Letter to the Editor

Radiotherapy plus hyperthermia is effective for painful bony metastases—optimal schedule unsettled

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We thank van Rhoon and van Holthe for their interests and comments on our article of combined hyperthermia (HT) and radiation therapy (RT) for painful bony metastases (1). In our study, a significant pain improvement and duration of response was demonstrated by HT + RT. We emphasized the complete response (CR) rate at the third month than the accumulated CR rate within 3 months, because the palliative goal for the good performance patients should focus more on long-lasting response (2). Our analysis was indeed limited by small patient size (58 patients). However, timing of preset analysis and the rule of early termination were performed according to protocol and were mandated by the institutional review board and health regulatory authorities for clinical trials.

The updated ASTRO guideline reported similar pain relief equivalency following different regimens (single fraction of 8 Gy, 20 Gy in 5 fractions, 24 Gy in 6 fractions, and 30 Gy in 10 fractions). Nevertheless, the retreatment rate (which means a shorter response duration) for single 8 Gy remained higher than conventional fraction (3). Therefore, we chose 30 Gy in 10 fractions as our study protocol.

HT plays a role of radio-sensitization between 39 to 45 ℃ by improving oxygenation of the tumor microenvironment, increased immune response and inhibition of DNA homologous recombination repair. During HT, mild heat shock stimulates tumor necrosis factor related apoptosis inducing ligand (TRAIL) to facilitate long-lasting apoptosis (4). T hermally enhanced immune effector cells (dendritic cells or natural killer cells) were also activated to migrate to tumor site and enhance killing (5). According to linear quadratic model of cell killing by HT in the range of 41 to 43 ℃, Franken et al had reported a decreased α/β ratio in various cell lines. The difference of α/β ratio is mainly caused by an increased β-value enhancement factor (6). Increased β-value is in favor of hypofractionated RT regimen too.

We are currently enrolling a phase II re-concurrent chemo-radiation protocol for unresectable recurrent head and neck cancer (NCT02567383). The RT schedule consist a subtotal of 10 Gy in 2 fractions a week to gross tumors and follow by 40 Gy in 20 fractions to clinical target volume. The total dose is 50 Gy in 22 fractions. HT (maximum temperature set on 42±0.5 ℃) and low dose chemotherapy (docetaxel 10 mg/m^2 and cisplatin 20 mg/m^2) were given weekly for 6 cycles. Interim analysis of 21 patients showed a surprisingly good CR rate of 60% and median overall survival for more than 2 years (Yang *et al.*, unpublished data). A synergistic effect must exist between high fraction size irradiation and HT. We support a higher dose per fraction treatment with HT to emphasize the importance of the β component of cell killing. We agree van Rhoon *et al.*'s opinion that HT with long course RT may work better based biologically on the reoxygenation of tumor microenvironment. However, the increased β component of cell killing by short course RT should also be highlighted.

In general, long course RT achieved longer response duration and should work better for patients in good performance status, while single fraction benefit more on

patients with poor performance status (3). The best RT schedule in which HT be implemented could only be answered by clinical trials. We were more than happy to see a new trial by 8 Gy in single fraction with HT or study with larger sample size to be launched.

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Footnote

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