



SYNERGO[®] RITE

FOR BLADDER CANCER

Radiofrequency-Induced ThermoChemotherapeutic Effect
for the treatment of Non-Muscle Invasive Bladder Cancer

LIST OF PUBLICATIONS
1991 - 2019

Witjes JA. Radiofrequency-induced Thermochemotherapy for Recurrent Non-muscle-invasive Bladder Cancer: A New Treatment for an Unmet Need? *Eur Urol*. 2019 Jan;75(1):72-73. doi: 10.1016/j.eururo.2018.09.039.

After summary on HYMN; The authors should be commended for conducting a multicenter RCT with a new treatment regimen in this patient population. This is a longstanding unmet need and the study has certainly generated information for further research. However, this trial did not meet my personal expectations, having worked with this technique since 2001. and is not in concordance with other previous reports. The study was closed after 104 patients were randomized (planned sample size 242), which makes the study underpowered, as acknowledged by the authors. Moreover, the 104 patients were included over a period of more than 3 yr from 14 centers, meaning an average number of 2.5 per center per year. Having used RITE for 18 yr for hundreds of patients, we have learned that this treatment requires experience and proper patient information to achieve effective therapy (eg, sufficient heating). No data on the temperature achieved are presented, although the target was $42\pm 2^{\circ}\text{C}$. A second concern, noted by most reviewers, is the patient selection at entry. The patients included had different treatments, which is a confounding factor. Although this trial started before the recent US Food and Drug Administration definition of BCG-unresponsive disease, the patients selected for the HYMN trial had clearly differing risk profiles. Other missing information with regard to treatment was the use of enhanced imaging and the use of perioperative chemotherapy. Apart from treatment history, pretrial pathology also remains an issue: was pathology reviewed, especially CIS? For example, a post hoc analysis shows a higher number of concurrent papillary and CIS tumors in the RITE arm than in the control arm (25% vs 16%; $p = 0.38$), which is a small bias. For subgroup analyses, however, the trial is too small. In addition, the treatment regimens deserve some attention. RITE was given with 40 mg of MMC, whereas, as again acknowledged by the authors, 40 + 40mg is the standard for these patients. They apparently followed “the manufacturer's guidance”, but the reference from 2004 (in the manuscript) refers to preliminary results from a study in papillary tumors for which no guidance is mentioned.

This dose is certainly one of the reasons for the lower results in this trial with RITE: the 24-mo DFS was 35% overall, and approximately 25% among CIS patients, versus results in the literature: 78.1% DFS in the RCT versus BCG in untreated patients, and 47% and 56% 2 year DFS in two large retrospective studies in patients also previously treated with BCG. The 3-mo response rate of 30% in CIS is also lower than results from a recent large retrospective analysis for CIS patients, for which the 6-mo CR rate was 46.0% among BCGunresponsive patients (n = 50), 71.7% among other patients previously treated with BCG (n = 50), and 83.0% among treatment-naïve patients. Furthermore the endpoint for CIS was 3 mo, whereas 6 mo is usually considered a better endpoint. The control group was treated according to the institutional standard, which is heterogeneous (BCG, MMC, or electromotive drug administration [EMDA]). Again, the numbers are too small for a subanalysis of the different results for different control treatments (what was the impact of EMDA in the control group?). There was also no pathology review after treatment, and no information on stage and grade for disease recurrence and progression was provided. Considering the visual appearance of hyperthermia necrosis after induction RITE, I certainly hope that recurrence or progression was histologically proven. The use of cytology to define response, as well as the definition of response, remains unclear. My conclusion is that treatment for BCG-unresponsive NMIBC is still an important unmet need, and in that sense I have to compliment the study group for conducting this trial with a new treatment regimen. However, the results should be interpreted with care. The patient selection, treatment regimens, and outcome measurement can be criticized. I have used RITE as a salvage treatment for similar patients for 18 yr now, and the results of the HYMN trial will not change my attitude after achieving successful results in many of my patients. How the current trials with other regimens such as cytokines, device-assisted strategies, new intravesical chemotherapy combinations, and PD(L)1 antagonists in BCGunresponsive NMIBC will change the landscape will become clear in the coming few years. In particular, there is increasing interest in PL(L)1 antagonists in bladder cancer, and after decades we will hopefully be able to offer new nonradical treatments to these patients in the near future.

Tan WS, Panchal A, Buckley L, Devall AJ, Loubiere LS, Pope AM, et al. Radiofrequency-induced Thermo-chemotherapy Effect Versus a Second Course of Bacillus Calmette-Guerin or Institutional Standard in Patients with Recurrence of Non-muscle-invasive Bladder Cancer Following Induction or Maintenance Bacillus Calmette-Guerin Therapy (HYMN): A Phase III, Open-label, Randomised Controlled Trial. *Eur Urol*. 2019 Jan;75(1):63-71. doi: 10.1016/j.eururo.2018.09.005.

Background: There is no effective intravesical second-line therapy for non-muscle-invasive bladder cancer (NMIBC) when bacillus Calmette-Guérin (BCG) fails. **Objective:** To compare disease-free survival time (DFS) between radiofrequency-induced thermo-chemotherapy effect (RITE) and institutional standard second-line therapy (control) in NMIBC patients with recurrence following induction/maintenance BCG. **Design, settings, and participants:** Open-label, phase III randomised controlled trial accrued across 14 centres between May 2010 and July 2013 (HYMN [ClinicalTrials.gov: NCT01094964]). **Intervention:** Patients were randomly assigned (1:1) to RITE (60 min, 40 mg mitomycin-C, 42 ± 2 °C) or control following stratification for carcinoma in situ (CIS) status (present/absent), therapy history (failure of previous induction/maintenance BCG), and treatment centre. **Outcome measurements and statistical analysis:** Primary outcome measures were DFS and complete response (CR) at 3 mo for the CIS at randomisation subgroup. Analysis was based on intention-to-treat. **Results and limitations:** A total of 104 patients were randomised (48 RITE: 56 control). Median follow-up for the 31 patients without a DFS event was 36 mo. There was no significant difference in DFS between treatment arms (hazard ratio [HR] 1.33, 95% confidence interval [CI] 0.84–2.10, p = 0.23) or in 3-mo CR rate in CIS patients (n = 71; RITE: 30% vs control: 47%, p = 0.15). There was no significant difference in DFS between treatment arms in non-CIS patients (n = 33; RITE: 53% vs control: 24% at 24 mo, HR 0.50, 95% CI 0.22–1.17, p = 0.11). DFS was significantly lower in RITE than in control in CIS with/without papillary patients (n = 71; HR 2.06, 95% CI 1.17–3.62, p = 0.01; treatment-subgroup interaction p = 0.007). Disease progression was observed in four patients in each treatment arm. Adverse events and health-related quality of life between treatment arms were comparable. **Conclusions:** DFS was similar between RITE and control. RITE may be a second-line therapy for non-CIS recurrence following BCG failure; however, confirmatory trials are needed. RITE patients with CIS with/without papillary had lower DFS than control. HYMN highlights the importance of the control arm when evaluating novel therapies. **Patient summary:** This study did not show a difference in bladder cancer outcomes between microwave-heated chemotherapy and standard of care treatment. Papillary bladder lesions may benefit from microwave-heated chemotherapy treatment; however, more research is needed. Both treatments are similarly well tolerated.

Abufaraj M, Mostafid H, Shariat SF, Babjuk M “What to do during Bacillus Calmette-Guérin shortage? Valid strategies based on evidence.”*Curr Opin Urol.* 2018 Nov;28(6):570-576. doi: 10.1097/MOU.0000000000000544.

Purpose of review: Over the last decade, the world has experienced health-threatening supply shortages of Bacillus Calmette-Guérin (BCG) immunotherapy for nonmuscle-invasive bladder cancer (NMIBC). We summarize the current literature to assist in treatment decisions in light of suboptimal supply. **Recent findings:** Currently available data do not support a superiority of one BCG strain over the other. Intravesical chemotherapy seems to provide similar results in term of disease progression but not recurrence in intermediate-risk patients. One trial has shown that a 3-year maintenance course of BCG in high-risk NMIBC has no advantage in term of progression or overall survival in comparison with 1-year maintenance. Synergo radiofrequency-induced hyperthermia is a reliable alternative in intermediate or high-risk NMIBC with at least similar recurrence rates compared with BCG. **Summary:** Patients with intermediate-risk NMIBC can be offered multiple instillations of intravesical chemotherapy for up to 12 months. In high-risk patients and in case of BCG shortage, BCG instillations can be terminated when the patient has completed 1 year of maintenance. Mitomycin C is an alternative in lowest risk high-risk (G3Ta) NMIBC, whereas patients with pT1/carcinoma in situ can be offered Synergo with mitomycin C when radical cystectomy is not feasible. Immediate radical cystectomy should always be considered in highest risk NMIBC after weighing up benefit to risk.

van Valenberg, F Johannes P et al. “Intravesical Radiofrequency-Induced Chemohyperthermia for Carcinoma in Situ of the Urinary Bladder: A Retrospective Multicentre Study” *Bladder Cancer* vol. 4,4 365-376. 29 Oct. 2018, doi:10.3233/BLC-180187

Objective: To examine the effect of intravesical radiofrequency-induced chemohyperthermia (RF-CHT) in carcinoma in-situ (CIS) patients overall and split according to previously received therapy. **Methods:** CIS patients that underwent an induction and maintenance phase of ≥ 6 RF-CHT instillations, and had either pathology or cystoscopy plus cytology available at 6 months of follow-up were retrospectively included. Complete response (CR), recurrences, cystectomy-free rate, overall survival (OS), and adverse events were evaluated. Analysis was performed for overall, bacillus Calmette-Guérin (BCG)-unresponsive, other BCG-treated, and treatment naïve patients. **Results:** Patients (n=150) had a mean of 17.5, 9.2, or 0 previous BCG instillations in the BCG-unresponsive (n=50), other BCG-treated (n=46, missing n=4), and treatment naïve groups (n=47, missing n=3), respectively. After 6 months, a CR of 46.0%, 71.7%, and 83.0% was found ($p < 0.001$). Subsequent 2-year recurrence rates were 17.4%, 27.3%, and 12.8%, respectively. The overall cystectomy-free rate and OS at mean follow-up (35.8 months) were 78.5% and 78.0%, respectively. These were 71.4% vs. 84.1% vs. 86.7% (cystectomy-free rate, $p = 0.006$) and 76.0% vs. 69.6% vs. 87.2% (OS, $p = 0.06$) for BCG-unresponsive vs. other BCG-treated vs. treatment naïve patients. Progression to muscle-invasive disease was seen in 13.3% of patients. Patients stopped induction or maintenance RF-CHT instillations due to adverse events in respectively 13.4% and 17.8%. **Conclusions:** Intravesical RF-CHT showed good results in both treatment naïve and BCG-treated CIS patients, avoiding the need for cystectomy in 78.5% of cases for at least 3 years with a modest risk of progression. Thus, RF-CHT proves an alternative to cystectomy in selected high-risk patients.

Ayres, B & Backhouse, Chris & Tomic, Domagoj & John, Babbin & Perry, M & Bailey, Mike & Issa, Rami. (2018). MP08-01 10-YEAR EXPERIENCE OF RITE THERMOCHEMOTHERAPY FOR HIGH RISK NON MUSCLE INVASIVE BLADDER CANCER THAT HAS FAILED BCG. The Journal of Urology. 199. e96. 10.1016/j.juro.2018.02.306.

Introduction and objectives: Patients with high risk non muscle invasive bladder cancer (NMIBC) who fail BCG should be offered a radical cystectomy. Alternative intravesical treatments have been tried in those unfit for cystectomy, such as radiofrequency induced thermochemotherapy (RITE). We present our 10-year experience with this device-assisted treatment. **Methods:** Between October 2006 and August 2017, 135 patients with high risk NMIBC (grade 3 or high grade and/or T1 and/or carcinoma in situ (CIS)) who failed BCG were considered for RITE thermochemotherapy at our institution. They had significant comorbidities making cystectomy a less desirable treatment option. Induction and maintenance thermochemotherapy was delivered using Synergo for 1 hour with 40mg mitomycin C. Surveillance cystoscopies +/- biopsies and urine cytology were performed 3-monthly for 2 years and then 6-monthly. The upper urinary tracts were imaged annually. Data was collected prospectively and Kaplan Meier analysis was performed. **Results:** 5 patients (4%) were unable to complete induction treatment due to significant side effects of pain, incontinence or severe rash. Of the 130 that completed treatments, 114 (88%) were male and median age was 74 years (IQR 68-80). 55 (42%) had T1G3 with CIS, 26 (20%) had TaG3 with CIS, 26 (20%) had CIS alone, 16 (12%) were T1G3 and 7 (5%) were TaG3. 45 (35%) were BCG unresponsive. 1-, 5- and 10-year recurrence free survival was 63%, 34% and 24% respectively. 1-, 5- and 10-year progression free survival was 92%, 71% and 62% respectively. Progression to muscle invasive disease occurred in 11 (8%), prostatic urethral stromal disease in 6 (5%) and metastatic disease in 6 (5%) including 2 with inguinal node involvement. 8 (6%) developed subsequent upper urinary tract recurrences. 30 patients (23%) eventually had a cystectomy for their disease, 20 for persistent CIS. 1-, 5- and 10-year overall survival was 98%, 63% and 54% respectively. 1-, 5- and 10-year cancer specific survival was 100%, 79% and 75% respectively. **Conclusions:** RITE thermochemotherapy has a role in the management of selected patients with high risk NMIBC who fail BCG, with a 5-year cancer specific survival rate of 79%. Just under a quarter of patients subsequently required a cystectomy for persistent or progressive disease and 5% developed metastatic disease whilst on the treatment. Urothelial cancer can recur in the upper urinary tracts and progress in the prostatic urethra despite initial negative scans and biopsies, so careful surveillance of these patients is required.

Kilb, J.-I., Hauptmann, A., Wagenlehner, F. & Luedecke, G . (2018) "Long-term results of organ preservation rate and progression risk in high-risk non-muscle-invasive bladder cancer (NMIBC) patients treated with radiofrequency-induced thermochemotherapy effect (RITE) with the Synergo system". Journal of Clinical Oncology 36, 456-456, doi:10.1200/JCO.2018.36.6_suppl.456 (2018).

Background: High risk NMIBC is a dangerous BC with a challenging treatment by BCG or early cystectomy to cure. The first has bad treatment tolerance and a remission of about 35%, whereas the last offer a curing perspective of 84% with extremely bad living conditions. RITE checked prospectively the therapy in respect to organ preservation, curing rate and risk of progression over 10 years in a single institution experience. **Methods:** All patients were EORTC high risk NMIBC. Treatment with induction phase: 8 treatments weekly with 2x40 mg Mitomycin C, 42°C intravesically induced by RITE. Followed by a re-resection of the bladder at week 11 to ensure complete remission and maintenance with treatments every 6 weeks with 2x20 mg Mitomycin C for 6 times. Cystoscopy controls were performed first 2 years every 3 month and following in 6 month until now. Study started in 2006 ongoing until today. **Results:** We enrolled 67 patients (4 female, 63 male), 65.7% Cis positive rate. 85% of the patients were treated alternatively to BCG with primary RITE whereas 15% were BCG failure patients treated alternatively to indicated cystectomy. Tumor persistence at week 11 after induction therapy proven by TURB was (10/67) 14.9% resulting in early cystectomy (4/10). Mean recurrence free time 3.5 years. In case of recurrence 10.4% progressed to MIBC including 6% metastatic tumors, high risk NMIBC was observed in 6% resulting in cystectomy and low risk NMIBC recurrence was 1.5% with organ preservation. BC death rate was 1 out of 67. Incomplete treatments induced by SAE of RITE was 9%. Bladder preservation rate was 80.6% with a long-lasting effectiveness (> 5 years) of 14/26 (53.8%). **Conclusions:** The RITE method is in short- and long-term manner a powerful procedure to cure and maintain a recurrence free BC status in high risk NMIBC with a very low risk for cystectomy and a minimal risk for systemic progression resulting in BC death. The organ preservation rate was achieved in 80.6% lasting for up to 11 years longest. RITE is an alternative to BCG and preferable to early cystectomy in high risk NMIBC.

van Valenberg, F. J. P. et al. (2017) "Intravesical radiofrequency induced hyperthermia enhances mitomycin C accumulation in tumour tissue". *Int J Hyperthermia*, 1-6, doi:10.1080/02656736.2017.1406618 (2017).

Introduction: Non-muscle invasive bladder cancer (NMIBC) is a highly recurrent disease with potential progression to muscle invasive disease despite the standard bladder instillations with mitomycin C (MMC) or Bacille Calmette–Guérin immunotherapy. Therefore, alternatives such as radiofrequency-induced chemohyperthermia (RF-CHT) with MMC are being investigated. The mechanism explaining the efficacy of RF-CHT is only partly understood. We examined whether RF-CHT results in higher MMC tissue concentrations as compared to cold MMC instillation.

Patients and methods: Prior to a planned transurethral resection of bladder tumour (TURBT), patients with stage Ta NMIBC were allocated to either (1) cold MMC instillation or (2) RF-CHT. After MMC instillation, three biopsies were taken of both normal and tumour tissue. Biopsies were snap-frozen and MMC tissue concentrations were analysed using ultra-performance liquid chromatography. **Results:** Eleven patients were included of which six received RF-CHT. Ten patients had TaG2-LG/HG papillary tumours at pathology. One patient in the RF-CHT group appeared to be free of malignancy and was excluded from the analysis as no tumour biopsies were available. The median MMC concentration in tumour tissue was higher in the RF-CHT group (median 665.00 ng/g vs. 63.75 ng/g, $U = 51.0$, $p = 0.018$). Moreover, in both techniques the MMC concentration was lower in normal tissue compared to tumour tissue. Tissue MMC concentration measurements varied substantially within, and between, different patients from the same group.

Conclusion: Intravesical RF-CHT results in higher tumour MMC concentrations vs. cold MMC instillation which contributes to its superior efficacy.

Benacka, M., Benamran, D. A., Wirth, G. & Iselin, C. E. (2017) "Intravesical microwave thermo-chemotherapy for the treatment of non-invasive bladder cancer". *Rev Med Suisse* 13, 2087-2091 (2017).

Abstract: Non-invasive urothelial carcinoma of the bladder is known for its significant rate of recurrence after transurethral resection (TURB) even after adjuvant intravesical chemotherapy or immunoprophylaxis. Therefore, new and more effective approaches for the management of non-invasive bladder tumors have been developed and are progressively introduced in clinical practice. Recently, the endovesical administration of a combined regimen using a cytostatic agent and microwave-induced hyperthermia appears to be highly efficient and possibly superior to intravesical chemotherapy alone for none invasive bladder cancer.

Pierconti, F. et al. (2017) "Cytological and histological changes in the urothelium produced by electromotive drug administration (EMDA) and by the combination of intravesical hyperthermia and chemotherapy (thermochemotherapy)". *Pathology - Research and Practice* 213, 1078-1081, doi:<https://doi.org/10.1016/j.prp.2017.07.026> (2017).

Abstract: The treatment of non muscle-invasive bladder cancer (NMIBC) encompasses a range of different procedures. Electromotive drug administration (EMDA) and chemo-hyperthermia (C-HT; Synergo) represent a minimally-invasive methods of intravesical instillation of therapeutic agents as mitomycin C (MMC). We selected patients with high grade NMIBC, BCG non responder, treated with EMDA/MMC and C-HT/MMC and we also examined the morphological changes in urine cytology samples During the period from 2012 to 2014, 110 patients with high grade NMIBC, BCG refractory were selected. All cases examined were classified according to The Paris System Classification as negative for high urothelial carcinoma (NHGUC) or atypical urothelial cells (AUC) with a mean of follow-up of 15 months and the cytological diagnosis were confirmed by histological biopsies. In particular 50 patients were treated with EMDA/MMC and 60 patients underwent to C-HT/MMC. The morphological changes were evaluated in urine samples processed by Thin Prep method. In the 50 patients treated with EMDA/MMC, 35 samples were classified as NHGUC and 15 cases were classified as AUC, while in the 60 patients treated with C-HT/MMC, 43 samples were NHGUC and 17 cases were classified AUC. The increase of cellularity and nuclear size with the alteration of nuclear/cytoplasmic ratio (N/C) were common in patients treated with EMDA/MMC and C-HT/MMC without clinical and histological evidence of recurrence of neoplasia. The hyperchromasia and irregular nuclear chromatin were rarely observed. The irregular nuclear membrane rarely identified in urine cytology after EMDA/MMC treatment, is a feature present in patients C-HT/MMC treated.

Campodonico, F. et al. (2017) "Intravesical Chemotherapy and Chemohyperthermia in Non-Muscle-Invasive Bladder Cancer; An Overview on Drug Administration Technologies and Pharmacokinetics". *Curr Drug Metab* 18, 657-665, doi:[10.2174/1389200218666170427092421](https://doi.org/10.2174/1389200218666170427092421) (2017).

Background: Tumor recurrence is the most expected clinical event after the resection of non-muscle invasive bladder cancer, depending on histological findings of the initial lesion. In patients with low and intermediate risk of disease, the intravesical instillation of chemotherapy agents is recommended as a standard treatment to reduce recurrences. **Methods:** A comprehensive review covering various aspects of different treatments with intravesical drugs is presented. **Results:** Drugs may be instilled into the bladder starting with a single, 'early' postoperative administration or, after tumor resection with adjuvant intent or, before tumor resection under a neo-adjuvant regimen. Both latter protocols would consist of weekly treatments followed by monthly maintenance treatments. Different methods of administering drugs intravesically have been proposed to enhance the depth of drug penetration and its absorption into the bladder wall thus increasing the rate of drug-DNA reaction. These device-assisted therapies therefore have set a goal to potentiate the drug's effect and efficaciousness. The Radiofrequency-Induced Thermochemotherapeutic Effect (RITE) and the Electromotive-Drug Administration (EMDA) are the two most relevant modalities used to increase the activity of intravesical chemotherapy. Despite the widely adopted international guidelines' recommendations, and recent clinical trials of device-assisted chemotherapy instillations showing markedly enhanced recurrence-free survival compared even to the standard of care, clinicians and pharmacologists are not familiar with the in-depth physical aspects, pharmacokinetics and systemic absorption of chemotherapeutic drugs following their intravesical administration. **Conclusion:** Knowledge of drug diffusion mechanisms into the tissue and cellular cytoplasm following bladder instillation is a key to understand the safety profile and clinical activity of chemotherapy.

Ayres B. et al. (2017) "5-year outcomes of RITE thermochemotherapy for BCG unresponsive high risk non muscle invasive bladder cancer" EAU 2017, Moderated Poster, London

Introduction & Objectives: Patients with high risk non muscle invasive bladder cancer (NMIBC) who fail BCG should be offered a radical cystectomy. Alternative intravesical treatments have been tried in those unfit for cystectomy, such as radiofrequency induced thermochemotherapy (RITE). The aim of this study was to assess 5-year recurrence, progression and survival following RITE device assisted thermochemotherapy. **Material & Methods:** Between June 2006 and June 2013, 64 patients with high risk NMIBC (grade 3 and/or T1 and/or carcinoma in situ) who failed BCG were considered for RITE thermochemotherapy at our institution if they were unfit for radical cystectomy. Induction and maintenance thermochemotherapy was delivered using Synergo for 1 hour with 40mg mitomycin C. Surveillance cystoscopies/biopsies and urine cytology were collected 3 monthly for 2 years then 6 monthly. Data was collected prospectively and Kaplan Meier analysis was performed. **Results:** 64 BCG failures had RITE thermochemotherapy. 84% were male, median age 74 years (68-78), median follow up 47 months (38-58). 1-year recurrence free survival was 70% and 5-year was 33%. 1-year progression free survival was 94% and 5-year 67%. Progression to muscle invasive disease occurred in 9%, prostatic urethral stromal disease in 5% and metastatic disease in 6%. 8% developed subsequent upper urinary tract recurrences. 5-year overall survival was 65%; 5-year cancer specific survival was 80%. **Conclusions:** RITE thermochemotherapy has a role in the management of selected patients with high risk NMIBC who fail BCG, with 80% 5-year cancer specific survival. Urothelial cancer can recur in the upper urinary tracts and progress in the prostatic urethra despite initial negative scans and biopsies, so careful surveillance of these patients is required.

Arends T.J. et al. (2017) "Reply to Sławomir Poletajew, Piotr Radziszewski, Juan Palou's Letter to the Editor re: Results of a Randomised Controlled Trial Comparing Intravesical Chemohyperthermia with Mitomycin C Versus Bacillus Calmette-Guérin for Adjuvant Treatment of Patients with Intermediate- and High-risk Non-Muscle-invasive Bladder Cancer" Eur Urol. 2017 Jan;71(1):e31-e32

We would like to thank Poletajew et al. for their response to our paper. They state correctly that this trial does not address the issues on risk of progression; however, a lower recurrence rate compared with bacillus Calmette-Guérin (BCG) is certainly worth reporting. Without any doubt, these results should be confirmed with a second multicenter trial, since this one was underpowered. Due to the high costs of such a new trial, it is questionable that this will be done. With regard to progression, long-term results from our trial are not available currently. In the meantime, we can only rely on the long-term results from Colombo et al. who reported progression-free survival (PFS) of 94% in their trial from 2004. Furthermore, two prospective cohort studies from Arends et al. and Maffezzini et al., with median follow-up of 75 and 38 mo, respectively, reported similar results with PFS of 96% and 88%, respectively, in high-risk patients. Poletajew et al. also reflected on the relatively high percentage of intermediate-risk patients in this trial. We applied the 2001 risk classification for the patients in this trial. With the newly announced 2016 risk classification, the number of high-risk patients is 85 in the intention-to-treat analyses, resulting in significantly higher recurrence-free survival for this subgroup of patients ($p = 0.043$). Another point that Poletajew et al. raised is the strength of the BCG strain used in this trial. Obviously, BCG strain differences were not an issue when the study was launched in 2002. Sylvester et al. did not observe this phenomenon in their meta-analysis in 2002. Furthermore, a study by Witjes et al. (unpubl. data) shows that a higher recurrence rate for BCG Tice compared with BCG Connaught was noted only in cases in which no maintenance was applied. When maintenance is applied, as in this trial, Tice seems at least as effective as Connaught. Regarding the side effects, the overall side effect rate was indeed higher for the chemohyperthermia (CHT) arm. This is mainly due to the relatively high frequency of mild symptoms of pain during or after CHT and catheterization difficulties. If we exclude these side effects, no difference was observed in the overall rate of adverse events. Moreover, CHT side effects are registered during CHT treatment, whereas BCG side effects are registered before the next instillation, at least 1 week later. In general, BCG and CHT both have side effects that should be weighed when treating patients. Finally, Poletajew et al. emphasized that CHT treatment is more expensive and time consuming compared with BCG. We totally agree with the statement that an analysis of the cost-effectiveness would be an asset.

Colombo, R., van Valenberg, H., Moschini, M. & Witjes, J. A. (2016) "Radiofrequency-induced thermo-chemotherapy effect (RITE) for non muscle invasive bladder cancer treatment: current role and perspectives". *Urologia* 83, 7-17, doi:10.5301/uro.5000197 (2016).

Abstract: Although many treatment modalities and schedules for nonmuscle invasive bladder cancer (NMIBC) exist, all yet prove to have limitations and the search for new therapeutic strategies continues. Among these, the combination of intravesical chemotherapy and microwave-induced local hyperthermia has been investigated and clinically tested during more than 15 years. An updated review of intravesical radiofrequency (RF)-induced thermo-chemotherapy effect (RITE) for NMIBC with regard to efficacy, adverse events (AEs) and perspectives. An extensive and sensitive search for RF-induced chemo-hyperthermia in Medline, Embase, Cochrane and ClinicalTrials.gov databases was performed. A table of published clinical trials up to 2016 was constructed. No meta-analysis could be performed on the basis of new papers. Recurrence was seen 59% less after RITE than after mitomycin C (MMC) alone in adjuvant clinical setting with an overall bladder preservation rate after RITE of 85%. The efficacy was proved to be comparable to that of Bacillus Calmette-Guèrin (BCG), based on a single comparative multicentric study. Due to short follow-up, no conclusions can be drawn about time to recurrence and progression. The AE rate in RITE was higher, although not statistically significant, than MMC alone and similar to that of BCG, albeit different in the type of AE. In almost all studies, no severe AEs are reported. RITE appears as a promising treatment option for NMIBC, particularly for high-risk patients with recurrent tumors, for those unsuitable for radical cystectomy and when Bacillus Calmette-Guèrin treatment is contraindicated. Further high-level evidence is needed for both reliable and reproducible data on efficacy and adverse events.

Arends T.J. et al. (2016) "Results of a Randomised Controlled Trial Comparing Intravesical Chemohyperthermia with Mitomycin C Versus Bacillus Calmette-Guèrin for Adjuvant Treatment of Patients with Intermediate- and High-risk Non-Muscle-invasive Bladder Cancer" Prize-Winning Mod. Abstract, EAU 2015, Madrid. Platinum Priority, *Eur Urol* 2016;69:1046–52

Background: Despite adjuvant intravesical therapy, recurrences in non-muscle-invasive bladder cancer (NMIBC) are still high; therefore, new treatment options are needed. The use of chemohyperthermia (CHT) as an alternative treatment is expanding in Europe. To date, however, there has been a lack of prospective randomised data. **Objective:** To compare CHT using mitomycin C (MMC) with bacillus Calmette-Guèrin (BCG) as adjuvant treatment for intermediate- and high-risk NMIBC. Design, setting, and participants: Between 2002 and 2012, 190 NMIBC patients were randomised in this controlled, open-label, multicentre trial for 1-yr CHT (six weekly treatments and six maintenance treatments) and 1-yr BCG immunotherapy (six weekly treatments and three weekly maintenance treatments at months 3, 6, and 12). Patients and physicians giving the interventions were aware of assignment. This study is registered with ClinicalTrials.gov (NCT00384891). Outcome measurements and statistical analysis: The primary end point was 24-mo recurrence-free survival (RFS) in the intention-to-treat (ITT) and per-protocol (PP) analyses in all papillary NMIBC patients (n = 147). Analyses were done with the log-rank test and Fisher exact test. All tests were two-sided. **Results and limitations:** The 24-mo ITT RFS was 78.1% in the CHT group compared with 64.8% in the BCG group (p = 0.08). The 24-mo RFS in the PP analysis was 81.8% in the CHT group compared with 64.8% in the BCG group (p = 0.02). Progression rates were <2% in both groups. Regarding the side-effects, no new safety concerns were identified. A concern is that this study closed prematurely and thus is underpowered. Furthermore, blinding of treatment for patients and physicians was impossible; this may have resulted in unavoidable bias. **Conclusions:** CHT is a safe and effective treatment option in patients with intermediate and high-risk papillary NMIBC. A significantly higher 24-mo RFS in the CHT group was seen in the PP analysis. Based on the results above, CHT is an option for BCG therapy as adjuvant treatment for intermediate- and high-risk papillary NMIBC. **Summary:** Recurrences in non-muscle-invasive bladder cancer are common, despite adjuvant therapies. We compared 24-mo recurrence-free survival (RFS) with chemohyperthermia (CHT) versus bacillus Calmette-Guèrin (BCG) therapy. According to these data, CHT therapy appears to be safe and has higher 24-mo RFS than BCG therapy.

Canepa G. et al. (2016) "Ten years experience with intravesical thermo-chemotherapy MMC 40mg for Non Muscle Invasive Bladder Cancer high/intermediate risk" Auro Italian National Congress, Rome, May 2016

Objective: Management of non muscle invasive bladder cancer (NMIBC) after transurethral resection of bladder tumor generally consists of surveillance and intravesical therapy. Particularly challenging is the treatment of patients who have not responded to first-line intravesical bacillus Calmette-Guérin (BCG) or that have high-risk features. For such patients, radical cystectomy remains a commonly recommended alternative treatment. High risk Non Muscle Invasive Bladder Cancer (HR-NMIBC), as stated by EORTC, is an important challenge for urologists and oncologists to avoid tumor progression and to preserve the bladder. The aim of the study is to evaluate the long-term experience on a treatment combining intravesical hyperthermia with Mytomycin C (HT-MMC) delivered with the Synergo® device.

Materials and Methods: Between 2004-2015, 146 patients (108 male and 38 female, mean age 68+/- 9 yrs, Range 40 – 84.) affected by high risk NMIBC were recruited. All of them were treated with endovesical thermo-chemotherapy MMC-C 40mg (HT-MMC) performing more than 1600 treatment sessions using the Synergo® device. After an initial induction of 4 weekly treatments with 2 x 40mg MMC, efficacy was checked in tumor eradication by TUR and cytology at week 6. Tumor-free patients continued with maintenance therapy with 2 x 40mg MMC, 3 sessions every 15 days, then 3 sessions every 21 days, then 3 sessions every 45 days, and in parallel cystoscopy and urine cytology every 3 months. The follow-up was conducted over an average period of 39.2 months (Range 2.4 mo.-7.9 yrs). The majority of patients were at high-risk including 64 pts. with G3 (44%), 79 T1 (54%) and 22 Cis (15%), high frequency of recurrences (2.1 +/- 2.7, Range 0–17 n° of recurrences before the first treatment). First aim of the study was the Recurrence-Free Survival (RFS) and disease progression for stage and grade (PFS), the secondary aim was the tolerability and adherence to the proposed schedule of treatment. **Results:** After the first 4 weekly sessions, only 11 patients (7.5%) stopped due to recurrences: 3 progressions and 8 recurrences. At the end of treatment 37/146 patients reported a recurrence and 14/146 patients presented a progression. RFS at 1, 2 and 5 years was 89.6%, 79.2 and 68.3 respectively. PFS at 1, 2 and 5 years was 98%, 96.2 and 83.7 respectively. The number of treatment sessions for each patients were 10.4+/- 4.7 with a median of 11 sessions, Range 4 – 31). The safety profile showed mainly grade 1 and 2 side effects. Ten patients complained grade 3 s.e. including 1 patient bladder spasms/pain during treatment, 3 patients dysuria and 6 patients urgency after treatment. **Discussions:** PFS was high considering the percentage of high-risk patients. Tolerability was good without relevant systemic side-effects and most of the patients demonstrated a complete adherence to the proposed schedule of treatment. **Conclusion:** To enhance the efficacy of MMC, a valid method for intravesical HT-MMC delivering was adopted in our department from 2004. We reported our experience over a period of more than 10 years. The results of RFS and PFS are encouraging to maintain this kind of protocol of treatment. Although the high dosage of MMC used with ablative intent, it is well tolerated by a good percentage of patients.

van Valenberg, H., Colombo, R. & Witjes, F. (2016) "Intravesical radiofrequency-induced hyperthermia combined with chemotherapy for non-muscle-invasive bladder cancer". *Int J Hyperthermia* 32, 351-362, doi:10.3109/02656736.2016.1140232 (2016).

Abstract: Although many treatment modalities and schedules for non-muscle-invasive bladder cancer (NMIBC) exist, all yet prove to have limitations. Therefore the search for new forms of therapy continues. One of these forms consists of combining intravesical chemotherapy, typically mitomycin C (MMC), with hyperthermia achieved by a microwave-applicator. We aimed to review the current status of intravesical radiofrequency (RF) induced chemohyperthermia (CHT) for NMIBC with regard to efficacy, adverse-events (AEs) and its future perspective. A search for RF-induced CHT in MEDLINE, Embase, Cochrane and ClinicalTrials.gov databases was performed. Relevant conference abstracts were searched for manually. If applicable, experts on the area were consulted. Papers were selected based on abstract and title. A table of newly published clinical trials since 2011 was constructed. No meta-analysis could be performed based on these new papers. Efficacy proved to be better for RF-induced CHT compared to both MMC alone and bacillus Calmette-Guérin (BCG) instillations, with the latter being based on just one abstract of a randomised controlled trial. The AE rate in CHT is higher compared to MMC instillation, but is similar compared to BCG, albeit different in the type of AE. In almost all studies no severe AEs are reported. Although heterogeneity in methodology exists, RF-induced CHT seems promising. However, alternative methods of applying hyperthermia are starting to present their first results, imposing as effective options too. Intravesical RF-induced CHT may become an alternative for BCG instillation, and possibly for cystectomy, although further level 1 evidence is required for both reliable and reproducible data on efficacy and adverse events.

Bahouth Z. (2016) "The role of hyperthermia as a treatment for non-muscle invasive bladder cancer" *Expert Rev Anticancer Ther.* 2016;16(2):189-98

Non-muscle invasive bladder cancer (NMIBC) has a high tendency for recurrence and progression. Currently, all known intravesical agents are associated with adverse effects (AEs) and limited efficacy. The combination of hyperthermia (HT) with intravesical Mitomycin C (MMC) chemotherapy has been shown to improve outcomes. The added efficacy of HT to MMC was first shown in preclinical studies. The reports on patients with NMIBC have indicated that the treatment is safe and well tolerated. Several clinical studies reported the efficacy of radiofrequency-induced chemotherapy effect (RITE) in the treatment of patients with NMIBC. This modality was shown to be superior to MMC alone. RITE was effective also in patients with high-risk NMIBC, including those who failed Bacillus Calmette-Guérin (BCG). This study provides an updated review of literature regarding the use of RITE in patients with NMIBC.

Sooriakumaran P. et al. (2016) "Predictive Factors for Time to Progression after Hyperthermic Mitomycin C Treatment for High-Risk Non-Muscle Invasive Urothelial Carcinoma of the Bladder: An Observational Cohort Study of 97 Patients". *Urol Int.* 2016;96(1):83-90

Introduction: Hyperthermic mitomycin (HM) is a novel treatment modality for selected patients with high-risk non-muscle invasive bladder cancer (NMIBC). We sought to determine predictors of response to this therapy. **Patients And Methods:** A longitudinal, cohort study of 97 patients with high-risk NMIBC treated with ≥ 4 HM instillations on a prophylactic schedule was conducted. The primary outcome was time-to-progression survival; secondary outcomes were overall survival, cancer-specific survival, and adverse events. Descriptive statistics, Kaplan-Meier survival analyses, Cox proportional hazards modelling, and univariate and multivariable regression were performed. **Results:** The presence of initial complete response (CR; no evidence of disease at first check video cystoscopy and urine cytology) post-HM treatment was an independent predictor of good response to HM. Female patients and those without carcinoma in situ (CIS) also appeared to respond better to the intervention. The overall bladder preservation rate at a median of 27 months was 81.4%; 17/97 (17.5%) patients died during the course of the study. **Conclusions:** High-risk NMIBC patients can be safely treated with HM and have good oncological outcome. However, those without an initial CR have a poor prognosis and should be counselled towards adopting other treatment methodologies such as cystectomy. Female gender and lack of CIS may be good prognostic indicators for response to HM.

Erturhan S. et al. (2015) "Thermochemotherapy in adjuvant treatment of primary high risk non-muscle invasive bladder cancers: Single center results" Arch Esp Urol. 2015 Oct;68(8):666-71

Objective: To evaluate the results of Thermochemotherapy in adjuvant treatment of primary high risk non-muscle invasive bladder cancer in our center. **Methods:** The study included 26 patients with an age of 51-78 years (mean: 62.4 years). All patients had transurethral tumor resection (TURB) after being diagnosed with a primary bladder tumor and were pathologically diagnosed with non-muscle invasive urothelial carcinoma. Thermochemotherapy (TCT) applications were performed via the Synergo® system SB-TS 101. **Results:** Of the study participants, 13 patients had T1 Grade III, six patients had T1 Grade III CIS (+), four patients had Ta Grade III, and three patients Ta Grade II multiple > 5 cm tumor. In all patients, six weeks plus six months protocol were completed. All patients completed the follow-up protocol. With a median follow-up time of 16.4 months (range: 6 - 48 months), recurrent urothelial carcinoma was identified in three patients. With a median follow-up time of 16.4 months, the recurrence-free survival was 88.4% in 26 patients included in the study. **Conclusions:** The obtained data suggest that the TCT method can be used effectively and safely in non-muscle invasive bladder cancers of primary high-risk. Prospective randomized studies will shed light on this subject which are BCG vs TCT in primary high risk patients and second course BCG vs TCT in the BCG insufficient patients.

Arends, T.J. et al. (2015) "Urinary cytokines in patients treated with intravesical mitomycin-C with and without hyperthermia" World J Urol. 2015 Oct;33(10):1411-7

Objectives: To explore whether urinary cytokine and chemokine (CK) levels differed between cold mitomycin-C (cold-MMC)-treated patients and chemohyperthermia (C-HT)-treated patients, to shed light on the possible molecular mechanisms that might explain the superior outcome of C-HT. Furthermore, CK-differences were explored between C-HT responders and C-HT non-responders. **Methods:** Twelve NMIBC patients were included. Nine received six-weekly C-HT, and three received four-weekly cold-MMC instillations. Urine was collected on 8–12 time points before and after every treatment. MDC, IL-2, IL-6, IL-8, IP-10, MCP-1 and RANTES were determined by Luminex®-analysis. **Results:** Elevated urinary CK levels were observed in both groups after treatment. In general, CK-peaks were lower in the cold-MMC group in comparison with levels in the C-HT group. Significant higher MCP-1 and IL-6 levels were observed in C-HT-treated patients. Additionally, significant cumulative effects were observed for IP-10 and IL-2. However, IP-10 and IL-2 levels did not significantly differ between treatments. MDC levels after the first week of treatment were significantly higher in the C-HT responders compared with the non-responders. **Conclusion:** MMC treatment leads to elevated urinary CK levels with significantly higher MCP-1 and IL-6 levels in C-HT-treated patients. Increased MDC levels after the first C-HT instillation appear to be related to good clinical outcome and might be of additional value to personalize treatment. Studies involving more patients and longer follow-up are needed to substantiate this observation.

Lüdecke G. et al. (2015) "Radiofrequency induced hyperthermia chemotherapy (RIHTC) in high-risk non-muscle invasive bladder cancer (NMIBC): Multiinstitutional, international outcome analysis of 271 treated patients with a follow-up time of more than 2 years" EAU, Moderated Poster, Madrid

Introduction & Objectives: In the actual situation of BCG shortage and the possibility that high-risk NMIBC patients couldn't get any BCG, urologists have to look for alternatives. In 7 international urological departments we have treated high-risk NMIBC patients with an ablative radiofrequency induced hyperthermia chemotherapy (RIHTC) under unique treatment protocols with a follow-up time of more than 2 years in mean (maximally 12.9 years). The prospective cohort study was performed to evaluate the effectiveness of RIHTC and will be discussed in comparison to the well documented historical data of BCG treatment and the clinical interferences like presence of carcinoma in situ (CIS) and BCG pretreatment. **Material & Methods:** In total 549 patients were treated with RIHTC in two indications (ablative 271; adjuvant 278) from 2000 to 2013. We focus here on the high-risk patients (pTis, pT1 G3, non complete resected NMIBC and BCG failures n=271) equal to a BCG treatment indication. They achieved an induction course of 8 treatments weekly with twice 40 mg per cycle followed by a control TUR-B at week 11-12 and a maintenance therapy of 6 treatments every 6 weeks with twice 20 mg per cycle if the re-resection documented a tumor free level. Follow-up controls by cystoscopy were made every 3 months for 2 years and thereafter every 6 months completed by urine cytology at each control. The results were achieved with an intention to treat analysis. **Results:** The study population had a mean age of 67.3 with a gender distribution of 78.2% male and 21.8% female patients. Average follow-up time 2.2 years (range 28 days-12.9 years). in this high-risk population 76.1% achieved a complete response, 7.6% a partial response and 16.3% no change in tumor status Out of the group of patients with completed induction and maintenance therapy 76.8% remained tumor free for 28 month in mean (range: 2.4m-10.8 y). The overall tumor-free rate for 2 year follow-up was 80.6% and the recurrence rate was 19.4% respectively. The interference of presence of CIS was documented. In respect to prior BCG treatment the rate of tumor free patients varied between 41.7% ("BCG resistance") and 66.7% ("early relapse") versus BCG naive patients (n=43) with a tumor free rate of 81.7% over 2 years. **Conclusions:** The effectiveness of RIHTC in high-risk NMIBC patients is impressive, and the overall tumor-free rate of 80.6% over a mean follow-up time of 2 years seems to be more potent than the historically documented BCG success rate in this indication. As expected the CIS status and a previous BCG-treatment are the main important interferences for increased recurrence rates. In the smaller subgroup of BCG-naïve patients we could achieve a recurrence rate of only 18.3% which is nearly 100% more effective than documented BCG results. In respect to the BCG shortage problem RIHTC is a potent alternative for organ preservation therapy in high-risk NMIBC patients.

Arends T.J. et al. (2014) "Results of a Randomized Controlled Trial Comparing Intravesical Combined Chemohyperthermia with Mitomycin-C versus BCG for Adjuvant Treatment of Patients with Intermediate and High Risk Non-Muscle Invasive Bladder Cancer" Urology 84 (4 Suppl 1) 2014 Oct

Introduction and Objectives: Despite regular adjuvant intravesical treatments, the incidence of recurrences in non-muscle invasive bladder cancer (NMIBC) is still high. Therefore, new treatment options are most welcome. This randomized, controlled, multicentre trial compares combined chemohyperthermia using Mitomycin- C (C-HT) with BCG as adjuvant treatment for intermediate and high risk NMIBC. **Materials and Methods:** Between 2002 and 2012, 190 NMIBC patients were eligible for inclusion and randomized between 1-year C-HT (induction: six weekly treatments and six maintenance treatments) and 1-year BCG immunotherapy (induction: six weekly and nine maintenance treatments). Median followup was 22 months in the C-HT group and 18 months in the BCG group. Recurrence-free survival (RFS) in all papillary NMIBC was the primary objective. The secondary objective was the safety-analysis of both treatments. **Results:** A total of 190 patients were included; 132 patients were eligible for RFS-analysis and 184 subjects were included in the safety analysis. Baseline characteristics were equally divided. Two-years RFS was 78.3% and 66.7% for the C-HT and BCG group, respectively (N=132, p=0.023). Although most side-effects didn't differ significantly between the two groups, systemic side-effects (fever, fatigue, arthralgia) were more reported in the BCG group. Bladder pain and spasms, however, were more frequent in the C-HT group. Muscle-invasive progression was low in C-HT and BCG treatment: 1.7% and 2.8%, respectively. **Conclusion:** C-HT is a safe and effective treatment option in patients with intermediate and high risk papillary NMIBC. The 2-years RFS is significantly higher in the C-HT arm in comparison to the BCG-arm. Furthermore, the systemic side-effects are higher in the BCG group. Accordingly, one should consider the option of C-HT treatment in intermediate and high risk NMIBC patients.

Arends T.J. et al. (2014) "Combined Chemohyperthermia: 10-Year Single Center Experience in 160 Patients with Nonmuscle Invasive Bladder Cancer"
J Urol. 2014 Sep;192(3):708-13

Purpose: Nonmuscle invasive bladder cancer is characterized by a high recurrence rate. New adjuvant treatments are needed to decrease this high number of recurrences. We present the results of more than 10 years of experience with chemohyperthermia in patients with nonmuscle invasive bladder cancer. **Materials and Methods:** Using standardized medical record forms we prospectively collected patient and tumor characteristics of patients treated with chemohyperthermia between 2002 and 2013. Median followup was 75.6 months. Recurrence-free survival was the primary objective. The secondary objective was to observe recurrence-free survival differences in 1) the epirubicin group vs the mitomycin group and 2) the highly recurrent (greater than 2 recurrences in 24 months) nonmuscle invasive bladder cancer group vs the other groups. **Results:** A total of 160 patients with nonmuscle invasive bladder cancer were included in study, including 20 (13%) treated with epirubicin and 129 (81%) previously treated with bacillus Calmette-Guérin. One and 2-year recurrence - free survival was 60% and 47%, respectively. Muscle invasive progression was seen in 4% of cases Two-year recurrence-free survival in the epirubicin and mitomycin groups was 55% and 46%, respectively ($p = 0.30$). The highly recurrent nonmuscle invasive bladder cancer group had significant decreased recurrence - free survival compared to other groups ($p < 0.01$). Patients treated with 2 or fewer vs greater than 2 transurethral bladder tumor resections before chemohyperthermia had higher recurrence-free survival ($p = 0.01$). On multivariable analysis the highly recurrent cancer criteria remained independently associated with decreased recurrence-free survival (HR 2.40, 95% CI 1.30-4.43, $p = 0.01$). **Conclusions:** Chemohyperthermia is an effective approach to nonmuscle invasive bladder cancer for which standard intravesical treatments fail. Patients with highly recurrent disease before chemohyperthermia have lower recurrence - free survival. Furthermore, recurrence-free survival appears to improve with earlier chemohyperthermia No significant differences were observed between the 2 chemotherapy agents.

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. 2014 May;73(5):925-30

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, Moderated Poster, Stockholm and Eur Urol Suppl 2014;13;e1109.

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, Moderated Poster, Stockholm and BJU Int vol.113 suppl. S5 June 2014

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 Clavian-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. April 2013 Volume 189, Issue 4, Supplement, Page 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, 2013 (suppl 6; 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 ablative 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 overall 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*. 2013 Apr-Jun;80(2):112-9

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. **Conclusions:** 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*. 2012;89(3):311-8

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.* 2012 Aug;8(8):1041-9

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.* 2011 Jul;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.* 2011 Mar;107(6):912-8

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.* 2011 May-Jun;29(3):259-64

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-Guerin" J Urol. 2009 Oct;182(4):1313-7

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 $42\pm 2^\circ\text{C}$. 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.

Witjes J.A. 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. 2009 Jun;27(3):319-24

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. 2007 Jun;25(3):303-8. Epub 2007 Feb 14

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. 2005 Apr;16(4):585-9. Epub 2005 Feb 25

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. 2005 Apr;173(4):1375-80

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. 2004 Mar;63(3):466-71

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.* 2004 Jul;46(1):65-71; discussion 71-2

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 videocystoscopy 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.* 2004 Nov;46(5):670-4

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 2.0×10^4 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 $\mu\text{g}/\text{ml}$ 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 μl 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.* 2003 Jun;84(3):145-52

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.* 2003 Aug;47(2):127-39

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 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 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 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. 2003 Dec 1;21(23):4270-6

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. 2001 Sep;52(3):273-8

Aims: To assess the effect of local hyperthermia 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⁻¹) occurred in a patient in group 3. This value was well below the threshold concentration (400 ng ml⁻¹) 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. 2001 Jan;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. 1998 Mar;159(3):783-7

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. 1997 Apr;43(4):615-8

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 porfirimycin 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. 1996 Apr;155(4):1227-32

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.

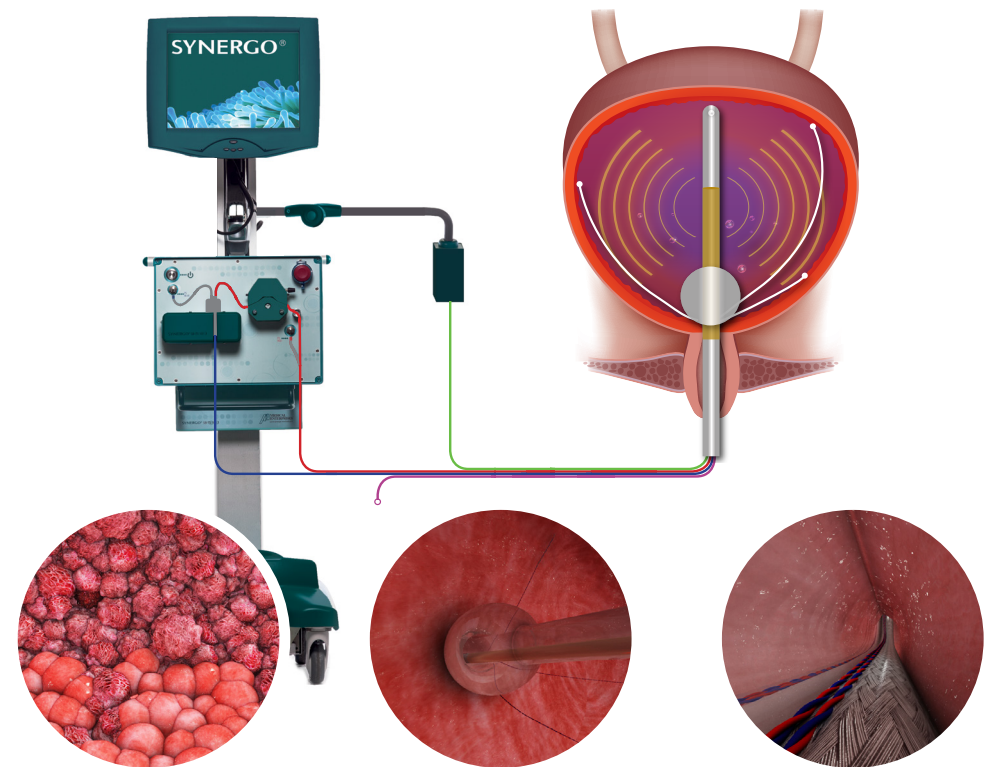
Colombo R. et al. (1995) "A new approach using local combined microwave hyperthermia and chemotherapy in superficial transitional bladder carcinoma treatment" J Urol. 1995 Mar;153(3 Pt 2):959-63

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. 1991;20(3):204-10

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.

SYNERGO® diagram and mechanism of action



RF radiation has demonstrated selective, non-thermal effects on different cancer cells including membrane microporing and adhesion loss in malignant tissue^{1,2} in addition to generating electric Foucault currents and direct tissue hyperthermia

Synergo® has shown to significantly increase uptake of chemotherapy selectively in bladder cancer tumors compared to regular instillations^{3,4} and exclusively caused irregularities in nuclear membranes⁵

Accurate real-time temperatures are measured in 5 predefined sites; 3 on bladder walls and 2 along the urethra

1 | Curley, S. et al. "The Effects of Non-Invasive Radiofrequency Treatment and Hyperthermia on Malignant and Nonmalignant Cells" *Int. J. Environ. Res. Public Health*, 11, 9142-9153; doi: 10.3390/ijerph110909142 (2014) | 2 | Ware, M.J. et al. "Radiofrequency treatment alters cancer cell phenotype" *Sci. Rep.* 5,12083; doi: 10.1038/srep12083 (2015) | 3 | Paroni, R. et al. "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.* 2001 Sep; 52(3): 273-278; doi: 10.1046/j.0306-5251.2001.01449.x (2001) | 4 | van Valenberg, F. J. P. et al. "Intravesical radiofrequency induced hyperthermia enhances mitomycin C accumulation in tumour tissue". *Int. J. Hyperthermia*, 1-6, doi:10.1080/02656736.2017.1406618 (2017) | 5 | Pierconti, F. et al. "Cytological and histological changes in the urothelium produced by electromotive drug administration (EMDA) and by the combination of intravesical hyperthermia and chemotherapy (thermochemotherapy)". *Pathol. Res. Pract.* 2017;213(9):1078-1081; doi: 10.1016/j.prp.2017.07.026 (2017)



**Medical Enterprises Europe B.V.
147A Amsterdamseweg,
1182GT Amstelveen,
The Netherlands**

Tel: +31 20 6423719

Fax: +31 20 6421161

E-mail: info@synergo-medical.com

Website: www.synergo-medical.com

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