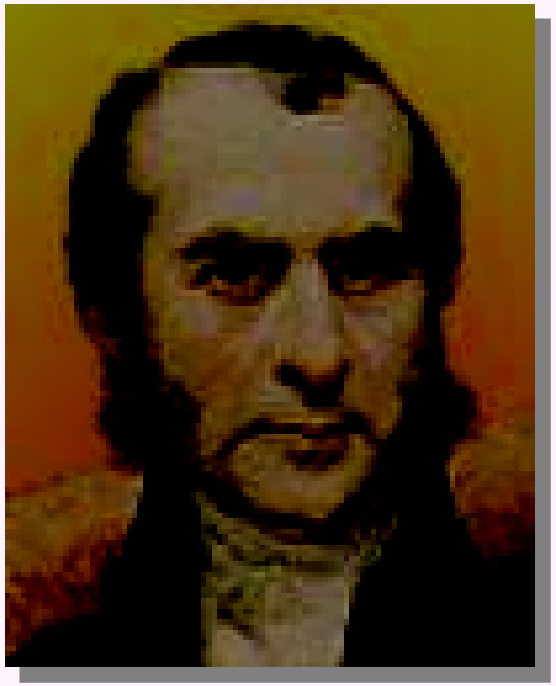
Recent Advances in Radiation Therapy in Hodgkin's Lymphoma

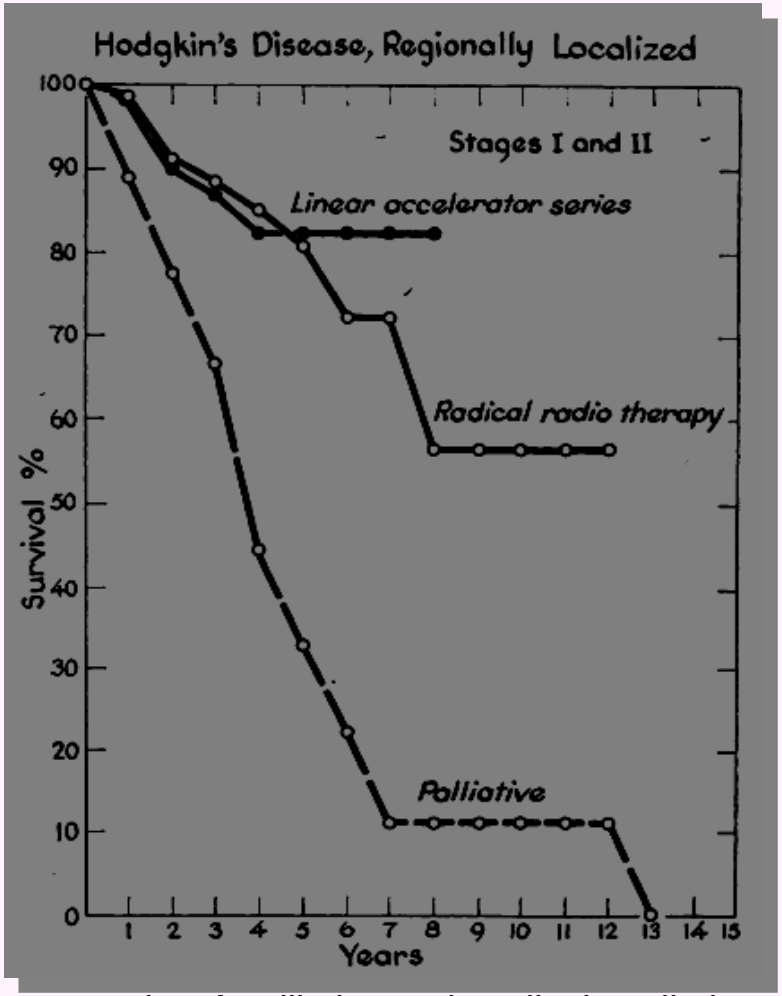
Introduction

- Hodgkin's Lymphoma described in 1832 by Dr Thomas Hodgkin
- Believed to be of B cell origin
- Reed Sternberg cell is the neoplastic cell
- Derived from the germinal cell of lymph nodes

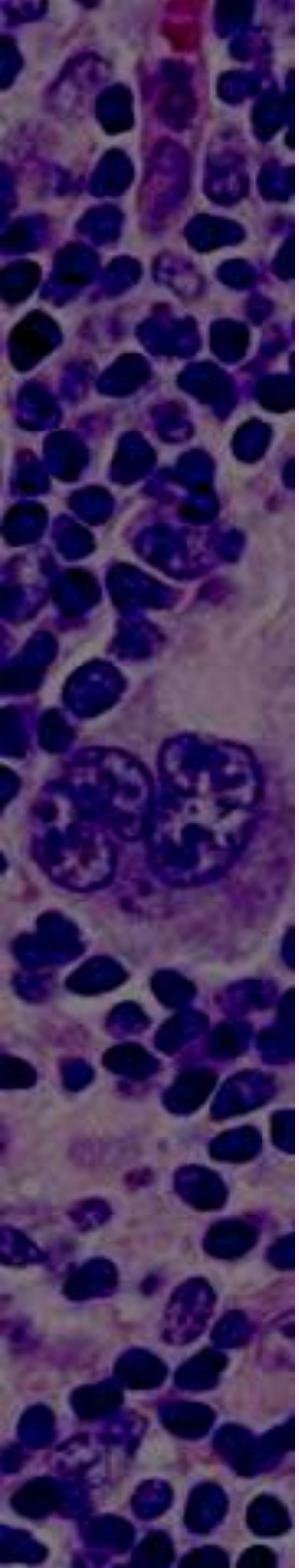


Historical Perspective

- The evolution of megavoltage radiation therapy closely linked to the treatment of Hodgkin's Lymphoma
- Magna field radiation resulted in unprecedented outcomes as reported by Kaplan et al

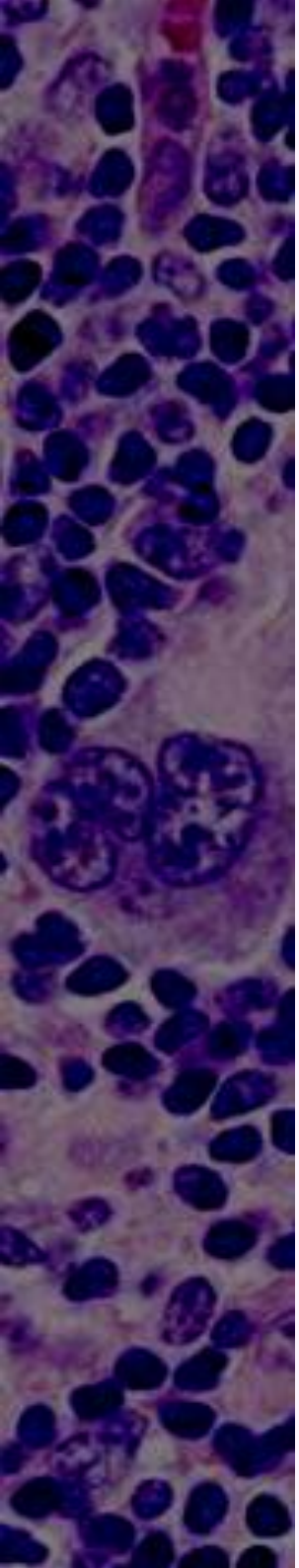


Long-Term Results of Palliative and Radical Radiotherap
Hodgkin's Disease Henry S. Kaplan Cancer Res 1966;26:125



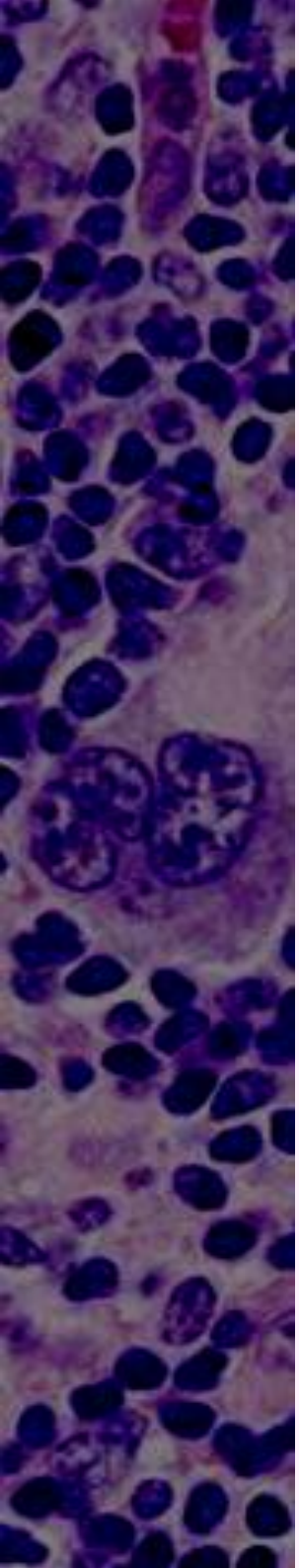
Historical Perspective..

- The introduction of Nitrogen mustard saw the introduction of one of the first RCTs in oncology
- The MOPP regimen proved its worth as the first combination chemotherapy agent
- ABVD found to the similar in efficacy as MOPP



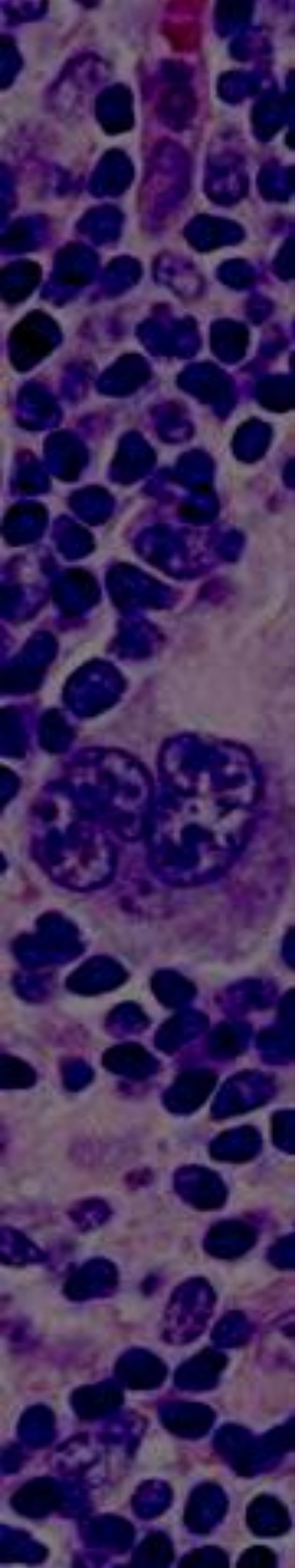
BBCI Experience

- Between 2010 -2011 16 patients registered (0.30% of total)
- Male : Female ratio : 11:5 (2.2)
- 40 patients identified registered between 2009-2011
  - Files retrieved :26
  - Hodgkin's disease: 22
  - Took treatment: 18



BBCI Experience

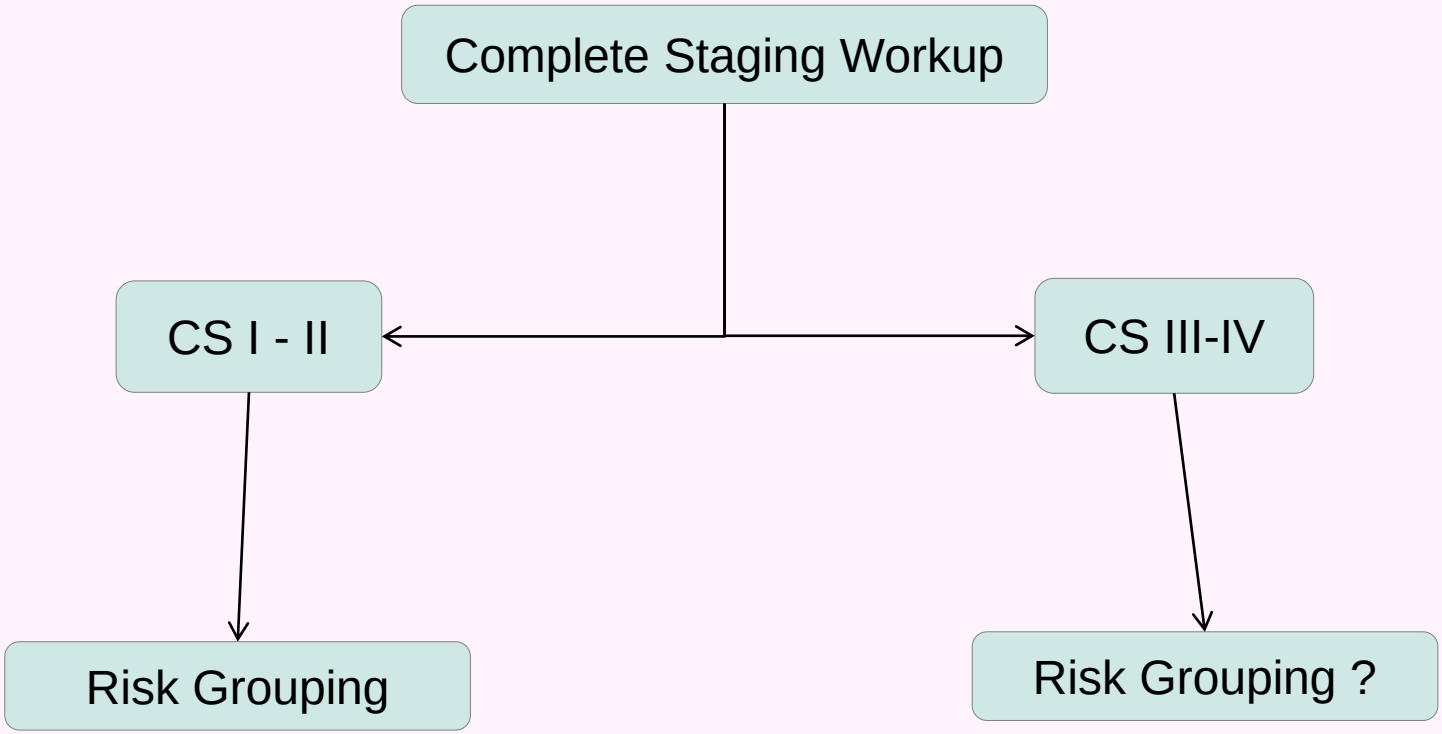
- Median age: 20 Years (7 – 77 years)
- 13 patients received RT (IFRT)
- All patients had received ABVD (2-6 cycles)
- IFRT dose ranged from 20 -46 Gy
- Cervical and mediastinal RT most commonly given
- Outcome data: Immature and incomplete but patients post CCT+RT (7) who came for followup are having CR

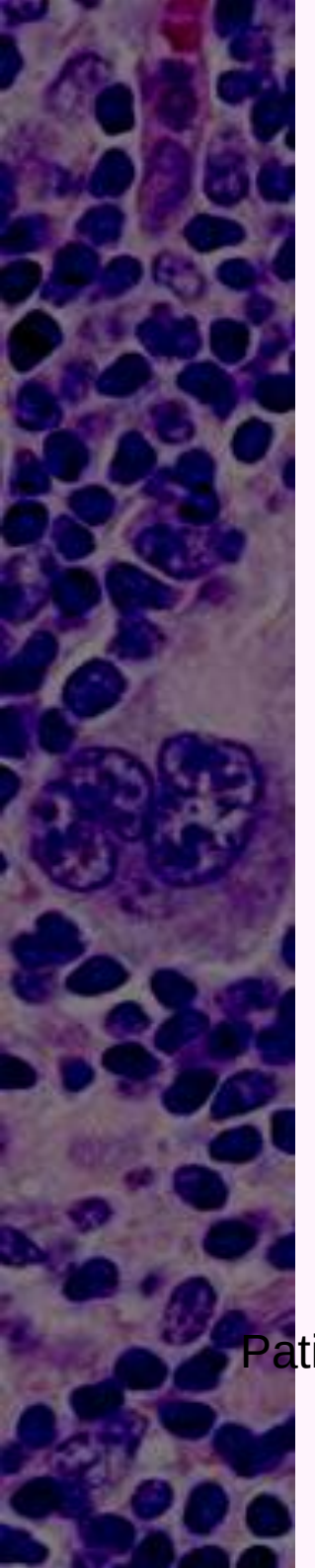


New Developments in RT

- When to give?
- How much to give?
- How to give?

Selection of Treatment

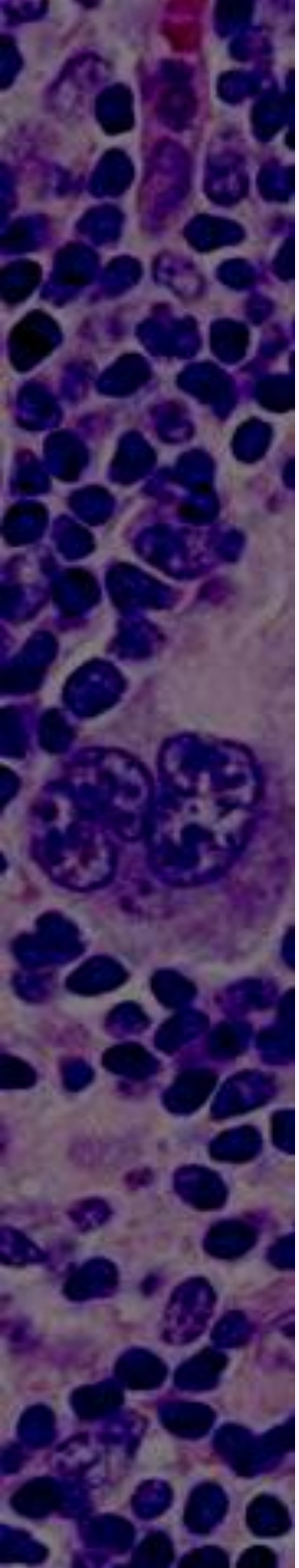




Risk Grouping Stage I-II

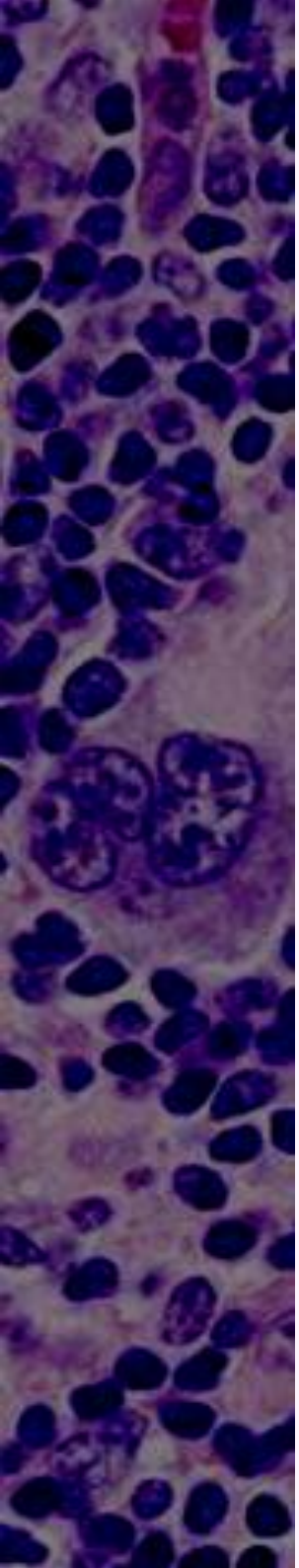
Criteria	NCIC-C	German HD	EORTC
Age	> 40 Years	> 50 Years	--
Bulky Mediastinal Disease	--	Absent	Absent
ESR without B symptoms	< 50 mm/hr	< 50 mm/hr without B symptom	< 50 mm/hr without B symptom
ESR with B symptoms	-	< 30 mm/hr with B symptoms	< 30 mm/hr with B symptoms
Sites of Involvement	< 3	< 3	< 4
Histology	LP/NS	--	--

Patients considered low risk (NCIC-C) or good prognosis if they have all the above factor



Stage I-II - CMT

- CMT is used in early stage disease following results from 5 major trials
- All showed equivalent or better results using CMT
- The long term increased risk of SMN finally swung the pendulum towards CMT



Stage I – II CMT

Trial	Study Arm	FU	OS
SWOG/ CALGB	STNI (36 -40 Gy)	3yr	96%
	AVx3 + STNI (36-40 years)		98%
GHSG HD-7	EFRT (30-40 Gy)	5yr	92%
	ABVD + EFRT (30-40 Gy)		94%
Milan	ABVD x 4 + STNI (30 -40 Gy)	12yr	96%
	ABVD x 4 + IFRT (36 -40 Gy)		94%
EORTC H7F	STNI (36-40 Gy)	10yr	92%
	EBVP x 6 + IFRT (36 -40 Gy)		92%
EORTC/GELA H8F	STNI (36 -40 Gy)	10yr	92%
	MOPP/ABV x 3 + IFRT (36-40 Gy)		97%

Stage I-II Good Prognosis

- Seminal trial : German HD10 trial
- 1370 patients – randomized into 4 groups
  - ABVD x4 > **IFRT 30 Gy**
  - ABVD x2 > **IFRT 30 Gy**
  - ABVD x4 > **IFRT 20 Gy**
  - ABVD x2 > **IFRT 20 Gy**
- Non-inferiority trial design :Difference in Freedom from treatment failure rate < 7% in pooled groups

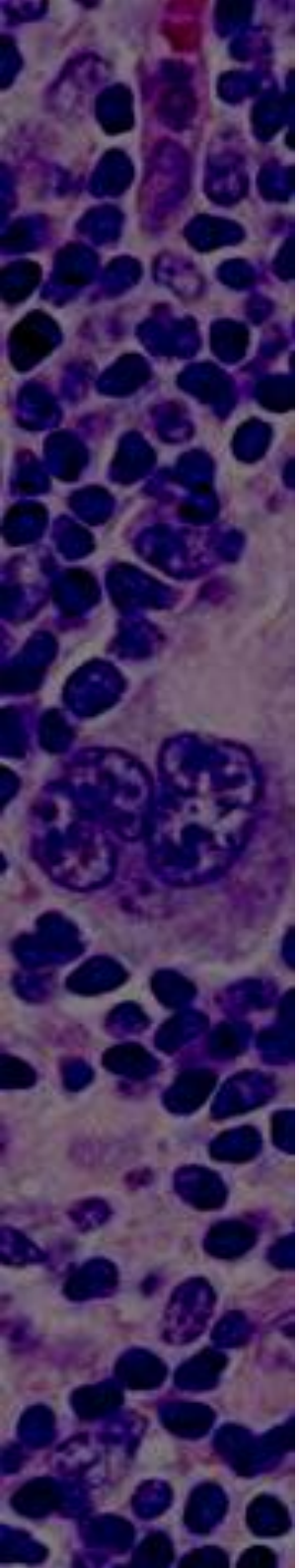
Reduced Treatment Intensity in Patients with Early-Stage Hodgkin's Lymphoma Engert et al N Engl J Med 363;7 Augu

Stage I-II Good Prognosis

Outcome	Treatment Group			
	Group 1: 4×ABVD + 30 Gy IFRT (N = 298)	Group 2: 4×ABVD + 20 Gy IFRT (N = 298)	Group 3: 2×ABVD + 30 Gy IFRT (N = 295)	Group 4: 2×ABVD + 20 Gy IFRT (N = 299)
Survival rate — % (95% CI)‡				
At 5 years				
Overall survival	96.9 (94.2–98.4)	97.3 (94.6–98.6)	96.6 (93.7–98.1)	96.6 (93.7–98.1)
Freedom from treatment failure	92.8 (89.1–95.3)	93.1 (89.4–95.5)	90.9 (86.8–93.8)	91.2 (87.1–94.1)
Progression-free survival	93.9 (90.3–96.2)	93.2 (89.5–95.6)	90.8 (86.7–93.7)	91.6 (87.6–94.4)
At 8 years				
Overall survival	94.4 (90.2–96.8)	94.7 (90.9–97.0)	93.6 (89.6–96.1)	95.1 (91.7–97.2)
Freedom from treatment failure	87.2 (81.3–91.4)	89.9 (85.2–93.1)	85.5 (79.5–89.8)	85.9 (80.2–90.1)
Progression-free survival	88.4 (82.6–92.4)	90.0 (85.4–93.2)	85.4 (79.4–89.8)	86.5 (80.9–90.6)

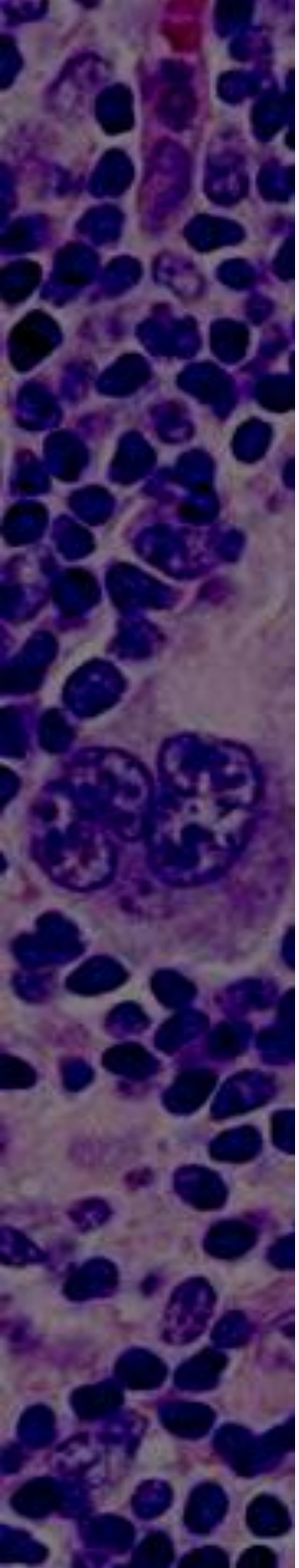
Stage I-II Good Prognosis

Outcome	Chemotherapy Comparison		Radiation Therapy Comparison	
	Groups 1 and 2 (N=596)	Groups 3 and 4 (N=594)	Groups 1 and 3 (N=575)	Groups 2 and 4 (N=588)
Survival rate — % (95% CI)‡				
At 5 years				
Overall survival	97.1 (95.4–98.2)	96.6 (94.7–97.8)	97.7 (96.1–98.7)	97.5 (95.9–98.5)
Freedom from treatment failure	93.0 (90.5–94.8)	91.1 (88.3–93.2)	93.4 (91.0–95.2)	92.9 (90.4–94.8)
Progression-free survival	93.5 (91.1–95.3)	91.2 (88.5–93.4)	93.7 (91.3–95.5)	93.2 (90.6–95.0)
At 8 years				
Overall survival	94.6 (92.0–96.4)	94.4 (91.9–96.1)	94.9 (92.2–96.6)	95.6 (93.2–97.1)
Freedom from treatment failure	88.4 (84.8–91.3)	85.7 (81.8–88.9)	87.8 (83.8–90.9)	88.6 (85.1–91.3)
Progression-free survival	89.1 (85.5–91.8)	86.0 (82.1–89.1)	88.1 (84.1–91.2)	88.9 (85.4–91.6)



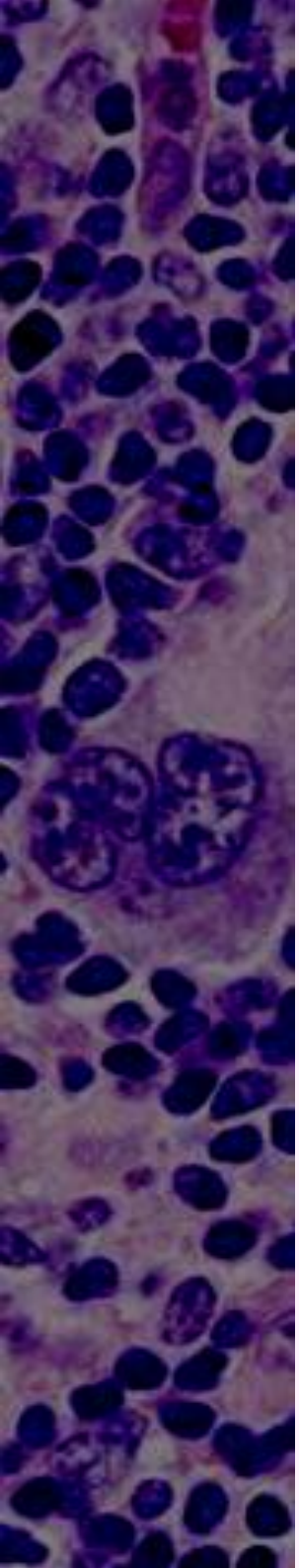
Stage I-II Good Prognosis

- Present standard of care for early stage I-II good prognosis / low risk disease is :
  - ABVD x 2 cycles
  - IFRT 20 Gy
- Reduces acute toxicity by almost 50%
- Presently results till 10 years.



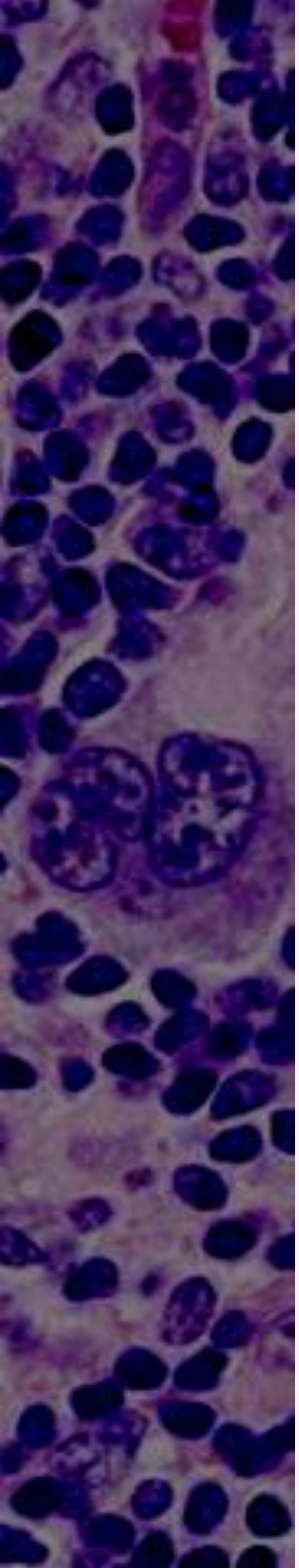
Stage I-II Good Prognosis

- Can we omit RT and replace by CCT alone?
- Unfortunately no ABVD containing trials !! (Two trials of older era employed STNI not IFRT)
- EORTC/GELAH9F :
  - EBVP x 6 + IFRT 36 Gy
  - EBVP x 6 + IFRT 20 Gy
  - EBVP x 6
- Patients randomized after **CR** to EBVP x 6



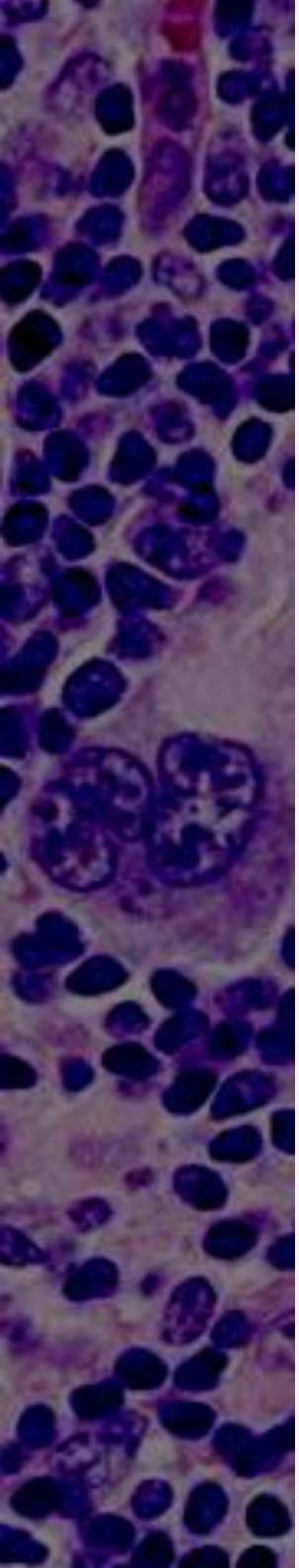
Stage I-II : Good Prognosis

- Despite CR to EBVP the 5 year RFS in no RT arm was 70% vs 86 - 89% in the RT arms
- Arm discontinued as met stopping rules (1 -β was kept at 77%).
- All relapsed at involved sites.
- Thus EBVP x 6 followed by even a CR is not a indication for omitting RT.



Stage I-II Poor Prognosis

- This group includes patients with:
  - Bulky disease
  - Age > 50
  - B symptoms
  - > 3 – 4 sites of involvement
  - Extranodal involvement
  - Elevated ESR
- Any <u>one</u> of the factors is enough

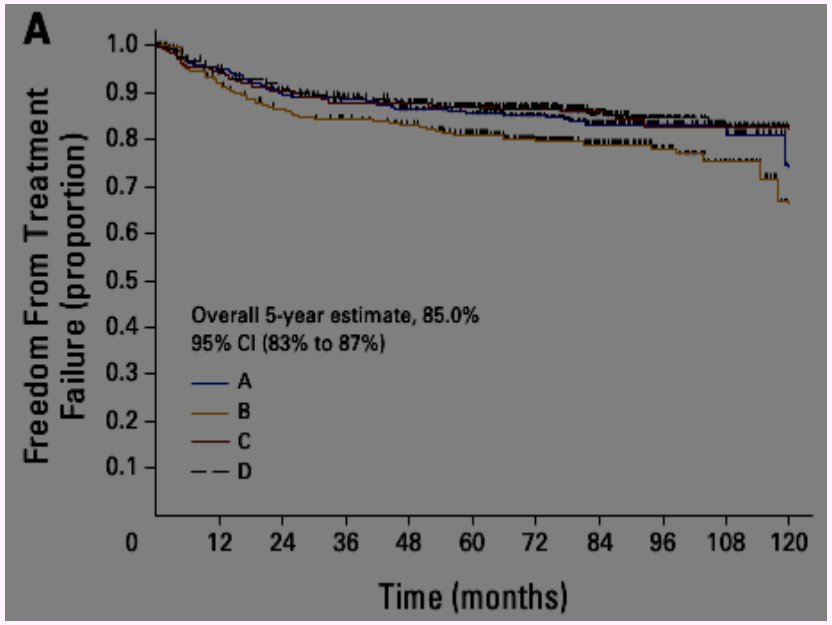


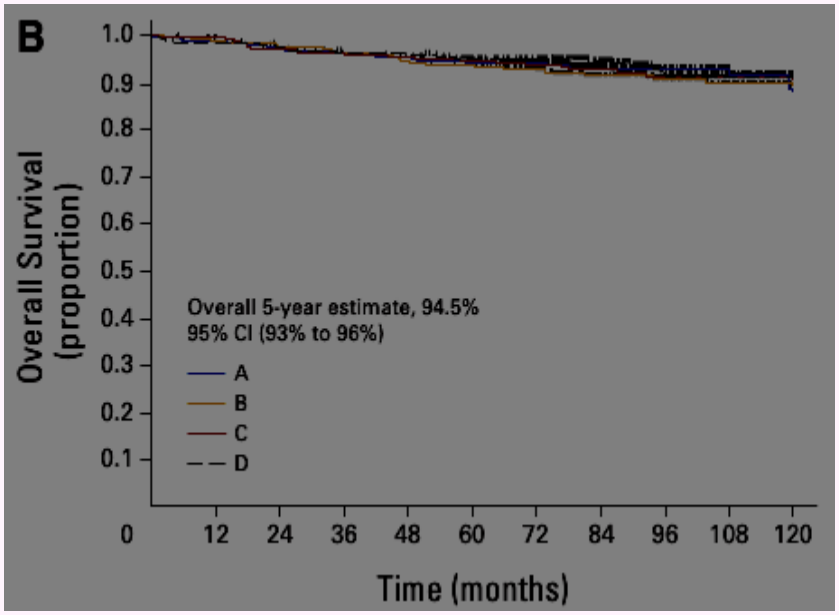
Stage I-II Poor Prognosis

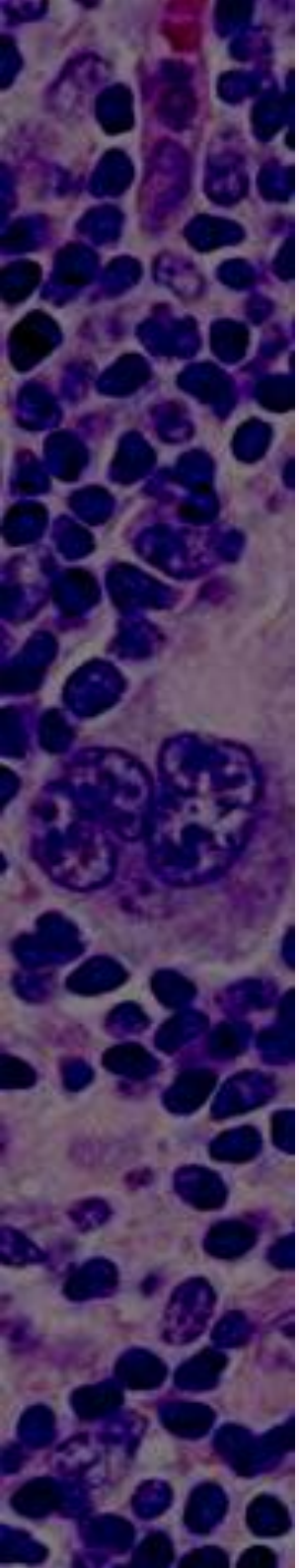
- German HD11 trial
- 2 x 2 factorial design 1395 patients
- Groups:
  - ABVD x 4 + **IFRT (30 Gy)**
  - ABVD x 4 + **IFRT (20 Gy)**
  - BEACOPP x 4 + **IFRT (30 Gy)**
  - BEACOPP x 4 + **IFRT (20 Gy)**

Stage I-II : Poor Prognosis

Arm	5 Year FFTF	5 Year OS
ABVD x 4 + 30 Gy	85.3%	94.3%
BEACOPP x 4 + 30 Gy	87.0%	94.6%
ABVD x 4 + 20 Gy	81.1%	95.1%
BEACOPP x 4 + 20 Gy	86.8%	93.8%

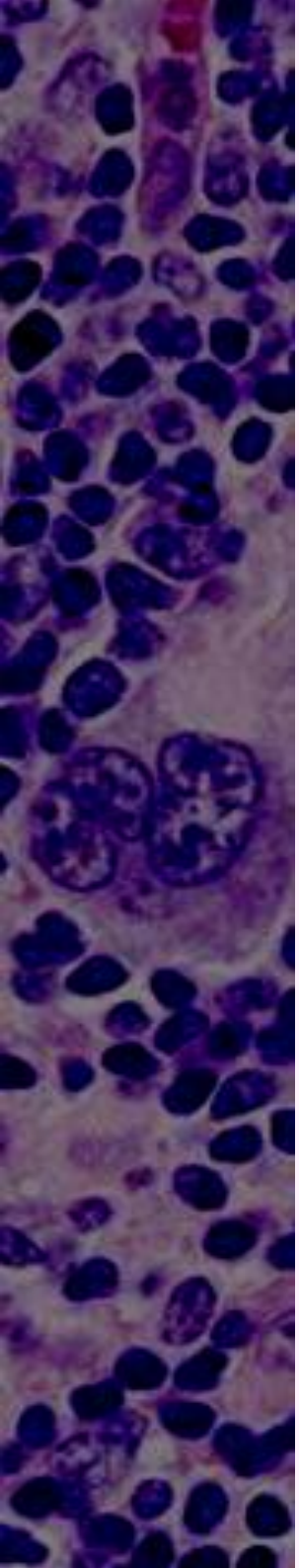






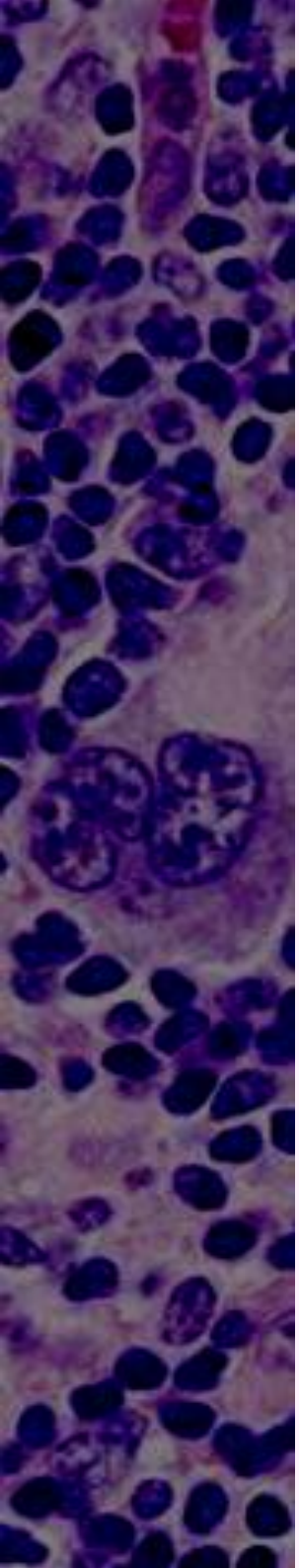
Stage I – II : Poor Prognosis

- Important Conclusions (HD 11):
  - ABVD x 4 followed by IFRT 20 Gy is suboptimal in terms of freedom from treatment failure and PFS
  - ABVD x 4 followed by IFRT 30 Gy is equivalent to BEACOPP arms (with IFRT 20 Gy or 30 Gy)
  - BEACOPP results in acute toxicity in 70% compared with 50% in ABVD
  - 30 Gy IFRT also was more toxic (12% vs 6%) than 20 Gy.



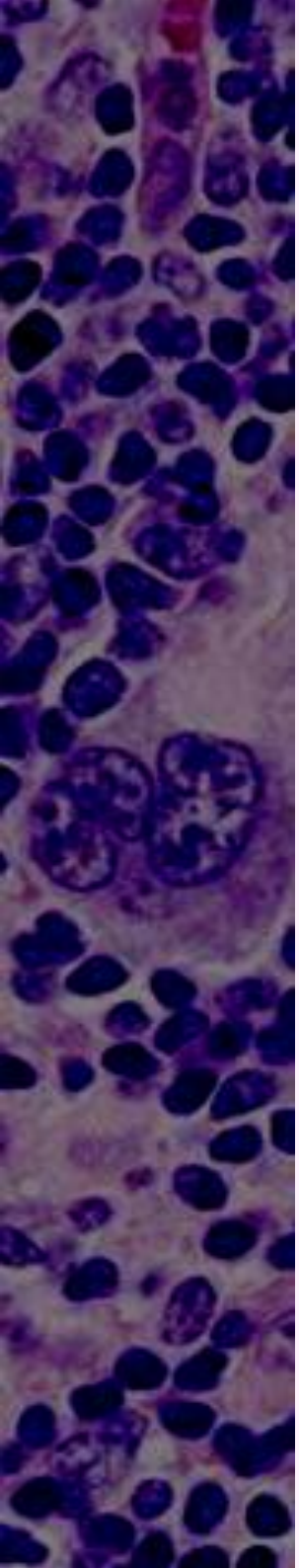
Stage I-II Poor Prognosis

- The EORTC/GELA H9 U trial compared 3 regimens:
  - ABVD x 4 + IFRT 30 Gy
  - ABVD x 6 + IFRT 30 Gy
  - BEACOPP x 4 + IFRT 30 Gy
- The cancer related outcomes were similar in 3 arms
- IFRT 30 Gy after ABVD 4 – 6 cycles is thus considered standard



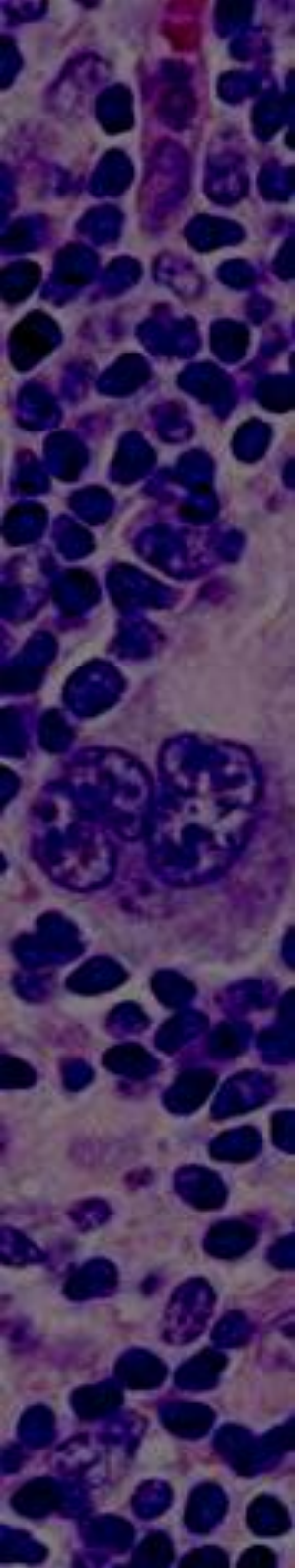
Stage III- IV

- The only positive study that supports the role of RT from TMH
- Included population : Heterogenous mainly bulky MC disease (more representative of Indian scenario?)
- The TMH study did show an improved OS if IFRT was added after 6 cycles of ABVD (89% vs 76%)



Stage III - IV

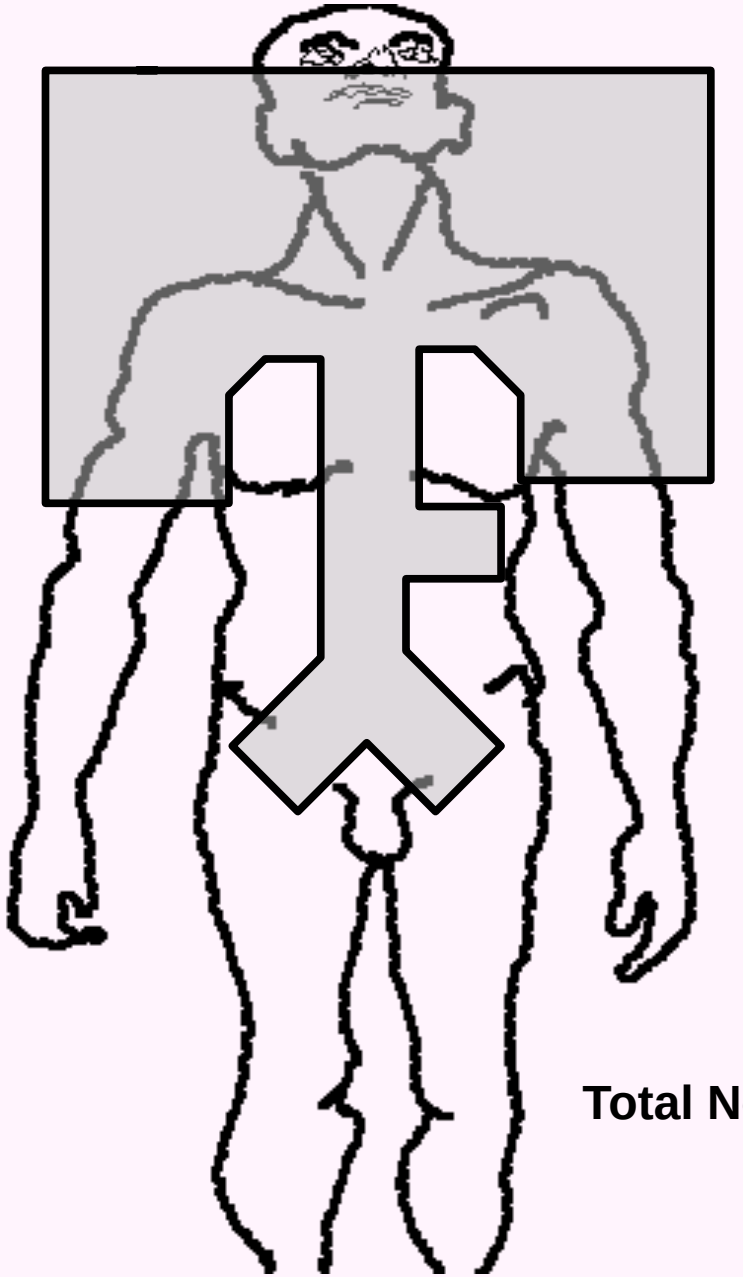
- Results from other studies including interim results from the HD 12 show that addition of RT adds little in terms of benefit
- However HD12 employed escalated BEACOPP not ABVD
- The HD 15 trial therefore employed RT in a selected population :
  - Residual Node > 2.5 cm
  - Positive PETCT
- In this group IFRT to 30 Gy resulted in 1 year



Radiation Volume

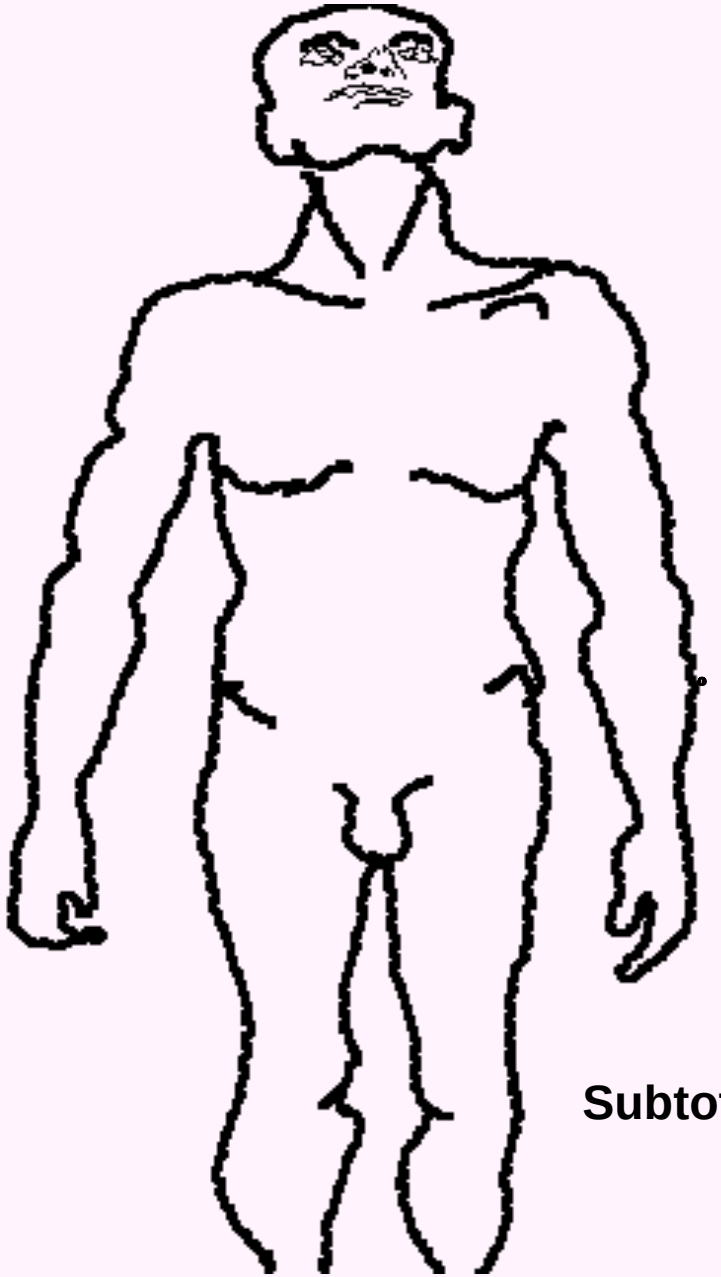
- As the dose has reduced so have the volumes
- Some Definitions:
  - TNI : Total Nodal Radiation
  - STNI : Subtotal Nodal Radiation
  - EFRT : Extended Field Radiation
  - IFRT : Involved Field Radiation
  - INRT : Involved Nodal Radiation

Radiation Volume: TNI



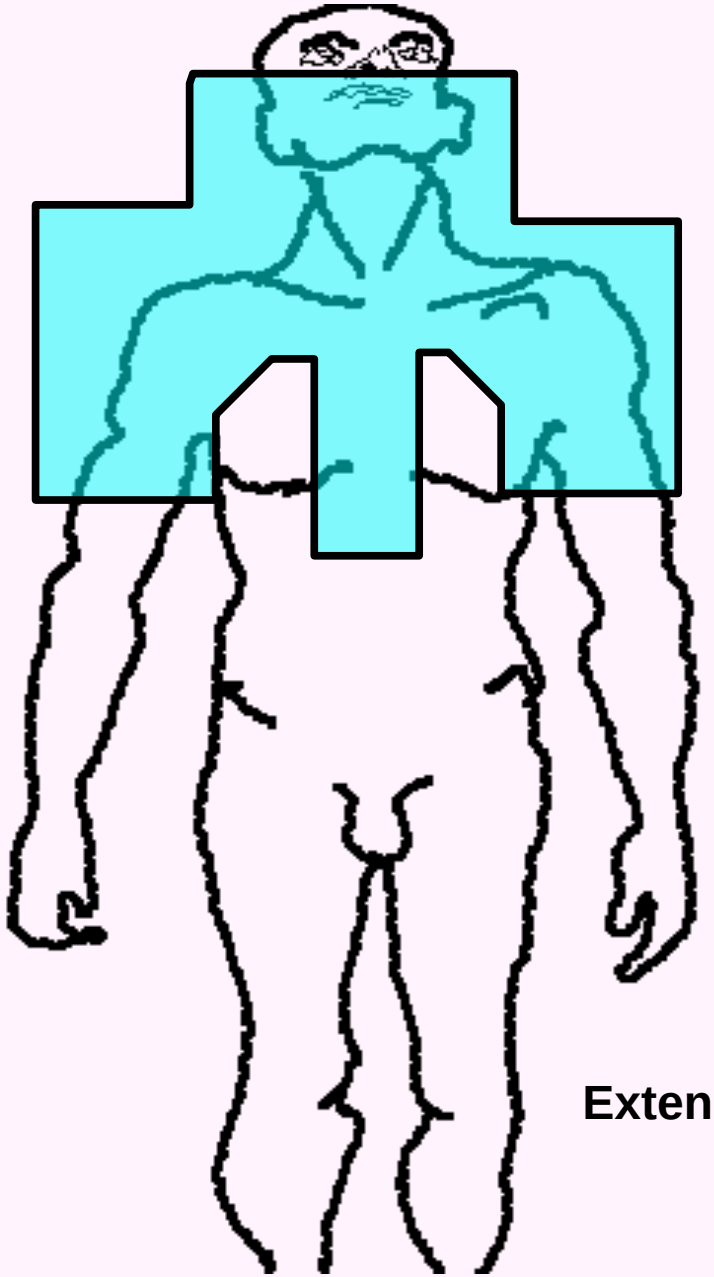
Total Nodal Irradiation

Radiation Volume: STNI



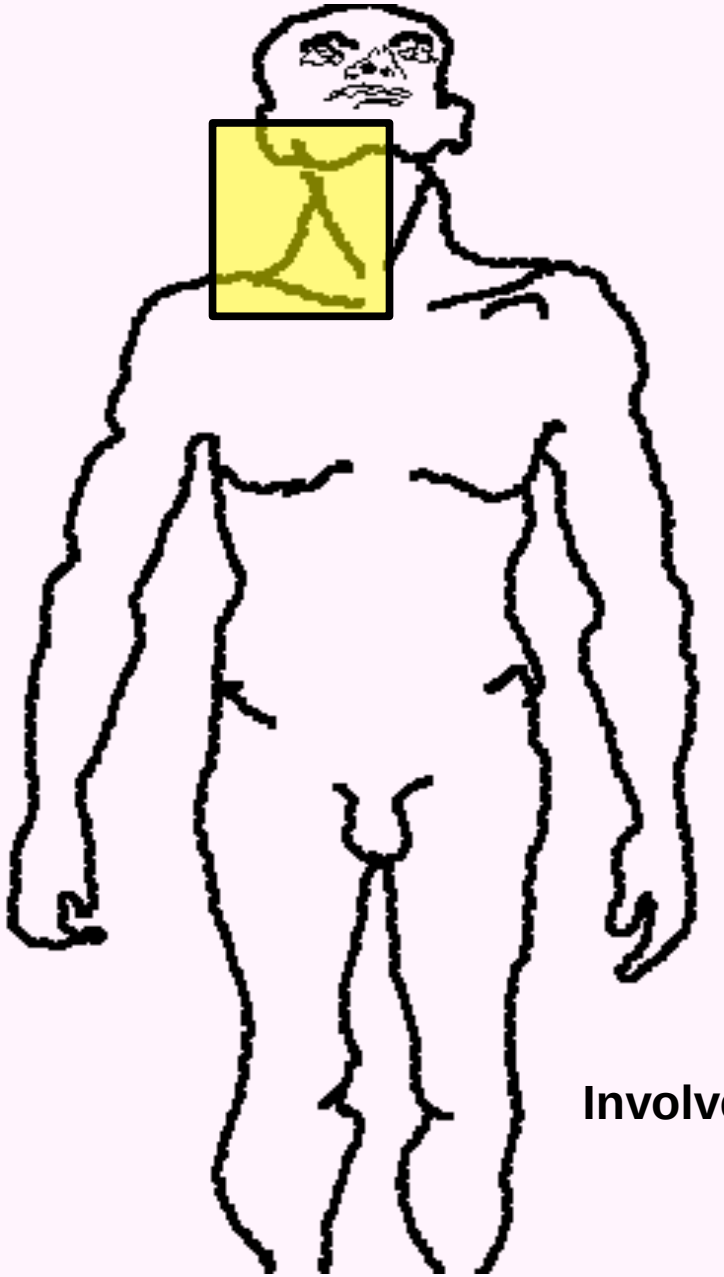
Subtotal Nodal Irradiation

Radiation Volume: EFRT



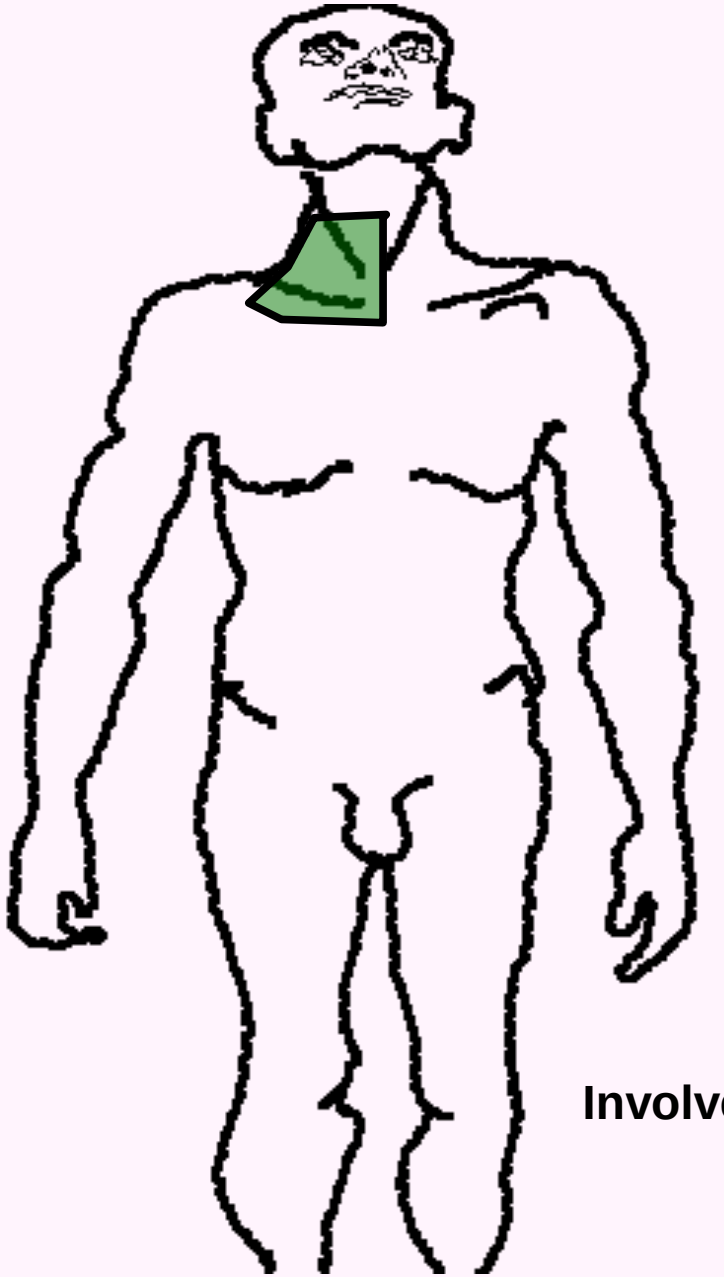
Extended Field Radiation

Radiation Volume: IFRT

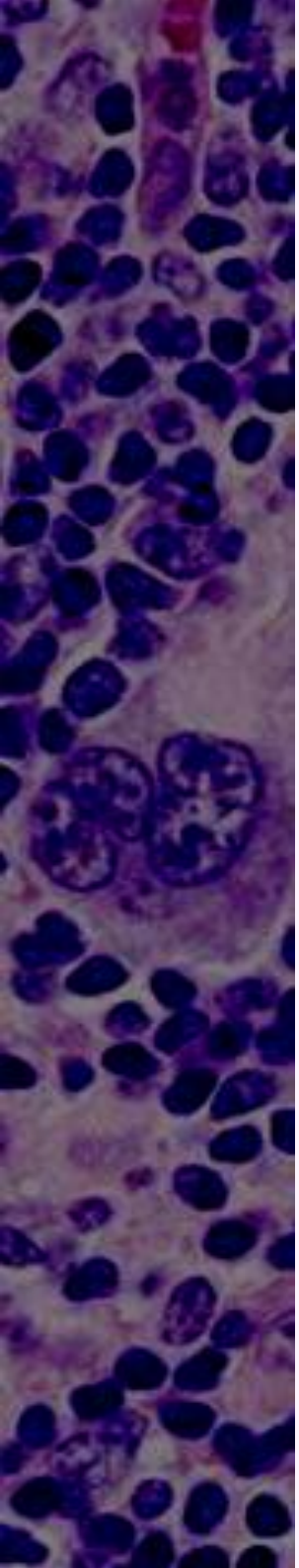


Involved Field Radiation

Radiation Volume: INRT



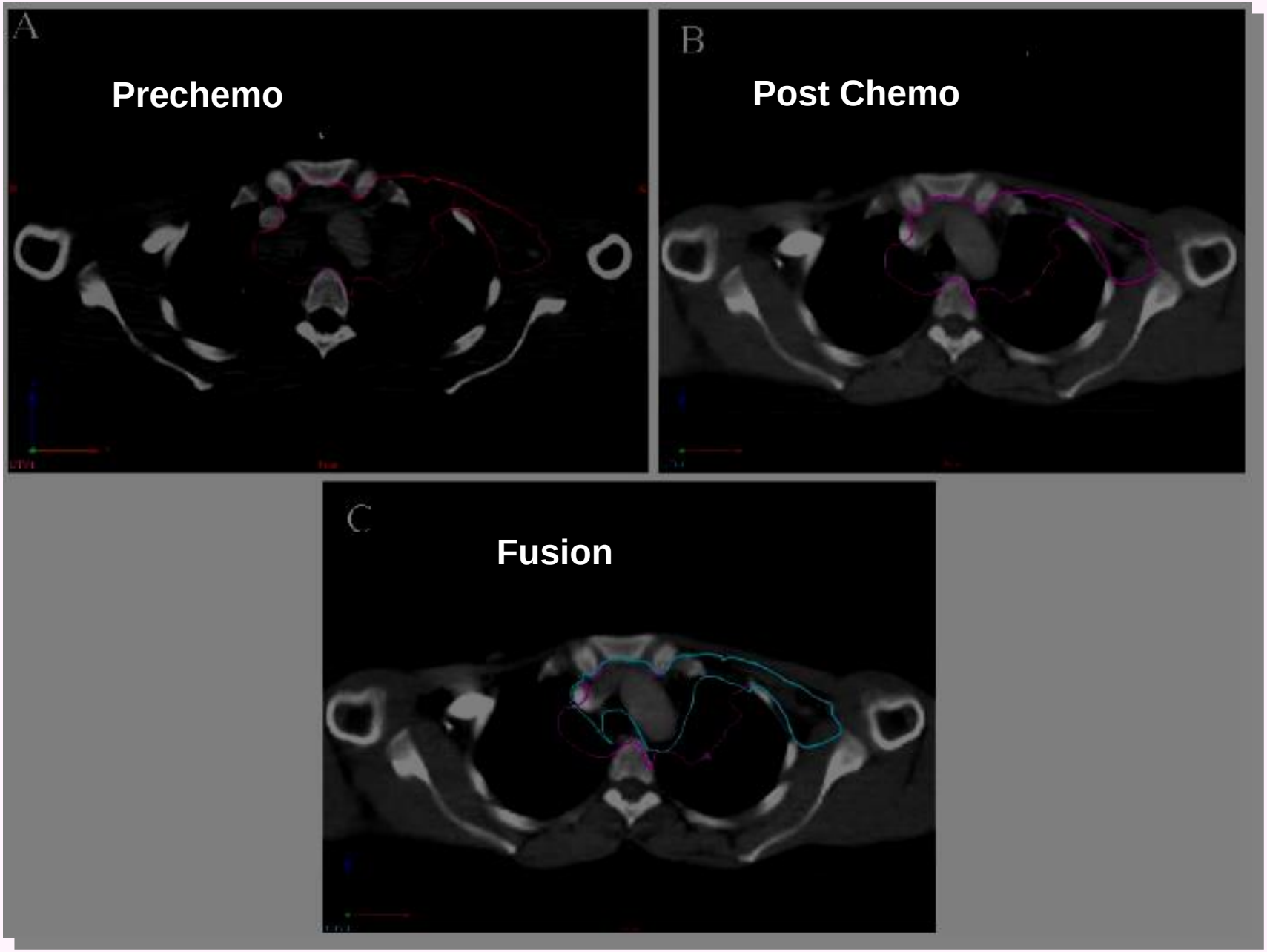
Involved Nodal Radiation

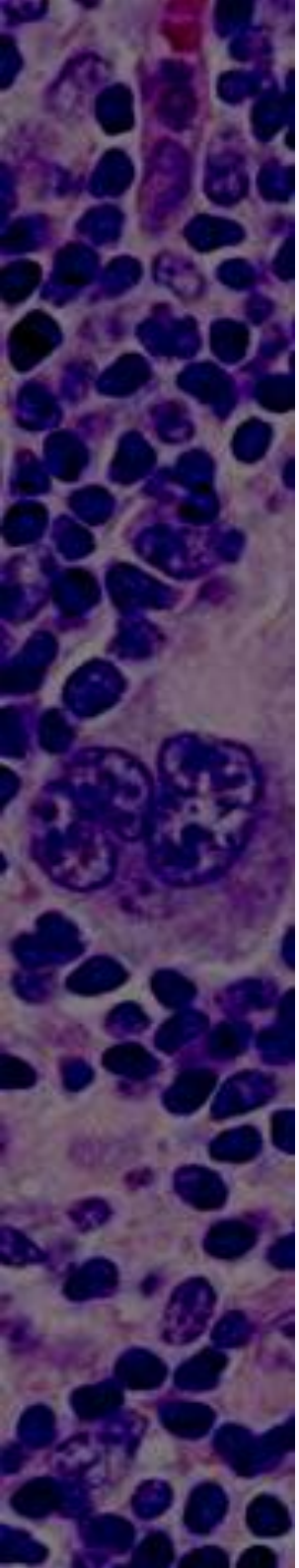


Involved Nodal Radiation

- Presently being evaluated in EORTC-GELA lymphoma trial
- Concept based on the finding that site of relapse is the initial node.
- Requirements for Implementation:
  - Rad Onc must see patient at initial evaluation
  - Full planning CT scan
  - If PET CT done pre-chemotherapy then it should also be done in planning position

Involved Nodal Radiation

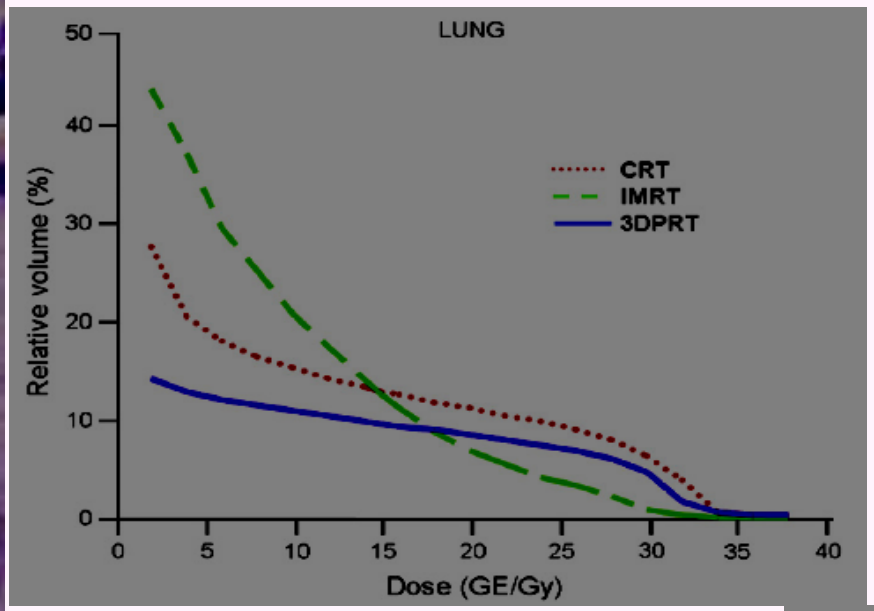


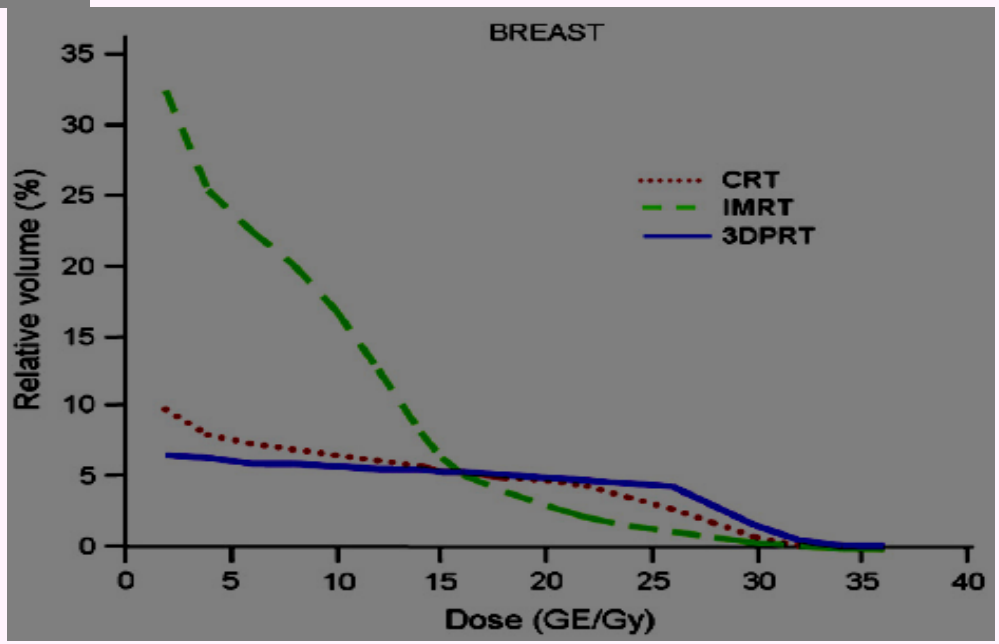


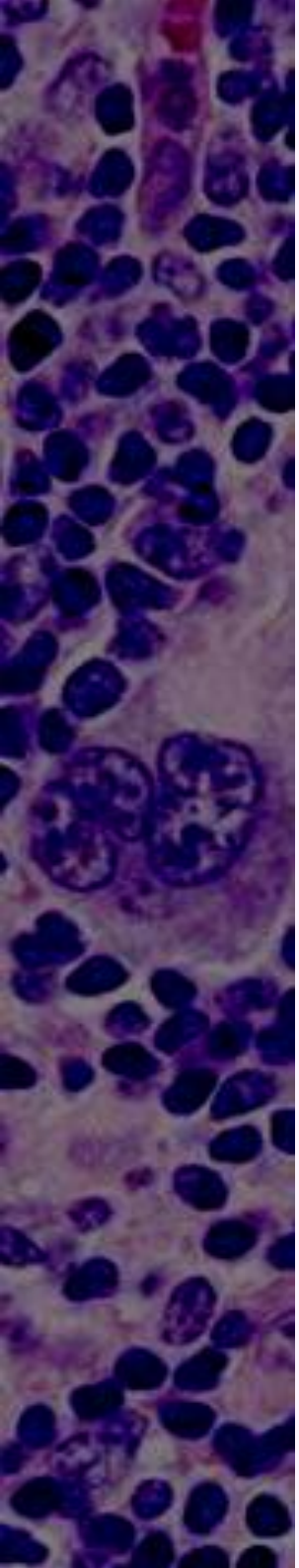
Delivery Improvements

- CT based planning now considered de rigueur in many western institutes
- Treatment planning studies have shown even further reductions in OAR doses using IMRT
- Important consideration in treating mediastinal HD.
- Proton therapy can help in further reductions in dose.

Delivery Improvements







Conclusions

- Radiation still a part of treatment modality in EHD.
- Volumes progressively reducing.
- Doses reduced to 20 Gy for favourable EHD and 30 Gy for unfavourable.
- Role in advanced stage HD likely to be increasingly determined by post chemo PET results.
- Reduction in long term morbidity to be expected but not proven.


DR. B. BOROOAH CANCER INSTITUTE
Regional Institute for Treatment & Research

Questions ?