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UNIVERSITY OF CALIFORNIA,
IRVINE

Comparison of Radiation Dose From Conventional and Triple-Bolus Computed
Tomography Urography Protocols in the Diagnosis and Management of Patients With Renal
Cortical Neoplasms

THESIS

Submitted in partial satisfaction of the requirements
for the degree of

MASTER OF SCIENCE

in Biomedical and Translational Science

By

Garen Abedi

Thesis Committee:
Professor Sheldon Greenfield, Chair
Professor Jaime Landman
Professor John Billimek

2015

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DEDICATION

To

my colleagues and mentors

in recognition of their support

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I also would like to acknowledge publisher of Urology Gold Journal, Elsevier for permission to include our original manuscript on the topic in this dissertation. The article can be accessed at the following link (A website statement has been included as supplementary file that permits use of previously published work as part of a thesis dissertation):

[http://www.goldjournal.net/article/S0090-4295\(14\)00610-4/abstract](http://www.goldjournal.net/article/S0090-4295(14)00610-4/abstract)

ABSTRACT OF THE THESIS

Comparison of Radiation Dose From Conventional and Triple-bolus Computed Tomography Urography Protocols in the Diagnosis and Management of Patients With Renal Cortical Neoplasms

By

Garen Abedi

Master of Science in Biomedical and Translational Science

University of California, Irvine, 2015

Dr. Greenfield Irvine, Chair

CT imaging predisposes patients to high levels of radiation. In this study, we retrospectively compared the radiation dose of triple-bolus computed tomography (TBCT) and conventional CT (CCT) urography protocols, analyzed the effects of body mass index (BMI) on radiation dose in each group and assessed image quality.

We retrospectively reviewed the images of patients who underwent CCT or TBCT imaging in the management of renal cortical neoplasms. We used standard volumetric CT dose index (CTDIvol) and dose length product (DLP) to estimate radiation exposure. In addition, 2 urologists rated the quality of 20 CT images from each group using a survey with a 5-point Likert scale. The survey consisted of 10 questions relating to the ability of the scan to identify relevant anatomy.

The study included 120 patients. CTDIvol and DLP were 28.7% and 40.4% lower in the TBCT protocol, respectively (both $P < .001$). Increased BMI was associated with a higher DLP for the CCT group compared with the TBCT group ($P < .001$). The effect of BMI on

CTDIvol did not differ between the CCT and TBCT groups. There was no difference in the urologists' assessments of CT image quality.

In patients with renal cortical neoplasms, TBCT provides comparable image quality to CCT, with lower ionizing radiation exposure without compromising image quality. Obese patients may benefit more from TBCT scans.

CHAPTER 1: INTRODUCTION

Personal Motivation for the Following Study

Ever since beginning medical school, I have had a strong interest in oncology and playing an active role in the treatment of cancer patients with the hope of curing them of their disease. Between the third and fourth year of medical school after I had decided that urology was the specialty I would pursue for a career, I had the privilege of working on multiple research projects with the Department of Urology at University of California, Irvine. My main project was the topic of this dissertation, which was evaluating the recently introduced triple bolus protocol in terms of effects of radiation, image quality, and other factors, which will be stated in further sections of this text. Given the vast amount of imaging that's intertwined in the field of urology and especially in the field of urologic oncology, having the opportunity to learn more about the risks and benefits of imaging in this population is one that can not be overstated.

Background

Since the invention of computed tomography (CT) by Godfrey Hounsfield in the early 1970s, technological advances have increased the efficiency of its use in the medical arena. In its early years, routine CT imaging only allowed acquisition of single slices at a time, which significantly lengthened the time needed to obtain a scan. Without multi-slice CT imaging, scan times were measured in minutes. In the 1980s, scan times began to decrease as the development of CT progressed. Starting in the 1990s, the introduction of the multi-detector CT scanners led to significant reduction in scan times¹. One of the other early limitations was image resolution. In the early 1970s, when CT imaging was in its

infancy, the image matrix was 320x320. Continued advancement in the imaging modality started leading to better image matrix in the late 1970s¹. By the late 1980s, image matrix capabilities had increased to a level permitting higher resolution imaging. From a historical and practical perspective, the addition of multi-detector CT scanners along with other improvements have led to faster scans and images with higher resolution; thus increasing medical efficiency to a level that is present today in the modern era.

The Problem

In recent years, CT scans have become more commonplace due to their tremendous utility for diagnosis, treatment, and follow-up of disease processes. Diagnostic CT scans have increased by 2000% since the 1990s^{2,3}. Increased utilization, however, comes with a price. CT imaging is associated with significant levels of ionizing radiation to patients and health care personnel. The consequences of ionizing radiation exposure and risks of cancer have been extensively examined and well documented in prior epidemiologic studies⁴⁻⁶. Brenner et al² demonstrated that ionizing radiation from CT imaging accounts for 1.5%-2% of all cancers in the United States. With the increasing use of imaging and its evident association with malignancy, radiation exposure has become an important consideration when CT imaging is ordered. Even without direct clinical trials assessing risks of ionizing radiation from CT imaging given the obvious unethical nature of such a study, the continuing increase in its utilization is concerning. Furthermore, the improved quality of CT images since the time of its invention makes radiation dose minimization of paramount importance given that CT will likely be highly utilized for the foreseeable future.

The diagnosis and treatment of renal cortical neoplasms (RCN) often involves CT imaging; indeed, CT is considered the standard imaging modality for these evaluations⁷. The potential harm from ionizing radiation is amplified by the multiple CT scans that are typically the standard of care in the management of RCN. All management strategies for RCN, including active surveillance and extirpative and ablative treatments, typically require patients to undergo multiple CT scans. Even with the addition of ultrasound and magnetic resonance imaging to the urologist's armamentarium during management of a patient with a RCN, CT still plays a significant role. Thus, radiation levels from imaging will remain to be a concern for patients with renal cancer. This concern is far greater especially for younger populations who will ultimately require a longer time of follow up with their urologists.

The Foundation

Concerns about ionizing radiation engendered the development of novel protocols to diminish the radiation exposure associated with CT imaging. One of these modifications to CT imaging protocols is triple-bolus CT (TBCT) urography, which was first described by Kekelidze et al⁸ in 2010. The TBCT protocol uses 3 intravenous (IV) bolus injections of contrast, followed by 1 post-contrast CT scan. Conventional CT (CCT) urography protocols, by comparison, use 1 bolus IV injection of contrast; followed by 3 post-contrast CT scans. With only 1 post-contrast scan, the TBCT protocol potentially decreases the patient's radiation exposure during CT imaging. The authors demonstrated an effective radiation dose decrease of 44% when using the TBCT protocol compared with their CCT protocols⁸. However, this study utilized only an average radiation dose level for their CCT protocols, which were used previously at their institution.

The Study

In the current study, we retrospectively compared the radiation dose exposure during a TBCT and CCT urography protocol performed in the diagnosis and treatment of RCN and also assessed the effects of body mass index (BMI) on the radiation dose associated with each protocol. Two urologists used a non-validated questionnaire to evaluate the quality of images from both protocols. In this study, the primary aims were to compare radiation dose between the two protocols in our patient database and assess the effects of BMI on radiation dose. The secondary aim was to compare image quality using a questionnaire. Given limited data about this protocol and its utilization in the management of patients with RCN, this study provides a platform with which future studies can standardize imaging in a way where radiation will be minimized without having a negative impact on image quality. Given the preliminary nature of the given study, a randomized prospective trial will need to be undertaken to assess the utility of TBCT in a larger population of patients.

CHAPTER 2: BACKGROUND

Ionizing Radiation, CT and Cancer Risk

Ionizing radiation has been studied in the past in animal models showing a propensity to induce mutations that are detrimental to survival. One of these deleterious mutations that is thought to result from ionizing radiation is those of proto-oncogenes, thus potentially increasing the risk of cancer over the baseline rate⁹. Proto-oncogenes once mutated turn into oncogenes, and thus start a cascade of protein expression leading to cell proliferation and uncontrolled cell division. One of the limiting factors in drawing direct correlations between ionizing radiation from imaging and cancer risk in humans is the relative absence of clinical trials examining this concern. However, studies on atomic bomb survivors in the late 20th century shed some light on the connection between ionizing radiation and human cancer risk as cases of leukemia and other solid malignancies were being uncovered⁹. In fact, when the Biological Effects of Ionizing Radiation (BEIR) VII report came out in 2006, it showed a linear relationship between atomic bomb survivors from Japan and patients that undergo medical imaging in terms of their exposures to radiation¹⁰. Although many of these cancers were seen in populations in high radiation dose areas, Pierce and Brenner have in their analysis showed the existence of a cancer risk even with low doses of ionizing radiation^{4,5}. Pierce et al. in their analyses looked at relative risk data and showed the presence of cancer risks even at very low doses. The issue that has also been raised is that sometimes, the risk of cancer for low radiation doses can be underestimated which may have profound implications outside of the atomic bomb survivor population^{4,5}.

Within medical imaging, CT remains a major source of ionizing radiation for both patients and health care personnel. In 2014, it was estimated that 81 million CT scans were performed in the United States alone¹¹. When compared to a general abdominal x-ray, abdominal CT exposes patients to 50 times more radiation². In their study, Brenner and Hall reported that extrapolation of CT risk data from original atomic bomb survivor data showed a small increase in cancer incidence in the United States just from CT imaging alone. Their analysis was based on a single CT scan and according to their analysis the lifetime risk of cancer attributable to CT may be well over 2% given the continuing increase in CT imaging². In another study, Berrington de Gonzales and colleagues used cancer risk projection models created by the “Biological Effects of Ionizing Radiation” committee to estimate risks of cancer from CT scans. In their analysis, they reported that in 2007, 29,000 cancers were likely to be due to CT¹². Additionally, they reported a higher risk of cancer in women due to the elevated breast and lung cancer risks in this population¹².

In a more recent retrospective study of a single institution, Sodickson and colleagues reported a lifetime attributable risk of CT induced cancer incidence ranging from 0.3 to 12%. They also reported that this risk may be higher in patients that get multiple CT scans¹³. This is particularly relevant in a population of patients that often undergo multiple CT images for their disease such as patients with suspected or diagnosed renal cortical neoplasms. The increased cancer risk is echoed in other more focused clinical situations such as in the emergency department and evaluation of endovascular aneurysm repair. In these studies, an increased risk is appreciated in younger patients given that they have a longer time to develop cancer from CT imaging^{14,15}.

Attempts of Radiation Dose Reduction in CT

Given the increasing concern of ionizing radiation, continued advancements in CT technology have attempted to control radiation dose or decrease patient and health care personnel exposure. Helical pitch and scan length have been two of the fundamental aspects of CT scanning to attempt to control patient radiation exposure. Helical pitch and scan length are both functions that can be controlled by a radiology technologist to change the speed at which the X-ray beams touch the patient and limit the length of body part scanned respectively³. Both these functions can be adjusted on the CT scanner and decrease the length of time the patient is in the CT scanner thus limiting radiation exposure. Another fundamental element of CT scanning that has been in use in CT scanning for a long time has been lead shields. The presence of lead shields in regions that do not need to be imaged have decreased unnecessary radiation exposure of organs and thus decreased the overall exposure of the patient to radiation.

Majority of work to reduce radiation dose is reported in the urologic imaging literature. Paulson and colleagues showed that by decreasing tube current in CT scans in a population of patients with renal and ureteral stones, the quality and detection were not significantly affected¹⁶. Although their group did not look at radiation dose reduction per say, tube current is directly proportional to exposure time; thus, they were able to show that reducing tube current offers adequate imaging while working to reduce radiation dose. In another study looking at urinary tract CT images, Yanaga and colleagues decreased the tube voltage and utilized adaptive noise reduction filter. In their results, it was shown that the radiation exposure was significantly less¹⁷. The idea behind their radiation dose reduction method was that they used a method that would improve the quality of images

that is thought to be decreased when the radiation dose is lowered. Yang and colleagues performed a similar study where they decreased the tube voltage in pediatric CT phantoms and found that radiation dose was significantly lower¹⁸. This finding is important given the increased lifetime risk of cancer in younger populations. Dahlman approached the idea of radiation dose in a small population of patients that had three-phase CT urography from a different angle. He was able to show that overall radiation could be reduced by lowering the radiation dose of the non-contrast and the excretory phases while keeping the dose of the corticomedullary phase the same. His major finding was that the image quality did not change significantly when making these alterations to reduce radiation exposure¹⁹. In their study, Juri et al. reported a 45% lower radiation dose in 30 patients when using a new method called the adaptive Iterative Dose Reduction 3D technique for their CT urography protocols. This new technique essentially decreases image noise and streak artifacts, the two of which allow for a reduced radiation dose indirectly^{20,21}.

In their study, Toepker and colleagues reported a radiation dose reduction of 40-60% in a split bolus CT technique in patients with suspected urolithiasis. Their split bolus technique consisted of two bolus injections of intravenous contrast²². In a prospective study looking at split bolus CT urography protocols, Takeuchi et al found a similar reduction in radiation dose. In their study, the CT scanner utilized was dual-energy, which the authors claimed to be behind the radiation dose reduction²³. In an unrelated study looking prospectively at cases of CT colonography, Nagata and colleagues reported a radiation dose reduction of 48.5 to 75.1% when using image reconstruction techniques such as iterative reconstruction. Given the breadth of research in the area of radiation dose reduction of CT imaging, one thing is clear: whether it has been the adjustment of CT

scanner settings or development of new techniques to acquire images, reduction of radiation dose remains a top priority especially in fields such as urology.

Body Mass Index and CT Radiation Dose

The relationship between BMI and radiation dose from CT imaging has been well documented. Image quality as explained by Lin in a review of medical imaging plays a significant role in terms of how much a given patient is exposed to radiation. It is well known that CT is a collection of x-ray beams that penetrate tissue in order to facilitate the creation of an image. To obtain an image of an organ or tissue of interest, the x-ray beams must first penetrate the overlying tissue. Thus, for obese patients and patients with higher body fat, a higher level of penetration must occur in order to acquire an image²⁴. As a result, patients with higher BMI's receive higher radiation doses secondary to a higher requirement for x-ray penetration. In the absence of alteration of radiation dose, it is typical for images to be of lower quality for higher BMI patients²⁴. The requirement for higher radiation dose has also been shown in a study of patients undergoing coronary angiogram²⁵. Given the increasing obesity epidemic especially in the United States, the concern of radiation exposure and methods of reduction become even more crucial in the diagnosis and management of patients.

Development of CT Urography

Over the years, CT urography has been utilized in the urology community for the original assessment of a patient who presents with symptomatology worrisome of a possible renal mass. CT urography was preceded originally by retrograde pyelography.

Although retrograde pyelography allowed for imaging of the kidney, its invasiveness and toxicity were some of the major reasons for the development of future methods of kidney imaging. The rise of intravenous contrast material allowed a transition from retrograde pyelography into intravenous urography. This transition also involved the development of less toxic substances used for imaging. CT urography ultimately took charge and is currently almost always the study of choice for initial imaging of renal masses²⁶. The benefits of CT urography are that it is not invasive, provides higher quality imaging than previous techniques and allows distinguishing renal masses better than previous techniques.

CHAPTER 3: METHODS

Literature Survey

The literature survey was performed using multiple strategies. Given this dissertation was adapted from a recently published manuscript, the literature search was begun using MeSH terms originally provided in the manuscript titled “Comparison of radiation dose from conventional and triple-bolus computed tomography urography protocols in the diagnosis and management of patients with renal cortical neoplasms” written by Abedi et al. In addition to works cited already in the published manuscript, MeSH terms of Kidney Neoplasms, radiation dose, CT urography, cancer risk and renal masses were utilized in no particular order. Given the low output of results when all of the above MeSH terms were combined in the search, renal neoplasms, renal masses and CT urography were removed from the advanced search bar, yielding more relevant articles not outputted previously. The alternative approach that was used for the literature survey process was through Google Scholar. A subset of article titles from PubMed was transferred to Google Scholar for expansion of literature search. The expansion process involved locating articles that had previously cited the article of interest.

The Project

In the remainder of this chapter, the methodology for comparing radiation dose and image quality of the triple bolus and conventional CT urography protocols in addition to assessing the effects of BMI on radiation dose will be presented. In the subsequent chapters of this dissertation, the results and conclusions of the study presented will attempt to

create a foundation for future studies on the subject and lead to better understanding of CT imaging of patients with renal masses.

Study Population and Research Design

After obtaining Institutional Review Board approval, we performed a retrospective review of consecutive patients who underwent CCT urography or TBCT urography between August 2010 and September 2013 at a single academic institution. Indications for imaging included active surveillance, preoperative planning, or postoperative follow-up for RCN. Patients with CCT urography images with all 3 phases (arterial, venous, and delayed) and available radiation dosage data were included in the study. All examinations in this study were performed using a Siemens Sensation 16-slice or 64-slice CT scanner. The indication for the examination did not alter the study protocol that was used, whether TBCT or CCT. We collected demographic data, including age, sex, estimated glomerular filtration rate (eGFR), and BMI. Renal function data were collected from pre- and post-scan periods closest to the scan date and within a year of the scan. In addition, we reviewed renal mass characteristics, including RENAL (radius, exophytic/endophytic properties of the tumor, nearness of tumor deepest portion to the collecting system or sinus, anterior/posterior descriptor, and the location relative to polar lines) nephrometry scores according to Kutikov et al²⁷. We compared the CCT and TBCT patients with respect to age, sex, BMI, renal function, renal mass size, and RENAL nephrometry scores.

CCT Urography Protocol

CCT urography imaging included 1 pre-contrast CT scan and 3 Post-contrast CT scans at 35 seconds, 70 seconds, and 10 minutes after IV administration of approximately 80-100 mL of contrast. The post-contrast scan time points correspond to arterial (corticomedullary), venous (nephrographic), and delayed excretory (urographic) phases, respectively. Example CCT urography images are shown in Figure 1.

Figure 1: Axial slices from conventional CT urography protocol. A. Arterial Phase, B. Venous Phase, C. Urographic phase.

TBCT Urography Protocol

The TBCT urography protocol included 1 precontrast CT scan, followed by 1 post-contrast CT scan. The TBCT protocol is a split-bolus technique, wherein 120-140 mL of Isovue 370 contrast is divided into 3 equal aliquots and injected at 3 different intervals. The waiting times after the first, second, and third aliquots of contrast are 15 minutes, 70 seconds, and 35 seconds, respectively, to acquire the corresponding urographic, venous, and arterial phases. Therefore, the TBCT urography protocol is the converse to CCT, in that the acquisition of the 3 phases is completed in reverse order compared with CCT protocols. After the final wait of 35 seconds, a single contrast-enhanced scan was acquired. The multiple boluses of contrast facilitate the effective imaging of arterial, venous, and urographic phases in a single acquisition. As such, TBCT urography included 2 CT scans rather than the 4 scans obtained with CCT urography⁸. Example CT images from a TBCT protocol are shown in Figure 2.

Figure 2: A. Axial slice from triple bolus CT urography protocol for a 7.0cm left renal mass. B. Coronal View

Radiation Dose Measurements

We collected radiation dose data from the patient protocol reports listed in our institutional picture archiving and communication system. Specifically, we recorded the total volumetric CT dose index (CTDIvol) and dose length product (DLP) from pre- and post-contrast scans for both protocols. The method of radiation dose data collections involved a series of steps. Each CT image in the study had a specific radiation dose data page where the CT scanner had recorded the CTDIvol and DLP for the different phases of the protocol. Thus, to obtain the overall radiation dose for a particular study, each individual radiation data recorded by the CT scanner was added together to arrive at the value recorded in our database.

Gender, Age and Radiation

Even though examining the relationship between age, gender and radiation was not part of the primary and secondary outcomes of the study, exploring this relationship was deemed essential as part of this dissertation. Age and gender are important factors in almost all disease states including renal cortical neoplasms. Management of patients with renal cortical neoplasms sometimes change based upon their age, either because of their comorbidities or an assessment of their life expectancy. Renal cortical neoplasm is thought to be gender neutral, however exploring gender differences in terms of radiation dose may lead to results that may play a role in imaging of patients. To explore the relationship between age, gender and radiation dose (both CTDIvol and DLP), exploratory analysis were performed on statistics software described later in this chapter.

Subjective Image Quality Assessment

A secondary end point of the study was to evaluate subjective assessment of image quality. We randomly selected a subset of 20 patients from each protocol, and 2 experienced urologists reviewed the corresponding CT images. Two CCT patients were excluded due to difficulty in reviewing the images. Before the urologists reviewed each image, they were de-identified using the video screen shot capabilities of computer video editing software. During the de-identification process, care was taken to capture video screen shots of all available views to simulate real-life viewing of a patient's CT image on our institutional picture archiving and communication system. Each urologist reviewed the CT images using the picture archiving and communication system and subsequently gave a rating of 1 to 5 (1 was defined as not interpretable, 2 as poor, 3 as fair, 4 as good, and 5 as excellent), using a nonvalidated 10-metric survey. The survey questions evaluated the ability of the reviewers to identify the renal anatomic structures, including the ability to visualize the main and segmental renal vessels, collecting system, and surrounding structures and their relationship to the RCN. In addition, they rated the ability to identify renal mass margins, renal mass characterization based on contrast enhancement, collecting system distension, and the venous drainage of the effected kidney. Finally, the image noise and overall image quality were also evaluated. (The full list of survey questions is provided in Table 1).

Table 1: Quality Assessment Survey of 40 random CT images of renal masses

Triple Bolus Radiation Dose Comparison Project: Quality Assessment of CT Imaging of Renal Masses

For the following 40 cases of renal masses, please rate the following on a scale of 1-5 as Shown below.

Case #1

Ability to Identify Renal Vessels and Relationship to Renal Mass

1	2	3	4	5
Not Interpretable	Poor	Fair	Good	Excellent

Ability to Identify Segmental Renal Vessels and Relationship to Renal Mass

1	2	3	4	5
Not Interpretable	Poor	Fair	Good	Excellent

Ability to Identify Ureter/Collecting System and Relationship to Renal Mass

1	2	3	4	5
Not Interpretable	Poor	Fair	Good	Excellent

Determination of the Relationship of Mass and Surrounding Structures

1	2	3	4	5
Not Interpretable	Poor	Fair	Good	Excellent

Renal Mass Characterization Based On Contrast Enhancement

1	2	3	4	5
Not Interpretable	Poor	Fair	Good	Excellent

Ability to Identify Margins of the Renal Mass

1	2	3	4	5
Not Interpretable	Poor	Fair	Good	Excellent

Collecting System Distension and Visualization

1	2	3	4	5
Not Interpretable	Poor	Fair	Good	Excellent

Tumor thrombus: Renal vein/IVC

1	2	3	4	5
Not Interpretable	Poor	Fair	Good	Excellent

Image Noise (*graininess)

1	2	3	4	5
None	Minimal	Mild	Moderate	Severe

Overall Image Quality

1	2	3	4	5
Not Interpretable	Poor	Fair	Good	Excellent

Statistical Analysis

Continuous data, including CTDIvol and DLP, were compared using the independent-samples t test, and categorical baseline data were compared using χ^2 analysis. Pearson correlation coefficients were calculated among CTDIvol, DLP, and BMI. Linear regression analysis was performed to analyze the effects of increasing BMI on CTDIvol and DLP for each CT protocol group. Subjective assessment scores were compared using the Mann-Whitney U test. Using data from the second reviewer, we assessed inter-rater reliability of the survey. Weighted k statistic generated by MedCalc 13.0.4.0 software was used for inter-rater reliability analysis. A P value of $<.05$ was considered statistically significant. SPSS 21.0 software (IBM, Armonk, NY) was used for all statistical analyses.

CHAPTER 4: RESULTS

We identified 120 patients who met the inclusion criteria. The indications for CT scanning included active surveillance of RCN (n. 30), presurgical planning (n. 29), and for follow-up after radical nephrectomy (n. 18), partial nephrectomy (n. 21), and cryoablation (n. 22). Patient demographic, clinical, and tumor characteristics are summarized in Table 2. There were 74 men (61.7%) and 46 women (38.3%), with a mean age of 66.1 years (range, 36-86 years). The mean BMI of the cohort was 28.1 kg/m² (range, 17.0-56.5 kg/m²). A Siemens 16-row CT scanner was used in 32.5% of the patients, and the Siemens 64-row scanner was used in 67.5%. There were no differences in sex, BMI, and type of scanner used between the CCT and TBCT groups. However, the mean age for the TBCT group was significantly younger than the CCT group (64.1 vs 68.6 years, respectively; $P = .032$; Table 2). The mean eGFR values for the TBCT group during the pre- and post-scan periods (73.87 and 67.64 mL/min/1.73 m²) were significantly higher than in the CCT group (56.80 and 56.65 mL/min/1.73 m²; $P = .010$ and $P = .029$, respectively). However, the mean change in eGFR after the scan was minimal for the CCT and TBCT groups (-1.94 and -0.57 mL/min/1.73m², respectively). In addition, the 2 groups did not differ in tumor size, RENAL nephrometry scores, and renal mass complexity.

Table 2. Baseline characteristics and RENAL nephrometry score data

Variables	CCT (n=54)	TBCT (n=66)	P Value
Age, mean (range), y	68.63 (50-86)	64.06 (36-86)	.032*
Gender, N (%)			.707
Male	32 (59.3)	42 (63.6)	
Female	22 (40.7)	24 (36.4)	
BMI, mean (SD) kg/m ²	29.02 (6.89)	27.31 (5.14)	.135
eGFR, mean (range) mL/min/1.73m ²			
Prescan	56.8 (4-130)	73.87 (4-329)	.010*
Postscan	56.65 (5-99)	67.64 (5-139)	.029*
CKD, N (%)			
Prescan			.110
1	2 (4.3)	9 (16.1)	
2	23 (48.9)	28 (50.0)	
3	22 (46.8)	19 (19)	
4	0 (0)	0 (0)	
Postscan			.294
1	1 (3.1)	5 (13.2)	
2	17 (53.1)	20 (52.6)	
3	14 (43.8)	13 (34.2)	
4	0 (0)	0 (0)	
CT scanner type, N (%)			.847
Siemens Sensation 16	17 (31.5)	22 (33.3)	
Siemens Sensation 64	37 (68.5)	44 (66.7)	
Tumor Size, mean (SD) cm	3.94 (2.01)	3.81 (2.45)	.747
Total RENAL nephrometry score, mean (range)	7.63 (4-12)	7.47 (4-12)	.719
Renal nephrometry categories, N (%)			
High (10-12)	15 (28.8)	18 (27.3)	.850
Moderate (7-9)	14 (26.9)	16 (24.2)	.740
Low (4-6)	23 (44.2)	32 (48.5)	.646

BMI, body mass index; CKD, chronic kidney disease; CT, computed tomography; eGFR, estimated glomerular filtration rate; SD, standard deviation; other abbreviations as in Table 1.

*Statistically significant

The mean CTDIvol for the CCT group was significantly greater compared with the TBCT group (124.03 ± 48.91 vs 88.36 ± 29.58 mGy, respectively; $P < .001$). In addition, mean DLP for the CCT group was significantly higher than for the TBCT group (1957.44 ± 797.25 vs 1166.40 ± 330.17 mGy-cm, respectively; $P < .001$). The results are shown in Figure 3.

Figure 3: Comparison of CTDIvol and DLP from Conventional and Triple Bolus CT Urography Protocols

We also found that CTDIvol and DLP both had significant positive correlations with BMI for the overall patient cohort ($r = 0.248$, $P = .006$ and $r = .569$, $P < .001$, respectively). Subgroup analysis showed that BMI did not have any significant difference in effect on CTDIvol when CCT and TBCT were compared ($P = .052$). However, CTDIvol increased by 2.338 for the CCT group with each point increase in BMI and stayed constant for the TBCT group ($P = .015$ and $P = .986$, respectively; Table 3 and Fig. 4). BMI had a significantly larger effect on DLP for the CCT group compared with the TBCT group ($P < .001$). With each BMI

point increase, DLP increased by 80.66 mGy-cm for the CCT group and by 26.17 mGy-cm for the TBCT group (both $P < .001$; Table 3 and Fig. 5).

Table 3. Subgroup analysis of effect of increasing body mass index on volumetric computed tomography dose index and dose length product

Variable	Effect	95% CI	<i>P</i> Value
BMI and CTDIvol			
Overall Sample	1.77	0.511-3.03	.006*
CCT	2.33	0.47-4.20	.015*
TBCT	-0.01	-1.44 to 1.42	.986
Protocol type x BMI	-2.35	-4.72 to 0.02	.052
BMI and DLP			
Overall Sample	66.66	49.094-84.228	<.001*
CCT	80.66	57.595-103.733	<.001*
TBCT	26.17	11.532-40.813	<.001*
Protocol type x BMI	-25.95	-31.769 to -20.134	<.001*

CI, confidence interval; CTDIvol, volumetric computed tomography dose index; DLP, dose length product; other abbreviations as in Tables 1 and 2.

*Statistically significant

Figure 4. Relationship between body mass index (BMI) and volumetric computed tomography (CT) dose index (CT DIvol) in conventional CT (CCT, blue) and triple-bolus CT (TBCT, green) urography protocols.

Figure 5. Relationship between BMI and dose length product (DLP) in CCT (blue) and TBCT (green) urography protocols.

Gender, Age and Radiation Data

Comparison of CTDI and DLP between the two genders showed a significantly higher DLP in males that were part of our database ($p=0.042$). CTDI was not significantly different between the two genders ($p=0.170$). (Table 4, Figure 6). Males with renal cortical neoplasms had higher mean CTDI, however, this difference did not reach statistical significance.

Figure 6 shows the relationship of age and radiation dose (CTDI and DLP) in our database of patients with renal cortical neoplasms. As age of patients increase, both CTDI and DLP remained stable (Figure 7).

Table 4. Comparison of Mean CTDI and DLP between genders.

Radiation Dose Measure	Male (N=74)	Female (N=46)	<i>P</i> Value
CTDI (SD)	109.13 (47.69)	96.83 (33.68)	0.170
DLP (SD)	1596.03 (747.06)	1403.87 (624.83)	<i>0.042*</i>

CTDI, Computed Tomography Dose Index; DLP, Dose Length Product

**Statistically Significant*

Figure 6: Comparison of CTDIvol and DLP Between Males and Females

Figure 7: Relationship between Age and Radiation Dose. CTDI is labeled in blue, and DLP is labeled in Green

Subjective Quality Assessment Data

Subjective quality assessment comparisons and inter-rater reliability test scores are reported in Table 5. After conducting inter-rater reliability analysis, we found that there was moderate inter-rater agreement for the following measures: ability to identify renal vessels and relationship to renal mass ($k=0.417$), determination of the relationship of mass and surrounding structures ($k=0.474$), renal mass characterization based on contrast enhancement ($k=0.474$), and collecting system visualization ($k=0.445$). The inter-rater agreement was fair for the measures of ability to identify segmental renal vessels ($k=0.388$), collecting system ($k=0.256$), tumor margins ($k=0.260$), and image noise ($k=0.257$). Inter-rater agreement was poor for visualization of tumor thrombus ($k=0.182$) and the overall image quality measure ($k=0.125$). There were no differences between the CCT and TBCT groups in the mean scores of each individual measure of our survey.

Table 5. Comparison of questionnaire scores of conventional computed tomography vs triple-bolus computed tomography urography

Assessment	CCT (Mean)	TBCT (Mean)	K Statistic+	P
Ability to identify renal vessels and relationship to RM	4.33	4.25	0.41	.51
Ability to identify segmental renal vessels and relationship to RM	4.44	4.05	0.38	.11
Ability to identify ureter/collecting system and relationship to RM	4.28	3.90	0.25	.17
Determination of the relationship of RM and surrounding structures	4.67	4.35	0.47	.09
RM Characterization based on contrast enhancement	4.28	4.05	0.47	.25
Ability to identify margins of the RM	4.61	4.20	0.26	.06
Collecting system distention and visualization	3.89	4.05	0.44	.89
Visualization of tumor thrombus: renal vein/IVC	4.44	4.20	0.18	.22
Image noise	2.44	2.35	0.25	.91
Overall image quality	4.33	4.25	0.12	.61

CCT, conventional computed tomography; IVC, inferior vena cava; RM, renal mass; TBCT, triple-bolus computed tomography. *Reviewer 1 data are presented. Reviewer 2 data were used to calculate inter-rater reliability. +K values: <0.2=poor, 0.21-0.40=fair, 0.41-0.60=moderate, 0.61-0.80=substantial, 0.81-1.0=almost perfect agreement²⁸.

Chapter 5: DISCUSSION

Cancer and Imaging

Every year in the United States, half a million individuals succumb to cancer. This is just the United States statistics; if one takes the entire world in to account, this number becomes only a small fraction. The evolution of cancer management is an interesting one. Where as before cancer was a “death sentence,” now with the addition of chemotherapy, and curative surgery, patients are living longer and even disease free for the rest of their life. One of the main factors that have played a role in the shift to longer life expectancies for cancer patients is earlier detection. How does earlier detection occur? Earlier detection is a product of better knowledge about disease processes, better training, and advanced medical imaging. Perhaps improved medical imaging is at the forefront of early disease diagnosis and better prognosis and survival. Renal cancer is a prime example of this phenomenon. Increased use of advanced medical imaging has increased the diagnosis of these tumors. A renal mass is often one where it’s staging and thus outcome depends on its size. For instance, a renal mass with greatest dimension of less than 4cm is considered a T1a and most likely is confined to the kidney parenchyma. Thus, early imaging makes RCN amenable to surgical treatment and thus cure. Increase the size of the mass and one runs in to the risk of a more complex case and possible metastatic disease, which ultimately puts the patient at higher risk of morbidity and mortality.

Current State of CT and RCN

CT imaging has become an integral part of the diagnosis and treatment of patients with RCN²⁹. Current American Urological Association guidelines recommend imaging

every 6 months to every year for patients on active surveillance for RCN. Moreover, routine follow-up imaging for the first few years after the procedure is recommended for patients treated with ablative or extirpative modalities²⁹. Therefore, the use of dose-efficient protocols is prudent^{9,12,13}. In addition to the use of dose-efficient protocols, contrast-enhanced ultrasonography and magnetic resonance imaging have been proposed as a no-radiation imaging substitutes for CT. However, the high spatial resolution capabilities of CT enables the detection of smaller masses with greater than 95% sensitivity. CT Scanning thus remains the preferred imaging modality for the evaluation of RCN^{30,31}.

Summary of Study Results

In this retrospective review, we demonstrated that a TBCT protocol is associated with significantly lower radiation dose compared with a CCT urography protocol. The 28.7% reduction in CTDIvol and 40.7% reduction in DLP followed a similar trend to previously reported data⁸. Clinical implications of these findings are significant. To the best of our knowledge, this is the first study demonstrating the feasibility of TBCT in the evaluation of RCN with satisfactory imaging quality.

Limitations of TBCT Protocol

TBCT has some significant limitations. The TBCT protocol requires the use of a larger volume of IV contrast material to enable 3-phase imaging in a single acquisition. The biological effects of contrast agents on renal function remain insufficiently understood. Renal function was monitored in all patients in our study in the standard course of their treatment for RCN, and no patient experienced a clinically noted episode of contrast

nephropathy. Patients in the TBCT group had better renal function than the CCT group. This difference was likely the result of surgeon selection bias. Due to the increased contrast requirements with the TBCT protocol, patients with compromised renal function were likely referred for CCT. However, in neither group did major deterioration occur in renal function after imaging. Although the risk of acute kidney injury (AKI) due to IV contrast is minimal in patients with no comorbidities, the risk for patients with poor baseline renal function and diabetes is higher³²⁻³⁵. In a meta-analysis, McDonald et al³⁶ compared the rate of AKI between patients who did and did not receive IV contrast. Their results demonstrated no significant differences in rates of AKI between the 2 groups regardless of the presence of poor renal function and diabetes³⁶. Furthermore, a recent study demonstrated that even though the risk of AKI increased with lower eGFR, this increase in risk was not associated with IV contrast administration in patients undergoing CT imaging³⁷. Given controversial results from prior studies, the increased volume of contrast material associated with the TBCT protocol should be considered when deciding among CT imaging protocols. Even with the use of IV contrast, methods have been developed to protect against the risk of renal damage in patients undergoing CT imaging. Two of the common ways that have been used in radiology departments have been IV fluids and N-acetyl cysteine. In one of the original studies on IV fluids and contrast induced kidney injury, Merten et al compared two types of fluids: normal saline and sodium bicarbonate. They were able to show close to 11% reduction in contrast induced kidney injury when using sodium bicarbonate as the source of IV fluid administration vs. normal saline³⁸. With regards to N-acetyl cysteine, in the first clinical trial, Tepel et al randomized around 80 patients undergoing CT scans to either N-acetyl cysteine arm or placebo arm. In their data,

they were able to show a 19% reduction in AKI in patients pretreated with N-acetylcysteine prior to their CT scans³⁹. Thus, in the midst of caution when utilizing the triple bolus protocol, safety mechanisms have been developed over the years whereby the use of a higher contrast volume protocol may have a lower risk to benefit ratio.

BMI and Radiation

BMI is a significant contributor to the amount of radiation a patient receives during CT imaging, with morbidly obese patients being exposed to almost twice the amount of radiation compared with patients a BMI within normal reference ranges^{40,41}. Our CCT data were consistent with previously published data. However, our TBCT group results showed that the CTDIvol stayed constant with increasing BMI, unlike the CCT group. A similar trend was also observed for the DLP. Even though what may be driving these trends is not clear, possible explanations may include the lack of effect of the scanning parameters, such as slice thickness, pitch, and filtration, on the CTDIvol during TBCT. The difference in relationship between BMI and radiation dose levels in the two CT protocols compared in this study if confirmed in larger trials is likely one of the groundbreaking findings of this study. Given the obesity epidemic of the United States, this may have major implications. If the results are confirmed, this may not only have clinical implications in renal mass patients, however, this will also play a significant role in patients getting CT scans for other indications.

Image Quality Implications

The lack of significant image quality difference combined with the noticeable radiation dose reduction makes TBCT a valuable alternative for patients with RCN. Our results demonstrated poor reproducibility with respect to measures of visualization of tumor thrombus and overall image quality. A possible explanation may be different training and experience in CT imaging. Limited familiarity with a relatively new TBCT protocol may also affect the results. Given that no validated questionnaire is available to assess the quality of CT imaging of a renal mass from the urologist's perspective, we developed a survey consisting of 10 questions partly adapted from the existing literature^{42,43} that we believed were mostly relevant to the evaluation of renal mass imaging. As more imaging protocols are introduced, it will be beneficial to examine their utility in clinical practice by using standardized and validated questionnaire. For any future studies, questionnaires used to assess image quality will have to be tested for reliability and validity.

Limitations of the Study

There are several limitations that are inherent to the retrospective design of this study. Our study sample size was relatively small, and our findings require further evaluation and validation with a larger cohort. In addition, risk calculation for adverse renal effects from the contrast was not performed. The current study is limited because CTDIvol and DLP are not exact measures of the radiation absorbed by the patient. However, these 2 metrics provide a relatively good estimate of how much radiation the patient is exposed to during a CT scan⁴⁴. In future prospective studies, methods such as the use of

thermoluminescent dosimeter strips can be implemented to obtain a more exact measure of patient radiation dose.

Advancement of Science

Advancement of science arises from drawing on conclusions of studies in the past. The ever-increasing concern of radiation dose from CT imaging arose from initial studies on atomic bomb survivors of the Second World War. Development of CT technologies led to the image qualities we have begun to appreciate in the modern era of medical imaging. Currently, a lot of work is being done on reducing radiation levels from medical imaging. Our study continues this effort as it highlights a significant radiation dose reduction using the triple bolus CT protocol in RCN patients. One of the novel findings in this study is also the difference in rate of increase in radiation dose with increasing BMIs of scanned patients between the two protocols analyzed in the study. This will undoubtedly change clinical decision-making both in the clinic and at the inpatient settings when planning to obtain a CT scan of a patient.

Future Directions

This dissertation is only a small part of what may come in the future in terms of CT imaging for patients with renal masses and other disorders. The overarching goal in future studies should remain the minimization of radiation dose to patients and healthcare personnel. The management of patients with RCN also involves surveillance with MRI and ultrasound imaging. However, CT is still the most common imaging modality urologists utilize for their patients. Perhaps, the movement that needs to occur in the urology world is

towards these two other modalities. Such a movement has many hurdles that will need to be overcome. First, MRIs are more expensive than CT scans and take a significantly longer time to obtain. So, cost will be a definite concern especially with the current health care economy of the United States. Second, ultrasound technology is very operator dependent and unless the quality can be substantially increased, it will need to remain a second line adjunct to CT and MRI in terms of evaluating patients with RCN.

Next Steps

At the University of California, Irvine, the triple bolus CT protocol is also utilized to assess patients that present with hematuria. Given the potential number of patients in such a cohort, we are well on our way into the Institutional Review Board process for a protocol of a larger prospective trial comparing conventional and triple bolus CT protocols. There are numerous changes that will be made before proceeding with a randomized control trial. The primary endpoints of our prospective randomized controlled trial will be comparing rates of diagnosis of urologic pathology in patients receiving CT scans for hematuria. There are numerous challenges that will have to be solved before a study of this kind can be executed. In our retrospective trial, two urologist reviewers examined the images to assess quality. However, image quality may be better evaluated if the reviewers come from the radiology department. Additionally, any questionnaire used for a future study to assess image quality will need to be tested for both reliability and validity. With regards to validity, anatomical findings on CT imaging with regards to renal mass and proximity and relationship to adjacent structures including renal vessels and collecting systems can be compared to intraoperative findings, which is the “Gold Standard.” To make

this comparison, surgeons will have to fill out a survey to indicate their thoughts into how closely the image findings correlated with actual intraoperative findings. Another challenge will be making certain that all CT scans are performed in the same exact manner in terms of CT scanner settings. CT scan settings may cause alterations in the amount of radiation that the patient receives during a CT scan, so it will be essential to control for this confounding variable. To accomplish this, before starting the trial, radiology technologists involved in obtaining CT imaging for urology patients will be trained on each protocol. For future larger studies, it will also be beneficial to include a multivariable model, which will examine contributions to the primary outcome and image quality from different factors such as CT scanner settings (pitch, length, etc), age, gender, and BMI.

Conclusions

The TBCT protocol significantly diminished the radiation dose compared with CCT, without compromising image quality in the diagnosis and management of RCN. TBCT radiation benefits may be more pronounced in obese patients. The larger IV contrast requirement associated with TBCT should be considered when selecting among CT imaging protocols. Further prospective randomized studies are needed to confirm our findings.

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