

Electrically-stimulated intravesical chemotherapy for superficial bladder cancer

1 Guidance

- 1.1 Current evidence on electrically-stimulated intravesical chemotherapy for superficial bladder cancer raises no major safety concerns. However, the evidence is based on methodologically inconsistent studies and the efficacy of the procedure is uncertain. Therefore, this procedure should only be used in the context of research.
- 1.2 Further research should take the form of randomised controlled trials (RCTs) with adequate duration of follow-up, comparing intravesical chemotherapy with and without the use of electrical stimulation. NICE may review the procedure upon publication of further evidence.

2 The procedure

2.1 Indications and current treatments

- 2.1.1 The most common form of bladder cancer is transitional cell carcinoma. Superficial disease is defined as cancer that is confined to the bladder lining and has not invaded the muscle layer.
- 2.1.2 Conventional treatment involves transurethral resection (TUR), in which malignant tissue is removed with an electrocautery device during cystoscopy. Intravesical chemotherapy with bacillus Calmette-Guérin (BCG) vaccine or other chemotherapeutic drugs may also be used, either alone, or as adjuvant therapy after TUR, to reduce the risk of cancer recurrence. Intravesical microwave hyperthermia has also been used in combination with intravesical chemotherapy. Cystectomy may be necessary in some patients.

2.2 Outline of the procedure

- 2.2.1 Electrically-stimulated intravesical chemotherapy can be used as neoadjuvant treatment before TUR or as adjuvant treatment following TUR. The procedure involves the use of a device to create an electric field across the bladder wall, with the aim of stimulating directional ionic and solute movement of the intravesical fluid, so increasing absorption of the chemotherapeutic solution which has been introduced into the bladder.
- 2.2.2 The procedure is usually performed with the patient under local anaesthesia. As in standard intravesical chemotherapy, a chemotherapeutic drug solution (usually mitomycin C [MMC] in saline or distilled water) is instilled into the bladder. Electrode pads are placed on the skin of the patient's lower abdomen and a catheter (with an intravesical electrode) is inserted into the bladder through the urethra. When the catheter and electrodes are in place the chemotherapeutic drug solution is introduced via the catheter into the bladder. The cutaneous and intravesical electrodes are then connected to a generator that creates a current of up to 25 mA. Treatment sessions usually last for approximately 30 minutes. After the procedure the bladder is drained and the catheter is removed.

Sections 2.3 and 2.4 describe efficacy and safety outcomes from the published literature that the Committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the overview, available at www.nice.org.uk/IP697overview

Interventional procedure guidance 277

Interventional procedures guidance makes recommendations on the safety and efficacy of a procedure. The guidance does not cover whether or not the NHS should fund a procedure. Decisions about funding are taken by local NHS bodies (primary care trusts and hospital trusts) after considering the clinical effectiveness of the procedure and whether it represents value for money for the NHS.

Interventional procedures guidance is for healthcare professionals and people using the NHS in England, Wales, Scotland and Northern Ireland. This guidance is endorsed by NHS QIS for implementation by NHSScotland.

2.3 Efficacy

- 2.3.1 An RCT of 212 patients with histologically proven pT1 transitional cell carcinoma of the bladder, including patients with carcinoma in situ, reported longer disease-free survival in patients treated by electromotive drug administration of MMC (EMDA–MMC) plus BCG (58%; 62/107) compared with BCG alone (42%; 44/105) at a mean follow-up of 88 months ($p = 0.0012$).
- 2.3.2 An RCT of 108 patients with bladder carcinoma in situ or papillary transitional cell carcinoma reported a significantly higher complete response rate among patients treated by EMDA–MMC (58%; 21/36) compared with those treated by MMC alone (31%; 11/36) ($p = 0.012$) at 6-month follow-up (complete response defined as negative histology and cytology). The same study reported no significant difference in estimated 5-year survival (all-cause mortality) between the three groups studied (EMDA–MMC 69%, MMC 63%, BCG 59%; $p = 0.782$). However, interpreting differences in efficacy between the treatments beyond 6-month follow-up is difficult, because patients for whom the initial treatment was judged to have failed at 6 months could cross over to a different treatment arm.
- 2.3.3 A non-randomised controlled trial of 80 patients reported complete response to treatment (defined as negative cystoscopy, cytology and histology) in 40% (6/15) of patients treated by EMDA–MMC, 28% (10/36) of patients treated by MMC and 66% (19/29) of patients treated by intravesical microwave hyperthermia combined with MMC at 7- to 10-day follow-up (significance not stated).
- 2.3.4 The Specialist Advisers considered key efficacy outcomes to include tumour recurrence, tumour progression and mortality. One Adviser stated that efficacy remains to be established in appropriate trials.

2.4 Safety

- 2.4.1 The RCT of 212 patients reported suspension of treatment owing to side effects in 3% (3/107) of patients treated by EMDA–MMC plus BCG and in 3% (3/105) of patients treated by BCG alone (nature of side effects not described). In a case series of 22 patients, 14% (3/22) of patients had

3 out of a total of 91 scheduled EMDA–MMC treatment sessions suspended because of bladder ulcer development in 1 patient, and leakage of the instillate solution because of bladder contractions in 2 patients.

- 2.4.2 The RCT of 108 patients reported urinary frequency in 19% (7/36) of patients following treatment with EMDA–MMC (duration of symptoms not described).
- 2.4.3 The RCT of 108 patients and a non-randomised controlled trial of 28 patients reported chemical/drug-induced cystitis in 36% (13/36) and 13% (2/15) of patients, respectively.
- 2.4.4 Across the studies, between 0% (0/15) and 22% (8/36) of patients treated with EMDA–MMC developed haematuria (defined differently across the studies; duration not reported).
- 2.4.5 The Specialist Advisers considered theoretical adverse events to include urethral stricture, systemic drug toxicity and transitory incontinence.

2.5 Other comments

- 2.5.1 The Committee noted that the available studies used different treatment protocols, comparators and outcomes. This made interpretation of the evidence complex and was an important reason for the uncertainty about efficacy.

3 Further information

- 3.1.1 NICE has published cancer service guidance on improving outcomes in urological cancers (www.nice.org.uk/CSGUC) and interventional procedures guidance on intravesical microwave hyperthermia with intravesical chemotherapy for superficial bladder cancer (www.nice.org.uk/IPG235) and laparoscopic cystectomy (www.nice.org.uk/IPG26).

Information for patients

NICE has produced information on this procedure for patients and carers ('Understanding NICE guidance'). It explains the nature of the procedure and the guidance issued by NICE, and has been written with patient consent in mind. See www.nice.org.uk/IPG277publicinfo

Ordering printed copies

Contact NICE publications (phone 0845 003 7783 or email publications@nice.org.uk) and quote reference number N1731 for this guidance or N1732 for the 'Understanding NICE guidance'.

This guidance represents the view of NICE, which was arrived at after careful consideration of the available evidence. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of healthcare professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

© National Institute for Health and Clinical Excellence, 2008. All rights reserved. This material may be freely reproduced for educational and not-for-profit purposes. No reproduction by or for commercial organisations, or for commercial purposes, is allowed without the express written permission of NICE.