

## Evaluation of the Risks and Benefits of Computed Tomography Urography for Assessment of Gross Hematuria



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<b>OBJECTIVE</b>	To model the risk of radiation-induced malignancy from computed tomography urography (CTU) in evaluation of gross hematuria and contrast this with the benefits of urinary tract cancer detection when compared to renal ultrasound.
<b>METHODS</b>	A PUBMED-based literature search was performed to identify model inputs. Estimates of radiation-induced malignancy rates were obtained from the Biological Effects of Ionizing Radiation VII report with dose extrapolation using the linear no-threshold model.
<b>RESULTS</b>	Male gender and age over 50 years were associated with a relative risk of upper tract malignancy of 2.04 and 2.95, respectively. The risk of upper tract malignancy missed by renal ultrasound ranged from 0.055% in females under 50 to 0.51% in males over 50. Risk of CTU-induced malignancy with associated loss of life expectancy ranged from 0.25% and 0.027 years in females under 50 to 0.08% and 0.0054 years in males over 50. For CTU to be superior to renal ultrasound, an undiagnosed upper tract malignancy would have to carry a loss of life expectancy of 49.2 years in females under 50, 13.4 years in males under 50, 2.6 years in females over 50, and 1.1 years in males over 50.
<b>CONCLUSION</b>	In low-risk patients, CTU for evaluation of gross hematuria may carry a significant risk of radiation-induced secondary malignancy relative to the diagnostic benefit offered over renal ultrasound UROLOGY 133: 40–45, 2019. © 2019 Elsevier Inc.

Gross, or visible hematuria, is a common indication for urologic referral, with an estimated prevalence of up to 2.5% in males over 50.<sup>1</sup> Patients with gross hematuria are recommended to undergo computed tomography urography (CTU) and cystoscopy due to a risk of urinary tract malignancy of approximately 20%-25%.<sup>2-4</sup> CTU is recommended over renal ultrasound or intravenous urogram due to increased sensitivity for detection of upper tract malignancy. CTU consists of precontrast, nephrographic, and excretory phases; due to being a tri-phasic study, CTU is associated with high doses of ionizing radiation.<sup>5</sup>

The Biological Effects of Ionizing Radiation (BEIR) VII Phase 2 report provides a framework for estimating the lifetime attributable risk of cancer incidence associated with radiation exposure.<sup>6</sup> This framework was previously applied to model the risk of radiation-induced malignancy from CTU in the evaluation of microscopic hematuria, defined as nonvisible hematuria with 3 or more red blood cells per

high-powered field. In this population, it was found that more patients would develop a radiation-induced malignancy from CTU than would have an upper tract malignancy undiagnosed if renal ultrasound were used as an alternative modality.<sup>7</sup> It is unknown to what extent these results could be extrapolated to patients with gross hematuria.

In this study, we apply the framework provided by the BEIR report to model the risk of secondary malignancy associated with CTU and compare this to the additional diagnostic benefit offered over renal ultrasound in patients with gross hematuria.

### MATERIALS AND METHODS

#### Identification of Model Inputs

A PUBMED-based literature review was performed to identify model inputs. These included age and gender distribution of gross hematuria patients, detection rates of upper tract malignancy in gross hematuria patients,<sup>3,4,8</sup> sensitivity of renal ultrasound for upper tract malignancy detection,<sup>4,9-11</sup> CTU radiation dose,<sup>12</sup> and the loss of life expectancy (LLE) from a radiation-induced malignancy.<sup>13</sup> The age and gender of patients with upper tract malignancy was used to calculate the relative risk of upper tract malignancy in gross hematuria patients based on those factors. Due to the rarity of upper tract malignancy, risk modification

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using additional factors such as smoking status could not be performed. Lower urinary tract malignancy was not modeled, as it is presumed that both cohorts would receive cystoscopy, which is the gold standard for evaluation of the lower urinary tract. The LLE from a radiation-induced malignancy was obtained from Baade et al,<sup>13</sup> who identified the LLE from a new malignancy diagnosis stratified by patient age through national registry data.

Estimates of age- and gender-specific radiation-induced malignancy rates were obtained from the BEIR VII Phase 2 report with dose extrapolation using the linear no-threshold model. Due to disparities in age grouping between studies of hematuria patients, which used 10-year age ranges, and the BEIR report, which reported malignancy risk for a specific age, the value at the upper end of the age ranges was selected. For example, when evaluating gross hematuria patients aged 50-60, the malignancy risk of a 60-year-old patient was used to create a conservative estimate.

### Data Analysis

Because male gender and age over 50 years were identified as significant risk factors for upper tract malignancy, the population was divided into 4 cohorts—men under 50, women under 50, men over 50, and women over 50. The risk of upper tract malignancy was identified for each cohort. The risk of an upper tract malignancy that would be undiagnosed on renal ultrasound was identified by multiplying the prevalence of upper tract urothelial carcinoma and renal cell carcinoma within each cohort by one minus the sensitivity of renal ultrasound for upper tract urothelial carcinoma and renal cell carcinoma, respectively.

The probability of secondary malignancy from exposure to CTU within each cohort was identified from the BEIR report. The average LLE from radiation exposure was obtained by multiplying the age-weighted LLE for a case of radiation-induced malignancy by the probability of developing said malignancy.

The LLE from an upper tract malignancy that went undiagnosed due to use of renal ultrasound instead of CTU is unknown. Rather than assign a value to that unknown, we identified the threshold LLE from an undiagnosed upper tract malignancy at which the LLE from potential undiagnosed malignancy is equal to the LLE from radiation exposure. This was calculated for each cohort by dividing the LLE from CTU radiation by the probability of an undiagnosed upper tract malignancy on renal ultrasound.

Sensitivity analysis was performed to test the robustness of our findings to variable model inputs. The model was programmed in and all calculations were performed using TreeAge Pro (version 2017, TreeAge Software Inc.).

## RESULTS

Model inputs and sources are summarized in Table 1. Three prospective series of gross hematuria patients were identified with pooled analysis consisting of 3671 patients. Prevalence of upper tract urothelial carcinoma and renal cell carcinoma was 0.63% and 1.20%, respectively. The age and gender distribution of gross hematuria patients was identified, of whom 72.7% were male and 72.5% were over age 50. Male gender and age over 50 years were associated with a relative risk of upper tract malignancy of 2.04 and 2.95, respectively. Renal ultrasound has a sensitivity of 77% for upper tract urothelial carcinoma and 82% for renal cell carcinoma. CTU radiation dose was found to be 31.7 mSv. The LLE from a case of secondary malignancy ranged from 11.2 years in patients under 40 to 3.9 years in patients over 70.

Based on these model inputs, individual risk of upper tract malignancy ranged from 0.45% in females under age 50 to 2.54% in males over age 50 (Table 2). The risk of undiagnosed upper tract malignancy on renal ultrasound ranged from 0.09%

**Table 1.** Model inputs and associated sources

Model Input		Sources		
Prevalence of UTUC and RCC in patients with gross hematuria		UTUC	RCC	Khadra et al, 2000; Edwards et al, 2006; Commander et al, 2017
		0.63%	1.20%	
Sensitivity of renal ultrasound		77%	82%	Cauberg et al, 2011; Warshaur et al, 1988; Jamis-Dow et al, 1996
Gross hematuria population	Age	Male	Female	Khadra et al, 2000
	<40	9.60%	5.43%	
	40-49	8.56%	3.86%	
	50-59	10.75%	4.70%	
	60-69	17.33%	5.95%	
	70+	26.40%	7.41%	
Radiation dose from CTU		31.7 mSv		Smith-Bindman et al, 2009 BEIR VII Phase 2 Report
Lifetime attributable risk of secondary malignancy from 31.7 mSv	Age	Male	Female	
	<40	0.201%	0.265%	
	40-49	0.183%	0.229%	
	50-59	0.142%	0.182%	
	60-69	0.106%	0.127%	
	70+	0.054%	0.066%	
Loss of Life expectancy from secondary malignancy	Age			Baade et al, 2012
	<40	11.2 years		
	40-49	10.5 years		
	50-59	8.0 years		
	60-69	6.0 years		
	70+	3.9 years		

CTU, CT urogram; RCC, renal cell carcinoma; UTUC, upper tract urothelial carcinoma.

**Table 2.** Comparison of the risk of undiagnosed upper tract malignancy on renal ultrasound with the risk of radiation-induced malignancy from CTU substratified by age and gender

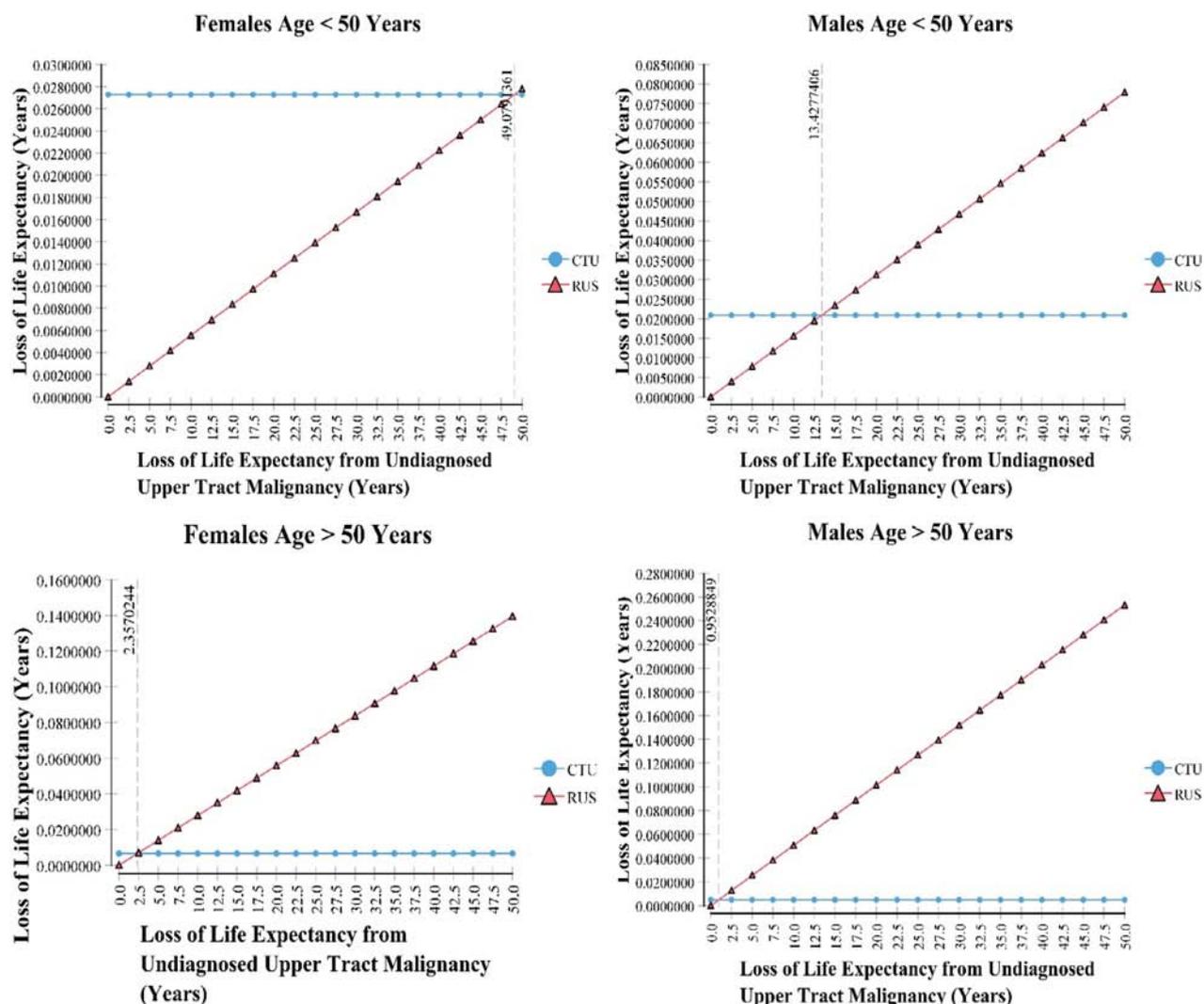
	Females Age <50	Males Age <50	Females Age >50	Males Age >50
Risk of upper tract malignancy	0.28%	0.79%	1.41%	2.57%
Risk of false negative ultrasound	0.06%	0.16%	0.28%	0.51%
Risk of CTU-induced malignancy	0.25%	0.19%	0.11%	0.51%
LLE from CTU (years)	0.027	0.021	0.007	0.005
Threshold LLE from undiagnosed upper tract malignancy at which CTU is superior to ultrasound (years)	49.04	13.43	2.36	0.95

CTU, CT urogram; LLE, loss of life expectancy.

in females under 50 to 0.50% in males over 50. The risk of radiation-induced malignancy ranged from 0.25% in females under 50 to 0.08% in males over 50, with a LLE of 0.027 years and 0.005 years, respectively. For CTU to be superior to renal ultrasound, a missed diagnosis of upper tract malignancy would have to carry a LLE of 49.0 years in females under 50, 13.4 years in

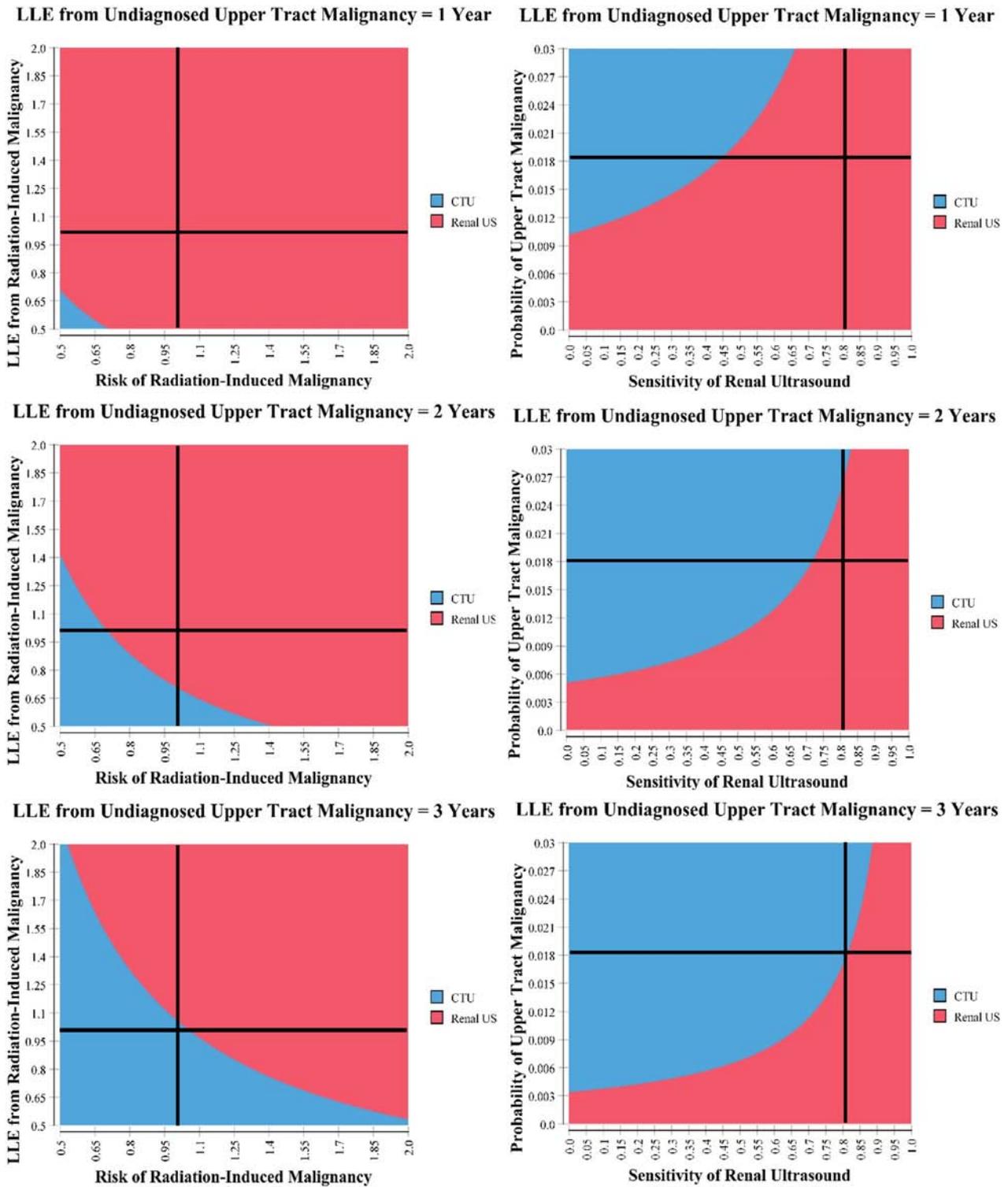
males under 50, 2.8 years in females over 50, and 1.1 years in males over 50 (Table 2, Fig. 1).

Sensitivity analysis demonstrated that these findings were robust to a range of model inputs. Figure 2 demonstrates a 2-way sensitivity analysis demonstrating the frontier of model inputs at which CTU is superior to renal ultrasound as the LLE from



**Figure 1.** One-way sensitivity analyses of loss of life expectancy from undiagnosed upper tract malignancy identifying the threshold at which the loss of life expectancy from CTU radiation exceeds the LLE from undiagnosed malignancy on RUS stratified by age and gender.

CTU, CT urogram; RUS, renal ultrasound. (Color version available online.)



**Figure 2.** Three-way sensitivity analyses performed as LLE from undiagnosed upper tract malignancy is varied from 1 to 3 years. Regions in red represent the frontier of inputs at which RUS is superior to CTU, while blue represents the range of inputs at which CTU is superior to RUS. Black lines represent model inputs as depicted in Table 1.

CTU, CT urogram; LLE, loss of life expectancy; RUS, renal ultrasound. (Color version available online.)

undiagnosed upper tract malignancy is varied. At a conservative estimate of 2-year LLE from undiagnosed upper tract malignancy, for CTU to be superior to renal ultrasound renal ultrasound would have to have a sensitivity for upper tract malignancy of less than 73%, LLE from a radiation-induced

malignancy would have to be less than 72% of predicted value, the risk of radiation-induced malignancy would have to be less than 70% of predicted value, or the risk of upper tract malignancy would have to be greater than 25% higher than estimated.

## DISCUSSION

This study demonstrates that the risk of malignancy related to CTU radiation is significant compared to the diagnostic benefit offered over renal ultrasound in patients with gross hematuria. This is most pronounced in younger or female patients, who have lower rates of upper tract malignancy and higher risk of radiation-induced malignancy. For CTU to be superior to renal ultrasound in the evaluation of gross hematuria, an undiagnosed upper tract malignancy would have to carry a LLE of greater than 49.0 years in females under 50, 13.4 years in males under 50, 2.8 years in females over 50, and 1.1 years in males over 50. While multiple studies have questioned the benefits of CTU in evaluation of asymptomatic microscopic hematuria, this is the first study we could identify to suggest a need for risk-stratification in evaluating patients with gross hematuria.

It is unknown what effect failing to diagnose an upper tract malignancy has on patient life expectancy; however, reasonable estimates can be obtained from evaluation of screening data for other malignancies. The National Lung Screening Trial, which evaluated the efficacy of CT screening for lung cancer, found that early diagnosis was associated with a 1.63 year gain in life expectancy.<sup>14</sup> Early detection of breast cancer via mammography was associated with a 1.16-year gain in life expectancy.<sup>15</sup> Secondary analysis of the European Randomized Study of Screening for Prostate Cancer trial estimated that (Prostate-Specific Antigen) PSA-based detection of prostate cancer was associated with a 0.69 year gain in life expectancy.<sup>16</sup> Additionally, Carter et al analyzed the SEER database to identify the LLE from malignancies stratified by primary site and estimated that renal cell carcinoma causes an average LLE of 3.36 years, while bladder cancer causes an average LLE of 2.19 years.<sup>17</sup> Unfortunately upper tract urothelial carcinoma was not similarly assessed. These estimates create a reasonable upper bound for the potential LLE from a false negative renal ultrasound. It would thus be reasonable to suggest that an undiagnosed upper tract malignancy carries a LLE of 1-2 years. Given these assumptions, CTU-based evaluation of gross hematuria patients in females under the age of 50 and potentially in females over the age of 50 is likely harmful and should be replaced with renal ultrasound.

It is reasonable to question whether practice should be altered based on modelled risks of radiation. Compared to an individual's lifetime risk of malignancy of 38%, the absolute risk of malignancy from CTU of 0.09%-0.25% is small.<sup>18</sup> However, it remains significant as it is an iatrogenic and entirely modifiable source of additional risk. Additionally, the validity of the linear no-threshold model has been questioned for low radiation doses. Current models are based on 3 primary sources: evaluation of malignancy patterns in the survivors of atomic explosions,<sup>19</sup> evaluation of malignancy patterns in exposed nuclear power workers,<sup>20</sup> and epidemiologic evaluations of patients receiving CT scans in the national health systems in England and Australia.<sup>21,22</sup> While each approach

carries methodologic limitations, the preponderance of evidence from these studies suggests a dose- and age-dependent risk of radiation-induced malignancy. In fact, radiation-induced malignancy risks may not decline as significantly in older patients as previously estimated, would cause this model to underestimate the risks of CTU.<sup>23</sup>

This study must be interpreted in light of its potential limitations. The quality of our results is limited by the quality of available input data. Due to limitations in the reporting of upper tract malignancy risk factors in the underlying studies, a more robust risk model incorporating additional risk factors such as smoking status could not be used. Data regarding LLE from a radiation-induced malignancy is based on evaluation of all malignancy cases, it is unclear to what extent this applies specifically to radiation-induced malignancies. Finally, our methodology fails to account for any additional benefits of CTU, such as improved detection of nephrolithiasis. These limitations are partially mitigated by sensitivity analysis demonstrating that our findings are robust across a range of model inputs.

## CONCLUSION

Based on current radiation risk models, CTU for the evaluation of gross hematuria may be associated with a small but significant risk of radiation-induced secondary malignancy. In low-risk patients, renal ultrasound should be considered as an alternative modality.

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## EDITORIAL COMMENT



The authors present data using a model to estimate the risk vs benefit of using computed tomography urography (CTU) in the evaluation of gross hematuria. Various models and data sources were used to construct the models used in this paper. The risk of radiation-induced malignancy was modeled using the Biological Effects of Ionizing Radiation VII Phase 2 report which assumes a linear, cumulative risk with no upper limit. The literature was then queried to assess the risk of an upper tract urothelial cell carcinoma (UTUC) in a patient with gross hematuria. The

sensitivity and specificity of renal ultrasound (RUS) and CTU were included in the model. Finally the loss of life expectancy was used to assess how a potential radiation-induced malignancy might limit the life span of patients. The data were then analyzed by gender as well as age (younger than age 50 vs those older than 50). The authors conclude that RUS may be the best study for females under the age of 50 with gross hematuria.

The data are provocative and the methodology attempts to assess the risks and benefits of CTU in the evaluation of gross hematuria from multiple vantage points. The data reported are based on multiple different data sets and multiple assumptions. The models used in this study do not account for smoking history which is a known risk factor for UTUC. It is important to point out that the authors still advocate for the use of cystoscopy in patients with gross hematuria. With regard to imaging the upper urinary tracts, the use of RUS has been promoted in the evaluation of patients with asymptomatic microscopic hematuria.<sup>1</sup> However, the use of RUS in patients with gross hematuria is less studied. The authors do point out that the absolute risk of CTU-induced malignancy is quite low (0.09%-0.25%). Furthermore, the validity of using the linear no-threshold model for radiation-induced injury is debatable.<sup>2</sup> Yet, CTU has increased costs compared to RUS and a 0.3%-1.6% risk of contrast-induced reactions.<sup>3</sup> Even with the use of CTU in the evaluation of gross hematuria, the rate of detection of UTUC is quite low. Commander et al found of the 652 patients who underwent CTU for gross hematuria, only 4 (0.006%) were diagnosed with UTUC, all of whom were current or former smokers.<sup>4</sup>

As we shift toward value-based care models, we should carefully consider how we evaluate patients with gross hematuria. This article focuses on the potential missed diagnosis of UTUC, yet many other disease states can also present with gross hematuria and therefore, providers should consider the patient's history, smoking history, and other symptomatology when deciding on the appropriate imaging test. For low-risk patients with gross hematuria, renal US may be a reasonable first imaging study, particularly those of younger age and of female gender.

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