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Review Article

Reducing Radiation Exposure in Patients with Hereditary Renal Cancers

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Abstract

Concern over radiation-induced cancers has increased over the last ten years. A number of spectacular overdoses with medical radiation has alarmed the public and caused a strong reaction in the professional and manufacturing communities. Medical imaging, particularly CT scanning is a major source of ionizing radiation after background radiation in all patients. However, in patients with von Hippel Lindau Disease and other Hereditary Renal Cancers (HRC), scans are performed on a regular basis to monitor the progress of the disease. As a result significant cumulative doses of radiation can occur resulting in doses for which the literature documents an increase risk of cancer. Meanwhile, due to germline mutations in tumor suppressor genes and oncogenes, patients with HRC are at increased theoretical risk for the development of radiation-induced cancers. This is, in part, balanced by increased surveillance in patients with HRC reducing the likelihood of death related to radiation-induced cancers. With improvements in Magnetic Resonance technology, more patients with HRC are scanned in this manner as opposed to CT since no ionizing radiation is involved. However, there have been a number of improvements in CT technology that are dramatically lowering the radiation doses to which HRC patients are exposed. Herein, we review the basis for concern over radiation-induced cancers in the general population and specifically in patients with HRC and describe methods to reduce radiation exposure on CT. These methods include automatic exposure control, modulation of voltage, iterative reconstruction and dual energy CT. Combined, these methods may enable patients with HRC to safely undergo CT as a method for monitoring the status of their renal disease.

ABBREVIATIONS

CT: Computed Tomography; MRI: Magnetic Resonance

Imaging; HRC: Hereditary Renal Cancer; Gy: Gray; Sv: Sievert; ACR: American College of Radiology; LNT: Linear-No-Threshold model; GFR: Glomerular Filtration Rate.

INTRODUCTION

Hereditary Renal Cancer (HRC) comprises a group of tumor syndromes characterized by a predisposition to the development of renal cancer. They include von Hippel Lindau (VHL), hereditary papillary renal cancer (HPRC), hereditary leiomyoma renal cell carcinoma (HLRCC), Birt Hogg Dube (BHD) Tuberos Sclerosis (TS) and Succinate Dehydrogenase (SD) among several others that are less well described[1]. Patients with HRC are at substantial risk for developing renal cancers and some of these cancers may prove to be lethal. As a consequence, imaging studies are commonly obtained to monitor the progress of disease in patients with HRC. The traditional method of monitoring patients with HRC is computed tomography (CT) which is quick, relatively inexpensive, reliable, reproducible and well understood by the medical community. However, over the past few years there has been rising concern about the cumulative effects of exposure to ionizing radiation from repeated CT scans obtained over many years in patients with hereditary predisposition to cancer. It is not uncommon to find 10-20 abdominal CT scans in the folder of a patient with HRC. Therefore, there has been increasing interest in exploring alternatives to CT or to find ways to reduce the dose of ionizing radiation during CT in order to allay these concerns.

In this article we will explore the basis for concern about exposure to ionizing radiation with special emphasis on patients with hereditary cancer syndromes, particularly HRC. Then we will compare different imaging modalities and focus on advances in CT technology that are aimed at reducing the burden of ionizing radiation in all patients but particularly in those with hereditary predispositions to cancer.

What is ionizing radiation?

Ionizing radiation is energy, in the form of photons (also called gamma or x-rays) or subatomic particles that is sufficient to knock an electron out of its orbit around the nucleus of an atom, thus ionizing it. Ionic compounds formed in this way are more chemically and biologically reactive and thus, more likely to cause degradation or radiolysis of molecules in its immediate environment. For instance, when a gamma ray hits a DNA molecule it can lead to reactive oxygen species that, in turn, damage the bonds between nucleic acids in DNA, leading to genomic mutations or instability. Such damage may occur at one time on one allele and then occur later, upon subsequent exposure, on the opposite allele leading to complete or partial loss-of-function in tumor-suppressor genes or gain-of-function in tumor promoting oncogenes. Such effects are usually delayed, not immediate responses to radiation. However, patients with hereditary renal cancers (HRCs) are born with genomes that harbor mutations, referred to as germline mutations, and therefore the acquisition of another DNA alteration (mutation, frame shift, deletion etc.) on top of the pre-existing mutation, is even more likely to result in a cancer than the normal genome in which two such "hits" are required at approximately the same location on the two different alleles of the chromosome. Patients with HRC are most likely to encounter ionizing radiation as part of diagnostic procedures such as CT and to a lesser extent, radionuclide studies and plain radiographs. Here, they are exposed to x-rays between the energy of 50kV to 150 kV, which are more than sufficient to cause ionization within DNA molecules. Most CT scans are obtained at

120-140kVp although this is changing as will be explained later.

Ionizing radiation is measured by the unit "Gray" and the "Sievert", recognizing these two pioneers in radiation research (Louis Harold Gray, 1905-1965, was a British physicist and Rolf Maximilian Sievert, 1896-1966, was a Swedish physicist). The old terminology for radiation exposure was the "Rad" and the "REM", the latter representing the acronym "Radiation equivalent man". The Gray (Gy) is equivalent to 100 Rads and is a measure of exposure to ionizing radiation. The Sievert (Sv), which is equivalent to 100 REMs, is a measure of absorption of ionizing radiation. For most gamma ray irradiation (e.g. CT scans) the radiation dose in Gy is equivalent to Sv but technically Sv is more meaningful as some high energy subatomic particles such as alpha and beta particles are more biologically damaging than gamma rays and therefore the Sv (absorption) may be several times the Gy (exposure). Most diagnostic imaging in the form of CT varies in dose from from 1-10 milliSv (abbreviated mSv) and mSv is the most commonly used designation of dose for CT. The commonly used term, Computed Tomography Dose Index (CTDI) is essentially equivalent to the dose in mGy or mSv while the term Dose Linear Product (DLP) takes into account the effect of the dose as it is translated over larger parts of the body (the more coverage of the body during a CT, the higher will be the DLP).

Mechanism of cancer induction by radiation

The most commonly feared impact of ionizing radiation at the doses encountered in medical imaging is the induction of cancer which occurs years or decades after exposure. Cancer induction by ionizing radiation is considered stochastic, meaning that its likelihood increases with radiation dose, but the severity of the disease is not predicted by the dose. For instance, a non-lethal cancer could be induced by radiation with no effect on the patient's longevity. The most common radiation induced cancer is leukemia but other cancers, particularly brain, lung and thyroid cancers have been definitively linked to radiation [2]. In theory, radiation could induce any cancer type, however, the most complete databases have been generated from radiologic disasters such as the Hiroshima/Nagasaki atomic bombs and the Chernobyl nuclear reactor explosion, and there is really very little data regarding the effects of highly fractionated diagnostic imaging ionizing radiation on cancer rates in adults [3]. Data is emerging in children (where the risks of ionizing radiation are substantially higher due to higher proliferation rates of cells) that diagnostic CT scans can result in increased rates of cancer, especially brain cancer in children exposed to diagnostic radiation [4,5]. An important aspect of the radiologic disaster databases is that they are based on exposures of the general population to radiation. In these single exposure scenarios there is little evidence of increased risk of radiation induced renal cancer although other cancers are reported. However, this should not imply that the kidney is resistant to the effects of radiation, but rather that other organs may be more sensitive. Little actual data exists concerning dose levels to patients undergoing CT as would be expected since the "CT era" is only 30 years old and cancers would probably only just now be emerging.

How does radiation exposure induce cancer? The most widely accepted model posits that the incidence of cancers increases linearly with effective radiation dose at a rate of 5.5% per Sv [6]. If this is correct, then natural background radiation

is the most hazardous source of radiation to the general public, followed by medical imaging as a close second. However, one problem with this data is that it is mostly derived from single exposures during radiologic emergencies such as atomic bombs or explosions at nuclear reactors. This is quite different than intermittent, fractionated low dose exposure at yearly intervals such as might occur during screening studies for HRC. The conservative estimate is that such exposures are cumulative, i.e. if one is exposed to 100 lifetime CTs at 10 mSv /CT scan, then, one's exposure is equivalent to 1000 mSv or 1 Sv and therefore there would be a 5.5% expected increase risk of cancer. But is that really true? Cells exposed to radiation can suffer double strand breaks (DSBs) at a rate of 35DSBs per cell per Gy [7]. But there is substantially less damage per 1-10 mGy exposure and some of that damage is likely to be repaired before the next exposure to radiation. In one study the majority of DSBs were repaired by 90 min after radiation [8]. Thus, it is unlikely that a single large exposure to ionizing radiation is directly equivalent to multiple small doses over time. However, beyond DSBs, radiation can induce epigenetic changes that do not affect the actual DNA helix but can alter the regulation of DNA synthesis and may be less subject to DNA repair processes. While DSBs are commonly repaired in cells within a day of exposure, approximately 25% of DSBs result in incorrect repair potentially leading to mutations [8]. The ability to repair DNA damage varies with health status and genetic background. For instance, some disorders like ataxia telangiectasia and xeroderma pigmentosa and BRCA (Breast cancer gene mutations) have specific DNA repair defects that make patients more susceptible to radiation induced cancers [9,10]. The HRCs do not fall into this category and have intact DNA repair mechanisms at least in the early stages of neoplasia. However, the diseases encompassed within HRC also involve germline damage to tumor suppressor genes or oncogenes and therefore, the genome is already impaired prior to exposure to ionizing radiation. It is also important to repeatedly note that the induction of cancer is not synonymous with death from cancer, as induced cancers vary significantly in their aggressiveness. To the extent that patients with HRC undergo more frequent screenings than the general population it could very well be that such induced tumors are detected and treated before they cause mortality.

There is general agreement that the risk of radiation is much higher for fetuses (10 fold) infants (4 fold) and adolescents (2 fold) than for adults and probably higher for women than for men [11]. Interestingly, because of the long lead times for radiation induced cancer, the risk may begin to fall above a certain age (e.g. above 60 years of age). Radiation induced cancers generally take 10-15 years to develop after exposure and may take as long as 40 years to become clinically apparent.

However, there remains controversy over whether the relatively low dose of radiation that most patients receive during medical examinations will impact cancer risk. Epidemiologic studies with exposures below 10mSv show equivocal increases in cancer. For instance, studies of occupational workers exposed to chronic low levels of radiation, above normal background, have provided mixed evidence regarding cancer and transgenerational effects. One of the most recent and extensive studies of workers was published by Cardis et al. [12]. There was no evidence

that low level, brief radiation exposures were harmful in these populations [13].

Thus, the prediction of cancer risk from radiation lies not in actual data but in projected models created by experts and agreed to in consensus. The "linear no threshold" (LNT) model is the most commonly accepted model as it is the most conservative one, and therefore, the largest consensus can be built around it. For instance the LNT is accepted by the International Commission on Radiation Protection (ICRP) and a variety of other global nuclear regulatory agencies [14]. It posits that there is no dose below which radiation exposure is safe and that every exposure damages biologic tissue in some way. According to the LNT model about 1% of the global population develops cancer as a result of natural background radiation at some point in their lifetime. For comparison, 13% of global deaths in 2008 were attributable to cancer, so background radiation is likely a small contributor to cancer formation in comparison to other environmental factors such as cigarette smoke, air pollution infections, inflammation and chemical exposure. CT scans alone, which account for half the medical imaging dose to the public, are estimated to be responsible for 0.4% of current cancers in the United States, and this may increase to as high as 1.5-2% with 2007 rates of CT usage [15]. Interestingly the number of CT scans performed in the United States peaked in 2007 and has been declining since then. However, regardless of the assumptions, this estimate is simply a projection based on current practices which are likely to change as will be explained below [16]. Recently, it has been reported that actual doses from CT are higher than previously reported [17].

From the US perspective, it has been estimated that CT scans performed in the US in 2007 alone will result in 29,000 new cancer cases in future years [18]. It is important to remember that not all or even most of these cancers will lead to death. Moreover, this estimate is criticized by the American College of Radiology (ACR), which maintains that the life expectancy of CT scanned patients is not that of the general population and that the model of calculating cancer is based on total-body radiation exposure and is thus faulty [11]. However, the ACR has some conflict of interest on this subject and has therefore been criticized. According to estimates based on the LNT model, a CT examination with an effective dose of 10mSv (which is not atypical for 3 phase abdominal CT scans) may be associated with an increase in the possibility of a fatal cancer of approximately 1 in 2000 [11]. This increase in the possibility of a fatal cancer from radiation can be compared to the 20% incidence of fatal cancer in the U.S. population. In other words, the risk of radiation-induced cancer is much smaller than the baseline risk of cancer. Other models such as the linear quadratic model suggest that radiation must be above a certain dose threshold (typically 10-50mSv) before biological effects are seen. Others suggest that low doses of radiation may actually promote health although this claim is difficult to prove in humans. However, as mentioned the highest consensus is reached by assuming the LNT model.

In summary, ionizing radiation causes irreversible double strand breaks or epigenetic changes that eventually lead to neoplastic transformation of the cell in a small percentage of cases. DNA repair processes probably repair the majority of such damage but not all, and in cases of impaired DNA repair

mechanisms or in the case of genetic predisposition to cancer, the risk of cancer is increased. However, this process may take decades to manifest from the time of maximal exposure. Aside from leukemia, brain cancer and thyroid cancer it is hard to measure actual increases in the rate of cancer in epidemiologic studies in exposed populations. Instead scientists rely on models, particularly the linear no-threshold model in which the doses that patients are exposed to during diagnostic CT could result in increases in cancers in the future. Clearly, if the LNT model is correct, lowering the dose of CT could lower the rate of cancer induction and is thus highly desirable.

Is the risk of radiation-induced cancer higher in hereditary cancer syndromes?

Some hereditary conditions such as nevoid basal cell syndrome and retinoblastoma, are more susceptible than average to developing cancer from radiation exposure [19]. This data has mainly been derived from larger therapeutic doses of ionizing radiation administered during radiation therapy with the subsequent development of secondary tumors years later at the site of irradiation. For instance, patients with retinoblastoma are at increased risk of developing sarcomas within the radiation field of treatment for the primary tumor. Patients with Nevoid Basal Cell Cancer Syndrome also developed recurrent basal cell cancers in irradiated regions. Neurofibromatosis type 1 and the Li Fraumeni syndrome are additional examples of this effect. Patients with neurofibromatosis 1 (NF1) with irradiated optic pathway gliomas have increased risks of developing additional cancers after radiotherapy. Patients with Li Fraumeni syndrome developed secondary malignancies at higher rates after radiotherapy [20,21]. There is no data for HRC. It is clear that genetically susceptible pediatric subpopulations of patients exist and radiation should be strongly avoided in these groups [22]. This data supports the concept that hereditary cancer syndromes of any type, including those considered within the HRC family of syndromes, are at increased risk for radiation induced cancers, however, the data only exists for much higher dose rate exposures such as those experienced during radiation therapy. No comparable data exists for the lower doses found with medical imaging.

Another approach to this problem is to examine animal models of cancer predisposition with and without exposure to radiation. Because of the cost of these models, few actual experiments have been reported but the evidence in the few studies that do exist, is compelling. For instance, in a mouse model of Lynch syndrome (Hereditary nonpolyposis, colon cancer or HNPCC), exposure to radiation in M1h1 knockout mice accelerated the growth of intestinal cancers [23]. Similar experiments in other models of cancer predisposition syndromes have found similar findings.

Thus, while there is no direct evidence of diagnostic radiation causing more cancers in patients with HRC, there is compelling circumstantial evidence. Interestingly, when specimens of patients with VHL are examined closely, it can be documented that the kidneys harbor literally thousands of microscopic tumors that may not progress over the patient's lifetime [1]. Only a small percentage of the total number of renal cancers manifest during the patient's life as visible lesions on CT. If after a lifetime exposure to 1Sv from 100 serial 10mSv CT scans it is calculated

that there is a 5.5% increase in the risk of cancer, say from 1000 tumors to 1055 tumors in the kidneys. It is interesting to speculate whether this small relative increase in number of tumor would really make a difference in the lifetime risk of dying from renal cancer. Once again, we emphasize that not all cancers are lethal and usually they require multiple additional genetic "hits" to turn into a lethal cancer. Moreover, these "extra" cancers would take decades to develop. In a patient with a life expectancy of less than 20 years at the time of the diagnostic procedure the presence of excess tumors from radiation would likely have little impact. Nonetheless, in the end, this is all speculative. The risks of cancer from diagnostic medical imaging in patients with HRC are not only unknown but likely unknowable. Therefore, a conservative approach should be taken. However, given the uncertainty, the patient should have the right to weigh in on the decision making regarding exposure to ionizing radiation as different patients can tolerate different levels of risk.

Thus, experimental evidence supports the concept that patients with hereditary forms of cancer, probably including HRC, are at increased risk for radiation induced cancers. Syndromes with the most obvious predisposition are those that include DNA repair mutations preventing correction of DSBs. However, even syndromes associated with tumor oncogenes or tumor suppressor genes (particularly the latter), have shown experimental evidence of radiation induced malignancy including retinoblastoma, models of hereditary non polyposis colon cancer, Li Fraumeni syndrome and NF1. Therefore, it would be predicted that even though no studies have been performed in tumor models harboring genetic abnormalities predisposing to renal cancer, it can be inferred by the preponderance of data that similar effects will be seen in HRC. It is important to note how difficult it would be to actually prove this in clinical studies as one would have to find a large group of HRC with no ionizing radiation exposure and compare it to a group of at least equal size with HRC who had been exposed to diagnostic radiation levels. These groups would then have to be monitored for decades. It is highly unlikely that such a study will ever be attempted so we must make do with inferences from other syndromes and models and conclude that radiation in patients with HRC should be avoided in patients under the age of 18 and generally avoided in adults if viable alternatives exist.



Figure 1 Ultrasound in a patient with von Hippel Lindau Disease. There is a small solid mass representing a renal cancer. Although ultrasound is often adequate in thin patients, it is much more operator dependent than other modalities and many areas of the body are obscured by overlying gas and bone.

IMAGING IN HEREDITARY RENAL CANCERS

There are three main imaging modalities that are used for screening and monitoring patients with HRC, Ultrasound (US), Magnetic Resonance Imaging (MRI) and computed tomography (CT) [24]. In the following sections we compare the advantages and disadvantages of each and demonstrate the technical developments in the field of CT that are aimed at lowering the ionizing radiation dose.

Ultrasound

From the perspective of ionizing radiation ultrasound would appear ideal for patients with HRC. It is a relatively low cost, portable method that avoids ionizing radiation. However, there are a number of significant issues that limits its use as a universal method. For evaluating the kidneys ultrasound is non-ideal. Ultrasound suffers from operator dependency; quality is highly dependent on experience. Moreover, patient body habitus can lead to inadequate surveys of the kidney. Large patients or patients with overlapping bowel will be poor ultrasound candidates. Furthermore, some HRC conditions such as von Hippel Lindau (VHL) disease also involve the adrenals and pancreas. Both organs are difficult to identify on ultrasound, and the latter is often obscured by overlying bowel gas. A study comparing ultrasound and CT for renal lesions (mostly VHL) revealed that ultrasound was far less sensitive and less specific than CT [25]. Thus, while having some favorable features ultrasound is not a suitable substitute in HRC imaging (Figure 1).

In particular instances, ultrasound can be very useful. For instance, where it is unclear whether a lesion is cystic or solid because of poor enhancement (as in the case of papillary renal cancers), ultrasound can be helpful. Ultrasound is also very good at identifying the inferior vena cava and rapidly detecting thrombus in cases of extension from a renal cancer. Finally, intraoperative ultrasound is often utilized during surgery to aid in identifying renal tumors deep to the kidney surface.

Magnetic resonance imaging

MRI has improved dramatically in quality in the last few years. As a result, the heterogeneity observed between MRI units and standardization of imaging has also improved. The standard MRI consists of a T1 and T2 weighted sequence in several planes (typically axial and coronal) and dynamic (images obtained every minute or so) contrast enhanced T1 weighted sequence after bolus administration of a gadolinium chelate. Diffusion weighted imaging has also become more common. Beyond this, specific manufacturers have speciality sequences that are typically added to the menu of standard options. Thus, the typical MRI is more complex than the typical CT in that there are more "series" of images to evaluate and techniques may vary from site to site.

A primary advantage of MRI is that it does not expose the patient to ionizing radiation. Compared to CT the spatial resolution is not as high. MRI requires more training than CT to interpret. MRI does not demonstrate calcifications well but this is a minor disadvantage in the setting of HRC. In patients with reduced renal function, specifically with estimated GFRs (eGFR) <30cc/min, Gadolinium based intravenous contrast agents should not be administered in order to prevent nephrogenic

sclecting fibrosis (NSF) a debilitating interstitial fibrosis that occurs with gadolinium chelates in the presence of renal failure. Some flexibility on this issue is possible because, some of the gadolinium chelates are more resistant to NSF than others. For instance, ProHance (gadoteridol) is a macrocyclic chelate of gadolinium that has a much stronger chelation of Gadolinium than other commercially available chelates. Thus, this agent can probably be used safely at even lower eGFRs. Moreover, some institutions use ferumoxytol, an FDA-approved iron containing agent as a substitute for Gadolinium in patients with severely reduced renal function. This off-label use of ferumoxytol enables contrast enhancement to be safely performed [26]. However, due to the relatively slow clearance of ferumoxytol from organs such as the liver, ferumoxytol should not be administered at frequent intervals.

MRIs take longer to obtain (30-45 min) than CT (5 min) and the patient must remain still for the duration of the study for high quality images to be obtained. A substantial minority of patients experience some degree of claustrophobia in an MRI unit often requiring some sedation. This, in turn, requires that the patient have an accompanying person to safely get them home from the imaging session. The same accompanying person

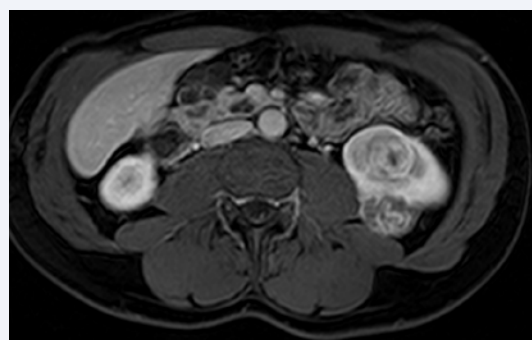


Figure 2 MRI in a patient with von Hippel Lindau Disease. This T1 weighted image is obtained after the administration of gadolinium chelate contrast media. It shows two masses in the lower pole of the left kidney (right side). MRI does not involve ionizing radiation but it is more expensive and time consuming than CT.



Figure 3 Conventional CT of a patient with von Hippel Lindau Disease obtained with "normal dose" settings. The left kidney contains a solid renal mass. It is of excellent quality but was obtained prior to current methods of limiting radiation dose.

may need to stay in the MRI room during the scan to reduce anxiety (Figure 2). Motion artifact can significantly degrade image quality whereas CT is so rapidly obtained that it is more tolerant of motion. Metallic artifacts such as hip replacement and other surgical remnants (e.g. surgical clips) can degrade image quality. MRI is contraindicated in some patients with pacemakers and other implanted electronic devices. Thus, MRI is often more complex and susceptible to artifacts than CT. Finally MRI is more expensive than CT by a factor of 1.5 to 2 fold and less available in non-urban settings.

Computed tomography

CT would be the first choice for patients with HRC were it not for the fact that it relies on ionizing radiation to produce images. It is fast, safe and efficient. The modern CT scan takes under 5 minutes and most of this is setup time and not scanning. However, the exposure to ionizing radiation is a decided disadvantage, especially in the HRC setting (Figure 3).

Public scrutiny of radiation from CT scanners has increased after several well publicized overexposures to radiation. In one instance, a child's head was repeatedly scanned leading to extremely high doses resulting in skin burns and local hair loss to the child. This story, amplified in the media, placed a spotlight on exposure to radiation from medical imaging and increased the level of caution on the part of patients. Somatic effects from CT such as hair loss are documented [27]. The concept that "radiation is harmful" is easily conveyed in stories but the concept that "the benefits of imaging outweigh the risks" is more difficult to convey. A positive outcome has been that patients and their physicians are more carefully considering whether scans are needed in the first place and to limit the scans to the relevant body parts and not freely scan through non-relevant body parts. For instance, in VHL, the risk of thoracic and pelvic disease is not above that of the general population and therefore, limiting the scans to the upper abdomen will reduce total dose to the patient. A negative outcome of the fear of radiation is that some patients who could benefit from CT scans refuse to have them. As always, children and adolescents are most susceptible to radiation exposure and therefore, all efforts should be made to avoid CT in these patients.

The public outcry over radiation exposure has led to a salutary response on the part of the CT manufacturers to lower the doses required to obtain diagnostic quality CT scans. Prior to this point, radiation exposure was hardly considered in determining what should be scanned and how it should be scanned. For instance, traditionally the standard HRC CT protocol involved a precontrast scan through the kidneys to identify hyperdense cysts that might masquerade as tumors, followed by an arterial phase (early after the arrival of intravenous iodinated contrast media) data set followed by a nephrographic phase (1-2 min after the intravenous injection). Of these three sequences the latter is clearly the most important. In the case of VHL, the advent of arterial phase imaging with CT revealed hitherto undiscovered pancreatic neuroendocrine tumors that demonstrate flash enhancement during the arterial phase but become extremely difficult to identify later. However, many of these newly discovered lesions were small and indolent and its unclear whether many patients benefited from their discovery.

Therefore, one way to reduce exposure would be simply to return to a single phase (nephrographic) CT scan. This would immediately reduce radiation exposure by a factor of 3 compared to current practice.

However, there are several remarkable developments in CT technology that are resulting in dramatic reductions (50-80%) in radiation exposure that could enable the current protocols to be maintained with less exposure to the patient. Patients, radiologists and physicians have become accustomed to spectacular high resolution CT scans. An important aspect of dose reduction is acceptance of degraded, but still useful, image quality. The field of CT spent its first 30 years developing better and faster CT scans. With the acknowledgement of limits to radiation dose we are now trying to find an acceptable level of image quality in order to reduce dose. Thus, one should no longer judge an image by its crispness, but by the effort employed to reduce dose while maintaining acceptable quality.

X-ray tubes work by aiming a high energy stream of electrons at a target. The interaction between the electrons and the target produces x-rays. Radiation dose is dependent on the number and energy of the electrons as measured by their current (millampere-seconds or mAs) and their peak voltage (kVp). One approach manufacturers have taken is to adjust the tube current depending on the thickness of the body. Thinner bodies require less radiation and thinner portions of the same body require less radiation. This can be automatically calculated in state of the art CT scanners and is known as automatic exposure control (AEC). Significant reductions in exposure can result especially if angular modulation of the tube current is employed. As the x-ray tube rotates around the patient and it traces different paths of the x-rays through the body; thus, depending on the angle of the tube there will be different attenuation of x-rays through the body. By modulating the x-ray output as the x-ray tube rotates around the patient in real time, substantial reductions in radiation exposure can be realized. The patient must be well centered in the CT gantry to achieve good results [28].

Another approach is to lower the kVp of the x-ray tube. This generally results in noisier images but they actually may be more sensitive for detecting the iodine in the intravenously administered contrast agents. Thus, lowering the kVp reduces

Table 1: Methods of Reducing Radiation exposure.

Method of Radiation Reduction	% Reduction in dose	Comments
Automatic Exposure control	20-80%	Reduces x-ray tube current
Automatic voltage control	25-50%	Reduces x-ray tube voltage
Iterative reconstruction	25% **	** No dose reduction per se but allows lower techniques to be used loss of image quality
Dual Energy CT	25-75%**	** No dose reduction per se but Reduces scans by creating virtual images
Limiting number of scans and reducing extent of coverage	0-100%	Relies on a philosophy of avoiding radiation exposure whenever possible.

overall exposure while maintaining or even improving sensitivity for enhancement which is critical for kidney cancers. This is very important in the case of HRC where enhancement within a lesion is a surrogate for the presence of cancer. Of course, there are limits to this approach. kVp cannot be substantially lowered in large patients as the penetrating power of the x-ray is dependent on kVp. Thus, the biggest gains in this approach are again seen in smaller, thinner patients. CT units are being introduced that modulate the kVp of the scanner according to patient size, analogous to modulating the current supplying the x-ray tube. Reductions in 25% of radiation dose can be achieved.

Another approach to reducing radiation exposure is to change the reconstruction of the image from traditional filtered back projection to iterative reconstruction (Table 1). This approach has long been used in nuclear medicine cameras but has only recently been applied to CT. It does not actually lower the radiation dose *per se*, but corrects for noise induced by lowering current and voltage thus permitting greater reductions to be made without affecting image quality. There are clear limits to how far this approach can be taken without resulting in uninterpretable images, however, depending on the application, substantial reductions (e.g. 80%) in radiation can be achieved while maintaining adequate image quality [29].

Finally, dual energy CT in which two separate x-ray tubes are simultaneously used at two different kVps enable the creation of synthetic images such as “virtual” non contrast scans and “virtual iodine scans”. This is based on the concept that iodine absorbs x-rays to a higher degree at lower kVp. Thus, by comparing the same image at two different kVps it’s possible to subtract out the iodine (i.e. create virtual non contrast images) and create iodine only images (virtual iodine scans) [30]. At first it is difficult to understand how doubling the number of x-ray tubes reduces radiation exposure (each tube uses about half of the typical exposure) but a more in depth understanding reveals the potential for this technology [31].

In a dual source system there are two x-ray tubes, one with a low kVp and the other with a higher kVp. An alternative technology is a single tube that alternates (<0.5ms) high and low kVp x-rays. Finally, a single tube with a sandwich detector that simultaneously differentiates high and low kVp x-rays is under development and is known as a photon counter. Regardless of the approach taken immediate benefits can be seen from virtual images by eliminating the need to obtain pre contrast scans and potentially reducing the need for arterial phase imaging. The iodine images detect the actual amount of iodine present rather than the relative attenuation value which is provided by Hounsfield Units (HUs) which is the most common method of measuring enhancement on CT. The lower kVp values enable detection of “flash” enhancing lesions such as pancreatic neuroendocrine tumors found in VHL without potentially requiring a separate arterial phase. This would greatly reduce exposure to patients.

An intriguing aspect of dual energy CT is to create virtual monochromatic CT scans. Currently CT tubes produce a spectrum of energies with a peak (the kVp). Using image processing algorithms, calculated single keV (kilo electron volts) images can be created. These may have the potential for image improvement



Figure 4 Low dose CT of a patient with von Hippel Lindau Disease. This scan is from a different patient from Figure 3. Even though the dose is about 30% of the scan shown in Figure 3, the quality of the scan is completely adequate for diagnostic purposes. Great strides have been made in dose reduction in CT.

with lower overall doses of radiation although this is still in the research domain.

Thus, while dual energy CT is dose neutral compared to conventional CT, with some systems, substantial gains can be made by avoiding direct acquisition of non contrast and arterial phase imaging. Instead, virtual versions of these scans can be generated without additional radiation. However, these benefits are still being evaluated in the research setting and may not be widely available for several years.

CONCLUSION

There is an increasing recognition that medical imaging is a substantial source of ionizing radiation exposure and probably surpasses background radiation in patients with HRC. The linear no-threshold model of radiation exposure posits that all radiation, no matter, how low, poses some risk to patients. Patients with HRC have a genetic predisposition to cancers and although radiation has never been shown to increase cancer rates in HRC, it would be quite difficult to show either in humans or animal models. Thus, we must assume the conservative stance that the linear no threshold model is correct, that low doses fractionated over a period of years are equivalent to higher doses obtained at one time and that germline mutations in HRC predispose to ionizing radiation damage. Under those conditions, MRI of the abdomen is the best modality to monitor HRC patients over time. However, MRI is not without its problems and new technologies in CT promise to substantially lower the exposure of patients to ionizing radiation. With radiation reductions of up to 80% it might be time to rethink the role of CT in HRC and to allow patients some input into which imaging modality should be used given differences in cost, availability and side effects. For instance, an approach whereby MRI and CT are alternated on a yearly basis would result in a 50% lifetime exposure reduction. Given the costs and inconveniences of MRI, some patients may very well elect low dose CT as an alternative (Figure 4). Healthcare providers must remain sensitive to the concerns of patients about radiation, especially those patients with HRC who must undergo repeated studies over their lifetime. An approach

that balances the concerns of the patient regarding cumulative radiation exposure, the medical benefits of CT vs. MRI and the reductions in risk offered by new CT technology should be included in the conversation.

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