CHEMO RADIATION IN CARCINOMA PANCREAS

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INTRODUCTION

- Pancreatic cancer is one of the most lethal cancers, as indicated by a mortality incidence ratio of 98%.
- Fourth leading cause of death from cancer
- Aggressive biology of the tumor and the lack of early disease specific signs and symptoms, only a small minority of patients present with potentially resectable disease at the time of diagnosis
- Periampullary cancers /Pancreatic head malignancies constitutes 70-80%.
- Surgery is the only curative treatment option

PATTERNS OF FAILURE AFTER SX RESECTION

	Surgical resection (N)	Local Recurrence (%)	Distant Metastasis (%)	2 yr & 5 yr survival (%)	Median survival (months)
Tepper et al (MGH)	45	50	15	-	11.5
Griffin et al	36	73	42-peritoneum 62-liver	32 & 17	-
Foo et al (mayo clinic)	29	59	38	-	-
Kayahara et al	45	80 LN- 47	53-peritoneum 66-liver	-	-
Willett et al	41	53	-	47 & 38	-

PATTERNS OF FAILURE AFTER SX RESECTION

- Local recurrence – 80%
- Distant mets – 75%
- Hepatic mets – 66%
- Peritoneal dissemination – 53%
- LN relapse – 47%

- Actuarial 5-year survival - 21% ; median survival of 15.5 mo
- With negative surgical margins -5-year survival of 26%
- With positive surgical margins -5-year survival of 8%.

RISK FACTORS FOR RECURRENCE

- Site –Body or Tail vs Head
- Size – >3cm
- Positive margins
- Residual disease
- Positive nodal status
- Grade –poorly diff.

ADJUVANT T/T AFTER CURATIVE RESECTION

- ***Rationale*** – to prevent local recurrence
  & distant mets
- ***Options***
  - RT
  - CCT
  - CCRT

WHY CHEMO RADIATION ?
RESULTS OF POST-OP ADJUVANT RT ONLY

	SURGERY f/b PORT (N)	Local Recurrence (%)	Distant Metastasis (%)	2 yr LC (%)	5 yr survival (%)
Foo et al (Mayo Clinic)	19 (S) 10 (Sx f/b RT) 45 -50 Gy	80% 7%	Liver – 43% Peritoneum-61%	-	-
Willett et al	29 (S) 12 (Sx f/b RT)	- 12% in T1 ,2 66% in T3,4	-	50% 83 % (p<0.05)	8% 23% (NS)
Bosset et al	14 (S) 14 (Sx f/b RT) 54 Gy	- 50%	-	-	 23 mths (MS)

ADJUVANT CCT & CRT

CCT

- Goal – to improve overall survival
- Regimens used – 5-FU infusion/ FAM/ FAP/ Gem/Capcitabine

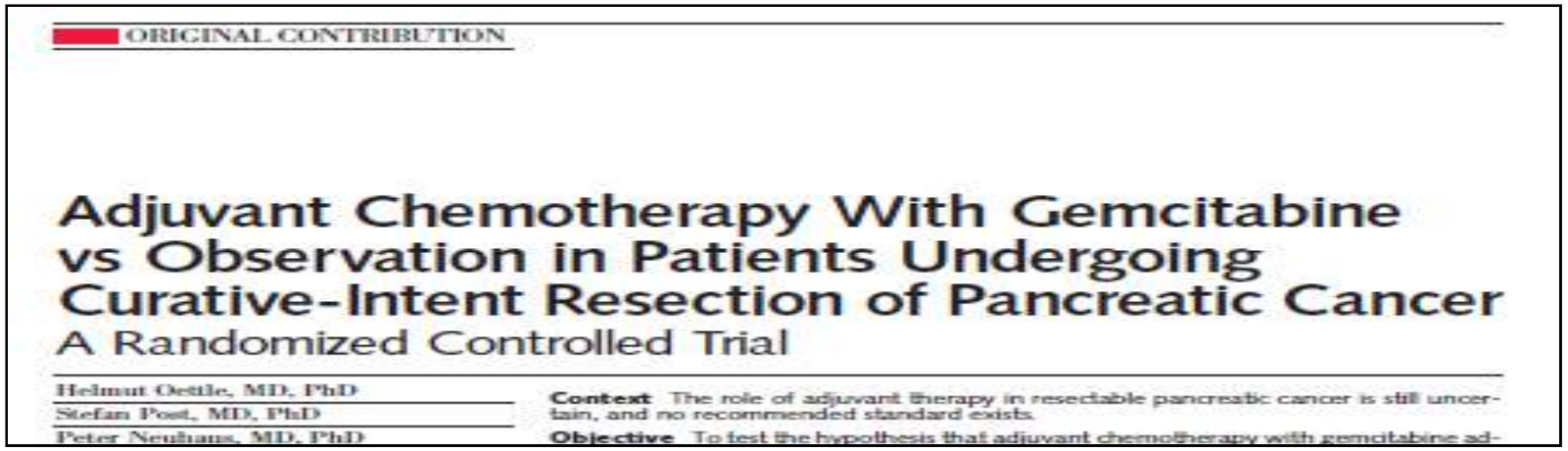
CCRT

- Goal: To improve local control & overall survival
- Types: Adjuvant and Neoadjuvant
- 5-FU based / Gemcitabine based

ADJUVANT CHEMOTHERAPY TRIALS IN RESECTABLE DISEASE

5 FU BASED INITIAL TRIALS

- Initial trials (1960s and 1970s) → as a single agent RR – 28%
- Recent trials of 5-FU bolus iv → no activity
- Bolus 5-FU + leucovorin daily for 5 days → no objective response
- Prolonged infusion 5-FU or capecitabine → modest activity
- infusional 5-FU and mitomycin C vs infusional 5-FU alone.
  - RR – 17.6% vs only 8.4%
  - median survival - 6.5 mo vs. 5.1 mo ; P = 0.34
- Older 5-FU combinations – FAM, SMF
  - Initial results in phase II trials were encouraging, but none of them demonstrated any significant survival advantage over single agent 5-FU in larger randomized trials.



ORIGINAL CONTRIBUTION

Adjuvant Chemotherapy With Gemcitabine vs Observation in Patients Undergoing Curative-Intent Resection of Pancreatic Cancer

A Randomized Controlled Trial

Helmut Oettle, MD, PhD
Stefan Post, MD, PhD
Peter Neuhaus, MD, PhD

Context The role of adjuvant therapy in resectable pancreatic cancer is still uncertain, and no recommended standard exists.

Objective To test the hypothesis that adjuvant chemotherapy with gemcitabine ad-

CONKO - 001

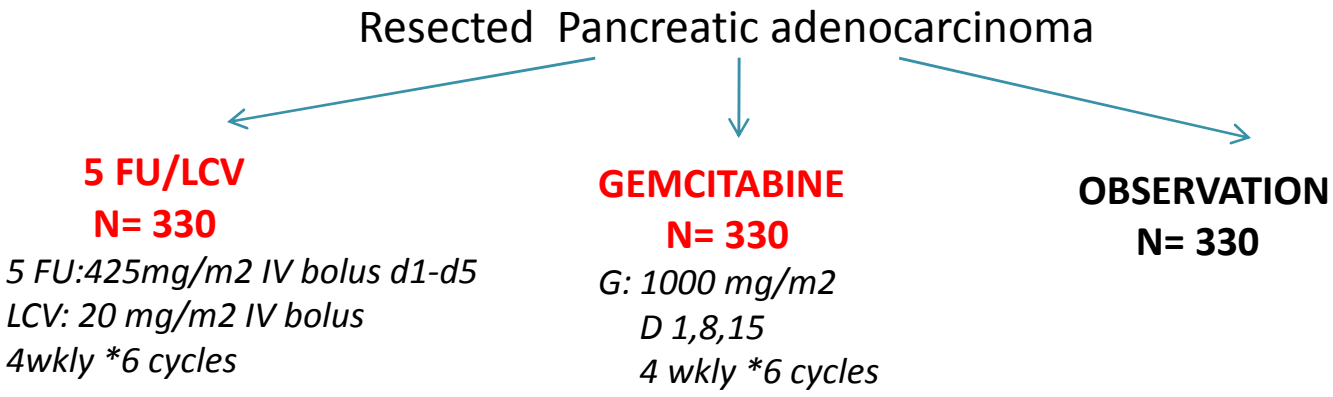
	N	SCHEDULE	5 yr LC (%)	DFS mo	OS mo	DFS (%)
CONKO-001	368 (R0 - 80% R1- 20%)	O 6 cycles gemcitabine (1,000 mg/m^2 IV over 30 min) on day 1, 8, and 15 every 4 wks	8% 26%	**6.9** **13.9** (P < 0.001)	20.2 22.1	**5.5%** **16.5%** (P<.001)

CONCLUSION: **Postoperative gemcitabine significantly delayed the development of recurrent disease in both R0 (13.1 vs 7.3 mths; p <0.001) and R1 (15.8 vs 5.5 mths; p<0.001) resections compared with observation alone.**

ESPAC -3/ NCIC –PA2

BACKGROUND: Adjuvant 5-FU/LCV (ESPAC-1 trial) and GEM (CONKO-001 trial) shown improved survival for patients with resected pancreatic cancer compared to no chemotherapy.

AIM :To compare 5FU/LCV vs GEM



Stratification: 515 patients in each arm

R0 (65%)

R1 (35%)

Grade (25% poorly diff)

LN + (71%)

Neoptolemos JP,et al. J Clin Oncol 2009; 27 (18 Supp): Abstract LBA4505

RESULTS:		
	5 FU/LCV	GEMCITABINE
TOXICITY: •Diarrhea •Stomatitis •T/t related hospitalizations •Thrombocytopenia	 13% 10% 10% less	 2% 0% 3.5% More
OVERALL SURVIVAL	23 mths	23.6 mths **(p = 0.39)ns**
Grade, stage, nodal status, resection margins are important prognostic factors		

CONCLUSION:

- **No difference between the two regimens**:
  --equal OS
  --Gemcitabine not superior to 5FU/LCV
- Safety, compliance, adverse events better with Gemcitabine
- No significant difference in the effect of treatment across subgroups according to R status
- Important study as there has been tendency to reject 5 FU/LCV in pancreatic cancer and now it is back on stage.

Neoptolemos JP,et al. J Clin Oncol 2009; 27 (18 Supp): Abstract LBA4505

CHEMORADIATION TRIALS IN ADJUVANT SETTINGS IN RESECTABLE DISEASE

RATIONALE :

- To increase local control by radiation
- To decrease chances of metastasis by concurrent use of chemotherapy
- To increase overall survival

ADJUVANT CHEMORADIATION STUDIES:

	N	SCHEDULE	MS mo	2 YR (%)	5 YR (%)	LR (%)	DM (%)
GITSG (1985)	22 21	O 40 Split + 5 FU Bolus	11 **20 (p<0.05)**	15 42	5 19	33 47	52 (LIVER) 40 (LIVER)
GITSG (1987)	30	40 Split + 5 FU Bolus	18	43	-	55	45 (LIVER)
CONCLUSION: ***Adjuvant chemoradiation beneficial but Dose of RT & 5 FU alone inadequate. T/t compliance poor***							
EORTC (1999)	54 60	O 40 Split + 5 FU CI	12.6 17.1 (P=0.09)	23 37	10 20	- -	- -
CONCLUSION: ***No benefit of chemoradiation in terms of survival Critized being underpowered***							

	N	SCHEDULE	MS mo	2 YR (%)	5 YR (%)	LR (%)	DM (%)
ESPAC -1 (2004)	69 73 72 75	O 40 Sp + 5 FU Bo 40 Sp + 5 FU Bo ; 5 FU- LCV 5 FU Bo(425 mg/m^2)- LCV(20 mg/m^2) *5 days	16.9 13.9 19.9 **21.6 (P=.009)**	30 40	8 21	- - - -	- - - -

CONCLUSION:

- **Survival benefit with adjuvant 5 FU –LCV chemotherapy but not with chemoradiation.**
- **Critized for having no radiation quality control in chemoradiation arm**

PHASE III TRIALS IN ADJUVANT SETTINGS IN RESECTABLE DISEASE

	N	SCHEDULE	MS mo	2 YR (%)	5 YR (%)	LR (%)	DM (%)
WHITTINGAN et al	33	O	15	35	-	85	23 (LIVER) 23 (PS)
	19	45 -48.6 + 5 FU Bolus	15	30	-	55	42 (LIVER) 21 (PS)
	20	45-48.6 + 5 FU CI	16	43	-	25	25 (LIVER) 15 (PS)
YEOH et al	53	O	14	30	-	-	-
John Hopkins	120	>45 + 5 FU Bo /CI	**20 (p=.003)**	40	-	-	-
PICOZZI et al ***Virginia***	53	45-54 + 5 FU + Cisp +IFN	46	53	45	-	-

CONCLUSION: **Adjuvant CRT with adequate RT doses and 5 FU CI, have shown benefit in patients.**

ORIGINAL CONTRIBUTION

Fluorouracil vs Gemcitabine Chemotherapy Before and After Fluorouracil-Based Chemoradiation Following Resection of Pancreatic Adenocarcinoma

A Randomized Controlled Trial

William F. Regine, MD
Kathryn A. Winter, MS
Rose A. Abrams, MD

Context Among patients with locally advanced metastatic pancreatic adenocarcinoma, gemcitabine has been shown to improve outcomes compared with fluorouracil.
Objective To determine if the addition of gemcitabine to adjuvant fluorouracil che-

RTOG 9704

Resected pancreatic cancer (n =538)

GEMCITABINE ARM

SCHEDULE :
G: 3 wks
↓
5 FU with RT (50.4Gy/28 #)
↓
G: 12 wks

5 FU ARM

SCHEDULE :
5 FU infusion 3 wks
↓
5 FU with RT (50.4Gy/28 #)
↓
5 FU infusion 12 wks

CONCLUSION: For pancreatic head tumors ONLY;

Median survival -	20.5 mths	16.9 mths
3 yr survival -	31%	22%

The addition of gemcitabine to adjuvant 5 FU based CRT was associated with a survival benefit, although this improvement was not statistically significant.

CONTRIBUTION OF ADVANCED RADIOTHERAPY TECHNIQUES IN CHEMORADIATION

RT PLANNING

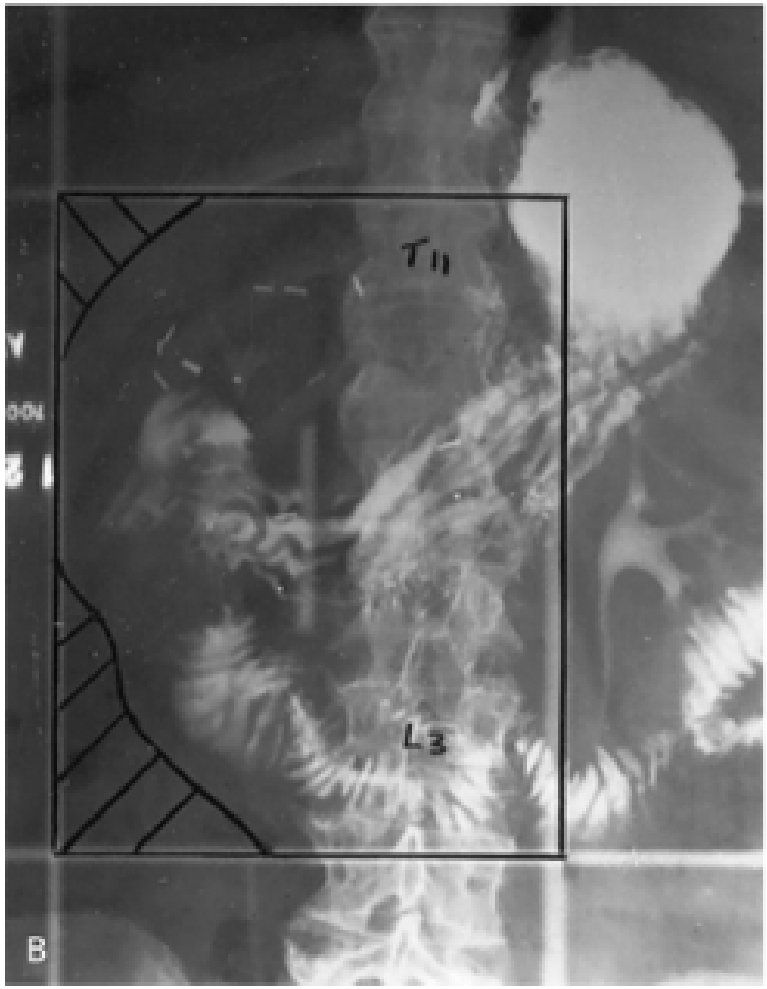
- ***Indications***
  - +ve margins
  - Gross residual tumor
  - LN involvement
  - Perineural involvement
- ***Goal***
  - Decrease local recurrence
- Should be given in even T1, T2 pts (high chance of local failure)
- ***Treatment volume*** – tumor bed, peripancreatic ln, PALN
- ***Fields*** – 4 field or 3D CRT
- ***Dose*** – 45 to 50 Gy in 1.8 Gy/#

RT PLANNING

- ***Information reqd***
  - Pre-op CT – location of tumor before resection
  - Post-op CT – persistent/ residual/ metastatic disease
  - Pre-op → barium/ ERCP/ angiography/ USG –findings
  - I/O findings
  - CT based planning
  - Renal contrast – delineation of kidneys
  - Oral contrast – stomach & duodenal C loop
  - Clips (extent of tumor)

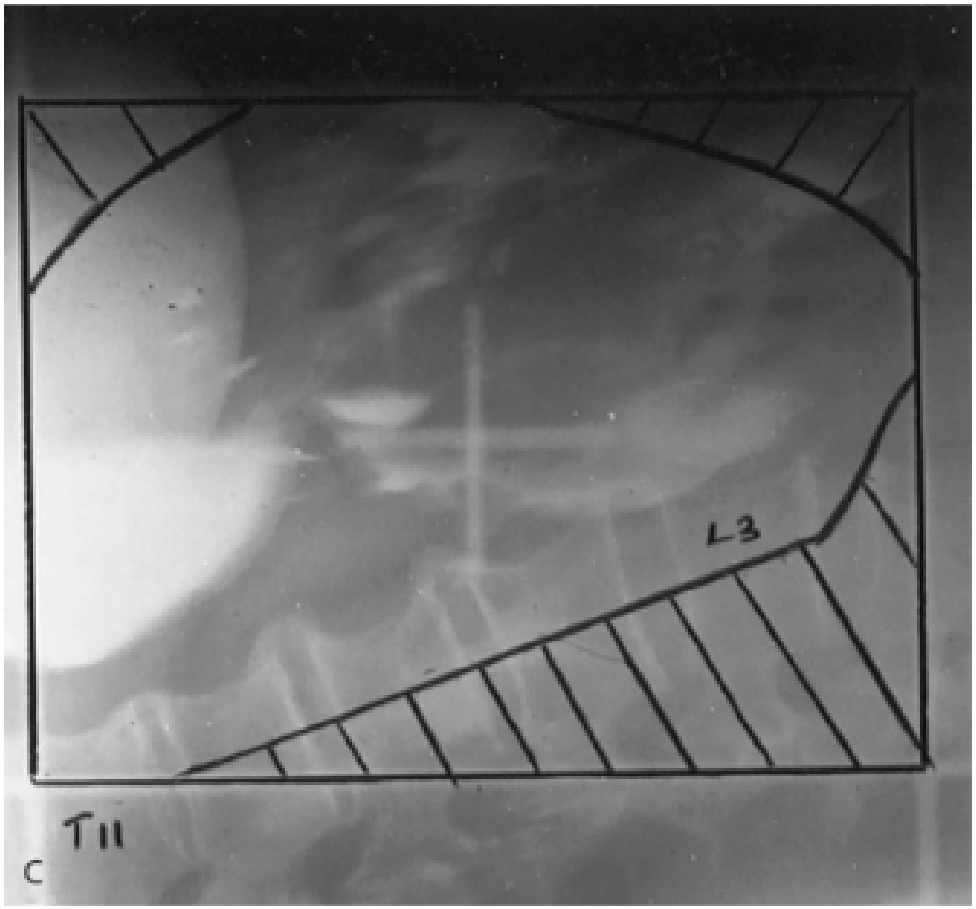
AP/PA fields

- Sup. – T10/T11
- Inf. – L3/L4
- R. lat – 2-3cm beyond gross disease
  - Head – lat 1/3- medial 2/3 jn of right diaphragm
  - Body & tail – 2-3 cm right to vertebral border
- L. lat –
  - Head - 2-3 cm left to vertebral border
  - Body & tail - lat 1/3- medial 2/3 jn of left diaphragm



LATERAL fields

- Sup. & inf. – same
- Ant. – 1.5-2 cm beyond gross disease as defined on pre-op CT
- Post. – spinal cord is blocked, but at least 1.5-2 cm of ant. Portion of vertebral body is in the field



DOSE CONSTRAINTS

- Lateral field contribution limited to 15-18 Gy (liver & kidney)
- Spinal cord – 45 Gy

DIFFICULTIES IN PLANNING

- Radiation field include tumor/tumor bed, peri-pancreatic nodes, para-aortic node.
- This volume is difficult to encompass without involvement of renal parenchyma.
- So, during early period when two dimensional radiotherapy technique was used dose was limited due to large volume of normal tissue to be encompassed.

Stepwise Approach to Contouring

- Delineate ROI's
  - Portal Vein (PV)
  - Pancreaticojenunostomy (PJ)
  - Celiac Artery (CA)
  - Superior Mesenteric Artery (SMA)
  - Aorta
  - Tumor Bed

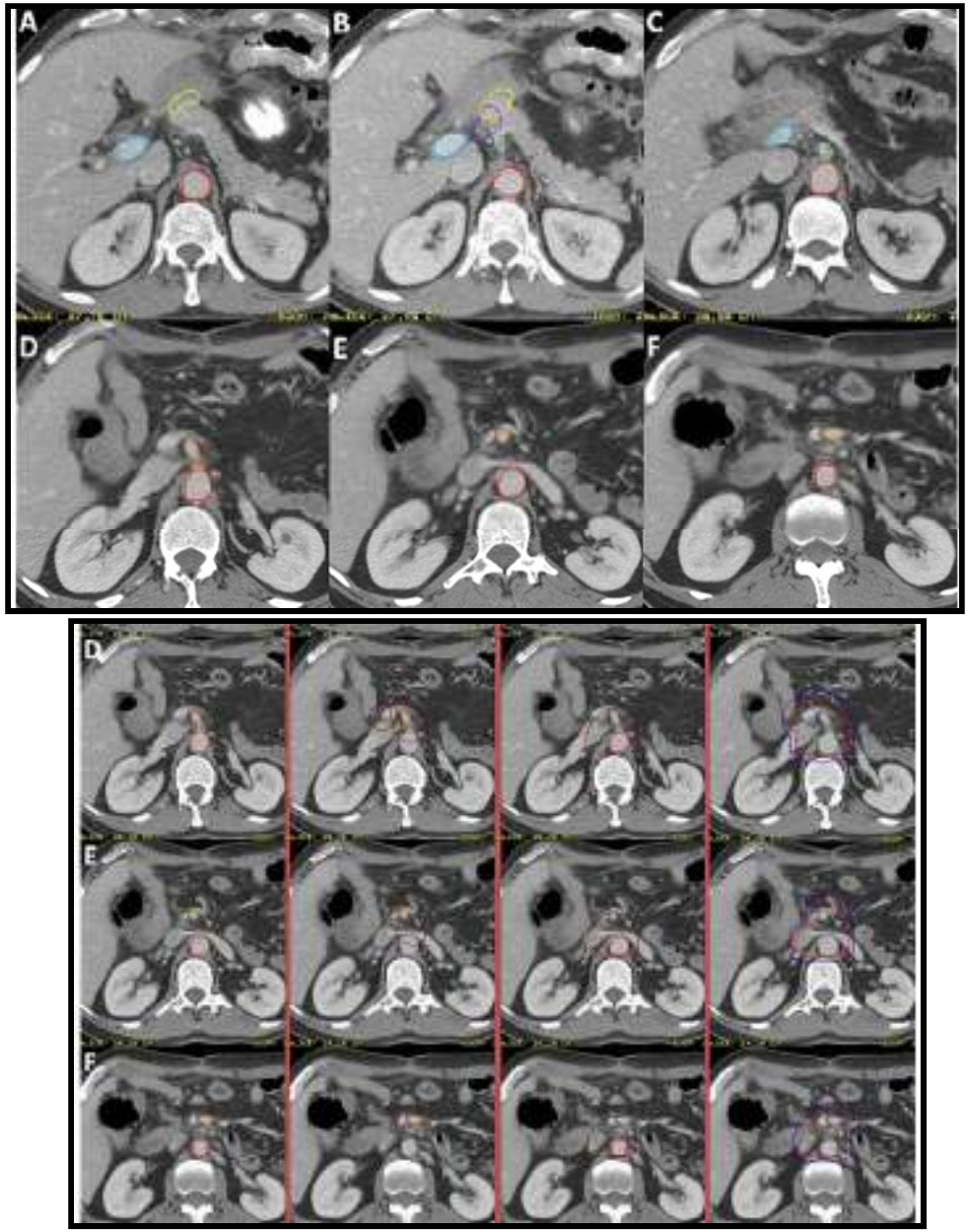
- Expansion 1
  - 1.0 cm expansion on PV, PJ, CA, and SMA

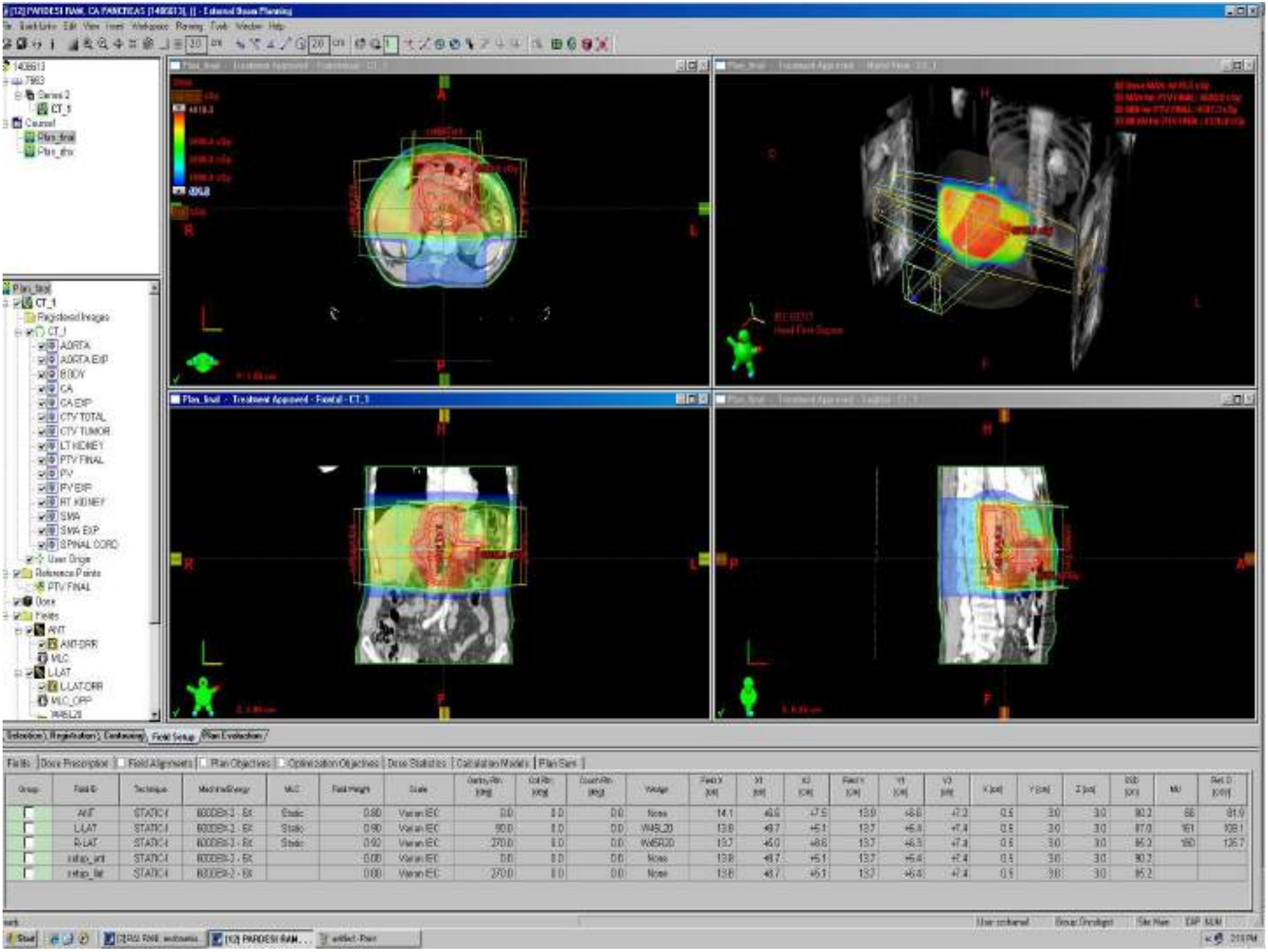
- Expansion 2
  - 2.5 to 3.0 cm to the right,1.0 cm to the left, 2.0 to 2.5 cm anteriorly, 0.2 cm posteriorly on Aorta

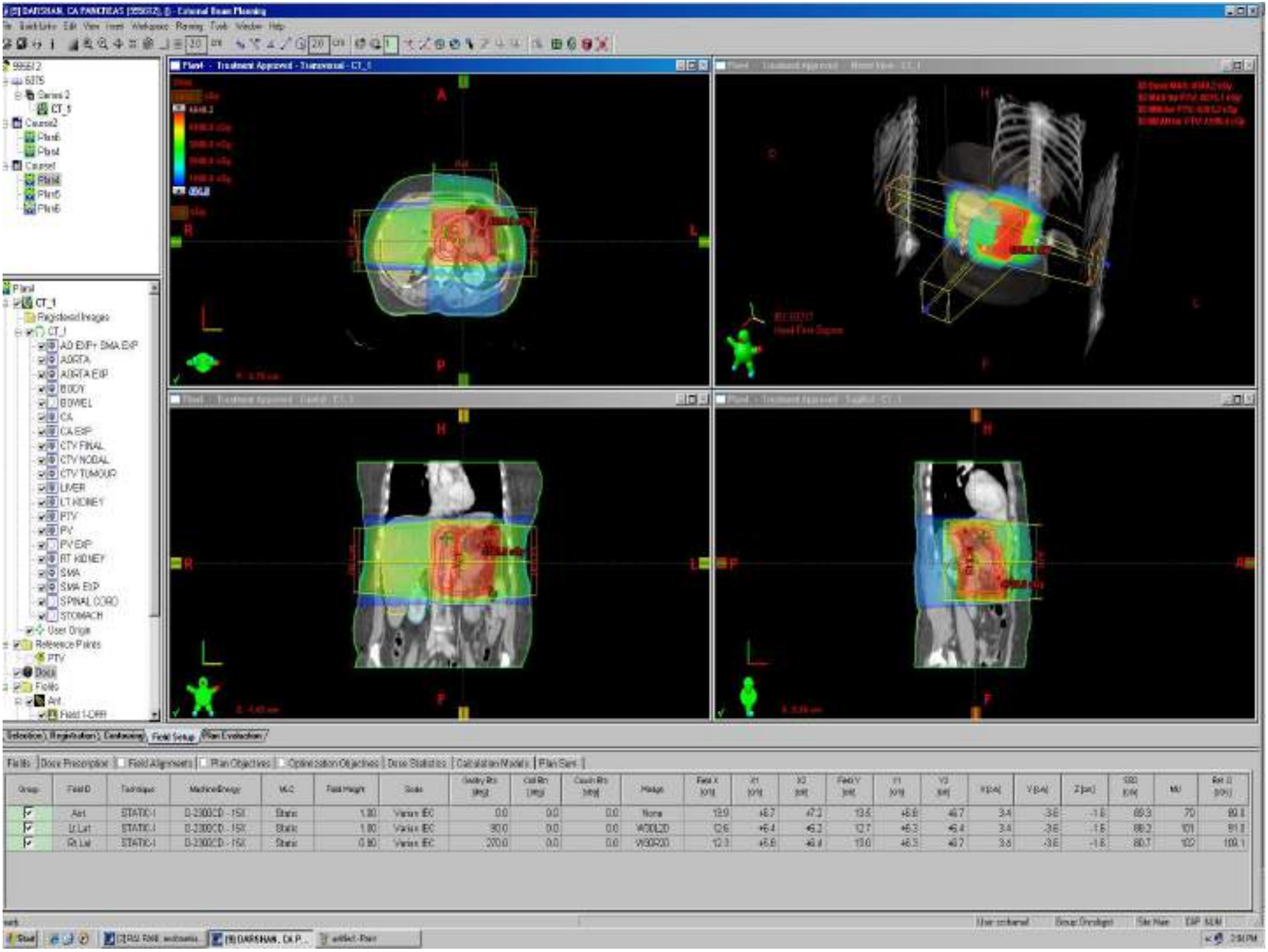
- CTV
  - Boolean addition (merging) of Expansion 1 and 2
  - Confirm that CTV encompasses tumor bed and contoured clips

- PTV
  - 0.5 cm expansion on CTV

CONTOURING




Plan_final - Treatment Approved - Frontal - CT_1
CT_1
Registered Images
AORTA
AORTA EXP
BODY
CA
CA EXP
CTV TOTAL
CTV TUMOR
LT KIDNEY
PTV FINAL
PV
PV EXP
RT KIDNEY
SMA
SMA EXP
SPINAL CORD
Reference Points
PTV FINAL
Fields
ANT
ANT-DRR
MLC
L LAT
L LAT-DRR
MLC_OPP
Field Setup
Plan Evaluation
Fields
Dose Prescription
Field Alignments
Plan Objectives
Optimization Objectives
Dose Statistics
Calculation Models
Plan Sum


Plan1 - Treatment Approved - Transversal - CT_1
CT_1
Registered Images
AO EXP+ SMA EXP
AORTA
AORTA EXP
BODY
BOWEL
CA
CA EXP
CTV FINAL
CTV NODAL
CTV TUMOUR
LIVER
LT KIDNEY
PTV
PV
PV EXP
RT KIDNEY
SMA
SMA EXP
SPINAL CORD
STOMACH
User Origin
Reference Points
PTV
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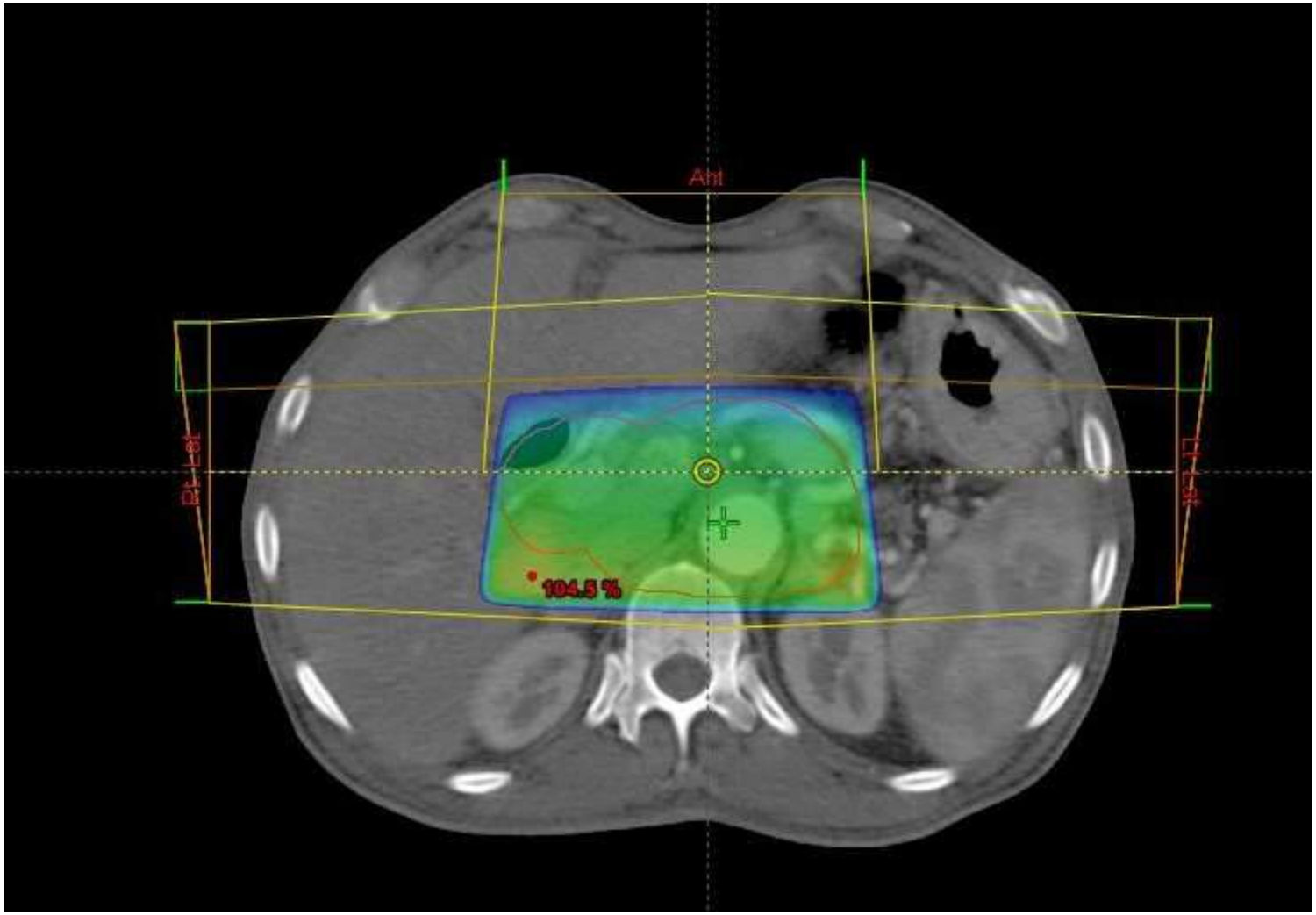
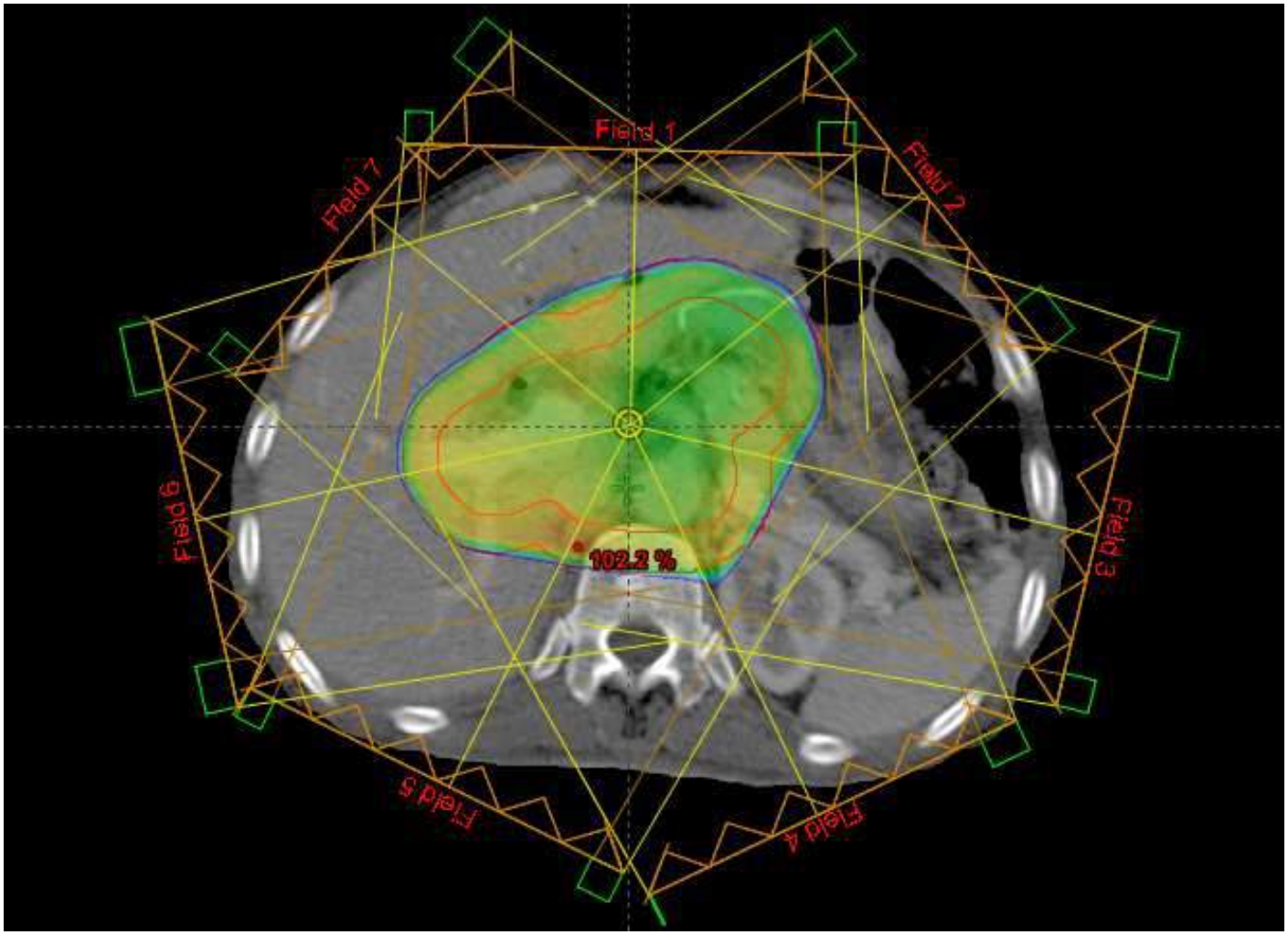

Ant
Rt. Lat
Lt. Lat
104.5 %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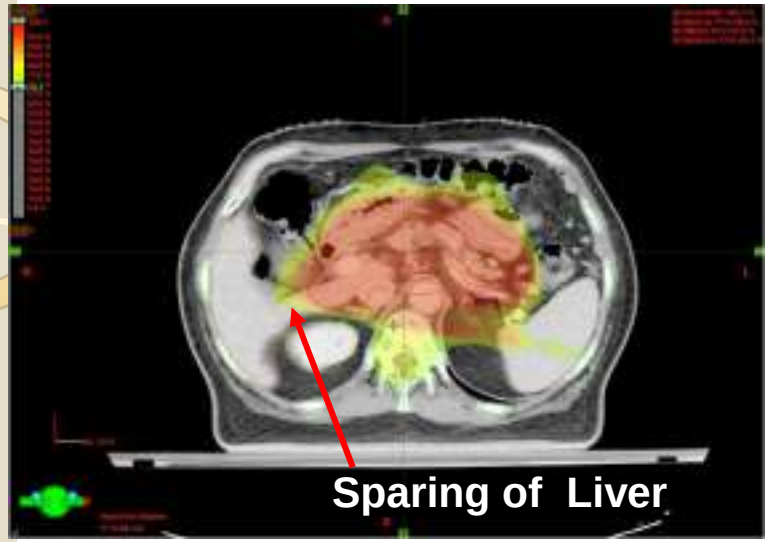
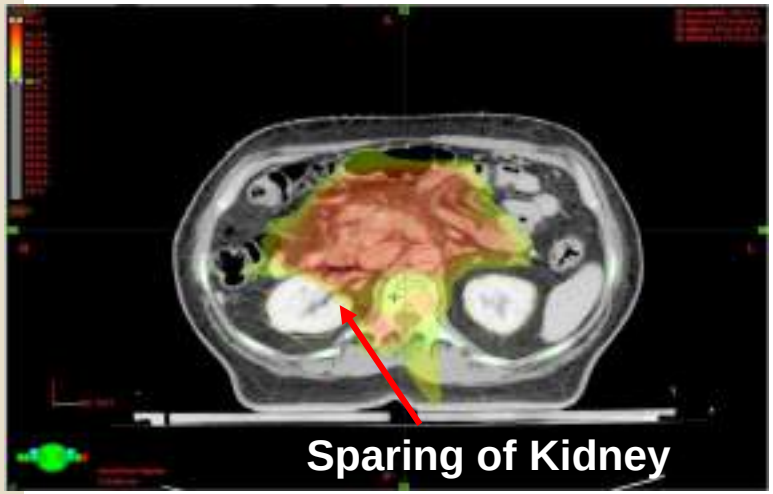
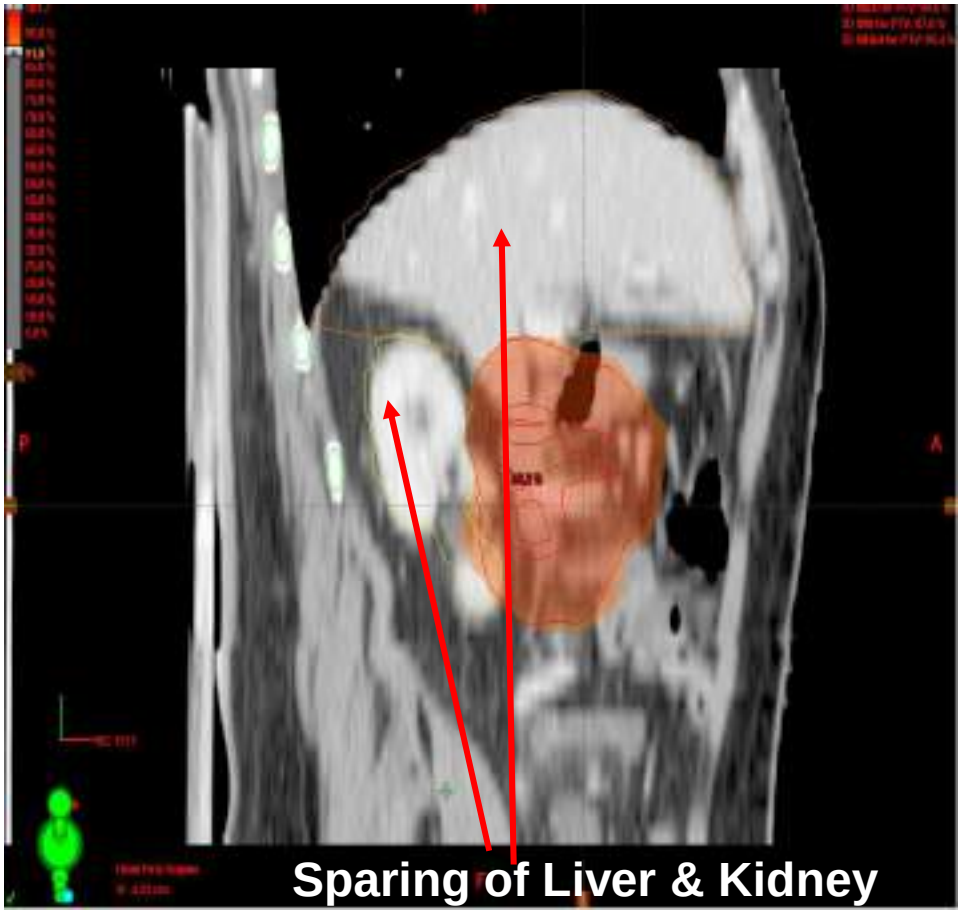
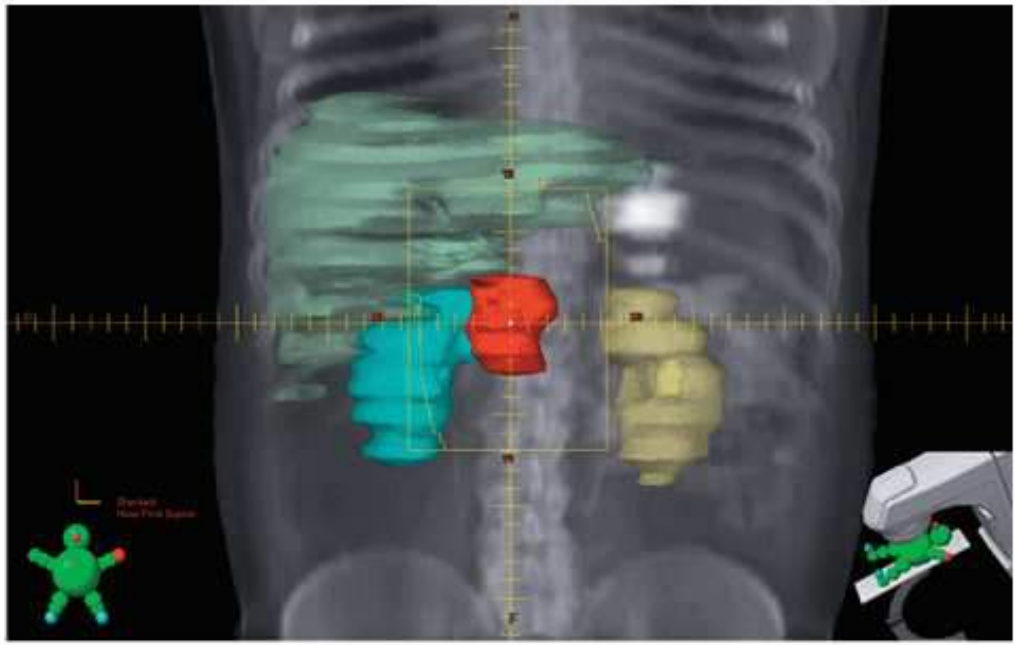
Field 7
102.2 %

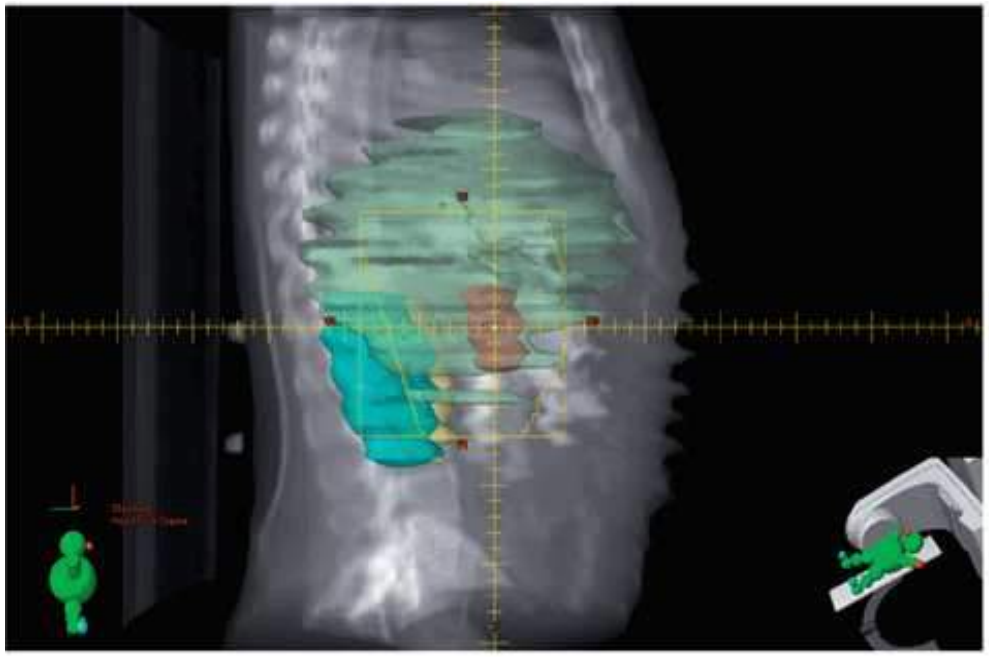




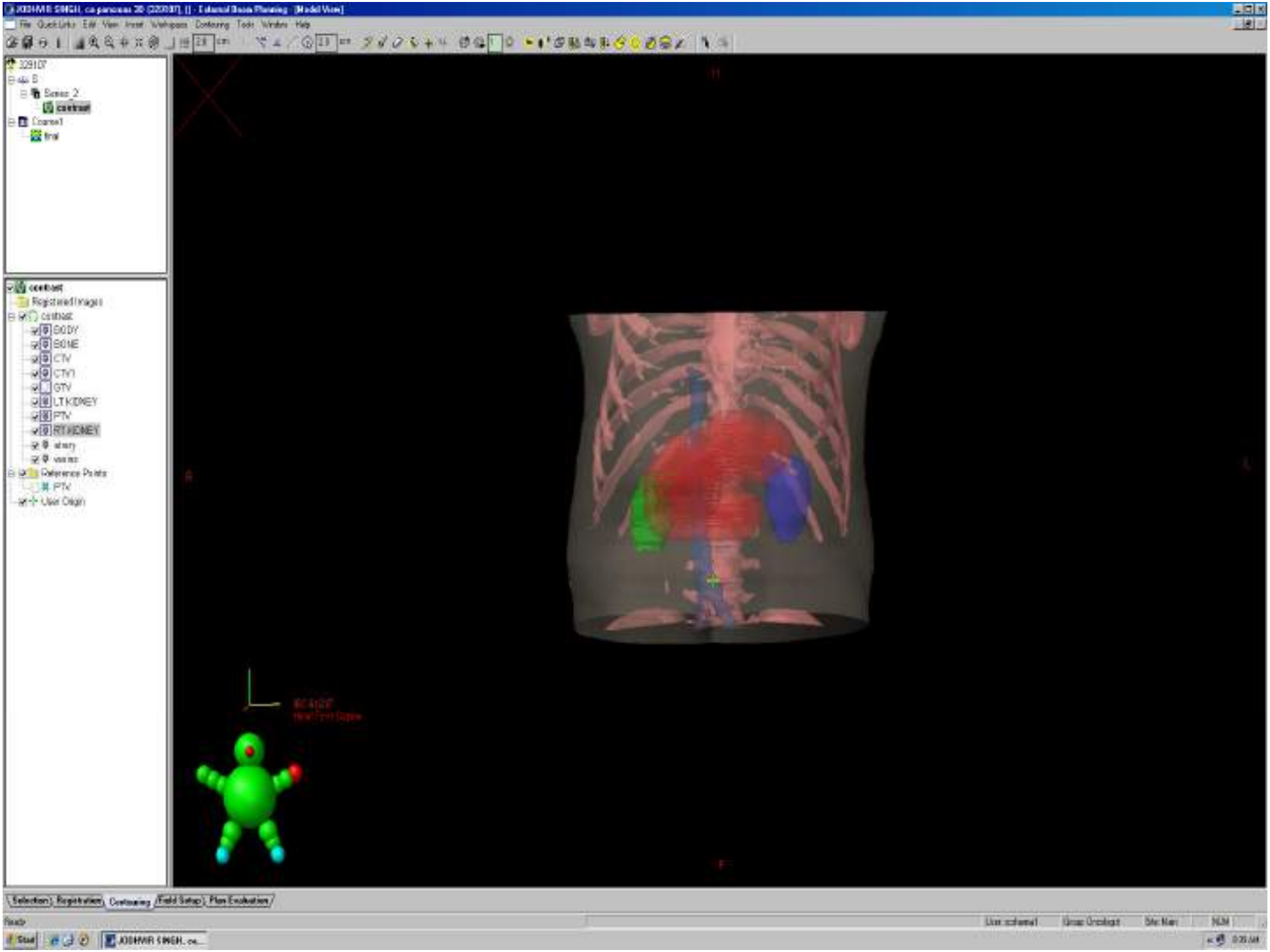


IMRT Dose Distributions





3 DCRT planning


File QuickLinks Edit View Insert Workspace Contouring Tools Window Help
229107
Beam 2
contour
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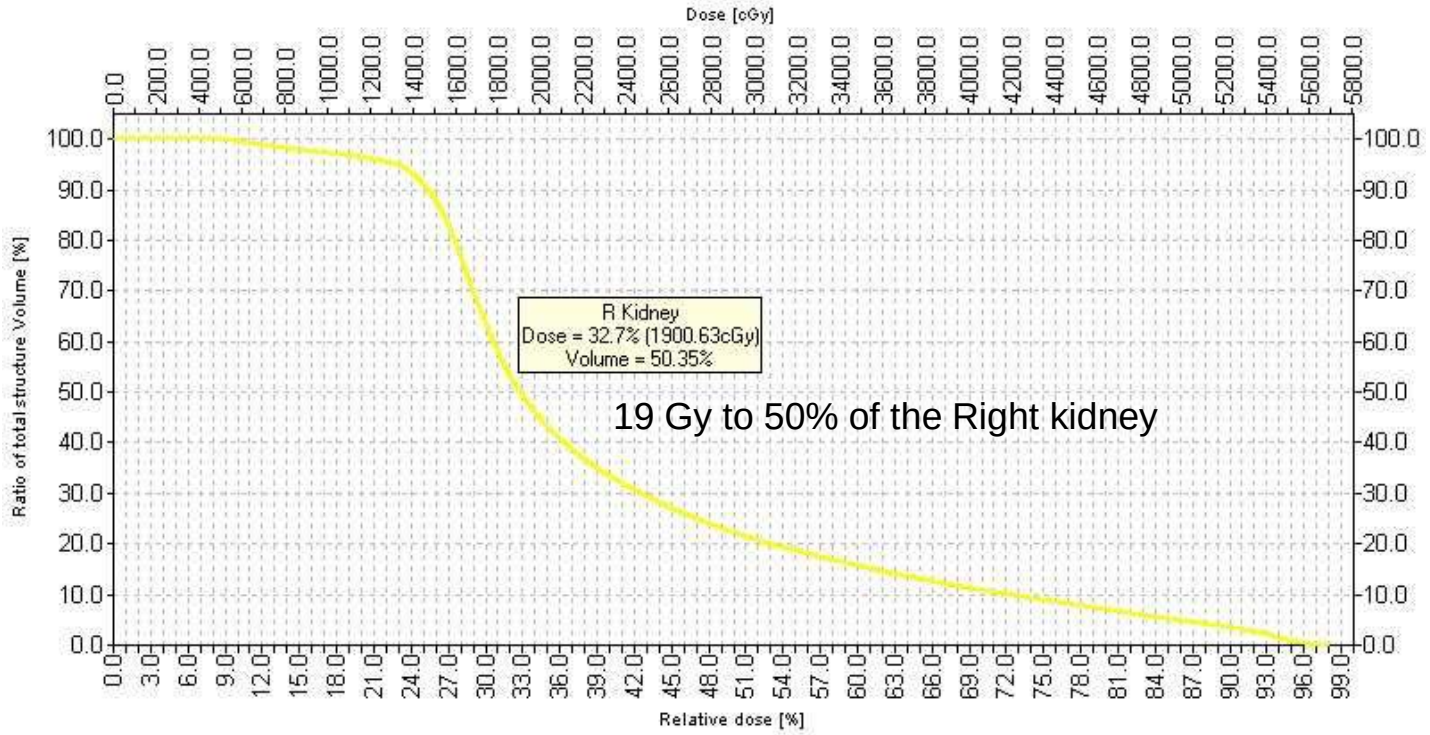
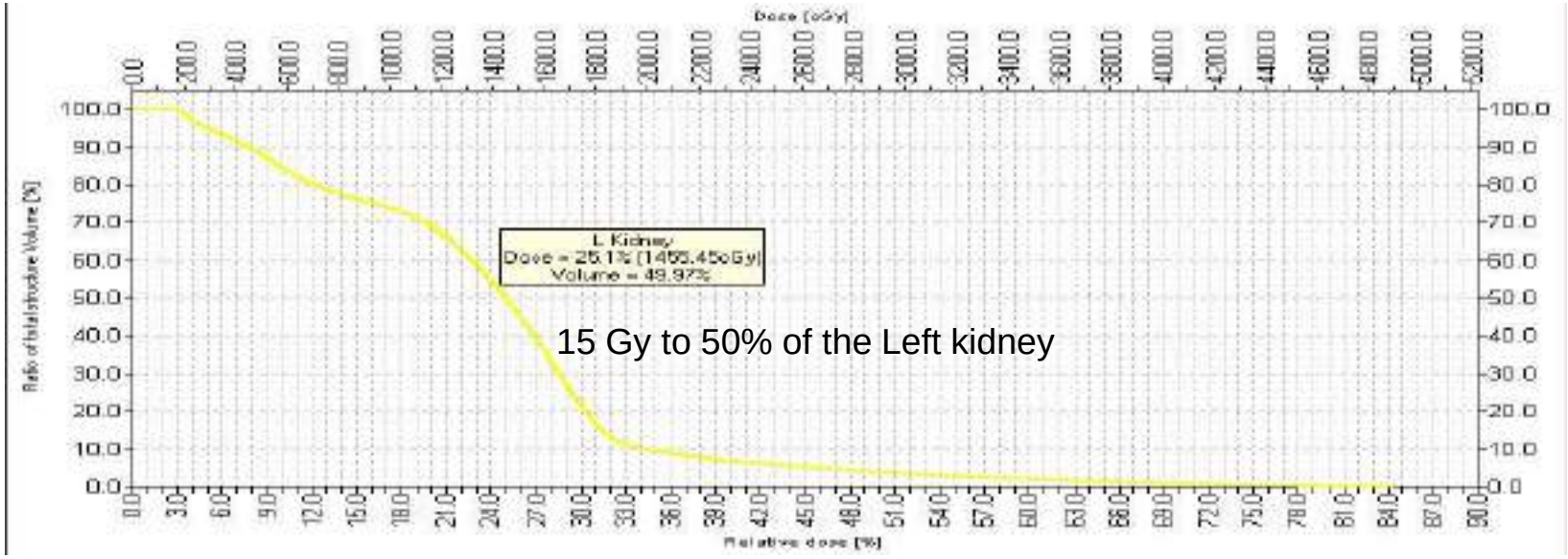
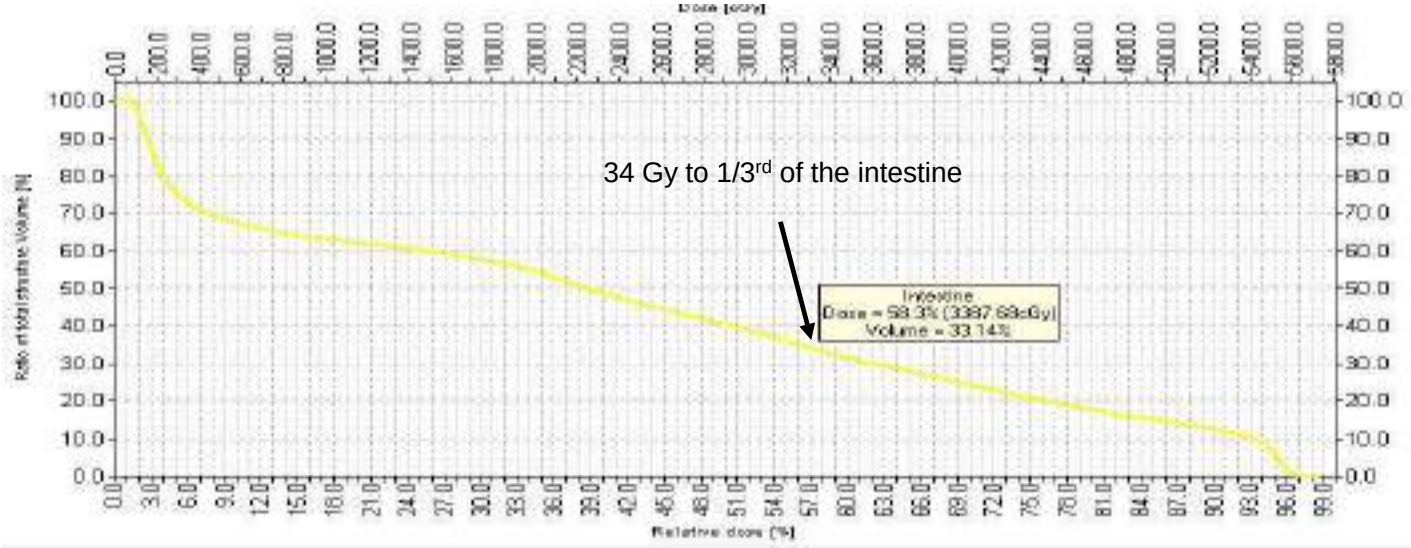
final
contour
Registered Images
contour
BODY
BONE
CTV
CTV1
GTV
LT KIDNEY
PTV
RT KIDNEY
Reference Points
PTV
User Origin
Selection
Registration
Contouring
Field Setup
Plan Evaluation
Ready
Start

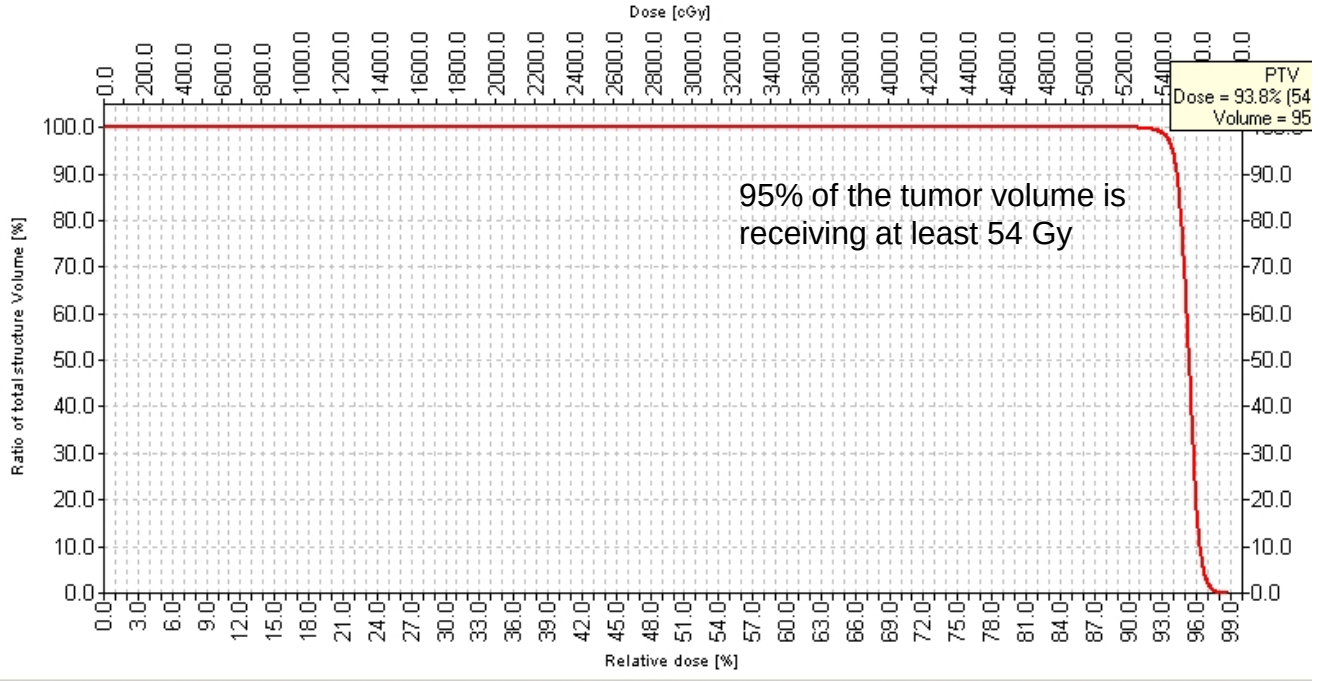


19 Gy to 50% of the Right kidney



15 Gy to 50% of the Left kidney


34 Gy to 1/3rd of the intestine
Intestine
Dose = 58.3% (3387.69cGy)
Volume = 33.14%


Dose [cGy]
PTV
Dose = 93.8% (54
Volume = 95
95% of the tumor volume is receiving at least 54 Gy
Ratio of total structure Volume [%]
Relative dose [%]

ADJUVANT CHEMORADIATION TRIALS WITH MODIFIED RADIATION TECHNIQUES

ESPAC 4:

- Comparing Gemcitabine (1000 mg/m2 D1,8,15 4 Wkly *6 cycles)

  vs

  Gemcitabine + Capecitabine (800 mg/m2 BD for 21 days 4 wkly)
- Capecitabine (Xeloda alone arm not been taken??)

RTOG 0848 :

- Comparing Gemcitabine (1000 mg/m2 D1,8,15 4 Wkly *6 cycles)

  vs

  Gemcitabine + Erlotinib (100 mg/day PO for 6 cycles)

  If no progression: then 2nd randomization to 5FU / Capecitabine based CRT (50.4 Gy/28#)

EORTC 40013:

- Comparing Gemcitabine 4 cycles

  vs

  Gemcitabine 2 cycles

  f/b Gemcitabine wkly concurrent with XRT 50.4 Gy/28#
- PH II results have shown that adjuvant gemcitabine based CRT is feasible, well-tolerated, and not deleterious. And 1st local recurrences are less in CRT arm

ACOSOG:

5-FU (200 mg/m^2/d for 5 weeks), weekly cisplatin (30 mg/m^2), and S/C interferon- (3 MIU s.c three times a week) combined with XRT 50 Gy f/b 2 cycles of CI 5-FU (200 mg/m^2/d) on days 64 to 105 and 120 to 161.

CHEMORADIATION TRIALS IN NEOADJUVANT SETTINGS IN UNRESECTABLE DISEASE

BORDERLINE RESECTABLE TUMORS

- ***Definition***
  - abutting 180 degrees or less (50% or less of the vessel circumference) of the superior mesenteric artery
  - encasing a short segment of the common hepatic artery,
  - causing segmental venous occlusion.

- ***Goal*** → sterilizing tumor at the periphery, where direct contact with arterial structures occurs → curative resection may be possible

- ***Treatment strategy*** → NA CRT f/b Sx

RATIONALE :

- Chemoradiation for unresectable pancreas was initiated after GITSG study demonstrated a survival advantage over external radiation alone.
- Chemoradiation is based upon the following premises:
  - Some patients may become **resectable** after chemoradiation which can improve their prognosis (downstaging)
  - The addition of chemotherapy adds to the **local control** by increasing the radiosensitivity of the tumor.
  - Chemotherapy in addition has the theoretical potential of **eliminating** systemic micrometastasis.

NEOADJUVANT CHEMORADIATION STUDIES

Series		N	Median Survival	Local Failure	1 yr Survival
Mayo Clinic[1]	RT only (35 – 40 Gy)	32	6.3	NA	6%
	RT + 5 FU	32	10.4	NA	22%
			Moertel CG.Lancet 1969; 2:865-7.		
GITSG[2]	RT (60 Gy) alone	25	5.3	24	10%
	RT (40 Gy) + 5FU	83	8.4	26	35%
	RT (60 Gy) + 5FU	86	11.4	27	46%
			Moertel CG. The Gastrointestinal Tumor Study Group. Cancer 1981; 48:1705-10.		
GITSG[3]	RT (60 Gy) + 5 FU	73	8.5	58	33%
	RT (40 Gy) + Adria	70	7.6	51	27%
GITSG[4]	RT (54 Gy) + SMF	22	9.7	45	41%
	SMF only	21	7.4	48	19%
ECOG[5]	RT(40 Gy) + 5FU	47	8.3	32	26%
	5 FU	44	8.2	32	32%
			Klaassen DJ. J Clin Oncol 1985; 3:373-8.		

GEMCITABINE BASED CCT+RT.(2000)

Series	N	Median Survival	Response	Toxicity (Gr III/IV)
Wilkowski et al[1] RT (45 -50 Gy) Gem 300mg/m^2 + Cisplatin	57	14.8	CR 12% PR 57.5%	54.7%(Hemat)
Crane et al[2] RT 30 – 33 Gy + Gem 250 – 500 mg/m^2 weekly	53	11	NA	24.5% (GI)
Brunner et al[3] RT 50.4 Gy + Gem 300 – 600 mg/m^2 weekly	36	14	PR 28.6% SD 71.4%	66.7% (Hemat) 19.4% (GI)
DeLange et al[4] 24Gy (3 x 8Gy) + Gem 300 mg/m^2	24	10	CR 4.2% PR 25%	37.5% (GI)

Neoadjuvant chemoradiation with Gemcitabine for locally advanced pancreatic cancer

Daniel Habermehl[1,4*], Kerstin Kessel[1], Thomas Welzel[1], Holger Hof[1], Amir Abdollahi[1], Frank Bergmann[3], Stefan Rieken[1], Jürgen Weitz[2], Jens Werner[2], Peter Schirmacher[3], Markus W Büchler[2], Jürgen Debus[1] and Stephanie E Combs[1*]

Radiation Oncology 2012, 7:28 doi:10.1186/1748-717X-7-28

- 215 patients with locally advanced pancreatic cancer
- NACRT: 52.2 Gy @1.8 Gy/# with concurrent gemcitabine (GEM) at a dose of 300 mg/m^2 weekly, followed by adjuvant GEM (1000 mg/m$^{2)}$
- RESULTS:

--- Resection rate : 26%

R0-resection : 39.2%

R1-resections : 41.2%,

R 2 resection: 11.8%

--- Median OS : 22.1 vs 11.9 months in non-resected patients.

--- In most cases the first site of disease progression was systemic with hepatic (52%) and peritoneal (36%) metastases

- CONCLUSION: Patients with locally advanced pancreatic cancer can undergo secondary resection after gemcitabine-based chemoradiation and has a relative long-term prognosis.

I.M.R.T. TRIALS

- Dose escalation
- Reduced dose to liver, kidneys, stomach & small intestine

Landry et al (2002)

- compared normal organ sparing of IMRT vs 3DCRT.
- Dose prescribed was 61.2 Gy to the gross tumor volume (GTV) and 45 Gy to the clinical treatment volume (CTV)
- Significant reducton in dose to small intestine.

Fuss et al (2005) -IMRT in 25 patients.

- 66 Gy to the gross tumor and 46 Gy to the subclinical disease.
- 14/25 (**56%**) patients were alive with median follow-up of 20 months (range 3-40 months)
- Actuarial 1-year survival was **26%**
- Four (**16%**) pts → **grade 3** or greater GI toxicity.
- A **single** patient exhibited grade 4 gastrointestinal bleeding immediately after completing the treatment course

OUR EXPERIENCE & RESULTS

Original Article

Role of neoadjuvant concurrent chemoradiation in locally advanced unresectable pancreatic cancer: a feasibility study at tertiary care centre

Rakesh Kapoor, Divya Khosla, Rajesh Gupta[1], Amit Bahl, Arvind K. Shukla, Suresh C. Sharma
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NEOADJUVANT CHEMORADIOTHERAPY

- N= 15 , Locally Advanced Pancreatic cancers
- Neoadjuvant treatment –

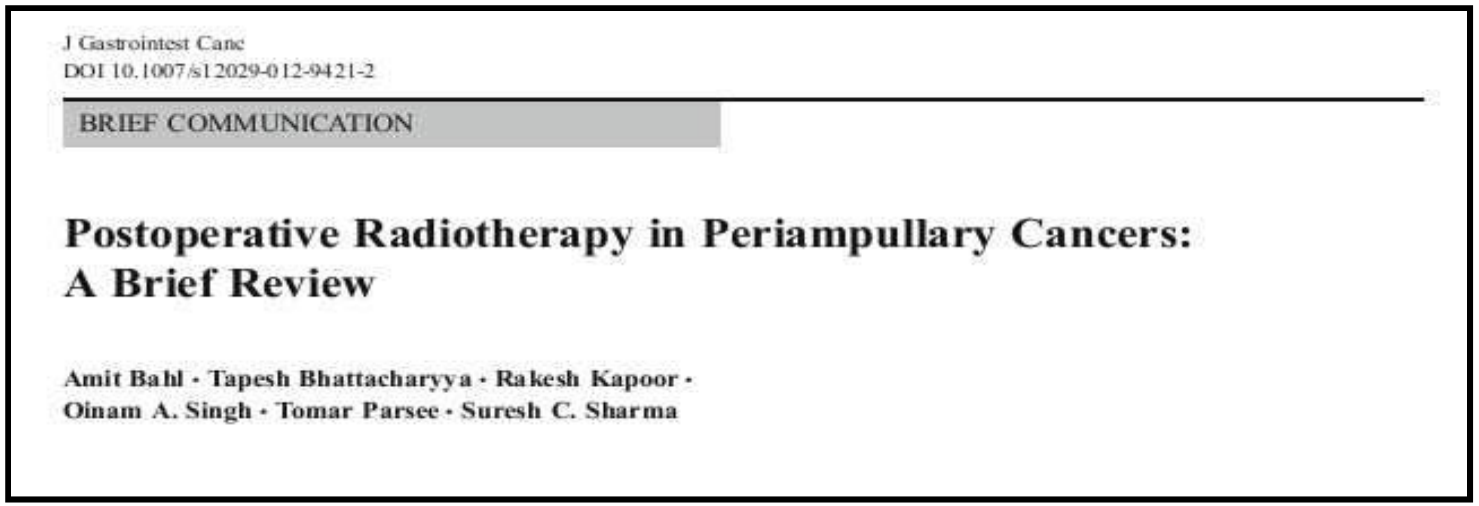
Oral Capecitabine 1000 mg/m2 daily in three divided doses, 5 days per week, coinciding with radiation therapy administration. Therapy continued for the entire duration of radiation therapy.

Radiotherapy : 30 Gy/ 10 # / 2 weeks

RESULTS : NACRT

- 4 patients underwent surgery
- 5 patients had partial response but were unresectable
- 2 patients had stable disease
- 3 patients had progressive disease
- Toxicity : Grade 1 -2
- Median survival : 15 months for resected & 8.5 months for unresected
- 2 year actuirial overall survival 34.6 months

RESULTS: PERIAMPULLARY CANCERS



J Gastrointest Canc
DOI 10.1007/s12029-012-9421-2

BRIEF COMMUNICATION

Postoperative Radiotherapy in Periampullary Cancers: A Brief Review

Amit Bahl · Tapesh Bhattacharyya · Rakesh Kapoor · Oinam A. Singh · Tomar Parsee · Suresh C. Sharma

- Retrospective analysis (2007-2009)
- N=40
- M:F – 33:7
- Whipples surgery followed by post operative radiotherapy 45Gy/25#/5 weeks
- Six cycles of adjuvant GEMOX chemotherapy

RESULTS: PERIAMPULLARY CANCERS

- At end of treatment

  Complete response-70%

  Partial Response - 7.5%

  Progressive Disease -15%

  Defaulted for treatment – 2.5%

  Dead - 5%

  At 2 year follow up DFS was 65%

CONCLUSIONS

- Addition of chemotherapy to radiation adds to the survival by 5 – 8 months in adjuvant setting.
- Chemoradiation makes tumors resectable in 10% -33% of the patients in neoadj settings.
- In the palliative setting chemoradiation improves pain relief by 30% - 40%.
- Either RT / CCT doses needs to be modified when given concomitantly
- Patient selection is of paramount importance in order to achieve desired results.
- Therefore, the ***realistic goal*** of chemoradiation for most patients is ***to delay local recurrence*** than to prevent it.


Thank
You