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Superficial thermoradiotherapy: Clinical result favor immediate irradiation prior to hyperthermia

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Purpose. *The aim of the present paper is to report the analysis of some relevant tumor and/or therapeutic parameters and to compare different treatment strategies used in our patients treated by local thermoradiotherapy (TRT).*

Methods and materials. *In the period 1989-1995, fifty-two patients with locally advanced tumors accessible to local TRT were treated at the Institute of Oncology in Ljubljana, Slovenia. A majority of 39 (75%) patients failed to respond to previous radiotherapy, while in 13 patients TRT was used as primary treatment. Interstitial TRT (ITRT) as primary treatment was used in 13 (25%) patients, interstitial hyperthermia combined with simultaneous external irradiation (STRT) in 7 (14%), and external TRT (ETRT) was applied in 32 (61%) patients.*

Results. *In all 52 patients a complete response (CR) rate of 60% was achieved, while 2-year recurrence-free and disease-specific survivals were 51% and 45%, respectively. Among tumoral and therapeutic parameters tested, CR rate was found to be significantly influenced by histology other than squamous cell carcinoma* (p=*0.045), tumor volume < 55 ccm* (p=*0.02), minimum intratumoral temperature* (T_{min}) $\geq$ *42.5C* (p=*0.015), total tumor dose (TTD) of radiotherapy* $\geq$ *45 Gy* (p=*0.048), fraction size of irradiation used concurrently to hyperthermia > 3 Gy* (p=*0.03), and by those TRT treatments where irradiation preceded hyperthermia* (p=*0.026). Repeating of hyperthermia (HT) treatments did not improve the CR rate. The use of RT immediately prior to HT resulted in a 2-year recurrence-free survival (RFS) of 66% compared to 38% for patients in whom HT treatment was followed by irradiation* (p=*0.07). For the subgroup of 20 patients in whom fraction size of >3 Gy was delivered immediately before HT treatment, an even better RFS of 85% was achieved* (p=*0.03) . The enhancement ratio of 1.7 was found between the dose response curves for 29 patients receiving RT prior to HT and 23 patients in whom HT was used before RT. Acute and late toxicity of grade 3 and/or 4 were recorded in 28% and 23% of treated patients, respectively. TRT-related acute toxicity was more pronounced in patients with maximum temperature measurements inside the heated volume* (T_{max}) *45C* (p=*0.006), while a higher grade of late toxicity correlated with a tumor volume* $\geq$ *55 ccm (p=0.02) and TD of RT > 45 Gy (p=0.04). There was no significant correlation found between a higher toxicity grade and CR rate.*

Conclusions. *Our clinical results are in favor of an application of somewhat higher fraction size of RT than conventional, employed immediately before heating, when combined with HT.*

Key words: neoplasms-radiotherapy; hyperthermice, induced; local thermoradiotherapy; advanced tumors; clinical results; prognostic parameters

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Introduction

When introduced to clinical practice, local thermoradiotherapy (TRT) proved useful first of all in the treatment of advanced and recurrent/residual tu-

mors, either applied with invasive technique,[1-7] non-invasive technique,[8-12] or in combination of both.[13, 14] The advantage of TRT over radiotherapy (RT) alone was proved in some non-randomized,[8, 9, 14-16] as well as in a few randomized clinical trials.[17-20] Believing in biological reasons for combining RT and hyperthermia (HT) treatment,[21-25] at the Institute of Oncology in Ljubljana, efforts were made to develop technical equipment and our own treatment strategies for the application of TRT prevalently in order to overcome radioresistance of locally advanced tumors[26] and tumor lesions which failed to respond to previous RT. The aim of the present paper is to report the analysis of some relevant tumor and/or therapeutic parameters in our patients treated by local TRT.

Materials and methods

The patients

Altogether 52 patients (42 male and 10 female) were treated by TRT between 1989-1995 at the Institute of Oncology in Ljubljana, Slovenia; 39 of these were with recurrent and/or residual tumors after previous standard RT and 13 with primary advanced malignancy. Tumor sites were as follows: head and neck region in 46 patients, breast and/or thoracic wall in 5, and inguinal lymphnodes in 1 patient. Histologically, 38 (73%) tumors were squamous cell carcinoma, 8 (15%) adenocarcinoma, 5 (10%) malignant melanoma, and 1 (2%) Mb Hodgkin. By the time of combined HT and RT treatment, patients were free of distant metastases and were not receiving any other concurrent cancer therapy. Only patients with Karnofsky performance score $\geq$ 70% were eligible for TRT. Tumor volume ranged from 10 - 180 ccm (median 54 ccm).

Hyperthermia devices

Interstitial heating was performed by means of interstitial water hyperthemia system. Prior to clinical utilization our device had been tested on experimental animals. The results of animal experiments were published elsewhere.[27, 28] First clinical experience using interstitial water hyperthermia system showed acceptable homogeneity of temperature distribution inside the heated volume.[29, 30] Intratumoral insertion of plastic or metal tubes for application of interstitial water hyperthermia technique was done under a general anesthesia in 20 patients. Percutaneous heating was performed in 32 patients by non-invasive 432 MHz microwave unit using two different antennae to cover adequately the total tumor surface within safety margins. In the majority of cases no water bolus was used. Extensive local anesthesia using 2% Xylocain was utilized with percutaneous application of thermotherapy.

Radiotherapy

In 13 patients brachytherapy was applied in combination with interstitial HT. Ir-192 wires were inserted through the same plastic tube implant as used for HT. In all implants, X-ray and/or ultrasound verification was used to assure that the implant encompassed the whole tumor volume. A dose-rate of 0.5 - 0.7 Gy/h was delivered to the tumor periphery. Total tumor dose (TTD) in patients treated by interstitial TRT (ITRT) ranged from 20 - 70 Gy (median 60 Gy). In 39 patients percutaneous RT was applied using a fraction size of 1.8 - 3 Gy. The fraction size of brachyradiotherapy was estimated from dose-rates at the tumor periphery given within 4 hours after HT treatment.

In 7 patients interstitial heating using metal tubes was performed combined with simultaneous irradiation (STRT) by teleradiotherapy using electron beam. In one patients STRT using single fraction of 5 Gy was the only therapy, while in 6 patients TTD of RT ranged from 25 - 60 Gy (median 55 Gy). For the rest of 32 patients percutaneous HT combined with external RT using either electron beam or Co-60 was employed with TTD of 20 - 70 Gy (median 40 Gy).

TTD of RT depended on the time interval from previous RT and TTD of previous RT. Total cumulative dose of radiotherapy did not exceed 100 Gy. Thirteen patients without previous irradiation received 45 - 70 Gy (median 60 Gy), while TTD for 39 previously irradiated patients ranged from 5 - 66 Gy (median 40 Gy). Fraction size of RT used concurrently with HT differed from 1.8 - 8 Gy (median 3.5 Gy).

Thermoradiotherapy and thermometry

Thirteen patients receiving interstitial hyperthermia were treated under general anesthesia once only. Hyperthermia session started after steady state temperature distribution inside the tumor volume had been reached and lasted 60 minutes. Placement of Ir-192 wires followed immediately after the heating session in 9 cases, while in 4 patients brachythera-

py had to be postponed for more than one hour due to a substantial swelling of the heated region.

Seven patients were treated with simultaneous interstitial hyperthermia and external irradiation. This specific therapeutic approach has been presented previously.[31] On the day before HT treatment, metallic tubes were implanted through the tumor volume under a general anesthesia. The next day, the patient was placed in a room close to the linear accelerator, and the implant was connected to a water HT unit. Approximately 30 minutes after the beginning of HT session, the patient and the HT device were moved together to the linear accelerator unit and irradiation using electron beam was performed while uninterrupted heating continued. After completed RT session, the patient was moved again to the nearby location and heating proceeded until total HT treatment time of 60 minutes elapsed. In all 7 patients treated simultaneously TRT was not repeated.

Combined percutaneous HT and RT was performed in 32 patients. After a TD of 10-20 Gy had been reached, the first HT treatment was performed. A single session of HT during the RT course was performed in 13 patients whereas 19 patients received 2-3 HT treatments. Repeated HT was applied once weekly. The total heating time depended on maximum and minimum temperature measured inside the heated volume and lasted 45 - 60 minutes for each HT session. Owing to technical problems, in 5/32 patients the time interval between the application of both modalities exceeded one hour. In 3 patients HT was performed immediately before irradiation while in the remaining 29 patients HT followed RT.

Altogether, there were 23 patients treated with HT preceding RT, and 29 patients in whom HT followed RT treatment.

Invasive thermometry was performed in 20 patients treated by interstitial HT using five-point manganin-constantan thermocouple probes which were moved stepwise through 2-3 (depending on tumor volume) plastic tubes inserted perpendicularly to the implant. It was considered that HT treatment started when intratumoral temperature of >=42.5°C was obtained at the tumor periphery. Temperatures were registered every five minutes during the heating session; minimum and maximum temperatures were recorded.

In 32 patients heated with an external HT device, 2-3 (depending on tumor volume) plastic tubes were inserted through the heated volume, and temperature measurements performed by means of a one-point non-conducting temperature probe. The same protocol for temperature monitoring as in invasive HT treatments was used. with the exception of an extra thermal probe on the skin surface.

Tmin i.e., mean minimum temperature measured in 3-5 measurement points at the tumor periphery during entire heating session was taken as a reference for estimation of HT treatment quality. In patients with multiple HT treatments, the highest Tmin observed was recorded. The mean value of maximum temperatures measured intratumorally and/or on skin surface was expressed as Tmax and was used for treatment toxicity estimation.

Estimation of response to treatment and toxicity

Only complete clinical disappearance of the treated tumors (CR-complete response) 2 - 3 months after completion of TRT was estimated as a therapeutic success. All other responses were considered as treatment failures. The results were analyzed using Biomedical Statistical Software Package (BMDP);[32] the survival was calculated from the end of treatment using Kaplan-Meier's method.[33] A log-rank, χ^2-test, and Fisher exact tests were used to analyze the difference between groups. Sigma-plot computer program was used for the dose-response curves drawing. In order to estimate treatment related toxicity RTOG/EORTC system was used,[34] introducing HT related formation of blisters as grade 3 early toxicity. Only the most severe grade of toxicity for each patient was recorded.

Results

In all 52 patients treated with TRT at the Institute of Oncology, Ljubljana, Slovenia, a CR rate of 60% and a 2-year recurrence-free survival of 43% were achieved. The observation time ranged from 3 - 42 months (median 11 months). The prognostic significance of some tumoral characteristics is evident from Table 1 while the prognostic importance of the observed therapeutic parameters is apparent from Table 2. Next to tumor histology, tumor volume was found to be the most prominent prognostic factor among tumoral parameters. The only significant parameter among hyperthermic factors was T_{min} while neither the type of HT used nor the number of HT treatments showed any prognostic significance. Among radiotherapeutic treatment parameters, except for the type of RT used, all three

Table 1. Prognostic importance of patients' and/or tumor characteristics.

Tested parameter		N° of pts.	CR (%)	*p*-value
Sex	Men	42	23 (55%)	
	Women	10	8 (80%)	0.11
Tumor site	Head & neck	34	19 (56%)	
	Other	18	12 (67%)	0.65
Histology	SCC	38	19 (50%)	
	Other	14	12 (86%)	0.045
Tumor volume	< 55 ccm	31	23 (74%)	
	≥ 55 ccm	21	8 (38%)	0.02
Previous RT	Yes	39	24 (62%)	
	No	13	7 (54%)	0.8
	≤ 50 Gy	22	15 (68%)	
	> 50 Gy	17	9 (53%)	0.5

CR – complete response, SCC – squamous cell carcinoma, RT – radiotherapy

Table 2. Prognostic significance of therapeutic parameters

Tested parameter		N° of pts.	CR (%)	*p*-value
Type of HT	Interstitial	20	10 (50%)	
	Percutaneous	32	21 (66%)	0.4
Type of RT	Interstitial	13	6 (46%)	
	Percutaneous	39	25 (64%)	0.1
N° of HT	1	33	23 (70%)	
	> 1	19	8 (42%)	0.1
T_{min}	≥ 42.5°C	43	29 (67%)	
	< 42.5°C	9	2 (22%)	0.015
TTD of RT	≥ 45 Gy	30	21 (70%)	
	< 45 Gy	22	10 (45%)	0.048
Fraction size/HT	> 3 Gy	28	21 (75 %)	
	≤ 3 Gy	24	10 (42%)	0.03
Sequence	RT + HT	29	21 (72%)	
	HT + RT	23	10 (43%)	0.026

CR – complete response, RT – radiotherapy, HT-hyperthermia, T_{min} – minimum intratumoral temperature, TTD – total tumor dose, Fraction size/HT – fraction size of RT concurrent to HT

remaining tested parameters, i.e. total dose of RT, fraction size of immediate irradiation, and sequence of RT showed a significant influence on local treatment outcome. While, all patients in RT + HT group were treated by external TRT (ETRT) only, CR rates in HT + RT group differed regarding the type of TRT applied. There were 6/13 (46%) CR recorded in patients using ITRT, 4/7 (57%) using STRT, while no CR was obtained in 3 patients treated by ETRT. Figure 1 presents a 2-year recurrence-free survival of 66% for the patients in whom RT was used immediately before HT, vs. 38% achieved in patients where RT followed HT (p=0.07). For 20 patients in whom an immediate fraction size of >3 Gy preceded HT, a recurrence-free survival of 84% was achieved (p=0.03). In Table 3 the two groups of patients treated with different sequence of the two modalities are compared regarding some prognostic parameters. It is shown that both treatment groups are acceptably comparable. Figure 2 presents dose response curves for the two groups of patients in whom different sequencing of both modalities was used. An enhancement ratio of 1.7 was found for the group of 29 patients in whom RT was used immediately prior to HT when plotted against those 23 patients in whom RT followed HT.

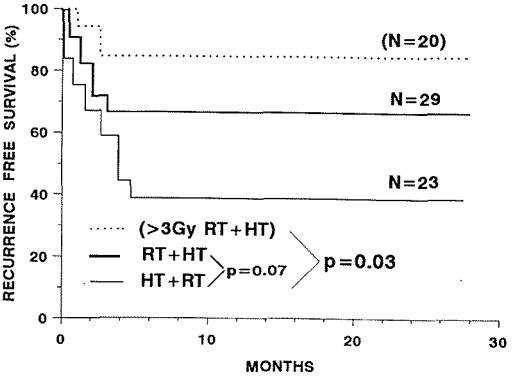

Figure 1. A 2-year recurrence-free survival (RFS) of 38% achived in 23 patients treated by TRT using HT prior to an immediate irradiation is compared to 66% for 29 patients in whom HT followed RT (p=0.07). Among those 29 patients in the latter group, there were 20 patients, refered in brackets, receiving a fraction size of > 3 Gy immediately before the heating. A significantly better RFS of 84% achieved in this subgroup of patients is presented by a dotted line (p=0.03).

The majority of our patients tolerated TRT treatment well, and there was no reason to terminate the therapeutic session before 45-60 min of HT treatment was reached. In 39 interstitial and/or percutaneous HT treatments, where no general anesthesia was used, generous infiltration of the heated volume with 2% Xylocain was employed. In a few patients pressure over the heated area was used in order to diminish the cooling effect of enhanced blood flow. Using RTOG/EORTC system, there were 29% of acute and 23% of late toxicities grade 3-4 recorded in our patients. Tables 4 and 5 present the prevalence of tested tumor and/or therapeutic

Table 3. The prevalence of prognostic parameters within the two groups of patients treated by different sequencing of the two treatment modalities.

Sequence of RT & HT	T_{min} ≥42.5°C (%)	Volume < 55 ccm (%)	TTD of RT ≥ 40 Gy (%)	Fr.size/HT > 3 Gy (%)	N° of HT > 1 (%)	Histology no SCC (%)
RT + HT	24/29 (83%)	19/29 (66%)	16/29 (55%)	19/29 (66%)	13/29 (45%)	8/29 (28%)
HT + RT	19/23 (83%)	12/23 (52%)	18/23 (78%)	9/23 (39%)	6/23 (26%)	6/23 (26%)
p-value	0.9	0.5	0.2	0.12	0.3	0.8

RT – radiotherapy, HT – hyperthermia, T_{min} – minimum intratumoral temperature, TTD of RT – total tumor dose, N° of HT – number of HT treatments, SCC – squamous cell carcinoma

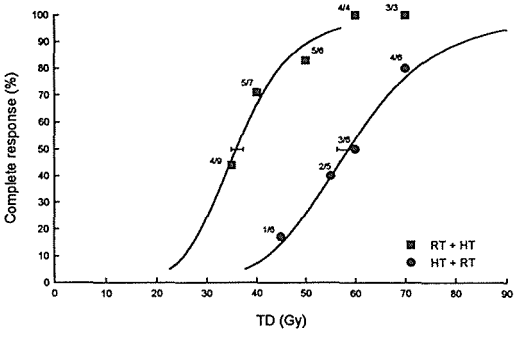

Figure 2. An enhancement ratio of 1.7 was found when the dose-response curve calculated for 29 patients receiving an immediate fraction of radiotherapy prior to the heat treatment had been compared to the dose-response curve for 23 patients in whom irradiation followed hyperthermia immediately.

Table 4. The influence of tumor and/or therapeutic parameters on acute toxicity grade.

Tested parameter		N° of pts.	Grade 3-4	*p*-value
Tumor volume	≥ 55 ccm	24	10	
	< 55 ccm	28	5	0.04
T_{max}	≥ 45°C	30	13	
	< 45°C	22	2	0.006
N° of HT	> 1	19	7	
	1	33	8	0.2
TTD of RT	> 45 Gy	30	11	
	≤ 45 Gy	22	4	0.1
Response	CR	31	9	
	no CR	21	6	0.2

T_{max} – maximum temperature measured in heated volume, HT – hyperthermia, TTD – total tumor dose, RT – radiotherapy, CR – complete response

Table 5. The influence of tumor and /or therapeutic parameters on late toxicity grade.

Tested parameter		N° of pts.*	Grade 3-4	*p*-value
Tumor volume	≥ 55 ccm	23	9	
	< 55 ccm	26	3	0.02
T_{max}	≥ 45°C	28	8	
	< 45°C	21	4	0.2
TTD of RT	> 45 Gy	27	7	
	≤ 45 Gy	22	5	0.3
Cumulative TTD	≥ 85 Gy	29	10	
	< 85 Gy	20	2	0.04

* In 3 patients evaluation of late toxicity was not possible because they died shortly after 3 months following TRT. T_{max} – maximum temperature measured inside the heated volume, TTD-total tumor dose, RT – radiotherapy

parameters at risk for the expression of higher grade toxicity. Tumor volume of 55 ccm was found equally significant for the appearance of both acute and late toxicity, T_{max} showed an important influence on acute toxicity rate, while higher cumulative TTD of RT was found to be responsible for a significant expression of high-grade late toxicity. There was no relation found in our patients between CR rate and the expression of either acute or late higher toxicity grade.

Discussion

Although, different treatment schedules of TRT were used at the Institute of Oncology, Ljubljana, it was possible to detect some important prognostic parameters with significant influence on local response rate. Next to tumor volume, TTD of RT, and T_{min} which has been previously recognized as prognostically important[16, 19, 35, 36] in our analysis also tumor histology, fraction size of RT concurrent to HT, and sequence of RT and HT were found of prognostic significance regarding CR rate (Tables 1

and 2). On the other side, tumor site, previous RT, type of RT and/or HT used, and more than one HT treatments showed no significant influence on response rate.

On basis of preclinical[21] and clinical data[37, 38] referring to the effects of HT treatment when combined with RT, it is possible to conclude that only appropriate heating should result in improvement of therapeutic effect when compared to RT alone. For multiple heatings used in clinical trials it was shown that CR rate, although strongly dependent of TTD of RT, is directly proportional to the cumulative equivalent time (CEM) at 43°C.[39, 40] Unfortunately, it is impossible to predict the sufficiency of heat treatment in clinical HT. In recently published randomized studies[18, 19] the planned intratumoral temperatures were reached only in a minority of treated patients. Although both trials failed regarding the planned threshold of minimum intratumoral temperatures, a significant influence of TRT over RT alone on CR rate (62% vs. 35%) was shown in a multicentric melanoma trial using ETRT,[19] while no benefit (57% vs. 54%) of combined treatment was recorded in RTOG study using ITRT.[18] From these data, regardless the differences in tumor histology, tumor volume, and TTD of RT for the patients treated in both series, two conclusions can be derived as follows: First, in external TRT where RT using a higher fraction size had been followed by an immediate heating, even "mild HT" significantly enhanced the treatment results. Second, "mild HT" followed by an interstitial low dose-rate brachyradiotherapy did not enhance already acceptable results achieved by RT alone. In meta analysis of clinical ETRT trials[15] it was found that the thermal enhancement ratios (TER) for different tumor types were similar regardless their response to RT alone. In the majority of published non-randomized series of head & neck tumors treated by TRT, the mean CR rate of 64% for ETRT[15] and 55% for ITRT[41] achieved were similar to the results of the two above mentioned randomized studies. In summary, although the heating in the majority of clinical trials has been equally inadequate, a constant superiority of ETRT over ITRT was recorded. It is hard to believe that thermal enhancement was more pronounced in ETRT trials, simply due to inferior results obtained by fractionated irradiation alone when compared to continual low-dose irradiation. It is more likely, that some other (presumably radiotheraputic) treatment parameters are responsible for the loss of thermal enhancement in ITRT.

In our treatments T_{min} of 42.5°C, measured at the tumor periphery throughout the 45 - 60 minutes of HT treatment course has been chosen as a therapeutic goal.[12] With respect to our HT strategy as much as 83% of patients (43/52) were adequately heated. Surprisingly, our overall CR rate of 60% was not found any better when compared to previously published TRT treatment series.[15, 42] However, when two groups of equally heated patients treated with different sequencing (i.e., RT + HT vs. HT + RT) (Table 3) were tested, a CR rates of 72% vs. 43% were estimated, respectively (p=0.025). RFS was significantly better for those 20 patients in whom >3 Gy of RT was used immediately before the heating (p=0.03) (Figure 1). When the dose response curves for the same two groups of equally heated patients has been drawn (Figure 2), the shape of the curve obtained in 23 patients in whom RT followed HT strongly resembled the curves for RT alone published in previous clinical trials.[15] According to the published data, similar effect are to be expected when HT is employed either before or after RT,[43] however in our patients an enhancement ratio of 1.7 was calculated in favor of TRT using RT immediately prior to HT. In one published animal study using ITRT,[44] the opposite findings were recorded, however, neither hyperthermic nor radiotherapeutic conditions used in aforementioned experiment are clinically obtainable.

The prediction that mild HT combined with low-dose rate RT would yield the best response[45] clinically failed.[18] On the other side, the possibility of tumor reoxygenation during mild HT[46] most likely does not affect tumors bigger than only few ccm.[26] If it would, the number of HT treatments should , by the process of reoxygenation, significantly improve the therapeutic results, not only in small experimental animal tumors,[47] but also in substantially larger human tumors.[48, 49] Though, in most of our patients cytotoxic level of intratumoral temperatures has been reached, still, practically no benefit of HT was recorded in patients in whom RT followed HT. The same observation was reported from animal experiments, when HT preceded RT.[50] It should be stressed that in a majority of our sufficiently heated patients the signs of circulatory collapse have been observed 30 minutes after T_{min} of 42.5°C at the tumor periphery has been reached. It is impossible to expect an enhancement of radiation damage in such a hypoxic situation. This is also a probable explanation for the achievement of only average treatment results (57% CR rate) achieved

in 7 patients in whom a really simultaneous TRT was employed, introducing the irradiation 30 minutes after HT treatment has been started. The fact, that in the majority of clinical trials an enhancement of TRT over RT alone was proved, although intratumoral temperatures achieved were far below from those proposed by results achieved from *in vitro* and *in vivo* experiments, is leading to a reasonable conclusion that in clinical circumstances tumors are more sensitive to HT. However, according to CEM,[40] it is not understandable that even more than 30 minutes of an "adequate heating" (i.e., $T_{min} > 42.5°C$), achieved in the majority of our patients, the therapeutic effect, obtained by HT + RT sequence, yielded the treatment results comparable only to those achieved by RT alone. The possible explanation for these findings is that the mechanism of thermal efficiency in clinical TRT most probably acts prevalently by inhibiting the ability of repair system for radiation induced damage. Because of somewhat greater sensibility of human tumors, in clinical conditions, to the heat, even non-cytotoxic HT could enhance an immediately preexisting radiation damage, however, sufficient heating probably results in better enhancement. Therefore, it looks like, it is not HT itself to be blamed for the disappointing treatment results obtained by ITRT, but more likely the placement and the amount of immediate irradiation used concurrently with HT. Our CR rate achieved in patients, where RT + HT sequencing has been used (i.e., CR rate of 72%), were even slightly better when compared to other randomized trials with similar sequencing employed.[15] Except for malignant melanoma, the positive influence of a higher fraction size of immediate RT, which in our case resulted in CR rate of 84%, in former clinical trials had not been found relevant. If radiosensitization induced by HT is a consequence of disturbances in DNA repair,[51] then only irradiation applied immediately before HT could result in the potentiation of radiation damage. A larger fraction size of RT should, therefore, result in more expressed potentiation of induced radiation damage. It is likely that higher intratumoral temperatures, rather than mild, interfere with the ability of repairing processes more effectively. Presumably, the recorded influence of somewhat higher fraction size on CR rate in our report is also related to the substantially higher level of intratumoral temperatures achieved in our HT treatments. Taking into account that in our report fairly good treatment results were achieved when RT was used immediately prior to somewhat more intense HT, even our higher rate of toxicity reported (Tables 4 and 5) could still be acceptable, considering the fact that the treatment by TRT was the only chance of prolonged survival due to a local cure in our patients.

It is true that a variety of tumor types and different treatment schedules used in our report can bias the final results. However, it is also true that by using strict protocols the differences would probably never show up.

It is our conclusion, that in the treatment of superficial human tumors by HT, either "mild" or "sufficient" heating, could be an important additive to RT, when appropriately employed. In our patients a significant influence of reasonably higher fraction size of RT on treatment results, when applied immediately before the heating session, was detected. Most likely, the low-dose irradiation, by having no ability to provide a productive amount of instant radiation damage to be increased by heat, rather than insufficient heating, was responsible for a poor expression of thermal enhancement in ITRT clinical trials.

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