ALBA

precision hyperthermia

ON4000D

RADIATIVE LOCOREGIONAL HYPERTHERMIA

HEAD AND NECK TUMORS

BREAST TUMORS

MELANOMA

SOFT TISSUE SARCOMA

CHEST WALL RECURRENCES

CUTANEOUS LYMPHOMA

MEDLOGIX
medical solutions

CONTENT

Rev.5 - 2021

HYPERTHERMIA RADIO-BIOLOGICAL RATIONALE

Hyperthermia (HT), heating tumors in the range 41-43°C, is a powerful radio and chemosensitizer. The effectiveness of HT as well as its safety, in combination with radiotherapy and chemotherapy, has already been proven in phase III clinical trials [1,3], particularly in patients with very large or very advanced stages of cancer and recurrent tumors. HT enhances the effect of radiotherapy on the tumor, without additional toxicity for nearby healthy tissue, by multiple synergistic mechanisms.

1. INHIBITION OF DNA DAMAGE REPAIR

HT enhances the effectiveness of radiotherapy by inhibiting the repair of DNA damage. [2,4,5,6]

2. REOXYGENATION

HT increases tissue perfusion resulting in reoxygenation, thereby reducing hypoxia and increasing radiosensitivity. [2,6,7]

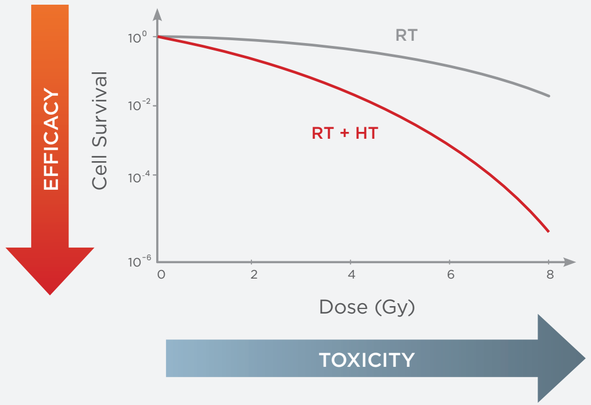
With regard to chemotherapy, hyperthermia targets its action within the heated tumor region without aggravating systemic toxicity. [8]

Local hyperthermia has also been shown to be capable of inducing systemic anti-tumor immune responses. [1]

3. DIRECT CELL KILLING

HT selectively kills radioresistant hypoxic tumor cells. [2]

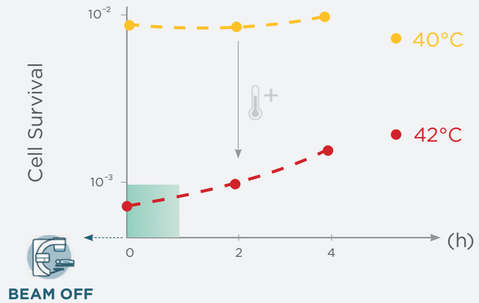
HYPERTHERMIA AS A CLINICAL DOSE-FRACTIONATION OPTIMIZER



LQ – MODEL TEMPERATURE DEPENDENT α & β

Clinical data show a significant hyperthermia-induced reduction of the α/β ratio, a.o. for recurrent breast cancer, head and neck cancer. [6,9]
This can be used to effectively optimize clinical dose-fractionation schedules.
The hyperthermic enhancement of the α and β parameters can vary per tumor type and is strongly temperature-dependent.

THERMORADIOTHERAPY DOSE ESCALATION INCREASES WITH: HIGH TEMPERATURE & SHORT TIME INTERVAL



TIME INTERVAL: from RT beam off to HT > 41°C

BOOST UP TO 10/20 Gy OR MORE WITH NO ADDITIONAL TOXICITY

HIGHER THERMO-DOSE
Higher temperature for reoxygenation and more direct cell killing for an effective thermodose escalation.

SHORT TIME INTERVAL
Achievable as the units allow for a short preparation time and ultrafast and precise Hyperthermia treatment delivery.

ALBA ON 4000D PLATFORM

The ALBA ON 4000D is a radiative hyperthermia system working at a fixed frequency of 434MHz. The unit is equipped with radiative technology curved high focused microstrip antennas with an integrated water bolus to safely and effectively heat targets, in the range of 41-43°C for 60 minutes, as required by the ESHO (European Society for Hyperthermic Oncology) guidelines. [11]

PRECISION

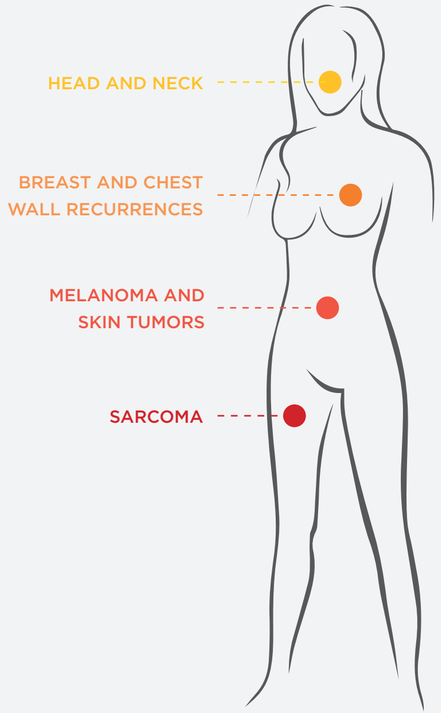
- Automatic focusing at tumor coordinates and optimal matching with heated tissue.

HIGH THERMAL DOSE

- Superior SAR homogeneity and maximum power deposition in the target result in a high dose escalation.

FAST HYPERTHERMIA TREATMENT DELIVERY

- Short preparation time of the patient set-up and dedicated tools for applicator positioning as well as the collimation of the center axis of the beam of the applicator with the center of the GTV/PTV.
- Faster temperature rise.

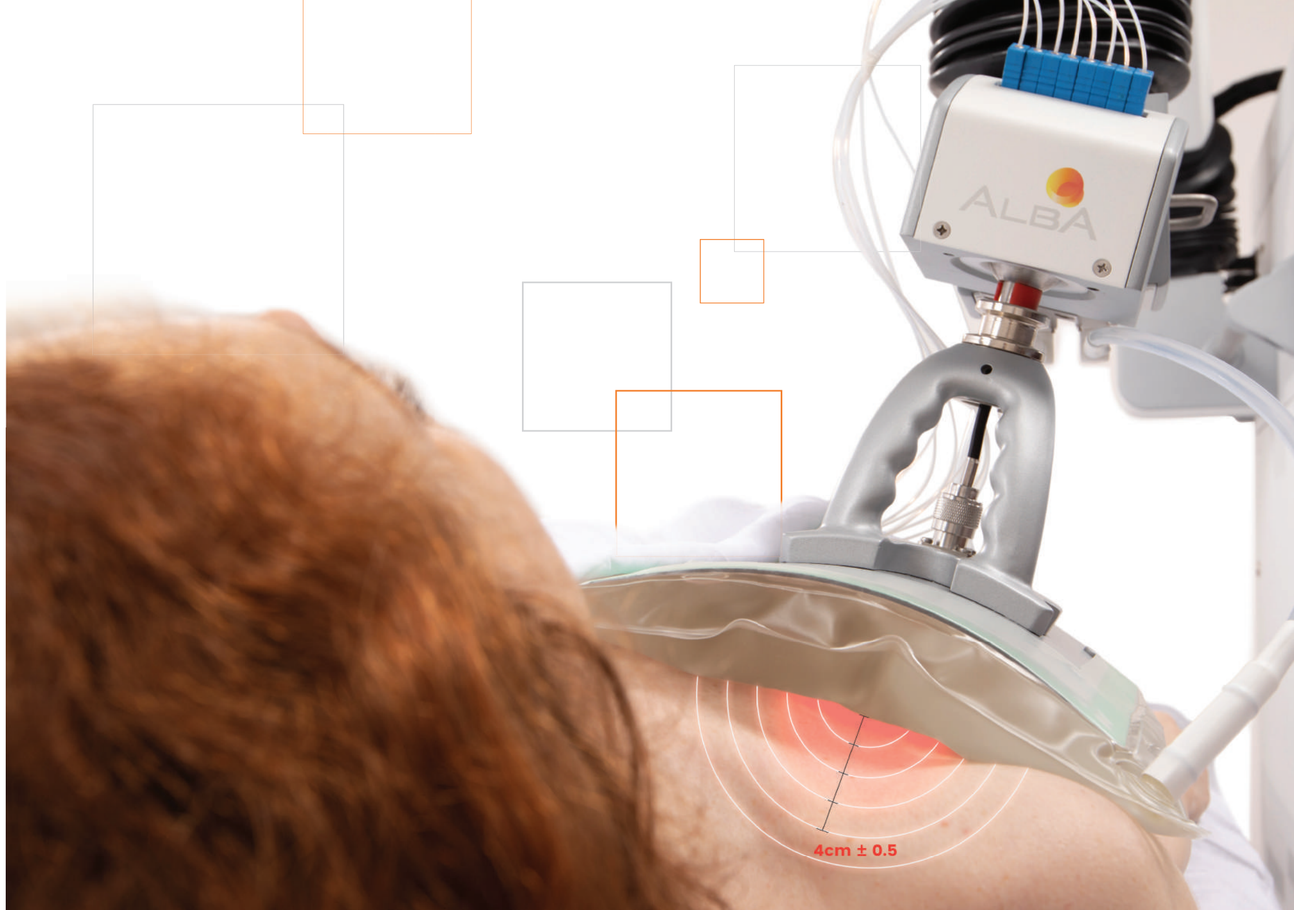


HIGH PATIENT COMFORT

- The curvature of the applicators together with the soft integrated water bolus allows an optimal adaptation to the shape of the anatomical sites to be treated, resulting in high patient comfort.

HIGH FOCUSED MOLDED BEAM ANTENNA

ALBA ON 4000D is provided with 4 different sized applicators based on CCMA (Contact Curved Microstrip Antenna) technology designed to properly heat at depth curved human anatomy with a wide range of target area (up to 609 cm^2). The integrated conformal water boluses are especially designed for different patient specific geometries, adaptive RF matching and surface cooling.



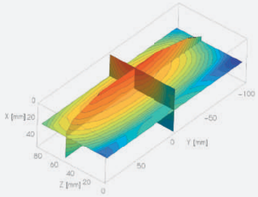
HEATING AT DEPTH

The curved surface with a fixed radius of curvature and the working frequency of 434 MHz allow to effectively heat both superficial and semi-deep lesions up to about **4 ± 0.5 cm** of depth as demonstrated both in phantoms [12,13] and in patients. [14,15]

FOCUS HOMOGENEITY

ALBA ON 4000D is ideal for delivering the superior therapeutic thermal dose due to the high SAR distribution homogeneity avoiding the occurrence of cold/hot spots.

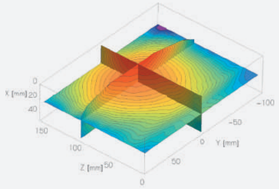
ALFA



Ideal for:

- Radiative area: 140 cm²
- Head and Neck lesions
- Axillary tumors
- Target with diameter < 4 cm

BETA



Ideal for:

- Radiative area: 225 cm²
- Supraclavicular tumors
- Breast tumors
- Target with diameter < 8 cm

Releasable holder for optimal patient skin surface adhesion. Bendable for maximum antenna applicator stability according to morphological structure of patient undergoing treatment.

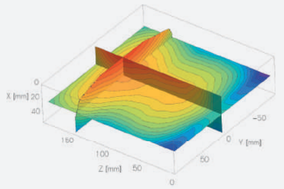
FAST TARGET HEATING

Fast temperature rise up to 41°C in less than 6 minutes (twice faster than the minimum requirement in the ESHO official guidelines [11]: temperature rise of at least 6°C in 6 minutes at 1 cm depth).

INCLUSION CRITERIA AND PRODUCTIVITY

An effective heating depth of up to **4 ± 0.5** cm allows the treatment of both superficial and many semi-deep lesions, increasing the ALBA ON 4000D clinical indications. The broad inclusion criteria enhance the system's productivity.

GAMMA

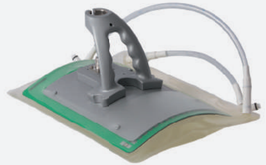


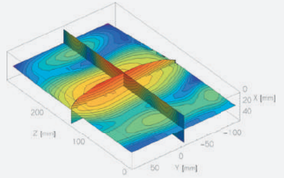
Ideal for:

- Radiative area: 400 cm²
- Breast tumors
- Sarcoma
- Target with diameter < 12 cm

Releasable holder for optimal patient skin surface adhesion. Bendable for maximum antenna applicator stability according to morphological structure of patient undergoing treatment.

DELTA





Ideal for:

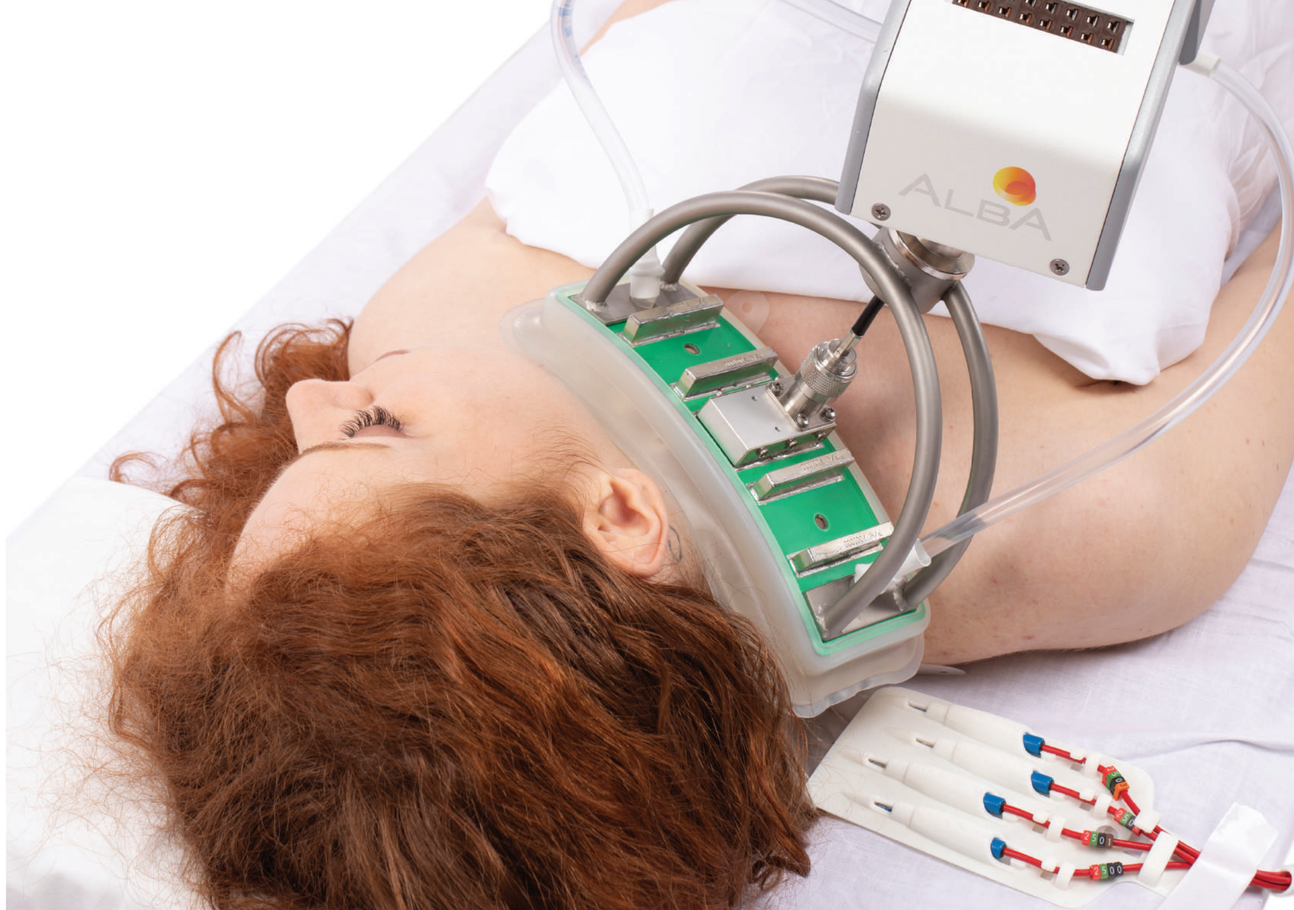
- Radiative area: 609 cm²
- Large chest wall recurrences
- Melanoma
- Target with diameter < 20 cm

Releasable holder for optimal patient skin surface adhesion. Bendable for maximum antenna applicator stability according to morphological structure of patient undergoing treatment.

ALBA TC MATRIX - 64 CH THERMOMETRY

Advanced dosimetry system for temperature measurement consisting in a high accuracy multichannel thermometer and an ultra-thin sheet integrated with up to 64 temperature sensors. [16]
Extensively sampled temperature data is displayed in real time via a thermal map overlapping the GTV/PTV.

**ALBA TC MATRIX - 64 CH CE marking in progress.*



- Extensive *in-vivo* dosimetry and real-time display of measured temperature at their real location for an effective and top-quality treatment.
- Automatic/Semi-automatic temperature sensor assignment with respect to the GTV/PTV for a more reliable GTV-PTV temperature dosimetry.
- Number of sensors 8 times higher than minimum ESHO recommendations to avoid under-dosage due to undetected cold/hot spots. [11,17]

MTU-64 CH MULTIPLE THERMOMETRIC UNIT

64-channel digital thermometer for real time target and normal tissue temperature dosimetry allowing simultaneous detection of the temperature in 64 points at known coordinates. The ALBA ON 4000D embedded multichannel digital thermometer guarantees very fast detection of the temperature sensors at an accuracy of +/- 0.2°C.

ALBA T-MATRICES

Devices designed to be used with ALBA MTU (Multichannel Thermometric Unit) and ALFA, BETA and GAMMA ALBA ON 4000D microstrip Antennas. T-Matrices allow a multi-point surface temperature detection up to 28 tips (ALFA) and 56 tips (BETA-GAMMA) for a real time EFS (Effective Field Size) dosimetry with temperature recognition at well-known coordinates thanks to ALBA optical guide solutions.

- **Enhances the quality and effectiveness of treatment accelerating its delivery.** [18]
- **Significant workflow optimization by a reduction of patient preparation and patient release times.** [18]

ALFA T-MATRIX UP TO 28 T-SENSORS EMBEDDED

Silicone matrix with spaced holes for probe insertion for ALFA Antenna.

BETA/GAMMA T-MATRIX UP TO 56 T-SENSORS EMBEDDED

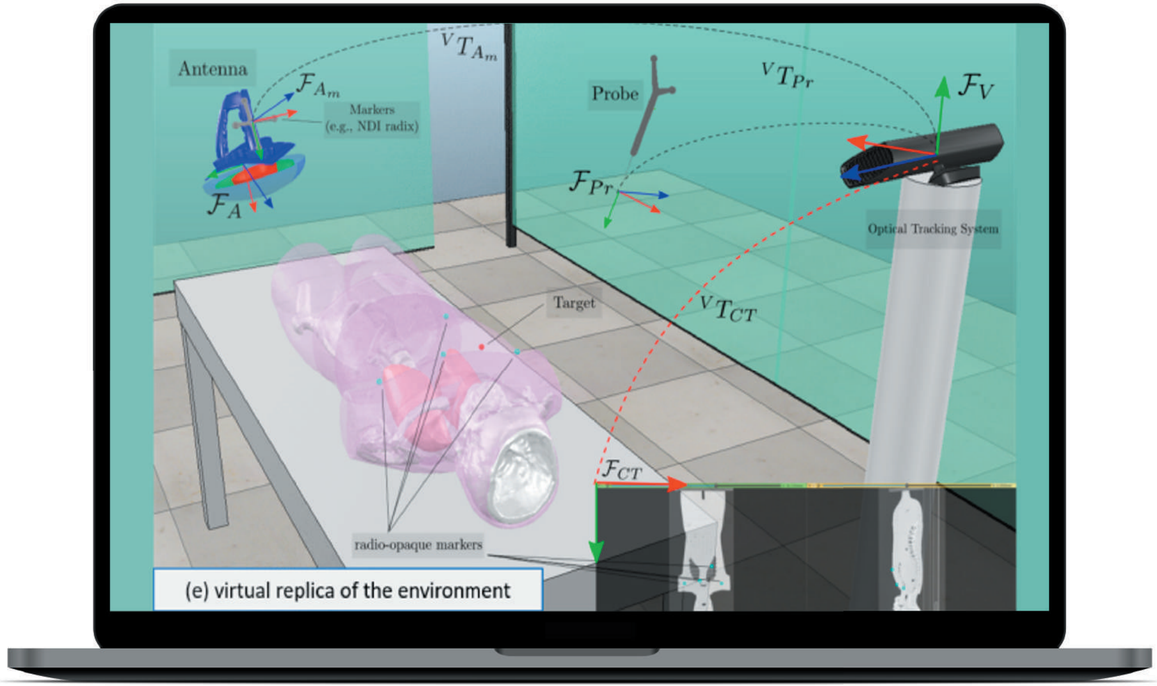
Silicone matrix with spaced holes for probe insertion for BETA, GAMMA and DELTA microstrip antennas.

ALBA OPTIX – OPTICAL GUIDED POSITIONING SYSTEM

The new optical guided positioning system aims to simplify and speed up the positioning procedure of the ALBA ON 4000D applicators and T-Matrices before performing the treatment, ensuring its accuracy and repeatability in subsequent treatment sessions. [19,20]

**ALBA OPTIX CE marking in progress.*

The system allows the operator to view and track the position of the applicator and matrix in real time with respect to the 3D reconstruction of patient DICOM CT image.



SYSTEM COMPONENTS

POLARIS VEGA OPTICAL SYSTEM

POLARIS VEGA optical system based on infrared technology produced by NDI and widely used in the medical field to calculate the 3D positions of markers attached to tools.

PASSIVE 4 MARKER PEN PROBE

Optical tracker pen for ALBA Matrices and GTV/PTV spatial registration.

FINGER MOUSE

Wireless finger mouse to move the cursor to the second monitor.

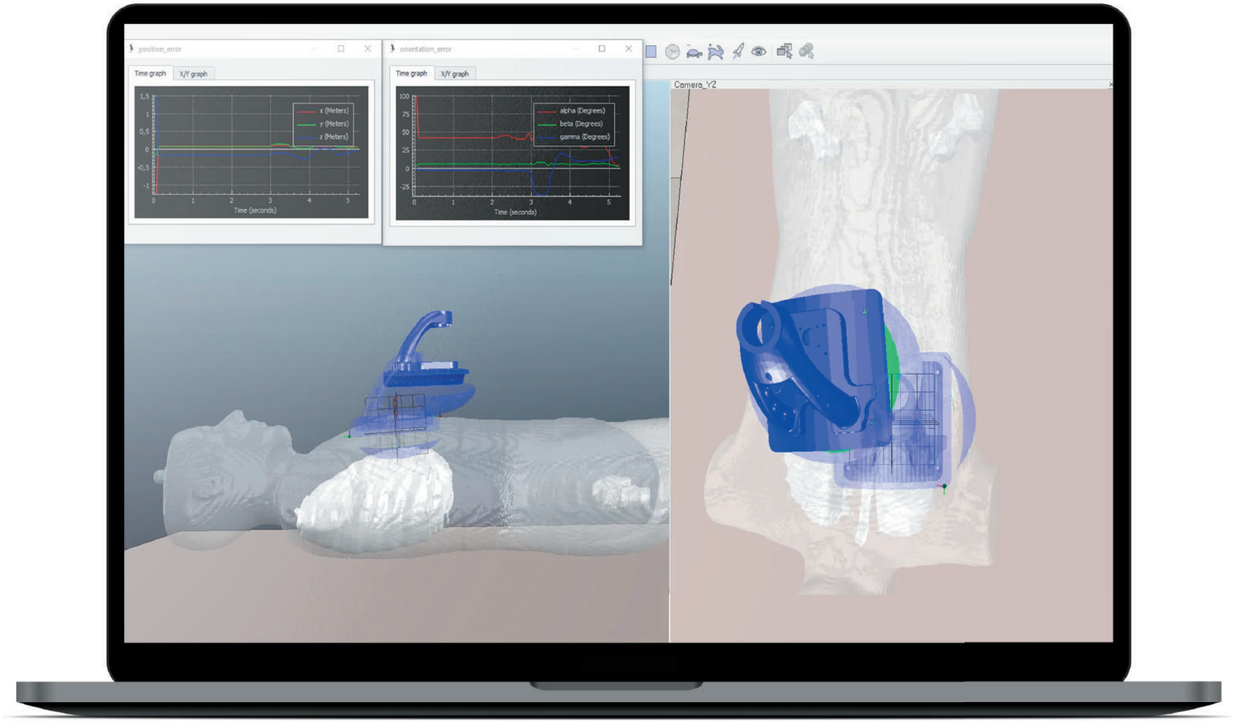
BETA APPLICATOR WITH PASSIVE MARKER

Rigid body passive markers mounted on antenna holder.

DEDICATED SOFTWARE INTERFACE FOR PRECISE HYPERTHERMIA AT REAL TARGET COORDINATES

Especially designed software for the 3D reconstruction of the patient's CT Images, virtual/real scenario registration, desired antenna and matrix pose acquisition and visualization, real time ALFA, BETA, GAMMA and DELTA antenna tracking, and visualization of positioning errors.

- Excellent precision delivery and treatment reproducibility;
- Optimal collimation between 3D power deposition pattern (SAR) that characterizes each ALBA ON 4000D antenna and the GTV/PTV;
- High quality dosimetry thanks to high-resolution and accurate positioning of temperature sensors on the treated surface.



PATIENT COMFORT AND ERGONOMIC SYSTEM

The curvature of the antenna together with the soft integrated water bolus allow for an optimal adaptation to the shape of the anatomical sites to be treated, resulting in high patient comfort as well as proper ergonomics for the operators.

- Light weight applicator resulting in high patient comfort.
- Easy operator-patient interaction in every treatment scenario.

3 rotation axes and 3 degrees of freedom for fine antenna positioning according to the morphological structure of patient anatomy.

Soft integrated water bolus for an optimal adaptation to the shape of the different anatomical sites to be treated.

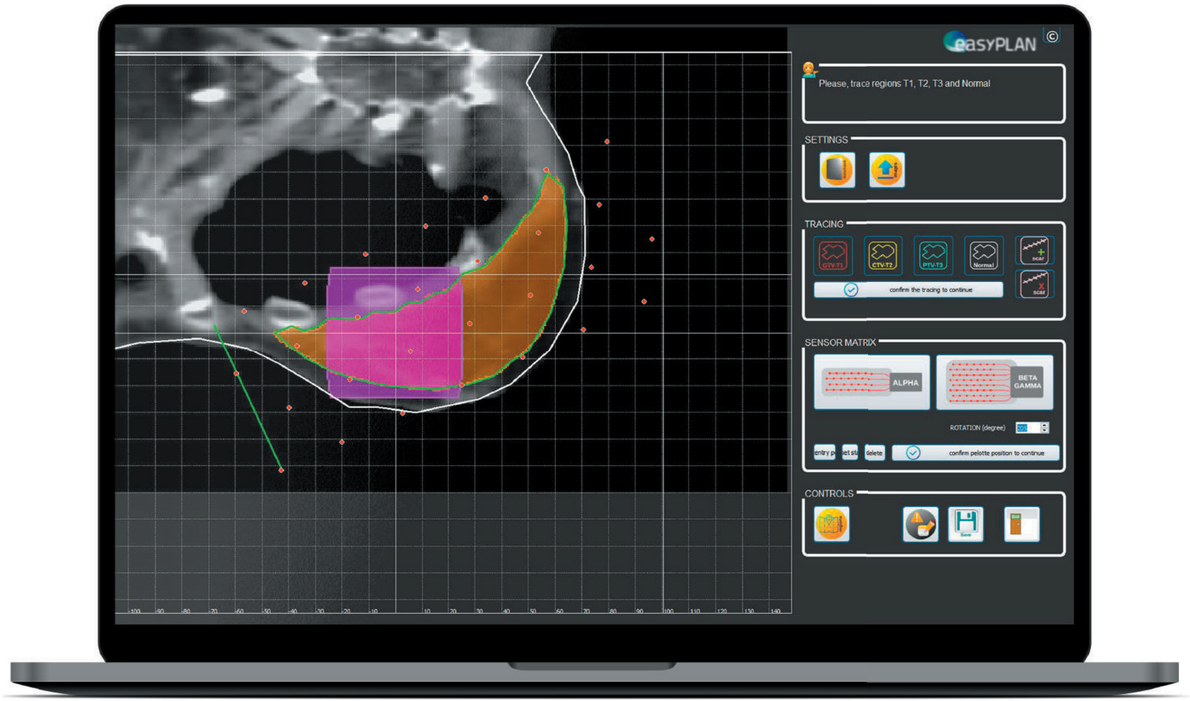
ALBA SOFTWARE TO FACILITATE HT TREATMENT

Dedicated software to ease treatment workflow, assist the user in planning treatments, correct treatment settings, and enhance treatment quality.

easyPLAN
geometrical planning

Software developed to facilitate the workflow and transfer of patient-specific data necessary for the treatment setting with ALBA ON 4000D from the radiation-oncologist/physicist to the RT technicians.
Easy-to-use GUI for recording the main geometrical data taken from any commercial imaging-TPS software (patient's radiological images, patient-specific anthropometric data).

**ALBA easyPLAN is not yet CE marked and therefore it is not yet a medical device. The purpose of the software is to speed-up and facilitate the flow of information from the physicist/radiotherapist to the hyperthermia operators.*



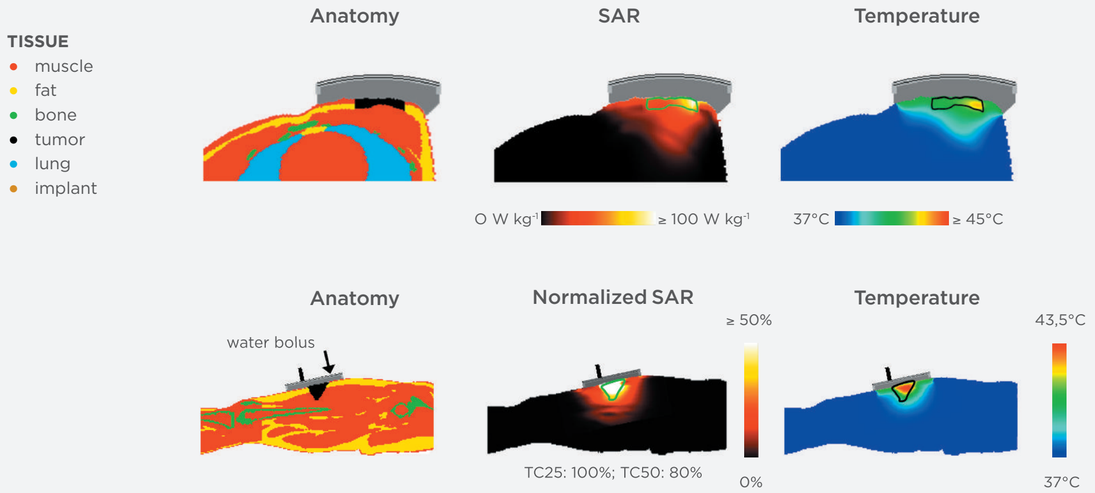
PLAN2heat
3D adaptive simulation

Dedicated hyperthermia treatment planning software to support treatment strategies consisting in a user-friendly streamlined Guided User Interface (GUI). [21]

1. Patient model generation: import of patient specific DICOM images (CT/MRI); automatic Hounsfield unit-based tissue segmentation and delineation of GTV, CTV, PTV, at risk organ contours or import from commercially available RT planning system; delineation and removal of any artifacts.
2. Automatic assignment of dielectric and thermal properties; assignment of thermal boundary conditions; definition of resolution for calculation and cubic grid generation.
3. Patient model-ALBA ON 4000D registration: import of ALBA ON 4000D array model; automatic antenna-patient gap filling with dielectric properties and thermal boundary conditions of the water bolus.
4. Electromagnetic field distribution calculation. Calculation is performed by solving Maxwell's equations applying the FDTD method.
5. SAR and temperature distribution calculation and visualization; temperature is calculated by solving the Pennes' bioheat equation. The user-friendly graphical user interface shows SAR and temperature distributions on the 3D image data sets (transverse, sagittal, coronal views). The user interface provides information about the amount of power absorbed in the tumor region and shows a temperature-volume histogram of the tumor, with a summary of the predicted minimum and maximum temperature and of the indexed temperatures T10, T50, and T90.

HTP can help with the following points:

- Adequate phase settings;
- Heating ability analysis;
- Hot spot suppression;
- Applicator selection;
- Evaluation of target coverage and heating depth.



Examples of SAR and T simulations in real patient anatomy. [21]

**ALBA PLAN2heat - for reserch purposes only.*

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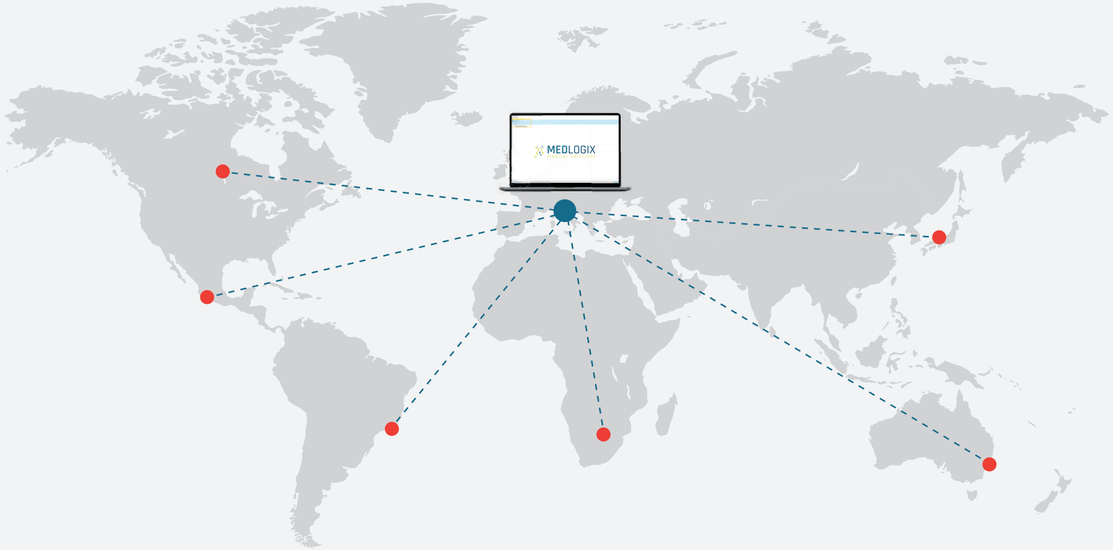
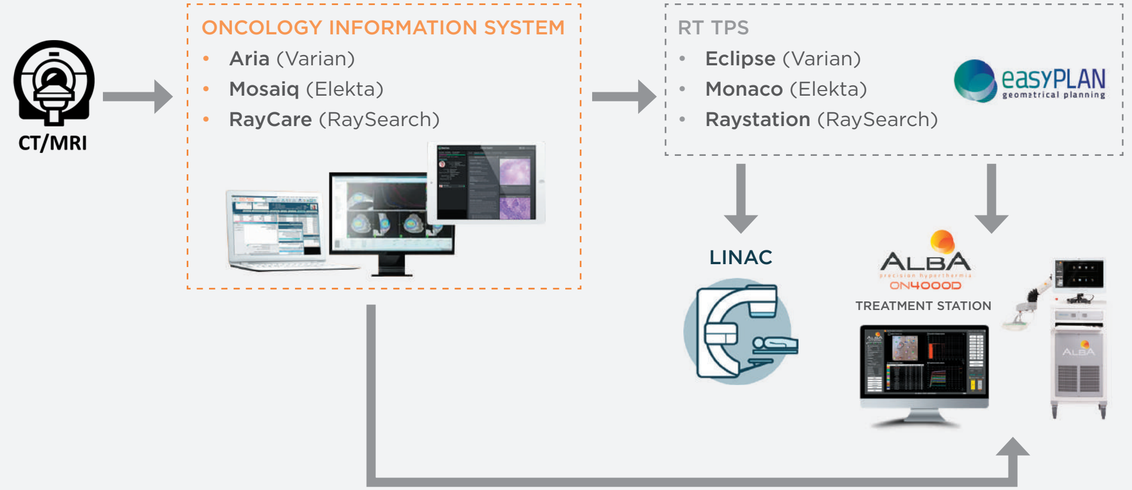


REAL TIME REMOTE TECHNICAL ASSISTANCE

ALBA ON 4000D allows the user to obtain real-time technical assistance via remote internet dial-up. Secure remote access is carried out through a high security software using encrypted communication to identify problems and find customized solutions for customers in a short time.

DATA MANAGEMENT SYSTEM AND INTEGRATION INTO RT WORKFLOW

- Patient personal data are imported as DICOM Worklist and treatment reports can be saved in PDF thanks to the data management system.
- Software fully integrated with HIS/OIS/PACS system to improve the integration of hyperthermia into the oncological information system.



ALBA ON 4000D MULTIPLE CONFIGURATIONS

ALBA ON 4000D can adapt its mechanical configuration to different patient anatomies, thus enhancing treatment efficiency and patient comfort.

The different console configurations allow an intuitive and easy installation in any outpatient room and meet the operational needs of the users.

CONFIGURABLE AND EASY TO USE SYSTEM

Easy movements and system configuration according to individual treatment needs and easy interaction with the patient thanks to:

- The 3D rotation wheels;
- 6 degrees of freedom double pantograph extendable arm;
- Special spherical antenna connectors for fine positioning of antenna applicator;
- Easy and flexible rotation of the monitor and the arm (up, down, right, left).

USER-FRIENDLY SOFTWARE INTERFACE TO EXPEDITE RTT WORKFLOW IN LEADING ONCOLOGY DEPARTMENTS

ALBA ON 4000D dedicated user-friendly treatment software consisting of a streamlined 5-step Guided User Interface (GUI) to ease treatment workflow and enhance treatment quality:

1. Self-test function;
2. Patient/Tumor selection;
3. Temperature Sensor Geometry Assessment;
4. Treatment Setting;
5. Treatment delivery and control.

Fully integrated with ALBA T-Matrix and ALBA Optix for advanced precision hyperthermia.

All relevant treatment data (applicator type, RF power level, bolus temperatures, measured temperatures) automatically recorded to allow easy treatment data extraction for publications and for exchange and comparison of data for multi-centric clinical trials.

EXTERNAL CONSOLE

External control station equipped with management software allows an ideal and easy remote control.

TWO ALBA ON 4000D WITH SINGLE CONSOLE

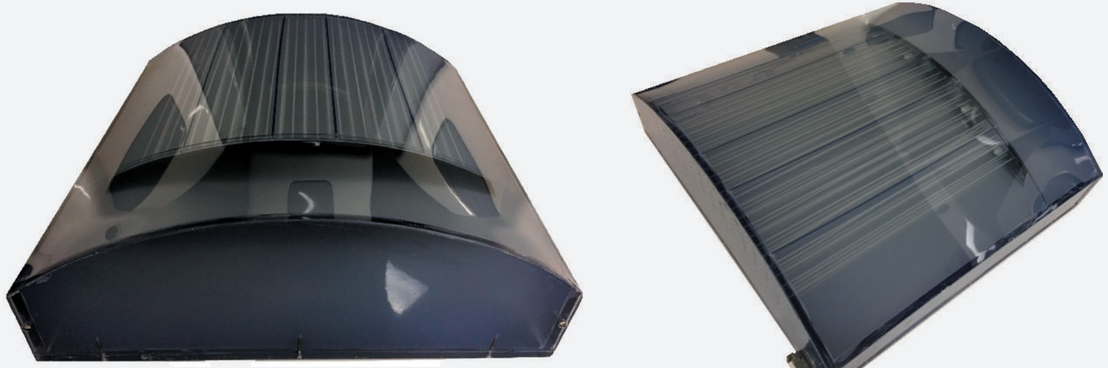
Optionally expandable with a second ALBA ON 4000D unit for simultaneous treatment of 2 tumor lesions or of very large tumor lesions (up to 880 cm^2).

QUALITY ASSURANCE

Dedicated tools in full compliance with the guidelines of the European Society of Hyperthermic Oncology (ESHO) guarantees high level, quality hyperthermia treatment over time. [22]

QA PHANTOM

Thorax Wall phantom reproducing the electromagnetic properties of the human body at the ALBA ON 4000D working frequency (434 MHz).
Equipped with embedded catheters to measure the temperature in real time at 1 cm to 6 cm depth for assessment of temperature profiles.



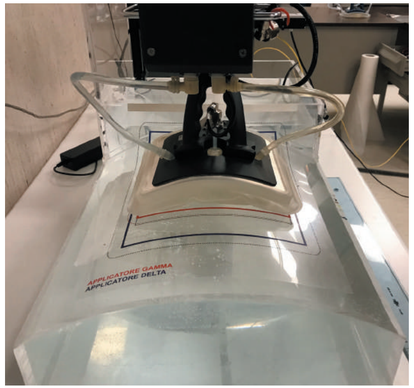
THERMOMETRIC CALIBRATION KIT

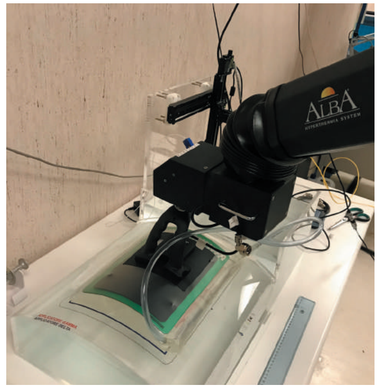
ESHO-approved Q.A. kit necessary for the calibration procedure of the thermometric system (thermometer + temperature sensors) with an accuracy of +/- 0.2°C, including thermostatic bath, calibrator and software tool.

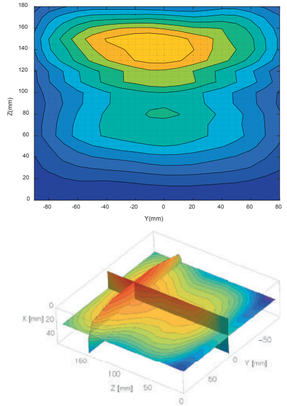
3D ANTENNA BEAM ELECTRIC FIELD MEASUREMENT

Specific QA tool designed to test and verify hyperthermia antenna performance in muscle equivalent phantom for qualitative 3D antenna beam assessment.

Quality assurance non-ionizing chamber consisting of a muscle equivalent curved shape liquid phantom, 3 axis EMC compatible motorized robot, high sensitive electric field probe and digital voltmeter. Dedicated software to acquire data, automatic 3D reconstruction and display of E-field data.

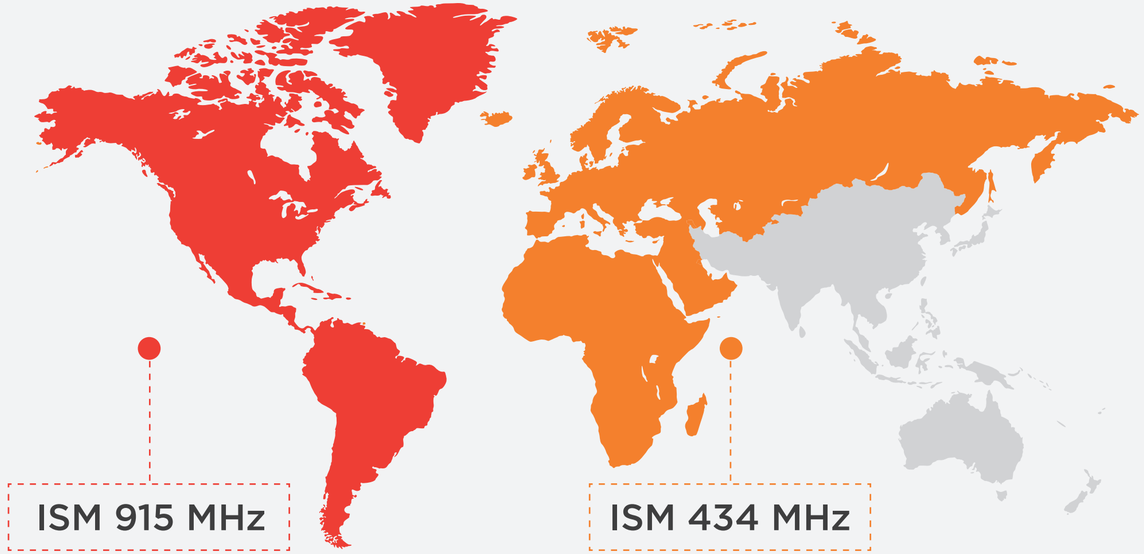






434 MHz ISM FREQUENCY IN REGION 2 (EMEA)

ALBA ON 4000D may be installed in any environment without the need of a Faraday cage.



Verification necessary according to local regulations, for all countries outside Region 2 (EMEA), whether a Faraday Cage is needed or not (e.g. 915 MHz is not an ISM frequency in region 2).

RESEARCH AND DEVELOPMENT

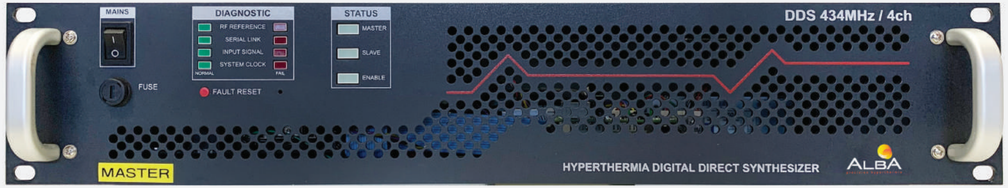
At Med-Logix we believe in continuous research and development performed with the precious support of clinical users in Hospitals and Academic Centers fighting every day to cure cancer patients.

All of today's and tomorrow's projects have the aim to bring hyperthermia technology to the standards of modern radiotherapy for routine daily use in the clinical environment, giving its contribution to the global oncological community.

434 MHz MULTICHANNEL RF GENERATOR WITH DIGITAL DIRECT SYNTHESIZER

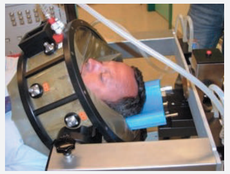
Designed to match the present and future demands of advanced multichannel phased array systems dedicated to treating tumors at complex locations such as lung and brain, Med-Logix has designed and produced the most advanced RF multichannel digital synthesizer fully dedicated to Hyperthermia environment.

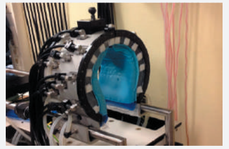
ALBA high frequency multichannel RF digital generator (up to 28 channels) with integrated phase and amplitude detectors are the core of the ultrafast ALBA phase collimator able to focus in real-time the RF energy irradiated by a multibeam antenna array at any target coordinate.



2400 W ALBA RF ENGINE POWERS HYPERCOLLAR PROJECT SINCE 2007 AT ERASMUS MC [23]

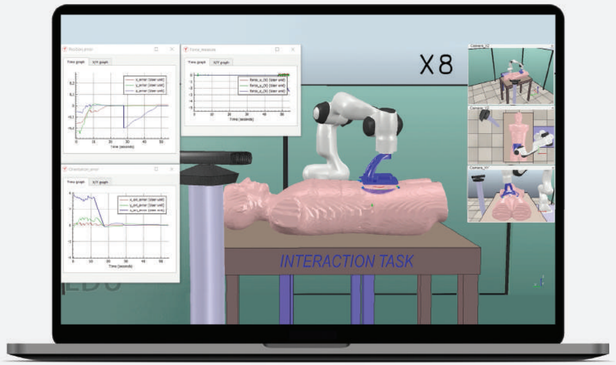
Since 2007, 12 x 434MHz ALBA RF amplifiers are powering a phased array antenna, called HYPERcollar, developed at ERASMUS MEDICAL CENTER in Rotterdam. HYPERcollar 3D powered by an ALBA RF engine have been used for more than 14 years to treat all patients affected by locally-advanced and recurrent head and neck carcinoma (HNC) at the Radiation Department of EMC Rotterdam.





ROBOT ASSISTED HYPERTHERMIA

Radiation oncology demands products able to offer automated, reproducible, fast and accurate procedures. Med-Logix has started a process of implementing a collaborative robot arm for computer-guided movement of the ALBA superficial and semi-deep hyperthermia systems. Bringing the HT systems into a new spatial precision domain is a mandatory element in a leading radiation therapy environment.



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BIBLIOGRAPHY

1. Datta, N. R. et al., 2015. Local hyperthermia combined with radiotherapy and-/or chemotherapy: Recent advances and promises for the future. *Cancer Treatment Reviews*, 11, Volume 41, p. 742–753.

2. Crezee, H. et al., 2015. Thermoradiotherapy planning: Integration in routine clinical practice. *International Journal of Hyperthermia*, 12, Volume 32, p. 41–49.

3. Issels, R. D. et al., 2018. Effect of Neoadjuvant Chemotherapy Plus Regional Hyperthermia on Long-term Outcomes Among Patients With Localized High-Risk Soft Tissue Sarcoma. *JAMA Oncology*, 4, Volume 4, p. 483.

4. Krawczyk, P. M. et al., 2011. Mild hyperthermia inhibits homologous recombination, induces BRCA2 degradation, and sensitizes cancer cells to poly (ADP-ribose) polymerase-1 inhibition. *Proceedings of the National Academy of Sciences*, 5, Volume 108, p. 9851–9856.

5. Oei, A. L. et al., 2015. Effects of hyperthermia on DNA repair pathways: one treatment to inhibit them all. *Radiation Oncology*, 8.Volume 10.

6. Franken, N. A. P. et al., 2013. Cell survival and radiosensitisation: Modulation of the linear and quadratic parameters of the LQ model. *International Journal of Oncology*, 3, Volume 42, p. 1501–1515.

7. Vujaskovic, Z. & Song, C. W., 2004. Physiological mechanisms underlying heat-induced radiosensitization. *International Journal of Hyperthermia*, 3, Volume 20, p. 163–174.

8. Issels, R. D., 2008. Hyperthermia adds to chemotherapy. *European Journal of Cancer*, 11, Volume 44, p. 2546–2554.

9. Datta, N. R. & Bodis, S., 2019. Hyperthermia with radiotherapy reduces tumour alpha/beta: Insights from trials of thermoradiotherapy vs radiotherapy alone. *Radiotherapy and Oncology*, 9, Volume 138, p. 1–8.

10. van Leeuwen, C. M. et al., 2017. Measurement and analysis of the impact of time-interval, temperature and radiation dose on tumour cell survival and its application in thermoradiotherapy plan evaluation. *International Journal of Hyperthermia*, 5, Volume 34, p. 30–38.

11. Trefná, H. D. et al., 2017. Quality assurance guidelines for superficial hyperthermia clinical trials: I. Clinical requirements. *International Journal of Hyperthermia*, 1, Volume 33, p. 471–482.

12. Kok, H. P. et al., 2010. SAR deposition by curved CFMA-434 applicators for superficial hyperthermia: Measurements and simulations. *International Journal of Hyperthermia*, 1, Volume 26, p. 171–184.

13. Marini, P., Guiot, C., Baiotto, B. & Gabriele, P., 2004. PC-aided assessment of the thermal performances of a MW applicator for oncological hyperthermia. *Computers in Biology and Medicine*, 1, Volume 34, p. 3–13.

14. Ichinoseki-Sekine, N. et al., 2007. Changes in muscle temperature induced by 434 MHz microwave hyperthermia. *British Journal of Sports Medicine*, 1, Volume 41, p. 425–429.

15. Gabriele, P. et al., 2009. Radio hyperthermia for re-treatment of superficial tumours. *International Journal of Hyperthermia*, 1, Volume 25, p. 189–198.

16. Bakker, A. et al., 2020. Two high-resolution thermal monitoring sheets for clinical superficial hyperthermia. *Physics in Medicine & Biology*, 9, Volume 65, p. 175021.

17. Bakker, A. et al., 2018. Analysis of clinical data to determine the minimum number of sensors required for adequate skin temperature monitoring of superficial hyperthermia treatments. *International Journal of Hyperthermia*, 4, Volume 34, p. 910–917.

18. Bakker, A. et al., 2020. Clinical Feasibility of a High-Resolution Thermal Monitoring Sheet for Superficial Hyperthermia in Breast Cancer Patients. *Cancers*, 12, Volume 12, p. 3644.

19. Ferro, M. et al., 2021. Marker-based registration for antenna positioning in superficial hyperthermia. 13th *International Congress of Hyperthermic Oncology*.

20. Ferro, M., Vendittelli, M., Ciampa, S. & Pavoni, P., 2019. Towards an image-guided positioning system for radiative applicators in oncological hyperthermia. *I-RIM Conference*.

21. Kok, H. P. et al., 2021. Treatment planning facilitates clinical decision making for hyperthermia treatments. *International Journal of Hyperthermia*, 1, Volume 38, p. 532–551.

22. Trefná, H. D. et al., 2017. Quality assurance guidelines for superficial hyperthermia clinical trials: II. Technical requirements for heating devices .*Strahlentherapie und Onkologie*, 3, Volume 193, p. 351–366.

23. Paulides, M. M. et al.,2007. The HYPERcollar: A novel applicator for hyperthermia in the head and neck . *International Journal of Hyperthermia*, Vol. 23, No. 7 p. 567-576.

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MED-LOGIX SRL
Polo Tecnologico Tiburtino
Via Adriano Olivetti, 24 - 00131 Roma
Tel: +39 06 40043808
Fax: +39 06 40043809

www.albahyperthermia.com
info@albahyperthermia.com

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