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Estimating Cancer Risk from Tc-99m Pyrophosphate Imaging for Transthyretin Cardiac Amyloidosis

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Abstract

Background—Increasing recognition that transthyretin cardiac amyloidosis (ATTR-CA) is much more common than previously appreciated, and the emergence of novel disease-modifying therapeutic agents, have led to a paradigm shift in which ATTR-CA screening is considered in high-risk populations, such as patients with heart failure with preserved ejection fraction (HFpEF) or aortic stenosis. Radiation risk from ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP) scintigraphy, a test with very high sensitivity and specificity for ATTR-CA, have not been previously determined.

Methods and Results—Radiation doses to individual organs from ^{99m}Tc-PYP were estimated using models developed by the Medical Internal Radiation Dose Committee and the International Commission on Radiological Protection. Excess future cancer risks were estimated from organ doses, using risk-projection models developed by the National Academies and extended by the National Cancer Institute. Excess future risks were estimated for men and women aged 40 to 80 and compared to total (excess plus baseline) future risks. All-organ excess cancer risks (90% uncertainty intervals) ranged from 5.88 (2.45,11.4) to 12.2 (4.11,26.0) cases per 100,000 patients undergoing ^{99m}Tc-PYP testing, were similar for men and women, and decreased with increasing age at testing. Cancer risks were highest to the urinary bladder, and bladder risk varied nearly twofold depending on which model was used. Excess ^{99m}Tc-PYP-related cancers constituted <1% of total future cancers to the critical organs.

Conclusion—Very low cancer risks associated with ^{99m}Tc-PYP testing suggest a favorable benefit-risk profile for ^{99m}Tc-PYP as a screening test for ATTR-CA in high-risk populations, such as such as patients with HFpEF or aortic stenosis.

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Keywords

Tc-99m pyrophosphate; ionizing radiation; cancer risk; cardiac amyloidosis

Introduction

Amyloidosis is a disease of protein deposition caused by misfolding of a precursor protein. This results in the formation of insoluble amyloid fibrils, which are deposited extracellularly in tissues, distorting tissue architecture and leading to organ dysfunction. While numerous proteins can misfold and cause amyloidosis, the vast majority of cases with cardiac dysfunction are caused by deposition of light chain (AL) or transthyretin (TTR) protein.

Imaging plays an important role in the diagnosis of cardiac amyloidosis(1) as well as in differentiating between AL and TTR-associated (ATTR) amyloidosis.(2) Initial reports of ^{99m}Tc-PYP scintigraphy for diagnosis of ATTR cardiac amyloidosis (ATTR-CA) date back to the 1980s and were in large part conflicting with variable sensitivity because they were performed in mixed populations before standardization of amyloid subtyping.(3–8) Contemporary studies have employed modern amyloid subtyping and have demonstrated that bone scintigraphy(9), and in particular(10) ^{99m}Tc pyrophosphate (^{99m}Tc-PYP) scintigraphy(4), have outstanding diagnostic performance for ATTR-CA. An international multicenter study of 1,217 patients with suspected cardiac amyloidosis demonstrated a sensitivity of >99%, specificity of 86%, and positive predictive value of 100% with respect to the histopathologic reference standard.(9) The consequent repurposing of ^{99m}Tc-PYP and bisphosphonate radiotracers for accurate noninvasive detection of ATTR-CA has led to the recognition that ATTR-CA is not so rare and that its prevalence among high-risk elderly patients is not insignificant. Therefore, the utility of ^{99m}Tc-PYP scanning is expanding from a confirmatory diagnostic test to a screening test for ATTR-CA.

Accordingly, a paradigm shift in which populations “at risk” for cardiac amyloidosis are actively screened has recently been proposed.(11) With the development of several classes of novel disease-modifying therapeutics to arrest amyloidosis progression(12), including TTR stabilizers, silencers of TTR gene expression(13,14), and degraders of amyloid fibrils, preclinical identification of ATTR is both possible and potentially clinically important. Nevertheless, 99mTc-PYP has not yet been established as a screening tool since to date there is no outcomes data with this approach.

At-risk elderly adults include those with HFpEF(15) or aortic stenosis(16), among other groups, which could involve millions of individuals potentially subject to ^{99m}Tc-PYP scanning. As such, concern regarding the safety of screening tests is a critical issue, since to recommend a screening test potential benefit should significantly outweigh potential harm.(17) For ^{99m}Tc-PYP scintigraphy, the primary safety concern relates to risk from ionizing radiation. To date, there have been no efforts to quantify this risk. In this paper, we use risk projection models developed in the National Academies’ Biological Effects of Ionizing Radiation (BEIR) VII report(18), as extended in the National Cancer Institute’s Radiation Risk Assessment Tool (RadRAT)(19), to estimate cancer risk from ^{99m}Tc-PYP scintigraphy,

and consider the effect of patient age, gender, comorbid conditions, and ^{99m}Tc-PYP dosimetry and protocol.

Methods

^{99m}Tc-PYP Organ Dosimetry

Dose coefficients(20) characterizing the organ absorbed dose of radiation per unit of administered activity (e.g., mGy/mCi), were determined primarily from a model for ^{99m}Tc-PYP developed by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine and Molecular Imaging.(21) These dose coefficients are used as well in one vendor's (Pharmalucence, Bedford, MA) package insert for ^{99m}Tc-PYP.(22) Secondarily, we compared these dose coefficients to those specified by the International Commission on Radiological Protection (ICRP) for ^{99m}Tc-PYP-labelled phosphates and phosphonates.(23) Organ doses were estimated from dose coefficients, assuming a ^{99m}Tc-PYP protocol with an administered activity of 10 mCi.(24) Dose coefficients for effective dose or effective dose equivalent, while not used in cancer risk modeling, were also determined from these sources.

Cancer Risk Estimation

Organ doses determined as above were used to estimate lifetime radiation-attributable cancer risks, based on the methods developed by the Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation of the National Academies in its BEIR VII report.(18) Since there are no cohorts of patients who underwent ^{99m}Tc-PYP scanning for whom long-term cancer rates are available, risk estimation necessitates the use of a risk projection model based on radiation exposure from other scenarios. The most widely used such model is BEIR VII, which uses a combination of excess relative risk and excess absolute risk models to estimate the absolute differences in cancer probabilities for exposed individuals in comparison to unexposed individuals. This model is based largely but not exclusively on data from Japanese atomic bomb survivors and controls from the same milieu. While BEIR VII estimates risks of 11 types of cancer and a remainder grouping, RadRAT adds 7 additional cancers, to include all cancers for which there were at least 100 incident cases identified in the Life Span Study cohort of over 105,000 individuals with a wide range of radiation exposures.(25) RadRAT also has small differences in its computational approach compared with BEIR VII, including propagating uncertainties using a Monte Carlo approach.(19)

We applied RadRAT to estimate three types of cancer risk predicted to occur in patients over their lifetime after ^{99m}Tc-PYP administration: excess future risk from ^{99m}Tc-PYP, baseline future risk, and the percentage of risk from ^{99m}Tc-PYP (excess divided by excess plus baseline). We estimated these risks for all organs with dose coefficients provided in the MIRD model, which constitute the critical organs in terms of radiation exposure: bladder, kidney, red bone marrow, and female ovary, as well as total risk. While absorbed dose to bone surfaces is somewhat higher than for other organs, bone cancer risk was not estimated because bone cancer is not included among the 18 types of cancer modeled; this is due to

few bone cancer cases identified in the Life Span Study, suggesting a low risk of radiation-attributable bone cancer. Testicular cancer risk is similarly not modeled in RadRAT.

We estimated risks using RadRAT for each combination of patient gender, and age of 40, 50, 60, 70, and 80 years; it is uncommon to perform ^{99m}Tc-PYP testing to diagnose ATTR-CA in younger individuals. Estimates assumed life tables for the general US population, with baseline cancer incidence rates based on Surveillance Epidemiology and End Results (SEER) data for the years 2000 to 2005. Associated 90% uncertainty ranges were determined using Monte Carlo simulations with Latin hypercube sampling, with a simulation sample size of 5000, taking into account statistical uncertainties in risk parameters as well as subjective uncertainties in several assumptions.(19)

Where there was a meaningful difference between MIRD and ICRP dose coefficients, cancer risks were re-calculated using ICRP dose coefficients.

Results

Dose coefficients

Dose coefficients for bladder, kidney, red marrow, and ovary were 8.87, 2.4, 2.33, and 1.4 mGy/10 mCi, respectively, using the MIRD models, and 17.39, 2.66, 2.18, and 1.33, respectively, using ICRP models. Effective dose coefficient using the ICRP model was 1.81 mSv/10 mCi. While an effective dose coefficient is not provided in the MIRD model (21) or package insert (22), a related older quantity, the effective dose equivalent, is reported in the package insert, at 2.2 mSv/10 mCi.

Cancer risks

Predicted cancer risks to men and women are summarized in Tables 1 and 2, respectively. The highest excess ^{99m}Tc-PYP-related risk of cancer was that to the urinary bladder, with a risk (90% uncertainty range) of 9.45 (2.48, 22.6) per 100,000 men scanned and 8.98 (2.61, 20.5) per 100,000 women scanned, at age 40. These risks roughly halved by age 80. ^{99m}Tc-PYP-related excess risks of leukemia were on the order of 1 to 2 cases per 100,000 persons scanned, with some age and gender dependence, and excess risks of other types of cancer were a small fraction of bladder risks. The percentage of future bladder cancer risk from ^{99m}Tc-PYP scanning was 0.74% in 40 year old women and 0.25% in 40 year old men; this decreased slightly with age. Thus, even if a 40 year old woman undergoing ^{99m}Tc-PYP scanning develops bladder cancer at some point later in life, subsequent to receiving ^{99m}Tc-PYP, the estimated probability that it is related to the scan is <1%. Overall, the lifetime risk of any cancer occurring attributable to ^{99m}Tc-PYP scanning was 12.2 (4.11, 26.0) per 100,000 in men and 11.5 (4.17, 23.6) per 100,000 in women scanned at age 40, and approximately half that in those scanned at age 80.

Differences between MIRD and ICRP Models

The only organ for which there was a meaningful (almost 2-fold) difference in dose coefficient between the MIRD and ICRP models was the urinary bladder. Excess ^{99m}Tc-PYP-attributable cancers (Table 3) were roughly doubled using the ICRP model, increasing

this risk to 18.8 (5.10, 44.0) per 100,000 in 40 year old men and 17.9 (5.39, 40.0) per 100,000 in 40 year old women.

Discussion

Using contemporary risk projection modeling, we found very low estimated excess future risks of cancer attributable to ^{99m}Tc-PYP scintigraphy. All-organ risks ranged from 6 to 12 cases per 100,000 patients exposed, depending on patient age and gender, and the upper limits of 90% uncertainty ranges, reflecting uncertainties in both risk parameters and model assumptions, fell between 11 and 26 cases per 100,000. Thus, in a very worst-case scenario, cancer risk associated with ^{99m}Tc-PYP scanning would be 1 in 4000 individuals.

With the emergence of novel treatments directed at ATTR-CA, these risks would seem to be far offset by potential benefits of screening and subsequent treatment in populations with high prevalence of undiagnosed TTR amyloidosis. Several disease-modifying therapies for ATTR-CA are under active clinical investigation and comprise candidates in three new TTR-targeted drug classes: stabilizers, silencers, and amyloid fibril degraders and reabsorbers.(12) Tafamidis, for example, is a TTR stabilizer approved by the European Medicines Agency for the treatment of mutated ATTR causing neuropathy(26), and has now been tested in a phase 3 human clinical trial for patients with ATTR-CA with results expected by mid-2018. Another drug, patisiran, a small interfering RNA delivered to hepatocytes in formulations of lipid nanoparticles has demonstrated knockdown of *TTR* gene expression by triggering enzymatic degradation of targeted messenger RNA.(13,27) A phase 3 randomized controlled trial in 225 patients with ATTRm polyneuropathy (APOLLO Study) showed that patisiran significantly improved the neuropathic primary endpoint at 18 months compared with placebo.(28) Although results of studies assessing the effect of patisiran in patients with ATTR-CA are expected soon, exploratory analyses from APOLLO also showed a significantly favorable effect of patisiran with respect to cardiac biomarker and echocardiographic endpoints at 18 months compared with placebo.

Thus, while no agents are currently FDA approved for ATTR-CA, it is clear that a new era in the treatment of this disease is rapidly approaching and that it will be imperative to identify patients at risk for ATTR-CA.(29) Several such populations have been suggested by recent data. For example, undiagnosed ATTR-CA has been described in at least 8% of black patients hospitalized with heart failure(30), in 13% of patients aged at least 60 with left ventricular hypertrophy and heart failure with preserved ejection fraction(15), and in 16% of patients with aortic stenosis undergoing transcatheter aortic valve replacement.(16) Moreover, the prevalence of ATTR-CA has been noted to be markedly increased in populations of patients with lumbar spinal stenosis(31), with ruptured biceps tendon(32), and with hip or knee arthroplasty.(33)

The primary limitation inherent to our findings is the numerous assumptions incorporated into the risk projection models we used. These include model selection (a weighted average of excess absolute risk and excess relative risk models), transfer of risk estimates from the Japanese to the US population, and the choice of a factor used to adjust epidemiological data for radiation dose and dose rate. These factors are reflected in the 90% uncertainty intervals

reported. The BEIR VII and RadRAT models both assume a linear no-threshold relationship between organ radiation dose and risk of cancer to that organ. This implies that risk increases linearly with dose, and that there is no dose threshold below which there is zero risk. While most expert consensus reports from national and international organizations—including the BEIR VII report of the US National Academies(18)—have determined this LNT relationship to best fit the available epidemiological data for purposes of radiological protection, it remains a matter of some debate.(34) Another limitation of our findings is that the MIRD dosimetry we used to estimate organ doses from ^{99m}Tc-PYP is based on data from only 15 patients (21), and the representation of various demographic groups among these patients is unclear.

One notable limitation in modeling is our assumption that individuals undergoing ^{99m}Tc-PYP testing here have life expectancies comparable to those of the general US population. At-risk elderly populations undergoing ^{99m}Tc-PYP screening for ATTR-CA, e.g., patients with HFpEF or AS have decreased life expectancy compared to the general population. In such populations, our models would overestimate excess ^{99m}Tc-PYP-related cancer risk, since patients have fewer years of life in which to develop an excess cancer While methods exist for adjustment of radiation-attributable cancer risk based on known life tables for a specific population(35), insufficient data are available to accurately determine these life tables for such at-risk populations. Nevertheless, the strongly favorable benefit-risk profile of ^{99m}Tc-PYP testing suggested by our data would only be enhanced in settings in which patients have decreased life expectancy.

A notable group of patients for whom these risk estimates are overestimates are those determined by ^{99m}Tc-PYP testing to have ATTR-CA. Recent data suggest a median life expectancy of just 25 to 41 months for patients diagnosed with ATTR-CA(12,36), and the vast majority of radiation-attributable cancers occur after a latency period of at least 5 to 10 years(18), suggesting that patients with positive tests are unlikely to live long enough to develop an excess ^{99m}Tc-PYP-related cancer. Thus, *post hoc* excess cancer risk for patients testing positive is virtually zero.

The only organ for which we noted a meaningful difference between MIRD and ICRP dose coefficients, and consequently in excess cancer risks, was the bladder. Estimated excess bladder cancer risks were nearly twice as high using the ICRP models, although still modest at between 3 and 18 cases per 100,000 patients tested. Two factors may account for this. Firstly, the MIRD dosimetry model used is specific to ^{99m}Tc-PYP, whereas the ICRP model is for ^{99m}Tc phosphates and phosphonates in general. In fact, the original MIRD paper(21) included models for four ^{99m}Tc phosphates and phosphonates—^{99m}Tc methylene diphosphonate, ^{99m}Tc hydroxymethylene diphosphonate, ^{99m}Tc hydroxyethylidene diphosphonate, and ^{99m}Tc-PYP—and doses to the bladder are indeed about a third lower for ^{99m}Tc-PYP and hydroxymethylene diphosphonate than for the other agents. Secondly, the MIRD models assume an initial bladder void at 2 hours and subsequent voids at intervals of 4.8 hours, whereas ICRP models assume a voiding period of 3.5 hours. This difference in dosimetry underscores the potential importance of hydrating patients and encouraging early micturition after ^{99m}Tc-PYP testing, to minimize bladder cancer risk. This recommendation holds for all ^{99m}Tc-based radiopharmaceuticals used in cardiac imaging.(20) Of course,

prudence should be exercised in hydration, to ensure that patients with heart failure do not become fluid overloaded.

Our risk estimates are based on a contemporary protocol for ^{99m}Tc-PYP imaging using 10 mCi of administered activity. A protocol with 10 mCi of ^{99m}Tc-PYP, 750,000 scintigraphic counts, one hour delay between injection and imaging, and 256×256 matrix has been found to provide excellent image quality, low extracardiac activity, and minimize study time and radiation dose, and thus is suggested for clinical use.(24) Several other protocols have been suggested, with administered activities ranging from 10 to 25 mCi.(24,37) For example, several laboratories perform 2–3 hour imaging for ^{99m}Tc-PYP (38) or other bone scintigraphic agents, and use doses of about 20 mCi. Since the RadRAT models, based on a comprehensive review of the radiation epidemiology literature found in the National Academies' BEIR VII report, assume a linear no-threshold relationship between radiation dose and risk, increasing administered activity to 20 mCi would multiply the risks here 2-fold, to 12 to 24 cases per 100,000, while increasing activity to 25 mCi would multiply risks 2.5-fold, to 15 to 31 cases per 100,000. While this represents only a modest increase in absolute risk, utilization of this optimized 10 mCi protocol provides another opportunity to minimize the low radiation risk from ^{99m}Tc-PYP testing.

In Europe, rather than performing ^{99m}Tc-PYP testing for ATTR cardiac amyloidosis, a different bone imaging agent is commonly used, viz. ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD)(39), which is not approved for use in the United States. We had sought to perform risk estimation for ^{99m}Tc-DPD as well, however we discovered that no specific biokinetic or dosimetric data is available for this radiopharmaceutical from MIRD, ICRP, or any other source.(40) Its European package insert(41) uses ICRP dosimetry for ^{99m}Tc-labeled phosphates/phosphonates in general, and remarkably does not have ^{99m}Tc-DPD-specific dosimetry.

In all cases, we observed that the proportion of expected cancers in patients undergoing ^{99m}Tc-PYP testing, which could be attributed to testing, was less than 1%. Thus, were a patient who underwent ^{99m}Tc-PYP testing to later develop a malignancy in one of the critical organs, the patient could be reassured that it is highly unlikely that this cancer is related to their previous testing. Given the low radiation effective dose associated with ^{99m}Tc-PYP testing of 2 mSv, which is less than the annual background radiation dose to the US population from natural sources, recommendations from an NIH-NHBLI/NCI-sponsored symposium suggest that informed consent for this testing need not require a detailed discussion of radiation risk or written consent.(42)

New Knowledge Gained

^{99m}Tc-PYP scintigraphy is associated with a very low estimated risk of radiation-attributable cancer, supporting its use in diagnostic and screening approaches for transthyretin-associated cardiac amyloidosis. With the active current development of several novel disease-modifying therapeutics to arrest amyloidosis progression, additional studies can quantitatively compare benefits of screening specific high-risk populations with radiation-associated risks.

Conclusion

Recognition that cardiac amyloidosis is markedly more prevalent than previously appreciated has expanded the utility of ^{99m}Tc-PYP scintigraphy beyond diagnostic confirmation towards a much greater potential use in screening. Using risk projection models, we found a very low risk of radiation-attributable cancer from ^{99m}Tc-PYP, with all-cancer excess future risks of 6 to 12 cases per 100,000 persons tested in the general population. Risks would be lower in populations with decreased life expectancy, such as patients with HFpEF or aortic stenosis. With the advent of emerging disease-modifying therapeutics for ATTR-CA, ^{99m}Tc-PYP testing is likely to offer a highly favorable benefit-risk balance in screening populations at high risk for cardiac amyloidosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ATTR-CA	transthyretin cardiac amyloidosis
HFpEF	heart failure with preserved ejection fraction
^{99m}Tc-PYP	^{99m}Tc-pyrophosphate
AL	light chain
TTR	transthyretin
BEIR	Biological Effects of Ionizing Radiation
RadRAT	Radiation Risk Assessment Tool
MIRD	Medical Internal Radiation Dose
ICRP	International Commission on Radiological Protection
SEER	Surveillance Epidemiology and End Results

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Table 1

Cancer Risks from ^{99m}Tc Pyrophosphate Imaging in Men. Assumes 10 mCi dose; for 20 mCi dose one should double these risks. In this and the following tables, future risks represent lifetime risks beginning from the time of ^{99m}Tc-PYP administration.

		Future Risk of Developing Cancer (chances in 100,000) for Men with 90% Uncertainty Range in Parentheses			
Age	**Type of Risk**	**Bladder**	**Kidney**	**Leukemia**	**Total**
40	Excess Future Risk from ^{99m}Tc-PYP	**9.45 (2.48,22.6)**	**0.771 (0.0587,2.32)**	**2.01 (0.680,4.43)**	**12.2 (4.11,26.0)**
	Baseline Future Risk	3840 (3770,3920)	1810 (1760,1860)	816 (783,850)	6468 (6316,6622)
	% Risk from ^{99m}Tc-PYP	0.25%	0.04%	0.25%	0.19%
50	Excess Future Risk from ^{99m}Tc-PYP	**9.39 (2.49,22.4)**	**0.705 (0.0541,2.12)**	**2.07 (0.567,4.83)**	**12.2 (3.85,26.0)**
	Baseline Future Risk	3910 (3840,3980)	1760 (1710,1800)	793 (762,825)	6458 (6311,6608)
	% Risk from ^{99m}Tc-PYP	0.24%	0.04%	0.26%	0.19%
60	Excess Future Risk from ^{99m}Tc-PYP	**8.87 (2.41,20.9)**	**0.573 (0.047,1.71)**	**2.17 (0.407,5.47)**	**11.6 (3.54,24.7)**
	Baseline Future Risk	3880 (3810,3940)	1570 (1530,1610)	759 (730,789)	6209 (6071,6348)
	% Risk from ^{99m}Tc-PYP	0.23%	0.04%	0.29%	0.19%
70	Excess Future Risk from ^{99m}Tc-PYP	**7.47 (2.14,17.5)**	**0.381 (0.0338,1.11)**	**2.09 (0.249,5.70)**	**9.93 (3.11,20.9)**
	Baseline Future Risk	3530 (3470,3590)	1180 (1150,1220)	685 (659,711)	5396 (5278,5515)
	% Risk from ^{99m}Tc-PYP	0.21%	0.03%	0.30%	0.18%
80	Excess Future Risk from ^{99m}Tc-PYP	**5.11 (1.54,11.8)**	**0.196 (0.0189,0.545)**	**1.52 (0.126,4.39)**	**6.82 (2.39,13.9)**
	Baseline Future Risk	2610 (2560,2660)	701 (677,726)	524 (503,545)	3836 (3743,3930)
	% Risk from ^{99m}Tc-PYP	0.20%	0.03%	0.29%	0.18%

Table 2

Cancer Risks from ^{99m}Tc Pyrophosphate Imaging in Women. Assumes 10 mCi dose; for 20 mCi dose one should double these risks.

		Future Risk of Developing Cancer (chances in 100,000) for Women with 90% Uncertainty Range in Parentheses				
Age		**Bladder**	**Kidney**	**Leukemia**	**Ovary**	**Total**
40	Excess Future Risk from ^{99m}Tc-PYP	**8.98 (2.61,20.5)**	**0.473 (0.0449,1.27)**	**1.57 (0.483,3.48)**	**0.522 (0.127,1.30)**	**11.5 (4.17,23.6)**
	Baseline Future Risk	1210 (1170,1250)	1040 (1010,1080)	613 (586,641)	1410 (1370,1450)	4274 (4131,4419)
	% Risk from ^{99m}Tc-PYP	0.74%	0.05%	0.26%	0.04%	0.27%
50	Excess Future Risk from ^{99m}Tc-PYP	**8.76 (2.59,19.9)**	**0.430 (0.0408,1.15)**	**1.60 (0.397,3.74)**	**0.458 (0.112,1.14)**	**11.3 (3.95,23.0)**
	Baseline Future Risk	1210 (1170,1240)	1000 (967,1030)	585 (560,611)	1310 (1280,1350)	4107 (3973,4243)
	% Risk from ^{99m}Tc-PYP	0.72%	0.04%	0.27%	0.03%	0.27%
60	Excess Future Risk from ^{99m}Tc-PYP	**8.06 (2.5,18.1)**	**0.354 (0.0332,0.936)**	**1.64 (0.283,4.06)**	**0.362 (0.0874,0.891)**	**10.4 (3.63,21.0)**
	Baseline Future Risk	1160 (1130,1200)	891 (862,921)	543 (521,567)	1110 (1080,1150)	3714 (3596,3836)
	% Risk from ^{99m}Tc-PYP	0.69%	0.04%	0.30%	0.03%	0.28%
70	Excess Future Risk from ^{99m}Tc-PYP	**6.55 (2.17,14.3)**	**0.248 (0.0228,0.633)**	**1.56 (0.180,4.16)**	**0.253 (0.0595,0.625)**	**8.61 (3.18,17.1)**
	Baseline Future Risk	1010 (985,1040)	684 (661,707)	474 (455,493)	831 (806,856)	3001 (2907,3097)
	% Risk from ^{99m}Tc-PYP	0.64%	0.04%	0.33%	0.03%	0.29%
80	Excess Future Risk from ^{99m}Tc-PYP	**4.42 (1.59,9.24)**	**0.134 (0.0119,0.322)**	**1.18 (0.0944,3.32)**	**0.148 (0.0326,0.381)**	**5.88 (2.45,11.4)**
	Baseline Future Risk	737 (716,757)	401 (386,416)	355 (341,369)	519 (502,536)	2011 (1945,2077)
	% Risk from ^{99m}Tc-PYP	0.60%	0.03%	0.33%	0.03%	0.29%

Table 3

Risks of Bladder Cancer estimated using ^{99m}Tc Pyrophosphate-specific dosimetry from Medical Internal Radiation Dose (MIRD) Committee and Package Insert, compared to risk estimated using ^{99m}Tc Phosphates and Phosphonates dosimetry from International Commission on Radiological Protection (ICRP) Publication 128. Assumes 10 mCi dose; for 20 mCi dose one should double these risks.

		Future Risk of Developing Bladder Cancer (chances in 100,000) with 90% Uncertainty Range in Parentheses			
		Men		Women	
Age	**Type of Risk**	**MIRD/Package Insert**	**ICRP 128**	**MIRD/Package Insert**	**ICRP 128**
40	Excess Future Risk from ^{99m}Tc-PYP	9.45 (2.48,22.6)	18.8 (5.1,44.0)	8.98 (2.61,20.5)	17.9 (5.39,40.0)
	% Risk from ^{99m}Tc-PYP	0.25%	0.49%	0.74%	1.46%
50	Excess Future Risk from ^{99m}Tc-PYP	9.39 (2.49,22.4)	17.7 (4.91,41.1)	8.76 (2.59,19.9)	16.5 (5.19,36.6)
	% Risk from ^{99m}Tc-PYP	0.24%	0.45%	0.72%	1.35%
60	Excess Future Risk from ^{99m}Tc-PYP	8.87 (2.41,20.9)	14.5 (4.17,33.1)	8.06 (2.50,18.1)	13.4 (4.51,28.9)
	% Risk from ^{99m}Tc-PYP	0.23%	0.37%	0.69%	1.14%
70	Excess Future Risk from ^{99m}Tc-PYP	7.47 (2.14,17.5)	8.99 (2.74,20.2)	6.55 (2.17,14.3)	8.62 (3.14,18.1)
	% Risk from ^{99m}Tc-PYP	0.21%	0.25%	0.64%	0.84%
80	Excess Future Risk from ^{99m}Tc-PYP	5.11 (1.54,11.8)	3.51 (0.945,8.41)	4.42 (1.59,9.24)	3.64 (1.24,7.75)
	% Risk from ^{99m}Tc-PYP	0.20%	0.13%	0.60%	0.49%