

radiotherapy is presently CT-guided three-dimensional conformal radiotherapy (3D-CRT), which enables targeting of the prostate with greater sparing of normal tissues. This technique allows escalation of the dose and increases disease-free survival.<sup>3</sup> With regard to androgen suppression, Radiation Therapy Oncology Group trials have confirmed the positive effect on survival of the combined approach, and both groups have optimised the role of neoadjuvant (6 months) and adjuvant (2–3 years) hormone therapy.<sup>4</sup> Hormone therapy alone has been assessed by the National Cancer Institute of Canada study, but the combination of radiotherapy and immediate androgen suppression is probably the best approach, as locoregional treatment plus tamoxifen is for locally advanced breast cancer.

I agree with Lane and colleagues and William Hrushesky that intermittent androgen suppression, which temporarily prevents the side-effects of hormonal therapy (eg, impotence, hot flashes), has to be assessed. First, we need to know the results of ongoing trials devoted to M1 disease, since we usually translate to less advanced disease the gain we obtain from the more advanced one. With respect to Lane and colleagues' preliminary data,<sup>5</sup> we ignore the breakdown of clinical and radiation data, and the cohorts of patients of this open study are quite small. Nevertheless we consider that a trial with a 2×2 factorial design, comparing 3D-CRT versus no 3D-CRT with continuous versus intermittent androgen suppression, is theoretically interesting, but it will face some pitfalls: locally advanced tumours are decreasing due to individual or mass screening; patients with locally advanced prostate cancer in the early 2000s have less tumour burden and are younger than those of the mid-1980s; and patients may be alarmed by our questioning of the role of radiotherapy, which is more and more tolerated and effective.

For locally advanced prostate cancers with high risk of relapse, I do not agree with Hrushesky that "less is more". Multivariate analysis has shown that, although the combined approach improves disease-free survival, more is required for moderately and poorly differentiated tumours.

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- 1 Fellows GJ, Clark PB, Beynon LL, et al. Treatment of advanced localized prostatic cancer by orchiectomy, radiotherapy, or combined treatment: a Medical Research Council Study. *Br J Urol* 1992; **70**: 304–09.

- 2 Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 1997; **337**: 295–300.
- 3 Pollack A, Zagars GK, Smith LG, et al. Preliminary results of a randomized radiotherapy dose-escalation study comparing 70 Gy with 78 Gy for prostate cancer. *J Clin Oncol* 2000; **18**: 3904–11.
- 4 Horwitz EM, Winter K, Hanks GE, et al. Subset analysis of RTOG 85-31 and 86-10 indicates an advantage for long-term vs short-term adjuvant hormones for patients with locally advanced nonmetastatic prostate cancer treated with radiation therapy. *Int J Radiat Oncol Biol Phys* 2001; **49**: 947–56.
- 5 Lane TM, Ansell W, Williams G, et al. Long term outcomes in patients managed with intermittent androgen suppression. *Br J Urol* 2002 (suppl 1): A82.

## Disarming Africa

Sir—Charles Wendo's report (August 17, p 554)<sup>1</sup> on the settlement of the long-standing wars of Africa is very encouraging, although he rightly warns that rebuilding the continent's health systems will take time.

Meanwhile, disposal of the small arms used in the various conflicts is essential. If new disputes arise in neighbouring countries, existing arms could be "recycled" to the disputants, as has regularly occurred in the past. Also, arms remain a direct threat to health. Civilian deaths from firearms continue after conflicts—eg, in domestic disputes and if children find and play with abandoned weapons.<sup>2</sup>

Attempts in the past by the United Nations to facilitate disarmament after regional conflicts have been disappointing. Most successful have been buy-back schemes in which compensation, perhaps in the form of retraining in agriculture, is offered to demobilising militias.<sup>3</sup>

Various measures to curb the market in the weapons supplying such conflicts were discussed at the UN Conference on the Illicit Trade in Small Arms in New York in July, 2001. Sadly, a legally-binding Convention to restrict trafficking was among the first multilateral international treaties to be obstructed by the George W Bush administration, although negotiations to bring it into being are continuing.

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- 1 Wendo C. Hope for health as Africa's wars subside. *Lancet* 2002, **360**: 554.
- 2 Meddings DR. Weapons injuries during and after periods of conflict: prospective cohort study. *BMJ* 1999; **315**: 1417–20.
- 3 Renner M. Small arms, big impact: the next challenge of disarmament. Washington DC: Worldwatch Institute, 1997: 47–54.

## Radiotherapy in soft-tissue sarcoma

Sir—In their report, Brian O'Sullivan and colleagues (June 29, p 2235)<sup>1</sup> compare the role of preoperative radiation therapy with that of postoperative radiation therapy for soft-tissue sarcomas of the limb.

An important point that was not entertained in this study is whether chemotherapy increases the rate of wound complications. This is an important question since chemotherapy—especially doxorubicin—is a major treatment option for this disorder. One of the main complications of radiation therapy associated with doxorubicin is "radiation recall". Skin reactions can be as mild as warmth and erythema,<sup>2</sup> but at times can involve desquamation and ulceration,<sup>3</sup> which may delay the healing process. For some limb sarcomas, chemotherapy is given before radiation and surgery to decrease the size of the tumour and surgical morbidity.<sup>4</sup> Whether recall reactions with doxorubicin occur with concurrent radiotherapy is unclear.

Nevertheless, the article is important because the prognosis for patients with sarcomas larger than 5 cm is inferior to those with tumours of less than 5 cm.<sup>5</sup> This finding is vital, because if the goal is palliation, then preoperative radiotherapy may not be the best approach.

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- 1 O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *Lancet* 2002; **359**: 2235–41.
- 2 Riggs CE. Antitumor antibiotics and related compounds. In: Perry MC, ed. The chemotherapy sourcebook. Philadelphia: Lippincott Williams and Wilkins, 2001: 234.
- 3 Donaldson SS, Glick JM, Wilbur JR. Adriamycin activating a recall phenomenon after radiation therapy. *Ann Intern Med* 1974; **81**: 407–08.
- 4 Edmonson JH, Petersen IA, Shives TC, et al. Chemotherapy, irradiation, and surgery for function-preserving therapy of primary extremity soft tissue sarcomas: initial treatment with ifosfamide, mitomycin, doxorubicin, and cisplatin plus granulocyte macrophage-colony-stimulating factor. *Cancer* 2002; **94**: 786–92.
- 5 Brennan MF, Alektiar KM, Maki RG. Sarcomas of the soft tissue and bone. In: Devita VT, ed. Cancer: principles and practice of oncology, 6th edn. Philadelphia: Lippincott Williams and Wilkins, 2001: 1874–75.

Sir—The randomised trial by Brian O'Sullivan and colleagues<sup>1</sup> would have been adequately powered to detect a difference in wound complications—its primary endpoint. Therefore, we cannot understand why the difference between the two groups in the incidence of serious wound complications (35% *vs* 17%) is regarded as significant, whereas an almost identical difference in overall mortality (15% *vs* 28%), or even in sarcoma-related deaths (7% *vs* 19%), qualifies as only “slightly better survival ( $p=0.0481$ )”. I am sure the authors have not just inversely related the significance of these results to the *p* value. The lower overall mortality is also internally consistent: the curves of preoperative radiotherapy group are always above those of the postoperative radiotherapy for local recurrence-free survival, distant relapse-free survival, or progression-free survival, although of course not having the power to lower the *p* value.

Preoperative radiotherapy could exercise survival benefit through several mechanisms including inhibition of angiogenesis at distant metastatic sites.<sup>2</sup> Before we dismiss it as a statistical quirk, it is essential that we await the long-term results of this trial and hopefully those of a much larger trial.

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- 1 O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *Lancet* 2002; **359**: 2235–41.
- 2 Hartford AC, Gohongi T, Fukumura D, Jain RK. Irradiation of a primary tumor, unlike surgical removal, enhances angiogenesis suppression at a distal site: potential role of host-tumor interaction. *Cancer Res* 2000; **60**: 2128–31.

#### Authors' reply

Sir—We acknowledge that other adjuvant treatments for sarcoma, such as chemotherapy, may have their own side-effects and complications, but their effect is often confounded by the combined use of several of these therapies. In our study, chemotherapy was not used and we cannot comment specifically from these results. Meric and colleagues<sup>1</sup> compared morbidity associated with radical surgery in soft-tissue sarcoma in 104 patients who received induction chemotherapy before surgery and 204 patients who had surgery first. The incidence of surgical complications was not different for patients undergoing preoperative chemotherapy from

patients who had surgery alone, in those with sarcomas of the limbs (34% *vs* 41%) and in those with retroperitoneal or visceral sarcomas (29% *vs* 34%).

With respect to “radiation recall”, we appreciate that this could cause difficulties for groups that use chemotherapy frequently and where scheduling issues of the type mentioned by Christian Schultheis and colleagues render it more likely. On the other hand, as they point out, the occurrence of such reactions is controversial and the data shown above indicate that much of the risk for surgical morbidity is unlikely to be due to chemotherapy on its own.

Finally we accept that a cut-point at 5 cm definitely declares patients at different risk of adverse outcome. Nevertheless, we do not consider that patients with lesions of greater than 5 cm should generally receive palliative approaches since a large proportion of such patients can be cured of their sarcoma.

Jayant Vaidya and Fausto Palazzo correctly note that our trial was powered and designed to detect a difference in major wound complications in soft-tissue sarcomas of the limbs undergoing preoperative or postoperative radiotherapy. Indeed, the trial was designed to be stopped early if the primary question was answered at an interim analysis after the midpoint of accrual (which is what took place). However, for practical reasons, the trial was not designed with sufficient power to reliably assess secondary endpoints such as survival and cancer-specific outcome.

Our reason for not emphasising the secondary endpoint was that our sample-size estimation was based on wound complication not overall survival. The observed significance should be adjusted for early comparison to avoid the possibility of potential bias due to small numbers of events, and the *p* value for survival should not be interpreted at its face value and must be interpreted with caution. Additionally, the *p* value is for time to event, based on the survival curve presentation for the secondary endpoints referred to, and not on the proportion of events which are different analytic approaches. Also, as we noted in the paper, the timing of the survival analysis was not specified before the trial started, whereas the primary endpoint analysis was clearly built into the trial design.

We respect Vaidya and Palazzo's comments concerning survival benefit. The biology of cancer and metastasis is complex and mediated

by numerous factors and pathways<sup>2,3</sup> that could be influenced at many levels. They mention angiosuppression by radiation,<sup>4</sup> but other mechanisms could also apply. The point is that we do not know. Future research is needed and, as Vaidya and Palazzo point out, longer follow-up from our trial and other trials. In the meantime we should not overinterpret the results that are available.

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- 1 Meric F, Milas M, Hunt KK, et al. Impact of neoadjuvant chemotherapy on postoperative morbidity in soft tissue sarcomas. *J Clin Oncol* 2000; **18**: 3378–83.
- 2 Blobel GC, Schiemann WP, Lodish HF. Role of transforming growth factor beta in human disease. *N Engl J Med* 2000; **342**: 1350–58.
- 3 Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000; **100**: 57–70.
- 4 Hartford AC, Gohongi T, Fukumura D, Jain RK. Irradiation of a primary tumor, unlike surgical removal, enhances angiogenesis suppression at a distal site: potential role of host-tumor interaction. *Cancer Res* 2000; **60**: 2128–31.

## Neonatal resuscitation for small for gestational age babies

Sir—In 2000, the International Cardiopulmonary Resuscitation and Emergency Cardiac Care conference formulated evidence-based recommendations for neonatal resuscitation.<sup>1</sup> The next conference to update these guidelines will be held in 2005. More up-to-date recommendations come from the Neonatal Resuscitation Program of the American Academy of Pediatrics.<sup>2</sup> One important issue that is not adequately addressed by international guidelines is use of radiant warmer and supportive care in small for gestational age babies.

Difficulties often arise when a baby is born at term with a low birthweight (<2500 g). As many as 30 million low birthweight babies are born each year—about 90% in developing countries.<sup>3</sup> Small for gestational age babies are at increased risk of birth asphyxia, hypothermia, hypoglycaemia, polycythaemia, infection, and death.<sup>4,5</sup> However, international guidelines place little emphasis on how to care for these infants. To improve neonatal care, international guidelines must be revised to include all low birthweight babies as an indication for assessment