

Case #7—Locally Advanced Stage IIB Cervical Carcinoma: Evaluating the Options



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Case #7

Cervical Carcinoma Stage IIb

Would you perform **surgical staging** including lymphadenectomy (either extraperitoneal or laparoscopic) in this patient with locally advanced cervical cancer?

- Yes
- No, but I will, in addition to clinical staging, do abdominal/pelvic contrast enhanced CT or MRI

Surgical Staging in Cervical Carcinoma

Large **randomized** phase III “**pure surgical**” trials in cervical carcinoma are **sparse or non-existing** eg,

- Laparoscopic, transperitoneal or retroperitoneal LN (n = 161)¹
- CT versus surgical staging (scopy/ extraperitoneal tomy) (n = 61)²
- ...??

Arguments Against Surgical Staging Laparotomy In Advanced Cervical Carcinoma

- High incidence of **gastrointestinal (GI) complications** after staging laparotomy and radiotherapy
- **Postponement** of radiotherapy during recovery period
- No proof of improved **survival** with surgical staging

Arguments in Favor of Laparoscopic Staging in Cervical Cancer

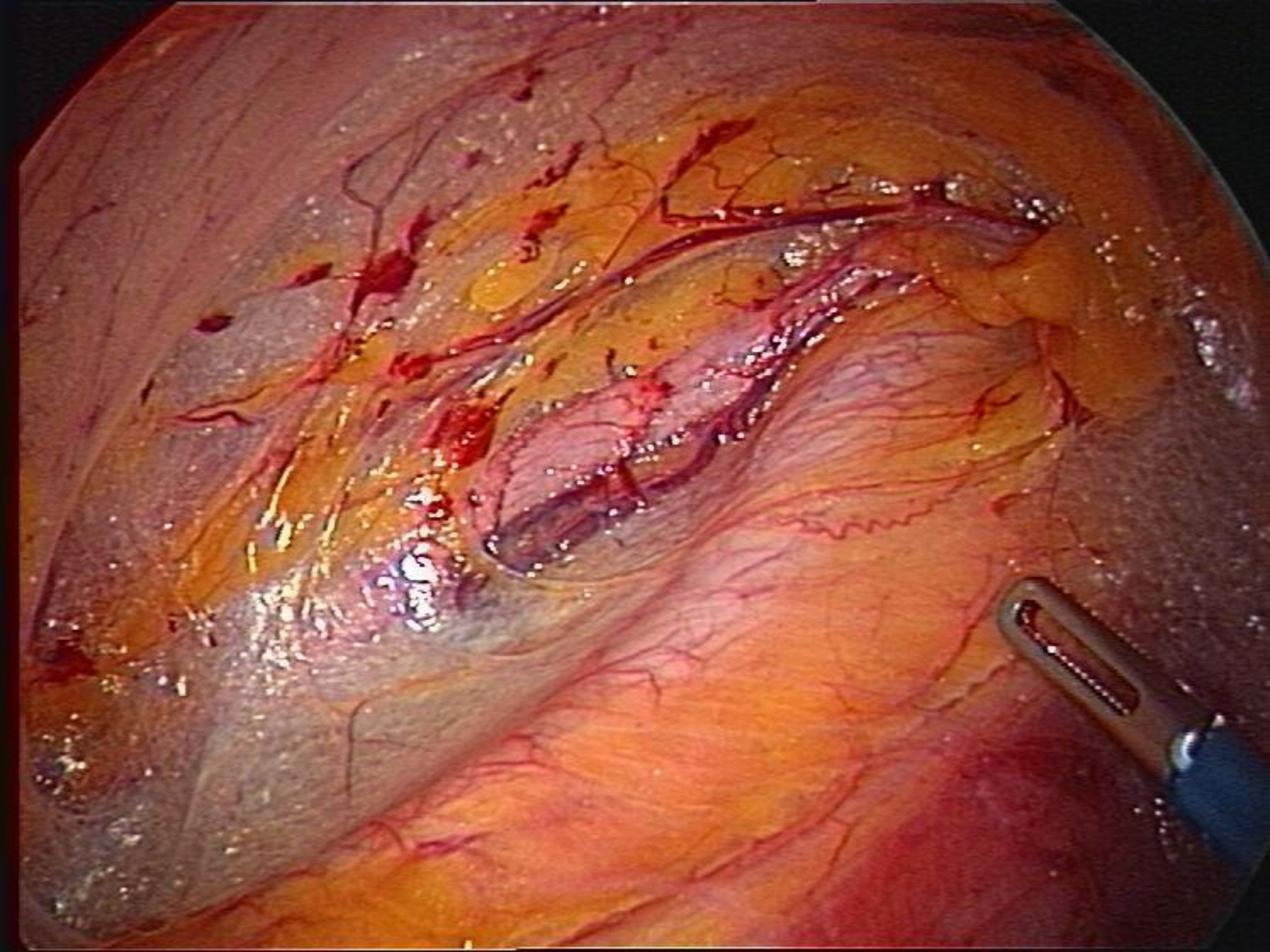
Laparoscopy

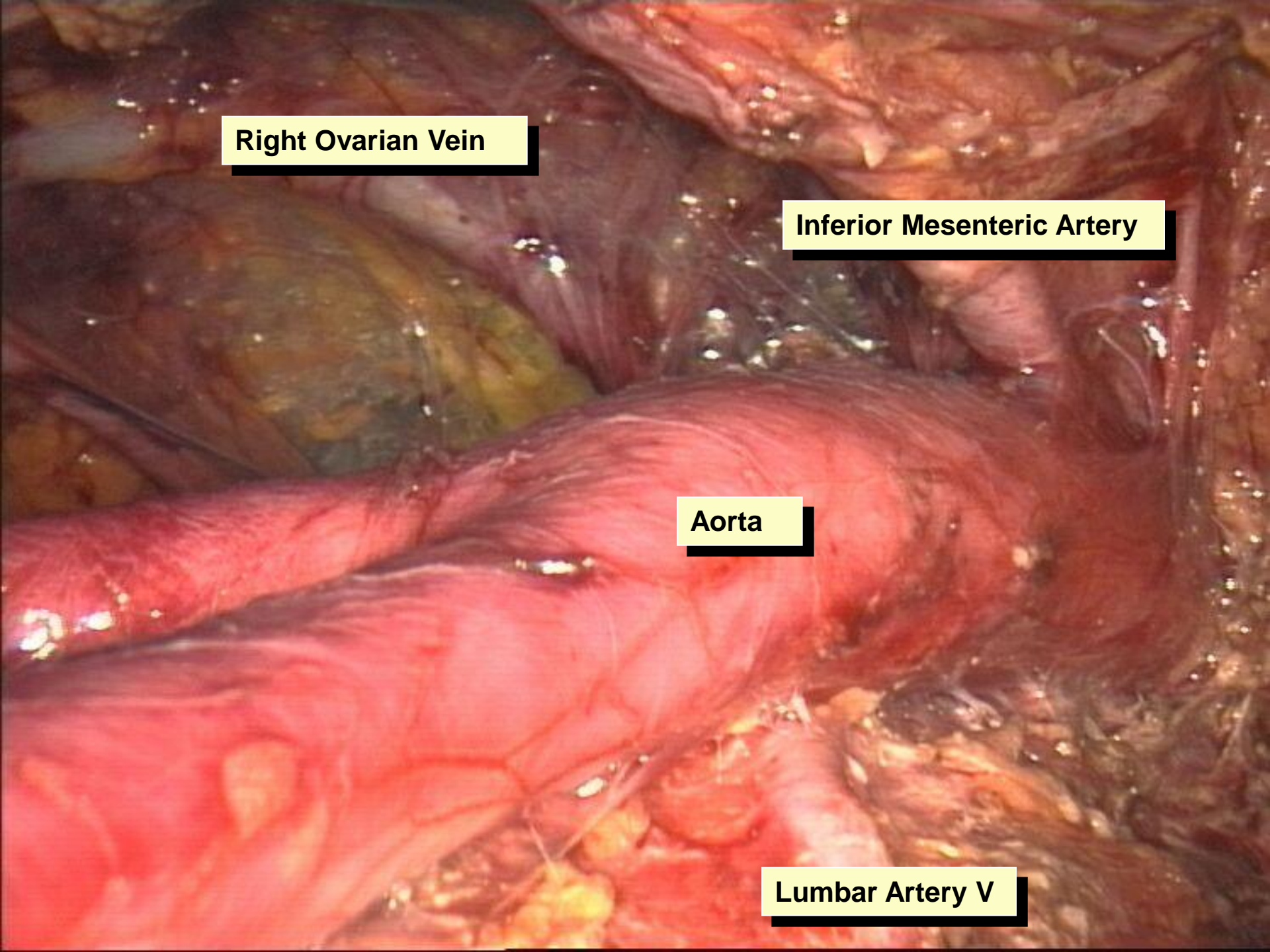
- Results in fewer **adhesions**
- The **retroperitoneal** approach does not interfere with radiotherapy
- The radiotherapy can be started **faster** than after laparotomy

Endoscopic Staging in Cervical Carcinoma IB2-IIIB (>4 cm) Leuven Policy 1997 - Today

- **No change in policy** (ie, radical pelvic lymphadenectomy may be curative and positive pelvic nodes are not a contraindication for radical hysterectomy)
- **No radical hysterectomy** in stage Ib-IIa if PAO lymph node metastases
- Radiochemotherapy to the pelvic field and **PAO boost** in stage Ib-III with positive PAO lymph nodes
- From October 1997 **endoscopic PAO** lymph nodes sampling as staging procedure
- Only the **lower** PAO lymph nodes removed as <2% patients have high paraaortic metastases without metastases in lower PAO area





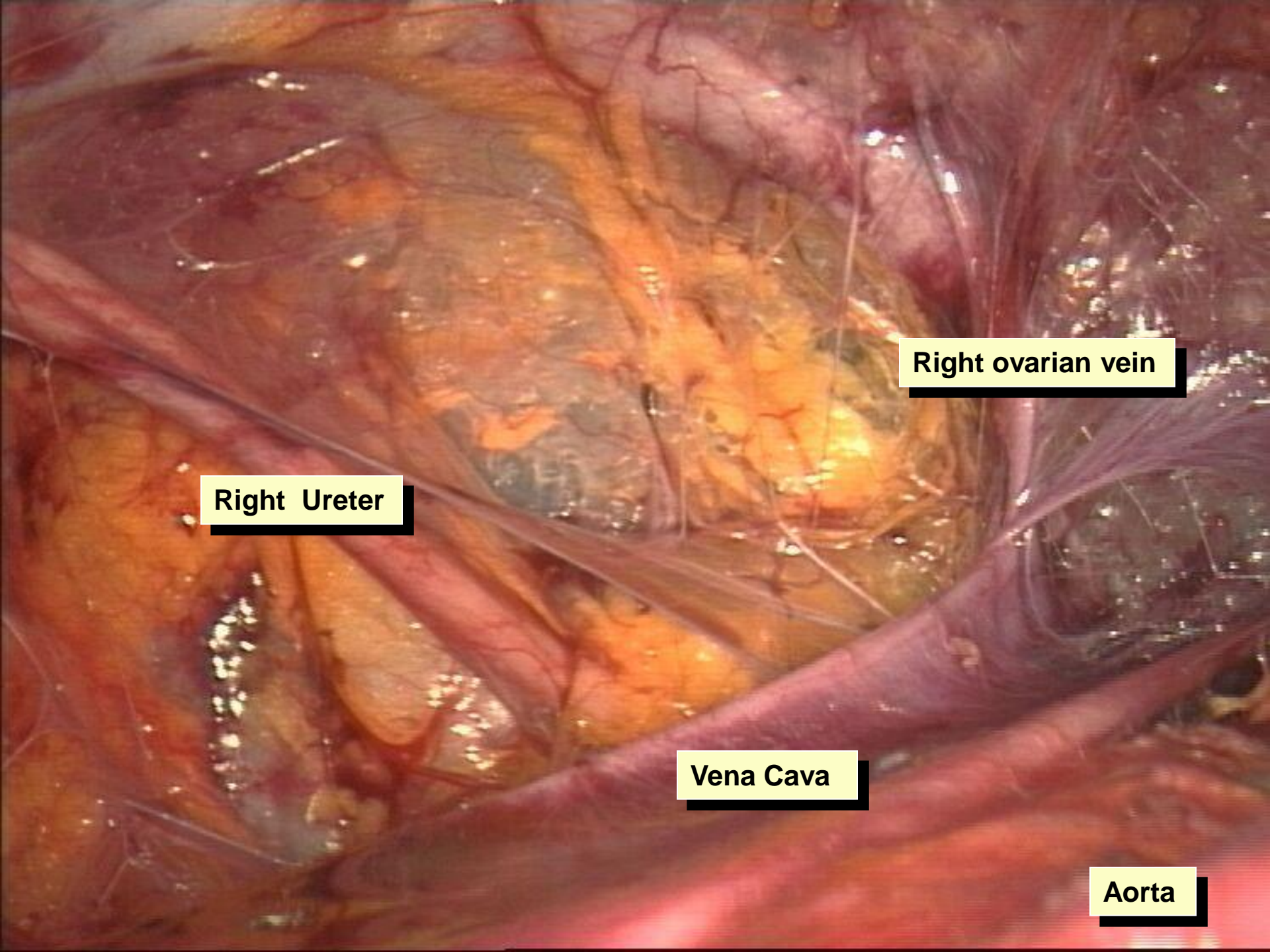
An anatomical dissection of the abdominal aorta and its branches. The aorta is the central, large, red vessel running horizontally across the middle. To its right, the inferior mesenteric artery branches off. To its left, the right ovarian vein is visible. At the bottom, the lumbar artery V is shown. The surrounding tissue is yellowish and fibrous.

Right Ovarian Vein

Inferior Mesenteric Artery

Aorta

Lumbar Artery V



Right Ureter

Right ovarian vein

Vena Cava

Aorta

Endoscopic Paraaortic Staging in Cervical Carcinoma IB2-IVa with Negative CT Paraaortic

	Pos PAO / Total	
Hertell (2002)	13/91	(14%)
Lai (2003)	8/38	(25%)
Chung (2005)	5/44	(11%)
Leblanc (2005)	39/156	(25%)
Vergote (2008)	10/80	(13%)

Endoscopic Paraaortic Staging in Cervical Carcinoma IB2-IVa—PET-CT

- N = 121 after **negative CT**, of which **85** after negative PET and CT or **PET-CT** in the PAO area
- After negative PET: 9/85 (**11%**) pos PAO nodes
- All metastatic lymph nodes were **smaller than 1 cm** and **none had capsular rupture**

Prognosis in PAO Pos Patients with Negative PET

Very poor prognosis even when treated with **PAO radiochemotherapy** (mostly relapses outside pelvic and APO area):

7 out of 9 died

(median 8 months, range 4 – 25 months)

Hence, **other treatment strategies** such as (neoadjuvant) chemotherapy or molecular targeted therapy should be evaluated in this group of patients

Laparoscopic Staging in Locally Advanced Cervical Cancer

Conclusions

1. Imaging, even **PET-CT**, **not sensitive** enough to detect paraaortic metastases (11% false negatives with PET-CT)
2. **Retroperitoneal** laparoscopic (robotic) paraaortic lymphadenectomy is preferred technique in this setting
3. Patients with negative (PET-CT) but with metastases to paraaortic nodes have **dismal** prognosis (median OS Leuven 8 months, Lille: 27 months). Currently treat patients first with **neoadjuvant chemotherapy** follow by radiochemotherapy (extended field)

Case #7

Cervical Carcinoma Stage IIb

Which of the following would you recommend for initial treatment of this patient?

1. Chemoradiation
2. Chemoradiation followed by surgery
3. Radiotherapy + concurrent gemcitabine/cisplatin followed by adjuvant gemcitabine/cisplatin
4. Neoadjuvant chemotherapy followed by surgery
5. Clinical trial of neoadjuvant chemotherapy and surgery versus concurrent chemoradiation therapy. (EORTC 55994)
6. Clinical trial of radiotherapy + bevacizumab + cisplatin

International Open Question

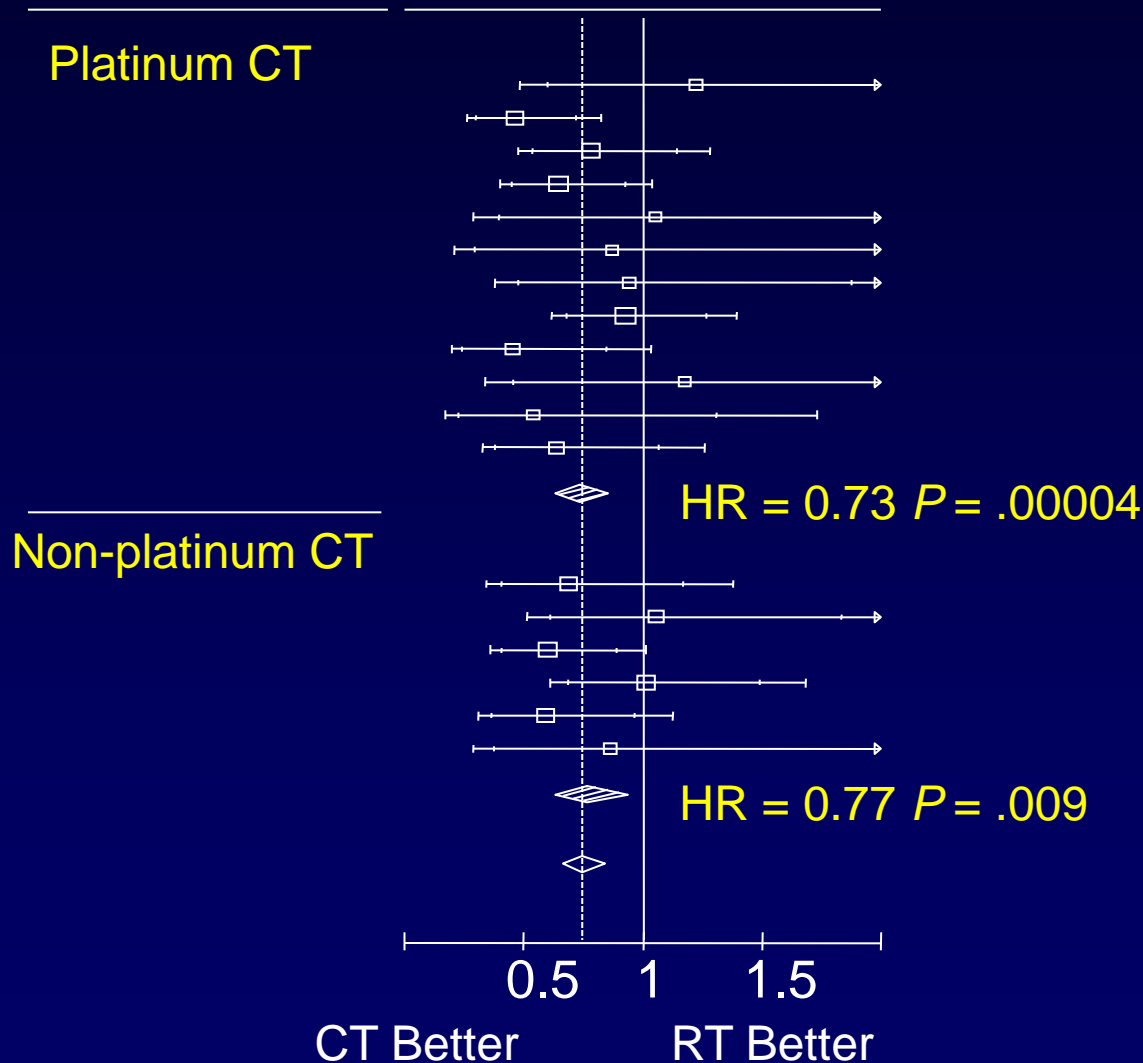
What is the best treatment
for FIGO stage IB 2/II B cervical cancer?

CT/RT

**Radical Hyst
+/-
adj CT/RT**

**NACT
+Rad Hyst
+/- adj CT/RT**

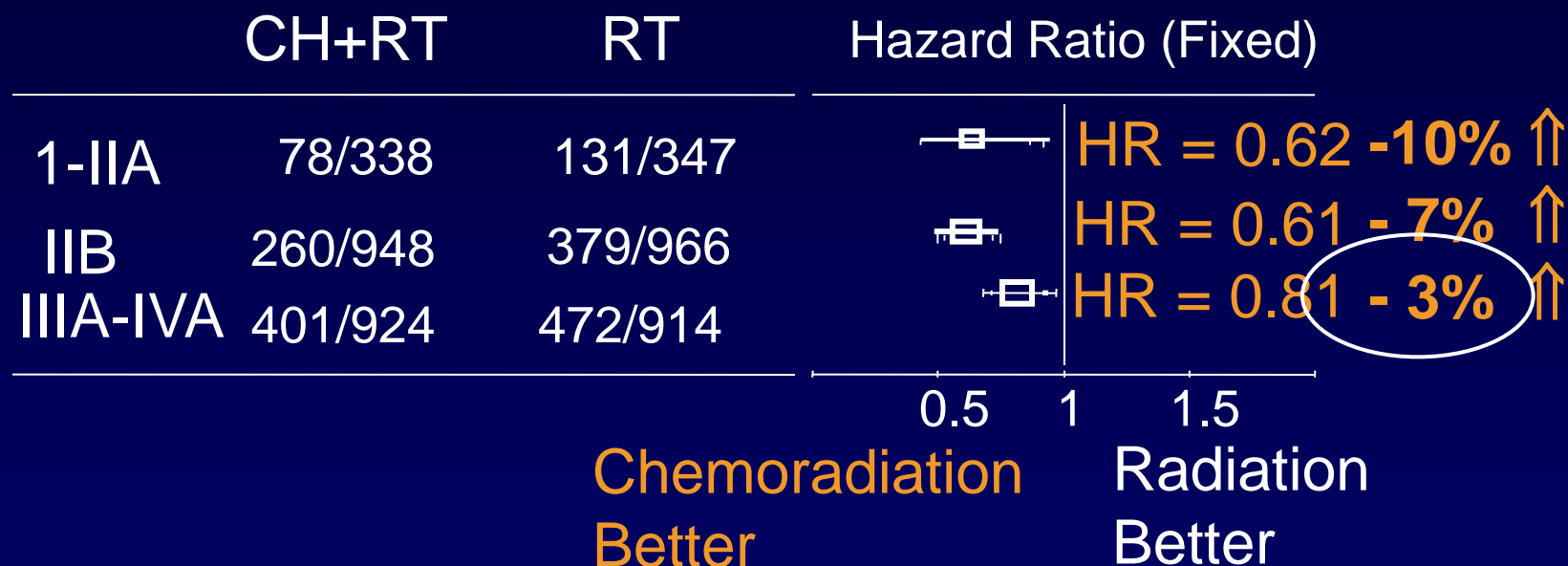
Concomitant CT/RT for Cervical Cancer Meta-Analysis Survival by CT Type



Survival All Trials and by Stage

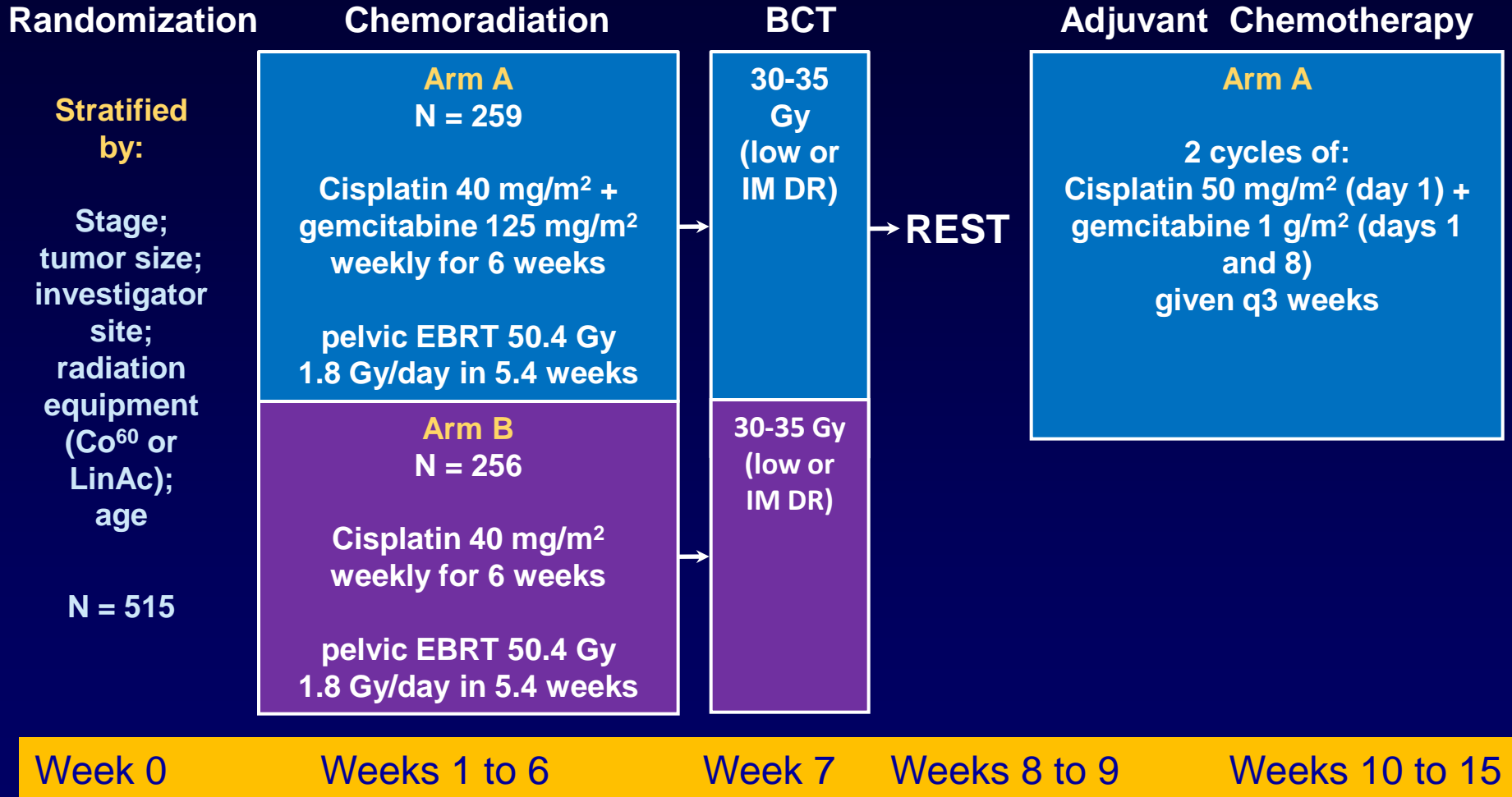
HR = 0.77 \Rightarrow Abs benefit at 5 years = 8% (from 60% to 68%).

Metastases Free S: HR = 0.81, \uparrow 7%

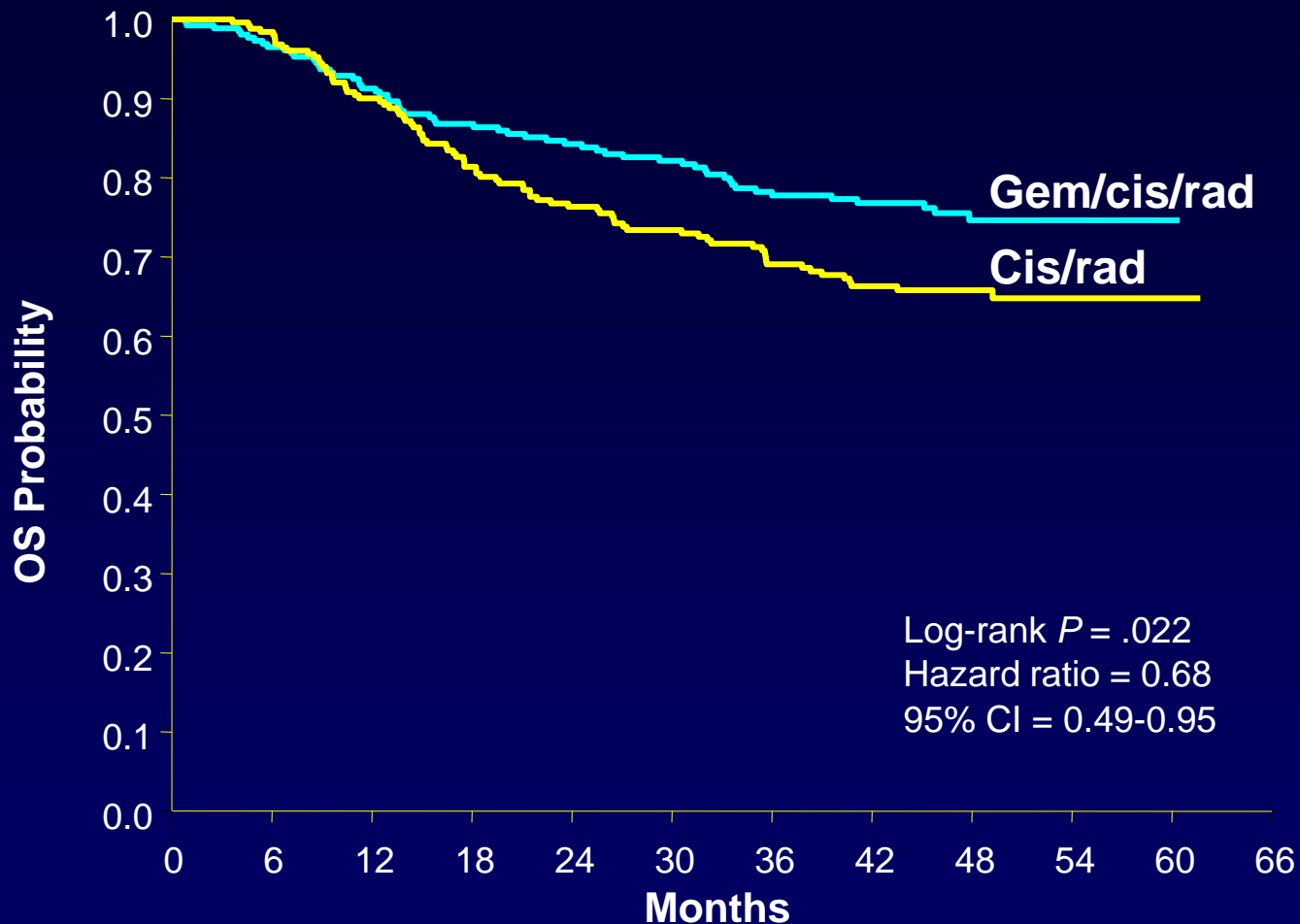


Magnitude of benefit is significantly higher in stage I-II B than in stage III

Dueñas-González ASCO 2009 Study Design



Overall Survival



- OS was statistically superior for Gem/cis/rad over Cis/rad
- OS at 3 years: 78.2% in Gem/cis/rad versus 69.1% in Cis/rad

Dueñas-González ASCO 2009 Comments

1. What is the effect of concomittant gemcitabine versus **adjuvant** postradiation chemotherapy?
2. Concomittant cis and gemcitabine was not tolerated in **other** studies (eg, GOG).
3. Not yet **published**

Locally Advanced Cervical Cancer

- Chemo-RT > RT YES
- NACT+RT > RT?
- NACT+surgery > RT ?
- NACT+surgery > Surgery?
- NACT+surgery > Chemo-RT?

Meta-Analysis

Neoadjuvant Chemotherapy Followed by Radiotherapy

- **24 trials (n = 2074)** were included but 3 excluded because one still ongoing and 2 concomittant
- Overall neoadjuvant chemotherapy prior to radiotherapy **did not improve survival**
- **Cisplatin** was the most important drug used
- **Dose intensity** (11% decrease in survival with dosages <25 mg/m²/week) and ...
- **Cycle length** appeared to be important variables (length <14 days: HR for death 0.83, *P* = .04):

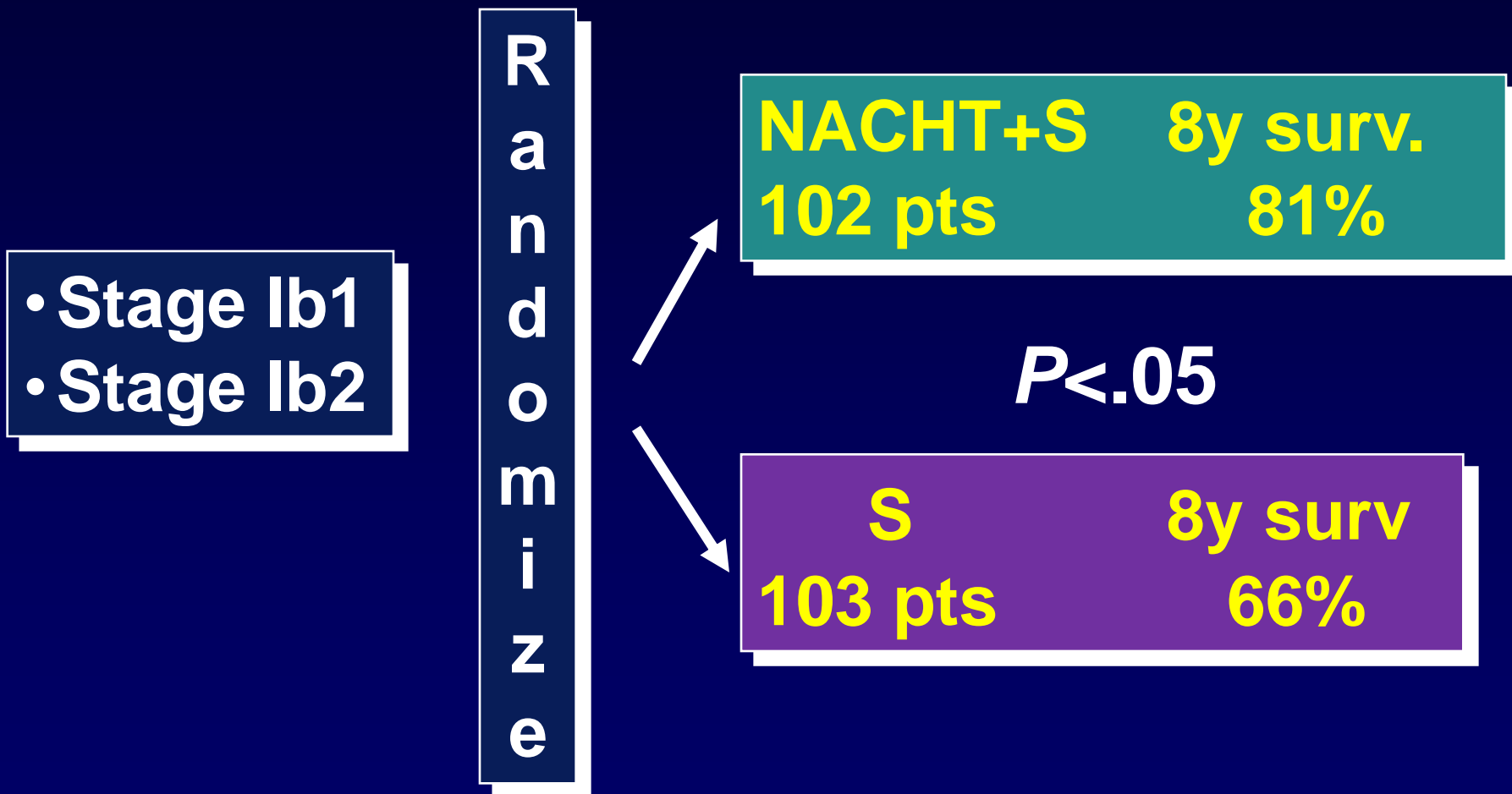
Locally Advanced Cervical Cancer

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- NACT+surgery > Surgery ?
- NACT+surgery > Chemo-RT ?

Potential Advantages of Neoadjuvant Chemotherapy Followed by Surgery

- **Uncompromised blood supply**
- **Better tolerance—no castration**
- **Tumor more chemosensitive**
- **Reduction of tumor bulk —→ operability**
- **Eradication of subclinical metastasis**

Randomized Trials of Neoadjuvant Chemotherapy in Cervical Carcinoma (NACHT)



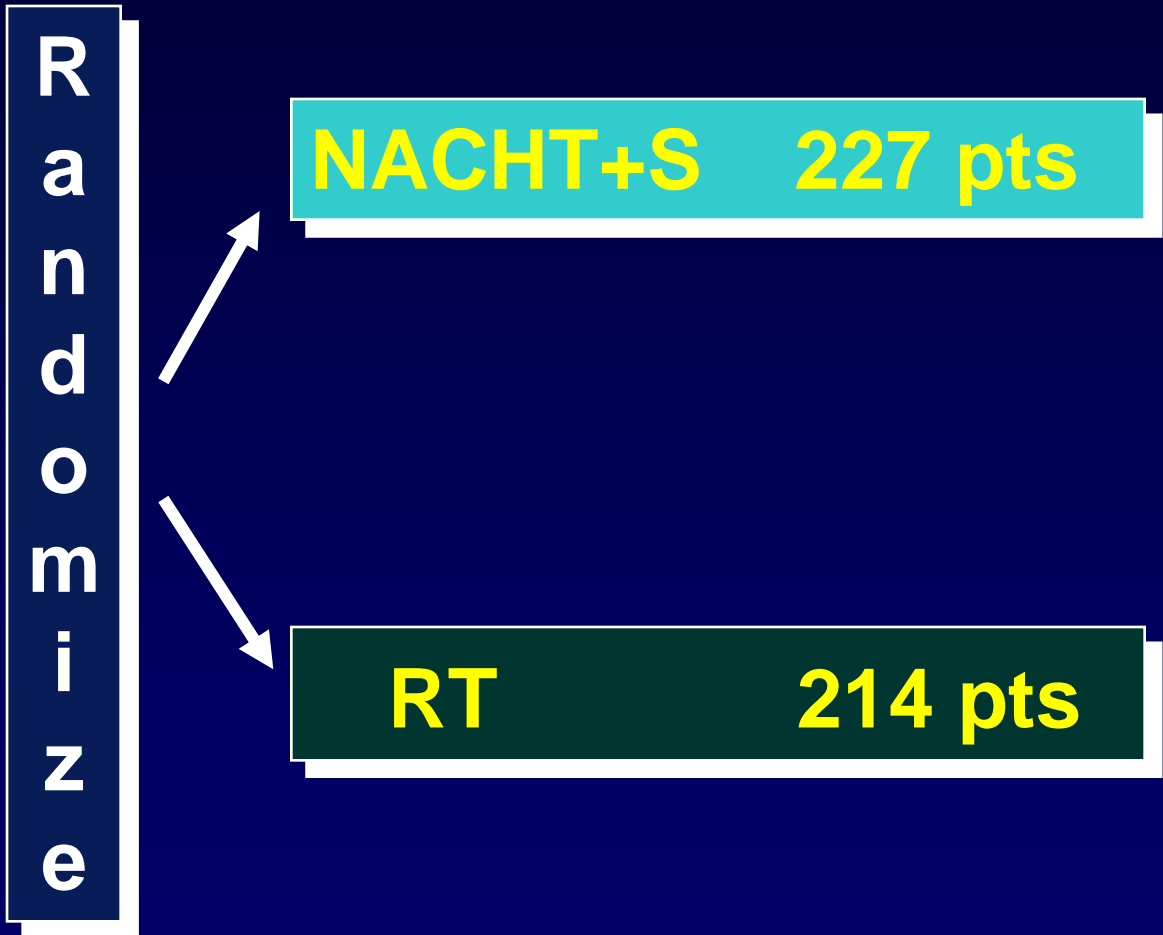
Randomized Trials of Neoadjuvant Chemotherapy in Cervical Carcinoma (NACHT)

	N	7-yr survival	
Stage IIb	RT:	73	48%
	S+RT:	75	41%
	NACHT+S:	76	65%
	NACHT+RT:	72	54%

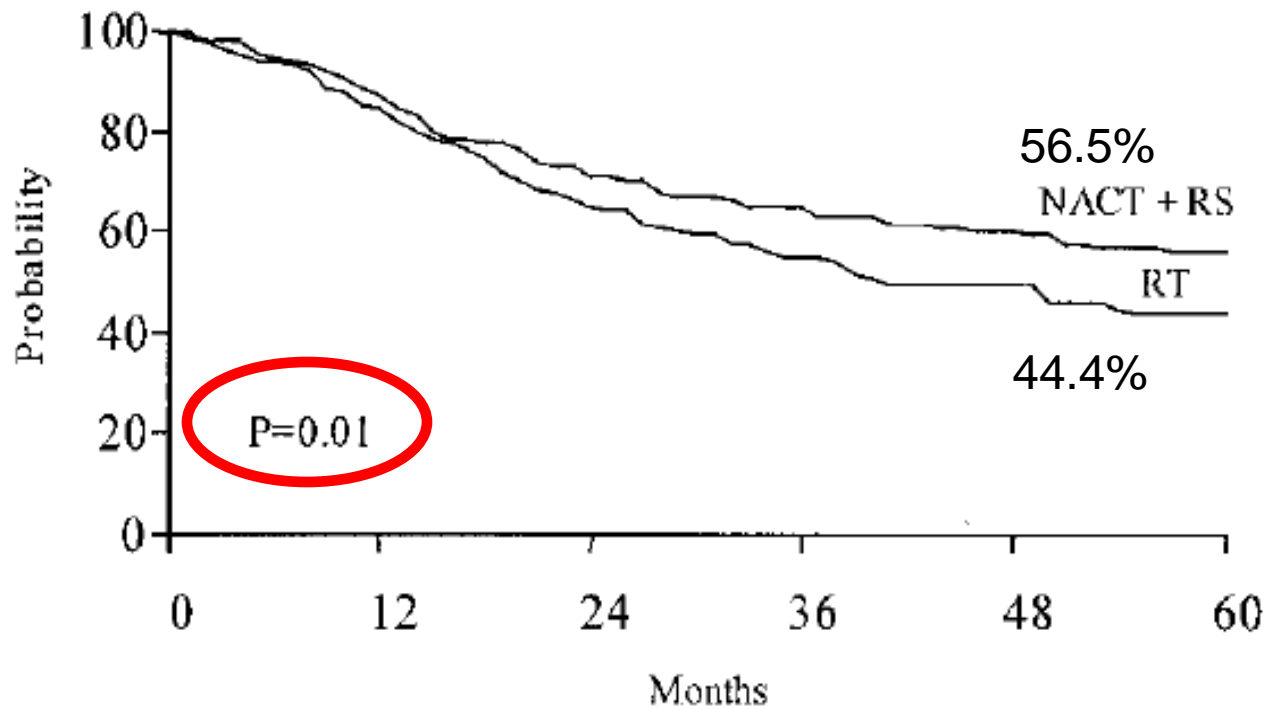
} $P < .001$

Italian Randomized Trial of Neoadjuvant Chemotherapy (NACHT) in Cervical Carcinoma

- Stage Ib2-IIb
- Stage IIIb

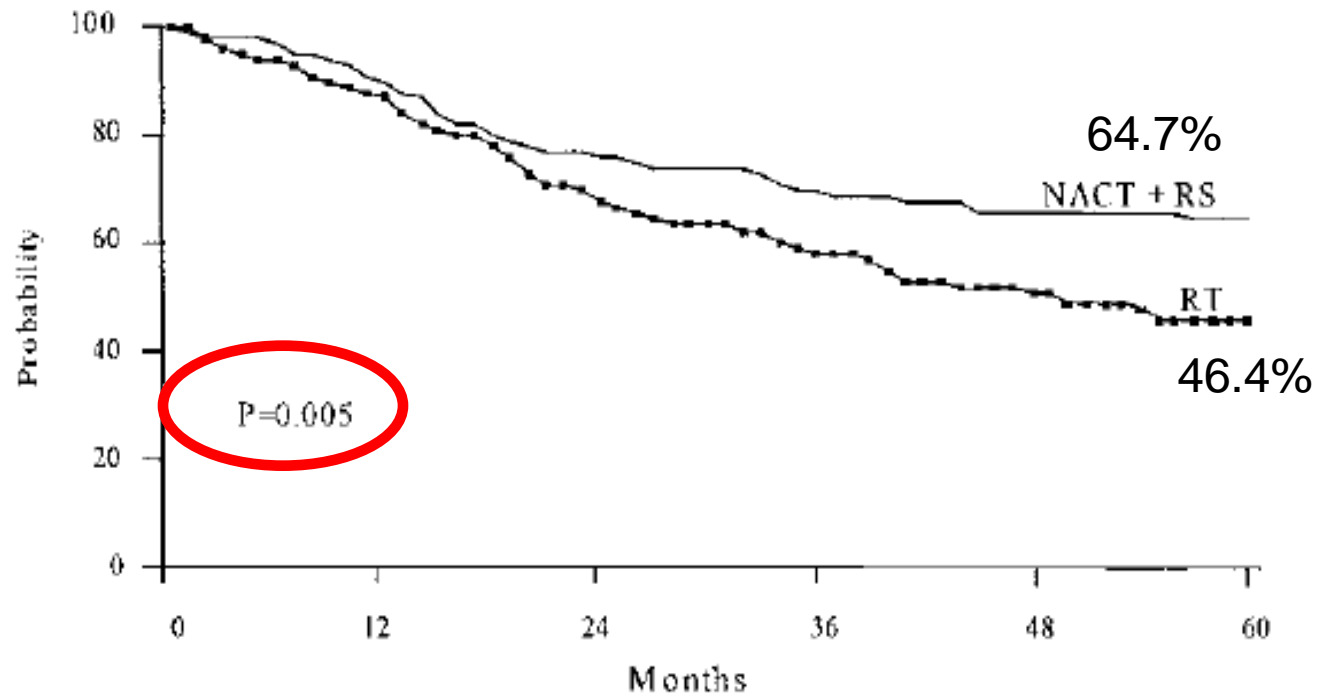


Overall Survival (Intention to Treat)



NACT + RS	227	194	153	120	81	42
RT	214	175	122	86	50	21

Overall Survival Stage IB2 to IIB (Intention to treat)



No. at Risk

NACT + RS

159

139

115

91

59

32

RT

163

140

99

73

43

18

Meta-Analysis

Neoadjuvant Chemotherapy Followed by Surgery

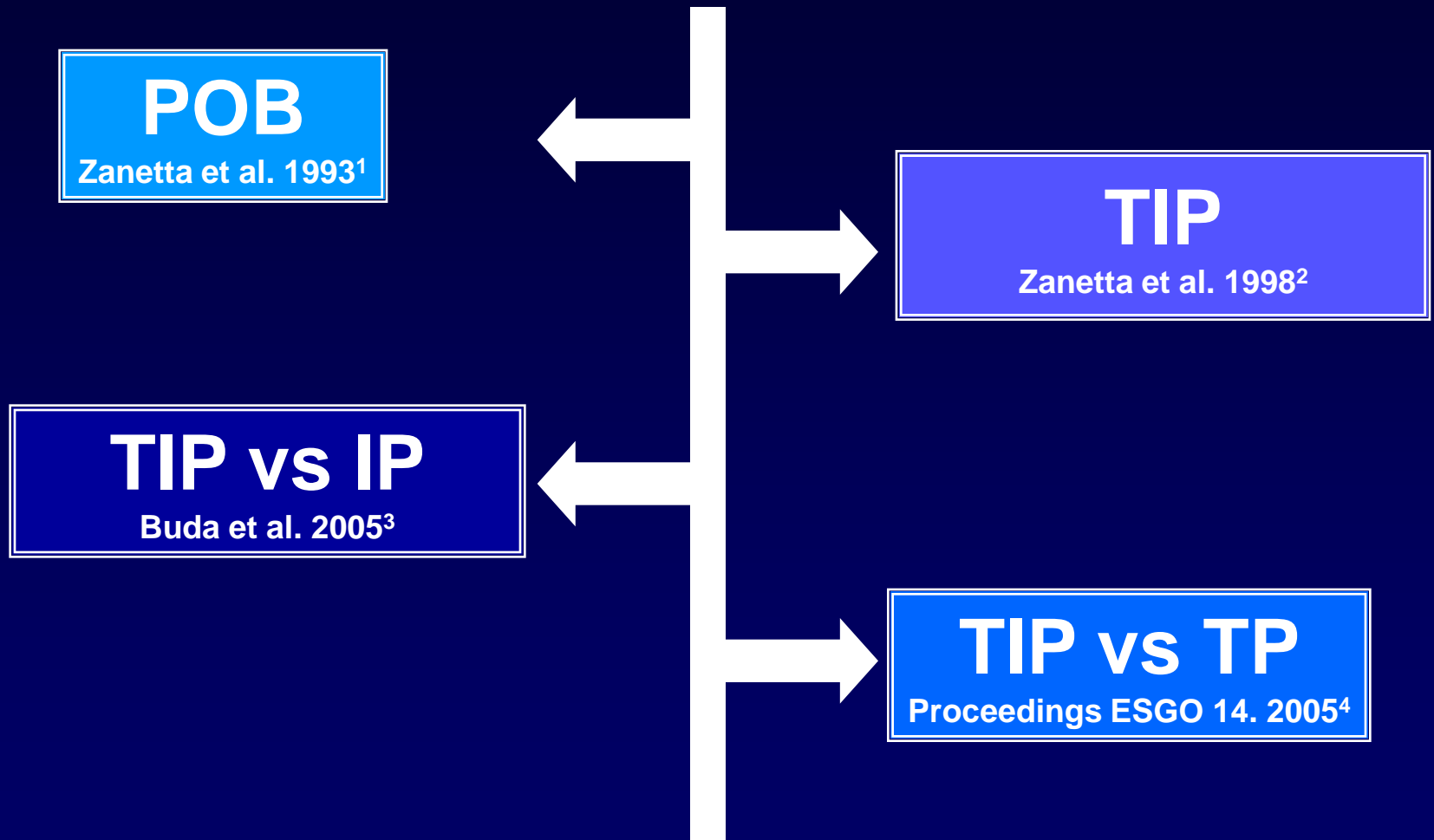
- ◆ **N = 872**
- ◆ **HR = 0.65 ($P = .0004$) translating into a 14% absolute improvement in 5-year overall survival with neoadjuvant chemotherapy compared to radiotherapy!**
- ◆ **Criticisms:**
 - 1. Low numbers**
 - 2. Quality of radiotherapy**
 - 3. No concomitant chemotherapy**

Locally Advanced Cervical Cancer

- Chemo-RT > RT YES
- NACT+RT > RT? NO
- NACT+surgery > RT ? YES
- NACT+surgery > Surgery?
- NACT+surgery > Chemo-RT?

Which Kind of Neoadjuvant Chemotherapy?

Studies to Define Our Standard Regimen of NACT



1. Zanetta G, et al. *Obstet Gynecol.* 1993;82(3):447-450. 2. Zanetta G, et al. *Ann Oncol.* 1998;9(9):977-980. 3. Buda A, et al. *J Clin Oncol.* 2005;23(18):4137-4145. 4. Presented at the 14th International Meeting of the European Society Gynaecological Oncology; Istanbul, Turkey: 25-29 September 2005.

SNAP 01 Trial

RANDOMIZED

TIP

IP

<i>IFO</i>	<i>5 g/mq</i>
<i>CDDP</i>	<i>75 mg/mq</i>
<i>Paclitaxel</i>	<i>175 mg/mq</i>

<i>IFO</i>	<i>5 g/mq</i>
<i>CDDP</i>	<i>75 mg/mq</i>

Main endpoint: Optimal response rate

SNAP-01 Neoadjuvant CT in Cervical Carcinoma. Response Evaluation

	IP		TIP	
	100		91	
CR	9%	} 23%	20%	} 47%
PR1*	14%		27%	
PR2	51%		41%	
SD	15%		10%	
PD	11%		2%	

OR 3.0 [IC at 95% 1.6-5.6] M-H: $c_1^2 = 12.33$; $P = .0004$

* <3 mm invasion or *in situ* residual tumor

Neoadjuvant CT in Cervical Carcinoma

SNAP 02

RANDOMIZED

TIP

TP

IFO 5 g/mq
CDDP 75 mg/mq
Paclitaxel 175 mg/mq

Paclitaxel 175 mg/mq
CDDP 75 mg/mq

Main endpoint: Optimal response rate

SNAP-02 Neoadjuvant CT in Cervical Carcinoma. Response Evaluation

n = 145

	TP, %	TIP, %
pCR	11	22
pPR1	16	20
Optimal response*	27	42
PR2	63	46
Total Response	90%	88%

*Optimal response: no residual or residual disease ≤ 3 mm stromal invasion

Leuven Dose Dense Paclitaxel Carbo Neoadjuvant Chemotherapy In Cervical Carcinoma

- Carbo AUC4, d1 AND 8, paclitaxel 90 mg/m² d1, aND d8 q 3 wks
- Stage IB2 – IIB
- Tumor size (mean):
before chemo: 49 mm → after chemo: 12 mm

Response

<i>Clinical</i>		<i>MRI</i>		<i>Pathologic “optimal” response*</i>		
PR	90% (19/21)	PR	95% (19/20)	pOR	Total	39% (7/18)
					Squamous	44% (7/16)
CR	10% (2/21)	CR	5% (1/20)		Adeno	0% (0/2)

*pOR = pathologic complete response or less than 3 mm residual infiltration

Which Neoadjuvant Chemotherapy Prior to Surgery?

1. **TIP is the most effective 3-weekly regimen**
2. Possibly it is important to have **short cycle** length (<14 days) prior to surgery, as it is important prior to radiotherapy
3. Therefore, the **Leuven dose dense paclitaxel/carboplatin** might be an interesting (less toxic) alternative

Locally Advanced Cervical Cancer

- Chemo-RT > RT YES
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- NACT+surgery > RT? YES
- NACT+surgery > Surgery?
- NACT+surgery > Chemo-RT?

NACT+Surgery vs Primary Surgery in Stage Ib2 – IIb Cervical Cancer (n = 140)

Main messages

- **Two cycles of high-dose short cycle-length NAC produced a response rate of 69%**
- **No adverse impact on postoperative morbidity**
- **Patients in NAC group showed lower lymph node metastases (25% vs 43%) and parametrial involvement (25% vs 41%)**
- **NAC did not harm survival of nonresponders**
- **NAC did not reduce the efficacy of postoperative RT**

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- NACT+surgery > Surgery? YES
- NACT+surgery > Chemo-RT?

Efficacy

Chemo-RT

Survival ranges from
68% to 82%

*depending on different
patient selection*

NACT+Surgery

Survival ranges from
63% to 86%

*depending on different
patient selection*

Toxicity

Chemo-RT

- Nausea
- Fatigue/anaemia
- Cystitis
- Altered bowel & bladder dysfunction
- Infertility
- Treatment induced menopause
- Skin reactions
- Vaginal stenosis
- Sexual dysfunction

NACT+Surgery

- Acute toxicity of chemotherapy
- Abdominal wound
- Urinary problems
- Nerve I thin morbidity?
- Need for adjuvant chemo-RT?

EORTC 55994

**Cervical Cancer
IB2, IIA >4 cm, IIB**

**Accrual 10/2009:
467/680**

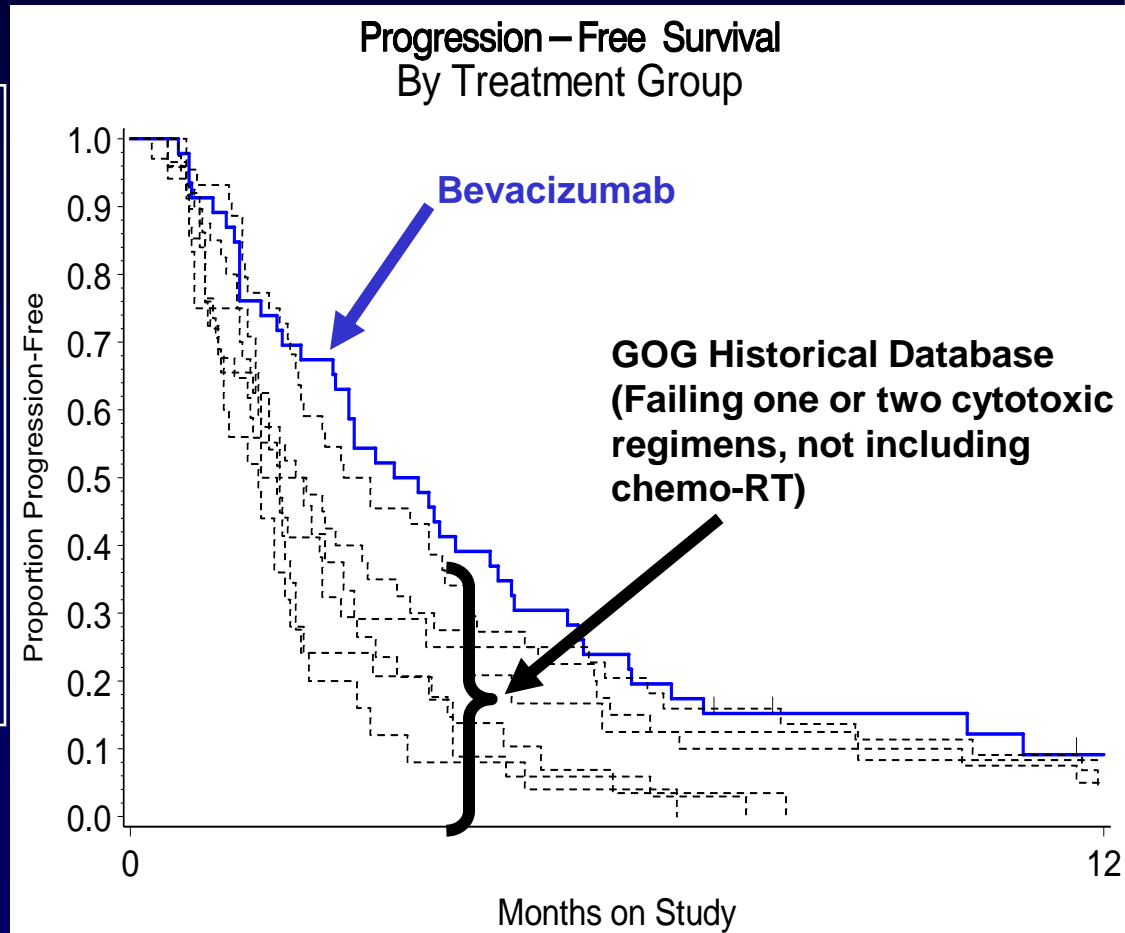
RANDOMIZED

**NACT +
Surgery**

**RT +
Cisplatin**

Bevacizumab in Cervical Carcinoma GOG 227-C

**PFS of Bev (Blue)
versus
GOG Historical
Database
(Failing one or two
cytotoxic
regimens, not including
chemo-RT)**



GOG 240 Schema

Eligibility:

1. Primary stage IVB or Recurrent/persistent carcinoma of the cervix
2. Measureable disease
3. GOG PS 0-1

R
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Regimen I

Paclitaxel 135 mg/m² IV d1 (24 h)
Cisplatin 50 mg/m² IV d2
Q21d to progression/toxicity

Regimen II

Paclitaxel 135 mg/m² IV d1 (24 h)
Cisplatin 50 mg/m² IV d2
Bevacizumab 15 mg/kg IV d2
Q21d to progression/toxicity

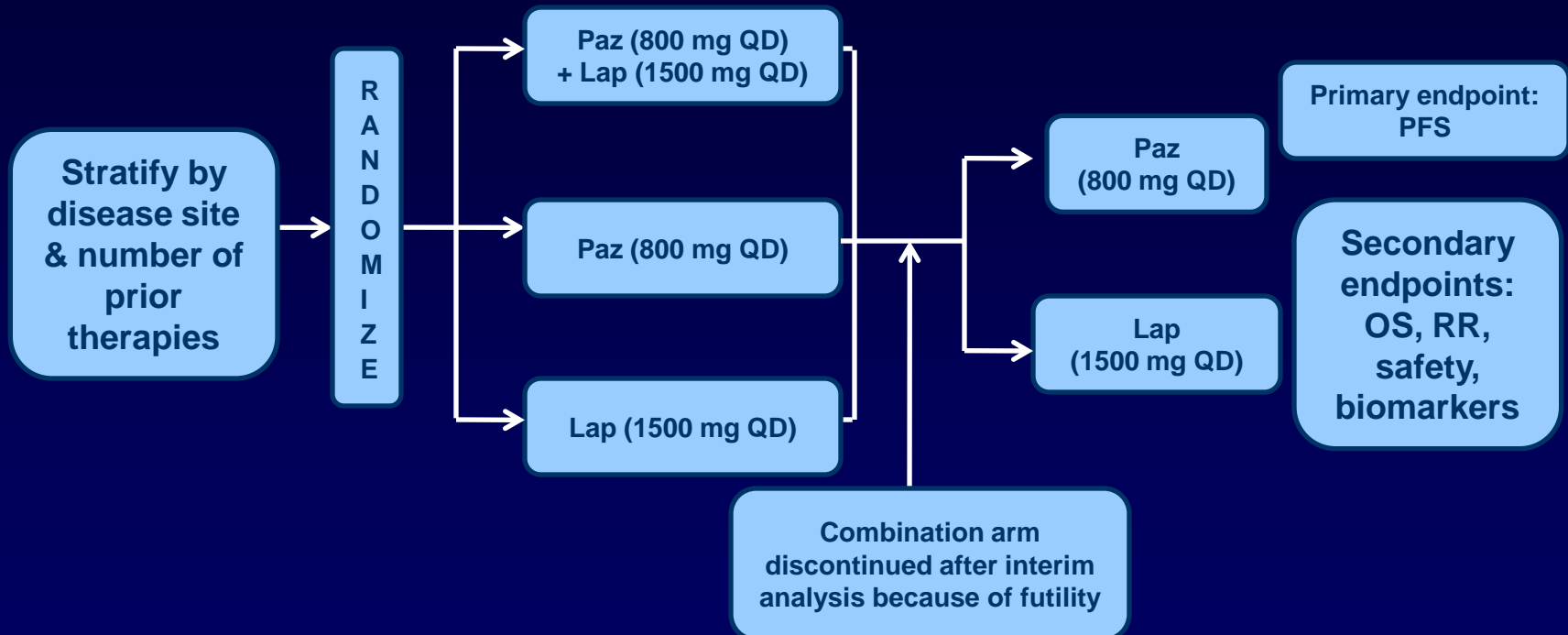
Regimen III

Paclitaxel 175 mg/m² IV d1 (3 h)
Topotecan 0.75 mg/m² d1-3 (30 m)
Q21d to progression/toxicity

Regimen IV

Paclitaxel 175 mg/m² IV d1 (3 h)
Topotecan 0.75 mg/m² d1-3 (30 m)
Bevacizumab 15 mg/kg IV d1
Q21d to progression/toxicity

Randomized, Open-Label, Phase II Trial



Schema GOG CVM 0902 Under Development

- FIGO Stage IB2, >4 cm IIA and IIB-IVA - limited to the pelvis
- Response to front-line weekly cisplatin and pelvic radiation

R
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Placebo



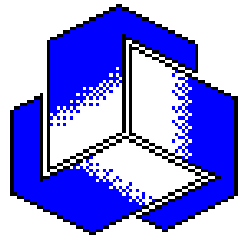
Pazopanib PO 800 mg/day

There Are Many Choices...



... and We Should Choose Carefully





What Would I Recommend in Leuven for This Patient with Cervical Carcinoma Stage IIb?



**Cervical Cancer
IB2, IIA >4 cm ,IIB**

RANDOMIZED

**NACT +
Surgery**

**RT +
Cisplatin**

EORTC 55994