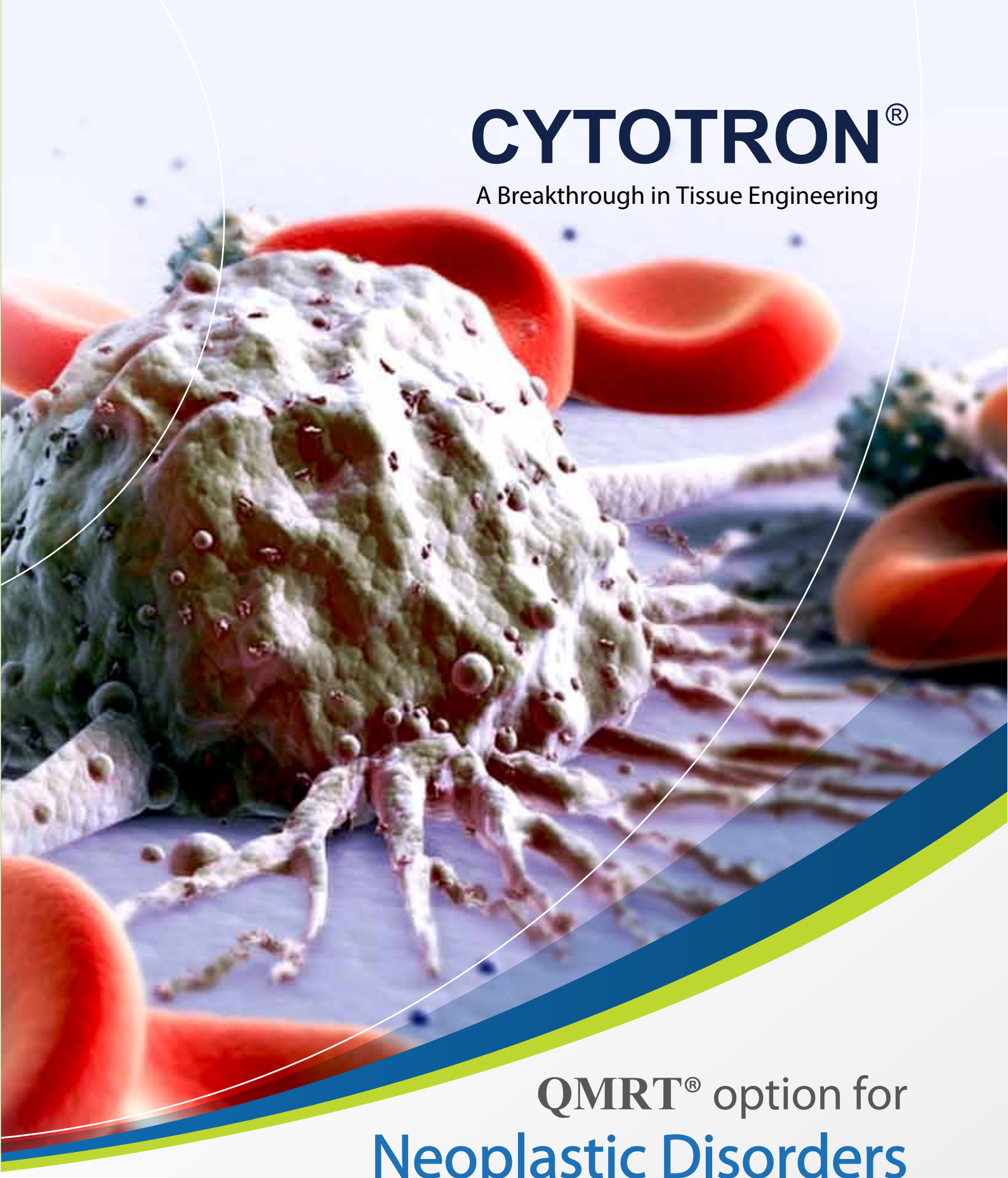
# CYTOTRON®

A Breakthrough in Tissue Engineering



## QMRT® option for
## Neoplastic Disorders

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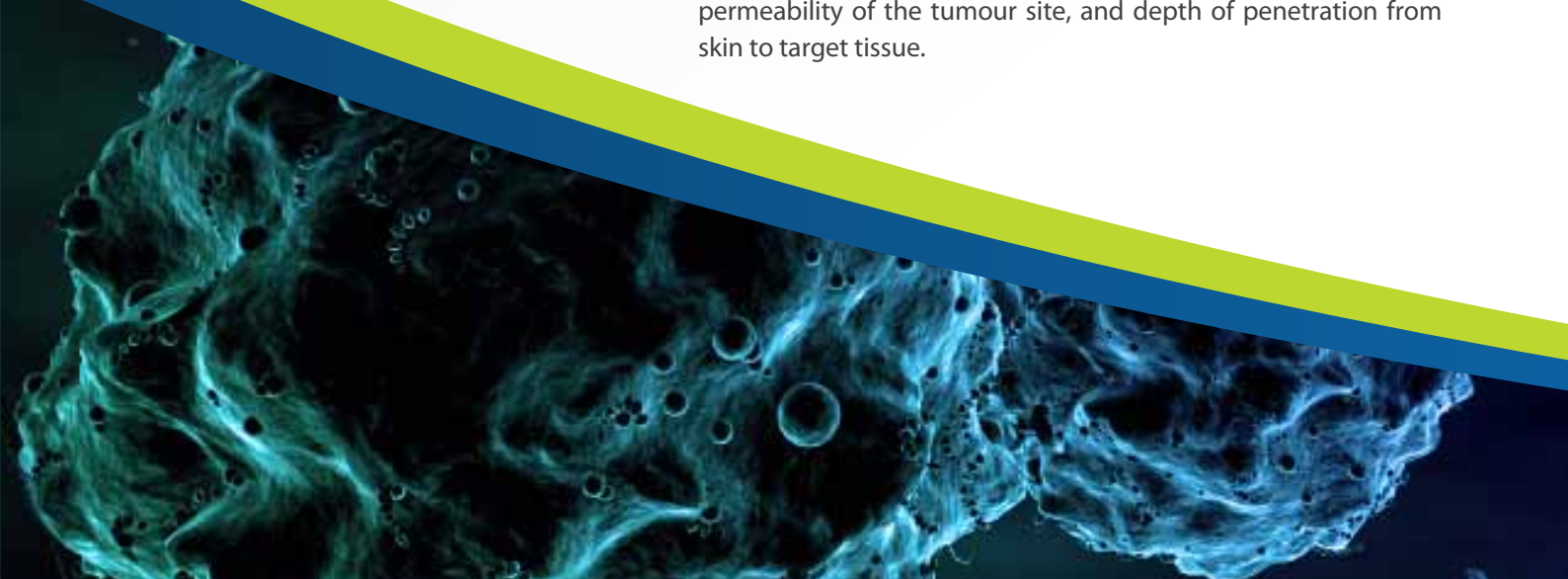
# Cell Signalling

Transmembrane Potential (TMP) is a well known cellular signaling pathway that regulates the synthesis of various proteins at the appropriate time in living cells. Many non-communicable illnesses like cancer, heart diseases and degenerative disorders like cartilage loss and different kinds of inflammation are also linked to disturbances in the protein transcription process (Cone CD, Variation of Transmembrane Potential as a basic mechanism of mitosis control: *Oncology*, 24: 438-470, 1970). It was thought during the last few decades that if an appropriate method could be developed to alter TMP in a controlled manner, most of these disorders that are protein linked could be corrected. The ion pump in the membrane activates the normal cellular channels for active synthesis and gene expression of appropriate proteins in different groups for a specific function. For instance the HSP group predominantly encourages tissue regeneration and can be useful in many chronic degenerative disorders, whereas the p53 group controls cell growth, thus playing an important role in arresting mitosis, thereby finding application in treating malignant neoplastic disorders. The p53 tumour suppressor gene stops the formation of tumours by its activities. If a person inherits only a copy of p53 gene from their parents, they are predisposed to cancer and usually develop several independent tumours in a variety of tissues in early adulthood (rare condition known as Li-Fraumeni Syndrome). Mutation in p53 is found in most tumour types and contributes to the complex network of molecular events leading to tumour formation. The p53 gene has been mapped to Chromomsome 17. In the cell, the p53 protein binds to the DNA, which in turn stimulates another gene to produce a protein called p21 which interacts with a cell- division- stimulating protein (CDK2). When p21 complexes with CDK2 the cell can not pass through to the next stage of cell division. When the p53 is mutated or fails to express, it can no longer bind to the DNA and as a consequence the p21 protein is not made available to act as the stop signal for cell division, thus the cell divides uncontrollably and forms tumours.

Tissue engineering is a field of science which involves altering, modifying and inducing controlled regeneration and degeneration in biological tissues. One of the methods of engineering the tissues is by altering the signaling pathways. These pathways can be altered by various intercellular parameters such as TMP, signal transduction (ligand, receptors, and signal propagation), cell cycle check points, telomere metabolism, RNA interference, etc.

Rotational Field Quantum Magnetic Resonance therapy or **QMRT®** is a functional method of altering one of the most prominent intercellular pathways i.e. the TMP pathways. It is hypothesized over the last 24 years of research that controlled altering of the TMP by application of specifically modulated radio frequency signals in the presence of a high instantaneous magnetic field can bring about changes relating to pro-apoptotic protein groups in the tumour cells. It is known that chromosomes, following the cell signaling received as a result of variation of potential (-70 to -90 mV in healthy cells, -40 to -60 mV when infected, -20 to -30 mV in neoplastic cells, 0 mV when the cell dies) in the cytoplasmic membrane, activate the emission of messages by the genes that regulate cell dynamics for normal cell function or for mitochondrial activities for ATP production, through electromechanical resonance (also called stress responsive).

The delivered, instantaneous mode, wide spectrum magnetic and RF modulations are highly cell and site specific. This is based on the proton density of the tumour tissue, the permittivity, permeability of the tumour site, and depth of penetration from skin to target tissue.



# Malignant Neoplastic Disorders

Malignant neoplastic disorder commonly known as cancer, is a chronic debilitating disease with genetic and environmental aetiology. It is predicted that there will be an increase in cancer incidence worldwide, with about 15 million new cases diagnosed annually. Currently available treatment modalities for cancer (surgery, chemotherapy, radiation therapy or hormonal therapy) are known for their side effects and invasive nature, despite their benefits. Thus the need for new treatments and palliative care modalities that can not only arrest tumour progression without the commonly experienced adverse effects, but can also help improve quality of life.

# Tissue Engineering in Malignant Neoplastic Disorders

- QMRT beams when appropriately controlled and modulated can alter the TMP to stimulate specific groups of proteins, thus initiating one or more signaling processes.
- Studies have shown that Nuclear Magnetic Resonance (NMR) exposure sensitizes tumour cells to apoptosis. (Ghibelli L, Cerella C, Cordisco S, et al: NMR Exposure Sensitizes Tumour Cells to Apoptosis. *Apoptosis* 11: 359-365, 2006)
- It is hypothesized that expression of p53 group of proteins is achieved by precisely altering the TMP pathway. This drives the tumour cells to apoptose.
- The cells continue to live in a quiescent state (vegetative form of life) until it finally attains apoptosis and are recycled by the body.

| Features | Benefits |
|---|---|
| QMRT® is non-invasive, non-thermal and non-ionizing | Improves quality of life in patients |
| Twenty-eight consecutive exposures of one hour daily | Relieves severe to extremely severe pain |
| Patients generally require no hospitalization | Enables tapering of powerful pain killers and opiates like morphine, etc |
| The device can also be installed in daycare centers with appropriate facilities | Improves appetite and weight gain, enhances social life, etc |
| The device is self-shielded and does not require shielding of the treatment room | Extends life expectancy |
| Fully-automatic dosimetry, requiring minimal training for technologist and specialist | Very likely aids in stabilizing the disease by arresting tumour progression |
| No consumables necessary | Very likely prevents tumour metastasis |
| | No known adverse effects |
| | Whole body treatment; multiple tumour sites can be exposed simultaneously |

# Clinical Efficacy of QMRT® in Neoplastic disorders

CYTOTRON®- **QMRT®** is a new modality for managing Neoplastic disorders with no known adverse effects. It is an emerging, stand-alone, adjuvant or neo- adjuvant therapy, poised to fill the unmet medical needs in terminally ill or advanced cancer patients. The treatment method involves exposure of the tumour site to the modulated radio signals generated by the Cytotron®. Each exposure lasts for about 60 minutes for 28 consecutive days. Special MRI-PD sequence is performed for precise dosimetry. A diagnostic MRI is required to evaluate the lesion status based on the Response Evaluation Criteria in Solid Tumours (RECIST v1.0) and the tumour's metastatic profile pre and post therapy.

In a clinical investigation carried out on 98 patients with histopathological confirmation of solid tumour, declared terminally ill or unwilling to undergo standard of care therapies, significant clinical outcomes were observed. Extension of life was determined by comparing predicted survival derived from a Palliative Prognostic Score (PaPS) model with actual survival. The quality of life (QOL) was recorded using the Functional Assessment for Cancer Therapy- General Population (FACT-GP) questionnaire and Karnofsky Performance Status (KPS) scores. Tumour status, pre- and post-treatment was evaluated using MRI/PET-CT. The patient follow up was for 12 months, with quarterly assessments, with periodic follow up and survival updates until close of the study. Paired 't' test as

applicable to dependent samples was applied for analysing KPS score and FACT-GP scores at completion of and one month after completion of therapy. Level of significance was set at $p<0.05$. However, exact significance is annotated in the tables presenting the outcome of analysis.

## Results and Outcome**

**Patient Cohort:** A total of 98 patients were assigned to the study after screening. There were 55 (56.1%) female and 43 (43.9%) male patients. The mean age was 54.5 ± 13.7 years, with ages ranging from 15 to 84 years. Out of the recruited patients, 86 (male 44%, female 56 %) completed the twenty-eight days exposure as per protocol.

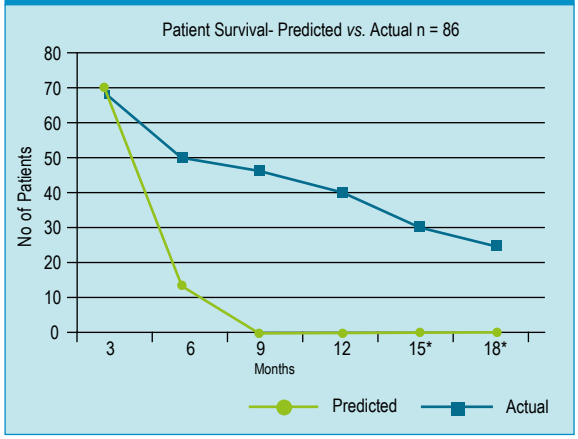
**Primary Outcome:** Thirty-one patients were still alive at the end of the study period of 4 years. Comparing predicted survival intervals with actual life expectancy during the follow up, there was a significant increase in life expectancy from the predicted mean of 117±46 days to the actual mean of 377±307 days, (t = - 8.21, p= 2.13 E-12).

**Table 1. Survival analysis at end of study period of 4 years.**

| Diagnosis | Total Cases (n = 86)* | Surviving | | Fatal | |
|---|---|---|---|---|---|
| | | No. | % | No. | % |
| BRAIN - Primary | 12 | 5 | 41.7% | 7 | 58.3% |
| BREAST- Primary | 15 | 8 | 53.3% | 7 | 46.7% |
| LUNG - Primary | 8 | 3 | 37.5 % | 5 | 62.5 % |
| LIVER – Primary | 8 | 0 | 0% | 8 | 100% |
| COLON- Primary | 6 | 2 | 33.3% | 4 | 66.7 % |
| PANCREAS-Primary | 7 | 1 | 14.3 % | 6 | 85.7 % |
| RENAL- Primary | 1 | 1 | 100% | 0 | 0% |
| PROSTATE- Primary | 2 | 1 | 50% | 1 | 50% |
| CERVICAL- Primary | 2 | 0 | 0% | 2 | 100% |
| OVARIES- Primary | 6 | 2 | 33.3 % | 4 | 66.7 % |
| Miscellaneous Tumours | 19 | 8 | 42.1 % | 11 | 57.9 % |
| | 86 | 31 | | 55 | |

*34 Cases had presented with single lesions; 52 cases had multiple metastasis.

**Fig 1. Graph showing patient survival during the follow up period.**




* Includes patients reviewed beyond the follow up period of 12 months.

**Secondary Outcome:** Significant improvement in Karnofsky Performance Status and FACT- GP scores. (Table 2)

**Table 2. Effect of QMRT® on Karnofsky Performance Score and FACT- GP Score**

| | Before Therapy* | At completion of therapy* | At one month after completion of therapy* | t- value | p- value |
|---|---|---|---|---|---|
| KPS† (n=86) | 74±15 | 80±12 | -- | t= -4.78 | p=7.25 E- 06 |
| Quality of life Score (FACT- GP‡) (n=86) | 71±22 | 78±18 | -- | t= -7.20 | p=1.71 E- 08 |
| Quality of life Score (FACT- GP‡) (n=77) | 76±19 | --- | 77±18 | t= -5.16 | p=1.91 E- 06 |

* Values in mean ± SD; † Karnofsky Performance Score; ‡ Functional Assessment of Cancer Therapy- General Population, © FACIT.org

**Table 3. Quality of Life Assessment - Post QMRT® (assessed as per KPS scoring pre and post therapy)**

| Study Cohort (n = 86) | Quality of Life | Number | % |
|---|---|---|---|
| Survivors 31 (36 %) | Better (Higher Score) | 8 | 26% |
| | No Change (Same Score) | 23 | 74 % |
| | Worse (Lower Score) | 0 | 0% |
| Deceased 55 (64%) | Better (Higher Score) | 24 | 44% |
| | No Change (Same Score) | 28 | 51% |
| | Worse (Lower Score) | 3 | 5% |

**Fig 2. Bar graph showing tumour status one month after completion of QMRT®**

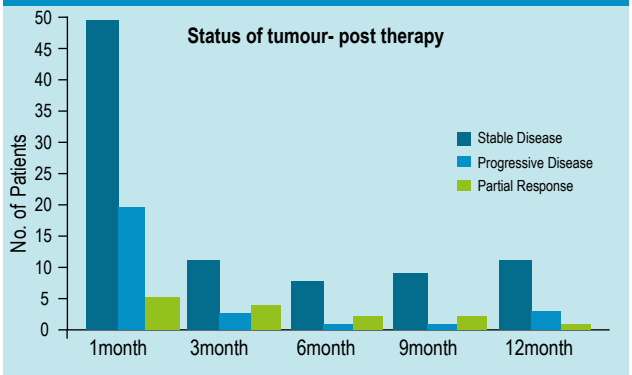



Fig 2. Bar graph showing tumour status post therapy (assessed based on RECIST v1.0)

*The data represents patients analyzed as an extension to the clinical investigation. Only 76, 18, 10, 11 and 16 patients reported for MRI follow up during the period of one, three, six, nine and twelve months post therapy respectively.*

**Results stated above is on the specific device designated model; CYTOTRON® - RTE - 6040 - 864 GEN. This data is awaiting publication.

| Table 4. Metastatic profile post QMRT®, based on MRI findings. | |
|---|---|
| Metastatic profile of tumour | No. of Patients *(%) |
| Presence of new metastasis | 20 (26.7%) |
| Absence of new metastasis | 55 (73.3%) |
| Total | 75 |

*Patients who reported for periodic post therapy MRI during a 4 year time frame.


# Conclusion

- Improves quality of life in patients by relieving pain, improving appetite and weight gain.
- Significant improvement in general quality of life.
- Significant extension in life expectancy
- Very likely aids in stabilizing the disease by arresting tumour progression.

This treatment can constitute a useful addition to standard of care therapy and may become a significant modality in the care of cancer patients in clinical practice and a safe therapy even in terminally ill cancer patients.

## Technical Specification of CYTOTRON®

**Classification:** Class IIa Medical Device.

**Indication of use:** The Device is intended to be used for Regenerative and Degenerative Tissue Engineering i.e. it can be used for regenerating tissues in-situ and to cause degeneration of uncontrolled growth of tissues.

Degeneration of tissues: The current indication is for use in protein linked abnormally regenerating disorders like neoplastic disease enabling tissue apoptosis and preventing metastasis.

**Contraindications:** Critically ill patients on life support system, pregnancy, patients unable to lie down for the duration of theraphy, Patients with electrically, Magnetically or mechanically activated implants. (e.g. cardiac pacemakers, Bio stimulators, Neuro stimulators, cochlear implants, hearing aids)

MRI Incompatible implants near the target region. E.g. intra medullary nail, intracranial aneurysm clips, stents, intra orbital metal fragments etc.

Patients with concomitant neoplastic disease especially chondrosarcoma.

**Drug interactions:** The following group of drugs that use the same or similar cellular pathways as QMRT® may interact with the CYTOTRON® exposure, like Calcium Channel Blockers and Proton Pump Inhibitors in cases of malignant neoplastic disorder. Patients should be advised to take medication with different mode of action.

### Product Specifications

The power supply Cytotron must meet these specifications:

a. Voltage fluctuation+/- 10% or less
b. Voltage imbalance +/- 3% or less
c. Frequency variation +/- 4% or less
d. Voltage distortion THD = 10% or less

### Recommended environmental specifications

Operating Temperature range 18°C to 30°C, Humidity range 10% to 75% RH, Atmospheric pressure 700 to 1060 hPa.

Transport / Storage Temperature range 10°C to 80°C, Humidity range 10% to 90% RH, Atmospheric pressure 500 to 1060 hPa

**Mode of usage:** Continuous
**Life of the equipment:** Typically assessed at about ten years
**Typical operating voltage:** 230 V, 50 Hz, single phase
**Maximum Operating current:** 12 Amps
**Typical operating current:** 6A
**IEC classification:** Type B, Class 1, IPX0
**MDD classification:** Class IIa
**Target resolution:** 11.25 degrees
**Power supply type:** Medical grade switch mode power supply complying with EN 60601-1, EN 60601-1-2
**Frequency band:** VLF, LF, HF and VHF radio bands
**Instantaneous magnetic field strength:** 1mT to 6T for the time duration 2.0µsec to10msec depends on the treatment and Dosimetry value.

**E-Field:** Broadband; average 100 dB V/m/MHz @ 4MHz
**H-Field:** Broadband; 20dB (below 1 kHz)
**Broadband common mode current in control cables:** 100dBmA/MHz @ 150 kHz
**Fuses:** Mains Fuse-12A, Isolation Transformer Fuse-2.5A

### Laser Guiding System

Output: 625 to 680 nanometer wave length less than 5 mill watt, Complies with CFR Part 1040.10 and 1040.11 Class III A LASER application

### QMRT Guns

**Magnetic field**

| | |
|---|---|
| Type: | MF6040-L |
| Guns: | K- _ Ferrite type; Near Field; gain; 10dB |
| Typical Voltage: | 60 Volts |
| Typical Current: | 4 Amps |

**Radio frequency**

| | |
|---|---|
| Type of antenna: | Helical |
| Q factor of the antenna: | 560 |
| Antenna gain: | 13 dB |
| Centre frequency: | 68.4 MHz |
| 3dB BW(Bandwidth): | ±4 MHz |
| 6dB BW(Bandwidth): | ±10 MHz |
| Input impedance: | 50 OHM |
| Input connector : | SMA |

### Physical Dimension

| | |
|---|---|
| **Cytotron device dimensions:** | 4500mm (L) x 1210mm (W) x 1600mm (H)<br>Weight: approx. 1900 Kg |
| **Central control unit dimensions:** | 1600mm (L) x 780mm (W) x 1455mm (H)<br>Weight: approx. 200 Kg |
| **Coating:** | Powder coating/Paint and Lacquer coating body for scratch protection and prevent from corrosion |
| **Patient weight:** | Max. 157 Kg |
| **Patient bed weight:** | 12.95 Kg (Part No: SCL-A-01-LB) |
| **Earthing clip weight:** | 50 Gms (Part No: SCL-A-02-EP) |
| **Patient transmission system: (Acrylic Sheet + Metal Frame)** | 22 Kg |
| **Total bed safe working load:** | 170 Kg |

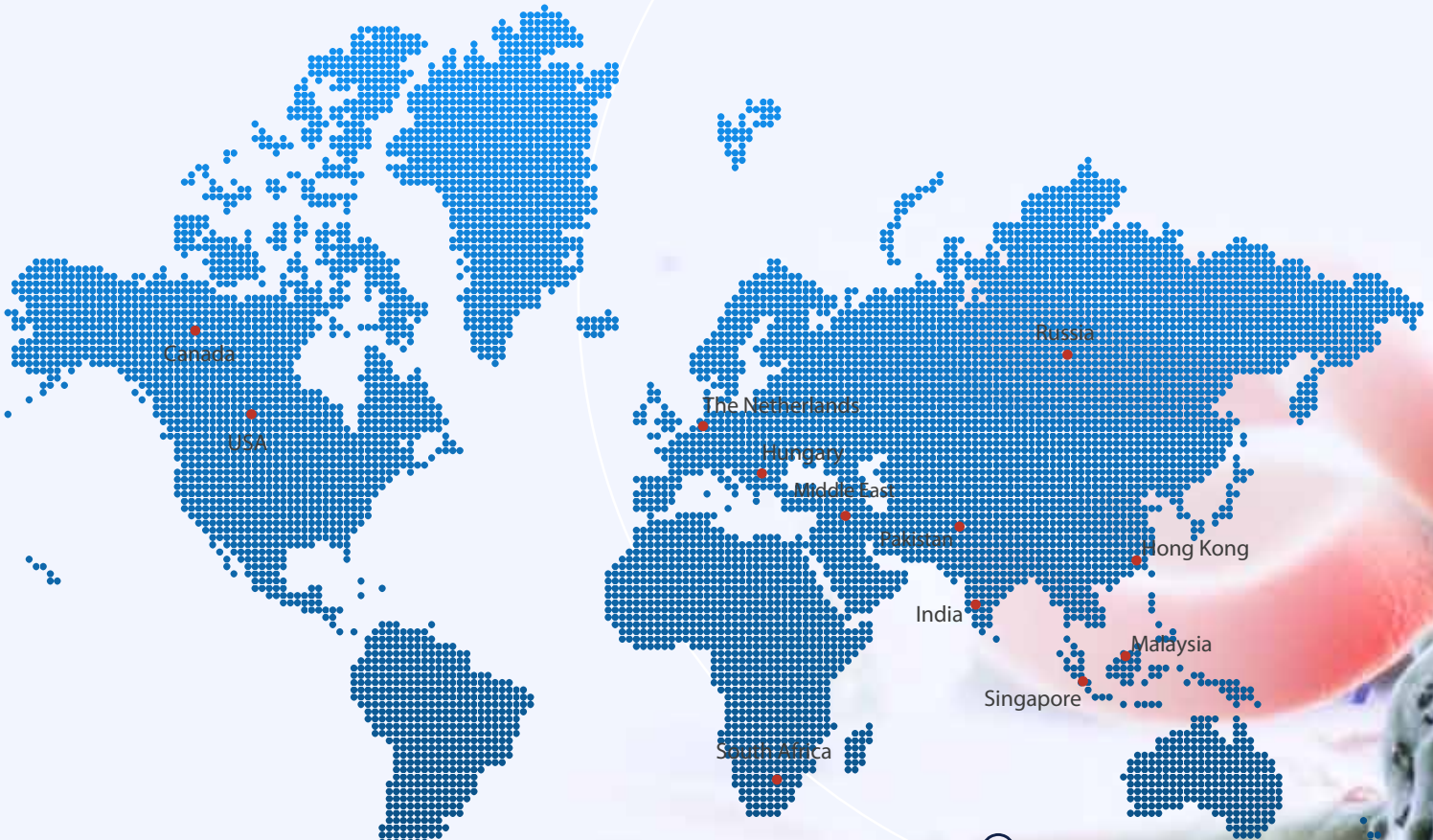
**Standard Applied:** BS EN 980:2008, BS EN 1041:2008, BS EN 62366:2008, IEC 60601-1, IEC 60601-1-1, IEC 60601-1-2, IEC 62304, ISO 9001:2008, ISO 13485:2003, ISO 14971:2007, ISO 14155-1:2003, ISO 14155-2:2003.

**Approvals:** ISO 9001:2008, ISO 13485:2003

**Accreditations:** ANAB, UKAS, CMDCAS

**Product Certification:** Annex II of MDD 93/42/EEC as Amended by 2007/47/EC

* Owing to continuous development, specifications are subject to change without notice.

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