

2003: Studie an verschiedenen Krebszentren, die in die Blase eingeführte Chemotherapie allein und mit lokaler Mikrowellen-Erwärmung zur Vorbeugung des Wiederauftretens von oberflächlichen Übergangszellen-Krebsgeschwüren vergleicht:

Multicentric Study Comparing Intravesical Chemotherapy Alone and With Local Microwave Hyperthermia for Prophylaxis of Recurrence of Superficial Transitional Cell Carcinoma

by Renzo Colombo, Mailand, Italien; Luigi Filippo Da Pozzo, Andrea Salonia, Patrizio Rigatti, Zvi Leib, Jack Baniel, Emanuele Caldarera; Michele Pavone-Macaluso;

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Zusammenfassung:

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 survival and the estimated probability of recurrence. The safety evaluation end points included subjective and objective 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.

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2009: In die Blase eingeführtes Chemotherapeutikum Mitomycin C kombiniert mit lokaler Erwärmung für Patienten mit T1G3 Übergangszellen Krebsgeschwür in der Blase:

Intravesical mitomycin C combined with hyperthermia for patients with T1G3 transitional cell carcinoma of the bladder

by Sarel Halachmi, Haifa, Israel; Boaz Moskovitz, Haifa, Israel; Massimo Maffezzini, Genua, Italien; Giario Conti, Como, Italien; Fabrizio Verweij, Mailand, Italien; Daniel Kedar, Petah-Tikva, Israel; Sandro D. Sandri, Magenta, Italien; Ofer Nativ, Haifa, Israel; Renzo Colombo, Mailand, Italien.

Zusammenfassung:

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°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.

**2009: In die Blase mit lokaler Erwärmung eingeführtes Chemotherapeutikum
Mitomycin C für Blasenkrebs carcinoma in situ (CIS):
Erfahrungen des Europäischen Synergo® Arbeitsausschusses**

**Intravesical hyperthermia and Mitomycin-C for carcinoma in situ of the urinary
bladder:
experience of the European Synergo® working party**

by **J. Alfred Witjes** , Nimwegen, Niederlande ; **Kees Hendricksen** , Nimwegen, Niederlande ;
O. Gofrit , Jerusalem, Israel ; **O. Risi** , Treviglio, Italien ; **O. Nativ** , Haifa, Israel .

Zusammenfassung:

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°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 pretreated 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.

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2010: Langfristige Ergebnisse einer randomisiert kontrollierten Studie zum Vergleich von (Mitomycin -C-) Hyperthermie-Chemotherapie mit Mitomycin -C allein als adjuvante Behandlung bei Nichtmuskelinvasiven Blasenkrebs (NMIBC)

Long-term outcomes of a randomized controlled trial comparing thermochemotherapy with Mitomycin-C alone as an adjuvant treatment of non-muscle-invasive bladder cancer.

by **Renzo Colombo** , **Andrea Salonia**, [University Vita-Salute San-Raffaele, Milan, Italy](#) ;
Zvi Leib, **Dov Engelstein**, [Rabin Medical Center Beilinson Campus, Petach Tikva, Israel](#) ;
Michele Pavone-Macaluso, [University of Palermo, Italy](#) .

Zusammenfassung:

Objectives: This study presents long-term efficacy of intravesical thermochemotherapy versus chemotherapy alone with Mitomycin C (MMC) randomly administered to patients with non-muscle-invasive bladder cancer as an adjuvant treatment after complete transurethral resection.

Subjects and methods: 83 patients with intermediate/high-risk non-muscleinvasive urothelial cell carcinoma of the bladder, following complete transurethral resection, were randomly assigned to receive either intravesical thermochemotherapy (by means of Synergo®) or intravesical chemotherapy alone, for prophylaxis of tumor recurrence. Two doses of MMC (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 examinations, tumor relapse or progression, and cause of death were collected and analysed.

Results: Updated complete data collection was available for 65/75 (87%) of the original patients. The median follow-up for tumor-free patients was 91 months. The 10-year disease-free survival rate for thermochemotherapy 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 discontinuation rate, still showed a significant advantage of the active treatment over the control treatment. Bladder preservation rates for thermochemotherapy and chemotherapy alone were 86% and 79%, respectively.

Conclusions: This is the first analysis of long-term follow-up of patients treated with intravesical thermochemotherapy. The high rate (53%) of patients documented to be tumorfree 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.