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COMMENTARY

Intensity Modulated Radiation Therapy and Second Cancer Risk in Adults

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Intensity modulated radiation therapy (IMRT) has been developed as an evolution of 3-dimensional conformal radiation therapy (3D-CRT) and was made possible by the enormous advances in the field of informatics and dose calculation algorithms (1, 2). Initially proposed by Brahme 30 years ago (3), IMRT has improved high-dose conformity around tumors with complex shapes, thus achieving maximal sparing of organs at risk. This "ideal" dose distribution can be achieved through an optimization process based on the definition of specific dose constraints for organs at risk and on the minimization of a so-called "cost function" (4). The result is a treatment plan consisting of multiple modulated static fields or 1 or more modulated volumetric or spiral rotational arcs (given that all modulated paradigms result in very similar dose distributions, all are referred to as "IMRT" for the purpose of this editorial). Intensity modulation also offers the unique opportunity to obtain nonhomogeneous dose distributions inside the target volumes, further refining the radiation therapy (RT) process. Even in randomized studies, IMRT translated into a significant reduction of dose-dependent nonstochastic acute and late RT-related side effects (for example, xerostomia in head and neck cancer patients) (5, 6). Intensity modulated radiation therapy also has the potential to reduce serious late effects in less obvious but very frequently encountered situations, such as the treatment of left-sided breast cancer (heart sparing) (7).

Since the early years, clinicians and radiobiologists have discussed the potential long-term side effects associated with IMRT's new dose-distribution paradigm, which tends to expand the volumes receiving lower doses while reducing the volumes receiving higher doses. It has been hypothesized that the low-dose "bath" typical of IMRT could result in an increased risk for second cancer (SC), on the basis of early estimations of dose-response relationships and the increased exposure of tissues located outside the treatment fields (8-10). This aspect assumed particular importance for adult patients with long life expectancy, such as those treated at a younger age and affected by curable cancers, such as germ cell tumors, lymphomas, and early-stage breast cancer, for which IMRT was therefore reluctantly used. The fear of treating large volumes to low doses in these patients was based on initial estimations of a relatively high impact of the low-dose component (derived from the A-bomb survivor study on whole-body exposures) on SC risk, and conversely a reduction in SC risk at higher doses, as a consequence of a higher cell death rate precluding the development of carcinogenic mutations (the "overkill" phenomenon) (8). The 2 concepts combined usually favored 3D-CRT versus IMRT with regard to SC risk in terms of radiobiological modeling

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risk comparisons (11-13). However, some factors precluded an accurate estimate of SC risk after fractionated RT, especially in the past: (*1*) an overall small number of events detected; (*2*) unclear effects of other factors (chemotherapy, hormonal therapy); (*3*) difficulties in collecting long-term follow-up data; and (*4*) uncertain dosimetry, mainly as a consequence of unreliable patient positioning together with a lack of availability of dosimetry data at the time of SC onset. Newly available data suggest that modern RT is associated with a lower than previously expected SC risk (14, 15), and IMRT may not induce significantly more SC than 3D-CRT (16). Moreover, the possibility cannot be excluded, as to our knowledge first explicitly suggested by Chargari et al (16), that SC risk might actually be reduced with modern IMRT.

Given that over the last 20 years IMRT a) has seen an impressively increased use, b) has been gaining traction dramatically between 2000 and 2005 (2, 17), and c) is now being used frequently across a wide array of adult and even pediatric indications (with a sufficient number of patients only recently crossing the crucial 10- to 15-year mark after treatment) this seems to be an appropriate point in time to reassess the situation, depicting a partially different landscape.

Advances in Modeling and Recent Clinical Data From Conventional RT Series That Also Provide More Insight as to Risk Conferred by IMRT

Radiobiological modeling studies no longer unequivocally predict significantly higher SC rates with IMRT. When based not only on A-bomb survivor series but also integrating data from clinical treatment—thus bridging extrapolated and epidemiologic data (18, 19)—new models may take into account organ-specific dose distributions and organ-specific dose-response relationships, better reflecting the situation after clinical RT and providing a more detailed theoretical evaluation of the SC risks associated with either 3D-CRT or IMRT (19). What emerges from these recent efforts, and from a meta-analysis of epidemiologic data, is that the SC risk from RT is generally linear, or linear-plateau shaped with the dose (with the exception of thyroid cancer), and seems to be not as high as previously predicted, at least for adults (20).

Clinical data on pediatric Hodgkin lymphoma with long-term follow-up clearly showed that second breast cancers develop in the high-dose region (21). A linear dose-effect relationship was also evident from the Yale University Hodgkin lymphoma cohort, analyzed for comparison of RT alone versus combined-modality therapy with reduced radiation fields; almost all second malignancies were diagnosed within the treatments field (22), even if some uncertainties do exist relative to appropriate dose reconstruction and site of origin of the second neoplasms (22, 23). A dose-volume linearity above 10 Gy for breast cancer induction was also evident from a cohort of patients treated at age <20 years (24) with whole-lung irradiation, thus including very large volumes of breast tissue to doses between 10 and 20 Gy; the cumulative incidence of second breast cancer was similar to that in children treated with high-dose mantle fields, well above 20 Gy. These data confirmed a strong linearity but also suggested a volume effect when whole organs such as breast are irradiated, even at low doses, at least in children and adolescents. Other findings on childhood cancer survivors showed that most of the SCs rise in the regions close to the planning target volume, but lower doses might still be at risk (25). This might not be the case for adults, and, for example, modern RT for mediastinal Hodgkin lymphoma avoids this situation, and the progressive reduction of treated volumes seems to already have reduced SC risk (26, 27). Because the volume effect might be more pronounced for children, special caution should be taken with IMRT, and all efforts for a better dose distribution and organ-at-risk sparing, achievable for example with protons, are justified.

Finally, very recently, Krul et al (28) published the latest data in this journal derived from a well-controlled cohort of patients treated for Hodgkin lymphoma, once more suggesting an at least linear dose−SC relationship with no hint at a plateau. Other findings imply similar conclusions for women with early breast cancer undergoing surgery plus RT: among large populations, the cumulative incidence of any second malignancy was generally in excess, although low, in high-dose regions close to the treated volumes (29, 30). One study showed that the risk of second lung cancer increased linearly, with 8.5% per delivered Gray, reinforcing the robustness of a linear relationship in a large number of clinical situations (31). In a similar study, on second esophageal cancer in Hodgkin lymphoma survivors, Morton et al (32) again showed linearity. The relative risk of SC was also increased, but only at a dose above 5 Gy, in a study in 647,672 adult cancer survivors followed for an average of 7 years (33). These data, in favor of a dose-response linearity for SC induction, indicate that the increase in out-of-field low dose typical of IMRT might be counter-balanced by a decrease in the intermediate-to-high dose region, thus not necessarily implying higher risks from IMRT. More recent modeling studies incorporating these concepts suggested at least an equivalence in SC risk induction between 3D-CRT and IMRT in different clinical presentations, for example adult mediastinal lymphomas or rectal cancer (34, 35).

Preclinical Data

Recent preclinical data also suggested a linear relationship between dose and SC occurrence, and potentially even a supralinear dependence. New evidence from a comprehensive set of experiments looking at SC incidence after RT resembling clinical fractionation schemes in murine models (36) leads to several interesting conclusions. The risk of postirradiation sarcoma after clinically relevant fractionated

exposures increased with total doses from 40 up to 80 Gy, with no evidence of a plateau, confirming that the dose-response relationship for high fractionated doses (in the range of what is clinically used for most solid tumors) is at least linear, but possibly supra-linear (which would favor IMRT in SC risk modeling studies). Two other new findings from this study should be highlighted: the difference in cancer induction between single doses (higher risk for same physical dose) and fractionated exposure, and the lack of a plateau at high doses for single-dose treatments, with a steep, almost binary, dose-response curve. This last finding is actually in line with historical data in a murine model (37) and the seminal canine intraoperative radiation therapy (IORT) series commissioned by the National Cancer Institute in preparation for later clinical IORT efforts (38). These data sets again suggest that fractionated IMRT may not carry a particularly elevated risk, whereas SC risk from IORT in patients with a long life expectancy after treatment (a more recent clinical development) should be closely monitored.

Clinical Data

The first data directly comparing the incidence of SC between adult patients treated with either 3D-CRT or IMRT are preliminarily emerging. In a cohort of 39,028 patients treated for prostate cancer, no difference in cumulative incidence between the 2 techniques with a median follow-up of 5.2 years was observed (39).

There was no difference in the risk of leukemia or myelodysplasia after IMRT versus 3D-CRT, and also the risks of other solid cancers and lymphomas did not significantly differ between IMRT and 3D-CRT. When analyzing the relative risk of different solid tumors, with crude incidence and adjusted relative risks, there was some preliminary evidence of reduced risks of colon and rectal cancers for IMRT, which is potentially consistent with lower volumes of these organs treated to high radiation doses, as also suggested by other studies taking into account dose distribution (40, 41). Although these data provided the first clinical insights directly addressing the IMRT versus 3D-CRT issue, it should be kept in mind that follow-up is still relatively short, the median age in the studied cohorts was high as a consequence of prostate cancer being the target disease, and that the usual caveats with Surveillance, Epidemiology, and End Results–based analyses (eg, all kinds of selection biases, overall data quality) apply.

A possible positive effect of the combination of smaller volumes through the typically combined use of image-guided RT and IMRT may also have contributed to these observations, given that sequential cohorts are compared and these paradigms emerged closely correlated in time. A reduction in SC risk for external beam RT when compared with the unchanged situation with brachytherapy, which the authors suggested to be a consequence of the increased use of IMRT in the latest period, was also observed in another analysis comparing SC risk between RT and surgery (42).

IMRT Versus Protons

The cumulative incidence of SC should theoretically be lower with proton therapy when compared with photons, as a consequence of the net lower integral dose with (ideally) no disadvantages regarding the dose distribution in the target. Nevertheless, modeling SC risk is even more complex for particle therapy than for photons, as recently outlined comprehensively by an expert group led by Stokkevag et al (43). So far, to our knowledge, the only clinical comparison between photons and protons (let alone IMRT vs protons) has been provided by Chung et al (44). They reported cases of SC in both a photon and proton cohort and suggested that protons do not confer a higher risk of SC in pediatric patients than photons. Being a two-center, noncontrolled comparison, this initial report leaves unclear, however, whether in addition to the other advantages of particle therapy it might measurably reduce clinical SC risk also a reduction in SC risk would be measurable. A considerable amount of clinical long-term observations will be needed to finally answer that question.

Conclusions

Accumulating evidence suggests that SC risk after IMRT is likely not higher than with more traditional techniques such as 3D-CRT. We believe that the new dose-response relationships derived from epidemiologic studies, the more recent modeling studies incorporating dose distributions, organ-specific parameters, and initial clinical observations, even with limited follow-up, all contribute to suggesting that IMRT use is safe in terms of SC risk. The biological basis is the high probability for a linear shape of the dose-response curve for most radiation-induced SC after fractionated RT (questioning the initial hypothesis for most solid tumors of a bell-shape relationship, with risk decreasing at higher doses). The potentially negative effect of the larger low dose component surrounding the target typical of IMRT is likely balanced by the potentially negative effect of the larger higher dose component typical of 3D-CRT. Clinical data undoubtedly to arrive over the next few years should be attentively monitored and will hopefully solidify the scientific basis for choosing a dose distribution that is optimal regarding tumor control, organs-at-risk sparing, and SC risk for every patient.

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