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Letters

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Letters to the Editor: Comments on *A Case of Radiation Myelopathy After 2 × 8.5 Gy for Inoperable Non-small Cell Lung Cancer*, Dardoufas *et al.*, *European Journal of Cancer*, 31A, Nos 13/14, pp. 2418–2419, 1995

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AN ALTERNATIVE explanation for the radiation myelopathy seen in a patient described by Dardoufas and colleagues [1] is that when radiotherapy is given as a parallel opposed pair with equal weighting on both beams, the midplane dose (mpd) is actually the minimum dose within the volume. Those parts of the volume closer to the entry point of either beam, such as the cord, actually receive higher doses.

Dardoufas and colleagues do not state the antero–posterior (AP) separation, but from the MRI illustration, the affected part of this man's cord was 5 cm below the surface. Using depth dose data from our 8 MV linear accelerator, an appropriate equivalent square actual cord dose at common AP diameters of chests is, at 20 cm, 8.65 Gy/fraction (plus 1.75%) and, at 25 cm, 8.93 Gy (plus 5.1%) of mpd and the discrepancy becomes greater with larger separation.

Using the same range of α/β ratio for late effects on cord of 1–2, the equivalent cord dose actually given to the cord is 44.6–53.8 Gy at 2 Gy/fraction for 17 Gy, but the received equivalent dose to cord in patients with a 20 cm separation is 46.1–55.7 Gy (plus 3.3%), and at a 25 cm separation 48.8–59.1 Gy (plus 9.5%). The biological effect is greater than expected if both total dose and dose per fraction are increased.

The cord tolerance dose is of crucial importance to radiation oncologists but is not precisely known. Schultheiss and Stephens suggest a threshold dose for radiation myelopathy of 50 Gy in 2 Gy fractions and estimate the dose required for a 5% risk of myelopathy at 5 years to be 57–61 Gy [2]. Emami and colleagues [3] estimate the dose for 5% myelopathy at 5 years to be 50 Gy for cord lengths of up to 10 cm.

There are some uncertainties extrapolating linear quadratic isoeffect formulae to very low numbers of fractions, but the actual dose to cord in this patient seems compatible with common estimates of dose sufficient to cause myelopathy without invoking any special mechanisms, and draws attention to variation in doses throughout the volume when prescribed to parallel opposed fields.

1. Dardoufas C, Plataniotis GA, Damatopoulou A, *et al.* A case of radiation myelopathy after 2 × 8.5 Gy for inoperable non-small cell lung cancer. *Eur J Cancer* 1995, **31A**, 2418–2419.
2. Schultheiss TE, Stephens L. Permanent radiation myelopathy. *Br J Radiol* 1992, **65**, 737–753.
3. Emami B, Lyman J, Brown A, *et al.* Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991, **21**, 109–122.

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WE WERE interested to read the case report by Dardoufas and colleagues (*Eur J Cancer* 1995, **31A**, 2418–2419), describing a case of radiation myelopathy (RM) following the use of the 2 × 8.5 Gy regimen for inoperable non-small cell lung cancer.

We have recently reported on the experience of this problem in three randomised trials run by the Medical Research Council Lung Cancer Working Party (*Clin Oncol*, in press). We identified 3 cases with clinical features suggestive of RM out of a total of 524 patients who received this regimen. We calculated the cumulative risk of RM to be 0.6% and 2.2% at 1 and 2 years, respectively, and suggested that α/β for human spinal cord is approximately 2 Gy.

We would like to comment on the radiobiological analysis made in the letter of Dardoufas and colleagues. It is incorrect to assume that the spinal cord will receive the same dose as that prescribed to the midplane (mpd). Because the spinal cord lies approximately 5 cm from the posterior surface, the dose received may be anything from 2 to 10% higher than the mpd, depending on the beam energy and antero–posterior (AP) separation. There may also be variation in AP separation in the superior–inferior direction. In our analysis, we assumed that the dose to the spinal cord might on average be 5% greater than the dose to mpd.

Table 1 shows the calculated values for the equivalent dose

Table 1. Values of biologically equivalent dose (LQED2) to spinal cord for the regimen of 17 Gy in two fractions, for different values of α/β and different percentage increases of cord dose above midplane dose (mpd)

Increase in spinal cord dose over mpd (%)	Fraction size (Gy)	LQED2 $\alpha/\beta = 1$	LQED2 $\alpha/\beta = 1.5$	LQED2 $\alpha/\beta = 2$
0	8.5	53.8	48.6	44.6
5	8.93	59.1	53.2	48.8
7.5	9.14	61.8	55.5	50.9
10	9.35	64.5	58	53.1

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if given in 2 Gy fractions (LQED2) for different values of α/β and the percentage increase in dose above mpd. Firstly, this shows that the calculations of Dardoufas and colleagues are misleading. For $\alpha/\beta = 1$, the LQED2 for $8.5\ Gy \times 2$ is less than 55 Gy and for $\alpha/\beta = 1.5$ less than 50 Gy. Secondly, if as is reasonable to assume, the cord dose will on average be 5% greater than mpd and $\alpha/\beta = 2$, then LQED2 will be approximately 48–49 Gy. In their review of the radiation response of the spinal cord, Schultheiss and Stephens considered the risk of RM with 45 Gy in 2 Gy fractions to be 0.2% [1].

As a result of this, we believe that there is a small and clinically significant risk of RM to the normal population if the regimen is used without taking precautions over the dose to the spinal cord. It is not necessary to invoke intrinsic idiosyncratic hypersensitivity to explain these cases as was suggested by Dardoufas and colleagues.

Oncologists who often treat patients with this regimen will see RM from time to time. If it is felt that the undoubted efficacy and convenience of the regimen justify its use, then the dose to the cord should be reduced. Our practice in Glasgow has been to shield the cord from the posterior field with a 2 cm midline block for the second fraction. This reduces the dose to the cord to about 16 Gy. There is a theoretical risk that the palliative efficacy will also be reduced, but the symptomatic disease is usually away from the midline. We have employed this technique for the past 4 years in over 400 patients and have seen no further cases of RM.

1. Schultheiss TE, Stephens LC. Invited review: permanent radiation myelopathy. *Br J Radiol* 1992, **65**, 737–753.

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Breast Metastases of Merkel Cell Carcinoma

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THERE IS increasing interest in Merkel cell tumours. This rare but very aggressive neuroendocrine carcinoma of the skin, which mainly occurs in elderly patients, was first described by Toker [1]. Some 100 cases have been reported in the literature over the past 30 years. The Merkel cell carcinoma has distinct ultrastructural and immunohistochemical characteristics. Demonstration of membrane-bound dense-core neurosecretory granules by electron microscopy, or immunohistochemical proof of neuron-specific enolase are required for diagnosis [2, 3].

The tumour has a very aggressive behaviour with frequent local recurrences, regional lymph node metastases and distant metastases, eventually leading to death. Merkel cell carcinomas mainly occur in the head and neck region of elderly patients, but also in other sites. Despite the chemo- and radiosensitivity of the tumour, optimal management has not yet been defined. Distant metastases may occur in lymph nodes, CNS, lung, liver and the skin [3–5]. We report here on 2 female patients with metastases of the breast. Clinical behaviour and treatment options will be outlined.

Case 1

An 85-year-old woman presented with a symptomless tumour on her right eyebrow. The radically excised mass measured 1.8 cm in diameter. After one month, a local recurrence appeared which was re-excised. Five months later three regional cutaneous metastases were removed and the patient was referred for radiotherapy. She had locoregional ^{60}Co external beam irradiation with 50 Gy including the right cervical lymph nodes and additional 10 Gy boost to the scars. Six months later multiple metastases appeared on her left cheek which were excised and the same postoperative radiotherapy was delivered. After several months, a painless mass in her right breast was detected at follow-up examination. Mammography revealed a round tumour measuring 1.5 cm. This lesion was excised under the assumption of a primary breast cancer but histopathological examination showed metastases of Merkel cell carcinoma. Postoperative radiotherapy of the whole breast was delivered with 50 Gy using CT-based individual treatment planning. The patient died one year later from intercurrent disease without local recurrence in the breast, but with recurrence on her left cheek.

Case 2

An 84-year-old woman presented with an axillary mass without detectable breast cancer. After axillary clearing, the histopathological diagnosis was metastases of a Merkel cell tumour. The patient subsequently reported that a tumour of 1.5 cm on her forearm had been removed 4 months previously. A review of the pathological specimen showed that this was the primary. An axillary recurrence occurred 3 weeks before radiotherapy was initiated. This recurrence was irradiated including the axillary, supra- and infraclavicular nodes with a dose of 60 Gy. The tumour regressed completely. CT and MRI did not show a lesion in the breast. Four months later the patient developed metastases in the oropharynx and cervical lymph nodes which again were irradiated with 60 Gy. The patient was then seen for regular follow-up in 4 week intervals. Three months after radiotherapy of the oropharynx, she presented with a lump in the right breast of 12×10 cm and two local skin metastases. She underwent radical mastectomy but during wound healing several locoregional metastases appeared which were subsequently excised. The patient died from abdominal dissemination 23 months after the diagnosis of the primary tumour.

Merkel cell carcinoma is seen in age groups ranging 7–96 years, but most of the patients tend to be elderly. The initial lesion is usually a small prominent nodule with pink or bluish

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