Radiation Therapy in the Management of Cervical Carcinoma

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Priorities

- Prevention, prevention, prevention
  - Life style changes
  - Vaccinations for HPV
- Effective screening
  - Pap smears
  - Pelvic examinations
  - Teaching the early signs

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FIGO Stage IA

- **IA - detected on microscopy only**

IA1 **≤ 3 mm deep**
≤ 7 mm wide

IA2 **3-5 mm deep**
< 7 mm wide

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Cure rates with surgery

- IA1 simple hyst 98-100%
- IA2 rad hyst 95-100%
- IB1-IIA rad hyst 79-92%

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Cure rates with radiation

▪ IA1	brachy alone	98-100%
▪ IA2	EBRT + brachy	95%
▪ IB1-IIA	EBRT + brachy	80-90%
▪ IB2	EBRT + brachy + C	75-85%

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Definitive Radiotherapy for Stage IB1

- Nodes negative on CT or MRI
  - Pelvic RT to 45 Gy
  - Brachytherapy doses 80-85 Gy to Pt. A
  - No chemo
- Nodes positive on CT or MRI
  - Same, plus platinum-containing regimen
  - Extended field RT if PA nodes positive

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Definitive Radiotherapy for Stage IB2

- Nodes negative
  - Pelvic RT to 45 Gy
  - Brachytherapy doses 80-85 Gy to Pt. A
  - Platinum containing regimen
- Nodes positive
  - Extended field RT if PA nodes positive

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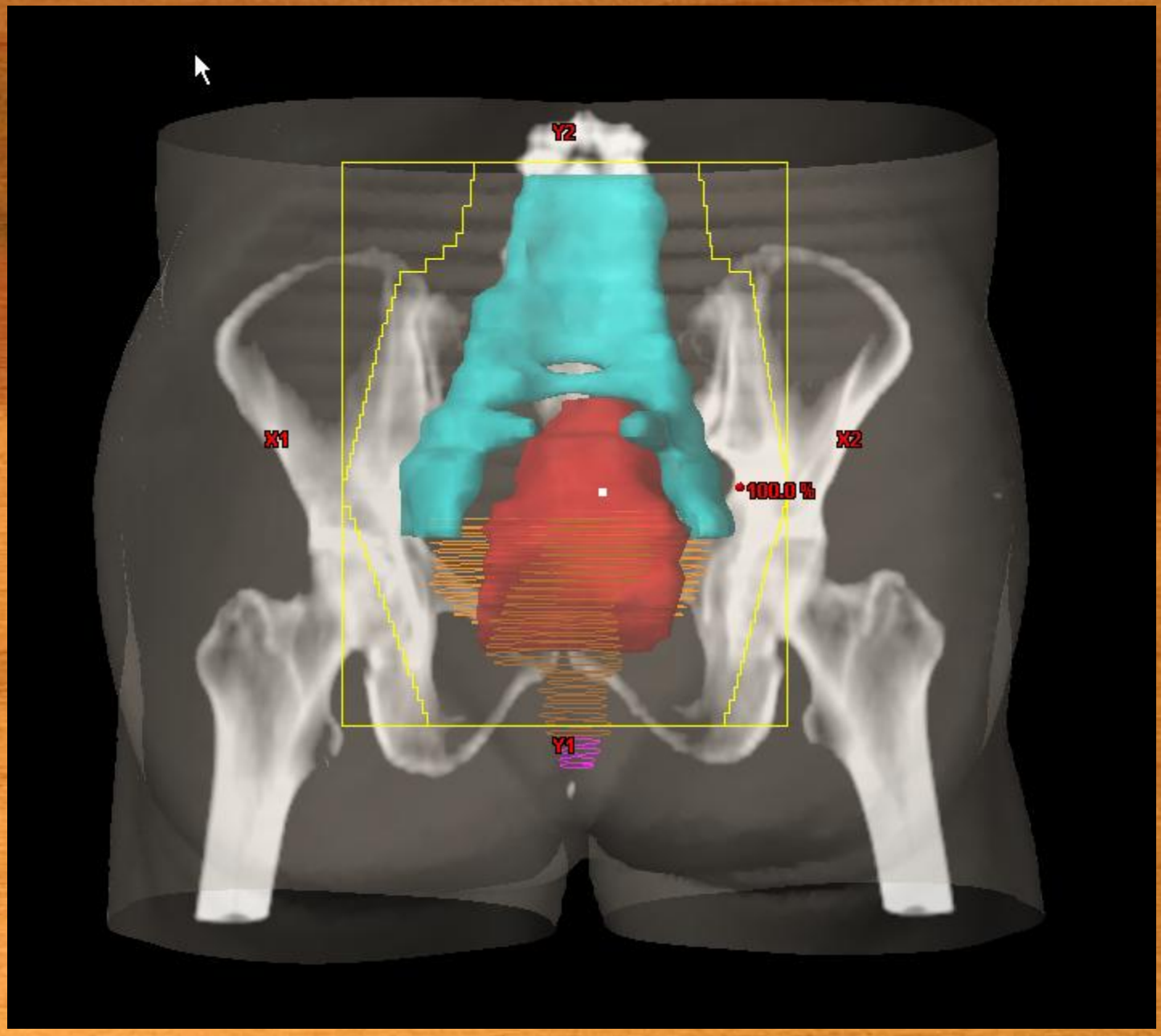

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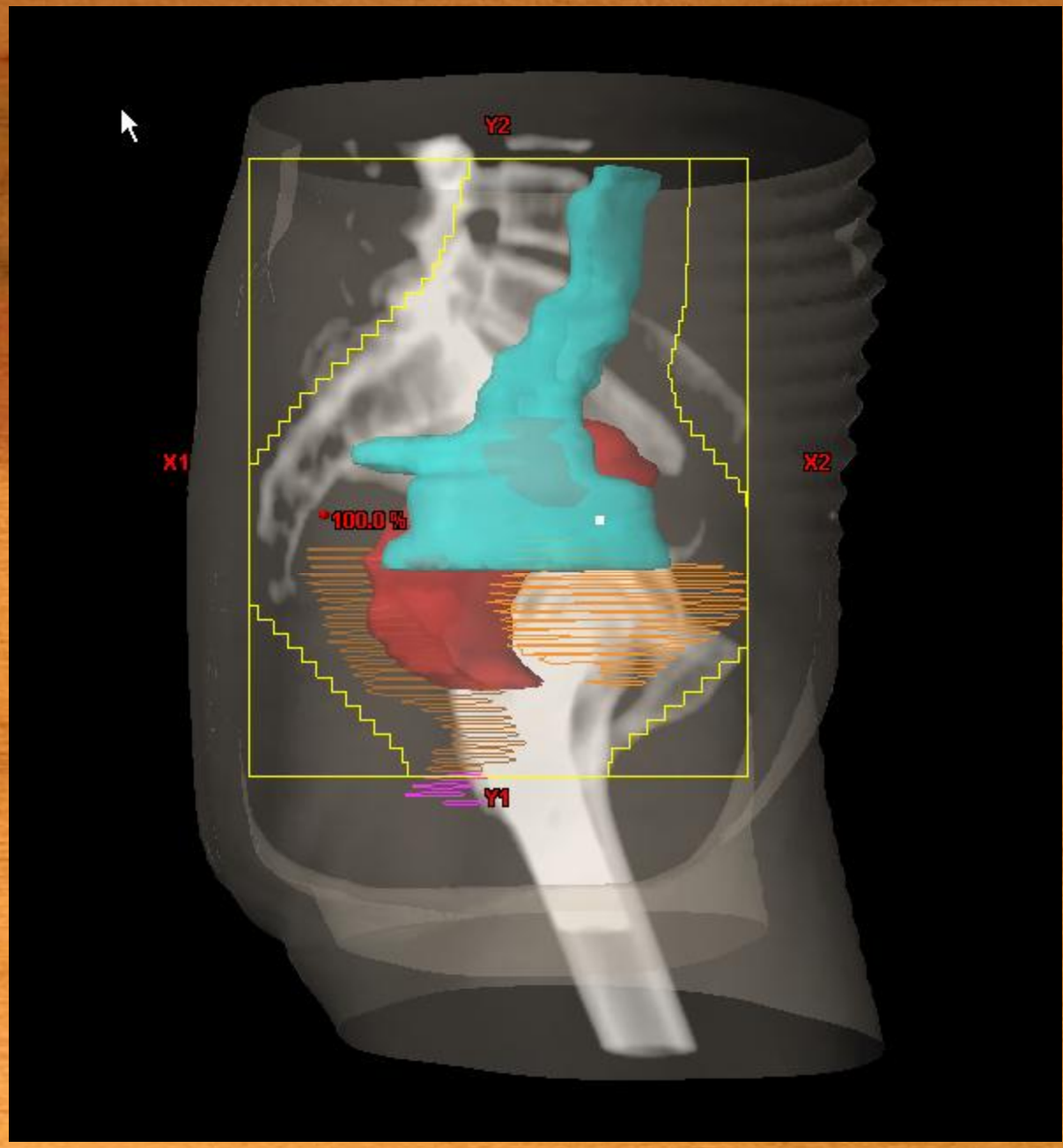

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FIGO Stage IB

- Clinically visible or microscopic > 5 mm
  - IB1 - ≤ 4.0 cm
  - IB2 - > 4.0 cm

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FIGO Stage II

- Tumor invades beyond the uterus but not to the pelvic wall or lower 1/3rd of vagina
- IIA - no parametrial invasion
- IIB - with parametrial invasion

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FIGO Stage III

- Tumor extends to pelvic sidewall, or lower 1/3rd of vagina, or hydronephrosis
- IIIA - lower third of vagina
- IIIB - pelvic wall or hydronephrosis

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FIGO Stage IV

- IVA - invades mucosa of bladder or rectum
- IVB - distant metastases

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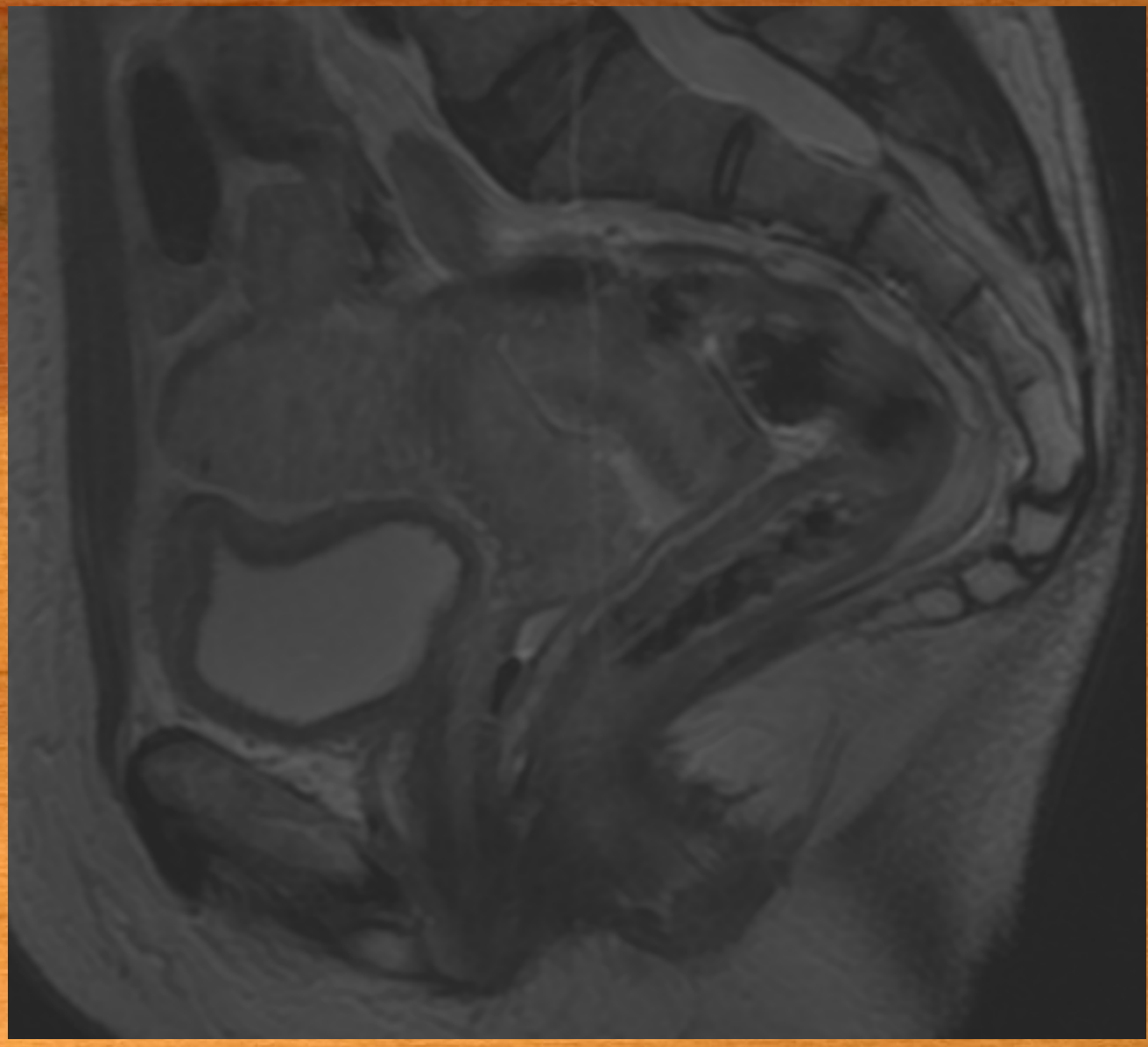

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Table 2:
Estimates of the Relative Risk of Death in Five Clinical Trials of Concurrent Chemotherapy and Radiotherapy.

Study	FIGO Stage	Control Group	Comparison Group	Relative Risk of Death in Comparison Group
Keys et al.	IB2	Radiotherapy	Radiotherapy plus weekly cisplatin	0.54
Rose, Bundy, Watkins et al.	IIB-IVA	Radiotherapy plus hydroxyurea	Radiotherapy plus weekly cisplatin	0.61
			Radiotherapy plus cisplatin, fluorouracil, and hydroxyurea	0.58
Morris et al.	IB2-IVA	Extended-field radiotherapy	Radiotherapy plus cisplatin and fluorouracil	0.52
Whitney et al.	IIB-IVA	Radiotherapy plus hydroxyurea	Radiotherapy plus cisplatin and fluorouracil	0.72
Peters et al.	IB or IIA (selected postoperatively)	Radiotherapy	Radiotherapy plus cisplatin and fluorouracil	0.50

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

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Chemoradiotherapy

- These 5 trials showed a 30-50% reduction in mortality for patients with stage IB2-IVA treated with radiation plus chemotherapy versus radiation alone
- The accepted regimens:
  - Weekly cis-platin (40 mg/m^2/4h)
  - Cis-platin (75 mg/m^2/4h)
  - plus 5FU (4 g/m^2/96 hr) on weeks 1 and 4 and 7

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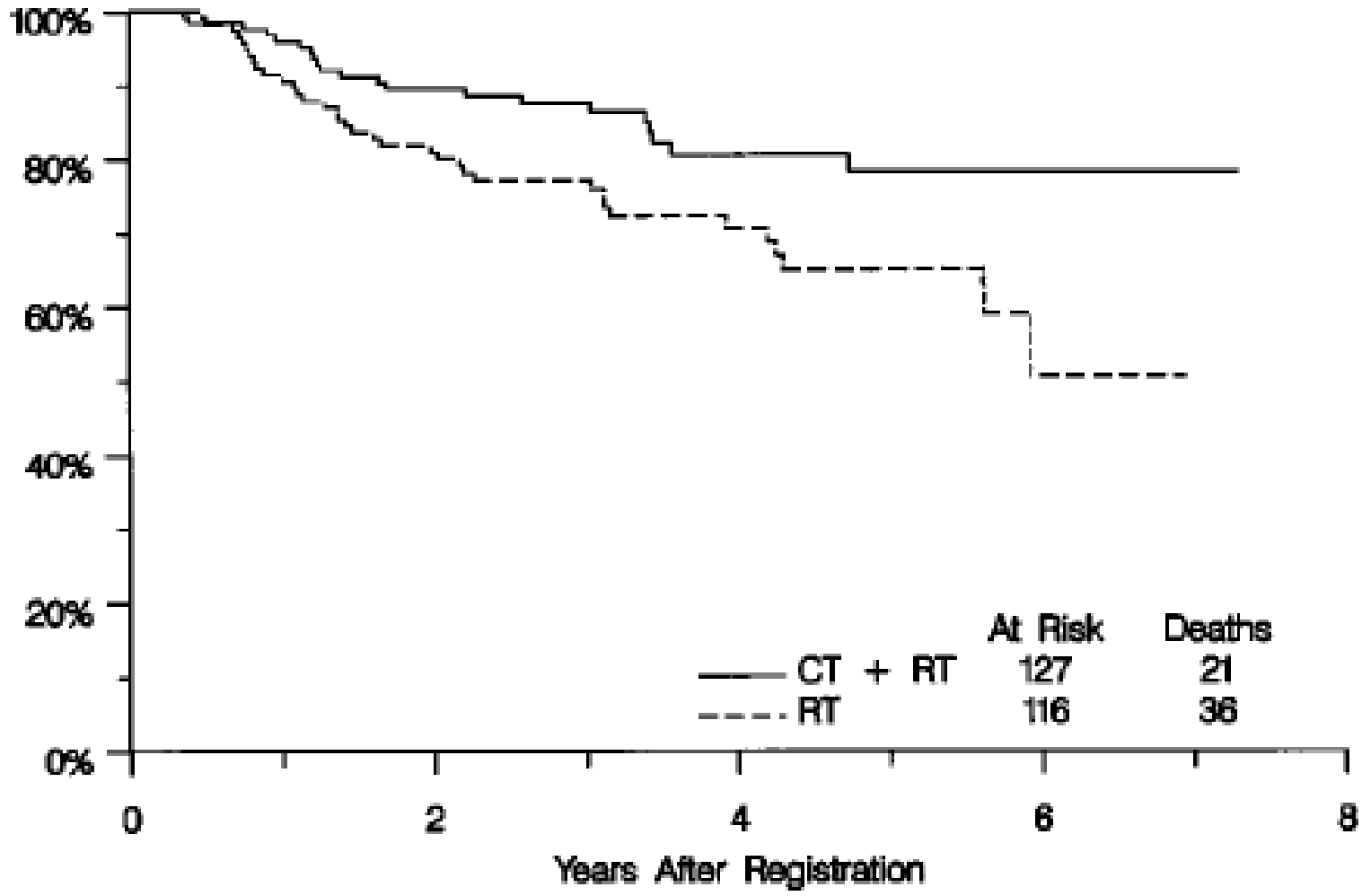

Fig 2. Overall survival for 127 patients randomized to receive CT + RT and for 116 patients randomized to receive RT alone.

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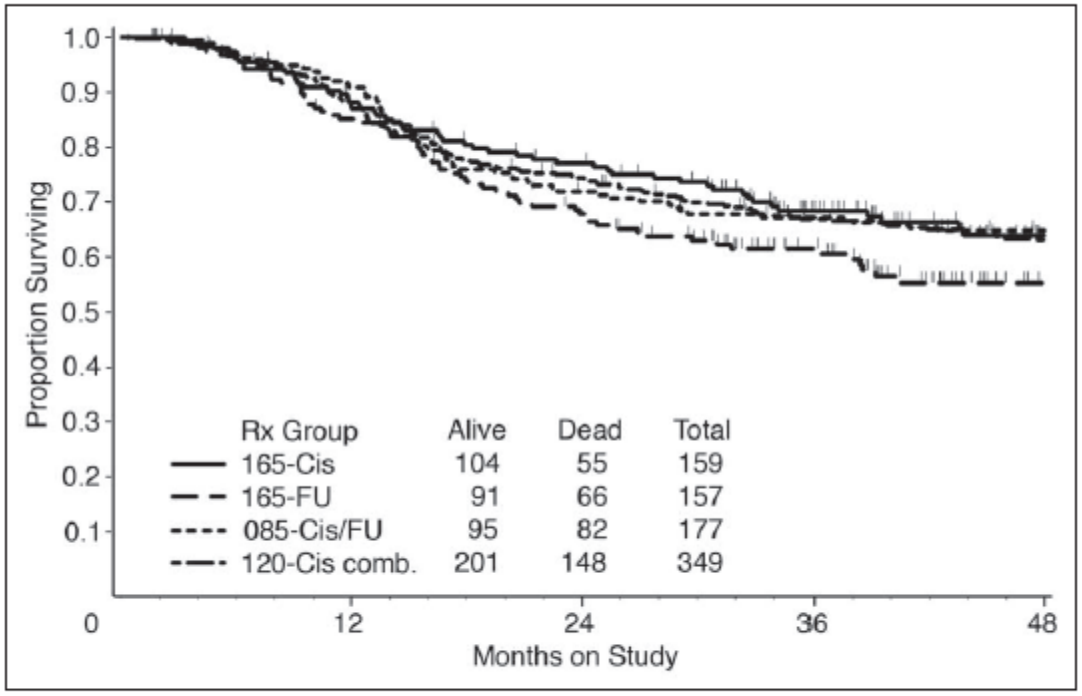

Fig 3. Comparison of Whitney,[1] Rose,[2] and present study. Rx, drug regimen; FU, fluorouracil; cis, cisplatin; comb, combination.

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Post-operative radiation alone

- High risk factors
  - Large primary tumor (> 4 cm)
  - Deep (> 1/3rd) stromal invasion
  - Lymphovascular space invasion

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GOG Phase III Trial

- Stage IB patients with no nodes
  - 2 or more high risk features
  - N=277 patients (137 RT, 140 no RT)
  - 46 - 50.4 Gy, no brachy

  - Rotman MZ, Sedlis A, Piedmonte MR et al, IJROBP, vol 65(1), pp169-176, 2006.

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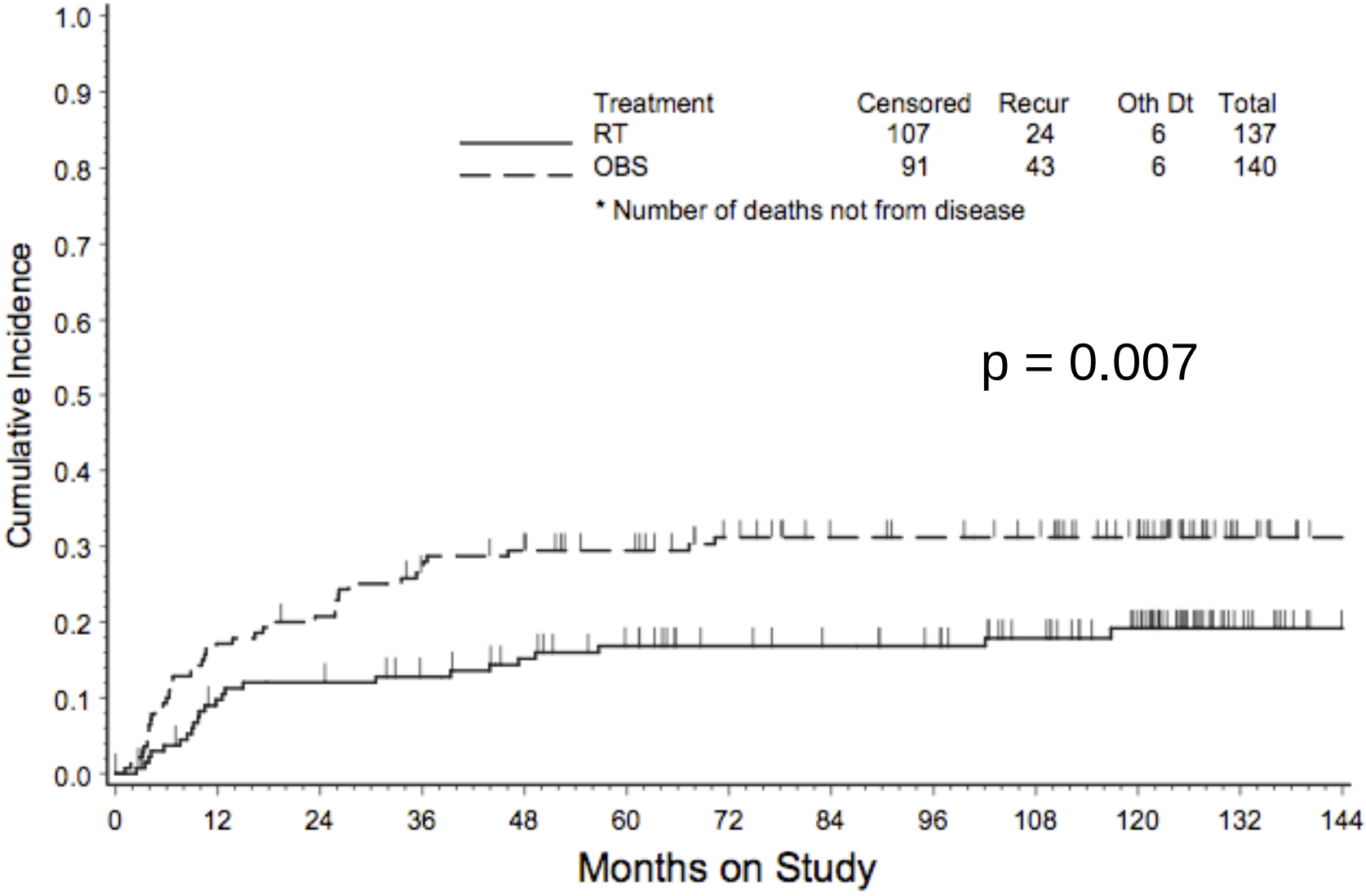
Cumulative Incidence of Recurrences
By Treatment Group



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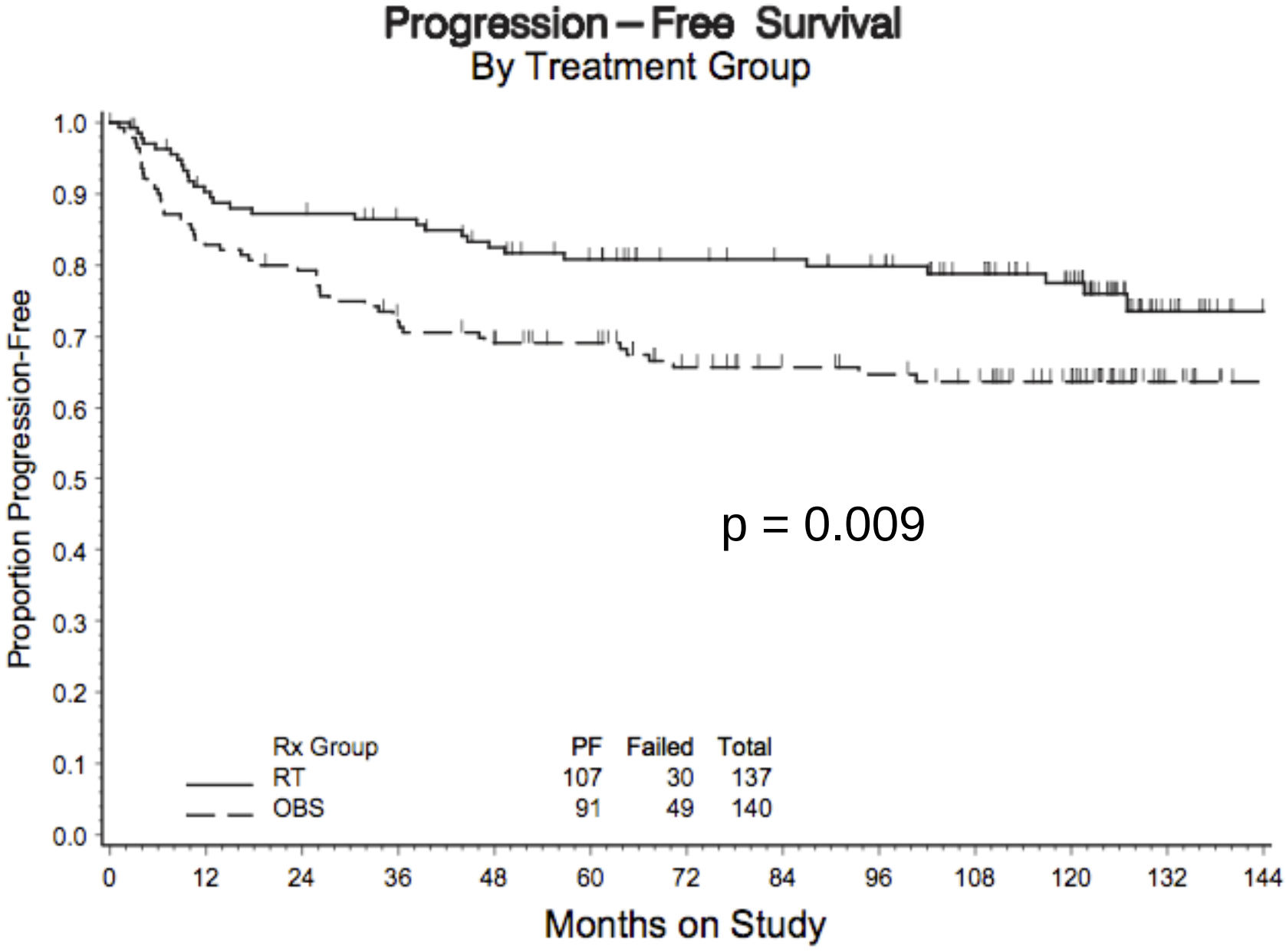

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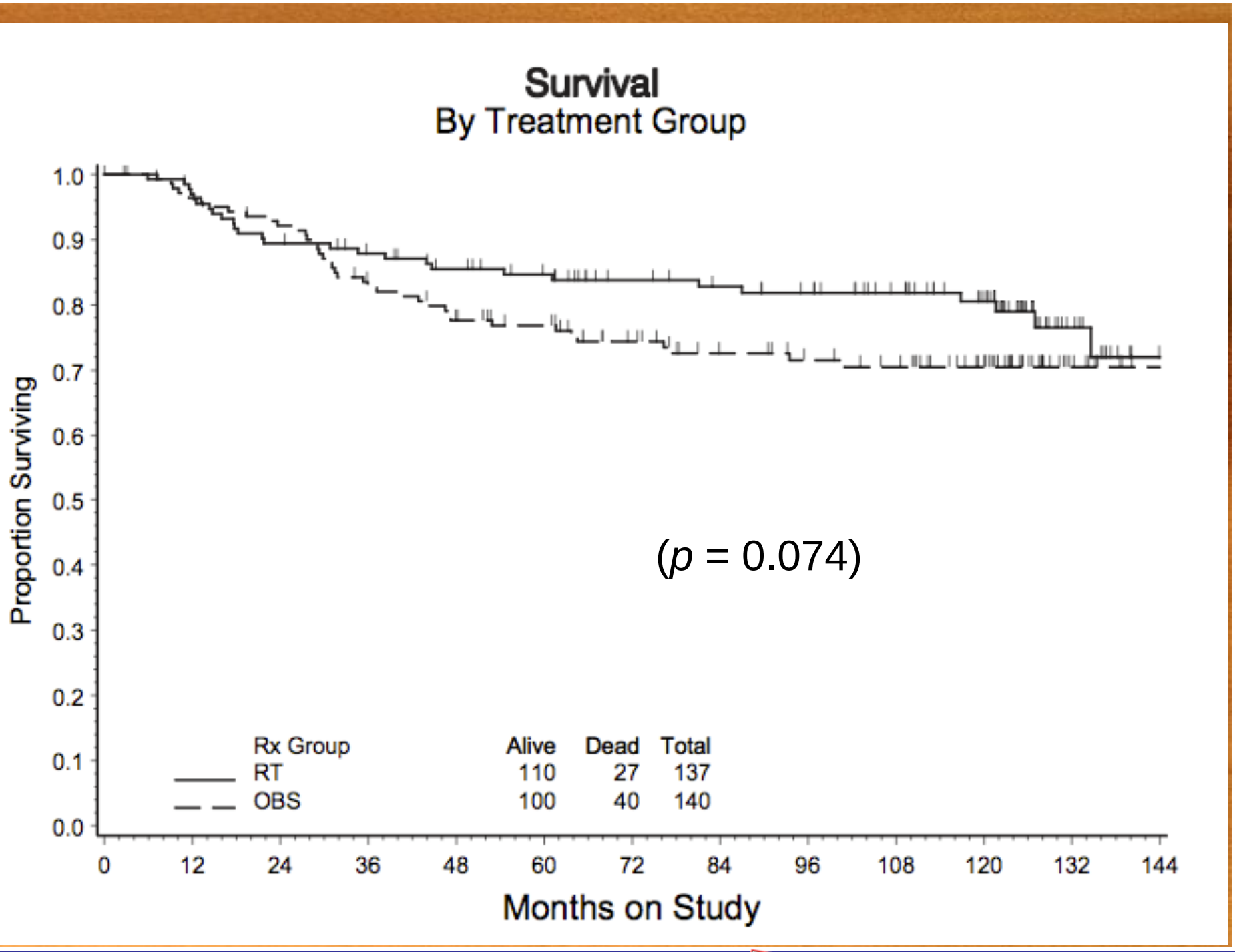

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Post-operative radiation plus chemotherapy

- Positive pelvic nodes (if > 1 node)
- Positive surgical margin
- Positive parametrial invasion

- Pelvic +/- PA nodal irradiation 45-50 Gy
- +/- vaginal brachytherapy
- Platinum-containing regimen

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Definitive Radiation for Stage IIB - IVA

- 45-50 Gy pelvis
- Brachytherapy 80-85 Gy to pt. A
- Concurrent chemotherapy
- Extended field radiation if pos. PA nodes
- Consider boosting positive nodes to 60 Gy

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Radiation Technique

- Multiple fields with conedowns
  - Shield small bowel in node pos disease
  - Shield rectum and bladder if using brachy
- Prone position
- IMRT - investigational uses

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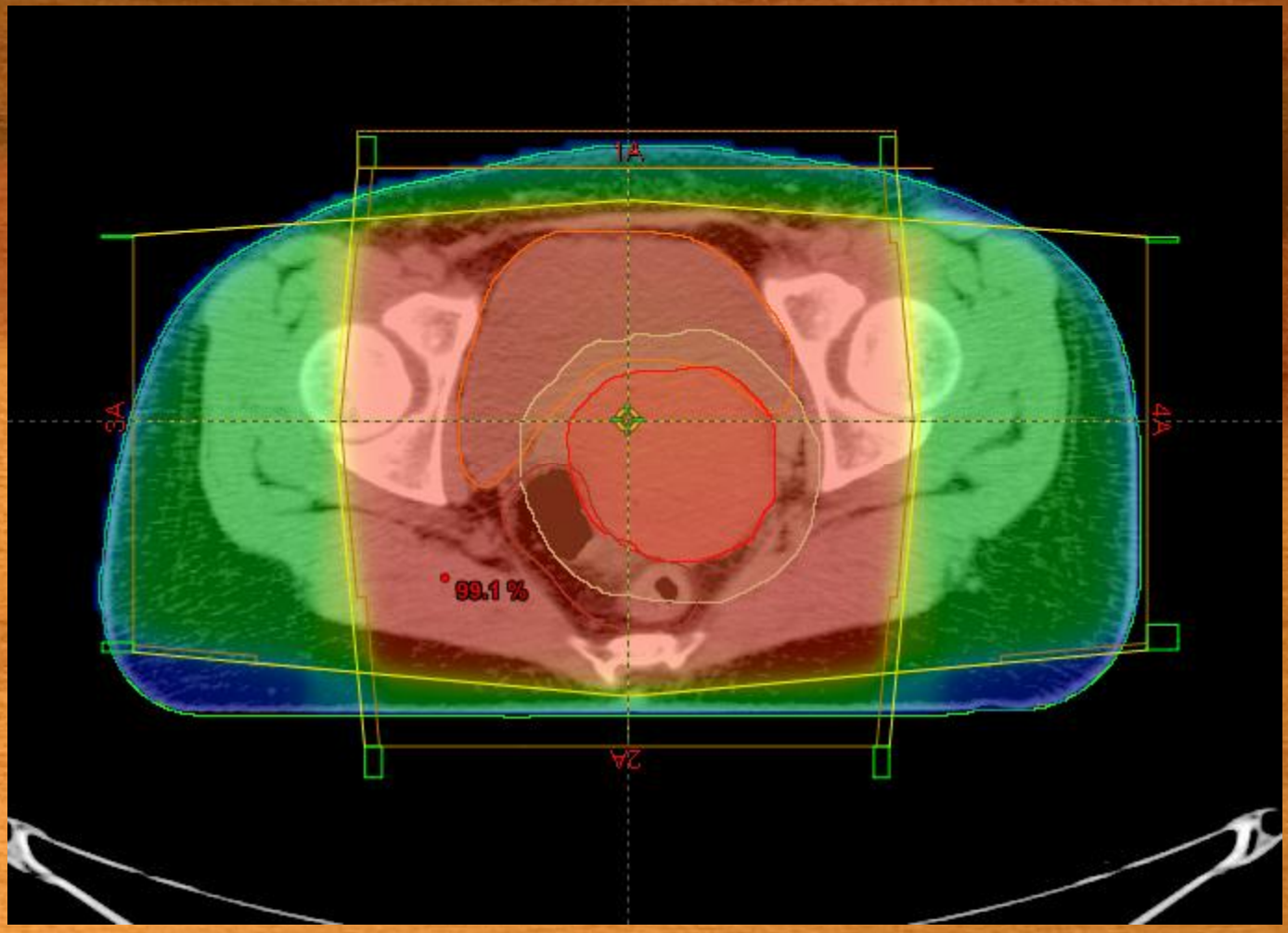

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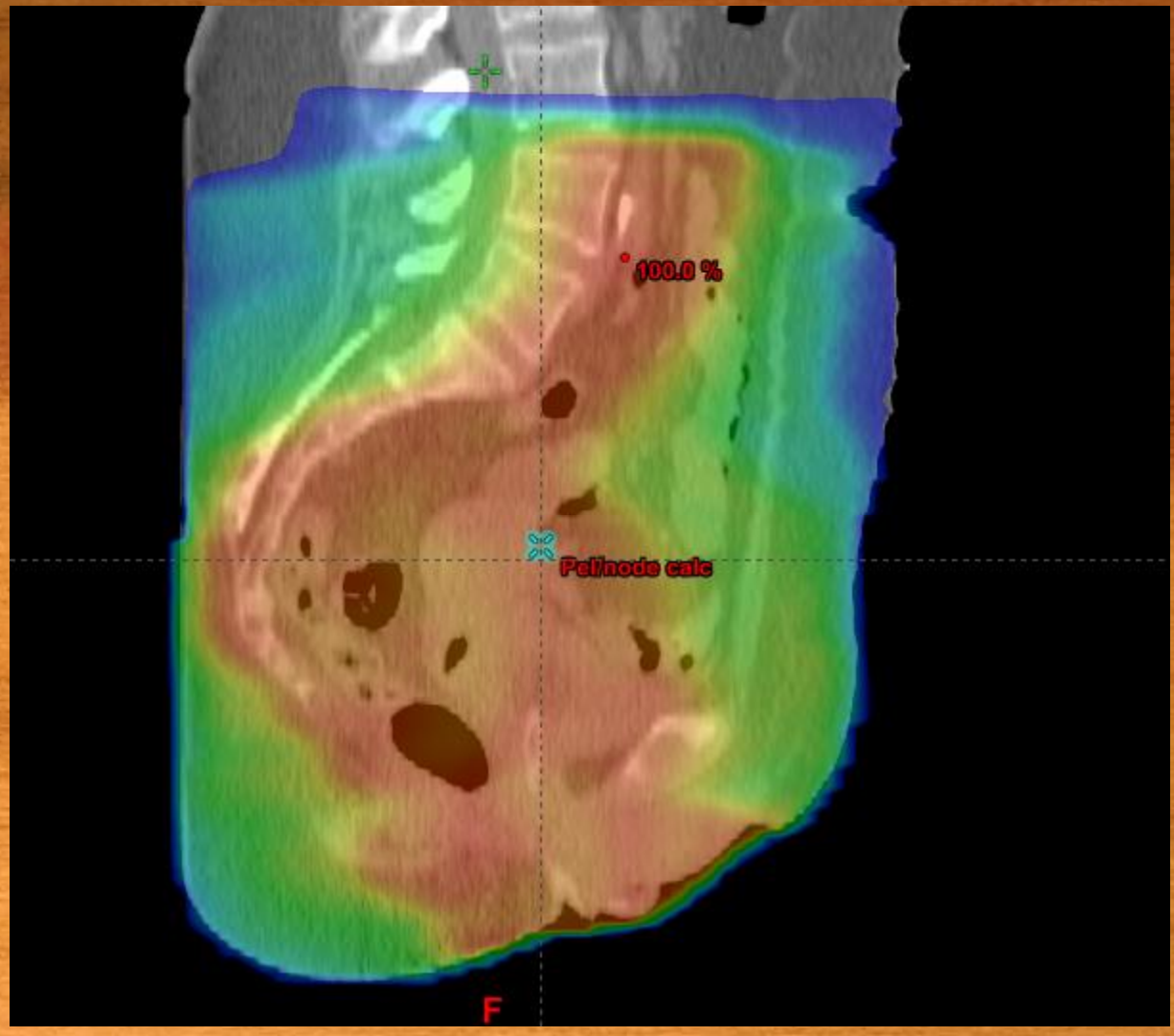

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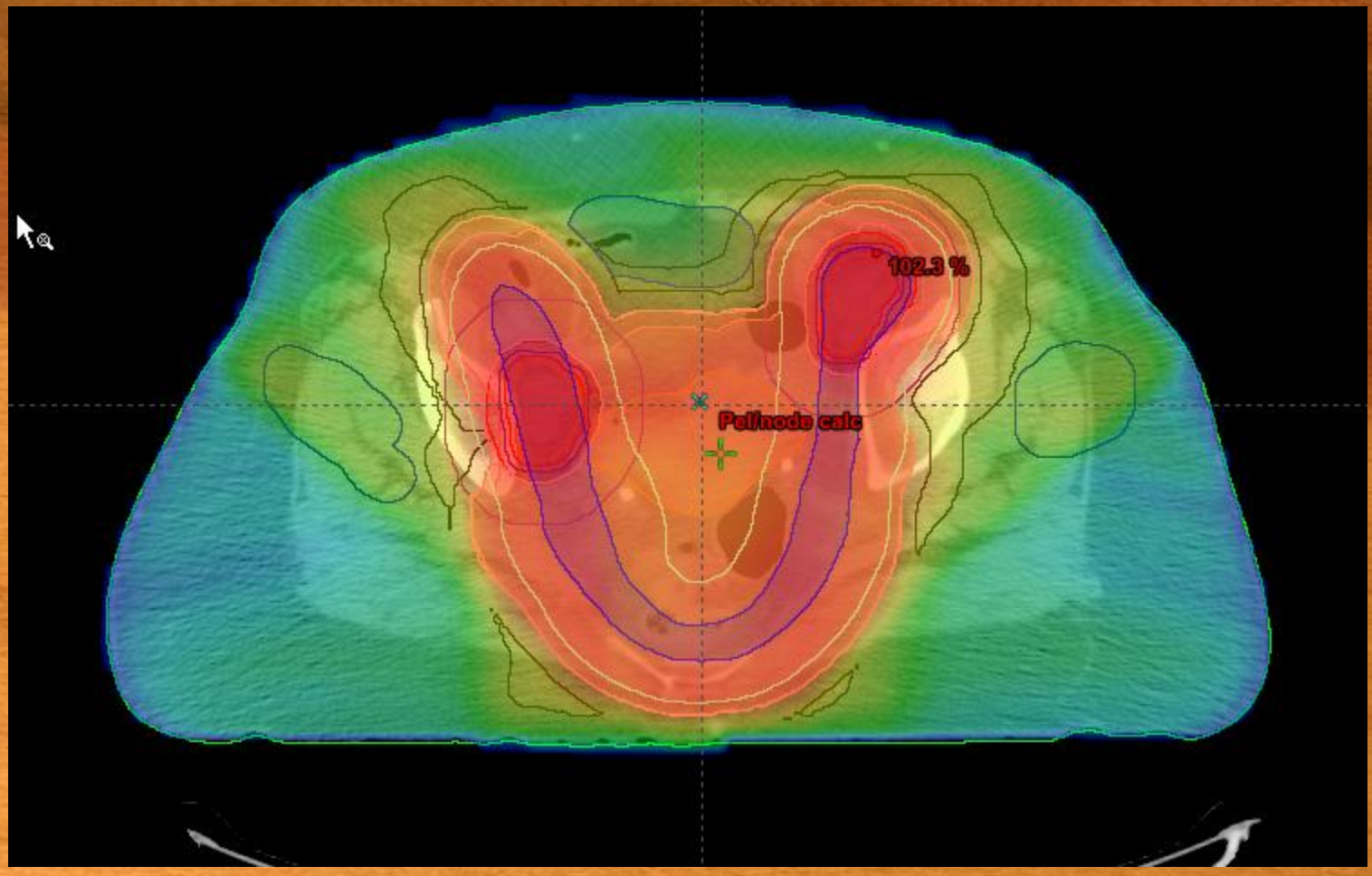

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 0417

A PHASE II STUDY OF BEVACIZUMAB IN COMBINATION WITH DEFINITIVE RADIOTHERAPY AND CISPLATIN CHEMOTHERAPY IN UNTREATED PATIENTS WITH LOCALLY ADVANCED CERVICAL CARCINOMA

SCHEMA (5/11/07)

REGISTER

Pelvic RT:

45 Gy given in 25 once-daily fractions (1.8 Gy/fraction) Monday-Friday over 5 weeks

↓

LDR x 2 or HDR x 5

↓

Parametrial boost (if indicated)

Bevacizumab (Avastin®): IV Q2 weeks (Days 1, 15 and 29, total of 3 doses) during chemoradiation, given before cisplatin, on the same day as cisplatin

Cisplatin: Weekly infusion x 6 weeks

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EORTC - 55994

Phase III Randomized Study of Neoadjuvant Cisplatin-Based Chemotherapy Followed By Radical Hysterectomy Versus Standard Therapy With Concurrent Radiotherapy and Cisplatin-Based Chemotherapy in Patients With Stage IB2, IIA, or IIB Cervical Cancer

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Investigational approaches

- Chemoradiotherapy +/- tirapazamine
  - A drug that is activated in settings of hypoxia (GOG)
- Pemetrexed
- Paclitaxel/Topotecan/Plat

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4 Year Overall Survival

- Stage IA 95-100%
- Stage IB1 80-90%
- Stage IB2 75-80%
- Stage IIB 68-73%
- Stage III/IVA 35-55%

- Prevention and Screening!!!!!!!

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