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Radiofrequency-Induced  
Thermochemotherapy Effect (RITE) for the  
treatment of Non-Muscle Invasive Bladder Cancer



Maffezzini, M., et al. (2014). "Intravesical mitomycin C combined with local microwave hyperthermia in non-muscle-invasive bladder cancer with increased European Organization for Research and Treatment of Cancer (EORTC) score risk of recurrence and progression." *Cancer Chemother Pharmacol*.

**Purpose:** to assess the activity of intravesical chemotherapy and local microwave hyperthermia (ICLMH) in increasing the disease-free interval (DFI) in patients with non-muscle-invasive bladder cancer (NMIBC) and treatment toxicity. **Methods:** forty-two patients with a diagnosis of high-risk NMIBC, according to the European Organization for Research and Treatment of Cancer (EORTC) criteria, were treated with an intensive schedule of ICLMH using 40 mg mitomycin C. The treatment consisted of 4 weekly sessions, followed by 6 sessions delivered every 2 weeks, and by 4 monthly sessions, for a total of 14 sessions over 8 months. The DFIs before and after treatment were compared in each patient. **Results:** the schedule was completed as planned by 32 patients (76.2 %). The percentage of disease-free patients the year before study was 14.9 % (95 % CI 5.5-28.8) versus 88.8 % (95 % CI 73.7-94.8) after ICLMH ( $p < 0.0001$ ). Patient EORTC scores, multifocality, and tumour stage were all associated significantly and independently with a higher risk of recurrence after ICLMH treatment with HR of 41.1 ( $p = 0.01$ ), 17.7 ( $p = 0.02$ ), and 8.5 ( $p = 0.02$ ), respectively. After a median follow-up of 38 months, 24 patients (57.1 %) did not show evidence of disease, whereas 13 patients (30.9 %) underwent disease recurrence and 5 patients (11.9 %) showed also stage progression. Toxicity consisted in grades 1 and 2 frequency, non-infectious cystitis, and haematuria. **Conclusions:** ICLMH significantly increases the DFI of NMIBC patients with high EORTC score for recurrence and progression. Toxicity of the intensive treatment schedule was generally mild.

Nair, R., et al. (2014). "Challenging the gold standard: A comparison of long-term disease specific outcomes for high-risk non-muscle invasive bladder cancer treated with mitomycin hyperthermia and radical cystectomy." *EAU* (Poster session pre-published), Stockholm.

**Introduction:** There has been a paradigm shift towards consideration of alternative intra-vesical chemotherapeutic agents in the management of primary or Bacillus Calmette–Guérin (BCG) failure high-risk non-muscle invasive bladder cancer (HR-NMIBC). Intra-vesical Mitomycin-C hyperthermia (MMC-HT) has been shown to be a viable option in such circumstances. Although the morbidity and medium-term outcomes of MMC-HT are well documented, there is still need for critical evaluation of long-term disease specific outcomes matched against the current gold standard therapy for HR-NMIBC; radical cystectomy (RC). **Patients and Methods:** A prospective single-centre review of 96 patients receiving MMC-HT was performed between June 2006 and October 2013 and matched against 47 cases undergoing RC for HR-NMIBC. Co-morbidities were quantified using the Charlson co-morbidity Index (CCI), and peri- and post-procedure complications were recorded in each group. Post operative pathology, recurrence and progression rates together with five-year overall and disease specific survival were evaluated. **Results:** The mean age of patients receiving MMC-HT was 72 (age range 51-91) compared to 68 (age range 54-84) undergoing RC. 30 percent of patients underwent primary-RC for HR-NMIBC versus 70 percent for BCG failure. This compared to 11 percent receiving primary MMC-HT versus 89 percent for BCG failure. The mean CCI score for patients receiving MMC-HT was significantly higher than RC group (6.1 vs 4.3). Significant complication rates classified as a Clavian-Dindo score of greater than 2, was significantly higher in the RC cohort (21 percent) compared to patients receiving MMC-HT (0 percent). There were no deaths associated with MMC-HT treatment compared to a ninety-day mortality of four percent in those receiving RC. Median follow-up was 36 months (3 to 88 months) for both cohorts. Disease specific survival at five years was observed at 85.2 and 74.6 percent in the MMC-HT and the RC cohorts respectively, whilst overall survival figures were 61.9 versus 68.4 percent. **Conclusion:** MMC-HT is both feasible and safe if offered to well selected patients. It provides durable long-term outcomes compared to RC for HR-NMIBC. We demonstrate that despite similar baseline characteristics in these groups, there is a clear advantage in complication rates favouring MMC-HT over RC without a significant difference in disease specific or overall survival.

Nair, R., et al. (2014). "The efficacy and safety of mitomycin-C hyperthermia in the treatment of high risk non-muscle invasive bladder cancer in a single regional centre."  
EAU (Poster session pre-published), Stockholm.

**Introduction and Objectives:** Intravesical BCG therapy is standard treatment after transurethral resection of high risk non-muscle invasive bladder cancer (HR NMIBC). However, up to 40% of patients do not respond to intravesical BCG. In addition, there are problems with patients who are intolerant or unsuitable for BCG. In these patients, radical cystectomy is the curative treatment of choice. However, a significant proportion of these patients are unfit or unwilling to undergo the morbidity of radical cystectomy. In these patients, mitomycin-C hyperthermia (MMC-HT) is a viable treatment option. We report our seven year experience of MMC-HT, and aim to establish whether it is efficacious in this high risk cohort of patients. **Materials and Methods:** 100 patients with HR NMIBC were treated with MMC-HT between June 2006 and August 2013 in a single regional centre. 3 patients did not complete induction regimen due to side effects. One patient developed clinical metastases during the first two weeks of her induction course. 96 patients completed induction treatment and had cystoscopy and biopsy at 3 months. Of these 96 patients, 84 had failed BCG or were intolerant to it. Patients were given an induction regimen with weekly treatments for 6-8 weeks with MMC-H on an outpatient basis with the Synergo® system SB-TS 101 (temperature range between 41 and 44°C). Patients were assessed with 3 monthly cystoscopy, biopsy and urine cytology. Patients who responded, were continued on maintenance MMC-HT. Data including response at 3 months, progression, survival and side effects at each session were entered into a prospective database. Progression was defined as muscle invasion, distant metastases, death from disease or requirement for cystectomy or radiotherapy. **Results:** 72% of patients (69/96) had complete response at 3 months, with 10% having partial response (10/96) and 18% (17/96) had recurrence. Median follow up was 34 months (3 to 88 months). Overall five year survival was 61.9%. Five year disease specific survival was 85.2%. Progression free survival five year survival was 46.9%. Twenty patients had radical cystectomy. Eighteen patients had organ confined disease and two patients had T3 disease at histology. Only one patient developed recurrence of disease after cystectomy. No patients suffered a Clavien-Dindo Complication above 2. **Conclusions:** MMC-HT has comparable five year survival to radical cystectomy in the treatment of high risk superficial bladder cancer after BCG failure. It is well tolerated and can be delivered effectively by a regional centre. In those patients who are medically fit, cystectomy is still a potentially curative option for those patients who fail MMC-HT.

Lüdecke, G., et al. (2013). "1702 Radiofrequency Hyperthermia Chemotherapy (HTC) in high - and extreme high-risk non-muscle-invasive bladder cancer (NMIBC) performed by the german htc study group: impressive high chance of organ preservation documented in a cohort study with long-time follow-up." *J Urol* **189**(4): e700.

**Introduction and Objectives:** A major objective in the clinical management of high-risk NMIBC is the prevention of progression and minimization of recurrence of the disease. AUA guidelines currently recommend that, unless contraindicated, all such patients should be treated with BCG and in recurrence with BCG plus interferon or cystectomy. To demonstrate the therapeutic efficacy of HTC we treated these high-risk patients and the extremely high-risk BCG failures (26% of the cohort) with an intensified HTC protocol plus follow-up of 11.8 years in maximum. **Methods:** There were 69 patients and more than 800 treatment sessions using the Synergo® device to deliver intravesical HTC with Mitomycin C (MMC). The follow-up were conducted over an average period of 24.1 months (range 1.7 month to 11.8 years). After an initial induction of 8 weekly treatments with 2x40 mg MMC we checked the initial efficacy in tumor eradication by TUR-B and urine cytology at week 11. Tumor-free patients continued with maintenance therapy every 6 weeks with 2x20 mg MMC and in parallel cystoscopy and urine cytology every 3-months. **Results:** All 69 patients treated in ablative mode (54 males and 15 females) could be evaluated for efficacy. 85.5% of the patients (59 of 69) reached complete remission at week 11 and this lasted for a mean period of 26.1 months. 69.6% of the patients (48 of 69) continued to be tumor-free over the whole investigation period. In total 8 patients (11.6%) underwent cystectomy including 3 patients (4.3%) with progression to metastatic TCC disease. The metastatic patients died subsequently. 5 TCC recurrences (7.2%) detected during maintenance and follow-up had new low-risk tumors, treated with TUR-B again. In total 61 patients (88.4%) achieved organ preservation despite high- and extremely high-risk disease. Side effects requiring medical intervention included allergy, UTI, hematuria, detrusor spasm, difficulties with catheterization and nocturia occurred in 1.4% to 5.6% of the cases. Treatment was stopped in 3 cases because of allergy and urethral trauma not influencing the efficacy. **Conclusions:** HTC is a very safe treatment and is an impressively effective therapy in high-risk and extremely high-risk NMIBC in preventing recurrence and ensuring organ preservation. We were able to demonstrate in this extremely at risk population of NMIBC patients that 69.6% remained tumor-free with their own bladder intact for an intermediate-to-long-lasting duration.

Lüdecke, G., et al. (2013). "The German study group of intravesical hyperthermia-chemotherapy in non-muscle-invasive bladder cancer presents their long-term results in efficacy and tolerability for optimized adjuvant therapy and bladder preservation." *J Clin Oncol* **31**, Suppl 6(0): abstr 268.

**Background:** In NMIBC recurrence and progression in high-risk BC are the dominant aspects for the clinical management. Intravesical chemotherapy and BCG treatment are the techniques to reduce both risks. HTC has a potentiating synergistic action in BC cell death induction. In consequence we proved HTC in the adjuvant indication and the ablativ indication in high-risk BC. **Methods:** We treated 138 patients in 1,443 treatment sessions in 3 institutions with intravesical hyperthermia-chemotherapy with Mitomycin C applied with the Synergo device. After an initial inductive weekly therapy for 6 to 8 weeks maintenance followed once every 6 weeks 6 times and cystoscopy every 3 month. Results: In the adjuvant indication 52 patients were treated. The over all recurrence free rate was 78.3% over 2.9 years in mean (3.6m – 6.9y). Only 10 patients recurred but none progressed or needed a cystectomy. In the ablative indication 86 patients were treated. For efficacy 69 could be evaluated. 17 patients must be excluded because of protocol violation or extra-vesical TCC or simultaneous second malignancy. 85.5% of the patients (58) reached CR and this persisted for 26.1 months in mean. 48 patients (69.6%) were tumor free over the whole investigation time. In total 8 patients (11.6%) needed a cystectomy. 3 patient (4.3%) progressed to metastatic disease and the other 5 demonstrated low-risk new tumors again treated transurethral. In total 53 patient (76.8%) achieved organ preservation in high-risk situation. Side effects included allergy, UTI, spasm, difficulties with catheterization and nocturia ascending from 1.4% to 5.6%. **Conclusions:** HTC is a safe and effective therapy in NMIBC to prevent intermediate risk BC patients for recurrence and to ensure organ preservation in high-risk BC patients in more than 75% with a long lasting efficacy.

Colombo, R. and M. Moschini (2013). "[Role of the combined regimen with local chemotherapy and Mw-induced hyperthermia for non-muscle invasive bladder cancer management. A systematic review]." *Urologia* **80**(2): 112-119.

**Objectives:** To give an updated review concerning the role of combined regimen (CT) based on microwave- induced hyperthermia (MwHT, CT-MwHT) with intravesical chemotherapy (ICT) as a treatment for non-muscle invasive bladder cancer (NMIBC). **Evidence Acquisition:** The review process followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. An electronic search of the Medline, Embase, Cochrane Library, CancerLit, and ClinicalTrials.gov databases was undertaken. Relevant conference abstracts and urology journals were also included. The primary end-point was the time to recurrence. Secondary end-points included time to progression, bladder preservation rate, and adverse event (AE) rate. **Evidence Synthesis:** A total of 24 studies met inclusion criteria and underwent data extraction. When feasible, data were combined using random-effects meta-analytic techniques. Recurrence was seen 59% less after CT-MwHT than after MMC alone, however, due to the short follow-up, no definitive conclusions can be drawn about the impact on the time to recurrence and progression. The overall bladder preservation rate after CT-MwHT was 87.6%. This rate appeared higher than after MMC alone, but valid comparison studies could not be drawn due to the absence of randomized trials in neo-adjuvant settings. AEs were higher with CT-MwHT than with MMC alone, but this difference was not statistically significant. Published data suggest that recurrence rates for chemo-hyperthermia are substantially reduced compared with chemotherapy alone in adjuvant settings. Patients with refractory disease fare worse than those being treated with chemo-hyperthermia for their first tumor. Progression rates to muscle-invasive disease are markedly lower after combination treatment than after chemotherapy alone, with very high rates of bladder preservation. Tolerability is good, with few dropouts in the clinical trials. The results support CT-MwHT in the future as a standard procedure for high-risk recurrent patients, for subjects in whom the treatment with Bacillus Calmette-Guérin is contraindicated, and those unsuitable for radical cystectomy.

Volpe, A., et al. (2012). "Thermochemotherapy for non-muscle-invasive bladder cancer: is there a chance to avoid early cystectomy?" *Urol Int* **89**(3): 311-318.

**Objectives:** Non-muscle-invasive bladder cancer is characterized by a high recurrence rate after primary transurethral resection. In case of bacillus Calmette-Guérin-refractory neoplasms, cystectomy is the gold standard. In this study the effects of thermochemotherapy with mitomycin C were evaluated in high-risk bladder cancer nonresponders to previous therapy. **Patients and Methods:** Between January 2006 and December 2009, 30 patients were enrolled with recurrent stage carcinoma in situ, Ta and T1, grade G1 to G3 non-muscle-invasive bladder cancer refractory to chemotherapy or immunotherapy and so becoming suitable for radical cystectomy. All patients underwent endovesical thermochemotherapy: 16 patients underwent a prophylactic scheme and 14 patients underwent an ablative scheme. **Results:** All the patients completed the study. The mean follow-up for all the patients enrolled was 14 months. Thirteen of 30 patients (43.30%) were disease free and 17 patients (56.70%) had recurrence. In the prophylactic group, 7 of 16 patients (43.75%) were disease free and 9 patients (46.25%) had tumor recurrence; no progression was observed. In the ablative group, 3 patients (17, 64%) had progression to muscle-invasive disease. Side effects were generally mild. **Conclusions:** Thermochemotherapy could be considered an additional tool in patients refractory to intravesical therapies before considering early cystectomy.

Moskovitz, B., et al. (2012). "10-year single-center experience of combined intravesical chemohyperthermia for nonmuscle invasive bladder cancer." *Future Oncol* **8**(8): 1041-1049.

**Aim:** Owing to the limited efficacy and significant toxicity of most topical intravesical agents for the management of nonmuscle invasive bladder cancer (NMIBC), a search for new therapeutic modalities continues. This study evaluates the safety and efficacy of a relatively new modality, combined intravesical chemotherapy and hyperthermia, using the intravesical chemohyperthermia system. **Methods:** The data summarize our 10 years of experience in the Department of Urology at Bnai Zion Medical Center, Israel. Ninety two patients with NMIBC (88 evaluable) were treated according to the adjuvant (66 patients) and the neoadjuvant (26 patients) protocols, with up to 7 years follow-up. **Results:** Over the follow-up period, 56 out of 64 patients (72%) treated according to the adjuvant protocol remained free from recurrences. The progression rate was 4.7% (three out of 64 patients). An initial complete response was documented in 19 out of 24 patients (79%) treated according to the neoadjuvant protocol. During the follow-up period, 16 out of these 19 patients (84%) remained free from recurrences. All of the recurrences in this group had stage Ta grade 1 tumors. **Conclusion:** Microwave-induced chemohyperthermia is a safe and effective treatment option for patients with NMIBC, both in the adjuvant and neoadjuvant settings. The use of this treatment modality did not expose the patients to an increased risk of progression.

Lammers, R. J., et al. (2011). "The role of a combined regimen with intravesical chemotherapy and hyperthermia in the management of non-muscle-invasive bladder cancer: a systematic review." *Eur Urol* **60**(1): 81-93.

**Context:** Due to the suboptimal clinical outcomes of current therapies for non-muscle-invasive bladder cancer (NMIBC), the search for better therapeutic options continues. One option is chemohyperthermia (C-HT): microwave-induced hyperthermia (HT) with intravesical chemotherapy, typically mitomycin C (MMC). During the last 15 yr, the combined regimen has been tested in different clinical settings. **Objective:** To perform a systematic review to evaluate the efficacy of C-HT as a treatment for NMIBC. **Evidence Acquisition:** The review process followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. An electronic search of the Medline, Embase, Cochrane Library, CancerLit, and ClinicalTrials.gov databases was undertaken. Relevant conference abstracts and urology journals were also searched manually. Two reviewers independently reviewed candidate studies for eligibility and abstracted data from studies that met inclusion criteria. The primary end point was time to recurrence. Secondary end points included time to progression, bladder preservation rate, and adverse event (AE) rate. **Evidence Synthesis:** A total of 22 studies met inclusion criteria and underwent data extraction. When possible, data were combined using random effects meta-analytic techniques. Recurrence was seen 59% less after C-HT than after MMC alone. Due to short follow-up, no conclusions can be drawn about time to recurrence and progression. The overall bladder preservation rate after C-HT was 87.6%. This rate appeared higher than after MMC alone, but valid comparison studies were lacking. AEs were higher with C-HT than with MMC alone, but this difference was not statistically significant. **Conclusions:** Published data suggest a 59% relative reduction in NMIBC recurrence when C-HT is compared with MMC alone. C-HT also appears to improve bladder preservation rate. However, due to a limited number of randomized trials and to heterogeneity in study design, definitive conclusions cannot be drawn. In the future, C-HT may become standard therapy for high-risk patients with recurrent tumors, for patients who are unsuitable for radical cystectomy, and in cases for which bacillus Calmette-Guerin treatment is contraindicated.

Colombo, R., et al. (2011). "Long-term outcomes of a randomized controlled trial comparing thermochemotherapy with mitomycin-C alone as adjuvant treatment for non-muscle-invasive bladder cancer (NMIBC)." *BJU Int* **107**(6): 912-918.

**Objectives:** This study presents long-term efficacy of intravesical chemochemotherapy versus chemotherapy alone with Mitomycin C randomly administered to patients with non-muscle-invasive bladder cancer as an adjuvant treatment after complete transurethral resection. **Subjects and Methods:** Eighty-three patients with intermediate/high-risk non-muscle invasive urothelial cell carcinoma of the bladder, following complete trans-urethral resection, were randomly assigned to receive either intravesical thermochemotherapy (by means of Synergo®) or intravesical chemotherapy alone, for prophylaxis of tumor recurrence. Mitomycin C (namely, two doses of 20 mg dissolved in 50 ml distilled water administered throughout two consecutive sessions) was used as the chemotherapeutic agent in both arms. Seventy-five patients completed the original study (35 of 42 in the treatment arm, 40 of 41 in the control arm), whose results at minimum 2-year follow-up have already been published. Recently, the files of these patients have been updated for long-term outcome definition. Data regarding general health, follow-up exams, tumor relapse or progression, and cause of death were collected and analyzed. **Results:** Updated complete data collection was available for 65/75 (87%) of the original patients. Median follow-up for tumor-free patients was 91 months. The 10-year disease-free survival rate for thermo-chemotherapy and chemotherapy alone were 53% and 15%, respectively ( $P < 0.0001$ ). An "intent to treat" analysis performed to overcome the potential bias introduced by the asymmetrical drop rate, still showed a significant advantage of the active treatment over the control treatment. Bladder preservation rates for thermo-chemotherapy and chemotherapy alone were 86% and 79%, respectively. **Conclusions:** This is the first analysis of long-term follow-up of patients treated with intravesical thermo-chemotherapy. The high rate (53%) of patients documented to be tumor-free 10 years after treatment completion as well as the high rate (86%) of bladder preservation, confirms the efficacy of this adjuvant approach for non-muscle invasive bladder cancer also at long term follow-up, even in patients with multiple tumors.

Halachmi, S., et al. (2011). "Intravesical mitomycin C combined with hyperthermia for patients with T1G3 transitional cell carcinoma of the bladder." *Urol Oncol* 29(3): 259-264.

**Objectives:** Non-muscle invasive bladder cancer (NMIBC) classified as T1G3 represents one of the most challenging issues in urologic oncology. Although it is still considered a lesion amenable for conservative management, the risk for recurrence and progression remains high. The aim of this study was to define both recurrence and progression rate in patients with T1G3 UCC treated by complete transurethral resection (TUR) and adjuvant thermochemotherapy approach. **Materials and Methods:** We retrospectively evaluated the clinical data of patients with T1G3 NMIBC who underwent TUR followed by thermochemotherapy (TCT) treatment. Data recorded included age, gender, previous resections, previous intravesical treatment, time to tumor recurrence, and progression. TCT was given once weekly for 6 consecutive weeks, followed by 6 maintenance sessions at 4 to 6 weeks intervals. During each treatment session, 40 mg of mitomycin C (MMC) was instilled into the bladder in combination with bladder wall hyperthermia of 42 +/- 2 degrees C for 60 minutes. Follow-up cystoscopy and urinary cytology were performed every 3 months for the first 2 years and then biannually. **Results:** A total of 56 T1G3 patients were treated with adjuvant TCT treatment at 7 urologic centers. Mean age was 68 years (range 35-91), 10 were females and 46 were males. Twenty-six patients failed on at least 1 previous intravesical treatment. Five patients who dropped out due to adverse events before reaching the first outcome evaluation cystoscopy were referred to another intravesical therapy, and were therefore excluded from the current analysis. A total 51 patients were available for analysis. Median follow-up time of tumor-free patients was 18 months (average 20, range 2-49 months). Seventeen patients (33.3%) had tumor recurrence and 4 of them progressed to muscle invasive disease. The median time to recurrence was 9 months (average 11, range 2-31 months). The Kaplan-Meier estimated recurrence rate for this group is: 42.9% at 2 years, 51.0% at 4 years. **Conclusions:** TCT can be an effective adjuvant treatment option after TUR to prevent recurrence in patients with T1G3 NMIBC. Progression rate after this treatment was low (7.9%). TCT treatment was documented to be effective also in those who failed previous intravesical BCG. Treatment was confirmed to be safe and well tolerated.

Nativ, O., et al. (2009). "Combined thermo-chemotherapy for recurrent bladder cancer after bacillus Calmette-Guérin." *J Urol* 182(4): 1313-1317.

**Purpose:** Despite an initial adequate response, many patients with non-muscle invasive urothelial cell carcinoma of the bladder eventually have recurrence after intravesical bacillus Calmette-Guérin treatments. We evaluated the efficacy of combined bladder wall hyperthermia and intravesical mitomycin-C instillation (thermo-chemotherapy) in cases of recurrence after bacillus Calmette-Guérin. **Materials and methods:** A total of 111 patients with recurrent papillary nonmuscle invasive urothelial cell carcinoma of the bladder after previous bacillus Calmette-Guérin treatment underwent complete bladder tumor resection and were referred to prophylactic (adjuvant) treatment with thermo-chemotherapy. Treatment was received on an outpatient basis weekly for 6 weeks, followed by 6 maintenance sessions at 4-6 week intervals. Each treatment included 2 30 minute cycles of 20mg of mitomycin-C and bladder wall hyperthermia to a mean  $\pm$ SD 42 $\pm$ 2 $^{\circ}$ C. Cystoscopy and urine cytology were performed after the completion of the induction treatment, and every 3 months thereafter. **Results:** The Kaplan-Meier estimated disease free survival rates was 85% and 56% after 1 and 2 years, respectively. No maintenance treatment was associated with decreased efficacy, that is the recurrence rate was 61% at 2 years vs. 39% in those with maintenance treatments ( $p=0.01$ ). Progression rate was 3%. **Conclusions:** Thermo-chemotherapy may be effective for papillary nonmuscle invasive urothelial cell carcinoma of the bladder that recurs after BCG treatment without increasing the risk for tumor progression. Maintenance therapy is important and improves outcome.

Alfred Witjes, J., et al. (2009). "Intravesical hyperthermia and mitomycin-C for carcinoma in situ of the urinary bladder: experience of the European Synergo working party." *World J Urol* 27(3): 319-324.

**Objectives:** To study the results of chemotherapy combined with intravesical hyperthermia in patients with mainly BCG-failing carcinoma in situ (CIS).  
**Methods:** Patients with histologically confirmed CIS were included retrospectively. Outpatient thermochemotherapy treatment was done with mitomycin-C (MMC) and the Synergo system SB-TS 101 (temperature range between 41 and 44 degrees C), weekly for 6-8 weeks, followed by 4-6 sessions every 6-8 weeks.  
**Results:** Fifty-one patients were treated between 1997 and 2005 from 15 European centers. Thirty-four were pre-treated with BCG. Mean age was 69.9 years. Twenty-four patients had concomitant papillary tumors. The mean number of hyperthermia/MMC treatments per patient was 10.0. Of the 49 evaluable patients 45 had a biopsy and cytology proven complete response. In two patients CIS disappeared, but they had persistent papillary tumors. Follow-up of 45 complete responders showed 22 recurrences after a mean of 27 months (median 22): T2 (4), T1 (4), T1/CIS (1), CIS (5), Ta/CIS (2), Ta (5) and Tx (1). Side effects (bladder complaints) were generally mild and transient.  
**Conclusions:** In patients with primary or BCG-failing CIS, treatment with intravesical hyperthermia and MMC appears a safe and effective treatment. The initial complete response rate is 92%, which remains approximately 50% after 2 years.

van der Heijden, A. G., et al. (2007). "The influence of thermo-chemotherapy on bladder tumours: an immunohistochemical analysis." *World J Urol* 25(3): 303-308.

To study the influence of microwave induced thermo-chemotherapy on high-grade urothelial cell carcinomas. Five groups of each three patients were formed of whom initial biopsies and cystectomy samples were collected. Patients were treated 2 days prior to cystectomy with mitomycin-C (group 1), hyperthermia (group 2) or thermo-chemotherapy (group 3). Group 4 patients had been treated with a cycle of six thermo-chemotherapy treatments prior to cystectomy and group 5 patients served as control (no treatment). Tumour samples were stained with Haematoxylin and Eosin, monoclonal antibody Ki-67 and the monoclonal antibody p53. In six out of the nine patients treated with hyperthermia a decrease in proliferation activity in the tumour was found. Seven out of nine patients treated with hyperthermia showed a decrease in p53 activity. A decrease in proliferation activity and p53 activity illustrate the potential role of thermo-chemotherapy as a promising intravesical treatment.

Moskovitz, B., et al. (2005). "Thermo-chemotherapy for intermediate or high-risk recurrent superficial bladder cancer patients." *Ann Oncol* **16**(4): 585-589.

**Background:** The purpose of this study was to evaluate the efficacy of combined local hyperthermia and intravesical mitomycin-C (MMC) in a selected group of patients with intermediate or high-risk recurrent transitional cell carcinoma (TCC) of bladder. **Patients and methods:** Forty-seven patients with multiple or recurrent Ta or T1 TCC of the bladder were treated with intravesical MMC and local hyperthermia of the bladder wall. Patients were treated with either a prophylactic protocol (40 mg MMC) after complete transurethral resection of all tumours or with an ablative protocol (80 mg MMC) in patients with viable tumours. **Results:** Thirty-two patients were eligible for analysis. The prophylactic protocol was administered to 22 patients. After a mean follow-up of 289 days, 20 patients (91%) were recurrence free. Two patients (9%) had tumour recurrence after a mean period of 431 days. The ablative protocol was administered to 10 patients. Complete tumour ablation was achieved in eight patients (80%) after a mean follow up of 104.5 days. **Conclusions:** Our efficacy and safety results confirm those reported in previously published studies, suggesting the promising value of this combined treatment modality for both prophylactic and ablative patients. The ablative protocol offers an alternative therapy for a selected patient population for whom no other treatment option exists.

van der Heijden, A. G., et al. (2005). "Effect of hyperthermia on the cytotoxicity of 4 chemotherapeutic agents currently used for the treatment of transitional cell carcinoma of the bladder: an in vitro study." *J Urol* **173**(4): 1375-1380.

**Purpose:** Hyperthermia combined with chemotherapy is not a novel cancer treatment. However, the working mechanism of this combination therapy is not fully understood. In the current in vitro study we investigated the differences in cytotoxicity of 4 chemotherapeutic agents at 37C or 43C. **Materials and Methods:** The human transitional cell carcinoma cell lines used were RT4, RT112, 253J and T24. Cells were seeded in 96-well microtiter plates. After 24 hours cells were treated for 60 minutes with increasing concentrations of mitomycin C, epirubicin, gemcitabine and EO9 at a temperature of 37C or 43C. After treatment cells were rinsed 3 times and left for 24 hours in the incubator at 37C. The influence of chemotherapy and temperature on cell survival was determined by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide) assay. **Results:** Decreased cell proliferation with increasing concentrations of chemotherapeutic agents was demonstrated. EO9 proved to be the most potent agent at each temperature. Hyperthermia alone did not demonstrate decreased cell proliferation. However, a synergistic effect on decreased cell proliferation was demonstrated in all cell lines and chemotherapeutic agents used, although each had a maximum at a different chemotherapy concentration and to a different extent. Synergism was most obvious in cell lines treated with low dose epirubicin. **Conclusions:** Synergism with hyperthermia and chemotherapy was clearly demonstrated for epirubicin, EO9, mitomycin C and to a lesser extent gemcitabine. Hyperthermia alone did not cause decreased cell proliferation. Synergism was most prominent with low drug doses and the most potent drug used in this in vitro study was EO9.

Gofrit, O. N., et al. (2004). "Combined local bladder hyperthermia and intravesical chemotherapy for the treatment of high-grade superficial bladder cancer." *Urology* **63**(3): 466-471.

**Objectives:** To evaluate the effectiveness of combined local bladder hyperthermia and intravesical chemotherapy for the treatment of patients with high-grade (G3) superficial bladder cancer. **Methods:** Patients with G3 bladder tumors (Stage Ta or T1) were treated with combined intravesical chemotherapy with mitomycin-C and local radiofrequency hyperthermia of the bladder wall. The patients were treated with either a prophylactic protocol (40 mg mitomycin-C) after complete transurethral resection of all tumors or with an ablative protocol (80 mg mitomycin-C) when visible tumor was seen on videocystoscopy or bladder biopsies were positive for carcinoma in situ. **Results:** Combined chemo-thermotherapy was administered to 52 patients with high-grade superficial bladder cancer (40 patients with Stage T1 tumor, 11 with Ta, and 3 with concomitant or isolated carcinoma in situ). At a median follow-up of 15.2 months (mean 23, range 6 to 90), no stage progression to T2 or disease-related mortality had occurred. The bladder preservation rate was 86.5%. The prophylactic protocol was administered to 24 patients. After a mean follow-up of 35.3 months, 15 patients (62.5%) were recurrence free. The bladder preservation rate was 95.8%. The ablative protocol was administered to 28 patients. Complete ablation of the tumor was accomplished in 21 patients (75%). After a mean follow-up of 20 months, 80.9% of these patients were recurrence free. The bladder preservation rate for the ablative group was 78.6%. **Conclusions:** Combined local bladder hyperthermia and intravesical chemotherapy has a beneficial prophylactic effect in patients with G3 superficial bladder cancer. Ablation of high-grade bladder tumors is feasible, achieving a complete response in about three quarters of the patients.

van der Heijden, A. G., et al. (2004). "Preliminary European results of local microwave hyperthermia and chemotherapy treatment in intermediate or high risk superficial transitional cell carcinoma of the bladder." *Eur Urol* **46**(1): 65-71; discussion 71-62.

**Introduction:** Superficial bladder cancer can be treated by transurethral resection (TUR) and adjuvant intravesical therapy. Intravesical bacillus Calmette-Gue´rin (BCG) has been proven to be more efficacious with respect to recurrence prevention than intravesical chemotherapy, although at the cost of more severe side effects. There is a need for a new treatment modality with higher efficacy and less toxicity. The subject of this study is the efficacy of local microwave hyperthermia and chemotherapy treatment in intermediate or high risk superficial transitional cell carcinoma (TCC) of the bladder. **Patients and Methods:** Ninety eligible patients received adjuvant treatment with a combination of mitomycin-C (MMC) and local microwave hyperthermia. All patients had multiple or recurrent Ta or T1 TCC of the bladder and were classified as intermediate or high risk according to EAU criteria. In total, 41 patients were BCG failures. The treatment regimen included 6 to 8 weekly sessions followed by 4 to 6 monthly sessions. Follow-up consisted of video-cystoscopy and urine cytology every 3 months. All patients were observed for 2 years. **Results:** Kaplan–Meier analyses of the total group (N=90) indicated that 1 year after treatment only 14.3% (SE 4.5%) of all patients experienced a recurrence. After 2 years of follow-up the risk of recurrence was 24.6% (SE 5.9%). No progression in stage and grade was observed. **Conclusion:** Microwave induced hyperthermia combined with MMC has promising value in intermediate or high risk superficial bladder cancer patients compared to literature data of BCG and/or intravesical chemotherapy, particularly where other treatments, i.e. BCG, have failed.

van der Heijden, A. G., et al. (2004). "The effect of hyperthermia on mitomycin-C induced cytotoxicity in four human bladder cancer cell lines." *Eur Urol* **46**(5): 670-674.

**Introduction:** Hyperthermia and mitomycin-C (MMC) have given very encouraging results in several clinical studies for the treatment of superficial transitional cell carcinoma of the bladder. However, a synergistic effect of hyperthermia and MMC on the decrease of cell proliferation has never been demonstrated accurately in vitro. We investigated the effect of MMC versus MMC combined with hyperthermia on the cytotoxicity in four human bladder cancer cell lines. **Material and Methods:** The RT112, RT4, 253J and T24 human bladder cancer cell lines were seeded in 96-well microtiter plates at  $2.0 \times 10^4$  cells per well and were left to attach for 24 hours. The cells were then treated for 60 minutes with MMC concentrations ranging from 0 to 400  $\mu\text{g/ml}$  at a temperature of 37°C or 43°C. After treatment cells were rinsed three times with culture medium and left for 24 hours in the incubator. Dimethyl thiazolyl tetrazolium (MTT) solution was added and after 4 hours of incubation the MTT containing media was aspirated from all wells and 100  $\mu\text{l}$  of dimethyl sulfoxide was added to each well. A spectrum analysis was performed at 595 nm light wavelength. **Results:** A decrease of cell proliferation after treatment with increasing concentrations MMC was demonstrated. Hyperthermia has a synergistic effect on the decrease of cell proliferation by different concentrations MMC. In the cells treated without MMC no significant difference in the extent of cell killing at 37°C and 43°C was observed. Furthermore, no difference was observed between cells with a p53 protein mutation (RT112 and T24) or without a p53 protein mutation (253J and RT4). **Conclusion:** A clear synergistic effect of MMC and hyperthermia has been demonstrated in four human bladder cancer cell lines.

Rath-Wolfson, L., et al. (2003). "Combined intravesical hyperthermia and mitomycin chemotherapy: a preliminary in vivo study." *Int J Exp Pathol* **84**(3): 145-152.

**Summary:** Previous clinical studies of the combination of local intravesical hyperthermia with cytostatic drugs for the treatment of Superficial Transitional Cell Carcinoma of the urinary bladder (STCCB) showed encouraging results both in reducing recurrence rate to 20–30% within 2 years and in ablative success rate of 79%. Our objectives were to evaluate bladder tissue and adjacent organs during and following hyperthermia treatment. An intravesical catheter equipped with a radio-frequency antenna (Synergo\_ SB-TS 101.1 System) was used for hyperthermia and intravesical chemotherapy (mitomycin C) was instilled in vivo for 60 min in two anaesthetized sheep. Thirteen to fifteen thermocouples were sewn surgically on the internal and external surfaces of the bladder wall and on adjacent organs to monitor the temperature during the treatment. We expected the intravesical temperature to be under 46°C and the external layers below 45°C. The bladder was filled with 50mL of chemotherapeutic solution (400 mg/mL of mitomycin C in distilled water). The sheep were sacrificed at the end of the treatment. Three other sheep, which underwent thoracic surgery, served as control group. Histological changes in both groups showed foci of oedema and haemorrhage with inflammation in the lamina propria and serosa. Foci of desquamation of the epithelium were noticed in the treated sheep. Histological analysis of the treated group showed no significant differences from the control group. The control group showed similar changes, some less pronounced. The combined treatment of hyperthermia with mitomycin C did not cause major damage to the urinary bladder or adjacent organs. All changes were superficial and reversible, and the control group showed similar changes, some less pronounced. Although this is an experimental model based on one single session treatment, rather than repeated treatments, it suggests that the approach may be useful in future studies both in models and man.

Colombo, R., et al. (2003). "Combination of intravesical chemotherapy and hyperthermia for the treatment of superficial bladder cancer: preliminary clinical experience." *Crit Rev Oncol Hematol* 47(2): 127-139.

The prevalence of superficial transitional cell carcinoma of the bladder (STCCB) is still increasing in spite of improved adjuvant chemotherapeutic and/or immunoprophylaxis approaches. Thus, there is certainly an urgent need to improve our ability to control this disease. Local hyperthermia has a therapeutic 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 antitumor 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 thermochemotherapy regimen in humans. In preliminary clinical experiences, insofar as mainly carried out as monoinstitutional 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.

Colombo, R., et al. (2003). "Multicentric study comparing intravesical chemotherapy alone and with local microwave hyperthermia for prophylaxis of recurrence of superficial transitional cell carcinoma." *J Clin Oncol* 21(23): 4270-4276.

**Purpose:** To compare the efficacy and local toxicity of the intravesical instillation of a cytostatic drug versus the same cytostatic agent in combination with local hyperthermia as an adjuvant treatment, after complete transurethral resection (TURB) of superficial transitional cell carcinoma (TCC) of the bladder. **Patients and Methods:** The study was designed as a prospective, multicentric, randomized trial. Eighty-three patients suffering from primary or recurrent superficial (Ta-T1) TCC of the bladder, after a complete TURB, were randomly assigned to receive intravesical instillations of mitomycin C (MMC) alone, for 41 patients, and MMC in combination with local microwave-induced hyperthermia, for 42 patients. For the combined approach, a new system, Synergo101-1 (Medical Enterprises, Amsterdam, the Netherlands) was used. The effectiveness evaluation end points of the study were evaluation of recurrence-free side effects and clinical complications. For the efficacy end point, Kaplan-Meier analysis was employed, with the log-rank test for significance. Minimum follow-up time was 24 months. **Results:** Of the 83 randomly assigned patients, 75 completed the study according to the protocol and had valid cystoscopy results. Survival analysis of the 75 assessable patients demonstrated a highly significant difference in the survival curves in favor of thermochemotherapy. Subjective intolerance and clinical complications were significantly higher but transient and moderate in the combined treatment group. **Conclusion:** In our series, endovesical thermochemotherapy appears to be more effective than standard endovesical chemotherapy as an adjuvant treatment for superficial bladder tumors at 24-month follow-up, despite an increased but acceptable local toxicity.

Paroni, R., et al. (2001). "Effect of local hyperthermia of the bladder on mitomycin C pharmacokinetics during intravesical chemotherapy for the treatment of superficial transitional cell carcinoma." *Br J Clin Pharmacol* 52(3): 273-278.

**Aims:** To assess the effect of local hypethermia on the systemic absorption of mitomycin C (MMC) during intravesical chemotherapy for the treatment of superficial transitional cell carcinoma of the bladder, and to establish the likely safety of this procedure. **Methods:** Group 1 (n=12) received 20 mg intravesical MMC plus local hyperthermia, group 2 (n=13) 20 mg MMC alone, group 3 (n=16) 40 mg MMC plus local hyperthermia and group 4 (n=10) 40 mg MMC alone. Patients in groups 1,2 and 4 underwent post-tumour resection adjuvant treatment, whereas those in group 3 still had tumour present and were treated to eradicate it. Intravesical instillation lasted 60 min, with the solution (50 ml) being replaced after the first 30 min. Blood samples were taken before, and every 15 min during instillation. MMC concentrations in plasma and in urine were determined by h.p.l.c. **Results:** The highest MMC plasma concentration (67.9 ng ml<sup>-1</sup>) occurred in a patient in group 3. This value was well below the threshold concentration (400 ng ml<sup>-1</sup>) for myelosuppression. Local hyperthermia associated with the intravesical chemotherapy enhanced plasma MMC concentrations at 30, 45 and 60 min compared with chemotherapy alone (Group 1 vs 2, P ≤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 greatest variability in pharmacokinetics between patients. **Conclusions:** Local hyperthermia enhances the systemic absorption of MMC during intravesical chemotherapy for bladder cancer. In the doses used, plasma MMC concentrations were always more than six times lower than those shown to cause toxicity.

Colombo, R., et al. (2001). "Thermo-chemotherapy and electromotive drug administration of mitomycin C in superficial bladder cancer eradication. a pilot study on marker lesion." *Eur Urol* 39(1): 95-100.

**Objective:** To assess the feasibility and safety of two novel methods for intravesical chemotherapy administration in patients suffering from superficial bladder carcinomas. To draw preliminary considerations concerning the ablative effect on marker lesion using novel approaches compared to standard intravesical chemotherapy. **Methods:** Eighty patients suffering from single, recurrent, low-stage, low-grade superficial bladder tumor entered a prospective nonrandomized study. Thirty-six of them were treated by means of mitomycin C instillation as a standard procedure. In 29 patients mitomycin C solution was administered in combination with local microwave-induced hyperthermia and in 15 patients the mitomycin C solution was administered according to the electromotive drug procedure. The treatment was scheduled as a short term neo-adjuvant regimen prior to transurethral resection. Feasibility and safety of the different procedures were evaluated on an outpatients basis. The local toxicity induced by different approaches was defined and compared using a subjective questionnaire. **Results:** Both intravesical chemotherapy administered in combination with hyperthermia and according to the electromotive drug technique appeared to be feasible and safe. Local toxicity induced by thermo-chemotherapy was more severe than that registered for electromotive drug technique and standard intravesical chemotherapy. Local toxicity was always short and self healing without early or delayed major complications. A higher complete response rate on marker lesion was observed after thermo-chemotherapy compared to other administration methods. **Conclusion:** The intravesical administration of mitomycin C can be safely performed in the form of both thermo-chemotherapy and electromotive drug approach with an increased ablative success rate on small superficial tumor involving only minimal local side effects.

Colombo, R., et al. (1998). "Local microwave hyperthermia and intravesical chemotherapy as bladder sparing treatment for select multifocal and unresectable superficial bladder tumors." *J Urol* **159**(3): 783-787.

**Purpose:** The role of a combined regimen of local hyperthermia and topical chemotherapy in patients with multifocal and recurrent superficial bladder tumors not curable by transurethral resection was evaluated in a neoadjuvant organ-sparing clinical study. **Materials and Methods:** A total of 19 patients with multifocal, superficial, grade 1 to 3 bladder tumors that recurred after intravesical chemoprophylaxis or immunoprophylaxis underwent local combined administration of microwave-induced hyperthermia and intravesical chemotherapy as a debulking approach. Due to extensive superficial involvement of the bladder walls, complete transurethral resection of all tumors seemed technically unfeasible in all cases and radical cystectomy was considered the treatment of choice. Endovesical hyperthermia at 42.5° to 45°C was delivered using the SB- TS 101 system based on a microwave transurethral applicator that irradiates the bladder filled with a circulating solution of mitomycin C. Patients underwent 8 weekly 1-hour sessions on an outpatient basis without anesthesia. When possible, after treatment patients underwent transurethral resection of residual tumors and all suspicious areas. **Results:** After treatment, transurethral resection appeared to be feasible and curative in 16 patients (84%). Histological study revealed complete and partial responses in 9 (47%) and 7 (37%) cases respectively. Due to extensive residual tumors, radical cystectomy was performed in 3 patients (16%). At a median 33-month follow-up, 8 superficial transitional tumor recurrences were documented and easily eradicated by transurethral resection or laser therapy in patients in whom the bladder had been saved. **Conclusions:** Microwave-induced hyperthermia combined with intravesical mitomycin C seems to be a feasible, safe and elective approach for conservative treatment of multifocal and recurrent superficial bladder tumors when other treatment strategies have failed.

Paroni, R., et al. (1997). "Plasma mitomycin C concentrations determined by HPLC coupled to solid-phase extraction." *Clin Chem* **43**(4): 615-618.

The aim of this study was to set up a method for quantification of plasma mitomycin C (MMC) concentrations during intravesical chemotherapy delivered in the presence of local bladder hyperthermia (HT). In comparison with existing methods, this assay, characterized by relative simplicity and efficiency, resulted in the facilitation of performance with nondedicated instrumentation or nonspecialized staff. Purification from plasma matrix was carried out by solid-phase extraction under vacuum. The purified drug was then collected directly into the vials of the HPLC autosampler. Chromatographic analysis was performed on a reversed-phase C18 column with water:acetonitrile (85:15 by vol) as the mobile phase and the UV detector set at 365 nm. The use of porfiromycin as internal standard provided a method with good within-day precision (CV 6.0% at 5 micrograms/L, n = 6), linearity (0.5-50 micrograms/L), and specificity. The lower limit of detection (< or = 0.5 microgram/L) proved to be suitable for plasma pharmacokinetics monitoring in two tested patients treated with MMC + HT for superficial bladder cancer.

Colombo, R., et al. (1996). "Neoadjuvant combined microwave induced local hyperthermia and topical chemotherapy versus chemotherapy alone for superficial bladder cancer." *J Urol* **155**(4): 1227-1232.

**Purpose:** We evaluated the effectiveness of local bladder hyperthermia and intravesical chemotherapy compared to intravesical chemotherapy alone in the treatment of superficial transitional cell carcinoma. **Materials and Methods:** A new system designed to deliver simultaneously local bladder hyperthermia and intravesical chemotherapy has been developed at our Institute. The system consists of a computerised 915 Mhz microwave source that directly heats the bladder walls (within a temperature range of 42.5 to 45.5°C) using a transurethral catheter. From February 1989 to December 1993, 52 patients 44 to 81 years old (mean age 64.3) with superficial stage Ta to T1, grade I to 3 transitional cell carcinoma of the bladder were selected for neoadjuvant intracavitary treatment. Tumors were left intact as marker lesions. Of the patients, 29 were randomly assigned to receive combined neoadjuvant intravesical chemotherapy and local hyperthermia (group 1), while 23 received intravesical chemotherapy alone (group 2). The treatment protocol included multiple sessions performed on an outpatient basis. Mitomycin C (40 mg in 50 cc distilled water) was used for intravesical chemotherapy in both groups. All patients underwent transurethral resection of residual tumors and of all suspicious areas 7 to 10 days after completion of treatment. Only a complete response was considered for statistical analysis. **Results:** A pathological complete response was documented in 19 cases (66%) in group 1 and in 5 cases (22%) in group 2 (chi-square  $p < 0.01$ ). **Conclusions:** According to these preliminary data, microwave-induced hyperthermia combined with local intravesical chemotherapy seems to be a feasible, safe and promising approach for neoadjuvant and minimally invasive treatment of superficial bladder cancer.

Colombo, R., et al. (1995). "A new approach using local combined microwave hyperthermia and chemotherapy in superficial transitional bladder carcinoma treatment." *J Urol* **153**(3 Pt 2): 959-963.

For some time hyperthermia, alone or in combination with radiotherapy or chemotherapy, has proved to be a promising method for treating several kinds of solid tumors. After intensive laboratory investigations, a new device based on a microwave source delivering local bladder hyperthermia together with intravesical mitomycin C chemotherapy has been clinically tested as a neoadjuvant approach in 44 patients suffering from superficial cancer of the bladder. The combined approach was administered on an outpatient basis without major complications and with acceptable local toxicity. Endoscopic and histological evaluations proved that combined local hyperthermia and chemotherapy can induce necrosis of transitional tumors. The overall response rate was 90.8%, with 70.4% complete and 20.4% partial, leaving 4 patients (9.2%) nonrespondent. Clinical and histological evaluations have confirmed the feasibility and safety of this combined treatment. Further multicentric studies have been initiated.

Rigatti, P., et al. (1991). "Combined intravesical chemotherapy with mitomycin C and local bladder microwave-induced hyperthermia as a preoperative therapy for superficial bladder tumors. A preliminary clinical study." *Eur Urol* **20**(3): 204-210.

Twelve patients suffering from superficial transitional cell carcinoma of the bladder underwent treatment combining simultaneous mitomycin C topical instillation and local endocavitary hyperthermia as a preoperative adjunct to transurethral resection in a preliminary clinical study. A specifically designed system to deliver and monitor local bladder hyperthermia was used. The feasibility, the subjective tolerance and the side effects of the combined treatment were the main target of our investigation. Endoscopic and histologic features, assessed before, during and after this combined approach, showed selective damage to neoplastic areas with minimal changes in the normal urothelium. Local intravesical concurrent chemotherapy and hyperthermia administration is found to be a safe and well-tolerated approach for superficial bladder tumor treatment. The preliminary results encourage further studies to define the limits and prospects of this regimen, in both superficial bladder tumor ablation and prophylaxis of recurrences.

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