INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY • BIOLOGY • PHYSICS
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PHYSICS CONTRIBUTION

The Relevance of High Temperatures and Short Time Intervals Between Radiation Therapy and Hyperthermia: Insights in Terms of Predicted Equivalent Enhanced Radiation Dose

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Received Jun 1, 2022; Accepted for publication Oct 13, 2022

Purpose: The radiosensitization effect of hyperthermia can be considered and quantified as an enhanced equivalent radiation dose (EQD_{RT}), that is, the dose needed to achieve the same effect without hyperthermia. EQD_{RT} can be predicted using an extended linear quadratic model, with temperature-dependent parameters. Clinical data show that both the achieved temperature and time interval between radiation therapy and hyperthermia correlate with clinical outcome, but their effect on expected EQD_{RT} is unknown and was therefore evaluated in this study.
Methods and Materials: Biological modeling was performed using our in-house developed software (X-Term), considering a 23- × 2-Gy external beam radiation scheme, as applied for patients with locally advanced cervical cancer. First, the EQD_{RT} was calculated for homogeneous temperature levels, evaluating time intervals between 0 and 4 hours. Next, realistic heterogeneous hyperthermia treatment plans were combined with radiation therapy plans and the EQD_{RT} was calculated for 10 patients. Furthermore, the effect of achieving 0.5°C to 1°C lower or higher temperatures was evaluated.
Results: EQD_{RT} increases substantially with both increasing temperature and decreasing time interval. The effect of the time interval is most pronounced at higher temperatures (>41°C). At a typical hyperthermic temperature level of 41.5°C, an enhancement of ∼10 Gy can be realized with a 0-hour time interval, which is decreased to only ∼4 Gy enhancement with a 4-hour time interval. Most enhancement is already lost after 1 hour. Evaluation in patients predicted an average additional EQD_{RT} (D95%) of 2.2 and 6.3 Gy for 4- and 0-hour time intervals, respectively. The effect of 0.5°C to 1°C lower or higher temperatures is most pronounced at high temperature levels and short time intervals. The additional EQD_{RT} (D95%) ranged between 1.5 and 3.3 Gy and between 4.5 and 8.5 Gy for 4- and 0-hour time intervals, respectively.

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This work was supported by the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No. 955625, Hyperboost.

Disclosures: none.

Data sharing statement: Research data are stored in an institutional repository and will be shared upon reasonable request to the corresponding author.

Summary: Thermoradiotherapy combines radiation therapy with hyperthermia (ie, tumor heating to 39-43°C for 1 hour) to enhance the effect of radiation therapy. This enhancement can be expressed as an equivalent dose (EQD_{RT}), that is, the radiation dose needed to achieve the same effect without hyperthermia. The effectiveness of thermoradiotherapy depends on achieved temperature and time interval between radiation therapy and hyperthermia. We provide insight into the relationship between these parameters and EQD_{RT}. Maximizing EQD_{RT} requires high temperatures and short time intervals.

Int J Radiation Oncol Biol Phys, Vol. 115, No. 4, pp. 994–1003, 2023
0360-3016/$ - see front matter
https://doi.org/10.1016/j.ijrobp.2022.10.023

Conclusions: Biological modeling provides relevant insight into the relationship between treatment parameters and expected EQD_{RT}. Both high temperatures and short time intervals are essential to maximize EQD_{RT}.

Introduction

Thermoradiotherapy combines radiation therapy with hyperthermia (ie, tumor heating to 39°C-43°C for 1 hour) to significantly enhance the therapeutic effect of radiation therapy. An increased response rate of 15% to 20%, has been demonstrated for several tumor sites, such as melanoma, cervix, recurrent breast, rectum, bladder, and head and neck tumors,[1] without significantly increasing the radiation-associated toxicity. Hyperthermia is applied once or twice a week, either before or after a radiation therapy session, and usually administered by a radiofrequency or microwave device.[2] The therapeutic enhancement realized by hyperthermia depends on the achieved tumor temperature. Clinical data demonstrate a clear thermal dose-effect relationship,[3-5] that is, higher temperatures improve treatment outcome. Furthermore, the time interval between radiation therapy and hyperthermia should preferably be as short as possible to maximize tumor control.[6,7]

During locoregional hyperthermia, a mild temperature rise in surrounding normal tissue is inevitable. This is not a problem because the effect of hyperthermia is largely tumor-selective. However, excessive temperatures (≥44°C-45°C) should be avoided to prevent thermal toxicity. These so-called "hot spots" will be experienced as pain by the patient. Treatment-limiting normal tissue hot spots can occur during locoregional hyperthermia delivery, due to strong differences in power absorption and blood perfusion in different tissues. Treatment planning is helpful to optimize the temperature distribution,[8,9] but due to the lack of patient-specific tissue properties and knowledge of hyperthermia-enhanced blood perfusion, the exact normal tissue temperature levels are difficult to predict accurately by pretreatment planning.[10] Therefore, online adjustments can be necessary and the operator then applies power steering to reduce the peak temperature at the treatment limiting hot spot location, either based on experience or with the help of online treatment planning.[11,12] Because of these hot spots, the maximum tolerable power level during a hyperthermia treatment is often limited. Consequently, in clinical practice, achieved temperatures may differ significantly between patients and between the sessions for an individual patient. Furthermore, because of logistic reasons, the time interval between radiation therapy and hyperthermia can vary largely from several minutes up to 4 hours. A relatively long time interval can occur, for example, when patients need to travel to another hospital to receive the hyperthermia treatment.

The quality of radiation therapy and hyperthermia treatments is judged separately by radiation dose parameters and temperature/thermal dose parameters. However, the interplay between radiation therapy and hyperthermia is also very relevant, but quite complex and dose and temperature distributions are heterogeneous. A single dose evaluation parameter that reflects the effect of the combined treatment would therefore be very helpful to evaluate the quality of thermoradiotherapy treatments. Such a dose parameter could also be useful in comparing different treatment strategies and optimizing treatment protocols.

Biological modeling is often used in radiation therapy to compare different fractionation schedules and to predict tumor control and normal tissue toxicity. The linear-quadratic (LQ) model is the most commonly used biological model in clinical situations.[13] The LQ model predicts cell survival as a function of the fraction dose, the number of fractions and the radiosensitivity parameters α and β. The α/β ratio distinguishes the responses of different tissues to radiation and tumor site and histology strongly determine the α and β parameters of malignant tumors.[14] Because hyperthermia leads to radiosensitization, an extended version of the LQ model with temperature-dependent α and β parameters can be used to model effects of hyperthermia treatments.[15-18] This way, an equivalent radiation dose (EQD_{RT}) can be estimated (ie, the dose that would be needed in a radiation therapy−only treatment to achieve the same biological effect as the combined radiation therapy and hyperthermia treatment). This EQD_{RT} provides intuitive insight into the radiosensitization effect of hyperthermia, and thereby in the effect of the combined treatment, which can be evaluated using conventional dose histograms and evaluation parameters.

A dedicated software package (X-Term) has been developed to model the biological effects of radiation therapy plus hyperthermia in terms of 3-dimensional equivalent dose distributions, thereby facilitating the evaluation of combined plans for individual patients and patient groups.[17] Using this software, first applications demonstrated that adding hyperthermia to standard radiation therapy schemes for prostate or cervical cancer is typically equivalent to a mean target dose escalation of ~10 Gy.[15,16]

Radiation therapy combined with hyperthermia is a standard treatment option for several indications, among which patients with locally advanced cervical cancer and a contraindication for platinum-based chemotherapy. Although clinical studies have shown that the treatment parameters (ie, achieved tumor temperatures and time interval between radiation therapy and hyperthermia) correlate with clinical outcome,[3,4,6] their effect on expected EQD_{RT} is unknown. Such insights would help to better judge the achieved treatment quality, and eventually to optimize treatment schedules and standardize clinical protocols among hyperthermia centers.

Biological modeling for combined radiation therapy and hyperthermia provides comprehensible dose parameters to evaluate different treatment scenarios and to obtain important insights into the overall treatment quality. Previous research evaluated the combination of realistic hyperthermia temperature distributions with radiation therapy plans for specific patient groups to predict the general effect of hyperthermia in terms of equivalent dose.[15,16] However, these studies evaluated only single treatment plans and ignored the fact that achieved temperatures and time intervals between radiation therapy and hyperthermia may vary between treatment sessions and patients, which influences treatment quality. Therefore, in this study, we extend the application of biological modeling to obtain relevant insight into the effect of temperature and time interval between radiation therapy and hyperthermia on treatment quality in terms of effective EQD_{RT} for a group of patients with locally advanced cervical cancer treated with thermoradiotherapy, selected from a larger cohort analyzed in a previous study. First, basic insight was obtained assuming homogeneous tumor temperature levels and evaluating a relevant range of temperatures and time intervals. Next, realistic heterogeneous hyperthermia treatment plans were combined with radiation therapy plans for 10 patients to determine the effect of temperature and time interval on the EQD_{RT} in realistic scenarios.

Methods and Materials

Biological modeling was performed for 10 patients with locally advanced cervical cancer. Patients were selected from a previous study that included patients with and without para-aortal lymph node involvement, who received thermoradiotherapy at the Academic Medical Center between 2009 and 2016.[19] Data were anonymized, and our Medical Ethics Committee confirmed that the Medical Research Involving Human Subjects Act did not apply for this study. To ensure a relatively homogeneous patient group in the present study, treated with the same radiation therapy schedule, we excluded patients with para-aortal lymph node involvement. All selected patients received 23- × 2-Gy external beam radiation therapy based on standard volumetric modulated arc therapy plans. For this patient category, hyperthermia is applied weekly during the course of the external beam irradiation and delivered with the 70 MHz locoregional ALBA-4D system.[20] This system has 4 waveguides, with individual phase-amplitude control. External beam irradiation plus hyperthermia is followed by a pulsed dose rate brachytherapy boost of 24 Gy. Because brachytherapy is administered several days later, hyperthermia has a negligible enhancement effect on the brachytherapy boost and only external beam irradiation plus hyperthermia was evaluated.

Hyperthermia treatment planning

Hyperthermia treatment planning was performed using the in-house developed planning software Plan2Heat.[21] Hyperthermia planning CT scans, recorded in treatment position on a water bolus and mattresses, were segmented into muscle, fat, bone, and air, based on Hounsfield units. The gross tumor volumes were delineated by the radiation oncologist. Dielectric and thermal tissue properties were assigned based on the literature.[22-24] Simulation resolution was 2.5 × 2.5 × 2.5 mm^3 and plans were optimized by an inverse planning algorithm, maximizing target T90 (ie, the temperature at least achieved in 90% of the target volume), subject to hard normal tissue constraints of 45°C.[25] The steady-state temperature distributions were used for the equivalent dose calculations.

Equivalent dose calculation

The in-house developed software package X-Term was used to calculate the equivalent radiation dose (EQD_{RT}).[17] X-Term can import radiation therapy and hyperthermia treatment plans to calculate EQD_{RT} for a specified treatment schedule. Three-dimensional dose distributions and dose-volume histogram information can be exported. Calculations are based on an extended LQ model, with parameters α and β depending on the local temperature and the time interval between radiation therapy and hyperthermia. The EQD_{RT} is then calculated as:

$$EQD_{RT}(T, t_{int}, D, d_{ref}) = \frac{\alpha(T, t_{int}) \cdot D + G \cdot \beta(T, t_{int}) \cdot D^2}{\alpha_{37} + \beta_{37} \cdot d_{ref}} + D_{direct\ cell\ kill} \quad (1)$$

with α_{37} (Gy^{-1}) and β_{37} (Gy^{-2}) the radiation sensitivity parameters without hyperthermia, and $\alpha(T,t_{int})$ and $\beta(T, t_{int})$ the radiation sensitivity parameters with hyperthermia at temperature T and a time interval between radiation therapy and hyperthermia t_{int} (h). In the case radiation therapy is applied before hyperthermia, t_{int} is the time between the end of the radiation therapy (beam off) and the start of the 1-hour steady-state hyperthermia period. When hyperthermia is applied first, t_{int} is the time between the end of the hyperthermia (power off) and the start of radiation therapy (beam on). G is the Lea-Catcheside protraction factor from the generalized LQ model, D (Gy) the total (physical) radiation dose and d_{ref} (Gy) the fraction size of the reference treatment.[17] Throughout this study, d_{ref} = 2 Gy, such that all calculated EQD_{RT} values are comparable to the conventional EQD_2. A temperature-dependent parametric model was used to determine the $\alpha(T,t_{int})$ and $\beta(T,t_{int})$ parameters for cervical cancer, which was derived based on extensive preclinical experiments.[26] These experiments showed the same level of radiosensitization when hyperthermia was applied either before or after radiation therapy, and the time interval t_{int} refers to both treatment orders. The first part of Equation 1 accounts for the radiosensitizing effect; the term $D_{direct\ cell\ kill}$ accounts for the direct cytotoxic effect of hyperthermia and is based on an Arrhenius relationship. For more details on the mathematical formulas the reader is referred to earlier publications.[19,26] Because previous studies showed a very small enhancement of the EQD_{RT} in normal

tissues (typically <3%),[19] this study evaluated only the effect of hyperthermia treatment parameters on tumor EQD_{RT}.

Evaluation of the effect of hyperthermia treatment parameters on EQD_{RT}

First, to obtain basic insight into the effect of hyperthermia treatment parameters on the EQD_{RT}, homogeneous temperature distributions were considered and the EQD_{RT} was evaluated for temperatures in the whole conceivable hyperthermic range between 37°C and 43°C, with 0.5°C intervals, considering time intervals t_{int} between radiation therapy and hyperthermia of 0, 0.5, 1, 1.5, 2.5, and 4 hours. In clinical practice, 0 hours would refer to simultaneous treatment because a 0-hour time interval would be very difficult to realize for sequential treatments. Nevertheless, because 0 hours reflects the highest enhancement achievable it yields a valuable upper limit. Because the model parameters α and β are subject to uncertainties, a 95% confidence interval (CI) for the parameters was translated into a CI for EQD_{RT}, as described by Van Leeuwen et al.[26]

Next, real treatment plans were evaluated for 10 patients with locally advanced cervical cancer. The radiation dose distribution was resampled onto the hyperthermia planning CT using intensity-based deformable image registration, as embedded in Velocity Medical Solutions (Varian Medical Systems, Palo Alto, CA).[15] EQD_{RT} in the tumor region was calculated for the original treatment plans, and the D95% was determined, assuming again time intervals t_{int} between radiation therapy and hyperthermia of 0, 0.5, 1, 1.5, 2.5, and 4 hours. Subsequently, we also evaluated the expected clinical effect of achieving lower or higher tumor temperatures compared with the originally planned temperature distribution. Achieving lower temperatures reflects the clinical situation of incidence of treatment limiting hot spots that requires to reduce the output power. An increase in temperature would be possible when treatment limiting hot spots remain absent. A typical clinical power level would be ~600 W and a reduction or increase in power in response to the incidence or absence of hot spots, respectively would be ~100 W. Considering a typical hyperthermic temperature of 41.5°C (ie, 4.5°C temperature rise), ~100 W reduction or increase would then be ~0.75°C. Therefore, predicted EQD_{RT} was evaluated for temperature distributions that were 0.5°C or 1°C lower or higher than in the originally planned temperature distribution. This was again evaluated for all indicated time intervals between radiation therapy and hyperthermia and the D95% was compared.

Results

Homogeneous temperature levels

To obtain basic insight into the effect of temperature and time interval t_{int} between radiation therapy and hyperthermia on the EQD_{RT}, the enhancement of a standard 23 × 2 Gy dose distribution by homogeneous temperatures was evaluated. Figure 1A shows the relationship between temperature and EQD_{RT} for t_{int} varying between 0 and 4 hours; Fig. 1B displays the relationship between time interval and EQD_{RT} for various temperature levels. The EQD_{RT} increases significantly with both increasing temperature and decreasing t_{int}. This implies that when t_{int} is increased, a higher temperature would be necessary to realize the same effect in terms of EQD_{RT}. For example, suppose that a patient receives the hyperthermia session with a time interval of 0.5 hours before or after a radiation therapy fraction and a temperature of 41.5°C is achieved; this yields a predicted EQD_{RT} of 54.3 Gy. When the time interval t_{int} increases to 2.5 hours for a next session, for instance because of logistic reasons, Fig. 1A predicts a drop in EQD_{RT} of 3.6 to 50.7 Gy. An almost 1°C-higher temperature would then be needed to realize again an EQD_{RT} of 54.3 Gy, which possibly cannot be achieved because of induction of treatment limiting hot spots.

The effect of t_{int} is largest close to 0 hours. For example, suppose that a temperature of 41°C is achieved; the predicted EQD_{RT} is 54.3 Gy when t_{int} is 0 hours. Increasing this to 0.5 hours reduces EQD_{RT} to 52.6 Gy. When the increase is with respect to a larger initial time interval t_{int}, for example, an increase from 2.5 to 4 hours, the effect on EQD_{RT} is much smaller: a decrease from 49.6 to 48.8 Gy. Thus, the EQD_{RT} rapidly decreases with increasing time interval between radiation therapy and hyperthermia. At a typical hyperthermic temperature of 41.5°C an enhancement of ~10 Gy can be realized when hyperthermia is applied immediately before or after the radiation therapy fraction; this decreases to only ~4 Gy enhancement when t_{int} would be 4 hours. As also indicated by Fig. 1B, the decrease of EQD_{RT} with time interval is stronger at higher temperature levels. Approximately half of the decay in dose enhancement that occurs between 0 and 4 hours occurs within the first hour.

The right side of Fig. 1 shows the influence of uncertainties in parameters $\alpha(T)$ and $\beta(T)$ (95% CI) on the predicted EQD_{RT}, determined as described by Van Leeuwen et al.[26] It is observed that the uncertainty in predicted EQD_{RT} increases for higher temperature levels, but the confidence band indicates that the chance of underestimation of EQD_{RT} is larger than the chance of overestimation. Furthermore, the shape of the profiles remains unchanged, so trends and basic relationships as derived previously remain valid, despite uncertainties in $\alpha(T)$ and $\beta(T)$.

Realistic treatment scenarios

Next, we evaluated realistic treatment scenarios, considering real volumetric modulated arc therapy plans and inhomogeneous temperature distributions for 10 locally advanced cervical cancer patients. Planned steady-state temperature distributions showed a mean T90, T50, and T10 of 40.4°C, 41.4°C, and 42.5°C, respectively (Fig. 2). Although planned

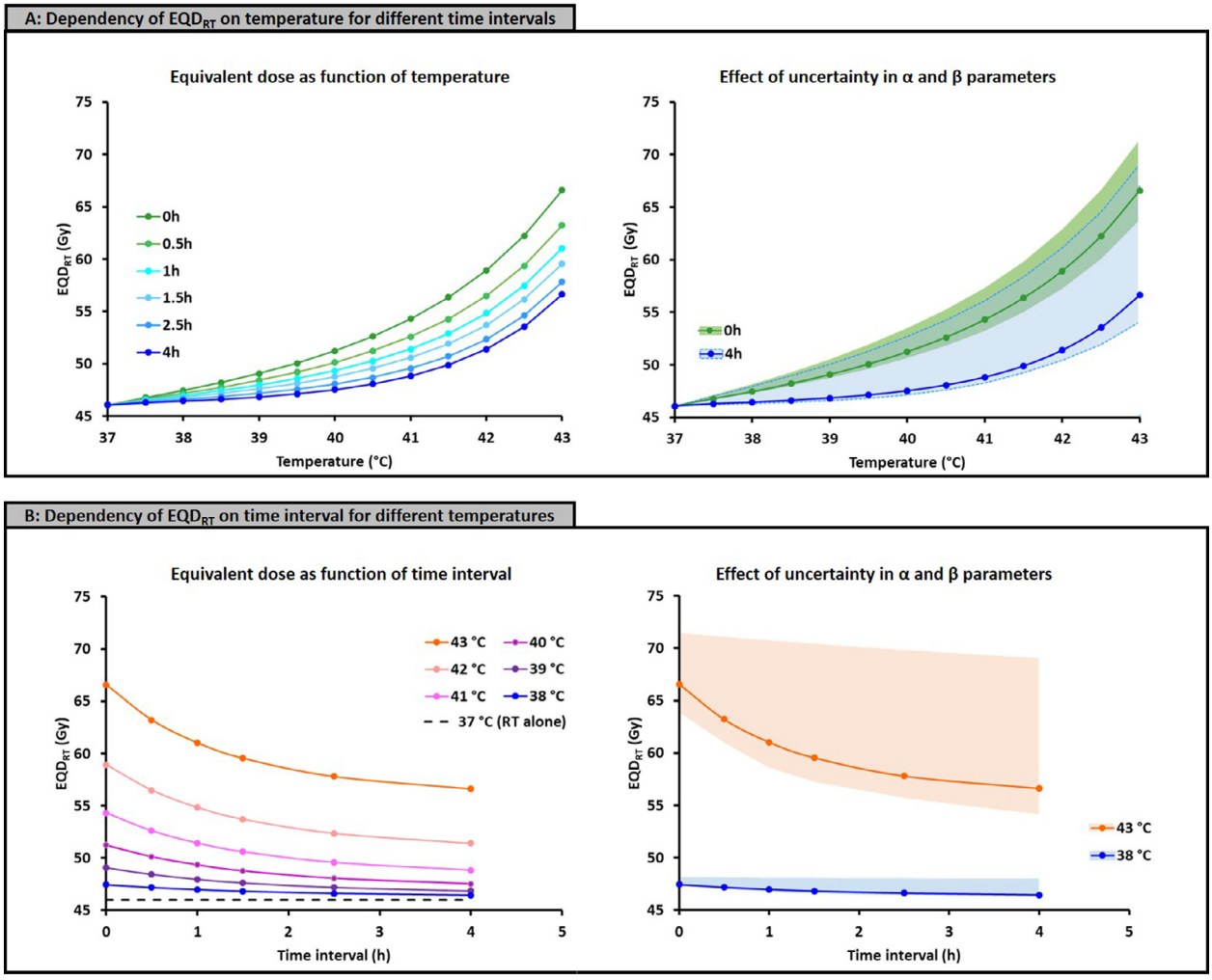

Fig. 1. (A) Dependency of the enhanced equivalent radiation dose (EQD_{RT}) on temperature for time intervals varying between 0 and 4 hours, and the effect of the uncertainty (95% confidence interval) in parameters $\alpha(T)$ and $\beta(T)$ on the predicted equivalent dose, expressed as a shaded confidence interval; for clarity only the 0- and 4-hour confidence intervals are shown. (B) Dependency of EQD_{RT} on time interval for temperatures varying between 38°C and 43°C, with the normothermic 37°C baseline as a reference (left). The graph on the right side shows the effect of the uncertainty in $\alpha(T)$ and $\beta(T)$, expressed as a shaded confidence interval; for clarity only the 38°C and 43°C confidence intervals are shown. Temperature-dependent linear-quadratic parameters for cervical cancer used in this evaluation were derived from extensive preclinical experiments.[26] Note that the time interval refers to both treatment orders (ie, hyperthermia before or after radiation therapy).

and actually realized temperature distributions might differ because of uncertainties in patient-specific tissue properties and blood perfusion, these planned temperature levels and heterogeneity are well in the range of actual temperatures and temperature heterogeneity typically encountered during locoregional hyperthermia treatments,[3,6] and these are thus suitable to evaluate effects of varying temperatures and time intervals between radiation therapy and hyperthermia on the predicted equivalent dose EQD_{RT}. Figure 2A shows the evaluation of EQD_{RT} for the standard treatment plan, comparing the predicted equivalent D95% dose EQD_{RT} for varying time intervals up to 4 hours with the D95% radiation dose without hyperthermia. In line with the uniform temperatures, a strong decay in equivalent dose is observed when the time interval between radiation therapy and hyperthermia increases. When hyperthermia is applied immediately before or after radiation therapy (time interval of 0 hours), the mean predicted D95% EQD_{RT} is 51.7 Gy. This is a gain of more than 6 Gy compared with radiation alone, where the mean D95% was 45.4 Gy. When the time interval increases to 4 hours, the mean predicted D95% EQD_{RT} drops to 47.6 Gy.

Figure 2B shows the effect of achieving 0.5°C or 1°C lower T50 temperatures compared with the planning predictions. This reflects the influence of lowering the output power in the case of incidence of treatment limiting hot spots. The effect on EQD_{RT} is most pronounced for a short time interval between radiation therapy and hyperthermia. For example, in the case of a 1°C-lower T50 and a time interval t_{int} of 0 hours, the mean predicted D95% EQD_{RT}

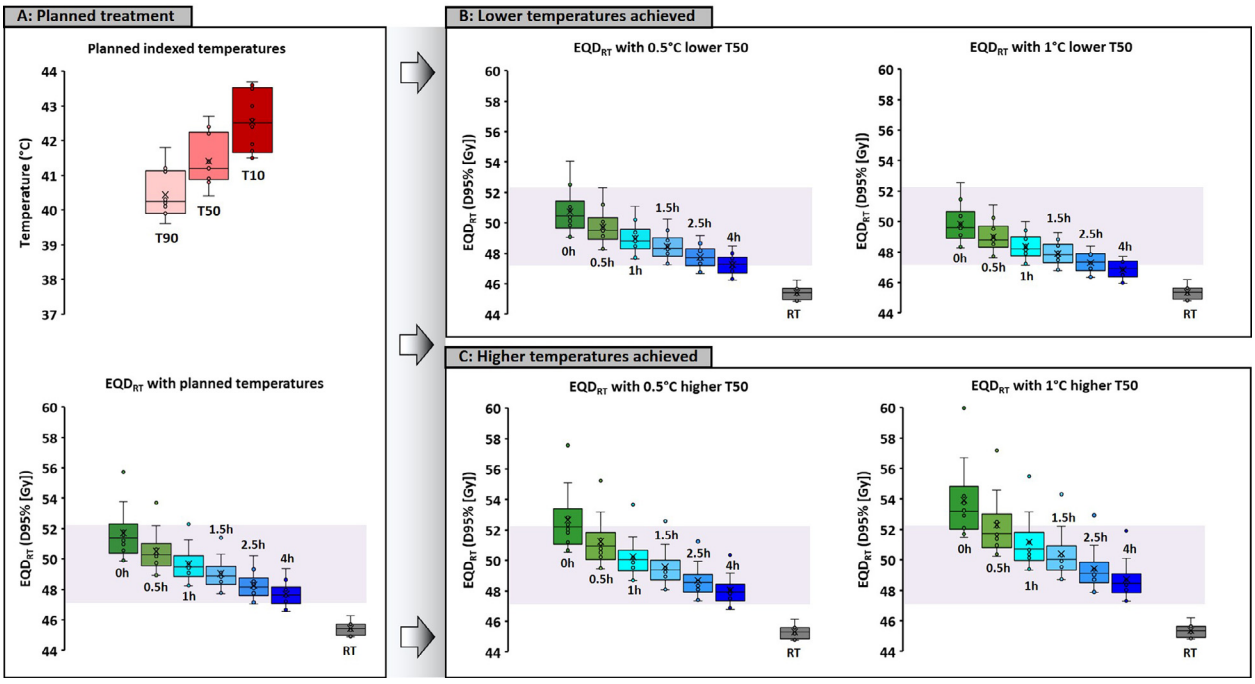

Fig. 2. (A) Effect of varying the time interval between radiation therapy and hyperthermia from 0 to 4 hours on the predicted enhanced equivalent radiation dose (EQD_{RT}) for 10 patients with locally advanced cervical cancer receiving 23- × 2-Gy external beam radiation therapy. The purple band represents the range spanned by Q1 and Q3 for time intervals of 4 and 0 hours, respectively, as indication of the overall improvement range compared with radiation alone. (B, C) Effect of achieving increased or reduced tumor temperatures during treatment on the EQD_{RT}, for varying time intervals. The purple band from (A) was redrawn here as baseline to better visualize the increase or decrease compared with (A). Results are based on simulations, using temperature-dependent linear-quadratic parameters for cervical cancer that were derived from extensive preclinical experiments.[26] Note that the time interval refers to both treatment orders (ie, hyperthermia before or after radiation therapy).

decreases with 1.8 Gy from 51.7 to 49.9 Gy; when t_{int} is 4 hours, the decrease is about 0.7 Gy: from 47.6 to 46.9 Gy.

Figure 2C shows the effect of achieving 0.5°C- or 1°C-higher T50 temperatures compared with the planning predictions. This temperature increase reflects the effect of increasing the output power, which is possible when no treatment limiting hot spots occur during treatment. In line with previous observations, the beneficial effect of realizing a higher temperature pays off most when the time interval between radiation therapy and hyperthermia is short. When a 1°C-higher T50 would be realized, the increase in mean D95% EQD_{RT} varies from more than 2 Gy for a 0-hour time interval, to about 1 Gy for a 4-hour time interval. Note that the exact gain in D95% EQD_{RT} depends largely on the individual temperatures achieved. For example, in the case of a 0-hour time interval and a 1°C increase in T50, the gain in D95% EQD_{RT} ranges between 1.7 Gy (T90 = 39.9°C) and 4.3 Gy (T90 = 41.8°C).

Thus, the influence of the time interval t_{int} on EQD_{RT} is most pronounced when relatively high temperatures are achieved and at higher temperature levels the effect of changes in temperature, that is, realizing a 0.5°C to 1°C higher or lower temperature, is also most pronounced. On average, the additional D95% EQD_{RT} ranged between 1.5 and 3.3 Gy and between 4.5 and 8.5 Gy for 4- and 0-hour time intervals, respectively. As illustration for a typical hyperthermia treatment, Fig. 3 shows an example of a patient with a planned T50 temperature of 41.2°C, which is a representative temperature level for an average clinical hyperthermia treatment. The effect of temperature and time interval between radiation therapy and hyperthermia on the planned EQD_{RT} is shown in equivalent dose distributions and dose-volume histograms, including the influence of uncertainties in parameters $\alpha(T)$ and $\beta(T)$ (95% CI). For radiation therapy only, the D95% was 45.7 Gy, which increases to 51.8 Gy (95% CI, 51.1-54.2 Gy), or 47.7 Gy (95% CI, 47.2-53.3 Gy) by adding hyperthermia with a time interval of 0 or 4 hours before or after radiation therapy, respectively. In the case the treatment operator is forced to reduce the power deposition because of treatment limiting hot spots and the achieved T50 would be 1°C lower, the predicted D95% EQD_{RT} would be 49.9 Gy (95% CI, 49.5-51.7 Gy) or 47.0 Gy (95% CI, 46.6-51.1 Gy) for a time interval of 0 or 4 hours, respectively. When treatment limiting hot spots would remain absent and the power could be increased during treatment, realizing a T50 of 42.2°C, the D95% EQD_{RT} would increase substantially with 8.5 to 54.2 Gy (95% CI, 53.2-57.2 Gy) for a time interval of 0 hours.

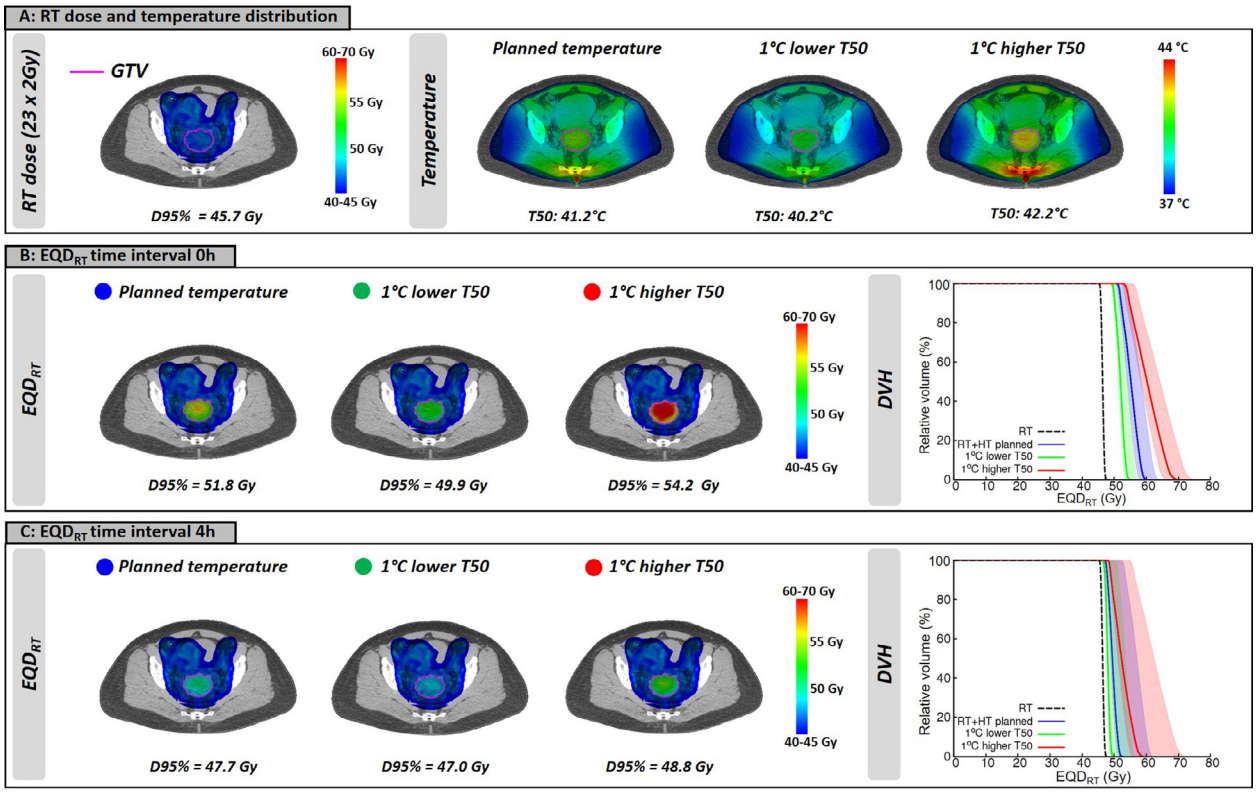

Fig. 3. Example of a patient with locally advanced cervical cancer receiving 23- × 2-Gy external beam radiation therapy plus hyperthermia. (A) Planned distributions and temperature distributions with a 1°C higher or lower T50 than the planned distribution. (B, C) Predicted equivalent dose distributions and dose-volume histograms for different time intervals between radiation therapy and hyperthermia (0 or 4 hours). The shaded regions in the dose-volume histogram plots indicate the confidence interval, represented by the 95% confidence interval for the α and β parameters. *Abbreviations*: DVH = dose-volume histogram; EQD_{RT}, = equivalent radiation dose distribution; GTV = gross tumor volume.

For a 4-hour time interval the increase is still about 3 Gy (48.8 Gy, with 95% CI of 48.5-56.0 Gy). For all situations, the lower bound of the confidence band is much closer to the maximum likelihood estimate than the upper bound limit. This indicates that, accounting for uncertainties in LQ parameters, underestimation of the EQD_{RT} levels is much more likely than overestimation. Also note that the dose-volume histograms for the combined treatment are less steep than those for radiation therapy only, which is due to the heterogeneity of the temperature distribution. This means that in parts of the target the enhancement effect will be much larger than reflected by the D95% EQD_{RT}.

Discussion

Radiation therapy plus hyperthermia is a standard treatment combination for locally advanced cervical cancer patients with a contraindication for platinum-based chemotherapy who are not eligible for standard chemoradiation. Clinical studies have demonstrated that both the achieved tumor temperatures and time interval between radiation therapy and hyperthermia correlate with clinical outcome,[3,4,6] but their expected quantitative effect on EQD_{RT} remains unknown. Therefore, this study evaluated the effect of these parameters on the predicted EQD_{RT}. Considering a 46-Gy external beam treatment schedule (23 × 2 Gy) and, for example, a 1-hour time interval between both modalities, biological modeling predicted an EQD_{RT} increase of 2 to 15 Gy over the hyperthermic temperature range from 39°C to 43°C (Fig. 1A), clearly underlining the strong thermal dose effect-relationship observed clinically. Given this strong increase in EQD_{RT} with increasing temperature, realizing the highest tolerable hyperthermic tumor temperature is of utmost importance to ensure optimal clinical outcome.

Biological modeling results showed that the effect of temperature on the EQD_{RT} is most significant for short time intervals close to 0 hours, and in turn that the beneficial effect of a short time interval is most pronounced when relatively high temperature levels are achieved (Fig. 1). A retrospective study of patients with cervical cancer treated with radiation therapy followed by hyperthermia showed a significantly lower risk of 3-year in-field recurrence (18% vs 53%) and improved 5-year survival (52% vs 17%) for those patients receiving hyperthermia with a time interval ≤79.2 minutes after radiation therapy, compared with patients treated with a longer time interval.[6] Evaluation of the DNA-

damage repair kinetics revealed that most of the DNA-damage repair takes place within 2 hours, thereby reducing the effectiveness of hyperthermia for longer time intervals.[6] Equivalent dose predictions evaluated in the present study as a function of time interval indicated that approximately half of the decay in dose enhancement that occurs between 0 and 4 hours occurs within the first hour. This indicates that in clinical protocols, time intervals between radiation therapy and hyperthermia delivery should be as short as possible to maximize clinical outcome.

To realize short time intervals between radiation therapy and hyperthermia, patients would preferably receive radiation therapy and hyperthermia in the same hospital. In the case this is not possible, logistics should be optimized to ensure the shortest possible time interval to realize optimal treatment quality. For hyperthermia, time is needed to install the patient with (minimally) invasive thermometry, and a 15- to 30-minute warming up time to reach tumor temperatures exceeding 41°C. Applying hyperthermia before radiation therapy can thus lead to significantly shorter time intervals, such that time intervals close to 0 hours become possible. Notter et al were able to apply radiation therapy within minutes after hyperthermia for patients with recurrent breast cancer, and achieved excellent tumor control with a low dose (5 × 4 Gy) reirradiation.[27] In the case hyperthermia is applied after radiation therapy, time intervals typically range between 30 minutes and 2 hours, depending on logistics[6] and even with optimized logistics implemented after the retrospective analysis of van Leeuwen et al[6] this can hardly get shorter than 30 minutes. This interval can increase up to 4 hours when the hyperthermia treatment is not delivered at the same hospital as the radiation therapy.[28]

The clinical relevance of the time interval between radiation therapy and hyperthermia is subject of an ongoing debate.[29-31] In contrast to the retrospective study by van Leeuwen et al, where a short time interval between radiation therapy and hyperthermia was shown to have a significant favorable effect on the risk of 3-year in-field recurrence,[6] another large retrospective analysis by Kroesen et al could not demonstrate an effect of the time interval on clinical outcome.[28] This could partly be explained by the temperature levels and time intervals achieved. Preclinical research has demonstrated that inhibition of DNA damage repair, an important working mechanism of hyperthermia, requires temperatures beyond 41°C.[32,33] In clinical practice, the achieved temperature level is largely determined by patient tolerance. When treatment limiting hot spots in surrounding normal tissue will not allow to further increase the applied power, this also limits achieved tumor temperatures. This could partly explain why a pronounced influence of time interval on clinical outcome was not observed by Kroesen et al.[28] When achieved temperatures remain below 41°C in a large part of the tumor, the DNA repair inhibition by hyperthermia is hardly activated and the effect of time interval will be less dominant.[30] And even when temperatures exceeding 41°C are achieved, the associated DNA repair inhibition is only relevant if also relatively short time intervals are achieved, because rapid DNA damage repair is reported, for instance for patients with locally advanced cervical cancer.[6,29] Furthermore, the definition of time interval was different in both studies. The time interval was defined as the time until steady state (aiming at T50 >41°C) was reached in one study, and as time until start power on for hyperthermia in the other study, which complicates direct comparison and interpretation.[29-31] Another factor influencing results could be different patient selection. Future well-designed clinical registration studies would be very valuable to obtain more evidence on the clinical effect of treatment variables such as temperature and time interval on patient outcome. In addition, such data would be very useful for further validation of the biological prediction models.

Although a clear thermal dose-effect relationship is observed both clinically and in terms of EQD_{RT}, some beneficial and clinically relevant effects can still be achieved at lower temperature levels (ie, between 39°C and 41°C). Next to DNA damage repair inhibition, hyperthermia exhibits also other important working mechanisms, for example, changes in perfusion, tumor reoxygenation and immunologic stimulation, which are activated at lower temperature levels.[34,35] Furthermore, many of these mechanisms also remain effective with longer time intervals between radiation therapy and hyperthermia. For example, reoxygenation effects occurring during mild heating are reported to last up to 24 hours,[35-38] and direct cytotoxic effects to hypoxic cells would be independent of the time interval. This explains that a clinically relevant benefit of hyperthermia is still reported also for patients treated with longer time intervals between radiation therapy and hyperthermia.[4]

This study evaluated the effect of treatment parameters on predicted EQD_{RT} for patients with locally advanced cervical cancer. Although predicted dose distributions and enhancement levels would be different for other tumor sites because of different temperature-dependent LQ parameters, basic insights and trends observed for increasing/decreasing temperatures and time intervals are likely to be similar. However, for more detailed insight in terms of EQD_{RT}, extensive preclinical experiments are required to derive mathematical models describing the dependency of the LQ parameters on temperature and time interval, as input parameters for biological modeling for other tumor sites.

The current biological model developed and implemented in X-Term accounts for DNA-repair inhibition by hyperthermia and heat-induced direct cytotoxicity.[17] Experimental cell survival data used to derive the mathematical model for the LQ parameters showed a symmetry around 0 hours, that is, the radiosensitization is the same regardless of whether hyperthermia is given before or after radiation therapy.[26] Ongoing research focuses on modeling of other relevant hyperthermia mechanisms, such as reoxygenation and immunologic effects, for which there will be a difference in applying hyperthermia before or after radiation. This difference, and thus the asymmetry in temperature-dependent

LQ parameters around 0 hours, is likely to increase with increasing time interval. For adequate modeling of these effects, reliable biological input data are very important. A major challenge here is derivation of temperature-dependent parameters to represent these mechanisms in equivalent dose calculations, which requires carefully designed in vivo experiments applying homogeneous heating to various specific temperature levels. Clinical application would then also require additional imaging protocols, for example, to determine patient-specific pO_2 maps.[39]

Biological modeling is commonly applied in radiation therapy to evaluate fractionation strategies and biological optimization and evaluation tools are available in modern commercial radiation therapy treatment planning systems, such as Eclipse and RayStation. Similarly, biological evaluation of combined radiation therapy and hyperthermia treatments is a useful tool to further optimize clinical treatments. A first research application showed a possible benefit in tumor control probability when applying hyperthermia combined with radiation therapy for high-risk prostate cancer,[16] and clinical feasibility studies confirm this potential benefit.[40,41] Another application evaluated the therapeutic gain (ie, the ratio between hyperthermic enhancement in the tumor and in organs and risk) in patients with cervical cancer for different time intervals, indicating that a short time interval is beneficial,[19] also confirmed by clinical data.[6] A recent study suggested that applying a hyperthermia boost to low-dose reirradiation for infield recurrent pediatric sarcoma in the pelvic region or in the extremities could possibly realize a curative equivalent radiation dose.[42] Thus, biological modeling could be very instrumental in the design of new clinical studies, as well as to optimize treatment schedules and to standardize protocols among clinical hyperthermia centers to ensure overall treatment quality.

Further developments in biological modeling for combined radiation therapy and hyperthermia aim to realize a planning platform that allows patient-specific biological evaluation and optimization of treatment plans. This is very challenging and requires multidisciplinary research combining advanced physical/mathematical models with biological and clinical data. One of the key aims of an ongoing European research consortium (Hyperboost, European Horizon 2020 MSCA-Innovative training network grant 955625) is to realize such an innovative planning platform. In the future, treatment planning combined with biological modeling will be important to further optimize combined radiation therapy and hyperthermia treatments, as well as to optimize clinical protocols and to guide further clinical studies.

Conclusions

Biological modeling is a very helpful instrument to obtain insight into the effect of treatment factors on the radiosensitization effect of hyperthermia in terms of an enhanced equivalent radiation dose (EQD_{RT}), that is, the radiation dose needed to achieve the same effect without hyperthermia. This way, treatment quality can be evaluated using standard dose-volume histograms and evaluation parameters. Our results indicate that the effect of the time interval between radiation therapy and hyperthermia on the EQD_{RT} is most pronounced at higher temperatures (>41°C). At a typical hyperthermic temperature level of 41.5°C the dose enhancement ranges between ~4 and 10 Gy, for time intervals between 4 and 0 hours. Enhancement decreases strongly with increasing time interval and most enhancement is already lost after a 1-hour time interval between radiation therapy and hyperthermia. For realistic heterogeneous temperature distributions in patients the average predicted additional EQD_{RT} (D95%) ranged between 1.5 and 8.5 Gy, strongly depending on the time interval and the temperature levels achieved. Biological modeling thus enhances the role of optimal treatment quality and logistics and can help to further optimize treatment protocols.

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