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Letters to Editor

'Tumour volume'

Sir

We were interested to read the paper on survival after resection of non-small-cell lung cancer (NSCLC) in relation to 'tumour volume' by Jefferson et al (1996).

By multiplying together the three dimensions of each tumour, the authors have assumed that the carcinomas are box shaped. The accuracy of this assumption was not validated. In a study of 54 resected lung cancers (Binks et al, 1996), we found that the most appropriate measures of tumour volume were to assume that the tumours were ellipsoidal or boxes. These measurements compared well with our gold standard methods (R = 0.887 and R = 0.910 respectively) of sequential 1-mm or 1-cm slices, for which the tumour area was measured and the volume derived from the sum of the areas. In contrast, measurement of the maximum dimension and assuming a spherical shape grossly overestimated the volume of some tumours (R = 0.632).

Although we expected ellipsoidal measurements to be more accurate than boxes, this was not the case. We support the authors statement that tumour volume is a useful piece of information that is easily collected, but three dimensions should always be measured for solid tumours.

Yours faithfully

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High-dose 5-fluorouracil infusional therapy is associated with hyperammonaemia, lactic acidosis and encephalopathy

Sir

Keywords: high-dose 5-fluorouracil; encephalopathy

Recently, weekly 24-h infusion of high-dose 5-fluorouracil (5-FU) and folinic acid has become a popular regimen (Ardalan et al, 1991; Aranda et al, 1995; Leichman et al, 1995). Although unusually high doses, up to 2600 mg m^{-2} per week of 5-FU and 500 mg m^{-2} per week of folinic acid, were administered, the toxicities of myelosuppression and mucositis were surprisingly low. In our institution, chemotherapeutic protocols incorporating 24-h infusion of high-dose 5-FU (2600 mg m^{-2} per week) and leucovorin (300 mg m^{-2} per week) (HDFL) have been used in treatment of various cancers, including colorectal cancer, gastric cancer, breast cancer, urological cancer, and head and neck cancer (Yeh et al, 1994*a*). Our experience of the treatment-related toxicities of HDFL has largely been in keeping with those reported by Ardalan et al (1991), except an unusual encephalopathy which first came to our attention in 1992 (Yeh et al, 1994*b*). Since then, we have encountered a spectrum of encephalopathy, including disorientation, confusion, agitation, neurosensory hearing impairment, seizure, stupor and deep coma, associated with the use of HDFL regimens. This encephalopathy was unique in that its development and severity were closely related to the emergence of hyperammonaemia and lactic acidosis. Thus, it should be distinguished from other 5-FU-associated toxicities previously reported.

Among 280 patients who had received HDFL in our institution between 1991 and 1995, 16 (5.7%) developed HDFL-related encephalopathy. The diagnostic criteria included: (1) development of encephalopathy *during* or *shortly after completion* of HDFL administration; (2) exclusion of other metabolic or physical factors that may have an effect on the consciousness level, such as hyperglycaemia, hypoglycaemia, azotaemia, hepatic failure, electrolyte imbalance, sepsis and central nervous system involvement of cancers; and (3) exclusion of a drug effect by concomitant medications. The incidence of this complication was highest in gastric cancer (12.1%), followed by breast cancer (4.3%) and colorectal cancer (2.4%). Thirteen (81.3%) of 16 patients had severe symptoms of stupor or coma; in two patients these symptoms were combined with seizure. Severe (grade III–IV) nausea and vomiting and a Kussmaul's respiration were noted in 15 (93.8%) and 16 (100%) patients respectively during the attack of encephalopathy. The median time of onset of encephalopathy was 19.5 h (range 10–30 h from the start of HDFL infusion, and the median duration of encephalopathy between discontinuation of HDFL and complete recovery was 15 h (range 3–72 h). All patients recovered completely, except one who developed a bilateral neurosensory hearing impairment that recovered partially. Electroencephalogram (EEG) examinations of eight patients revealed diffuse cortical dysfunction with diffuse slow waves or diffuse intermittent theta waves, suggesting metabolic or toxic encephalopathy. Since our first experience of this complication in 1992 (Yeh et al, 1994*b*), arterial blood gas, plasma ammonia and plasma lactic acid were routinely examined in the patients who had developed encephalopathy. Hyperammonaemia (149 to >500 μmol l^{-1}, median 345) (reference level 19–43 μmol l^{-1}, checked by ammonia-selective electrode), lactic acidosis (4.0 to > 12 mg dl^{-1}, median 9.2) (reference level 0.3–1.3 mg dl^{-1}) and hypocapnia (pCO_2 15–30.1 mmHg, median 18.6) (reference level 35–45 mmHg) were found to parallel the development of encephalopathy.