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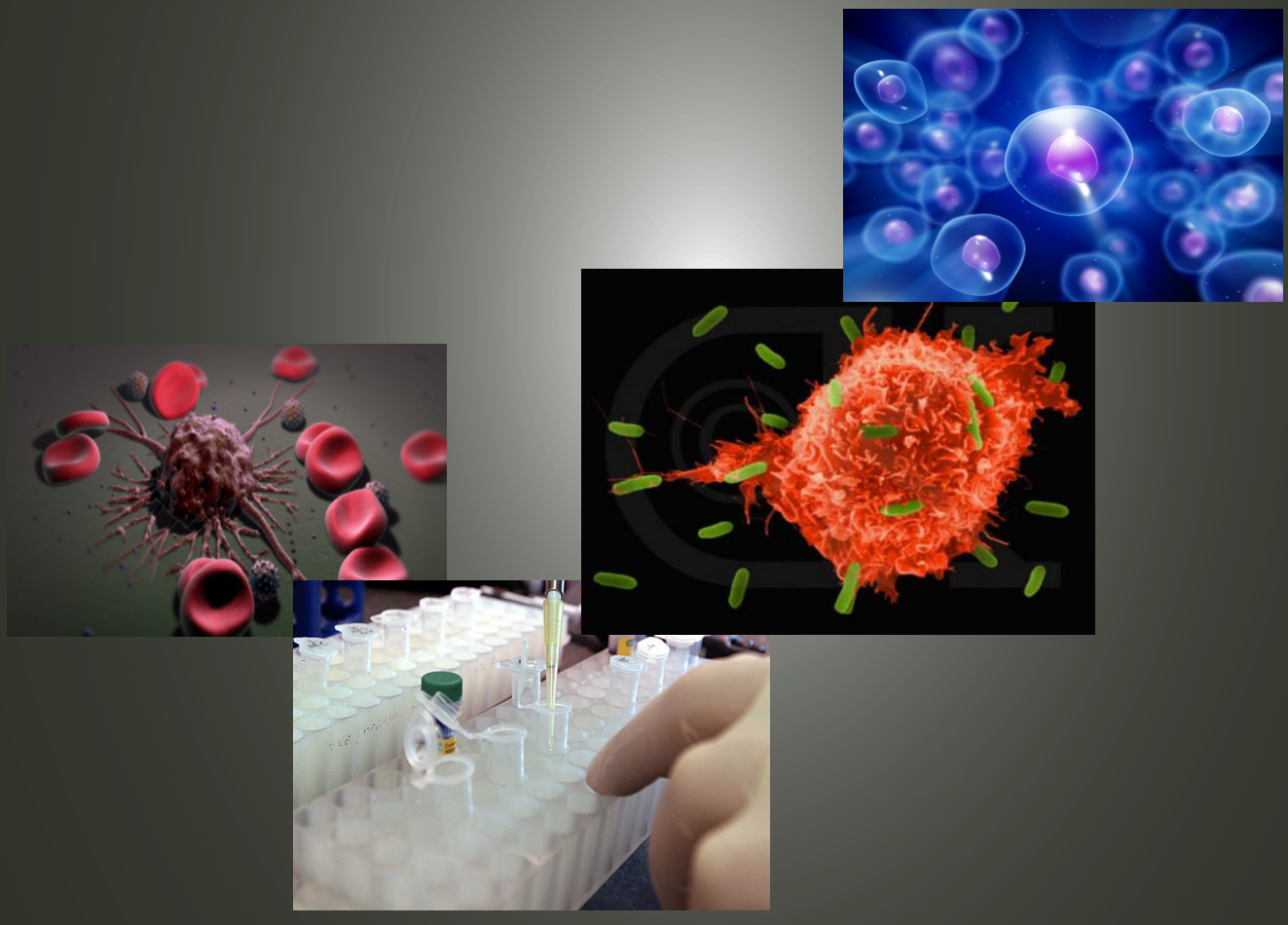

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Research Article

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Quantum Magnetic Resonance Therapy: Targeting Biophysical Cancer Vulnerabilities to Effectively Treat and Palliate

Ranjit Kumar[1‡], Meena Augustus[2‡*], Anjana Rani Nair[1‡], Reinhard Ebner[2], Gopalapillai Sreedharan Nayar[3], Rajah Vijay Kumar[1]

Abstract

Background: Radical paradigm shifts in traditional thinking is paramount to winning the war on cancer and understanding why this disease survives despite state of the art, advanced therapies. There is mounting evidence that biophysical signals are integral to the cycle of initiation, progression and death of cancer cells. Innovative technologies that manipulate this vulnerability in solid tumors could effectively be used to perturb only diseased cells and tissues. Not compromising normally functioning cells while controlling tumor progression, is the ultimate goal for evolving cancer therapeutics like Quantum Magnetic Resonance Therapy, headed promisingly in that direction.

Methods: A patented, CE marked device, the CYTOTRON® delivers rotating, target-specific, modulated, safe Radio Frequencies in the presence of an integrated, instantaneous magnetic field. The presumed modulation of the transmembrane potential of tumor cells and downstream cellular signalling by RF for tissue degeneration in cancer underlies Rotational Field Quantum Magnetic Resonance platform technology. Whole body MRI for tissue proton density determinations was used to compute individualized dosimetry to target solitary or multiple regions of interest in the whole body, simultaneously. Exposure to QMRT was for 1 hour daily for 28 consecutive days. Quality of Life assessments, overall survival and tumor stability using RECIST v1.1 were evaluated and followed up for 12 months.

Results: Significant increase in life expectancy from the predicted to the actual mean (p=2.13 E-12), improvements in Karnofsky Performance Scale scores (p=7.25 E-06) and Quality of Life scores (p=1.71 E-08 and p=1.91 E-06) were noted. Thirty six of 51 (71 %) terminally ill patients had stable disease one month after completion of QMRT or longer.

Conclusions: Exposure to radiofrequency-mediated QMRT improved life expectancy and quality of life, along with arrest of tumor progression. This therapy can be safely positioned in a palliative care setting, transitioning to mainstream cancer care with more rigorous clinical validation.

Keywords

CYTOTRON; Electromagnetic spectrum; Quantum Magnetic Resonance Therapy; Rotational field quantum magnetic resonance technology; Palliative care; Radiofrequency; Transmembrane potential; Solid tumors; Quality of life; Terminally ill

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Abbreviations: QMRT: Quantum Magnetic Resonance Therapy; RFQMR: Rotational Field Quantum Magnetic Resonance Therapy; MRI: Magnetic Resonance Imaging; TMP: Transmembrane Potential; PD: Proton Density; RF: Radiofrequency; MR: Magnetic Resonance; KPS or K: Score-Karnofsky Performance Scale Score; FACT-GP: Functional Assessment of Cancer Therapy-General Population; ROI: Regions of Interest; QoL: Quality of Life; RECIST: Response Evaluation Criteria in Solid Tumors

Introduction

Clinical cancer research is currently gaining new momentum under the umbrella of precision medicine. Oncologists /scientists the world over has been charged with the responsibility of finding better treatments and faster cures in the war on cancer [1]. Recently, a multidisciplinary task force identified critical gaps and translational priorities in breast cancer research and treatment. One of the ten major gaps listed was the need to develop interventions that support and improve the survivorship experience [2]. Some of the seminal advances surround ways to attack cancers' vulnerabilities [3-5]. To this end, the importance of manipulating the cell's biophysical signalling, to improve therapeutic impact on the disease has been gaining momentum stressing the need to integrate these improvements into clinical research [6]. Rotational Field Quantum Magnetic Resonance (RFQMR) platform technology and Quantum Magnetic Resonance Therapy (QMRT) introduced here has been the focus of our pioneering efforts into the realm of tissue engineering and translational medicine to treat human diseases like cancer [7], reported here for the first time. Traditionally, cytotoxic chemotherapy and radiotherapy randomly target both cancerous and non-cancerous cells, resulting in a range of mild to very severe adverse effects [8]. Depression, hopelessness, dependence, distressing pain, lack of appetite and loss of body weight are all very common problems in these patients requiring close monitoring, in addition to monitoring treatment outcomes [9-13]. A peaceful and dignified end of life (EoL) for such patients could be achieved through improved palliative interventions, including pain relief and other enhancements to Quality of Life (QoL). There is an urgent need for new treatments and integrated palliative care modalities that can not only arrest tumour progression without the commonly experienced side effects, but can also positively impact QoL [10,11]. Quantum Magnetic Resonance Therapy, or QMRT®, is based on an innovative technology platform deploying Rotational Field Quantum Magnetic Resonance (RFQMR). This emerging treatment modality is currently filling an unmet medical need in the management of solid tumors in a palliative care setting, with the promise to eventually transition into mainstream medicine. In QMRT®, poly-dimensional, rotating target-specific, modulated Radio Frequencies (RF) are delivered in the presence of an instantaneous magnetic field. Dose selection in QMRT® is tailored to the target tissue proton density, obtained using MRI. The CYTOTRON® device (Figure 1A) that delivers QMRT® operates at the safe end of the electromagnetic spectrum (EMS) (Figure 1B). It is poised as an emerging, stand-alone, adjuvant or neo-adjuvant modality, to manage disease progression in terminally ill or advanced cancer patients. The primary objective of the study was to observe the effect of QMRT® on life expectancy in advanced cancer patients. Since the study population was terminally ill, any

Figure 1A: The CYTOTRON® whole body device. The CYTOTRON-RTE–6040-864GEN (Class IIA Medical Therapeutic Device; developed by Scalene Cybernetics Ltd, Bengaluru, India) is seen in the foreground. The wide-bore gantry houses 864 guns distributed in 9 axes, with each axes bearing 96 guns to deliver RF & MR as per protocol; a moving patient bed and built in device control unit. The central control & command computer for dosimetry planning is seen in the background.

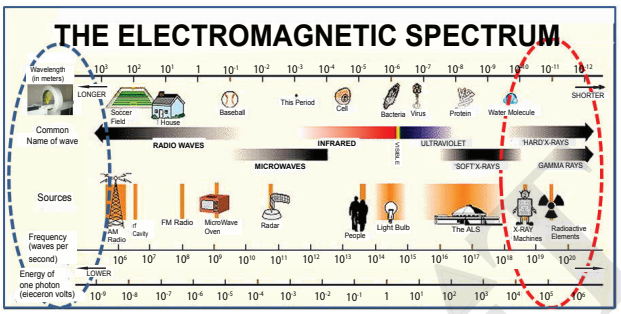

Figure 1B: Product-positioning of the CYTOTRON® at the safe end of the Electromagnetic Spectrum. A cross-section of the CYTOTRON® device is shown positioned in the non-ionizing radio frequency (RF) range - lower than cell phones and microwaves- within the blue oval; the red oval indicates the typical wavelength range for ionizing radiotherapy (RT) devices in human use today.

extension of lifespan beyond established standard prediction averages could indicate that the treatment played a role in extension of life. While a randomized, controlled trial (RCT) would help confirm these observations, the patients enrolled in the study were part of an all-comer, compassionate clinical study to test potential efficacy of the CYTOTRON®. For purposes of this pilot study, comparisons could only be projected to include reported survival outcomes in similar patients routinely treated with other conventional standard of care modalities; in other words, historical control groups. An associated primary objective was to analyse the impact of QMRT® on QoL of these patients. Quality of life is an important concept in cancer care, helping to evaluate effects of treatment in clinical trials. QoL determination indicates how the disease and the treatment affect the individual's wellbeing and relies largely on subjective patient responses. Functional Assessment of Cancer Therapy (FACT) and Karnofsky Performance Scale (KPS) scores are frequently used to assess the effects of treatment. In addition to overall survival and QoL, the effect of QMRT on tumor stability and disease progression was the secondary study endpoint, followed up using Magnetic Resonance Imaging (MRI) criteria. The emphasis on the importance of QoL and prolonged survival achieved by QMRT was integral to this study. In conventional therapies, QoL is negatively impacted by repeated cycles of therapy in advanced disease, in an effort to achieve the elusive cure. In countries where early detection and precision diagnosis is still in its infancy, significant delays in initiation of treatment are commonplace. QMRT has a distinct niche in managing such patients even concurrently with conventional therapies, for palliation and effective control.

Methods

Study population

Patients of either gender, predominantly adult, with confirmed pathological diagnosis of cancer, having solid tumors and declared terminally ill by the attending Oncologist, were included in the study. Three patients with primary cancer, who were unwilling to undergo conventional treatment but elected to undergo QMRT®, were also inducted into the study (Figure 2) on compassionate grounds. Patients were a diverse group coming from different parts of the world like India, Europe, South East Asia, United States and Africa. Written informed consent was obtained from patients fulfilling the selection/inclusion criteria. Enrolled patients were subjected to a thorough clinical examination, complete blood count (CBC) and biochemistry investigations. Other laboratory tests were advised as required for individual patient management. Almost all patients had previously undergone conventional treatment for cancer and had no other treatment / palliative care options available to them. Exclusion criteria included: (a) non-solid tumour(Leukemia and Multiple Myeloma); (b)pregnancy; (c) those with electrically, magnetically or mechanically activated implants (cardiac pacemakers, bio-stimulators, neuro-stimulators, cochlear implants, hearing aids); (d) MRI incompatible implants (intra medullary nails, intracranial aneurysm clips, intra-orbital metal fragments, stents near target area; (e) critically ill patients needing life support; (f)mentally challenged

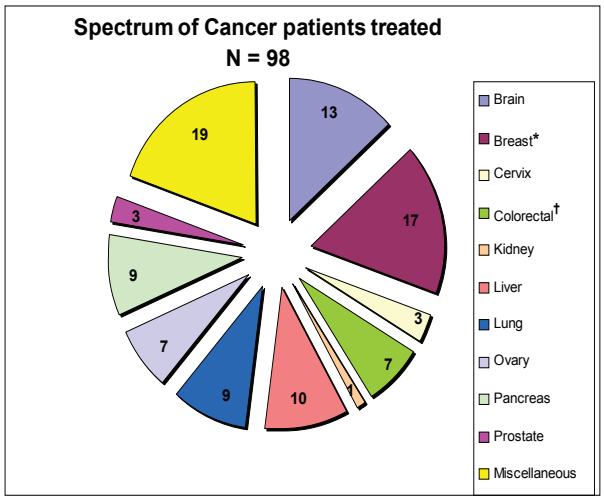

Figure 2: Patient cohort and distribution of solid tumors treated with QMRT. The all-inclusive range of solid tumors treatable with the QMRT protocol underpins this targeted technology. The miscellaneous group includes carcinoma of upper gastro-intestinal tract (GIT), appendix, gall bladder, nasopharynx, sino-nasal, thyroid, urinary bladder, endometrium, sarcomas, mesenchymal chondrosarcoma, melanoma and non-Hodgkin's lymphoma. *Includes two cases of primary ductal cell carcinoma without metastasis.† Includes one carcinoma of the ascending colon without metastasis.

patients unable to provide informed consent; (g) inability to lie in a supine position with minimal movement for the duration of the therapy.

Study design

This was an investigator-initiated, open label, prospective, single center, non-randomized pilot study conducted at the Scalene Center for Advanced Research and Development (S-CARD), in Bengaluru, India, from February 2006 to March 2010. Approval was obtained from the Institutional Ethics Committee (IEC) duly constituted as per guidelines of the Indian Council of Medical Research (2000) [12-14].

Device

CYTOTRON-RTE–6040-864GEN (Class IIA Medical Therapeutic Device; developed by Scalene Cybernetics Ltd, Bengaluru, India), is a patented (U.S. Patent 9162076 B2 awarded 20/10 2015, European Patent EP 175350831, awarded 3/11/2015, Chinese Patent issued 2010, 09/08), CE marked device. It is in use for tissue regeneration or degeneration in man by applying rotational field, narrow-focused, quantum magnetic resonance targeted at the region(s) of interest (ROIs) using RFQMR platform technology. The device consists of multiple guns in 9 sequential axes (designated A to I) to deliver the computed Radio Frequency (RF) and pulsed, instantaneous quantum magnetic resonance (MR); a traveling platform or bed to bear the person undergoing treatment; an electronic switching system for controlling the guns; which in turn is controlled by a main computer through an on board microprocessor. There is provision for cooling and dispersing the heat generated during the operation. It is a full-body, wide-bore device with 864 guns using specialized near field antennae (K- μ ferrite type; near-field; gain; 10 dB) and a parabolic reflector delivery system. The device operates at the safe, non-ionizing and non-thermal end of the electromagnetic spectrum [15]. The CYTOTRON® can focus frequencies to a maximum of 300 MHz. For treatment of cancer patients with solid tumors, the delivered RF does not exceed 100 MHz in the presence of a high, instantaneous magnetic field ranging from 1mT (Tesla) to 6 T, for the time duration of 2.0 μsec to 10 msec, depending on the dosimetry. This therapeutically effective RF range is known to be non-ionising and non-thermal. Before the study commenced, specific tests were conducted by the Electronics and Radar Development Establishment (LRDE), Ministry of Defence, Government of India [16] (Ref: EMI/EMC/95527/RES/PVT dated December 9, 2005). Device risk from the point of view of performance, electromagnetic hazard, patient and operator safety, in accordance with the recommendations of the International Commission for Non-Ionizing Radiation Protection (ICNIRP), was evaluated. It was observed by the agency that both electric and magnetic field emissions from the CYTOTRON® are well below the hazardous levels specified by the ICNIRP for the measured frequency band and safe to be used on human biological systems. The device failure mode was assessed by the use of Failure Mode and Effects Analysis (FMEA) [17]. Therapeutic dosimetry is individualized and computed using proprietary and automated machine algorithms that combine inherent physical tumor characteristics and RF related delivery criteria [7].

Magnetic Resonance Imaging (MRI) Protocol

Pre-treatment

For brain lesions: Routine MRI (T1 and T2 weighted sequence) with contrast, diffusion, perfusion and spectroscopy is mandatory. For other solid tumors, routine MRI (T1 and T2 weighted sequence), with contrast and diffusion is adequate. MRI of the affected region (e.g. thorax, abdomen etc.) or the whole body (in cases of widespread metastasis) was done to obtain proton density (PD) data of lesions to be targeted as well as to archive base-line images prior to QMRT for tumor status determinations. Response Evaluation Criteria in Solid Tumors (RECISTv1.1) [18-20] was completed post QMRT and compared to pre-QMRT tumor measurements.

Proton Density (PD) evaluation

A 2D Proton density sequence of the tumor was obtained on film and copied to a compact disc (CD) by the radiologist for use at the treatment center for dose planning.

Surface marking

Very low intensity Computerized Tomography (CT) guided surface marking of the target tissue is made on the patient's body by the radiologist.

Treatment planning

Dosimetry: The dosimetry of QMRT® is based on the proton density of the tumor mass obtained using MRI. The CD containing PD images is loaded into the device computer, and the region(s) of interest (ROIs) is/are identified. Individual gun files are generated using software to obtain PD data spanning from skin to target and simulated as gun paths (Supplemental data Figure 1A). The largest and smallest diameter of each lesion is marked. A margin of 1-2 mm beyond the target area is marked to include any infiltrating, rapidly growing tumor cells around the lesion, and included in the region of interest (ROI). The planning film covers a 360^0 field for each lesion targeted. The sequence of dose planning is set in motion automatically by the computer, applying pre-planned proprietary algorithms. This dosimetry procedure is repeated for each lesion (primary and/or metastatic) for simultaneous targeting at one sitting with the whole body device. Supplemental data Figure 1B shows examples of dosimetry planned for several targets simultaneously in a patient with multiple metastases.

QMRT® protocol: The body surface marking is transferred to a transparent plastic sheet as a template for use in targeting the region(s) of interest (ROIs) during daily patient exposure in the CYTOTRON®. The template is placed on the body, and the markings are aligned with prominent anatomical landmarks (Supplemental data Figure 1C). For precise focusing of RF beams on the ROI, a laser guide pointing system (625-680 nM wavelength) is focused on the template to indicate and mark the position of the specific axes (A to I) used to target underlying ROI(s). The marked template is removed, and the laser guide lights switched off. The patient is moved into a precise position in the gantry and exposed to individualized QMRT® in the CYTOTRON® for one hour every day for a period of 28 consecutive days. Patients were periodically reviewed for one year from the day of completion of their treatment, till death or to the end of the study, whichever occurred earlier.

MRI protocol for determining tumor status post therapy and follow up

During follow up, the same MRI sequence that was performed prior to therapy (except PD determination) was obtained. Comparisons were made with the pre-therapy images in terms of measurable changes in dimensions, tumor volume and signal intensity differences between pre and post-treatment images of targeted lesions (as per RECISTv1.1).

Evaluation of life extension

Patient prognosis (expected days of survival) was determined at baseline (before therapy) using a proprietary palliative prognosis score (PaPS) model and insights from previous studies on prognostic factors [21-29]. This PaPS model has been widely assessed and used in different palliative care settings. In cases where blood samples are available, or for a more accurate prediction, the Pa PS, among other more recent scoring indices, was utilized - being more appropriate [24] for our study design. In this model, parameters considered are total white blood cell count, lymphocyte percentage, dyspnea, anorexia, pain and KPS Scores. The model supports normal total white blood cell counts with increased lymphocyte percentage, absence of anorexia and dyspnea, low pain score and high KPS as indicators for good prognosis. Patients were followed up for the period until their demise or the end of the study period. For the purpose of statistical analyses in the study, patients who were still alive at the end of the study period were 'counted' as 'deceased' immediately following the 'putative' end of the trial (23rd March, 2010). Actual survival refers to number of days the patients survived after the completion of 28 days of QMRT®, whereas expected survival refers to the number of days patients were expected to survive without therapy as calculated using the PaPS model [21-29].

Evaluation of Quality of Life (QoL)

Karnofsky performance scale score (KPS/ K- score) [30] was used to assess QoL. It was recorded at baseline (before therapy) and at the completion of 28 days of therapy.

The functional assessment of cancer therapy general population (FACT – GP version 4): A subtype of Functional Assessment of Chronic Illness Therapy (FACIT) [31,32] Quality of Life questionnaire was used. This is a 21-Likert type scale with physical wellbeing (PWB - 6 items), social wellbeing (SWB - 5 items), emotional wellbeing (EWB - 4 items) and functional wellbeing (FWB - 6 items) subscales. Total scores ranged from 0 to 108, with higher scores indicating better health-related QoL. Patients were asked to respond to each item with a score ranging from 0 - 4 (0 - not at all; 1 - a little bit; 2 - somewhat; 3 - quite a bit; 4 - very much). Final scoring was done based on specific scoring guidelines provided by FACIT.org, USA [32] duly licensed for use at S-CARD. Higher scores indicate better health-related QoL. Since KPS only deals with physical performance of the patients, both tools were deemed important in this study. The FACT-GP questionnaire was recorded at baseline (before therapy), at the completion of therapy, one month after completion of therapy and then every quarter for a period of 12 months.

Adverse event reporting

Patients were examined every day by the Investigator and a nurse for any adverse effects/events during treatment. The description, severity, date of onset and end of adverse events/adverse device effects, as well as outcome of the event/ effect were recorded.

Time Lines for Reporting Serious Adverse Events (SAEs)

In case of an unexpected SAE, the study investigator had to report immediately (within 24 hours) to the sponsor and within 7 working days of its occurrence to the ethics committee who had accorded approval for the study protocol. The sponsor had to report any SAEs to the Licensing Authority and other investigators participating in the study within 14 calendar days (as per ICH-GCP) [33].

Statistical analysis: Statistical software called 'STATISTICA' and Excel spreadsheets were used for data analysis. The Shapiro-Wilk Test was used to examine normality. The two way (mixed design) analysis of variance (ANOVA) was employed for survival data and FACT-GP scores. An independent variable was gender, and the dependent variables were the survival data and FACT- GP scores at two levels (before and after treatment). Paired 't' test as applicable to dependent samples was also applied for analyzing survival data, KPS and QoL at completion, and one month after completion of therapy. Level of significance was set at $p<0.05$. Only patients completing therapy (n=86) were included for statistical analysis and follow up. To analyze the data obtained during follow up, only the data set for patients who reported for the first review, i.e. one month after completion of therapy was included. Supplemental data Figure 2 shows the flow chart of patient compliance / iteration during study period with follow up. The data from patients, who reported late for scheduled follow up were excluded as the sample size of this patient group was small and not considered a statistically acceptable patient subset.

Results

Patient cohort

A total of 98 patients were assigned to the study after screening and applying inclusion/exclusion criteria. The study population comprised of Asian (81%), Caucasian (15%), Mongoloid (3%) and Negroid (1%) patients. 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. The spectrum of patients treated in this all-comer study is shown in Figure 2. Breast cancer, including two primary cases without metastasis, was the most common type of cancer in the study, followed by brain cancer. One primary carcinoma of the ascending colon (without metastasis) also underwent QMRT. A total of 86 patients (88%) completed the study. Twelve patients (12%) discontinued treatment for reasons that included progressive disease, concomitant other illness and related complications, inability to follow the protocol schedule due to personal compulsion or death. Supplemental data Table 1 provides the list of all the patients in the study, with relevant clinical data points and tumor response data based on RECIST v1.1.

Primary outcome

It was observed that 40 patients (n=86; 47%) who completed treatment, survived for 12 months after therapy as compared to the 0% predicted survival. Twenty-two patients (26%) survived for 6 months beyond the planned study period, when 0% was the predicted survival. Thirty-one patients were still alive at the end of the study period, i.e. on 23rd March 2010. Survival statistics are summarized in Figures 3A and 3B. Comparing predicted survival intervals with actual life expectancy during the follow up, there was a significant increase from the predicted mean of 117± 46 days to the actual mean of 377 ± 307 days, ($t = -8.21$, $p= 2.13$ E-12). A significant effect ($F=69.58$, $p=1.26$ E-12) of therapy alone on life expectancy was noted (Table 1) (Supplemental data Figure 3).

Secondary outcome

At completion of therapy (n=86), the KPS/K-Score had increased significantly ($p=7.25$ E-06), from its baseline value of 74 ± 15 (before therapy) to 80 ± 12 (post-therapy). FACT-GP scores showed

Table 1: Median survival (in days) observed in the study, is compared to expected survival times. Median expected survival times and confidence intervals are taken from a comparator study [22]. The confidence limits were determined using actual values of survival associated with ranked data. Median survival showed an increase of 375 days between the 2 groups and p<0.5 probability.

	Median (days)	Lower value of 95% Confidence Interval	Lower value of 95% Confidence Interval
Comparator study (n=127)	76	67	87
Present Study (n=78)	375	246	489

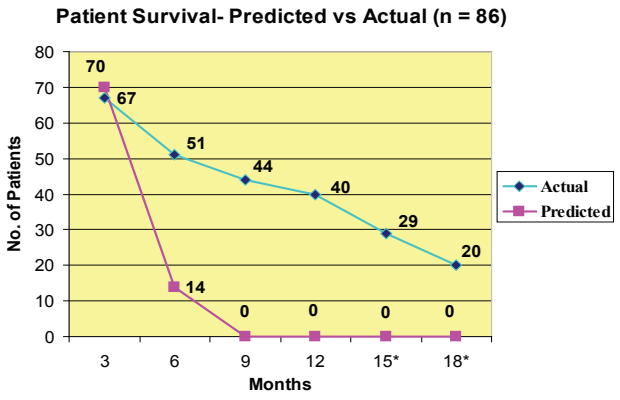

Figure 3A: Survival Outcome in QMRT treated patients. Predicted survival curve indicates no. of patients who were predicted to survive for the specified period without therapy according to the palliative prognostic score model [21-29]. Actual survival curve indicates no. of patients who survived after undergoing QMRT.* Includes patients reviewed beyond the follow up period of 12 months.

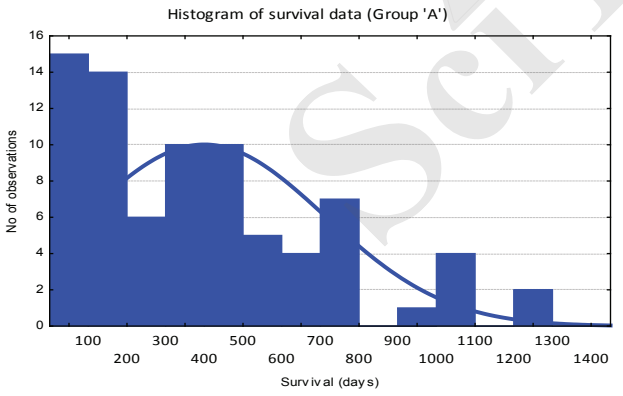

Figure 3B: Overall Survival. Bar graph summarizing number of patients per survival period, grouped into 100 day periods. *Note: only Maltoni [22] risk group A cases (78 out of 86) are shown in this graph. The number of observations in Group 'B' and 'C' was too low to permit any viable statistical analysis. (Of all cases followed up, only 5 and 3 patients were assigned to risk groups B or C, respectively.)*
Distribution of survival in our data (Group 'A') exhibited significant departure from the assumptions of normality (Shapiro-Wilk W=0.907; p=0.00003).

significant improvement from 71 ± 22 to 78 ± 18. At first review, i.e. one month after completion of therapy a small yet significant improvement (p=1.91 E-06, n=77) was reported (Table 2). Significant effect of therapy was observed on the QoL score; F=36.71, p=3.73 E-08 (Supplemental data Table 2).

Tumor stability and disease progression based on MRI findings

Fifty-one of the 86 patients (59%) who had completed treatment, reported for the first review, i.e. one month after QMRT completion. During the first review it was seen that 36 (71%) of these 51 patients showed no interval change and no deterioration or increase in tumor size on MR imaging, indicating stable disease. Measurable reduction in the size of the tumor was seen in 4 (8%) patients during the first review; whereas the tumor progressed in 22% of patients during this follow up period. Of the 36 who had no interval change in tumor characteristics after one month, 8 remained stable, 2 showed complete resolution and 2 had progressed at 12 months after completion of therapy. The data is summarized in Figure 4. Representative before and after QMRT evaluations of patients' MRIs reflecting tumor status based on RECIST 1.1,are provided in supplemental data Figures 4-9.

Adverse event/adverse device effect monitoring [16,33]

No adverse event or adverse device effect severe enough-either superficial or systemic -to prompt therapy termination, were noted during therapy or in the follow up period. All vital parameters remained within normal limits during the 28 days of therapy. In case of any minor discomfort reported during therapy; patients were managed by the in-house physician or referred to a hospital. The most commonly encountered adverse effects were mild headache and giddiness in patients with brain tumors, and a local tingling sensation or mild bleeding per-urethra in a case of nasopharyngeal carcinoma and advanced urinary bladder cancer, respectively, none of which prevented patients from completing QMRT.

Discussion

Cancer is a globally debilitating disease that is tipping the balance between rising health care costs, affordability and the socio-economic burden of the disease. Although overall cancer incidence trends for 2016 are predicted to be stable in women and marginally decreasing in men in the US, it is forecasted that there will be an increase in cancer incidence worldwide, with about 15 million new cases diagnosed annually; the burden weighing heavily on developing countries, accounting for more than 65% of cancer deaths world-wide [34-36]. Weighing down on this increasing burden is the futility of conventional treatment modalities in advanced disease, particularly palliative cancer chemotherapy or radiotherapy; with minimal clinical benefit [37-39], and the treatment abandonment (TxA) common in childhood cancers due to related toxicity issues [40]. There is an urgent need for integrated treatment or palliative care modalities that can increase life expectancy and afford better QoL. In view of this important primary objective, the study was aimed to evaluate the efficacy of an innovative treatment modality, QMRT®, on life expectancy and QoL in advanced cancer patients. Recently, an article in the American Society of Clinical Oncology's Connection Magazine cited Jamie H. Von Roenn, MD, of North-Western University who commented that "people equate palliative care with the end of life when in fact it is part of care throughout the continuum [41,42]." The article further states that palliative care is often perceived as an EoL measure and provided as an option ONLY when curative or life-prolonging therapy is no longer beneficial [43]. However, experts in palliative medicine recognize that some form of palliative care - including symptom management - should be incorporated into oncology care earlier on in the treatment planning, especially for patients presenting with advanced disease. In this study, the FACT-GP and KPS used to evaluate the QoL and physical performance,

Table 2: Values shown are +/- standard deviations, for Karnofsky Performance Scores and for FACT-GP QoL scores for 86 patients after completion of therapy and 77 patients one month thereafter.

	Before Therapy (mean ± SD)	At completion of therapy* (mean ± SD)	At one month after completion of therapy† (mean ± SD)	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

*At the end of 28 days of QMRT®; † One month after completion of 28 days of therapy; ‡ Karnofsky Performance Score; § Functional Assessment of Cancer Therapy-General Population, © FACIT.org [31].

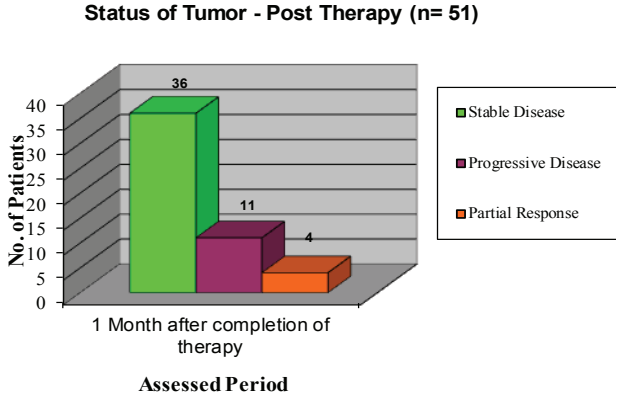

Figure 4: Tumor Response Evaluation. Tumor stability and partial responses were more commonly encountered with very few patients showing progressive disease among the survivors, post-QMRT. The total number of patients in each subset is given above respective bars.

respectively, showed significant improvements with an associated increase in life expectancy. In contradistinction to the known drawbacks of conventional modalities, QMRT® positively impacts QoL parameters as evidenced by the KPS and FACT-GP tool scores. KPS Scores for these patients improved significantly (p=7.25 E-06), from 74 ±15 (before therapy) to 80 ± 12 (at completion of therapy). FACT- GP derived QoL scores also exhibited significant increase (p=1.71 E-08 and p=1.91 E-06) at the completion and 1 month after completion of therapy, respectively. This significant improvement in KPS (p=7.25 E-06) indicates that the therapy had a positive effect on the physical well-being of the patients at completion of therapy. Substantially significant improvement was seen in FACT-GP scores when compared to KPS at completion of therapy. This can be attributed to overall improvement in social, functional and emotional well-being of patients undergoing QMRT. Significant increase in life expectancy from the predicted mean of 117 ± 46 days to the actual mean of 377 ± 307 days (p=2.13 E-12) was noted. Such statistically significant increase in survival implies that the finding is not a chance occurrence. It was remarkable that 31 of the 86 treated patients (with an average predicted survival of less than 6 months) were still alive at the end of study on 23rd March 2010. These include 29 patients surviving for 3 months and 22 patients surviving for 6 months beyond the study period (Figure 3A). An incidental finding of the study was the comparably similar impact on QoL and increased life expectancy in male and female patients treated by QMRT (Supplemental data Table 2). Very compelling data was seen with MRI evaluation one month after completion of therapy. Thirty six of 51 patients (71%) had stable disease, maintained during the study period. This disease stability - as evidenced by the unchanged tumor size - suggests that the therapy had slowed the progression of cancer, contrary to the commonly encountered progression rate observed in treatment refractory end-stage cancer. The decrease in tumor size in 4 patients also provides evidence for arrest of tumor progression in some cases. Of the 36 stabilized cases, 8 patients remained stable and 2 showed complete tumor regression 12 months after therapy. This finding suggests that QMRT® can be effective in controlling tumor growth for an extended duration, with both progression free survival (PFS) and disease free survival (DFS) endpoints in terminal cancer patients. We are well aware that the presumptive arrest of cellular proliferation and tumor progression based on tumor size measurements, as evidenced by MRI, as is routinely acceptable, is an outcome that needs to be investigated further in a larger sample cohort, using specific and appropriate functional biomarkers, and the more recently amenable PERCIST v1.0 using Positron Emission Tomography-Computerised Tomography (PET-CT) for metabolically active disease and end-point evaluations [44]. The study population included patients from different parts of the world. Cancer does not grossly differ (histopathologically or symptomatically) in a particular ethnic group or geographical boundary, even though the incidence of a particular cancer may be higher in a given population. Since diverse types of tumors were included in the study using individual PD measurements as the basis of QMRT® the relevance of the results may be universally applicable to all solid tumors, irrespective of pathological sub-type, grade or stage of the tumor. Studies to tease out these distinctions in larger cohorts might be very valuable in positioning QMRT® earlier within standard of care regimens / main lines of treatment. However, we recognize that the number of cases was small for some tumor types in this open label, all comer compassionate study setting. Following FDA's Investigational Device Exemption (IDE), clinical trials will be carried out here in the United States using larger patient cohorts in RCT settings, in distinct tumor types, to throw more light on the role of QMRT® in routine cancer management. No adverse effects of therapy were recorded. The lack of adverse events or adverse device effects during the therapy or at defined follow up time points indicates that the therapy can be safely given to patients in palliative care settings without further deteriorating their QoL or increasing life support requirements. The emotional, functional and psycho-social well-being of the patients was impacted positively by QMRT®, along with vastly enhanced physical well-being. The improved QoL and overall 'wellness' of these cancer patients with extended survival was a hallmark in this study.

Presumptive Mechanism of Action (MoA) of QMRT®

QMRT has evolved using Magnetic Resonance Imaging (MRI) based on intrinsic proton density (PD) measurements of target tissue to manipulate biophysical cellular signalling. Highly complex

electromagnetic beams in the safe radio frequency ranging from 30 kHz to 300 MHz, in the presence of controlled, high, instantaneous MR, can be precisely focused on target tissues to alter the cell membrane potential of cells, which in turn stimulates tissue growth in degenerative diseases such as osteoarthritis [45] or triggers apoptosis (programmed cell death) and impacts growth in solid tumors, as reported here. Membrane potentials (*Vm*) are created by the differences in the concentration of ions inside and outside the cell creating an electrochemical force across the membrane. The *Vm* of normal cells is around -70mV to -90 mV [46]. Cone's theory proposing a general correlation between proliferation and *Vm* [46,47] was supported by previous studies which demonstrated significant *Vm* depolarization during malignant transformation of normal cells [48,49]. More recently, a review of transmembrane potential (TMP) in Frontiers in Physiology, states that membrane depolarization might be important for the emergence and maintenance of cancer stem cells (CSCs) that are essential for sustained tumor growth [50]. This more recent elucidation provides a broad understanding of *Vm* in the process of bioelectrical signalling in cancer cells, contributing to the regulation of proliferation, migration, and differentiation. They also suggest that *Vm* could even be "artificially modified" in order to inhibit tumor growth and metastasis. Although the precise physiological mechanism of action of QMRT® is not explicit at this time, the research leading up to use of specific RF delivered in the presence of an instantaneous magnetic field, led to triggering the modulation of the aberrant TMP of tumor cells in man. Electromagnetic field exposure has been demonstrated to elicit a wide variety of physiological effects on individual cell types and tissues [51-55]. For example, pulsed electromagnetic fields have been used to elicit therapeutic benefits in a variety of diseases [56], predominantly in the treatment of chronic defects of the musculoskeletal system such as osteoarthritis [57-60], osteoporosis [61,62], multiple sclerosis [63,64], wound healing [65-67], fibromyalgia [68], tendonitis and pain [69,70], to name but a few. We have also applied QMRT® to treat patients with other chronic degenerative diseases, such as osteoarthritis (OA) [45] reported earlier, and Multiple Sclerosis (MS) more recently, in a clinical trial setting [71]. Non-withstanding impressive clinical benefits, mechanistic details of the MoA have not been elucidated at the cellular/molecular level for QMRT®. However, many interesting biochemical consequences of electromagnetic fields (EMF) and MR have been described in the literature, including enhanced mesenchymal cell differentiation via the induction of a variety of cytokines, namely transforming growth factor beta [61]. Use of radio frequency (RF) in the treatment of cancer is also not new. Procedures like radiofrequency ablation (RFA) are performed routinely on tumors of the lung, liver, kidney and bone [72-74] and, less frequently, other organs [75,76]. In the majority of these regimens however, RF waves passing through a locally inserted probe increases tissue temperature, resulting in the destruction of tumors by heat, unlike the non-thermal RF range used in QMRT. Interestingly enough, differences in resting cell membrane potential values between normal and proliferating cancer cells - extensively demonstrated long ago [77-82], is the target of QMRT modulation conceptualized and harnessed by this platform technology. Very few studies have been carried out in the low-frequency non-thermal RF range we deploy, but examples of interesting responses do exist. For example, cytotoxic or cytostatic effects of low power RF directed toward cancer cells - while sparing the surrounding stroma - have been reported in preclinical models [82-84]. The TMP of resting, dividing, proliferating or inflammatory cells is unique and dynamic. In fact, differences in resting cell membrane potential values between normal, proliferating and cancer cells have long been demonstrated [80-85]. Transformed cells use altered cellular signalling pathways to regulate protein synthesis to disrupt the normal process of apoptosis or programmed cell death. One such very seminal pathway is the p53/p73 group of proteins [86], that needs to be activated at appropriate times within the life cycle of normal cells. Many proliferating illnesses like cancer and degenerative diseases like multiple sclerosis and osteoarthritis are linked to disturbances in the protein synthesis process. Several studies have also shown that magnetic fields may play an important role in the control or alteration of cell activity in such tissues [87]. The QMRT® field may act on the mitochondrial membrane and interfere with communication between the gene transcription machinery and the protoplasmic glycoproteinic complexes involved in the promotion of cellular mitosis. Further, it is also surmised that the impedance of the mitochondrial membrane induced by certain gene products increases with QMRT® exposure, particularly in advanced malignant states. In fact, it has been reported that the highest impedance is observed in highly undifferentiated tumours [78,80]. Studies have also shown that Nuclear Magnetic Resonance (NMR) exposure sensitizes tumor cells to undergo apoptosis [88]. The responsible protein-signalling pathway here was the p53 /p73 mediated pathway. Based on the outcomes reported in treating malignant lesions, the CYTOTRON® induces such alterations of the TMP in a controlled manner, to modify cellular command and control and alter cellular activity. One possible way by which delay of tumor progression could be achieved in our protocol is by eliciting irreversible bio-physical modulation of cancer cells. During the time this study data was being consolidated, Chernet and Levin [3] reported that bioelectric signals that reveal, induce and normalize cancer could have mastery over somatic voltage gradients and lead to normalization of cancer or induce rebooting strategies, resulting in transformative advances in basic biology and oncology! This statement in hindsight aptly summarizes the approach taken by RFQMR technology to induce apoptosis and cancer cell death. Over the last two decades, the phenomenon of irreversible electroporation of tumor cells has been employed in the clinic to enhance the utility of classical chemotherapy [74]. In fact, use of an extension of the Rotational Field Quantum Magnetic Resonance (RFQMR) technology for Focused Resonance Nano-permeabilization (FORN) of target tissue to optimize cancer drug delivery is currently under active investigation [89-92]. Irreversible cell membrane permeabilization by exposure to electric or pulsed magnetic fields, has only recently received greater attention as a means for minimally invasive tissue ablation. Non-thermal irreversible electroporation (IE) is now considered as a technique in surgery, treating nervous system disorders and vascular tissue regeneration [93-95]. Several efforts to apply such methods to treat cancer are reportedly underway and data from these studies in clinical practice are gradually gaining relevance [74,96,97]. Finally, guided by studies showing that low levels of electromagnetic fields (EMF) modify cancer cell growth, several laboratories have set out to systematically identify tumor tissue-specific field parameters to evaluate the therapeutic potential of EMF. Sets of tumor-specific frequencies were indeed identified and shown to have efficacy in patients with advanced cancer [98-101], particularly in human brain tumors [102]. Trials using such low intensity tumor-treating fields (TTF) have been reported [103,104] and at least one instrument, Optune™ (Novo-Cure, Israel), has recently gained US-FDA approval [105]. The claim is that TTF create low intensity, alternating electric fields within a tumor by exerting physical forces on electrically charged cellular components, preventing the normal mitotic process and causing cancer cell death. Even more 'out of the box' approaches,

like finding therapeutic interventions that can effect biophysical changes in ion 'channelopathies' are also currently being explored [106]. Although, as mentioned earlier, definitive assignment of a mechanistic explanation for the effects observed with the CYTOTRON® is pending further investigation, some of the aforementioned phenomena assisting the modulation of TMP in diseased cells, by combining RF and MR, is very likely to be integral to the clinical benefit observed with QMRT®. Pathological cells are different from healthy cells due to inherent tissue-specific compositions that affect proton density, permittivity, conductivity and depth of penetration parameters of RF and MR. The CYTOTRON® is programmed to affect target tissue (proton-dense tumors) non-invasively, sparing surrounding normal tissues. This is in contradistinction with conventional ionizing radiotherapy, which explains the absence of any adverse effects like radiation sickness, radiation-induced necrosis, normal tissue scarring etc. Other typical treatment consequences like systemic chemotherapy induced myelo-suppression, loss of appetite and related weight loss etc. are also not experienced with QMRT®. This study is the first of its kind, demonstrating the use of the emerging RFQMR® technology and QMRT® in the management of cancer patients. Failure of several treated patients to report for the quarterly follow up (Supplemental data Figure 2) due to personal reasons (good response, death, no response, protocol non-compliance), or logistic and other personal constraints, despite repeated reminders from the study team, limited the scope and outcome of the study. More studies are necessary to enroll patients with larger representation of specific tumor types (freshly diagnosed cases with or without metastasis) to establish the efficacy of this therapy in the earliest stages of the disease, as a stand-alone therapy or in conjunction with other available anticancer therapies. It is hoped that more studies of this kind will help shed additional light on its effectiveness and spur advanced studies on the mechanism of action of QMRT® in cancer. A good understanding of "The Body Electric" as described by Becker and Selden in their seminal book [107] would help to enhance one's overall understanding of how electromagnetism could underlie the very foundations of life, and allow exquisite biophysical manipulations to achieve therapeutic benefit.

Conclusion

Further evidence is being accumulated on the role of QMRT® in primary and metastatic disease in a larger number of patients. Based on our overall experience and findings in this study, it can be concluded that exposure to QMRT® extends life expectancy and improves QoL. Stabilizing the disease and arresting tumor progression in a very unique way, without collateral damage, is a break through. This emerging treatment modality can be a very useful addition to standard of care therapies and soon become integral to mainstream cancer medicine.

Note of Attribute

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Conflicts of Interest/Disclaimers

The investigators Dr. Ranjit Kumar MD, and Dr. Anjana Rani Nair, BAMS MSc. employed during the study by S-CARD, in Bengaluru, India, and Dr. Reinhard Ebner PhD, Scientific Advisor to Shreis Scalene Sciences LLC, have no conflicts of interests. The senior author, Dr. R.V. Kumar DSc is the inventor and IP holder for the Cytotron® device, RFQMR® technology and QMRT®. He heads a public company, Scalene Cybernetics Ltd., in Bengaluru, India.

Prof. Meena Augustus PhD is CEO& CSO of Shreis Scalene Sciences (N. & S. America)-an LLC registered in the United States currently working towards seeking approval for the Cytotron® through the Mexican-COFEPRIS, Health Canada & US-FDA.

Dr. G.S. Nayar M.D. (Retd. Indian Air Force) is a practising Cytotron user and QMRT practitioner currently running a commercial clinic to treat musculo-skeletal diseases and malignancies with QMRT, in Bengaluru, India.

Authors Contribution

‡All 3 authors contributed equally.

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Sl.No	Pat_ID	Type of Cancer	Histopathological Dx	Metastasis	TNM staging/treatment history	Tumor Status* One month after completion of therapy	Predicted Survival (days)	Actual Survival (days)	Increase in Survival (days)	% Increase	Alive/ Deceased at end of study period (23/03/2010)	KPS Score		FACT GP		
		n= 86	n= 86	n= 86	n= 86	n= 51	n= 86	n= 86	n= 86	n= 86		Pre Therapy (n = 86)	At completion of 28 days of therapy (n = 86)	Pre Therapy (n = 86)	At completion of 28 days of therapy (n = 86)	At one month after completion of therapy (n= 77)
1	012/07	Brain	Glioblastoma Mutiforme- Rt Frontal Lobe- Recurrent	Nil	High grade	ND	95	128	33	35	Deceased	40	80	98.3	103.3	103.3
2	016/07	Pancreas	Periampullary CA- Head of Pancreas	Nil	Stage T2	ND	100	334	234	234	Deceased	70	70	90.5	87	87
3	025/07	Breast	Carcinoma Breast (ER/ PR Negative)	Pelvis, proximal femur and spine	Post Surgery TxN0 M1	SD	138	1,011	873	633	Alive	60	80	97.7	98.3	98.3
4	029/07	Ovaries	Cyst Adenocarcinoma Ovaries	Liver, inguinal & axillary lymphnodes	Stage IV	ND	42	80	38	905	Deceased	60	70	57.8	68.7	68.7
5	005/06	Brain	Glioma Frontal Lobe	Nil	Glioma Frontal Lobe	SD	154	1,232	1,078	700	Alive	40	90	105.7	105.7	105.7
6	006/07	Breast	CA Breast (Rt) (Histopath Not available)	Lungs (Rt), liver, mediastinal Lymphadenopathy	Post Surgery Tx N0 M1	ND	133	489	356	268	Deceased	90	90	73.8	69.9	---
7	008/06	Pancreas	Periampullary carcinoma- Pancreas	Abdominal Lymphadenopathy	T2 N1M0	ND	165	367	202	122	Deceased	80	90	78.1	87.3	87.3
8	018/07	Endometrium	CA Endometrium	Pulmonary	Post Surgery Grade IVb	PD	3	110	107	3567	Deseased	40	80	20.5	47.7	47.7
9	013/07	Pancreas	Periampullary CA- Head of Pancreas	Nil	Post Surgery Tx	SD	145	1,079	934	644	Alive	80	90	101.5	102.7	102.7

10	**022/07**	Liver	Hepatocellular carcinoma	Nil	NON RESECTABLE	ND	118	91	-27	-23	Deceased	70	80	70.2	80.2	80.2
11	**011/07**	Brain	Anaplastic Medulloblastoma Recurrent	Nil	Anaplastic Medulloblastoma	SD	145	128	-17	-12	Deceased	80	90	65.7	77.5	---
12	**002/06**	Pancreas	Adenocarcinoma- Head of Pancreas	Nil	Post Surgery Tx	ND	93	187	94	101	Deceased	80	90	87.9	91.4	---
13	**011/06**	Breast	Invasive Lobular carcinoma breast (Lt)	multiple bone, cerebellum, cerebral	T2 N1 M1	ND	100	358	258	258	Deceased	80	90	52.7	79.5	79.5
14	**033/07**	Synovial Sarcoma	High Grade Synovial Sarcoma	Pulmonary (Both)	High Grade	SD	198	127	-71	-36	Deceased	90	90	106.8	103.3	---
15		Pancreas	Periampullary CA	Hepatic	T3 N0 M1	PR	108	516	408	378	Deceased	50	80	72.4	88.1	88.1
16		Breast	CA Breast (Lt) (Histopath Not available)	Axillary Lymphnode (Lt)	Post Surgery Top Nx M0	SD	178	1,044	866	487	Alive	90	90	71.8	83	83
17	**010/07**	Pancreas	Carcinoma Tail of Pancreas	Liver, Lt paraaortic Lymphnodes	T3 M1	PD	66	133	67	102	Deceased	80	90	49.2	49.2	49.2
18	**004/07**	Brain	Glioblastoma Mutiforme WHO Grade IV	Nil	Glioblastoma Grade IV	ND	111	66	-45	-41	Deceased	40	90	45.4	52.4	52.4
19	**034/07**	Appendix	Adenocarcinoma Appendix	Retrocaval, paraaortic , mesenteric lymphnodes	TX N1 M1	PD	125	394	269	215	Deceased	70	80	84.2	98.9	98.9
20	**006/06**	Liver	Hepatocellular carcinoma	Nil	NON RESECTABLE	ND	95	38	-57	-600	Deceased	70	80	59.7	79.5	---
21	**007/06**	Brain	Glioma	Nil	Glioma	ND	175	1,211	1,036	592	Alive	80	90	67.5	80.5	---
22	**001/06A**	Colon	Adenocarcinoma - Ascending colon- Grade II -III	Nil	T1 N0 M0	SD	201	752	551	274	Deceased	80	90	60.2	72.9	72.9
23	**004/06**	Ovaries	Carcinoma Ovaries	Pelvis, Liver, mesentric lymph nodes	Stage IV	PD	128	389	261	204	Deceased	80	90	65.2	65.2	---

24	**006/08**	Peritoneum	Serous Primary Peritoneal carcinoma	Pelvic Lymphnodes	no data	PD	5	264	259	5180	Deceased	40	60	47.5	70.5	70.5
25	**019/07**	Lungs	Adenocarcinoma Lungs (Rt)	cervical, mediastinal lymphnodes	T4 N2 M1	ND	81	53	-28	-35	Deceased	70	90	87.3	92.3	92.3
26	**003/07**	Liver	Hepatocellular carcinoma	Nil	Not Resectable	ND	88	134	46	52	Deceased	60	80	79.8	84.5	84.5
27		Breast	Infiltrating Ductal cell carcinoma (Rt) Grade III	Pelvic bone, Liver, Brain	Post Surgery T0 Nx M1	SD	76	1,075	999	1314	Alive	70	90	73.9	76.2	76.2
28	**002/07**	Prostate	Adenocarcinoma- Prostate	Inguinal Lymphnodes	Tx N1 M1b	SD	21	594	573	2729	Deceased	40	80	91.7	104.2	104.2
29		Lungs	Non small cell Carcinoma Lungs	Ribs, Vertebrae, Pelvis, Femur, brain	Stage IV	SD	125	950	825	660	Alive	70	90	91.4	94	94
30	**028/07**	Ovaries	Cyst Adenocarcinoma Ovaries	Liver	Post Surgery Grade IV	ND	122	417	295	242	Deceased	80	90	77.7	87.5	87.5
31	**003/06**	Brain	Anaplastic Astrocytoma Grade III	Nil	Anaplastic Astrocytoma Grade III	SD	153	389	236	154	Deceased	50	70	50.2	72.5	61.2
32	**001/08**	Ovaries	Not available	Liver, Vertebrae, abdomina/ axillary lymphnodes, peritoneum	Tx N M4 Stage IV	SD	84	210	126	150	Deceased	70	80	58.2	72	70.8
33	**002/08**	Ovaries	Moderately differentiated serous cacrcinoma of ovaries (both)	Extensive metastasis in abdominal cavity and anterior abdominal wall	Tx N0 M1 Stage IV	SD	129	795	666	516	Alive	80	80	94.5	98.7	98.7
34	**005/08**	Breast	Carcinoma Breast (both)- Recurrent (Histopath Not available)	Abdominal and Skeletal metastasis	no data	ND	66	60	-6	-9	Deceased	70	70	29.8	42.2	42.2

35	**007/08**	Bladder	Papillary Carcinoma-Bladder	Nil	pT3b N0 M0	ND	177	172	-5	-3	Deceased	90	90	100.3	100.3	100.3
36	**008/08**	Oesophagus	Adenocarcinoma GE Junction	Liver	T1 N0 M1	PD	141	88	-53	-38	Deceased	90	90	77.8	80.2	80.2
37	**009/08**	Breast	CA Breast (Lt) (Histopath Not available)	Pulmonary, pleural , osseous and nodal metastasis	post op Tx pN1 M1	ND	33	65	32	97	Deceased	70	70	37.3	50.9	50.9
38	**010/08**	Gall Bladder	Cholangiocarcinoma	Nil	T post op N0 M0 Recurrent	ND	117	763	646	552	Alive	90	90	46.8	61.5	61.5
39	**012/08**	Spinal Astro	Spinal Astrocytoma	Nil	WHO Grade II	SD	177	755	578	327	Alive	90	90	52.3	68.7	68.7
40	**013/08**	Brain	? Cranial Nerve Neuroma/ Meningioma	Nil	WHO Grade I- II	SD	87	748	661	760	Alive	80	90	35.2	89.8	89.8
41	**014/08**	Lungs	Bronchogenic Carcinoma	Lymphnodes Prevascular space, Pratracheal region, Brain	T2 N2 M1 Grade IV	ND	132	156	24	18	Deceased	70	70	57.4	57.4	57.4
42	**015/08**	Colon	Adenocarcinoma Colon	Skeletal Metastsis	T3 N1 M1 Stage IV	SD	153	701	548	358	Deceased	90	90	70.1	71.3	71.3
43	**017/08**	Colon	Adenocarcinoma Ascending colon and caecum Grade II	Nil	T3 N0 M0 Stage IIA	SD	75	720	645	860	Alive	90	90	42.7	61.3	61.3
44	**019/08**	Lungs	Bronchogenic Carcinoma	Mediastinal Lymph nodes	T2 N2 M0 Stage IIIA	PD	51	65	14	27	Deceased	80	80	44.3	47.6	47.6
45	**020/08**	Brain	Glioblastoma Mutiforme	Nil	Grade IV Recurrent Glioblastoma	ND	162	136	-26	-16	Deceased	80	80	94.3	94.3	---
46	**021/08**	Lungs	Non small cell adenocarcinoma Lungs (Lt)	Nil	T1 N0 M0 Stage III B	SD	102	687	585	574	Alive	90	90	77.5	97.5	97.5
47	**022/08**	Breast	Ductal cell carcinoma	Dorsal , lumbar vertebrae, Illiac bone,	T1 N0 M1	SD	162	675	513	317	Alive	90	90	89.7	89.7	89.7

48	**024/08**	Colon	Adenocarcinoma- Sigmoid colon	Nil	T0 (post op)N2 M0	SD	177	574	397	224	Deceased	90	90	95.8	95.8	95.8
49	**025/08**	Cervix	Squamous cell carcinoma-Cervix	Skeletal Metastsis	T0(post op) N1 M2	ND	90	45	-45	-50	Deceased	90	90	97.7	95.3	95.3
50	**028/08**	Duodenum	Moderately differentiated Adenocarcinoma-Duodenum	Head of Pancreas, Liver, Peripancreatics and coeliac lymphnode	T0 N1 M2	ND	54	28	-26	-48	Deceased	70	70	46.6	38.9	38.9
51	**030/08**	Breast	Invasive Ductal carcinoma (Rt)	Axillary Lymphnode (Rt)	Tic pN1 M0 Grde IIIc	SD	174	629	455	261	Alive	80	80	74.9	74.9	74.9
52	**031/08**	Pancreas	CA Head and Uncinate process	Hepatic, Local Lymph node	T2 N1 M1	ND	54	84	30	56	Deceased	90	90	50.5	54	54
53	**032/08**	Breast	Infiltrating Ductal cell carcinoma	Hepatic	T1 N1 M1	PD	162	52	-110	-68	Deceased	80	80	101	101	101
54	**033/08**	Brain	Glioblastoma Mutiforme	Nil	Glioblastoma Grade IV	SD	96	252	156	163	Deceased	30	40	42	42	--
55	**036/08**	Colon	Adenocarcinoma Ascending colon	Nil	T0 N0 M0 post op	ND	177	602	425	240	Alive	90	90	95.7	95.7	95.7
56	**037/08**	Breast	Ductal Cell Carcinoma (Lt)	Nil	Tic N0 M0	SD	129	581	452	350	Alive	90	90	88.7	96	96
57	**038/08**	Breast	Infiltrative Ductal Carcinoma (Lt)	Liver, Pleural (?)	Tx N0 M1	SD	162	573	411	254	Alive	90	90	89.5	91	91
58	**039/08**	Ovaries	Papillary Cystadenocarcinoma Ovaries (both)	Omentum, Pelvic nodes, Peritoneal Nodes,	Stage IV	SD	159	564	405	255	Alive	80	90	81.6	84.6	84.6
59	**040/08**	Stomach	Well Differentiated Adenocarcinoma- Stomach	Nil	T1 N1 M0	PD	129	218	89	69	Deceased	80	80	89.3	97.5	97.5
60	**041/08**	Breast	Invasive Ductal Carcinoma (Rt)	Liver	Tx N0 M1	SD	132	91	-41	-31	Deceased	90	90	57.3	67.4	67.4
61	**044/08**	Skull Bone	Mesenchymal Chondrosarcoma Recurrent	Locally Invasive	Recurrent Mesenchymal Chondrosar	SD	132	497	365	277	Alive	90	90	80.3	81.5	81.5

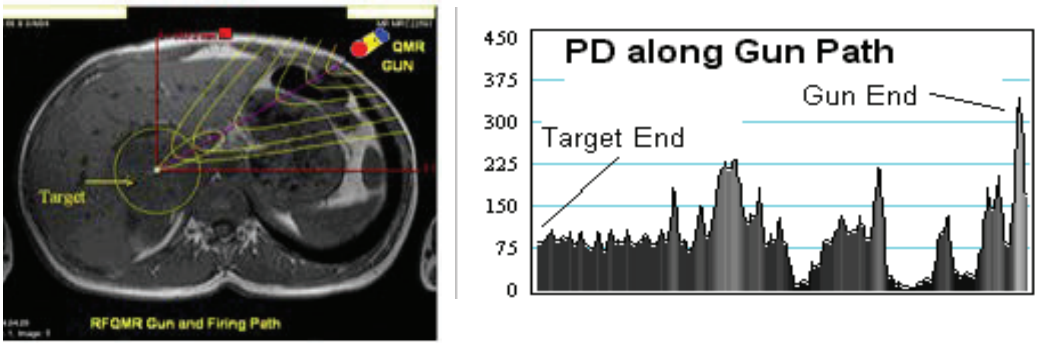
62	**047/08**	Naopharynx	Transitional Cell Carcinoma of Nasopharyx	Nil	T4b N1 M0 (IV B)	SD	75	491	416	555	Alive	80	80	35.4	51.6	47.3
63	**049/08**	Brain	Anaplastic Astrocytoma/ glioblastoma WHO Grade IV	Nil	Glioblastoma Grade IV	SD	90	488	398	442	Alive	80	80	68.6	68.6	68.6
64	**050/08**	Brain	Anaplastic Astrocytoma	Nil	Astrocytoma Grade II	SD	105	484	379	361	Alive	70	70	94	99	97
65	**051/08**	Sino nasal	Sino nasal squamous cell carcinoma	Nil	T4a N0 M0 Stage IVA	ND	99	472	373	377	Alive	60	60	66.2	73.8	73.8
66	**057/08**	Liver	Intrahepatic Cholangiocarcinoma	Hepatic	T N0 M1 Stage IV	ND	58	80	22	38	Deceased	60	60	44.5	65.6	65.6
67	**001/09**	Thyroid	Papillary Carcinoma - Thyroid	Pelvic Bone	Tpost op N0 M1	SD	57	266	209	377	Deceased	60	60	58.3	72.4	77
68	**002/09**	NHL	Non-Hodgkin Lymphoma	Nil	Stage IV AX	ND	162	441	279	172	Alive	90	90	98.9	108	108
69	**003/09**	Breast	Invasive Ductal carcinoma (Lt)	Lungs, Sternum, C6 Vertebrae, Frontal lobe	post op Tx N0 M1	ND	129	246	117	91	Deceased	80	80	70.8	67.7	67.7
70	**004/09**	Brain	Astrocytoma Grade II	Nil	WHO Grade II astrocytoma	PR	117	180	63	54	Deceased	60	70	87.5	85.8	95.1
71	**005/09**	Colon	Moderately differentiated Adenocarcinoma- Colon and Anus	Hepatic and Lungs	post opTx N0 M1 Stage IV	PD	159	185	26	16	Deceased	70	70	92.8	100.7	87.8
72	**006/09**	Lungs	Non small cell carcinoma Lungs (Rt)	hepatic and mediastinal lymphnode	T2a N2 M1b Stage IV	SD	87	239	152	175	Deceased	70	60	51.8	48.7	50.1
73	**007/09**	Cervix	Squamous cell carcinoma-Cervix	Lungs	post op Stage IVb	ND	96	118	22	23	Deseased	80	80	64.8	53.7	53.7
74	**008/09**	Breast	Ductal cell carcinoma (Lt)-Her2Neu- (+), ER(+), PR (-)	Hepatic and Rt scapula (?)	post op Tx N0 M1	SD	162	418	256	158	Alive	90	90	72.2	86.2	73.8
75	**010/09**	Melanoma	Malignant melanoma	Multiple skeletal Metastasis	Stage IVC T1b N3 M1	ND	177	412	235	133	Alive	70	70	65.6	62.1	62.1

76	**011/09**	Sarcoma	High grade angiosarcoma-Inguinal region	Lung	T1a N1 M1a Stage IV	ND	105	71	-34	-32	Deceased	80	80	42.2	73.7	71.6
77	**012/09**	Liver	Hepatocellular carcinoma	Paraaortic Lymphnodes	Non Resectable HCC, M0	ND	48	45	-3	-6	Deceased	70	50	36.8	44.9	44.9
78	**013/09**	Liver	Hepatocellular carcinoma	Nil	Non Resectable HCC, M0	SD	183	109	-74	-40	Deceased	70	60	102.8	78.8	57.1
79	**015/09**	Kidneys	Renal Cell Carcinoma (Lt)	Lung (Rt)	Tx N0 M1 Stage IV	SD	177	400	223	126	Alive	70	70	94.5	103.6	100.6
80	**017/09**	Lungs	Bronchoalveolar Carcinoma	Lungs, Adrenal glands (Lt)	T2 Nx M1b Stage IV	ND	105	56	-49	-47	Deceased	80	80	60.3	54.4	54.4
81	**018/09**	Liver	Hepatocellular carcinoma	Lungs	Non Resec Mets in Lungs	SD	54	150	96	178	Deceased	70	70	78.2	69.2	79.2
82	**019/09**	Prostate	Adenocarcinoma Prostate	Nil	T2c N0 M0 (Gleason 6 (3+3) Grade 2	PR	174	385	211	121	Alive	80	80	75	90	90
83	**020/09**	Sarcoma	Pleomorphic sarcoma/ Metastatic Phyllodes tumor from breast (?)	Left lung and gluteal muscle	T2b N0 M1a Stage IV	ND	90	383	293	326	Alive	50	50	52.2	63.8	63.8
84	**022/09**	Liver	Hepatocellular carcinoma	Nil	Non-Resectable N0 M0	PD	138	112	-26	-19	Deceased	80	80	67.1	83.3	83.3
85	**026/09**	Endometrium	CA Endometrium	Sacrum, L5 vertebral body, rt piriformis muscle	No data	ND	63	78	15	24	Deceased	60	60	31.3	54	54
86	**029/09**	Lungs	Adenocarcinoma lung (Lt)	Nil	T2b N0 M0 (Stage II A)	PR	150	362	212	141	Alive	80	80	104	104	103

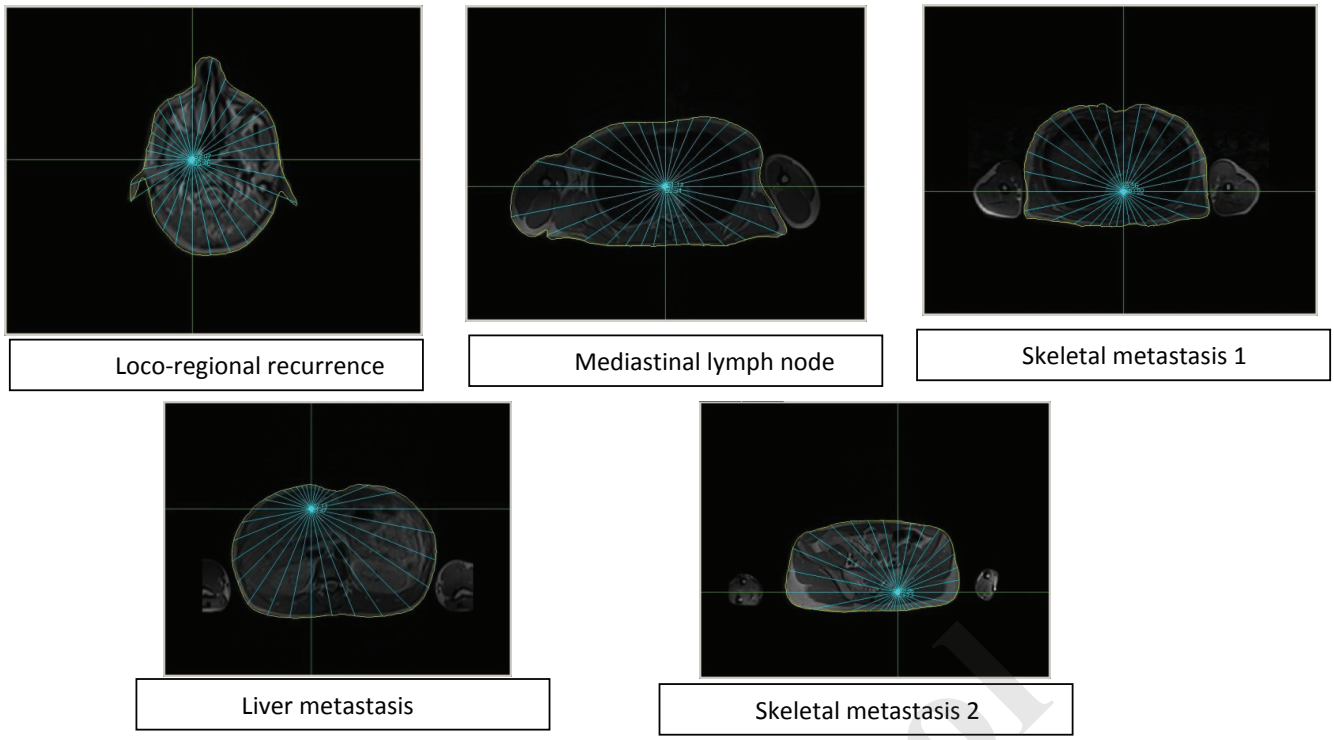
Supplemental Data Table 1: Patient Cohort –Pathology & Survival Data. Data for the 86 patients who completed QMRT is summarized in this table with relevant histopathological, clinical staging RECISTv1.1 criteria for tumor stability, survival data. KPS Scores and FACT-GP scores.

Supplemental Data Table 2: Effect of therapy and gender alone, and the interaction of both on Survival and QOL (ANOVA). Listed are F-distribution values and p-probability values for the effect of therapy alone, for gender and for the interaction of both on Survival and QOL by analysis of variance (ANOVA) analysis.

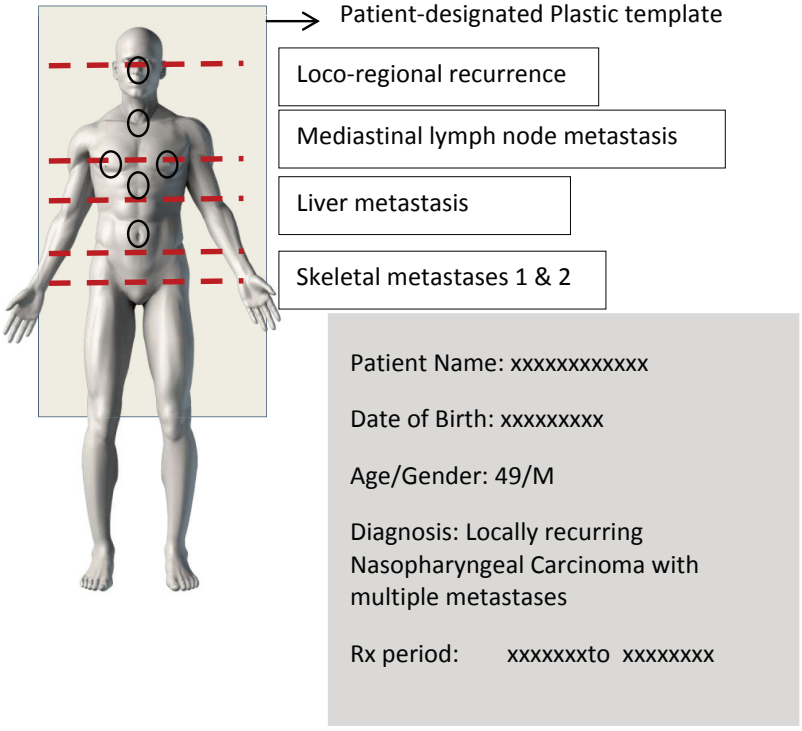
	Main Effect Therapy (1)	**Main Effect Gender (2)**	**Interaction Effect (1x 2)**
Survival (days) (n=86)	F=69.15, p=1.41E-12	F=3.34, p= 0.071	F=1.44, p=0.234
Survival (months) (n=86)	F=69.58, p=1.26 E-12	F= 3.42, p = 0.068	F=1.29, p=0.260
QOL* (FACT-GP) (n= 86)	F=36.71, p=3.73 E-08	F = 3.02, p = 0.086	F=2.35, p=0.129
*Assessed on completion of therapy			



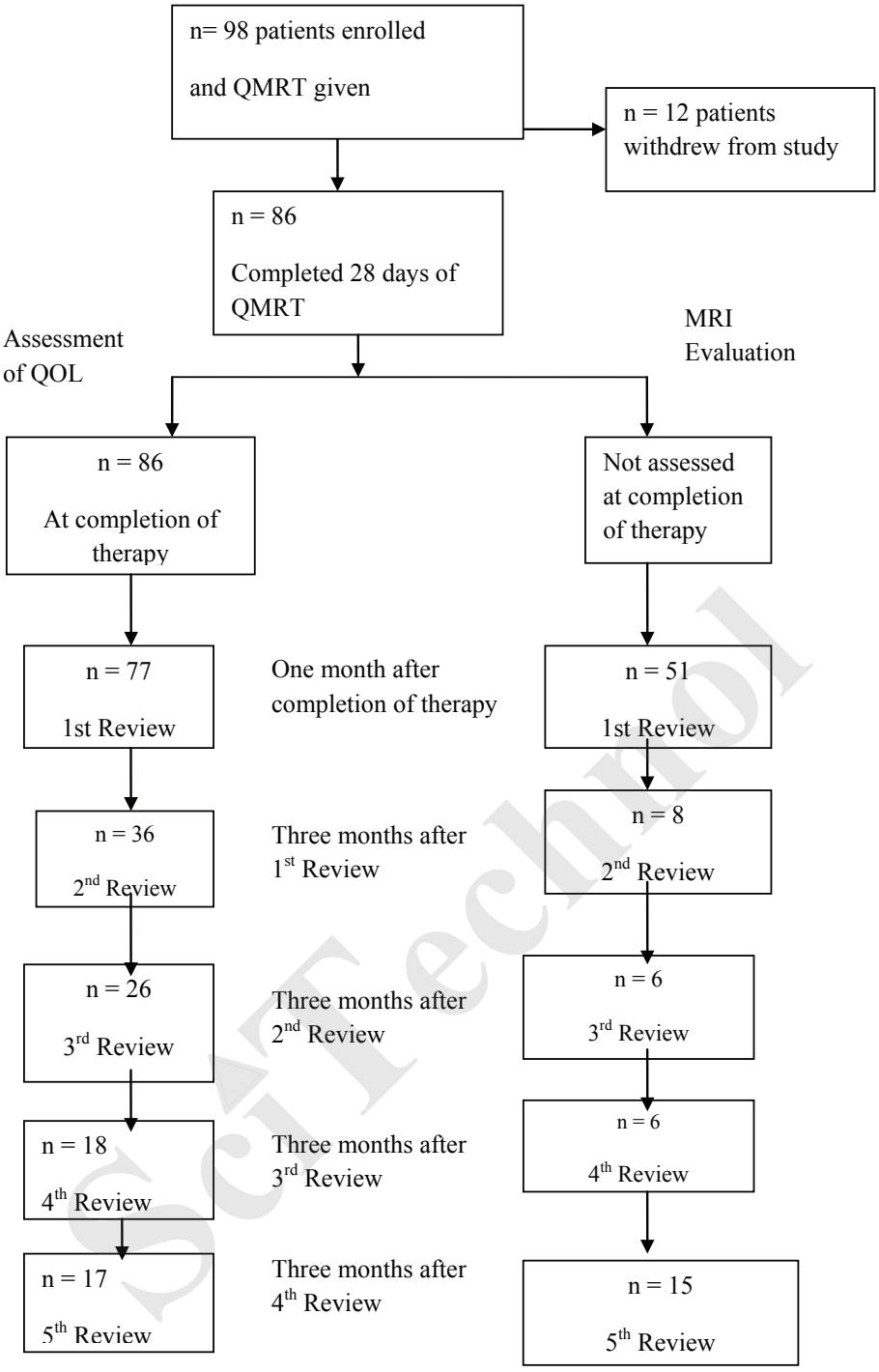
Supplemental Figure 1A: Proton Density (PD) determination and automated RF/MR gun targeting for automated dose-planning and simulation on the central control computer. A.RF /MR gun emission is based on tissue proton density (PD) of the region of interest (ROI) in the gun path of the targeted lesion and the PD assessments of Region(s) of Interest (ROIs) from skin to target. (Left)The pre-treatment MR Imaging is used to measure inherent tissue proton density (PD) of each (axial view of abdomen showing liver PD) and all lesions to be targeted by QMRT. The film is marked by the radiologist and images are transferred from the CD to the device central control computer for automated dosimetry and gun path simulation. (Right) The PD from the skin (gun end) to the target obtained from the MRI is computed to generate the RF files for individualized dosimetry.



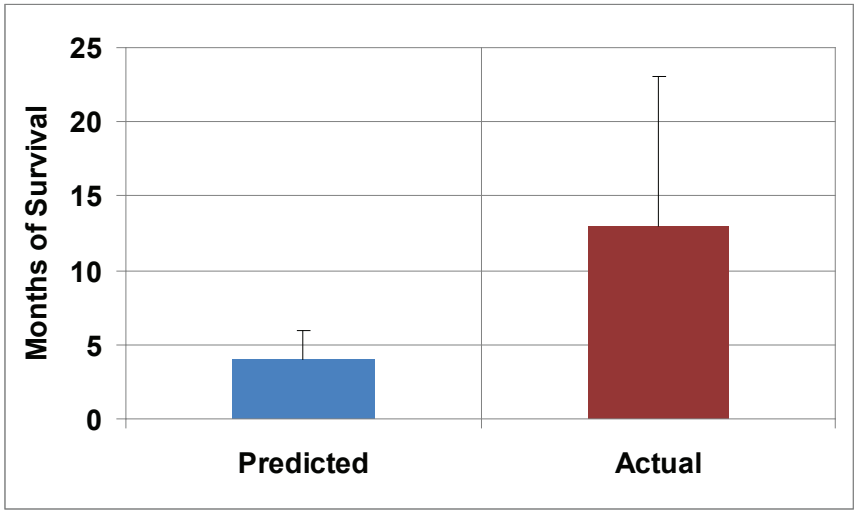
Supplemental Figure 1 B: Dosimetry computed for multiple regions of interest (ROIs) for simultaneous targeting during 1 hour of QMRT. Any or all lesions can be simultaneously targeted by QMRT in the same sitting for patients with disseminated disease/multiple metastasis as shown for one patient as an example. The underlying regions of interest (ROIs) marked on the body template indicate the areas targeted by the RF guns. The dosimetry is computed on the device computer from the PD sequence data derived from patient specific MRI images for each of the ROIs (blue lines converging on the ROI are the computed gun paths). Each region targeted in the whole body is simultaneously targeted during the 1-hour daily treatment exposure for 28 consecutive days.



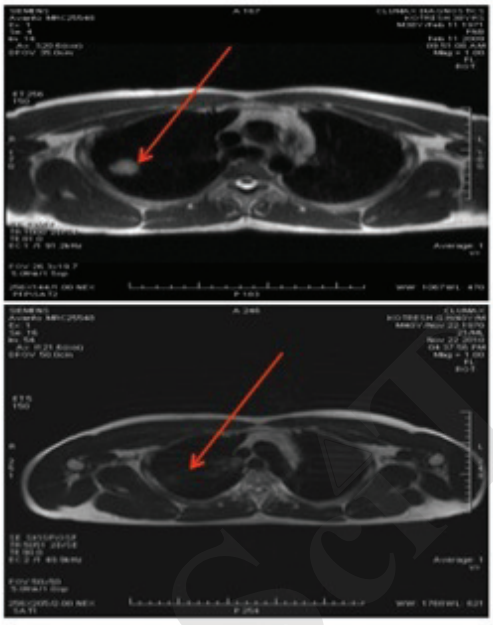
Supplemental Figure 1C: Body surface marking and patient template. Prior to exposing the patient to QMRT in the Cytotron® device, a transparent plastic template is prepared and used to precisely position every patient in the gantry daily for 28 consecutive days. Body surface markings are made under very low intensity CT guidance by the radiologist after PD sequence data is obtained on MRI. These surface markings are transferred on to a template positioned on the patient with anatomical reference points (black oval) at the nose, suprasternal notch, nipples, xiphisternum and umbilicus. The patient is positioned on the Cytotron bed and the gun axes to be used to deliver the dose planned is aligned and marked on the template at targeted ROIs (red hatched lines). Patient specific information is also referenced on the template for daily verification prior to treatment being initiated.



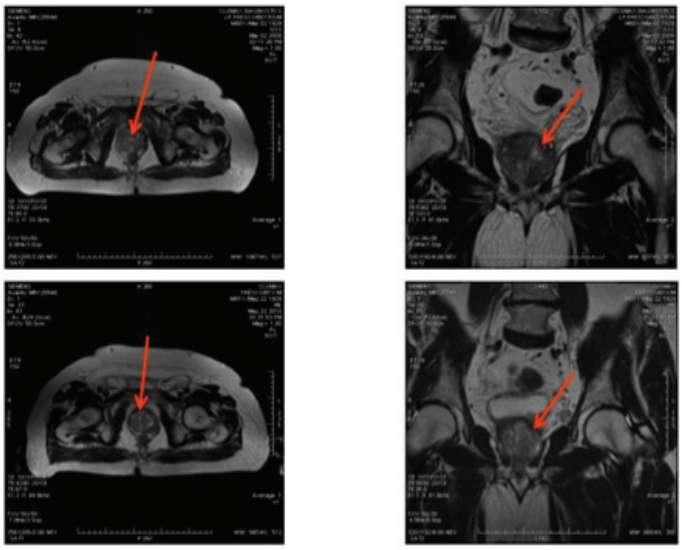
Supplemental Figure 2: Flow-chart of patient accrual, therapy duration, compliance follow up and iteration (lost to follow up). Patient compliance and adherence to follow up review dates was accurately tracked as it was critical for primary and secondary endpoint analysis, particularly survival statistics.



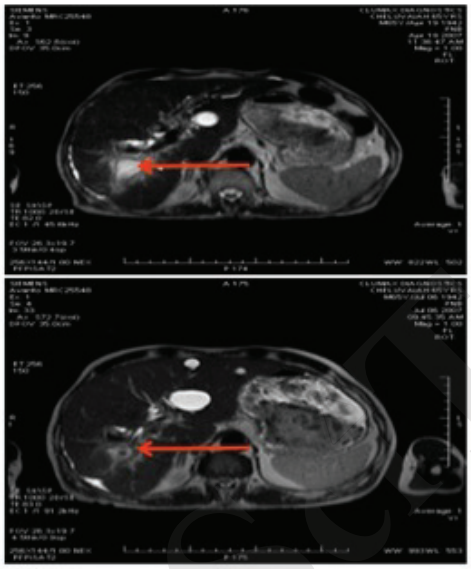
Supplemental Figure 3: Bar graph showing Predicted *vs* Actual (derived at end of study period) in months of survival (n = 86). Bars represent mean ± SD.



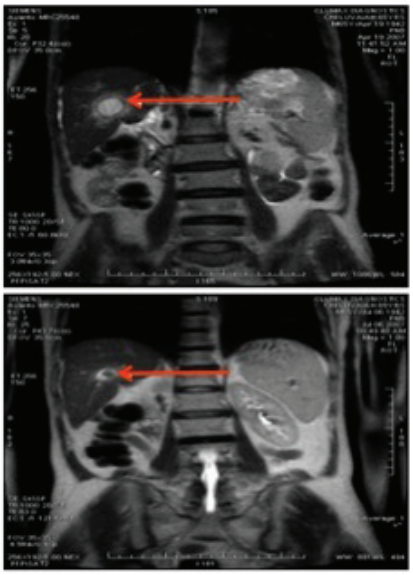
Supplemental Figure 4: Male 38yrs, Renal cell carcinoma with lung metastasis showing (top arrow) complete response post-QMRT (bottom arrow).



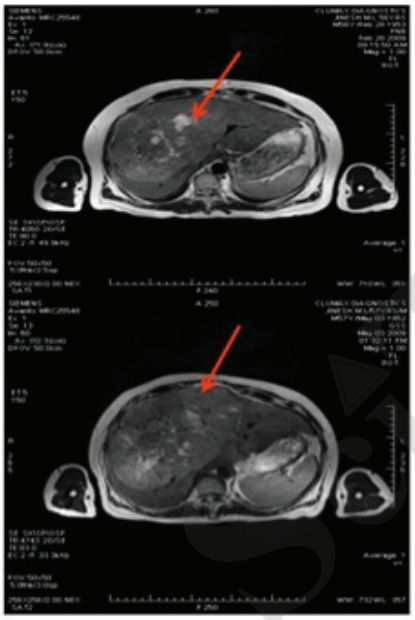
Supplemental Figure 5: Carcinoma prostate showing partial response post-QMRT. Pre RFQMR (First Row), March 2009, Prostate lesion: 6.0 (AP) × 5.5 (T) × 6.0 (SI) cms, 14 months Post RFQMR (Second row), May 2010, Prostate lesion: 2.98 (AP) × 1.88 (T) cms.



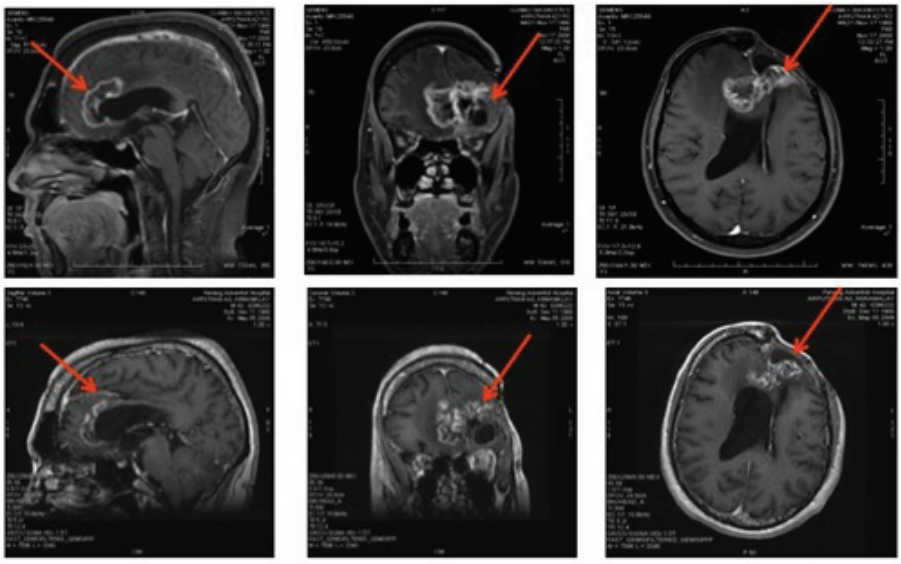
Supplemental Figure 6A and 6B: Male 65yrs, Carcinoma Pancreas- Periampullary with Hepatic Metastasis showing Partial response (Axial Section) Ca. Pancreas with liver metastasis (top arrow) showing partial response post-QMRT (bottom arrow).



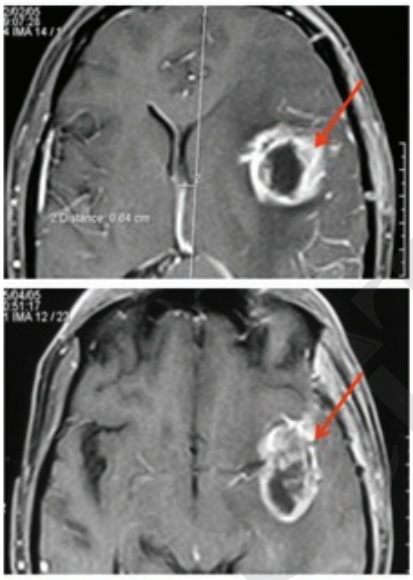
Supplemental Figure 6 C and 6 D: Male 65yrs, Carcinoma Pancreas- Periampullary with Hepatic Metastasis showing Partial response (Coronal Section). Ca Pancreas with liver metastasis (top arrow) showing partial response post-QMRT (bottom arrow).



Supplemental Figure 7A and 7B: Hepatocellular Ca. with lung metastasis. Hepatic lesion (top arrow) showing progressive disease (bottom arrow) after and beyond QMRT.



Supplemental Figure 8: Glioblastoma Grade IV with stable disease (bottom row) 6 months post QMRT and doing well and usefully employed until and beyond the end of the study.



Supplemental Figure 9: Glioblastoma Grade IV post-QMRT currently alive and professionally active. The residual lesion (bottom arrow) observed in the MRI has been inert and metabolically inactive over a long period of disease free survival.

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