# Adjuvant Treatment in Endometrial Cancer: Addressing Dilemmas


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# Definition

- Adjuvant treatment is defined as the treatment imparted after the main treatment
- Adjuvant Treatment: A compulsion
- Avoid if possible
- But do not hesitate, if there is a need

# Why Adjuvant Treatment ?

- Despite curative resection, some pts actually have remaining viable tumor cells
- These cells, if not treated, will grow & lead to clinical recurrence later
- Rx of clinical recurrence is mostly difficult
- Effectiveness of adjuvant Rx like RT is inversely related to tumor burden (more effective when tumor is microscopic)

# Aim of adjuvant treatment

- Reduction in the recurrence rate
- Improvement in survival
- Improved quality of life

# General principles of Adjuvant Rx

- Significant risk of recurrence (>10-15%)
- Salvage probability
- Rx should be effective
- Toxicity should be within acceptable limits
- Team approach

# Adjuvant RT in Endometrial cancer

- Stage I : Role of adjuvant RT is debatable
- Stage II onwards : Not controversial
- Why debatable in Stage I ?
- Overtreatment (toxicity)  vs under-treatment (Rec)
- Therefore adjuvant therapy should have balance between local control and associated toxicity

# Adjuvant RT in Stage I : Surgeon's Perspective

- Additional treatment will lead to higher toxicity
- Literature does not show survival gain
- Local recurrences are salvageable
- Confidence

# Adjuvant RT in Stage I :

## Radiation Oncologist's Perspective

- Consistent reduction in local recurrence: robust literature
- Toxicity within acceptable limits
- Local recurrences are hardly salvageable
- Comfort

# Adjuvant RT Endometrial Carcinoma : other Issues

- Nature & extent of surgery
- Lymph node Sampling/dissection
- Adequacy of lymph node removal
- Appropriate no. of L nodes
- Emerging role of chemotherapy

# Current Protocol

| | G I | G II | G III |
|---|---|---|---|
| IA | Observation | Observation | Observation or IVBT* |
| IB | IVBT | EBRT+ IVBT | EBRT+ IVBT |
| II | EBRT + IVBT | | |
| III | EBRT + IVBT + Chemotherapy | | |

*Adverse risk Factors [Myoinvasion, Age >60 years, LVSI]

** Stage IV: Palliative RT/ Chemotherapy

# Stage I

| | G I | G II | G III |
|---|---|---|---|
| IA | | | |
| IB | | | |


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**CLINICAL INVESTIGATION**

# FIFTEEN-YEAR RADIOTHERAPY OUTCOMES OF THE RANDOMIZED PORTEC-1 TRIAL FOR ENDOMETRIAL CARCINOMA

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FOR THE PORTEC STUDY GROUP

# STUDY DESIGN

- Multicenter RCT involving19 institutions of Netherlands
- 715 patients of FIGO stage I EC recruited from 1990 to 1997
- 354 patients were randomly assigned to EBRT & 361 to NAT
- 5 yr and 10 yr results published in 2000(Lancet) and 2005(IJROBP)
- Median FU= 13.3 years
- EBRT-46Gy/23#/4.5 weeks delivered by AP-PA parallel opposed fields (30%), 3-field (18%) or 4-field techniques (52%)

# LOCOREGIONAL RELAPSE

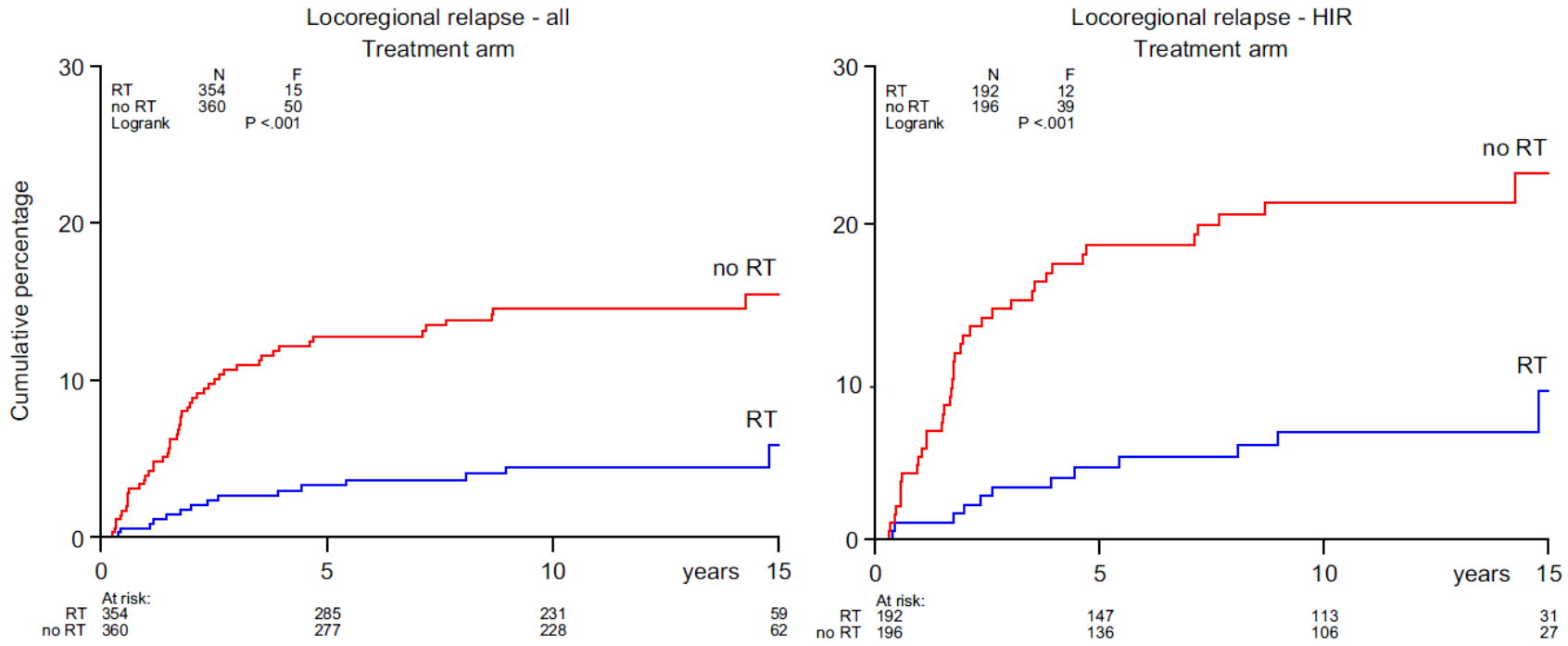



Fig. 1. Probability of locoregional (vaginal and/or pelvic) relapse for patients assigned to postoperative radiotherapy (RT) or no additional treatment (NAT) for the total group (left) and for patients with high-intermediate-risk (HIR) features (right).

# FAILURE FREE SURVIVAL

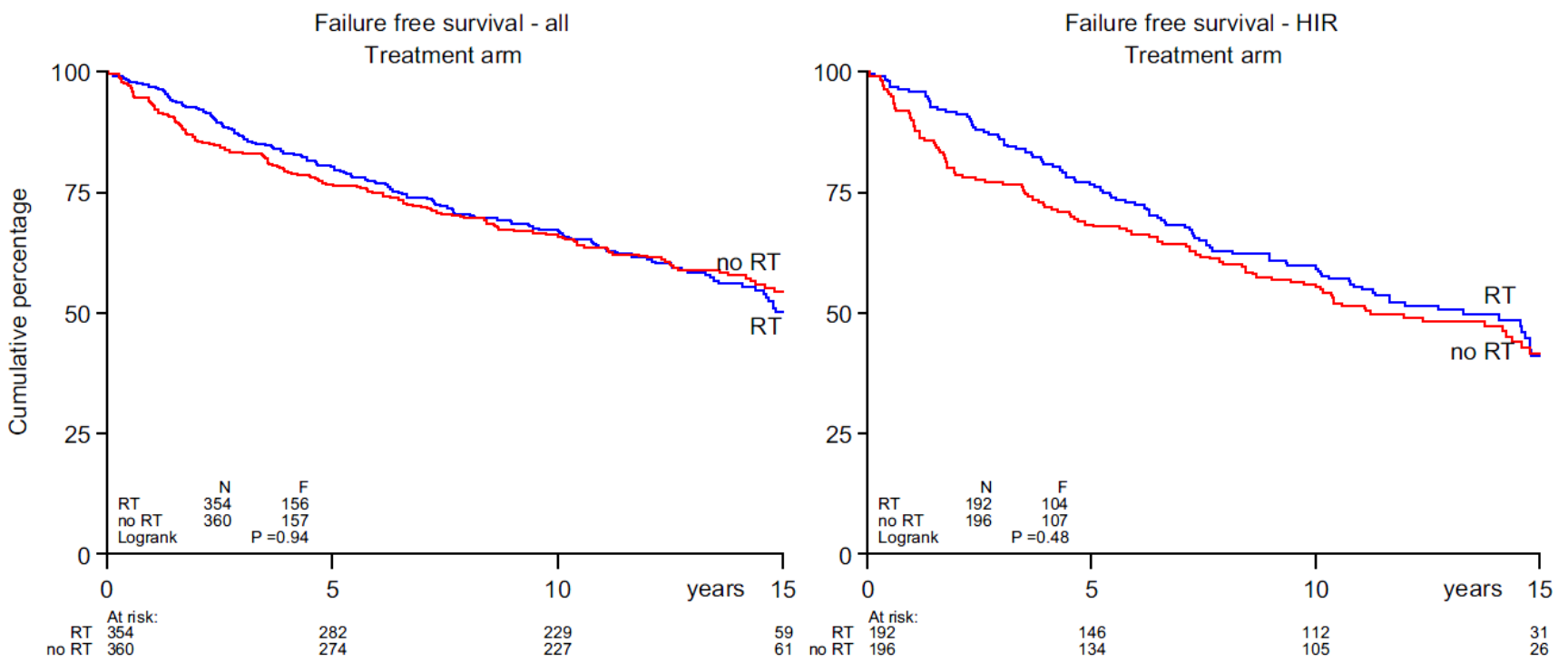



Fig. 2. Probability of failure-free survival for patients assigned to postoperative radiotherapy (RT) or no additional treatment (NAT) for the total group (left) and for patients with high-intermediate-risk (HIR) features (right).

# STUDY FINDINGS

- No difference in overall survival with EBRT
- Reduction in locoregional recurrence in HIR group receiving EBRT
- No significant difference in LRR in LIR group receiving adjuvant radiation


# GOG 99 TRIAL

- 392 patients with stage IB, IC, or IIA, all grades (surgical LN-ve)
- TAH+BSO and selective lymph node dissection
- Adjuvant EBRT vs observation
- 2yr recurrence → 3% vs 12% in favour of EBRT ($p < 0.01$)

| Outcome | EBRT (%) | Observation (%) |
|---|---|---|
| Vag recurrence | 1 | 6.4 |
| Distant failure | 5.3 | 6.4 |
| 4yr OS | 92 | 86 |
| 2yr recurrence (HIR) | 6 | 26 |

*Key et al. Gynecol Oncol 2004; 92: 744-751.*


# PORTEC-II TRIAL

- 427 patients of EC (age>60yrs, IBG3/ IC G1-2)
- After TAH+BSO pts randomized to VBT vs. pelvic EBRT
- Median FU→ 3.75 years

| Outcome | VBT | EBRT | P value |
|---|---|---|---|
| 5yr vaginal recurrence | 1.8% | 1.6% | 0.74 |
| 5yr LRR | 5.1% | 2.1% | 0.17 |
| Isolated pelvic recurrence | 1.5% | 0.5% | 0.3 |
| Distant metastasis | 8.3% | 5.7% | 0.46 |
| 5yr overall survival | 85% | 80% | 0.57 |

*Nout RA et al. Lancet 2010 ;375:816-23.*

**Table 1.** Summary of classic landmark trials on adjuvant treatment of stage I and II endometrial cancer

| | Histology | Risk groups | Lymph node dissection | Study arms | Locoregional recurrence | Survival |
|---|---|---|---|---|---|---|
| PORTEC-1 | Endometrioid<br>Clear cell<br>Papillary-serous | Intermediate risk:<br>Grade 1, >50% myometrial invasion<br>Grade 2, any myometrial invasion<br>Grade 3, <50% myometrial invasion<br>High-intermediate risk:<br>Age >60 years, grade 1 or 2, >50% myometrial invasion<br>Age >60 years, grade 3, <50% myometrial invasion | Not required | EBRT vs. observation | EBRT improved over observation at 5 years (intermediate risk – 4 vs. 14%, $P<0.001$) (HIR – 5 vs. 18%, $P<0.001$) | EBRT equivalent to observation at 5 years for overall survival (81 vs. 85%, $P=0.31$) |
| GOG-99 | Endometrioid | Intermediate risk: any grade, stage IB, IC, or occult IIA or IIB[a]<br>High-intermediate risk:<br>Age <50 years with three risk factors<br>Age 50–69 years with two risk factors<br>Age ≥70 with one risk factor<br>Risk factors: grade 2 or 3, +LVSI, outer 1/3 myometrial invasion (stage IC[a]) | Comprehensive | EBRT vs. observation | EBRT improved over observation at 2 years (all – 3 vs. 12%, $P$ 0.007) (HIR – 6 vs. 26%, $P<0.001$) | EBRT equivalent to observation at 4 years for overall survival (92 vs. 86%, $P=0.55$) |
| ASTEC/EN.5 | Endometrioid<br>Clear cell<br>Papillary-serous | Intermediate risk:<br>Endometrioid, stage IA or IB[a], grade 3<br>Endometrioid, stage IC or IIA[a], grade 1 or 2<br>High risk:<br>Endometrioid, stage IC and IIA[a], grade 3<br>Endometrioid, stage IIB[a]<br>Clear cell or papillary-serous histology | Not required | EBRT vs. observation<br>VBT allowed for both arms | EBRT improved over observation at 5 years for isolated vaginal recurrence (3.2 vs. 6.1%, $P=0.02$) | EBRT equivalent to observation at 5 years for overall survival (84 vs. 84%, $P=$NS) |
| PORTEC-2 | Endometrioid | Intermediate risk:<br>Endometrioid, stage IA or IB[a], grade 3<br>Endometrioid, stage IC or IIA[a], grade 1 or 2 | Not required | EBRT vs. VBT | EBRT equivalent to VBT at 5 years for isolated vaginal recurrence (1.6 vs. 1.8%, $P=0.74$) and all locoregional recurrences (2.1 vs. 5.1%, $P=0.17$) | EBRT equivalent to VBT at 5 years for overall survival (79.6 vs. 84.8%, $P=0.57$) |

# Current Protocol

| | G I | G II | G III |
|---|---|---|---|
| IA | Observation | Observation | Observation or IVBT* |
| IB | IVBT | EBRT+ IVBT | EBRT+ IVBT |

# Radiotherapy options

- Intra-vaginal Brachytherapy : IVBT alone
- Pelvic EBRT +/- IVBT
- Extended field RT : Pelvis + PA nodes
- Whole abdominal RT : WART
- Interstitial Brachytherapy
- IMRT, IGRT

# Dose Practices

**Brachytherapy alone**

- **HDR**

  **7 Gy ( at 0.5 cm from surface of applicator ) X 3 sessions, each 1 week apart.**

**Brachytherapy in Combination with EBRT**

- **HDR**

  **6 Gy ( at 0.5 cm from surface of applicator ) X 2 sessions 1 week apart**

**EBRT doses**

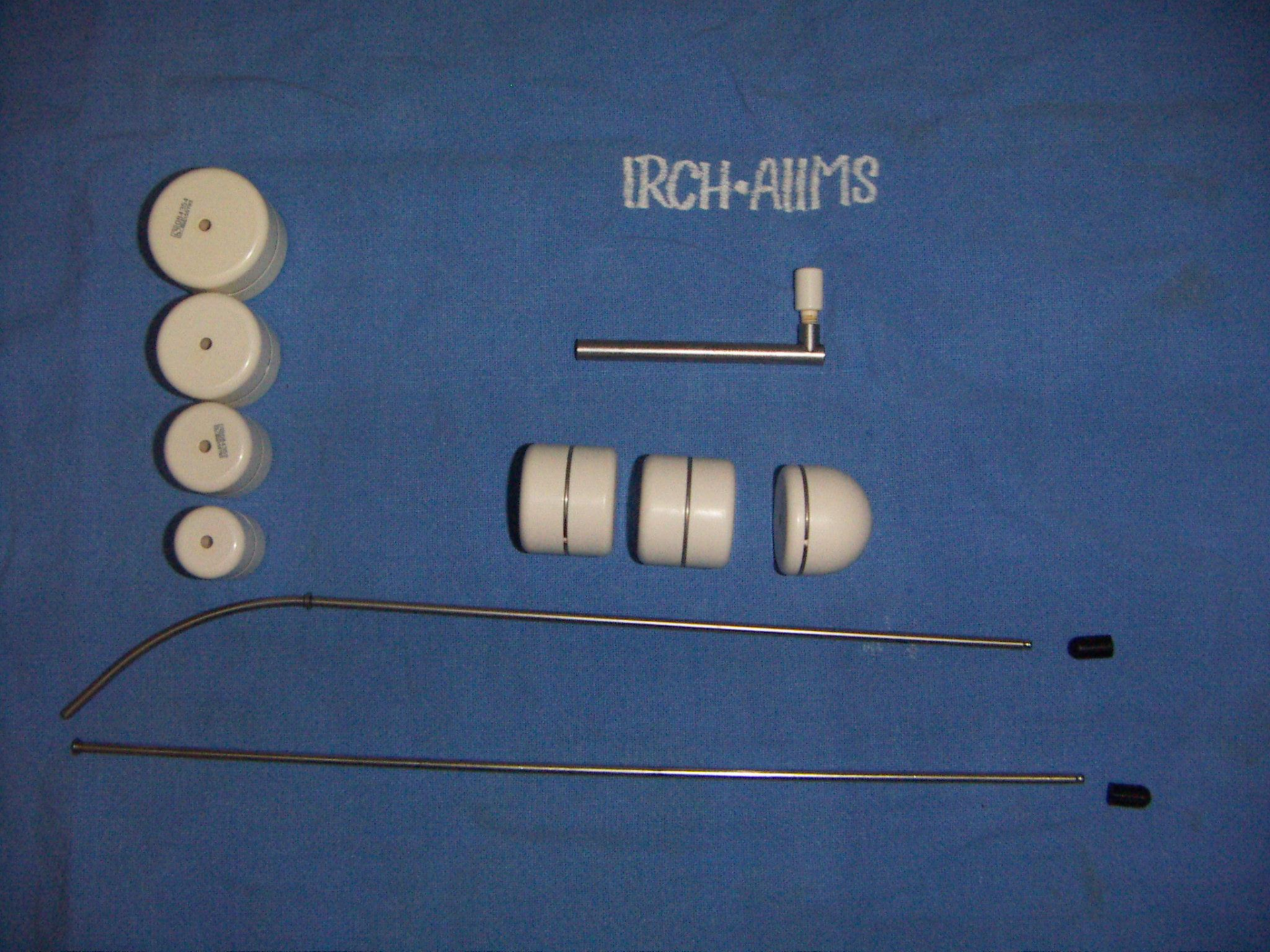
- **45 Gray in 25# over 5 weeks (stage I)**
- **50.4 Gray in 28# over 5.5 weeks (stage II-III)**

**Chemotherapy (Stage III)**

- **Sandwich/Sequential 6 cycles of chemotherapy (Paclitaxel/Carboplatin)**

# IVBT alone

- Vagina is a potential site of recurrence
- Pelvic node rec. is negligible
- About 10-15% risk (Intermediate risk group)
- Common site of recurrence in both trials
- Pelvic RT may be effective but sign. toxicity
- Vaginal RT alone may be of same efficacy, more convenient, less toxic
- Various trials have shown the risk reduction from 12-15% to <5%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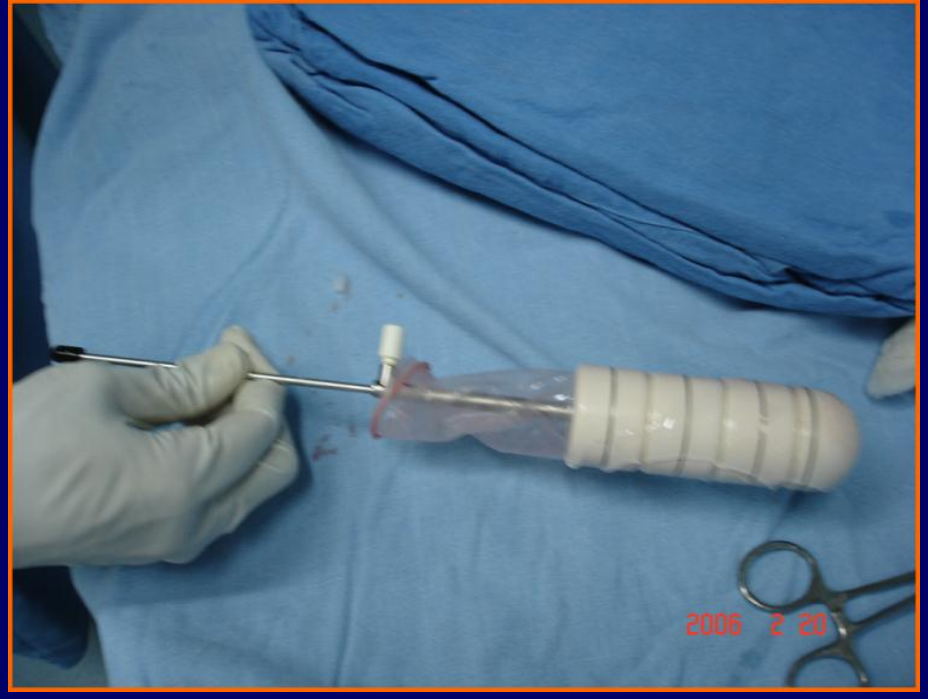
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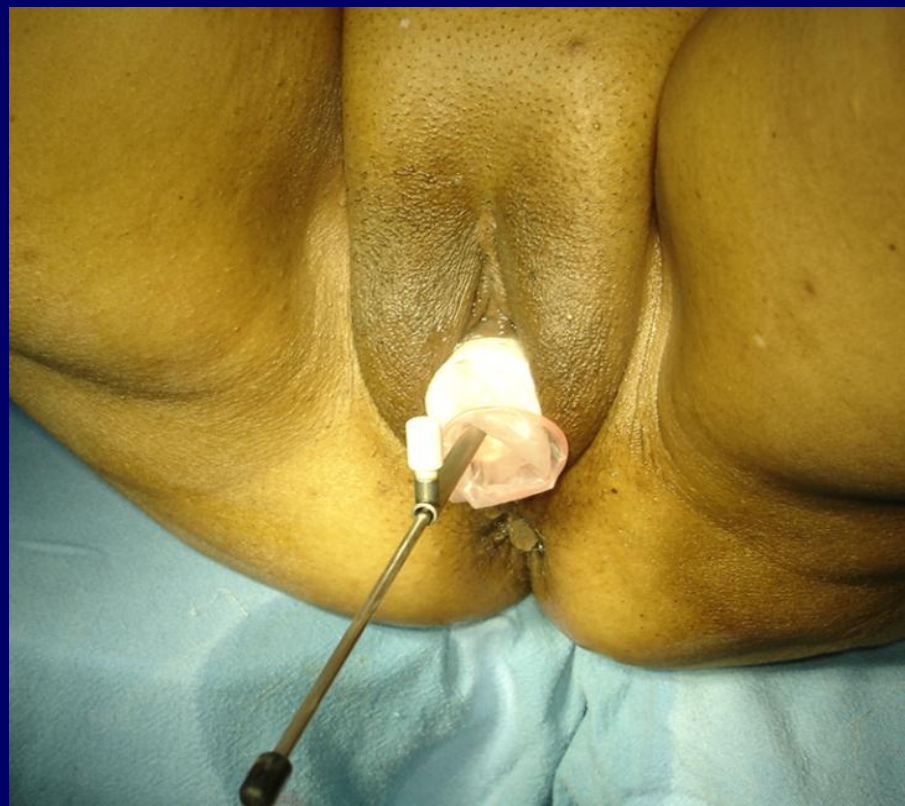

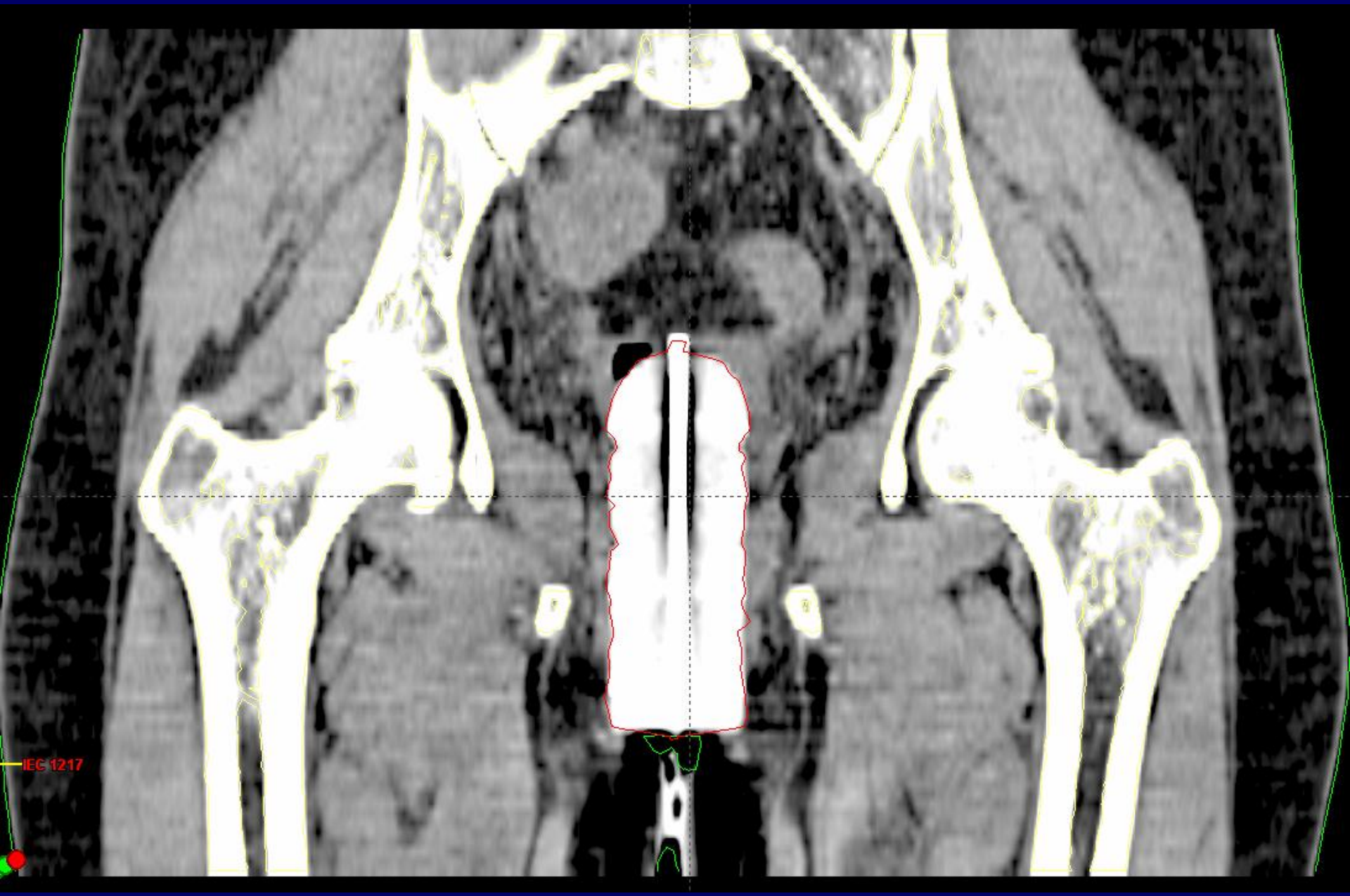
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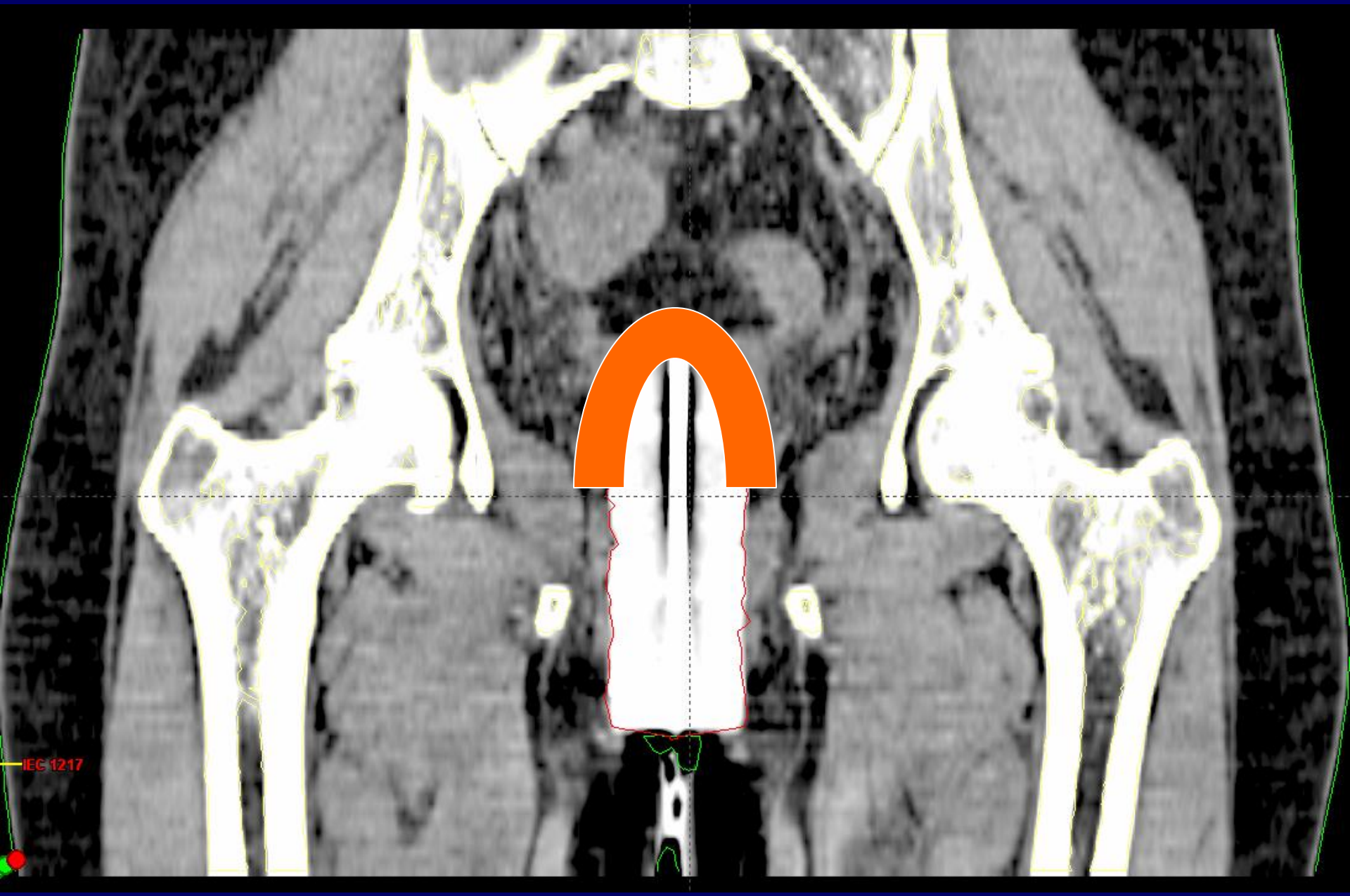
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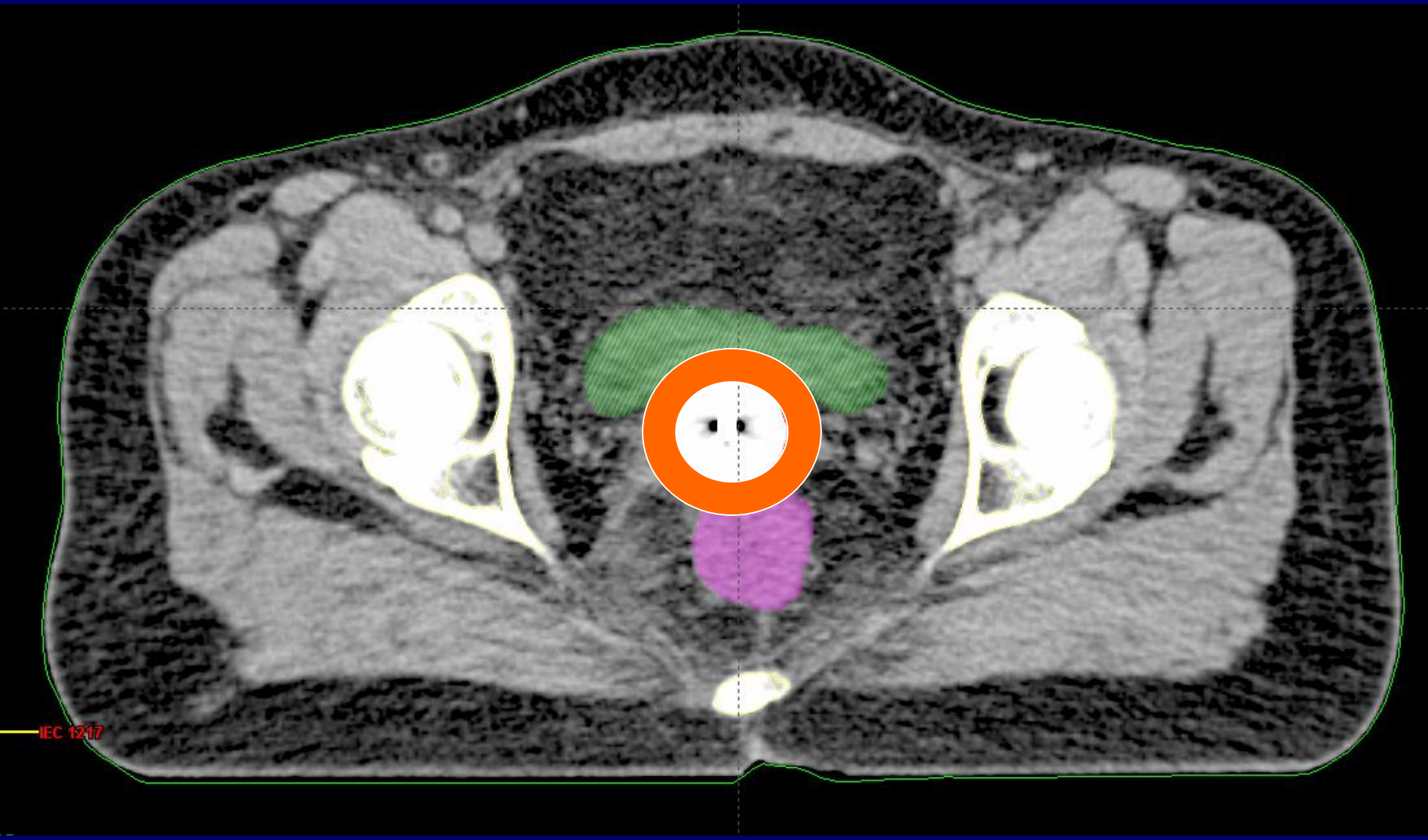
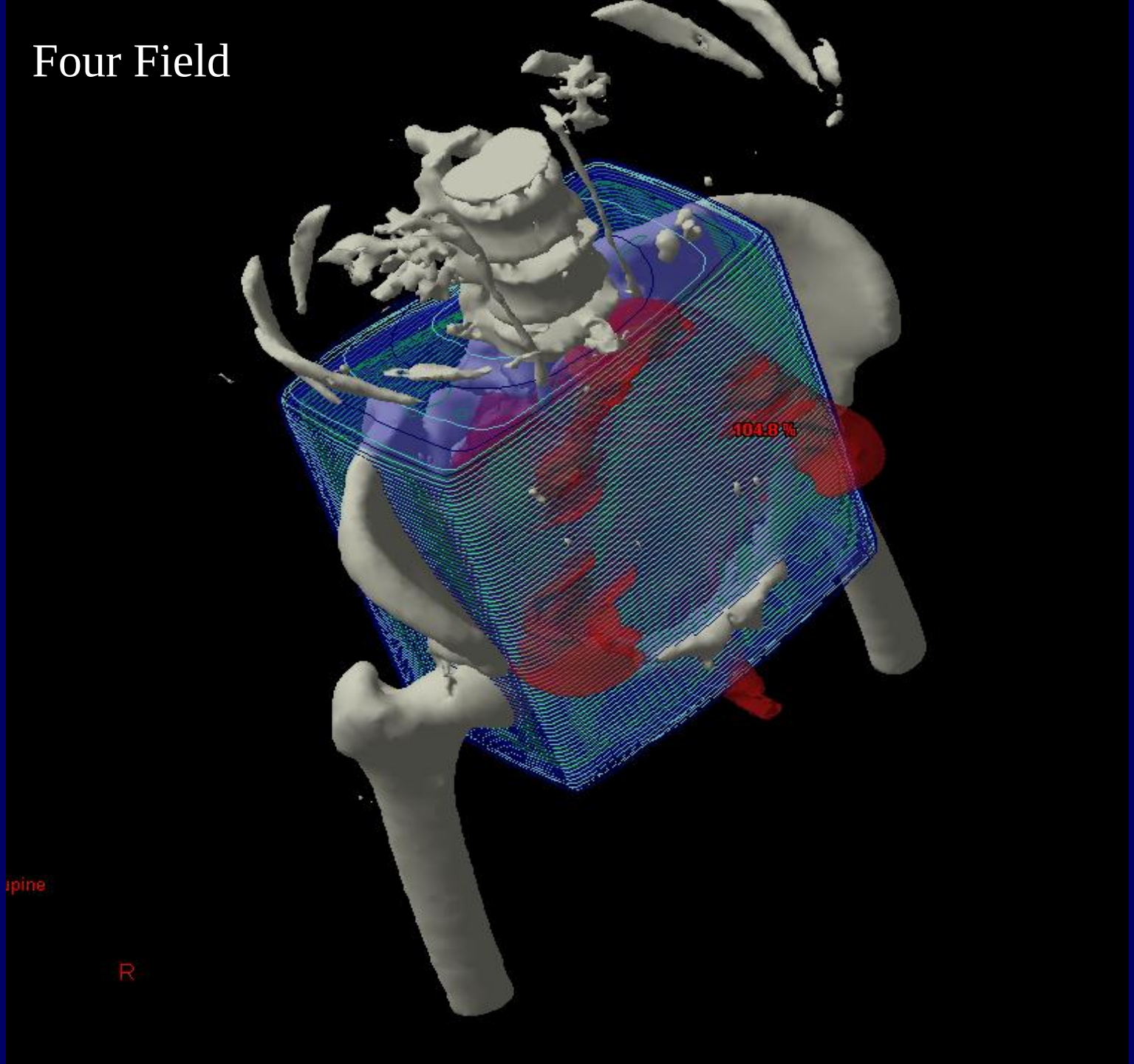
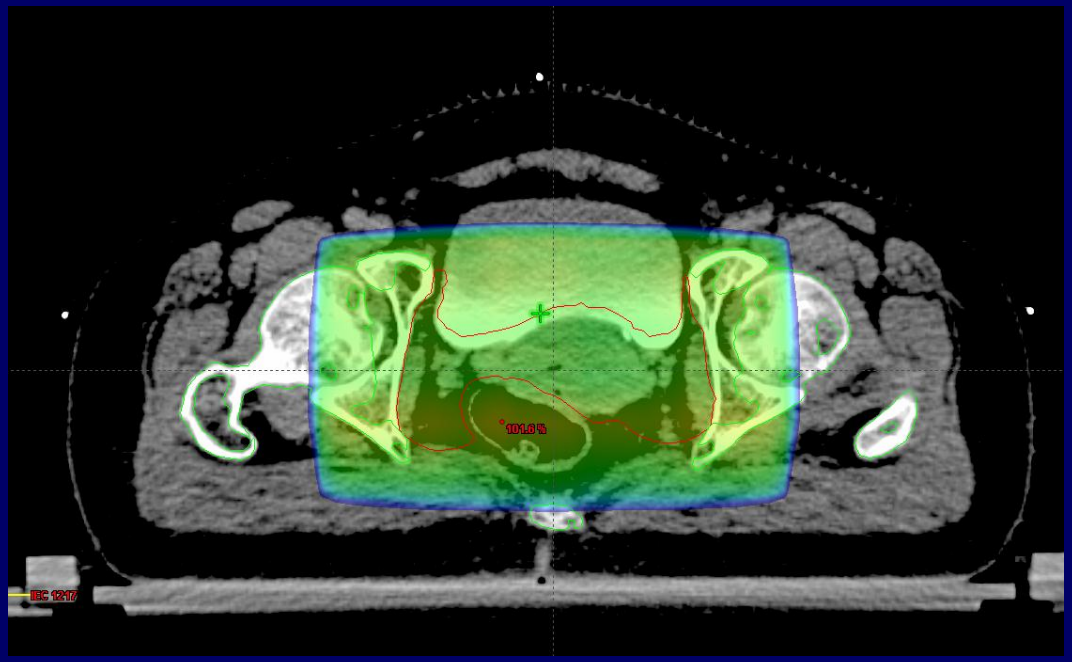

IEC 1217

# Four Field

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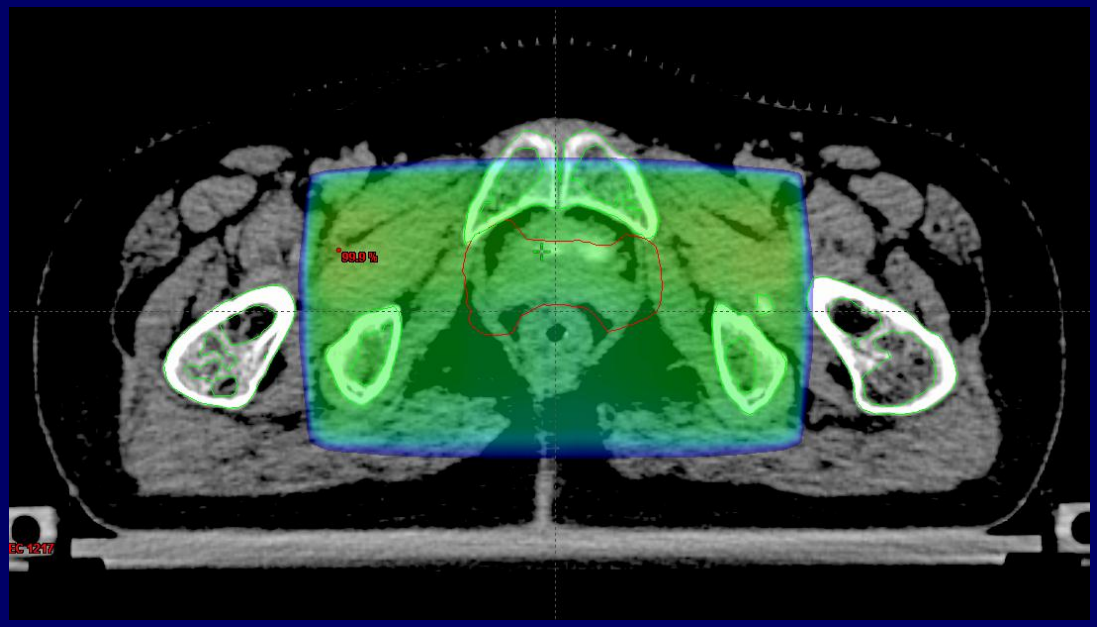
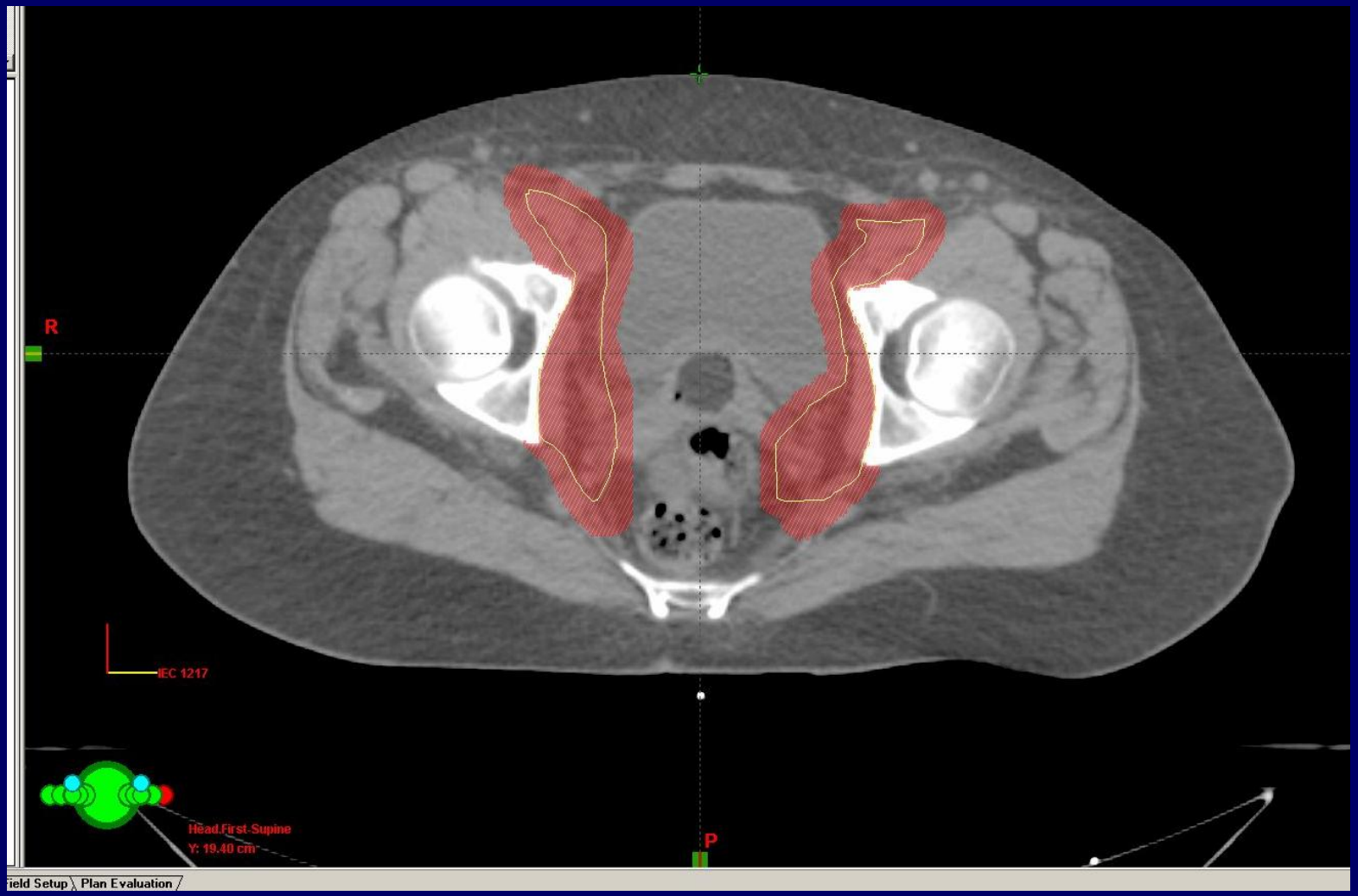
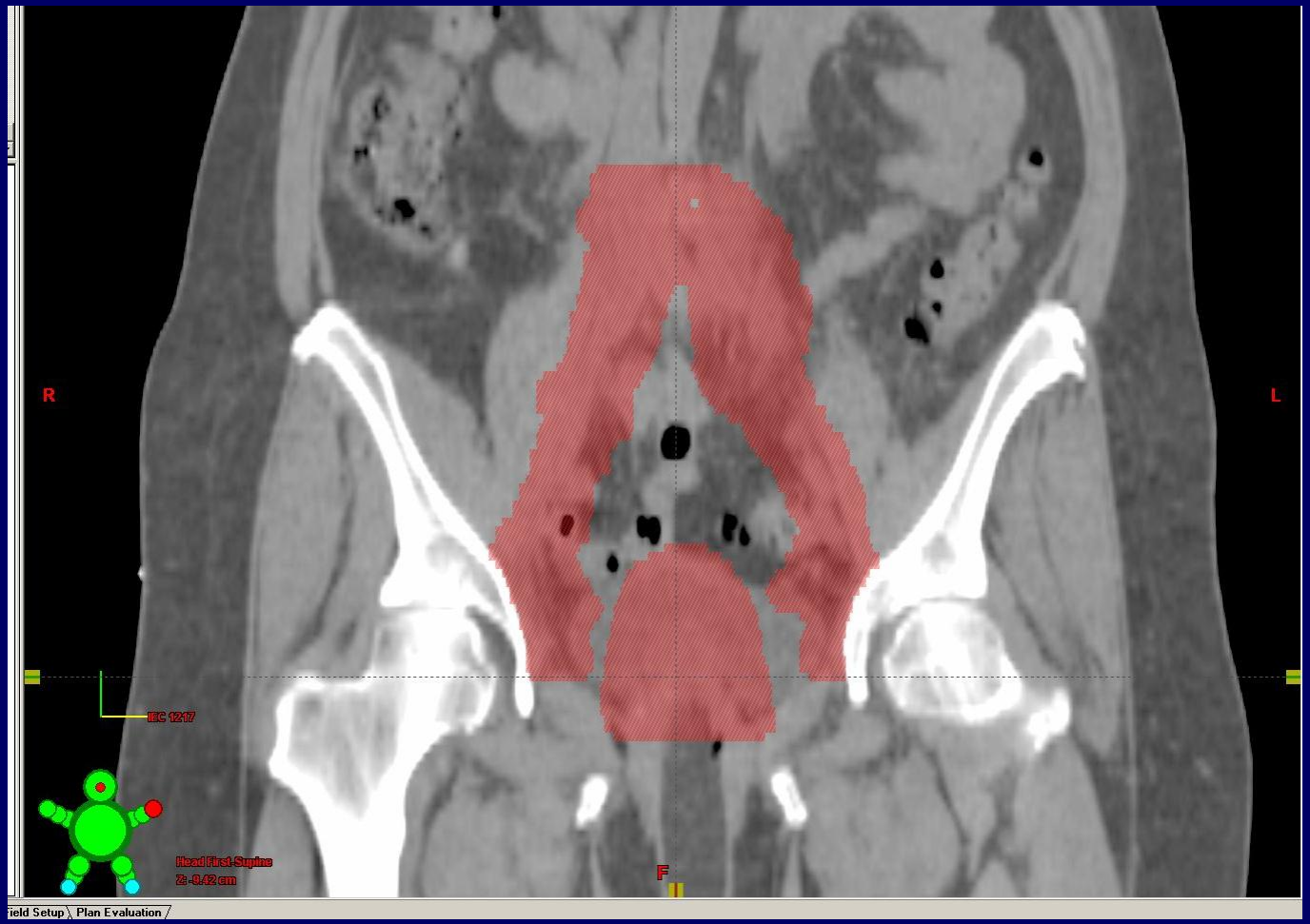
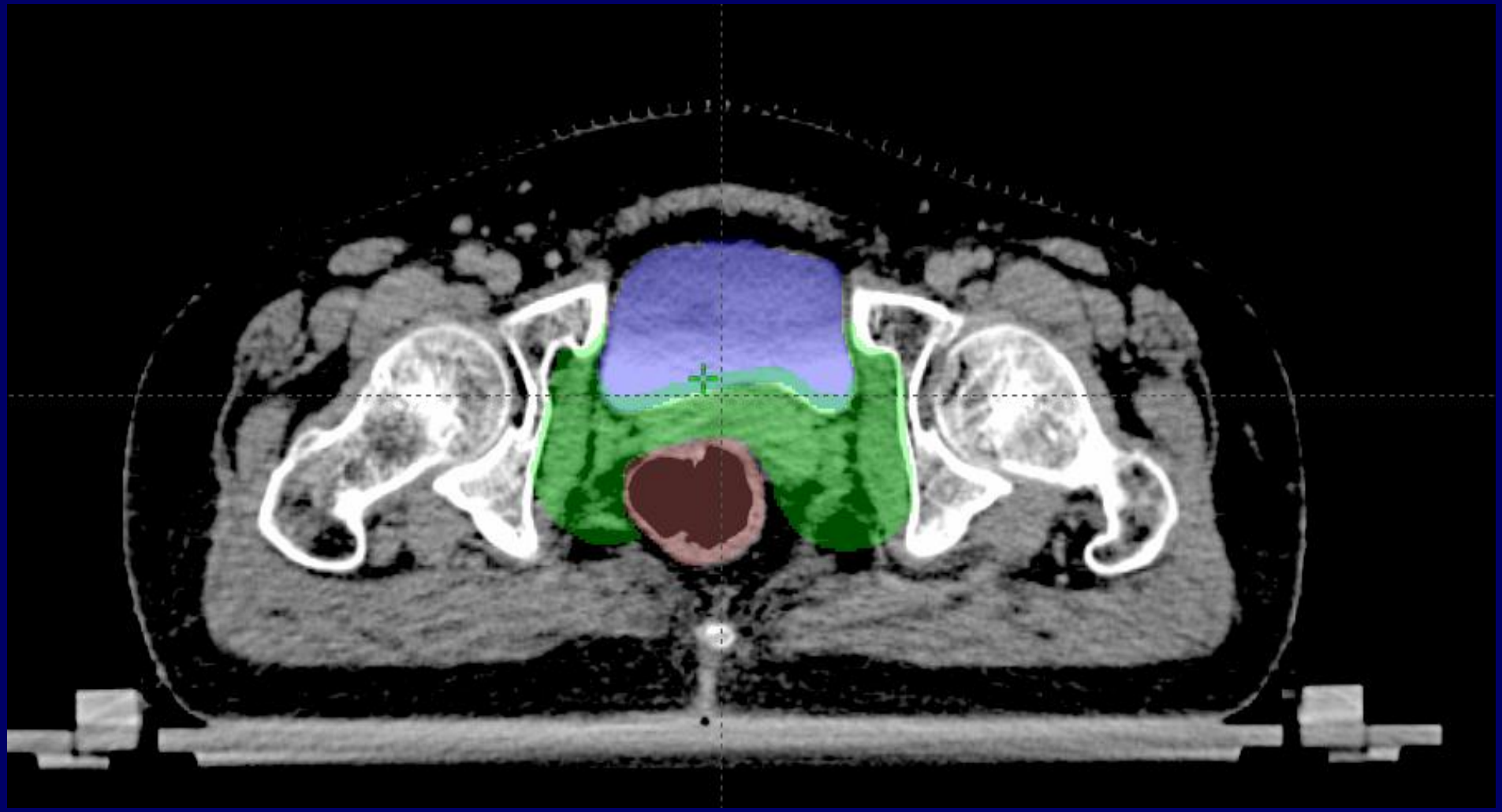
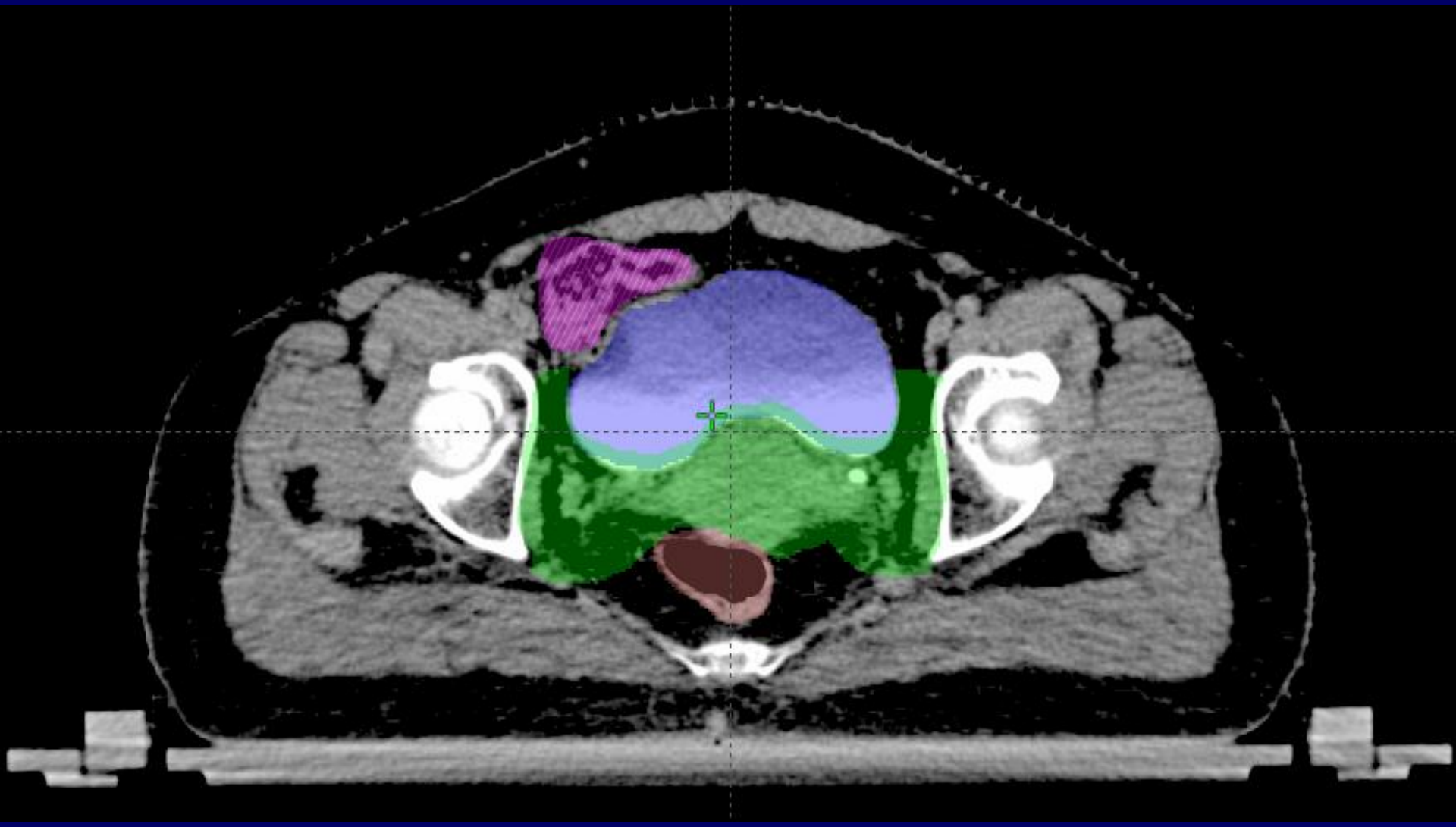

99.0 %
IEC 1217


R
IEC 1217
Head First-Supine
Y: 19.40 cm
P
ield Setup
Plan Evaluation


R
L
IEC 1217
Head First-Supine
Z: -8.42 cm
F
Field Setup \ Plan Evaluation





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** Stage IV: Palliative RT/ Chemotherapy

# THANK YOU