocol	Effective dose (mSv)
Brain contrast-enhanced	1.6
Brain unenhanced	1.4
Neck contrast-enhanced	1.0
Neck unenhanced	1.0
Chest contrast-enhanced	3.5
Chest unenhanced	2.6
Chest biopsy	2.5
Abdomen contrast-enhanced	4.2
Abdomen unenhanced	2.8
Liver multiphase	7.1
Kidneys and urinary tract multiphase	7.2
Abdomen biopsy	3.9
Liver tumor microwave ablation under CT guidance	27.2

2.4. Cumulative radiation burden and lifetime attributable risk of cancer incidence and mortality

Cumulative effective dose in each patient was calculated based on the average effective dose for each CT protocol in adults at our institution. The average effective dose (E, in mSv) per protocol was calculated as mean dose-length product (in mGy × cm) × k (in mSv × mGy^{-1} × cm^{-1}), with k denoting a conversion factor for different body regions as published previously [11]. Mean dose-length product per protocol was determined based on all CT examinations that had been performed in adults at our institution between January 2014 and June 2019. Table 1 summarizes the average effective doses for the most commonly used CT protocols in adults at our institution, which were relevant for this study. The Biological Effects of Ionizing Radiation (BEIR) VII model was then used to estimate the radiation-induced lifetime attributable risk (LAR) of cancer incidence and mortality, taking into account patient's age and gender [12]. Patient's age at time of first CT scan after November 2007 was used as input for this calculation.

2.5. Cumulative volumes of injected CT contrast agents, allergic reactions, and kidney function

Volume of intravenously injected iomeprol was extracted for each CT scan that was performed, and cumulated volumes were calculated for each patient. Occurrence of contrast agent-induced allergic reactions, and kidney function before the first CT scan (i.e. baseline) and after the last CT scan in the predefined 10-year period were determined.

2.6. Data analysis

The percentage of patients who underwent 40 or more CT scans within the predefined 10-year period was calculated, as a proportion of all patients who underwent at least one CT scan in this time frame. Patient characteristics, cumulative radiation burden and LAR of cancer incidence and mortality, cumulatively administered volumes of iomeprol, and number of patients who developed chronic severely decreased kidney function (i.e. eGFRs ranging between 15 and 29 mL/min per 1.73 m^2 [13]) or chronic kidney failure (i.e. eGFRs below 15 mL/min per 1.73 m^2 [13] for at least 3 months), were descriptively presented. It should be emphasized that the latter analysis can neither determine any causal relationship nor any association between the amount of injected contrast agents and kidney function, and that it merely has an explorative, hypothesis-generating purpose. Number of patients with a newly developed malignancy and number of patients who deceased

during follow-up, were also described. Quantitative data were presented using mean ± standard deviation (SD) for normally distributed data or median with interquartile range (IQR) for not normally distributed data, as assessed with the Shapiro-Wilk test in Medcalc version 18.5 statistical software (MedCalc, Ostend, Belgium).

3. Results

3.1. Patient selection

A total of 100,966 unique patients underwent at least one CT scan at our hospital between November 2007 and November 2017. These patients underwent a total of 273,893 CT scans, with a median of 2 CT scans (IQR: 1–3 CT scans) per patient. Fifty-six patients (0.06 %) underwent 40 or more CT scans in this 10-year period, and they were included in this study.

3.2. Patient characteristics

The included patients consisted of 35 men and 21 women, with a median age at time of first CT scan of 58 years (IQR: 47–65 years; range: 19–80 years), a median of 47 CT scans (IQR: 44–52 CT scans; range: 40–92 CT scans) per patient, and a mean time span ± SD between first and last CT scan of 71.1 ± 22.9 months (range: 33–115 months). Contrast-enhanced CT of chest-abdomen (n = 968), neck-chest-abdomen (n = 131), brain-chest-abdomen (n = 36), chest (n = 86), and abdomen (n = 74) comprised 94.1 % of all CT scans performed. The main reason for CT scanning in all 56 patients was oncological, with non-small cell lung cancer (17.9 %), melanoma (16.1 %), colon cancer (14.3 %), renal cell cancer (12.5 %), and rectal cancer (10.7 %) comprising the majority of malignancies (Table 2). All but one patient (with non-metastatic hepatocellular carcinoma) had metastatic disease (either already before or developed after the first CT scan in the 10-year study period). Twenty-six patients (45.6.0 %) had received chemotherapy, 35 (62.5 %) radiation therapy, 38 (67.9 %) targeted therapy, 12 (21.4 %) liver tumor microwave ablation under CT guidance, 44 (78.6 %) major surgery, and 34 (60.7 %) had participated in a therapeutic trial.

3.3. Cumulative radiation burden and associated cancer risk

Mean cumulative effective dose ± SD due to recurrent CT scanning was 187.4 ± 38.0 mSv (range: 120.7–278.4 mSv). Median estimated radiation-induced LAR of cancer incidence was 1.0 % (IQR: 0.86–1.30 %; range: 0.20–2.36 %) (Fig. 1). Mean estimated radiation-induced LAR of cancer mortality ± SD was 0.68 ± 0.22 % (range: 0.18–1.37 %) (Fig. 1).

Table 2
Types of malignancies in the 56 included patients.

Malignancy	No.
Non-small cell lung cancer	10 (17.9 %)
Melanoma	9 (16.1 %)
Colon cancer	8 (14.3 %)
Renal cell cancer	7 (12.5 %)
Rectal cancer	6 (10.7 %)
Breast cancer	3 (5.4 %)
Hepatocellular carcinoma	2 (3.8 %)
Hürthle cell thyroid cancer	2 (3.8 %)
Neuroendocrine tumor	2 (3.8 %)
Anaplastic large cell lymphoma	1 (1.8 %)
Follicular thyroid cancer	1 (1.8 %)
Hodgkin lymphoma	1 (1.8 %)
Mantle cell lymphoma	1 (1.8 %)
Ovarian cancer	1 (1.8 %)
Hepatocellular carcinoma and mucosa-associated lymphoid tissue lymphoma	1 (1.8 %)
Melanoma and follicular lymphoma	1 (1.8 %)

3.4. Cumulative volumes of injected CT contrast agents, allergic reactions, and kidney function

Mean volume of intravenously injected iomeprol ± SD per patient was 2339 ± 509 mL (range: 540 − 3605 mL). No contrast agent-induced allergic reactions were reported in any of the patients. Three patients (5.4 %) had developed severely decreased kidney function as measured after the last CT scan; pre-CT eGFRs in these patients were 85, 95, and 99 mL/min per 1.73 m^2, with corresponding post-CT eGFRs of 21, 27, and 25 mL/min per 1.73 m^2 (Fig. 2), after having received cumulative volumes of iomeprol of 2510 mL, 2500 mL, and 2700 mL, respectively. None of the other patients had developed either severely decreased kidney function or kidney failure (Fig. 2).

3.5. Follow-up

Twenty-five patients (44.6 %) died during follow-up due to reasons unrelated to the radiation burden. Mean overall survival from the moment of first CT scan ± SD was 80.8 ± 30.8 months (range: 0–136 months).

4. Discussion

The results of this study show that a very small proportion of patients (0.06 % of all patients with at least one CT scan at our institution within a 10-year period) undergoes disproportionate recurrent CT imaging. Disproportionate recurrent CT imaging was defined as 40 or more CT scans within a 10-year period. Although it is acknowledged that this cut-off is somewhat arbitrary and that determining whether these CT scans were clinically useful or not was outside the topic of this study, it serves its purpose by providing insight into the population that is subjected to multiple repeated CT scans. All subjects who underwent disproportionate recurrent CT imaging, were oncological patients, and almost all of them had metastatic disease. Thanks to the success of both traditional anticancer therapies (surgery, radiation therapy, and chemotherapy) and relatively newer treatments such as targeted therapies (applied in 67.9 % of patients) and liver tumor ablation (applied in the patients with colorectal metastases), mean overall survival in these patients was relatively long with 80.8 ± 30.8 months. Moreover, the majority of patients (60.7 %) had participated in a therapeutic trial that included imaging follow-up. This explains the fact that the vast majority of CT scans was performed for therapy response assessment or surveillance imaging.

The estimated overall radiation-induced LARs of cancer incidence and mortality due to multiple repeated CT scanning in our study population were 1.0 % and 0.68 %, with extremes up to 2.36 % and 1.37 %, respectively. These numbers are non-negligible, and should raise awareness among oncologists, surgeons and radiologists who take care of these patients. Awareness in clinical practice may be increased by implementing software for automatized individual patient dose tracking [14], and this information should be available to both the referring physician and the radiologist in the electronic patient files. The presented data also reemphasize the need to carefully consider the need of each CT scan, and to exercise restraint when CT results are unlikely to have a clinical benefit or management consequences, in line with the ALARA principle [15]. In addition, replacement of CT by radiation-free (whole-body) magnetic resonance imaging, which has become a clinically feasible, yet underutilized technique for early diagnosis, staging, and assessment of therapeutic response in oncology [16], should be considered when the need for repeated imaging is anticipated.

Post-contrast kidney injury refers to a decrease in renal function that follows intravascular administration of contrast media, and is a marker for increased short- and long-term morbidity and mortality and

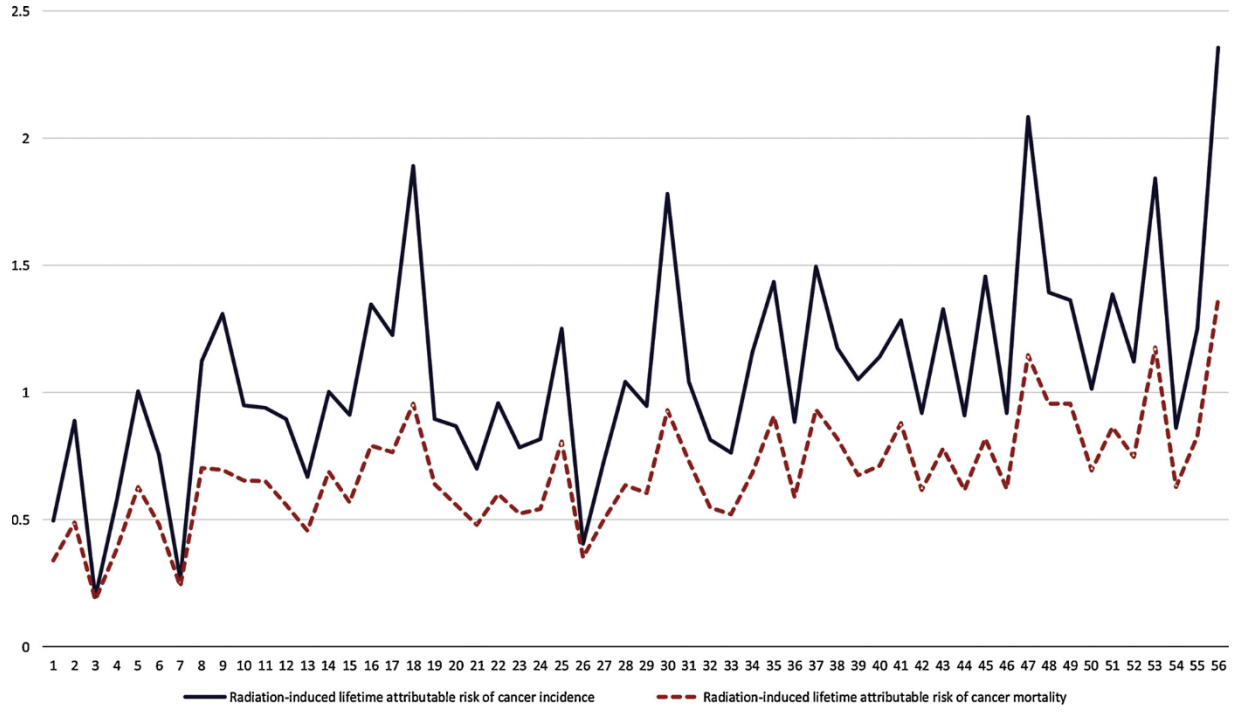

Fig. 1. Graph with individual patients on the x-axis (ordered according to increasing acquired effective dose) and percentage on the y-axis, with radiation-induced LAR (%) of cancer incidence (continuous blue line) and mortality (dashed red line). Of interest, the five cases who showed a relative peak with regard to LAR of cancer (patients 18, 30, 47, 53, and 56) involved one female aged 24 years, one male aged 15 years, and three females aged 31, 46, and 38 years, respectively.

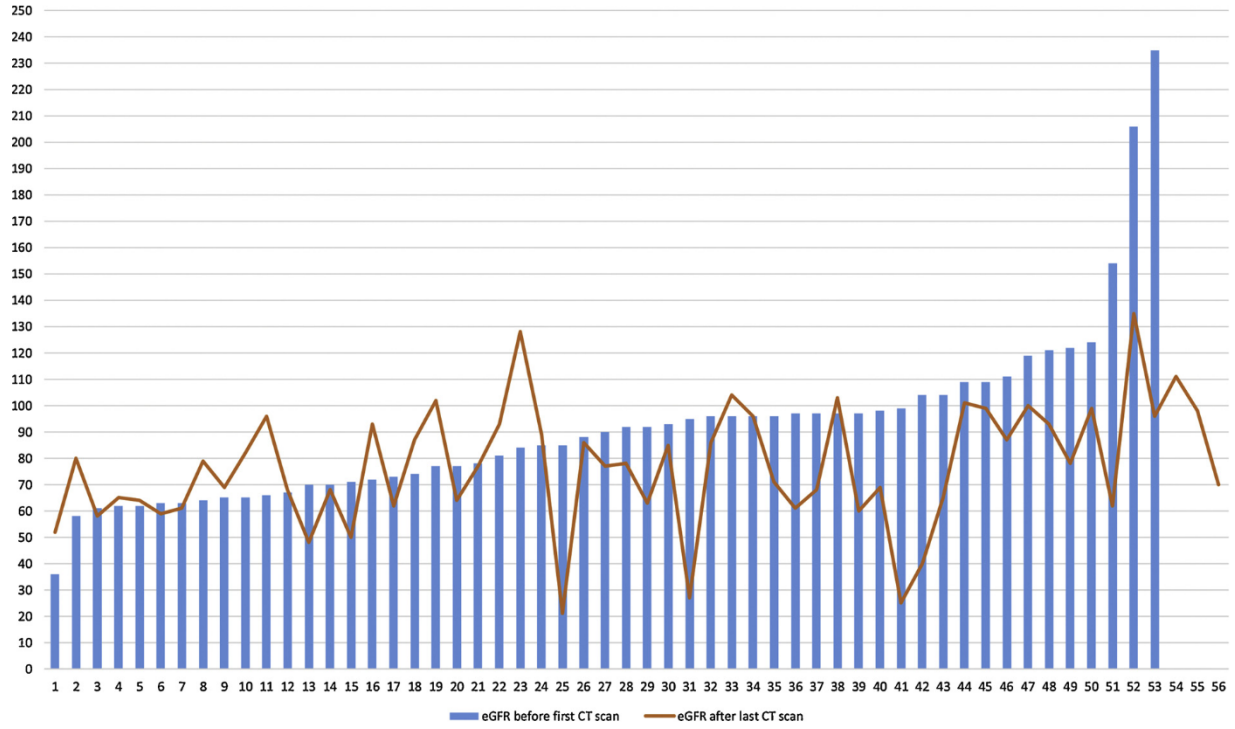

Fig. 2. Graph with individual patients on the x-axis (ordered according to increasing eGFR value before first CT scan, i.e. baseline) and eGFR (in mL/min per 1.73 m^2) on the y-axis, with eGFR before first CT scan (light blue bars) and eGFR after last CT scan (orange line). Note that eGFR before first CT scan was not measured in three patients (no. 54-56).

prolonged hospital stay [17,18]. It is a highly debated topic, with some research showing that the administration of intravenous contrast material does not increase the risk of acute kidney injury, even in patients with substantially compromised renal function [19–21]. Regardless of this debate, the effect of large cumulative amounts of injected contrast media on kidney function in patients who underwent multiple repeated CT scans, has never been investigated. In the present study, patients had received a mean volume of 2339 mL and extremes up to 3605 mL of contrast agent. Despite these high volumes, only three patients (5.4 %), who had received cumulative volumes of iomeprol of 2510 mL, 2500 mL, and 2700 mL, had developed chronic severely decreased kidney function and none of the other 53 patients (94.6 %) had developed

chronic severely decreased kidney function or kidney failure. Furthermore, there may be multiple other causes that have caused chronic kidney disease in these three patients that could not be corrected for [22]. Although these explorative data appear somewhat reassuring, further research into this topic is necessary before any definitive conclusions can be drawn.

Several previous studies have investigated the cumulative radiation burden and associated LAR of cancer due to repeated CT scanning in specific predefined populations such as trauma [23], shunted hydrocephalus [24], suspected renal colic [25], testicular cancer [26] and lymphoma patients [27]. However, their scope was different due to the predefined patient spectra in these studies. Furthermore, the patients in these previous studies by far did not reach the high number of CT scans that were performed in the patients included in the present study. In an older study by Sodickson et al. [7] that retrospectively evaluated a cohort of 31,462 adult patients who underwent CT in 2007, 1% underwent more than 38 examinations in the prior 22 years [7]. However, the characteristics of the 1% of patients who underwent these multiple repeated CT scans, their radiation burden with associated LAR of cancer, and kidney function were not described [7]. Nevertheless, overall, it was reported that patients who underwent large amounts of recurrent CT imaging generally have “substantial underlying disease”. In addition, 85 % of the patients with estimated LAR of cancer greater than 1% had a malignancy diagnosis [7], which corresponds to the patient spectrum of the present study. A more recent study by Rehani et al. [8] that combined data from different institutions in the United States and Central Europe showed that in a population of 2,504,585 patients who underwent 4,819,661 CT examinations during a period of between 1 and 5 years (between 2013 and 2019), a total of 33,407 (1.33 %) patients received a cumulative effective dose of ≥100 mSv. In another study by Rehani et al. [9] that investigated a subset of 8952 patients who received a cumulative effective dose of ≥100 mSv with a median of 19 CT examinations per patient [range: 1–110 CT scans per patient]) at a single institution in the United States between 2013 and 2017, it was reported that 9.6 % had non-malignant conditions and 1.4 % were aged ≤40 years. The fact that none of the patients in the present study had a non-malignant condition may be explained by factors such as different inclusion criteria (≥40 CT scans within a 10-year period in the present study vs. cumulative effective dose of ≥100 mSv within a 5-year period in the studies by Rehani et al. [8,9]) and different patient populations (with the current study having been performed at a tertiary care center with oncological care as one of the top priorities).This study had several limitations. First, it was performed in a tertiary care center in Europe, and results may be different in other institutions and countries with different patient populations and CT utilization habits. Second, the average effective dose for each of our CT protocols is on the low end compared to other institutions and countries [28]. Therefore, CT radiation-induced LAR of cancer is likely higher in most other hospitals. On the other hand, it also shows that thanks to dose optimization strategies the risk of second CT radiation-induced cancers can be relatively contained, even in patients who undergo multiple repeated CT scans. Third, the calculated cancer risks using the BEIR VII report, which is based on a linear-no-threshold model of carcinogenesis estimation for low-dose radiation exposures, are subject to uncertainties at a factor of 2–3 [12]. In addition, patients who already developed cancer may be more prone to develop a second radiation-induced cancer due to issues like DNA repair problems, but this is not taken into account by the BEIR VII data. Fourth, the cumulative risk of recurrent CT exposures was estimated as the summation of the risks of N separate exposures, where in general the cumulative probability that an event will occur is the complement of the probability that the event will not occur. However, previous work showed the differences between these two approaches to be small and that both methods can be applied [29]. Fifth, not all individual dose-length products were stored in the patient records between 2007 and 2017. Therefore, the effective dose was calculated using the mean dose-length product for each CT examination that was performed in adults at our institution between January 2014 and June 2019. This may have introduced some uncertainty in dose estimation. Sixth, (oncological) patients may also have been subjected to ionizing radiation from other sources than CT only, such as SPECT/CT, PET/CT, fluoroscopy-guided interventions, and radiation therapy (with second cancers due to out-of-field doses [30]). However, this was beyond the scope of the present study. Seventh, all of the 56 included patients suffered from cancer, and 25 patients (44.6 %) died during the relatively short-term follow-up. The incidence of estimated CT radiation-induced deaths may have been substantially lower when taking into account the disease-related reduction in life expectancy in the calculations [27]. However, correction for this factor was not possible because of the different types of cancer and the unknown survival of these patients with the advent of newer and promising therapies such as targeted therapies.

In conclusion, patients with metastatic disease who experience a relatively long survival may be prone to undergo disproportionate recurrent CT imaging. The non-negligible CT radiation-induced cancer risk and mortality should be taken into account in these patients, while the effect of cumulatively administered CT contrast agents on kidney function requires further investigation.

Funding

None.

IRB statement

The institutional review board of the University Medical Center Groningen approved this retrospective study (registered in the UMCG research register with number 201900012) and waived the requirement for written informed consent (see attached letter).

This study has been performed in accordance with the ethical standards in the 1964 Declaration of Helsinki.

This study has been carried out in accordance with relevant regulations of the US Health Insurance Portability and Accountability Act (HIPAA).

Declaration of Competing Interest

The authors declars no potential conflicts of interest.

Acknowledgement

None.

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