Radiology

Patients with Testicular Cancer Undergoing CT Surveillance Demonstrate a Pitfall of Radiation-induced Cancer Risk Estimates: The Timing Paradox[1]

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Purpose: To demonstrate a limitation of lifetime radiation-induced cancer risk metrics in the setting of testicular cancer surveillance—in particular, their failure to capture the delayed timing of radiation-induced cancers over the course of a patient's lifetime.

Materials and Methods: Institutional review board approval was obtained for the use of computed tomographic (CT) dosimetry data in this study. Informed consent was waived. This study was HIPAA compliant. A Markov model was developed to project outcomes in patients with testicular cancer who were undergoing CT surveillance in the decade after orchiectomy. To quantify effects of early versus delayed risks, life expectancy losses and lifetime mortality risks due to testicular cancer were compared with life expectancy losses and lifetime mortality risks due to radiation-induced cancers from CT. Projections of life expectancy loss, unlike lifetime risk estimates, account for the timing of risks over the course of a lifetime, which enabled evaluation of the described limitation of lifetime risk estimates. Markov chain Monte Carlo methods were used to estimate the uncertainty of the results.

Results: As an example of evidence yielded, 33-year-old men with stage I seminoma who were undergoing CT surveillance were projected to incur a slightly higher lifetime mortality risk from testicular cancer (598 per 100 000; 95% uncertainty interval [UI]: 302, 894) than from radiation-induced cancers (505 per 100 000; 95% UI: 280, 730). However, life expectancy loss attributable to testicular cancer (83 days; 95% UI: 42, 124) was more than three times greater than life expectancy loss attributable to radiation-induced cancers (24 days; 95% UI: 13, 35). Trends were consistent across modeled scenarios.

Conclusion: Lifetime radiation risk estimates, when used for decision making, may overemphasize radiation-induced cancer risks relative to short-term health risks.

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Many authorities demand that physicians do a better job of considering radiation-induced cancer risks when ordering computed tomographic (CT) scans, but there is little evidence available to guide related decision making (1–5). The most commonly used resource for projecting radiation-induced cancer risks is the Biological Effects of Ionizing Radiation VII report, the product of a federally commissioned initiative to better understand health effects of low levels of ionizing radiation (6). Biological Effects of Ionizing Radiation VII investigators use outcomes data from atomic bomb survivors to project cancer risks corresponding to specified exposure levels and present results as lifetime attributable risk estimates of cancer development and death (6). For example, for a cohort of 20-year-old U.S. men exposed to 10 mSv (a level reached or exceeded during many CT scans), the reported lifetime attributable risk for cancer development is approximately one in 1000, meaning that one in 1000 men is projected to develop a secondary radiation-induced cancer at some time in his life (6).

We describe a pitfall—here termed the *timing paradox*—that can result from the use of lifetime attributable risk estimates in clinical decision making. This paradox arises when a physician weighs health risks from both a diagnostic test and the diagnosis of concern, but fails to account for when, over the course of a patient's lifetime, each risk is most relevant. The tendency to overlook differences in the timing of risks is natural; in many health care settings, risks of diagnostic tests and diseases play out concurrently (eg, endoscopy and upper gastrointestinal bleeding). In the case of CT, however, risks of radiation-induced cancers begin years after the initial exposure and continue for a lifetime, while risks associated with the disease for which CT is being performed tend to be more proximate (6).

Lifetime attributable risk estimates fail to capture the delayed timing of radiation-induced cancer risks and therefore can distort interpretation of cancer risks from CT. Consider a scenario where a patient has a small risk of dying of a disease at—or soon after—the time of a CT scan, and an equal risk, based on a lifetime attributable risk estimate, of dying later in life of a radiation-induced cancer attributable to the CT examination. If a physician compares these risks directly, without taking into consideration the difference in timing, these risks may appear similar. However, if given the choice between equal risks of dying now, versus dying several years from now, most patients would understandably choose the latter; these "equal" risks are not equal.

How can the delayed timing of secondary cancer risks from CT be captured in clinical decision making? One way would be to consider life expectancy losses attributable to radiation-induced cancers. Life expectancy losses, unlike lifetime risk metrics, inherently account for the timing of risks; more life expectancy is lost when a population faces the same risk early as opposed to later in life. To illustrate this phenomenon, we used computer modeling techniques to project outcomes in young patients with testicular cancer who were undergoing frequent surveillance CT after orchiectomy. In the years immediately after orchiectomy, this population has a low risk of dying of testicular cancer (7–9). As the risk of dying of testicular cancer diminishes, a low risk of dying of radiation-induced cancers emerges and remains for a patient's lifetime (6). We compared life expectancy losses and lifetime risks of cancer death from testicular cancer with life expectancy losses and lifetime risks of death attributable to radiation-induced cancers from CT. Our purpose was to demonstrate a limitation of lifetime radiation-induced cancer risk metrics in the setting of testicular cancer surveillance—in particular, their failure to capture the delayed timing of radiation-induced cancers over the course of a patient's lifetime.

Advances in Knowledge

- Lifetime risk metrics do not account for the delayed timing of radiation-induced cancers over the course of a patient's lifetime; as a result, radiation-induced cancer risks may be overemphasized relative to more immediate health risks in many clinical settings.
- Projections of life expectancy loss, unlike lifetime risk metrics, account for the timing of health risks over the course of a patient's life.
- In a Markov model of patients with stage I seminoma undergoing CT surveillance, patients incurred only a slightly greater lifetime mortality risk from testicular cancer than from radiation-induced cancers; however, life expectancy loss attributable to testicular cancer was more than three times greater than life expectancy loss attributable to radiation-induced cancers, because testicular cancer poses a more immediate risk of death.

Implication for Patient Care

- Lifetime radiation risk estimates, when used for decision making, may overemphasize radiation-induced cancer risks relative to immediate health risks.

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Abbreviations:
NSGCT = nonseminomatous germ cell tumor
UI = uncertainty interval

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Materials and Methods

Institutional review board approval was obtained, and the study was Health Insurance Portability and Accountability Act compliant. Informed consent was waived.

Model Overview

We developed a Markov model to project outcomes for patients with stage I testicular cancer who underwent orchiectomy followed by CT surveillance for possible cancer recurrence. For stage I cancers, all patients undergo orchiectomy. Although subsequent treatment options vary, the vast majority of patients undergo CT surveillance alone in lieu of additional adjuvant chemotherapy or radiation therapy. This is because salvage therapies for recurrent disease have high rates of cure, allowing favorable long-term outcomes without cardiovascular, secondary malignancy, and infertility risks associated with adjuvant therapies (9,10).

Our model was designed to differentiate deaths resulting from testicular cancer from deaths resulting from radiation-induced cancers associated with CT. The model also enabled projections of lifetime risks of radiation-induced cancer development. We designated, as our "base case," 33-year-old men with seminoma, which was on the basis of the median age of testicular cancer diagnosis in the United States (11). We also modeled multiple additional clinically relevant scenarios, including nonseminomatous germ cell tumor (NSGCT) subtypes and two additional age cohorts (23 and 43 years). We modeled our institution's current effective dose levels and CT surveillance schedules for the base case, but we also modeled low-dose and low-frequency imaging strategies to estimate effects of dose-reduction efforts on patient outcomes.

Our Markov model included two health states (alive and dead), a lifetime horizon, and a 1-month cycle length. Multiple competing risks of death were modeled. Patients were susceptible to death from testicular cancer during their first 10 years after diagnosis and were susceptible to death from all other causes at all times (12). Probabilities of radiation-induced cancer incidence, which were modeled at the organ level, and death were introduced following latent periods after CT scans and were continued until death of the entire cohort.

For each combination of tumor subtype (seminoma or NSGCT), age at diagnosis, and imaging schedule, our model yielded the following results: life expectancy losses and lifetime risks of cancer death from testicular cancer and life expectancy losses and lifetime risks of death attributable to radiation-induced cancers from CT.

Modeling Deaths Attributable to Testicular Cancer

To estimate cancer-specific mortality for patients with stage I testicular cancer, we used publicly available Surveillance Epidemiology and End Results *Stat software to query the Surveillance Epidemiology and End Results national cancer registry (13). Query details are provided in Appendix E1 (online). Our approach yielded 5-year cause-specific survival estimates of 99.70% (95% confidence interval: 99.48%, 99.83%) for stage I seminoma and 98.87% (95% confidence interval: 98.27%, 99.26%) for NSGCT (13). Cause-specific survival estimates were converted to monthly mortality rates by using standard exponential assumptions according to the equation $r_m = -\ln(p_{5\text{-yr-css}})/60$ months, where r_m is monthly mortality rate and $p_{5\text{-yr-css}}$ is the 5-year cause-specific survival probability, and were applied for 10 years after initial cancer diagnosis (14,15).

Modeling Organ-specific Secondary Cancer Risks from CT

We projected radiation-induced cancer outcomes on the basis of core elements of the Biological Effects of Ionizing Radiation VII report, including the following: *(a)* the assumption of a linear nonthreshold relationship between risk and exposure for all solid cancers; *(b)* suggested methods of cancer risk transport from Japanese atomic bomb survivors and medically exposed cohorts to a contemporary U.S. population; and *(c)* organ-specific parameters governing cancer risk, extracted from the Biological Effects of Ionizing Radiation VII report and Berrington de González and colleagues (6,16) (Appendix E1 [online]). We used the Surveillance Epidemiology and End Results registry (17–19) to inform U.S. background cancer incidence and mortality rates necessary for modeling radiation-induced cancer risks specific to a contemporary U.S. population.

We modeled radiation-induced cancer incidence and mortality risks for 13 solid organs (lung, esophagus, stomach, pancreas, liver, colon, rectum, kidney, bladder, prostate, central nervous system, thyroid, and oral cavity) and for leukemia, specifically accounting for expected anatomic regions of imaging coverage. For the majority of organs, we computed cancer risks as a geometric mean of excess relative risk and excess absolute risk, which was in keeping with Biological Effects of Ionizing Radiation VII methods for risk transport (6). Risk estimates were divided by a dose and dose rate effectiveness factor of 1.5 to account for further assumed reductions in the setting of low exposure levels (6). General excess absolute risk and excess relative risk equations for most cancers and alternate models used for thyroid cancer and leukemia are included in Appendix E1 (online).

After undergoing a CT scan, patients were continuously susceptible to death from solid cancers after 5 years and from leukemia after 2 years (6,20). Incidence risks were applied analogously to survivors in each cycle. As patients underwent more scans, cancer incidence and mortality risks from each were cumulatively applied. In this way, the model was used to incorporate and compute life expectancy losses and cancer risks attributable to radiation exposures from CT for all cohorts.

Imaging Schedules and CT Effective Doses in the Model

Abdominopelvic CT surveillance schedules we used are included in Table 1and were in keeping with institutional protocols as well as National Comprehensive Cancer Network guidelines (21). We also modeled imaging schedules

in which only alternate CT scans were performed. In these schedules, after the first CT scan, every other CT scan detailed in Table 1 was skipped, resulting in a total of 11 abdominopelvic CT scans (instead of 21) in patients with stage I seminoma and six (instead of 11) in patients with stage I NSGCT.

We modeled two effective doses for abdominopelvic CT. Institutional doses were derived, with institutional review board approval, from a sample of 500 consecutive abdominopelvic CT scans performed at our institution in May 2010. Dose-length product data were used to compute effective doses for each scan (22). The mean effective dose was 8.3 mSv ± 2.7 (standard deviation) (mean weight = 74 kg). A low dose was designated as 1 mSv (effective dose). This level is not yet routinely achievable but was modeled to quantify benefits of future dose-reduction technologies. To compute organ-specific cancer risks in our model, organ-specific equivalent doses were estimated by using effective dose values and CT dosimetry software (ImPACT, London, England), which accounted for expected anatomic coverage during abdominopelvic CT, as described in Appendix E1 (online) (23,24).

Given that some practitioners request chest CT to be performed with surveillance abdominopelvic CT in patients with NSGCT (21,25), we modeled this scenario as well. For this purpose, we used the mean effective dose derived, with institutional review board approval, from 500 consecutive chest CT scans performed during the same time period (4.1 mSv ± 1.5 [effective dose], mean weight = 72 kg).

Markov Chain Monte Carlo Uncertainty Analysis

We used Markov chain Monte Carlo methods, described in Appendix E1 (online), to estimate the uncertainty of model results (26). By using these methods, the uncertainty of each projected outcome was informed by the composite uncertainty of testicular cancer survival estimates derived from the Surveillance Epidemiology and End Results cancer registry (13) and most model parameters governing radiation risks (Table E1 [online]) (26). Because of the lack of evidence to inform latent period and dose and dose rate effectiveness factor uncertainty, effects of varying these parameters were instead evaluated by using one-way deterministic analyses. Latent periods for solid cancers were varied from 5 to 10 years, and, for leukemia, from 2 to 5 years; the dose and dose rate effectiveness factor was varied from 1 to 3 (6).

Table 1

CT Surveillance Schedule for Patients with Testicular Cancer in the Model

Disease	Total No. of Abdominopelvic CT Scans	Schedule
Seminoma	21	Years 1–3, scanned every 4 months; years 4–7, scanned every 6 months; and years 8–10, scanned every 12 months
NSGCT	11	Year 1, scanned every 4 months; year 2, scanned every 6 months; years 3–5, scanned every 12 months; and years 6–9, scanned every 24 months

Results

Base Case Results and the Timing Paradox

Primary model results are summarized in Table 2. For 33-year-old men with stage I seminoma who were undergoing a full schedule of abdominopelvic CT scans at institutional doses, the projected lifetime mortality risk attributable to testicular cancer (598 per 100000; 95% uncertainty interval [UI]: 302, 894) was slightly higher than that for radiation-induced cancers (505 per 100000; 95% UI: 280, 730). The projected life expectancy loss attributable to testicular cancer (83 days; 95% UI: 42, 124) was substantially higher than that for radiation-induced cancers (24 days; 95% UI: 13, 35).

Our findings support the timing paradox; similar lifetime mortality risks from two different causes correspond to discrepant projections of life expectancy loss. The cause of this paradox is illustrated in the Figure, where projected testicular cancer deaths and radiation-induced cancer deaths are plotted according to decade of life after orchiectomy. Because testicular cancer deaths occur much earlier, they result in greater life expectancy loss relative to radiation-induced cancers, even when lifetime mortality risks are similar.

Seminomatous Tumors versus NSGCTs

In a corresponding cohort of 33-year-old men with NSGCT, the projected lifetime mortality risk attributable to testicular cancer was comparatively higher (2243 per 100000; 95% UI: 1411, 3075) relative to that from radiation-induced cancers (262 per 100000; 95% UI: 145, 379), because of higher testicular cancer–specific mortality associated with NSGCT and lower CT surveillance requirements (13,21) (Table 2). Life expectancy losses from testicular cancer (311 days; 95% UI: 196, 426) compared with radiation-induced cancers (12 days; 95% UI: 6, 18) were again more discrepant than respective mortality risks, because of the described timing paradox.

When chest CT was added in patients with NSGCT, the lifetime mortality risk attributable to testicular cancer—and associated life expectancy loss—remained the same, while that attributable to radiation-induced cancers increased (454 per 100000; 95% UI: 227, 681), corresponding to a life expectancy loss of 22 days (95% UI: 11, 33).

Effects of Varied Cohort Ages

The timing paradox was more pronounced in younger than older men; meaning that in younger men, differences in life expectancy loss—attributable to testicular cancer versus radiation-induced cancers—were more pronounced than differences in lifetime mortality risks (Table 2).

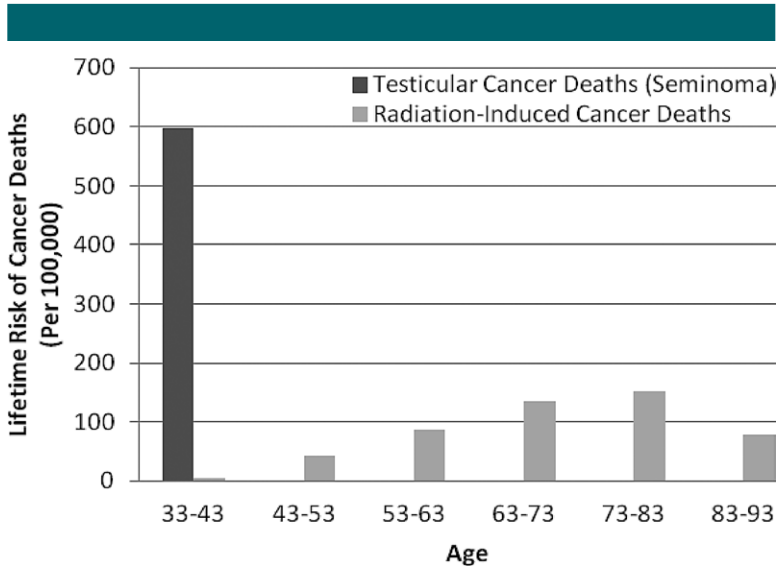
Table 2

Lifetime Mortality Risks and Life Expectancy Losses Attributable to Primary versus Secondary Cancers in Patients with Testicular Cancer Undergoing Surveillance Abdominopelvic CT

Cancer Type and Model Output	Cohort of 23-year-old Men	Cohort of 33-year-old Men (Base Case)*	Cohort of 43-year-old Men
Seminoma			
Testicular cancer deaths (per 100 000)	600 ± 297	598 ± 296	591 ± 293
Radiation-induced cancer deaths (per 100 000)	566 ± 254	505 ± 225	481 ± 212
Life expectancy loss due to testicular cancer (d)	103 ± 51	83 ± 41	63 ± 31
Life expectancy loss due to radiation-induced cancers (d)	28 ± 13	24 ± 11	20 ± 9.1
NSGCT			
Testicular cancer deaths (per 100 000)	2251 ± 835	2243 ± 832	2217 ± 823
Radiation-induced cancer deaths (per 100 000)	300 ± 135	262 ± 117	251 ± 111
Life expectancy loss due to testicular cancer (d)	388 ± 144	311 ± 115	235 ± 87
Life expectancy loss due to radiation-induced cancers (d)	15 ± 6.9	12 ± 5.6	11 ± 4.8

Note.—All model projections are reported with 95% UIs. Estimates are based on an effective dose level of 8.3 mSv for abdominopelvic CT (institutional dose).

* In 33-year-old men with seminoma, deaths attributable to testicular cancer are only slightly greater than those attributable to radiation-induced cancers, but life expectancy loss attributable to testicular cancer is more than three times greater, demonstrating a pitfall in lifetime risk estimates. This effect is generalizable to all cohorts evaluated.



Graph shows relative timing of deaths due to testicular cancer versus radiation-induced cancers. Testicular cancer risks predominate immediately after orchiectomy; radiation-induced cancer risks peak in the 7th–8th decades of life. If weighing lifetime mortality risk metrics only—and thereby disregarding the timing of such risks—one would compare the black bar (representative of testicular cancer deaths) against all gray bars combined (representative of radiation-induced cancer deaths). This type of comparison would make these risks seem more "equal" than they are.

For example, compared with 33-year-old men, for 23-year-old men with seminoma who were undergoing a full schedule of abdominopelvic CT scans at institutional doses, we projected a smaller difference in lifetime mortality risks between causes (testicular cancer: 600 per 100 000, 95% UI: 303, 897; radiation-induced cancers: 566 per 100 000, 95% UI: 312, 820) but a greater difference in life expectancy loss (testicular cancer: 103 days, 95% UI: 52, 154; radiation-induced cancers: 28 days, 95% UI: 15, 41).

Compared with younger men, in 43-year-old men, the difference in lifetime mortality risks between causes was greater (testicular cancer: 591 per 100 000, 95% UI: 298, 884; radiation-induced cancers: 481 per 100 000, 95% UI: 269, 693), but the difference in life expectancy loss was smaller (testicular cancer: 63 days, 95% UI: 32, 94; radiation-induced cancers: 20 days, 95% UI: 11, 29). This effect was expected; with increasing age at exposure and shorter life expectancy, both radiation-induced cancer risks and issues of timing decrease substantially in importance.

Effects of Radiation Dose Reduction

For the same cohort of 33-year-old men with seminoma who were undergoing a full schedule of abdominopelvic CT scans, when moving from institutional to low doses for each CT, radiation-induced cancer risks decreased substantially (Table 3). The projected lifetime risk of radiation-induced cancer mortality was 61 per 100 000 (95% UI: 34, 88), which corresponded to an attributable life expectancy loss of 2.9 days (95% UI: 1.6, 4.2).

In a corresponding cohort of 33-year-old men who were undergoing an alternating schedule of abdominopelvic CT scans at institutional doses (eg, skipping each alternate CT scan after the first), radiation-induced cancer risks decreased substantially (Table 3).

Table 3

Effects of Varying CT Dose and Schedule in 33-year-old Patients with Testicular Cancer Undergoing Surveillance Abdominopelvic CT

Cancer Type and Model Output	Institutional CT Dose		
	Full CT Schedule (Base Case)	Alternating CT Schedule	Low CT Dose (Full CT Schedule)
Seminoma			
Testicular cancer deaths (per 100 000)	598 ± 296*	…	…
Radiation-induced cancer deaths (per 100 000)	505 ± 225	265 ± 118	61 ± 27
Life expectancy loss due to testicular cancer (d)	83 ± 41*	…	…
Life expectancy loss due to radiation-induced cancers (d)	24 ± 11	12 ± 5.7	2.9 ± 1.3
NSGCT			
Testicular cancer deaths (per 100 000)	2243 ± 832*	…	…
Radiation-induced cancer deaths (per 100 000)	262 ± 117	143 ± 64	32 ± 14
Life expectancy loss due to testicular cancer (d)	311 ± 115*	…	…
Life expectancy loss due to radiation-induced cancers (d)	12 ± 5.6	6.8 ± 3.1	1.5 ± 0.7

Note.—All model projections are reported with 95% UIs. Institutional dose corresponds to an effective dose level of 8.3 mSv. Low dose corresponds to an effective dose level of 1 mSv. Patients undergoing a full schedule of CT scans adhered to the schedule outlined in Table 1, whereas those undergoing an alternating schedule of CT scans underwent alternate abdominopelvic CT scans only.

* Projected testicular cancer–related deaths and associated life expectancy loss varied minimally across the presented cohorts because our model accounted for competing risks of death; however, variability was not reflected within the significant figures provided.

The projected lifetime risk of radiation-induced cancer mortality was 265 per 100 000 (95% UI: 147, 383), which corresponded to an attributable life expectancy loss of 12 days (6,18). Trends were consistent across all scenarios.

Lifetime Risks of Cancer Development

There is no metric similar to life expectancy loss that can quantitatively account for the timing of cancer development over the course of a lifetime. Here, we provided projections of cancer development primarily for reference purposes. For 33-year-old men with stage I seminoma who were undergoing a full schedule of abdominopelvic CT scans at institutional doses, we projected 1074 per 100 000 (95% UI: 560, 1588) would develop radiation-induced cancers. For corresponding patients with NSGCT, we projected 557 per 100 000 (95% UI: 290, 824) would develop radiation-induced cancers. When chest CT was added in patients with NSCGT, an expected higher proportion of patients (784 per 100 000; 95% UI: 417, 1151) were projected to develop radiation-induced cancers.

Sensitivity Analysis

Markov chain Monte Carlo analysis results, reflecting the composite uncertainty of most model parameters, are presented as 95% UIs alongside all model results (Tables 2, 3). Increasing latent periods from 5 to 10 years for solid cancers and from 2 to 5 years for leukemia minimally improved outcomes. For 33-year-old men who were undergoing surveillance CT for seminoma at institutional doses, we projected a slightly decreased risk of radiation-induced cancer mortality (490 per 100 000) and life expectancy loss (22 days). In the same cohort, varying the dose and dose rate effectiveness factor from 1 to 3 resulted in predictably varied projections of radiation-induced cancer death (290–719 per 100 000) and life expectancy loss (14–34 days).

Discussion

Concerns about radiation-induced cancer risks from CT are largely based on lifetime risk projections, with multiple investigators using lifetime attributable risk estimates to highlight the potential harms of current CT practices (3,4,16,27). Critics of lifetime attributable risk estimates have primarily focused on the uncertainty associated with risks extrapolated from Japanese atomic bomb survivors and the relevance of lifetime attributable risk estimates in settings where disease-specific risks overwhelm radiation-induced cancer risks (28–30). Pitfalls associated with the use of lifetime attributable risk estimates in clinical decision making have received less attention (31,32). In this study, we highlighted a limitation of lifetime attributable risk estimates—their failure to account for the delayed timing of radiation-induced cancer events—that creates the potential for misuse of these metrics in routine clinical decision making.

In the case of testicular cancer, we demonstrated how the combination of a highly favorable primary cancer prognosis, substantial CT surveillance requirements, and a young age at initial CT exposure may lead to circumstances under which lifetime mortality risks attributable to testicular cancer are only slightly higher than those projected from radiation-induced cancers. Life expectancy losses attributable to testicular cancer, however, are more than three times higher, because risks of testicular cancer relapse are more immediate than radiation-induced cancer risks (6–9). This counterintuitive characteristic of lifetime risk estimate comparisons, here termed the *timing paradox*, renders providers susceptible to distorted perceptions of radiation-induced cancer risks in essentially all imaging

scenarios; all referring providers must weigh immediate risks imparted by a disease with future risks of radiation-induced cancers.

A similar clinical scenario occurs in the setting of young patients with limited-stage Hodgkin lymphoma. While this population has an excellent prognosis, most patients are exposed to multiple follow-up CT and positron emission tomography/CT scans during treatment and surveillance (33–36). In the past, radiation doses associated with diagnostic imaging were not a primary concern, because most patients received therapeutic radiation doses during treatment; however, stand-alone chemotherapy has recently emerged as an acceptable alternative, renewing concerns about radiation-induced cancer risks from imaging (35). As in the case of testicular cancer, physicians must be careful to consider the delayed timing of these risks relative to recurrent lymphoma; differences in life expectancy loss from lymphoma versus radiation-induced cancers are expected to be much greater than differences in corresponding lifetime mortality risks.

Acute settings in which young patients undergo CT scans (eg, for a suspicion of perforated appendicitis or subarachnoid hemorrhage or as part of a trauma protocol) also highlight the importance of considering the timing of radiation-induced cancer risks. In most related scenarios, the risks of life-threatening disease processes and injuries are immediate and, even if low, exceed lifetime risks of radiation-induced cancers (6,37–39). The delayed timing of radiation-induced cancer risks should further reduce their weight in a physician's real-time risk-benefit analysis.

Do life expectancy loss metrics have a role in risk communication? From a practical standpoint, life expectancy loss can be difficult to interpret at the patient level. For example, we projected a cohort of 33-year-old men with seminoma to have an average life expectancy loss of 24 days from radiation-induced cancers; however, this number is averaged across a cohort. Most individuals will lose no days of life, and a few will lose much of their life. Both lifetime risk metrics and life expectancy losses have shortcomings as stand-alone metrics of risk, but each carries distinct information that is important to convey. Further work is needed that investigates patient and provider risk perception in this setting to optimize the quality of risk communication.

Our study illustrated the relatively high magnitude of radiation-induced cancer risks in patients undergoing CT surveillance after orchiectomy for stage I cancers. Tarin and colleagues (25) reported lifetime attributable risk estimates (for development of radiation-induced cancers) of 1.9% and 1.2%, respectively, for 18- and 40-year-old patients with testicular cancer undergoing CT surveillance; their analytic design precluded calculation of life expectancy losses (25). Their lifetime risk estimates were slightly higher but reasonably comparable to our lifetime risk projections (1.2% for 23-year-old and 1.0% for 43-year-old patients). In part, this difference may be because they did not incorporate mortality risks attributable to testicular cancer itself.

van Walraven and colleagues reported follow-up data in 2569 patients with testicular cancer with substantial diagnostic radiation exposure (40). During a median follow-up period of 11.2 years, 14 developed new cancers (40). While this low number was reassuring, interpretation of results was limited by the short follow-up period, which reflected only a small portion of the population's future lifetime of susceptibility to radiation-induced cancers (41). To demonstrate the shortcoming of this approach, when applying our base case analysis to a cohort of 2569 men, we would project less than one radiation-induced cancer to develop in the first 11 years after diagnosis, but approximately 28 to develop over the course of the cohort's lifetime.

We quantified benefits to be gained by reductions in the dose or frequency of CT scans. O'Malley and colleagues (42) demonstrated that diagnostically acceptable images can be generated with a mean dose reduction of 55% compared with standard protocols. However, further research is needed to ensure that this translates into equivalent test performance (for identifying cancer recurrence) and relapse end points. In a randomized controlled trial comparing two versus five follow-up CT scans for patients with stage I NSGCT, Rustin and colleagues (43) could not identify a substantial benefit for patients to undergo five CT scans by using intermediate or poor-prognosis disease at relapse as a primary end point. Further similarly designed studies would be beneficial for determining the safety of dose-reduction measures in patients with testicular cancer. While magnetic resonance (MR) imaging may be used for surveillance purposes instead of CT, definitive comparisons of CT and MR imaging test performance have not yet been reported (44,45). Should MR imaging emerge as an acceptable technology for testicular cancer surveillance, our results would remain valuable, because they quantify the extent of risks that may be averted.

Mathematic models such as ours rely on simplifying assumptions about biologic processes (46). In our model of radiation risks, most parameters governing cancer risk were derived from outcomes of atomic bomb survivors, many of whom were exposed to much higher radiation levels than CT. The linear nonthreshold assumption that provides the theoretical framework for this approach remains controversial (6,47–49). However, given its empirical basis and the lack of clearly superior alternate methods of risk estimation, its use in our model was considered consistent with current standards (6,47,48,50).

Because of the lack of available data to inform benefits imparted by each individual CT scan for testicular cancer surveillance, these benefits could not be explicitly weighed against CT risks in the current analysis. To an extent, aggregate benefits of CT are represented within testicular cancer–specific survival estimates used in our model, which were extracted from the Surveillance Epidemiology and End Results cancer registry (13). However, the goal of the current analysis was not to perform a direct comparison of CT risks

and benefits. Instead, our goal was to contrast radiation-induced cancer risks and testicular cancer–specific risks to demonstrate a pitfall that can occur when making similar comparisons.

In this study, we illustrated how lifetime risk metrics, when used to compare risks that occur at different times in a patient's life, can lead to a practical overestimation of the effect of risks incurred later in life. This paradox, here termed the *timing paradox*, has important implications in the context of radiation-induced cancer risks from CT. In circumstances of CT referral, providers are commonly comparing proximal risks imparted by a disease with more distant radiation-induced cancer risks but are equipped only with lifetime radiation risk metrics. The timing paradox illustrates a way in which radiation-induced cancer risks may be distorted by many stakeholders and supports the need for further work in patient and provider risk perception to understand its effect in clinical decision making.

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