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Radiotherapy combined with deep regional hyperthermia in elderly and frail patients with muscle-invasive bladder cancer: quality analysis of hyperthermia and impact on clinical results

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ABSTRACT

Purpose: Radiotherapy (RT) in combination with deep regional hyperthermia (HT) after transurethral removal of bladder tumor (TURBT) can be offered to elderly and frail patients with muscle-invasive bladder cancer (MIBC).

Methods: In total, 21 patients (mean age 84 years) with unifocal or multifocal MIBC received radiation to a dose of 48–50 Gy/16–20 fractions with weekly HT. The primary endpoint was the variation in temperature metrics, thermal dose expressed as cumulative equivalent minutes at 43 °C when the measured temperature is T_{90} ($CEM43T_{90}$) and net power applied in target volume per each HT session. Secondary endpoints were three-year overall survival (OS), disease-free survival (DFS), local progression-free survival (LPFS) and toxicity.

Results: The temperature metrics, $CEM43T_{90}$, mean and maximum net power applied did not differ significantly among the HT sessions of the 21 patients. With a median follow-up of 65 months, 52% (95% CI 32–72%) of patients had died 3 years after treatment. The three-year DFS and LPFS rates were 62% (95%CI 41–79%) and 81% (95%CI 60–92%), respectively. The three-year bladder preservation rate was 100%. Three out of four patients with local failure received a thermal dose $CEM43T_{90}$ below a median of 2.4 min. The rates of acute and late grade-3 toxicities were 10% and 14%, respectively.

Conclusion: The reproducibility of HT parameters between sessions was high. A moderately high $CEM43T_{90}$ (> 2.4 min) for each HT session seems to be preferable for local control. RT combined with HT is a promising organ-preservation therapy for elderly and frail MIBC patients.

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KEYWORDS

Radiotherapy; deep regional hyperthermia; muscle-invasive bladder cancer; temperature metrics; thermal dose; hyperthermia sessions

1. Introduction

Muscle invasive bladder cancer (MIBC) invades the detrusor muscle and has a high tendency to spread to lymph nodes and other organs, rendering it a challenging malignancy requiring a multidisciplinary approach to treatment [1,2]. The current standard of care for MIBC is either neoadjuvant chemotherapy followed by radical cystectomy or trimodality therapy consisting of transurethral resection of bladder tumor (TURBT) followed by chemoradiotherapy (CRT) [3,4].

Data from meta-analyses [5,6] and a recent multi-institutional propensity score-matched analysis [4] show that in well-selected patients with MIBC, bladder-sparing therapy can offer equal oncological outcomes compared with radical cystectomy. Based on these study results, there is an increasing interest in bladder preservation treatment strategies, which could provide patients with a choice of treatments and improvement of the quality of life, especially for elderly patients with associated comorbidities who are often deemed unfit for radical cystectomy [7]. Furthermore, if patients are given the choice, most patients would prefer a bladder-sparing technique, as it is considered tolerable due to its minimal invasiveness and manageable toxicity [8,9].

The BC2001 randomized trial in MIBC patients, which compared whether CRT would improve locoregional control of cancer if compared with radiotherapy (RT) alone, showed that only 11% of patients underwent radical cystectomy after being treated with neoadjuvant chemotherapy followed by CRT [10]. Currently, the most effective strategy for bladder-sparing therapy consists of maximal TURBT followed by CRT [11] with bladder preservation rates of 79–71% [11]. This treatment strategy is primarily used for the elderly, frail patients who are ineligible for radical cystectomy [12].

One limiting issue with regard to bladder preservation is that patients who are unfit for radical cystectomy are often also unfit for concurrent chemotherapy. RT alone for such patients has a limited therapeutic benefit in MIBC [13]. Therefore, deep regional hyperthermia (HT), can be offered

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as a radiosensitizer in combination with RT after TURBT, as an alternative treatment modality in elderly MIBC patients [14]. HT is a clinical treatment for cancer which heats tumor cells to a temperature of 40–43 °C for an hour [15]. HT induces direct cytotoxicity, radiosensitization by various effects on the microenvironment and tumors cells, as well as immune modulation when it is used in combination with RT [16]. The cell lethality induced by HT at temperatures 40–43 °C results from disruptions in cancer cell metabolism, inhibition of DNA repair, and triggering of cellular apoptotic pathways [17,18]. Several randomized clinical trials have demonstrated the effectiveness of HT in combination with RT for different cancer types [19,20].

To assess treatment quality, temperature is monitored and recorded during HT sessions using temperature probes, which may be placed directly or in the vicinity of the target volume [21]. The temperature metrics are derived from the recorded temperature data after each HT session to clinically evaluate the quality of heating in the target volume [22]. The concept of thermal dose, expressed as cumulative equivalent minutes at 43 °C (CEM43), is also estimated using the Arrhenius relationship to account for the biological effects induced by HT in terms of both temperature and heating duration [23].

In clinical studies, the temperature metrics and thermal dose CEM43 are reported as mean or median values using the temperature data across all HT sessions. However, no clinical analysis has been performed to assess the variation of temperature and thermal dose CEM43 between HT sessions. In this clinical study, we examined whether the temperature metrics and thermal dose vary significantly between each HT sessions in MIBC patients treated with RT combined with HT. Additionally, we report 3-year overall survival (OS), disease-free survival (DFS), local progression-free survival (LPFS) evaluated by cystoscopy with or without biopsy and including acute and late toxicity symptoms following RT and HT for MIBC.

2. Methods

2.1. Patients

Patients with MIBC treated with TURBT followed by RT in combination with HT in the Radiation Oncology Center at Cantonal Hospital Aarau from December 2012 and July 2022 were included in this analysis. The hospital study protocol was approved by Cantonal Ethics Committee in Aarau, Switzerland. This study's research adheres to guidelines of the Declaration of Helsinki and was approved by the Institutional Ethics Committee Northwest and Central Switzerland (protocol code 2023-01512), which granted an exemption from obtaining individual informed consent. All data used in this study were treated in accordance with ethical and legal standards to ensure the confidentiality and rights of the individuals involved. Pilot clinical data without analysis of hyperthermia parameters were published in 2019 [14].

2.2. Treatment

2.2.1. Radiotherapy

For multifocal bladder tumors, 50 Gy in 20 fractions were delivered over four weeks to the entire empty bladder along with proximal urethra, prostate and prostatic urethra (in men). For unifocal tumors, 36 Gy in 12 fractions were delivered to the partially filled bladder three times a week. Additionally, a sequential boost to unifocal tumors was delivered once weekly to a dose of 12 Gy in four fractions.

2.2.2. Deep regional hyperthermia

HT was delivered with a BSD-2000 with Sigma-60 or Sigma-Eye phased array applicator (BSD Medical Cooperation/ Pyrexar, Salt Lake City, UT, USA) at frequency of 75–120 MHz in accordance with the European Society of Hyperthermic Oncology (ESHO) quality guidelines [24,25]. The choice of applicator was based on the patient's size and typically, the Sigma-Eye was used for smaller-sized patients.

A geometric HT treatment plan was generated in the Eclipse™ treatment planning system version 16.0 (Varian Medical Systems, Palo Alto, USA) for all patients. A CT scan with a reference marker was undertaken in the HT treatment position (patient lying in the treatment hammock). The importance of the marker in the planning CT for HT is to define the reference position for the image registration, treatment planning and repositioning of patient during the treatment course.

Image registration was performed to use the gross target volume contoured for the RT treatment plan to generate the geometric HT plan. The heating target volume and the rectal probe were also contoured on the co-registered CTs, as shown in Figure 1. The probes were contoured for bladder or organs at risk (e.g., rectum and vagina) for each patient as appropriate, to understand the location of thermometer measurement points with respect to the planning target

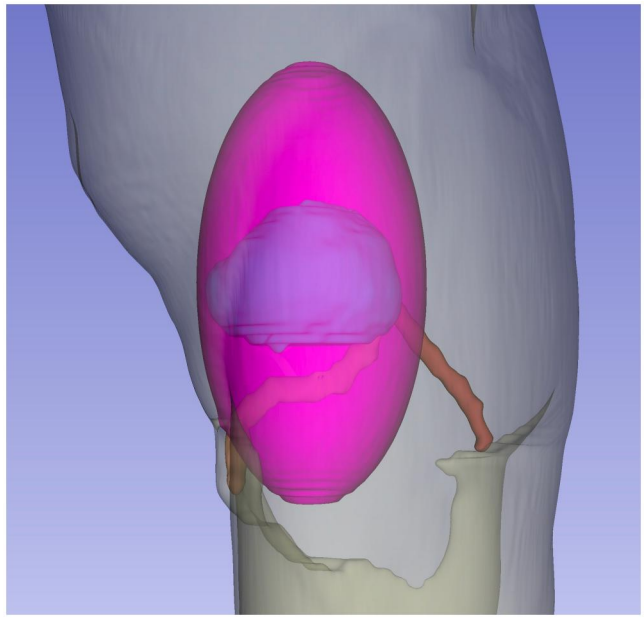

Figure 1. The geometric HT treatment plan.

volume (PTV) and the heating target volume (Figure 1). The evaluation of temperature in the PTV was evaluated based on measurement points from the probe inserted in the bladder only.

The relative shift in 3D heating volume and the marker in the registered planning CT for HT was automatically estimated.

After specifying the location of the tumor relative to the marker on the planning CT scan, the frequency of the radiofrequency (RF) field and the power were selected. After a 15–30-min preheating phase, a therapeutic temperature between 40 and 43 °C was applied for one hour. The catheter-guided temperature probes were inserted in the bladder, rectum or vagina to read and monitor the temperature during the HT session. During HT treatment sessions, the temperature with respect to the position of the temperature measurement points were monitored for bladder, rectum and vagina. The objective was to sustain a steady 40–43 °C temperature within the bladder (PTV) for an hour, following the pre-heating period, while ensuring that the temperature in the rectum and vagina, whether close or distant to the PTV, remained below 40 °C, respectively. Any hotspots in the rectum and vagina were managed by phase steering.

The temperature was measured at 10 s intervals, starting before treatment and stopping either immediately or five minutes after switching off the radiofrequency power. Thermal mapping was performed every 8 min with a step size of 1 cm and a maximum map length of 18 cm. Patients were treated with deep regional HT sessions once a week before RT.

2.3. Outcomes and statistical analysis

The patient-, disease- and treatment-related characteristics at baseline are summarized by descriptive statistics. The continuous variables are summarized using mean ± standard deviation or median with a range interval. The categorical variables are reported as frequency and percentages.

The primary outcomes of this analysis were temperature metrics, thermal dose expressed at cumulative equivalent minutes at 43 °C when the measured temperature is T_{90} ($CEM43T_{90}$), the mean and maximum net power applied (Watts, W) in the bladder target volume. The temperature metrics and thermal dose $CEM43T_{90}$ were estimated using a single temperature-specific measurement point which was used to represent the tumor temperature data in the bladder target volume.

The following temperature metrics were estimated for this analysis:

- T_{20}, T_{50}, T_{90} are the temperatures achieved in 20%, 50% and 90% of the temperature-specific measurement point in the bladder target volume, respectively.
- T_{max}, T_{mean}, T_{min} are the maximum, mean and minimum temperatures achieved in the temperature-specific measurement point in the bladder target volume.

Thermal dose $CEM43T_{90}$ was calculated using the concept proposed by Saparto and Dewey [23]: $CEM43T_{90} = \sum \int_0^t R^{(43^\circ C - T_{90}(\tau))} d\tau$ where $R = \begin{cases} 0.5 \ if \ T \geq 43^\circ C \\ 0.25 \ if \ T < 43^\circ C \end{cases}$, t is the duration of one HT treatment session and $T_{90}(\tau)$ is the time-dependent temperature T_{90} measured in °C.

The main research question was "Do temperature metrics and thermal dose $CEM43T_{90}$ vary significantly per each HT session?". The variation of temperature metrics, thermal dose $CEM43T_{90}$ including the mean and maximum net power applied applied for each HT session were compared using multiple pairwise paired t-tests. The *p*-values were adjusted with the Bonferroni multiple testing correction method.

The secondary outcomes were 3-year OS, DFS, LPFS and toxicity. The survival endpoints OS, DFS and LPFS were computed using the Kaplan-Meier survival estimator. OS measured from treatment start to death, DFS from treatment start to local progression or metastasis, and LPFS to local progression based on cystoscopy with or without biopsy result or evidence of metastases based on radiological examinations. Patients still alive at the analysis time were censored at their last available follow-up data for the respective outcome. The median follow-up was calculated using the reverse Kaplan–Meier survival estimator. The relationship between clinical outcomes and thermal dose $CEM43T_{90}$ are descriptively analyzed. In addition, the acute and late toxicities were evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) toxicity scale version 4.0. The acute and late toxicities are reported using frequency and percentages.

All statistical tests were two-tailed and p-values ≤ 0.05 were considered significant. All statistical analyses were performed in R studio (Version 4.0.5, R studio, Inc. Boston) using the main packages 'rstatix', 'survival' and 'binom'.

3. Results

In total, 21 patients (19 male and two female) with median age 84 (57-90) years, were enrolled in this analysis. There were 14 and 7 patients with multifocal and unifocal tumors, respectively. Histopathologically, all patients had a grade-3 urothelial malignancy. Baseline patient and tumor characteristics are shown in Table 1.

3.1. Primary outcomes: Variation of temperature metrics and thermal dose among HT sessions

All patients received the prescribed total radiation dose without unplanned treatment interruptions. One patient had to interrupt HT treatment due to a urinary tract infection and received only two HT sessions. The remaining 20 patients received all HT sessions as planned.

The average of T_{20}, T_{50}, T_{90}, T_{max}, T_{mean}, T_{min} estimated in 21 patients during their HT treatment course were 41.63 ± 0.14, 41.37 ± 0.15 °C, 40.66 ± 0.16 °C, 41.84 ± 0.14 °C, 41.29 ± 0.14 °C, 40.51 ± 0.15 °C, respectively. Among four HT sessions, none of the temperature metrics (T_{20}, T_{50}, T_{90}, T_{max}, T_{mean}, T_{min}) varied significantly as shown in Figure 2.

The mean thermal dose CEM43T_{90} was 4.23 ± 1.12 min. No significant difference in thermal dose CEM43T_{90} among the four HT sessions was found (supplementary Figure S1). The average and maximum net power applied during the HT sessions in all patients was 641.92 ± 22.71 W and 719.45 ± 30.84 W, respectively. The applied (mean and maximum) power did not differ significantly among HT sessions (supplementary Figure S2a and Figure S2b).

For unifocal and multifocal tumors, the temperature metrics (T_{20}, T_{50}, T_{90}, T_{max}, T_{mean}, T_{min}), thermal dose CEM43T_{90}, maximum and minimum power applied during HT sessions are summarized in Table 2.

Table 1. Patient and tumor characteristics.

Variables	
Age	81 ± 8.9
Sex	
Male	19 (90%)
Female	2 (10%)
Weight before treatment [kg]	71 ± 3.2
T stage	
T1	2 (9.5%)
T2	17 (81%)
T3	0 (0%)
T4	2 (9.5%)
N stage	
N0	19 (90.5%)
N+	2 (9.5%)
M stage	
M0	19 (90.5%)
Mx	2 (9.5%)
Tumor lesions	
Unifocal	7 (33%)
Multifocal	14 (67%)
Tumor grading	
G3	21 (100%)

3.2. Secondary outcomes: survival outcomes and toxicity symptoms

After a median follow up of 65 (95%CI: 56-74) months, 52% (95% CI 32-72%) of patients had died 3 years after treatment (Figure 3a). The median DFS was 22 months as shown in Figure 3b. The 3-year rate of DFS and LPFS were 62% (95%CI 41-79%) and 81% (95%CI 60-92%), respectively. The Kaplan Meier for 3-year LPFS is shown in Figure 3c. In total, four patients (19%) experienced local progression, two of four patients underwent a repeat TUR-BT and thereby retained their bladder. One patient died due to progressive disease, i.e., local failure and distant metastases. The fourth patient with local failure underwent bladder neck incision and transurethral prostate resection. Three of four patients who experienced a local failure had received a thermal dose CEM43T_{90} below the median of 2.4 min. A trend to increased local control was observed in patients who were treated with a thermal dose CEM43T_{90} above the estimated median 2.4 min. The 3-year bladder preservation rate in these patients was 100%.

One patient who was diagnosed with distant metastases in the spleen and pancreas 15 months after MIBC treatment underwent splenectomy with pancreaticodudenectomy. The patient was alive and locally free of cancer in the bladder 38 months after surgery. Three other patients developed distant metastases without local failure. Three of these four patients who developed metastases were treated with CEM43T_{90} below 2.4 min.

The incidence of acute and late grade 2 toxicity was 29% and 21%, respectively (Table 3). The rates of acute and late

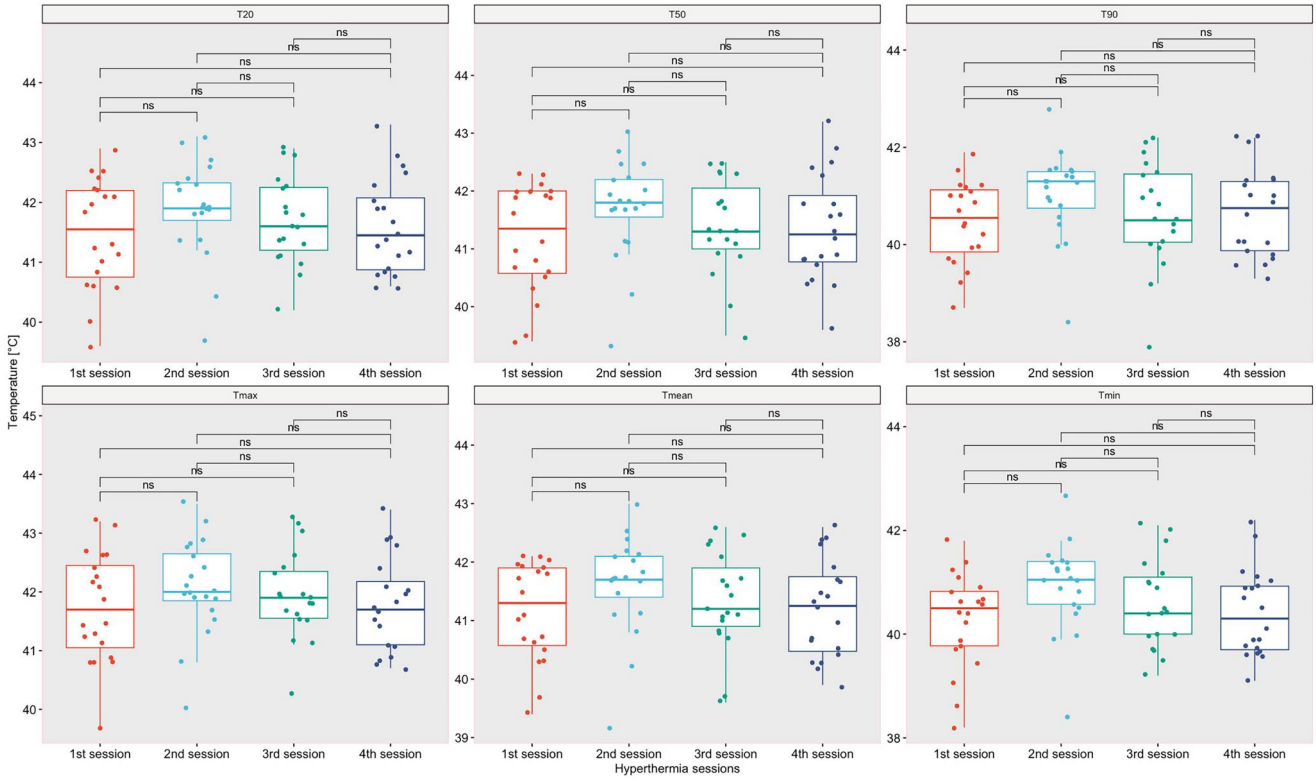

Figure 2. Temperature metrics (T_{20}, T_{50}, T_{90}, T_{max}, T_{mean}, T_{min}) for each HT sessions in 21 patients. ns: nonsignficant statistical difference (p-value > 0.05).

Table 2. Mean and standard deviation (SD) of temperature metrics (T_{20}, T_{50}, T_{90}, T_{max}, T_{mean}, T_{min}), thermal dose CEM43T_{90}, mean and maximum power in 7 and 14 patients with unifocal and multifocal muscle invasive bladder cancer patients, respectively.

Variables	Unifocal tumors ($n = 7$) Mean ± SD	Multifocal tumors ($n = 14$) Mean ± SD
T_{20} [°C]	41.47 ± 0.97	41.71 ± 0.49
T_{50} [°C]	41.18 ± 1.04	41.47 ± 0.51
T_{90} [°C]	40.42 ± 0.96	40.78 ± 0.61
T_{max} [°C]	41.68 ± 0.97	41.93 ± 0.50
T_{mean}[°C]	41.10 ± 0.96	41.39 ± 0.50
T_{min} [°C]	40.34 ± 0.88	40.60 ± 0.60
Thermal dose CEM43T_{90} [minutes]	4.66 ± 7.71	4.02 ± 3.68
Mean Power [W]	618.73 ± 130.52	651.74 ± 91.53
Maximum Power [W]	682.73 ± 168.97	750.35 ± 118.65

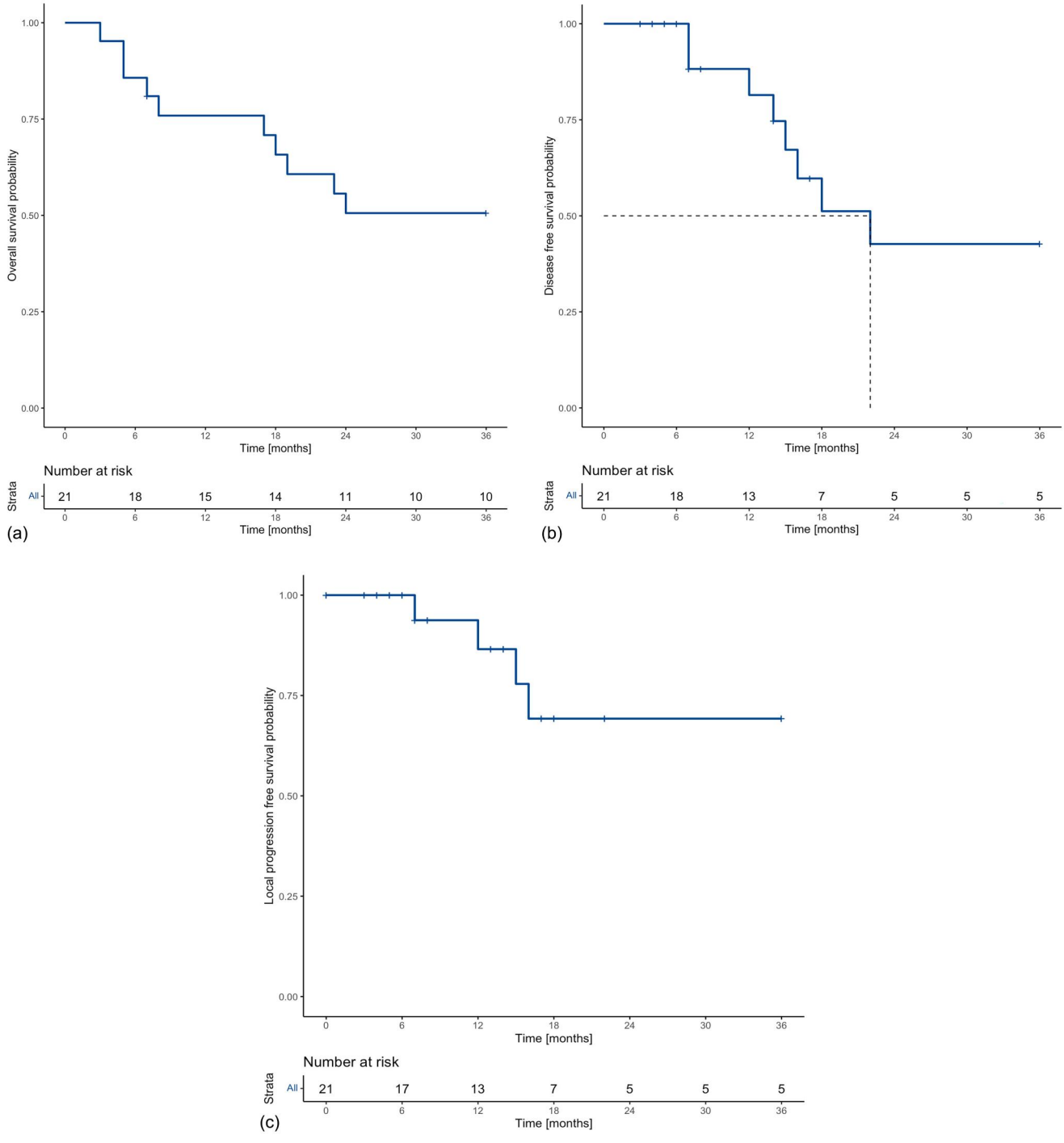

Figure 3. Kaplan Meier Curves representing 3-year a) overall survival, b) disease free survival; c) local progression free survival after post-TURBT HT and RT.

Table 3. Acute and late toxicity according to CTCAE v.4.0.

	Acute toxicity $n = 21$	Late toxicity $n = 15$
Grade 2 toxicity		
Dermatitis	1 (5%)	0
Hematuria	2 (10%)	0
Diarrhea	3 (14%)	0
Abnormal urination frequency with nocturia	0	2 (14%)
Pain in pelvic region	0	1 (7%)
Grade 3 toxicity		
Obstipation	1 (5%)	0
Urinary tract infection	1 (5%)	0
Hematuria	0	1 (7%)
Bladder infection	0	1 (7%)

grade 3 toxicity were 10% and 14% (Table 3). The acute grade 2 toxicities included dermatitis ($n = 1$), hematuria ($n = 2$) and diarrhea ($n = 3$). The grade 3 acute symptoms were constipation ($n = 1$) and urinary tract infection ($n = 1$). Late toxicity data were available for 15 patients. Grade 2 symptoms were: frequent and abnormal urination with nocturia ($n = 2$) and pelvic pain ($n = 1$). Grade 3 late toxicity symptoms included hematuria ($n = 1$) and bladder infection ($n = 1$).

Patients who experienced grade 3 late toxicities (hematuria and bladder infection) were treated with thermal dose $CEM43T_{90}$ of 2.72 min (above the median $CEM43T_{90}$ of 2.4 min) and 2.17 (below the median $CEM43T_{90}$ of 2.4 min) minutes, respectively. Moreover, patients with symptoms of grade 2 late toxicity were all treated with thermal dose $CEM43T_{90}$ lower than 2.4 min.

4. Discussion

This is the first clinical study in patients with MIBC that investigates the quality of HT and its impact on clinical outcomes. We investigated whether tumors were heated to the desired temperature for the recommended time (an hour at 40–43 °C). All 21 patients were treated with a moderately high thermal dose $CEM43T_{90,}$ with median of 2.4 (range: 0.3–14.6) minutes, indicating that the bladder target volume was heated at the desired temperature during each weekly HT session. Pleasingly, the temperature metrics (T_{20}, T_{50}, T_{90}, T_{max}, T_{mean}, T_{min}), thermal dose $CEM43T_{90}$, mean and maximum net power applied in the target (bladder) volume between HT sessions did not differ significantly, despite the numerous challenges of effectively heating the bladder target volume, including heat dissipation, blood flow (perfusion) and maintaining patient comfort during each HT session.

The three-year OS, DFS, LPFS rates, in MIBC patients treated to 40–43 °C for an hour weekly, were 52% (95%CI 32–72%), 62% (95%CI 41–79%) and 81% (95%CI 60–92%), respectively. These results are comparable with the preliminary results reported in 24 elderly MIBC patients treated with hypofractionated RT (50 Gy/20 fractions) combined with concomitant weekly chemotherapy [26]. Due to the intense chemotherapy treatment regime, 4% of patients experienced acute grade 3 gastrointestinal or genitourinary toxicities and 17% of patients had acute grade 3 or 4 hematologic toxicities, liver toxicities, or both [26], whereas in our analysis only two patients (10%) experienced grade 3 toxicity. Thus, MIBC patients who were treated with CRT experienced higher side effects and toxicity symptoms in comparison with patients treated with RT in combination with HT.

Recently, our group reported that patients with various tumor types treated with combined radio(chemo)therapy and HT had significantly improved or stable quality of life scores according to the symptoms and functional scale items of the EORTC Core Quality of Life questionnaire [27]. The use of HT in combination with RT does not markedly enhance acute or late toxicities, when thermal hotspots are continuously monitored and managed during HT sessions [28]. In this analysis, we showed that no hotspots above 43 °C were recorded at one single specific measurement point in the bladder.

Various treatment strategies for MIBC without the addition of chemotherapy have been investigated. Hypofractionated RT (36 Gy/6 fractions) alone and in combination with an immune checkpoint inhibitor showed no further improvement of clinical outcomes but considerable toxicity [29,30] and cannot be recommended. A meta-analysis conducted to assess which RT schedule is more effective for bladder preservation in MIBC showed that 55 Gy/20 fractions can be considered as standard of care when compared to 64 Gy/32 fractions, with regard to locoregional control rates and toxicity [31]. The elderly patients with unifocal and multifocal tumors in our analysis, received 48 Gy/16 fractions or 50 Gy/20 fractions respectively, which is a lower dose suited to the very fragile patient cohort with shorter life expectancy.

Monitoring and recording temperature during HT is one of the main challenges in routine clinical practice and has hindered the clinical expansion of HT. Not all clinical studies that investigate the effect of HT report the quality of HT applied or the temperatures achieved in the region of the tumor. The process of inserting temperature probes to monitor and record the temperature during HT is considered invasive and uncomfortable, and sometimes the tumor site is inaccessible for the insertion of such probes. In comparison to other cancer sites, it is relatively easy to monitor and measure the temperature in the bladder invasively with a transurethral probe, which is why we performed the analysis of temperature metrics and thermal dose in this group of patients. We excluded bladder cancer patients treated with HT and CRT because HT is also a recognized sensitizer of several chemotherapeutic drugs which could bias the analysis [32]. Another obstacle to HT is the non-standardized methodology for describing the temporal and spatial variance of the temperature fields. The study by Oleson et al. showed that T_{min}, tumor volume, radiation dose, and heating technique play significant roles in predicting treatment response for patients treated with RT in combination with HT [33]. In contrast, Leopold et al. reported in patients with soft tissue sarcomas that the more robust parameters T_{90}, T_{50}, and T_{10} are better temperature descriptors and predictors of histopathologic outcome than T_{min} and T_{max} [34]. In our analysis, we included all the above temperature metrics for the clinical evaluation of the HT sessions. Due to the relatively small number of available patients, it was not feasible to develop a prediction model. Larger patient cohorts are required to

determine which temperature parameters may predict clinical outcomes. The predictive role of thermal dose has been investigated in a few studies [34–37], but no conclusion has been drawn regarding the thermal dose that should be obtained during HT to maximally enhance the effect of RT. A randomized trial in 122 dogs with sarcomas was designed to evaluate prospectively the effect of high thermal dose 20-50 $CEM43T_{90}$ vs low thermal dose 2-5 $CEM43T_{90}$ on clinical outcome. This study showed a significant association between prescribed thermal dose $CEM43T_{90}$ and duration of local tumor control [38]. The outcomes of this study were reaffirmed in a randomized clinical trial in human cancer patients with superficial tumors which reported a significant difference in the duration of local control between the patients who received HT with a high thermal dose (10 CEM43T90) combined with RT in comparison to RT alone (OR = 2.8, 95%CI: 1.2–6.3, $p = 0.02$) [39]. Furthermore, a few retrospective studies have reported that thermal dose, CEM43, is an adequate predictor of treatment response and its best prognostic descriptor is $CEM43T_{90}$ [34,36,37]. Dinges et al. reported that $CEM43T_{90}$ was significantly associated with local tumor control for patients with uterine cervix carcinomas, treated with RT in combination with HT [40]. Similarly, Kroesen et al. showed that $CEM43T_{90}$ is a predictive factor of local control in cervix cancer [35]. Recently, a prospective phase II study investigating neoadjuvant triplet therapy in patients with rectal cancer showed that patients with a good tumor regression had higher values for CEMT43 (7.2 min vs. 4.5 min, $p = 0.012$) [41]. The retrospective analysis of thermometric parameters of the prospective study by Harima et al. [42] showed that >1 min $CEM43T_{90}$ is the threshold value, which significantly correlates with treatment response (complete remission and DFS rates). Not only tumor stage, performance status, radiotherapy dose and tumor size but also $CEM43T_{90}$ emerged as significant predictors of the various oncological outcomes [36].

Two studies reported that a high power applied during HT results in higher temperatures [43,44]. In contrast, a large analysis of 444 patients with primary cervical cancer treated with HT in combination with RT did not find any correlation between the net power and temperature metrics [45]. In this analysis, it was also concluded that lower target temperatures are achieved in patients >70 kg and such patients are more challenging to heat adequately [45]. In our analysis, patients had a mean weight of 71 ± 3.2 kg before treatment and the narrow range may be one of factors behind the non-significant variation of temperature and power between HT sessions.

The promise of the bladder-sparing 'RT and HT after TURBT' combined modality approach in elderly MIBC patients has also been shown in a large retrospective analysis by the research group in Erlangen [46]. The favorable clinical outcomes in our cohort can be explained by the maximal radiosensitization achieved by the constant and good quality heating of the bladder target volume during each HT session. We showed that a homogenous temperature was achieved in the bladder target volume due to non-significant variation of the temperature metrics, thermal dose and applied power during the HT sessions. A homogenous adequate temperature plays an important role in increasing efficacy thus leading thus to a high local tumor control.

Based on these results, the use of HT in combination with RT in MIBC patients, who are unfit for radical cystectomy and chemotherapy and/or who decline these treatment options, should be assessed in a larger cohort to evaluate the efficacy of the treatment and the association of temperature metrics and thermal dose on clinical outcomes.

5. Conclusion

The present study showed that high quality HT can be achieved in elderly and frail patients with MIBC and the combined treatment with HT and RT is efficient, with a high and persistent local control rate during the remaining life span of these patients.

Ethic statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee Northwest and Central Switzerland (protocol code 2023-01512).

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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