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Critical Reviews in Oncology/Hematology 47 (2003) 127–139

Critical Reviews in Oncology Hematology

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Combination of intravesical chemotherapy and hyperthermia for the treatment of superficial bladder cancer: preliminary clinical experience

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Accepted 16 December 2002

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1040-8428/03/$ - see front matter
doi:10.1016/S1040-8428(03)00076-3

Abstract

The prevalence of superficial transitional cell carcinoma of the bladder (STCCB) is still increasing in spite of improved adjuvant chemotherapic and/or immunoprophylaxis approaches. Thus, there is certainly an urgent need to improve our ability to control this disease. Local hyperthermia has a therapeutical potential for the treatment of many solid tumors, especially when used in combination with other treatments, such as radiation and chemotherapy. In particular, a synergistic or, at least, supra-additive anti-tumor cell killing effect was documented when local hyperthermia was administered in combination with selected cytostatic drugs. Recently, advances in miniaturized technology have allowed the development of a system specifically designed for delivering an endovesical thermo-chemotherapy regimen in humans. In preliminary clinical experiences, insofar mainly carried out as mono-institutional investigations, the combined treatment using this system was demonstrated to be feasible, minimally invasive and safe when performed on out-patient basis. Moreover, the anti-tumoral efficacy seemed to be significantly enhanced when compared with that obtained using intravesical chemotherapy alone for both adjuvant (prophylaxis) and neo-adjuvant (ablative) approaches to superficial bladder cancer.

Keywords: Bladder cancer; Local hyperthermia; Chemotherapy

1. Introduction

Epidemiological studies show a progressive increase in the prevalence of superficial transitional cell carcinoma of the bladder (STCCB) and the treatment of this disease still remains a major problem in oncology [1,2]. As a matter of fact, standard procedure for its removal is still represented by transurethral resection (TUR). However, as well known, following this procedure as a single step, tumor recurrence-rate is dramatically high. In order to reduce this high recurrence rate, several endovescical adjuvant cytostatic agents or immuno-modulating drugs have been widely introduced and used in the last 20 years. However, in spite of these adjuvant regimens, 30–50% of STCCB tumors recur within 24 months and 15–30% progress to infiltrating stage according to different tumor characteristics and schedule of administration adopted [3–5]. As a consequence, new and more effective ways of investigating procedures are needed when treating superficial bladder cancer for both ablation of neoplasm and prophylaxis of recurrence.

At present, intravesical treatment is administered following TUR and recurrence-rate reduction remains the only indicator available to define treatment efficacy [6–9]. However, the neo-adjuvant pre-TUR chemotherapy on native tumors, seems to be the most adequate way to assess the anti-tumoral potential of any intravesical therapy [10,11].

The combined administration of local hyperthermia and selected cytostatic agents represents an innovative and encouraging modality for treating different kinds of solid tumors, mainly when refractory to standard therapies. Due to its endocavitary location, superficial bladder cancer has represented an exciting field for the clinical application of this promising association for a long time. However, so far, lack of suitable technology has strongly limited the application of this intriguing approach in clinical practice. After extensive laboratory and animal investigations a novel technically advanced system, specifically designed for handling superficial bladder cancers, was realized and clinically tested. This system allows for a combined approach using local endocavitary microwave-induced hyperthermia and intravesical chemotherapy. In over 10 years, many clinical investigations have been carried out in order to test its technical feasibility, efficacy and safety.

2. Background and rationale

After sporadic evidences of therapeutic effects of hyperthermia, early in the last century [12,13], many therapeutic applications of local hyperthermia (LHT) in the oncological field have been organized enthusiastically in the following decades, achieving interesting but often disappointing results. The most recent interesting attempts have been focused on the combination of LHT together with chemo and/or radiotherapy.

The basic rationale of this approach has been well known for a long time: a synergistic or at least a supra-additive anti-tumoral cell killing effect can be expected in vitro and in vivo when LHT is administered in combination with selected cytostatic agents in treating many malignancies, including transitional cell carcinoma. At present, the reason for this synergistic effect is still not completely clear. However, according to several in vitro observations, different mechanisms seem to explain this improved anti-tumoral effect that also depends on temperature, time of exposure, and of course on the cytostatic drug used [14–16].

As a matter of fact, in the mid-60s and mid-70s the endovesical administration of local hyperthermia was performed by the use of hot water irrigations of the bladder cavity achieving poor or controversial clinical outcomes. In fact, when using this kind of procedure, only superficial anti-tumoral effect can be obtained, through the whitening of the tumor surface, whilst

leaving the underlying tumoral mass unaffected [17]. The main technical limitations of the hot water perfusion method were: (1) the necessity to heat the solution at very high temperatures outside the body in order to obtain some acceptable therapeutic temperature inside the bladder, (2) the risk of overheating the urethral tissue and (3) a heterogeneous and unreliable distribution of heating at different points of the bladder wall.

Since then, various techniques for local hyperthermia delivering have been proposed. Among these ultrasounds and electromagnetic non-ionizing radiations such as radiofrequencies have also been tested by different Authors [18–21] including ourselves. When we started our project an electromagnetic radiation (microwave) was used. Technical implementations were developed through specifically designed pre-clinical studies.

3. Pre-clinical studies

3.1. Laboratory investigations

With the use of the liquid phantom (Fig. 1) we demonstrated that electromagnetic radiation is transmitted from the applicator in a cylindrical symmetrical mode and that there is no electromagnetic radiation in undesired zones. Investigations on liquid phantom also documented that electromagnetic radiation energy has a typical shape, with higher energy transmitted towards distant bladder wall and lower energy to the near bladder wall. The particular radiation pattern would allow for more homogeneous energy deposition in all of the bladder wall, once the bladder is inflated in a controlled manner. In addition, it could be demonstrated that the electromagnetic radiation propagating from the applicator does not decay exponentially, because, as expected, the whole volume of interest is in the near field.

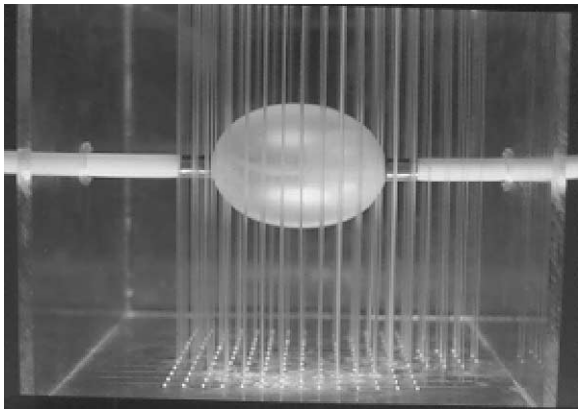

Fig. 1. Liquid phantom used for the definition of physical proprieties of the Synergo® system RF-applicator. The configuration of the catheter during the measurement of heat deposition and of energy profile of the microwave applicator is shown.

A special solid phantom simulating a bladder embedded in a special material equivalent to the muscle tissue [22] was used to study the dielectric properties of the specific electromagnetic frequency.

With this phantom we simulated treatments with the use of a catheter. We measured the heat deposition in the vicinity of the bladder wall in the area corresponding to the lamina propria, the muscle as well as in areas of the urethra. The measurements were also taken to verify heat deposition further in depth.

It was also demonstrated that the heat absorption rate to the electromagnetic radiation from the applicator, in the circumstances resembling treatment, indeed gave homogeneous heating of bladder wall surface, decayed rapidly with depth (typically at 5 mm) and that there was no potentially harmful heating in any undesired area, such as in the urethra. The investigation on temperature profiles, using a solid phantom showed two important aspects. The first is that the temperature gradients over the bladder predicted by Specific Absorption Rate (SAR) of the tissue at any given point on the bladder walls is small and of the order of 10% which means temperature variation of $\pm 0.8\,^{\circ}C$ or less. The second important aspect is that the temperature drop in the depth of the bladder is predicted to fall 90% in few millimeters [23].

3.2. Animal investigations

Female pigs were treated with catheters and the applicator inserted through the urethra while thermocouples measured the temperature on the internal surface of the bladder. With such a thin bladder wall, the pig's bladders were surgically exposed (under complete anesthesia and having the Ethics Committee approval for the experiments) and another set of thermocouples was attached to the external surface of the bladder. Using this procedure it was demonstrated that the heating mechanism of the bladder wall was direct and actually due to the heating by the electromagnetic radiation and not to the heating of the medium (distilled water) inside the bladder. The temperatures measured by both sets of thermocouples were also compared, demonstrating that the internal thermocouples were measuring the bladder wall temperature correctly and were not influenced by the electromagnetic radiation or by the medium temperature.

In a following animal investigation, some adult sheep were used, in order to simulate the actual conditions and methods utilized during the treatment with the device. With the treated sheep fully anesthetized, the catheter with the special microwave delivering applicator was placed inside the bladder and a full session of treatment took place after the thermocouples were sewn to the

internal and external bladder surfaces. The bladder and adjacent organs were, thereafter, macroscopically and microscopically evaluated. The main observation was ulceration of the epithelium, mild oedema and inflammation of the lamina propria, as well as foci of fresh hemorrhage in the serosa. All changes observed were of transient nature and attributed to surgical procedure and not to the treatment. The harvested organs were also macroscopically and histologically examined for possible damage, using the control sheep samples for comparison purposes. The temperature mapping and following pathological findings of the bladder, clearly showed that the treatment could be delivered safely with no risks of irreversible damage to the urinary bladder or adjacent tissues [23].

3.3. System and procedure

Laboratory and animal investigations gave physical and biological information for the realization of a specifically designed system for superficial bladder cancer treatment in clinical practice.

This technically advanced system was named Synergo® SB-TS:101-1. In its final version, the system used for clinical applications consists of a 915 MHz intravesical microwave applicator, which delivers hyperthermia to the bladder walls via direct irradiation [24]. The applicator is inserted into the bladder through a special operative transurethral 20 F balloon catheter which also allows, through different and separate ways, for the intravesical administration of the cytostatic solution and for the insertion of a set of thermocouples for measuring the temperature at the superficial layer of the bladder walls. More precisely, two thermocouples are located inside the catheter in the prostatic urethra (only one for the urethral sphincter zone in the female patients), one is inserted in the applicator and the other three are spread out from the catheter and pushed tangentially against the bladder neck and the posterior and lateral walls of the bladder during the operative session. The tips of these thermocouples are very thin and well isolated from the cytostatic solution instilled into the bladder, thus ensuring that the actual temperature of the superficial bladder wall layers is measured. To avoid the risk of urethral overheating, the drug solution is automatically and continuously pumped out of the bladder and re-instilled after being cooled. The closed circulatory circuit allows the control of the temperature of the solution at the urethral tract and in the bladder. All physical parameters including the power at the microwave source, radiofrequencies and temperatures, are monitored by means of a computerized unit and specific software (Fig. 2).

We can assume that using this system the combined endovesical administration of hyperthermia and chemotherapy can be achieved given a controlled, uniform and prolonged contact of the cytostatic drug solution with the bladder wall as well as a controlled and quite

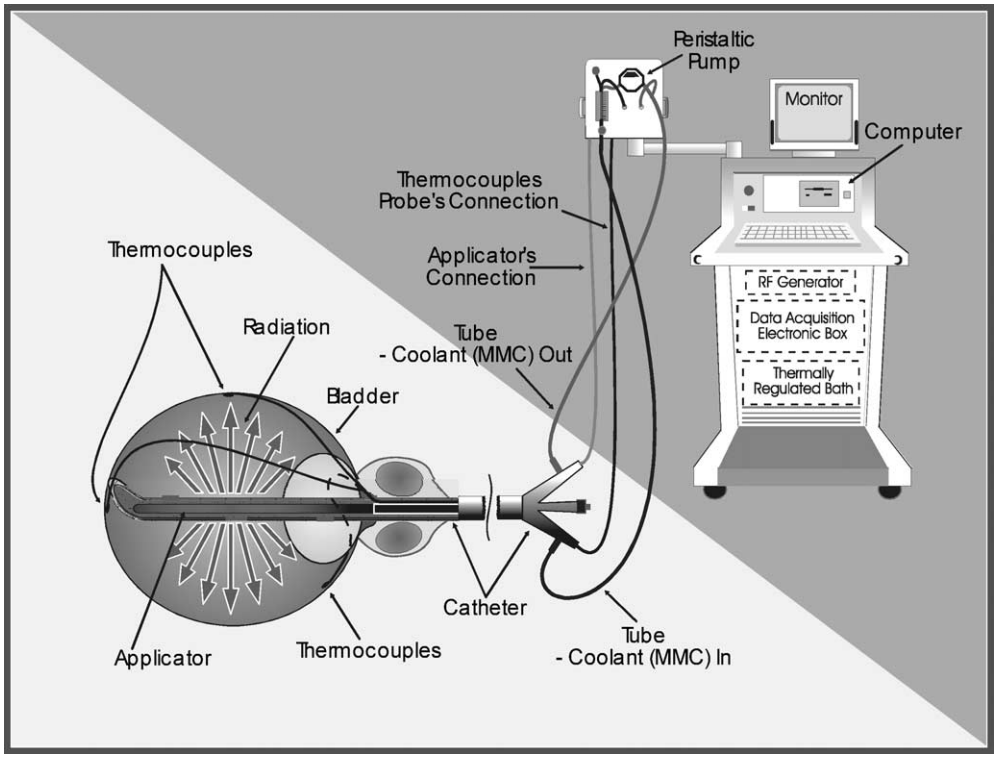

Fig. 2. The schematics of the Synergo® system used for clinical trials. The catheter with the Mw-applicator loaded inside, the position of the thermocouples and the closed circulatory circuit connected to the computerized unit are shown.

homogeneous MW-induced heating of the bladder tissue. In addition, the cytostatic solution filling the bladder can be kept at the expected conditions for volume, concentration and temperature during the whole treatment session.

4. Clinical studies

4.1. Local hyperthermia and chemotherapy for superficial bladder tumor ablation

A preliminary study was carried out from 1987 to 1992 as neoadjuvant pre-TUR ablative approach. The key points of this investigation were to verify technical feasibility and treatment safety [25]. The patient population included 128 patients suffering from low and intermediate risk, mainly recurrent, superficial bladder cancer. For this trial, the schedule of administration included 8 weekly 60 min sessions, performed on out-patient basis without anesthesia except for the use of an anaesthetic urethral gel. Local hyperthermia was delivered by means of the Synergo® system at average bladder temperature of 42.5 °C and as cytostatic drug, a solution of Mitomycin C (MMC) at the dosage of 40 mg in 50 ml of distilled water was used. From the beginning of our experience, MMC was adopted as a synergist drug for many reasons: MMC is widely and successfully used for adjuvant and neo-adjuvant protocols for STCCB, acceptable local and very limited systemic side effects due to its high molecular weight are expected and a proved synergistic or at least additive anticancer effect, when used in combination with local hyperthermia in treating solid tumors, is supported by several laboratory and clinical studies [26–31]. All patients completed the scheduled protocol and 7–10 days after treatment completion underwent TUR which documented 70% tumor complete response (CR) and 20% partial response (PR). This study clearly demonstrated that the combined thermo-chemotherapy regimen using the Synergo® system was feasible and minimally invasive on out-patient basis, subjectively well tolerated with a consistent tumor response-rate.

From 1989 to 1993 a randomized clinical study to compare the ablative effect of the combined regimen by means of the Synergo® system versus intravesical chemotherapy alone was performed as neo-adjuvant approach [32]. Fifty-two patients suffering from intermediate and high-risk STCCB entered the study and were randomly assigned to receive the combination treatment (29 patients) or intravesical chemotherapy alone (23 patients). All patients completed the scheduled treatment (similar to that of the preliminary study reported above) and underwent TUR within 10 days after treatment completion. Histology on specimens taken by TUR documented 66 and 22% CR after combination regimen and intravesical chemotherapy alone, respectively. The difference in tumor eradication efficacy resulted highly significant from a statistical point of view ($P < 0.001$) in favor of thermo-chemotherapy. In order to evaluate local toxicity, a special subjective questionnaire including symptoms such as dysuria, nocturia, haematuria, urethrorrhagia, urethral burning, suprapubic pain, was designed and completed by all patients before, during and after treatment. When comparing the subjective symptoms score questionnaire, as expected, cystitis syndrome symptoms appeared to be clearly higher for patients who underwent combined treatment. However, all these symptoms completely and spontaneously disappeared without special medication within a few days of the end of the treatment. In addition, no major complication or increased systemic toxicity was documented in the combination regimen group.

In 1992 a different clinical study [33] was designed in order to evaluate the possible role of thermo-chemotherapy regimen when applied to a special subset of patients suffering from low grade, highly recurrent, multifocal STCCB tumors unresponsive to any conservative treatment. To these patients, due to the above mentioned characteristics and mainly for the extensive involvement of the bladder surface, radical cystectomy was suggested, given that TUR was considered technically unfeasible or not curative in one single step. In this study, the combined thermo-chemotherapy treatment was tested as a powerful debulking approach with the main intent of saving the bladder. Here, a more aggressive schedule of administration, including an inductive cycle (8 weekly, 60 min sessions) and a maintenance cycle (4 monthly sessions) was used. In addition, in order to keep the dose concentration of the drug throughout the entire session as constant as possible, the solution of MMC at 40 mg in 50 ml distilled water was replaced every 30 mins during each session and hyperthermia was delivered at an average bladder temperature of 43 °C. This study, however, is still ongoing. Up to now 28 patients have been treated and are evaluable at 33-month minimum follow-up. All patients but two completed the scheduled treatment due to local toxicity. At the end of the treatment all patients underwent TUR which appeared to be feasible and complete in a single step. TUR documented a CR (no residual endoscopic or histologic finding after treatment) in 16 cases, while a PR (more than 50% eradication of the overall initial tumoral mass) was observed in 12 cases. During follow-up, among all patients treated, three underwent early radical cystectomy due to limited tumor response to thermo-chemotherapy treatment and seven delayed radical cystectomy for high-risk recurrence within 2 years. However, 18 patients could have had their bladder preserved after treatment and post-treatment TUR

Table 1
The combination of intravesical chemotherapy and hyperthermia: results of four clinical trials

	Study type	Number of patients	Tumor type	Dose and regimen	Median follow-up	Results
Rigatti et al. [24]	Ablative	128	Low and intermediate risk STCCB	40 mg MMC	–	70% CR, 20%PR
Colombo et al. [31]	Ablative	52	Intermediate and high risk STCCB	40 mg MMC	–	66% CR
Colombo et al. [32]	Ablative	28	Low grade, highly recurrent, multifocal and refractory STCCB	40+40 mg MMC	–	57% CR, 43% PR
Colombo et al. [33]	Prophylaxis	83	Intermediate and high risk STCCB	40+40 mg MMC	24 months	79% CR

STCCB, superficial transitional cell carcinoma of the bladder; MMC, Mitomycin C; CR, complete tumor response: no residual endoscopic or histologic finding after treatment; PR, partial tumor response: more than 50% complete disappearance of tumor at endoscopy; Ablative, neo-adjuvant; Prophylaxis, adjuvant.

alone or after some adjunctive TUR or lasertherapy for small and low-risk recurrence in long term follow-up. Among patients who underwent delayed radical cystectomy two major complications occurred in the form of bladder contraction with severe urinary incontinence. The clinical results of the studies mentioned above are summarized in Table 1.

4.2. Local hyperthermia and chemotherapy for superficial bladder tumor prophylaxis

In order to test efficacy and tolerability of the combined regimen as prophylaxis treatment, a prospective, multicentric and randomized study was carried out between 1994 and 2000 [34]. Eighty-three STCCB patients, after a complete (confirmed) TUR of their tumors, were randomized and assigned either to receive the combination treatment by means of the Synergo® system or MMC alone under identical experimental conditions. The end point of the study was the evaluation of the recurrence-rate at minimum 24-month follow-up and the definition of the time at first recurrence.

According to the inclusion criteria only intermediate and high risk STCCB (primary CIS were excluded) after complete TUR were recruited. Most patients were recurrent in spite of many previous intravesical chemo or immunoprophylaxis adjuvant treatment. Clinical pre-treatment assessment included cystoscopy with biopsies of any suspect areas to confirm the complete removal of tumor, ultrasound evaluation of the abdomen and pelvis, uroflowmetry and measurement of post-void residual urine. All patients were also requested to complete the detailed questionnaire, concerning subjective urinary symptoms. Patients were then randomized to receive local microwave-hyperthermia and intravesical chemotherapy (HT+MMC) or intravesical chemotherapy alone (MMC) as a standard treatment in 42 and 41 cases, respectively. For both groups of patients the scheduled treatment regimen included an induction cycle consisting of 8 weekly sessions and a subsequent maintenance regimen of 4 monthly sessions.

The duration of each session was 60 min and all sessions were performed on an out-patient basis using only some urethral anaesthetic gel. In the combined treatment group hyperthermia was delivered at medium temperature of $42.0 \pm 2\,^{\circ}C$ for at least 40 min per session, while a MMC solution at 40 mg in 50 ml of distilled water was replaced after 30 min.

Follow-up started at the end of the induction cycle and included rigid or flexible cystoscopy with biopsy of every suspicious area. Urinary cytology and cystoscopy were performed every 3 months for 24 months. In only a few cases when cytology was positive and cystoscopy was negative, multiple random biopsies of the bladder mucosa were performed. As cellular atypia was detected, in no case recurrence rate was evaluated according to cystoscopic findings. Ultrasound evaluation of the abdomen and pelvis was also performed every 6 months. For high risk patients, CT was requested every year. For the primary efficacy analysis, the difference in tumor recurrence-rate between the two treatment groups was investigated by the Kaplan–Meier Survival Analysis with the Log Rank test for significance.

Of the 83 randomized patients 75 were assessed with a minimum follow-up of 24 months. Three patients in thermo-chemotherapy and five who received chemotherapy alone were taken off the study due to subjective intolerance (two cases), personal decision (two cases) or protocol violations (four cases).

There was no significant difference in both demographic and baseline tumor characteristics between the centers participating in the study.

As far as recurrence-rate is concerned, 6 and 23 recurrences were seen in group 1 and 2, respectively. The Kaplan–Meier curve (Fig. 3) shows that tumor recurrence in the chemotherapy alone group occurs significantly earlier and more frequently after chemotherapy alone. The Log Rank test used for statistics demonstrated a highly significant difference ($P < 0.0001$) in

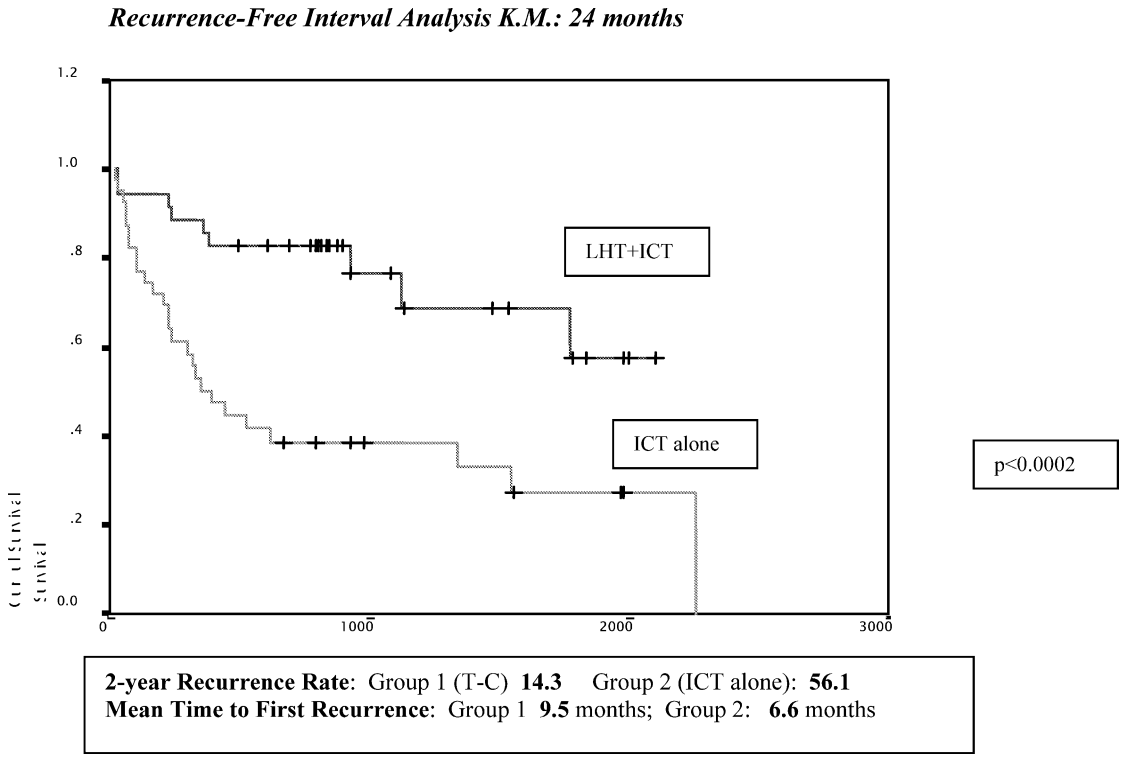

Fig. 3. KM curve; recurrence-free interval analysis. The 2 year recurrence rate and mean disease free interval for thermo-chemotherapy and intravesical chemotherapy alone groups at minimum 24-month follow-up are shown, respectively.

favor of the combined approach. This tendency seems to be confirmed also in a longer follow-up ($P = 0.0002$).

The demographic factors (age, gender) had no significant effect on recurrence rate in either treatment group ($P > 0.05$) and previous local chemotherapy did not influence the results. Previous recurrence rate had an obvious impact on subsequent recurrence rate after treatment. The difference between treatment arms was more pronounced in the patients with highly recurrent tumors (>3 recurrences), insofar as 79% were recurrence-free in thermo-chemotherapy group versus 38% in chemotherapy alone group. Also regarding multifocality, the difference between treatment arms was more pronounced in patients with more than five tumors.

The evaluation of the time at recurrence showed that recurrence was delayed (9.8 months) in patients receiving the combined treatment when compared with chemotherapy alone treatment (6.2 months).

The follow-up is still not long enough to show any difference in progression rate between the two treatment arms. However, both treatments were subjectively well tolerated. According to the local symptoms questionnaire results, local toxicity was higher during and after the combination treatment, as expected. As usual, all these cystitic symptoms spontaneously disappeared a few days after the procedure.

No severe clinical complication was observed, except one case of slightly reduced bladder capacity with urge incontinence in the thermo-chemotherapy group. Voiding patterns, as expressed by uroflowmetry and measurement of residual urine, remained unchanged in both groups. Table 1 summarizes the characteristics and results of this study.

5. Histologic changes

The histologic investigations performed on specimens taken by cold cup biopsies and by TUR at different periods of time during neo-adjuvant treatment, documented many interesting findings. These alterations are similar to those caused by alkylating agents (i.e. MMC and Thiotepa), but frequently more marked and simultaneously represented. After a few operative sessions of thermo-chemotherapy, predominant changes are represented by degenerative modifications such as vacuolization and ballooning of the cytoplasm and hyperchromatism and pyknosis of the nuclei (apoptotic changes) of the urothelial cells resulting in mucosal exfoliation and hyalinization of the papillary stroma of the tumor. Sometimes, areas of keratinized or non-keratinized squamous metaplasia can be observed. During treatment (e.g. after three to five sessions) histology shows irreversible changes at the superficial cells with complete destruction of the tips of the papillae, loss of the stratification of the neoplastic

urothelium or progressive stromal sclerosing hyalin necrosis, particularly around the vessels of the neoplastic papillae (Fig. 4). Submucosal stromal cells often showed cytological pseudoatypical changes, such as increased volume, mild hyperchromatism, multinucleation and nuclear irregularity. The vascular response in the submucosa of T1 tumor stage usually appears to be more intense and scattered than for Ta stage. At the end of the treatment (6–12 sessions) the tumor is generally involved in an extensive sclerosing hyalin and/or coagulative necrosis and sometimes, in a massive calcification necrosis. Interestingly, during thermo-chemotherapy treatment, histologic modifications seem to start from the stroma of the tumor leaving some layers of superficial cancer cells still suffering (apoptotic) or alive around the sclerotic root of the tumor. We can assume that using this procedure the neoplastic tissue is primary heated and that chemotherapy works on the heated cells. This aspect is probably different from that observed after chemotherapy alone treatment, where predominant findings are microcalcifications, flattening, lengthening and stretching of the urothelial cells and where degenerative and necrotic changes generally start from the urothelium with subsequent stromal involvement. As a remarkable feature, the smooth muscle bundles of the detrusor, as well as peri-vesical fat, were never significantly affected by treatment. This fact correlates with the physical properties of the system and procedure used for inducing local hyperthermia, which involve only the superficial layers (urothelium and submucosa) with minimal involvement of the deeper layers of the bladder wall. This histologic evidence confirms that this kind of approach is only indicated for treating superficial bladder tumors in clinical practice.

In addition, only light and transitory inflammatory changes such as hyperemia and oedema at the urothelial surface could be documented in non tumoral areas. The inflammatory modifications, including focal squamous metaplasia appeared to be reversible within a short time of treatment completion. Based on this crucial observation, we can assume that this treatment actually works selectively on tumor sites, whilst it spares normal tissue.

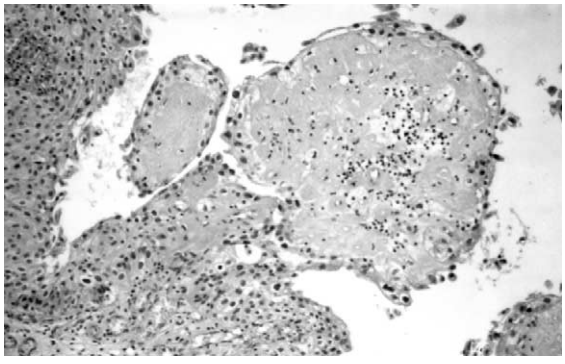

Fig. 4. Histology of a specimen after thermo-chemotherapy procedure. The extensive sclerosing hyalin and coagulative necrosis of the papillary tumor is shown.

6. Safety evaluation

6.1. Local toxicity and side effects

Local toxicity and subjective tolerability to thermo-chemotherapy regimen were assessed by means of a detailed questionnaire that patients were asked to complete before treatment, after four sessions, and then again 7–10 days after completion of treatment. This questionnaire included a 1–4 score (best to worst) for daytime frequency, nocturia and dysuria and a 1–3 score (best to worst) for urgency, haematuria, urethrorrhagia and urethral pain. Subjective symptoms were expressed as the mean value of these scores. When comparing the questionnaire score before and after treatment, the integrated thermo-chemotherapy approach was generally well tolerated but most patients complained of cystitis symptoms such as urgency, urethral burning and nocturia occurring immediately after each treatment session and generally lasting for 12–24 h. However, only 6% of the sessions was interrupted in advance and only 4% of patients could not complete their schedule of treatment due to local toxicity. As previously mentioned the cystitis symptoms resolved almost completely in all cases within 7–10 days and only occasionally were anti-cholinergic drugs administered. Uroflowmetry performed after treatment showed a mean improvement, not statistically significant, in maximum flow rate of 3.4 ml/s. No major complications (i.e. urethral stricture or a contracted bladder) related to the procedure were observed after an average follow-up of 36 months.

Local side effects in the form of cystitis symptoms, suprapubic pain and posterior bladder wall necrosis after thermo-chemotherapy are generally more severe than after standard intravesical chemotherapy. However, local side effects did not influence the completion of the treatment and were documented to be transitory, asymptomatic and self-recovering without medical intervention in a short time after the end of therapy.

The most frequent side effect, as revealed by cystoscopy, was in the form of superficial and confined (no larger than 3 cm) necrosis of the posterior bladder wall.

This effect can be explained by the location of the RF antenna in the bladder during the operative procedure which is responsible for an accumulative effect of the dissipated heat in the area around the tip of the antenna, causing in some cases a small and localized area of necrosis in the posterior bladder wall. This condition, when occurred, was painless and usually self-recovering

without any residual effects. In the rare case of severe posterior wall necrosis, resulting in posterior wall ulceration or burn, this would be considered as a complication or unanticipated adverse event.

As clinical major complications, only a few cases of reduced bladder capacity were observed after aggressive thermo-chemotherapy regimen in patients previously treated by many TURs. No significant changes in blood tests were documented. No urinary tract infection was registered in either groups of patients and no significant urodynamics modifications were registered.

6.2. Systemic toxicity

Systemic side effects related to thermo-chemotherapy treatment were evaluated from a clinical and pharmacokinetics point of view.

The only clinical aspect of systemic toxicity was represented by some cases of skin rash related to MMC. However, the rate of this effect (6%) was not dissimilar to that described in literature reporting the use of MMC alone.

In most patients blood analysis was performed before, during and a few days after treatment completion and no modification concerning blood cell count, liver and renal function was documented. No sign of mylosuppression was noted.

In order to assess the effect of local hyperthermia on the systemic absorption of MMC during the combined treatment and to establish the likely safety of this procedure a pharmacokinetics study was carried out [35]. In this study patients were assigned to four groups. In group 1, 12 patients received 20 mg intravesical MMC plus local hyperthermia; in group 2, 13 patients received 20 mg MMC alone; in group 3, 16 patients received 40 mg MMC plus local hyperthermia and in group 4, ten patients underwent treatment using 40 mg MMC alone. Patients in groups 1, 2, and 4 underwent post-tumor resection adjuvant treatment, whereas those in group 3 still had tumor present and were treated for eradication purpose. Intravesical instillation lasted 60 mins with the solution (50 ml) being replaced after the first 30 min. Blood samples were taken before, and every 15 min during each session. MMC concentration in plasma and in urine was determined by HPLC [36].

The highest MMC plasma concentration (67.9 ng/ml) occurred in one patient in group 3. This value was well below the threshold concentration (400 ng/ml) generally assumed for risk of myelosuppression. Local hyperthermia associated with the intravesical chemotherapy enhanced plasmatic MMC concentrations at 30, 45 and 60 mins when compared with chemotherapy alone (group 1 vs. 2, $P \leq 0.008$). Systemic exposure to MMC was not significantly increased by doubling the intravesical dose when intravesical chemotherapy alone was administered. Patients in group 3 displayed the highest degree of MMC absorption and the highest variability in pharmacokinetics between patients (Fig. 5).

Based on these results we can assume that local hyperthermia increases the plasmatic absorption of MMC and that this influence is temperature and dose dependent. However, in the doses used, plasma MMC concentrations were always more than six times lower than those shown to cause toxicity even when thermo-chemotherapy is used with the more aggressive schedule of administration. This fact ensured the systemic safety of the combined treatment when performed according to the described procedure.

6.3. Potential pitfalls and unknowns

6.3.1. Basic investigations

Although it has been unquestionably demonstrated that the interaction of local hyperthermia and chemotherapeutic agents frequently induces a potentiated cytotoxicity against tumor cells over that predicted for an additive effect, many aspects of this interaction remain unclear or fully unknown. Not all cytostatic drugs become more cytotoxic at elevated temperature and the effect of the heat-drug interaction is often variable even for the same drug when tested in different in vitro and in vivo models. It has also been proved that different human cell lines greatly differ in their thermosensitivity without relation with the level of temperature and time of exposure. As a consequence, at present, a definitive in vitro model for investigating the combination of heat and drug interaction has not be defined.

6.3.2. In vivo investigations

Presumably, some human cell lines are intrinsically more resistant to either high temperatures or cytostatic

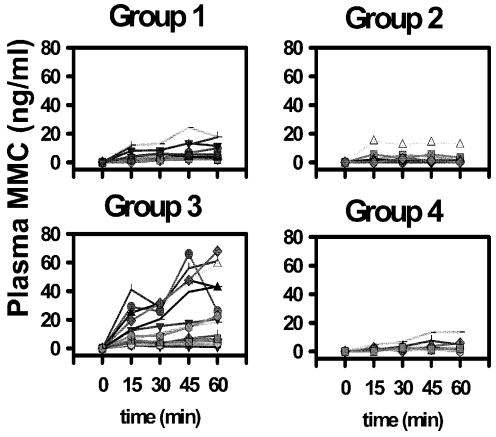

Fig. 5. Pharmacokinetics of plasmatic concentrations of intravesical MMC administered alone and combined with local hyperthermia. Individual concentration–time profiles of MMC in plasma during a 60 min intravesical instillation. Group 1, ICT (20 mg) combined with hyperthermia. Group 2, ICT alone at the same dose as Group 1. Group 3, ICT (40 mg) combined with hyperthermia. Group 4, ICT alone at the same dose as group 3.

agents for genetic reasons. The rapid induction of thermo-tolerance is another well known source of resistance, depending on the cell line and the timing of heat application. Moreover, in vivo many other biological parameters play a crucial role for interpreting the varaible effects of the heat-drug application. When applying the endovesical thermo-chemotherapy in human, the homogeneous distribution and the prolonged contact of the drug with the bladder surface, as well as the homogeneous distribution of the thermal energy, are of pivotal importance for obtaining positive clinical outcomes. In addition, the effect on the heat dissipation and penetration due to the blood circulation, which can differ in different and diverse portions of the bladder, should also be considered when interpreting some unexpected results.

6.3.3. Schedule of administration

We decided to use 42.5–43.5 °C range of temperature for an effective minimum 40 min exposure time, because that seems to be a reasonable and acceptable time frame in clinical applications. We also decided to include both an inductive (6 weekly sessions) and a maintenance (4 monthly sessions) cycles in our schedule of administration in order to balance suitable tumor response rate, subjective tolerability and treatment cost. However, at present, we still do not know if better results could be obtained using a different schedule of administration. How many sessions should be delivered during the inductive cycle? Are there actually advantages performing an additional maintenance cycle and how should it be administered? Which is the best drug to use for an optimal expected synergism with hyperthermia? These questions still remain to be answered.

6.3.4. Drug

The optimal drug for local thermo-chemotherapy should combine the maximum synergistic result against tumor with the lowest side effects. At present the optimal drug remains uknown.

So far, we have mainly used MMC, because literature supports that this drug is effective in both ablation and prophylaxis of superficial bladder cancer and because its toxicity is very low. However, many other drugs could be adopted. Preliminary studies based on Epirubicin showed a similar tumor response rate with a slight additional local toxicity, while using Mitoxantron highly variable dose dependent clinical outcome. In addition, the synergistic effect expected when using chemotherapy and hyperthermia in combination, should allow for a reduction of dose-concentration of the drug when compared with chemotherapy alone. At present, it is still unclear how much of the synergistic effect is attributable to the drug and how much to the hyperthermia and the optimal dose of the drug is still totally to be defined.

6.3.5. Site related tumor response

Most of the residual tumors documented, when thermo-chemotherapy was performed with ablative intent, were located to the dome of the bladder and near to the trigone. We presume that this can be explained by a heterogeneous distribution of the heat related to some technical limitations of the delivering system (endovesical applicator energy profile) and/or trans-urethral catheter configuration, radio-frequency dissipation and others.

6.3.6. Subjective tolerance, side effects and complications

The treatment is generally well tolerated. However, patients suffering from prostatic hyperplasia and reduced bladder capacity should be excluded. In addition, 4–8% of our overall patients required treatment suspension due to severe cystitis syndrome.

In an overall 12 years experience, major complications such as urethral strictures and contracted bladders have been registered very rarely. However, our series of patients are limited and for some patient cohort the follow-up does not exceed 5 years. The safety of this treatment in a long term follow-up is still to be defined.

6.3.7. Costs and benefits

This treatment requires a well trained staff and a consistent cost for both start up and disposables. The time required for each session and for completing the entire scheduled administration per patient is long. Exhaustive information and a complete assistance once at home are also necessary for achieving the expected results. As a consequence, we should consider that this procedure is certainly more onerous in terms of cost, time and engagement of personnel, when compared with other procedures. However, when considering that the goals of this procedure are to replace TUR for the eradication of primary superficial bladder tumor, to reduce the number of TURs (and related hospitalization and anesthesia) for tumor recurrences and to avoid radical cystectomy in some select cases, we can expect a significant advantage also in terms of cost in favor of this novel approach. The definitive cost–benefit evaluation will certainly require a long-term follow-up.

6.3.8. Indications

The present experience is mainly a single-institutional experience and due to the limited number of patients and short follow-up, no conclusive consideration can be drawn for the clinical indications of the treatment. Moreover, at present, no study has been conducted on a homogeneous population of patients suffering from bladder carcinoma in situ, while a prospective, multicentric and randomized study comparing thermo-chemotherapy versus BCG in prophylaxis of recurrence of the intermediate and high risk superficial bladder cancer is still ongoing.

Based on the presented preliminary clinical results, the best candidates to this procedure seem to be the highly recurrent superficial bladder tumor patients and those patients suffering from a superficial bladder tumor refractory to any standard conservative approach and unresectable by TUR, due to the extension of the disease and for whom radical cystectomy remains the only alternative indication.

7. Conclusions

It is well known from the literature that malignant cells are more sensitive to heat than normal cells [37,38]. Hyperthermia causes an inhibition of cellular respiration and the synthesis of deoxyribonucleic acid and ribonucleic acid and protein, blocking the cell in S phase. These injuries may be lethal to the cell if repair mechanisms are not effective. Normal cells not only dissipate the heat but also have more time and more efficient mechanisms for repair before the next mitosis. Tumor cells exposed to hyperthermia become more immunogenic, thus, potentially can stimulate host defences. The delivery of hyperthermia to the tumor ideally would produce uniform heating of the tumor volume while sparing normal structures as much as possible. Homogeneous heating of the tumor depends on the volume, the temperature applied and the thermal dissipation via the blood supply. When used as monotherapy, local hyperthermia obtained only limited results in clinical trials. However, local hyperthermia has certainly proved to develop a selective synergistic or supra-additive antitumoral cell-killing effect when used in combination with selected cytostatic agents for the eradication of many solid tumors including transitional cell carcinomas [39,40]. Superficial bladder tumors, due to their endocavitary location, have long represented an intriguing field and the simultaneous administration of local hyperthermia and intravesical chemotherapy is not an original way of treating this disease. However, so far, the lack of suitable technology has strongly limited the clinical application of this promising regimen. After laboratory and animal investigations, a novel, technically advanced system based on a transurethral radiofrequency applicator, was specifically realized and clinically tested in STCCB patients. During the last decade this system was mainly used for STCCB eradication as an alternative or complementary approach to trans-urethral resection of the bladder (TURB).

These results are preliminary but certainly encouraging. Thus, extensive prospective multicenter studies involving more consistent cohorts of patients, although difficult and onerous to perform, are certainly needed.

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Acknowledgements

The authors would like to thank Mrs. Anastasia Negro, Dr Avigdor Lev and Giuseppe Collura for their precious collaboration and Mrs. Lorraine Wood for reviewing the linguistic style of the manuscript.

References

[1] Jensen OM, Estève J, et al. Cancer in the European community and its member states. Eur J Cancer 1990;26:1167–256.
[2] Black RJ, Bray F, et al. Cancer incidence and mortality in the European Union: cancer registry data and estimates of national incidence for 1990. Eur J Cancer 1997;33:1075–107.
[3] Torti FM, Lum DL, Aston D. Superficial bladder cancer: the primacy of grade in the development of invasive disease. J Clin Oncol 1987;5(1):125–30.
[4] Soloway MS, Murphy WM, Johnson DE, et al. Initial evaluation and response criteria for patients with superficial bladder cancer. Br J Urol 1990;66:380–5.
[5] Herr HW, Laudone WP, Withmore WF, Jr. An overview of intravesical therapy for superficial blòadder tumors. J Urol 1987;138:1363–8.
[6] Lum BL, Torti FM. Adjuvant intravesicular pharmacotherapy for superficial bladder cancer. J Natl Cancer Inst 1991;83:682–94.
[7] Soloway MS. The management of superficial bladder cancer. Cancer 1980;45(Suppl.):1856–8.
[8] Huland H, Otto U, Droese M, Kloppel G. Long term Mitomycin C instillation after transurethral resection of superficial bladder carcinoma: influence on recurrence, progression and survival. J Urol 1994;132:27–9.
[9] Lamm DL. Long term results of intravesical therapy for superficial bladder cancer. Am Urol Clin North Am 1994;19:573–7.
[10] Heney NM, Ahmed S, Flanagan MJ, et al. Superficial bladder cancer: progression and recurrence. J Urol 1983;130:108–1083.
[11] Herr HW. Intravesical therapy. A critical review. Urol Clin North Am 1987;14:399–404.
[12] Busch W. Uber den Einfluss, welchen heitigere Erysipeln zuweilen auf organisierte neubildungen ausuben. In: Verhandl Naturh. Westphal: Preuss Rhein, 1866:23–8.
[13] Coley WR. The treatment of malignant tumors by repeated inocluation of erysipelas. With a report of ten original cases. Am J Sci 1893;105:487–9.

[14] Herman TS, Teicher BA, Jochelson M, et al. Rationale for the use of local hyperthermia with radiation therapy and selected anticancer drug in locally advanced human malignancies. Int J Hyperthermia 1988;4:143–58.
[15] Millaer RC, Richards M, Baird C, et al. Interaction of hyperthermia and chemotherapy agents: cell lethality and oncogenic potential. Int J Hyperthermia 1994;10:89–99.
[16] Oleson JR, Calderwood SK, Coughlin CT, et al. Biological and clinical aspects of hyperthermia in cancer therapy. Am J Clin Oncol 1988;11(3):368–80.
[17] England HR, Anderson JD, Minasian H, et al. The therapeutic application of hyperthermia in the bladder. Br J Urol 1976;47:849–52.
[18] Le VH, Wapnick PV, et al. Tumor eradication by radiofrequency therapy. Response in 21 patients. J Am Med Assoc 1976;235:2198–200.
[19] Debicki P, Okoniewska E, Oboniewski M. Superficial and intraurethral applicators for microwave hyperthermia. Adv Exp Med Biol 1990;267:321–6.
[20] Yerushalmi A, Fishelovitz Y, Singer D, et al. Localized deep microwave hyperthermia in the treatment of poor operative risk patients with benign prostatic hyperplasia. J Urol 1985;133:873–8.
[21] Moffat FL, Gilas T, Calhoun K, et al. Further experience with regional radiofrequency hyperthermia and cytotoxic chemotherapy for unresectable hepatic neoplasia. Cancer 1985;55:1291–5.
[22] Chou CK, Chen GW, Guy AW, Luk KH. Formula for preparing phantom muscle tissue at various radiofrequencies. Bioelectromagnetics 1984;5:435–41.
[23] Rigatti P, Lev A, Da Pozzo LF, Salonia A, Colombo R. Locally induced hyperthermia in bladder cancer. In: Syrigos KN, Skinner DG, editors. Bladder cancer. Biology, diagnosis and management. Oxford Medical Pubblications, 1999:393–406.
[24] Colombo R, Lev A, Da Pozzo LF, et al. A new approach using local combined microwave hyperthermia and chemotherapy in superficial transitional bladder carcinoma treatment. J Urol 1995;153(3 Pt. 2):959–63.
[25] Rigatti P, Lev A, Colombo R. Combined intravesical chemotherapy with Mitomycin C and local bladder microwave-induced hyperthermia as a preoperative therapy for superficial bladder tumors. Eur Urol 1991;20:204–10.
[26] Mauroy B, Bonnal JL, Prevost B, et al. Study of the synergy of microwave hyperthermia/intravesical chemotherapy in the prevention of recurrences of superficial tumors of the bladder. Prog Urol 1999;9(1):69–80.
[27] Matzkin H, Rangel MC, Soloway M. In vitro study of hyperthermia on normal bladder cell line and on five different transitional cell carcinoma cell lines. J Urol 1992;147:1671–4.
[28] Teicher BA, Kawal CD, Kennedy KA, et al. Enhancement by hyperthermia in the in vitro cytotoxicity of Mitomycin C toward hypoxic tumoral cells. Cancer Res 1981;41:1096–112.
[29] Wallner K, Banda M, et al. Hyperthermic enhancement of cell killing by Mitomycin C in Chinese hamster ovary cell. Cancer Res 1987;47:1308–12.
[30] Sugimachi K, Inokuchi K, Kai H, et al. Preoperative hyperthermo-chemo-radiotherapy effective for carcinoma of the esophagous. Cancer Res 1984;27:199–204.
[31] Sthelin JS, giovenella BC, De Ipolyi PD, et al. Results of 11 years experience with heated perfusion for melanoma of the extremities. Cancer Res 1979;39:2255–7.
[32] Colombo R, Da Pozzo LF, Lev A, et al. Neoadjuvant combined microwave induced local hyperthermia and topical chemotherapy versus chemotherapy alone for superficial bladder cancer. J Urol 1996;155:1227–32.
[33] Colombo R, Da Pozzo LF, Lev A, et al. Local microwave hyperthermia and intravesical chemotherapy as bladder sparing treatment for select multifocal and unresectable superficial bladder tumors. J Urol 1998;159:783–7.
[34] Colombo R, Da Pozzo LF, Salonia A, et al. Comparative study of intravesical chemotherapy alone versus intravesical thermo-chemotherapy for prophylaxis of recurrence of superficial transitional cell carcinoma. A multicentric study, J Clin Oncol, in press.
[35] Paroni R, Salonia A, Lev A, et al. Effect of local hyperthermia of the bladder on Mytomicin C pharmacokinetics during intravesical chemotherapy for the treatment of superficial transitional cell carcinoma. Br J Pharmacol 2001;52:278–9.
[36] Paroni R, Arcelloni C, De Vecchi E, Fermo I, Mauri D, Colombo R. Plasma Mitomycin C concentrations determined by HPLC coupled to solid-phase extraction. Clin Chem 1997;43:615–8.
[37] Song CW, Kang MS, Rhee JG, et al. Th effect of hyperthermia on vacular function, pH and cell survival. Radiology 1980;137:795–803.
[38] Meyer JL. The clinical efficacy of localized hyperthermia. Cancer Res 1984;44(Suppl. 10):4745s–51s.
[39] Hall RR, Wadehra V, Towler JM, et al. Hyperthermia in the treatment of bladder tumors. Br J Urol 1976;48:603–8.
[40] Ludgate CM, McLean N, Carswell GF, et al. Hyperthermic perfusion of the distended urinary bladder in the management of recurrent transitional cell carcinoma. Br J Urol 1975;47:841–8.

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