



Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic:	Radiofrequency-induced thermochemotherapy for the treatment of non-muscle-invasive bladder cancer.
Topic exploration report number:	TER172

Introduction and aims

Treatment of non-muscle invasive bladder cancer (NMIBC) can include delivery of chemotherapy into the bladder via a catheter (intravesical chemotherapy). Some technologies combine delivery of local chemotherapy to the bladder tissue with heating via controlled radiofrequency radiation (non-ionising microwave radiation). This treatment is known as radiofrequency-induced thermochemotherapy.

Health Technology Wales researchers searched for evidence on the clinical and cost effectiveness of radiofrequency-induced thermochemotherapy to treat NMIBC.

Evidence

Synergo is a CE-marked class IIb medical device that delivers radiofrequency-induced thermochemotherapy. Although alternative devices exist that deliver thermochemotherapy by other methods, as of December 2020 Synergo is the only device known to be available for radiofrequency-induced thermochemotherapy to treat NMIBC.

Existing Guidance

European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (last updated 2020) include a chapter on intravesical chemotherapy. This includes a statement that 'promising data have been presented on enhancing the efficacy of MMC using microwave-induced hyperthermia in patients with high-risk tumours' but no specific recommendations are made on this method of chemotherapy delivery.

In 2018, NICE published Interventional Procedures Guidance (IPG628) on intravesical microwave hyperthermia and chemotherapy for non-muscle-invasive bladder cancer. When this Guidance was issued, NICE concluded that the evidence regarding this intervention was limited in quality

and that the procedure should be only be used with special arrangements for clinical governance, consent and audit or research. Furthermore, patient selection should be undertaken by bladder cancer multidisciplinary teams and the procedure should only be done in specialist centres. NICE encouraged further research into the topic, especially randomised controlled trials (RCTs) which stratify patients by risk and give adequate follow-up as well as report frequency of adverse events, patient-reported outcome measures, overall and disease-free survival and quality of life.

Subsequently, in 2020, NICE published a Medtech Innovation Briefing (MIB226) on Synergo, summarising the evidence on this technology specifically. Production of NICE Medical Technologies Guidance on Synergo is also ongoing.

Randomised Trials

We identified three randomised trials investigating radiofrequency-induced thermochemotherapy to treat NMIBC. All trials used the Synergo system, and compared it to various types of intravesical chemotherapy without radiofrequency-induced heating. All three trials included people with intermediate or high risk NMIBC. Each trial is described in further detail below.

Arends et al. (2016) recruited 190 patients with new or recurrent intermediate- and high-risk non-muscle invasive bladder cancer from Israel and Europe. Patients were randomised to radiofrequency-induced thermochemotherapy with mitomycin C in the intervention arm (n = 92) or bacillus calmette-guérin (BCG) immunotherapy in the control arm (n = 98). After 24 months follow up there was no significant difference in recurrence-free survival between people treated with radiofrequency-induced thermochemotherapy and BCG (78.1% compared with 64.8%, p=0.08). Disease progression occurred in 0 patients who received radiofrequency-induced thermochemotherapy and 1 who received BCG.

Colombo et al. (2011) was a multi-centre randomised controlled trial of 83 people with new or recurrent intermediate- or high-risk non-muscle invasive bladder cancer. Patients were randomised to radiofrequency-induced thermochemotherapy with mitomycin C (n = 42) or mitomycin C alone (without radiofrequency-induced heating, n = 41). Seventy five patients completed the study (35 of 42 in the treatment arm, 40 of 41 in the control arm) and were followed up for at least 2 years and for a maximum of 12 years. The 10-year disease-free survival rates for radiofrequency-induced thermochemotherapy and mitomycin C alone were 53% and 15%, respectively (p<0.001). Overall survival did not differ significantly between the two treatment groups. Bladder preservation rates for radiofrequency-induced thermochemotherapy with mitomycin C and mitomycin C alone were 86% and 79%, respectively.

Tan et al. (2019) was a study in the UK that compared radiofrequency-induced thermochemotherapy and standard second-line therapy (BCG or institutional standard of care) in NMIBC patients with recurrence following induction/maintenance treatment with BCG. Median follow-up for the 31 patients without a disease-free survival event was 36 months. The rates of disease free survival after 24 months in the radiofrequency-induced thermochemotherapy group and the standard therapy group were 35% and 41%, respectively (HR 1.33, 95% confidence interval 0.84-2.10, p = 0.23). Pre-planned subgroup analysis also compared disease free survival in people with carcinoma in situ. DFS of RITE-treated patients was significantly lower than that of control in patients with baseline CIS (HR 2.06, 95% CI 1.17-3.62, p = 0.01). In people with non-carcinoma in situ tumours, disease free survival was higher in the radiofrequency-induced thermochemotherapy group but the difference between the treatments was not statistically significant.

Observational studies

We also identified a number of other non-randomised studies investigating radiofrequency-induced thermochemotherapy in people with NMIBC. These studied radiofrequency-induced thermochemotherapy given either as tumour ablation or as a prophylactic treatment after tumour resection. None of the studies included a control group. Details of the studies identified can be found in the Brief Literature Search Results section.

Areas of uncertainty

Radiofrequency-induced thermochemotherapy has been studied in people with NMIBC at different points in the care pathway. The target patient population that might most benefit from treatment is unclear. For example, it is not clear whether radiofrequency-induced thermochemotherapy shows the most benefits as an adjuvant treatment after tumour resection, or could be used as a first-line treatment.

Synergo is the most well-studied device that delivers radiofrequency-induced thermochemotherapy in people with NMIBC, and is the only known device CE-certified for this purpose as of December 2020. However, interventions that deliver chemo-hyperthermia by other methods are available and the performance of these, in isolation or in comparison to Synergo, is not known. No evidence highlighting the cost effectiveness of the intervention with Synergo was identified in the literature.

Conclusions

Synergo has been studied as part of three randomised controlled trials. These are the same trials included in NICE MIB226 and we did not identify any randomised controlled trials of other radiofrequency-induced thermochemotherapy systems. The results of the trials suggest radiofrequency-induced thermochemotherapy may have some benefits over alternative therapies for the treatment of NMIBC, but further scrutiny of the evidence is needed to establish where in the care pathway this type of treatment could offer benefits.

Brief literature search results

Resource	Results
HTA organisations	
Healthcare Improvement Scotland:	We did not identify any relevant information from this source.
Health Technology Assessment Group	We did not identify any relevant information from this source.
Health Information and Quality Authority	We did not identify any relevant information from this source.
UK guidelines and guidance	
SIGN	We did not identify any relevant information from this source.
NICE	<p>NICE. (2018). Intravesical microwave hyperthermia and chemotherapy for non-muscle-invasive bladder cancer. Interventional Procedures Guidance [IPG628]. https://www.nice.org.uk/guidance/ipg628 (Accessed December 2020).</p> <p>NICE. (2020) Synergo for non-muscle-invasive bladder cancer. Medtech innovation briefing [MIB226]. https://www.nice.org.uk/advice/mib226 (Accessed December 2020)</p>
Secondary literature and economic evaluations	
ECRI	We did not identify any relevant information from this source.
Cochrane library	We did not identify any relevant information from this source.
Medline	<p>We identified two evidence reviews of potential relevance. However, both included different types of thermochemotherapy (i.e. not only radiofrequency-induced thermochemotherapy).</p> <ul style="list-style-type: none"> Lammers RJM, Witjes JA, Inman BA, et al. (2011). The Role of a Combined Regimen With Intravesical Chemotherapy and Hyperthermia in the Management of Non-muscle-invasive Bladder Cancer: A Systematic Review. <i>European Urology</i>. 60(1): 81-93. doi: https://doi.org/10.1016/j.eururo.2011.04.023 van Valenberg H, Colombo R, Witjes F. (2016). Intravesical radiofrequency-induced hyperthermia combined with chemotherapy for non-muscle-invasive bladder cancer. <i>Int J Hyperthermia</i>. 32(4): 351-62. doi: 10.3109/02656736.2016.1140232
Randomised trials	
Medline	<ul style="list-style-type: none"> Arends TJ, Nativ O, Maffezzini M, de Cobelli O, Canepa G, Verweij F, Moskovitz B, van der Heijden AG, Witjes JA. Results of a Randomised Controlled Trial Comparing Intravesical Chemohyperthermia with Mitomycin C Versus Bacillus Calmette-Guérin for Adjuvant Treatment of Patients with Intermediate- and High-risk Non-Muscle-invasive Bladder Cancer. <i>Eur Urol</i>. 2016 Jun;69(6):1046-52. doi: 10.1016/j.eururo.2016.01.006. Epub 2016 Jan 20. Colombo R, Da Pozzo LF, Salonia A, et al. (2003). Multicentric study comparing intravesical chemotherapy alone and with local microwave hyperthermia for prophylaxis of recurrence of superficial transitional cell carcinoma. <i>J Clin Oncol</i>. 21(23): 4270-6. doi: 10.1200/jco.2003.01.089

	<ul style="list-style-type: none"> Colombo R, Salonia A, Leib Z, et al. (2011). Long-term outcomes of a randomized controlled trial comparing thermochemotherapy with mitomycin-C alone as adjuvant treatment for non-muscle-invasive bladder cancer (NMIBC). <i>BJU international</i>. 107(6): 912-8. Tan WS, Panchal A, Buckley L, et al. (2019). Radiofrequency-induced Thermo-chemotherapy Effect Versus a Second Course of Bacillus Calmette-Guerin or Institutional Standard in Patients with Recurrence of Non-muscle-invasive Bladder Cancer Following Induction or Maintenance Bacillus Calmette-Guerin Therapy (HYMN): A Phase III, Open-label, Randomised Controlled Trial. <i>Eur Urol</i>. 75(1): 63-71. doi: 10.1016/j.eururo.2018.09.005
Observational studies	
Medline	<ul style="list-style-type: none"> Gofrit O, Shapiro A, Pode D, et al. (2004). Combined local bladder hyperthermia and intravesical chemotherapy for the treatment of high-grade superficial bladder cancer. <i>Urology</i>. 63(3): 466-71. Halachmi S, Moskovitz B, Maffezzini M, et al. (Year) Published. Intravesical mitomycin C combined with hyperthermia for patients with T1G3 transitional cell carcinoma of the bladder. <i>Urologic Oncology: Seminars and Original Investigations</i>, 2011. Elsevier. 259-64 Accessed]. Kiss B, Schneider S, Thalmann GN, et al. (2015). Is thermochemotherapy with the Synergo system a viable treatment option in patients with recurrent non-muscle-invasive bladder cancer? <i>Int J Urol</i>. 22(2): 158-62. doi: 10.1111/iju.12639 Maffezzini M, Campodonico F, Canepa G, et al. (2014). Intravesical mitomycin C combined with local microwave hyperthermia in non-muscle-invasive bladder cancer with increased European Organization for Research and Treatment of Cancer (EORTC) score risk of recurrence and progression. <i>Cancer Chemother Pharmacol</i>. 73(5): 925-30. doi: 10.1007/s00280-014-2423-y Moskovitz B, Meyer G, Kravtsov A, et al. (2005). Thermo-chemotherapy for intermediate or high-risk recurrent superficial bladder cancer patients. <i>Annals of oncology</i>. 16(4): 585-9. Moskovitz B, Halachmi S, Moskovitz M, et al. (2012). 10-year single-center experience of combined intravesical chemohyperthermia for nonmuscle invasive bladder cancer. <i>Future Oncol</i>. 8(8): 1041-9. doi: 10.2217/fon.12.90 Tan WS, Panchal A, Buckley L, et al. (2019). Radiofrequency-induced Thermo-chemotherapy Effect Versus a Second Course of Bacillus Calmette-Guerin or Institutional Standard in Patients with Recurrence of Non-muscle-invasive Bladder Cancer Following Induction or Maintenance Bacillus Calmette-Guerin Therapy (HYMN): A Phase III, Open-label, Randomised Controlled Trial. <i>Eur Urol</i>. 75(1): 63-71. doi: 10.1016/j.eururo.2018.09.005 van Valenberg FJP, van der Heijden AG, Lammers RJ, et al. (2018). Intravesical radiofrequency induced hyperthermia enhances mitomycin C accumulation in tumour tissue. <i>International Journal of Hyperthermia</i>. 34(7): 988-93. Witjes JA, Hendricksen K, Gofrit O, et al. (2009). Intravesical hyperthermia and mitomycin-C for carcinoma in situ of the urinary bladder: experience of the European Synergo® working party. <i>World journal of urology</i>. 27(3): 319-24.
Cochrane library	We did not identify any relevant information from this source.
Ongoing research	

Clinicaltrials.gov	<ul style="list-style-type: none"> • Mitomycin C Intravesical Chemotherapy in Conjunction With Synergo® Radiofrequency-Induced Hyperthermia for Treatment of Carcinoma in Situ Non-Muscle Invasive Bladder Cancer Patients Unresponsive to Bacillus Calmette-Guérin, With or Without Papillary Tumors. (RITE-USA). Interventional Clinical Trial, Single Group Assignment, Open Label, Multicentre, NCT03335059. Status: Terminated due to poor recruitment.
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Date of search:	December 2020
Concepts used:	Synergo, radiofrequency-induced thermochemotherapy, chemo-hyperthermia, intravesical microwave hyperthermia, non-muscle-invasive bladder cancer.