Cutaneous Lymphoma; Total Skin Electron Therapy

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INTRODUCTION

- Heterogenous group of B & T cell lymphocytes
- Cut T-Cell Lymphoma (CTCL) arise from T lymphocytes of helper T phenotype having affinity for skin and epidermis
- Mycosis Fungoides - most common CTCL
- Incidence as low as 0.4 /1 lakh

Frequency

Lymphomas Type	Percentage
▪ Mycosis / Sezary	82.3%
▪Lymphatoid Papulosis	12.6%
▪B cell Lymphoma	4.5%
▪Peripheral T cell lymphomas	2.9%
▪CD30+ anaplastic large cell lymphomas	0.9%

MYCOSIS FUNGOIDES

- Rare often indolent T cell lymphoma
- About 1000 new cases in US /year
- Av age at diagnosis 50-60 yrs
- Children and adolescents not spared
- Median duration between onset of skin lesions and diag 8 -10 yrs
- Lesions can occur anywhere in body -- predilection for body folds

PHASES OF MF

- Patch or premycotic phase
- Plaque phase
- Tumor phase
- Sezary syndrome
- Erythroderma

Patch Phase

- Thin, non- palpable, erythematous & eczematous lesions
- Histologic features - diagnosis of MF
- DD: psoriasis, eczema, fungal infections, pityriasis rosea, drug eruptions
- Pruritus: most common symptom

Plaque Phase

- Clinically perceptible palpable lesion

Tumor Phase

- Neoplastic infiltrate extends below the upper dermis.
- Cutaneous ulceration
- Secondary infection

Erythroderma

Stanford Staging System

Stage I : Limited to skin. No Tum, ulcer, adenopathy or visc involvement

Stage Ia : Limited skin invol < 25%

Stage Ib : Invol. of more than 25%

Stage II : Skin Tum or Bx proven LN

Stage III : Invol skin with Bx proven LN or Spleen No other visc invol

Stage IV : Cut and extracut MF with documented visc invol

TNM(B) Classification

T1- Limited patch/plaque (<10% of skin surface involved)

T2- Generalized patch/plaque (>/=10% of skin surface involved)

T3- Cutaneous tumors (one or more)

T4- Generalized erythroderma (± patch, plaque or tumors)

N0- LN clinically uninvolved

N1- LN clinically enlarged, histologically uninvolved

N2- LN clinically unenlarged, histologically involved

N3- LN clinically enlarged and histologically involved

M0- No visceral disease

M1- Visceral disease present

B0- No circulating atypical cells (<1000 Sezary cells[CD4+CD7-]/ml)

B1- Circulating atypical cells (>/=1000 Sezary cells/ml)

Stage classification of MF

IA	T1	N0	M0
IB	T2	N0	M0
IIA	T1-2	N1	M0
IIB	T3	N0-1	M0
IIIA	T4	N0	M0
IIIB	T4	N1	M0
IVA	T1-4	N2-3	M0
IVB	T1-4	N0-3	M1

The B classification does not alter clinical stage

Prognostic factors

- Age
- Stage
- Lymph node involvement
- Visceral involvement

DIAGNOSTIC WORK UP

- General
  - History (attn to pace of evolution)
  - Derma eval and proper lesion charting
  - Routine physical exam – LN, liver, spleen etc
- Imaging studies
  - CXR
  - CT Scan Chest, Abd & Pelvis

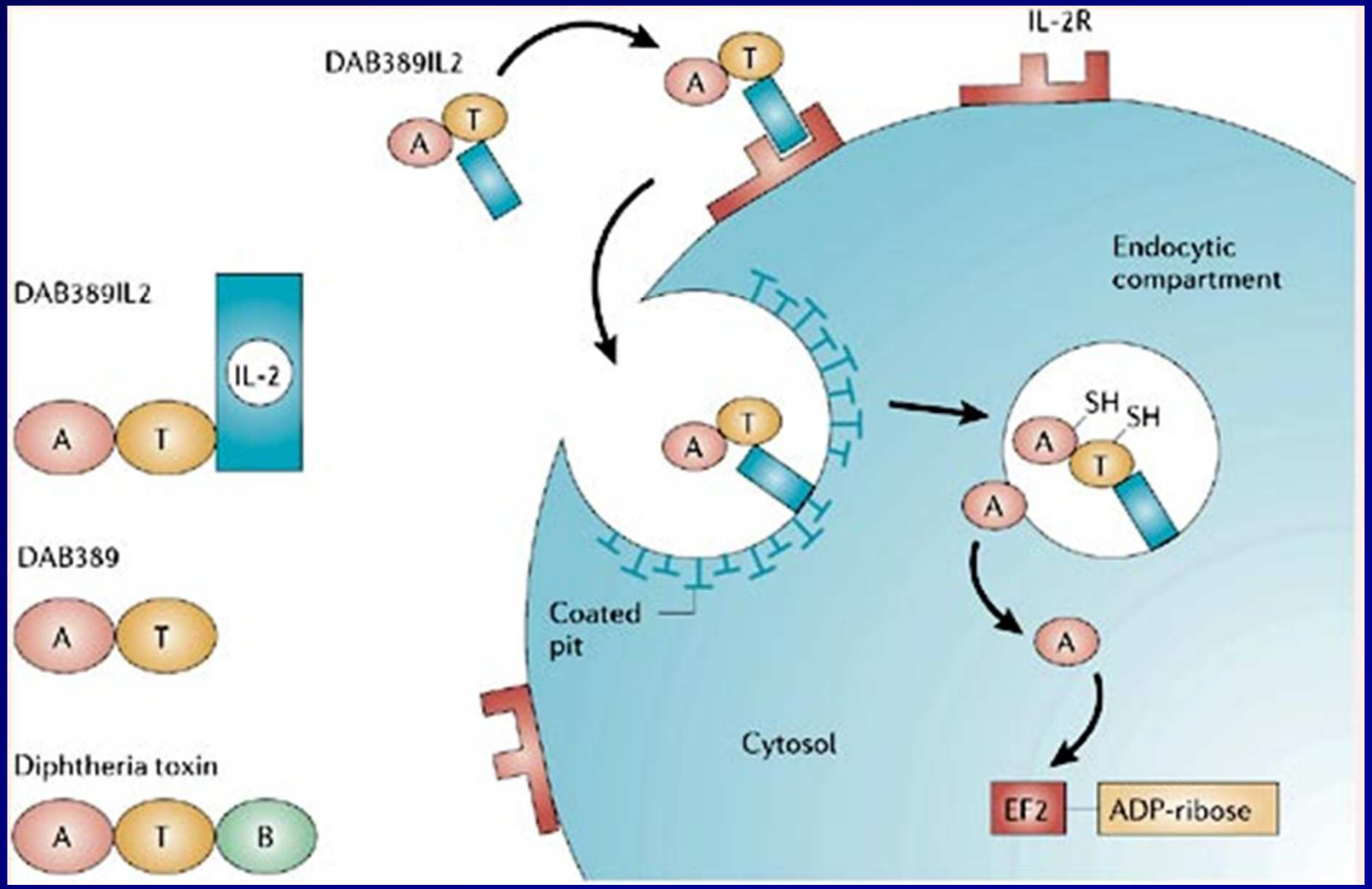
Diagnostic workup contd.

- Laboratory studies
- CBC, blood chemistry, LDH
- Peripheral Blood smear for Sezary cells
- Flow cytometry of peripheral blood
- Biopsy
- Punch biopsy of lesion
  Biopsy of palpable LN
  Bone marrow biopsy

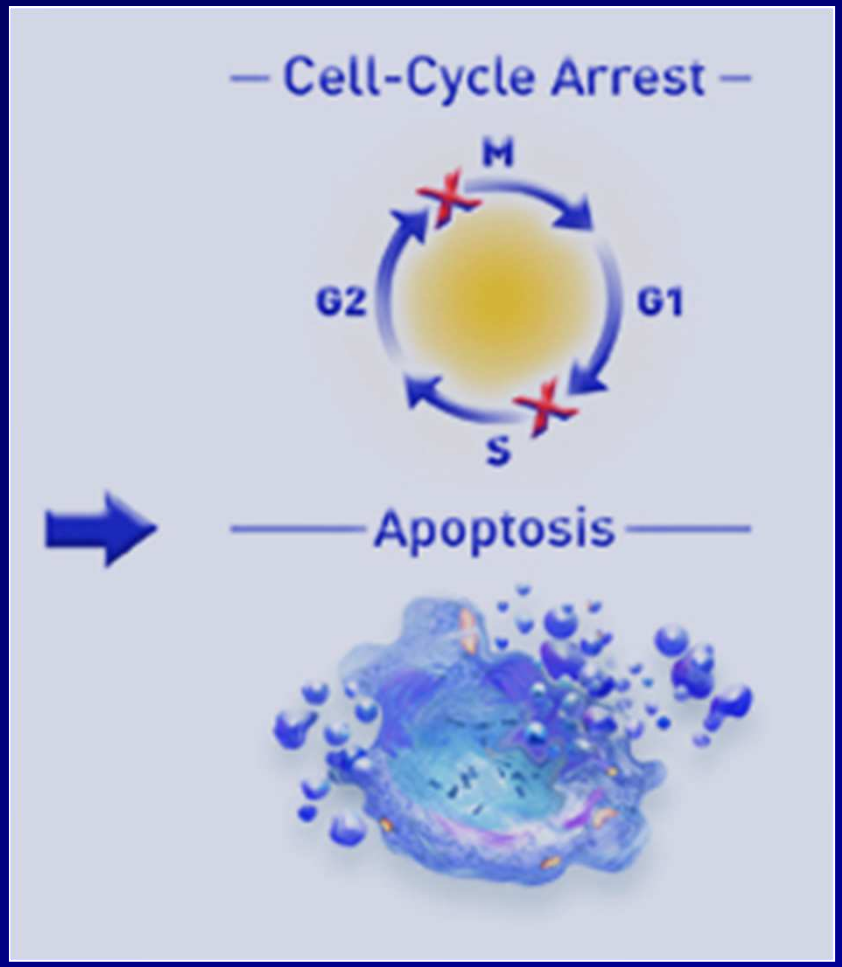
Treatment modalities

- Skin- directed therapy
  - Localized EBRT
  - Topical chemotherapy (NM, BCNU)
  - Topical retinoids (Bexarotene)
  - Total skin electron beam therapy (TSET)-**Most effective**
  - Phototherapy
- Biologic response modifier
  - Extracorporeal photopheresis
  - Interferon alpha
  - Systemic retinoids
  - Recombinant fusion protein (e.g. denileukin difitox)
  - Vorinostat
- Systemic chemotherapy (CHOP, COPP)
- Combined modality therapy

Denileukin Diftitox



HDAC Inhibition on Cancer Cells With Vorinostat



Anticancer Effects of Vorinostat

Marks PA et al. Nat Rev Cancer. 2001;1:194–202.

TREATMENT BY STAGE

- **Stage Ia**
  - **generalized *topical HN2***
  - **Unable to tolerate topical HN2 – *PUVA, Re-PUVA, topical BCNU***
  - **Progression/refractory to trt – TSET, *PUVA with Interferon alpha***

- **Stage Ib /IIa**
  - Chronic dis - topical HN2 or PUVA
  - Rapidly prog disease with thick plaques
    - *TSET* with *optional follow up therapy* - topical HN2, PUVA, Photopheresis to maintain remission
    - Refractory to these trt - *systemic drugs* exa- Interferon alpha, retinoid, or single agent CT exa- MTX

- **Stage IIb:**

- ***TSET*** **with boost to tum with optional follow-up topical trt/ photopheresis to maintain response**
  - ***sequential topical therapies*** **for refractory lesions**
  - **Disease progression – *photopheresis***
  - **No response - *systemic therapy***

- **Stage III**
  - ***Photopheresis***
  - **Progression or unresponsive –add MTX to photopheresis**
  - **Progression - *palliative PUVA*, *palliative topical HN2*, *interferon,* syst CT, *retinoids, exp protocols* exa-*fludarabine,* MAB or BMT**

- **Stage IVa**
  - ***Individualized palliative trt***
    - **Interferon-alpha, syst CT**
    - **local radiation to sympt dis**
    - **Photopheresis**
    - **Retinoids**
    - **exp protocols**

Stage IVb

- *Individualized palliative trt*
  - Syst CT
  - Interferon, retinoids, exp protocols

Radiation Therapy Technique

- Skin thickness
  - Average : 2-3 mm
  - min (eyelid) : 0.5 mm
  - Max (back) : 5 mm
- Cellular infiltration in MF
  - Mainly superficial portion of skin
  - Often extend in deeper tissue exa- hair follicle
  - Tumor formation : 15 mm

RT Techniques used in MF

- β-rays from Sr^{90}
  - superficial lesion
- Superficial irradiation (80-140 KV)
  - Infiltrated plaque
- Orthovoltage irradiation
- TSET

Conventional Radiation Therapy

- Markedly infiltrated plaques & tumors
  - High energy ortho-voltage(200-280 KV) or local-field electron beam irradiation (10-15 MeV)
- Discrete lesion
  - 10-20 Gy / 3-4#/ 3-4 days OR
    20-30 Gy /10-15# / 2-3 weeks
  - Generous portals
  - Document the trted area (photograph, portal drawing or tattooing)
  - Possible need of subsequent irradiation

Conventional Radiation Therapy

- Cotter et al. (*IJROBP* 1983;9 :1477)
  - 20 patients (110 lesions)
  - RT for cutaneous MF
  - Superficial X-ray, Co60, electron beam
  - Plaque (50%), tumor<3 cm(20%), tumor>3 cm(27%)

	10 Gy	10-20 Gy	20-30 Gy	30-40 Gy
No. of lesion	27	46	28	9
Complete response	26 (96%)	41 (89%)	28(100%)	9(!))%)
Partial response	1	5	0	0
Recurrence after CR	11/26 (42%)	13/41(32%)	6/28 (21%)	0/9
Mean time to recurrence	5 mon	10 mon	16 mon	No fail.
Treatment failure	12/27 (44%)	18/46(39%)	6/28 (21%)	0/9

Conventional Radiation Therapy

- Micaily et al. (*IJROBP* 1998;9:475)
  - 18 patients with unilesional MF
  - Local electron beam irradiation only
  - Median dose 30.6 Gy
  - 10 Yr relapse free SR = 86.2%
  - 10 Yr overall SR = 100%
- TSET is not indicated for unilesional MF

Total Skin Electron Beam Therapy

- Only in major radiotherapy centers
- Aims to irradiate the patient's whole skin
  - Radiation dose by proper choice of electron energy
  - Dose to epidermis and upper dermis
  - Sparing deep dermis & subcutaneous tissues
- First used by Trump et al.* using a van de Graaff generator
- Stanford technique**

*Trump et al. Am J Roentgenol.1953;69:623
**Page et al. Radiology.1970:94;635

Various TSET Techniques

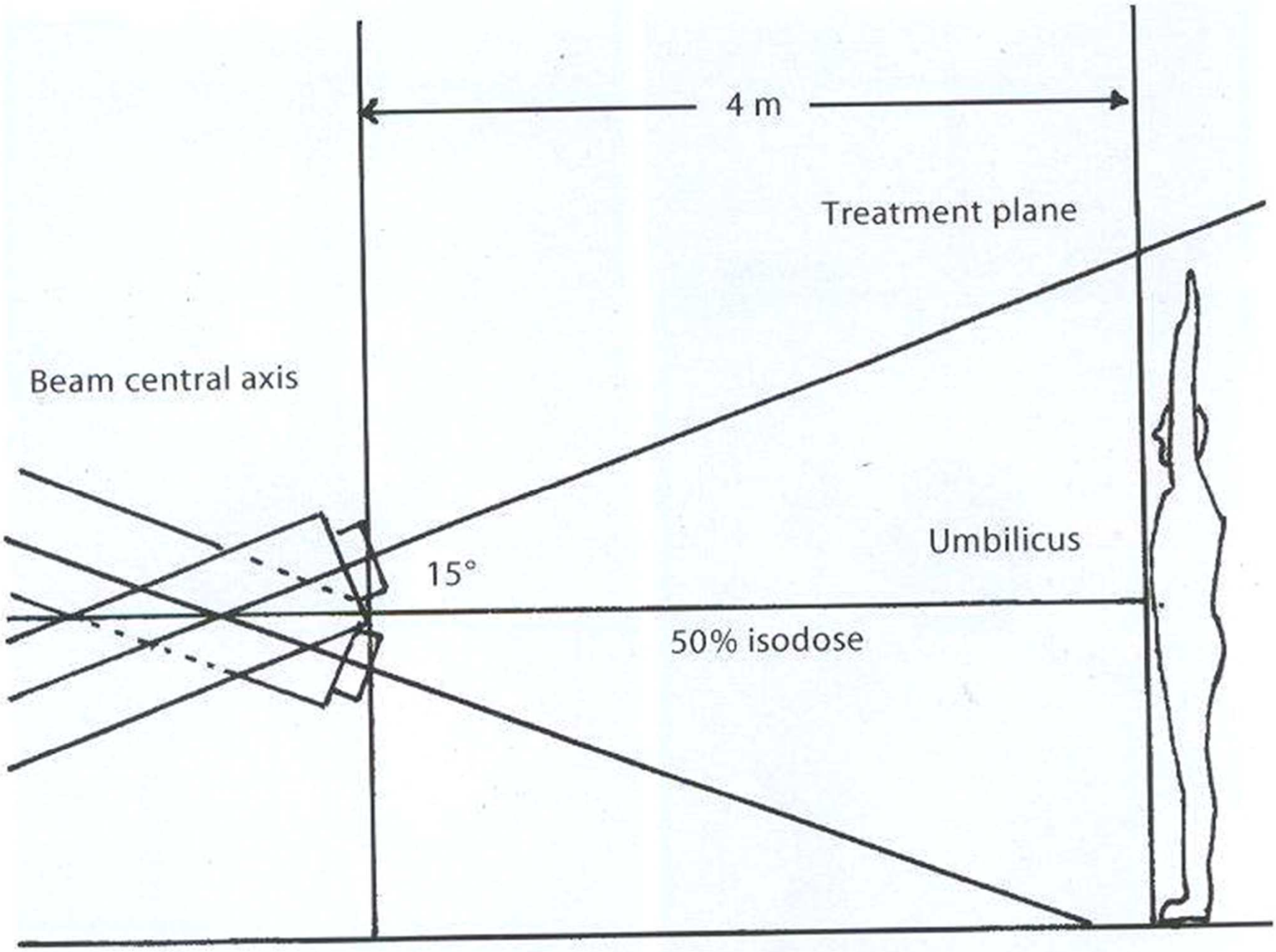
Modified Stanford technique

- Six field
- Two beams (15 degree above & below horizontal)
- 1st day- Ant, RPO & LPO
- 2nd day- Post, RAO & LAO
- Dose – 30-40 Gy / 8-10 wks – one wk gap at 18-20 Gy, 1.5-2Gy/#.
- 3 fields /day
- Boost - 15-20Gy ; 1-2Gy/# to soles , scalp perineum and inframammary

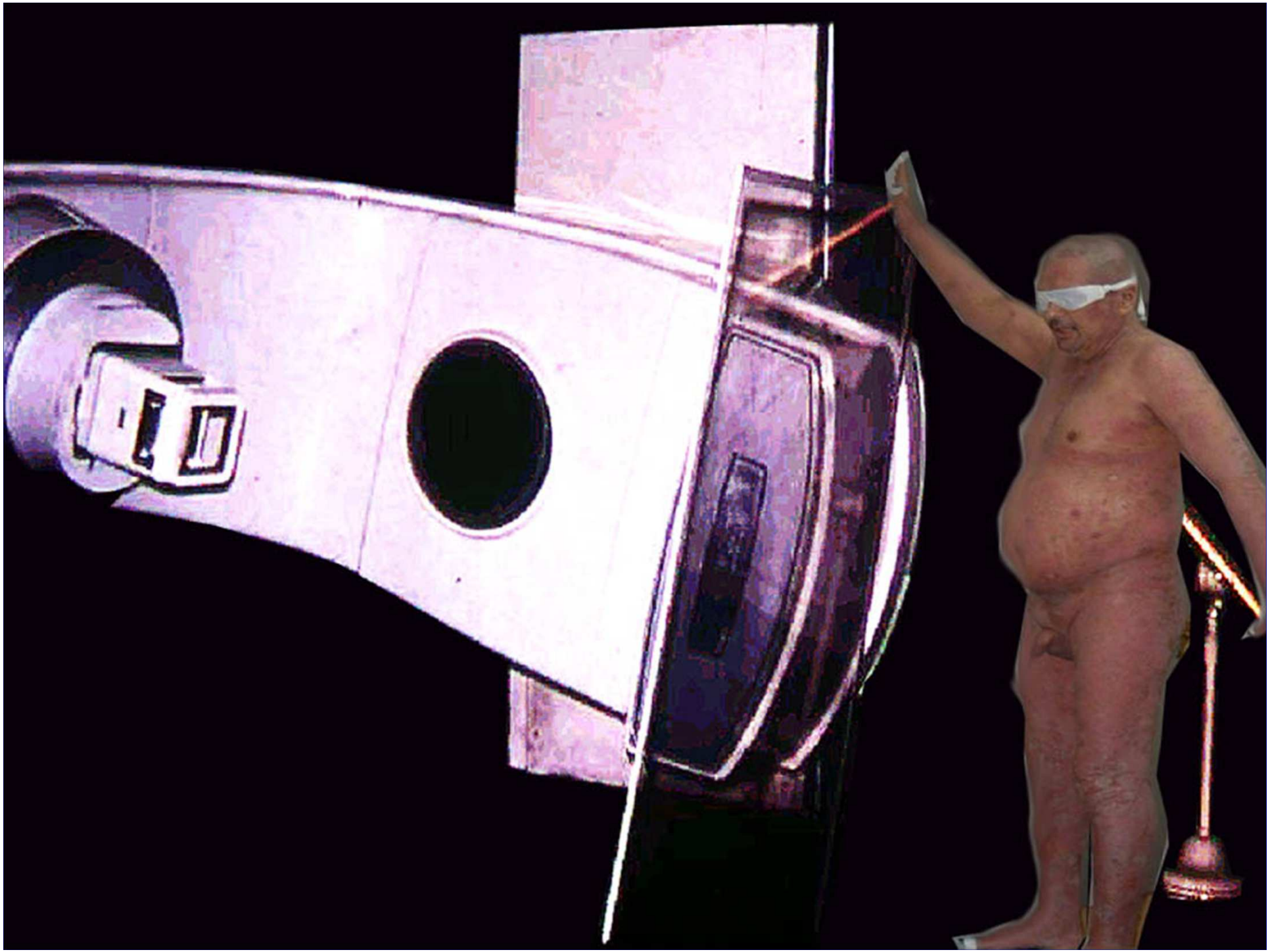
Page et al. Radiology 1970; 94:635-41

Shielding

- Eye
- Finger Nails
- Toe nails


4 m
Treatment plane
Beam central axis
Umbilicus
15°
50% isodose

TSET Applicator



ANT

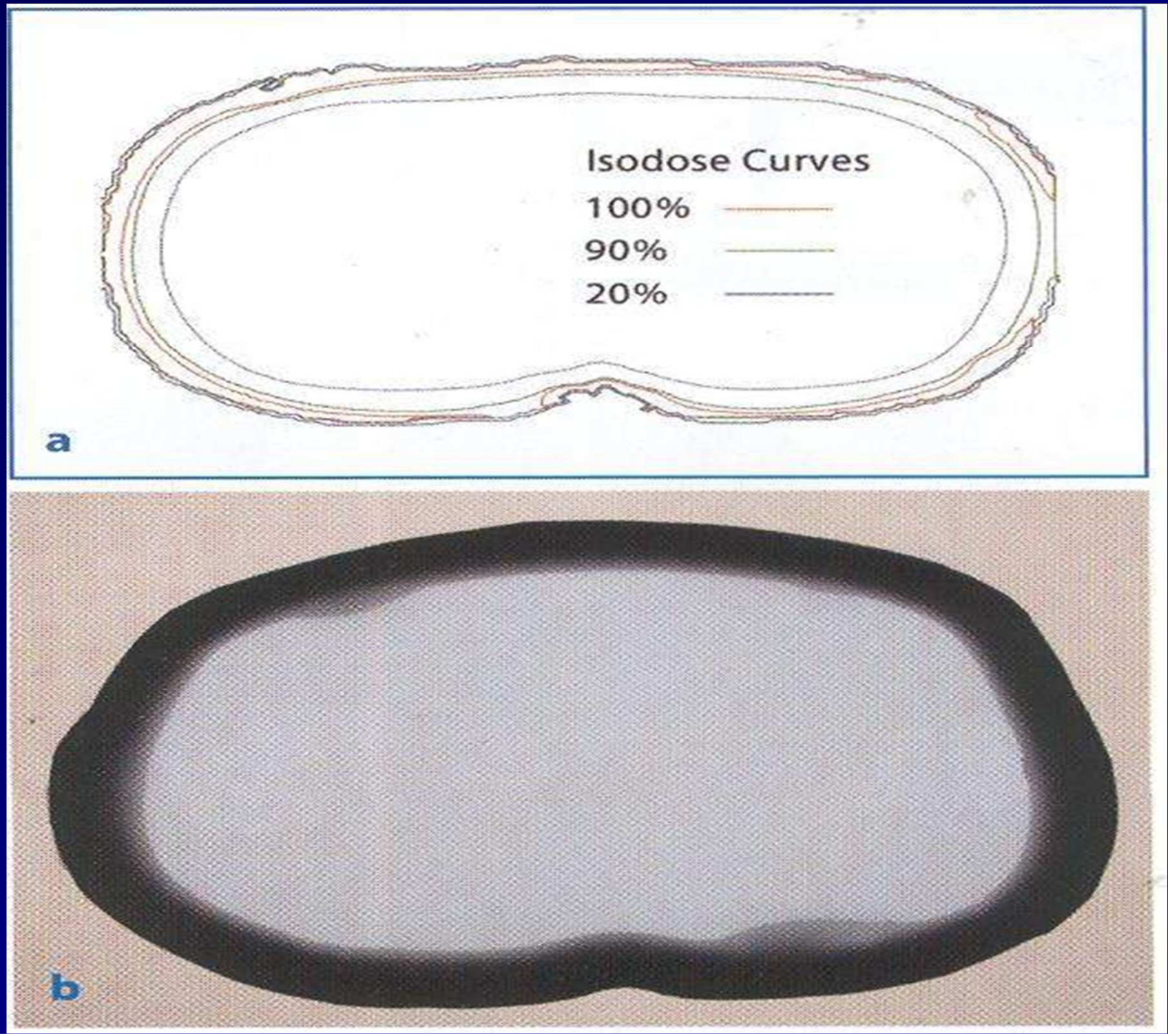
RAO

RPO

POST

LPO

LAO


Isodose Curves
100%
90%
20%
a
b

BOOST TO SCALP

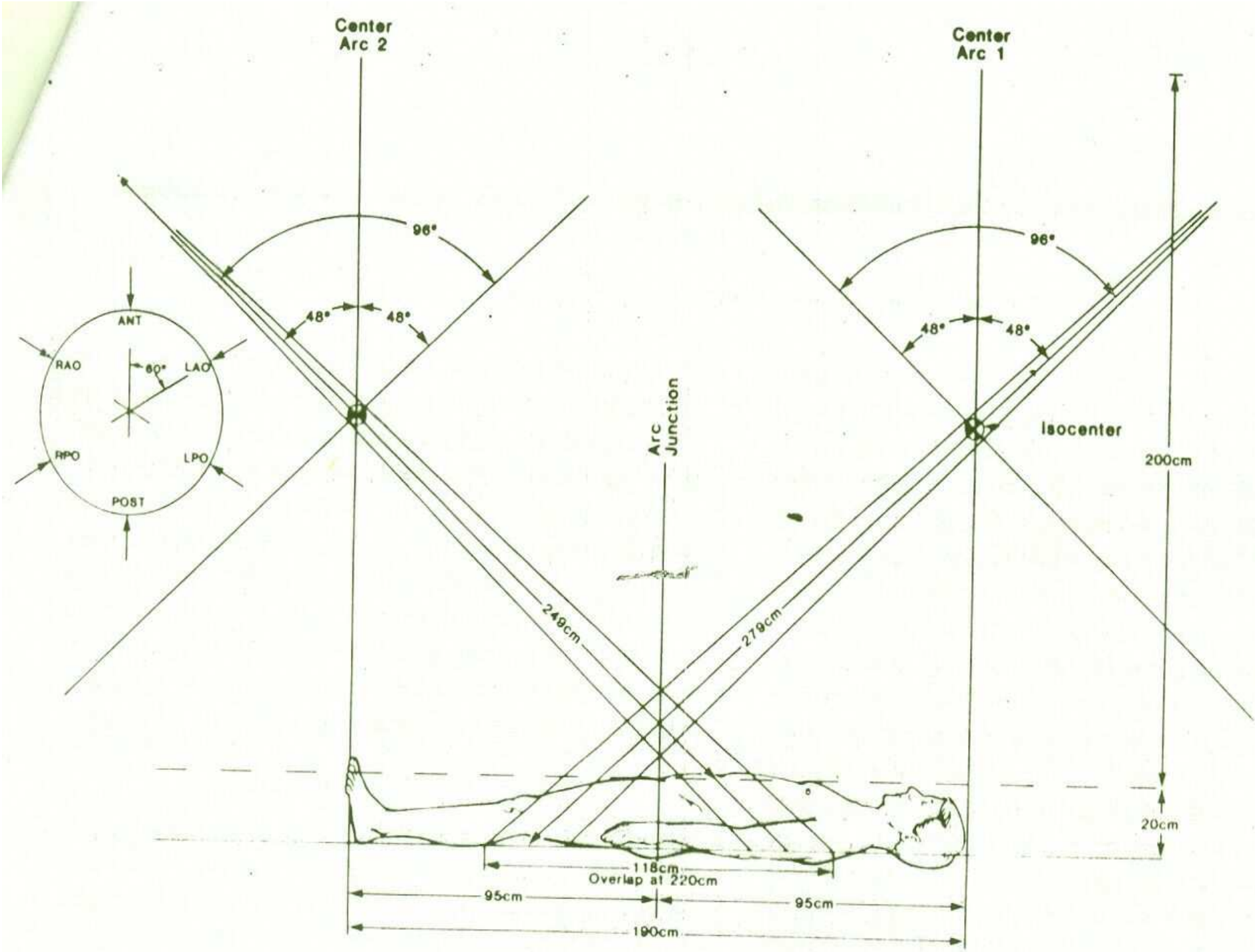
BOOST TO SOLES

BOOST TO PERINEUM

Reclined patient position

- For pts who cannot stand
- Pt lies reclined on a low couch close to the floor
- Two symm 48 deg electron arc fields
- Field uniformity of 5%
- 6 positions - Ant, Post & 4 obliques , over a 2 day period
- Disadv - More time consuming (because of low electron dose rate)

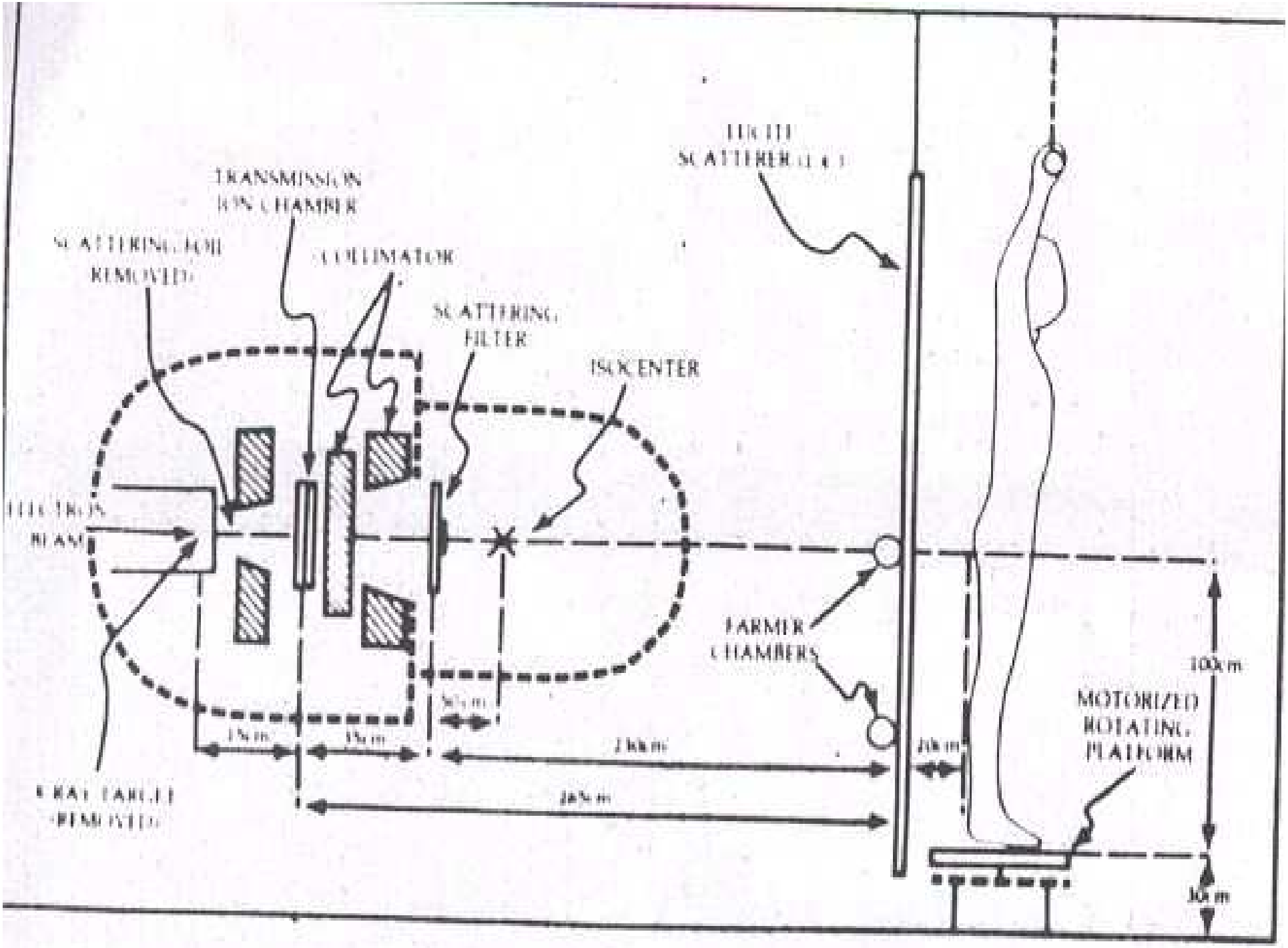
Gerbi et al. Int J Radiat Oncol Biol Phys 1989; 17:397-404.


Center
Arc 2
Center
Arc 1
96°
48°
48°
96°
48°
48°
ANT
RAO
60°
LAO
RPO
LPO
POST
Arc
Junction
Isocenter
200cm
249cm
279cm
20cm
118cm
Overlap at 220cm
95cm
95cm
190cm

Rotational total skin electron irradiation

- Improved surf dose homogeneity
- Simplify pt positioning
- Pt stands on rotational platform - dist 285 cm
- 6 MeV electron HDR mode
- Trt time reduced < 10 min
- Skin dose homogenous - within +10% to -20%

Kim TH et al: Br J Radiol 1984; 57:501-6


TRANSMISSION
ION CHAMBER
SCATTERING FOIL
REMOVED
COLLIMATOR
SCATTERING
FILTER
ISOCENTER
FARMER
CHAMBERS
MOTORIZED
ROTATING
PLATFORM

AIIMS PROTOCOL

- **Modified Stanford tech**
- **Machine used Cl 20/2300CD,SL 20/Precise**

- **6 trt positions – Ant, Post , RAO, LAO,RPO, LPO**
- **All 6 fields trted every day; 120cGy/day**
- **5 days/week**
- **Trt dist - 10 feet from isocenter**

AIIMS PROTOCOL cont.

- 4 MeV/6MeV electron (with beam spoiler)
- LDR (500 cGy/min) in the initial years
- Now HDR mode (2500-3000 cGy/min)
- Dose - 36 Gy/30 #
- Boost to scalp, perineum, sole & residual tum
- Nails, eyes shielded

Rationale of treating with 6 fields

- Better dose uniformity
- Entire body surface get better exposure
- Self shielding regions are better irradiated

Radiation accompaniments

- Acute
  - generalized erythema, itching
  - edema
  - moist desquamation
  - Alopecia
- Late
  - hyperpigmentation
  - telangiectasia
  - dry skin
  - Necrosis of nails

ACUTE RADIATION ACCOMPANIMENTS

LATE SEQUEL

RADIATION DERMATITIS

Recurrence and re-irridiation

- Frequent in MF
- Relapse with diffuse cut inv not amenable to other topical modalities may be offered a second course of TSEI
- Criteria for re-irridiation
  - Long gap following first course of TSEI
  - Diffuse cut invol
  - Failure of other adj modalities

Review of literature

- **Karzmark et al (Radiology: 1960; 74:633-44)**

  Suggested a technique for large field electron therapy

- **Bjarngard et al (Int J Radiat Oncol Biol Phys 1977; 2:381-2)**

  Increasing the no of fields improves dose homogeneity

A randomized trial comparing combination electron-beam radiation and chemotherapy with topical therapy in the initial treatment of mycosis fungoides

- N=103
- Randomized: 3000 cGy of electron-beam + CT(n = 52) or seq topical trt (n = 51)
- Comb therapy produced considerable toxicity
- Comb therapy pts-- sig higher rate of CR than conserv therapy (38% vs. 18% P = 0.032)
- FU 75 mo-- no sig diff between the trt groups in DFS or OS

Kaye FJ et al. N Engl J Med. 1989; 321:1784-90

Ultimate results of radiation therapy for T1-T2 mycosis fungoides (including reirradiation)

- 1975 - 2001; n=14
- 3 mo after TSET OR - 94.7%
- CR - 87.5% of T1 and 84.8% of T2
- 31(54.4%) had a skin failure (8 with T1 and 23 with T2) within 1 year
- 18/ 31 received a reirradiation
- For the whole group, 5-year DFS was 50%
- 5/10/15-year OS were 90%/65%/42%
- TSET is highly effective in early-stage MF without adjuvant therapy
- Second TSET is feasible, time-saving, and cost-effective

Ysebaert et al. Int J Radiat Oncol Biol Phys. 2004; 58:1128-34

Total skin electron beam therapy with or without adjuvant topical nitrogen mustard or nitrogen mustard alone as initial treatment of T2 and T3 mycosis fungoides

- T2 and T3
- TSET +/- topical HN2 Vs HN2 alone
- N=148, Stanford, 1970-1995
- TSET +/- HN2 : higher CR rates than HN2 alone for T2 and T3
- 76% vs 39%, p = 0.03 for T2
- 44% vs 8%, p < 0.05 for T3

Chinn et al. Int J Radiat Oncol Biol Phys. 1999; 43:951-8

Local superficial radiotherapy in MF

- Local superficial RT studied in early stage IA MF
- Failure is unusual
- Pt should receive a min surface dose of 20 Gy
- Sequela -- minimal

Wilson et al. Int J Radiat Oncol Biol Phys 1998; 40:109-15

Our publications

- **Rath et al. Electron Irradiation for Mycosis Fungoides – Report of two cases and review of literature. Ind J Cancer. Total Skin 1986; 23:146-150**

- **Rath et al. Total Skin Electron Irradiation with Clinac-20, Clinical experience in treating Mycosis Fungoides. AMPI Bull 1986; 11:91-92**

Pharmacology and therapeutics

Cutaneous T-cell lymphoma treated with electron beam irradiation in Indian patients

Dillip K. Parida, MD, Kaushal K. Verma, MD, Subhash Chander, MD, R. C. Joshi, MSC, Dip RP and Goura K. Rath, MD

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Abstract

Background Cutaneous T-cell lymphoma (CTCL) is a rare occurrence in India. Total skin electron irradiation (TSEI) is a well-accepted therapeutic modality for the treatment of CTCL throughout the world. The aim of this study was to retrospectively analyze the treatment outcome of TSEI in Indian patients with CTCL and to determine the different parameters affecting the disease-free survival in these patients.

Methods Fourteen male patients between 27 and 82 years of age with CTCL (duration of disease, 4 months to 2 years) were treated with TSEI between 1985 and 1998. Seven patients had early stage disease, while the other seven had advanced disease. Two patients had lymph node involvement at the time of presentation. The TSEI was performed according to the Stanford technique delivering a total dose in the range 8–36 Gy.

Results Of the 14 patients, 10 showed complete remission following TSEI. The total follow-up period was 4–110 months (median, 52 months). Five patients were disease free at the end of 5 years. Two patients died due to rapid progression of the disease, while the cutaneous lesions relapsed in three patients after 2–27 months and one patient developed visceral metastasis.

Conclusions TSEI was an effective therapeutic modality for the treatment of CTCL in this group of patients, both as a curative and palliative measure, although the long-term prognosis is poor.

International Journal of Dermatology 2001, **40**, 295–297

Results

Total no. of patients	14
Complete remission	10
NED at 5 years	5
Relapsed skin lesions	3
Liver metastasis	1
Mortality	2

Follow-up period 4-110 months (mean 52 months)

Total skin electron irradiation therapy in mycosis fungoides using high-dose rate mode: a preliminary experience.

Parida DK, Verma KK, Chander S, Joshi RC, Rath GK

Department of Radiation Oncology and Dermatology*, All India Institute of Medical Sciences, New Delhi -110029, India

Int J Dermatol. 2005; 44:828-30.

Results

- **Total no. of patients** **7**
- **MFU** 9 Mo
- **Complete remission** **6**
- **NED at 2 years** **4**
- **Relapsed skin lesions** **2**
- **Mortality** **1**

Total skin electron irradiation treatment for mycosis fungoides with a new alternate daily treatment schedule to minimize radiation-associated toxicity: a preliminary experience.

Parida DK, Verma KK, Rath GK

Department of Radiation Oncology and Dermatology*, All India Institute of Medical Sciences, New Delhi -110029, India

Clin Exp Dermatol. 2009; 34:e37-9.

Results

- N : 4
- T2 : 1
- T3 : 3
- RT Dose : 5 days/week X 2 wks followed by treatment on alternate days to deliver a total dose of 36 Gy.

- Follow up Period : 60-84 months
- All without any evidence of disease at FU
- Minimal toxicity, less OTT, good clinical remission and prolonged DFS

Thank you