Sonodynamic Photodynamic Therapy

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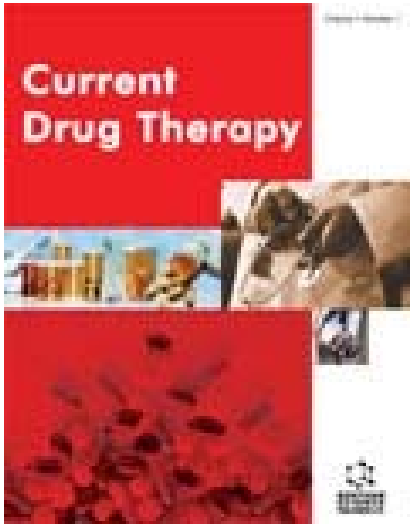
(Click or use arrow keys to move through the slideshow)

Sonodynamic Photodynamic Therapy

- *** We do not claim that any of these treatments, investigative procedures, or blood tests are cancer cures**.

- This presentation is intended to provide background information to healthcare practitioners about an integrated medical approach called Sonodynamic Photodynamic Therapy and focuses on information presented in a recent medical journal publication.

Publication Details– Sept 2009



- "Activated Cancer Therapy Using Light and Ultrasound - A Case Series of Sonodynamic Photodynamic Therapy in 115 Patients over a 4 Year Period"

- ***Current Drug Therapy, 2009, Vol. 4, No. 3***
- ***J N Kenyon, R J Fuller, T J Lewis***

The Case Series Publication

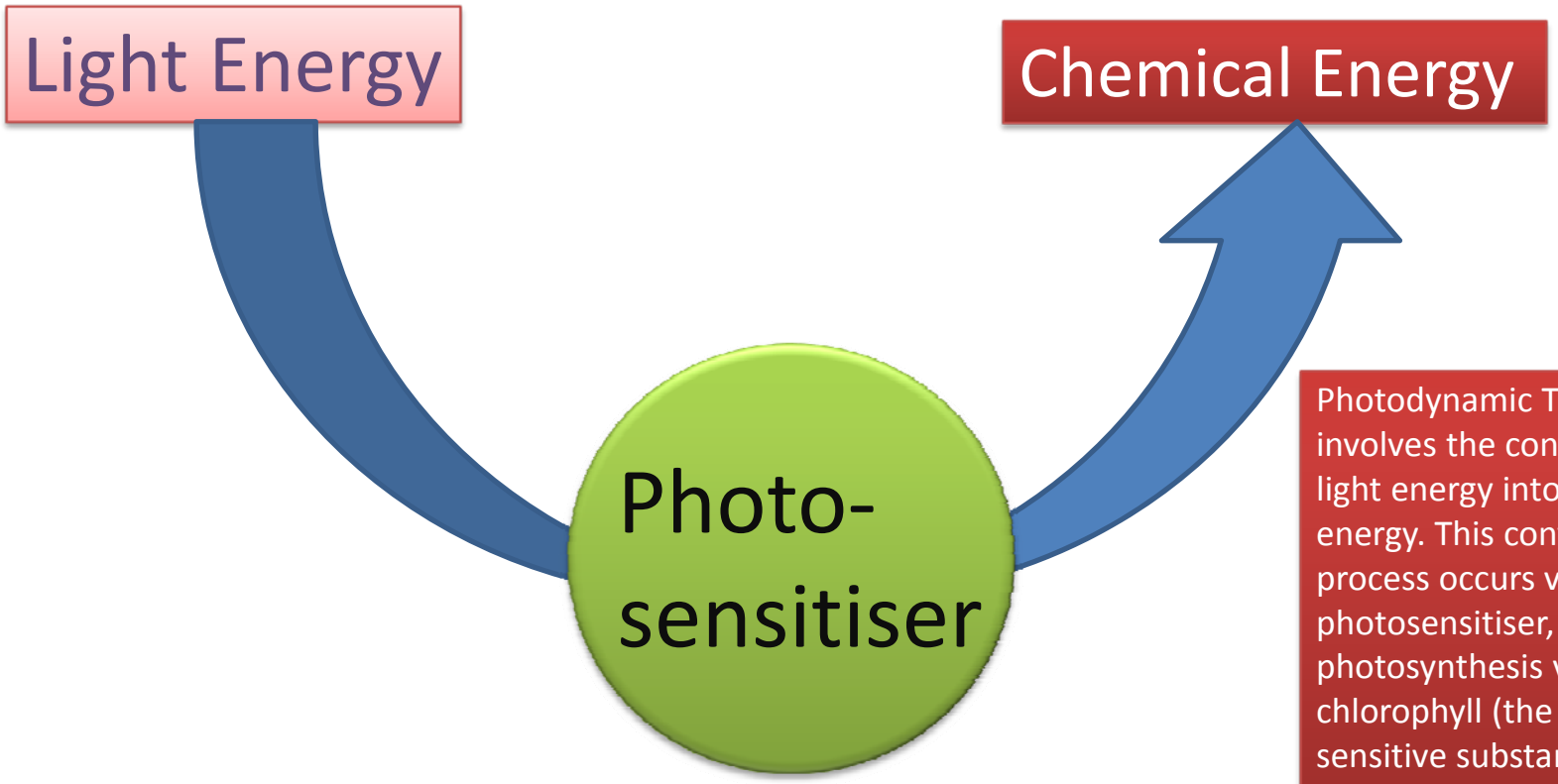
- 115 consecutive cases
  - Variety of cancer diagnoses
  - April 2005 – Feb 2009
  - Most cases - late stage/ secondary spread
  - Many did not respond previously to chemotherapy or were unable to tolerate side-effects
  - Further details outlined anonymously (categorised by type of primary tumour) in the journal article

Introduction - Sonodynamic Photodynamic Therapy (SPDT)

- **What is SPDT?**
- **How does it work?**
- **Is it safe?**
- **Is it effective?**

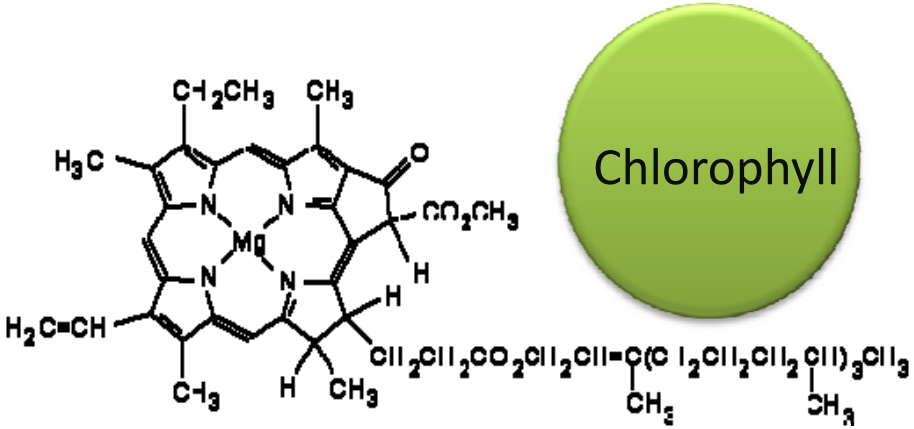
What is Photodynamic Therapy?

Light/ Photo-Activation



Photodynamic Therapy involves the conversion of light energy into chemical energy. This conversion process occurs via a photosensitiser, similar to photosynthesis via chlorophyll (the green light sensitive substance in plants)

Conversion of Light to Chemical Energy



Photodynamic Therapy - History

- **Light-activated treatment**

- **Ancient Egypt**
  - Ancient Egyptians used the plant Amni Majus (Psoralen) and Sunlight to effectively treat vitiligo 4000 years ago.

- **Modern Cancer Treatment**
  - LED and laser light are used in modern medicine to treat a variety of problems including non-melanoma skin cancer, Barret's Oesophagus, Endobronchial and Head and neck tumours.

- **Review Reference**: Zheng Huang. A Review of Progress in Clinical Photodynamic Therapy. Technol Cancer Res Treat. 2005 June; 4(3): 283–293

Photodynamic Therapy - Overview

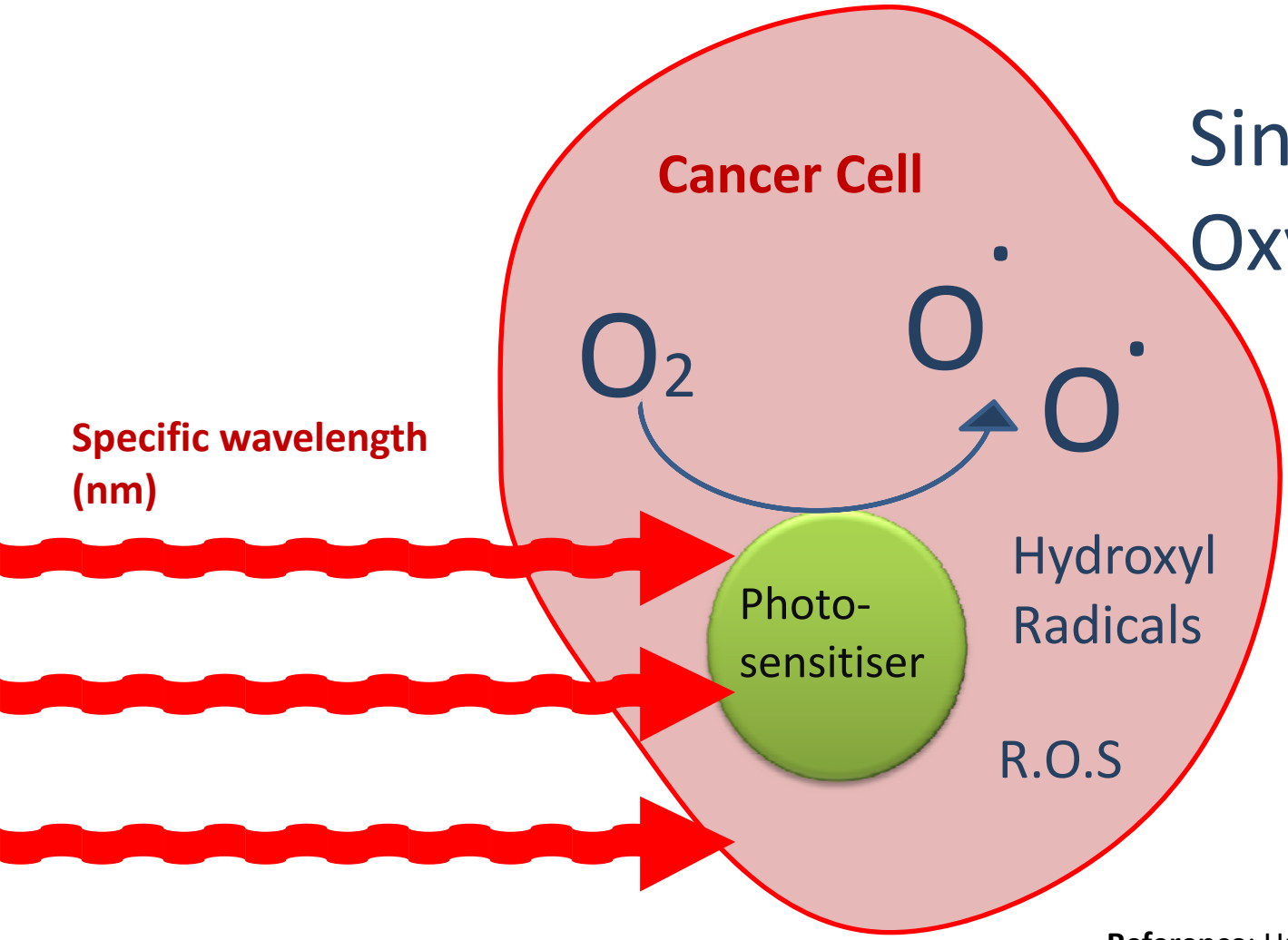
Step 1. Administration

- A Light-sensitive medicine (photosensitiser) is administered IV, orally or onto the skin.
- Photosensitisers typically have a Chlorophyll or porphyrin ring structure which provides sensitivity to light.
- Photosensitisers have the characteristic of being preferentially taken up by tumour cells rather than by healthy cells.

Step 2. Activation

- Photosensitisers are non-toxic. They are sensitive to specific wavelengths of light which are absorbed by the sensitiser. As the light energy is given out again by the sensitiser this breaks molecular oxygen O2 into singlet oxygen causing damage to the cancer cell.

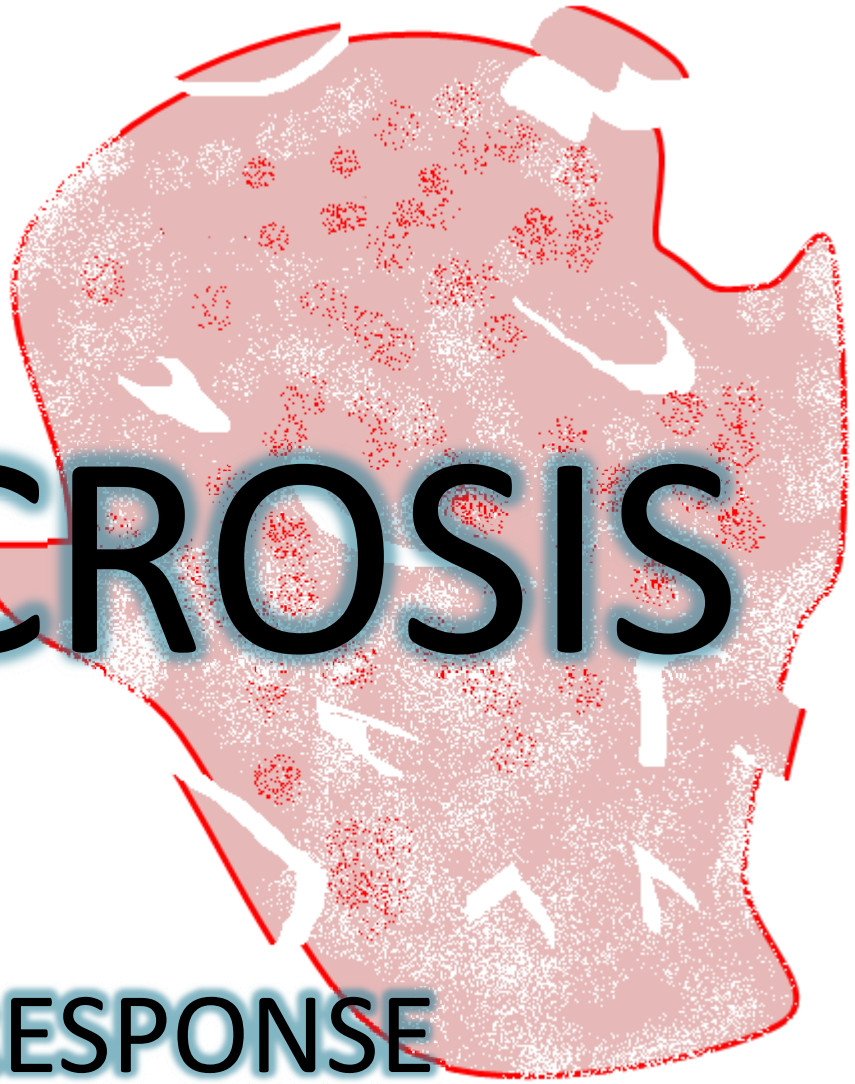
Mechanism of Action - Necrosis



Activation of the sensitiser by specific light energy leads to the breakdown of molecular oxygen into singlet oxygen and free radicals within the cancer cell. This leads to cell death (necrosis)

Reference: Huang Z. A review of progress in clinical photodynamic therapy. Ther Technol Cancer Res Treat 2005; 4(3): 283-93.

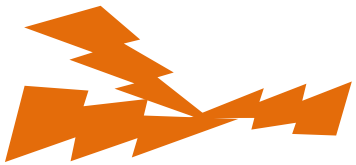
Mechanism of Action



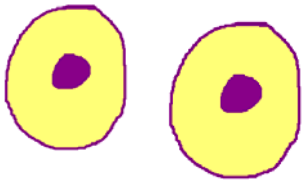
NECROSIS

IMMUNE RESPONSE

Phagocytic Cells



Dendritic Cells



Cytotoxic T Cells (CD8+)

Benefits

- Photosensitisers are non-toxic
- Treatment effect targeted to the tumour – minimal effect on healthy tissue
- No total dose limitation
- Does not suppress immune function
- Vaccine-like response – “immunogenic” cancer cell necrosis and cancer-specific immune response

- **Reference**: Korbelik M, Stott B, Sun J. Photodynamic therapy-generated vaccines: relevance of tumour cell death expression. *Brit J Cancer* 2007; 97: 1381-7.

Limitations – Light Activation?

– Light Penetrance limits the depth of activation

Sufficient light needs to reach the tumour in order to activate the breakdown of oxygen and kill the cancer cell

– Light is absorbed into surrounding tissues making treatment of deep-sited tumours technically challenging.

Solution – Ultrasound?

- Ultrasound is used widely for the very fact that it travels safely deep into body tissues, therefore ultrasound-activated treatment potentially allows treatment of deep-sited tumours using an ultrasound probe placed on the skin, similar to a pregnancy scan, over areas of cancer tissue.
- Activation of a sensitiser using ultrasound rather than light is called **Sonodynamic Therapy**

Sonodynamic Therapy

- Ultrasound was first found to enhance the treatment effect of chemotherapy drugs in 1976

- Later it was found that several photosensitisers are also activated by ultrasound (“sonosensitiser”)

- Ultrasound creates a mechanical effect on the Sonosensitiser, causing:

  - **Oxygen free radical production**
  - **Sonoporation** (physical destabilisation of cell membrane)
  - **Cavitation**

- **Reference** - Rosenthal et al. **Sonodynamic therapy—a review of the synergistic effects of drugs and ultrasound**. Ultrason Sonochem; 2004.11: 349-63.

Sonodynamic Photodynamic Therapy (SPDT) in this Case Series – Possible due to a new Dual-Activation Sensitiser

- Ultrasound activation is achieved using a new light and ultrasound sensitive molecule (sonnelux). This has been developed from a photodynamic therapy sensitiser and has a similar structure to chlorophyll in plants (chlorophyllin) with a specific side chain that increases sensitivity to ultrasound.

- It is administered as a solution under the tongue

- Unlicensed medication – imported under MHRA guidance and approval

Safety – Photo Sono-sensitiser

- Safety studies using a Zebra Fish Model (a widely used safety test) have shown an excellent safety profile even at maximal soluble concentrations (Author: T J Lewis)
- No side-effects have been associated with sonnelux administration over the 4 year period
- Advice is given to avoid bright sunlight during treatment but no cases of skin sensitivity have been noted.
- Sonnelux is registered as non-hazardous by OSHA and EU standards

Potential of Sonodynamic Therapy?

- Treat deep tumours
- Non-invasive
- Targetted
    - Selective cancer cell sensitiser uptake
    - Ultrasound probe

What's the evidence for the ultrasound theory?

Animal Cancer Studies

- Animal cancer studies have been performed and published using the same sensitiser and ultrasound strength as used in the case series.

- **Reference:**
  - **The tumoricidal effect of sonodynamic therapy (SDT) on S-180 sarcoma in mice.** Integr Cancer Ther 2008; 7: 96-102. Wang X, Lewis T, Mitchell D.

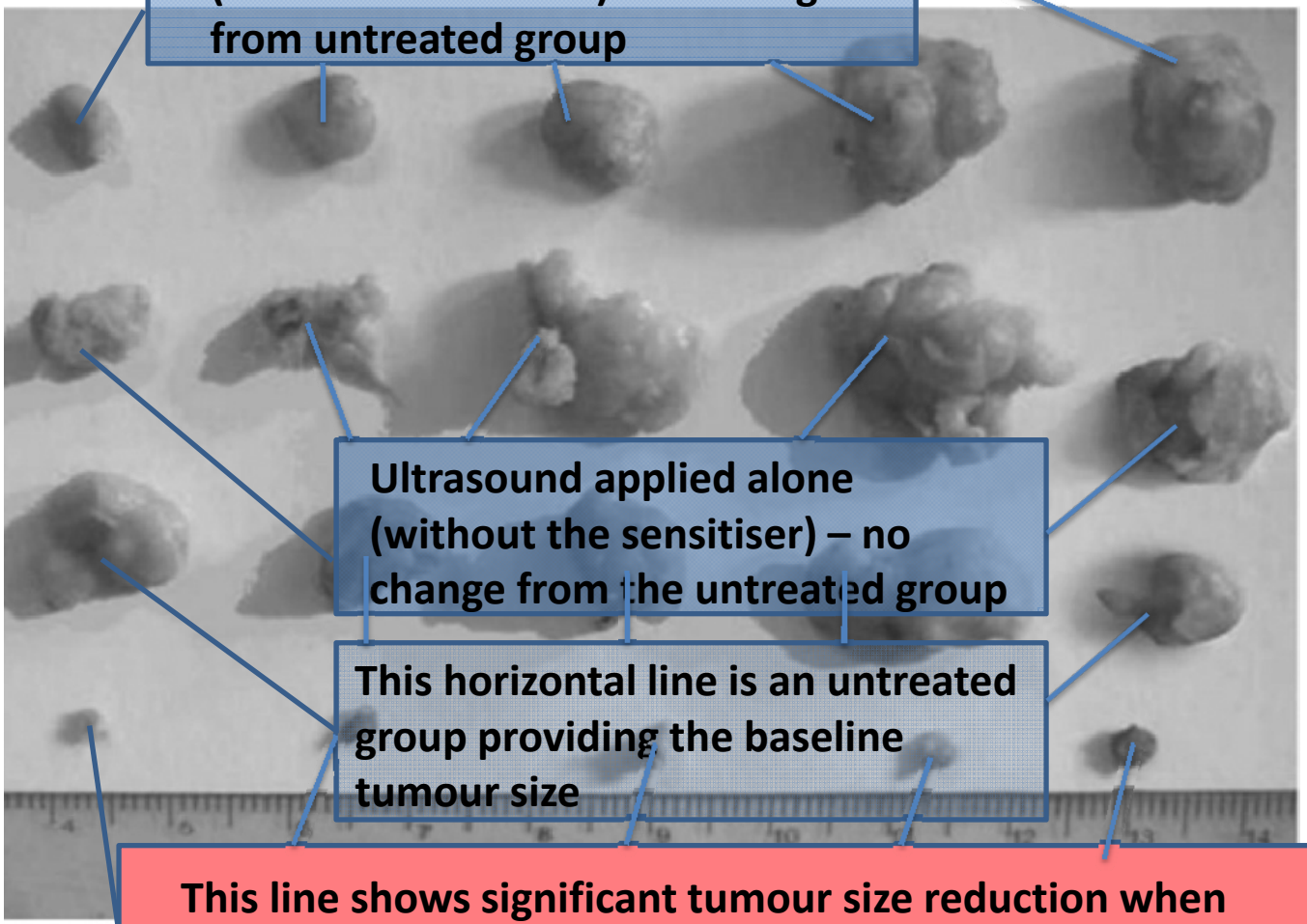
Synergistic Effect - Sonosensitiser + Ultrasound

Sonnelux Only

Ultrasound 1.2W/cm2 Only

Control

Ultrasound 1.2W/cm2 + Sonnelux



Sonnelux sensitiser admistered only (without ultrasound)– no change from untreated group

Ultrasound applied alone (without the sensitiser) – no change from the untreated group

This horizontal line is an untreated group providing the baseline tumour size

This line shows significant tumour size reduction when BOTH ultrasound and the sonnelux sensitiser are applied

Ultrasound Intensity - Dose Dependent

The most effective reduction in tumour size is seen with the highest ultrasound intensity (1.2 W/cm2). This is the strength of ultrasound used in clinical practice to optimise the effect but is still very safe and well tolerated at an intensity used in ultrasound scans and physiotherapy.

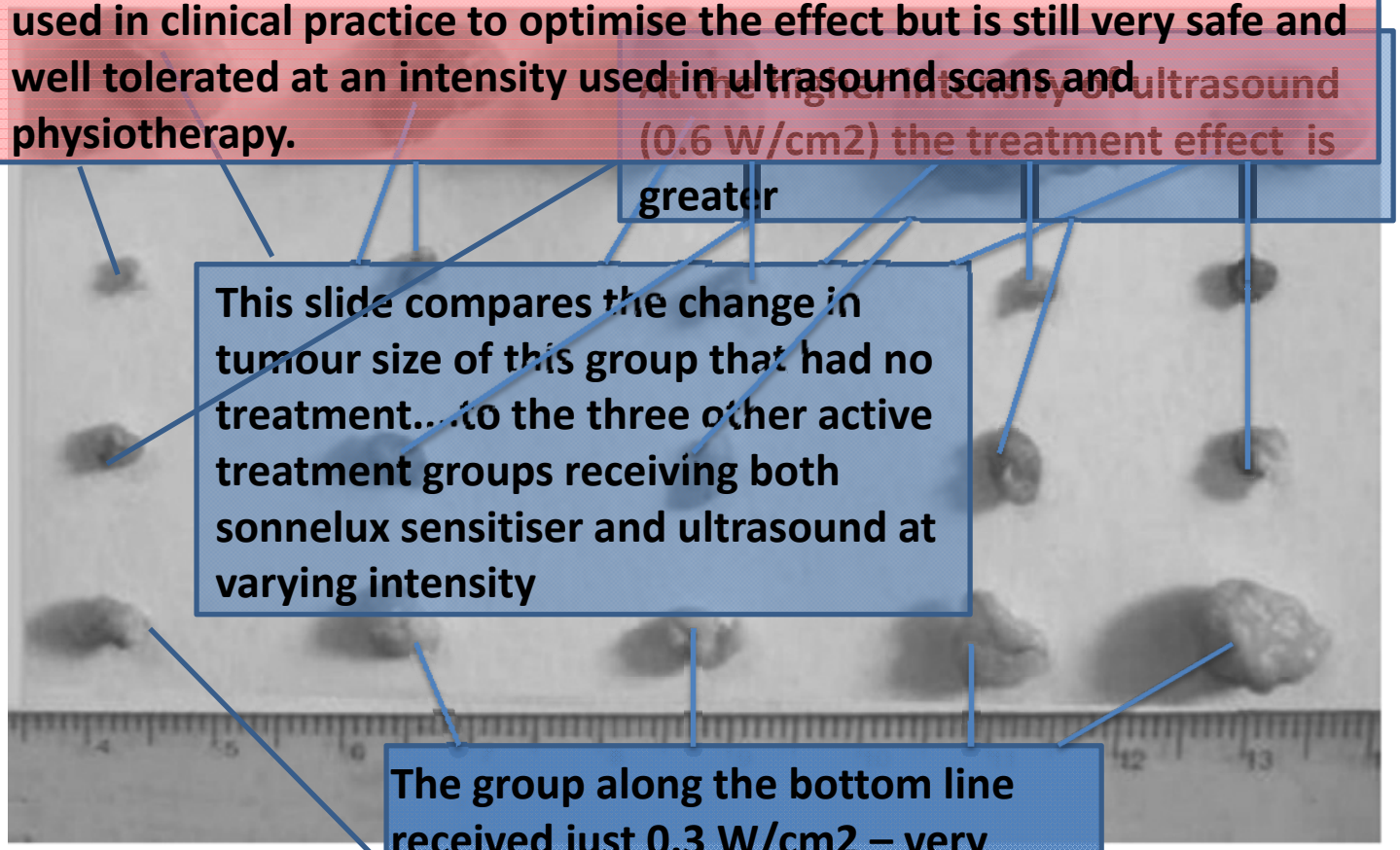
At the higher intensity of ultrasound (0.6 W/cm2) the treatment effect is greater

Control

1.2 W/cm2 + sonnelux

0.6 W/cm2 + sonnelux

0.3 W/cm2 + sonnelux



This slide compares the change in tumour size of this group that had no treatment...to the three other active treatment groups receiving both sonnelux sensitiser and ultrasound at varying intensity

The group along the bottom line received just 0.3 W/cm2 – very low ultrasound intensity and had the smallest treatment effect

Reference: Wang et al Integr Cancer Ther 2008; 7: 96-102

Histology – SPDT induced Necrosis

- This next slide shows the changes under a microscope in pathology samples taken from the treated tumours. It shows areas of tumour cell breakdown (necrosis) which start to occur shortly after SPDT treatment.

Histology – SPDT induced Necrosis

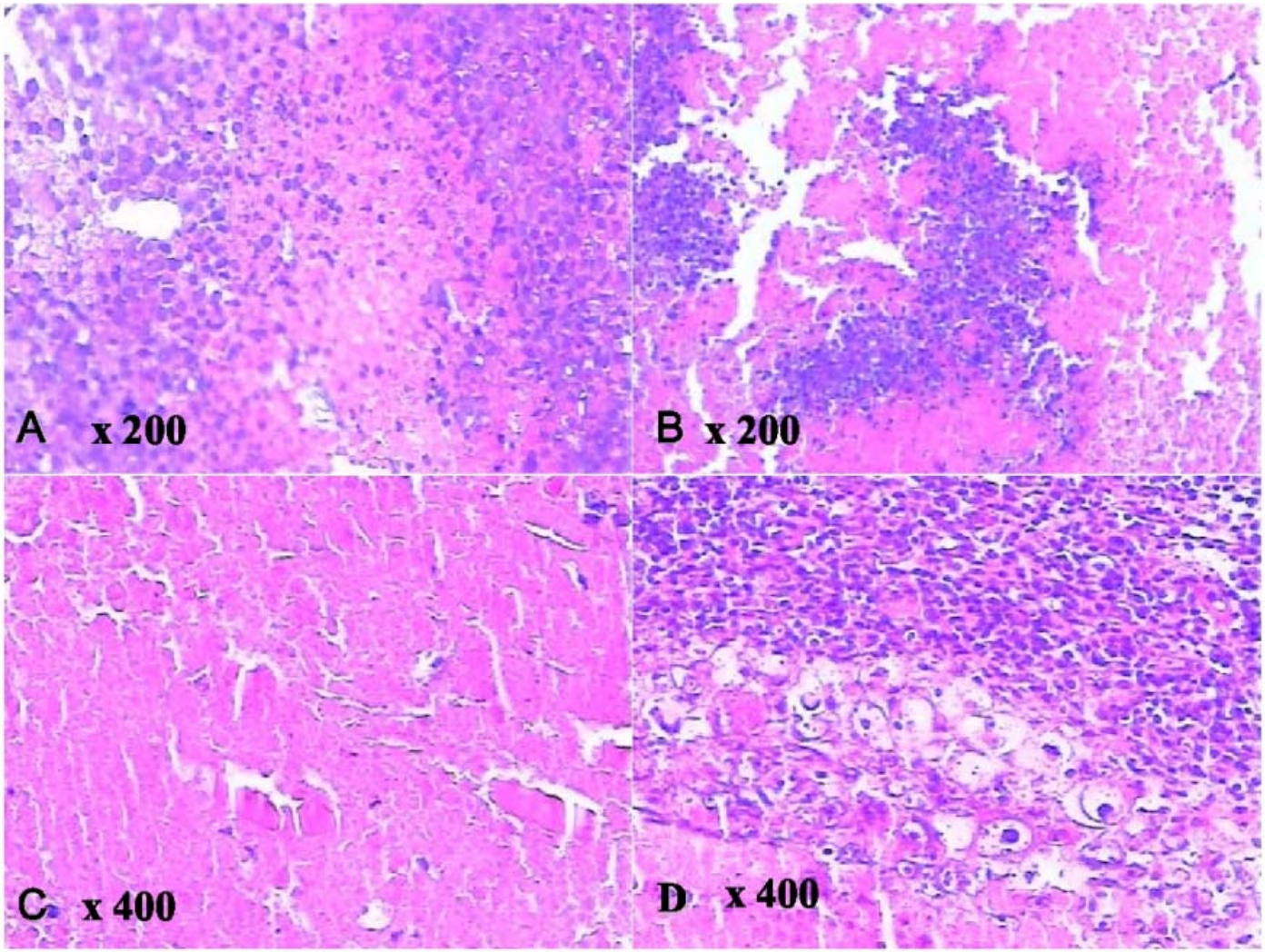
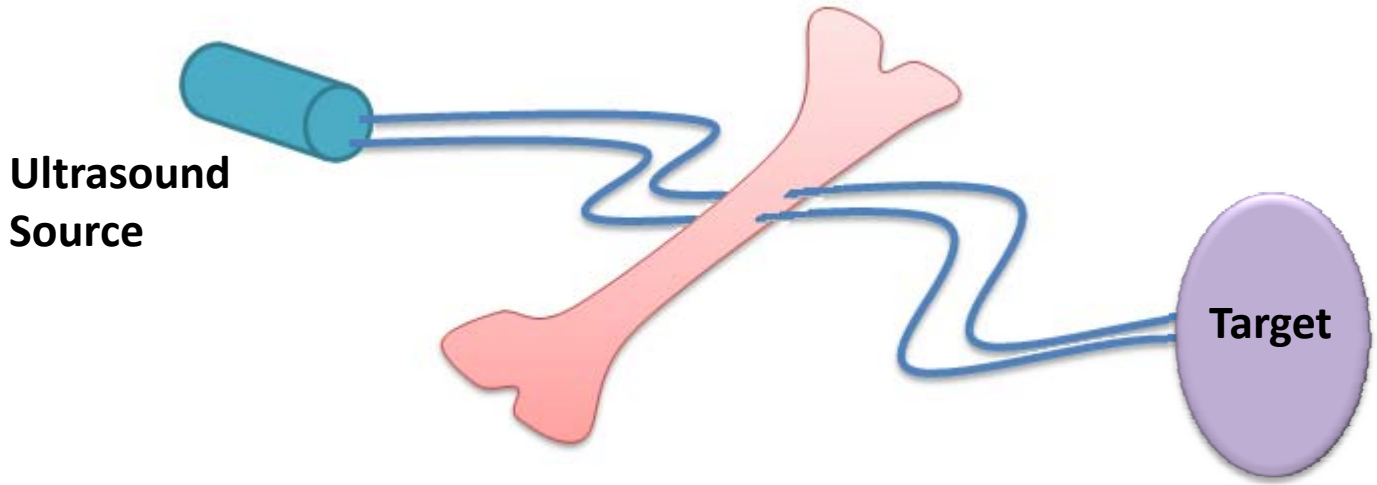


Figure 4: Histological slices of the tumour in a group of mice following sonnelux-1 plus ultrasound plus light exposure showing coagulated tumour cell necrosis, inflammatory changes and metamorphic tissue.

Slice taken
A. 2 hours after treatment
B. Slice taken 36 hours after treatment
C & D. Slices taken 15 days after treatment

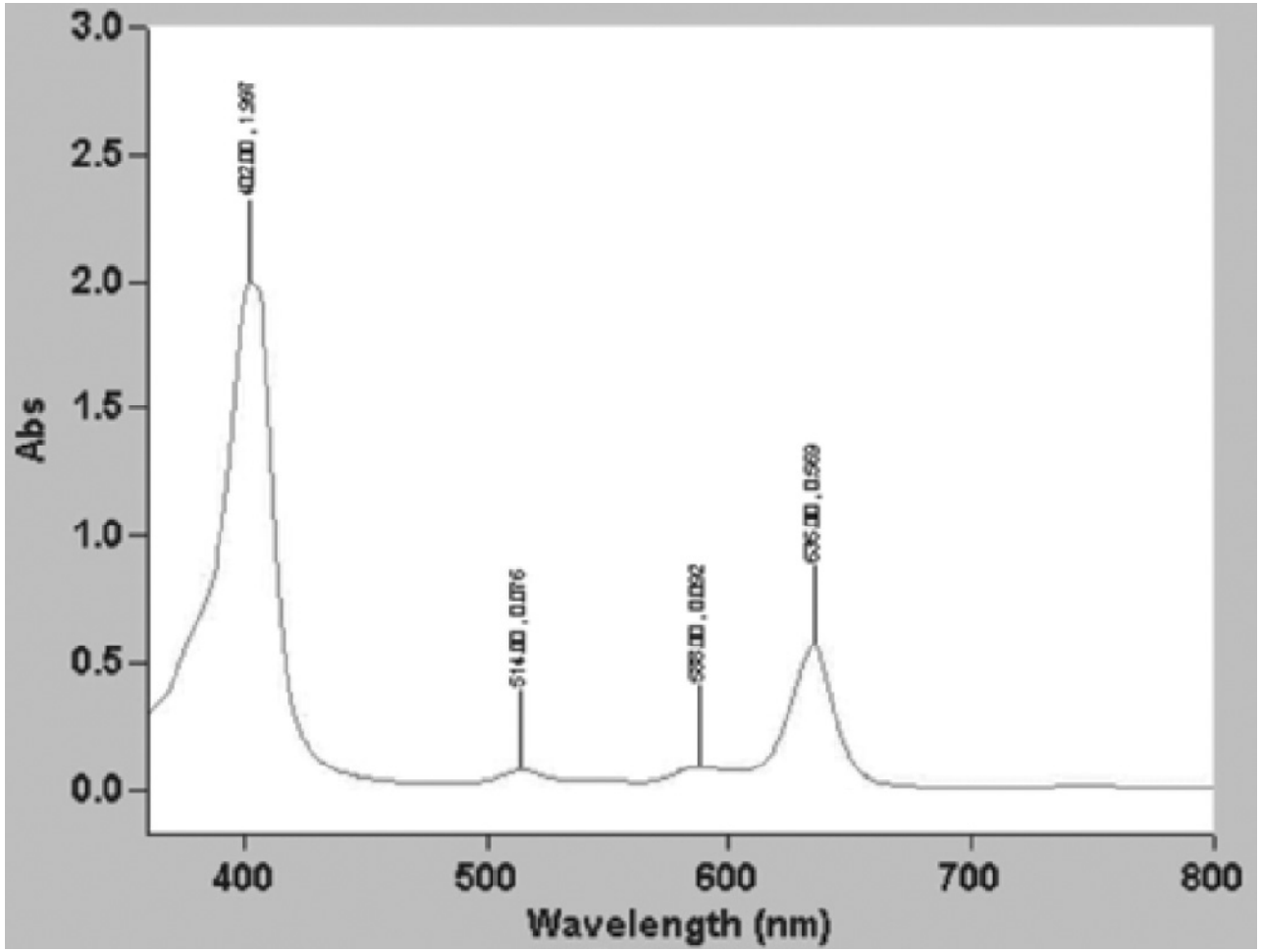
Activation Through Bone Barrier

- This study also showed successful ultrasound activation with a bone barrier between the probe and tumour i.e effective treatment through bone.



Reference: Wang et al Integr Cancer Ther 2008; 7: 96-102

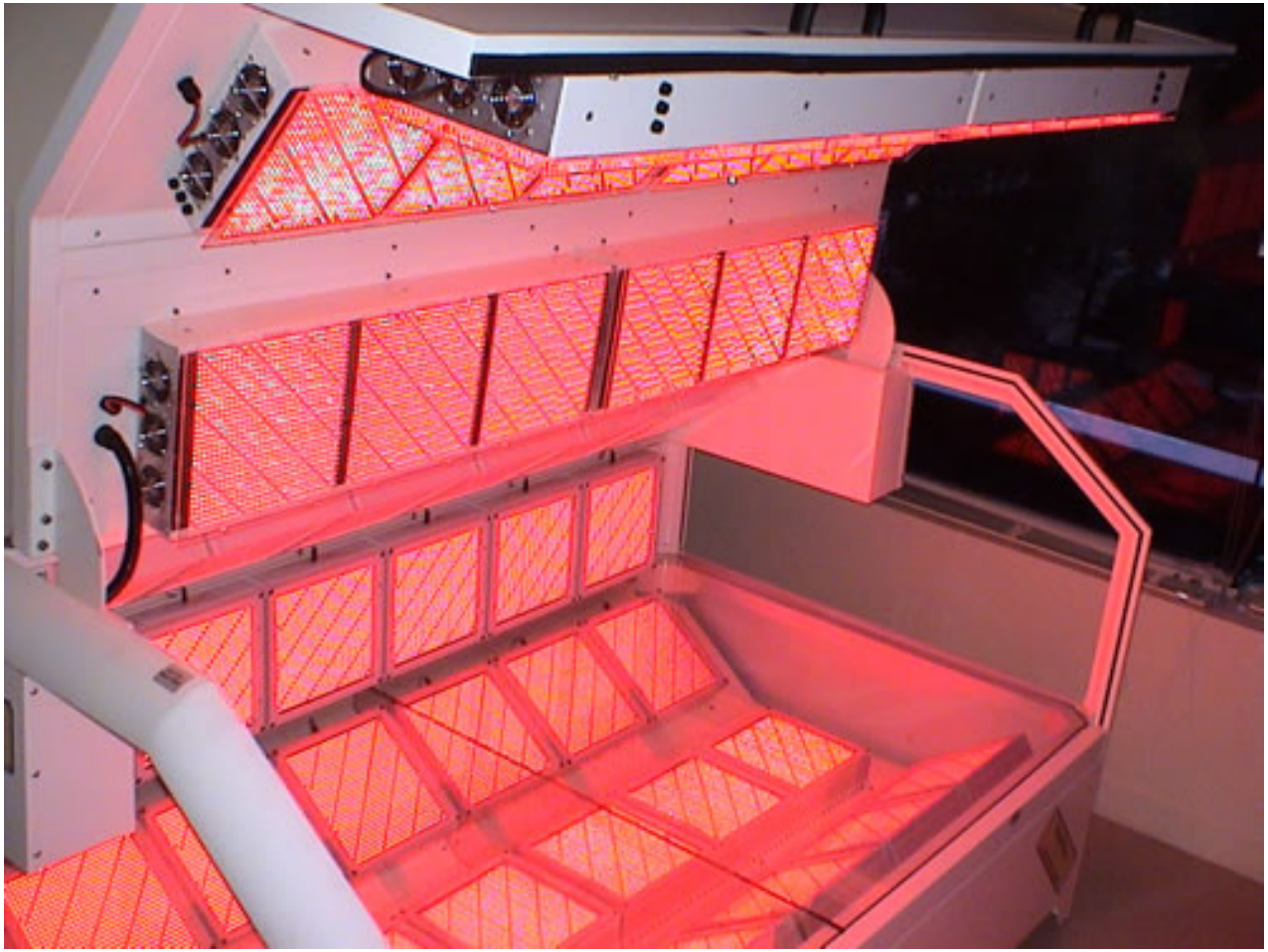
Activation – Sensitiser Light Absorption



The ultrasound sensitive medicine shows specific light absorption properties – therefore light and ultrasound are both used to activate singlet oxygen production.

Reference: Absorption Scan (ChemLab) Wang et al Integr Cancer Ther 2008; 7: 96-102

LED Light Activation – 660 and 940 nm



This specially designed light bed emits light at specific wavelengths corresponding to the activation properties of the sensitiser medication.

SPDT Case Series Protocol

Sublingual administration

48 hours

LED Light Bed

Ultrasound
1W/cm2
1MHz
CT/ MRI/ Bone scan

An SPDT treatment cycle involves administration of the sonnelux drops under the tongue followed by a 48 hour period to allow release from healthy tissue and skin. Light and ultrasound are used then for 3 consecutive mornings or afternoons. The total time and sites treated vary case by case. The cycle is then repeated with further sonnelux for a second week to complete a treatment cycle.

Integrated Approach - Supplementation

- Specific nutritional supplementation and dietary advice is provided on a case by case basis, including:

- Refined 1-3 1-6 beta glucan, Vitamin D (Immiflex)
- Pancreatic enzymes
- EGCG – Green tea extract
- Omega 3 - EPA
- Specific plant-based angiogenesis inhibitors
- Other supplementation and support

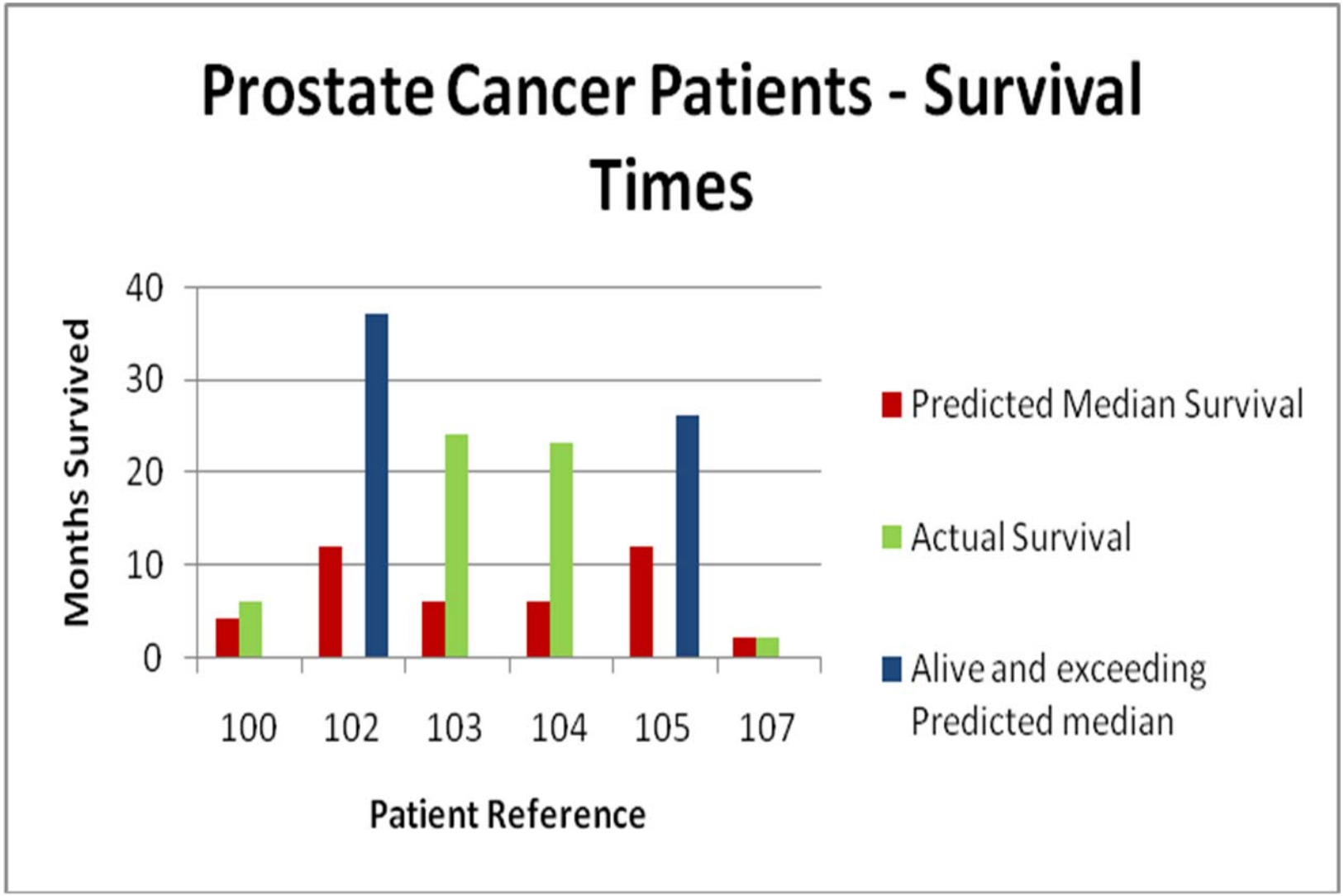
Tumour Hypoxia + Ozone Autohaemotherapy

- **Tumours are low in oxygen (hypoxic)**
- **Poor oxygenation can reduce the effectiveness of chemotherapy, radiotherapy and sonodynamic photodynamic therapy.**
- **Ozone autohaemotherapy is performed 15 minutes prior to SPDT light and ultrasound activation with the aim of increasing tumour oxygenation.**
- **Tumour oxygenation was demonstrated to increase following ozone administration in previous research.**

Reference: Hoogsteen et al. The hypoxic tumour microenvironment, patient selection and hypoxia-modifying treatments. Clin Oncol (R Coll Radiol) 2007; 19(6): 385-96.

Reference: Clavo et al. Ozone Therapy for Tumor Oxygenation: a Pilot Study. eCAM 2004;1(1)93–98

Outcomes - Case Series



Case 1 – Non Hodgkin's Lymphoma

- 60 year old female
- Recurrence of non-Hodgkin's Lymphoma (T cell) – Aug 2004
- Resistant/ partial response only to second line chemotherapy and IV Vitamin C - Continued to have progressive disease
- Abdominal Radiotherapy 36Gy - 2005
- Predicted Median Survival **6 months**

- SPDT was completed in July 2005. At the time of writing, she is in full remission and has no recurrence of her tumour

- Actual survival – alive and well at **41 months**

Case 2 – Brain Tumour

- 50 year old female patient presented in April 2008
- Grade 3 Ependymoma first diagnosed in April 2003.
- At first consultation her clinical state was poor
- Predicted median survival time of 6 months
- Previous surgical de-bulking and whole brain radiotherapy had been performed.
- She had refused management with chemotherapy (Temozolamide)

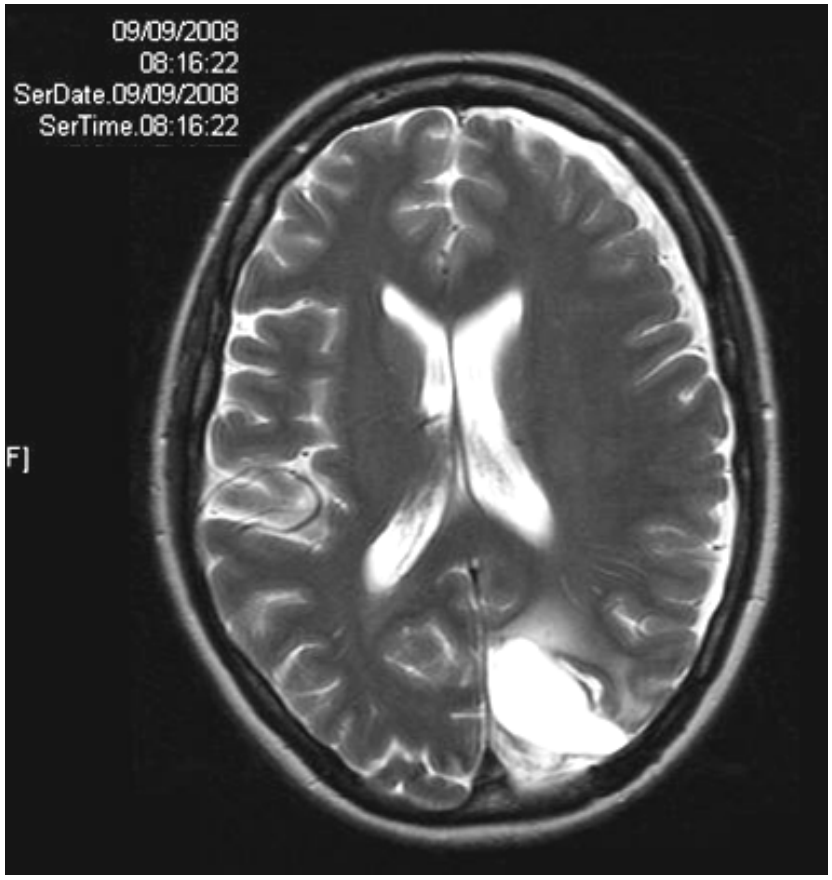
- SPDT in April 2008
- Dexamethasone was prescribed for the treatment course (2mg twice a day).

Case 2 – Brain Tumour

- **Outcome**
- A month after treatment she felt well enough to go on a 2 month holiday abroad.
- She has remained relatively symptom free.
- A further course of SPDT was performed in October 2008.
- Actual survival – 10 months + (alive and well)
- Repeat MRI scans in December 2008 – stable from April

MRI Scans

9/9/08 (after 1st course)



2/12/08 (after 2nd course)

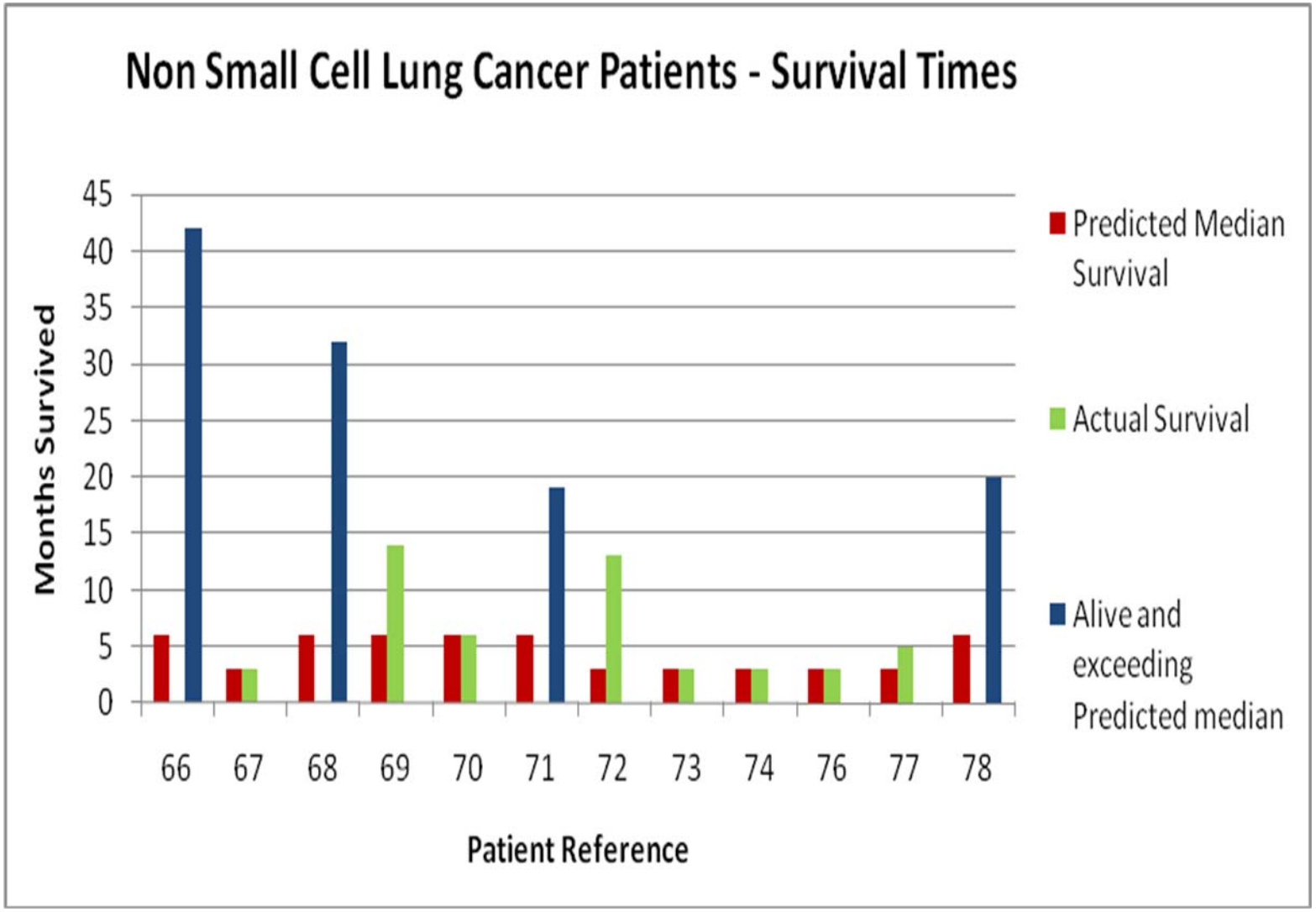
Case 3 - Non Small-Cell Lung Cancer

- 80 year old female patient
- Inoperable 8cm non small-cell lung cancer (squamous cell) in the left lung diagnosed June 2005.
- Refused palliative radiotherapy
- Presented in August 2005
- Given a predicted median survival of **6 months**.
- SPDT was completed in September 2005.

Case 3 - Non Small-Cell Lung Cancer

- Following treatment she developed an inter-scapula (back) ache, but tolerated the treatment well.
- Until March 2007 she had stable disease, as determined by regular chest x-rays.
- In June 2007 she was demonstrated to have tumour progression and underwent a second course of SPDT.
- She tolerated the second course well and at the time of writing she still has stable disease on chest x-rays with a good quality of life.
- Actual survival **42 months**, alive and well

Case 3 - NSCLC Cases Overview



Case 4 – Recurrent breast cancer

- Breast cancer – left side 1990
- Previous mastectomy and radiotherapy
- June 2008
  - Developed Right sided visual symptoms and severe eye pain
  - CT Sept 2008 – found a mass encasing right optic nerve
  - CT scan body - Metastasis in spine and right sided breast lump – malignant on biopsy
  - Too high risk for biopsy of the mass around eye
  - Started anastrazole

Case 4 – Recurrent breast cancer

- SPDT December 2008
- Pain – eye reduced within 2 weeks then resolved
- Visual fields assessment at hospital improved
- Breast tumour reducing in size on follow up
- Exercise tolerance and wellbeing increased
- Follow-up scan of orbit awaited

Objective evidence of tumour destruction, via scans, histology and visual inspection

Case 1 - Non-small cell Lung Cancer

- NSCLC – left lung with right adrenal metastasis; female age 58.
- First seen in May 2007 with a prognosis of weeks.
- SPDT July 2007 – cough cleared up and air entry restored to left lung within 2 months of treatment.
- No other treatment used

Case 1 - continued

- Cough returned end of 2007, had another course of SPDT
- Cough cleared up again
- Follow-up scan showed stable disease and reduction of left sided pleural effusion
- Scan also showed reduction in right adrenal metastasis
- Patient still alive as of November 2009

Case 2 - Tumour Cell Necrosis on Histology

- 56 year old female, previous carcinoma of anus in April 2006
- Found to have 16mm liver lesion in August 2007
- Partial hepatectomy planned with neo-adjuvant chemotherapy
- Patient refused chemotherapy

Case 2 - continued

- Carried out SPDT in October 2007
- Right hepatectomy in December 2007
- Histology showed extensive tumour cell necrosis
- Patient alive and well, tumour free, as of November 2007.

Case 3 – Visible Tumour Cell Destruction

- Female aged 66, breast cancer, oestrogen and HER2 positive, diagnosed in 2007
- Widespread tumour across the majority of the chest when she came to see us in August 2007
- This was followed by a marked inflammatory response lasting nearly 3 months; Dexamethasone cover was used for the SPDT

Case 3 – Visible Tumour Cell Destruction

- Tumour visibly disappeared from the area treated by ultrasound
- Tumour recurred mid 2008 in area above and below ultrasound treated area – the demarcation between treated (now tumour free) area and recurrence was as precise as a straight line above and below the ultrasound treated area
- Further SPDT, using ultrasound over recurrent tumour area under Dexamethasone cover. This resulted in further tumour destruction

Case 4 – Breast Cancer

- Female age 45, right sided breast cancer November 2004 – right mastectomy. Refused chemotherapy, radiotherapy and Tamoxifen
- Recurrence of tumour over both sides of chest when patient came to see us in August 2008 including several fungating ulcers.
- SPDT under Dexamethasone cover carried out in September 2008.
- Extensive inflammatory reaction followed by disappearance of all tumour in treated area over the following 3 months

Case 4 – continued

- Recurrence of tumour in January 2008 directly above and below ultrasound treated area
- A clear distinction visible between ultrasound treated area form SPDT treated area, now replaced by fibrous/scar tissue and area of recurrent tumour
- A further one week course of SPDT administered in January 2009
- No other form of treatment was used

Thank you for watching this presentation.

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