Life Years Lost—Comparing Potentially Fatal Late Complications After Radiotherapy for Pediatric Medulloblastoma on a Common Scale

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BACKGROUND: The authors developed a framework for estimating and comparing the risks of various long-term complications on a common scale and applied it to 3 different techniques for craniospinal irradiation in patients with pediatric medulloblastoma.

METHODS: Radiation dose-response parameters related to excess hazard ratios for secondary breast, lung, stomach, and thyroid cancer; heart failure, and myocardial infarction were derived from large published clinical series. Combined with age-specific and sex-specific hazards in the US general population, the dose-response analysis yielded excess hazards of complications for a cancer survivor as a function of attained age. After adjusting for competing risks of death, life years lost (LYL) were estimated based on excess hazard and prognosis of a complication for 3-dimensional conformal radiotherapy (3D CRT), volumetric modulated arc therapy (VMAT), and intensity-modulated proton therapy (IMPT).

RESULTS: Lung cancer contributed most to the estimated LYL, followed by myocardial infarction, and stomach cancer. The estimates of breast or thyroid cancer incidence were higher than those for lung and stomach cancer incidence, but LYL were lower because of the relatively good prognosis. Estimated LYL ranged between 1.90 years for 3D CRT to 0.28 years for IMPT. In a paired comparison, IMPT was associated with significantly fewer LYL than both photon techniques.

CONCLUSIONS: Estimating the risk of late complications is associated with considerable uncertainty, but including prognosis and attained age at an event to obtain the more informative LYL estimate added relatively little to this uncertainty.


KEYWORDS: life years lost, radiotherapy, late effects, secondary cancers, risk modeling.

INTRODUCTION

Cancer survivors are subject to elevated risks of adverse effects, such as cardiac disease, blindness, pneumonitis, neurocognitive impairment, and secondary cancers (SCs). Information from cohort studies can be used to model the risk of late complications, for example, to compare different treatment modalities or strategies. Risk estimates usually are expressed as a percentage excess risk or a relative risk (RR) compared with the general population. One problem is that different treatment options may give rise to different complications, and it is not straightforward to trade-off, say, an increased lifetime excess risk of severe late cardiac events with a decreased risk of inducing an SC.

In this report, we propose life years lost (LYL) as a tool for comparing multiple risks of potentially fatal late complications. This takes into account the age-dependent risk of a given late event as well as its prognosis. Furthermore, a treatment-related fatality occurring at a young age will cause a greater average loss of life expectancy than the same event occurring late in life. The measure is easy to interpret and can be used to prioritize between risks, for example, of cardiac events and SCs. In this study, LYL are applied to compare 3 craniospinal irradiation (CSI) techniques for 10 pediatric patients with medulloblastoma (MB).

MATERIALS AND METHODS

Concept Methodology

LYL are estimated from the age-specific excess hazard ratio (hr_excess) of cancer survivors compared with the general population. To facilitate treatment-specific risk assessment, the dependency of hr_excess on the radiation dose, D, must be obtained for each of the studied endpoints. Also, the optimal dosimetric descriptor (eg, mean dose, median dose, or maximum...
dose) will have to be established for each endpoint as well as the dependency on age at exposure \( (e) \), patient sex \( (s) \), and attained age \( (a) \), or other relevant characteristics. Here, age at exposure and attained age are only included in the risk estimation model if they had a statistically significant effect on the \( hr_{\text{excess}} \).

The age-specific and sex-specific hazard rates of the general population, \( h_{\text{gen.pop.}} \), were extracted from the Surveillance, Epidemiology, and End Results (SEER) Program unless otherwise noted.\(^6\)

\[
\dot{h}_{\text{excess}}(D, e, s, a) = hr_{\text{excess}}(D, e, s, a) \cdot h_{\text{gen.pop.}}(a, s) \tag{1}
\]

This yields an \( \dot{h}_{\text{excess}} \) per year of attained age for developing the studied complication.

To account for competing risks of death from the primary disease, treatment-related mortality, or noncancer-related events, the probability of reaching age \( a \), \( S(a; s) \) was estimated using survival curves from the Childhood Cancer Survivor Study (CCSS) cohort relative to an age-matched and sex-matched US general population.\(^7\) These data cover 30 years since diagnosis but were linearly extrapolated beyond this period by assuming the same trend in survival ratio between the CCSS cohort and the general population (see Figure 1). The childhood cancer survival curve is normalized to the survival from the primary disease assuming a 5-year survival rate of 80%. The sensitivity of LYL to this extrapolation was tested by recalculating the survival curve, assuming that the survival ratio between the CCSS cohort and the general population remained constant after the last empirical observation.

The age-dependent and sex-dependent life expectancy (LE) after a complication at age \( a \) is estimated from empirical survival data assuming the same prognosis as that for a spontaneous event extracted from national registries. Integrating the survival probability yields the LE after the corresponding event. The LYL attributable to a specific endpoint occurring at age \( a \) is then the difference in LE relative to an individual of the same age in the general population, conditional on having survived until that age. Hence:

\[
LYL(D, e, s, a) = S_{\text{survivor}}(a, s) \cdot \dot{h}_{\text{excess}}(D, e, s, a) \cdot (LE_{\text{gen.pop.}}(a, s) - LE_{\text{endpoint}}(a, s)) \tag{2}
\]

Figure 2 provides a flowchart illustrating the methodology with a corresponding example of calculating the LYL for a specific case. The total LYL attributable to each endpoint can then be derived by integrating the LYL for all attained ages after the age at exposure.

\[
LYL(D, e, s) = \int_{e+1}^{\infty} S_{\text{survivor}}(a, s) \cdot \dot{h}_{\text{excess}}(D, e, s, a) \cdot (LE_{\text{gen.pop.}}(a, s) - LE_{\text{endpoint}}(a, s)) da \tag{3}
\]

The upper limit of the integral was taken as 110 years, because \( S_{\text{survivor}} \) for older ages was effectively zero.

**Application to Pediatric Medulloblastoma Patients**

Different radiotherapy treatment techniques were compared with respect to LYL for 10 pediatric patients with MB ages 4 to 15 years who received treatment during 2007 to 2009 with postsurgical chemotherapy and CSI at our institution. Table 1 summarizes literature data on radiation dose-response and effect of age at exposure, attained age, and patient sex. Data from pediatric studies were used where possible; alternatively, data from Hodgkin lymphoma survivors were used. The \( hr_{\text{excess}} \) as a function of radiation dose is normalized to that of unirradiated individuals, because the case-control design does not allow for absolute risk estimates. This assumes that deriving \( hr_{\text{excess}} \) from nonirradiated cancer patients is identical to deriving it from the US general population.

Age-specific and sex-specific hazard rates and survival data for thyroid, breast, and lung cancer were obtained from the SEER registry.\(^6\) Data for cardiac events were obtained as hospital discharge rates from the Centers for Disease Control and Prevention (CDC) database.\(^16\) After a heart failure diagnosis, however, the same patient may be hospitalized repeatedly. Therefore, age-specific mortality rates, \( h_{\text{mört}} \), were obtained from the CDC database and LYL estimated as:

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**Figure 1.** This chart illustrates age-specific and sex-specific survival probabilities of the US general population and the Childhood Cancer Survivor Study (CCSS) cohort. Values were extrapolated based on data obtained up to 30 years after primary cancer diagnosis.
Treatment plans for the 10 patients with MB delivering 36 gray (Gy) to the craniospinal axis and 54 Gy to the posterior fossa were generated in accordance with published guidelines, using 3-dimensional conformal therapy (3D CRT); volumetric modulated arc therapy (VMAT); and spot-scanned, intensity-modulated proton therapy (IMPT) with the Eclipse treatment planning system (version 8.9; Varian Medical Systems, Palo Alto, Calif). The 3D CRT plans consisted of 2 lateral opposed cranial fields to cover the whole brain and a spinal posterior-anterior field to cover the spinal canal extending caudally to the junction of spinal segments 2 and 3. The lateral extent of the 3D CRT spinal field was the planning target volume plus 10 mm, because this best represented the
set-up from the treatment records of the patients. The boost plans were created using 4 fields to cover the posterior fossa. The VMAT plans were generated using the RapidArc (Varian Medical Systems) implementation with a 360-degree cranial arc and one or two 140-degree spinal arcs. The spinal arcs were not planned as full rotations to avoid irradiating through the arms and ventral parts of the patient. The VMAT boost plans consisted of a 220-degree arc covering the posterior fossa without incident irradiation through the anterior part of the head.

The IMPT plans were generated using 3 fields incident from the posterior direction. One field was set to cover the caudal part of the spinal canal, and the other 2 fields were set to cover the brain and remaining part of the spinal canal. The IMPT boost plans consisted of a single posterior field covering the posterior fossa. The clinical target volume-to-planning target volume margins for the VMAT and IMPT plans were 5 mm for the cranial part and 7 mm for the spinal part. Note that changing the margins would change the doses to the organs at risk (OARs) close to the target and, thus, would affect the relative comparison between treatment techniques.

Further details regarding treatment planning and margins have been described elsewhere. It should be noted that, although the dosimetric input in the current study was based on Brodin et al, the risk estimates provided here were based on a different methodology and dose-response data. The same treatment margins were applied for IMPT as for the VMAT technique, although, in practice, larger margins are sometimes applied with proton therapy because of the range uncertainty in proton dose deposition. OARs were delineated by an experienced radiologist (A.K.-B.).

Estimated, organ-specific, secondary neutron doses were obtained from a spot-scanned proton beam that was simulated using Monte Carlo methods on a pediatric mathematical phantom receiving craniospinal proton irradiation. The induction of late effects attributable to secondary neutrons is subject to large uncertainty. Therefore, as a conservative approach, the recommended relative biologic effectiveness of neutrons compared with photons was multiplied by a factor of 5 in our estimates. Even so, the secondary neutrons inherent to proton irradiation will contribute to added uncertainty in our estimates. Also, because our estimates are based on a simulated, spot-scanned proton beam, they may not be valid for a passively scattered beam.

Dose-response relations for the heart, breast, lung, and stomach endpoints were approximately linear, so the mean dose was used for these calculations.
response for secondary thyroid cancer, however, is best modeled as a bell-shaped function. Consequently, the differential dose-volume histogram of the thyroid was weighted to obtain an organ equivalent dose.

\[ hr_{\text{excess, thyroid}} = \frac{1}{V} \sum_{i=1}^{N} v_i \beta_1 D_i \cdot \exp(-\beta_4 D_i^2) \]  

(5)

where \( v_i \) is the fractional volume of the thyroid receiving dose \( D_i \), and \( N \) is the number of voxels in the total volume \( V \). The \( \beta_1 \) parameter describes the linear ascending part of the dose-response, and \( \beta_4 \) is the exponential-quadratic descending part (see Table 1).

**Statistical Analysis**

Uncertainty in estimating LYL comes mainly from the dose-response parameters. To obtain a robust comparison of LYL between treatment modalities, a paired difference Monte Carlo method was used. Samples were randomly drawn from a log-normal distribution with mean and 95% confidence interval (CI) corresponding to the published dose-response data. Thus, we sampled over the uncertainty in dose-response for each endpoint derived from the corresponding epidemiological studies. However, this does not include systematic components; for example, if the true functional form of the dose-risk curve is different from the assumed form or if the dose descriptor used here is not the best fit to the outcome data, then such uncertainties cannot be represented by the uncertainty in the model parameters.

For each endpoint, the difference in LYL between pairs of modalities was calculated, and the overall LYL with 95% CI were extracted by inverse variance weighting. To avoid underestimation of the variance because of the small number of patients in this study, a bootstrapping procedure was applied in which 10,000,000 samples from the 10 patients were drawn with replacement. The average point estimate and CI was calculated as stated above for each sample, and a normal distribution was matched to the result. Finally, a sample was randomly drawn from each of these 10,000,000 normal distributions. The final difference in LYL with 95% CI was taken as the mean and percentiles 2.5 to 97.5 of the randomly drawn samples. This provided estimates of the uncertainty in the paired comparison between modalities, resulting from uncertainty in the parameters derived from the published dose-response data.

**RESULTS**

Age-specific hazard rates for cancer and cardiac events in the general population were not published for individuals aged ≥85 years. It was assumed that these rates are constant for all those aged >90 years and equal to the rates published for the group aged ≥85 years in the Surveillance, Epidemiology, and End Results registry. The LYL curves are left-shifted compared with the hazard rate curves, illustrating more LYL after an event that occurred at younger age. Despite similar hazard rates for contracting breast and lung cancer, there is a large difference in LYL attributable to breast and lung cancer as a result of the different prognosis of the diseases.

![Figure 3](https://example.com/figure3.png)

**Figure 3.** This chart illustrates the mean values of estimated hazard rates and life years lost (LYL) attributable to radiation-induced, secondary breast and lung cancer for 10 patients with medulloblastoma based on the volumetric modulated arc therapy plans. Data are shown for attained ages ≤90 years, after which, it was assumed that the hazard remained constant at the level reported for the group aged ≥85 years in the Surveillance, Epidemiology, and End Results registry. The LYL curves are left-shifted compared with the hazard rate curves, illustrating more LYL after an event that occurred at younger age. Despite similar hazard rates for contracting breast and lung cancer, there is a large difference in LYL attributable to breast and lung cancer as a result of the different prognosis of the diseases.

The treatment-related mean (95% CI) LYL differences between VMAT and IMPT was 1.09 years (95% CI, 0.80-1.42 years) and 0.37 years (95% CI, 0.23-0.52 years) between 3D CRT and VMAT. LYL attributable to SC was higher for VMAT than for 3D CRT, reflecting the spread of radiation dose to OARs typical of intensity-modulated treatment. Conversely, the LYL attributable to cardiac events were lower for VMAT than for 3D CRT, reflecting the considerably reduced mean heart dose (7.3 Gy vs 18.9 Gy). The difference between 3D CRT and VMAT depends on the relative weight of cardiac events compared with SC events and, thus, is subject to a...
systematic uncertainty that is not included in the statistical uncertainty and should be cautiously interpreted. The width of the spinal treatment field in 3D CRT for MB affects the risk of radiation-induced heart failure, because it directly affects the mean heart dose. The same holds true for the mean lung dose. Hence, the relative merits of these techniques depend critically on the margins used.

The sensitivity analysis of extrapolating the survival curve of the CCSS cohort to older ages indicated that assuming a constant rather than a linearly decreasing ratio after the last follow-up yielded 12% higher LYL estimates for all 3 treatment techniques but did not affect their relative merits. The paired samples statistical test revealed a small but significant difference in LYL between 3D CRT and VMAT, although it should be noted that any systematic uncertainty that may change the relative weights of SCs compared with cardiac events is not considered in the statistical analysis, and there is a risk of a systematic error stemming from a mismatch between the assumed shape and the true shape of the underlying dose-response relation. The strength of the paired Monte Carlo test is that only differences in risks are considered, rendering the conclusion insensitive to uncertainties in parameters that describe a monotonous dose-response curve. However, as most statistical tests, the method relies on the assumption that the dose descriptor (typically, the mean dose) is indeed the correct descriptor and that the dose response has the correct parameterization. Figure 5 illustrates the paired Monte Carlo test with bootstrapping for this comparison. The LYL because of secondary thyroid cancer were less for 3D CRT compared with VMAT despite a higher thyroid dose because of the bell-shaped dose-response relation.

Figure 6 illustrates the lifetime cumulative risk of developing an SC and the corresponding LYL, clearly illustrating the impact of disease prognosis on LYL. The most frequent SCs were breast cancer and thyroid cancer; however, the LYL attributable to these malignancies were small compared with the LYL attributable to lung cancer. The mean lifetime cumulative risk of developing any of the studied SCs was 33%, 40%, and 18% for 3D CRT, VMAT, and IMPT, respectively.

**DISCUSSION**

A framework was developed for estimating the LYL attributable to late complications of radiation therapy, such as SC and cardiac events. The advantage of the LYL estimate over assessment of lifetime cumulative risks is that the time to event and the prognosis are taken into account. The uncertainty in relating radiation dose to excess hazard dominates the uncertainty of both the LYL estimate and estimates of lifetime cumulative risk. The additional data needed for estimating LYL are extracted from population-based registries and, thus, are known with comparatively high precision. A required assumption is that the prognosis after SCs or radiation-induced nonmalignant toxicity is similar to that observed after an event of nonradiation-related etiology. Consequently, LYL are easier to interpret when assessing the relative merits of alternative radiation therapy plans than lifetime cumulative risks and is associated with only a minor increase in uncertainty. Although it is informative, the LYL measure is a result of modeling various risks based on epidemiological studies and, thus, should be used with caution at the individual patient level. Further validation of the model is required, and the conclusions regarding the relative merits of radiation modalities should be tested in independent data sets.

In the current study, dose-response relations were extracted from large clinical series and from hazard rates documented for the US general population. When interpreting case-control study data for an endpoint, we assumed that \( h_{\text{excess}} \) for an unirradiated cancer survivor was identical to that of an age-matched and sex-matched individual in the general population, thus assuming no impact of chemotherapy or genetic predisposition. A similar problem was identified by Travis et al when estimating cumulative absolute risks of secondary breast cancer after treatment for Hodgkin lymphoma based on a nested case-control study. Those authors proposed treating the
RR from the case-control study as an internal risk, estimating an external risk for the same cohort related to the general population breast cancer incidence, then combining these to estimate absolute risks. This approach requires individual patient-level data from the case-control study. In addition, it is unclear whether age at exposure and attained age significantly affect the late complication risk. The estimates provided in Figure 4 primarily represent the possibility of affecting the LYL by redistribution of radiation dose. Including nonradiation-related risks more closely represents the absolute treatment-induced LYL of a cancer survivor. It is indeed possible to include risks like anthracycline-related cardiac complications in the presented framework, but the required data could not be extracted from the current literature.

The statistical uncertainty illustrates the need for higher quality dose-dependent risk data reported as standardized incidence ratios (SIRs) relative to the general population. However, the dose-dependence of complication risks and the risk-modifying effect of patient-related factors often are not reported in sufficient detail for optimal estimation of LYL. In the current analysis, the dependence on age at exposure was only available for the thyroid cancer estimates. Ideally, fitting parameters with CIs and the functional form of the multivariate model should be reported (for example, see the report by Bhatti et al13).

The translation of risk estimates derived from large epidemiological studies with retrospective dosimetry into estimates for the patients in our study contributes to the overall uncertainty. This is especially true for endpoints in which the dose response was based on adult data, because

![Figure 5. These are results from statistical analyses of the difference in life years lost (LYL) with 3-dimensional conformal radiotherapy (3D CRT) and volumetric modulated arc therapy (VMAT). The mean differences with corresponding 95% confidence intervals (CIs) are listed for each patient from the Monte Carlo sampling along with the resulting distribution of difference estimates obtained from bootstrapping and final estimates of mean and 95% CI.](image-url)
A general concern is that a developing child may be more susceptible to radiation-induced cancers. Also, long-term follow-up studies like the CCSS reflect the risk of treatment given some 20 to 30 years ago, making it difficult to extrapolate the results to modern treatment techniques like VMAT or IMPT. These uncertainties mean that validation against independent data sets is crucial if an LYL measure is to be trusted for clinical decision support.

A recent publication estimated the nonrelapse-associated LYL in MB survivors at 4.3 years based on published mortality data from the CCSS. This value is larger than our estimates, probably because only a few causes of mortality are considered here. The estimated lifetime cumulative risks of SC of 33% for 3D CRT and 40% for VMAT are roughly in agreement with other estimates for pediatric patients with MB at 20% to 55%. It is noteworthy that Mertens et al reported no cardiac deaths among MB survivors, possibly because the patients they studied had not reached an age at which the risk of cardiac events in the general population becomes apparent.

The current study assumes a similar prognosis after a treatment-induced event and a spontaneous event. Cancer survivors may be followed more closely than the general population, possibly leading to earlier detection of an SC. The SC also may be of a different phenotype, more or less difficult to manage, than its spontaneous counterpart. Treatment-related cardiac complications may have a worse prognosis because of the relatively high prevalence of cardiac risk factors among cancer survivors. Such nuances can easily be incorporated into the LYL estimation if the appropriate data become available.

A logical, but challenging, extension of the LYL concept would be the inclusion of late relapse of the primary disease. Curing the primary disease must be the highest priority in cancer care, and failure to do this would yield a large number of LYL. Including estimates of tumor control requires reliable clinical dose-response data and, ideally, a quantification of the loss of tumor control if part of the target volume is under treated. Another extension of our model would be to include nonlethal late complications that affect quality of life to estimate quality-adjusted LYL (QALYL). QALYL theoretically would allow optimization of both health-related quality of life and life expectancy and thereby allow assessment of the cost-benefit of advanced therapy options, such as proton therapy. Finally, LYL or QALYL could form the basis for radiotherapy plan optimization.

In summary, LYL estimates attributable to late effects are objective, easy to interpret, and take prognosis and time to the event into account when comparing alternative treatment options. Our current limited knowledge of treatment-induced late effects does limit the accuracy of long-term risk estimates. However, several large clinical studies are in progress that will reduce the uncertainty of dose-response and clinical risk factor data and thereby improve the accuracy of LYL estimates.

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REFERENCES