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Letter to the Editor

Radical Irradiation of Localized Inoperable Lung Cancer with Concurrent Chemotherapy and Misonidazole: a Phase I/II Study

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TUMOURS contain hypoxic cells which are relatively resistant to irradiation. An initial course of fractionated irradiation was followed by concurrent administration of radiation, chemotherapy [1,2-chloroethyl-3-cyclohexyl-1-nitrosourea (CCNU) and mitomycin C] and a radio- and chemosensitizer (misonidazole) aimed at sterilizing the presumed persisting clonogenic hypoxic cells.

Twenty patients with inoperable non-small cell lung cancer were entered into the study between March 1983 and November 1984. The study was approved by our regional ethical committee and informed consent was obtained from all patients. The patient had T3 and/or N2 disease [1] without metastases (MO). The median age was 61 years (range 40–75 years). The median forced expiratory volume in 1 s (FeVI) at presentation was 1630 ml (range 860–2800 ml).

The initial radiation fractionation schedule consisted of 3, 6 Gy fractions × 8 with three fractions per week (because of therapy unit availability at the time of the study). This was followed by 6 Gy × 2 (1/week). MISO was administered orally at a dose of 3.0 g/m^2 4 h prior each radiation fraction of 6 Gy and the cytotoxics 2 h prior each fraction of 6 Gy. The dose of CCNU was 60 mg/m^2 orally and the dose of mitomycin C was 10 mg/m^2 with each of the two fractions.

Irradiation was given with opposed anterior and posterior portals with shielding of the spinal cord posteriorly after six fractions.

The 1 year survival rate (life table) was 60% and the 2 year survival rate 15%. Two of the three patients who were alive at 2 years subsequently died of disease. First relapse was lung disease within the radiation port in eight patients, lung disease outside the radiation port in six patients and with cerebral metastases in five patients.

A complete response was noted radiologically in five patients and a partial response (50% decrease of the surface area of the tumour on chest X-ray) in eight patients for an overall response rate of 65%. The overall median survival was 15 months. The median survival in patients with a complete response, partial response and no response was 18, 15 and 11 months, respectively. The difference in survival between the responding and non-responding patients was not statistically significant (log-rank $P < 0.08$).

The nadir of the white blood and platelet count occurred between 4 and 6 weeks after therapy. The median nadir of the white blood count was 2800/mm^3 (range of 500–55,000/mm^3). The median nadir of the platelet count was 135,000 (range of 28,000–429,000).

The median radiation portal size was 12 cm^2 equivalent (range 9–14 cm^2 equivalent). The median serial FeVI lung function tests in patients alive at 12 months were 1620 ml at presentation, 1760 ml at 6 and 1570 ml at 12 months follow-up. This is interpreted as indicating an initial improvement in lung functions because of therapy

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followed later by a deterioriation in lung functions with the onset of radiation induced lung fibrosis. The latter was not thought to be more severe than that noted with radiation alone.

There has been one major late complication. A patient developed radiation myelitis 9 months after therapy which resulted in a spastic paraplegia. This complication has not been previously seen at our clinic in patients treated with radiation alone with similar biological effective doses to the spinal cord. The patient was a disguised alcoholic. She died 21 months after presentation and a *post mortem* examination revealed persistent local lung cancer without metastases and extensive centrilobular liver necrosis.

In a study in experimental mice, the combination of MISO, CCNU and irradiation resulted in significantly improved tumour responses when compared with the use of only two of the modalities [2]. Mitomycin C had been shown to be preferentially cytotoxic to hypoxic cells *in vitro* [3] at the time of the design of this study. This has not subsequently been verified *in vivo* [4].

It is concluded that the use of concurrent chemo- and radiotherapy together with MISO has in this study resulted in a major complication and the survival rates do not warrant further evaluation in a phase III study.

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