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Editorial Comment

High-energy Photons in IMRT: Uncertainties and Risks for Questionable Gain

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In this issue of Technology in Cancer Research and Treatment de Boer and colleagues (1) present an article dealing with a fairly controversial subject in radiation oncology – photon energy in intensity modulated radiation therapy (IMRT). Much of this debate is based on purely theoretical grounds and, thus, real data is invaluable in settling the issue.

Because high-energy photons (*e.g.*, greater than 10 MV) have dosimetric advantages in some situations thanks to of their greater depth of penetration and skin-sparing potential, such energies are commonly used in 3D conformal radiotherapy. With IMRT, however, high-energy photons may present more disadvantages than advantages.

For a start, although integral dose is generally assumed to be improved by the use of higher energy photons, there is concern that some treatment planning systems might not effectively model the "beam narrowing" at depth observed with high energy photons in the small radiation beamlets encountered in IMRT. This phenomenon is caused by lateral beam degradation due to penumbra widening (8); when very small fields are used, there is greater loss of electron equilibrium laterally with higher energy photons (8, 9). This is especially problematic at high gradients, leading to dose reduction near the beam edge and along the central axis (10). The clinical solution to this problem is to use wider beams – which negates the hypothetical gain from high-energy photons as far as integral dose is concerned.

Dose modulation is the key to successful IMRT and this modulation is heavily dependent on the lateral fall-off provided by the leaves of the multi-leaf collimator. The ability to modulate is impaired at high energy because the lateral range of electrons widens the lateral fall-off (penumbra). The lateral range increase is the result of the same fundamental physics that produces a deeper depth of maximum dose for high-energy photons. The electrons are being set in motion at higher energies, but not so high that they do not scatter. A typical initial kinetic energy of an electron set in motion by an 18 MV photon beam is about 4 or 5 MeV. At this initial kinetic energy an electron travels about 2 or 3 cm and scatters considerably, even if it is originally set in motion in the same direction as the photon. This leads to blurring of the lateral boundary and inherently limits the modulation that can be achieved. There is a simple test that can illustrate this phenomenon. Irradiate a film with every second leaf pair closed together producing a picket fence irradiation pattern. Do this for both high energy and low energy beams and it will be evident that the valleys under the lower energy beam are deeper than under the high-energy beam. In signal processing, the definition of "modulation" is the peak minus valley signal divided by the peak plus valley signal. This

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simple experiment will show that the modulation that can be achieved at low energy is superior to the modulation that can be achieved at high energy. IMRT is all about the modulation. Having said that, a conventional IMRT prostate radiotherapy plan that does not assign a lot of importance to avoidance of the rectum and bladder will not yield highly modulated IMRT patterns and this high vs. low energy effect will not be obvious. However, high modulation *is* required when avoidance of the rectum has been assigned high priority in the optimizer. Such high priority demands a very steep gradient between the prostate and rectum. This gradient becomes obviously less steep if a high-energy beam is used with its wider lateral penumbra. As a clinical aside, placing high gradients between the prostate and rectum should probably only be done if there is daily image guidance to ensure that the prostate is receiving a high dose and the rectum a low dose.

Another disadvantage of high-energy IMRT commonly cited is the neutron "contamination" when photon energy exceeds the threshold of photonuclear reactions. Beyond the threshold for this (γ,n) reaction, there is a giant resonance where the probability of neutron production is greatly increased. The giant resonance curve varies from element to element with the midpoint given by the general formula $E_o = 80\ A^{-1/3}$ (when E_o is in MeV and A is atomic weight). Photoneutron production by and large is possible when bremsstrahlung x-rays are generated by electrons of 8 MeV or higher. In such situations, elements within the gantry, collimator, flattening filter, wedge filter, and blocks may undergo photonuclear disintegration yielding unwanted neutrons that contribute to the patient dose. Neutrons are of considerable importance in radiation safety because for any given absorbed dose, neutron irradiation typically yields a much higher biologically effective dose (BED) than photons for practically any biological endpoint. The quality factor (Q) used in radiation protection is only a very general approximation of the relative increased toxicity of neutrons but typically has quoted values between 2 to 11, depending on energy. Neutrons of 2-5 MeV are particularly biologically damaging because they generally can enter the body but do not have enough energy to exit. Thus, all the energy is deposited within the body. Neutron dose equivalent is obtained from quality factors, which are defined in terms of LET (the amount of energy deposited over distance traveled). A quality factor of 10 is used for radiation safety calculations involving neutrons. That is, for any given dose, neutron irradiation delivers about 10 times more damage to cells.

Since "low energy" photons (*e.g.*, 6 MV bremsstrahlung) are normally below the threshold for neutron generation, such concerns are avoided. With conventional radiation therapy or 3D conformal radiotherapy, the time during which the linac beam is on (*i.e.*, the monitor units) is relatively brief and therefore, regardless of photon energy, significant amounts of neutron contamination are not likely. The increased monitor units required with IMRT greatly increase the odds of neutron generation when high-energy photons are used (as is discussed in the paper by de Boer *et al.*). Howell *et al.* (2, 3) measured neutron doses from the delivery of 18 MV conventional and IMRT treatment plans. They found that the IMRT treatment resulted in a higher neutron fluence and higher dose equivalent. These increases were approximately the ratio of the monitor units used.

Concerns about IMRT neutron contamination are illustrated by estimates by Chbani and Ma (4). They found that the dose equivalent from photoneutrons at 50-cm off-axis distance produces up to a 2.0% likelihood of fatal secondary cancer for a 70 Gy treatment delivered by a Varian 18 MV beam. Hall and Wuu (5) have estimated that IMRT is likely to almost double the incidence of second malignancies compared with conventional radiotherapy from about 1% to 1.75% for patients surviving 10 years with much of this increased risk due to neutron dose. Kry *et al.* (6) also found that neutrons were a significant contributor to the out-of field dose equivalent for beam energies >15 MV. They estimated risks of fatal secondary malignancy associated with IMRT and conventional external-beam approaches for prostate cancer and calculated a maximum risk of fatal second malignancy of 1.7% for conventional radiation therapy but up to 5.1% for IMRT using 18 MV photons. IMRT using 6 MV photons yielded calculated risks of 2.9% for treatment with a Varian accelerator and 3.7% with a Siemens accelerator; whereas for 15 MV photons the figures were 3.4% (Varian) and 4.0% (Siemens). The authors concluded that the estimated risk of fatal secondary malignancy differed substantially between IMRT and conventional therapy for prostate cancer but also between different IMRT approaches (*e.g.*, high energy vs. low energy photons).

In addition to neutron contamination, several other factors have to be weighed and considered when choosing energy for IMRT. Because IMRT typically requires more "beam-on" time than conventional radiation therapy (*i.e.*, more monitor units), leakage through the collimator and scatter from the gantry have to be considered. de Boer *et al.* (1) showed that IMRT with 18 MV photons required 18% less monitor units than similar plans with 6 MV. Others have found, however, that the amount of leakage radiation between leaves is significantly higher with high-energy photons thereby, possibly negating the lower monitor unit advantage. For example, Hug *et al.* (7) identified a 40% increase in leakage between leaves with high energy photons compared to low energy; the measured average leakage was 2.5% and 3.5% for 6 MV and 25 MV, respectively. This photon leakage may lead to a higher dose to the patient outside the (intended) irradiated volume from high energy IMRT than with low energy despite the fewer required monitor units. Also, estimations of dose

within the irradiated volume are hindered by uncertainties with existing treatment planning systems when dealing with doses below 10% of the target dose.

Often-overlooked are the potential radiation safety concerns for the therapists who must walk in and out of the room following IMRT treatments. Because IMRT exposes the linac and associated hardware to more radiation, when the energy of such radiation is sufficient, it can photoactivate certain elements within this hardware. The primary and daughter products may be radioactive and could increase radiation exposure to staff as well as patients. Elements within commercial linac collimators that can result from such photoactivation include ^{28}Al ($t_{1/2}$ = 2.24 min), ^{56}Mn ($t_{1/2}$ = 2.58 h), and ^{24}Na ($t_{1/2}$ = 14.96 h). Rawlinson *et al*. (11) using a Varian Clinac 21EX have estimated that with 18 MV photons and a linac workload of 60,000 monitor units per week, therapy staff would receive about 60 microSv with conventional treatments but up to 330 microSv per week if high-energy IMRT were used. Thus, staff doses could be nearly 6-fold greater with IMRT using high-energy photons. They recommended avoiding high-energy IMRT whenever possible, but if high-energy photons are used, these IMRT patients should be scheduled as late in the day as practical to minimize unnecessary exposure to personnel and other patients. Investigations have demonstrated differences in the induced activity from one linac brand to another. For example, Perrin *et al*. (12) have estimated the maximum annual whole body dose for a treatment therapist, with the machine treating with 18 MV, for 60,000 monitor units per week was 2.5 mSv using an ELEKTA Precise accelerator; whereas, the published value for a Varian Clinac 21EX was 2.9 mSv. We (13) have recommended that linac manufacturers strive to design collimators that have reduced susceptibility to photonuclear activation to minimize this risk. A similar potential concern for the patient exists if there is any form of implanted medical hardware in the near the target area (*e.g*., a hip replacement in a prostate cancer patient), as the elements in these implants may be photoactivated. This activation could result in unwanted and underestimated dose to the adjacent tissues near the device.

While the debate about photons energy continues, the data provided by de Boer *et al*. may be helpful to clinicians when choosing nominal photon energies for IMRT. Overall, our interpretation of their data and the balance of the literature strengthen our conviction that high-energy photons pose more risks and uncertainties than gains. We continue to advocate the use of 6 MV photons for IMRT.

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