but we fail to discuss the implications of a possible increase in metastatic potential of tumour cells which have recovered from hypoxic exposure [2].

Unfortunately, Senan has somewhat misinterpreted our comments. Our editorial was an attempt, based on experimental results, to suggest possible ways in which radio-resistant acutely hypoxic cells may be eliminated. Such hypoxic cells have now been shown to normally occur in tumours [3]. The methods suggested were either to use certain drugs to actually prevent acute hypoxia from happening; to employ treatments which can directly kill these cells or sensitise them to radiation; or finally make these acutely hypoxic cells chronically hypoxic and then attack them with hypoxic cell cytotoxins which preferentially kill such cells. If, with this latter treatment, some of the hypoxic cells are not killed by the cytotoxin, then it is possible that they may become re-oxygenated or remain hypoxic. The ultimate fate of these surviving cells will depend on what treatment was used to make the tumour hypoxic in the first instance. If the hypoxia was induced by agents that damage tumour vasculature, then the resulting hypoxia could last for 24 h or longer [4], thus any cell surviving subsequent treatment with the hypoxic cell cytotoxin could remain hypoxic long enough to have the potential to interfere with any conventional therapy likely to be used against the aerobic population. However, physiological modifiers of tumour blood flow result in hypoxia lasting only a few hours [4]. With hydralazine, for example, which is the agent we use to illustrate our proposal, tumour blood flow is substantially reduced and results in full radiobiological hypoxia which lasts for less than 2 h [5]. This is more than sufficient time to enhance the action of hypoxic cell cytotoxins like hyperthermia [5] and bioreductive drugs [6] and, therefore, physiological modifiers of tumour blood flow are probably the best way to induce chronic hypoxia in tumours.

It has been shown experimentally that prolonged exposure of tumour cells to hypoxia [7] or acidosis and glucose starvation [8] may increase their metastatic potential when they are subsequently incubated in normal aerobic conditions, but the exposure times to these adverse conditions were for 18–24 h. Moreover, one study suggested that at least 6–12 h exposure under hypoxic conditions was necessary before any increase in metastatic potential was seen [9]. This is not an acute exposure as Senan suggests and it is far longer than the chronic conditions we recommend, so although long-term hypoxia followed by reoxygenation may lead to an increase in metastasis, it has no relevance to our proposals.

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Overcoming Tumour Radiation Resistance Resulting from Acute Hypoxia

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IN DISCUSSING the induction of acute hypoxia in tumours as a means of exploiting hypoxic cytotoxins, Horsman and Overgaard [1] have mentioned both the lack of consistent reduction in blood flow by the currently available agents and the often prolonged period (greater than 24 h) of resulting reduction in blood flow. They fail, however, to discuss the implications of a possible increase in metastatic potential of tumour cells which have recovered from hypoxic exposure.

Following a period of *in vitro* reoxygenation, cells isolated from the hypoxic regions of murine tumours (identified by proximity to functional vasculature) have been shown to have an increased lung colonisation ability [2]. In addition, a 24–48 h recovery from acidosis or glucose starvation has been shown to result in a marked (30-fold) increase in metastatic ability [3]. The changes in metastatic potential associated with cells cycle position were between 0.5- and 2-fold following hypoxic exposure, and cannot account for this finding [3]. All three conditions (hypoxia, acidosis and glucose starvation) have been shown to introduce a class of stress proteins [4] which may confer a survival advantage in adverse conditions, including the metastatic process.

These findings are relevant as resumption of blood flow following the induction of acute hypoxia will allow tumour cells access to blood vessels. With highly selective hypoxic cytotoxins such as SR-4233 and E09 currently undergoing clinical trials, the option of inducing acute hypoxia in an attempt to increase tumour cell kill must be approached with caution.

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