Dose-painting by numbers: a feasible approach?

Treatment of cancer by radiation has benefited greatly from technological advances. In fact, it is not an exaggeration to say that technology has revolutionised radiotherapy.[1]

The spin-off from the World War II development of radar led to linear accelerators, which produce high-energy x-rays that are much more penetrating than the low-energy x-rays available in the 1930s, so that deep-seated cancers can be treated effectively. The development of fast computers, together with the diagnostic techniques of CT and MRI, allow more accurate treatment planning, so that the dose distribution could be tailored to the shape of the tumour. In parallel with these advances in technology there have been few major contributions from biology. Now, in a *Personal View* in this issue, Søren Bentzen[2] attempts to marry some present advances in biology with those in physics, which, he claims, will shape the future of radiation oncology.

The step forward in biology is the use of imaging techniques to identify regions in a tumour that might need a higher dose.[3] Such regions include: hypoxic regions, and those in which cells are refractive to killing by x-rays, are dividing rapidly, are more malignant and aggressive, and express known characteristics of malignant disease. Thus, the notion of a tumour as a homogeneous soup of identical cells is replaced by a complex pattern—with small regions needing a boost dose because of resistance or aggressive growth.

The corresponding step forward in physics is intensity-modulated radiation therapy (IMRT), in which many small pencil beams are used, under computer control, to conform the volume irradiated to any irregular shape. Such a technique allows the design of tailored hot-spots within the overall tumour mass that receive much higher local doses;[4] IMRT also improves sparing of local unaffected tissue.

Dose-painting, which is already in use in a few institutions, depends on the ability to visualise subvolumes of the tumour that are potentially radioresistant and then paint some additional dose restricted to those volumes. However, this is an all-or-nothing idea. Bentzen now proposes to plan treatment to adjust the dose on a pixel by pixel basis to conform to the degree of radioresistance within resistant volumes—on the level of hypoxia, on the rate of cell division, and on the level of tumour aggression. This is dose-painting by numbers, but at present it is a long way from practical application.

See page 112 for a **Personal View** on theragnostic imaging

Bentzen predicts that theragnostic imaging for radiation oncology will revolutionise the whole process of radiotherapy prescription and planning. At present, of course, the gains are strictly theoretical, since no clinical advantage has yet been shown for IMRT, much less for dose-painting by numbers. It is important not to be carried away with the enthusiasm for a new technology without a careful examination of the potential downside. In his *Personal View*, Bentzen deals with the two most frequently aired arguments against IMRT. The first, based on the complex IMRT technology, which offers many opportunities for error, is that quality assurance becomes too demanding. Bentzen deals adequately with this objection, citing effective quality-assurance programmes in clinical use on both sides of the Atlantic. However, Bentzen's answers for the second point, the predicted increase in radiation-induced secondary malignant disease in long-term survivors of IMRT, are less convincing. IMRT typically requires that the linear accelerator operates for two to three times as long as in conventional treatment, even longer for dose-painting. Linear accelerators leak radiation through the treatment head and collimator, so that a patient lying on a treatment couch receives a small total body dose in addition to the radiation concentrated in the tumour; this leakage radiation is doubled or tripled in the case of IMRT.

Bentzen quotes Hall and Wuu's estimate[5] that IMRT should increase the incidence of second cancers in patients surviving to 10 years to 1·75% compared with 1·0% after conventional radiotherapy, and that this small increase will be more than offset by the (as yet undocumented) gain in control of the primary tumour. But this estimate is for late-to-middle-aged patients, whereas IMRT is often used in children,[6] because of the immediate benefit of sparing healthy tissues from growth arrest. However, children are 10–15 times more sensitive to radiation-induced cancers compared with adults, altering the equation.[7] Although the gains in tumour cure are theoretical, the downside of an increase in radiation-induced cancers is almost a certainty in children and very likely in adults.

Bentzen has done a service to the specialty by discussing this exciting new research area in this most interesting and comprehensive *Personal View*, but I suspect it will be a while before dose-painting by numbers moves into the realm of evidence-based medicine.

Eric J Hall
Center for Radiological Research, Columbia University, New York, NY 10032, USA
ejh1@columbia.edu

I declare no conflicts of interest.

1 Bernier J, Hall EJ, Giaccia A. Radiation oncology; a century of achievements. *Nat Rev Cancer* 2004; **4:** 1–11.
2 Bentzen SM. Theragnostic imaging for radiation oncology: dose-painting by numbers. *Lancet Oncol* 2005; **6:** 112–17.
3 Ling CC, Humm J, Larson S, et al. Towards multidimensional radiotherapy (MD-CRT): biological imaging and biological conformality. *Int J Radiat Oncol Biol Phys* 2000; **47:** 551–60.
4 Intensity Modulated Radiation Therapy Collaborative Working Group. Intensity-modulated radiotherapy: current status and issues of interest. *Int J Radiat Oncol Biol Phys* 2001; **51:** 880–914.
5 Hall EJ, Wuu CS. Radiation-induced second cancers: the impact of 3D-CRT and IMRT. *Int J Radiat Oncol Biol Phys* 2003; **56:** 83–88.
6 Huang E, Teh BS, Strother DR, et al. Intensity-modulated radiation therapy for pediatric medulloblastoma: early report on the reduction of ototoxicity. *Int J Radiat Oncol Biol Phys* 2002; **52:** 599–605.
7 International Commission on Radiological Protection. Publication 60: 1990 recommendations of the International Commission on Radiological Protection. Oxford: Pergamon Press, 1990.