Radiotherapy in Management of Neuroblastoma

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Neuroblastoma: Factsheet

477,000 new cancer cases per year *(GLOBOCAN, IARC 2012)*

7600 – 22800 childhood cancer,<15yrs age *(Arora et al, IJC 2009)*

304-912 neuroblastoma cases per year *(Jignasa B et al, NJCM India 2011)*

750-800 new cases per year in US

Radiotherapy in Neuroblastoma

- Whom to treat?
- When to treat?
- What to treat?
- How to treat?

"It is a capital mistake to theorize before you have all the evidence. It biases the judgment"…

Sherlock Holmes

Neuroblastoma

- Unique biology
- Commonest malignancy in infants & 3rd most common in children
- Molecular biological assays influence treatment and prognosis

Natural History

- **Arise from any site in Sympathetic NS**
  - Adrenal medulla, paraspinal ganglia, thorax, H&N.
- **>70% metastatic disease at presentation**
  - nodes, bone, liver, marrow, skin.
- **Spontaneous remission known**

Pathology

Blue Round Cell Tumor

- Ganglioneuroma
- Ganglioneuroblastoma
- Neuroblastoma

Shimada Grading System -
Favorable OR Unfavorable

Stromal Development, MKI, neuroblastic differentiation

Shimada H et al, J Natl Cancer Inst 1984

BE ReD RAM With MeN!!

- **B**urkitt's lymphoma and other lymphoblastic lymphoma
- **E**wing Sarcoma
- **Re**tinoblastoma
- **D**esmoplastic small round blue cell tumor
- **R**habdomyosarcoma
- **A**cute lymphoblastic Leukemia
- **M**edulloblastoma, and other PNET
- **Wi**lms tumor
- **Me**sothelioma, small cell
- **N**euroblastoma

International Neuroblastoma Staging System (INSS)

Stage 1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive).
Stage 2A	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.
Stage 2B	Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically.
Stage 3	Unresectable unilateral tumor infiltrating across the midline,[a] with or without regional lymph node involvement; *or* localized unilateral tumor with contralateral regional lymph node involvement; *or* midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement.
Stage 4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for stage 4S).
Stage 4S	Localized primary tumor (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, and/or bone marrow[b] (limited to infants, 1 year of age).

[a]The midline is defined as the vertebral column. Tumors originating on one side and "crossing the midline" must infiltrate to or beyond the opposite side of the vertebral column.

[b]Marrow involvement in stage 4S should be minimal, that is, less than 10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate. More extensive marrow involvement would be considered to be stage 4. The MIBG scan (if done) should be negative in the marrow.

Brodeur GM, JCO 1993

COG Risk Grouping

International neuroblastoma staging system	Age (Days)	*MYCN*	Histology	Ploidy	Risk
1	Any	Any	Any	Any	Low
2A/2B	Any	Nonamplified	Any	Any	Low
	Any	Amplified	Any	Any	High
3	<547	Nonamplified	Any	Any	Intermediate
	Any	Amplified	Any	Any	High
	≥547	Nonamplified	Favorable	–	Intermediate
	≥547	Nonamplified	Unfavorable	–	High
	≥365 <547	Nonamplified	Any		Intermediate
4	<547	Nonamplified	Any	Any	Intermediate
	Any	Amplified	Any	Any	High
4S	<365	Nonamplified	Favorable	DI > 1	Low
	<365	Nonamplified	Favorable	DI = 1	Intermediate
	<365	Nonamplified	Unfavorable	Any	Intermediate
	<365	Amplified	Any	Any	High

Treatment of Neuroblastoma

Surgery –

- Pivotal role both diagnostic & therapeutic
- Second look surgery
- Extent of Resection – ‘Controversial’

Chemotherapy –

- Dominant modality in IR and HR disease
- Low Risk patients with symptomatic involvement of vital organs

Radiotherapy –

- Radiosensitive BUT not a radiocurable tumor
- Limited role –
  High Risk patients, Unrersectable, Progressive disease, Palliation, TBI

Treatment Recommendations and Role of Radiation

Low Risk Group

Low Risk Group

INSS Stage	Age (days)	MYCN	Histology	Ploidy
1	Any	Any	Any	Any
2A/2B	Any	Non amplified	Any	Any
4S	<365	Non amplified	Favorable	DI>1

Treatment: Low Risk NB

Surgical removal in Stage 1 and 2

No role of radiotherapy in INSS 1 or 2
(even with macroscopic residual disease)

Role of chemotherapy or RT –

- ✓ **Cord compression, respiratory compromise**
- ✓ **In Unresectable tumors after chemotherapy**

Treatment: Low Risk NB

Surgical removal in Stage 1 and 2

Perez et al, *JCO 1991*:
93% EFS for Stage 1 with Surgery alone

6/10 recurrences – distant, OS - 99%

Atkinson JB et al, CCG Study, *JCO 2000*:
233 stage 2 pts, no MYCN amplification, Sx alone

4yr EFS – 81%, 4yr OS – 98%

Low Risk NB

No role of chemotherapy or radiotherapy in INSS 1 or 2 (even with macroscopic residual disease)

Strother D et al, COG P9641, *JCO 2012* –

Prospective study, 915 INSS Stage 2A/2B pts

Sx alone, Chemotherapy for<50% resection or progression

Stage 2A/2B – 5yr EFS: 89%, OS: 97%
Stage 1 – 5yr OS:99%
Stage 4S – 5yr OS:91%

Role of chemotherapy or RT –

Cord compression, respiratory compromise

In Unresectable tumors as pre-op chemotherapy

Chemotherapy or Radiation Did not Improve DFS

Matthay's series, non randomized, EDIIA disease

# of pts	Treatment	6 yr DFS
75	Surgery alone	89%
66	Surgery+ Chem or RT	94%, p=NS
40 (R1/R2)	Surgery alone	92%
59 (R1/R2)	Surgery+RT	90%, p=NS

No improvement in DFS with RT in patients with gross or microscopic residual disease!

Matthay KK et al, JCO, 1989

Radiotherapy in Neuroblastoma
Low Risk

- Whom to treat?
  Cord compression, Respiratory compromise
- When to treat?
  Immediate or Sx/chemotherapy failure
- What to treat?
- How to treat?

No role in low risk, completed resected, localized disease

Treatment Recommendations and Role of Radiation

Intermediate Risk Group

Intermediate Risk NB

INSS Stage	Age (days)	MYCN	Histology	Ploidy
3	<547	Non amplified	Any	Any
	≥547	Non amplified	Favorable	-
	≥365 <547	Non amplified	Any	
4	<547	Non amplified	Any	Any
4S	<365	Non amplified	Favorable	DI=1
	<365	Non amplified	Unfavorable	Any

Treatment: IR NB

Options –

- Surgery + Adjuvant Chemotherapy
- Pre-op CT (if unresectable) followed by Surgery
- Surgery + Observation in infants
- Radiotherapy – Limited role/Controversial

Successful Treatment of Stage III Neuroblastoma Based on Prospective Biologic Staging: A Children's Cancer Group Study

By Katherine K. Matthay, ... nada, James B. Atkinson, C. Thomas Black, ... and John N. Lukens

- CCG Study, Evans Stage 3
- 143/228 pts met IR criteria
- CT f/b Sx. RT for R2 resection

Results –

1. Normal MYCN, Fav Shimada/ Low Sr Ferritin:
   4yr EFS = 100%

2. Infants with at least one unfav factor:
   4yr EFS = 90%, OS = 93%

3. >1yr and atleast one unfav factor:
   4yr EFS = 75%

4. RT not prognostic for EFS

Multivariate analysis – Age, MYCN

Purpose: To identify ... unfavorable subset of ... neuroblastoma and to ... stratification would imp... (EFS) for high-risk patien... for the lower-risk patient...

Patients and Methods: ... formed by age, *MYCN* ... histopathologic classifica... Lower-risk patients were ... Children's Cancer Group ... patients were treated a... more intensive multimo... cases, autologous bone m...

Results: Of 228 Evans ... the study, 92% also met the definition of International Neuroblastoma Staging System (INSS) stage 3. One hundred forty-three patients met the lower-risk criteria, which included 89 patients less than 1 year of age and 54 patients 1 year of age or greater, and favorable biology, whereas 85 patients were 1 year of age or greater and biologically unfavorable. Biologically unfa-... ge or greater who under-... n had improved survival, ...nts or biologically favor-... hange according to resec-... was 100% for the patients ...y age, 90% for those less ... at least one unfavorable ... Evans stage III patients 1 ...unfavorable biology. Age, ...ber, Shimada histopathol-...inal extension were signifi-...ctors for all patients, but ...d age were independent ...es. ...survival of the biologically favorable group and the historically improved EFS of the biologically unfavorable group suggest that biologic staging should be used to define the prognosis and treatment of stage III neuroblastoma.

J Clin Oncol 16:1256-1264. © *1998 by American Society of Clinical Oncology.*

Radiotherapy Improves the Outlook for Patients Older Than 1 Year With Pediatric Oncology Group Stage C Neuroblastoma

By R.P. Castleberry, L.E. Kun, J.J. Shuster, G. Altshuler, I.E. Smith, R. Nitschke, M. Wharam, N. McWilliams, V. Joshi, and F.A. Hayes

- **Phase 3 Trial**
- **>1yr <21, POG Stage C, +ve regional nodes**
- **Randomised to CT alone or CT+RT**

RT –

24Gy (age 12-24mths), 30Gy (age>24mths)@1.5Gy/#

Results –

Significant increase in EFS & OS with RT

Children older t… f 29 eligible
toma with comp… ved CR, and
tumor and posi… hs (median,
ric Oncology G… 33 eligible
higher-risk sub… 19 are NED
importance of … erapy. Local
neuroblastoma… rms. Differ-
of adding concu… rvival rates
therapy (CT) in t… 08, respec-
conducted. Eligible patients received cyclophospha- tively. Surgical compliance was excellent and complica-
mide 150 mg/m² orally days 1 to 7 and Adriamycin tions uncommon. Therapy was tolerable in both groups
mg/m² day 3 (CDP/VM) for two courses each. Second- therapy.
ary CT with CDP/VM alone was available for patients
not achieving complete response (CR) following induc-

DeBernardi et al. *Cancer* 1987– Italian Cooperative Group for Neuroblastoma

Prospective randomized trial
age > 1 yr
minimal gross residual post-op or involved nodes
Randomization: (1) RT (20-30 Gy) OR (2) no RT
No difference in RFS rate

J Clin Oncol 9:789-795.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Outcome after Reduced Chemotherapy for Intermediate-Risk Neuroblastoma

David L. Baker, M.D., Mary L. Schmidt, M.D., Susan L. Cohn, M.D., John M. Maris, M.D., Wendy B. London, Ph.D., Allen Buxton, M.S., Daniel Stram, Ph.D., Robert P. Castleberry, M.D., Hiroyuki Shimada, M.D., Anthony Sandler, M.D., Robert C. Shamberger, M.D., A. Thomas Look, M.D., C. Patrick Reynolds, M.D., Ph.D., Robert C. Seeger, M.D., and K

Prospective study, 479 pts
IR, normal MYCN
Pre-op CT –
4 cycles – pts with fav features
8 cycles – unfav profile or incomplete response

Results –
3yr OS – 96%
Fav biology – 98%, Unfav features – 93%

BACKGROUND
The survival
dose-intensi
receive reduc

METHODS
We conducte
3-year estima
tions in the
therapy assig
roblastoma w
of age) who
tumors with
ease with a
who had dis
assigned to
either unfavorable feature were assigned to eight cycles.

RESULTS
Between 1997 and 2005, a total of 479 eligible patients were enrolled in this trial (270 patients with stage 3 disease, 178 with stage 4 disease, and 31 with stage 4S disease). A total of 323 patients had tumors with favorable biologic features, and 141 had tumors with unfavorable biologic features. Ploidy, but not histopathological features, was significantly predictive of the outcome. Severe adverse events without disease progression occurred in 10 patients (2.1%), including secondary leukemia (in 3 patients), death from infection (in 3 patients), and death at surgery (in 4 patients). The 3-year estimate (±SE) of overall survival for the entire group was 96±1%, with an overall survival rate of 98±1% among patients who had tumors with favorable biologic features and 93±2% among patients who had tumors with unfavorable biologic features.

CONCLUSIONS
A very high rate of survival among patients with intermediate-risk neuroblastoma was achieved with a biologically based treatment assignment involving a substantially reduced duration of chemotherapy and reduced doses of chemotherapeutic agents as compared with the regimens used in earlier trials. These data provide support for further reduction in chemotherapy with more refined risk stratification. (Funded by

ncess Margaret Hospital for rth, Australia (D.L.B.); the Illinois at Chicago College (M.L.S.), and the Comer ospital and the University of .C.) — both in Chicago; the spital of Philadelphia and the Pennsylvania School of Medelphia (J.M.M.); Children's ston and Harvard Medical n (W.B.L., R.C. Shamberger); s Oncology Group Statistics ter, Arcadia, CA (A.B.); Chiltal of Los Angeles, Universirn California, Los Angeles .C. Seeger); the University of mingham (R.P.C.); the Chilnal Medical Center and the hington University Medical Center, Washington, DC (A.S.); St. Jude Children's Research Hospital, Memphis, TN (A.T.L.); Texas Tech University Health Sciences Center, Lubbock (C.P.R.); and the University of California San Francisco Benioff Children's Hospital and University of California San Francisco School of Medicine, San Francisco (K.K.M.). Address reprint requests to Dr. Matthay at the Department of Pediatrics, University of California at San Francisco School of Medicine, 505 Parnassus Ave., Rm. M 647, San Francisco, CA 94143-0106, or at matthayk@peds.ucsf.edu.

*Investigators participating in the Children's Oncology Group study are listed in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2010;363:1313-23.

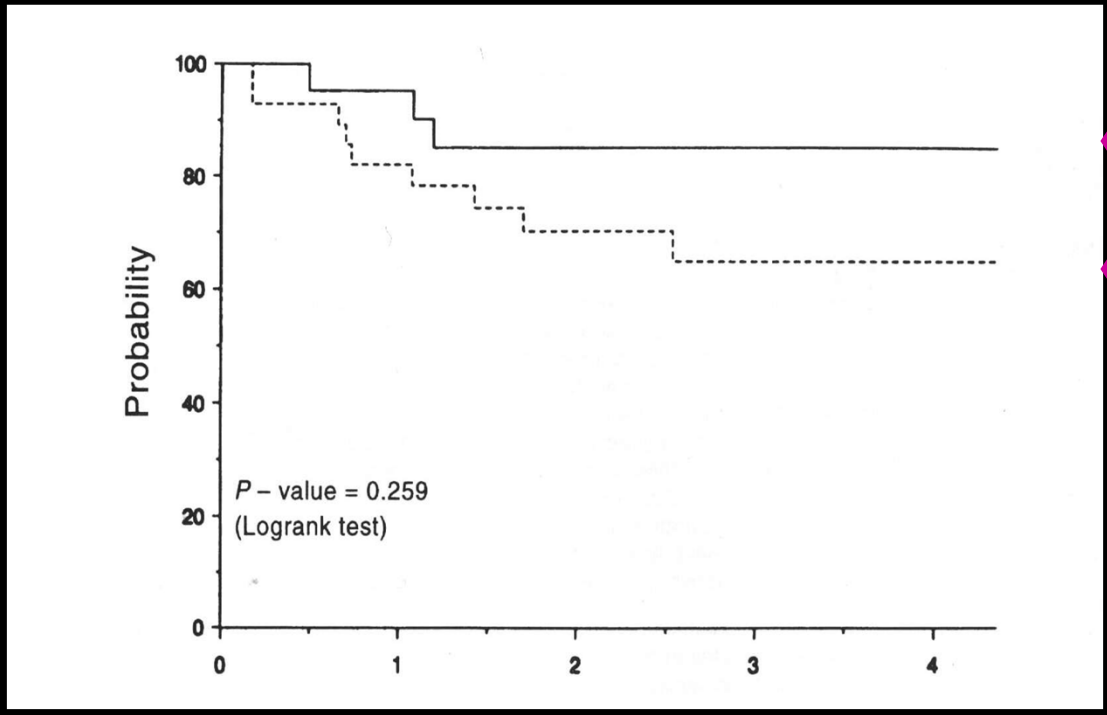
Role of Radiation in Neuroblastoma

Intermediate Risk, EDII, LN- pts

Institution	Radiation	Patients	Survival
CCSG	No	76	89%
SJCRH	No	15	100%
POG	No	61 (14III)	87%
CCSG	Yes	66	94%
Duke	Yes	7	86%
SJCRT	Yes	9	100%
HSC,UK	Yes	24	79%

Radiation is therefore not warranted for this group

Results of Surgery and Chemotherapy
Intermediate Risk



Complete resection

Incomplete resection

Event free survival with INSS stage 2B or 3, treated by POG 8742 and 9244

Positive surgical margin does not warrant postoperative radiation therapy in intermediate risk neuroblastoma

Strother et al, Eur. J. Cancer, 1997

Role of Radiation in Neuroblastoma

Intermediate Risk, EDIII/POG C or LN+pts

Institution	Radiation	Patients	Survival
SJCRT	No	27	41%
CHOP	No	9	11%
POG	No	29	41%
ICGN	No	129 (B&C)	52%
Duke	Yes	13	69%
JCRT	Yes	16	81%
CHOP	Yes	7	86%
ICGN	Yes	14	64%
POG	Yes	33	73%

Radiation may improve tumor control & survival rates in this group

Radiotherapy in Neuroblastoma
Intermediate Risk

- **Whom to treat?**

  Unresectable Primary s/p Chemotherapy

  Progressive disease post Surgery/Chemotherapy

  Stage 3, node +ve pts (Level III evidence)

- **When to treat?**

  Post surgery for node +ve pts
  Post chemotherapy for unresectable disease

- **What to treat?**

- **How to treat?**

No unequivocal recommendations in Stage 3 disease

Treatment Recommendations and Role of Radiation

High Risk Group

High Risk NB

INSS Stage	Age (days)	MYCN	Histology	Ploidy
1 2A/2B	Any	Amplified	Any	Any
3	Any	Amplified	Any	Any
	≥547	Non amplified	Unfavorable	-
4	Any	Amplified	Any	Any
4S	<365	Amplified	Any	Any

Treatment: High Risk NB

- Poor survival rates (15-30% @ 5yrs)
- Intensive protocols
- Three phases –
  Induction Therapy – max reduction in bulk at primary & metastatic sites
  Consolidation Therapy – eliminate resistant tumor clones
  Maintenance Therapy – eradicate any residual tumor cells

Local control (Stage 4 Neuroblastoma)

- Predilection of recurrences in previous sites of disease
- Surgical resection of primary a/w improved local control & survival
- Role of RT @ Primary site & bulky metastatic sites to improve tumor control rates

Matthay KK, JCO 1993; Sibley GS, IJROBP 1995

Int. J. Radiation Oncology Biol. Phys., Vol. 46, No. 4, pp. 969–974, 2000

0360-3016/00/$–see front matter

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CLINICAL INVESTIGATION **Pediatric Tumors**

LOCAL CONTROL WITH MULTIMODALITY THERAPY FOR STAGE 4 NEUROBLASTOMA

SUZANNE L. WOLDEN, M.D.,* SMITHA V. GOLLAMUDI, M.D.,* BRIAN H. KUSHNER, M.D.,† MICHAEL LAQUAGLIA, M.D.,‡ KIM KRAMER, M.D.,† NANCY ROSEN, M.D.,§ SARA ABRAMSON, M.D.,§ AND NAI-KONG V. CHEUNG, M.D., PH.D.†

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Purpose: To evaluate the efficacy of 21 Gy hyperfractionated radiotherapy for local control in conjunction with surgery and intensive systemic therapy for patients with Stage 4 neuroblastoma.

Methods and Materials: After achieving a partial or complete remission, 47 children, ages 1–10 years, with Stage 4 neuroblastoma were treated on four consecutive institutional protocols (N4–N7) with dose-intensive multi-agent chemotherapy, maximal surgical debulking, and hyperfractionated radiotherapy (1.5 Gy twice a day to 21 Gy). Radiotherapy fields encompassed the initial tumor volume and regional lymph nodes plus a 3-cm margin. This was followed by consolidation with either autologous bone marrow transplantation (N4 and N5) or immunotherapy (N6 and N7).

Results: Forty-five of 47 patients had a complete response to surgery and chemotherapy prior to radiotherapy. Five-year actuarial rates of local control, progression-free survival, and overall survival were 84%, 40%, and 45%, respectively. Among 26 patients who relapsed, 1 failed only at the primary site, 22 developed distant metastases exclusively, and 3 had both local and distant failures. There were no acute complications of radiotherapy.

Conclusion: Hyperfractionated radiotherapy to 21 Gy, in conjunction with dose-intensive systemic therapy and aggressive surgical resection, is well tolerated and is associated with durable local control for most patients with Stage 4 neuroblastoma. © 2000 Elsevier Science Inc.

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doi:10.1016/S0360-3016(02)04506-6

CLINICAL INVESTIGATION **Pediatrics**

IMPACT OF RADIOTHERAPY FOR HIGH-RISK NEUROBLASTOMA: A CHILDREN'S CANCER GROUP STUDY

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Purpose: To assess the effect of local radiation administered to primary disease sites in children with high-risk neuroblastoma.

Methods and Materials: A total of 539 eligible patients were entered on protocol CCG-3891, consisting of chemotherapy, primary surgery, and 10 Gy of external beam radiation therapy (EBRT) to gross residual disease, followed by randomized assignment to continuation chemotherapy (CC) or autologous bone marrow transplantation (ABMT). ABMT patients received total body irradiation (TBI).

Results: Estimated event-free survival and overall survival at 5 years were 25% ± 2% and 35% ± 2%, respectively. Estimated 5-year locoregional recurrence rates were 51% ± 5% and 33% ± 7% for CC and ABMT patients ($p = 0.004$). For patients who received 10 Gy of EBRT to the primary, the addition of 10 Gy of TBI and ABMT decreased local recurrence compared with CC (22% ± 12% and 52% ± 8%, $p = 0.022$). EBRT did not increase acute toxicity, except for increased total parenteral nutrition administration.

Conclusions: In combination with EBRT to the primary tumor site, the addition of 10 Gy of TBI as a component of high-dose chemotherapy with ABMT improved local control compared with CC without TBI. Results suggest a dose–response relationship for local EBRT. Short-term toxicity of local EBRT is limited.

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CLINICAL INVESTIGATION **Pediatric**

EXCELLENT LOCAL CONTROL FROM RADIATION THERAPY FOR HIGH-RISK NEUROBLASTOMA

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Purpose: Local recurrence has been demonstrated in previous studies to be one of the obstacles to cure in neuroblastoma. Radiation therapy indications, optimal dose, and technique are still evolving. Here we report our experience of high-risk neuroblastoma patients who received local radiation therapy as part of their cancer management.

Methods and Materials: We conducted a retrospective study of 34 high-risk neuroblastoma patients who received radiation therapy to local sites of disease from March 2001 until February 2007 at our institution as part of their multimodality therapy.

Results: At a median follow-up of 33.6 months, 6 patients died of disease, 7 patients were alive with disease, and 21 patients were in clinical remission. Eleven patients relapsed, all distantly. Two patients failed locally in addition to distant sites. Both of these patients had persistent gross disease after induction chemotherapy and surgery. Our 3-year local control, event-free survival, overall survival were 94%, 66%, and 86%, respectively.

Conclusion: Patients with high-risk neuroblastoma in our series achieved excellent local control. Doses of 21–24 Gy to the primary tumor site appear to be adequate for local control for patients in the setting of minimal residual disease after induction chemotherapy and surgery. Patients with significant residual disease may benefit from radiation dose escalation, and this should be evaluated in a prospective clinical trial.

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Clinical Investigation

Radiation Therapy to the Primary and Postinduction Chemotherapy MIBG-Avid Sites in High-Risk Neuroblastoma

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Received May 14, 2014, and in revised form Jun 17, 2014. Accepted for publication Jul 14, 2014.

Summary

Radiation therapy to the primary site and postinduction metaiodobenzylguanidine (MIBG)-positive metastatic sites were associated with favorable local control in children with high-risk neuroblastoma. The number of MIBG-avid sites present after induction chemotherapy and surgery was predictive of progression-free and overall survival.

Purpose: Although it is generally accepted that consolidation therapy for neuroblastoma includes irradiation of the primary site and any remaining metaiodobenzylguanidine (MIBG)-avid metastatic sites, limited information has been published regarding the efficacy of this approach.

Methods and Materials: Thirty patients with high-risk neuroblastoma were treated at 1 radiation therapy (RT) department after receiving 5 cycles of induction chemotherapy and resection. All patients had at least a partial response after induction therapy, based upon international neuroblastoma response criteria. The primary sites were treated with 24 to 30 Gy whereas the MIBG-avid metastatic sites were treated with 24 Gy. RT was followed by high-dose chemotherapy with autologous stem cell rescue and 6 months of *cis*-retinoic acid.

Results: The 5-year progression-free survival (PFS) and overall survival (OS) rates were 48% and 59%, respectively. The 5-year locoregional control at the primary site was 84%. There were no differences in locoregional control according to degree of primary surgical resection. The 5-year local control rate for metastatic sites was 74%. The 5-year PFS rates for patients with 0, 1, 2, and >3 postinduction MIBG sites were 66%, 57%, 20%, and 0% ($P<.0001$), respectively, whereas 5-year OS rates were 80%, 57%, 50%, and 0%, respectively ($P<.0001$).

Conclusions: RT to the primary site and postinduction MIBG-positive metastatic sites was associated with 84% and 74% local control, respectively. The number of MIBG-avid sites present after induction chemotherapy and surgery was predictive of progression-free and overall survival.

Radiotherapy in Neuroblastoma
High Risk

- Whom to treat?

  Primary site (regardless of extent of resection)

  Sites of metastatic disease with MIBG activity

- When to treat?

  Post surgery before Consolidation phase

- What to treat?

- How to treat?

Radiotherapy in Neuroblastoma
RT Planning

- Patient Positioning & Immobilisation
- Target volumes & Critical structure delineation
- Dose
- Techniques

Radiotherapy in Neuroblastoma

Positioning & Immobilization

- Supine position, usually sedated
- Arms overhead
- Thermoplastic mould or Vac-Lock
- Contrast CT/MRI scans (3mm axial images)

Radiotherapy in Neuroblastoma

Target Delineation

- Pre surgery or Pre chemo (if unresectable) imaging studies determine volume of irradiation

- Nodal sites –
  - If radiologically/pathologically involved
  - Routine un-involved or next echelon nodal irradiation not done
  - Symmetrical irradiation of bone

Radiotherapy in Neuroblastoma

Target Delineation

GTV – if any residual disease or volume of tumor prior to Sx, but after CT

CTV – GTV+1.5-2cm margin
(include all areas of μscopic disease as per I/o and Path findings)

PTV – Institution protocol (5-10mm)

OARs – Kidneys, Spleen, Liver, Stomach, Iliac crests, Bowel, Gonads

Radiotherapy in Neuroblastoma

Dose

- Debatable (10-45Gy)
- Conventional or Hyperfractionated RT
- May be age dependent *(Jacobson GM, Am J Clin Oncol 1984, Rosen EM, JCO 1984)*
- Presence of residual disease

Am J Clin Oncol. 1984 Dec;7(6):693-7.

Dose response analysis of pediatric neuroblastoma to megavoltage radiation.

Jacobson GM, Sause WT, O'Brien RT.

Abstract

Children with **neuroblastoma** treated in Salt Lake City from 1966 through 1982 were analyzed in an attempt to develop guidelines fo ar attention was addressed to time-dose relationships in those t-resection (Stages II and III). Altogether, 76 patients were ana ge I--100%; Stage II--84%; Stage III--69.2%; Stage IV--14.3%; Sta e correspondingly better in younger children and in infants. on therapy in this population were: unresectable or gross remaining amina; tumor spill during surgery; positive regional lymph nodes or positive surgical margins. Local control was achieved in a majority of patients undergoing surgery and radiation for limited disease. In children younger than 1 year of age, no local failures were observed at doses above 1200 rad. In children between 1-2 years of age, no local failures were observed with doses as low as 1440 rad. In children older than 3 years, local failures were observed up to 4500 rad.

RT Dose

< 1 yr – 12Gy

1-2 yrs – 14.4Gy

>3yrs – 45Gy

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CLINICAL INVESTIGATION **Pediatric Tumors**

LOCAL CONTROL WITH MULTIMODALITY THERAPY FOR STAGE 4 NEUROBLASTOMA

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RT Dose

21Gy, 1.5Gy BID

Purpose: To evaluate the efficacy of 21 Gy hyperfractionated radiotherapy for local control in conjunction with surgery and intensive systemic therapy for patients with Stage 4 neuroblastoma.

Methods and Materials: After achieving a partial or complete remission, 47 children, ages 1–10 years, with Stage 4 neuroblastoma were treated on four consecutive institutional protocols (N4–N7) with dose-intensive multi-agent chemotherapy, maximal surgical debulking, and hyperfractionated radiotherapy (1.5 Gy twice a day to 21 Gy). Radiotherapy fields encompassed the initial tumor volume and regional lymph nodes plus a 3-cm margin. This was followed by consolidation with either autologous bone marrow transplantation (N4 and N5) or immunotherapy (N6 and N7).

Results: Forty-five of 47 patients had a complete response to surgery and chemotherapy prior to radiotherapy. Five-year actuarial rates of local control, progression-free survival, and overall survival were 84%, 40%, and 45%, respectively. Among 26 patients who relapsed, 1 failed only at the primary site, 22 developed distant metastases exclusively, and 3 had both local and distant failures. There were no acute complications of radiotherapy.

Conclusion: Hyperfractionated radiotherapy to 21 Gy, in conjunction with dose-intensive systemic therapy and aggressive surgical resection, is well tolerated and is associated with durable local control for most patients with Stage 4 neuroblastoma.

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ELSEVIER

doi:10.1016/S0360-3016(02)04506-6

CLINICAL INVESTIGATION **Pediatrics**

IMPACT OF RADIOTHERAPY FOR HIGH-RISK NEUROBLASTOMA: A CHILDREN'S CANCER GROUP STUDY

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RT Dose

10Gy EBRT + 10Gy TBI

Purpose: To assess the effect of local radiation administered to primary disease sites in children with high-risk neuroblastoma.

Methods and Materials: A total of 539 eligible patients were entered on protocol CCG-3891, consisting of chemotherapy, primary surgery, and 10 Gy of external beam radiation therapy (EBRT) to gross residual disease, followed by randomized assignment to continuation chemotherapy (CC) or autologous bone marrow transplantation (ABMT). ABMT patients received total body irradiation (TBI).

Results: Estimated event-free survival and overall survival at 5 years were 25% ± 2% and 35% ± 2%, respectively. Estimated 5-year locoregional recurrence rates were 51% ± 5% and 33% ± 7% for CC and ABMT patients ($p = 0.004$). For patients who received 10 Gy of EBRT to the primary, the addition of 10 Gy of TBI and ABMT decreased local recurrence compared with CC (22% ± 12% and 52% ± 8%, $p = 0.022$). EBRT did not increase acute toxicity, except for increased total parenteral nutrition administration.

Conclusions: In combination with EBRT to the primary tumor site, the addition of 10 Gy of TBI as a component of high-dose chemotherapy with ABMT improved local control compared with CC without TBI. Results suggest a dose–response relationship for local EBRT. Short-term toxicity of local EBRT is limited.

Strahlenther Onkol. 2006 Jul;182(7):389-94.

FULL-TEXT ARTICLE

Intensified external-beam radiation therapy improves the outcome of stage 4 neuroblastoma in children > 1 year with residual local disease.

Simon T[1], Hero B, Bongartz R, Schmidt M, Müller RP, Berthold F.

Author information

Abstract

BACKGROUND AND PURPOSE: In **neuroblastoma**, the value of radiation therapy in high-intensive first-line treatment protocols is still not exactly known but radiation-associated long-term effects need to be considered. The impact of external-beam radiation therapy (EBRT) on event-free (EFS) and overall surv 397 trial was analyzed.

RT Dose

36Gy to the residual disease

PATIENTS AND MET 10 stage 4 **neuroblastoma** patie high-dose chemotherapy with stem cell transplantation without relapse. Intensified local EBRT (36 Gy) of the residual tumor volume was reserved for patients with residual viable tumor documented by MRI and corresponding metaiodobenzylguanidine (MIBG) uptake.

RESULTS: 13 patients who received EBRT for local residual disease had similar outcome (3-year EFS 85 +/- 10%, 3-year OS 92 +/- 7%) as 74 patients without any MIBG residual (3-year EFS 61 +/- 6%, 3-year OS 75 +/- 6%). Outcome was worse in 23 children without EBRT to residual primary (3-year EFS 25 +/- 10%, 3-year OS 51 +/- 11%). Separate analysis of 14 patients with isolated localized residual disease found far better outcome of eight patients with EBRT (3-year EFS 100%, 3-year OS 100%) compared to six patients without EBRT (3-year EFS 20 +/- 18%, 3-year OS 20 +/- 18%). Multivariate analysis identified EBRT as influential on EFS (hazard ratio 0.27) and OS (hazard ratio 0.17) in addition to MYCN amplification and presence of primary tumor site MIBG residual.

CONCLUSION: EBRT appeared effective in high-intensive treatment of stage 4 **neuroblastoma**. It seems to compensate the disadvantage of incomplete response to induction chemotherapy. These retrospective results need confirmation by a prospective randomized trial.

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Clinical Investigation

Radiation Therapy to the Primary and Postinduction Chemotherapy MIBG-Avid Sites in High-Risk Neuroblastoma

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Received May 14, 2014, a[ccepted]

RT Dose

Primary site – 24 to 30Gy
MIBG avid Mets – 24Gy

Summary

Radiation therapy to the primary site and postinduction metaiodobenzylguanidine (MIBG)-positive metastatic sites were associated with favorable local control in children with high-risk neuroblastoma. The number of MIBG-avid sites present after induction chemotherapy and surgery was predictive of progression-free and overall survival.

Purpose: Although it is generally accepted that consolidation therapy for neuroblastoma includes irradiation of the primary site and any remaining metaiodobenzylguanidine (MIBG)-avid metastatic sites, limited information has been published regarding the efficacy of this approach.

Methods and Materials: Thirty patients with high-risk neuroblastoma were treated at 1 radiation therapy (RT) department after receiving 5 cycles of induction chemotherapy and resection. All patients had at least a partial response after induction therapy, based upon international neuroblastoma response criteria. The primary sites were treated with 24 to 30 Gy whereas the MIBG-avid metastatic sites were treated with 24 Gy. RT was followed by high-dose chemotherapy with autologous stem cell rescue and 6 months of *cis*-retinoic acid.

Results: The 5-year progression-free survival (PFS) and overall survival (OS) rates were 48% and 59%, respectively. The 5-year locoregional control at the primary site was 84%. There were no differences in locoregional control according to degree of primary surgical resection. The 5-year local control rate for metastatic sites was 74%. The 5-year PFS rates for patients with 0, 1, 2, and >3 postinduction MIBG sites were 66%, 57%, 20%, and 0% ($P<.0001$), respectively, whereas 5-year OS rates were 80%, 57%, 50%, and 0%, respectively ($P<.0001$).

Conclusions: RT to the primary site and postinduction MIBG-positive metastatic sites was associated with 84% and 74% local control, respectively. The number of MIBG-avid sites present after induction chemotherapy and surgery was predictive of progression-free and overall survival.

Radiotherapy in Neuroblastoma
Dose Recommendations

Completely resected tumor –

- ✓ 21Gy, either 1.8Gy daily or 1.5Gy BD

Residual disease – boost up to 30-36Gy

- ✓ Microscopic disease, min 15 Gy wide field, followed by 5-10 Gy boost
- ✓ Gross disease 15-20 Gy initial volume, followed by 5-10 Gy boost
- ✓ For gross disease, age dependent:
  <1 Yr - 12 Gy, 1-4 Yr - 25 Gy , >4Yr - >25 Gy

Jacbson GM Am J Clin Oncol 1984
Michalski JM, Proc Am Radium Society, Paris 1995

Radiotherapy in Neuroblastoma

Ongoing trial

ANBL0532, COG High Risk Phase III Trial

Incompletely resected pts -

RT – 21.6Gy to pre-op primary tumor volume
14.4Gy to the gross residual volume

Radiotherapy in Neuroblastoma

Dose Recommendations

Liver –

- Dose to whole liver not to exceed 19Gy. 21Gy is acceptable for one lobe
- <50% to receive 9Gy and <25% more than 18Gy

Spinal Cord –

A dose of 21Gy is acceptable for any length of spinal cord

Kidney –

- If single kidney, then dose should not exceed 12Gy
- A dose of 21Gy is acceptable for up to half a kidney, if the patient has both kidneys
- Contralateral Kidney - <50% to receive >8Gy & <20% to receive >12Gy

HR-NBL-1/SIOPEN Study Protocol

Radiotherapy in Neuroblastoma

Dose Recommendations

Bone –

- Maintain the symmetry by irradiation of whole vertebra
- If possible, shield the epiphysis of bone

Gonads –

<5Gy if possible

Radiotherapy in Neuroblastoma

Technique

- Parallel opposed, 3DCRT, IMRT, VMAT
- Individualization for each patient
- IMRT for abdominal/pelvic disease, Re- irradiation
  - Better renal sparing
  - Watch for mean doses to stomach, spleen etc
- Lateralised tumor – either of the technique

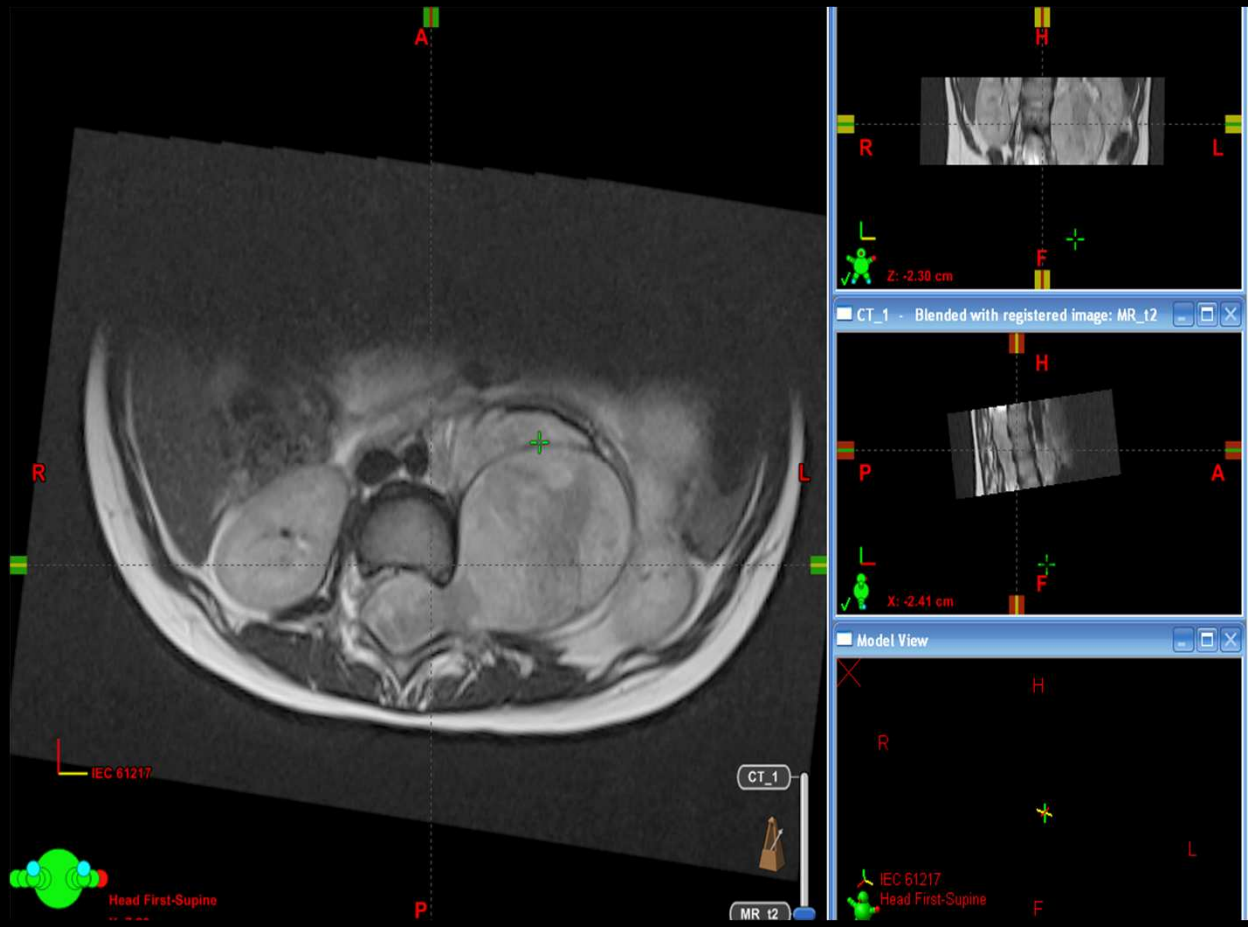
Case 1

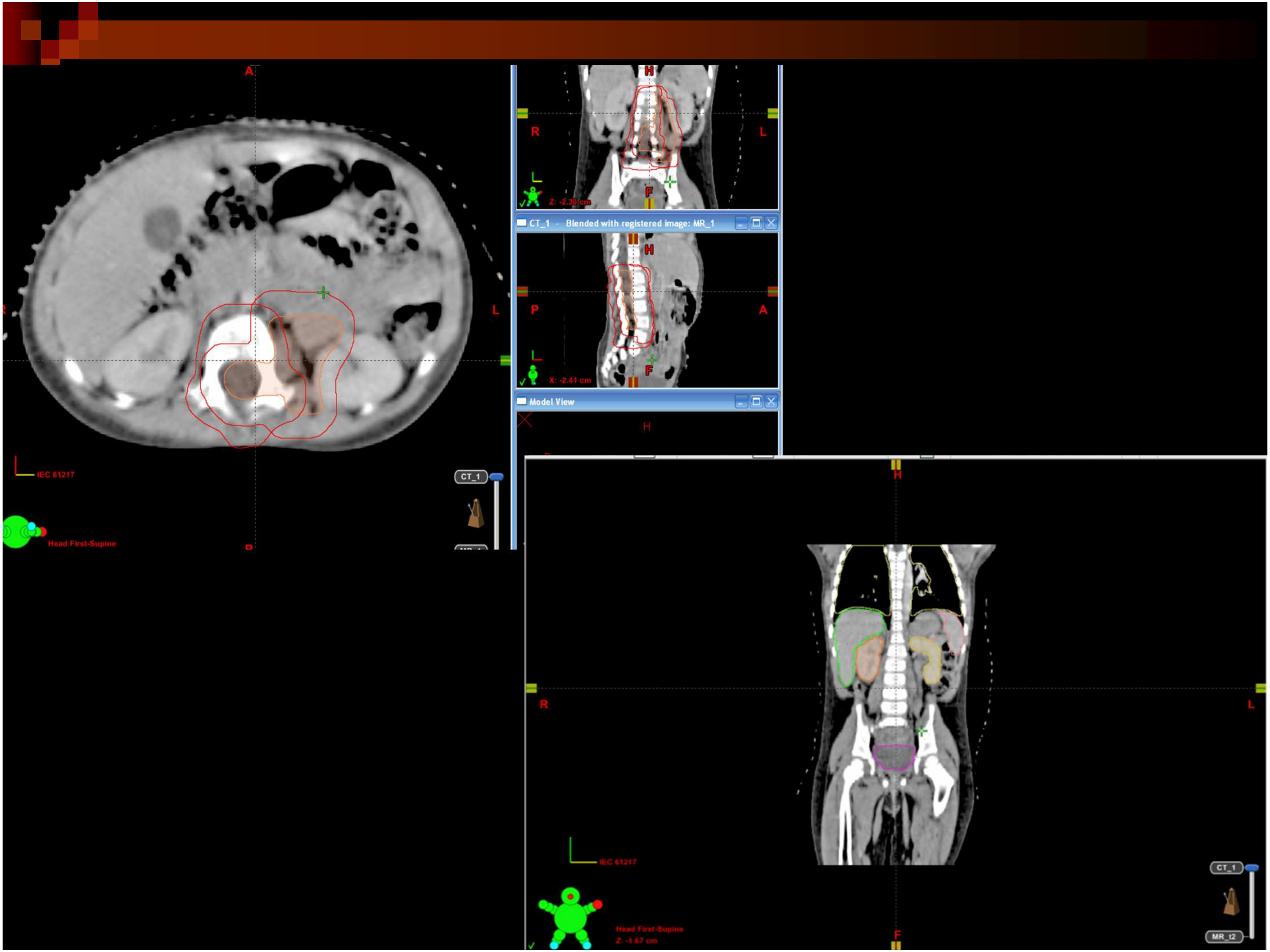
2/F

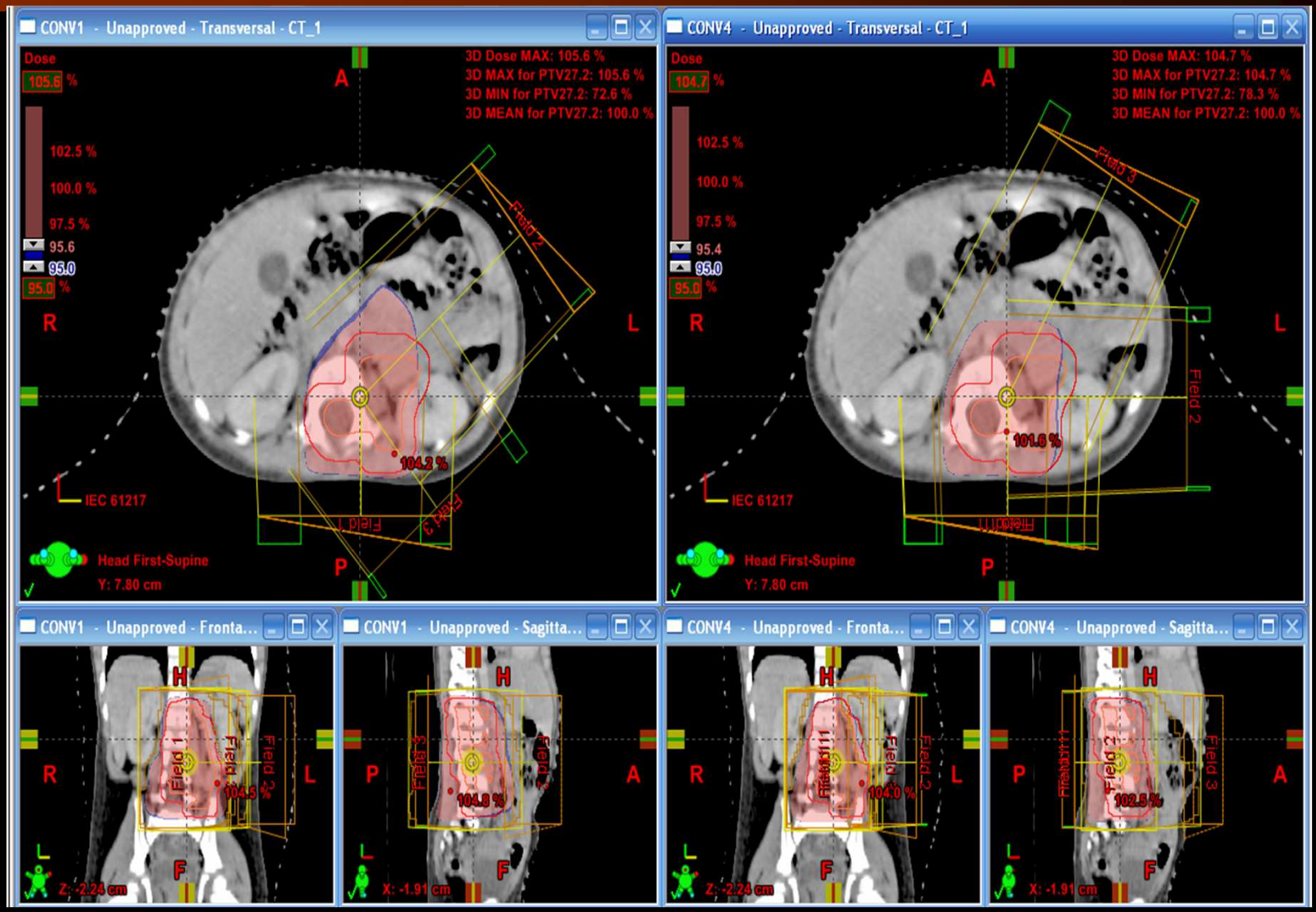
L1-L3 Paraspinal mass

Dumbbell NB, ‘IR’

Limited Excision + CT

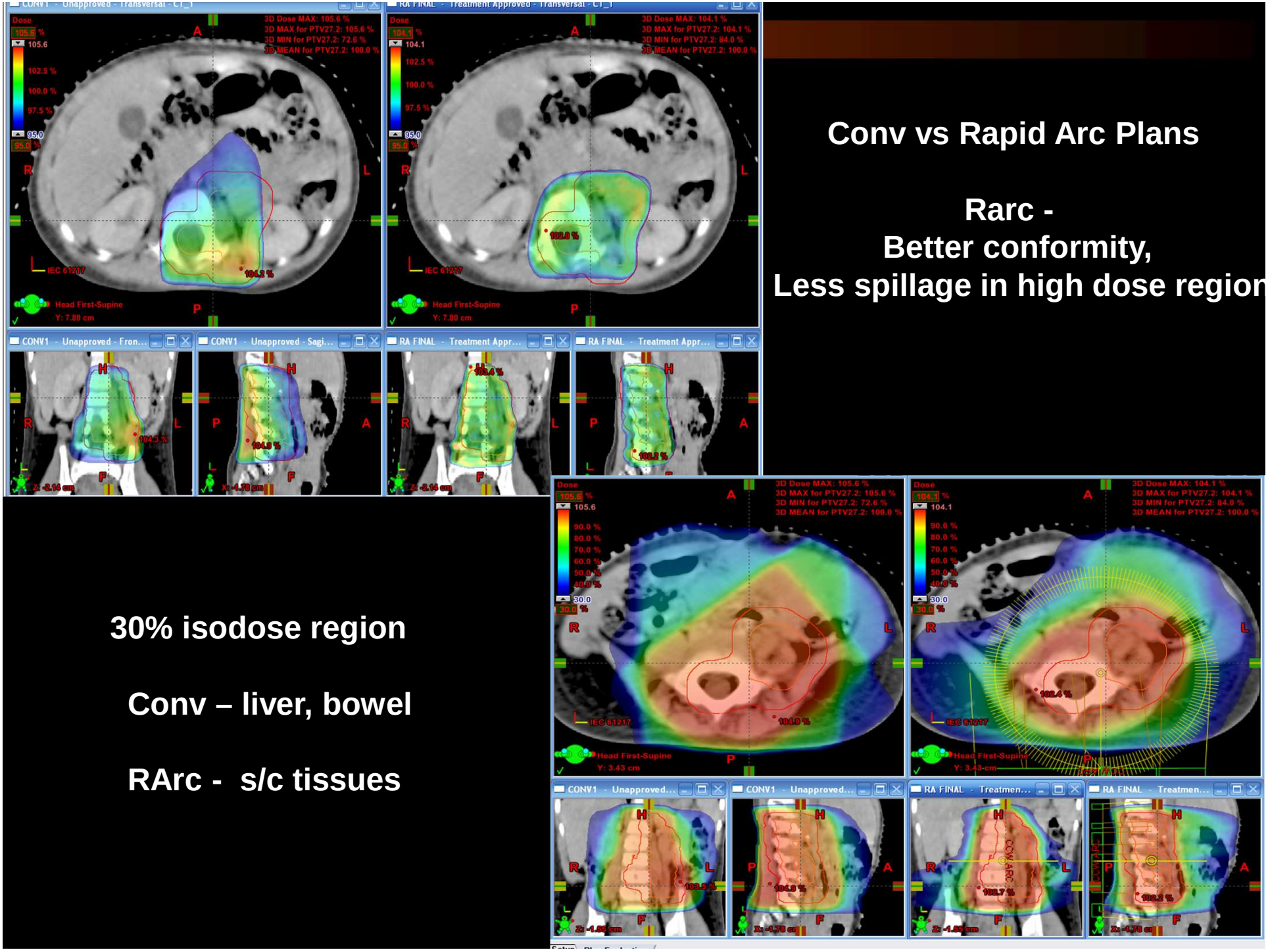


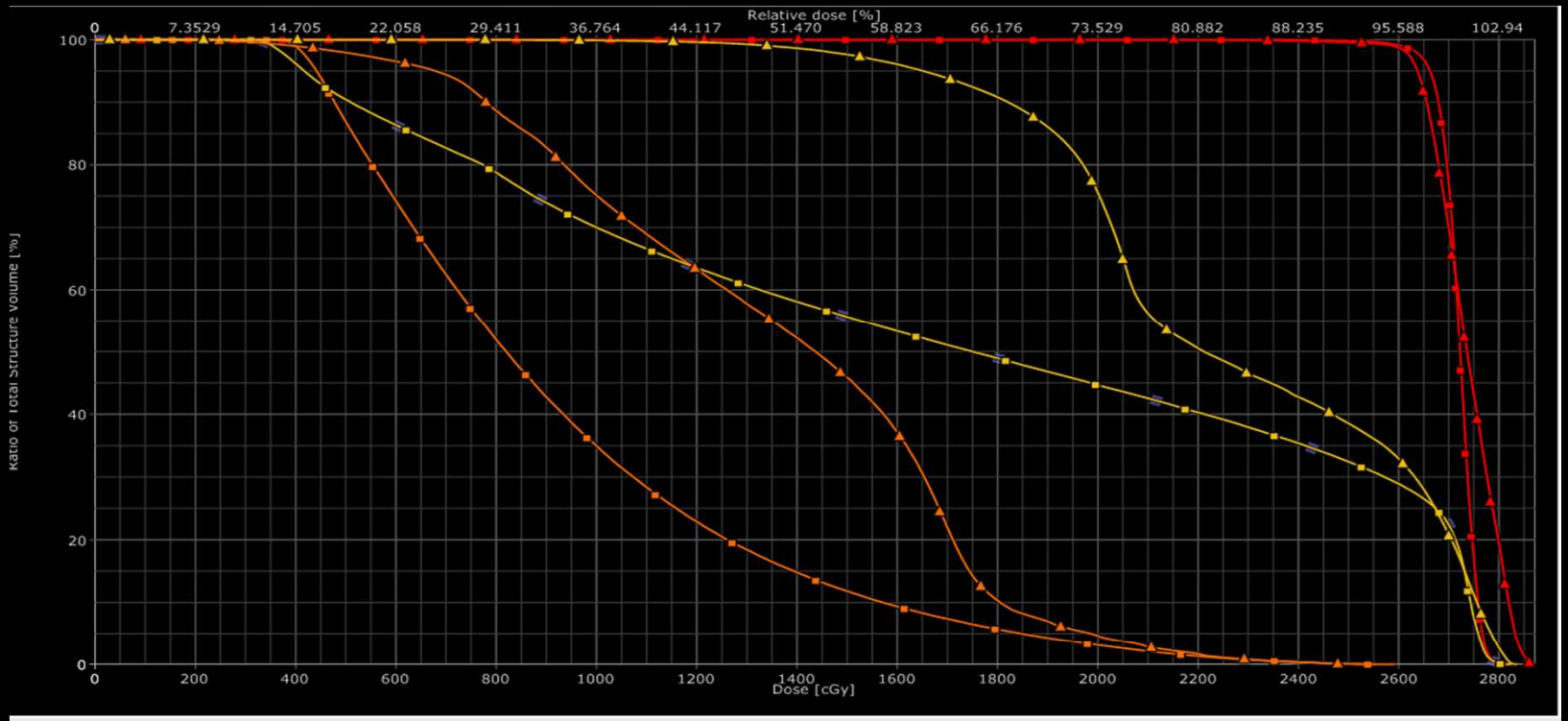

A
L
IEC 61217
Head First-Supine
CT_1
H
R
L
F
Z: -2.30 cm
CT_1 - Blended with registered image: MR_1
P
A
X: -2.41 cm
Model View
Z: -1.67 cm
MR_t2



Two 3DCRT plans

Ist Plan - more spillage in bowel, better conformity


Conv vs Rapid Arc Plans
Rarc -
Better conformity,
Less spillage in high dose region
30% isodose region
Conv – liver, bowel
RArc - s/c tissues



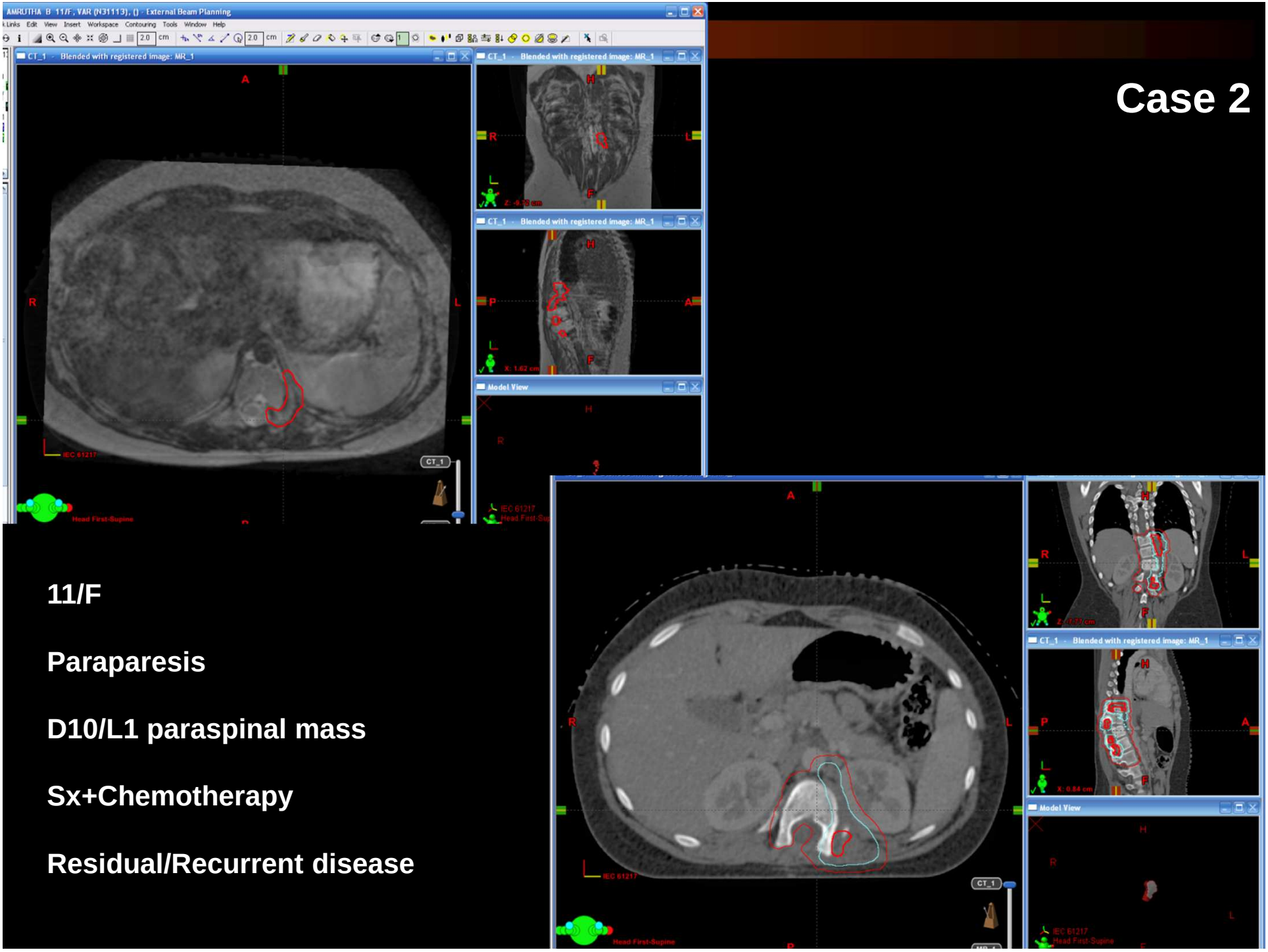
egistration | Contouring | Field Setup | Plan Evaluation

e Prescription | Dose Statistics | Plan Sum

Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover...	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
	LIVER	Approved	CONV1	C1	316.7	100.0	100.0	42.1	2546.9	524.9
	LT KIDNEY	Approved	RA FINAL	C1	32.9	100.0	100.0	305.1	2824.4	1716.9
	LT KIDNEY	Approved	CONV1	C1	32.9	100.0	100.0	729.0	2836.9	2278.5
	LT.KIDNEY-PTV	Approved	RA FINAL	C1						
	LT.KIDNEY-PTV	Approved	CONV1	C1						
	Lungs	Approved	RA FINAL	C1						
	Lungs	Approved	CONV1	C1						

Rarc Plan –
Better conformity & homogeneity
Lower doses to OARs

Case 2



11/F

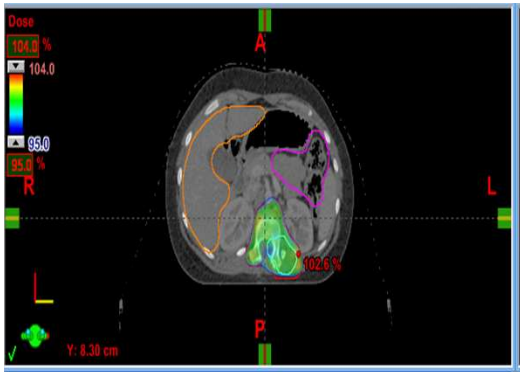
Paraparesis

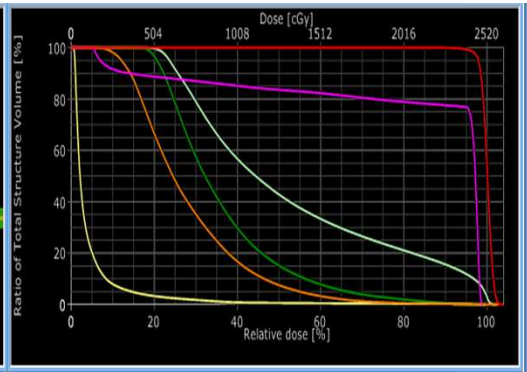
D10/L1 paraspinal mass

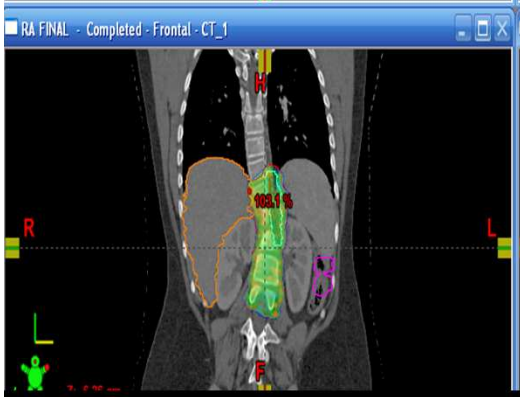
Sx+Chemotherapy

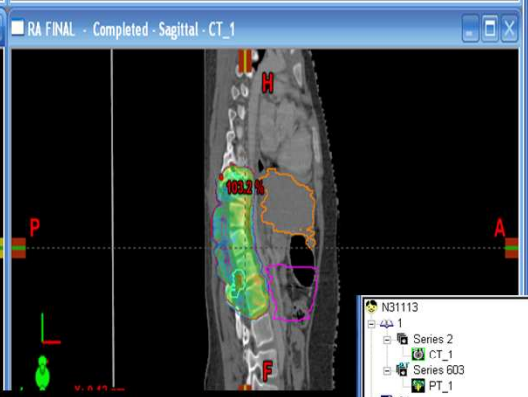
Residual/Recurrent disease

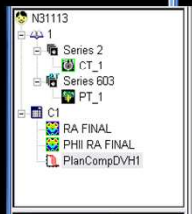
Case 2

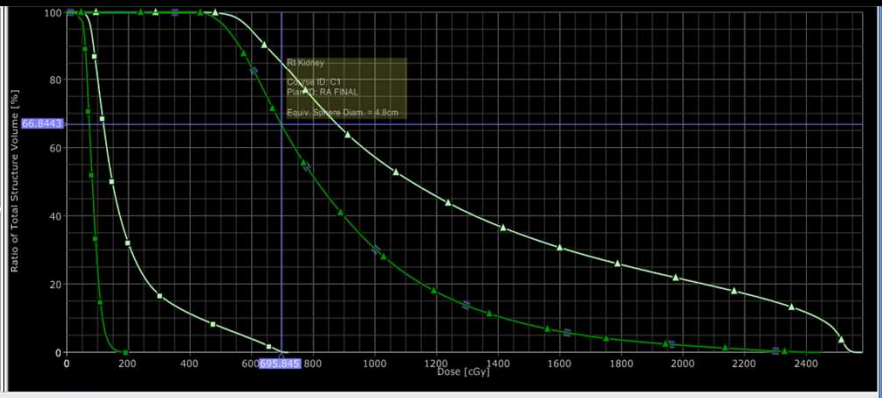


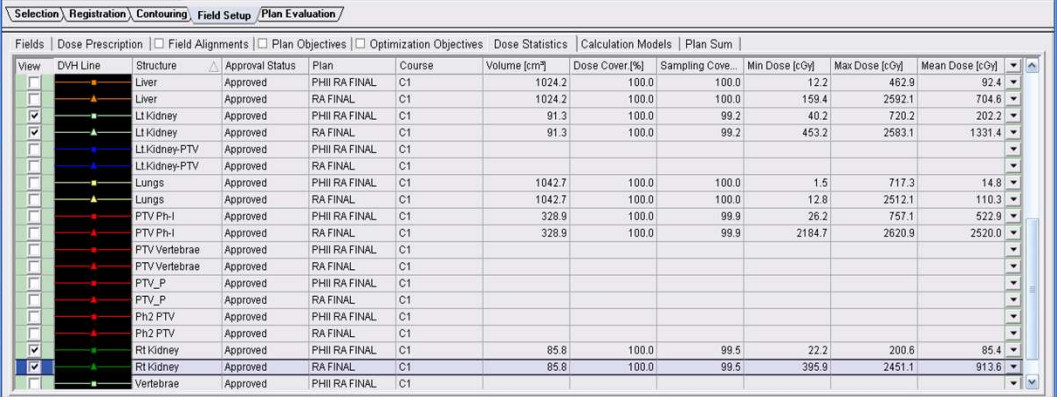












View	DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cove...	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
☐		Liver	Approved	PHII RA FINAL	C1	1024.2	100.0	100.0	12.2	462.9	92.4
☐		Liver	Approved	RA FINAL	C1	1024.2	100.0	100.0	159.4	2592.1	704.6
☑		Lt Kidney	Approved	PHII RA FINAL	C1	91.3	100.0	99.2	40.2	720.2	202.2
☑		Lt Kidney	Approved	RA FINAL	C1	91.3	100.0	99.2	453.2	2583.1	1331.4
☐		Lt Kidney-PTV	Approved	PHII RA FINAL	C1						
☐		Lt Kidney-PTV	Approved	RA FINAL	C1						
☐		Lungs	Approved	PHII RA FINAL	C1	1042.7	100.0	100.0	1.5	717.3	14.8
☐		Lungs	Approved	RA FINAL	C1	1042.7	100.0	100.0	12.8	2512.1	110.3
☐		PTV Ph-I	Approved	PHII RA FINAL	C1	328.9	100.0	99.9	26.2	757.1	522.9
☐		PTV Ph-I	Approved	RA FINAL	C1	328.9	100.0	99.9	2184.7	2620.9	2520.0
☐		PTV Vertebrae	Approved	PHII RA FINAL	C1						
☐		PTV Vertebrae	Approved	RA FINAL	C1						
☐		PTV_P	Approved	PHII RA FINAL	C1						
☐		PTV_P	Approved	RA FINAL	C1						
☐		Ph2 PTV	Approved	PHII RA FINAL	C1						
☐		Ph2 PTV	Approved	RA FINAL	C1						
☑		Rt Kidney	Approved	PHII RA FINAL	C1	85.8	100.0	99.5	22.2	200.6	85.4
☑		Rt Kidney	Approved	RA FINAL	C1	85.8	100.0	99.5	395.9	2451.1	913.6
☐		Vertebrae	Approved	PHII RA FINAL	C1						

Dose -

Phase 1 PTV – 21.6/12frs

Phase2 PTV – 32.4Gy/18frs

Mean dose:

Lt Kidney – 15Gy

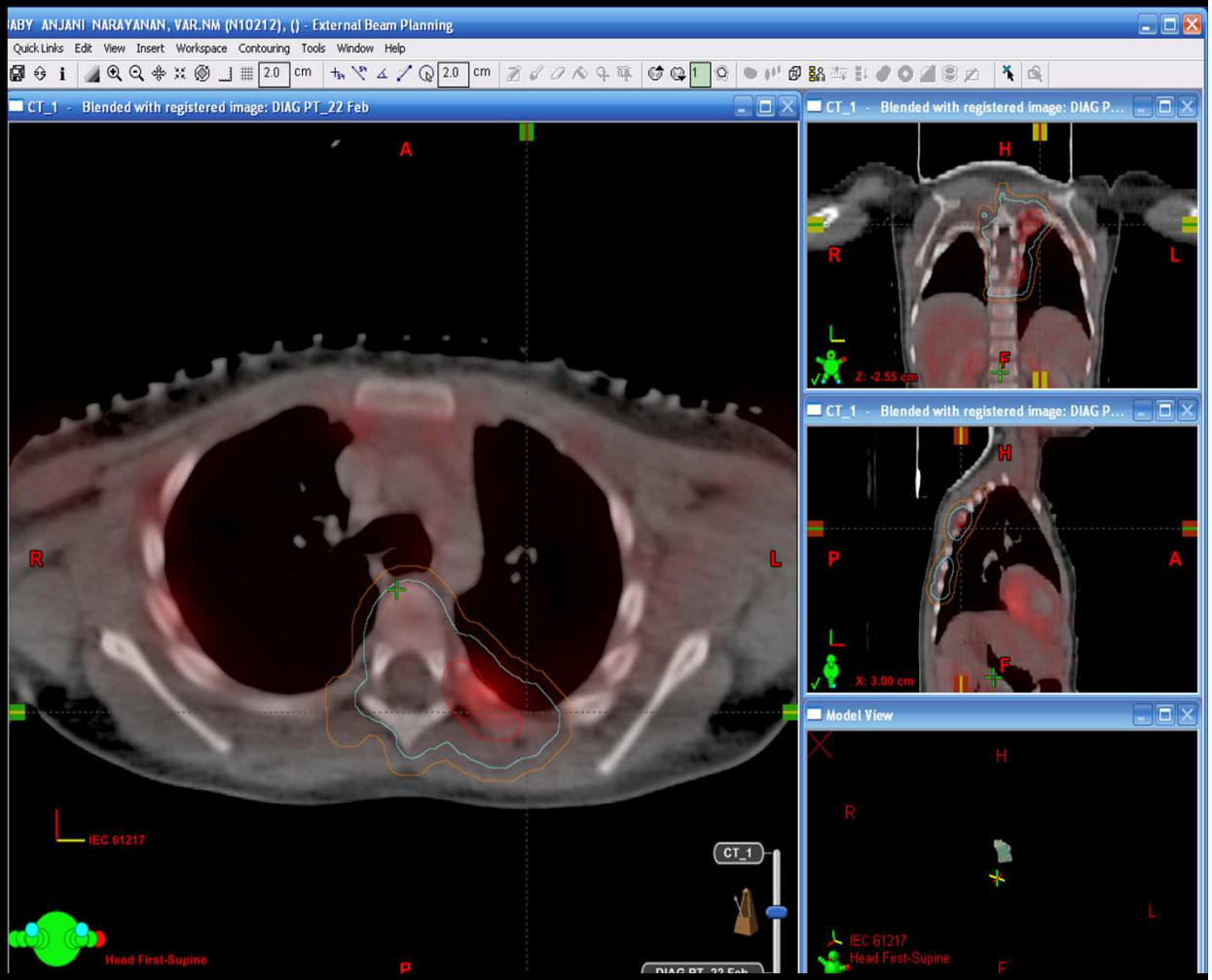
Rt Kidney – 10Gy

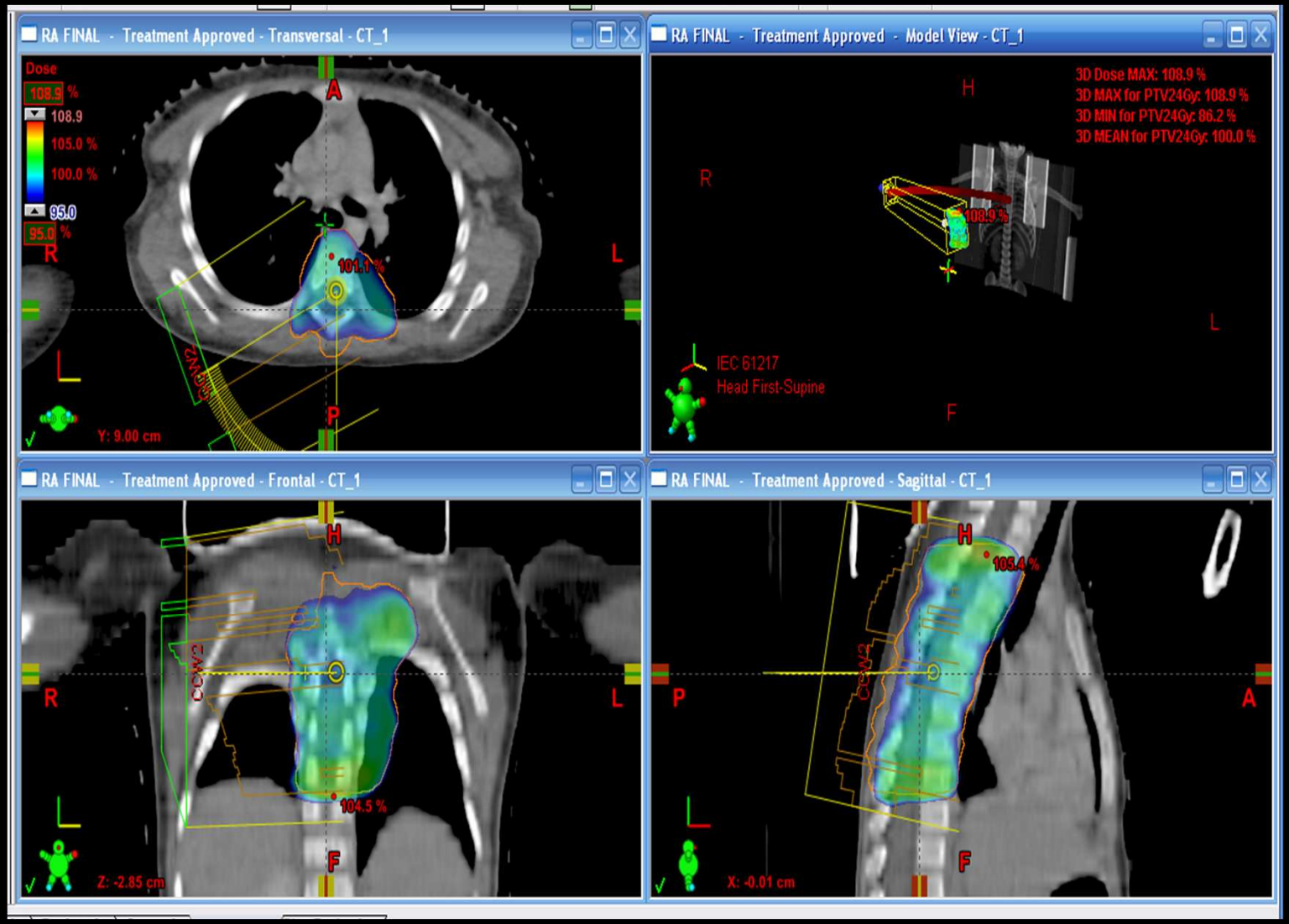
Case 3

1/F

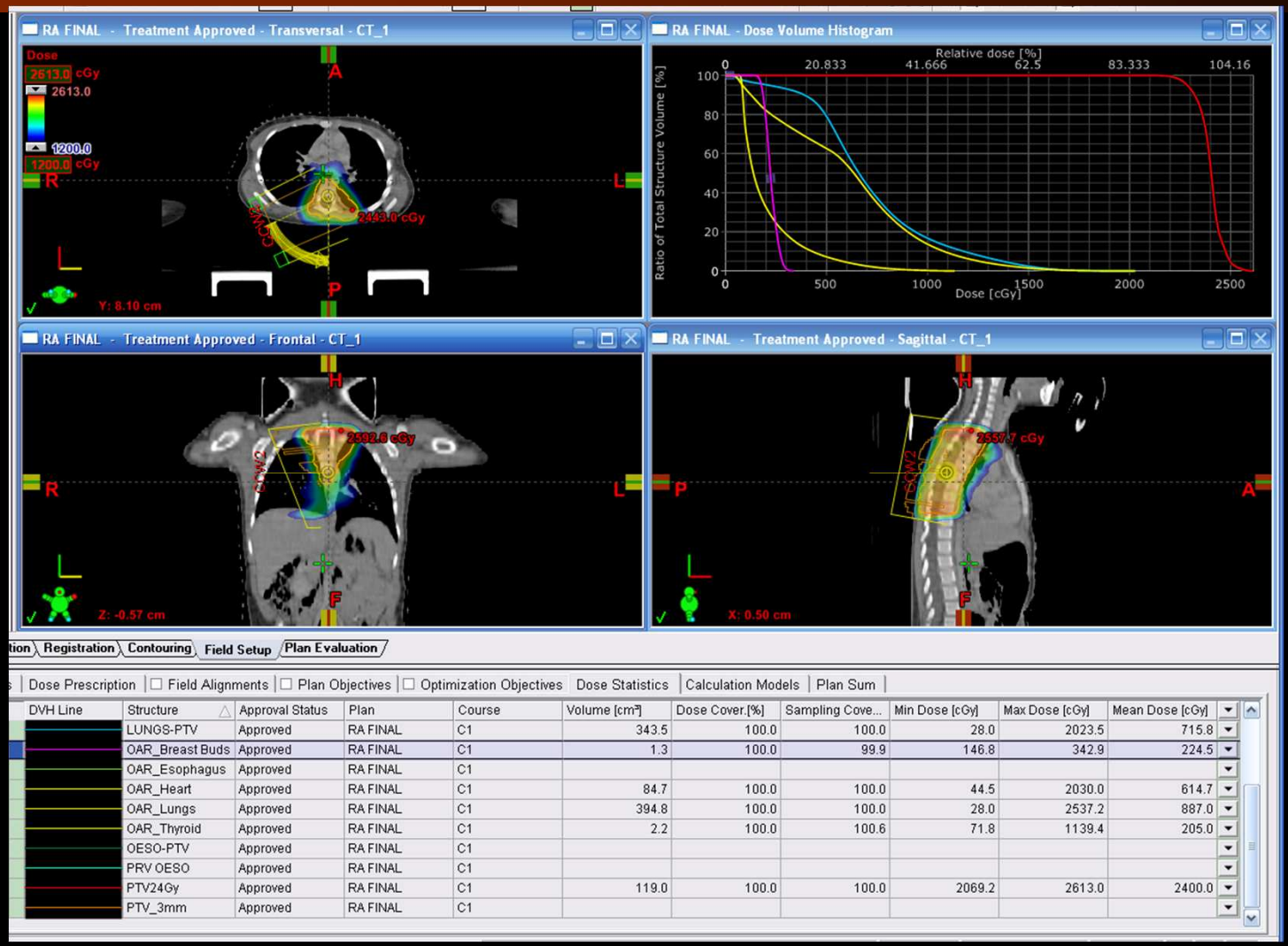
D1-8 Pre/Para vertebral mass

Limited Excision+Chemo





Rapid Arc Plan
24Gy/15frs, 1.6Gy/fr



DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cove...	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
	LUNGS-PTV	Approved	RA FINAL	C1	343.5	100.0	100.0	28.0	2023.5	715.8
	OAR_Breast Buds	Approved	RA FINAL	C1	1.3	100.0	99.9	146.8	342.9	224.5
	OAR_Esophagus	Approved	RA FINAL	C1						
	OAR_Heart	Approved	RA FINAL	C1	84.7	100.0	100.0	44.5	2030.0	614.7
	OAR_Lungs	Approved	RA FINAL	C1	394.8	100.0	100.0	28.0	2537.2	887.0
	OAR_Thyroid	Approved	RA FINAL	C1	2.2	100.0	100.6	71.8	1139.4	205.0
	OESO-PTV	Approved	RA FINAL	C1						
	PRV OESO	Approved	RA FINAL	C1						
	PTV24Gy	Approved	RA FINAL	C1	119.0	100.0	100.0	2069.2	2613.0	2400.0
	PTV_3mm	Approved	RA FINAL	C1						

Less spillage in low dose region
Low dose to OARs – Lungs, Breast buds, Heart

Case 3

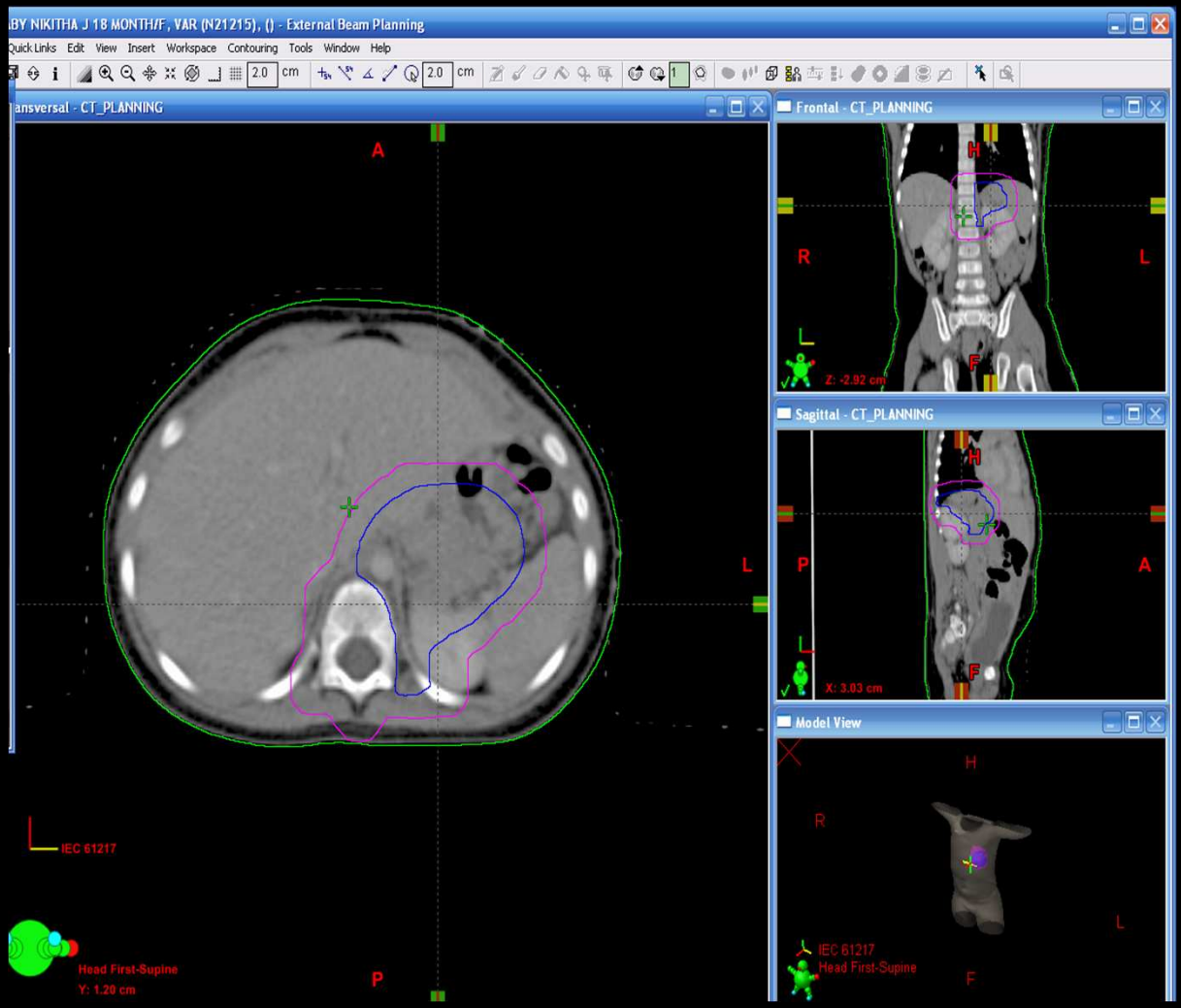
1yr/F

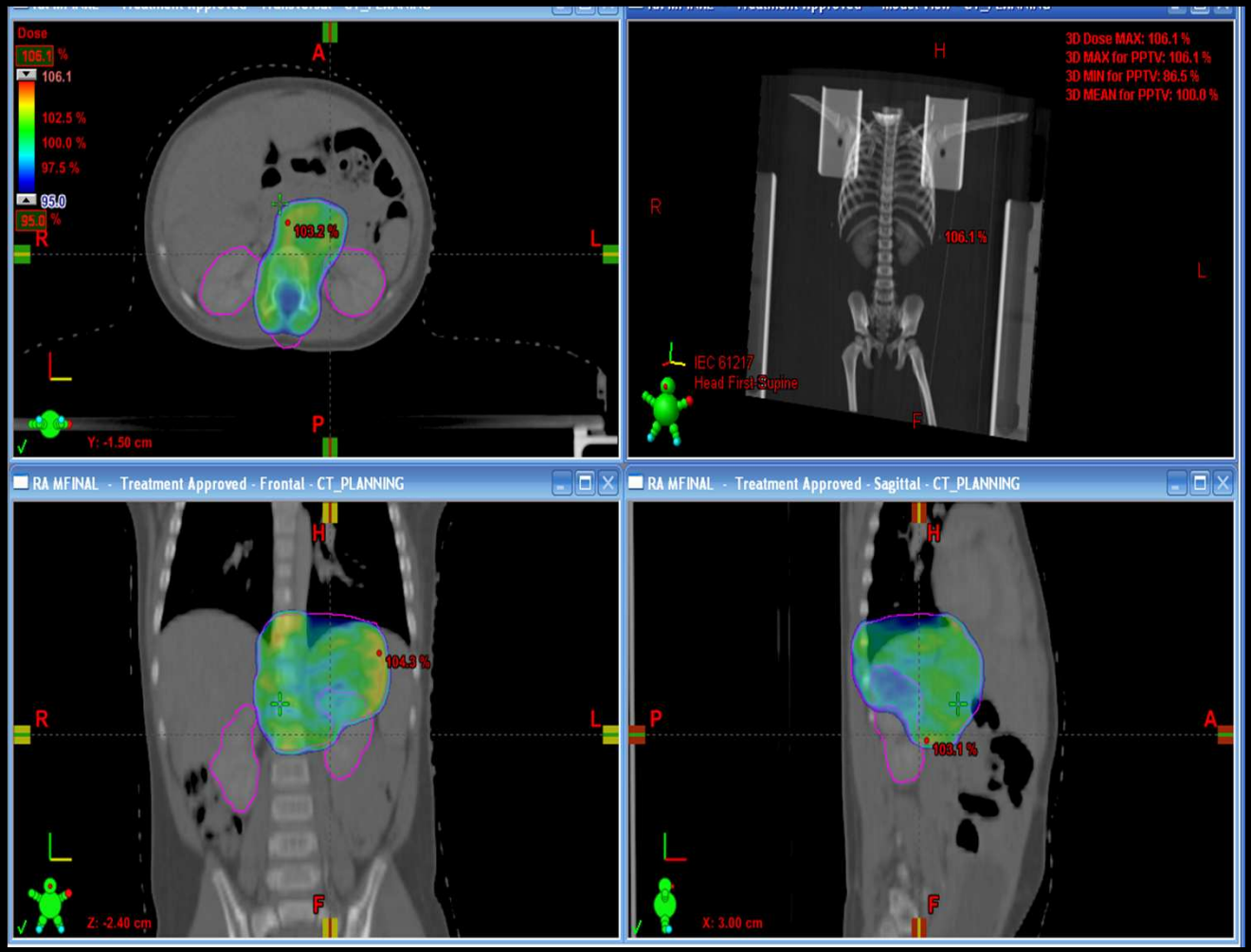
Lt Suprarenal mass

Stage 4S, liver mets

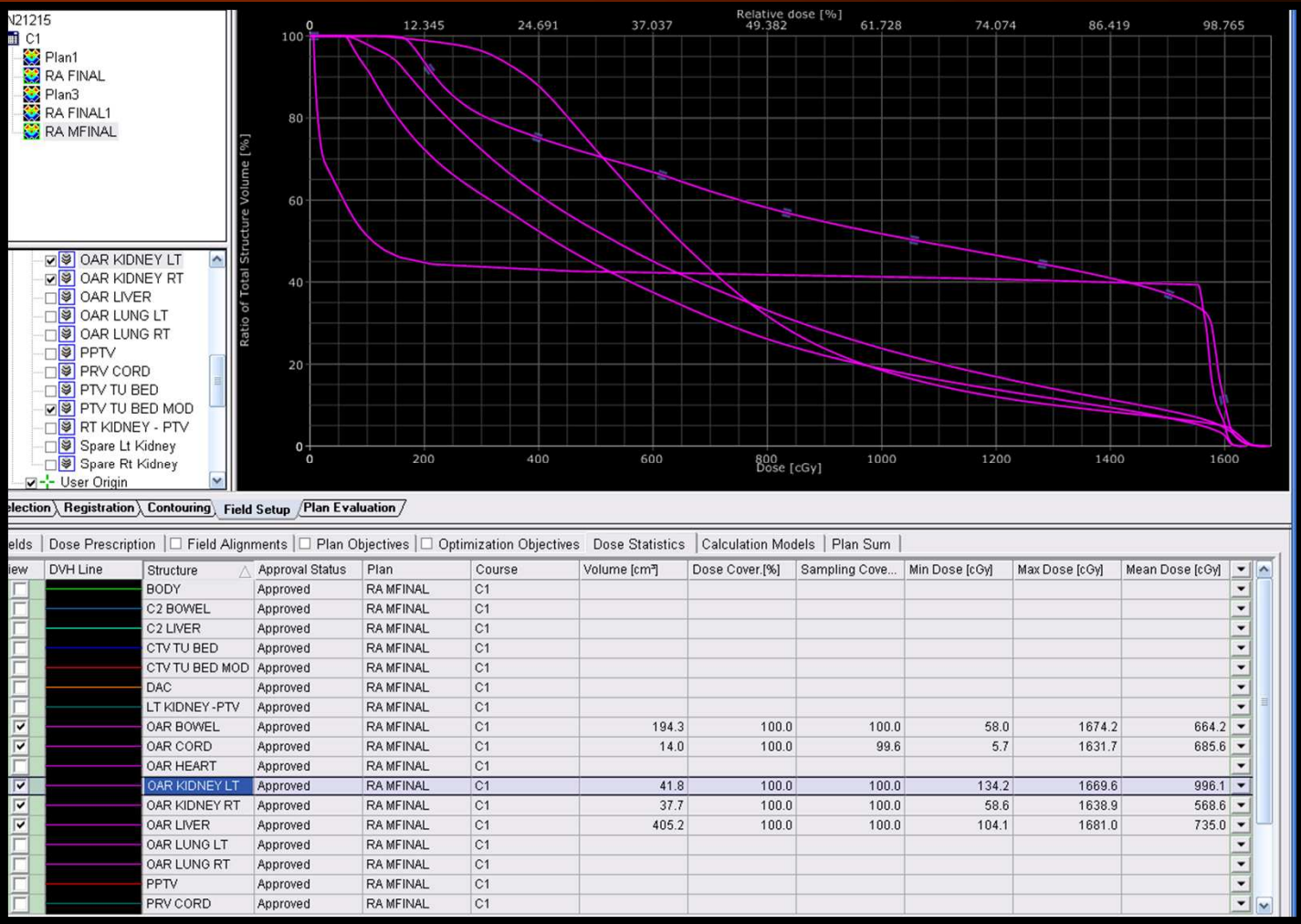
Post Chemo – CR

Recurrent Tm – s/p Sx





Rapid Arc Plan, 25.2Gy/14frs
Good conformity



View	DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cove...	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
		BODY	Approved	RA MFINAL	C1						
		C2 BOWEL	Approved	RA MFINAL	C1						
		C2 LIVER	Approved	RA MFINAL	C1						
		CTV TU BED	Approved	RA MFINAL	C1						
		CTV TU BED MOD	Approved	RA MFINAL	C1						
		DAC	Approved	RA MFINAL	C1						
		LT KIDNEY -PTV	Approved	RA MFINAL	C1						
☑		OAR BOWEL	Approved	RA MFINAL	C1	194.3	100.0	100.0	58.0	1674.2	664.2
☑		OAR CORD	Approved	RA MFINAL	C1	14.0	100.0	99.6	5.7	1631.7	685.6
		OAR HEART	Approved	RA MFINAL	C1						
☑		OAR KIDNEY LT	Approved	RA MFINAL	C1	41.8	100.0	100.0	134.2	1669.6	996.1
☑		OAR KIDNEY RT	Approved	RA MFINAL	C1	37.7	100.0	100.0	58.6	1638.9	568.6
☑		OAR LIVER	Approved	RA MFINAL	C1	405.2	100.0	100.0	104.1	1681.0	735.0
		OAR LUNG LT	Approved	RA MFINAL	C1						
		OAR LUNG RT	Approved	RA MFINAL	C1						
		PPTV	Approved	RA MFINAL	C1						
		PRV CORD	Approved	RA MFINAL	C1						

Mean Dose –
Lt Kidney – 9.9Gy
Rt Kidney – 5.6Gy
Liver - 7.3Gys

Radiotherapy in Neuroblastoma

Metastatic sites

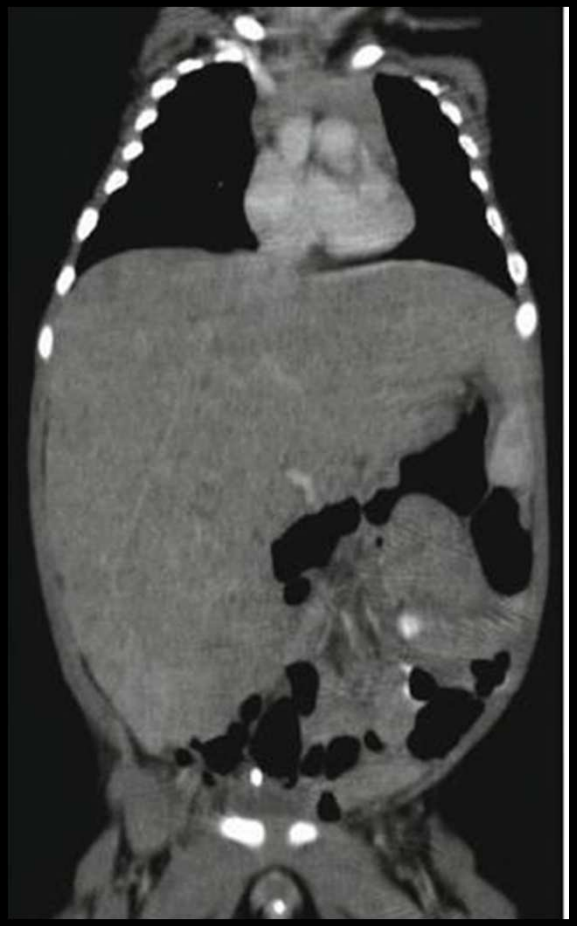
- Generous margins for the bony lesions
- Orbital mets – treat entire orbit
- Liver mets – adquate margins (no whole liver irradiation)
- Dose/# -
  symptoms, volume, life expectancy
  16-20Gy in 4/5fractions
  Or 20-30Gy in 2 to 3Gy/fraction, if large fields

Radiotherapy in Neuroblastoma

Hepatomegaly in Stage 4S –

- Entire liver need not be irradiated
- Spare kidneys, ovaries
- Usually lateral opposed
- 2-6Gy in 2-4 fractions

Borders –
Anterior – 2cm ant to liver
Posterior –anterior vertebral body
Superior –2cm sup to liver
Inferior – superior iliac crest to avoid ovarian exposure



Radiotherapy in Neuroblastoma

Intraoperative Radiotherapy –

Rationale:

Increased risk of late toxicities with EBRT as large volume of normal tissue exposed

Reduced renal function which may compromise tolerance to chemotherapy with SCT

Higher dose deliverable with minimal exposure to normal tissues

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CLINICAL INVESTIGATION **Pediatric Tumors**

LONG-TERM OUTCOME AND TOXICITIES OF INTRAOPERATIVE RADIOTHERAPY FOR HIGH-RISK NEUROBLASTOMA

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Well tolerated
Good local control
Late sequelae

Purpose: To review a historical cohort of consecutively accrued patients with high-risk neuroblastoma treated with intraoperative radiotherapy (IORT) to determine the therapeutic effect and late complications of this treatment.
Methods and Materials: Between 1986 and 2002, 31 patients with newly diagnosed high-risk neuroblastoma were treated with IORT as part of multimodality therapy. Their medical records were reviewed to determine the outcome and complications. Kaplan-Meier probability estimates of local control, progression-free survival, and overall survival at 36 months after diagnosis were recorded.
Results: Intraoperative radiotherapy to the primary site and associated lymph nodes achieved excellent local control at a median follow-up of 44 months. The 3-year estimate of the local recurrence rate was 15%, less than that of most previously published series. Only 1 of 22 patients who had undergone gross total resection developed recurrence at the primary tumor site. The 3-year estimate of local control, progression-free survival, and overall survival was 85%, 47%, and 60%, respectively. Side effects attributable to either the disease process or multimodality treatment were observed in 7 patients who developed either hypertension or vascular stenosis. These late complications resulted in the death of 2 patients.
Conclusions: Intraoperative radiotherapy at the time of primary resection offers effective local control in patients with high-risk neuroblastoma. Compared with historical controls, IORT achieved comparable control and survival rates while avoiding many side effects associated with external beam radiotherapy in young children. Although complications were observed, additional analysis is needed to determine the relative contributions of the disease process and specific components of the multimodality treatment to these adverse events.

Radiotherapy in Neuroblastoma

Complications

Acute Side-effects:

Nausea/Vomiting
Diarrhea, Abdominal pain
Hematological toxicity

Long term Sequelae:

Musculoskeletal –
Kyphoscoliosis, bone shortening

Hearing loss

Hypothyroidism , ovarian dysfunction

Vascular – Middle Aortic syndrome

Radiation in Neuroblastoma
Conclusions

- Radiation is only indicated in very rare occasion in Low risk patients
- Radiation is controversial in Intermediate risk patients
- In High risk group, local radiation may be used as a boost to primary or bulky metastatic site, TBI as a part of BMT, palliative measure in life threatening situations
- Structure Delineation:
  - Pre surgery CT/MIBG scans
  - Nodal irradiation for involved nodes ONLY
  - Symmetrical irradiation of vertebrae
- Dose - 21Gy for R0 resection, 30-36Gy for R1/R2 resection

Thank You