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THE AUSTRALIAN NATIONAL HEALTH AND MEDICAL RESEARCH COUNCIL's REVIEW INTO DR JOHN HOLT'S UHF RESONANCE TREATMENTS – MORE ANALYSES & HYPOTHESES (NUMBER 5)

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ABSTRACT

Dr John Holt (Radiotherapist, Western Australia) trialled radiowave UHF 434 MHz to treat cancer. This was controversial, and after some expressed concerns, the Federal Health Minister directed the National Health and Medical Research Council to conduct a Review of the techniques. Analyses here follow-on from the more statistical analysis of patient survival, and concentrate on scientific explanations. **Conclusion:** UHF 434 MHz does have effects: with Radiotherapy (RT) to cancer there is increased sensitivity. With the "GBA," there is probably a "futile-like" cyclic reaction with NQO1 & disulphides with the production of damaging ROS and electrons, hence Holt's UHF resonance (Traill, 2022a)

Index terms: Cancer, UHF, Microwave, futile-like, NQO1, cytokeratins, glutathione, ROS & electrons – hence Holt's UHF resonance.

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INTRODUCTION

Re-examination of the NH&MRC Review of Dr Holt's UHF treatments

Parts of the Conclusions of the publication "Microwave Therapy for the Treatment of Patients with Cancer" published as a Review by the National Health and Medical Research Council of Australia (NH&MRC) stated (as modified) are:

- 'UHF in combination with Radiotherapy (RT) was inferior compared to standard conventional radiotherapy with respect to disease control and survival for patients with breast cancer, lung cancer, lymphoma or prostate cancer
- There was no significant difference to survival between RT alone or reduced radiotherapy (rt) + UHF for patients with head and neck, colorectal or bladder cancer
- There is insufficient information to make a reliable assessment of the safety of UHF in combination with RT, or UHF in combination with "Glucose Blocking Agents" (GBA) for the treatment of patients with cancer
- UHF+GBA appeared to have a lower rate of toxicity than UHF + rt and RT alone.' (p.7)

Table 49 of the Review (p.104) presents Adjusted Survivals at 5 [and 10] years after diagnosis, with extracts from Table 48 (Hazards Ratio and Significance) (p103.): 5 year

Site	RT	UHF+rt	Hazard Ratio	P
Bladder	20% (13-30)	28% (12-66)	0.78 (0.38-1.57)	0.48
Breast	72% (68-76)	56% (46-69)	1.75 (1.22-2.50)	0.002
Colorectal	17% (11-25)	9% (4-19)	1.33 (0.92-1.93)	0.12
Head & Neck	36% (28-46)	42% (27-67)	0.84 (0.48-1.48)	0.55
Lung	4.4% (2.7-7.2)	1.5% (0.6-3.9)	1.34 (1.06-1.70)	0.013
Lymphoma	72% (64-81)	50% (31-83)	2.09 (1.01-4.35)	0.048
Prostate	56% (50-62)	34% (23-51)	1.81 (1.23-2.66)	0.003

The Review

From the Review (Traill, 2022b) visual assessments of the results are probably adequate when assessing how the various treatments performed. Examining these and, despite the knowledge that most of the UHF cohorts have blurred figures denigrating the UHF treatment arm (Traill, 2022b) some trends from visual inspection may be possible. Survivals for those with Head and Neck cancers seemed better with the UHF-rt regime, whilst survivals of patients with bladder cancers seemed less so. :

The best UHF-rt treatment appears to be that for head and neck cancers (usually squamous cell cancers derived from the skin, mouth, throat, pharynx and oesophagus, which may be subjected to considerable stretching stresses. The next best result is for a cancer from the urinary bladder, which is subjected to less stretching stresses. Seeking to explain these features, an examination was made of some of the intercellular adhesion molecules, such as the Desmoglein-2 component of the desmosomes.

Such a comparison of the Desmoglein-2 patterns (Myo Min *et al.,* 2023) with the various cancers did not reveal any clear match, so attention was given to intracellular components:

The different responses to the UHF treatments may be related to the cytokeratins:

The main cytokeratin patterns in benign tissues are (from Kalabusheva *et al.,* 2023):

Organ/Cancer Type	Markers
Urinary bladder	8/18, 7, 19, 5/47, 1, 20, 13
Breast	5/14, 8/18, 19

Intestine	8/18, 7, 19, 20, 21
Oesophagus	5/14, 15, 4/13
Lung (mixed types ?)	5/15, 8/18, 6a, 19, (14)

Cancer Types and Markers

In cancers, the main cytokeratin patterns are:

Breast 5/14, 17, 8/18 (Gusterson *et al.,* 2005)
Head and neck cancers (Typically squamous cell carcinomas):
CK5, CK6, CK14, CK13 (often in more differentiated tumours) (Fillies 2006)
Urothelial carcinomas (Typically transitional cell carcinomas)
Southgate *et al.,* (1999)
Main cytokeratins: ("The intensification of immunolabelling with some CK and CK18 antibodies may underlie an active role in tumour invasion."
CK8, CK18
Additional commonly expressed cytokeratins:
CK17/CK14
Colorectal carcinoma:
CK20, CK19, CK18, CK14, CK8 (Knösel 2006)
Prostate adenocarcinoma:
CK8, CK18, CK19 (Heatley *et al.,* 1995)

Noticeable, was the frequent appearance of the twin cytokeratins (CK8 & CK18). This pair is of interest because Leech *et al.,* (2008) found that, between the two, there were displayed nine acetylated groups. The hypothesized activation of the deacetylase SIRT2 by the action of the applied UHF (Traill, 2002a) to the tumour may be expected to inactivate, modify or cause destruction of one or both of these cytokeratins. This could result in the destruction of both, as reported by Kulesh and Oshima (1988) because injury to one of the pair resulted in melting away of its mate. This could mean that for tumours with a high proportion of the pair, the UHF application could see the CK8/CK18 cortical mesh melting away, possibly having some similarities to the fate of cortical actin (Traill, 2023). So, with a disconnect between the cells' desmosomes and the EB1s of the microtubules' tips, there would be insufficient structural components capable of conducting the UHF electrical energy into the interior (or exterior) of the cancer cells.

Thus, when the UHF is first applied and the state of the SIRT2 activated, the cortical electrical conducting meshworks could be attenuated, meaning that the effective UHF power would be reduced - a negative feedback effect that could reduce the UHF's cell-killing effectiveness.

Head and neck cancers, typically squamous cell cancers, arise from benign epithelia that do not display appreciable amounts of CK8 & CK18 (Fillies *et al.,* 2006). This group studied cancers of the oral cavity and noted that, within their group, out of 287, the CK8/18 pair was detected in 154 (53.7%). This acquired status implies more an auxiliary role rather than a replacement, with the implication that, if the CK8/18 pair was damaged, the cytoplasmic CK status/functioning would approximate the pre-malignant status. This would leave the cortical CK filament meshwork status remaining to occupy the desmosome-EB1 space and the electrical conduction at a functional level.

Transitional cell (urothelial) cancers seem to acquire the CK8 & CK18 pair with the active role of tumour invasion (Southgate et al. 1999) – a presumed limited axillary role similar to that in head and neck cancers (see above). The limited distribution may explain the less impressive survival response to the UHF/RT.

The other cancer groups with the CK8 & CK18 in the tumours from the start may have disappointing responses to UHF/RT because, with the application of the UHF, the (presumed) SIRT2 effect on the CK filament meshes will be to reduce electrical energy transfer, as discussed above.

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More Thoughts

UHF & RADIOTHERAPY (RT)

There seems no overall, tabulated display of these, such as showing total doses, fraction sizes and duration of the treatment courses, except for what was in text.

Abbreviations	Markers
RT: Radiotherapy, [planned, orthodox/standard, doses never displayed]	
Rts: Radiotherapy dose to survivors	
rt: Radiotherapy, [reduced, as used by Holt, doses rarely displayed]	
rts: Radiotherapy, rt to survivors	
ρT: Difference in the radiation doses Rts-rts	
UHF: UHF 434 MHz as used by Holt +/- 2 MHz (4 transmitters, unsynchronized)	
GBA: Glucose Blocking Agent; one or more intravenous adjunctive substances used by Holt in the (probably incorrect) belief that they blocked the metabolism of Glucose (see later).	

GBAs

Holt proposed that the Glutathione/Glutathione disulfide system formed in an energy unit, like an organelle, enclosing a circular redox reaction:

Reduced Glutathione
NH_2 CH_2SH
| |
$HOOCCHCH_2CH_2CONHCHCONHCH_2COOH$ (Abbreviated GSH)
(γ-Glu-Cys-Gly)

GSH + GSH x2 reduced glutathione
▲ |
+2e' | ▼ -2e'
Oxidized Glutathione: GSSG (Glutathione disulphide)

With the Glutathione (oxidized, in a futile-like, cycling reaction with reduced Glutathione). He hypothesized that if one electron entered the continuous cycling process, two electrons would emerge!

This perpetual-motion-like reaction was supposedly supported by Kosower & Kosower (1976). However, these authors do not propose an ongoing 1 electron in, with two electrons out possibility; such would not seem credible.

Formal processes mentioned are: Two-electron oxidation
RS'→ RS+
One-electron oxidation-reduction
RS' + RS+ → RSSR

That both one and two electron reactions could involve NQO1 means that "futile-like" cycling reactions may be possible (Silvers *et al.,* 2017). Futile-like recycling produces elevated superoxide levels and eventually massive hydrogen peroxide concentrations that lead to substantial DNA damage and endoplasmic reticulum Ca2+ release*, with a resultant spray of Reactive Oxygen Species (ROS), as cited by

Luo *et al.,* (2024) and Khan *et al.,* (2024) and electrons, potentially damaging bystander molecules and feed Holt's UHF resonance (Traill 2022a) (*2 patients who received Holt's rt+GBA protocol developed clinical hypercalcaemia in the second week.)

So, when the GBA (Oxidized Glutathione) is infused into a cancer patient prior to the UHF being applied in preparation for a reduced RT-dose treatment (rt) "[cancer] cells may adept to oxidative stress in the short term by metabolic reprogramming and, in the longer term, by genetic reprogramming. Upon acute exposure to ROS, NADPH production by glucose-6-phosphate dehydrogenase (G6PD) plays a pivotal role in mitigating oxidative stress... (e.g.) by re-routing glucose metabolism from glycolysis through the oxidative arm of the pentose phosphate pathway (PPP) towards nucleotide synthesis, thereby allowing increased reduction of NADP+ to NADPH..." (Hayes, *et al.,* 2020; the authors do not mention possible futile processes).

(a) The cancer cells will be put under oxidative stress. This may then stimulate the production of the enzyme NQO1 which may be important for those cancers which may produce little. Khan et al. 2024 present a histogram of the production of NQO1 by some 22 cancer types. Six, (Bile duct cancer, Cervical cancer, Gall bladder cancer, prostate cancer and Thyroid cancer) show low levels, with 'outlier' appearances. Perhaps there may be rapid stimulation of these latter, perhaps not…..

(b) Entry of oxidized glutathione (disulphide) into cancer cells will have the cytoplasm enriched, being through-which the microtubules and attached NQO1 molecules course. With the UHF applied these will be the conduits of the UHF power, driving the NQO1 molecules into acrobatic flexibility with the UHF energy (Siegel, 2017). The latter are well placed to reduce the Glutathione disulphide to single molecules (Siegel, *et al.,* 2018; Ross & Siegel 2021). "The diverse functionality of NQO1 and its roles in redox control. 2021)." With the UHF applied (x4 power units asynchronized) any electrons not attached will be churned and come into contact with the glutathione molecules and NQO1 can oxidize pairs of them to form the disulphide, completing the futile cycle.

--ooOoo--

Another thought:

Performance of UHF

The median radiotherapy dose for patients with bladder carcinoma who received RT was 60 Gy in 32 fractions (i.e. 1.875 Gy/fraction) whereas for patients who received UHF+rt (+GBA) the median dose was 51 Gy in 34 fractions (i.e. 1.5 Gy/fraction) and the dose per fraction was lower.' (p.106) (Fortunately, the bladder cancer group seemed to have fewer discrepancies, Traill, 2022b).

Taking the stated median survival differences between RTs and UHF+rts for bladder carcinoma as statistically similar (see earlier), then $\rho_T \approx 0$, meaning that UHF confers an augmentation effect to the rts as being roughly equivalent to 9 Gy, presumably the futile-like effect. The review makes no mention of this difference and what it may mean. (Refer above to futile-like metabolism).

Performance of GBA with UHF

To the Review panel, (p.181) Holt claimed that "this modality is a significant curative or therapeutic benefit (at least equal to that of conventional treatments.." (p.191). for this,

"One of three GBA is administered,

1. Cyclophosphamide (2.5-5 mg/day)
2. Cystine disulphide (1g/day)
3. Penicillamine disulphide (1mg/day)," (p.181)

But in a publication of the time (Holt, 2004) he sets out:

1. "Oxidized glutathione
2. Cystine and
3. Other disulphides, (including insulin)." (p.180)

Expectations (Holt's)

a) "All tumours <1-1.5 cm may result in complete remission.

b) Tumours <2 cm can be reduced in size with treatment (i.e. not necessarily curative expectation.)

c) Tumours >2 cm are difficult to treat."

Holt noted a place for UHF+GBA for palliation. "Dr Holt believes that glucose Blocking analogue (sic) (GBA) and the UHF provides effective palliation in 100% of patients." (p.179). In regard to this, most patients referred to him would have had advanced disease: tumours <2 cm would be uncommon; primary tumours <1.5 cm diameter would be very rare. The Review found that treatments with curative intent were RT alone, 32, 94% (N=34); UHF+rt+GBA 11, 92% (N=12); UHF+GBA 14, 78% (N=18); (p.97) and those tumours with any macroscopic residual following surgery were, for RT alone, 19, 56%, rt+UHF 33%, UHF+GBA 4, 22%. (p.96).

The UHF dose (mean +- range), UHF+RT = 128 kW (92-176), UHF+rt+GBA = 94 (54-144).(p.97) The reasons for the difference are not clear, other than increased sensitivity. The operator would need to be skilled to assess the doses for rt but the criteria that were applied have not been presented.

Attempts to find similar dosage details for other cancer groups were unsuccessful!

These augmentation or sensitization effects would seem consistent with Holt's claims regarding sensitization (Traill, 2023d). In the context of the administrations of Oxidized Glutathione, the possibility of futile-like reactions involving a GBA, with the energy from the UHF and the enzyme NQO1, the effective equivalence to 9 Gy RT (see above) may be attributed (in part) to futile-like reactions with emitted ROS products and electrons.

After ~1991, Holt applied UHF+GBA to patients until he retired. The preferred GBA at about the year 2000 seemed to be Oxidized Glutathione, with other disulphides (cystine and insulin, Holt 2004) tried.

His results applying treatments without rt:

Disease and Patient Status at Last Follow-up or Death (p.101)

Status Category / Outcome	RT alone (N=34)	UHF+RT (N=12)	UHF+GBA (N=18)
Complete remission	14 (41%)	2 (17%)	2 (11%)
Partial remission	1 (3%)	1 (8%)	0

Stable disease	4 (12%)	2 (17%)	2 (11%)
Progressive disease	5 (15%)	4 (33%)	10 (56%)
Not known	10 (29%)	3 (25%)	5 (28%)
Alive	33 (97%)	11 (92%)	11 (61%)
Dead, cancer related	1 (3%)	1 (8%)	5 (28%)
Dead, non ""	0	0	2 (11%)

Clinical Performances (From Table 44 of the Review, p.101),

For Bladder cancer. (Head and neck cancer would probably have produced better results.)

Holt considered that this treatment had a place for palliation. Most patients going to a clinic such as Holt's, would be expected to have incurable disease, meaning that the expectation for a cure was "wishful thinking," so note the results for complete remission, stable disease and progressive disease (78%). The Palliation role seemed to be of little concern to those conducting the Review. Contrast the results rather than comparing them.

CONCLUSION

- Dr Holt's UHF (~434 MHz) when applied with routine RT to patients with cancer appeared to improve the survival of the patients with head and neck tumours and bladder tumours. The remainder showed little difference; any difference may be related to intracellular structures
- That the head and neck tumours and bladder tumours could show any difference implies that the UHF+GBA+rt has a measurable effect
- The "Glucose Blocking Agents; GBA" may have an effect by supplying a 2 electron redox milieu for futile-like reactions with the enzyme NQO1. The latter, being attached to the Microtubules along which the UHF is (presumably) conducted, (Traill 2022a), produces sprays of ROS to damage nearby structures and electrons to drive Holt's UHF resonance
- Differences in sensitivity may be related to the intracellular cytokeratins.

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