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Regional hyperthermia: new standard for soft-tissue sarcomas?

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In this issue of *The Lancet Oncology*, Issels and colleagues[1] describe a large, randomised phase 3 study assessing the effects of local hyperthermia in addition to chemotherapy and local therapy (surgery whenever possible with or without radiation) in a group of selected patients with intermediate or high-grade soft-tissue sarcomas greater than 5 cm, and deep.[1] The trial was a multicentre study, although three institutions with major previous experience of using hyperthermia contributed 310 of the 341 patients, with the remainder distributed among another six centres. Including this small subset of patients had no effect on the results, and the reader is left to wonder whether the findings of the study could be extrapolated for widespread use or whether the technique should be limited to centres of expertise. If hyperthermia is to be considered a standard treatment, studies of more than 31 patients in six centres are needed.

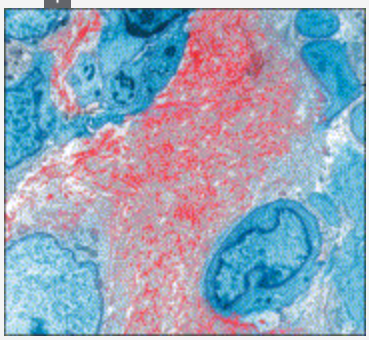
Any attempt to extrapolate the data to a typical group of soft-tissue sarcomas should be avoided. Issels and colleagues' series was heavily weighted towards retroperitoneal sarcomas, where local recurrence is the primary reason for treatment failure, and local progression is a major cause of death.[2] None of the series referenced by Issels and colleagues contains such a preponderance of retroperitoneal tumours. The main local adjuvant treatment for soft-tissue sarcomas is radiation, which often cannot be administered to large retroperitoneal tumours, particularly postoperatively. The high local recurrence rate seen even in patients with extremity sarcomas might be due to the fact that radiation was given only to patients with R1 or R2 resections, while it would be standard practice for the tumours included in this study, at least in North America. The risk reduction from the addition of hyperthermia to radiation was less than 0·2, and was not statistically significant.

Owing to the extremely high number of local recurrences in this series, the data on disease-free survival are superfluous, and could mislead those who would apply the data to other series where disease-free survival is highly influenced by freedom from metastasis.

The authors present a survival analysis of patients who had sarcomas and received the induction therapy prescribed by the protocol unless they progressed before. That analysis shows different results from the intention-to-treat analysis presented in the body of the manuscript. I applaud this inclusion: it matters whether the patient had the disease under study and what treatment was given rather than what treatment was planned. Should this not be the standard for all analyses rather than the statistically correct but clinically misleading approach of intention-to-treat?

So, should hyperthermia become the new standard in treating soft-tissue sarcomas? Not yet. The authors provide compelling evidence that it should be considered carefully as a potential advance in the management of retroperitoneal sarcomas, at least for those where local failure is crucial to survival; but patients with atypical lipomatous tumours (ALT; also known as well differentiated liposarcomas), where

this is most crucial, were excluded from the trial. Two new studies would be needed before hyperthermia can take its place in standard sarcoma management. The most important would look only at hyperthermia in addition to preoperative radiation for retroperitoneal tumours that could be irradiated, or without radiation for those deemed unsuitable to receive it. The study should include patients with ALT and stratify accordingly. A more contemporary preoperative and postoperative chemotherapy regimen could be included for those with high-grade tumours. The second, necessary only if the first were positive, would look at the same question for extremity tumours. The studies would need to be done with adequate numbers of patients treated at centres other than those currently specialising in this technique. At present, we know only that local control is improved by hyperthermia in patients whose tumours are inadequately managed by surgery alone, and who are treated at centres of expertise with experience of regional hyperthermia.



Full-size image (29K) National Cancer Institute/SPL Download to PowerPoint

The author declared no conflicts of interest.

References

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2 Gronchi A, Casali PG, Fiore M, et al. Retroperitoneal soft tissue sarcomas: patterns of recurrence in 167 patients treated at a single institution. *Cancer* 2004; **100**: 2448-2455. PubMed

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