IMPROVING THERAPEUTIC RATIO

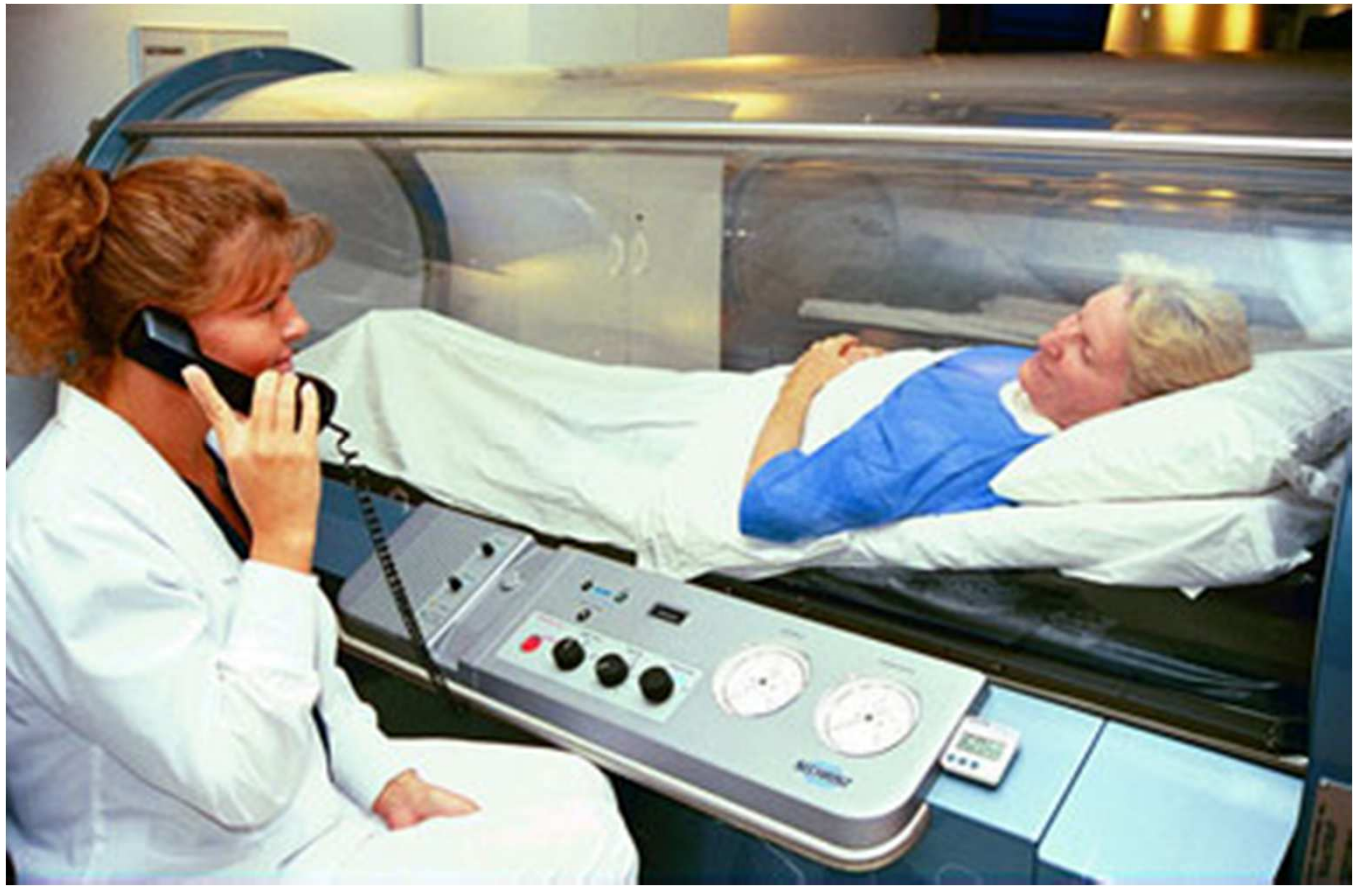
DR GIRI G. V.

KIDWAI MEMORIAL INST OF ONCOLOGY

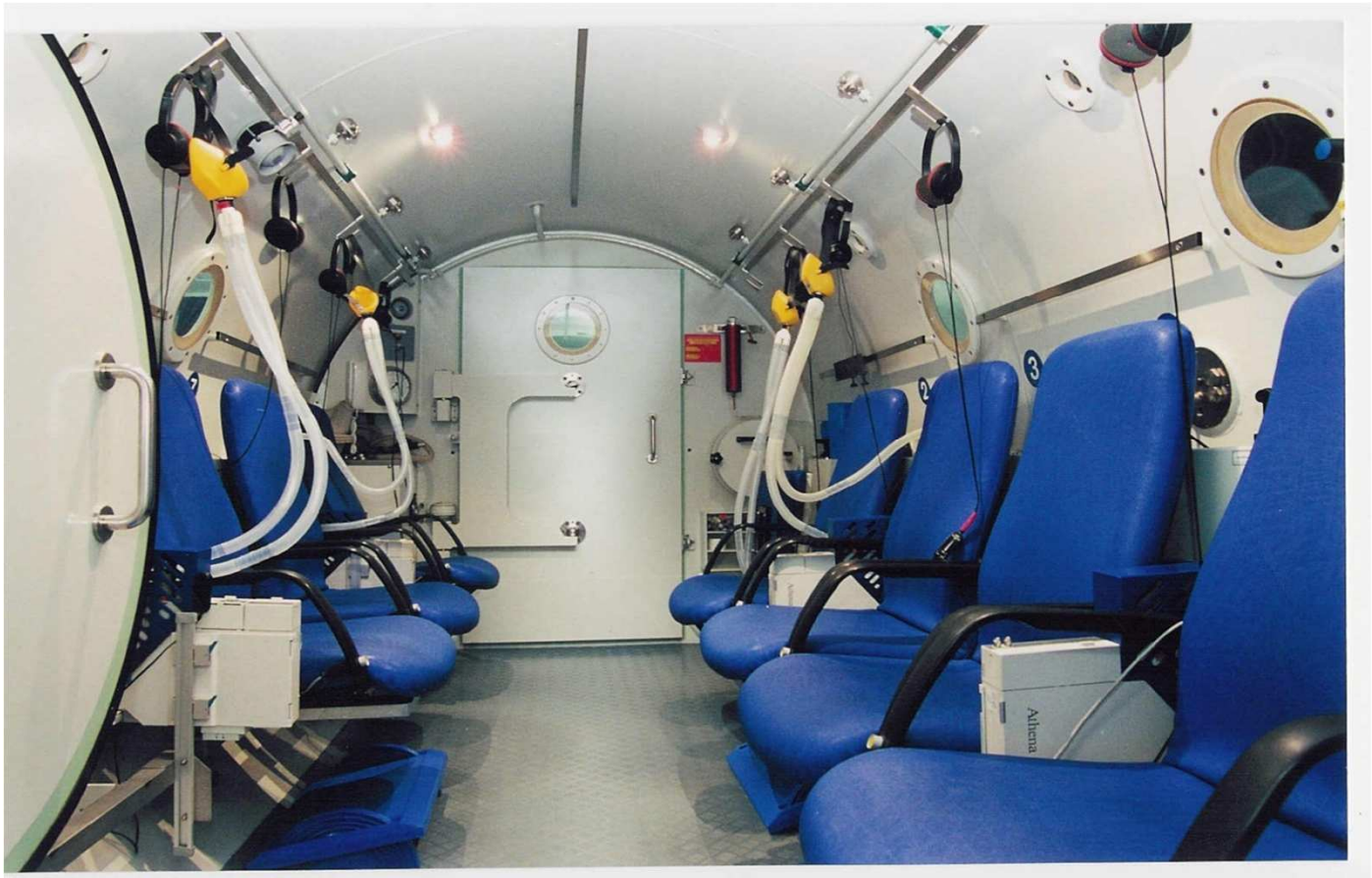
ICRO, VARANASI 2011

- HYPERBARIC OXYGENATION
- PHOTODYNAMIC THERAPY
- PARTICLE BEAM THERAPY
- HYPERTHERMIA

HYPERBARIC OXYGENATION



MONOPLACE CHAMBER

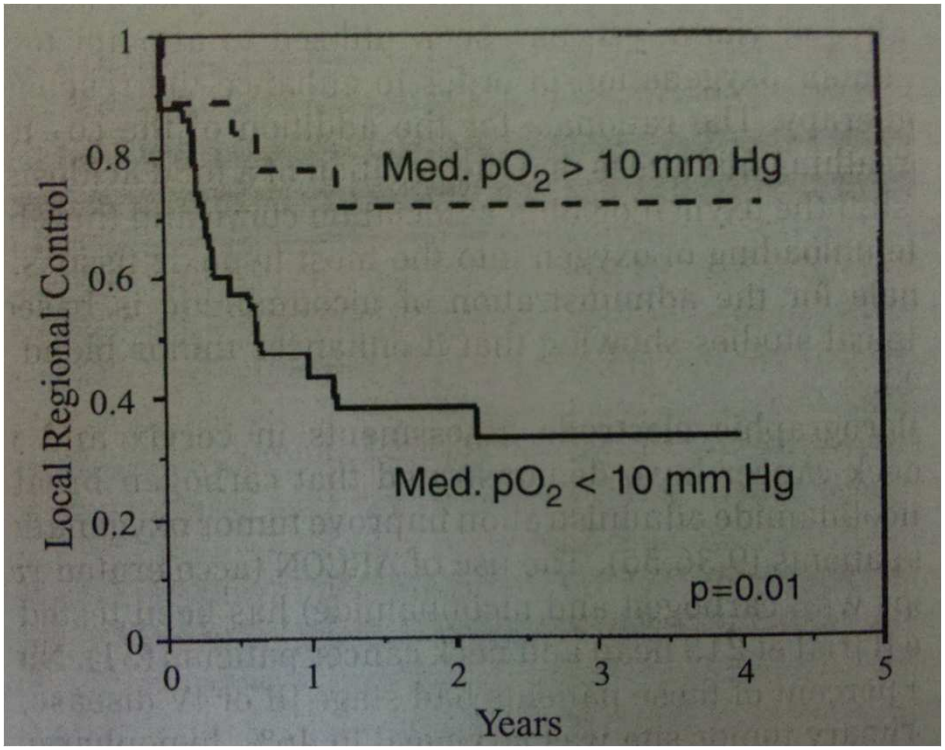


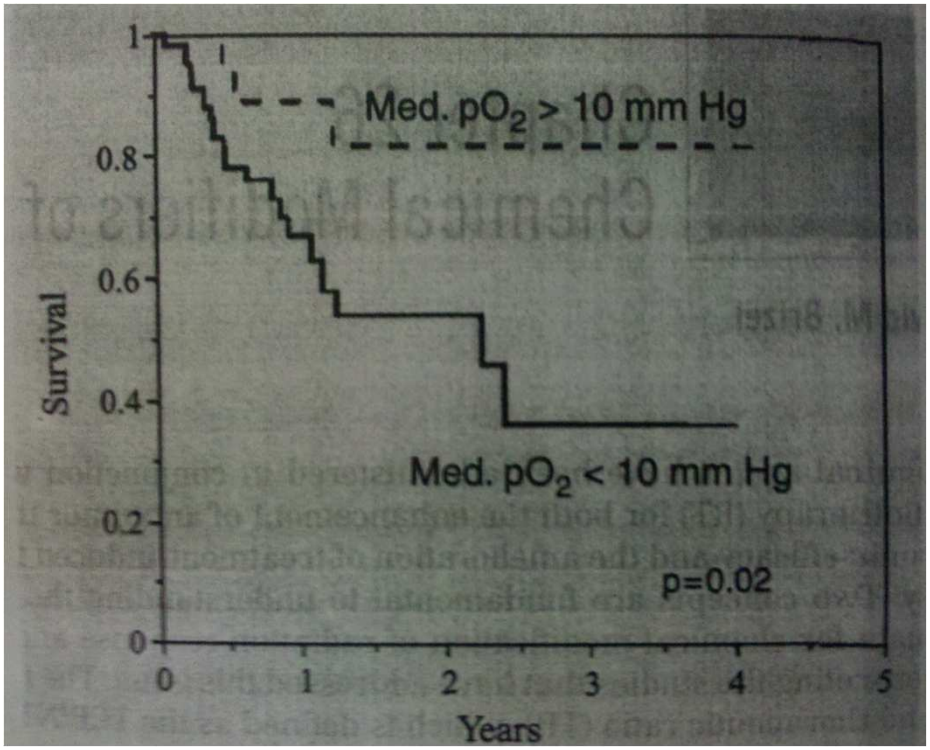
MULTIPLAC E CHAMBER

BASIS OF OXYGENTION----FREE RADICAL FORMATION AND IN THE PRESENCE OF OXYGEN --FIXATION OF DAMAGE BY THE INDIRECT EFFECT OF RADIATION.

UNDER NORMOBARIC CONDITIONS OXYGEN ISOLUBLE IN PLASMA BUT UNDER HYPERBARIC CONDITIONS (2-3 ATM)OXYGEN DISSOLVED IN PLASMA AND HENCE AVAILABLE FOR DELIVERY

WELL OXYGENATED CELLS PO_2 > 10 mm Hg ARE APPROX. 2.5 TIMES MORE SENSITIVE TO A GIVEN DOSE OF RADIATION THAN HYPOXIC CELLS.


Local Regional Control
1
0.8
0.6
0.4
0.2
0
Med. pO_2 > 10 mm Hg
Med. pO_2 < 10 mm Hg
p=0.01
0
1
2
3
4
5
Years


Survival
1
0.8
0.6
0.4
0.2
0
Med. pO_2 > 10 mm Hg
Med. pO_2 < 10 mm Hg
p=0.02
0
1
2
3
4
5
Years

CHOCHRANE REVIEW – SEPT 2008

19 RCT'S > 2000 PTS

BENEFITS OF BREATHING HBO Vs AIR

1103 PATIENTS---HBO

1153 PATIENTS---CONTROL

REDUCTION IN MORTALITY 1YR 5YR

H & N P=0.03 0.03

LOCO REGIONAL CONTROL

H & N P=0.0001 0.01

CERVIX AT 2 YEARS P = 0.04

RADIATION TISSUE INJURY P = 0.0001

SEZIURES P = 0.03

MRC TRIALS --1963 - 1976

CUMBERSOME

DIFFICULT TO PRACTICE

WITH THE AVAILABLITY OF DRUGS ACTING IN THE SAME MANNER IT IS SIMPLER TO ADMINISTER THE DRUGS THAN SUBJECTING PATIENTS TO HYPERBARIC OXYGENATION

CONCLUSIONS -

- HBO IMPROVES LOCAL CONTROL AND MORTALITY FOR CANCERS OF THE H & N AND CANCER OF THE CERVIX.

- BENEFITS ARE SEEN IN UNUSUAL FRACTIONATION SCHEMES

- ASSOCIATED WITH SIGNIFICAT ADVERSE EFFECTS INCLUDING OXYGEN TOXIC SEZIURES AND SEVERE RADIATION TISSUE INJURY.

- DIFFICULT TO RECOMMEND IN OTHER ANATOMICAL SITES
- CUMBERSOME
- DIFFICULT TO PRACTICE

WITH THE AVAILABLITY OF DRUGS ACTING IN THE SAME MANNER IT IS SIMPLER TO ADMINISTER THE OXYGEN MIMETICS THAN SUBJECTING PATIENTS TO HYPERBARIC OXYGENATION

PHOTODYNAMIC THERAPY

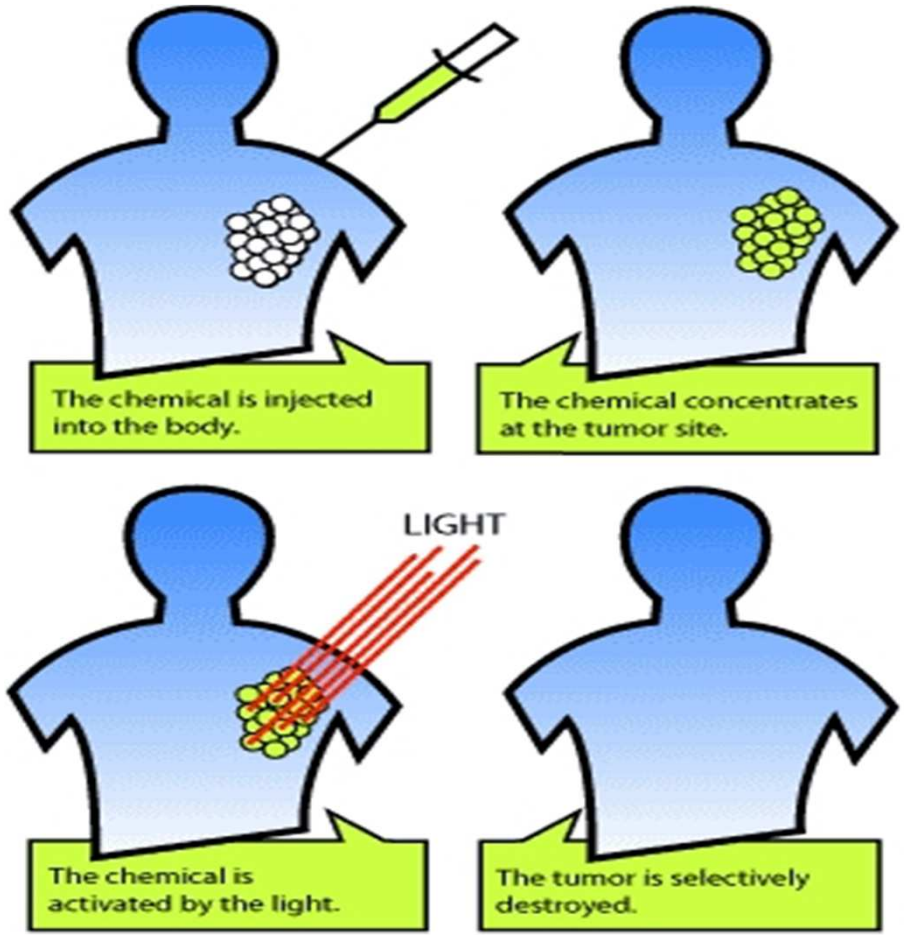
PHOTOSENSITIZERS ---- CONVERT LIGHT ENERGY ---> CHEMICAL ENERGY.

PHOTOSENSITIZER EXCITED – TYPE I REACTION---FREE RADIACAL FORMATION

TYPE II REACTION → $^{1}02$ CELL MEMBRANE DAMAGE-- NECROSIS

UPREGULATION OF IMMUNE SYS.

APOPTOSIS


The chemical is injected into the body.
The chemical concentrates at the tumor site.
LIGHT
The chemical is activated by the light.
The tumor is selectively destroyed.

PORFIMER SODIUM

TEMOPORFIN

BENZOPORPHYRIN DERIVITIES

VERTEPORFIRIN

HPPH

AMINO LEUVLINIC ACID (ALA)

ILLUMINATION --- 400 – 800 nm

400-- BLUE LIGHT

630-- RED LIGHT , 1 CM PENETRATION

ORDINARY LIGHT, LASERS AND L.E.D

CURRENT STATUS OF PDT

NO RCT ‘ S COMPARING -- PDT ALONE Vs RT , RT+PDT

LOCAL TREATMENT---PATIENTS AT RISK FOR NODAL METS.ARE NOT SUITABLE FOR PDT ALONE.

HOWEVER TREATMENT MAY BE REPEATED ANY NUMBER OF TIMES.

- LATE EFFECTS HAVE NOT BEEN REPORTED WITH PDT
- LIMITED LIGHT PENETRATION IN TISSUE AND HENCE LIMITED DEPTH OF NECROSIS THUS ALSO LEADING TO RELATIVE LACK OF FIBROSIS
- IMPORTANT ROLE IN TREATING RECURRENT TUMORS ?

H & N CANCERS – SURGERY AND OR RADIATION

5 YR SURVIVAL - 55 % - 70 %

COSMESIS

XEROSTOMIA

TRISMUS

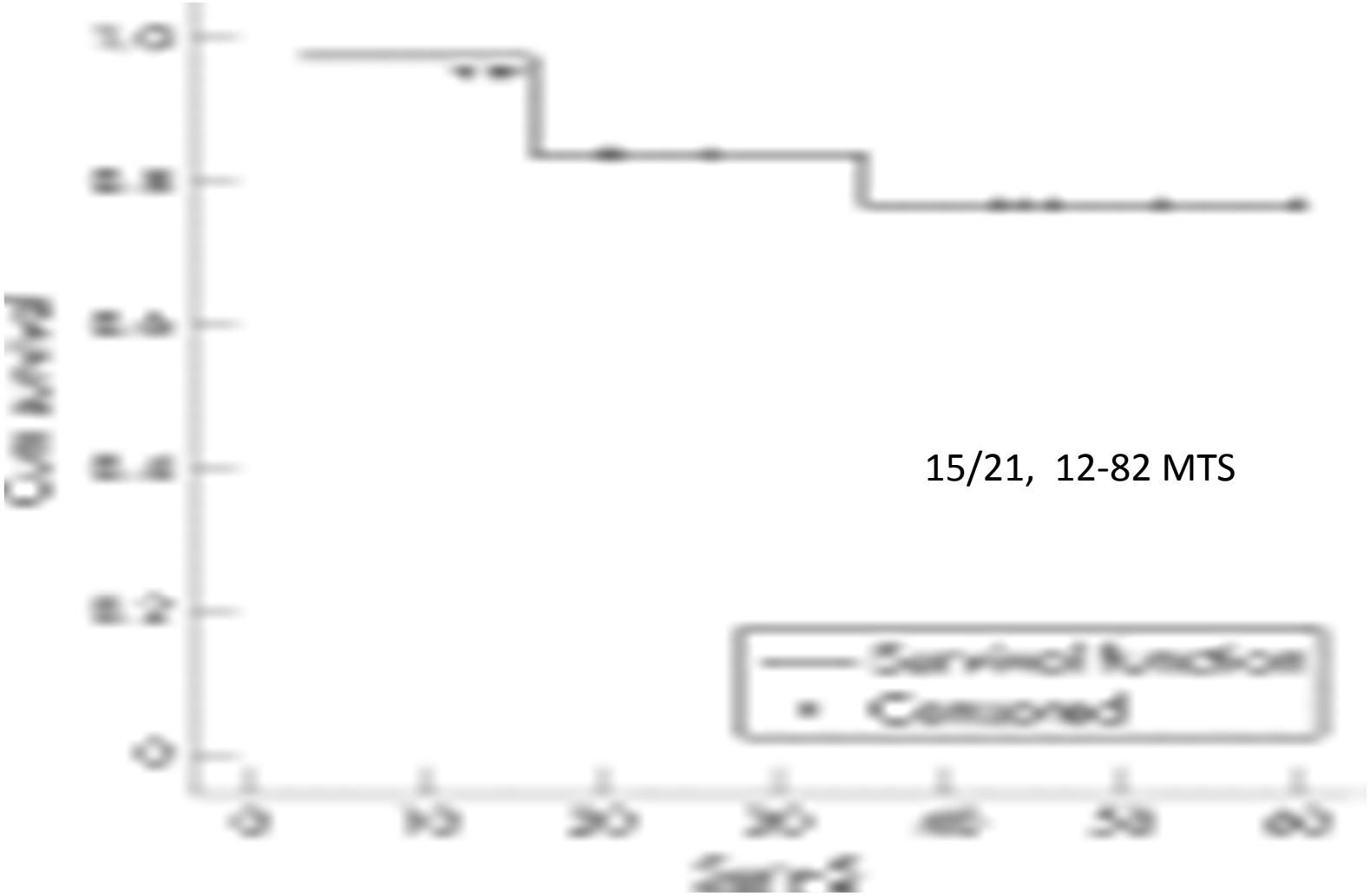
FIELD CANCERIZATION DIFFICULT TO TREAT

BIEL MA ET AL – METHODS MOL. BIOL 2010

518 PATIENTS –Cis, T1 AND T2 ORAL CAVITIY LESIONS, 89.1 % (462/518) OBTAINED COMPLETE CLINICAL RESPONSE AFTER PDT.

RESPONSE OF PATIENTS WITH ‘FIELD CANCERIZATION’ WAS OBTAINED IN UPTO 65%

21 PATIENTS EARLY ENDOBRONCHIAL LESIONS— MOGHISSI ET AL , THORAX 2007



15/21, 12-82 MTS

OTHER SITES PDT COMMONLY USED

SKIN

BREAST

ESOPHAGUS

CIN AND VAGINAL VAULT TUMORS

BLADDER CANCERS

CURRENTLY THE FDA HAS APPROVED PDT ONLY FOR PALLIATION OF OBSTRUCTION OF THE ESOPHAGUS AND BRONCHUS WITH QOL AS THE FOCUS

CONCLUSION

PDT - ESSENTIALLY A THERAPY BEST SUITED FOR TREATMENT OF SUPERFICIAL CANCERS WHERE ADEQUATE SURGERY OR RADIOTHERAPY IS DIFFICULT OR LEADS TO MUTILATING SIDE EFFECTS.

PARTICULATE RADIATION

FAST NEUTRONS

PROTON BEAMS

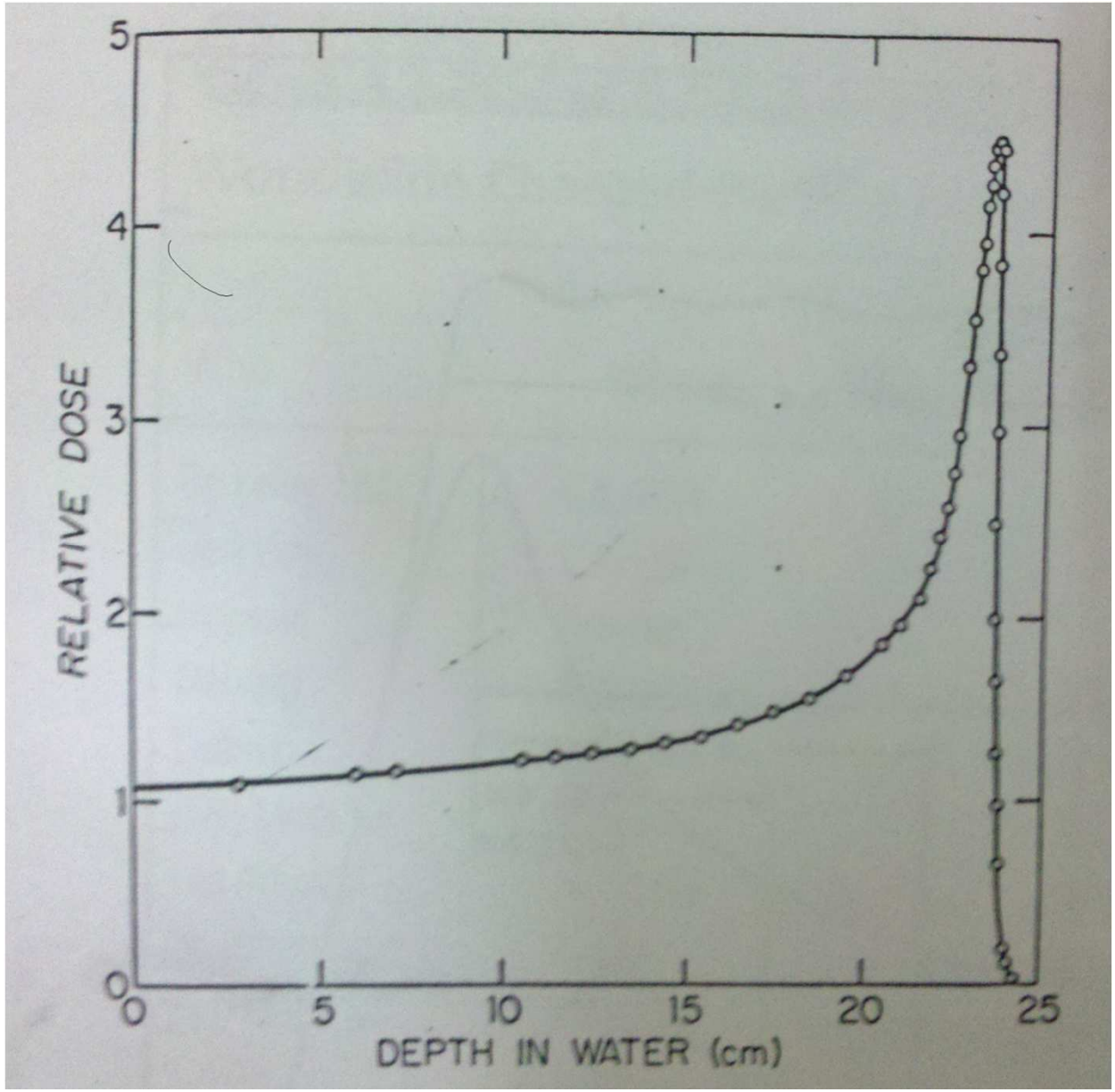
CARBON ION BEAMS

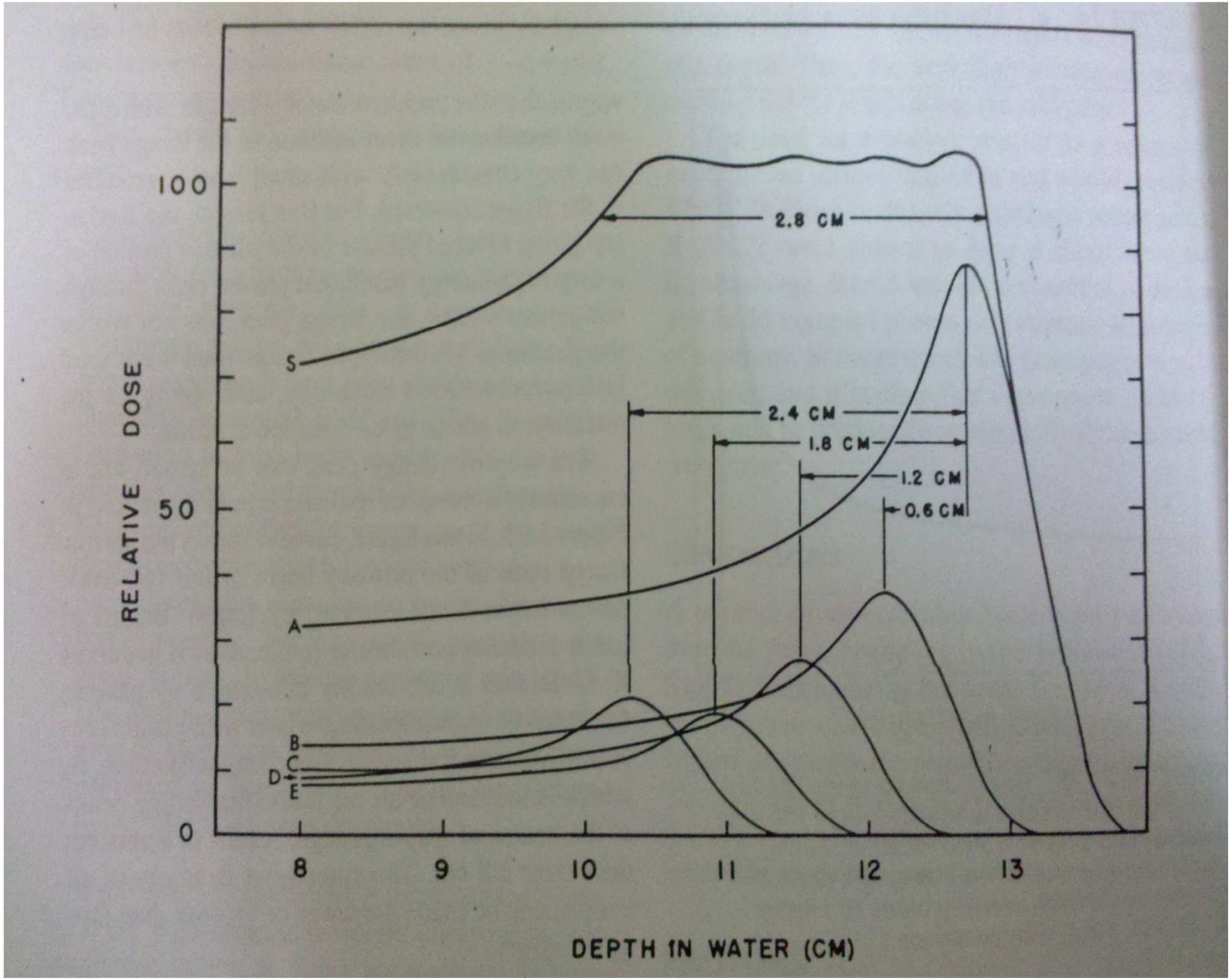
NEON ION BEAM

HELIUM BEAM

PROTON BEAM RADIATION THERAPY

- CHARGED PARTICLES----DEPOSIT ENERGY IN TISSUE THROUGH MULTIPLE INTERACTIONS WITH ELECTRONS IN ATOMS OF CELLS.
- THE ENERGY LOSS PER UNIT LENGTH IS SMALL AND CONSTANT UNTIL THE END OF THE RANGE
- THE RESIDUAL ENERGY AT THE END OF THE RANGE IS LOST OVER A VERY SHORT DISTANCE RESULTING IN THE STEEP RISE OF ABSORBED DOSE-----BRAGG PEAK.

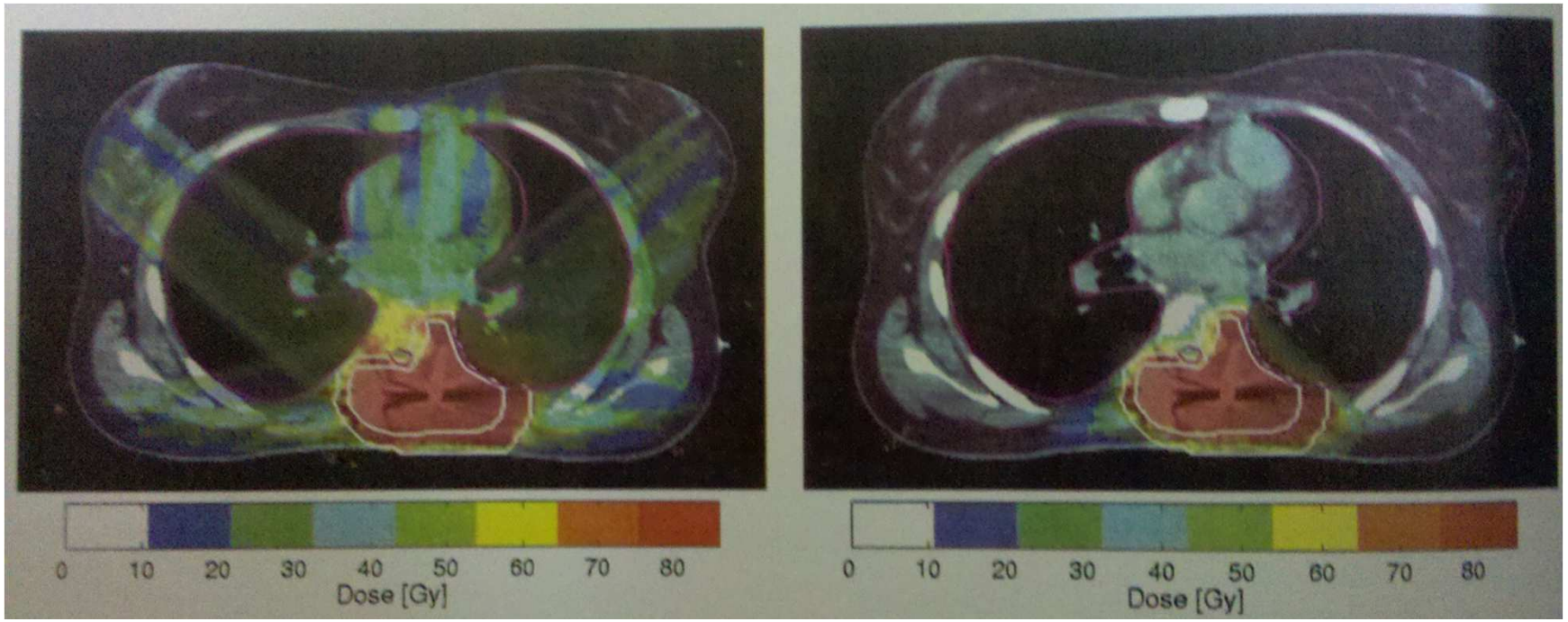

RELATIVE DOSE
0
1
2
3
4
5
0
5
10
15
20
25
DEPTH IN WATER (cm)

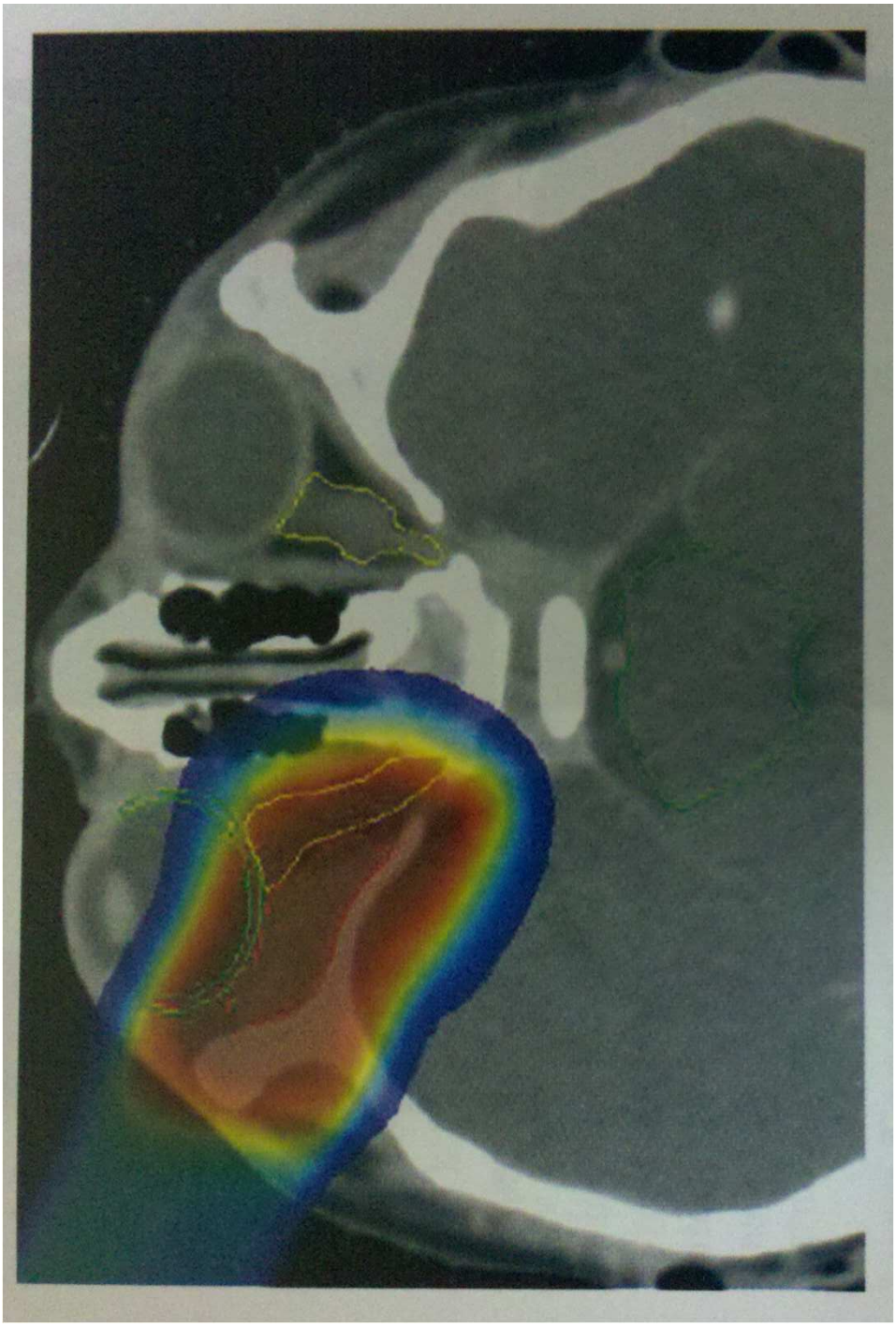

100
50
0
RELATIVE DOSE
2.8 CM
2.4 CM
1.8 CM
1.2 CM
0.6 CM
S
A
B
C
D
E
8
9
10
11
12
13
DEPTH IN WATER (CM)

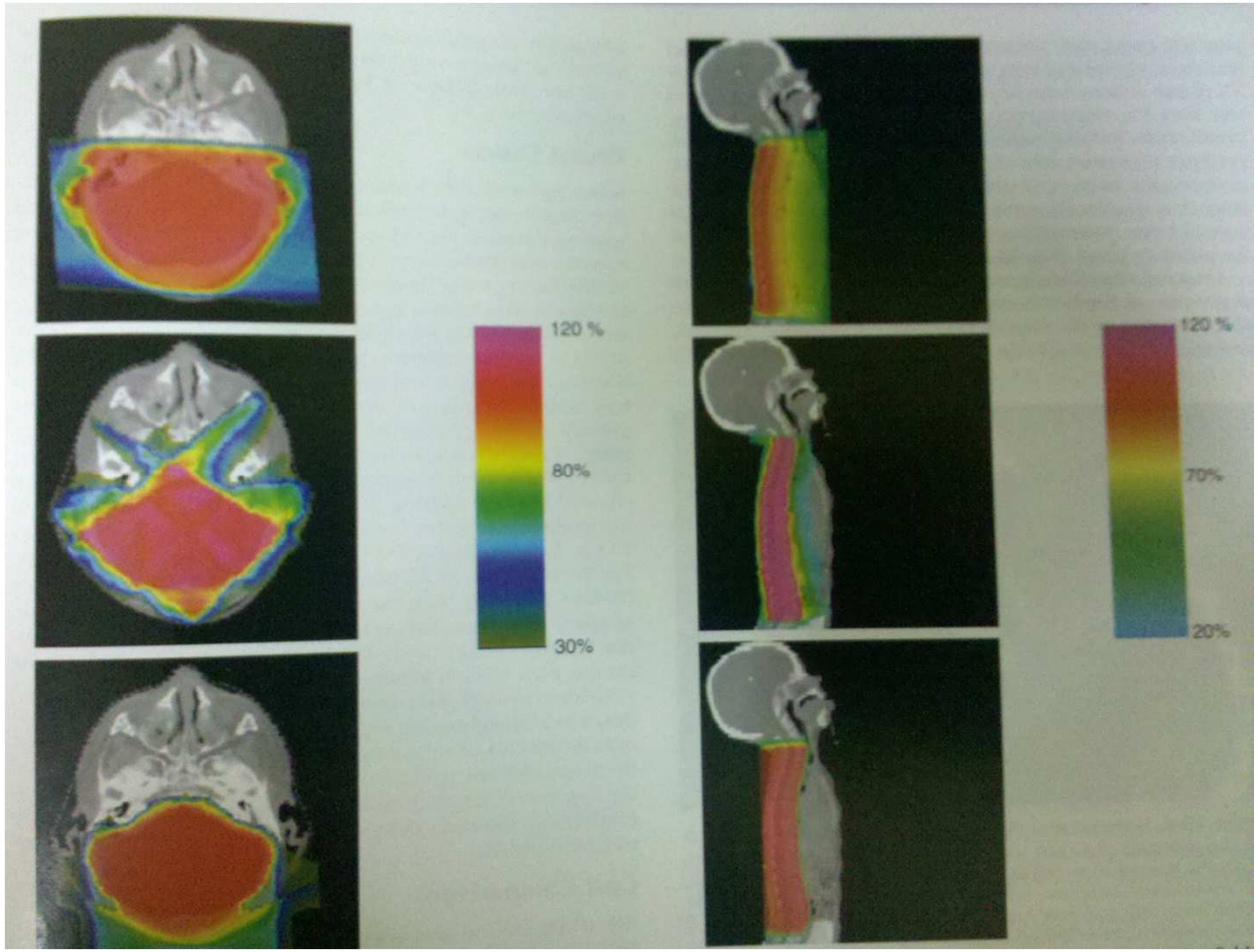
INTEREST IN CHARGED PARTICAL BEAM

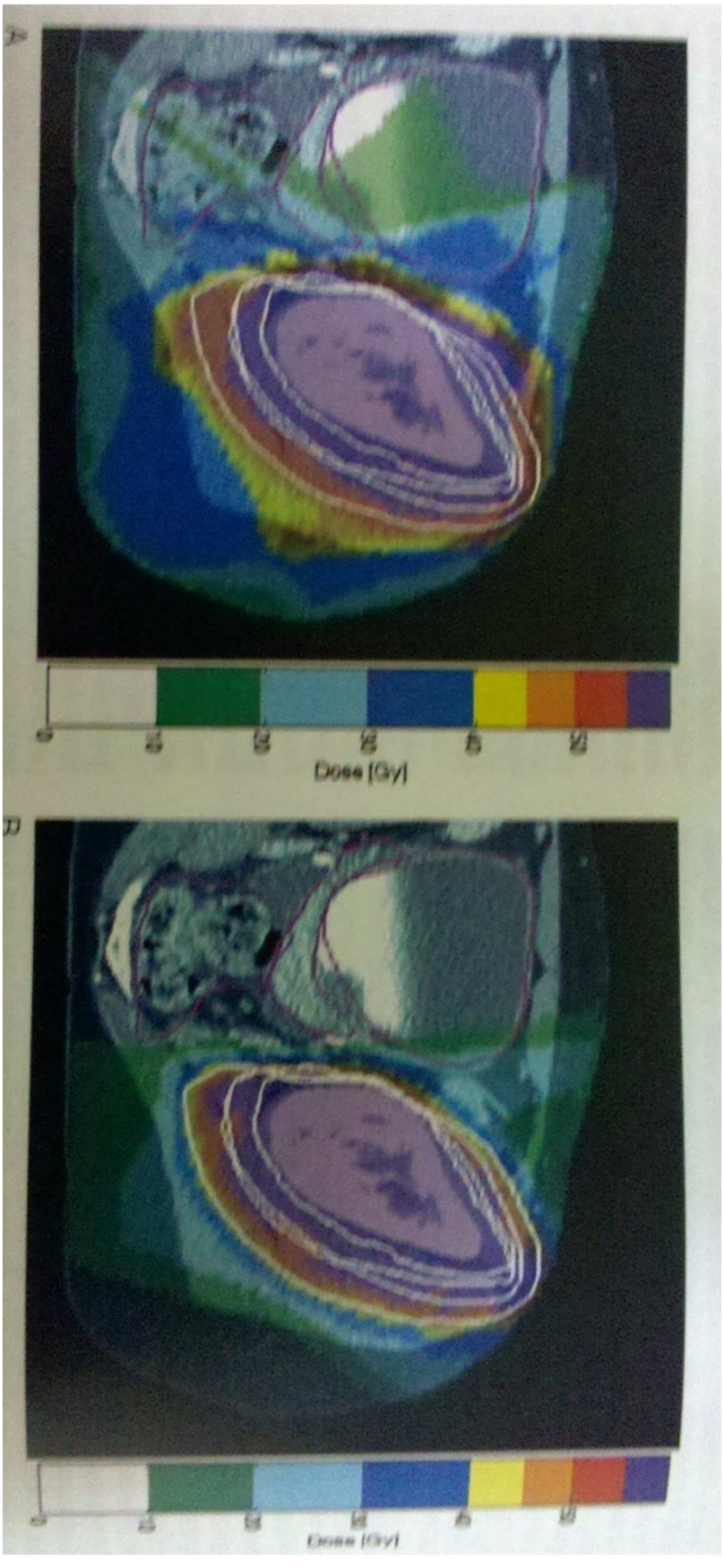
- THERAPY DEVELOPMENT OF HOSPITAL BASED CYCLOTRONS WITH HIGER ENERGIES CAPABLE OF REACHING DEEP SEATED TUMORS UPTO 30CM , 235 MeV ENERGY
- FIELD SIZES COMPARABLE TO LINEAR ACC.
- ROTATIONAL GANTRIES

THIS TECHNOLOGICAL DEVELOPMENT WAS STIMULATED BY THE SUPERIOR DOSE DISTRIBUTIONS THAT CAN BE ACHIEVED WITH PROTONS WHEN COMPARED TO STANDARD PHOTON THERAPY TECHNIQUES.


0 10 20 30 40 50 60 70 80
Dose [Gy]
0 10 20 30 40 50 60 70 80
Dose [Gy]




120 %
80%
30%
120 %
70%
20%


Dose [Gy]
Dose [Gy]

COMMON SITES WHERE PROTON BEAMS USED TILL DATE

- UVEAL MELANOMAS
- SARCOMAS OF THE BASE SKULL AND SPINE
- OPTIC PATHWAY GLIOMAS
- ASTROCYTOMAS
- PARANASAL SINUS TUMORS
- CA PROSTATE
- PEDIATRIC MALIGNANCIES

MIRALBEL R ET AL, INT J RADIAT ONCOL BIOL PHYS. 54, 2002

POTENTIAL INFLUENCE OF IMPROVED DOSE DISTRIBUTION WITH PROTON BEAMS COMPARED TO CONVENTIONAL BEAMS AND IMRT ON THE INCIDENCE OF TREATMENT INDUCED 2^{ND} MALIGNANCIES IN CHILDREN.

2 CHILDREN ,

1 PARAMENINGEAL RHABDOMYOSARCOMA

1 MEDULLOBLASTOMA

TREATMENT PLANS GENERATED

4 FOR RHABDOMYOSARCOMA CONVENTIONAL, IMRT, PROTON BEAM AND IMPT.

3 FOR MEDULLOBLASTOMA, CON., IMRT , PROTONS

SECONDARY CANCER INCIDENCE WAS ESTIMATED USING A MODEL BY THE ICRP

ALLOWED TO ESTIMATE THE ABSOLUTE RISK BASED ON THE DVH FOR NON TARGET ORGANS.

PROTON BEAMS REDUCED THE EXPECTED INCIDENCE BY A FACTOR OF >2 FOR THE RHABDO. AND BY FACTOR OF 8 TO 15 FOR THE CHILD WITH MEDULLOBLASTOMA COMPARED WITH IMRT AND CONVENTIONAL TREATMENT.

CONCLUSION –GOAL OF RT IS TO ERADICATE TUMOR BUT ALSO TO MINIMIZE THE RISK OF RADIATION INDUCED TOXICITY.

ALL THE CLINICAL AND TREATMENT PLANNING INDICATES THAT PROTON BEAM OFFERS SIGNIFICANT POTENTIAL FOR IMPROVING THERAPEUTIC INDEX

HOWEVER IF ONE WAS TO ESTIMATE THE COSTS INVOLVED, IT IS AT THE MOMENT PROHIBITIVE

FAST NEUTRON THERAPY

- REFERS TO USING NEUTRONS HAVING TENS OF MeV
- GENERATED BY ACCELARATING PROTONS OR DEUTRONS AND IMPACTING A TARGET—BERYLLIUM
- BEAMS COLLIMATED AS IN A LINAC
- LET RANGES 20 – 100 KeV/u COMPARED TO 0.2 – 2.0 KeV/u FOR MEGAVOLTAGE—DENSLY IONIZING

RBE -3.0 – 3.5 NORMAL TISSUE LATE EFFECTS

4.0 –4.5 CNS DAMAGE

8.0 SALIVARY GLANDS

TYPICAL NEUTRON DOSE FOR SALIVARY GLAND TUMORS—20nGy ~ 60 – 70 Gy EQV, FOR NORMAL TISSUE , BUT 160 Gy FOR TUMOR

THUS THE THERAPEUTIC GAIN FOR SALIVARY GLAND TUMORS IS IN THE RANGE OF 2.3 -2.6

DOUGLAS ET AL, ARCH OTOLARYNGOL H & N SURGERY, 129 : 2003

279 PATIENTS WITH SALIVARY GLAND TUMORS (20nGy)

DFS – 67 %

MULTIVARIATE –STAGES I / II, TUM < 4Cm

MINOR SALIVARY GLAND TM

LACK OF BASE OF SKULL INVOL.

PRIMARY AND NOT REC. TUMORS

RTOG 77 – 04, AM J CLINICAL ONCOL 16: 1993

PROSTATE CANCER T3 N0/N1

36PTS—PHOTONS (70 Gy)

55 PTS---MIXED BEAMS , NEUTRONS AND PHOTON, DOSE EQV. 70 Gy

	LRC	10 YR SUR	
MIXED	70%	46%	(P=0.04)
STD TREAT	29%	58%	

NO SIG. IN COMPLICATIONS

CONCLUSIONS—HIGH LET OF NEUTRONS CAUSES A DENSE CHAIN OF IONIZING EVENTS TO BOTH STRANDS OF DNA THUS MAKING DNA REPAIR MORE DIFFICULT

HIGH LET RADIATION OF FAST NEUTRONS – LESS SENSITIVE TO HYPOXIA

NEUTRON BEAMS IS BEST USED IN THE TREATMENT OF CERTAIN TUMORS THAT EXIBIT A "RESISTANCE" TO LOW LET RADIATION

HYPERTHERMIA

HYPERTHERMIA – ELEVATION OF TEMP. TO A SUPRAPHYSIOLOGICAL LEVEL.

WHEN CELLS ARE EXPOSED TO TEMP. > 41^{0} C

- HT. CAN KILL CELLS IN ITS OWN RIGHT
- CAN SENSITIZE TUMOR CELLS TO RADIATION
- INDUCE REOXYGENATION
- CHANGE IN THE MICROVASCULATURE PORE SIZE
- AUGMENT THE HOST IMMUNE RESPONSE AGAINST TUMOR CELLS

MECHANISM OF ACTION PREDOMINANTLY ON THE MOLECULAR PROTIENS----SYNTHESIS OF ALL PROTIENS STOPPED ON EXPOSURE TO HEAT EXCEPT HSP WHICH ARE UPREGULATED.

HSP 27 AND HSP 70

THERMOTOLERANCE – TRANSIENT ADAPTATION THAT RENDERS SURVIVING HEATED CELLS MORE RESISTANT TO ADDITIONAL HEAT STRESS

DEVELOPS -- DURING THE HEAT STRESS OR AFTER

THERMOTOLERENCE CAN PERSIST FOR SEVERAL DAYS AND IF NOT EXPOSED TO HEAT STRESS AGAIN WILL DECAY

HENCE A MINIMUM OF 48 HRS HAS BEEN SUGGESTED BETWEEN HT FRACTIONS IN ORDER TO AVOID RETREATMENT DURING THERMOTOLERENCE PHASE.

RATIONALE FOR COMBINING HT WITH RT

- S PHASE CELLS MOST RESISTANT TO RT, WHILE MOST SENSITIVE TO HT.
- HYPOXIA RENDERS 2.5 X MORE RESISTANT TO RT, WHILE NO DIFFERENCE IN SENSITIVITY BETWEEN HYPOXIC CELLS AND OXYIC CELLS
- RE-OXYGENATION DURING HT
- INHIBITION OF REPAIR OF SUBLETHAL AND POTENTIALLY LETHAL DAMAGE

SIMULTANEOUS TREATMENT BECAUSE NORMAL TISSUE IS NOT AS WELL HEATED AS TUMOR TISSUE

- DIFFERENCE OF THE HEAT TRANSFER CAPACITY OF TUMORS Vs NORMAL TISSUE
- POWER IS DEPOSITED PREFERNTIALLY IN TUMOR

LITTLE EVIDENCE TO SUGGEST HT ENCHANCES THE INCIDENCE OR SEVERITY OF LATE NORMAL TISSUE COMPLICATIONS.

REGIONAL HT OFTEN ASSOCIATED WITH A PHYSIOLOGIC STRESS SIMILAR TO AN EXERCISE WORK OUT

COMPROMISED CARDIAC STATUS

METAL IMPLANTS

PACE MAKERS

VAN DER ZEE ET AL, LANCET 355, 2000

RT Vs RT + HT IN LOCALLY ADVANCED PELVIC TM

MULTICENTRIC TRIAL –358 PTS

		LC 3YR	
RECTAL 143 ,	71 RT Vs 72 RT +HT	26 %	38%
BLADDER 101,49	RT Vs 52 RT+ HT	33%	42%
CERVICAL 114, 56	RT Vs 58 RT+ HT	41%	61%

(P< .05)

PEREZ ET AL, AM J CLINC ONCOL, 14, 1991, FINAL REPORT

COMPARISON OF RT Vs RT + HT IN SUPERFICAL MESURABLE TUMORS – 236 PTS H&N CA.

		OVERALL CR	< 3 CM
117	RT ALONE	30%	25%
119	RT + HT	32%	52 %
		(P>0.05)	

DATTA ET AL, INT J HYPERTHRMIA 6, 1990

COMPARISON OF THERMORADIOTHERAPY Vs RADIOTHERAPY -- HEAD AND NECK CA.- 65 PTS

	CR @ 8 WK
32 PTS RT ALONE	31 %
33 PTS RT + HT	55 %

(P< 0.05 FOR DFS AND OS IN STGS III/IV)

SUMMARIZING ROLE OF HYPERTHERMIA

RESULTS ARE INTRIGUING

MANY OF THE TRIALS SHOW BENEFITS

SIGNIFICANT DESIGN AND IMPLEMENTATION PROBLEMS AND THERMAL GOALS NOT ACHIEVED

CONTROL ARMS DID NOT RECEIVE OPTIMAL STANDARD THERAPY.

THANK YOU