

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

Lüdecke G., Schäfer L., Nativ O., Witzsch U., Hanitzsch H., Hasner F., Issa R., Witjes F., Weidner W.
Gießen, Haifa, Frankfurt, Bonn, München, London, Nijmegen: Germany, Israel, United Kingdom, Netherlands

Abstract

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: 2.4 m - 10.8 y). The overall tumor-free rate for 2 year follow-up was 80.6% and the recurrence rate was 19.4% respectively.

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.

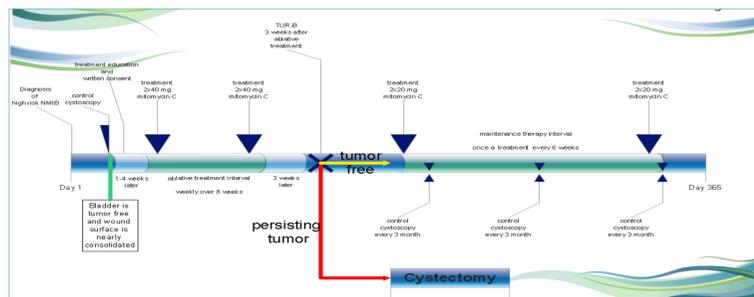
Conclusions: The effectiveness of RIHTC in high-risk NMIBC patients is impressive, and the overall tumor-free rate of 80.6% over a mean follow-up time of 2 years seems to be more potent than the historically documented BCG success rate in this indication. As expected the CIS status and a previous BCG-treatment are the main important interferences for increased recurrence rates. In the smaller subgroup of BCG-naive 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.

Material and Methods:

Ablative Indication

Inductive phase:
2x40 mg MMC in 2x30 minutes therapy; Weekly; 8 times
Quality control:
TUR-B 3 weeks after last inductive RIHTC
For all tumour free patients after quality control
Maintenance phase:
2x20 mg MMC in 2x30 minutes therapy; Every six weeks; 6 times
Control cystoscopy before first maintenance followed 3 monthly over 2 years

Study design



Results:

Study Populations

ablative	Total	Average Age
No. Patients	271	67.3
Male	212 (78.2%)	67.9
Female	59 (21.8%)	66.3

Response rates

Induction phase	Number	Percent
No. Patients	271	
Complete response	206	76.1
Partial response	21	7.6
No change	44	16.3

Former BCG treatment influence recurrence rate

Recurrence free rate	Number	percent
Never BCG	49	81.7
Early BCG relapse	16	66.7
BCG resistant	10	41.7

Synopsis of comparison between BCG and RIHTC

RIHTC is extremely more potent than BCG at 1 and 5 years follow-up time for RIHTC responding high-risk NMIBC patients, especially under the aspect of 59.8% of BCG failure patients included.

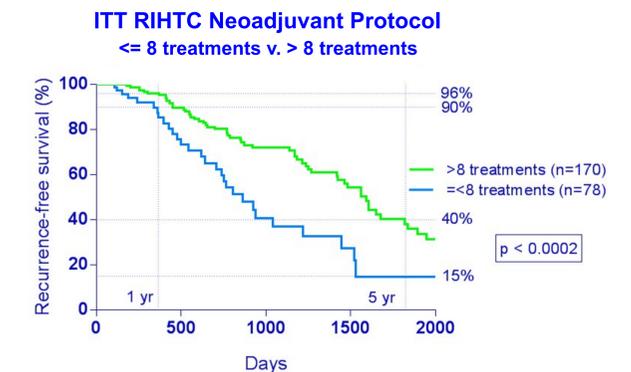
Side effects under RIHTC

Symptom	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)
Nocturia pre-treatment	28.4	15.8	6.3
Nocturia during	26.0	14.7	9.0
spasm	15.5	6.6	0.5
pain	17.8	3.1	0.8
Difficult catheterization	10.4	4.0	0.8
hematuria	8.1	1.7	0.7
incontinence	7.9	1.9	0.9
UTI	5.5	2.3	0.3
allergy	4.9	1.8	0.3
Urethral stricture	0.4	0.4	0

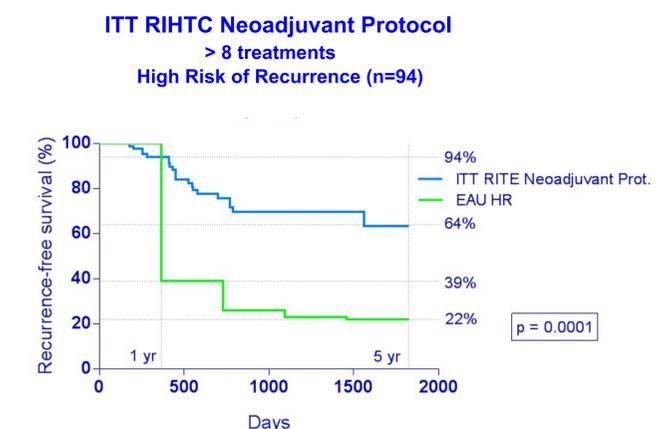
Duration of efficacy

Follow up of complete response	Number (percent)	Follow-up time
No. Patients	206	
Tumor-free	166 (80.6%)	2 years
recurrence	40 (19.4%)	1.8 years

Optimal ablative treatment with > 8 sessions



Comparison RIHTC with BCG Meta-analysis



Take home message

- RIHTC is a well tolerable treatment.
- Our high-risk population is an extremely high-risk group with 59.8% BCG-failures including.
- In this high-risk cohort we can achieve a primary response rate in tumor ablation after 8 inductive treatment sessions with 76.1% (206 out of 271)
- The rate of tumor-free organ preservation over 2 years for responder is 80.6%.
- In the time of BCG shortage RIHTC is a powerful alternative for high risk NMIBC patients.
- Increase of recurrence free rate at 1 year = 241%.
- Increase of recurrence free rate at 5 years = 291%.