



Radiotherapy plus hyperthermia shows effectiveness in painful bony metastases – indicated only for selected patients with extended live expectancy and radiotherapy resistant tumor!

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Introduction

Solid tumors are known to frequently metastasize to the bony structures with incidence varying strongly by tumor type and stage (1). Having bone metastasis is associated with a poor prognosis and a survival expectancy of several months. Bone metastases have a large impact on the quality of life as they cause severe and debilitating effects, like pain, spinal cord compression, hypercalcemia, pathologic fractures and neurologic deficits (1-3). Radiotherapy has an important role in the treatment of bone metastases. It is recognized for its low incidence of side effects and considered time efficient.

Most recently, the first randomized controlled trial to investigate the benefit of external beam radiotherapy combined with hyperthermia *vs.* external beam radiotherapy in the treatment of patient with painful bony metastases was published (4). The authors motivated their study by the short duration of the pain-free period: 50% of the patients experienced pain relapse after 12 weeks. In an attempt to improve response rate and duration they considered addition of hyperthermia to external beam radiotherapy a promising option to enhance treatment effectiveness.

Hyperthermia has long been recognized as one of most potent cellular sensitizers for radiotherapy and chemotherapy. During hyperthermia the tumor is heated to 40–44 °C for 30–90 minutes and is repeated once or twice weekly during radiotherapy or chemotherapy. Hyperthermia

induces various biological and physiological effects. All effects depend on the applied thermal dose, i.e., temperature and time, often reported as cumulative equivalent minutes at 43 °C expressed as CEM43T90 (5). Direct cytotoxicity and sensitization of radiation typically occurs at tumor temperatures above 43 °C. Tumor temperatures from 41 to 43 °C are required to inhibit DNA damage repair by affecting the homologous recombination and non-homologous end joining pathways (6). At lower temperatures, 40–42 °C, hyperthermia increases perfusion, causing increased tumor oxygenation as well as improved drug delivery (7). Multiple, randomized controlled trials have demonstrated that adding hyperthermia increases the effectiveness of radiotherapy and chemotherapy for a large variety of tumor pathologies (8,9). Currently, addition of hyperthermia to radiotherapy, i.e., thermoradiotherapy, is commonly considered regular treatment for recurrent tumors in previously irradiated areas (9). In some European countries thermoradiotherapy is available as first line treatment for patients with locally advanced cervical cancer (10). The combination of chemotherapy and hyperthermia finds a growing application for patients with high-risk soft tissue sarcoma (11), high risk non-muscle invasive bladder cancer (12), hyperthermic intraperitoneal chemotherapy (13,14) and in children and adolescents with refractory or recurrent non-testicular malignant germ-cell tumors (15). Overall, the trials show that adding hyperthermia to radiotherapy and/or chemotherapy can result in an

impressive improvement in treatment outcome, i.e., enhanced local control, prolongation of disease free survival or even a doubling of overall survival (8-10), under the condition that good quality hyperthermia is applied (16).

Chi *et al.* (4) have to be commended for conducting their phase III study in which they randomized patients with painful bony metastases between radiotherapy-alone, 30 Gy in 10 fractions in 2 weeks (RT-alone), and radiotherapy plus hyperthermia (RT + HT). Hyperthermia was applied for 40 minutes, 2 fractions per week and 4 totals, using the Thermotron RF-8 device. Hyperthermia intensity was according the principle of maximum acceptable power level, i.e., RF-power input is increased until the patient complains of discomfort. Temperatures during hyperthermia were measured at tumor indicative locations. In three patients direct intratumoral temperature was measured, average highest tumor temperature: 41.9 ± 1.2 °C.

Patients were randomized to RT-alone (n=28) and RT + HT (n=29). At 3 months after treatment the RT + HT patient group showed a significant higher complete response (CR) than the RT-alone group, i.e., 37.9% *vs.* 7.1% [P=0.006; CR defined as a zero score on the Brief Pain Inventory (BPI)]. Also, the accumulated CR at the third month after treatment was higher for the RT+HT group, i.e., 58.6% *vs.* 32.1% respectively (P=0.045). Besides an improved CR-rate the study also reports a statistically significant prolongation of duration of pain relief: median time to pain progression was 7.9 weeks for the RT-alone group, while for the RT + HT group median time to progression was not reached after the 24 weeks of observation. In the group of patients with radiologic response evaluation a higher response for the combined treatment arm at week 12 was noted: complete plus partial radiological response for RT+HT was 11/15 *vs.* RT-alone 3/12.

How to continue?

No doubt, the study of Chi *et al.* (4) is another confirmation of the great potential of hyperthermia to boost the effectiveness of radiotherapy. Their findings are in good agreement with many other phase III studies. However, identifying whether and how this study will contribute in the design of future protocols is less clear. Chi *et al.* (4) conclude that additional prospective trials are still needed to better define the role of radiotherapy plus hyperthermia for the treatment of bony metastases. In this respect, the decision of the safety monitoring committee to

early terminate the study appears to be premature. As a consequence, comparison of the results between RT-alone and RT + HT is limited to two small groups, which constrains the statistical persuasiveness of the study (17,18).

The small sample size makes it also difficult to position the results of Chi *et al.* (4) in a broader perspective. Internationally, there is common acceptance that radiotherapy provides successful palliation of painful bone metastasis in 50–80% of patients, with up to one-third of patients achieving complete pain relief at the treatment site. Complete or partial pain relief is typically experienced within 4 weeks after radiotherapy with a mean remission duration of approximately 19 weeks (2,3). In the Chi *et al.* (4) study the accumulated rate of complete pain relief of 58.6% for RT + HT and 32.1% for RT-alone appear to be at the lower range of the response reported in literature. A similar remark appears appropriate with regard to duration of pain remission for the RT-alone group (7.9 weeks), whereas with >24 weeks the duration of pain remission in the RT + HT group is in the higher range of the literature values. However, the exact response rate is of course fully defined by the specific composition of the patient group and therefore comparison to literature values might not be valid.

Is it realistic and feasible to add hyperthermia to modern palliative radiotherapy in which the growing preference is to treat patients with severe pain complaints, by a single 8 Gy fraction?

Discussion on what should be the optimum number of radiotherapy fractions is still ongoing. In recent years, several reviews comparing multiple radiotherapy schedules with varying fraction numbers and radiotherapy dose have been published (19,20). The ASTRO guideline for palliative radiotherapy for bone metastases (3) concludes that “*numerous prospective trials have shown that 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions but also 8 Gy in a single fraction provide excellent pain control and minimal side effects*”. As single fraction radiotherapy is highly convenient for the patient, modern palliative radiotherapy is characterized by a growing preference for a single 8 Gy fraction schedule.

Based upon the biological mechanisms of hyperthermia one could argue that adding hyperthermia to radiotherapy in high fraction schedules is advantageous over a single fraction. In the current 10 RT-fraction schedule the

observed improved treatment outcome reflects at least two biological mechanisms induced by hyperthermia: improved oxygenation through increased perfusion and reduced repair of DNA damage. For single fraction radiotherapy plus hyperthermia (with hyperthermia after radiotherapy), the thermal enhancement will be mainly through the reduced DNA-repair effect (21). The latter put stronger demands on the minimum required tumor temperature ($T > 41$ °C) to effectively obstruct DNA repair. Hence, a new trial is required to demonstrate whether the beneficial effect of adding hyperthermia to single fraction radiotherapy will remain.

Tolerance to hyperthermia by patients treated by single fraction 8 Gy radiotherapy?

Treatment tolerance for patients with painful bone metastases is severely compromised. In general, the patients have a poor condition (WHO performance status ≤ 2) and a poor prognosis with short life expectancy. These patients benefit strongly from a fast, comfortable and effective treatment procedure, i.e. single fraction 8 Gy radiotherapy. The poor condition of this specific patient group seems to be in conflict with the essential requirements to apply a high-quality hyperthermia: the patient should be able to lay still and tolerate local heating to 41–42 °C during 30–60 minutes. In most of these patients' pain complaints will be high which will degrade the quality of hyperthermia (22,23).

Single 8 Gy radiotherapy plus hyperthermia only for selected patients!

In our experience for patients with painful bony metastases treatment with a single fraction of 8 Gy is considered highly effective and efficient, and therefore the best option. Adding hyperthermia to single fraction radiotherapy could be considered in the selected group of patients who have a good condition and an extended live expectancy, but where RT-alone will result in an insufficient response, i.e. large tumor or recurrent pain complaints after previous single 8 Gy radiation to the bony metastasis.

Conclusions

The results reported in the randomized trial of Chi *et al.* (4) for palliative treatment of painful bony metastases with radiotherapy and hyperthermia, again confirm the great potential of hyperthermia to sensitize the tumor to

radiotherapy. However, in modern palliative radiotherapy, treatment of patients with painful bony metastases is more and more dominated by a single fraction of 8 Gy. As feasibility and tolerance of the hyperthermia treatment is crucial for effectiveness, the indication for combined radiotherapy plus hyperthermia appears to be best suited for patients with a good condition and extended live expectancy under treatment, but where we expect that RT-alone will result in an insufficient response.

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