NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Interventional Procedures Programme

Specialist Adviser questionnaire

Before completing this questionnaire, please read Conflicts of Interest for Specialist Advisers. Certain conflicts exclude you from offering advice, however, please return the questionnaire to us incomplete for our records.

Please respond in the boxes provided.

Please complete and return to: Deonee.Stanislaus@nice.org.uk

Procedure Name:	**Intravesical microwave hyperthermia with intravesical chemotherapy for superficial bladder cancer**
Name of Specialist Advisor:	Mr Mark Johnson
Specialist Society:	British Association of Urological Surgeons (BAUS)

1 Do you have adequate knowledge of this procedure to provide advice?

☑ Yes.

☐ No – please return the form/answer no more questions.

1.1 Does the title used above describe the procedure adequately?

☑ Yes.

☐ No. If no, please enter any other titles below.

Comments:

2 Your involvement in the procedure

2.1 Is this procedure relevant to your specialty?

☑ Yes.

☑ Is there any kind of inter-specialty controversy over the procedure?

☐ No. If no, then answer no more questions, but please give any information you can about who is likely to be doing the procedure.

Comments:

The next 2 questions are about whether you carry out the procedure, or refer patients for it. If you are in a specialty that normally carries out the procedure please answer question 2.2.1. If you are in a specialty that normally selects or refers patients for the procedure, please answer question 2.2.2.

2.2.1 If you are in a specialty that does this procedure, please indicate your experience with it:

☐ I have never done this procedure.

☑ I have done this procedure at least once.

☐ I do this procedure regularly.

Comments:

2.2.2 If your specialty is involved in patient selection or referral to another specialty for this procedure, please indicate your experience with it.

☐ I have never taken part in the selection or referral of a patient for this procedure.

☑ I have taken part in patient selection or referred a patient for this procedure at least once.

☐ I take part in patient selection or refer patients for this procedure regularly.

Comments:

2.3 Please indicate your research experience relating to this procedure (please choose one or more if relevant):

☐ I have done bibliographic research on this procedure.

☐ I have done research on this procedure in laboratory settings (e.g. device-related research).

☐ I have done clinical research on this procedure involving patients or healthy volunteers.

☐ I have had no involvement in research on this procedure.

☑ Other (please comment)

Comments:

Our unit used the SYNERGO machine within the HYMN study to treat one patient. The HYMN study then closed to recruitment. We also treated 2 more patients outside of the trial.

3 Status of the procedure

3.1 Which of the following best describes the procedure (choose one):

☐ Established practice and no longer new.

☐ A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.

☑ Definitely novel and of uncertain safety and efficacy.

☐ The first in a new class of procedure.

Comments:

The procedure status remains virtually unchanged since the last NICE publication in this area. It probably remains novel and its status remains one of uncertain safety and efficacy.

3.2 What would be the comparator (standard practice) to this procedure?

There remains a variety of options as comparator – including surgical interventions for non-muscle invasive tumours by transurethral resection (TUR), intravesical Bacillus Calmette-Guérin (BCG) vaccine or chemotherapeutic drugs may be instilled directly into the bladder, either as a treatment in itself, or as adjuvant therapy after TUR. Cystectomy may also be necessary in some patients.

3.3 Please estimate the proportion of doctors in your specialty who are doing this procedure (choose one):

☐ More than 50% of specialists engaged in this area of work.

☐ 10% to 50% of specialists engaged in this area of work.

☑ Fewer than 10% of specialists engaged in this area of work.

☐ Cannot give an estimate.

Comments:

4 Safety and efficacy

4.1 What is the potential harm of the procedure?

Please list adverse events and major risks (even if uncommon) and, if possible, estimate their incidence, as follows:

1. Adverse events reported in the literature (if possible please cite literature)

Reports of side effects are common and include urgency/frequency (52%), pain (38%), gross haematuria (24%). More major complications include allergic reaction (10%) and urethral stricture (10%). Bladder spasm sufficient to discontinue to stop treatment in 20% of cases. *Kiss etal Int. Journal of Urology (2015)* 22, 158-162

2. Anecdotal adverse events (known from experience)

3. Theoretical adverse events - Reduced bladder capacity due to scarring / thermal injury.

4.2 What are the key efficacy outcomes for this procedure?

Rates of recurrence and rates of progression to muscle invasive bladder cancer.

4.3 Are there uncertainties or concerns about the *efficacy* of this procedure? If so, what are they?

There are a variety of small non-controlled single centre cohort studies using this procedure that report a wide variety of outcomes from a very mixed group of patients in terms of risk. There is no level 1 evidence of efficacy to support its general adoption

4.4 What training and facilities are needed to do this procedure safely?

The manufacturer provided training to use the equipment including a visit to another centre and support once the machine was delivered.

4.5 Are there any major trials or registries of this procedure currently in progress? If so, please list.

There is no current trial or registry of this procedure in the UK as far as I am aware.

4.6 Are you aware of any abstracts that have been *recently* presented/ published on this procedure that may not be listed in a standard literature search, for example PUBMED? (This can include your own work). If yes,

please list.
Please note that NICE will do a literature search: we are only asking you for any very recent or potentially obscure abstracts and papers. Please do not feel the need to supply a comprehensive reference list (but you may list any that you think are particularly important if you wish).

No I am not aware of anything else.

4.7 Is there controversy, or important uncertainty, about any aspect of the way in which this procedure is currently being done or disseminated?

The urological community in the UK remains sceptical about the safety and efficacy of this procedure in the UK. It is also quite a difficult treatment to deliver and there is an alternative method of delivering heated Mitomycin C into the bladder that is easier and anecdotally far better tolerated by patients.

5 Audit Criteria

Please suggest a minimum dataset of criteria by which this procedure could be audited.

Total numbers. Numbers completed course of treatment. Reasons for discontinuation.

5.1 Outcome measures of benefit (including commonly used clinical outcomes, both short and long - term; and quality-of-life measures). Please suggest the most appropriate method of measurement for each:

Cystoscopic and biopsy pathology evidence of recurrence and progression.

5.2 Adverse outcomes (including potential early and late complications). Please state timescales for measurement e.g. bleeding complications up to 1 month post-procedure:

Pain, bleeding, urinary tract infection, urethral injury / false passage up to 1 month post procedure. Stricture upto 3 months post procedure.

6 Trajectory of the procedure

6.1 In your opinion, how quickly do you think use of this procedure will spread?

No I do not think this procedure will be adopted by UK urologists.

6.2 This procedure, if safe and efficacious, is likely to be carried out in (choose one):

☐ Most or all district general hospitals.

☐ A minority of hospitals, but at least 10 in the UK.

☐ Fewer than 10 specialist centres in the UK.

☑ Cannot predict at present.

Comments:

Evidence of its safety and efficacy is lacking.

6.3 The potential impact of this procedure on the NHS, in terms of numbers of patients eligible for treatment and use of resources, is:

☐ Major.

☐ Moderate.

☑ Minor.

Comments:
Given that is very unlikely to be adopted then I think the impact will be limited.

7 Other information

7.1 Is there any other information about this procedure that might assist NICE in assessing the possible need to investigate its use?

8 Data protection and conflicts of interest

8. Data protection, freedom of information and conflicts of interest

8.1 Data Protection

The information you submit on this form will be retained and used by the NICE and its advisers for the purpose of developing its guidance and may be passed to other approved third parties. Your name and specialist society will be published in NICE publications and on the NICE website. The specialist advice questionnaire will be published in accordance with our guidance development processes and a copy will be sent to the nominating Specialist Society. Please avoid identifying any individual in your comments.

☐ I have read and understood this statement and accept that personal information sent to us will be retained and used for the purposes and in the manner specified above and in accordance with the Data Protection Act 1998.

8.2 **Declarations of interest by Specialist Advisers advising the NICE Interventional Procedures Advisory Committee**

Nothing in your submission shall restrict any disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

Please submit a conflicts of interest declaration form listing any potential conflicts of interest including any involvement you may have in disputes or complaints relating to this procedure.

Please use the "Conflicts of Interest for Specialist Advisers" policy as a guide when declaring any conflicts of interest. Specialist Advisers should seek advice if needed from the Associate Director – Interventional Procedures.

Do you or a member of your family[1] have a **personal pecuniary** interest? The main examples are as follows:

Consultancies or directorships attracting regular or occasional payments in cash or kind	☐ YES ☑ NO
Fee-paid work – any work commissioned by the healthcare industry – **this includes income earned in the course of private practice**	☐ YES ☑ NO
Shareholdings – any shareholding, or other beneficial interest, in shares of the healthcare industry	☐ YES ☑ NO
Expenses and hospitality – any expenses provided by a healthcare industry company beyond those reasonably required for accommodation, meals and travel to attend meetings and conferences	☐ YES ☑ NO
Investments – any funds that include investments in the healthcare industry	☐ YES ☑ NO
Do you have a **personal non-pecuniary** interest – for example have you made a public statement about the topic or do you hold an office in a professional organisation or advocacy group with a direct interest in the topic?	☐ YES ☑ NO

Do you have a **non-personal** interest? The main examples are as follows:

Fellowships endowed by the healthcare industry	☐ YES ☑ NO
Support by the healthcare industry or NICE that benefits his/her position or department, eg grants, sponsorship of posts	☐ YES ☑ NO

If you have answered YES to any of the above statements, please describe the nature of the conflict(s) below.

Comments:

Thank you very much for your help.

[1] 'Family members' refers to a spouse or partner living in the same residence as the member or employee, children for whom the member or employee is legally responsible, and adults for whom the member or employee is legally responsible (for example, an adult whose full power of attorney is held by the individual).

Dr Tom Clutton-Brock, Interventional Procedures Advisory Committee Chair

Professor Carole Longson, Director, Centre for Health Technology Evaluation.

Jan 2016

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU

Deonee.stanislaus@nice.org.uk
www.nice.org.uk

DATA PROTECTION

In order to comply with the Data Protection Act 1998 we ask you to read the following statement and to sign it if you are willing for your data to be used in the way described.

Any personal data such as your name, job title, mailing address, email, telephone, specialist societies and specialist interests will be used by the National Institute for Health and Clinical Excellence (NICE) to carry out its work on interventional procedures and will be kept on a NICE database for future reference.

Your name and specialist society will be placed in the public domain, in future publications and on our website (www.nice.org.uk) and is therefore viewable worldwide. This information may be passed to third parties connected with the work on interventional procedures.

A copy of the completed Specialist Advisor advice will be sent to the Specialist Society who nominated the Specialist Advisor.

Specialist Advisors should be aware that full implementation of the Freedom of Information Act 2000 may oblige us to release Specialist Advice on request from 2005. The Freedom of Information Act 2000 favours the disclosure of information however requests will be considered on a case by case basis against the exemptions in the Act. If information is made available, personal information will be removed if its disclosure would contravene the Data Protection Act 1998.

I agree for the above information to be used on the aforementioned website and in any relevant publications.

Signed:.....

Print name: Mark Johns

Date: 24/01/18

Please return this form via email to: *Deonee.Stanislaus@nice.org.uk*

Alternatively you can return this via post to: Interventional Procedures Programme, 10 Spring Gardens, London SW1A 2BU. Please note forms returned by email must be from an email address associated with your name

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Interventional Procedures Programme

Specialist Adviser questionnaire

Before completing this questionnaire, please read Conflicts of Interest for Specialist Advisers. Certain conflicts exclude you from offering advice, however, please return the questionnaire to us incomplete for our records.

Please respond in the boxes provided.

Please complete and return to: Deonee.Stanislaus@nice.org.uk

Procedure Name:	**Intravesical microwave hyperthermia with intravesical chemotherapy for superficial bladder cancer**
Name of Specialist Advisor:	Mr Rami Issa
Specialist Society:	British Association of Urological Surgeons (BAUS)

1 Do you have adequate knowledge of this procedure to provide advice?

✓ Yes.

☐ No – please return the form/answer no more questions.

1.1 Does the title used above describe the procedure adequately?

✓ Yes.

☐ No. If no, please enter any other titles below.

Comments:

2 Your involvement in the procedure

2.1 Is this procedure relevant to your specialty?

✓ Yes.

☐ Is there any kind of inter-specialty controversy over the procedure?

☐ No. If no, then answer no more questions, but please give any information you can about who is likely to be doing the procedure.

Comments:

The next 2 questions are about whether you carry out the procedure, or refer patients for it. If you are in a specialty that normally carries out the procedure please answer question 2.2.1. If you are in a specialty that normally selects or refers patients for the procedure, please answer question 2.2.2.

2.2.1 If you are in a specialty that does this procedure, please indicate your experience with it:

☐ I have never done this procedure.

☐ I have done this procedure at least once.

✓ I do this procedure regularly.

Comments:

2.2.2 If your specialty is involved in patient selection or referral to another specialty for this procedure, please indicate your experience with it.

☐ I have never taken part in the selection or referral of a patient for this procedure.

☐ I have taken part in patient selection or referred a patient for this procedure at least once.

☐ I take part in patient selection or refer patients for this procedure regularly.

Comments:

2.3 Please indicate your research experience relating to this procedure (please choose one or more if relevant):

✓ I have done bibliographic research on this procedure.

☐ I have done research on this procedure in laboratory settings (e.g. device-related research).

✓ I have done clinical research on this procedure involving patients or healthy volunteers.

☐ I have had no involvement in research on this procedure.

☐ Other (please comment)

Comments:

3 Status of the procedure

3.1 Which of the following best describes the procedure (choose one):

✓ Established practice and no longer new.

☐ A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.

☐ Definitely novel and of uncertain safety and efficacy.

☐ The first in a new class of procedure.

Comments:

3.2 What would be the comparator (standard practice) to this procedure?

No universal standard but possible options would be cystectomy, re-challenge with BCG, and endoscopic surveillance.

3.3 Please estimate the proportion of doctors in your specialty who are doing this procedure (choose one):

☐ More than 50% of specialists engaged in this area of work.

✓ 10% to 50% of specialists engaged in this area of work.

☐ Fewer than 10% of specialists engaged in this area of work.

☐ Cannot give an estimate.

Comments:

4 Safety and efficacy

4.1 What is the potential harm of the procedure?

Please list adverse events and major risks (even if uncommon) and, if possible, estimate their incidence, as follows:

1. Adverse events reported in the literature (if possible please cite literature)

Commonly local urinary symptoms such as cystitis symptoms, dysuria, frequency, urgency, haematuria, urgency and urge incontinence.

Urethral and bladder pain during and after the procedure. Rash type allergic reaction to mitomycin

2. Anecdotal adverse events (known from experience)

Reduction in bladder capacity and compliance, urethral strictures

3. Theoretical adverse events

4.2 What are the key efficacy outcomes for this procedure?

This is used mainly for high risk non muscle invasive bladder cancer in patients who failed BCG therapy or can't tolerate BCG. In my opinion the most important outcome would be disease specific survival and rate of bladder preservation (avoiding cystectomy). Cancer free status is to a degree less important as recurrence of low risk disease in less clinically significant in this group of patients

4.3 Are there uncertainties or concerns about the *efficacy* of this procedure? If so, what are they?

We do not know fully the nature history of high risk non muscle invasive after BCG failure and as we have no gold standard non surgical treatment for this condition it is difficult to ascertain the true efficacy of this procedure.
We know from several RCTs (mostly by R. Colombo) that this procedure is more effective than intravesicle chemotherapy (without hyperthermia) in cohorts of mostly intermediate risk non muscle invasive bladder cancer. Another more recent RCT by J. Alfred Witjes showed that this procedure is at least as effective as BCG in high risk BCG naïve non muscle invasive bladder cancer. However, the HYMN trial gave inconclusive results and was closed early as patients without CIS did reasonably well with this procedure whereas patients with BCG did not have any benefit from this procedure.

4.4 What training and facilities are needed to do this procedure safely?

This procedure can be delivered by a clinician (a doctor or specialist nurse) after a short period of theoretical and practical training. An average of 10 hands on treatments is necessary to become proficient and independent in delivering this procedure. If a nurse is to be delivering this treatment they need to be proficient in male and female catheterisation.
An on-site oncology pharmacy is required to mix and prepare different doses of chemotherapy drugs.

4.5 Are there any major trials or registries of this procedure currently in progress? If so, please list.

Tom J.H. Arends, Ofer Nativ, Massimo Maffezzini, Ottavio de Cobelli, Giorgio Canepa, Fabrizio Verweij,
Boaz Moskovitz, Antoine G. van der Heijden, J. Alfred Witjes
Results of a Randomised Controlled Trial Comparing
Intravesical Chemohyperthermia with Mitomycin C Versus Bacillus Calmette-Gue´rin for Adjuvant Treatment of Patients with Intermediate- and High-risk Non–Muscle-invasive Bladder Cancer
European Urology, Volume 69 Issue 6, June 2016, Pages 1046-1052

Prasanna Sooriakumaran, Virginia Chiocchia, Susan Dutton, Aakash Pai, Benjamin E. Ayres, Pieter Le Roux, Michael Swinn,
Michael Bailey, Matthew J.A. Perry, Rami Issa
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;96:83-90

Sakıp Erturhan, Haluk Sen, Asaf Demirbag, Omer Bayrak, Faruk Yagcı, Iker Seckiner and Ahmet Erbagcı.
Thermo-Chemotherapy in adjuvant treatment of primary high risk non muscle invasive bladder cancers: single center results
Arch. Esp. Urol. 2015; 68 (8): 666-671

Lüdecke G, Schäfer L, Nativ O, Witzsch U, Hanitzsch H, Hasner F, Issa R, Witjes F, Weidner W
Radiofrequence 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, 2015, Moderated Poster, Madrid

Tom J. H. Arends, Johannes Falke, Rianne J. M. Lammers, Diederik M. Somford, Jan C. M. Hendriks, Mirjam C. A. de Weijert,
Harm C. Arentsen, Antoine G. van der Heijden, Egbert Oosterwijk, J. Alfred Witjes
Urinary cytokines in patients treated with intravesical mitomycin-C with and without hyperthermia
World J Urol. 2014 Dec DOI 10.1007/s00345-014-1458-3

Arends TJ, van der Heijden AG, Witjes JA
Combined Chemohyperthermia: The 10-Years Monocentric Experience in 160 Non-Muscle Invasive Bladder Cancer Patients
J Urol. 2014 Apr 1. pii: S0022-5347(14)03189-9. doi: 10.1016/j.juro.2014.03.101. [Epub ahead of print]

Massimo Maffezzini · Fabio Campodonico · Giorgio Canepa ·Egi Edward Manuputty · Stefania Tamagno · Matteo Puntoni
Intravesical mitomycin C combined with local microwavehyperthermia 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 Published online March 2014

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

Lüdecke G, Schäfer L, Weidner W, Schmidt M, Hanitzsch H, Hasner F
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
Journal of Urology, The Vol. 189, Issue 4, Supplement, p700 2013

G. Luedecke, F. Hasner, H. Hanitzsch, M. Schmidt
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
ASCO 2013, 2013 Genitourinary Cancers Symposium

A. Volpe M. Racioppi L. Bongiovanni D. D'Agostino A. Totaro A. D'Addessi F. Marangi G. Palermo F. Pinto E. Sacco P.F. Bassi Thermochemotherapy for Non-Muscle-Invasive Bladder Cancer: Is There a Chance to Avoid Early Cystectomy?
Urologia Internationalis September 2012

Boaz Moskovitz, Sarel Halachmi, Michal Moskovitz, Omri Nativ, Ofer Nativ
10-year single-center experience of combined intravesical chemohyperthermia for nonmuscle invasive bladder cancer
Future Oncol. August 2012

Rianne J.M. Lammers, J. Alfred Witjes, Brant A. Inman, Ilan Leibovitch, Menachem Laufer, Ofer Nativ, Renzo Colombo
The Role of a Combined Regimen With Intravesical Chemotherapy and Hyperthermia in the Management of Non-muscle-invasive Bladder Cancer: A Systematic Review
European Urology, Volume 60 Issue 1, July 2011, Pages 81-93

Renzo Colombo, Andrea Salonia, Zvi Leib, Michele Pavone – Macaluso, and Dov Engelstein
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 International, 10/05/2010

Ofer Nativ, J. Alfred Witjes, Kees Hendricksen, Michael Cohen, Daniel Kedar, Ami Sidi, Renzo Colombo and Ilan Leibovitch.
Combined Thermo-Chemotherapy for Recurrent Bladder Cancer After Bacillus Calmette-Guerin.
J Urology October 2009

Halachmi S, Moskovitz B, Maffezzini M, Conti G, Verweij F, Kedar D, Sandri SD, Nativ O, Colombo R.
Intravesical mitomycin C combined with hyperthermia for patients with T1G3 transitional cell carcinoma of the bladder.
Urol Oncol. 2009 Apr 21. V

J. A. Witjes, K. Hendricksen, O. Gofrit, O. Risi, O. Nativ
Intravesical hyperthermia and Mitomycin-C for (BCG refractory) Carcinoma in Situ of the urinary bladder.
World J Urol (2009)

Antoine G. van der Heijden, Christina A. Hulsbergen Van de Kaa, J. Alfred Witjes.
The Influence of Thermo-Chemotherapy on Bladder Tumours: An Immunohistochemical Analysis.
World J Urol (2007) 25:303-308

Moskovitz B, Meyer G, Kravtzov A, Gross M, Kastin A, Biton K, Nativ O.
Thermo-Chemotherapy for intermediate or high-risk recurrent superficial bladder cancer patients.
Ann Oncol.2005 Apr,16(40:585-9)

Van der Heijden A.G, Verhaegh G, Cornelius F. J. J, Schalken J.A, Witjes J.A.
Effect of Hyperthermia on the Cytotoxicity of Four Chemotherapeutic Agents Currently Used for the Treatment of
Transitional Cell Carcinoma of the Bladder - An in Vitro Study. J Urol Vol. 173, 1375-1380, 2005

Van der Heijden A.G, Cornelius F. J. J, Verhaegh G, O'Donnell M.A, Schalken J.A, Witjes J.A.

The Effect of Hyperthermia on Mitomycin-C Induced Cytotoxicity in Four Human Bladder Cancer Cell Lines.
Eur Urol. 2004 Nov;46(5):670-674

Van der Heijden A.G, Kiemeney L.A, Gofrit O.N, Nativ O, Sidi A, Leib Z, Colombo R, Naspro R,
Pavone M, Baniel J, Hasner F, Witjes J.A.
Preliminary European Results of Local Microwave Hyperthermia and Chemotherapy Treatment in
Intermediate or High Risk Superficial Transitional Cell Carcinoma of the Bladder.
Eur Urol 46:65-72;2004

Gofrit O.N, Shapiro A, Pode D, Sidi A, Nativ O, Leib Z, Witjes J.A, Van Der Heijden A.G, Naspro R, Colombo R.
Combined Local Bladder Hyperthermia and Intravesical Chemotherapy for the Treatment of High Grade
Superficial Bladder Cancer.
Urol 63(3):466-471;2004

Colombo R, Da Pozzo L.F, Salonia A, Rigatti P, Leib Z, Baniel J, Caldarera E, Pavone-Macaluso M.
Multicentric Study Comparing Intravesical Chemotherapy Alone and With Local Microwave Hyperthermia for
Prophylaxis of Recurrence of Superficial Transitional Cell Carcinom
J Clin Oncol. 2003

Wolfson L.R, Moskovitz B, Dekel Y, Kugel V, Koren R.
Combined intravesical hyperthermia and mitomycin chemotherapy: a preliminary in-vivo study.
Int J Exp Path. 84:145-152;2003

Colombo R, Salonia A, Da Pozzo L.F, Naspro R, Freschi M, Paroni R, Pavone-Macaluso M, Rigatti P.
Combination of intravesical chemotherapy and hyperthermia for the treatment of superficial bladder cancer:
preliminary clinical experience.
Crit Rev Oncol Hematol. 47(2):127-39;2003

Van Der Heijden A.G, Witjes J.A.
Future strategies in the diagnosis, staging and treatment of bladder cancer.
Curr Opin Urol 13(5):389-95;2003

Van Der Heijden A.G, Witjes J.A.
Intervesical Chemotherapy: An Update - New Trends and Perspectives.
EAU Update Series 1:71-79;2003

Paroni R, Salonia A, Lev A, Da Pozzo L.F, Cighetti G, Montorsi F, Rigatti P, Colombo R.
Effect of local hyperthermia of the bladder on mitomycin C pharmacokinetics during intravesical chemotherapy
for the treatment of superficial transitional cell carcinoma.
Br J Clin Pharmacol 52:273-278;2001

Colombo R, Brausi M, Da Pozzo L.F, Salonia A, Montorsi F, Scattoni V, Roscigno M, Rigatti P.
Thermo-chemotherapy and electromotive drug administration of mitomycin C in superficial bladder cancer eradication.
Eur Urol 39:95-100;2001

Rigatti P, Lev A, Da Pozzo L.F, Salonia A, Colombo R.
Locally induced hyperthermia in bladder cancer. Bladder Cancer: Biology, Diagnosis and Management,
Chapter 22, Oxford Medical Publication, Ed. K.N. Syrigos & D.G. Skinner, 1999

Colombo R, Da Pozzo L.F, Lev A, Salonia A, Rigatti P, Leib Z, Servadio C, Caldarera E, Pavone-Macaluso M.
Local microwave hyperthermia and intravesical chemotherapy as bladder sparing treatment for select multifocal
and unresectable superficial bladder tumors.
J Urol 159:783-787;1998

Paroni R, Arcelloni C, De Vecchi E, Fermo I, Mauri D, Colombo R.
Plasma mitomycin C concentrations determined by HPLC coupled to solid-phase extraction.
Clin Chem 43:615-618;1997

Colombo R, Da Pozzo L.F, Lev A, Freschi M, Gallus G, Rigatti P.
Neoadjuvant combined microwave induced local hyperthermia and topical chemotherapy versus
chemotherapy alone for superficial bladder cancer.
J Urol 155:1227-1232;1996

Colombo R, Lev A, Da Pozzo L.F, Freschi M, Gallus G, Rigatti P.
A new approach using local combined microwave hyperthermia and chemotherapy in superficial
transitional bladder carcinoma treatment.
J Urol 153:959-963;1995

Rigatti R, Lev A, Colombo R.
Combined intravesical chemotherapy with mitomycin C and local bladder microwave-induced hyperthermia
as a preoperative therapy for superficial bladder tumors - A preliminary clinical study.
Eur Urol 20:204-210;1991

4.6 Are you aware of any abstracts that have been *recently* presented/ published on this procedure that may not be listed in a standard literature search, for example PUBMED? (This can include your own work). If yes, please list.
Please note that NICE will do a literature search: we are only asking you for any very recent or potentially obscure abstracts and papers. Please do not feel the need to supply a comprehensive reference list (but you may list any that you think are particularly important if you wish).

Ayres B. Sri D. Perry M. Issa R.
5-year outcomes of RITE thermochemotherapy for BCG unresponsive high risk non muscle invasive bladder cancer. Eur Urol Suppl 2017; 16(3);e1158

Ayres B et al
10-year experience of RITE thermochemotherapy for high risk non muscle invasive bladder cancer that has failed BCG
Abstract accepted to the American Urological Association meeting 2018

4.7 Is there controversy, or important uncertainty, about any aspect of the way in which this procedure is currently being done or disseminated?

There is some variability in the chemotherapy agent doses used and the number of treatments delivered as the introductory course (4-8)

5 Audit Criteria

Please suggest a minimum dataset of criteria by which this procedure could be audited.

In addition to the obvious oncological outcomes such as recurrence and progression rate (including developing TCC in upper tract and urethra), bladder preservation and survival in relation to the original risk groups of these patients, one has to look carefully at rate and severity of side effects including QOL in relation to urinary symptoms and health status.

5.1 Outcome measures of benefit (including commonly used clinical outcomes, both short and long - term; and quality-of-life measures). Please suggest the most appropriate method of measurement for each:
please see above

5.2 Adverse outcomes (including potential early and late complications). Please state timescales for measurement e.g. bleeding complications up to 1 month post-procedure:
The local side effects (urinary symptoms and allergic reactions) should be measured during every treatment visit and 1, 3 months after finishing the introductory course and the each maintenance course. Long term side effects related to bladder capacity and compliance and urethral strictures should be assessed at 1, 3 and 6 months after the introductory course and each maintenance course

6 Trajectory of the procedure

6.1 In your opinion, how quickly do you think use of this procedure will spread?

This procedure has been in use in the UK for over 10 years. Its popularity has been slowed down by its financial and practical demands in comparison to standard intravesicle therapies and fact that there is no agreed tariff for this procedure. However, with the on/off availability of BCG recently and in the future combined with the aging population where cystectomy is challenging and BCG is less successful one would expect an increase in its use over the next 5-10 years. This procedure is not the only way to combine chemotherapy and hyperthermia for treatment of bladder cancer and there has been several other options available in the country which could impact negatively on the use of this particular procedure.

6.2 This procedure, if safe and efficacious, is likely to be carried out in (choose one):

☐ Most or all district general hospitals.

☐ A minority of hospitals, but at least 10 in the UK.

☐ Fewer than 10 specialist centres in the UK.

☐ Cannot predict at present.

Comments:

6.3 The potential impact of this procedure on the NHS, in terms of numbers of patients eligible for treatment and use of resources, is:

☐ Major.

☐ Moderate.

☐ Minor.

Comments:

7 Other information

7.1 Is there any other information about this procedure that might assist NICE in assessing the possible need to investigate its use?

8 Data protection and conflicts of interest

8. Data protection, freedom of information and conflicts of interest

8.1 Data Protection

The information you submit on this form will be retained and used by the NICE and its advisers for the purpose of developing its guidance and may be passed to other approved third parties. Your name and specialist society will be published in NICE publications and on the NICE website. The specialist advice questionnaire will be published in accordance with our guidance development processes and a copy will be sent to the nominating Specialist Society. Please avoid identifying any individual in your comments.

I have read and understood this statement and accept that personal information sent to us will be retained and used for the purposes and in the manner specified above and in accordance with the Data Protection Act 1998.

8.2 Declarations of interest by Specialist Advisers advising the NICE Interventional Procedures Advisory Committee

Nothing in your submission shall restrict any disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

Please submit a conflicts of interest declaration form listing any potential conflicts of interest including any involvement you may have in disputes or complaints relating to this procedure.

Please use the "Conflicts of Interest for Specialist Advisers" policy as a guide when declaring any conflicts of interest. Specialist Advisers should seek advice if needed from the Associate Director – Interventional Procedures.

Do you or a member of your family[1] have a **personal pecuniary** interest? The main examples are as follows:

[1] 'Family members' refers to a spouse or partner living in the same residence as the member or employee, children for whom the member or employee is legally responsible, and adults for whom the member or employee is legally responsible (for example, an adult whose full power of attorney is held by the individual).

Consultancies or directorships attracting regular or occasional payments in cash or kind	☐	**YES**
	☐	**NO**
Fee-paid work – any work commissioned by the healthcare industry **– this includes income earned in the course of private practice**	☐	**YES**
	☐	**NO**
Shareholdings – any shareholding, or other beneficial interest, in shares of the healthcare industry	☐	**YES**
	☐	**NO**
Expenses and hospitality – any expenses provided by a healthcare industry company beyond those reasonably required for accommodation, meals and travel to attend meetings and conferences	☐	**YES**
	☐	**NO**
Investments – any funds that include investments in the healthcare industry	☐	**YES**
		NO
Do you have a **personal non-pecuniary** interest – for example have you made a public statement about the topic or do you hold an office in a professional organisation or advocacy group with a direct interest in the topic?	☐	**YES**
	☐	**NO**

Do you have a **non-personal** interest? The main examples are as follows:

Fellowships endowed by the healthcare industry	☐	**YES**
	☐	**NO**
Support by the healthcare industry or NICE that benefits his/her position or department, eg grants, sponsorship of posts	☐	**YES**
	☐	**NO**

If you have answered YES to any of the above statements, please describe the nature of the conflict(s) below.

Comments: Medical Enterprises Europe B.V made a donation of £4500 to the charity fund at the urology department, St George's Hospital, London to support audio-visual material related to the EAU meeting.

Thank you very much for your help.

Dr Tom Clutton-Brock, Interventional Procedures Advisory Committee Chair

Professor Carole Longson, Director, Centre for Health Technology Evaluation.

Jan 2016

Conflicts of Interest for Specialist Advisers

1 Declarations of interest by Specialist Advisers advising the NICE Interventional Procedures Advisory Committee

1.1 Any conflicts of interest set out below should be declared on the questionnaire the Specialist Adviser completes for the procedure.

1.2 Specialist Advisers should seek advice if required from the Associate Director – Interventional Procedures.

2 Personal pecuniary interests

2.1 A personal pecuniary interest involves a current personal payment to a Specialist Adviser, which may either relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as **'specific'** or to the industry or sector from which the product or service comes, in which case it is regarded as **'non-specific'**. The main examples are as follows.

2.1.1 **Consultancies** – any consultancy, directorship, position in or work for the healthcare industry that attracts regular or occasional payments in cash or kind (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place).

2.1.2 **Fee-paid work** – any work commissioned by the healthcare industry for which the member is paid in cash or in kind (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place).

2.1.3 **Shareholdings** – any shareholding, or other beneficial interest, in shares of the healthcare industry that are either held by the individual or for which the individual has legal responsibility (for example, children, or relatives whose full Power of Attorney is held by the individual). This does not include shareholdings through unit trusts, pensions funds, or other similar arrangements where the member has no influence on financial management.

2.1.4 **Expenses and hospitality** – any expenses provided by a healthcare industry company beyond that reasonably required for accommodation, meals and travel to attend meetings and conferences (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place.

2.1.5 **Investments** – any funds which include investments in the healthcare industry that are held in a portfolio over which individuals have the ability to instruct the fund manager as to the composition of the fund.

2.2 No personal interest exists in the case of:

2.2.1 assets over which individuals have no financial control (for example, wide portfolio unit trusts and occupational pension funds) and where the fund manager has full discretion as to its composition (for example, the Universities Superannuation Scheme)

2.2.2 accrued pension rights from earlier employment in the healthcare industry.

3 **Personal family interest**

3.1 This relates to the personal interests of a family member and involves a **current payment** to the family member of the Specialist Adviser. The interest may relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as '**specific**', or to the industry or sector from which the product or service comes, in which case it is regarded as '**non-specific**'. The main examples include the following.

3.1.1 Any consultancy, directorship, position in or work for a healthcare industry that attracts regular or occasional payments in cash or in kind.

3.1.2 Any fee-paid work commissioned by a healthcare industry for which the member is paid in cash or in kind.

3.1.3 Any shareholdings, or other beneficial interests, in a healthcare industry which are either held by the family member or for which an individual covered by this Code has legal responsibility (for example, children, or adults whose full Power of Attorney is held by the individual).

3.1.4 Expenses and hospitality provided by a healthcare industry company (except where they are provided to a general class of people such as attendees at an open conference)

3.1.5 Funds which include investments in the healthcare industry that are held in a portfolio over which individuals have the ability to instruct the fund manager as to the composition of the fund.

3.2 No personal family interest exists in the case of:

3.2.1 assets over which individuals have no financial control (for example, wide portfolio unit trusts and occupational pension funds) and where the fund manager has full discretion as to its composition (for example, the Universities Superannuation Scheme)

3.2.2 accrued pension rights from earlier employment in the healthcare industry.

4 **Personal non-pecuniary interests**

These might include, but are not limited to:

4.1 a clear opinion, reached as the conclusion of a research project, about the clinical and/or cost effectiveness of an intervention under review

4.2 a public statement in which an individual covered by this Code has expressed a clear opinion about the matter under consideration, which could reasonably be interpreted as prejudicial to an objective interpretation of the evidence

4.3 holding office in a professional organisation or advocacy group with a direct interest in the matter under consideration

4.4 other reputational risks in relation to an intervention under review.

5 Non-personal interests

5.1 A non-personal interest involves payment that benefits a department or organisation for which a Specialist Advisor is responsible, but that is not received by the Specialist Advisor personally. This may either relate to the product or service being evaluated, in which case it is regarded as **'specific,'** or to the manufacturer or owner of the product or service, but is unrelated to the matter under consideration, in which case it is regarded as **'non-specific'**. The main examples are as follows.

5.1.1 **Fellowships** – the holding of a fellowship endowed by the healthcare industry.

5.1.2 **Support by the healthcare industry or NICE** – any payment, or other support by the healthcare industry or by NICE that does not convey any pecuniary or material benefit to a member personally but that does benefit his/her position or department. For example:

- a grant from a company for the running of a unit or department for which a Specialist Advisor is responsible
- a grant, fellowship or other payment to sponsor a post or member of staff in the unit for which a Specialist Adviser is responsible. This does not include financial assistance for students
- the commissioning of research or other work by, or advice from, staff who work in a unit for which the specialist advisor is responsible
- one or more contracts with, or grants from, NICE.

5.2 Specialist Advisers are under no obligation to seek out knowledge of work done for, or on behalf of, the healthcare industry within departments for which they are responsible if they would not normally expect to be informed.