

Synergo for non-muscle-invasive bladder cancer

Medtech innovation briefing

Published: 10 September 2020

www.nice.org.uk/guidance/mib226

Summary

- The **technology** described in this briefing is Synergo. Synergo uses radiofrequency-induced thermo-chemotherapeutic effect (RITE) to give chemotherapy (mitomycin C, MMC). It is a treatment for non-muscle-invasive bladder cancer.
- The **innovative aspects** are that it uses radiofrequency radiation (non-ionising microwave radiation) to deliver controlled electromagnetic energy directly to the walls of the bladder. It then infuses chemotherapy into the bladder via a catheter inserted through the urethra.
- The intended **place in therapy** would be as an add-on intervention for treating non-muscle-invasive bladder cancer.
- The **main points from the evidence** summarised in this briefing are from 3 trials and 3 observational studies including a total of 829 people with non-muscle-invasive bladder cancer. Results from 2 trials showed that there was no significant difference in disease-free survival when the group of people who had RITE given by Synergo was compared with the control group. The results of an earlier trial showed significantly higher survival rate in people who had device-assisted intravesical thermo-chemotherapy compared with those who had chemotherapy alone.

- **Key uncertainties** around the evidence are that limited evidence from randomised controlled trials for the technology is available. This is because 2 trials were terminated prematurely. The evidence would benefit from well-controlled comparative studies to capture treatment clinical benefits.
- **Safety issues** identified in [NICE's interventional procedures guidance on intravesical microwave hyperthermia and chemotherapy for non-muscle-invasive bladder cancer](#) include thermal bladder damage. The company noted adverse events including haematuria, pain or heat sensation during treatment and posterior bladder wall thermal reaction.
- The cost of the Synergo System is £9,500 (excluding VAT) per year on lease. As an add-on intervention, the **resource impact** of using Synergo would result in additional costs to standard care. The cost of mitomycin for 40 mg of powder and solvent for intravesical solution vials is £135 ([BNF for mitomycin](#)). The cost of standard care for people with high-risk non-muscle-invasive bladder cancer using a white-light-guided transurethral resection of bladder tumour is £1,500 per person.

The technology

Synergo is a technology known as radiofrequency-induced thermo-chemotherapeutic effect (RITE). It is designed to improve how chemotherapy is given to treat non-muscle-invasive bladder cancer. The treatment is based on controlled radiofrequency radiation (non-ionising microwave radiation) of the bladder tissue, along with instillations of the bladder with chemotherapy (thermo-chemotherapy). Synergo circulates and continuously cools the chemotherapy and flushes the bladder. At the same time a miniature antenna in the catheter emits radiofrequency radiation. The radiofrequency energy is directed at the bladder wall tissue, at a depth which goes past the superficial layer of the blood vessels but does not generate heat past the bladder. This avoids injuries to surrounding organs.

Synergo is an intravesical irrigation system combined with an energy-delivering unit. The system has a radiofrequency generator that delivers radiofrequency energy at 915 MHz (the lower limit of microwave electromagnetism). It also includes a drug circulating unit, and a microprocessor with application-specific software. The drug solution is continuously pumped out of the bladder and re-instilled after being cooled by the device. The user interface consists of a computer, monitor with touch screen, and barcode reader. The software monitors and records treatment parameters in real time during the treatment session. The patient is treated as an outpatient and there is no need for anaesthesia during treatment.

Expert advice suggests that people with high-risk non-muscle-invasive bladder cancer whose disease has not responded to Bacille Calmette-Guérin (BCG) treatment (a form of immunotherapy), or are intolerant to BCG treatment, would be most likely to benefit from this technology.

The company noted adverse events reported include haematuria; dysuria; nocturia; pain or heat sensation during treatment; bladder spasm; urinary frequency or urgency; urethral stricture; posterior bladder wall thermal reaction. No safety issues have been reported.

Innovations

Synergo uses microwaves and infuses chemotherapy into the bladder via a catheter inserted through the urethra. The hyperthermia range is between 41°C and 44°C. This is controlled by 5 thermocouples integrated in a specially designed size 18 French treatment catheter.

Current care pathway

People diagnosed with bladder cancer would have papillary tumours removed in a transurethral resection of bladder tumour (TURBT). The pathology and the person's history indicate if they have low, intermediate or high risk. Treatment for people with a confirmed diagnosis of non-muscle-invasive bladder cancer are guided by risk classification.

Treatment includes using intravesical mitomycin C for people with intermediate-risk non-muscle-invasive bladder cancer. People should have another TURBT as soon as possible, and no later than 6 weeks after the first resection if the first TURBT shows high-risk non-muscle-invasive bladder cancer. People with high-risk non-muscle-invasive bladder cancer are offered intravesical BCG or radical cystectomy.

[NICE's guideline on bladder cancer: diagnosis and management](#) is relevant to this care pathway.

[NICE interventional procedures guidance on intravesical microwave hyperthermia and chemotherapy for non-muscle-invasive bladder cancer](#) recommends this procedure should only be used with special arrangements for clinical governance, consent, and audit or research.

Population, setting and intended user

Synergo is intended to give the intravesical mitomycin C solution with local microwave-induced hyperthermia when treating people with intermediate and high-risk non-muscle-invasive bladder cancer.

The company states that Synergo could be used:

- as first-line treatment for intermediate and high-risk non-muscle-invasive bladder cancer if BCG immunotherapy is not available
- as second-line treatment for intermediate and high-risk non-muscle-invasive bladder cancer patients if previous treatment has failed
- in people with high-risk non-muscle-invasive bladder cancer who cannot have or do not want to have a cystectomy
- in people with intermediate or high-risk non-muscle-invasive bladder cancer who are either intolerant to, or cannot have, BCG immunotherapy.

The system could be set up in outpatient clinics. It is most likely to be used by healthcare professionals such as bladder cancer nurse specialists in secondary and tertiary care in the NHS.

Costs

Technology costs

The Synergo system costs £9,500 (excluding VAT) per year on lease. Synergo applicators (disposable, single use) cost £7,350 per box of 15 units (excluding VAT). This results in a cost of £490 (excluding VAT) per treatment, which is the cost for consumables only.

Costs of standard care

The cost of delivering a single 40-mg dose of intravesical mitomycin C in an operating theatre will be £295 per person. This will include an administration cost of £160 ([National tariff 2020/21](#)) and £135 for the cost of mitomycin 40 mg powder and solvent for intravesical solution vials ([BNF for mitomycin](#)).

The cost of standard care for people with high-risk non-muscle-invasive bladder cancer using a white-light-guided TURBT is £1,500 per person ([National tariff 2020/21](#)). BCG is generally used for high-risk tumours and first-line treatment for carcinoma in situ, and the average total BCG treatment cost was \$1,936 (equivalent to £1,490) per person ([Sievert et al. 2009](#)).

Resource consequences

Synergo has been used in 3 hospitals in the UK.

Costs include provision of the system and staff training. This includes additional refresher training or new user training when needed. Training consists of bespoke professional education on using the technology in a clinical setting. This usually takes 1 day, and a certificate is issued for completed training.

Minimal changes in facilities or infrastructure are needed because chemotherapy is routinely given in hospitals.

If adopted, the technology would be used in addition to chemotherapy. However, it could be resource releasing by improving cancer survival rates and reducing recurrence of bladder cancer.

Regulatory information

The Synergo system is a CE-marked class IIb (or In Vitro Diagnostic Directive Annex II list B, or In Vitro Diagnostic Device Regulation class C).

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Bladder cancer is more common in men than in women, and most cases happen in people aged 60 and over. Bladder cancer is more common in white people than in black or Asian people. Age, sex and race are protected characteristics under the Equality Act. People with cancer are considered to have a disability under the Equality Act.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the [interim process and methods statement](#). This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

Six studies are summarised in this briefing, selected based on the most relevant technology and

outcomes. They include 3 trials and 3 observational studies. There were 829 people with non-muscle-invasive bladder cancer in the selected studies.

The clinical evidence, and its strengths and limitations, is summarised in the overall assessment of the evidence.

Overall assessment of the evidence

Evidence was collected from an open label trial ([Tan et al. 2018](#)). This showed that there was no significant difference in disease-free survival. Also, there was no significant difference in complete response rate of carcinoma in situ between people having radiofrequency-induced thermo-chemotherapeutic effect (RITE) and a control group who had Bacille Calmette-Guérin (BCG) instillation. People included in the study were from 14 sites throughout the UK, but the trial terminated early and did not reach its target number of people. A proportion of people in the control group (up to 23%) also had electromotive drug administration, and no subgroup analysis of this group was included in the study. There was also no difference in recurrent-free survival between the chemohyperthermia and BCG group ([Arends et al. 2016](#)). But the results of an early trial ([Colombo et al. 2011](#)) reported a significantly better survival rate for thermo-chemotherapy than chemotherapy alone.

One comparative observational study compared disease-free survival in people who had treatment with Synergo with those who had electromotive drug administration ([Ragonese et al. 2019](#)). The study is reported as an abstract with no details of methods. Two non-comparative studies reported outcomes including recurrence-free survival ([van Valenberg et al. 2018](#), [Arends et al. 2014](#)). The limitations of the studies are retrospective study design and selection bias.

Two studies ([Arends 2016](#), [Colombo 2011](#)) used Synergo in people who had not had BCG before. There were 4 other studies that used Synergo in people whose disease had not responded to BCG treatment. More evidence is needed from randomised controlled trials for this technology in the NHS, and on benefits and costs. A multicentre prospective randomised trial could address the overall risks and benefits of the Synergo system.

Ragonese et al. (2019) (an abstract)

Study size, design and location

A retrospective single-centre interventional study. The study evaluated 142 people who had non-muscle-invasive bladder cancer and whose disease did not respond to BCG treatment (a form of immunotherapy). They either had chemohyperthermia (n=72, group A) or radical cystectomy

(n=70, group B).

Intervention and comparator

Synergo for chemohyperthermia (device-assisted therapy). Electromotive drug administration of mitomycin C (EMDA-MMC system) was the comparator.

Key outcomes

The median follow up was 59 months (standard deviation 5.3). Overall high-grade disease-free survival (HGDFS) was 51.4% in group A and 84.3% in group B ($p < 0.05$). Within group A, 42 patients had chemohyperthermia using Synergo and 30 patients had electromotive drug administration (EMDA-MMC system). HGDFS was 50% in EMDA and 52.4% in Synergo group ($p < 0.05$).

Strengths and limitations

This is a retrospective comparative study. In group A only 42 patients had chemohyperthermia using Synergo.

Tan et al. (2018)

Study size, design and location

An open-label, two-arm, phase 3 randomised controlled trial done in the UK. The study included 104 patients with recurring intermediate or high-risk non-muscle-invasive bladder cancer who either had RITE (n=48) or BCG instillation and then maintenance therapy.

Intervention and comparator

Synergo was used for RITE, comprised of 2 30-minute cycles, each with 20 mg mitomycin C at 42°C (range 40°C to 44°C, 40 mg mitomycin C in total).

People in the control arm had either 6 consecutive weekly BCG instillations followed by maintenance therapy, or institutional standard of care defined at randomisation.

Key outcomes

All people were followed up for a minimum of 24 months. No significant overall benefit was seen in disease-free survival when comparing RITE with the control group (HR=1.33, 95% confidence interval [CI] 0.84 to 2.10, $p=0.23$). There was no significant difference in the complete response

rate of carcinoma in situ at 3 months between RITE and the control group (odds ratio 0.43, 95% CI 0.18 to 1.28, $p=0.15$). There were 5 people in RITE group who did not complete 6 or more instillations because of adverse events. These included skin rash, urinary urgency and nocturia. There were 42 patients in the RITE group who experienced one or more adverse events, and there was no difference seen in adverse events between each treatment group.

Strengths and limitations

The trial stopped early at interim analysis stage and did not reach its target number of people. People having treatment in the control group also had electromotive drug administration (23%).

van Valenberg et al. (2018)

Study size, design and location

A retrospective study including 150 people with histologically proven carcinoma in situ of non-muscle invasive bladder cancer. People were treated with radiofrequency-induced chemohyperthermia using mitomycin C (MMC). People included in the study were from 6 international centres including 2 units in the UK.

Intervention and comparator

Synergo was used for radiofrequency-induced chemohyperthermia. Typically, MMC was used in a dose of 40 mg/50 ml with a total of 80 mg MMC in an hour. People were treated weekly for 4 weeks to 8 weeks depending on the planned induction schedule. This was followed by maintenance instillations (one instillation every 4 weeks to 8 weeks). The study had no comparator.

Key outcomes

The complete response rate after 6 months was 66.2%. For people whose disease did not respond to BCG, the complete response was 46.0%. This significantly differed from other people who had BCG treatment and people who had not had treatment before (71.7% and 83.0% respectively, $p<0.001$). In patients with a complete response, the subsequent recurrence rate and recurrent-free survival after 2 years of follow up were 18.8% and 74.5%. The rates did not differ significantly regardless of treatment history. In 13.3% of people, progression to muscle-invasive bladder cancer with or without lymph node or distant metastasis at final follow up was seen. This consisted of 16.0% in people whose disease did not respond to BCG treatment, 13.0% in others who had BCG treatment, and 10.6% in people who had not had treatment before ($p=0.74$). There were 13.4% of people who stopped induction because of adverse events, and 17.8% of people who stopped maintenance RF-CHT instillations because of adverse events.

Strengths and limitations

The study is a retrospective review of people who had treatment with RF-CHT. The authors noted that the collected data were very heterogeneous because of randomly missing values and different standards of treatment and follow up between the participating centres. Study population was selected based on pathology or combined cystoscopy and cytology availability. This may result in potential bias towards higher tumour rates or non-response in the study.

Arends et al. (2016)

Study size, design and location

A multicentre prospective randomised controlled trial of 190 patients with intermediate- and high-risk non-muscle invasive bladder cancer from 6 countries.

Intervention and comparator

Synergo was used for intravesical chemohyperthermia with MMC (n=92). The comparator was BCG immunotherapy (n=98).

Key outcomes

All people were followed up at least 24 months after randomisation. There was no significant difference in recurrent-free survival when comparing chemohyperthermia with the BCG group in people with no carcinoma in situ (intention-to-treat analysis, 78.1% compared with 64.8%, p=0.08). The complete response rate of people with carcinoma in situ at 3 months was 88.9% in the chemohyperthermia group compared with 85.7% in the BCG group. No statistically significant difference was seen (p=1).

In the chemohyperthermia group, 0 patients (0.0%) showed progression to muscle-invasive disease, compared with 1 (1.4%) in the BCG group. The most common adverse events during chemohyperthermia treatment sessions were bladder spasms (n=206, 14.4%) and bladder pain (n=202, 14.1%). The most prevalent adverse events after treatment were dysuria (n=167, 11.7%), nocturia (n=147, 10.3%) and urinary frequency (n=141, 9.9%).

Strengths and limitations

The authors noted that the trial closed prematurely and so is underpowered. This is a randomised trial but blinding of treatment for patients and physicians was impossible, which may have resulted in bias. Survival outcomes were not reported in people with carcinoma in situ.

Arends et al. (2014)

Study size, design and location

A retrospective observational study of 160 people who had treatment with chemohyperthermia for non-muscle invasive bladder cancer.

Intervention and comparator

The Synergo system simultaneously gave local microwave-induced hyperthermia and intravesical chemotherapy. There was no comparator.

Key outcomes

Of those included in the study, 20 people (13%) had treatment with Epirubicin and 129 (81%) had previous BCG treatment. Median follow up was 75.6 months. The 1- and 2-year recurrence-free survival was 60% and 47%, respectively. Muscle-invasive progression was seen in 7 patients (4.3%). Adverse events were mild, transient and mostly limited to the genitourinary tract.

Strengths and limitations

The retrospective study design is subject to selection bias and information bias. There was no comparator.

Colombo et al. (2011 and 2003)

Study size, design and location

Two publications of 1 study. The most recent publication was a long-term outcome of a multi-centre randomised controlled trial of 83 people with intermediate- or high-risk non-muscle invasive bladder cancer, after complete transurethral resection.

Intervention and comparator

The Synergo system gave intravesical thermo-chemotherapy. The comparator was intravesical chemotherapy alone.

Key outcomes

All 75 people who completed the study (35 of 42 in the treatment arm, 40 of 41 in the control arm) were followed up for a minimum of 2 years. The median follow up for people who were tumour free

was 91 months. The 10-year disease-free survival rate for thermo-chemotherapy and chemotherapy alone was 53% and 15%, respectively ($p < 0.001$). An intention-to-treat analysis also showed a significant higher survival using thermo-chemotherapy compared with the control treatment. Bladder preservation rates for thermo-chemotherapy and chemotherapy alone were 86% and 79%, respectively (p value was not reported).

Strengths and limitations

An analysis of long-term follow up was done of people who had intravesical thermo-chemotherapy. The risk of bias cannot be assessed based on the information in the abstract (Colombo et al. 2011).

Sustainability

The company claims that the technology could support sustainability by reducing the need for cystectomy in some patients and reducing the need for in-hospital theatre resources. This is because Synergo is used in an outpatient setting. There is no published evidence to support these claims.

Recent and ongoing studies

Severity of overactive bladder symptoms in patients after Synergo treatment (OACSYNERGO). ClinicalTrials.gov Identifier: NCT01955408. Status: recruitment completed. No interim results published. Indication: overactive bladder, bladder cancer. Devices: Synergo. Last update on 6 October 2017.

Expert comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

Three experts were familiar with or had used this technology before.

Level of innovation

All expert commentators considered the technology to be innovative compared with standard of care. One expert thought that this would be an alternative treatment option particularly for people whose disease did not respond to Bacille Calmette-Guérin (BCG) treatment. The experts described

other technologies to assist chemotherapy such as the COMBAT BRS system (offering passive hyperthermia) and electromotive drug administration (EMDA). They noted that these technologies use different methods of heating or improving drug delivery but data on the effectiveness of these technologies remain unclear.

Potential patient impact

The main benefit identified by 3 experts is the potential of less invasive treatment for non-muscle-invasive bladder cancer in people whose cancer does not respond to, or who cannot tolerate, BCG. All experts agreed that these people were most likely to benefit from the technology. The experts noted that patients may need cystectomy when BCG has not worked, which is major surgery. Synergo could avoid a more invasive procedure and improve overall treatment experience. However, Synergo would not be suitable for all people whose disease has not responded to BCG.

Potential system impact

The experts generally agreed that the technology could reduce the number of cystectomies and reduce the need for hospital stay. Synergo could move treatment from inpatient to outpatient clinics. The cost impact of using Synergo is uncertain. One expert explained that Synergo used as first-line treatment was likely to be more expensive than standard care such as mitomycin C, for people with intermediate-risk non-muscle-invasive bladder cancer or BCG for high-risk non-muscle-invasive bladder cancer. But, Synergo may be cost saving compared with standard care in some people when BCG has not worked. Another expert suggested that Synergo could be more expensive if there was no improvement in disease-free survival. It was likely to be cost neutral or even cost saving if there was a reduced recurrence and progression. One expert noted that space would be needed to store the Synergo device. All experts thought that healthcare professionals would need training to give the treatment.

General comments

The experts thought that Synergo would be used as an alternative treatment to BCG in people with high-risk non-muscle-invasive bladder cancer. Two experts were not aware of any safety issues, but 1 commentator suggested the possibility of local toxicity using Synergo. The main barrier to adoption identified by 2 commentators was the technology cost.

Expert commentators

The following clinicians contributed to this briefing:

- Benjamin Ayres, consultant urological surgeon, St Georges University Hospital NHS Foundation Trust. Has received funding to attend conferences and lecture fees for teaching. Was also involved in a trial of pembrolizumab in high-risk non-muscle-invasive bladder cancer as chief investigator for the UK.
- James Catto, professor in urological surgery, University of Sheffield, Sheffield Teaching Hospitals NHS Trust. Involved in a trial of using erdafitinib in people whose disease did not respond to Bacille Calmette-Guérin (BCG) treatment and a clinical trial comparing BCG with radical cystectomy in people who had not had BCG treatment.
- Sanjeev Madaan, consultant urological surgeon and lead cancer clinician, Darent Valley Hospital. Did not declare any interests.

Development of this briefing

This briefing was developed by NICE. The [interim process and methods statement](#) sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

ISBN: 978-1-4731-3871-1