

National Institute for Health and Care Excellence

IP395/2 Intravesical microwave hyperthermia and chemotherapy for superficial bladder cancer

IPAC 12/07/18

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response
1	Consultee 1 NHS Professional	3.6	<p>What is your evidence that "superficial" (I assume you mean non-muscle-invasive) bladder cancer is increasingly being diagnosed in patients where alternative more invasive treatments such as cystectomy may not be considered clinically appropriate ?</p> <p>I do not know of any.</p>	<p>Please respond to all comments</p> <p>Thank you for your comment.</p> <p>The committee was advised that the patient population is getting older and that more invasive treatments may not be suitable for some elderly patients with non-muscle-invasive bladder cancer.</p>

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2	Consultee 1 NHS Professional	1.3	There is a risk of understaging in people who have failed to respond to BCG. Outcomes in series of cystectomy for people who have failed to respond to BCG suggest that the rates of unsuspected muscle-invasive disease (poor prognosis) may be as high as 20%-30%. So when offering treatment other than cystectomy to people who have failed BCG, this significant risk must be borne in mind and discussed by a suitable clinician (member of specialist multidisciplinary team, not local one) after review by a specialist multidisciplinary team, to avoid people who may have undiagnosed muscle-invasive cancer being offered this treatment, which will not be effective for that sort of bladder cancer and will considerably disadvantage them.	Please respond to all comments Thank you for your comment. Section 1.3 of the guidance has been changed to include 'specialist'.
3	Consultee 1 NHS Professional	General	Please avoid very outdated terminology - "transitional cell carcinoma" and "superficial". Please use the long-recognised term urothelial carcinoma (of bladder), and non-muscle-invasive, respectively.	Thank you for your comment. The term 'superficial' has been changed to 'non-muscle-invasive' throughout. The committee was advised that the term 'transitional cell carcinoma' is still commonly used.

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4	Consultee 2 Healthcare Other	2.3	<p>I would like to emphasize that this committee has only reviewed evidence obtained using the microwave-induced (or radiofrequency-induced, as claimed by the manufacturer) hyperthermia. Clause 2.3 should therefore be rephrased</p> <p>from :</p> <p>"Intravesical hyperthermia combined with intravesical chemotherapy can be used as neoadjuvant therapy before transurethral resection, with the aim of eradicating tumours."</p> <p>to state</p> <p>"Microwave-induced intravesical hyperthermia..."</p> <p>to assure clarity and avoid misinterpretation of the recommendations.</p>	<p>Please respond to all comments</p> <p>Thank you for your comment.</p> <p>The first sentence of section 2.3 of the guidance has been changed to include the word 'microwave'.</p>
5	Consultee 2 Healthcare Other	3.9	<p>It would be plausible to expand the target population to include BCG-intolerant patients and patients for whom BCG is contraindicated.</p>	<p>Thank you for your comment.</p> <p>The committee comment has been changed.</p>

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6	Consultee 3 Bnai Zion Medical Center	2.4	The mechanism of this technology i.e. the RF induced effect needs to be mentioned	Thank you for your comment. Section 2.4 of the guidance has been changed to include the term 'radiofrequency'. Section 3.6 of the guidance has been changed to include the following sentence: 'The committee was informed that the microwave energy itself may have some action on the cancer cells.'
7	Consultee 3 Bnai Zion Medical Center	General	An important indication of this technology is the ablative indication which is by more effective than any other intravesical agent	Thank you for your comment. Section 3.6 of the guidance has been changed to include the following sentence: 'The committee was informed that the microwave energy itself may have some action on the cancer cells.'
8	Consultee 3 Bnai Zion Medical Center	General	I would consider all subgroups of patients who are not suitable to receive BCG as optimal candidates for this technology	Thank you for your comment. Section 3.8 3.8 of the guidance has been changed to 'The committee was informed that the technology may be useful when treatment with Bacillus Calmette-Guérin (BCG) vaccine is contraindicated or unsuitable, has been unsuccessful, or when the vaccine is not available.'

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9	Consultee 4 Medical Enterprises Europe	1.1	<p>the draft document states: “well-recognised adverse events”™. We believe it is mostly based on the comments of Mr. Johnson:</p> <p>On page 4 of his questionnaire, under clause 4.1, Mr. Johnson states/cites Kiss et al as a reference on adverse events associated with the treatment. It is unclear why was this publication, describing a very limited and worse selected patient cohort (n=21), chosen to provide an estimate of safety, while a systematic review of safety is available in:</p> <p>Lammers RJ, Witjes JA, Inman BA, Leibovitch I, Laufer M, Nativ O, et al. 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;60(1):81-93.</p> <p>and provides a much more reliable estimate of safety aspects associated with the treatment.</p>	<p>Please respond to all comments</p> <p>Thank you for your comment.</p> <p>The statement in section 1.1 was based on all of the evidence that was presented in the overview and discussed by the committee, as well as the specialist adviser questionnaires. This evidence included the systematic review by Lammers et al, 2011.</p>

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10	Consultee 4 Medical Enterprises Europe	1.1	<p>The draft document states: “current evidence on its efficacy is limited in quality”™. We believe it is mostly based on the comments of Mr. Johnson:</p> <p>on page 4 of his questionnaire, under clause 4.3, he states that “there is no level 1 evidence of efficacy to support its general adoption”. It is unclear what grading system Mr. Johnson refers to, however, it is plausible to assume that he adopts the Oxford Centre for Evidence-based Medicine Levels of Evidence, as modified in the EAU guidelines on NMIBC (Table 1). This grading system maintains the following:</p> <p>Evidence level 1a: Evidence obtained from meta-analysis of randomised trials.</p> <p>Evidence level 1b: Evidence obtained from at least one randomised trial.</p> <p>Randomized studies have been reviewed during the NICE open review session in March. And as shown, there are a couple of such published.</p>	<p>Please respond to all comments</p> <p>Thank you for your comment.</p> <p>The statement in section 1.1 was based on all of the evidence that was presented in the overview and discussed by the committee, as well as the specialist adviser questionnaires. When considering the quality of the evidence on efficacy, the committee takes several factors into account, including study design, study size, follow-up duration and completeness, and patient-focused efficacy outcomes.</p>

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11	Consultee 4 Medical Enterprises Europe	3.3	The concern regarding the thermal bladder damage may be, at least partly, alleviated by stating that the side effect may appear as hyperemia, mild inflammatory changes or even the appearance of necrotic tissue, yet these events are superficial (no muscle involvement), asymptomatic, usually resolve without medical intervention and no clinically significant sequelae have been noted to date. The company hereby declares that with about 40,000 (40,000) treatments to-date, no bladder perforation occurred due to the treatment and the above description (being asymptomatic etc) is true.	Please respond to all comments Thank you for your comment. The committee considered this comment but decided not to change the guidance.
12	Consultee 4 Medical Enterprises Europe	Overview	Sorry I missed but people drew my attention that in the "Overview" document page 29 you make reference to EAU Guidelines which are quite old and in the new ones our LE is 1B! thank you	Thank you for your comment. The overview currently refers to a 2016 version of the EAU guidelines. This will be updated to the most recent version (http://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/)

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13	Consultee 4 Medical Enterprises Europe	General	There is an manuscript on one of the largest sub-groups of CIS patients ever ever published submitted for publication with impressive results the author told us.	Please respond to all comments Thank you for your comment. The consultee refers to a study that had not yet been accepted for publication. The Committee was given a copy of the manuscript in confidence and reviewed it for safety events. The NICE Interventional Procedures programme only uses peer reviewed published data to assess efficacy. NICE may update its guidance in the event of new peer reviewed published information becoming available.

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