HYPERTHERMIA IN ONCOLOGY : LUNG & ESOPHAGUS

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History of Hyperthermia

• Greek HYPER ("to raise") and THERME ("to heat").

• 3,000 B.C., Egyptian doctors treated tumors with heat (i.e. hot clay, and hot water) and in Indian Auyerved hot baths were mentioned.

•Hyperthermia as a therapeautic modalitiy in epic of Ramayana.

• Hyperthermia was given legal status as an approved medical procedure in 1984.

•There has been a disconnect between therapeautic and clinical practice.

History

1866	W. Bush	Germany
1893	William Coley	USA
1898	F. Westermark	Sweden
*1909	H. Schmidt	Germany
*1910	C. Mueller	Germany
1912	R.A. Lambert	USA
*1913	A. Teilhaber	Germany
*1921	P. Liebensy	Austria
*1921	Rhodenberg & Primo	Germany
1927	N. Westermark	Sweden
1934	K. Overgaard	Holland
*1937	J. Arons	USA
*1958	Selawary	USA
1961	Crile	USA
1967	Cruke	USA
2002	Vander Zee	Netherlands
2002	Nagraj G.Huilgol	INDIA

* Hyperthermia combined with radiation

Conventional Strategies

Fractionation

- **CHART**
- **MDF**
- **Hypofractionation**

Dose Escalation

Chemo-radiation

Hyperthermia with radiation

Chemo-radiation with hyperthermia

Targets for Hyperthermia

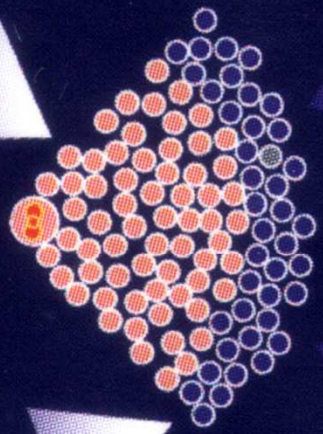
- Plasma Membrane
- Cytoskeleton
- Nucleolus

Therapeutic options in combating tumour hypoxia

Hypoxia modification
- hyperbaric oxygen
- vasoactive drugs
- blood transfusion
- erythropoietin

Elimination of oxic cell compartment
- radiation hyperfractionation
- cytotoxic drugs

Molecular targeting
- antiangiogenic agents
- COX-2 inhibitors
- EGFR inhibitors



Hypoxic cell toxins
- bioreductive drugs
- hyperthermia
- hypoxia-activated gene therapy

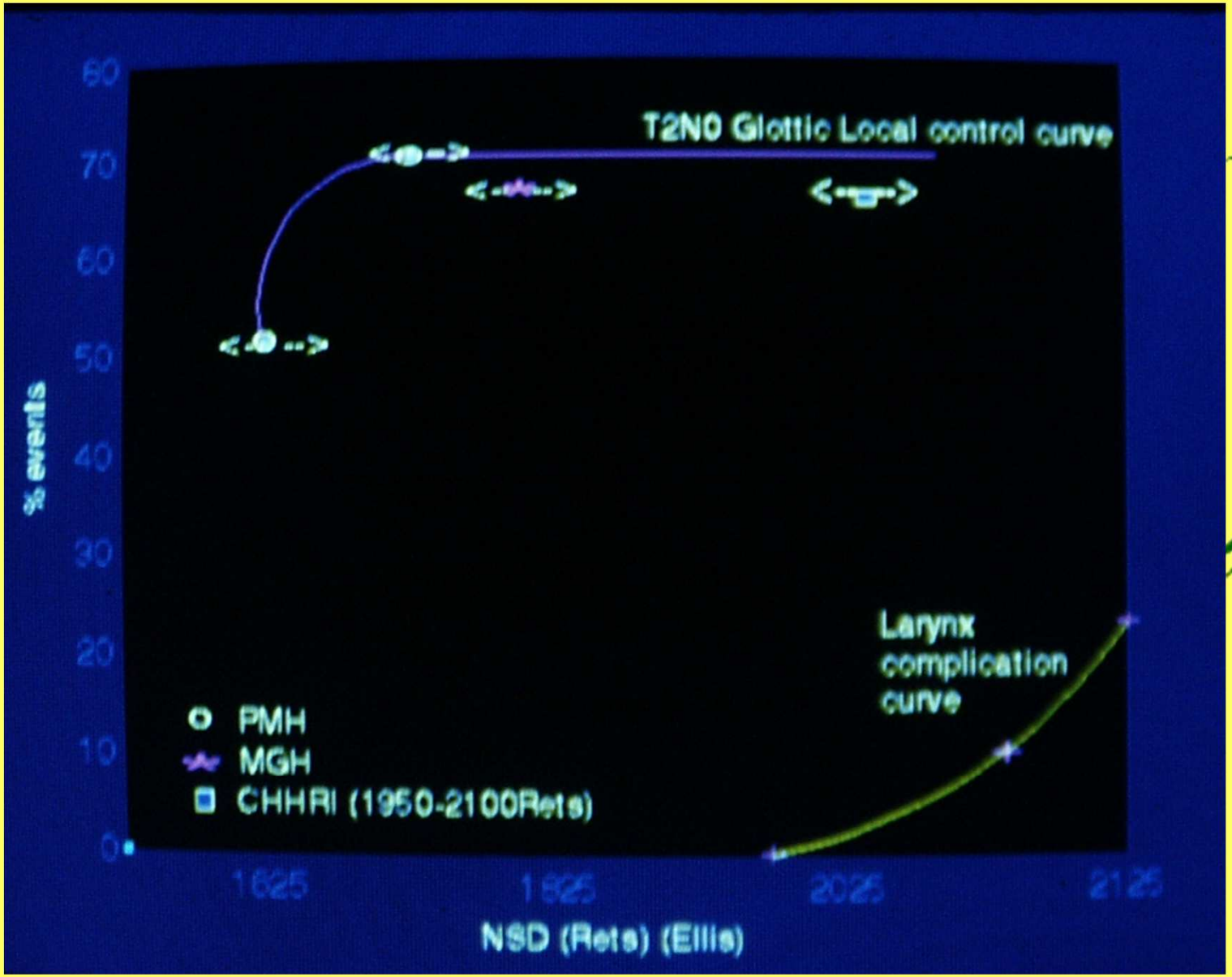
Hypoxic cell radiosensitisers
- nitroimidazoles

Techniques & Technologies for Regional Hyperthermia

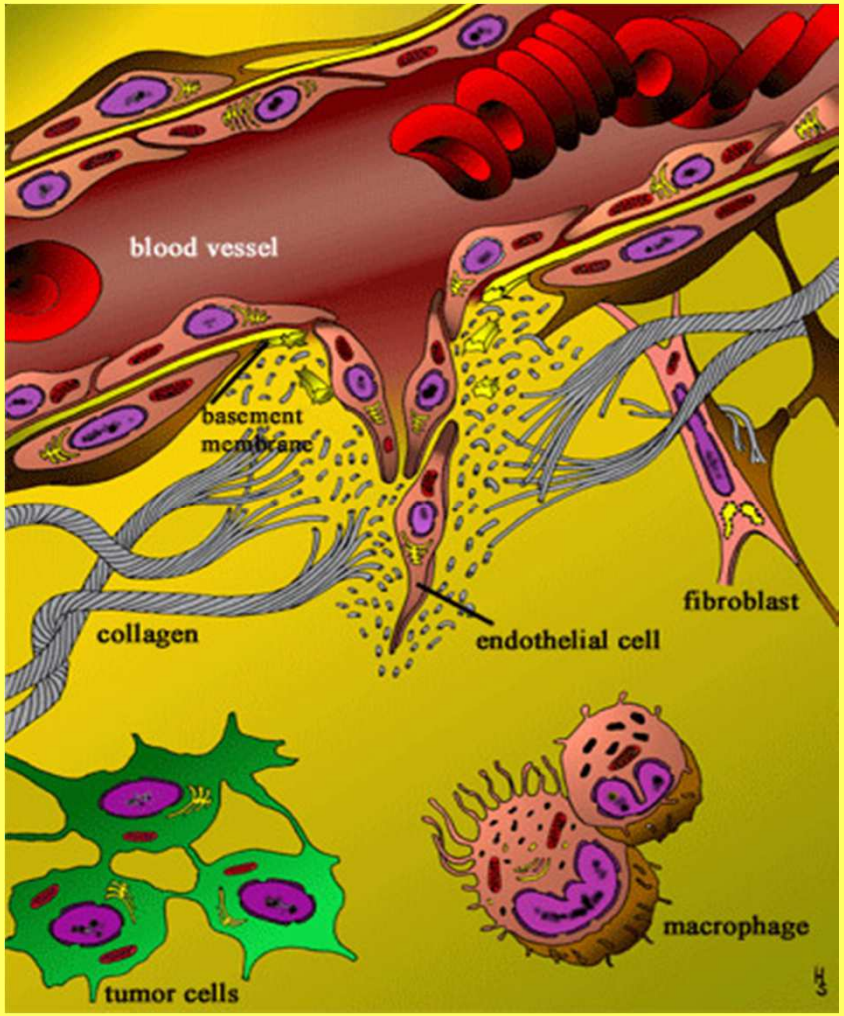
- Microwave
- Radiofrequency
- Ultrasound

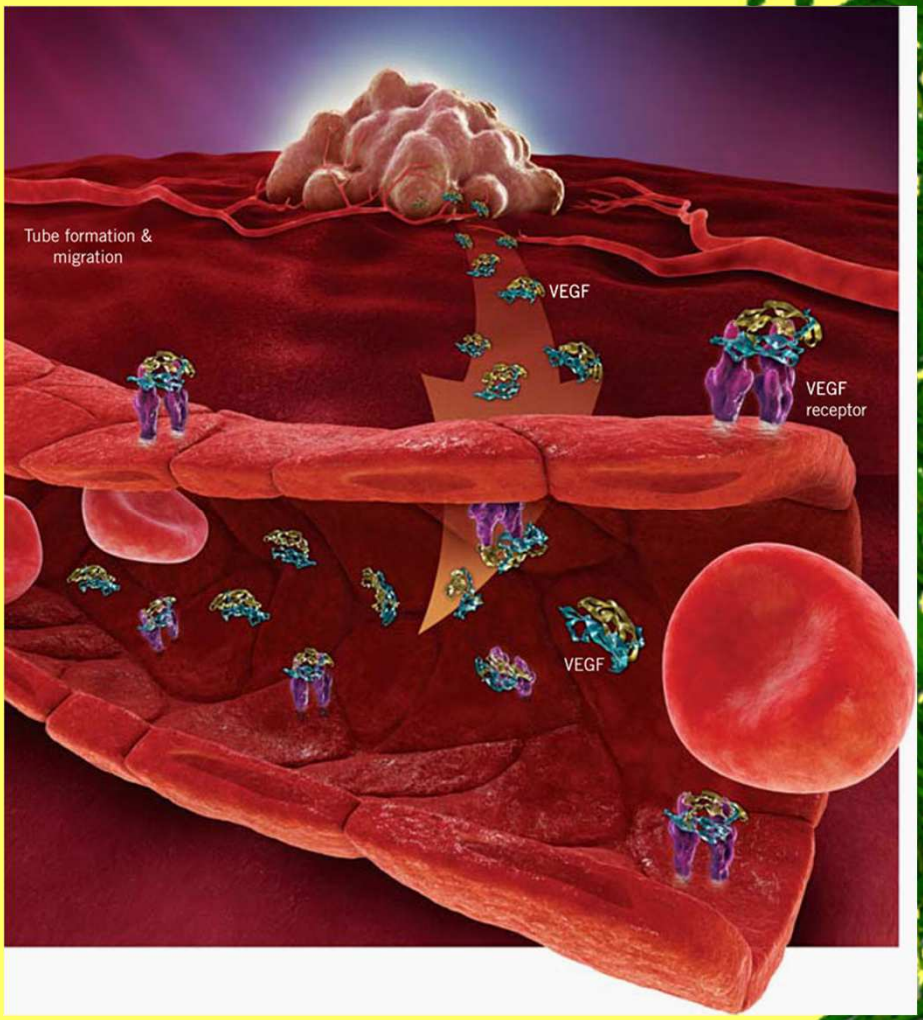
Biological Basis of Hyperthermia

- Cells in S phase are sensitive to HT and not for RT
- Cells in acidic pH are sensitive
- Targets of HT are different for than that for RT
- Can improve perfusion at low temperature.


T2N0 Glottic Local control curve
Larynx complication curve
PMH
MGH
CHHRI (1950-2100Rets)
% events
NSD (Rets) (Ellis)
60
70
60
50
40
30
20
10
0
1625
1825
2025
2125

ANGIOGENESIS





Specification of the RF Heating System

Power Source	**Single phase, 200V, 50~60Hz, 30A**
Max. Input	**4KVA**
RF Output	**8MHz**
Electrode	**Twin plate electrodes, ϕ10cm, ϕ14cm, ϕ25cm**
Temp. Measurement	**Micro thermocouple sensor (0.64mm diameter)**
Temperature Control	**On-Off control**
Heating Method	**RF Capacitive coupling heating**

Physical agents and techniques in Hyperthermia

MW-External (Waveguide applicator)	MW-Interstitial (Co-axial antennas)	RF-External (Plates , coils)	RF-Interstitial (Needle arrays)	Ultrasound arrays
300-2450MHz	300-1000 MHZ	0.1-27 MHz	0.1-1 MHz	0.3-5MHz
Up to 3 cm 20-300 W Superficial tumors	1-1.5 cm 10-200 W Tumors that can be implanted	Up to 8 cm 20-400 W Deep seated	1-1.5 cm 10-200 W Tumors that can be implanted	Up to 6 cm 10-100 W Deep seated tumors with focused beam

FACTORS AFFECTING RESPONSE TO HYPERTHERMIA

- Temperature
- Duration of heating
- Rate of heating
- Temporal fluctuations in temperature
- Spatial distribution of temperature
- Environmental factors (such as pH and nutrient levels)
- Combination with radiotherapy, chemotherapy, immunotherapy, etc.
- Previous history
- Intrinsic sensitivity

Thermal Sensitizers

- Hyperglycemia
- Amiloride
- Hydralazine
- Nitroprusside
- Arsenic Trioxide

Changes in Tissue pH

- Accumulation of lactic acids
- Changes equilibrium of intra and extra cellular buffer state
- Increase in ATP hydrolysis
- Increase in pCO^2 level
- Inhibition of the Na^+/H^+ ion pump

Sequence of HT

HT ——— RT

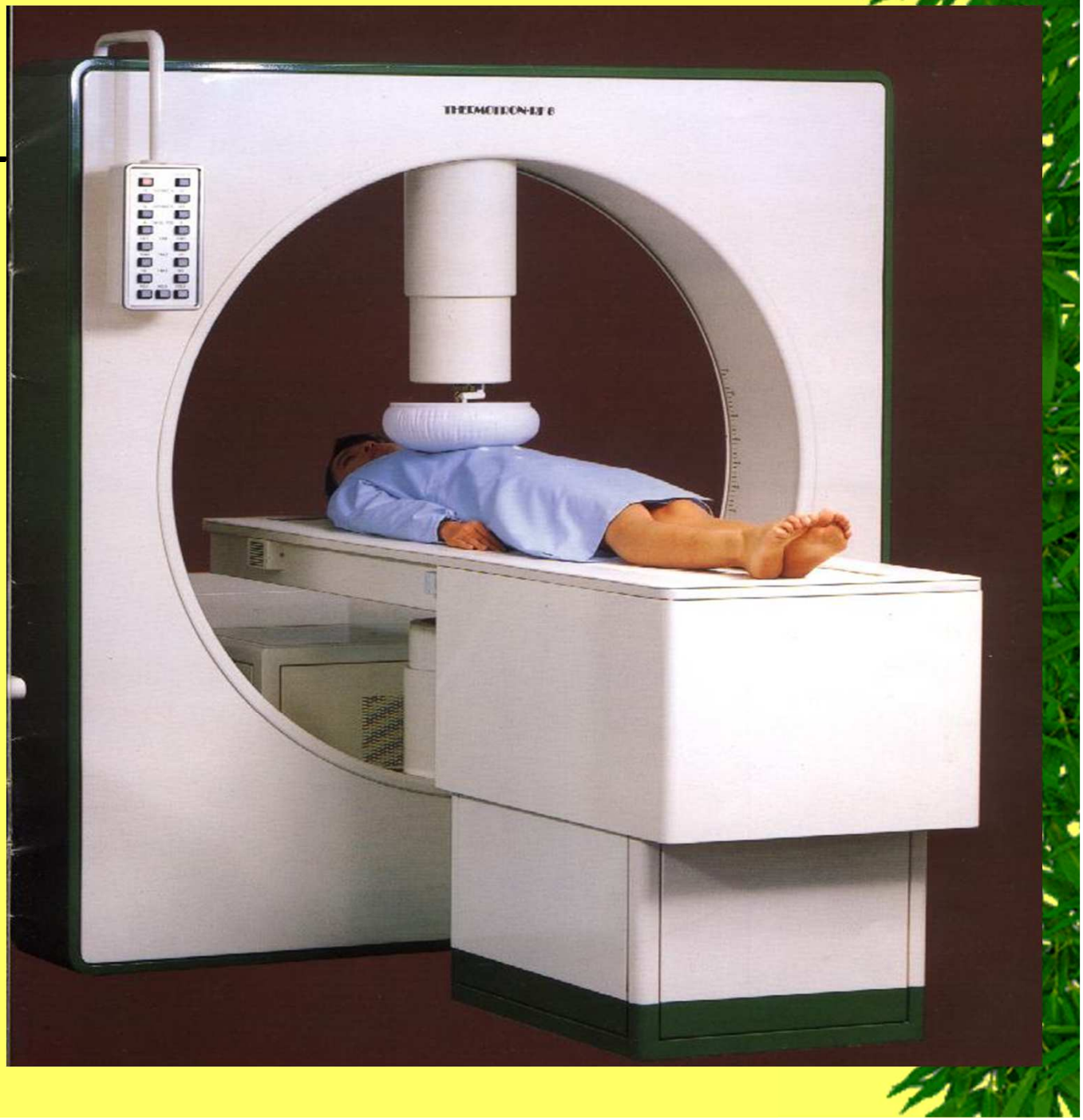
RT ——— HT

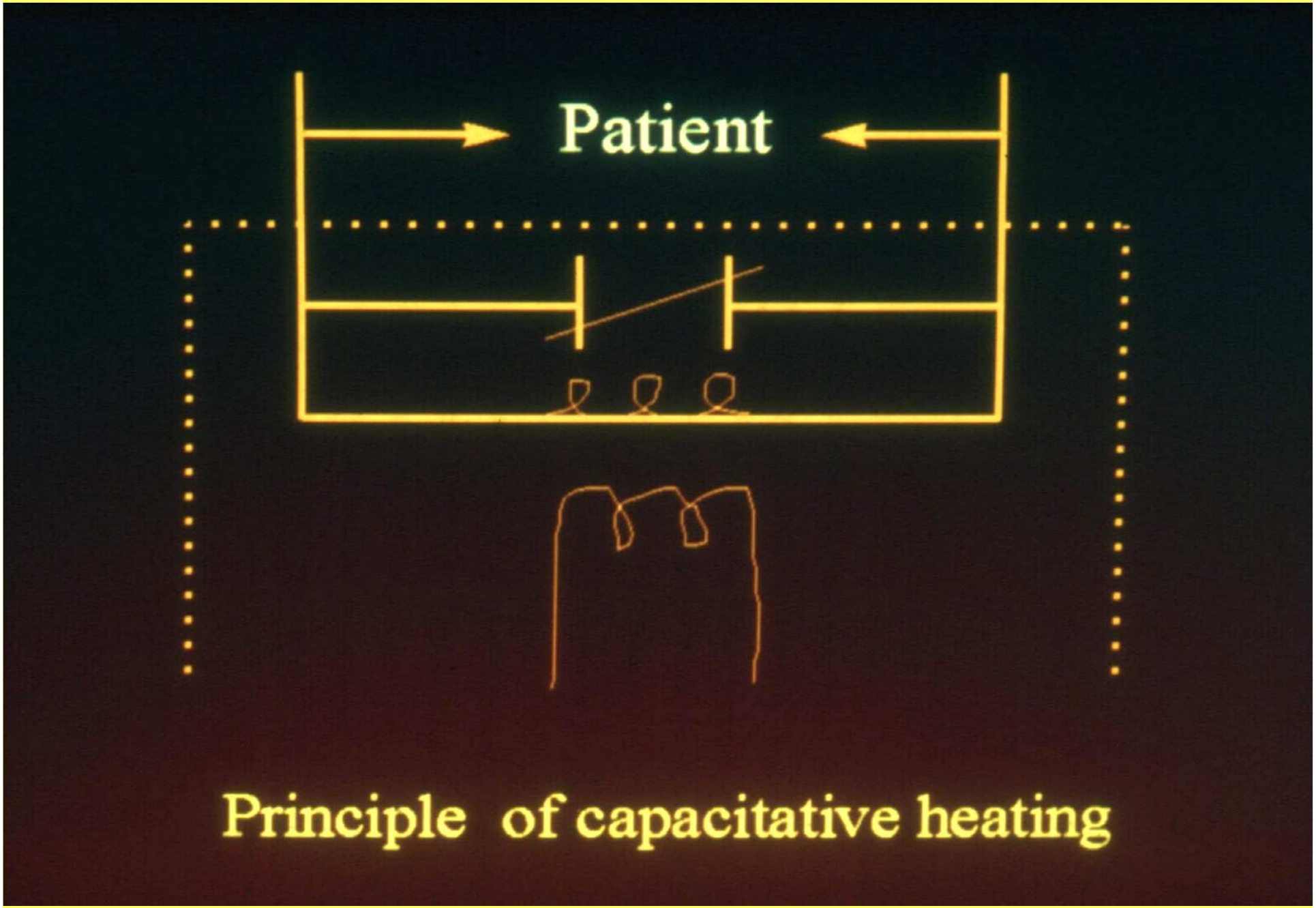
Simultaneous HT & RT

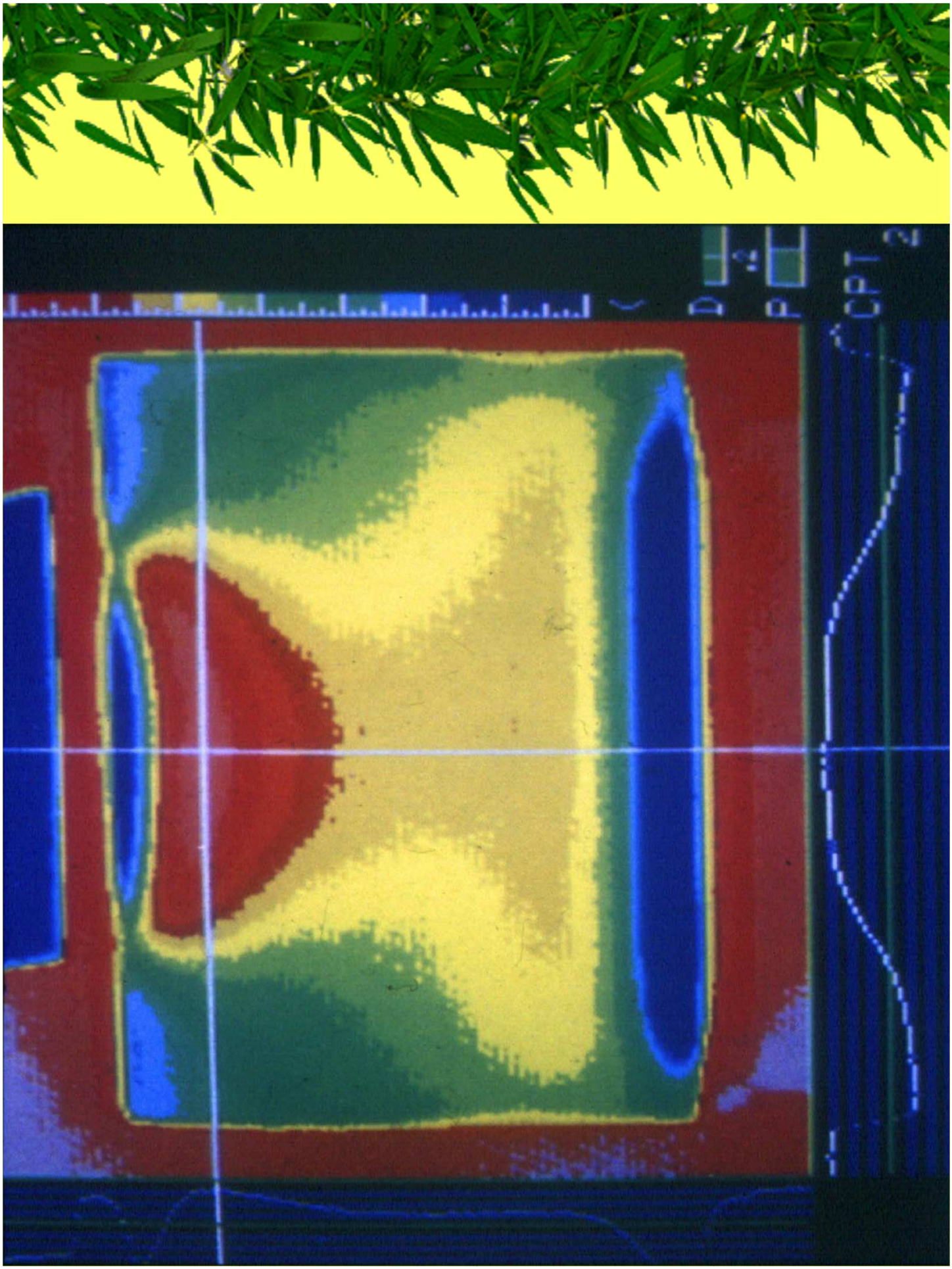
Thermotron:

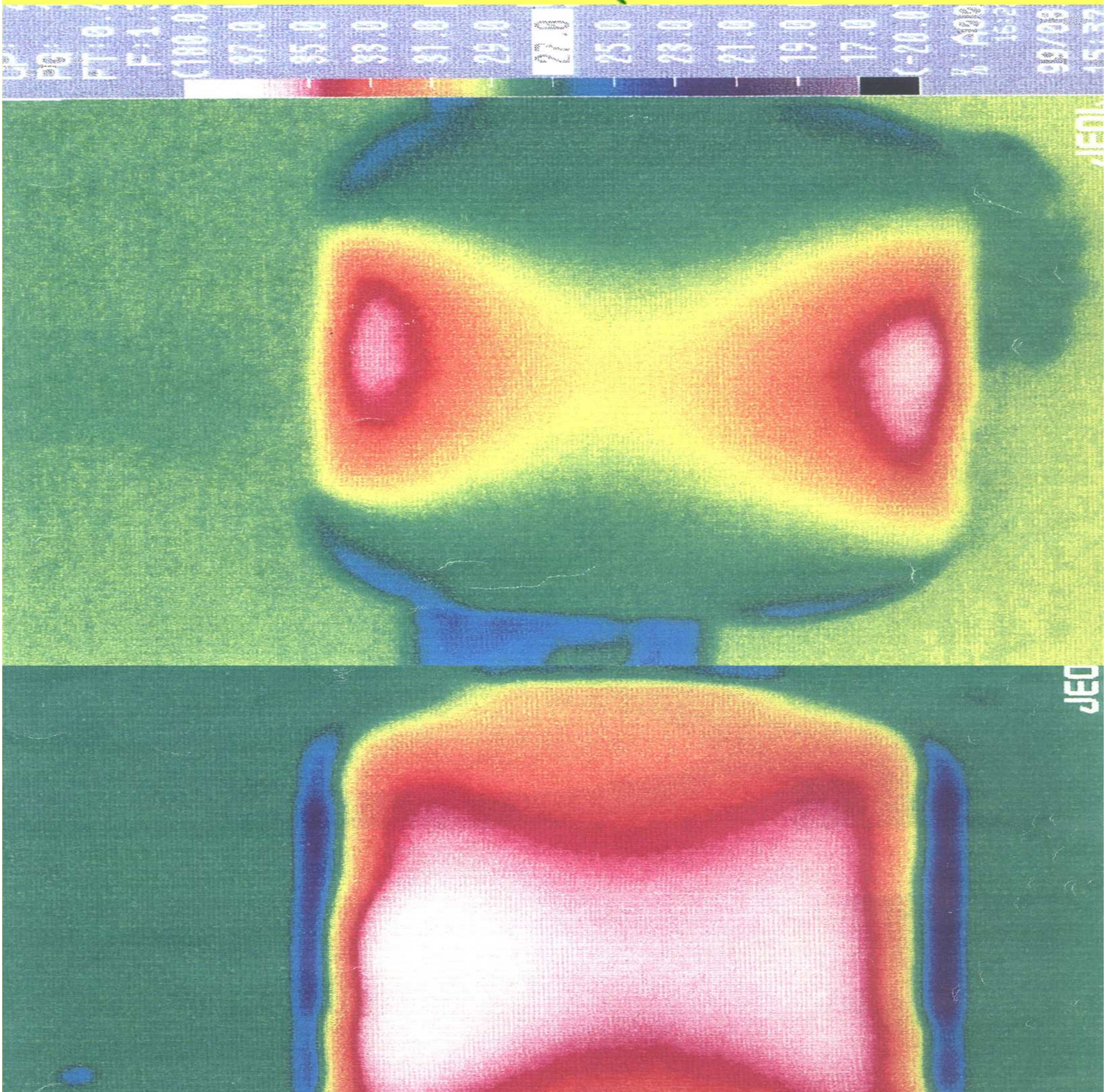
Capacitive heating

(photograph by N. Huilgol)




Patient
Principle of capacitative heating


CPT 2



IRF: Temperature vs. Time Profile.

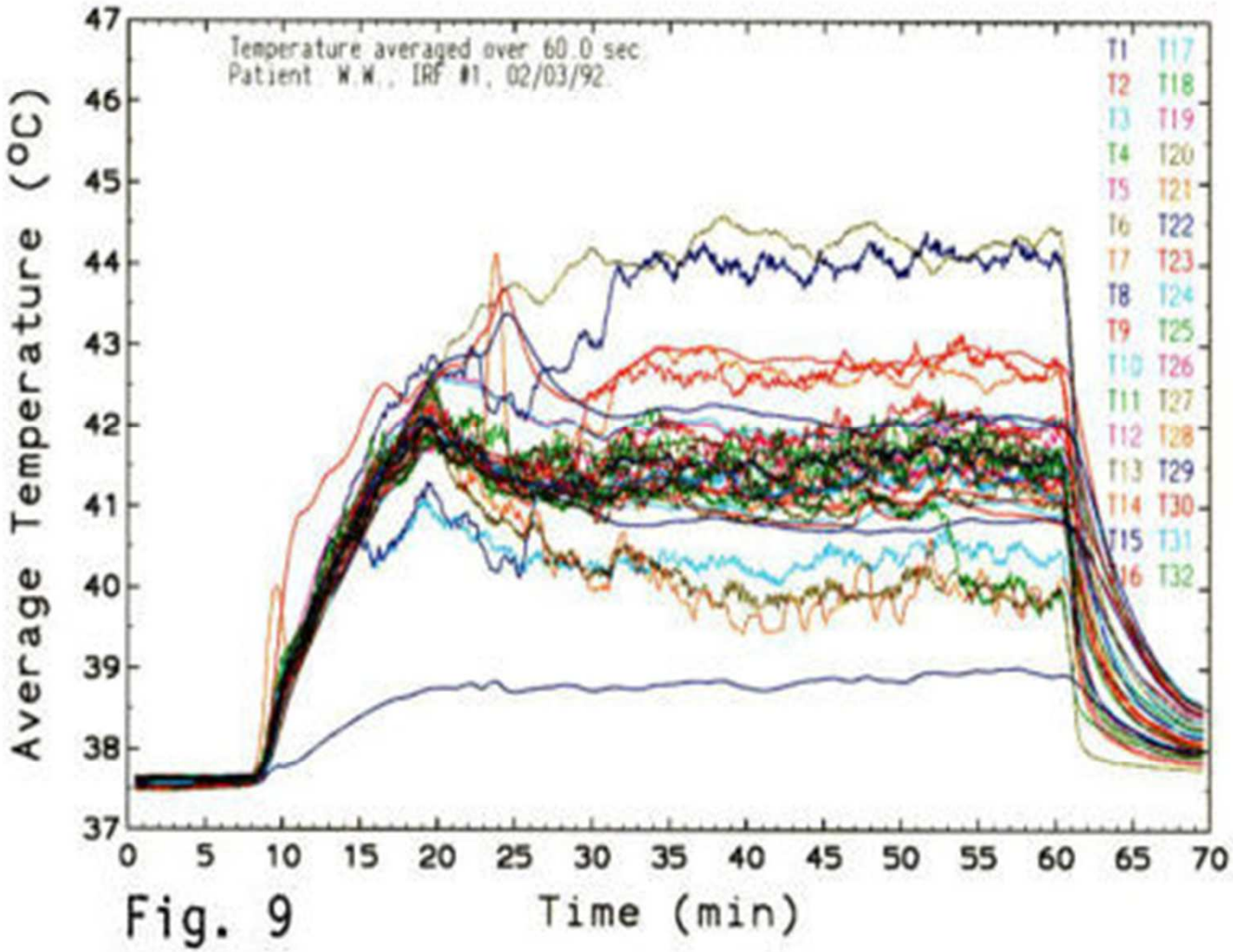


Fig. 9

Pre-cooling

Pre-cooling spares the fat and increases penetration of EM field

THERMOMETRY

- **Thermometry is a procedure to measure the intra-tumoural temperature**
- **Angiocath is inserted in the tumour at a point, which is perpendicular to the direction of the electrical flow**
- **Temperature is measured by putting a thermocouple in the angiocath**
- **Lowest Thermal Dose (lowest temperature x time) and Maximum Thermal Dose (highest temperature x time) are recorded**

Thermometry

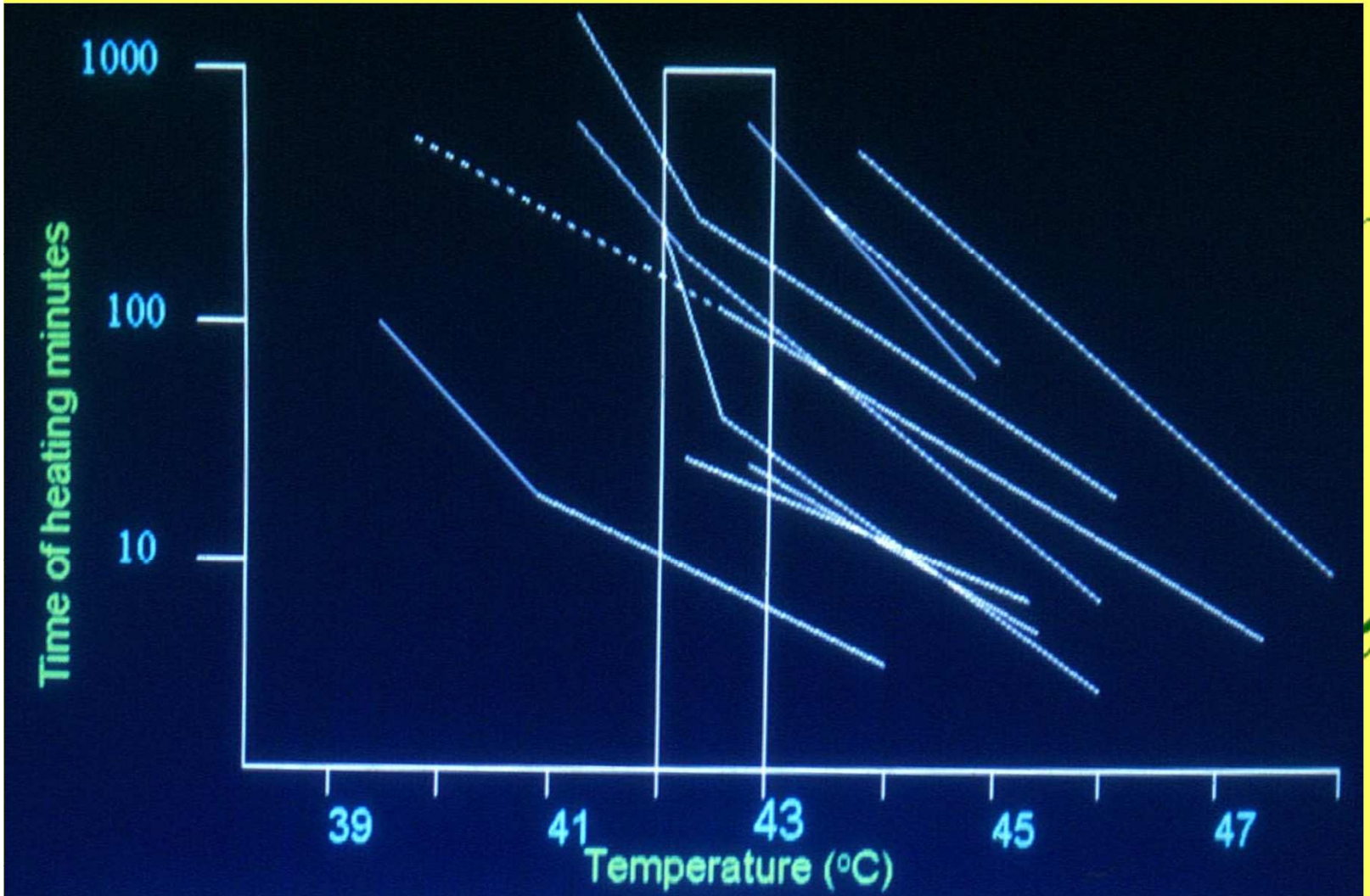
T_{max}

T_{AV} $EQ_{Min} - T_{50}$

T_{min} $EQ_{Min} - T_{90}$

T_{90}

T_{min} **has shown to have bearing on tumour outcome**

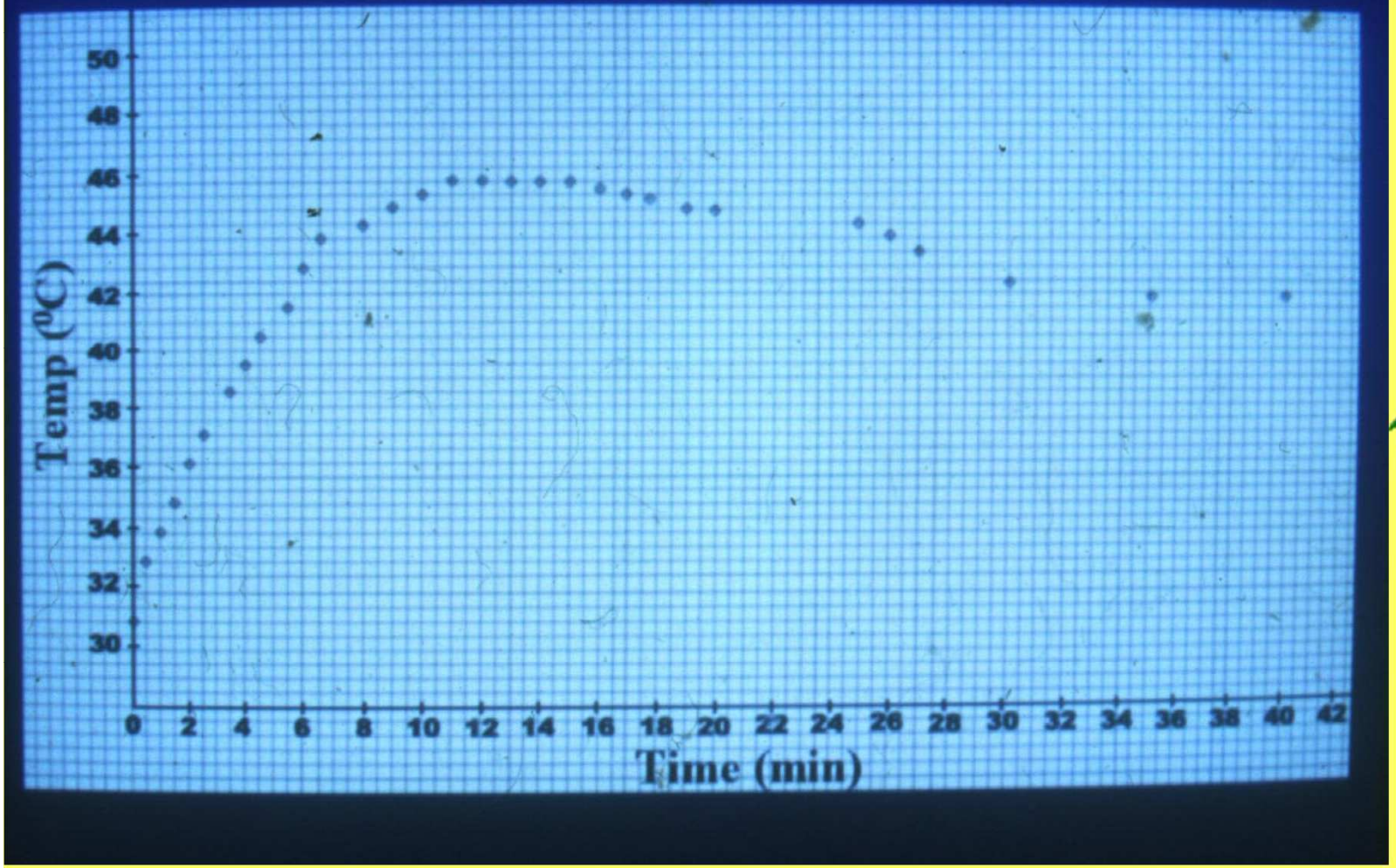


Relationship between time of heating temperature to produce a given effect in a range of normal tissues and tumours in situ. At temperatures above the break point 1°C is equivalent to a factor of two in heating time: below the break 1°C is equivalent to a factor of six.

Thermometry

Temperature x Time

THERMOMETRY



Interstitial Hyperthermia with Microwaves

- Miniature antennas fabricated from microwave co-axial cables are implanted
- Utilises higher microwave frequency such as 3000 to 1000 MHz
- Energy propagates through tissue as EM waves instead of low frequency currents unlike in RF
- Routinely compatible with Ir-192
- Nylon implants used in Brachytherapy

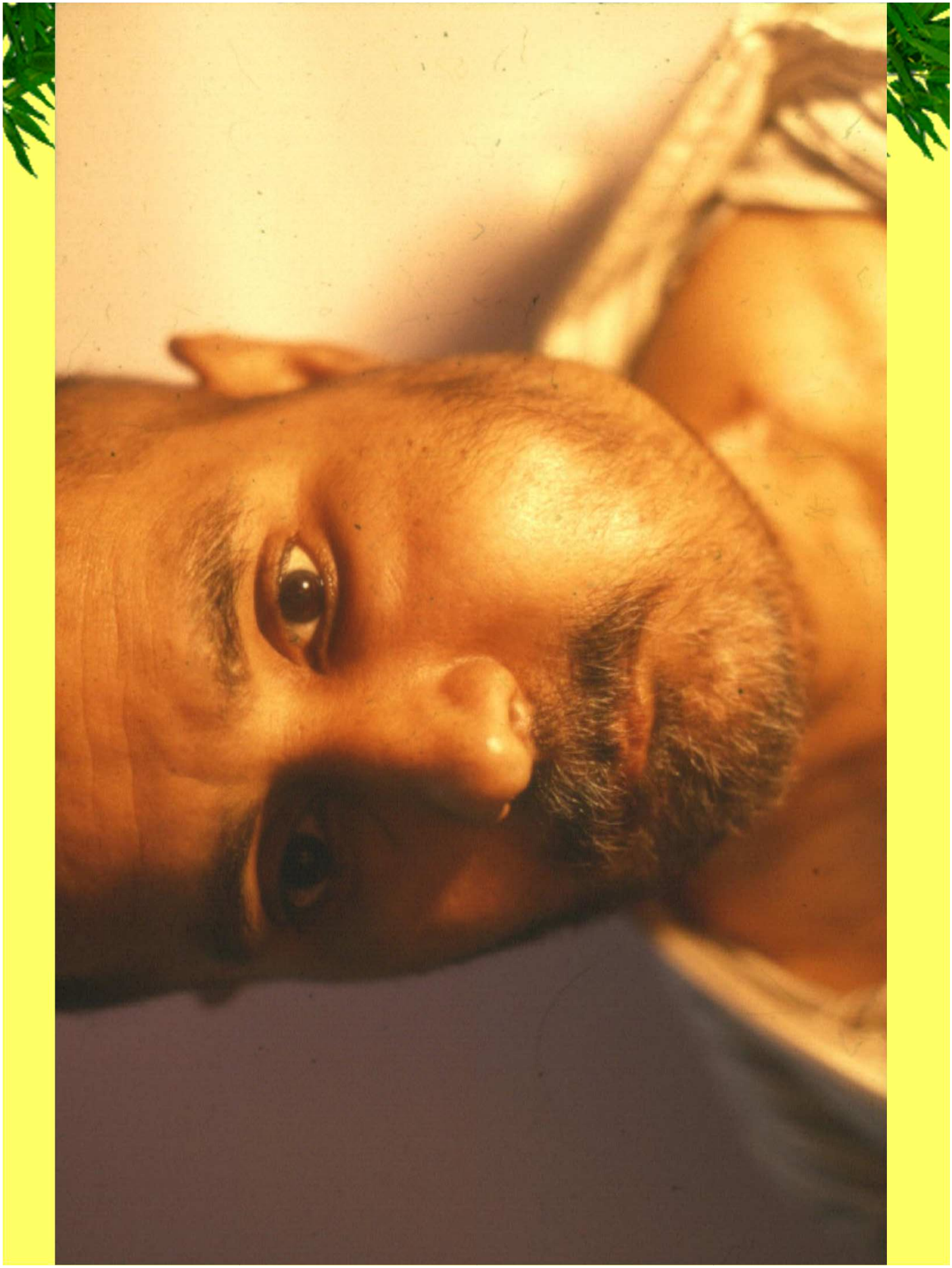
Effect of heat alone

- (46-43 ^{0}C)-Vascular destruction in highly perused tissue
- 43^{0}C -Vascular destruction in poorly perused tissue
- 42-41^{0}C-Celluar Cytotoxicity enhanced at low pH and S-Phase
- 40^{0}C-increased perfusion in all tissue types
- 38-36^{0}C-Normothermia

Interaction with XRT

- 44^{0}C-Increaded Thermal cytotoxicity
- Thermal radiosensitisation
- Improved nutrients & Oxygen supply of radioresistent hypoxic cells inhibited repair of XRT.
- Normothermia

ICMR TRIAL OF HT+RT HYPERTHERMIA IN HEAD AND CANCER



DEMOGRAPHIC DATA

Parameters	RT-Group	RT + HT-Group
No. of Cases	26	28
@Age (yrs) Mean SD Range	58.42 11.39 40-76 yrs	57.71 12.93 31-78 yrs
#Sex (%) Male Female	24(92.3) 02(07.7)	22(78.6) 06(21.4)

@ By Student‘t’ Test P > 0.05 Not Significant

By Chi-square Test

In this data, RT group patient’s mean age was 58.42 and ranged from 40-76 yrs which was statistically comparable with mean age of 57.71 of RT+HT group patients which ranged between 31-78 yrs. In RT group 92.3% were male which was more than 78.6% in RT+HT group but it did not made statistical significance.

PROFILE OF SITES OF DISEASE

Site	RT-Group (N=26)		RT + HT-Group (N=28)	
	No	%	No	%
Oropharynx	17	65.4	10	35.7
Hypopharynx	05	19.2	12	42.9
Oral cavity	04	15.4	06	21.4

Patients in RT group with Oropharynx as the site of disease were 65.4% followed by 19.2% with disease at Hypopharynx and 15.4% diseased in oral cavity. In case of RT+HT group patients 35.7% suffered at Oropharynx, then 42.9% with Hypopharynx and rest affected by oral cavity

COMPARISON OF RESPONSE BETWEEN TWO TREATMENT GROUPS

Response	RT-Group (N=26)		RT + HT-Group (N=28)	
	No	%	No	%
Complete Response	11	42.4	22	78.6
Partial Response	13	50.0	03	10.7
No Response	01	03.8	-	-
PD	01	03.8	03	10.7

By Chi-square test P > 0.05 Significan

There is a statistical significance in getting complete response from the patients in both the groups as it was 42.4% in RT group and 78.6% in RT+HT group.

Partial response was also a significant one as 50.0% cases was observed in RT group and only 10.0% cases in RT+HT group.

In RT+HT group 10.7% of subjects showed PD response which was more than 03.8% in RT group but difference was not statistically significant.

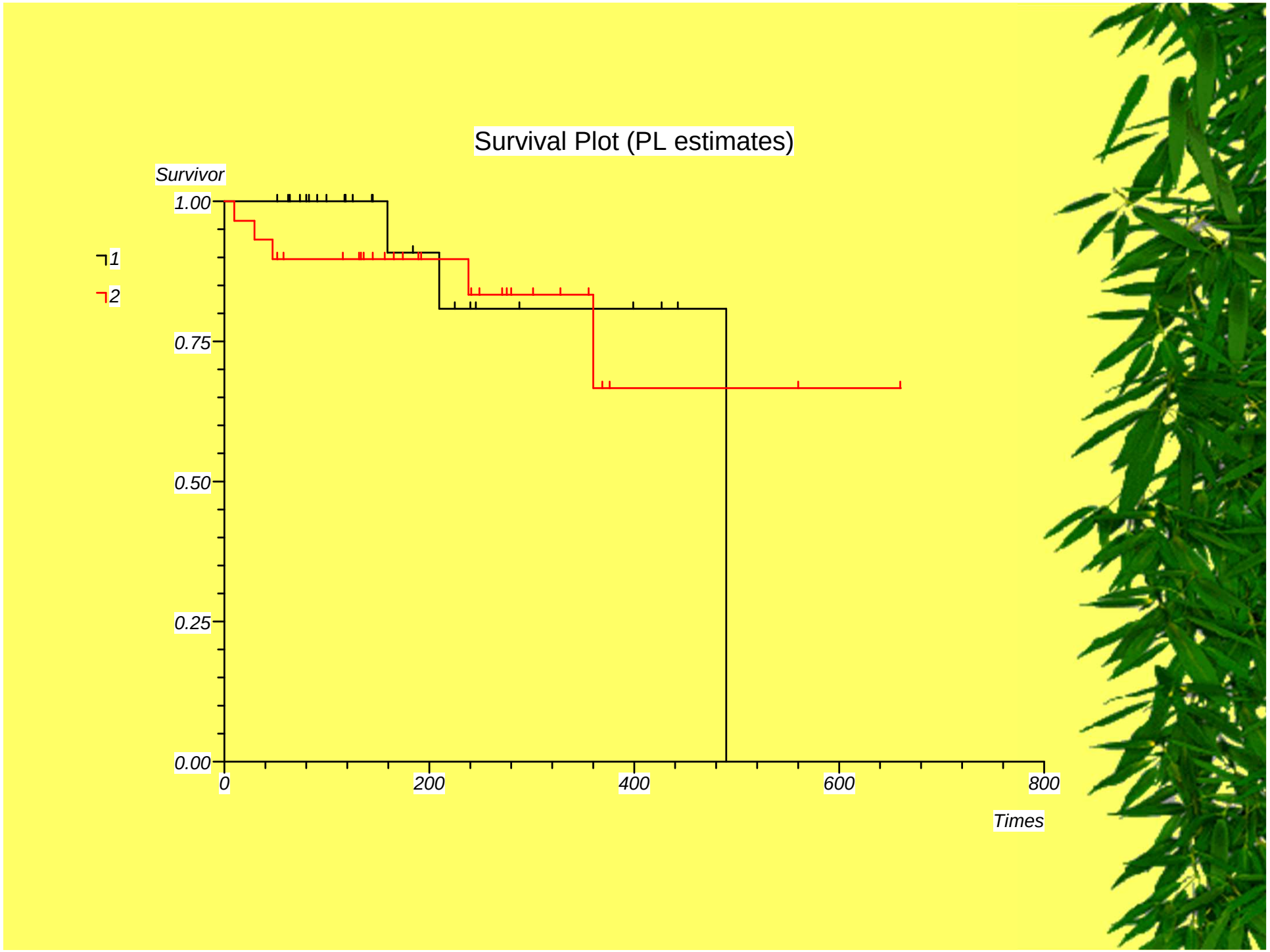
PROFILE OF FOLLOW UP PERIOD

Durations	RT-Group (N=26) No.	%	RT + HT-Group (N=28) No.	%
< 6 months	16	61.5	11	39.3
6-12 months	08	30.8	12	42.8
> 12 months	02	07.7	05	17.9

By Chi-square test P > 0.05 Not Significant

Included subjects were assessed according to their follow-up period, where 61.5% of subjects in RT group had followed up for less than 6 months as compared to 39.3% in RT+HT group which was not a significant difference.

17.9% subjects in RT+HT group followed up for more than 12 months which was more than 07.7% in RT group but was not a significant difference.


Survival Plot (PL estimates)
Survivor
1.00
0.75
0.50
0.25
0.00
1
2
0
200
400
600
800
Times

Treatment Protocol

- Patients were treated by conventional EBRT with concurrent weekly Hyperthermia and Chemotherapy (with Taxane or Cisplatin)
- RT Dose was planned conventional - 200 cGy/#, total dose of 60-70 Gy.
- Weekly Hyperthermia was administered at 42°C for 40 min after pre cooling for 10 mins.
- Weekly chemotherapy was administered according to the protocol regimen.

Our Data-Hyperthemia and chemoradiation in Head and neck cancer

Out of 40 patients, 38 were evaluated-

Out of 38

CR – 29 (76.32%)

PR – 09 (23.68%)

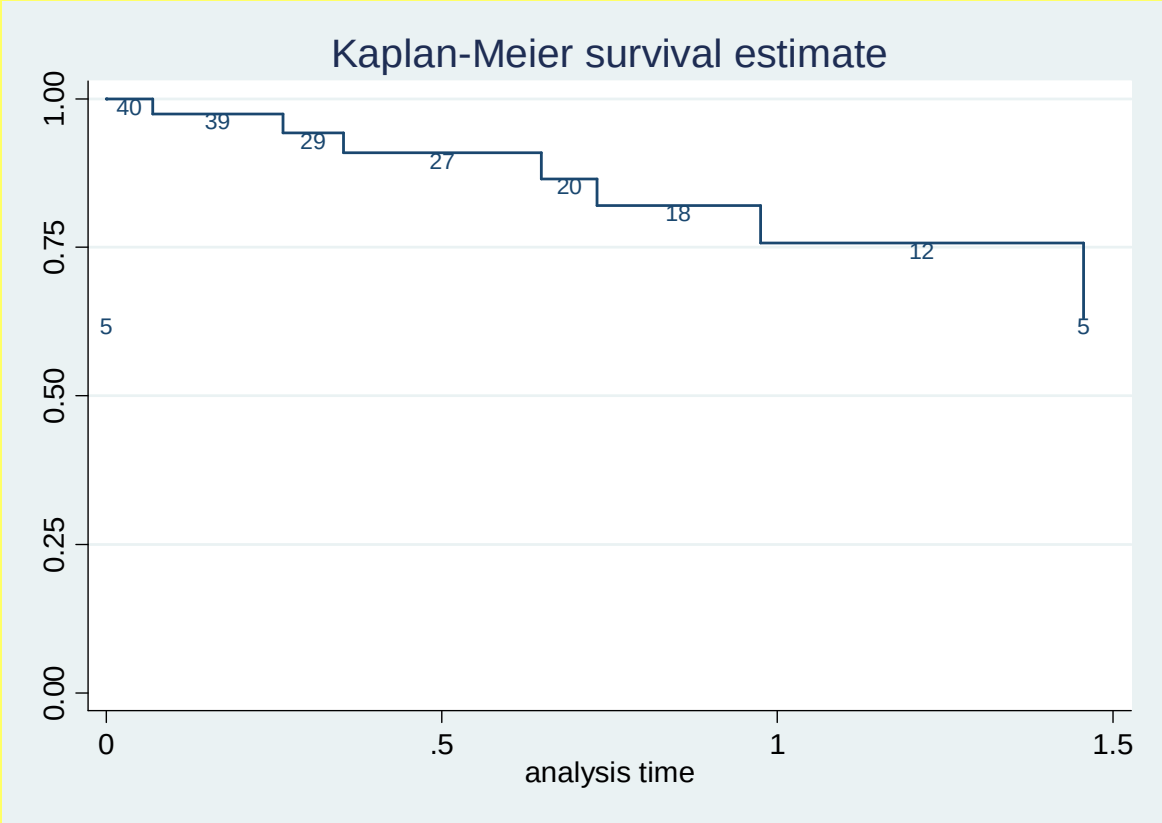
Dr Nagraj.G.Huilgol

Dr Sapna Gupta

Our data-38/40 patients- Overall survival by the Kaplan−Meir method is 75.69%

at 1 year(95%Confidence interval(CI)-51.88−88.85) and at 2 years, it was

63.08% (with 95% CI-30.98−83.43).



HEATING TECHNIQUE

- THERMOMETRY – AT LEAST ONCE, WITH INVASIVE THERMISTOR PROBES
- PRIMARY – HEAD & NECK NOT DONE
- APPROPRIATE ANTENNAE ARE ARRANGED IN PARALLEL WITH ACTIVE SIDE TOWARDS THE LESION
- POWER : - 400 – 900 W
- RF – 8 MHz – THERMATRON – CAPCITATIVE HEATING

Toxicities

- ✓ Thermal burns – generally Grade I
- ✓ Pain
- ✓ Systemic stress

Acute Toxicities
Thermal Burns

Grade I	**5**
Grade II	**2**
Grade III	**1**

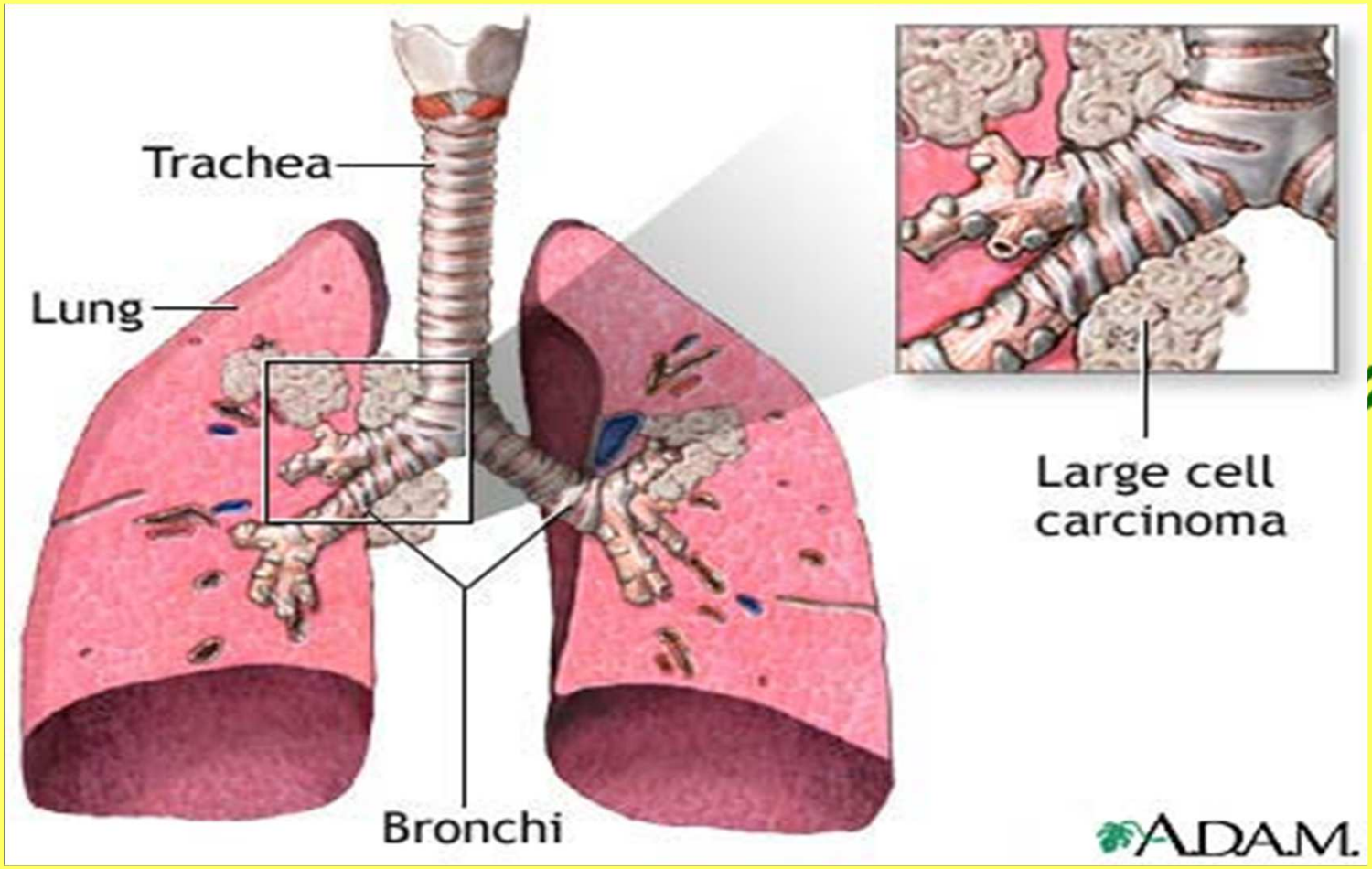
Phase –III Hyperthermia Studies

		Pts Number	RT	RT +HT	Signif.
1.	Valdagni et al.1998,1993: H&N , N2/3	44	37% 0%	83% CR 53% 5yrs	+ +
2.	Rotterdam (Van der zee 1994) Pelvin tumors (Cervical carcinoma)	147	37%	58% CR Survival	+
3.	Berdov, Metshashviii 1990: T4 Rectal carcinoma	115	27% 7%	56% Resectability 30% 5 yrs	+ +

Comparison with Published Literature

Studies	No. of pts.	RT+ HT	
		CR	PR
Valdagni et.al.	44	83	17
Huilgol et.al.	47	72.34	23.4

Lung Carcinoma



Two Lung Cancer Cells, Classified

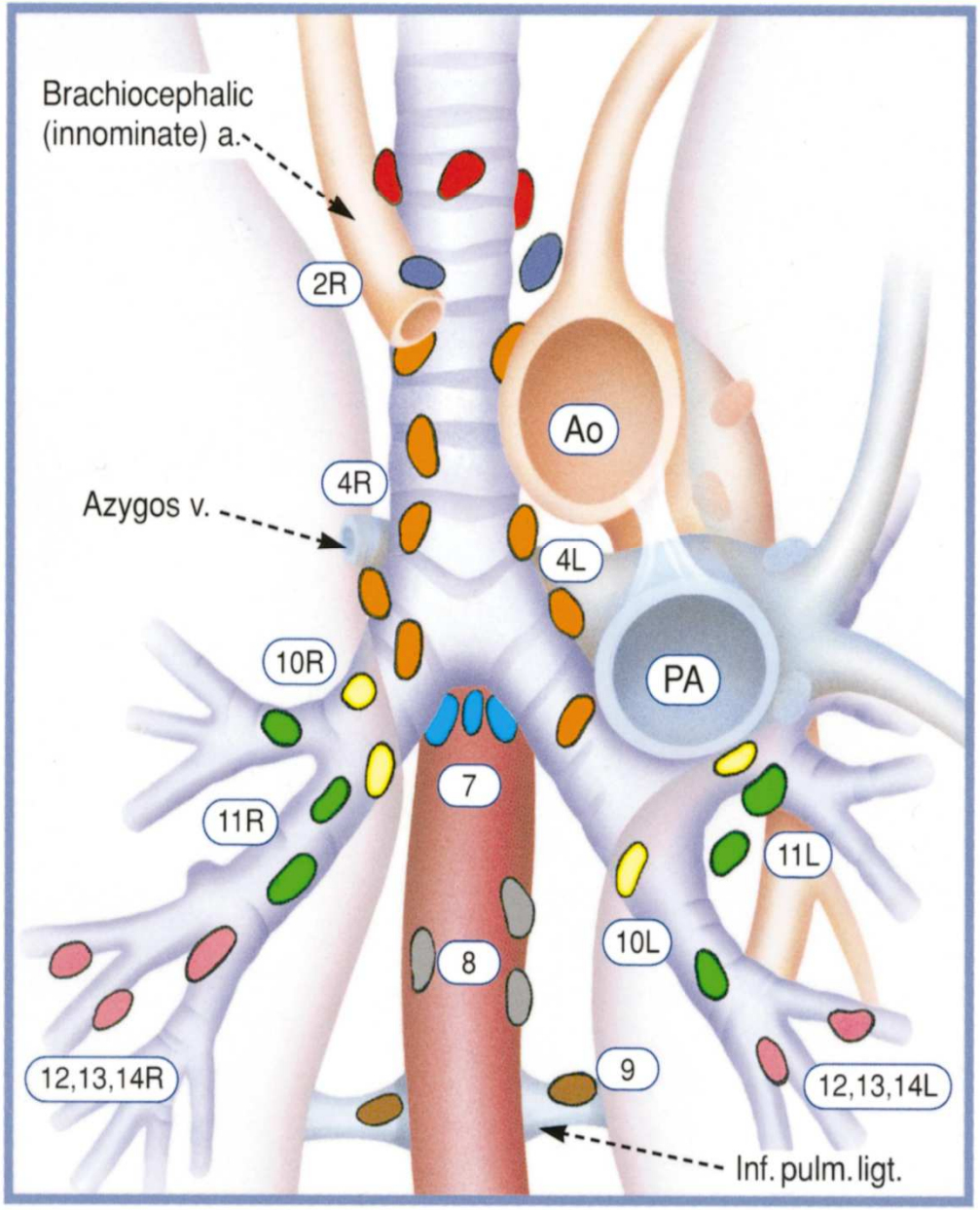
Non Small Cell Lung Cancer (NSCLC)

- Adenocarcinoma
- Squamous Cell Carcinoma
- Large Cell Carcinoma

Small Cell Lung Cancer (SCLC)

- Oat Cell
- Intermediate
- Combined

Lymph node classification for lung cancer staging



Superior Mediastinal Nodes

- **1** Highest Mediastinal
- **2** Upper Paratracheal
- **3** Pre-vascular and Retrotrachea
- **4** Lower Paratracheal (including Azygos Nodes)

N_2 = single digit, ipsilateral
N_3 = single digit, contralateral or supraclavicular

Aortic Nodes

- **5** Subaortic (A-P window)
- **6** Para-aortic (ascending aorta or phrenic)

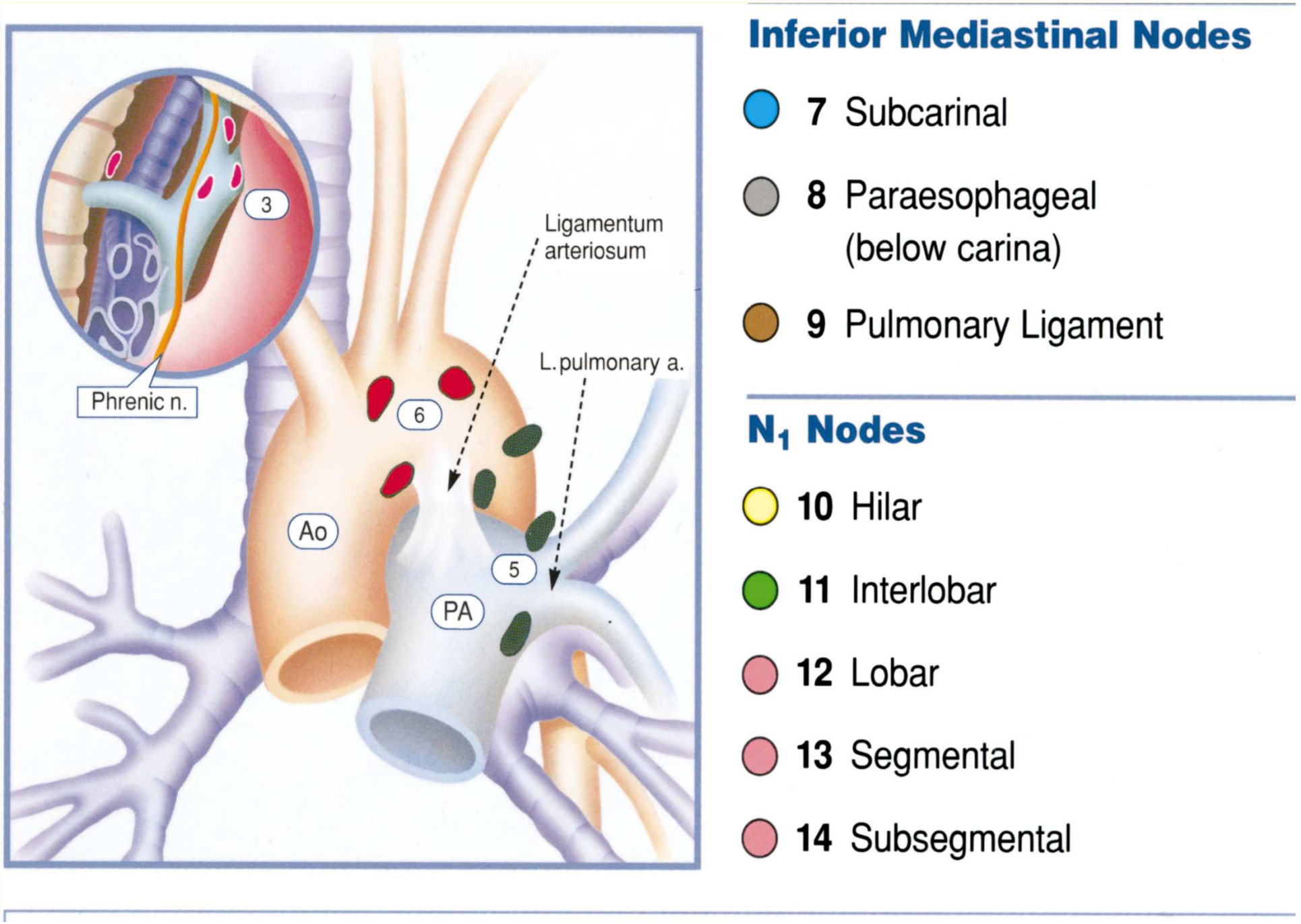


Figure 1. Regional lymph node stations for lung cancer staging. Adapted from Naruke et al,6 and the ATS/North American LCSG2 (copyright 1996, Mountain and Dresler; may be reproduced for educational purposes without permission).

Treatment and Staging NSCLC

Stage	Description	Treatment Options
Stage I a/b	Tumor of any size is found only in the lung	Surgery
Stage II a/b	Tumor has spread to lymph nodes associated with the lung	Surgery
Stage III a	Tumor has spread to the lymph nodes in the tracheal area, including chest wall and diaphragm	Chemotherapy followed by radiation or surgery
Stage III b	Tumor has spread to the lymph nodes on the opposite lung or in the neck	Combination of chemotherapy and radiation
Stage IV	Tumor has spread beyond the chest	Chemotherapy and/or palliative (maintenance) care

Esophageal carcinoma

- CLASSIFICATION
  - Squamous carcinoma
  - Adenocarcinoma
    - -Type-1
      Intestinal metaplasia of tubular oesophagus
    - -Type-2
      True junctional tumor of the gastric cardia
    - -Type-3
      Subcardial tumors which is infiltrate superiorly

Staging

Primary tumors(T) invades

T1 L.propria/submucosa

T2 M.propria

T3 Adventitia

T4 Adjacent structures

Regional LNs(N)

N1 Regional LN mets

Metastases(M)

Lower oesophagus

M1a coeliac axis node

M1b distant mets

Mid/upper oesophagus

M1a not applicable

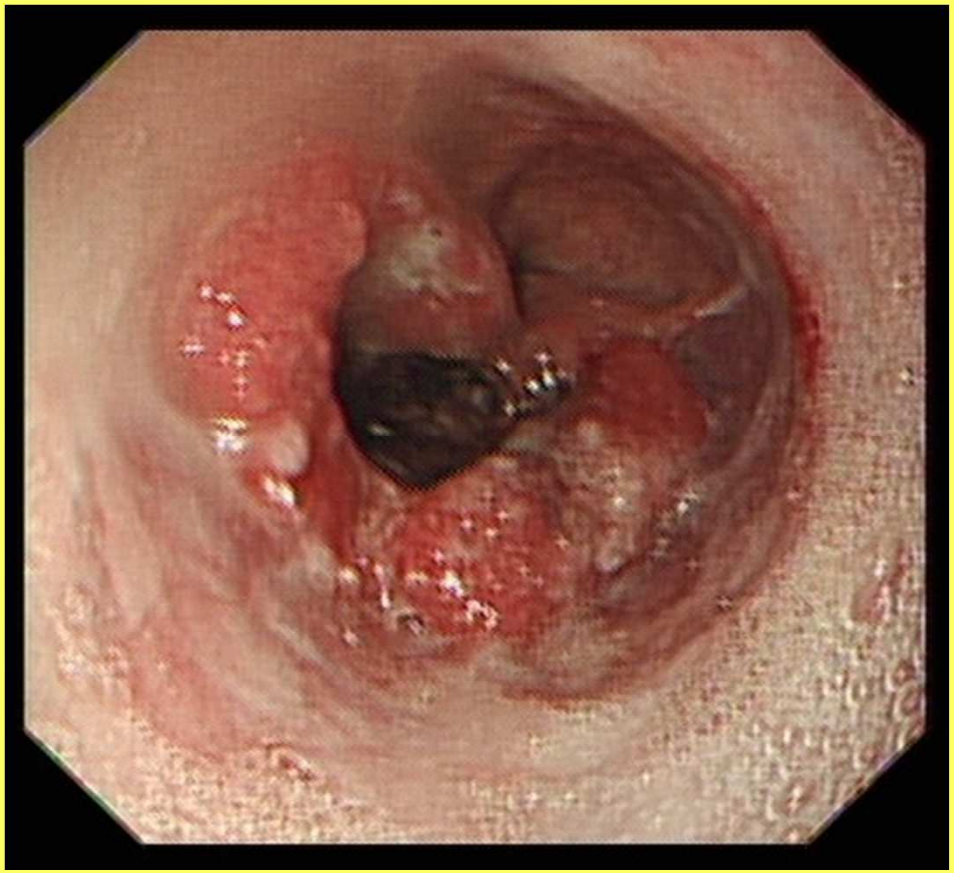
M1b distant metastases

DIAGNOSIS - Barium Swallow

- Shouldering at both proximal and distal ends.
- Evidence of mucosal destruction and filling defects
- Free flow of barium

Endoscopy

Small flat tumor at distal end of oesophagus occupying <20% lumen



Thermal ablative therapy

RADIOTHERAPY WITH 8-MHz RADIOFREQUENCY-CAPACITIVE REGIONAL HYPERTHERMIA FOR STAGE III NON-SMALL-CELL LUNG CANCER: THE RADIOFREQUENCY-OUTPUT POWER CORRELATES WITH THE INTRAESOPHAGEAL TEMPERATURE AND CLINICAL OUTCOMES

TAKAYUKI OHGURI, M.D.,* HAJIME IMADA, M.D.,* KATSUYA YAHARA, M.D.,* TOMOAKI MORIOKA, M.D.,* KEITA NAKANO, M.D.,* HIROMI TERASHIMA, M.D.,† AND YUKUNORI KOROGI, M.D.*

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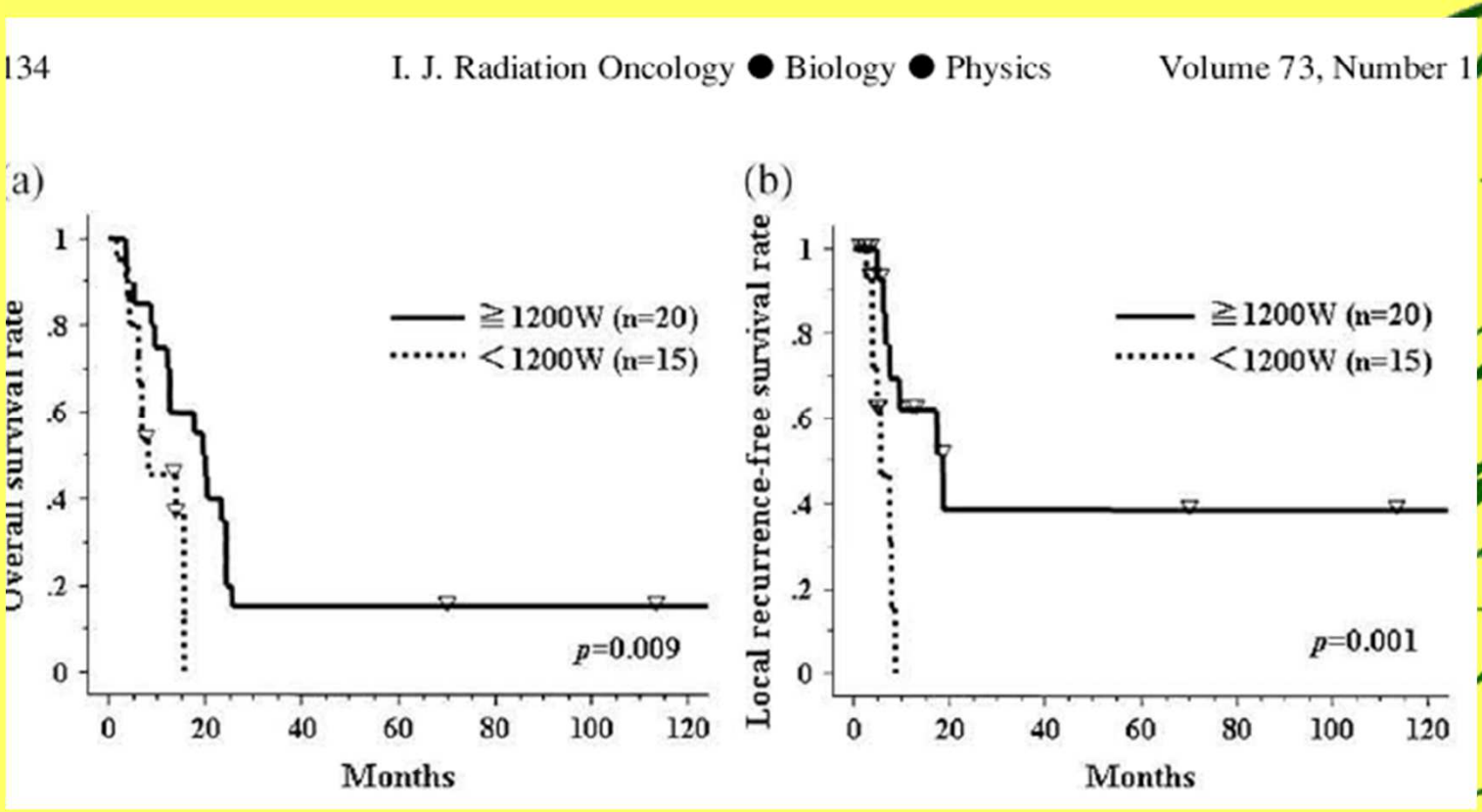
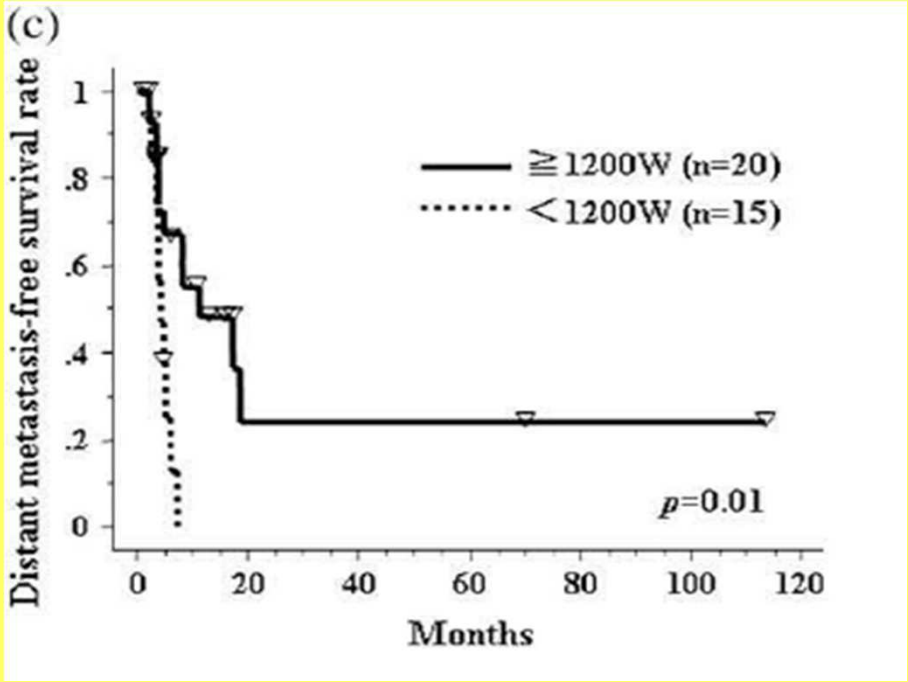
Lung Cancer


134
I. J. Radiation Oncology ● Biology ● Physics
Volume 73, Number 1
(a)
Overall survival rate
1
.8
.6
.4
.2
0
≧1200W (n=20)
＜1200W (n=15)
p=0.009
0
20
40
60
80
100
120
Months
(b)
Local recurrence-free survival rate
1
.8
.6
.4
.2
0
≧1200W (n=20)
＜1200W (n=15)
p=0.001
0
20
40
60
80
100
120
Months


(c)
Distant metastasis-free survival rate
1
.8
.6
.4
.2
0
0
20
40
60
80
100
120
Months
≧1200W (n=20)
＜1200W (n=15)
p=0.01

Oesophageal cancer

CLINICAL INVESTIGATION Esophagus

PROGNOSTIC SIGNIFICANCE OF LYMPHOCYTE INFILTRATION FOLLOWING PREOPERATIVE CHEMORADIOTHERAPY AND HYPERTHERMIA FOR ESOPHAGEAL CANCER

MASARU MORITA, M.D.,* HIROYUKI KUWANO, M.D.,† KOHSHI ARAKI, M.D.,* AKINORI EGASHIRA, M.D.,* HIDETOSHI KAWAGUCHI, M.D.,* HIROSHI SAEKI, M.D.,* KAORU KITAMURA, M.D.,* SHINJI OHNO, M.D.,* AND KEIZO SUGIMACHI, M.D., F.A.C.S.*

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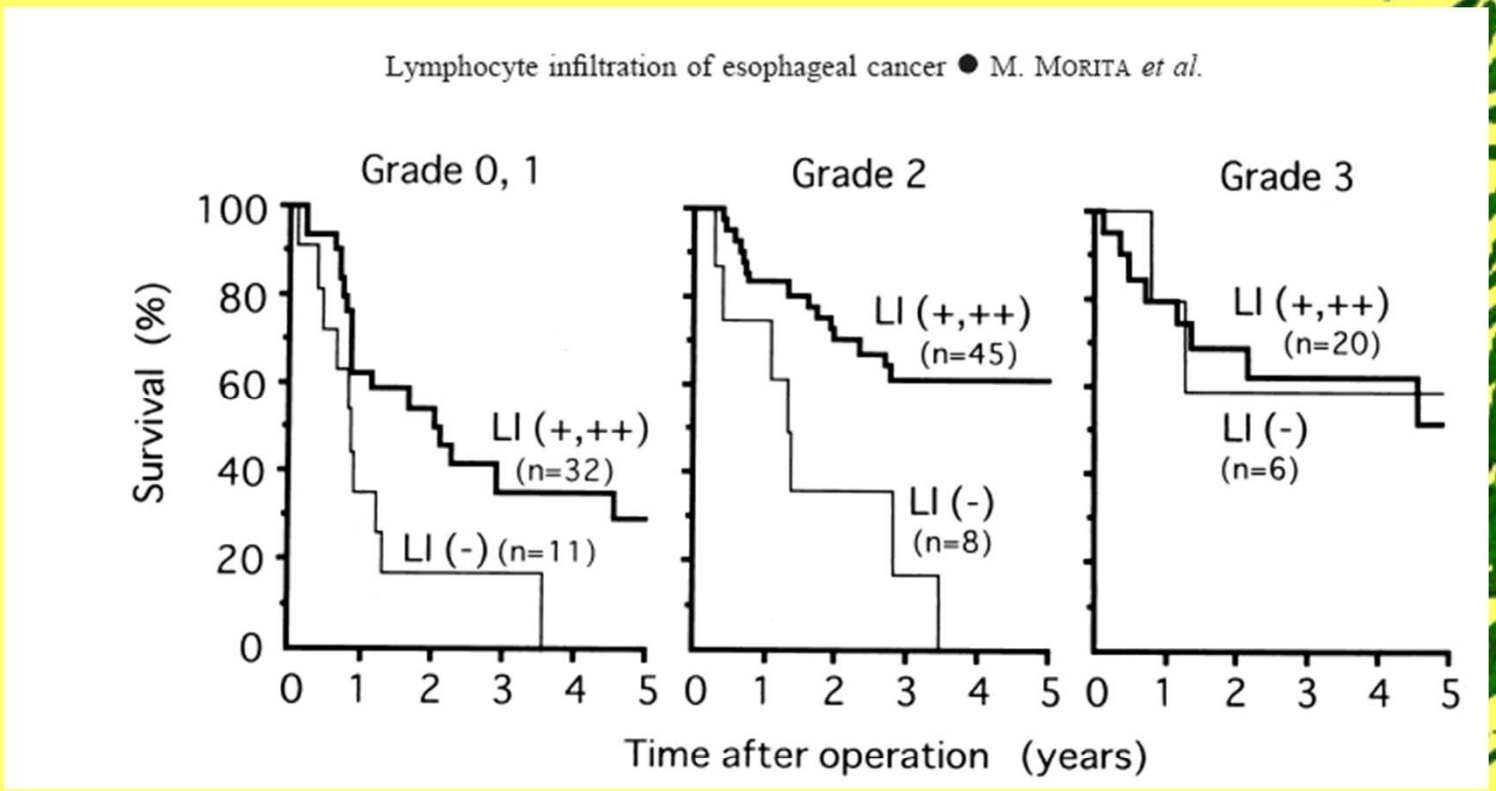
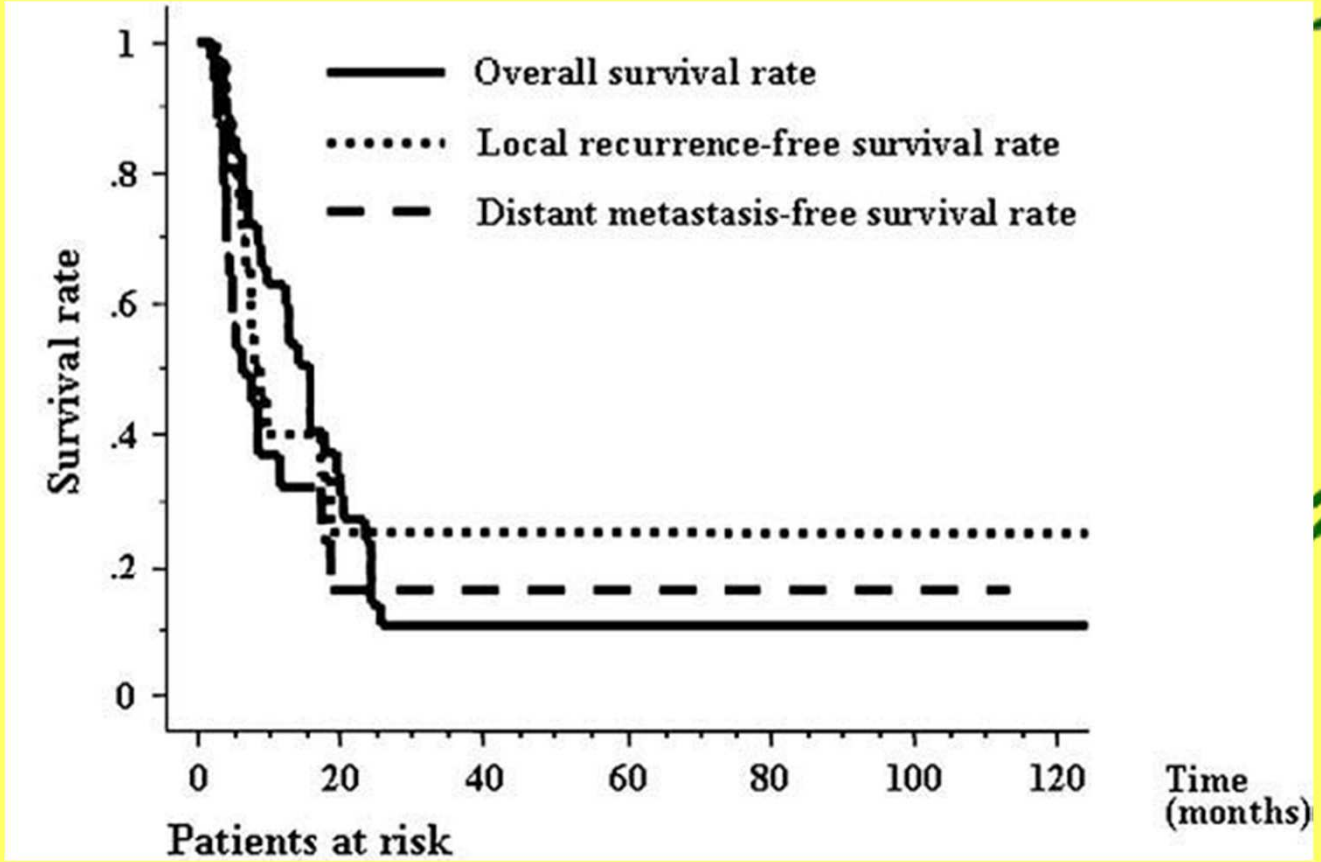
Table 4. Relationship between preoperative treatment and lymphocyte infiltration

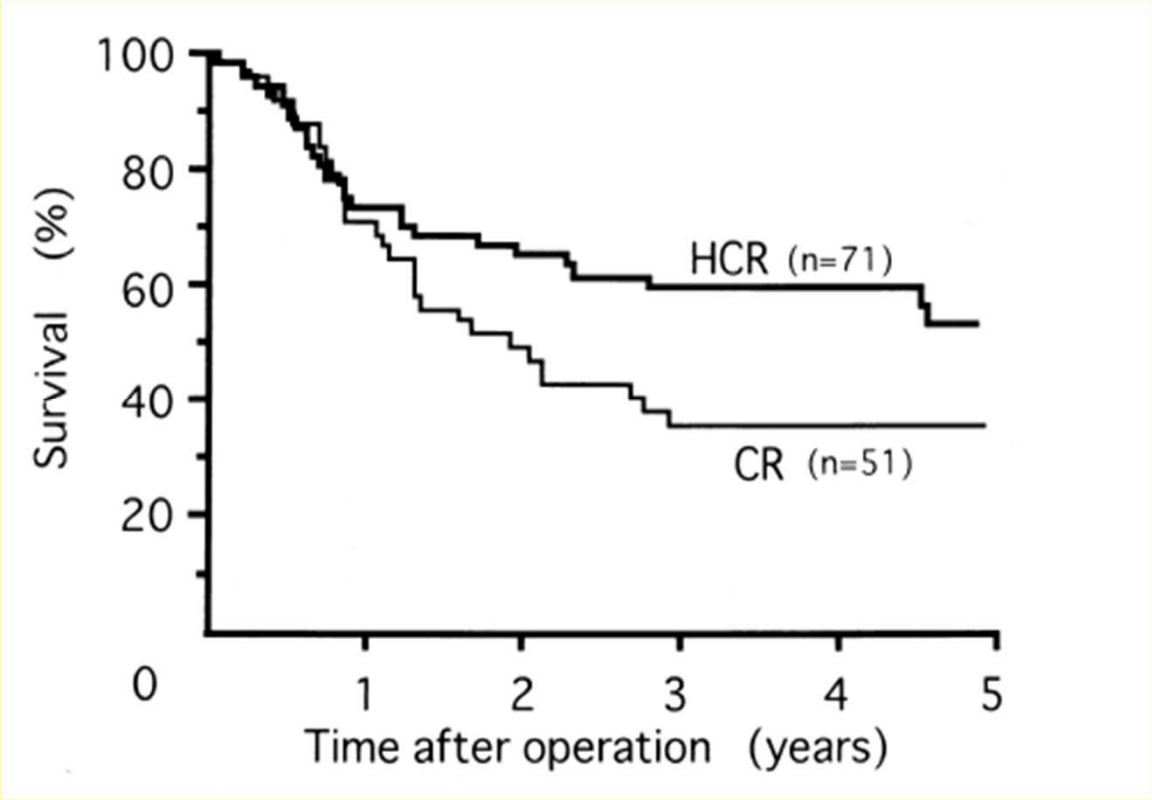
Preoperative treatment	*n*	Lymphocyte infiltration		
		LI (−)	LI (+)	LI (++)
Chemotherapy				
Bleomycin	47	8 (17.0)	33 (70.2)	6 (12.8)
Cisplatin	75	17 (22.7)	51 (68.0)	7 (9.3)
Hyperthermia				
Performed (HCR therapy)	71	11 (15.5)	48 (67.6)	12 (16.9)*
Not performed (CR therapy)	51	14 (27.5)	36 (70.6)	1 (2.0)*

* $p < 0.01$.
Numbers in parentheses represent percentages.


Lymphocyte infiltration of esophageal cancer ● M. MORITA et al.
Grade 0, 1
Grade 2
Grade 3
Survival (%)
100
80
60
40
20
0
LI (+,++)
(n=32)
LI (-) (n=11)
LI (+,++)
(n=45)
LI (-)
(n=8)
LI (+,++)
(n=20)
LI (-)
(n=6)
0 1 2 3 4 5
Time after operation (years)


Overall survival rate
Local recurrence-free survival rate
Distant metastasis-free survival rate
Survival rate
1
.8
.6
.4
.2
0
0
20
40
60
80
100
120
Time
(months)
Patients at risk

HT+RT+CT in Oesophageal cancer

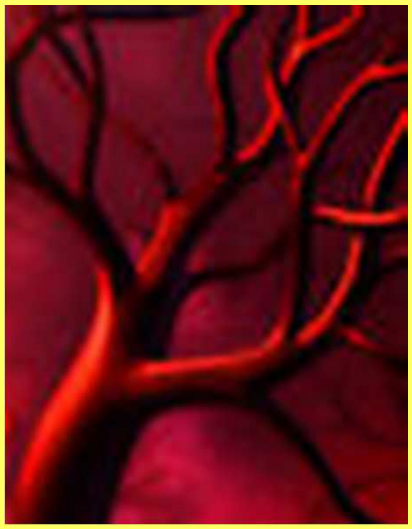


Future Direction

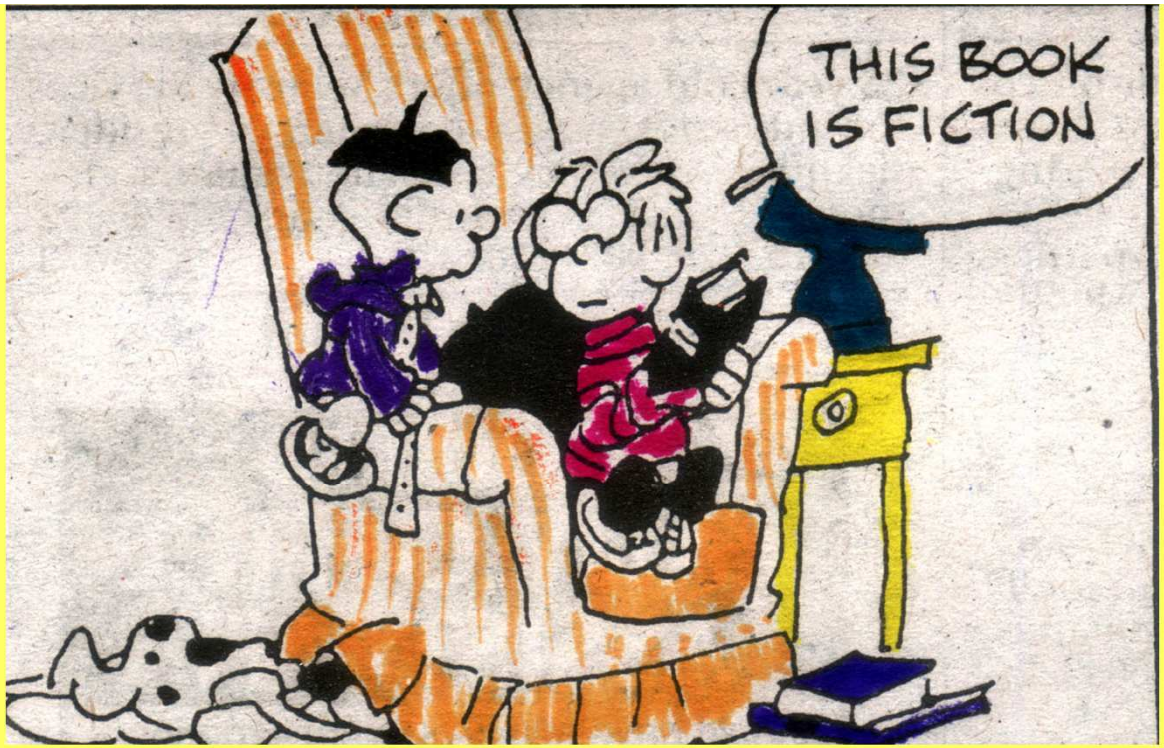
Hyperthermia with Radiation and Chemotherapy with drugs encapsulated in heat sensitive liposomes

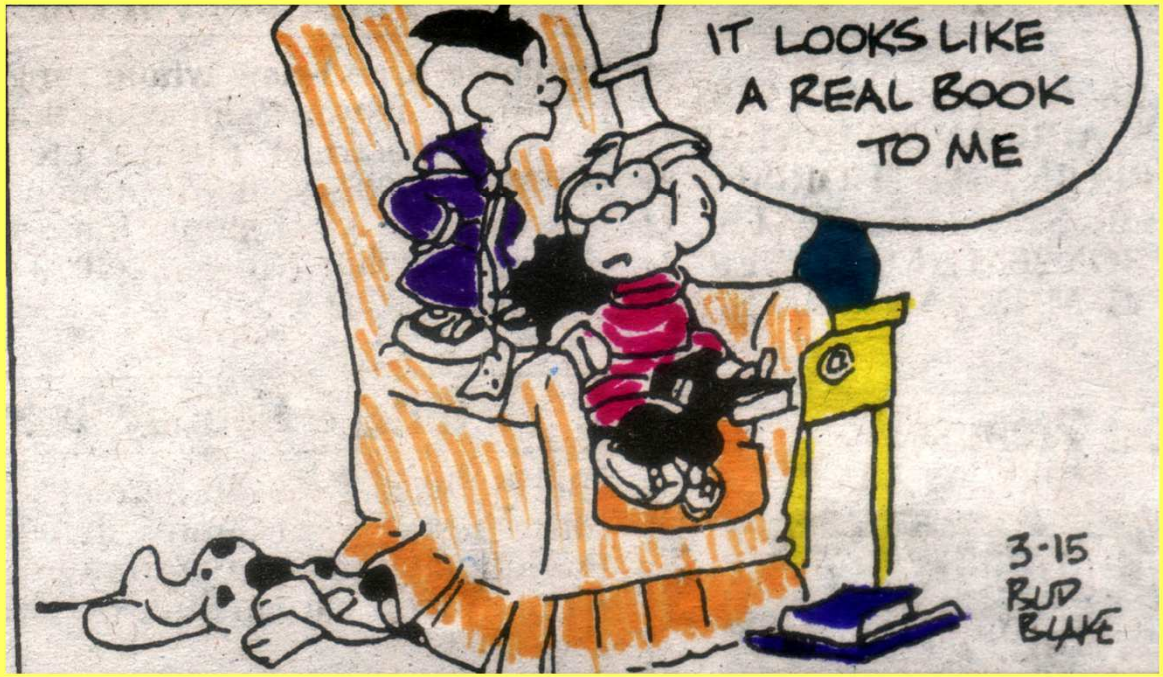
Hyperthermia is an useful adjunct to Radiotherapy and Chemotherapy

Hyperthermia is an option to explore now instead of waiting for an exotic treatment to arrive to increase survival




SURVIVOR


THIS BOOK IS FICTION


IT LOOKS LIKE A REAL BOOK TO ME
3-15
BUD BLAKE