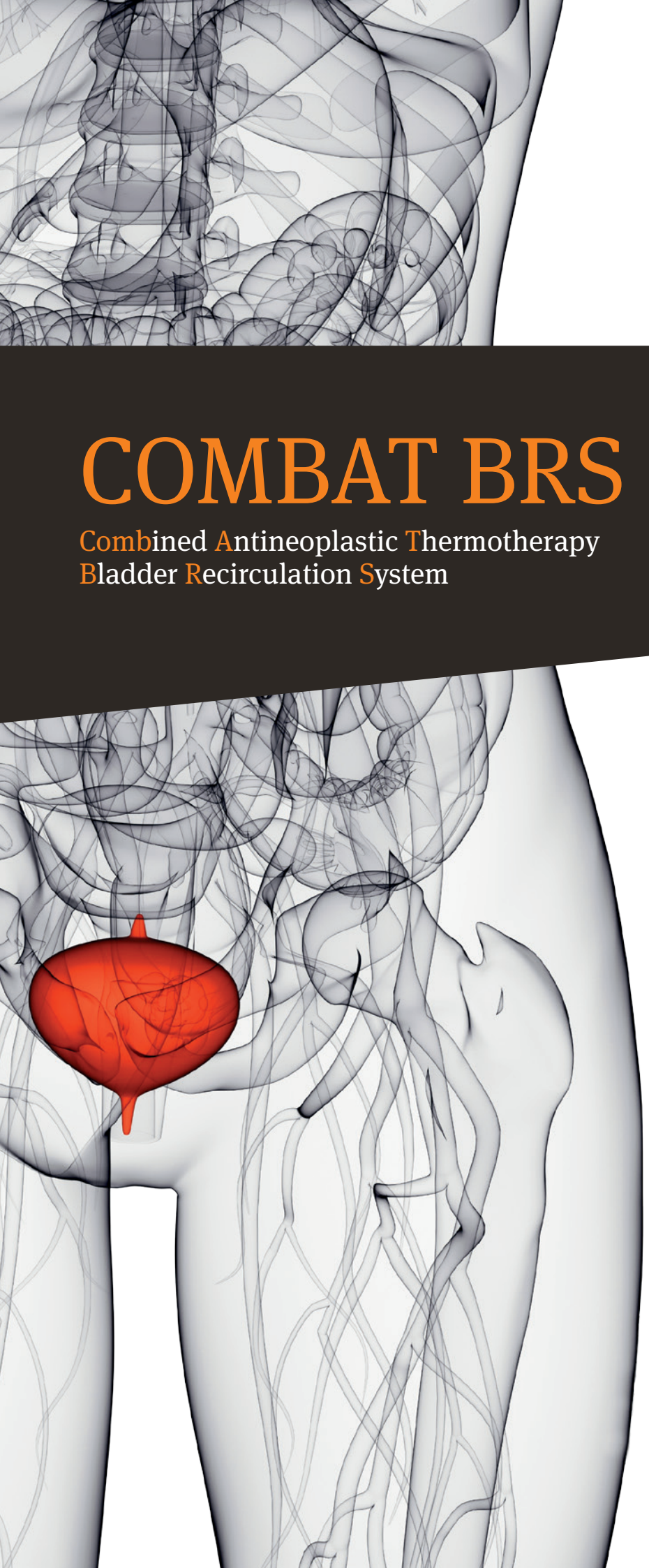
COMBAT MEDICAL

COMBAT BRS

Combined Antineoplastic Thermotherapy
Bladder Recirculation System



www.combat-medical.com

"Our mission is to drive change in order to optimise the efficacy of the conventional chemotherapy instillation, reducing recurrence and progression rates in Non-Muscle Invasive Bladder Cancer in a cost effective way that fits alongside current practices."
Edward Bruce-White, Combat Medical CEO

Combat Medical helping to combat bladder cancer through thermotherapy

Efficacy

The Combat BRS system is an innovative and patented recirculation system for the delivery of Hyperthermic Intra-VEsical Chemotherapy (HIVEC™). Hyperthermia has been shown to significantly increase the effectiveness of Mitomycin C (MMC) in Non-Muscle Invasive Bladder Cancer (NMIBC)[1-2]. The Combat BRS system has been in clinical use since 2011, it is safe for patients and healthcare professionals, has similar patient tolerability to MMC at room temperature and is easy to use and adopt[3].

Safety

The Combat BRS system uses an external dry conductive recirculation system. Our innovative and patented aluminium heat exchanger ensures efficient heat transfer and accurate temperature control within ±1°C of the set temperature, whilst providing homogeneous drug distribution throughout the bladder. Patient safety and comfort are paramount and the Combat BRS system has a range of safety features including over temperature and high pressure audio and visual alarms and system auto cut off. At the end of a treatment the BRS system also enables the removal of the MMC from the patient for safe disposal.

Synergy

The Combat BRS system harnesses accurate and effective heat control and the proven synergistic effects of chemo-hyperthermia to target NMIBC. The mutually enhancing effects of chemotherapy drugs and hyperthermia are well documented for their cytotoxic effects and are widely used in treating several types of cancer including bladder cancer[4]. Cancer cells become more permeable and are increasingly affected on many levels because of their inability to dissipate heat while the heat enhances the body's natural immune responses[5-7]. See synergistic effects of hyperthermia.

Simplicity

The Combat BRS system is portable, robust and easy to use. Simple to integrate into current treatment practice it requires minimal set up, no continuous monitoring and therefore minimal additional resources either physically, logistically or financially. Both the BRS system and disposable sets are affordable and through improving patient outcomes, the overall treatment cost can be reduced.

"I now have over 400 uses of the Combat BRS system and in my experience the system only takes 5 minutes more to set up compared to normal installations of MMC or BCG. During the 60 minute treatment I am able to continue my normal clinical routine because the system doesn't require continuous monitoring. I also particularly like that you are able to safely remove and dispose of the drug after the treatment."
Alfonso Piñeiro, Urology Nurse, Hospital Comarcal de Monforte, Galicia (Spain)

COMBined Antineoplastic Thermotherapy Bladder Recirculation System

COMBAT BRS System

Touch Screen
Simple user interface. Automated setup checking procedure. Continuous monitoring and graphical temperature readings.

USB Port
Data can be stored to USB drive in csv or txt format.

Pressure Sensor and Tube Detection
Ensures correct setup and use of disposable set. Pressure sensor detects overpressure situations with automated cut off to ensure patient safety and comfort.

Peristaltic Pump
Maintains accurate and continuous recirculation and flow rates.

Safety Alarms
Audible and visible alarms for high and low temperature and overpressure.

Heat Exchanger
Easy to insert our innovative aluminium foil heat exchanger provides effective and accurate heat control and transfer. Low priming volume, ensuring minimal dilution of chemotherapy agent.

Temperature Probe Port
In line fluid temperature probe for continuous and accurate monitoring throughout treatment.

Catheter
Flexible soft 16F 3-way catheter with coude tip to help ease of insertion.

Synergistic effects of hyperthermia

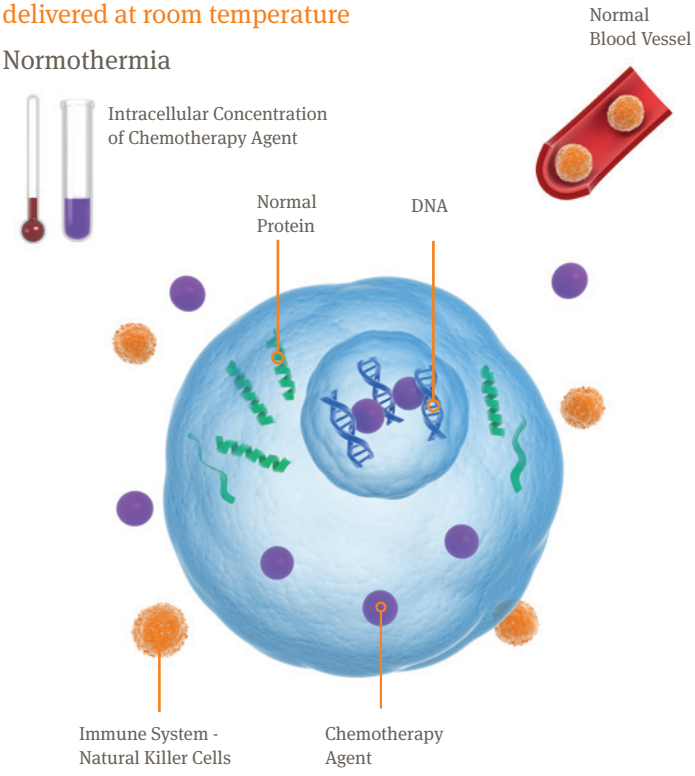
Clinical hyperthermia is defined as the therapeutic use of temperature between 40°C to 44°C [5]. The introduction of thermal energy at these temperatures into cancer tumours affects the cancer cells more because of their inability to manage the heat as well as good cells [6]. **Mitomycin C (MMC)** an alkylating chemotherapy agent is stable at temperatures up to 50°C, but importantly it has shown to be **1.4 times more active at 43°C** [8]. Hyperthermia **inhibits the formation of new blood vessels** (angiogenesis) by the tumour mass [9]. At 43°C the **cytotoxicity increases by 10 times**, importantly without any increase in the toxicity to the patient [8]. At elevated temperatures the lipid-protein cellular membrane bilayer will become more permeable, due to the unfolding (denaturing) of the cellular membrane and cytosolic proteins, resulting in **higher intracellular concentration of the chemotherapy agent**. Direct affects on the DNA include; **strand breaking, impaired transcription** (production of messenger RNA for protein synthesis), **reducing replication and cell division** [5]. Thermotherapy has profound effects on the immune system resulting in **increased activation of more natural killer cells** (NKC) that target heat stressed cancer cells as they signal heat shock proteins on the cancer cell surface [7]. The consequence of all these actions on the cancer cells is that they actively participate in their own demise through the natural process of **apoptosis.**

Chemo-hyperthermia multifactorial modes of action create a strong synergistic effect, ensuring cancer tumours and cells are specifically targeted. **Therefore hyperthermia substantially increases the effectiveness of chemotherapy compared to instillation at room temperature.** The Combat BRS has the potential to be the first system to allow the delivery of thermotherapy within the tight parameters necessary to optimise the delivery of chemo-hyperthermia without compromising patient safety or increasing resources required.

Based on the strong body of evidence cited above to achieve the best results with the Combat BRS system in adjuvant treatment it should be used at a temperature setting of 43°C for 1 hour using 40 mg dose of Mitomycin C.

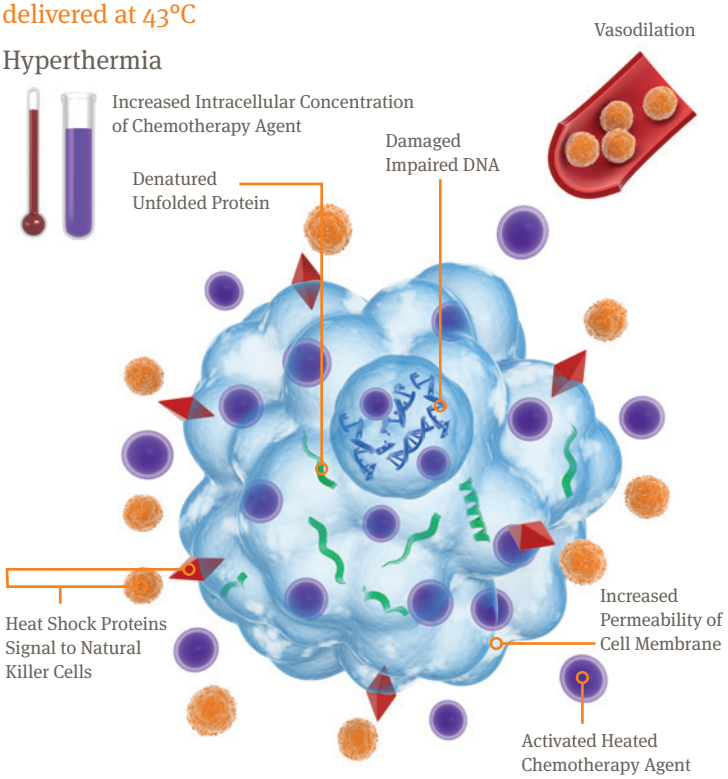
Cancer cell with Mitomycin C
delivered at room temperature

Normothermia



Cancer cell with Mitomycin C
delivered at 43°C

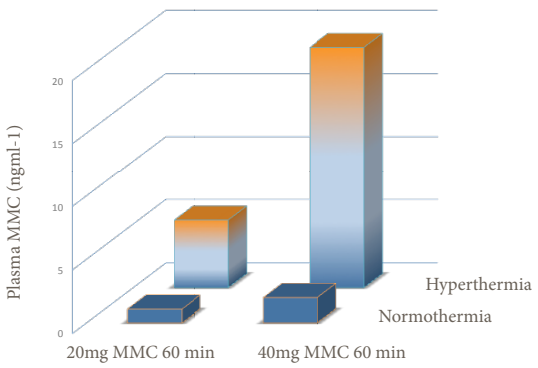
Hyperthermia



Effect of hyperthermia on alkylating agents
Teicher et al (1981) demonstrated activation rates
1.3 – 1.4 times higher at 41°C, 42°C, and 43°C compared to 37°C [8].

Mitomycin C remains stable at higher temperatures [10]						
Temp.	Solvent	Parameter	Storage Period			
			0 hr*	1 hr	3 hr	6 hr
37°C	5 ml water	Content %	100.0	94.9	92.8	91.6
	5 ml of saline	Content %	100.0	94.2	90.6	90.4
50°C	5 ml water	Content %	100.0	91.0	88.0	87.3
	5 ml of saline	Content %	100.0	91.3	90.2	89.7
*0 hr : immediately after reconstitution.						

Mitomycin C (MMC) plus hyperthermia achieves greater plasma concentration than MMC alone [11], but is well below 400 ng/ml associated with systemic side effects like myelosuppression [12].



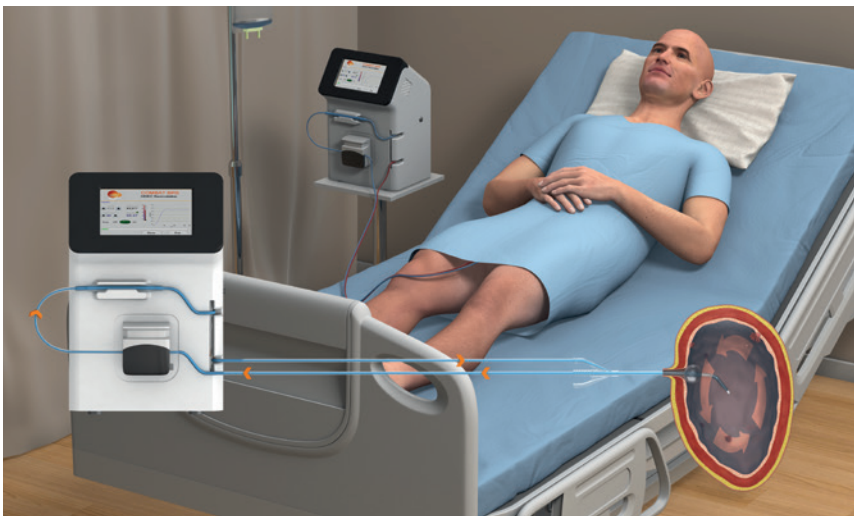
HIVEC I & II trials are already underway

Hyperthermic Intra-VEsical Chemotherapy

HIVEC I

HIVEC II

Prospective, Randomized International Multicentre Clinical Trials in 494 NMIBC Intermediate Risk Patients.
For more information please contact Combat Medical
www.combat-medical.com



Combat Medical leading the current investigation in thermotherapy device assisted therapies for NMIBC

Combat Medical is committed over the next 5 years to creating its own clinical bibliography of fact based evidence supporting the BRS system in it's fight against bladder cancer. By harnessing the powers of chemo-hyperthermia in an innovative and unique way we hope to prove beyond doubt that the BRS system in combination with Mitomycin C (40mg) can significantly reduce recurrence and progression rates in NMIBC bladder cancer.

Combat Medical is equally committed to improving outcomes without healthcare providers having to significantly alter their treatment model or adding additional resources, in fact we believe over time we will be able to reduce the overall treatment cost due to our streamlined approach and through the reduction in recurrence and progression rates.

We have demonstrated this potential in phase I trials and through its clinical use over the last 3 years. During this time Combat BRS has shown it is easy to use and is well tolerated by the patient with similar side effects to standard MMC instillations, but importantly with little impact in terms of time and effort for the healthcare professional in delivering Combat's new HIVEC™ treatment.

Bibliography:

1. Lammers, R. J. M. 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. 60, 81–93 (2011).
2. Colombo, R., Salonia, A., Leib, Z., Pavone-Macaluso, M. & Engelstein, D. 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 Int. 107, 912–8 (2011).
3. Sousa-Escando, A., Piñerio, A. & Uribarri, C. MP–04.22: Neoadjuvant Chemohyperthermia for the Treatment of High Risk Non Muscle Invasive Bladder Cancer (NMIBC): A Phase I Study. Urology 78, Supp 3A, S57 (2011).
4. Van der Zee, J. Heating the patient: a promising approach? Ann. Oncol. 13, 1173–84 (2002).
5. Dahl, O., Dalene, R., Schem, B. C. & Mella, O. Status of clinical hyperthermia. Acta Oncol. 38, 863–73 (1999).
6. Song, C. W. Effect of Local Hyperthermia on Blood Flow and Microenvironment : A Review. Cancer Res. 44, 4721s – 4730s (1984).
7. Fuse, T., Yoon, K. , Kato, T. & Yamada, K. Heat-induced apoptosis in human glioblastoma cell line A172. Neurosurgery 42, 843–9 (1998).
8. Teicher, B. A., Kowal, C. D., Kennedy, K. A. & Sartorelli, A. C. Enhancement by Hyperthermia of the in Vitro Cytotoxicity of Mitomycin C toward Hypoxic Tumor Cells. Cancer Res. 41, 1096–1099 (1981).
9. Fajardo, L., Prionas, S., Kowalski, J. & Kwan, H. Hyperthermia inhibits angiogenesis. Radiat Res 114, 297–306 (1988).
10. Adapted from Company Data Kyowa *http://www.mitomycin.net/professionals/about03.html*
11. Paroni, R. et al. 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, 273–8 (2001).
12. Crooke, S. T., Henderson, M., Samson, M. & Baker, L. H. Phase I study of oral mitomycin C. Cancer Treat. Rep. 60, 1633–6 (1976).

Technical Specifications:

Physical characteristics
COMBAT BRS System

Equipment external dimensions:
Height 400 mm
Width 250 mm
Depth 255 mm

Equipment weight:
BRS system 9.6 Kg plus portable stand

Safety alarms:
High & Low temperature alarms
High pressure alarm
Auto safety cut off
End of treatment alarm & auto stop

Electrical risk classification:
Class II, Type B

Fluid ingress protection:
IPX2

Function mode:
Continuous delivery at set temperature between 40 – 44°C ± 1°C

Certification:
UL 60601-1; IEC 60601-1; IEC 60601-2; EN 55011; CAN/CSA-C22.2; CE 0120

For more information contact:
Combat Medical Ltd.
Lamer House Office, Lamer Lane, Wheathampstead, Herts AL4 8RL
Tel/Fax: +44 1582 83 44 66 Email: contact@combat-medical.com
Visit: www.combat-medical.com

COMBAT MEDICAL