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Communication

DR JOHN HOLT'S UHF TREATMENT – COLORECTAL CANCER TRIAL : AN HYPOTHESIS

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ABSTRACT

An "Once-in-a-lifetime" clinical trial seeking an improved survival for patients with rectal cancer, compared standard radiotherapy (RT) and RT+ Radio wave (UHF) irradiation at 434 MHz. Whilst no significant difference was recorded, the Kaplan-Meier graphs revealed a trend towards a worsening of the RT+UHF treatment arm. This, and more recent research findings, gives insight into possible UHF stimulatory effects on some cancers.
Conclusion: UHF applied to patients with cancers carrying some mutations of the APC gene may stimulate cancer.

Keywords: Rectal cancer, stimulation, UHF, APC, β-Catenin, microtubule, TGF-β.

INTRODUCTION

Early in 1973, Dr John Holt of Western Australia (Radiotherapist) examined a machine being sold in Germany. It irradiated cancer patients with radio waves of 434 MHz UHF* with up to 2,000 Watts of power. He noticed that when a patient with stomach cancer was in the radiation field, the current drawn by the output stage of the machine was 225 W, but when a person without cancer entered the field, the current was 195 W. That started his interest in the topic. It was developed further with a spectrum analyser.

*Here, VHF=UHF=Microwave

After empirical trials he, and an Associate Dr A Nelson, conducted a formal trial using the UHF as an adjuvant treatment prior to standard radiotherapy for Head and Neck cancers. This, and follow-up were published (Nelson & Holt, 1978 & 1985). The results seemed gratifying, but the lack of a scientific explanation was a barrier for acceptance by the profession. Doubts in the profession led to another group planning a trial of the protocol. Patient accrual proved difficult, so the group settled for a trial treatment of rectal cancer. Nelson and Holt protested on the basis that, as assessed by their empirical studies, they had little success using the treatment for this condition. Nevertheless, the trial for rectal cancer treatment went ahead, was completed and published (Trotter, 1996). The results were disappointing; statistical analysis provided no significant difference between the radiotherapy (RT) arm and the RT+UHF survival arms (and other end-points) and the comment was

> *". . . VHF* microwave therapy in conjunction with radiotherapy produces no therapeutic advantage over conventional radiation therapy. . . . ."*

The survival figures were presented as Kaplan-Meier (K-M) graphs with derived patient survival numbers at 6 monthly intervals. These have been graphed here (Figures 1 & 2) for clarity.

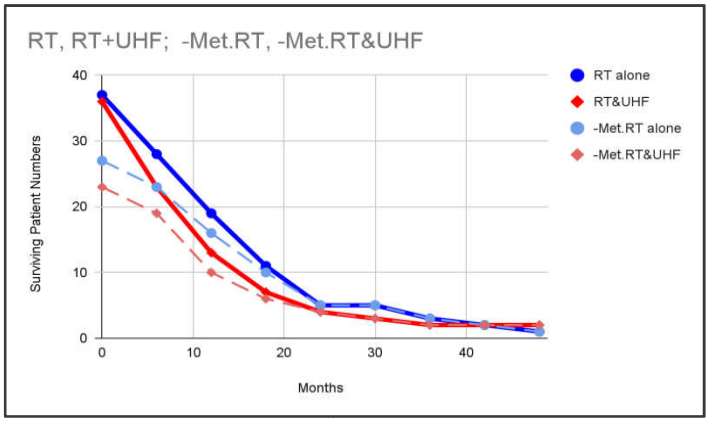

Figure 1: Graphs of patient numbers provided by Trotter *et al.,* 1996. The increasing death rate for the RT&UHF is apparent early (at 6 months), and seems to peak at ~12 months. After subtraction of those with metastases at the start ("-Met."), the patterns become similar to the full-complement arms at about 12+ months.

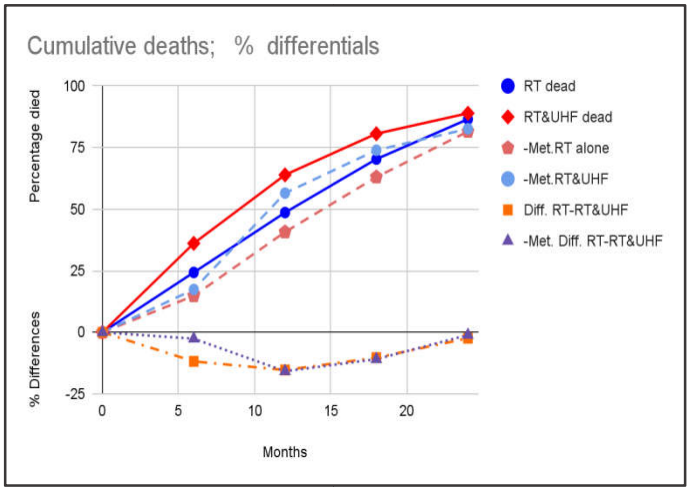

Figure 2: The death toll with time (upper); (lower) the differences between the percentages (RT – [RT&UHF]). "-Met." refers to the cohort remaining after deletion of those with known metastases at the start. (After Trotter *et al.,* 1996)

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However, close examination of the graphs reveals that the RT+UHF arm shows a distinct early drift, with a **worsening** of survivals, the maximum difference being at ~12 months, after which the worsening rate falls. When the figures are re-drawn showing deaths, the increased mortality seems broad-based, with similar trends between the RT alone and the arm with the known metastases at the start excluded (-Met. RT). Note that at 6 months, the number of deaths in the -Met. RT alone and the -Met. RT&UHF are very similar, with the difference (Diff.) RT-RT&UHF small, yet the RT+UHF deaths exceeds the RT alone. This seems to indicate that there is some quality in the tumours yet to metastasize (line RT+UHF) which sensitizes them to **grow** following the UHF, whereas those that had already metastasized at the start (and therefore excluded) in the -Met. RT&UHF arm, lack this quality. The suggestion to be examined (**Hypothesis**) is that this may be related to the truncated APC molecule and the possibility of Epithelial to Mesenchymal Transition (EMT) changes in the UHF-irradiated tumours.

The APC molecule
Total Length (amino acids, aa): 2,843 aa
Central region 959-2129 aa
MCR* 1284-1580 aa
(Usual) Truncation follows 1450. . . . . aa
C-terminal 2130-2843 aa
β-Catenin binding site 1 – 1020 - 1169 aa
β-Catenin binding site 2 – 1342 - 2075 aa
*Mutation cluster region
(From Juanes, 2020)

Table 1

With the derived figures provided, losses at 12 months were; RT 48.6%, RT+UHF 63.9% (difference 15.3); those with metastases excluded, RT 40.7%, RT+UHF 56.5% (difference 15.8). A visual assessment (K-M) was that the difference amounted to an increased mortality at 12 months of ~12.6%. The authors make no mention of what appears to be a worsening influence from the UHF. Perhaps they did not consider such a deleterious effect possible. This effect seems to select specifically a cohort having (presumably) similar defects, with more cases represented in the treatment/early post-therapy stage, within ~50 days.

Since colorectal tumours are reported to have a high incidence of mutations/losses involving the *Adenomatous Polyposis Coli* (*APC*) gene and APC protein, with mismatched repair (MMR) and microsatellite instability (MSI; e.g. Müller *et al.,* 2016 ~13% [with DNA MMR]; Kinzler & Vogelstein, 1996 [composite] 13%; Carethers & Jung 2015, [hyper-mutated] 16%; Schell *et al.,* 2016, [MSI-High] 13%), the hypothesis proceeds by suggesting that this higher-mortality cohort may have mismatched repair/microsatellite instability abnormalities in the *APC* gene, supplying truncated APC molecules, resulting in stimulated tumour growth. (Faux *et al.,* 2004; Juanes *et al.,* 2020). To explain the result, the UHF may have a number of stimulatory effects, such as providing more β-Catenin to the nuclear promoters, +/- E-Cadherin perturbation involved in cell-to-call cohesion, +/- release of TGF-β, including effects on the microtubules and associated molecules.

APC truncated molecule
Most binding sites lost
β-Catenin binding site 2
Axin
Microtubules
Formin
Actin
Kinesins
Miro
Milton
EB1
DLG
(From Juanes, 2020)

Table 2

THERE APPEAR TO BE THREE POINTS:

1) Based upon Nelson's & Holts' empirical experience, the colorectal cancers seemed generally resistant to UHF treatments. The study by Trotter *et al.,* (1996) confirms this. The explanation may be that, with the (almost certain) presence of truncated APC molecules in most colorectal cancers, the plus ends (the plasma membrane association) of the microtubules are effectively unattached (Mogensen *et al.,* 2002; Faux *et al.,* 2010; see Tables 1 & 2), so that the radio wave energy cannot be conducted into the interiors of the cells (e.g. to the centrosomes/centrioles), as hypothesized (Traill, 2022) for cancers generally; these are "open circuits." And so, the centrosomal events (with the proposed production of PARP, SIRT2, and cADPR etc.) cannot occur. The therapeutic resistance then matches the explanation in the hypothesis, giving some support to the hypothesis. Similar resistance could occur with other tumour types if they have similar APC molecular truncations.
2) The similarity of the early death cohort percentage (noted here) and the percentage figures documented for APC Mismatch Repair/Micro-satellite Instability raises the possibility that these genetic defects may be the cause for the (assumed) APC truncation in these cases (although other combinations may be possible). The early, increased mortality following the UHF treatment in a ~13% cohort, is shown fully at ~12 months. Excluding those with known metastases at the start, the difference at 12 months is less, indicating that the state of metastasizing (e.g. Epidermal to Mesenchymal Transition) may be a phenotype that has a worse prognosis if subjected to UHF treatment. Key cytological features of this state are leading edges for motility. Despite APC truncation, APC puncta are still found in the leading edge cytoplasm (Faux *et al.,* 2010; Parker *et al.,* 2020), but are bereft of microtubule connections. (The junctional cell membranes [cell-to-cell] also attract APC puncta, but these are less mobile.) The high level of microsatellite instability involved in the MSI-H/MMR abnormalities would be expected to make the remaining APCs' distal molecules unstable sites for the binding of β-Catenin (one of 2 originally). The application of UHF radio wave power may be sufficient to displace the β-Catenin from the truncated APC by molecular agitation. The freed and phosphorylated β-Catenin may then be dephosphorylated by the (generic) Protein Phosphatase PP2A in the cytoplasm, leaving the β-Catenin able to move to the nucleus and stimulate tumour growth. An appreciable resonance effect by the UHF would seem unlikely without a resonator, meaning that growth stimulation may be caused by a wide UHF spectrum; and, or -
3) The cells, for their interactions with the extracellular matrix (ECM), gather together a posse of interacting players, some being (Matsumoto *et al.,* 2010): - microtubules* and kinesins*, Wnt, dishevelled, APC, frizzled, focal adhesion kinase, paxillin, axin*, actin* and integrins. (*Indicate the factors for APC binding for which the sites are lost by typical APC truncation.) The stabilizing influence of APC may be lost, so that the interface may be susceptible to physical/molecular agitation caused by the UHF. This may modulate the release of TGF-β from the ECM (O'Connor & Gomez, 2014) and could affect the direction of EMT↔MET (Aiello & Kang, 2019), and hence the metastasis or seeding of cancer cells. There may be others.

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