

# RADIATION THERAPY FOR HODGKIN'S LYMPHOMA CURRENT CONSENSUS



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INDIA

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A microscopic image of tissue, likely a histological section, showing numerous cells with dark, round nuclei and lighter, granular cytoplasm. The cells are densely packed. A teal rectangular box with a black border is overlaid on the upper portion of the image, containing white text.

**THOMAS HODGKIN**

**“1832”**

**“On Some Morbid Appearances of the  
Absorbent Glands & Spleen”**

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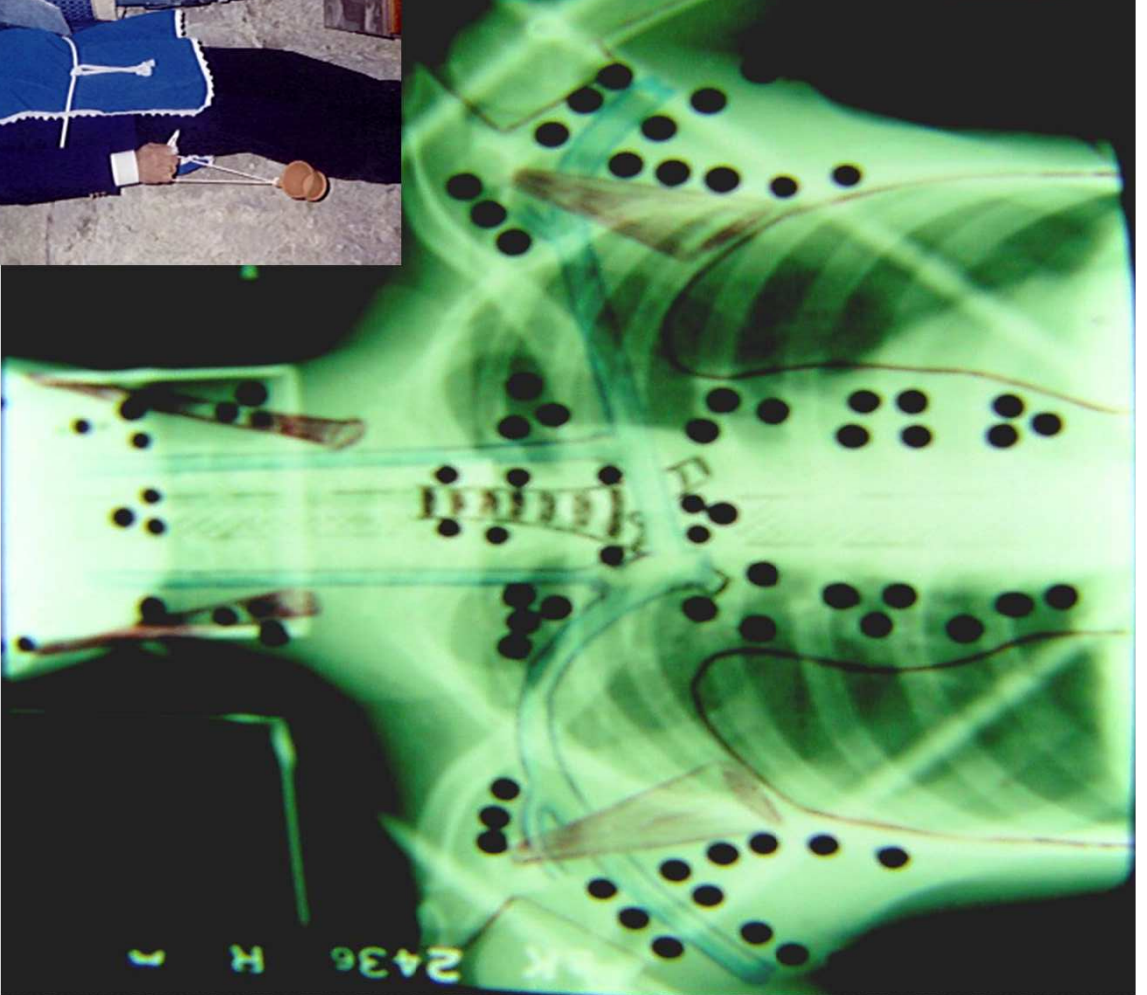
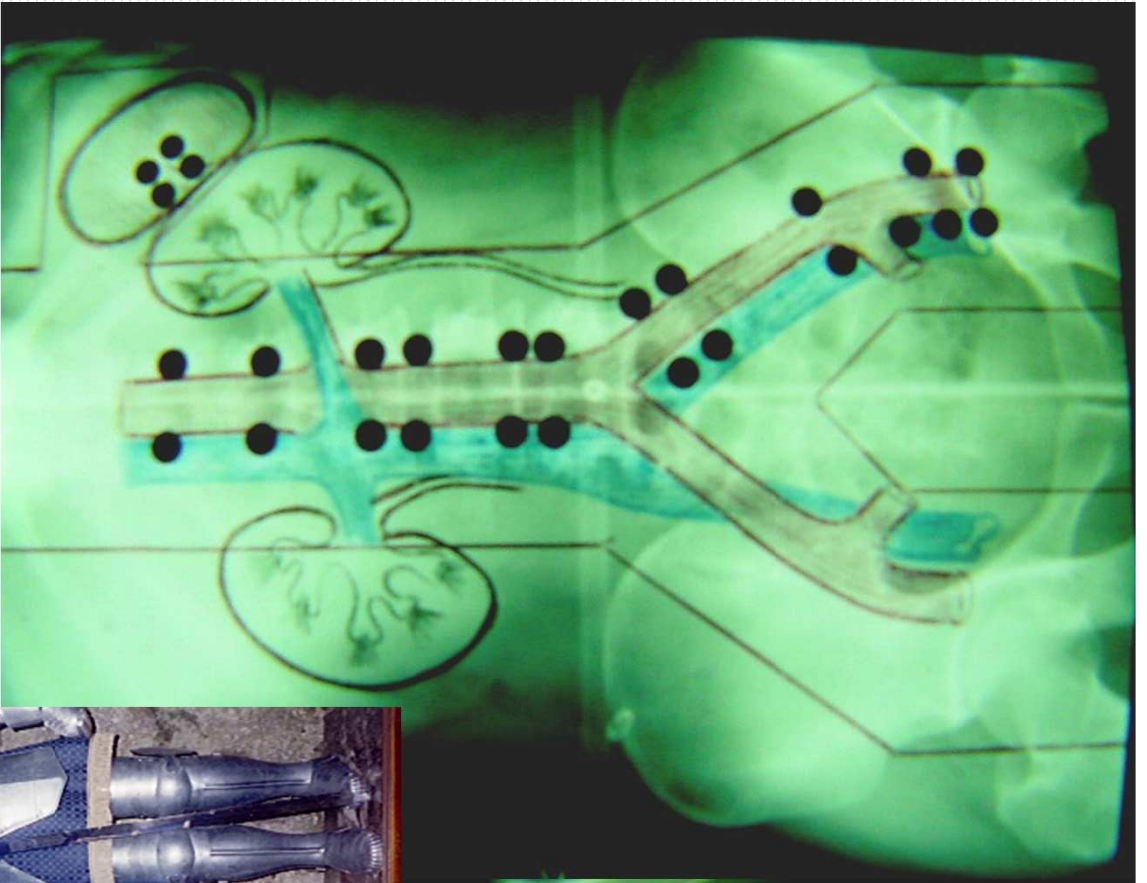
Vera Peters (1950): The first physician to present definitive evidence of curability of Hodgkin's disease.

Reviewed the records 113 patients treated at the Ontario Institute of Radiotherapy from 1924 – 1942 and reported 10 year survival rates of 79% for stage I Hodgkin's disease using high dose fractionated extended field radiation therapy

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*Am J Roentgenol 1950; 63: 299-311.*







## 1960's

Development of the MOPP regimen

Appreciation of adverse effects of “High Dose Radiation”

Investigation of “Combined Modality Therapy”

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## 1970's & 80's

Development of better imaging facilities (CT scan)

Diminished importance of staging laparotomy

GHSG HD 78 – all pts lap staged

GHSG HD 82 – all lap staged, splenectomy only if visible abnormalities at lap

GHSG HD 85 – lap staging only if abnormal USG/ CT scan

GHSG HD 90 – laparotomy abandoned

Risks of Infertility / Leukemogenesis – Alkylating agents

Development of ABVD regimen

Development of MOPP/ ABVD hybrid regimen

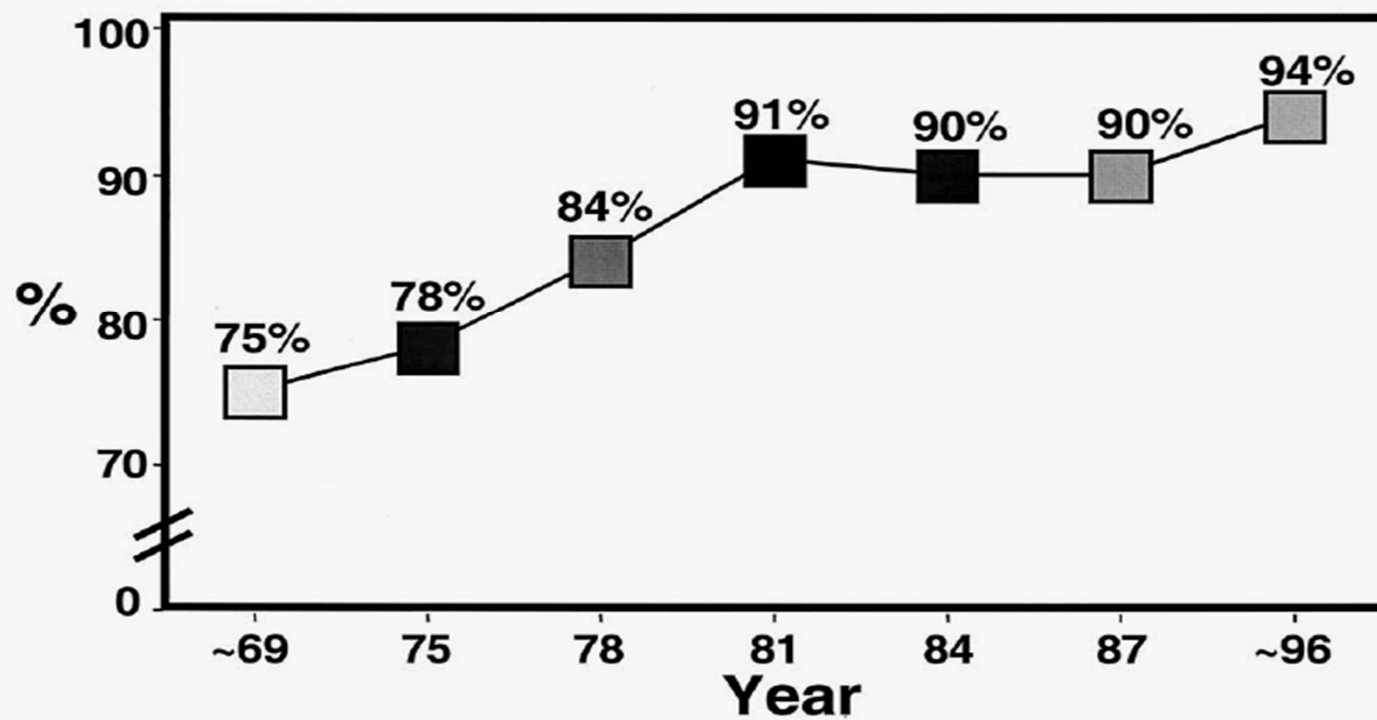
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Reduction in doses of radiotherapy when used with chemo

# IMPROVEMENT IN SURVIVAL

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## COTSWALDS MODIFICATION OF ANN ARBOR STAGING

**Table 1. Cotswolds staging classification**

Stage	Description
Stage I	Involvement of a single lymph-node region or lymphoid structure (eg, spleen, thymus, Waldeyer's ring) or involvement of a single extralymphatic site
Stage II	Involvement of two or more lymph-node regions on the same side of the diaphragm (hilar nodes, when involved on both sides, constitute stage II disease); localised contiguous involvement of only one extranodal organ or site and lymph-node region(s) on the same side of the diaphragm (IIIE). The number of anatomic regions involved should be indicated by a subscript (eg, II <sub>2</sub> )
Stage III	Involvement of lymph-node regions on both sides of the diaphragm (III), which may also be accompanied by involvement of the spleen (III <sub>s</sub> ) or by localised contiguous involvement of only one extranodal organ site (IIIE) or both (IIISE)
III1	With or without involvement of splenic, hilar, celiac, or portal nodes
III2	With involvement of para-aortic, iliac, and mesenteric nodes
Stage IV	Diffuse or disseminated involvement of one or more extranodal organs or tissues, with or without associated lymph-node involvement
<b>Designations applicable to any disease stage</b>	
A	No symptoms
B	Fever (temperature >38°C), drenching night sweats, unexplained loss of more than 10% of body weight within the previous 6 months
X	Bulky disease (a widening of the mediastinum by more than one third of the presence of a nodal mass with a maximal dimension greater than 10 cm)
E	Involvement of a single extranodal site that is contiguous or proximal to the known nodal site

# RISK FACTORS & TREATMENT GROUPS

Early Stage	Risk Factor	Treatment Group
EORTC	Bulky Mediast. Mass Age $\geq$ 50 yrs Elevated ESR B Symptoms $\geq$ 4 nodal regions	Fav: St. I-II without risk factors Unfav: St. I-II with risk factors
GHSG	Bulky Medist. Mass Elevated ESR B Symptoms $\geq$ 3 nodal regions	Fav: St. I-II without risk factors Intermed: St. I-IIA with risk factors Unfav: St. IIB with Elevated ESR
ECOG & NCI-C	Histology (MC, LD) Age $\geq$ 40 yrs Elevated ESR B Symptoms $\geq$ 4 nodal regions	Fav: St. I-II without risk factors Unfav: St. I-II with risk factors
Advanced Stage		
International Prognostic Score	Serum Albumin $\leq$ 4 g/dl Hemoglobin $\leq$ 10.5 g/dl Male Age $\geq$ 45 yrs WBC Count $\geq$ 15 thousand Lymphocyte Count $\leq$ 8% of WBC	



## The 90's

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Recognition of the need to optimize therapy (Chemo & RT)

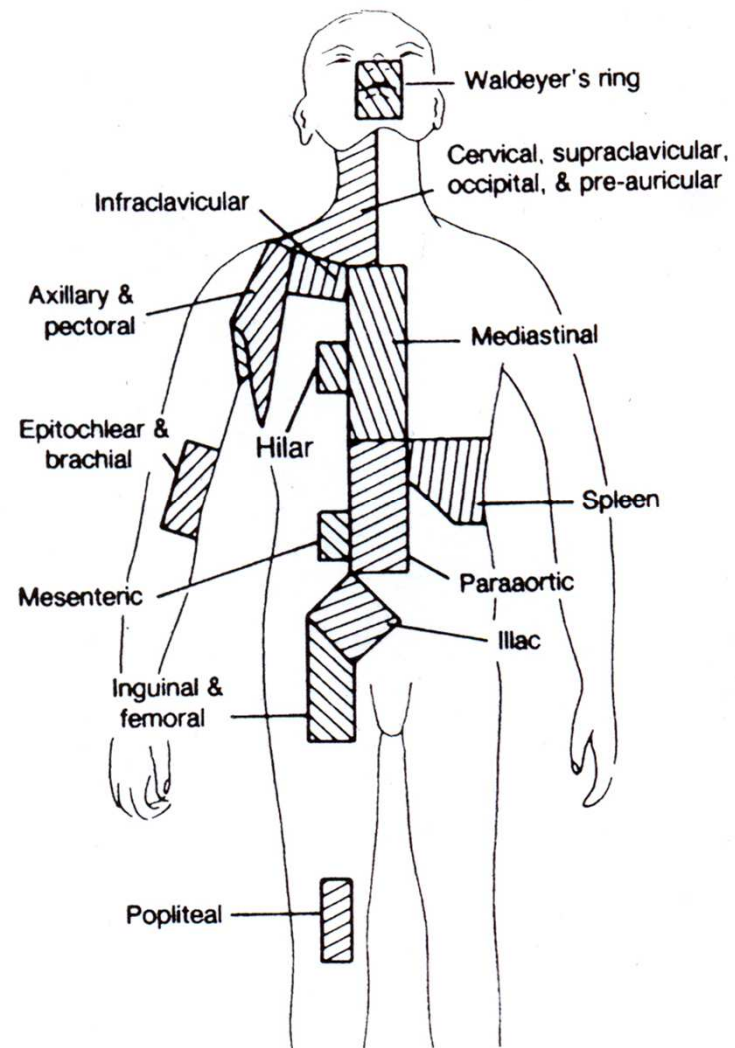
Recognition of prognostic groups

- Early Stage Favourable
- Early Stage Unfavourable
- Advanced Stage Disease

Development of risk adapted therapy

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# LYMPH NODAL REGIONS





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CAN WE AVOID CHEMOTHERAPY FOR EARLY STAGE  
FAVOURABLE DISEASE ?

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# Two Cycles of Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine Plus Extended-Field Radiotherapy Is Superior to Radiotherapy Alone in Early Favorable Hodgkin's Lymphoma: Final Results of the GHSG HD7 Trial

Andreas Engert, Jeremy Franklin, Hans Theodor Eich, Corinne Brillant, Susanne Sehlen, Claudio Cartoni, Richard Herrmann, Michael Pfreundschuh, Markus Sieber, Hans Tesch, Astrid Franke, Peter Koch, Maike de Wit, Ursula Paulus, Dirk Hasenclever, Markus Loeffler, Rolf-Peter Müller, Hans Konrad Müller-Hermelink, Eckhart Dühmke, and Volker Diehl

## A B S T R A C T

### Purpose

To investigate whether combined-modality treatment (CMT) with two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by extended-field radiotherapy (EF-RT) is superior to EF-RT alone in patients with early favorable Hodgkin's lymphoma (HL).

### Patients and Methods

Between 1993 and 1998, 650 patients with newly diagnosed, histology-proven HL in clinical stages IA to IIB without risk factors were enrolled onto this multicenter study and randomly assigned to receive 30 Gy EF-RT plus 10 Gy to the involved field (arm A) or two cycles of ABVD followed by the same radiotherapy (arm B).

### Results

At a median observation time of 87 months, there was no difference between treatment arms in terms of complete response rate (arm A, 95%; arm B, 94%) and overall survival (at 7 years: arm A, 92%; arm B, 94%;  $P = .43$ ). However, freedom from treatment failure was significantly different, with 7-year rates of 67% in arm A (95% CI, 61% to 73%) and 88% in arm B (95% CI, 84% to 92%;  $P \leq .0001$ ). This was due mainly to significantly more relapses after EF-RT only (arm A, 22%; arm B, 3%). No patient treated with CMT experienced relapse before year 3. Relapses were treated mainly with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, or with the combination cyclophosphamide, vincristine, procarbazine, and prednisone/ABVD; treatment of relapse was significantly more successful in arm A than in arm B ( $P = .017$ ). In total, there were 39 second malignancies, with 21 in arm A and 18 in arm B, respectively. The incidence was approximately 0.8% per year during years 2 to 9 and was highest in older patients ( $P < .0001$ ) and those with "B" symptoms ( $P = .012$ ).

### Conclusion

CMT consisting of two cycles of ABVD plus EF-RT is more effective than EF-RT alone.

RT Alone: 67%  
CTh + RT: 88%

## RT vs. CT + RT FOR EARLY STAGE FAVOURABLE HD

Trial	Treatment	Outcome	OS
EORTC H7	STNI (36-40Gy) 6 EBVP+IFRT (36-40Gy)	10 yr EFS 78% 88%	10 yr 92% 92%
SWOG 9133	STNI (36-40Gy) 3 x Dox + Vinblast + STNI	3 yr EFS 81 94	3 yr 96 98
GHSB HD7	EFRT 30Gy (IF 40Gy) 2 x ABVD + EFRT 30Gy (IF 40Gy)	2 yr FFTF 84 96	2 yr 98 98
EORTC/ GELA H8	STNI 36Gy (IF 40Gy) 3 x MOPP/ ABV + IFRT (36Gy)	4 yr FFTF 77 99	4 yr 95 99



# COMBINED MODALITY

## Metaanalysis

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13 randomized clinical trials

Multiagent CT+RT

Vs

Radiation alone

- At 10 years RFSR 85% and 67%  $p=0.00001$
- 10-year OAS 79% and 76% ( $p=0.07$ ).

Effective salvage of relapses in the RT alone arm  
↑RR in radiation alone balanced by the ↑ treatment  
related mortality (cardiac, second malignancies)  
combined arm

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CAN WE AVIOD RADIATION AFTER MULTIAGENT CHEMO ?

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# Consolidation Radiation After Complete Remission in Hodgkin's Disease Following Six Cycles of Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine Chemotherapy: Is There a Need?

S. Laskar, T. Gupta, S. Vimal, M.A. Muckaden, T.K. Saikia, S.K. Pai, K.N. Naresh, and K.A. Dinshaw

## A B S T R A C T

### Purpose

Combined modality treatment using multidrug chemotherapy (CTh) and radiotherapy (RT) is currently considered the standard of care in early stage Hodgkin's disease. Its role in advanced stages, however, continues to be debated. This study was aimed at evaluating the role of consolidation radiation in patients achieving a complete remission after six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy using event-free survival (EFS) and overall survival (OS) as primary end points.

### Patients and Methods

Two hundred and fifty-one patients with Hodgkin's disease attending the lymphoma clinic at the Tata Memorial Hospital (Mumbai, India) from 1993 to 1996 received induction chemotherapy with six cycles of ABVD after initial staging evaluation. A total of 179 of 251 patients (71%) achieved a complete remission after six cycles of ABVD chemotherapy and constituted the randomized population. Patients were randomly assigned to receive either consolidation radiation or no further therapy.

### Results

With a median follow-up of 63 months, the 8-year EFS and OS in the CTh-alone arm were 76% and 89%, respectively, as compared with 88% and 100% in the CTh+RT arm ( $P = .01$ ;  $P = .002$ ). Addition of RT improved EFS and OS in patients with age < 15 years ( $P = .02$ ;  $P = .04$ ), B symptoms ( $P = .03$ ;  $P = .006$ ), advanced stage ( $P = .03$ ;  $P = .006$ ), and bulky disease ( $P = .04$ ;  $P = .19$ ).

### Conclusion

Our study suggests that the addition of consolidation radiation helps improve the EFS and OS in patients achieving a complete remission after six cycles of ABVD chemotherapy, particularly in the younger age group and in patients with B symptoms and bulky and advanced disease.



## CT + RT FOR EARLY STAGE FAV. HD

Trial	Treatment	Outcome	OS
Milan Group	4 ABVD + STNI 30Gy (36-40Gy) 4 ABVD + IFRT (36-40Gy)	12 yr EFS 87% 91%	12 yr 96% 94%
GHSG HD 10	2 ABVD + IFRT 30Gy 2 ABVD + IFRT 20Gy 2 ABVD + IFRT 30Gy 2 ABVD + IFRT 20Gy	2 yr EFS 96.6%	2 yr 98.5%
EORTC/ GELA H9F	6 EBVP + IFRT 36Gy 6 EBVP + IFRT 20Gy 6 EBVP	4 yr FFTF 87% 84% 70%	4 yr 98% 98% 98%

## CT + RT FOR EARLY STAGE UNFAV. HD

Trial	Treatment	Outcome	OS
EORTC-GELA H8-U	6 MOPP/ABV + IFRT (36-40Gy) 4 MOPP/ABV + IFRT (36-40Gy) 4 MOPP/ABV + STNI (36-40Gy)	4 yr TFFS 89% 92% 92%	4 yr 90% 94% 92%
GHSG HD 8	2 COPP/ABVD + EFRT 30Gy 2 COPP/ABVD + IFRT 30Gy	% yr FFTF 86% 84%	5 yr 91 92
EORTC-GELA H9U	6 EBVP + IFRT 36Gy 6 MOPP/ABV + IFRT 36Gy	10yr EFS 68% 88%	10 yr 79% 87%
GHSG HD-11	4 ABVD + IFRT 30Gy 4 ABVD + IFRT 20Gy 4BEACOPP + IFRT 30Gy 4 BEACOPP + IFRT 20Gy	FFTF 89.9%	OS 97.4%

## CT + RT FOR ADVANCED STAGE HD

Trial	Treatment	Outcome	OS
GHSG	3 COPP/ABVD + 1 3 COPP/ABVD + IFRT (20Gy)	7yr TFFS 59.4%	7 yr 76.2%
Laskar Trial	6ABVD 6 ABVD + IFRT 30Gy	8 yr RFS 59% 78%	8 yr 80% 100%
GELA H89	8 ABVPP 8 MOPP/ABV 6 MOPP/ABV + STNI 30Gy 6 ABVPP/ABV + STNI 30Gy	10yr EFS 70% 76% 79% 76%	10 yr 90% 78% 82% 77%

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# Randomized Comparison of Low-Dose Involved-Field Radiotherapy and No Radiotherapy for Children With Hodgkin's Disease Who Achieve a Complete Response to Chemotherapy

By James B. Nachman, Richard Sposto, Philip Herzog, Gerald S. Gilchrist, Suzanne L. Wolden, John Thomson, Marshall E. Kadin, Paul Pattengale, P. Charlton Davis, Raymond J. Hutchinson, and Keith White for the Children's Cancer Group

**Purpose:** Current standard therapy for children and adolescents with Hodgkin's disease includes combination chemotherapy and low-dose involved-field radiation (LD-IFRT). Because radiation may be associated with adverse late effects, the Children's Cancer Group (CCG) investigated whether radiation could be omitted in patients achieving a complete response to initial chemotherapy without jeopardizing the excellent outcome obtained with combined-modality therapy.

**Patients and Methods:** Between January 1995 and December 1998, 829 eligible patients were enrolled onto CCG 5942. A total of 501 patients who achieved an initial complete response after risk-adapted combination chemotherapy were randomized to receive LD-IFRT or no further treatment. Event-free survival (EFS) and overall survival were assessed from the date of study entry or the date of randomization, as appropriate.

**Results:** The projected 3-year EFS from study entry for the entire cohort was  $87\% \pm 1.2\%$ . Among patients

who achieved a complete response to initial chemotherapy,  $92\% \pm 1.9\%$  of those randomized to receive LD-IFRT were alive and disease free 3 years after randomization, versus  $87\% \pm 2.2\%$  for patients randomized to receive no further therapy (stratified log-rank test;  $P = .057$ ). With an "as-treated" analysis, 3-year EFS after randomization for the radiation cohort was  $93\% \pm 1.7\%$  versus  $85\% \pm 2.3\%$  for patients receiving no further therapy (stratified log-rank test;  $P = .0024$ ).

Three-year survival estimates for patients treated with and without LD-IFRT were  $98\% \pm 1.1\%$  for patients who received radiation and  $99\% \pm 0.5\%$  for patients who did not receive radiation.

**Conclusion:** LD-IFRT after an initial complete response to risk-adapted chemotherapy improved EFS. At this time, there is no survival advantage for LD-IFRT, but follow-up remains short.

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3 Year EFS CTh Alone: 85%

3 Year EFS CTh + RT: 93%,  $p=0.0024$

# Randomized comparison of consolidation radiation *versus* observation in bulky Hodgkin's lymphoma with post-chemotherapy negative positron emission tomography scans

MARCO PICARDI<sup>1</sup>, AMALIA DE RENZO<sup>1</sup>, FABRIZIO PANE<sup>1</sup>, EMANUELE NICOLAI<sup>2</sup>, ROBERTO PACELLI<sup>3</sup>, MARCO SALVATORE<sup>3</sup>, & BRUNO ROTOLI<sup>1</sup>

<sup>1</sup>*Department of Biochemistry and Medical Biotechnology, Federico II University Medical School, Naples, Italy,*

<sup>2</sup>*SDN, Istituto di Ricerca Diagnostica-Nucleare, Naples, Italy, and* <sup>3</sup>*Department of Biomorphological and Functional Sciences, Federico II University Medical School, Naples, Italy*

## Abstract

This study aimed at evaluating the role of consolidation radiation in a setting of Hodgkin's lymphoma (HL) patients, using event-free survival (EFS) as end point. Among 260 patients treated with induction chemotherapy for bulky HL, 160 patients achieved negative residual masses at 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scans. They were randomly divided into two well-matched groups to receive either 32 Gy radiotherapy to bulky area or no further therapy. At a median follow-up of 40 months, histology showed a malignancy in 14% of patients in the chemotherapy-only group (HL, 11 patients) and in 4% of patients in the chemotherapy + radiotherapy group (HL, 2 patients; carcinoma in previously irradiated area, 1 patient) ( $P=0.03$ ). All the relapses in the chemotherapy-only group involved the bulky site and the contiguous nodal regions. Thus, the overall diagnostic accuracy of FDG-PET to exclude future relapses in the patients nonprotected by radiotherapy was 86% with a false-negative rate of 14%. Our study suggests that the addition of irradiation helps improve EFS in HL patients with post-chemotherapy FDG-PET-negative residual masses.

**Keywords:** *Hodgkin's lymphoma, bulky disease, radiotherapy, FDG-PET*

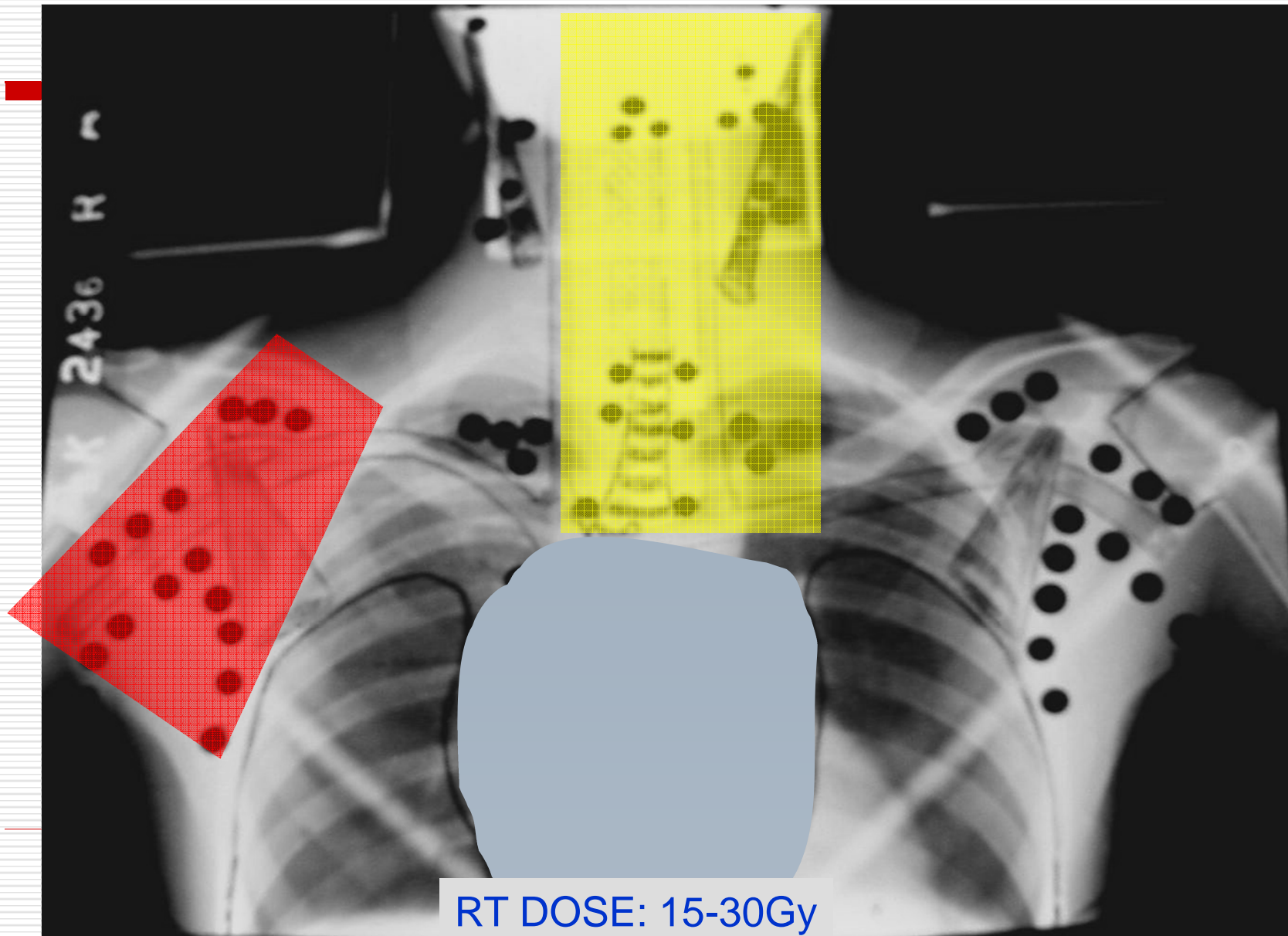
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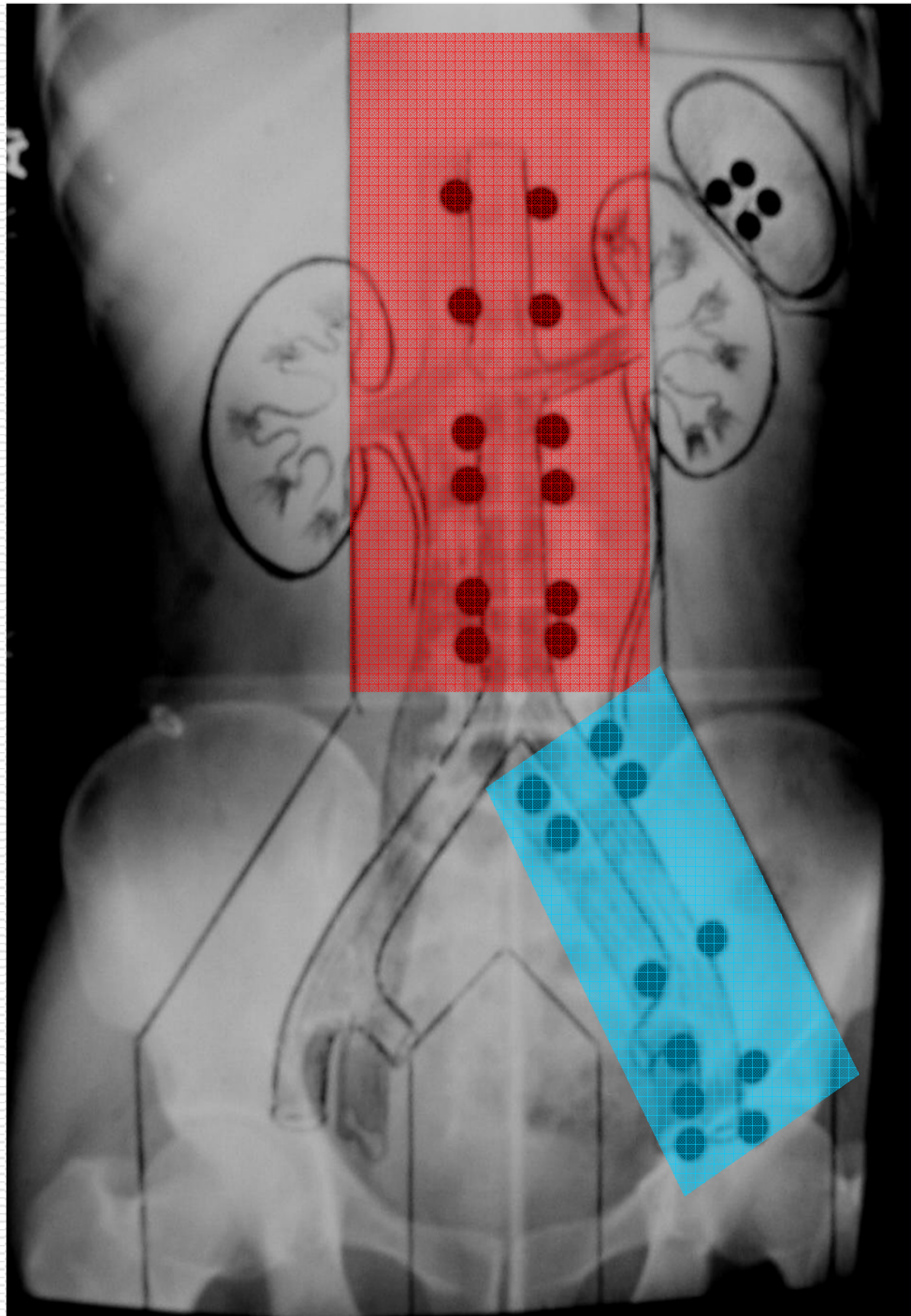
**WHAT IS THE OPTIMAL RADIATION VOLUME ?**

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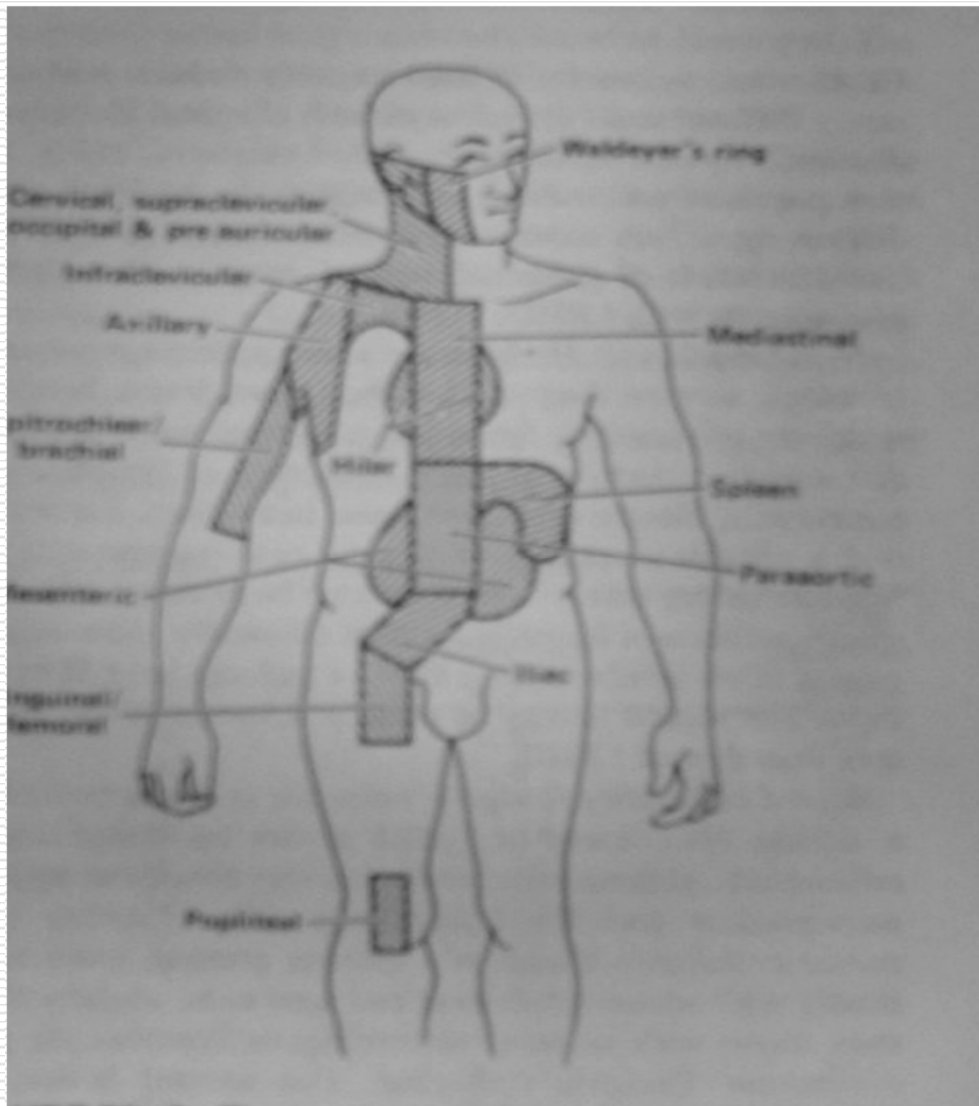


## MANTLE FIELD FOR TREATMENT OF SUPRADIAPHRAGMATIC NODAL REGIONS





## **INVERTED “Y” FIELD FOR TREATMENT OF INFRADIAPHRAGMATIC NODAL REGIONS**



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## **INRT (Involved Nodal RT)**

IFRT

Mini Mantle

Mantle

Extended Mantle

Inverted "Y"

Hemi Inverted "Y"

Spade Field

Subtotal Nodal Irradiation

Total Nodal Irradiation

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# Involved-Field Radiotherapy Is Equally Effective and Less Toxic Compared With Extended-Field Radiotherapy After Four Cycles of Chemotherapy in Patients With Early-Stage Unfavorable Hodgkin's Lymphoma: Results of the HD8 Trial of the German Hodgkin's Lymphoma Study Group

By Andreas Engert, Petra Schiller, Andreas Josting, Richard Herrmann, Peter Koch, Markus Sieber, Friederike Boissevain, Maïke de Wit, Jörg Mezger, Eckhart Dühmke, Normann Willich, Rolf-Peter Müller, Bernhard F. Schmidt, Helmut Renner, Hans Konrad Müller-Hermelink, Beate Pfister, Jürgen Wolf, Dirk Hasenclever, Markus Löffler, and Volker Diehl

**Purpose:** To investigate whether radiotherapy can be reduced without loss of efficacy from extended field (EF) to involved field (IF) after four cycles of chemotherapy.

**Patients and Methods:** Between 1993 and 1998, patients with newly diagnosed early-stage unfavorable HD were enrolled onto this multicenter study. Patients were randomly assigned to receive cyclophosphamide, vincristine, procarbazine, and prednisone (COPP) + doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) for two cycles followed by radiotherapy of 30 Gy EF + 10 Gy to bulky disease (arm A) or 30 Gy IF + 10 Gy to bulky disease (arm B).

**Results:** Of 1,204 patients randomly assigned to treatment, 1,064 patients were informative and eligible for the arm comparison (532 patients in arm A; 532 patients in arm B). The median observation time was 54 months. Five years after random assignment, the overall survival ( $OS_{ran}$ ) for all eligible patients was 91% and freedom from treatment

failure ( $FFTF_{ran}$ ) was 83%. Survival rates at 5 years after start of radiotherapy revealed no differences for arms A and B, respectively, in terms of  $FFTF$  (85.8% and 84.2%) and  $OS$  at 5 years (90.8% and 92.4%). There also were no differences between arms A and B, respectively, in terms of complete remission (98.5% and 97.2%), progressive disease (0.8% and 1.9%), relapse (6.4% and 7.7%), death (8.1% and 6.4%), and secondary neoplasia (4.5% and 2.8%). In contrast, acute side effects including leukopenia, thrombocytopenia, nausea, gastrointestinal toxicity, and pharyngeal toxicity were more frequent in the EF arm.

**Conclusion:** Radiotherapy volume size reduction from EF to IF after COPP + ABVD chemotherapy for two cycles produces similar results and less toxicity in patients with early-stage unfavorable HD.

*J Clin Oncol* 21:3601-3608. © 2003 by American Society of Clinical Oncology.

## Reduction in field sizes

Metaanalysis BY Specht 1998

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8 randomized controlled trials

Extensive portals (e.g. subtotal mantle, total nodal irradiation etc)

Vs

less extensive portals (e.g. mantle, mini mantle, involved field radiation etc).

Results –

- At 10 years, the risk of recurrence was 31% vs. 43% (  $p=0.00001$ ).
- Subgroup analysis showed similar results.
- 10-year actuarial OAS- 77% in both groups ( $p=0.1$ )

effective salvage of relapses with CT

↑ relapse rates in mantle gp was balanced by the increased treatment related mortality in TNI



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**WHAT IS THE OPTIMAL RADIATION DOSE ?**

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# RADIATION DOSE

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## HD-10 trial

1131 patients  
(1998-2002)

Randomized into 4 arms:

- a) ABVD x 2 + (30Gy)
- b) ABVD x 2 + IFRT (20Gy)
- c) ABVD x 4 + IFRT (30Gy)
- d) ABVD x 4 + IFRT (30Gy).

- ❑ **Results:** interim analysis conducted in August 2003 of 847 pts (75%)
  - ❑ Complete remission rates-98.4%
  - ❑ FFTF after two years – 96.6% with no statistical differences between arms
  - ❑ Overall survival- 98.5% without any statistical differences in CT and RT comparisons.
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# Final Results of a Prospective Clinical Trial With VAMP and Low-Dose Involved-Field Radiation for Children With Low-Risk Hodgkin's Disease

*Sarah S. Donaldson, Michael P. Link, Howard J. Weinstein, Shesh N. Rai, Sam Brain, Amy L. Billett, Craig A. Hurwitz, Matthew Krasin, Larry E. Kun, Karen C. Marcus, Nancy J. Tarbell, Jeffrey A. Young, and Melissa M. Hudson*

## A B S T R A C T

### **Purpose**

To evaluate outcome and assess complications in children and adolescents with low-risk Hodgkin's disease treated with vinblastine, doxorubicin, methotrexate, and prednisone (VAMP) chemotherapy and low-dose, involved-field radiation therapy (IFRT).

### **Patients and Methods**

One hundred ten children with low-risk Hodgkin's disease were treated with four cycles of VAMP and 15 Gy IFRT for those who achieved a complete response (CR) or 25.5 Gy for those with a partial response after two cycles of VAMP.

### **Results**

With median follow-up of 9.6 years (range, 1.7 to 15.0), 5- and 10-year overall survival were 99.1% and 96.1%, respectively, and 5- and 10-year event-free survival (EFS) were 92.7% and 89.4%. Factors contributing to 10-year EFS were: early CR ( $P = .02$ ), absence of B symptoms ( $P = .01$ ), lymphocyte predominant histologic subtype ( $P = .04$ ), and less than three initial sites of disease ( $P = .02$ ). Organ toxicity has been limited to correctable hypothyroidism in 42% of irradiated patients, and one case of cardiac dysfunction. Seventeen healthy babies have been born to 106 survivors. There have been two malignant tumors: one thyroid cancer within the radiation therapy field and one Ewing's sarcoma outside the radiation therapy field.

### **Conclusion**

Risk-adapted, combined-modality therapy using VAMP chemotherapy with radiation is effective and well tolerated. Pediatric patients with low-risk Hodgkin's disease can be cured with therapy without an alkylating agent, bleomycin, etoposide, or high-dose, extended-field radiotherapy. Thus, these children are expected to retain normal fertility, organ function, and be at low risk of a second malignant tumor.

## DOES BULKY DISEASE AT DIAGNOSIS INFLUENCE OUTCOME IN CHILDHOOD HODGKIN'S DISEASE AND REQUIRE HIGHER RADIATION DOSES? RESULTS FROM THE GERMAN-AUSTRIAN PEDIATRIC MULTICENTER TRIAL DAL-HD-90

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**Purpose:** The identification of risk factors is required for risk-adapted treatment strategies in the treatment of Hodgkin's disease. To assess the influence of bulky disease at diagnosis as compared with other risk factors on event-free survival (EFS) in pediatric Hodgkin's disease such as stage, B-symptoms, number of involved lymph node regions, histology, and remission status after chemotherapy, we analyzed the outcome of 552 patients treated with a risk-adapted treatment strategy consisting of OPPA(OEPA)/COPP (vincristine, procarbazine, etoposide, prednisone, adriamycin, cyclophosphamide) and involved-field radiotherapy.

**Methods and Materials:** Between 1990 and 1995, 578 patients with primary Hodgkin's disease (HD) were enrolled in the German/Austrian Pediatric Hodgkin's Disease Study Group (DAL) Multicenter Study (HD-90). Patients were stratified into three treatment groups (TGs) for early, intermediate, and advanced stage. All patients received induction chemotherapy (CT) with two cycles of OEPA for boys and two cycles of OPPA for girls. Patients in TG2 and TG3 received another two or four cycles, respectively, of COPP. Chemotherapy was followed by involved-field radiotherapy. The radiation field, which was prescribed by the study center, was treated with a dose of 25 Gy/25 Gy/20 Gy (TG1/TG2/TG3), and in case of insufficient remission with a local boost of 5 Gy to 10 Gy. The following prognostic factors were analyzed with regard to their impact on EFS: bulky disease, mediastinal tumor, number of involved lymph node regions, histology, treatment group, B-symptoms, sex, age, and remission status after chemotherapy.

**Results:** Significant univariate predictive factors for EFS were: nodular sclerosis type 2 (NS2) histology (relative risk [RR] 3.43;  $p = 0.0002$ ), presence of B-symptoms (RR 2.70;  $p = 0.0014$ ), number of involved regions (1.55;  $p = 0.019$ ), and treatment groups (RR 1.33;  $p = 0.017$ ). There was a higher risk (RR 1.92;  $p = 0.040$ ) for patients with bulky compared with nonbulky disease (5-year EFS 89.6%/94.6%). In the multiple regression model, only NS2 and B-symptoms remained strong predictive factors. The remission status after chemotherapy did not correlate with EFS ( $p = 0.66$ ).

**Conclusion:** Treatment strategies in Hodgkin's disease have an impact on different risk factors. In the risk-adapted treatment strategy of the HD-90 study, tumor burden indicated as bulky disease or as number of involved lymph nodes loses its importance, whereas NS2 histology and B-symptoms have a major impact on treatment outcome. Bulky disease at diagnosis might require higher radiation doses only in case of insufficient remission. © 2003 Elsevier Inc.



# RESPONSE-ADAPTED RADIOTHERAPY IN THE TREATMENT OF PEDIATRIC HODGKIN'S DISEASE: AN INTERIM REPORT AT 5 YEARS OF THE GERMAN GPOH-HD 95 TRIAL

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**Purpose:** A multinational trial on pediatric Hodgkin's disease (HD) with the aim to reduce the risk of long-term toxicity of combined modality treatment by restricting dose and volume of radiation therapy (RT) while maintaining the excellent treatment results of previous German multicenter trials (DAL-HD82-90).

**Methods and Materials:** Patients were treated according to stage of disease (CS) and defined risk factors in three treatment groups (TG) with 2, 4, or 6 cycles of combination chemotherapy. When a complete remission (CR) had been achieved, treatment was terminated without RT independent of initial stage or tumor bulk. Patients with a partial remission (PR) of >75% tumor regression were irradiated with 20 Gy using modified involved fields; in the case of PR <75% RT dose was 30 Gy, residual masses >50 mL received 35 Gy.

**Results:** From August 1995 to July 2000 a total of 956 patients have been registered, 830 as trial patients, 39% in TG1, 27% in TG2, 34% in TG3. 827 patients were evaluable by June 2001 with a median follow-up of 38 months. Chemotherapy (CTx) resulted in CR in 22%, PR >75% in 62%, PR <75% in 12%. Event-free survival (EFS) for the entire group is 90% (SD 0.01), for TG1 94%, TG2 91%, and TG3 84%; the overall survival is 97% in Kaplan-Meier-analysis. Relapse-free survival (RFS) is superior for patients with RT after PR (93%) than for those without RT after CR (89%); the difference is significant ( $p = 0.01$ ) for advanced stages, however not in TG1. Seventy-two events were observed by June 2001: 28 progressions during the initial therapy or within the first 3 months, 38 relapses, 3 second malignancies, three fatal accidents or infections; 18 patients have died.

**Conclusion:** Treatment results of the GPOH-HD 95 trial are excellent thus far. The reduction of RT dose and volume in PR has not caused a significant impairment of overall and event-free survival in comparison to the previous German trials; however, failure rates are higher in advanced stages when RT is omitted after achieving a CR. It is too early to tell whether the HD 95 protocol will be successful in reducing late toxicity. © 2001 Elsevier Science Inc.



# HODGKIN'S DISEASE CURRENT GUIDELINES

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**Early Stage Favourable (Low Risk)**  
**Multiagent CTh x 2 - 4 cycles + IFRT**

**Early Stage Unfavourable (Intermediate Risk)**  
**Multiagent CTh x 4 cycles + IFRT**

**Advanced Stage (High Risk)**  
**Multiagent CTh x 6-8 cycles ± IFRT**

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# INDICATIONS FOR ADJUVANT RADIATION THERAPY

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Bulky Disease at Presentation (Irrespective of Response to CT)

Residual Disease/ Partial Response after Chemotherapy

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# **RADIATION DOSE GUIDELINES**

## **(Tata Memorial Hospital)**

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### **WITHIN CLINICAL TRIAL**

#### **Adults:**

**Microscopic: 19.8Gy/11#/3wks @ 1.8Gy / fr.**

**Gross: 30.6Gy/17#/3wks @ 1.8Gy / fr**

#### **Paediatric:**

**Microscopic: 14.4Gy/8#/2wks @ 1.8Gy / fr.**

**Gross: 25.2Gy/14#/3wks @ 1.8Gy / f**

### **OUTSIDE CLINICAL TRIAL**

#### **Adults:**

**Microscopic: 25.2Gy/14#/3wks @ 1.8Gy/fr.**

**Gross: 34.2Gy/19#/4wks @ 1.8Gy/fr.**

#### **Paediatric:**

**Microscopic: 19.80Gy/11#/3wks @ 1.8Gy/fr.**

**Gross: 30.60Gy/17#/3wks @ 1.8Gy/fr.**

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## Guidelines

# Involved-node radiotherapy (INRT) in patients with early Hodgkin lymphoma: Concepts and guidelines

Theodore Girinsky<sup>a,\*</sup>, Richard van der Maazen<sup>b</sup>, Lena Specht<sup>c</sup>, Berthe Aleman<sup>d</sup>, Philip Poortmans<sup>e</sup>, Yolande Lievens<sup>f</sup>, Paul Meijnders<sup>g</sup>, Mithra Ghalibafian<sup>a</sup>, Jacobus Meerwaldt<sup>h</sup>, Evert Noordijk<sup>i</sup>, on behalf of the EORTC-GELA Lymphoma Group

<sup>a</sup>Department of Radiation Oncology, Institut Gustave Roussy, Villejuif, France, <sup>b</sup>Department of Radiotherapy, Nijmegen, The Netherlands,

<sup>c</sup>The Finsen Centre Rigshospitalet, Copenhagen University Hospital, Denmark, <sup>d</sup>Department of Radiotherapy, The Netherlands Cancer

Institute, Amsterdam, The Netherlands, <sup>e</sup>Department of Radiotherapy, Dr Bernard Verbeeten Instituut, LA Tilburg, The Netherlands,

<sup>f</sup>Radiotherapy Department, Leuven, Belgium, <sup>g</sup>Department of Radiotherapy, Antwerpen, Belgium, <sup>h</sup>Department of Radiation Oncology,

Medisch Spectrum Twente, Enschede, The Netherlands, <sup>i</sup>Department of Clinical Oncology,

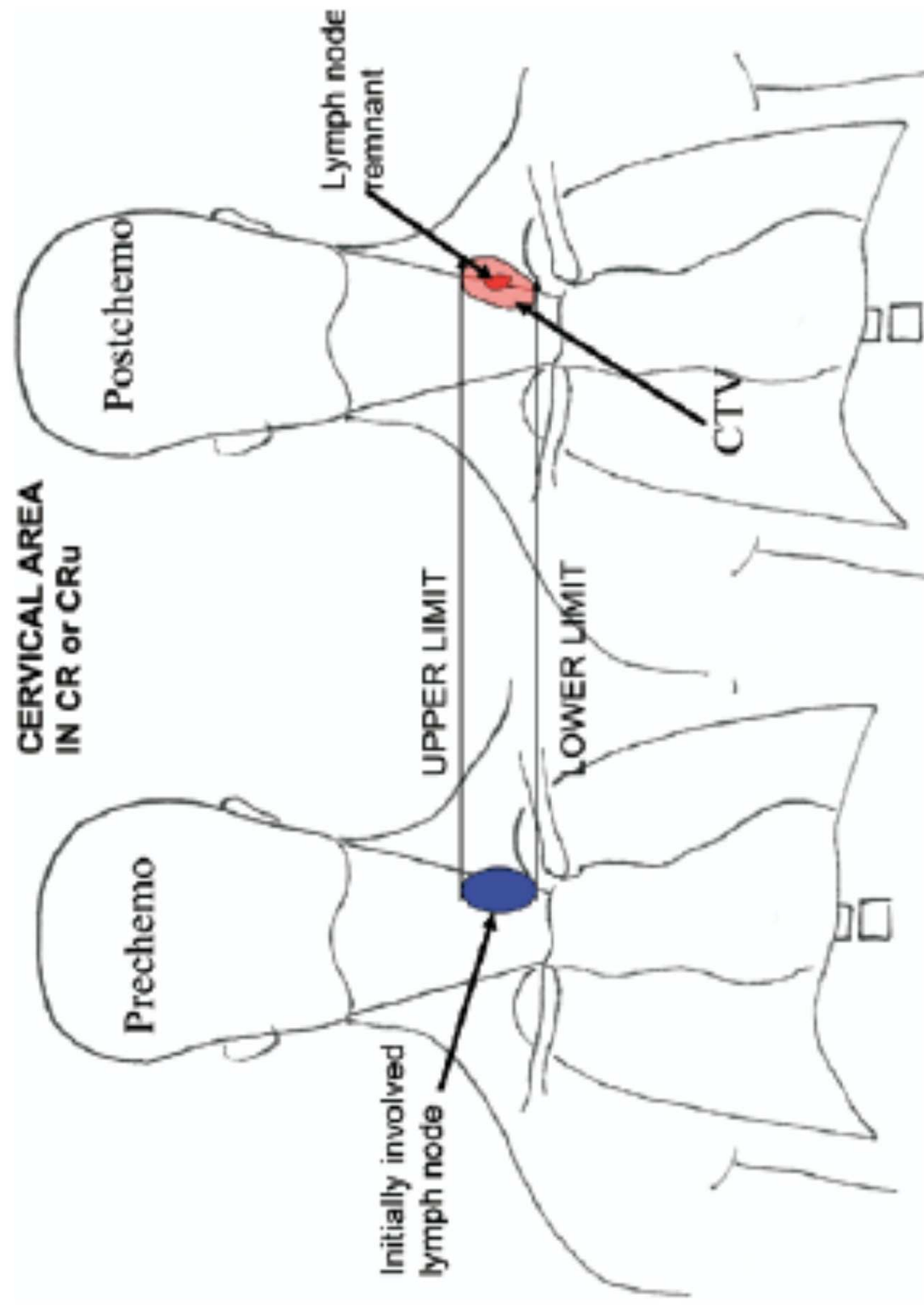
Leiden University Medical Center, The Netherlands

# BASIC RULES

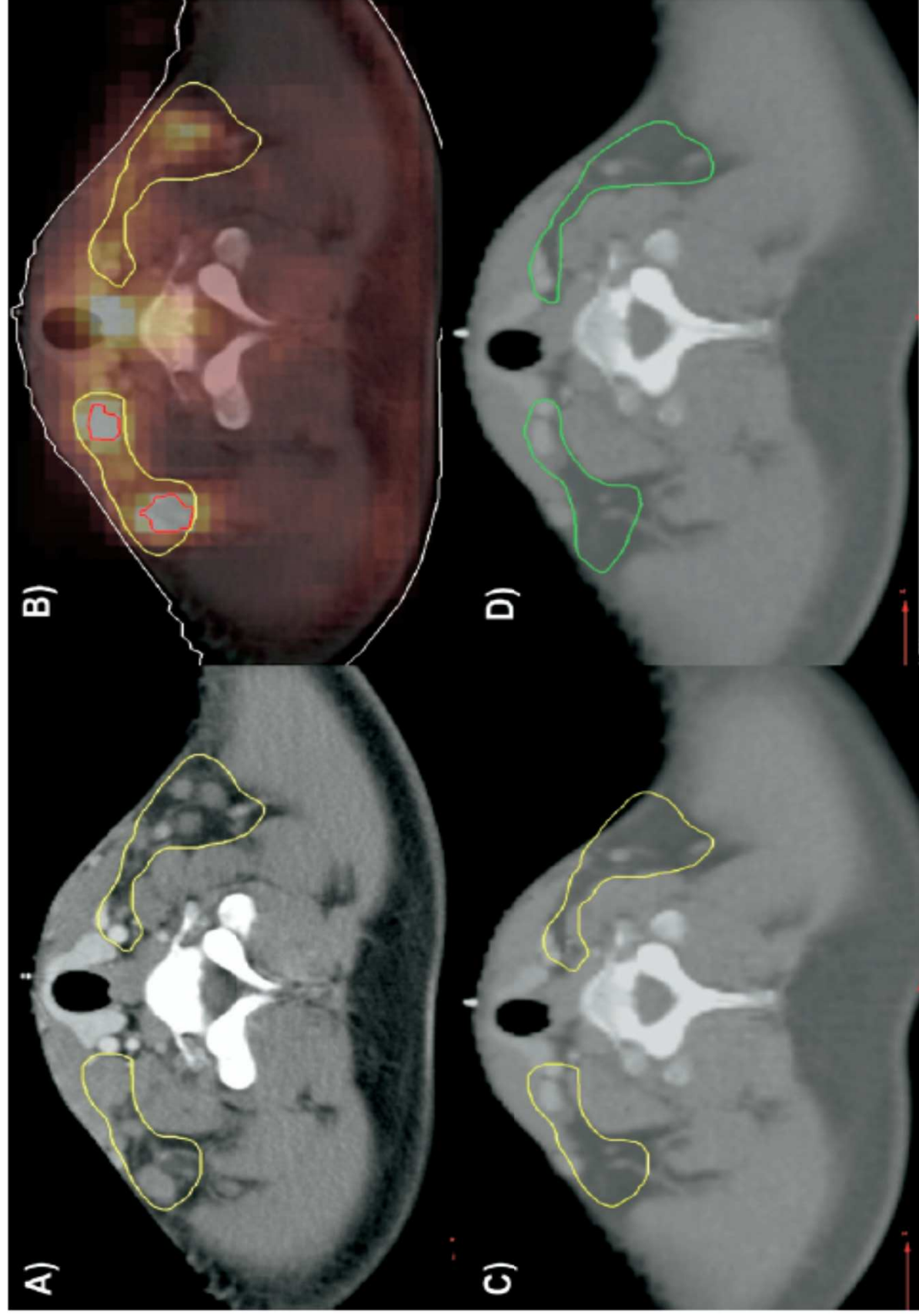
- Examination of patient by Radiation Oncologist.

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  - Pre and Post chemotherapy CT and FDG-PET scan performed in the treatment position.
  - Scans should encompass cervical, axillary, and mediastinal areas.
  - Remission status – For each initially involved lymph node should be determined exclusively on CT scans.
  - Modern Radiation techniques
    - Immobilization.
    - CT simulation.
    - Fusion techniques.
    - 3D-CRT.
    - Intensity modulated Radiotherapy.
    - Respiratory Gated Radiotherapy.
-

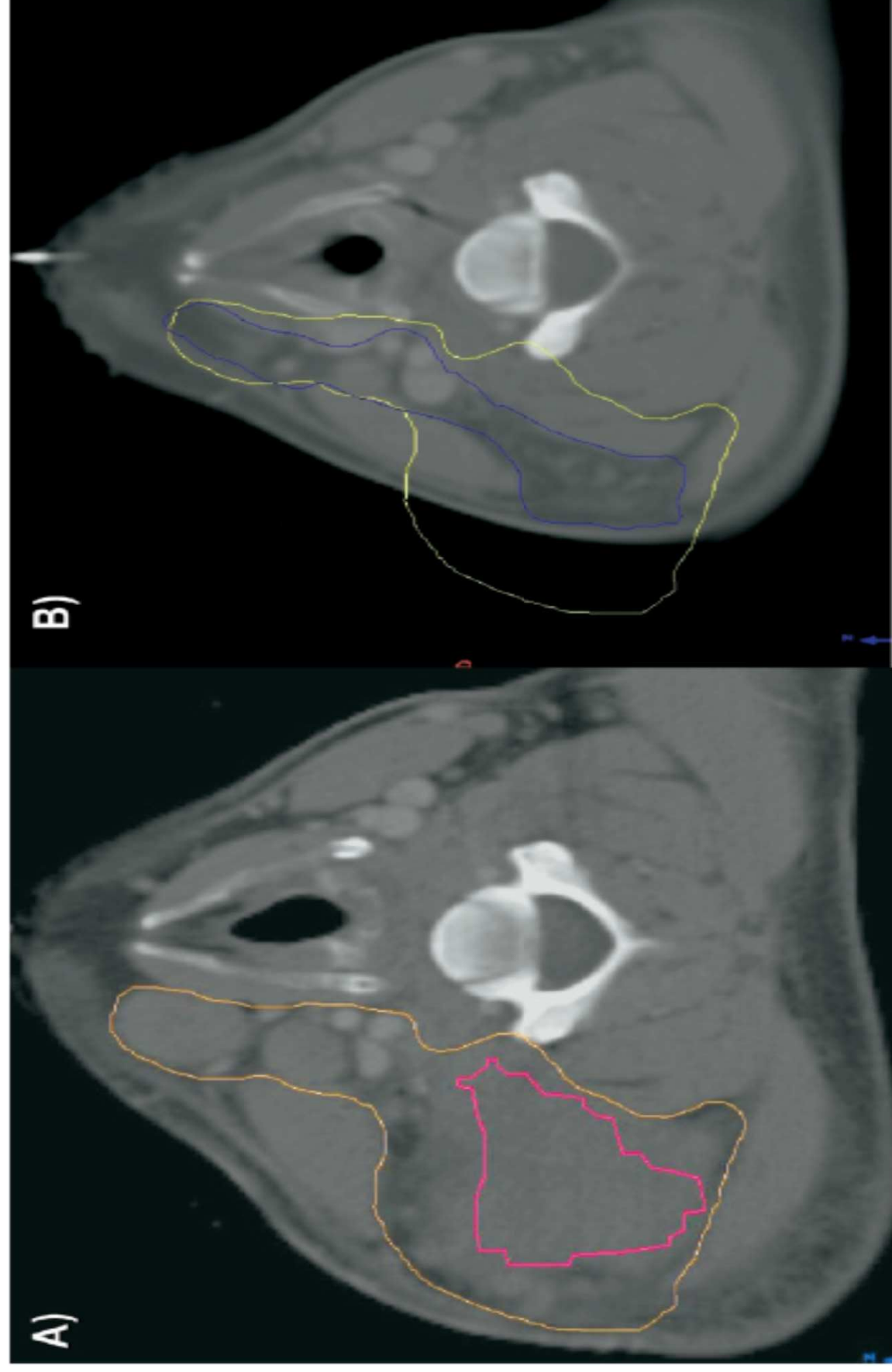




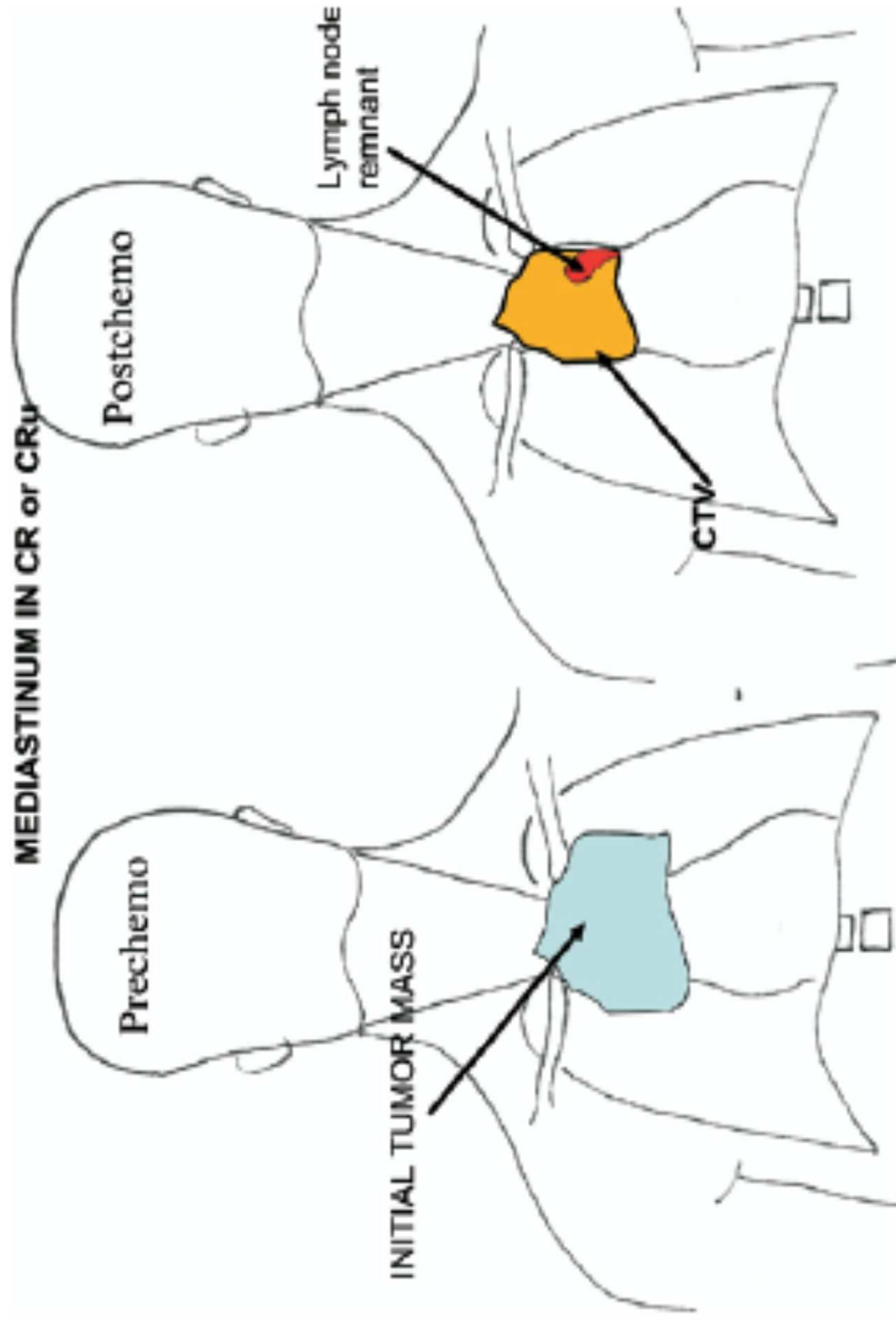
**Figure 1** Determination of a CTV in a cervical area in CR or CRu after chemotherapy.



**Figure 2** (A) Yellow contouring outlines the initial volume on a prechemotherapy axial CT scan. (B) Red outlines the PET+ areas on the prechemotherapy CT scan. (C) Initial volume superimposed on a postchemotherapy axial CT scan. (D) Adequate CT contouring on the postchemotherapy CT scan (green contouring).

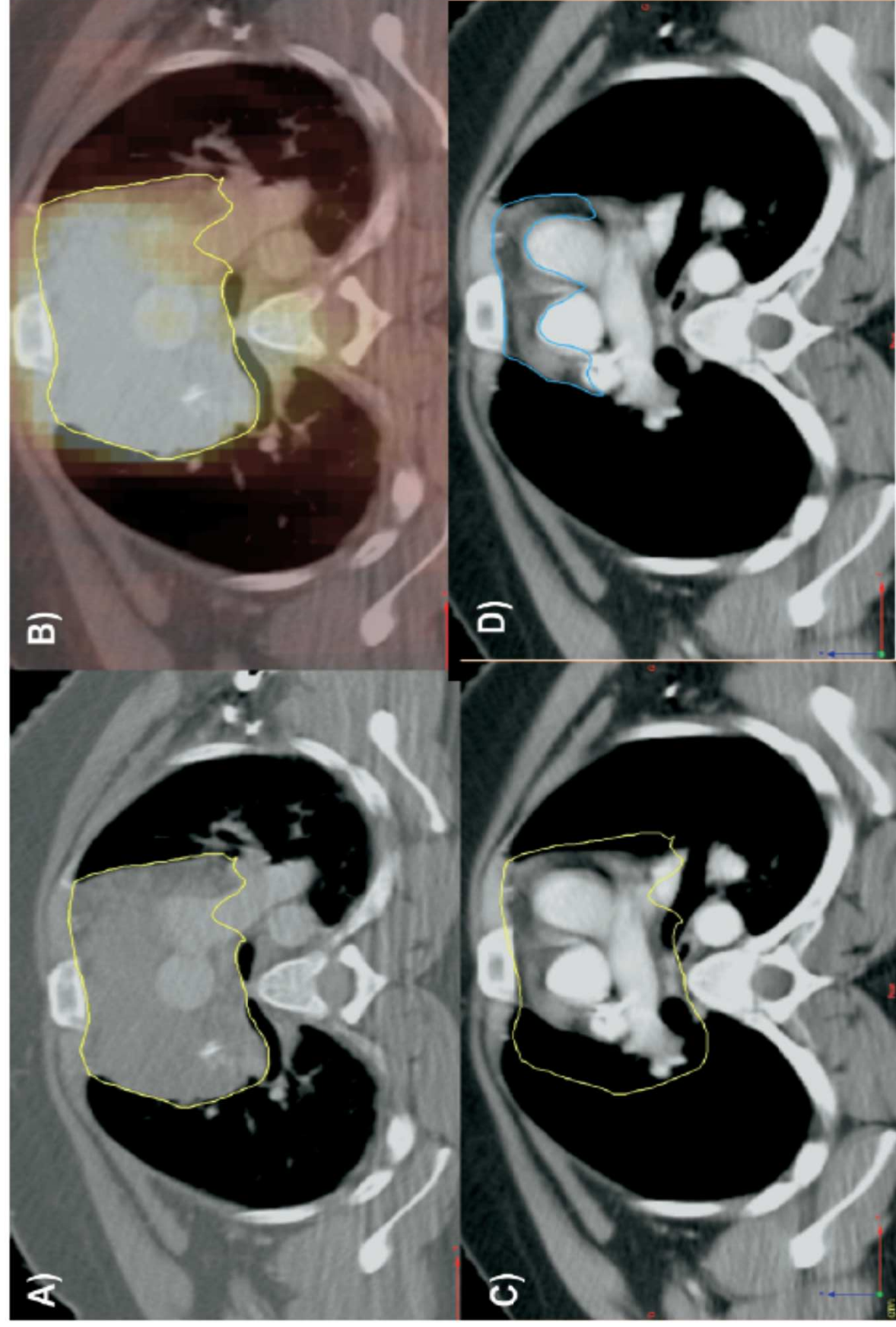


**Figure 3** (A) Orange contouring outlines the initial volume on a prechemotherapy axial CT scan and red outlines the PET+ areas. (B) Initial volume superimposed on the postchemotherapy axial CT scan (yellow contouring); blue outlines the CTV.



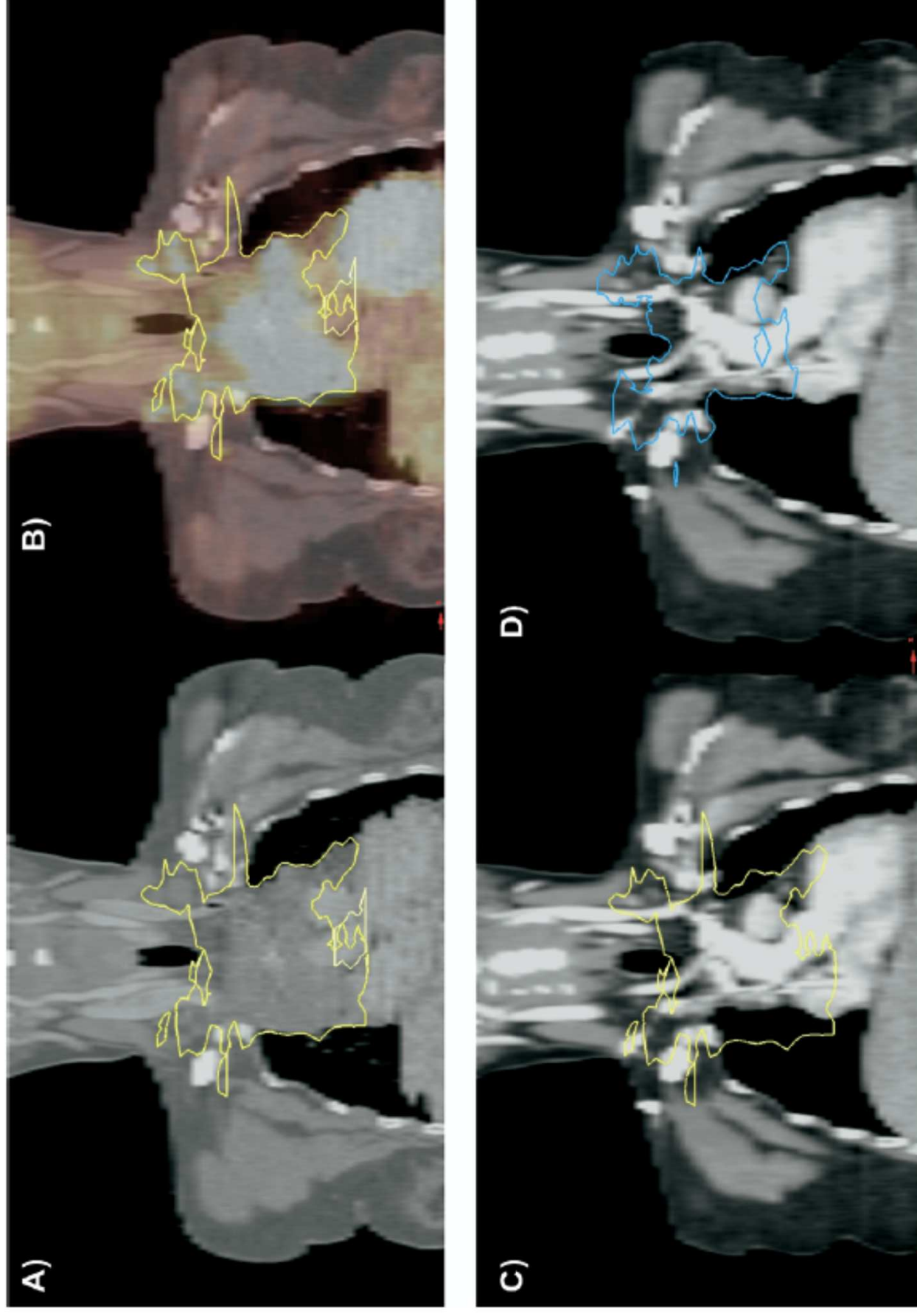
**Figure 4** Determination of a CTV in a mediastinal area in CR or CRu after chemotherapy.





**Figure 5** (A) Yellow contouring outlines the initial volume on a prechemotherapy axial CT scan. (B) Coregistration of the prechemotherapy CT scan and FDG-PET. (C) Initial volume (yellow contouring) superimposed on a postchemotherapy axial CT scan. (D) Adequate CT contouring on the postchemotherapy CT scan (blue contouring).





**Figure 6** (A) Yellow contouring outlines the initial volume on a prechemotherapy coronal CT scan. (B) Coregistration of the initial CT scan and FDG-PET. (C) Initial volume (yellow contouring) superimposed on a postchemotherapy coronal CT scan. (D) Adequate CT contouring (blue contouring) on the postchemotherapy CT scan.

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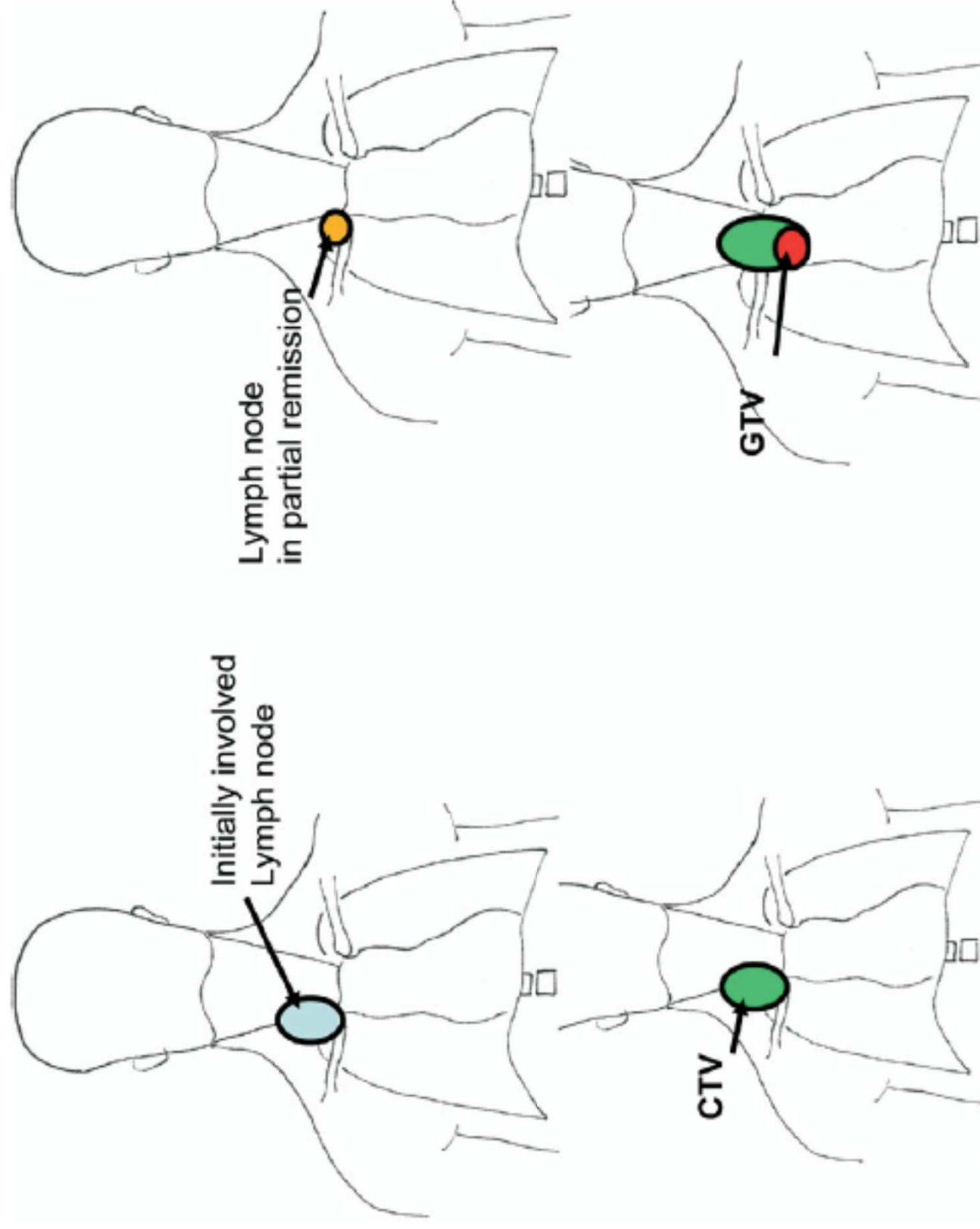
Initially involved lymph nodes in PR  
(Partial Remission)

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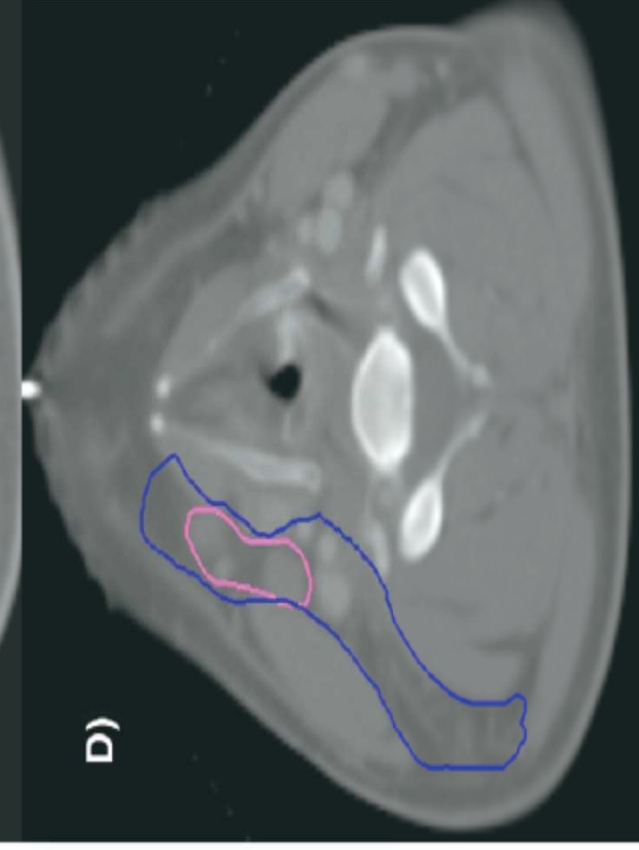
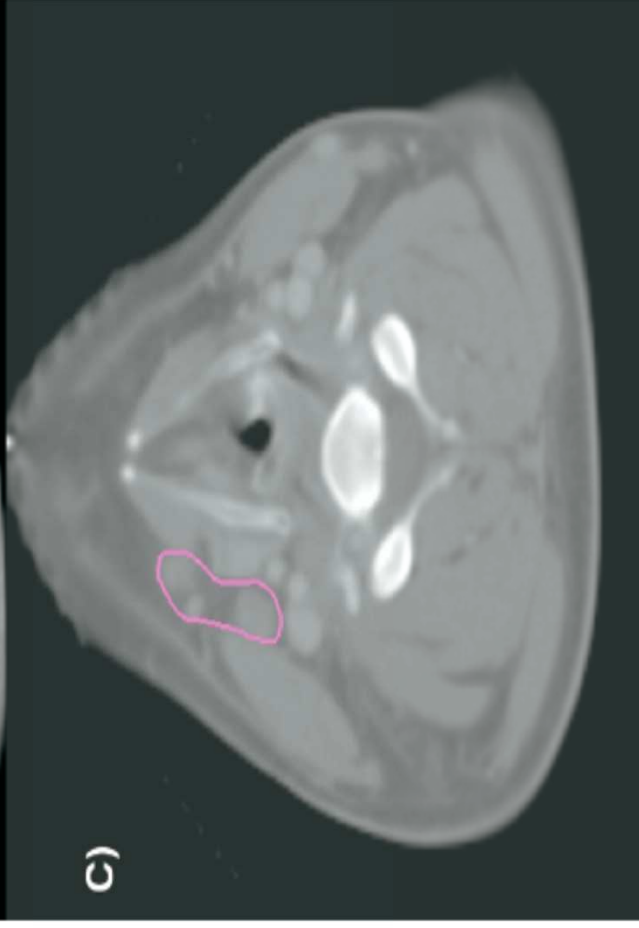
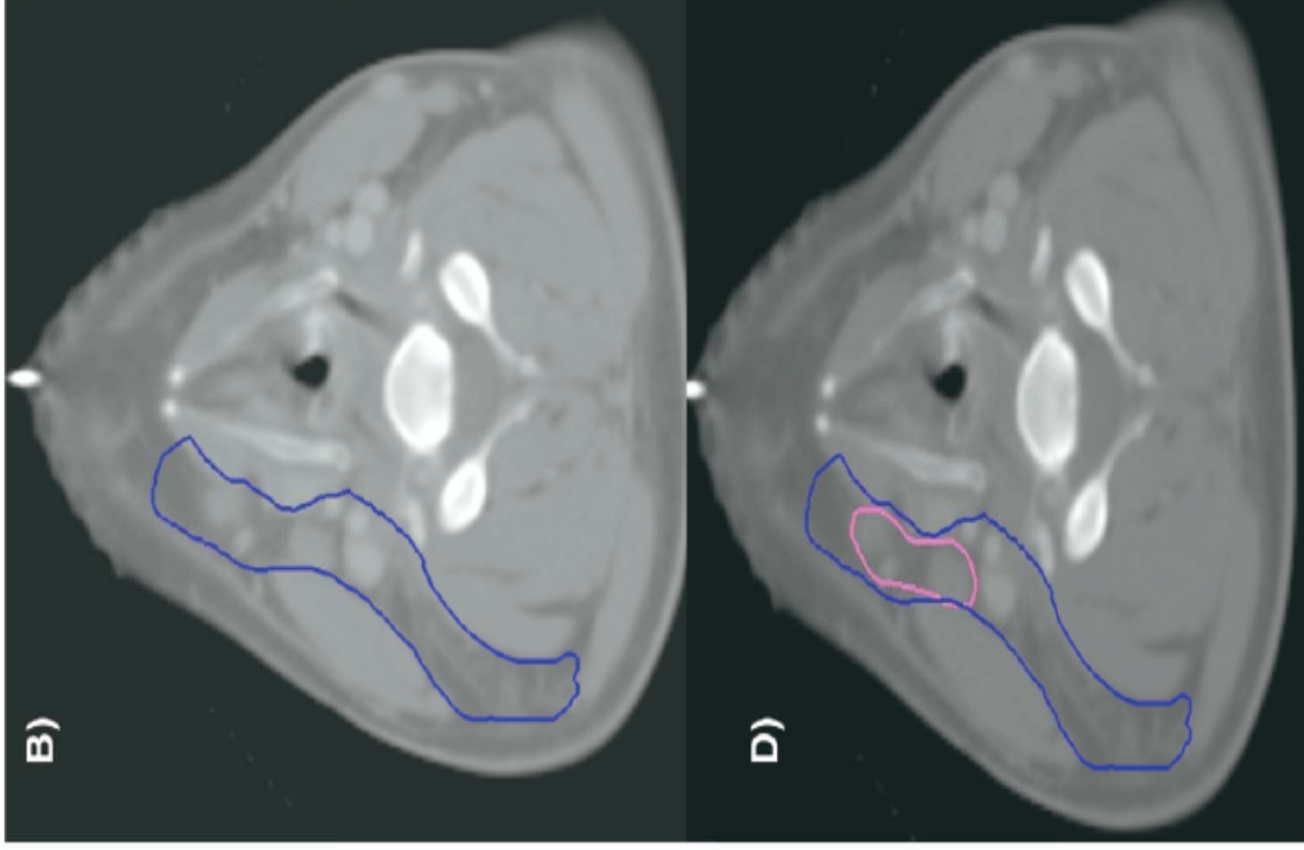
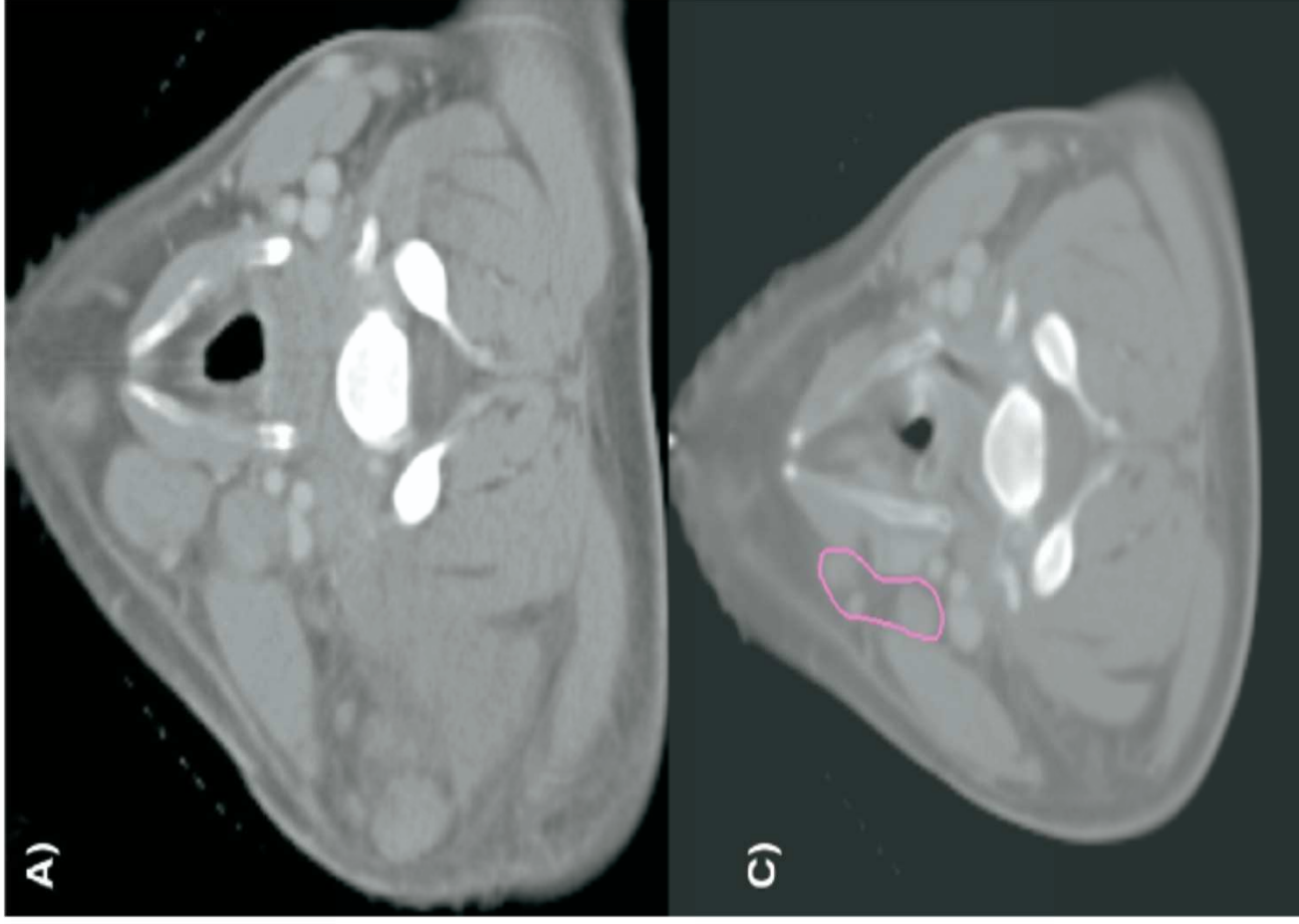
# CERVICAL AND AXILLARY LYMPH NODES

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- **GTV** - The lymph node remnant(s).
  - **CTV** - The initial volume of the lymph node(s) before chemotherapy.
  - **PTV1** - The CTV including the GTV [i.e. initial tumor mass and lymph node remnant(s)] with a margin.
  - **PTV2** - The GTV alone with a margin.
-



**Figure 7** Definition of CTV and GTV for a cervical node in partial remission.



**Figure 8** (A) Prechemotherapy axial CT scan. (B) Blue outlines the CTV. (C) Pink outlines the GTV that will receive the radiation boost. (D) CTV and GTV on the same axial cervical CT scan slice.

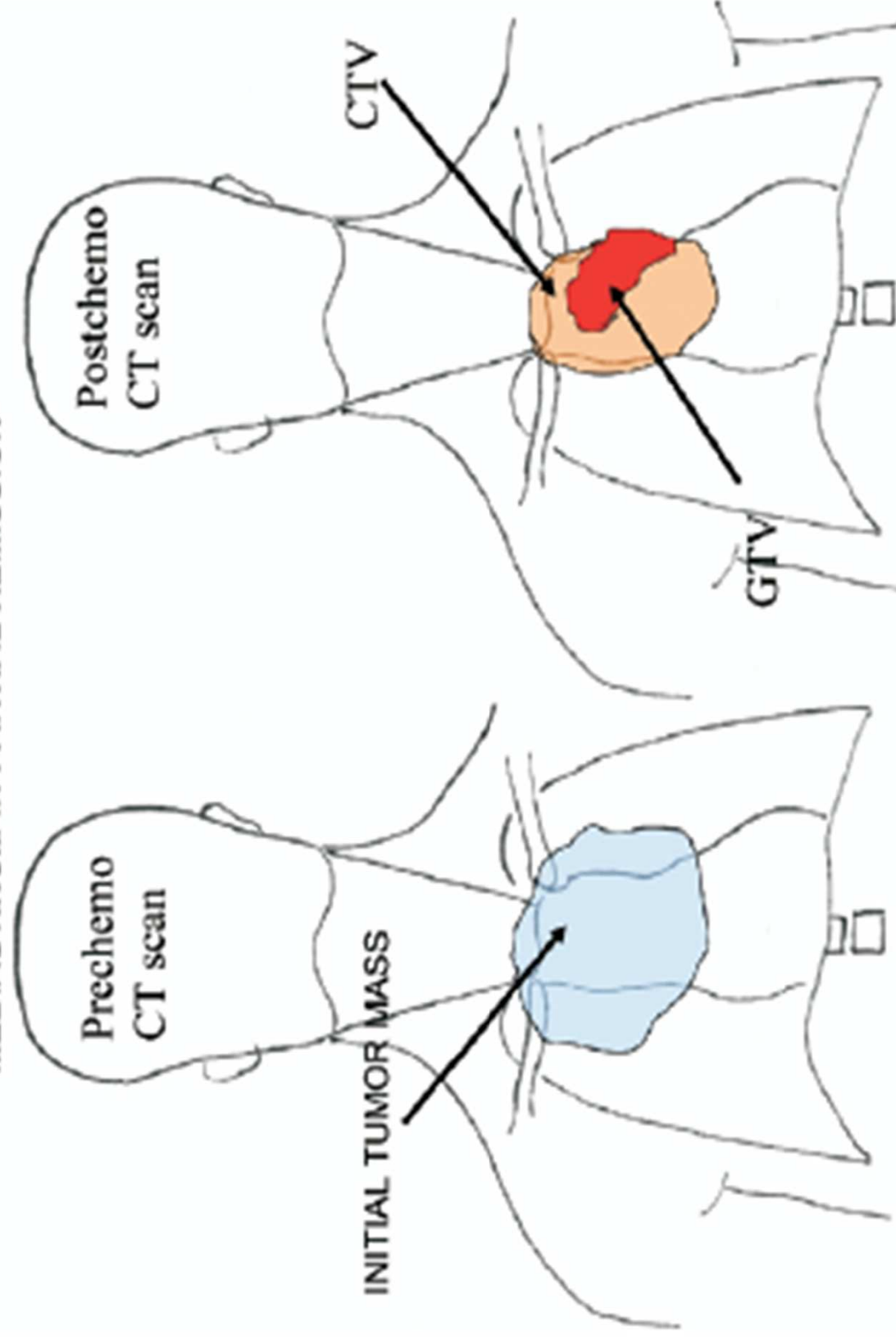


# MEDIASTINAL AREA

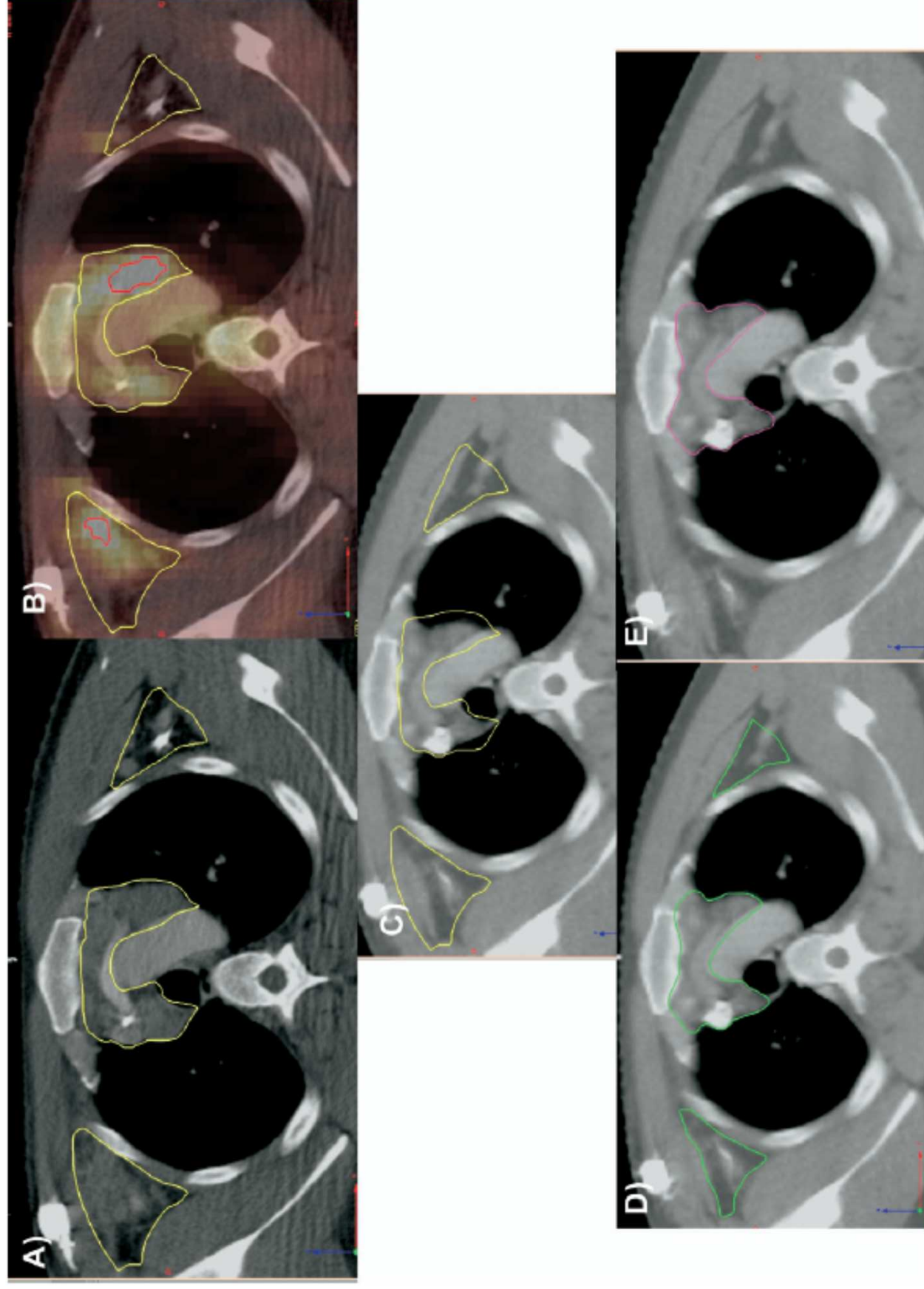
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- **GTV** - Lymph node remnant(s) or the remaining mass alone.
  - **CTV** - The initial volume of the mediastinal mass.
  - **PTV1** - The CTV including the GTV (i.e. the initial tumor mass and the lymph node remnant(s) with a margin.
  - **PTV2** - The GTV alone with a margin.
-

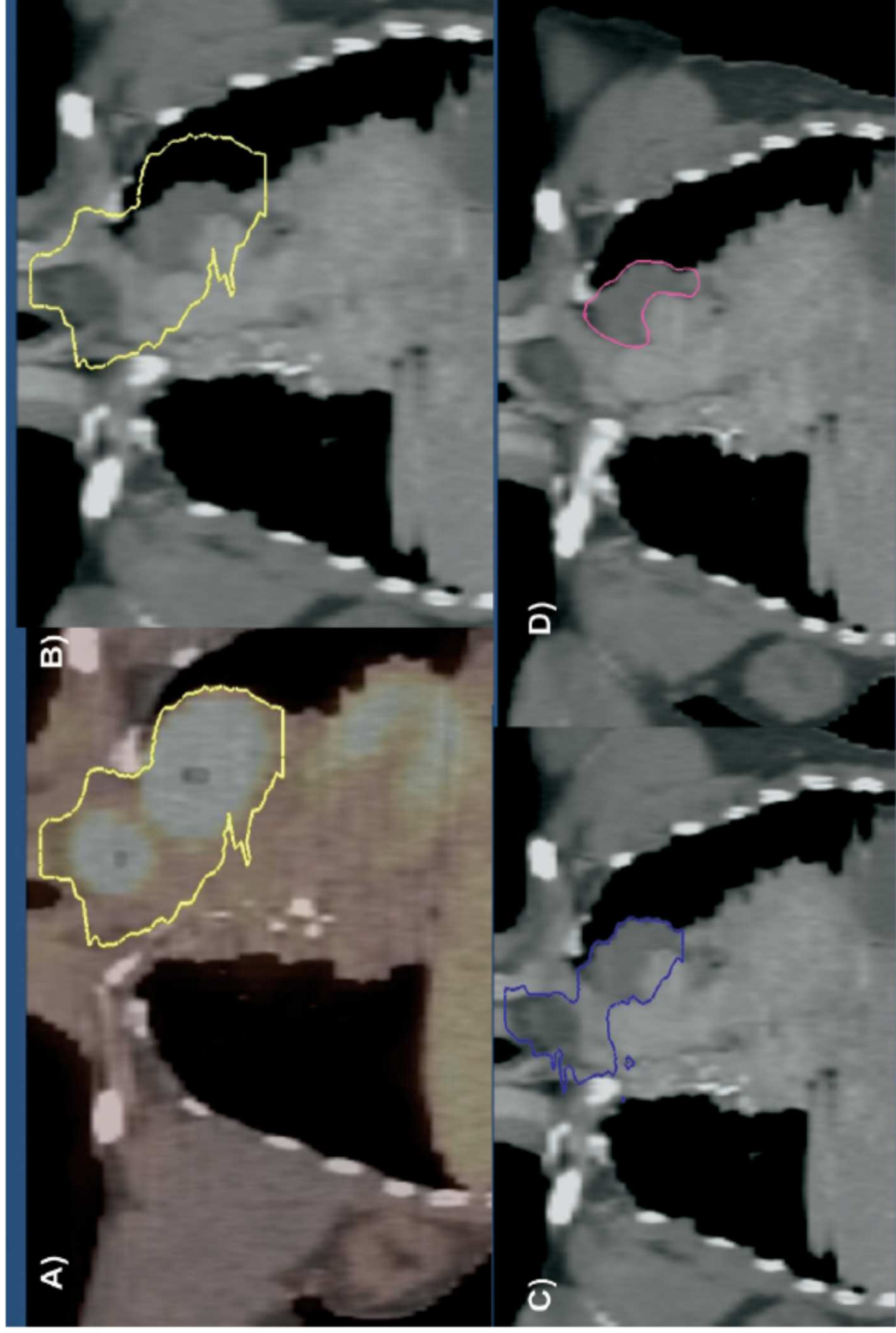
## MEDIASTINUM IN PARTIAL REMISSION



**Figure 9** Determination of a CTV and a GTV in a mediastinal area in PR after chemotherapy.



**Figure 10** (A) Yellow contouring outlines the initial volume on a prechemotherapy axial CT scan. (B) Red outlines PET+ areas on the coregistered prechemotherapy CT and FDG-PET. (C) Initial volume superimposed on the postchemotherapy CT scan. (D) Green outlines the CTV. (E) Pink outlines the GTV which will receive the additional boost.



**Figure 11** (A) Yellow outlines the initial volume on a prechemotherapy coronal CT scan. (B) Initial volume superimposed on the postchemotherapy CT scan. (C) Blue outlines the CTV. (D) Pink outlines the GTV which will receive the additional boost.

# TREATMENT AND DOSE PRESCRIPTION

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PTV1 – 30 GY

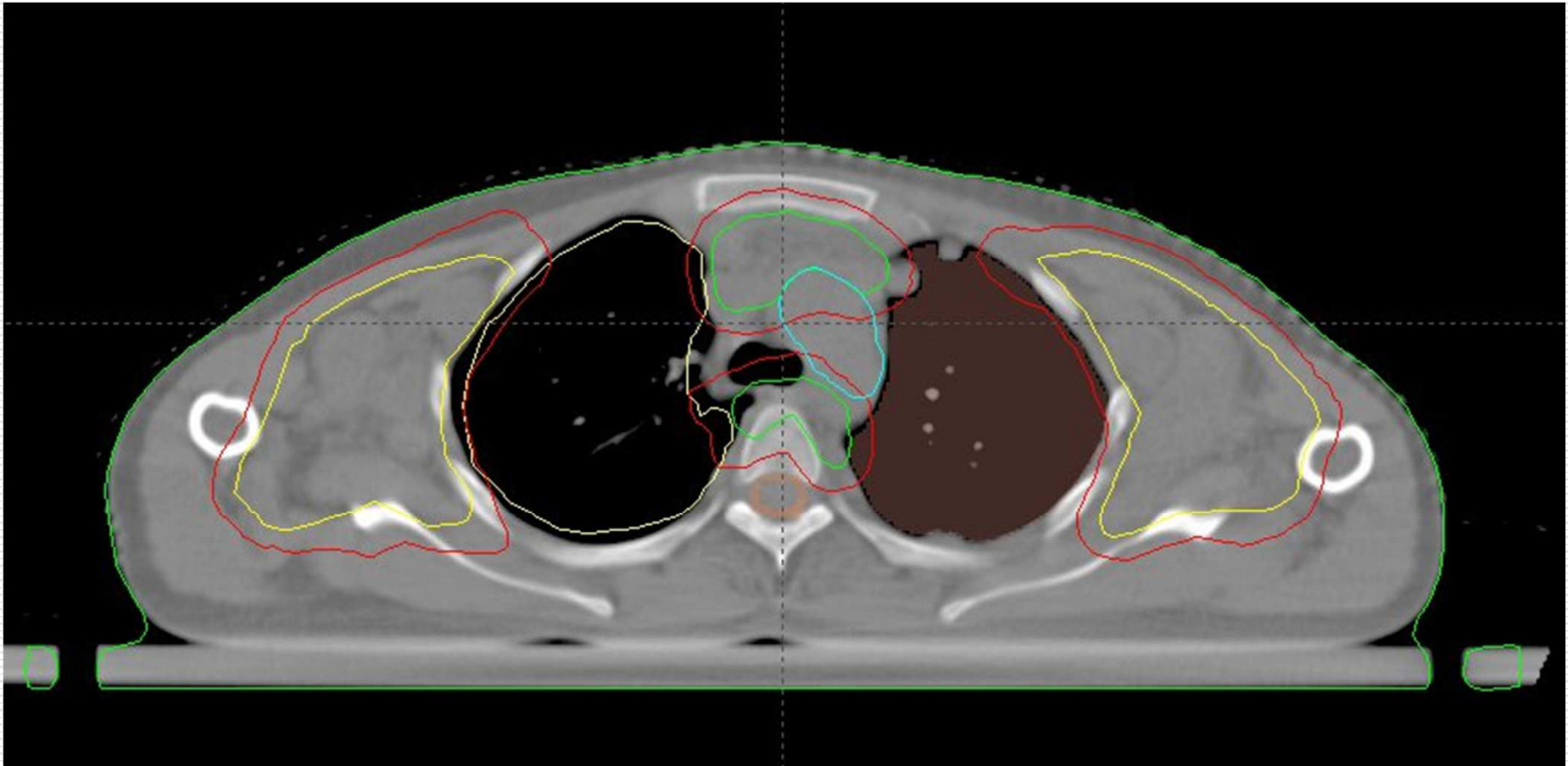
PTV2 – 6 GY

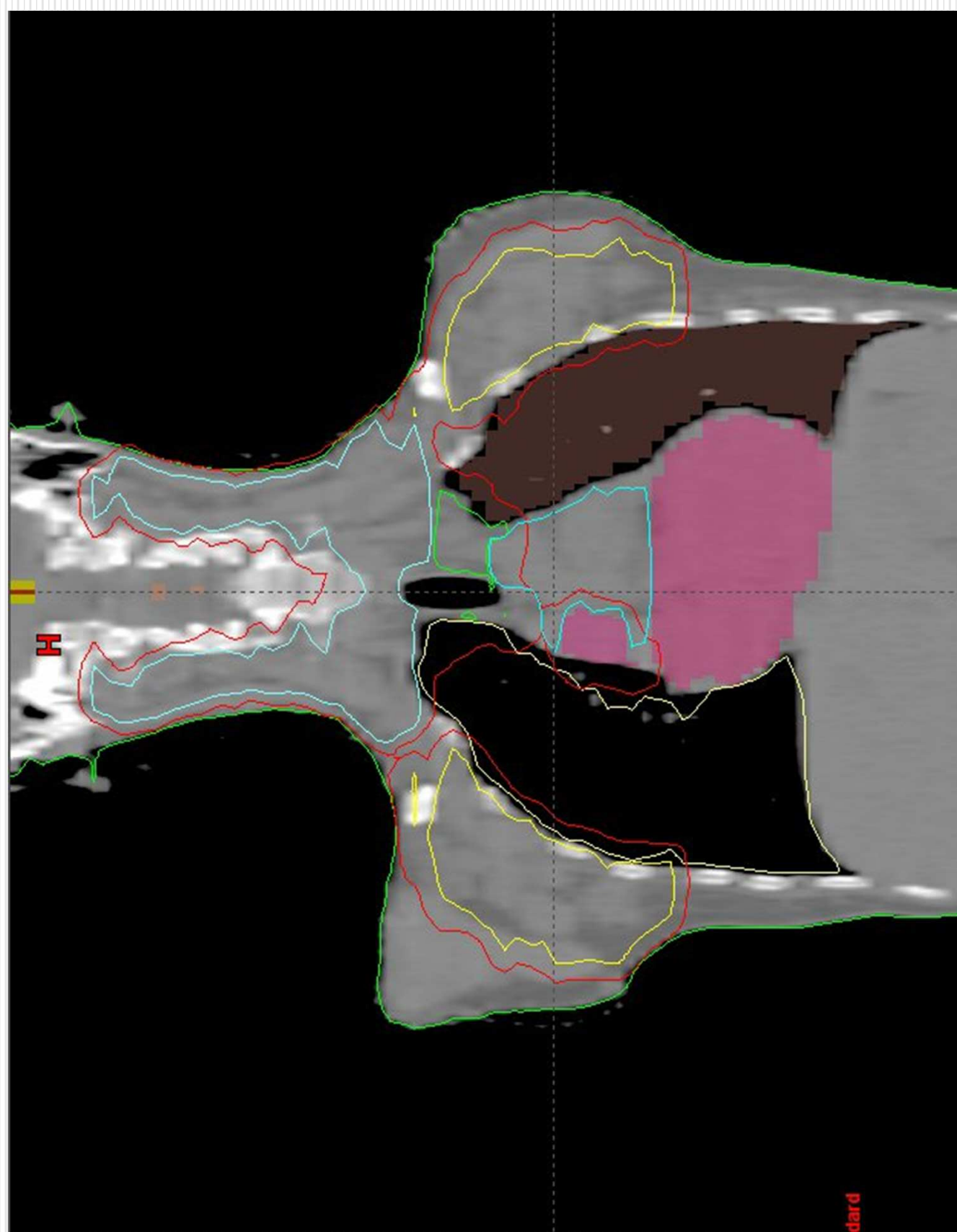
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## HODGKIN'S DISEASE

ABVD X 6 Cycles ----- Relapsed Salvage MINE X 2 cycles  
Progressive Disease + Chest Wall Nodule







Patient: [REDACTED]

No Photo  
DOB: Jul 9, 1986  
ID: BZ/14658  
Sex: F  
Plan date: Feb 1, 2008 11:34:41 AM  
Oncologist:  
Disease: 1

Plan: Plan\_02  
Plan status: Approved  
DOA plan: Plan\_01  
Patient position: HFS

What's Next



#### Define Rx Constraints

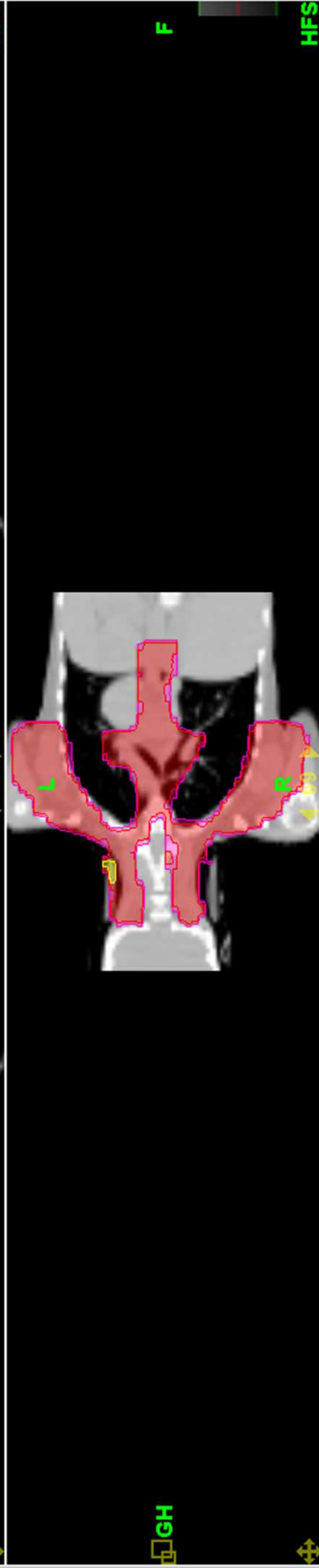
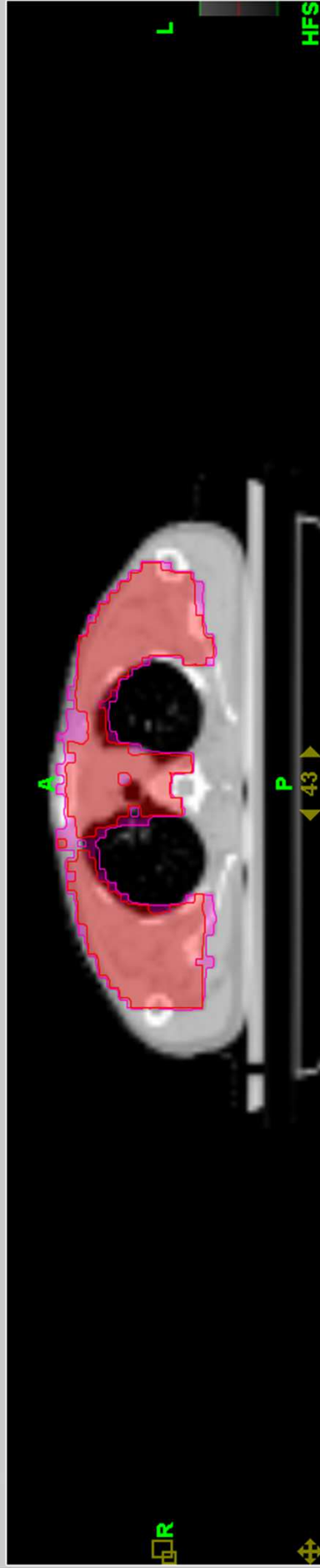
- Define constraints for tumors.
- Define constraints for sensitive structures.
- Set isodose display options.
- When you are satisfied, click **Start** to begin optimization.

User: Physicist



ROIs Optimization Fractionation Delivery QA Setup Delivery QA Analysis

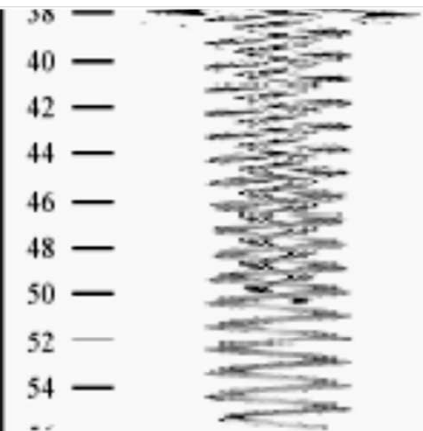
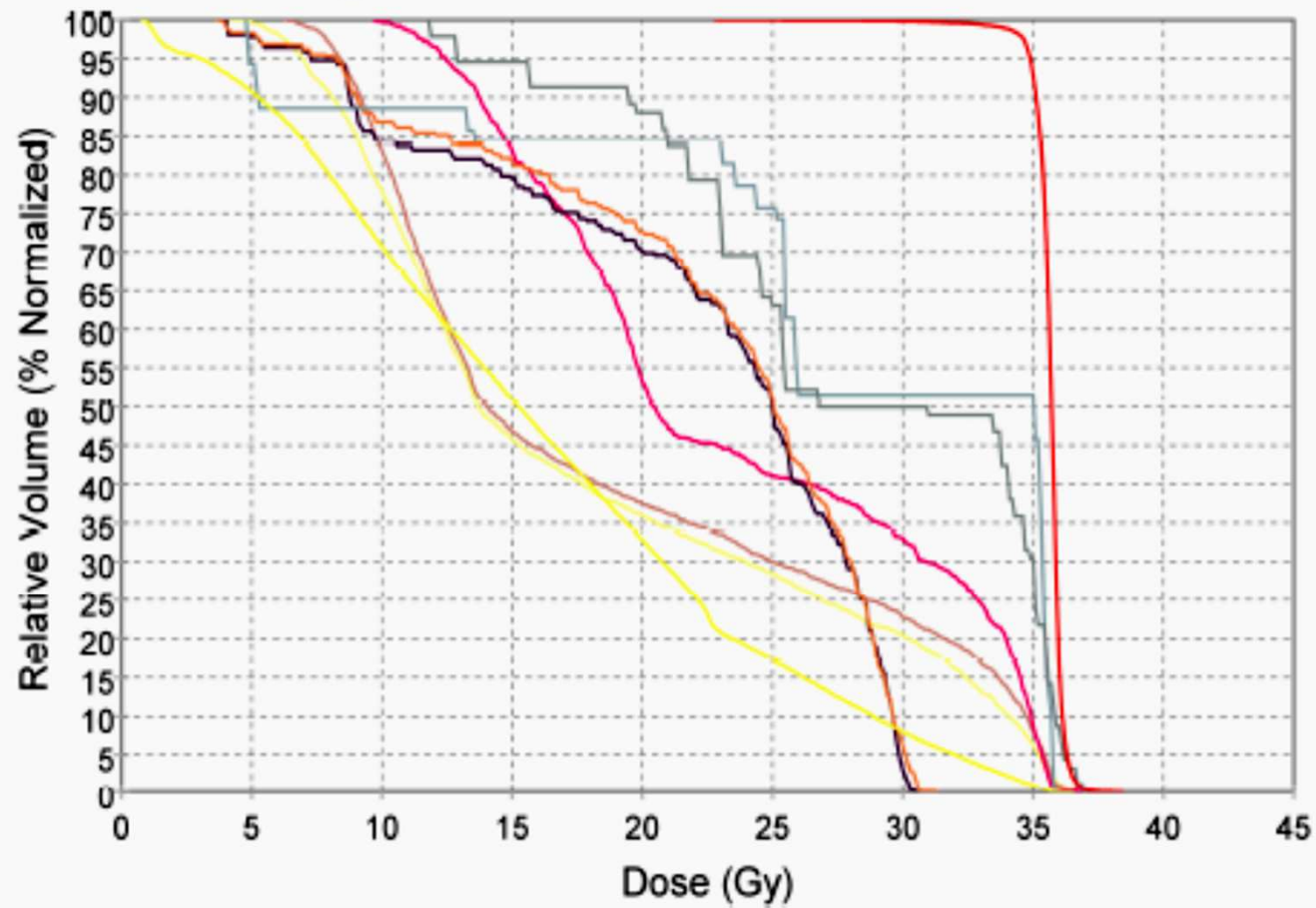
Patient Images





# TOMOTHERAPY DVH

Dose-Volume Histogram - Cumulative Mode Relative



Legend	
LUNG RT	
Lung(L)	
Heart	
PRV CORD	
Parotid(L)	
Parotid(R)	
PTV All	
PTV Shell	



# PTV Dose

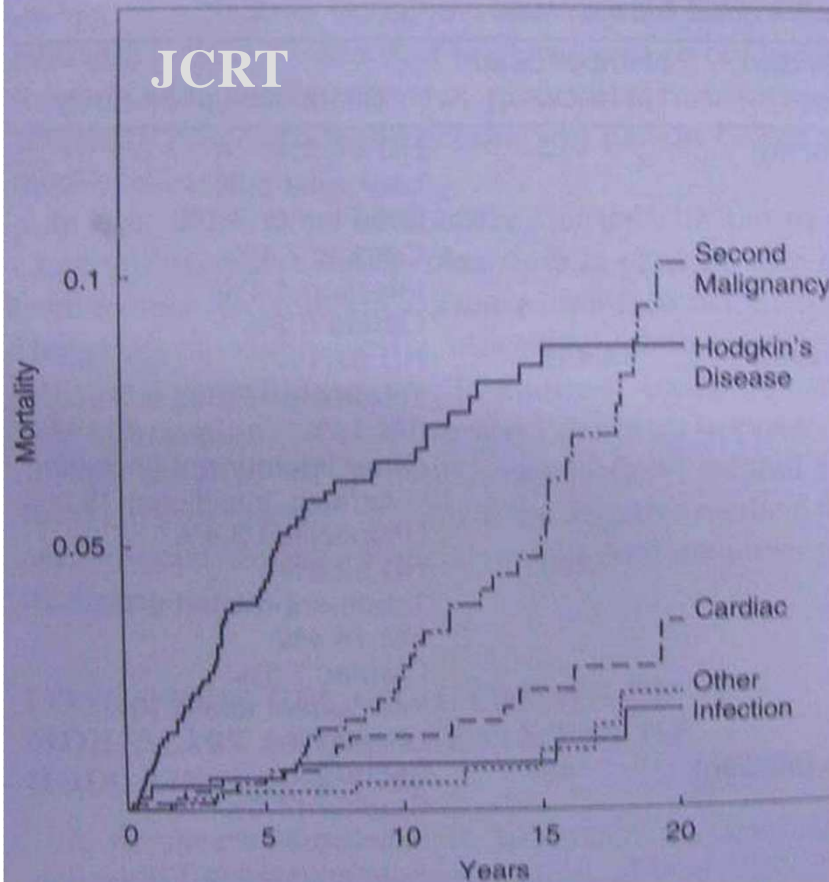
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	Tomotherapy	Con. IMRT
V95 %	99.44%	69%
V99%	98.44%	53%
V107%	0.1%	15%

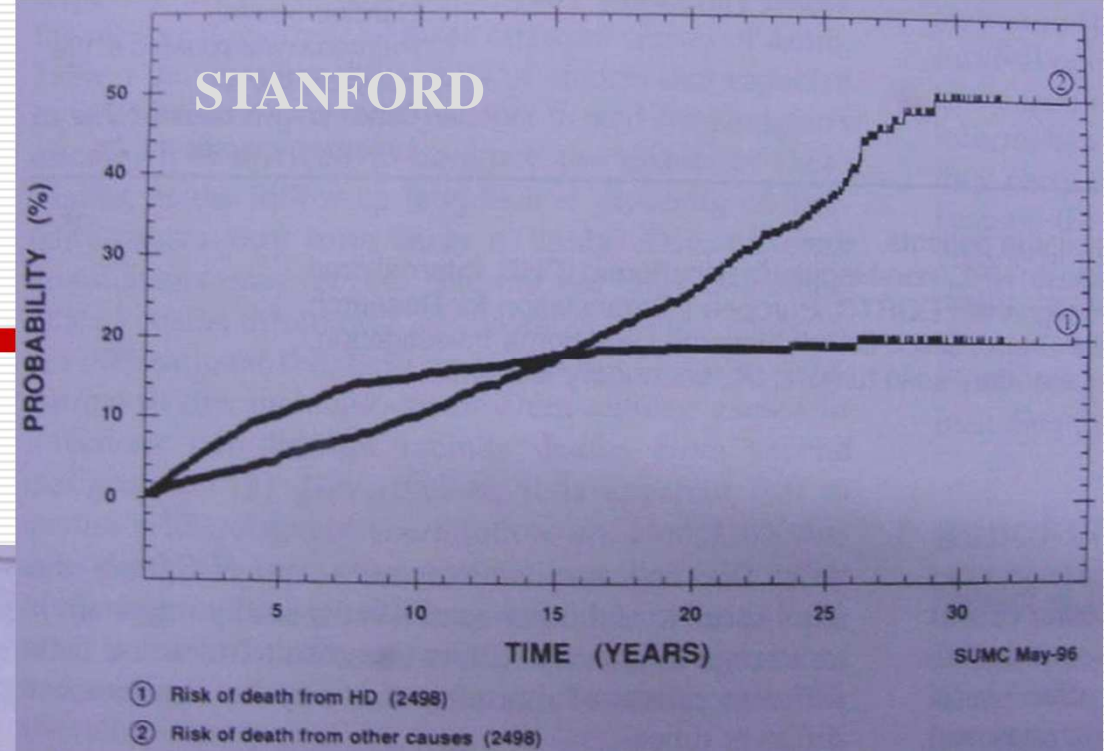
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# LATE CAUSES OF DEATH IN HODGKIN'S DISEASE

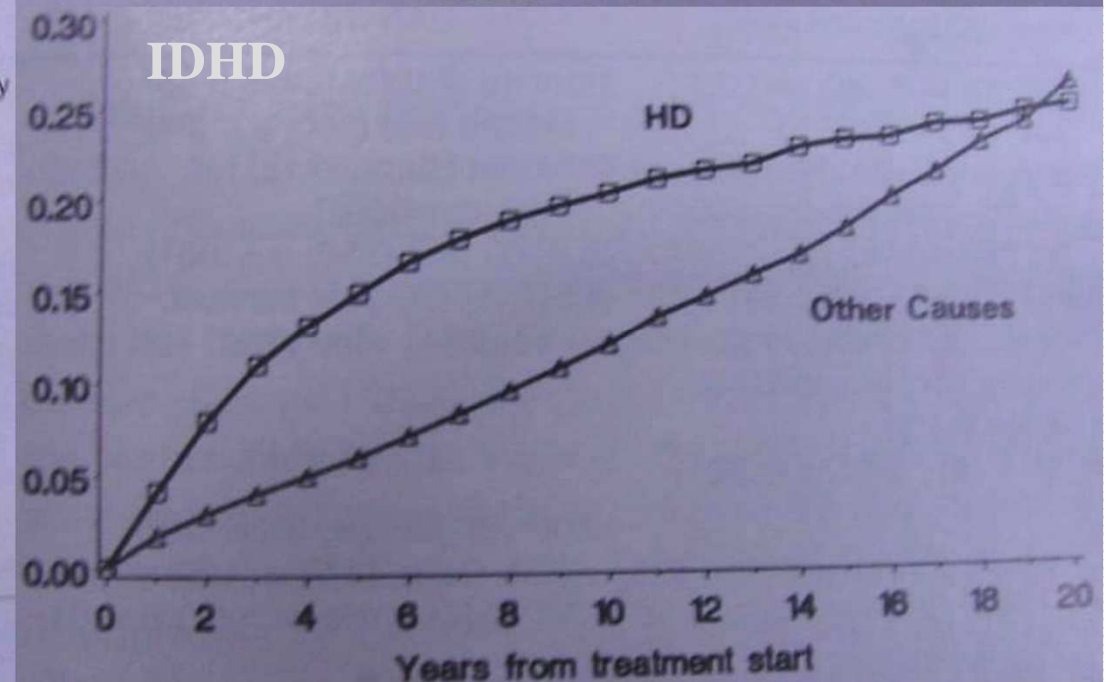
JCRT



STANFORD



IDHD



# LATE EFFECTS OF HODGKIN'S DISEASE TREATMENT

Musculoskeletal abnormalities

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Pulmonary Sequelae

Cardiovascular Sequelae

Thyroid dysfunction

Second Malignancies

Leukemogenesis

NHL

Solid Tumors

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# GROWTH, HEIGHT, MUSCULOSKELETAL EFFECTS

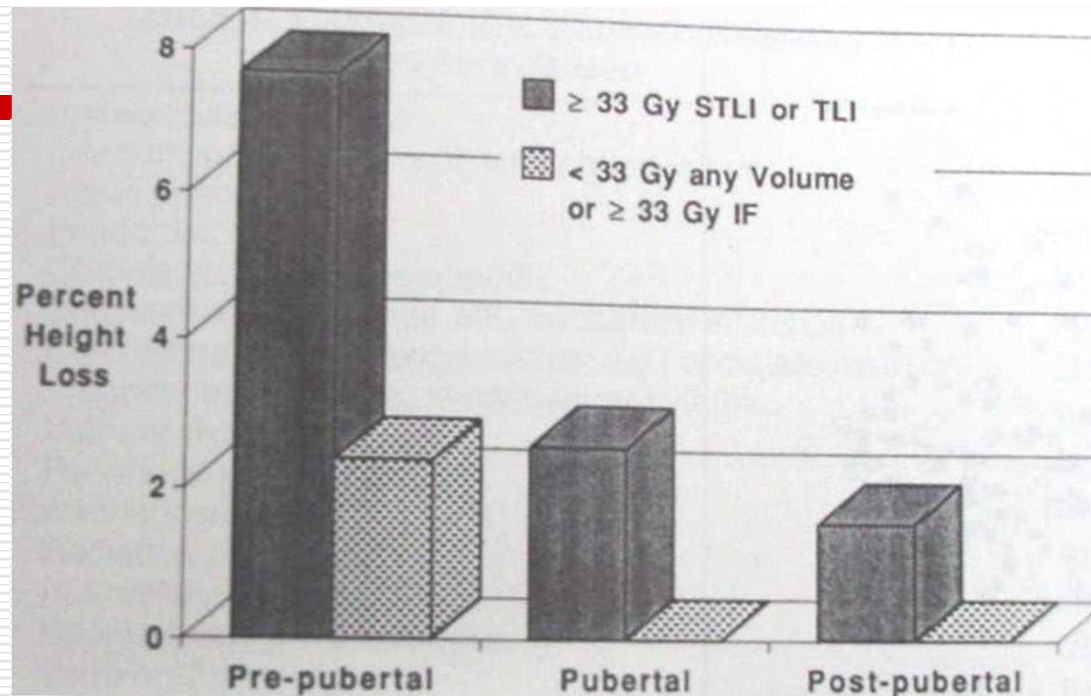
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## Factors Influencing Growth

- Chronological age at treatment
- RT volume
- Total RT dose
- RT dose per fraction
- Site of treatment
- Homogeneity of growth plate irradiated
- Surgery
- Chemotherapy



## RELATIVE LOSS OF ADULT HEIGHT



- 7.7% (13cm) with RT dose  $> 33$ Gy, Entire spine (pre-pubertal age)
- No clinically significant loss of height with low dose RT
- IFRT associated with clinically insignificant height loss
- No disproportion between sitting & standing height

## CARDIOVASCULAR LATE EFFECTS

<b>STANFORD (1960-1995)</b>	2498 Pts.	754 Deaths	16% CV disease
<b>JCRT (1969-1996)</b>	794 Pts.	124 Deaths	14% CV disease
<b>EORTC (1963-1986)</b>	1449 Pts.	240 Deaths	7% CV disease
<b>BNLI</b>	1043 Pts.	43 Deaths	14% CV disease

Decreasing CV deaths with improving therapy (CT & RT)

Stage I & II at Stanford (CV deaths after 15yrs of treatment)

1962 - 1980: 812 pts. ----- 5.4%

1980 – 1996: 628 pts. ----- 0.8%

## RISK OF SECOND CANCERS

TYPE/ SITE	RELATIVE RISK	ABSOLUTE RISK /10,000 pts, Per Yr.	RELATIVE RISK In 10yr survivor	ABSOLUTE RISK In 10yr survivor Per 10,000 pts, Per Yr.
All cancers	3.5 (3.1 – 3.8)	56.2	4.7 (3.8 – 5.7)	111.7
Leukemia	32.4 (25.5 – 40.6)	16.8	16.2 (6.5 – 33.3)	9.9
NHL	18.6 (13.8 – 24.6)	10.7	32.7 (19.7 – 51.1)	27.8
Solid tumors	2.4 (2.1 – 2.7)	29.3	3.6 (2.8 – 4.6)	74.4
Female breast	2.5 (1.8 – 3.4)	11.3	4.6 (3.0 – 6.6)	39.5
Lung	4.2 (3.3 – 5.2)	13.5	7.3 (4.7 – 10.6)	33.8

*Van Leeuwen FE, J Clin Oncol 1994;12:312*

*Swerdlow AJ, Br Med J 1992;304:1137*

*Tucker MA, NEJM 1988;318:76*