XVI
ASSEMBLEA MANGO

RICERCA BIOLOGICA E FARMACOLOGICA
SUL TUMORE DELL'OVAIO: LABORATORIO E CLINICA

REGGIO EMILIA
21-22 GIUGNO 2019

EORTC
The future of cancer therapy

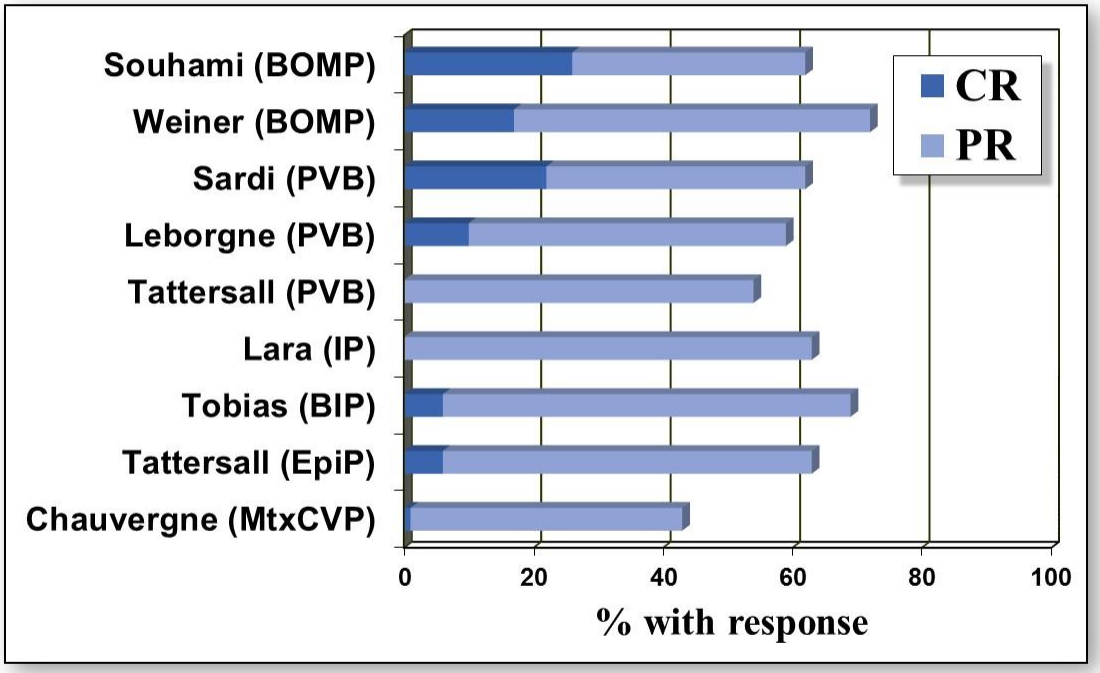
GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative

Results from neoadjuvant chemotherapy followed by surgery compared to chemoradiation for stage Ib2-IIb cervical cancer EORTC GCG 55994

G. Kenter, S. Greggi, I. Vergote, D. Katsaros, F J. Kobierski, L. Massuger, H. van Doorn, F. Landoni, J. van der Velden, E. Van Dorst, N. Reed, N. Colombo, C. Coens, I. van Luijk, P. Ottevanger, A. Casado Herráez

Cervical cancer – The evolution of multi-modality treatment

- 1990s: 1st neoadjuvant trials (RT +/- neoadjuvant CT)
  - Encouraging response rates



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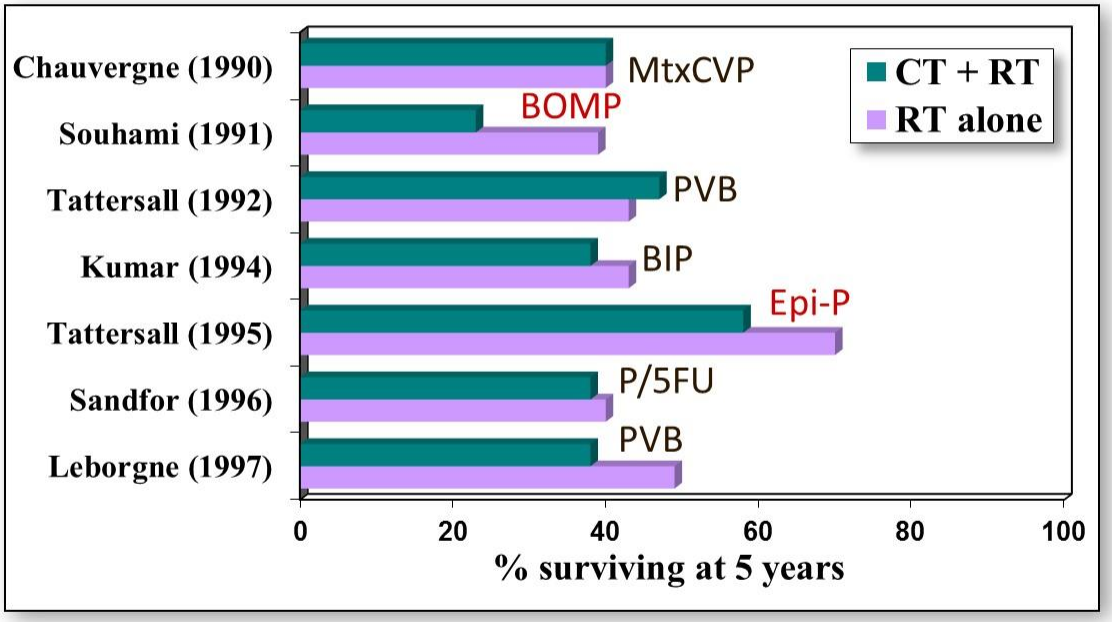

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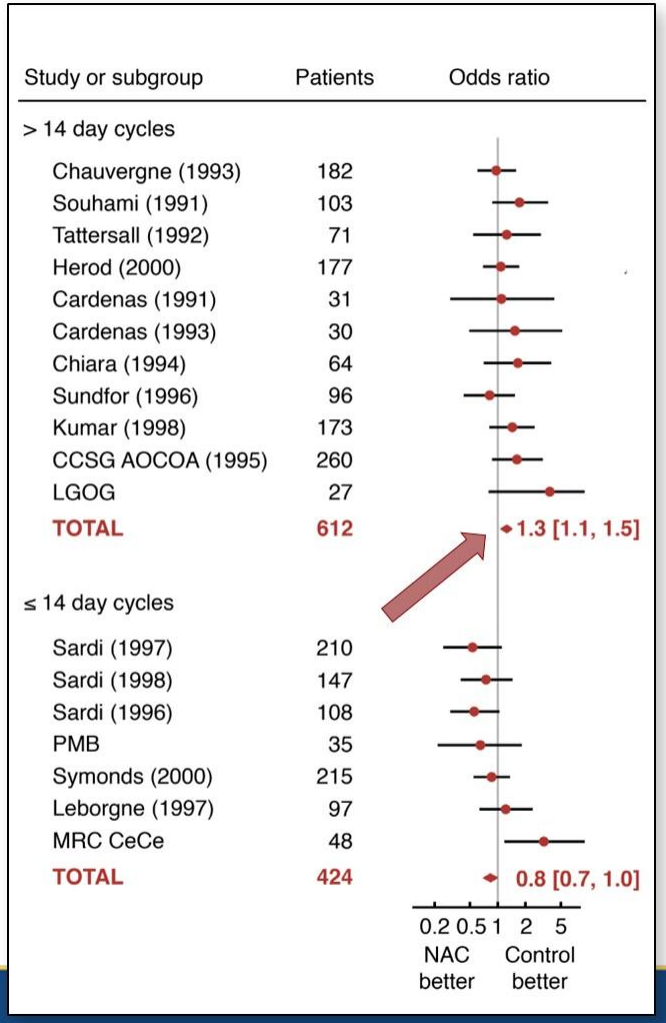
  - No evidence of improved OS
- 2004: Cochrane meta-analysis of neoadjuvant CT before definitive RT
  - Possible slight improvement with short cycles
  - Poorer outcomes after more prolonged neoadjuvant CT



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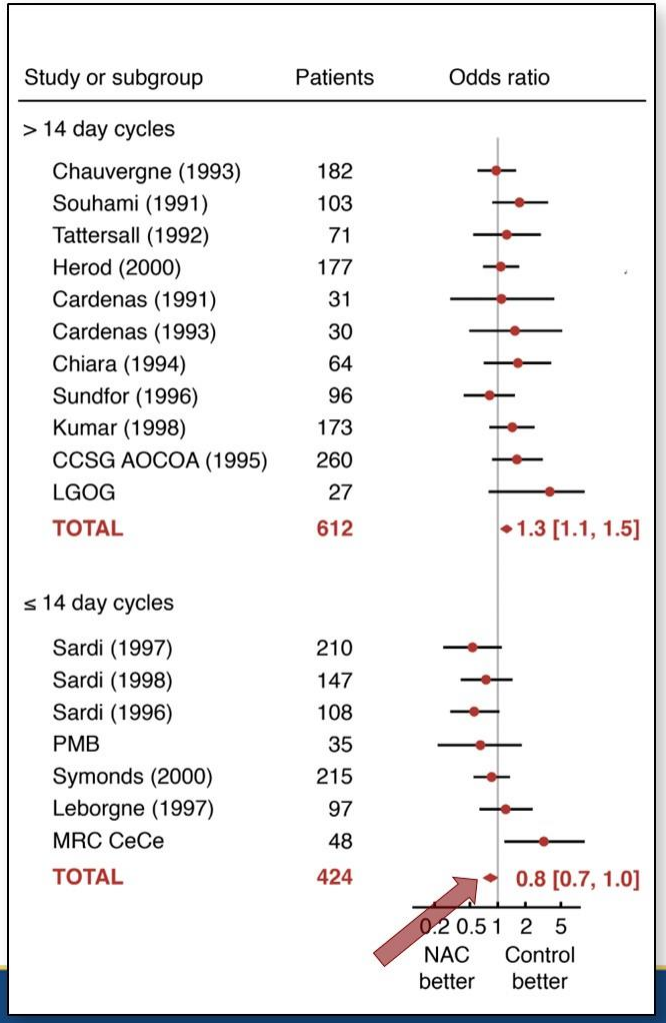

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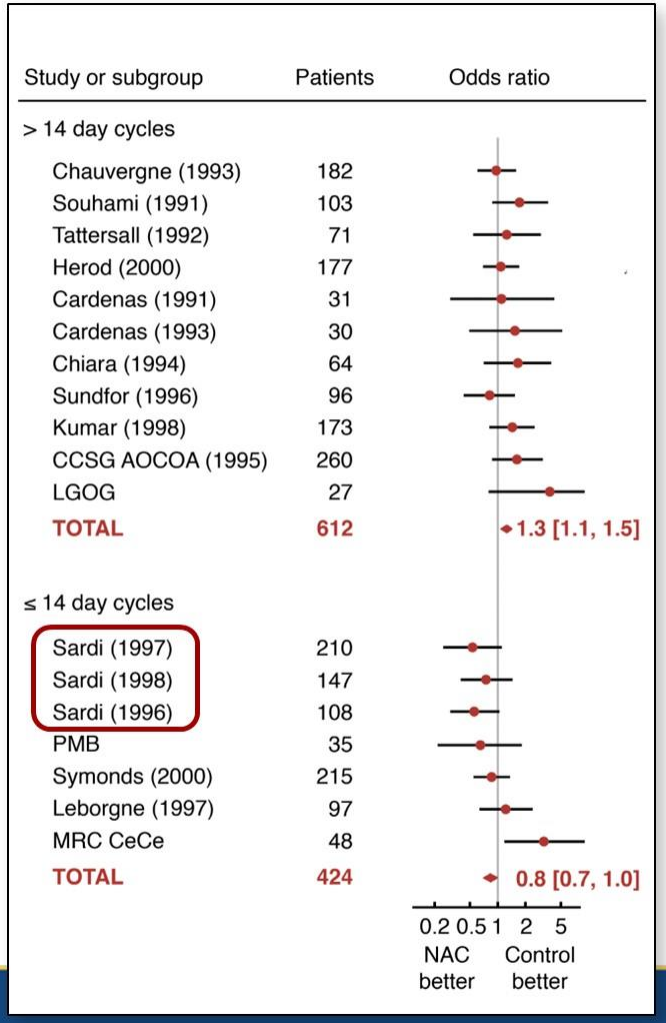
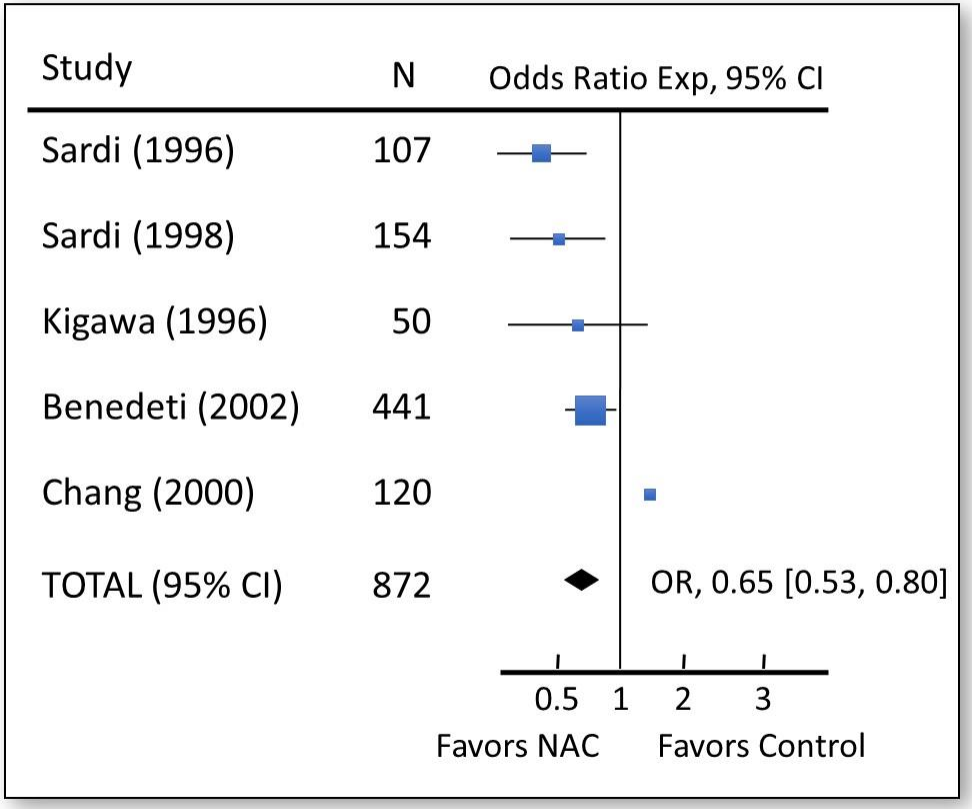


Neoadjuvant chemotherapy before surgery vs definitive RT for locally advanced disease (Cochran meta-analysis, 2004)

- OS improved with NAC
- Critiques:
  - GOG-188 not included (negative trial)
  - Most gave postop RT in NAC/hyst arm
  - Definitive RT often suboptimal
    - Low dose, protracted (often >10 wks)



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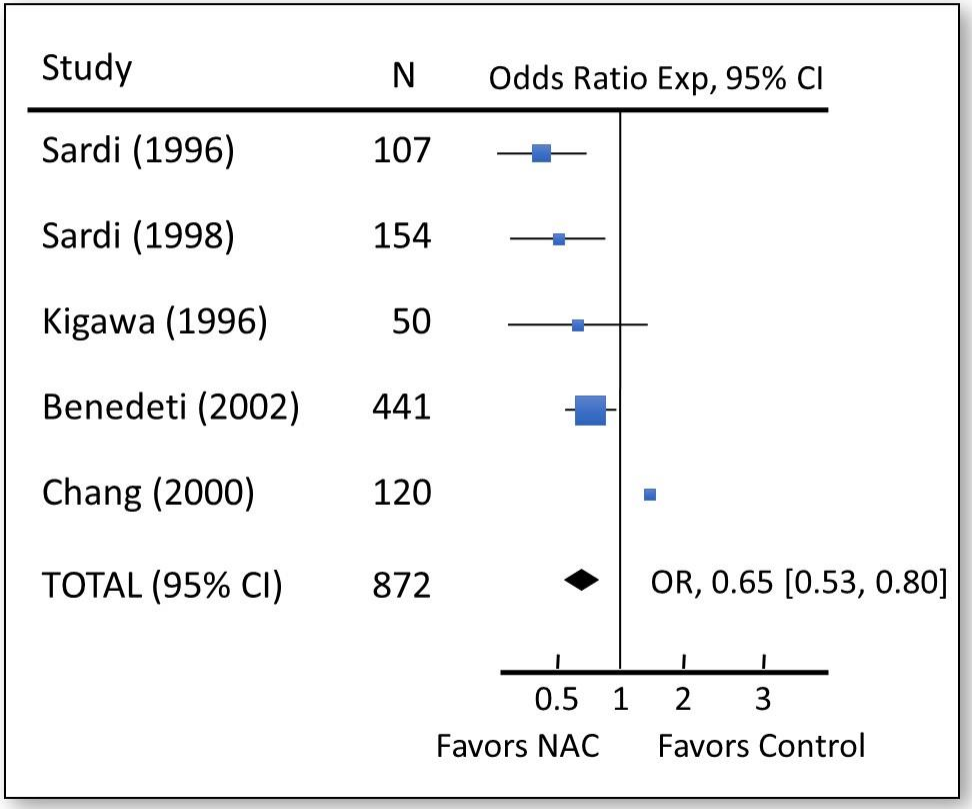
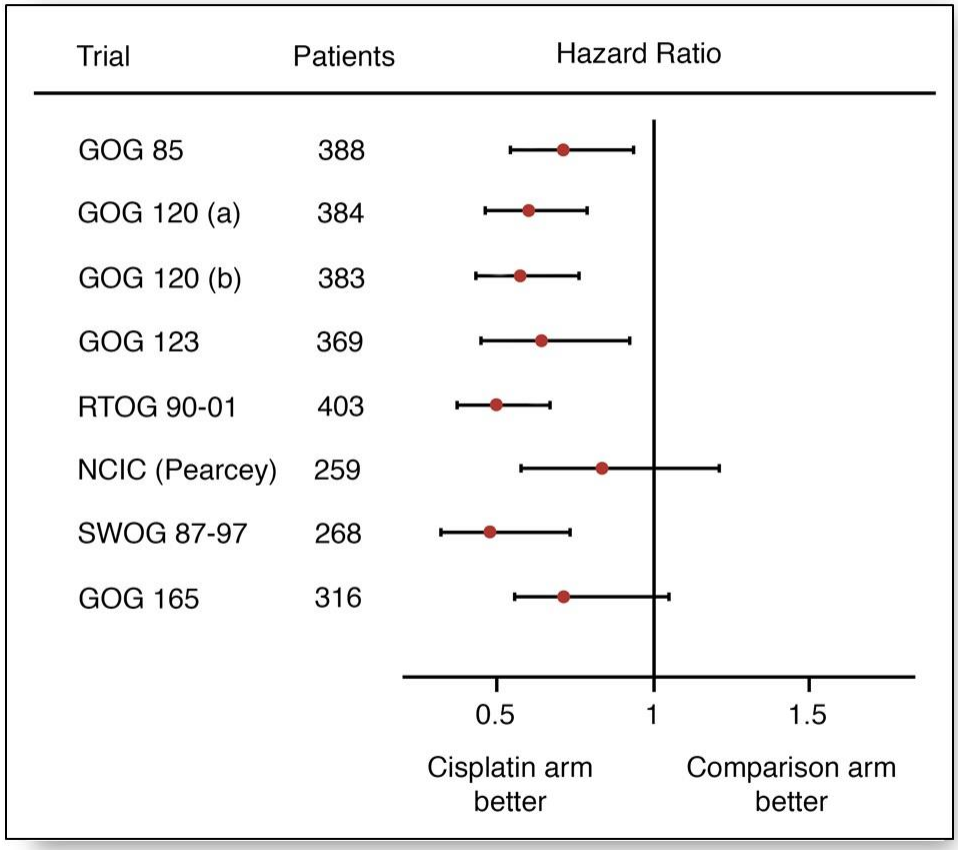
  - **Control was RT only (no CT)**



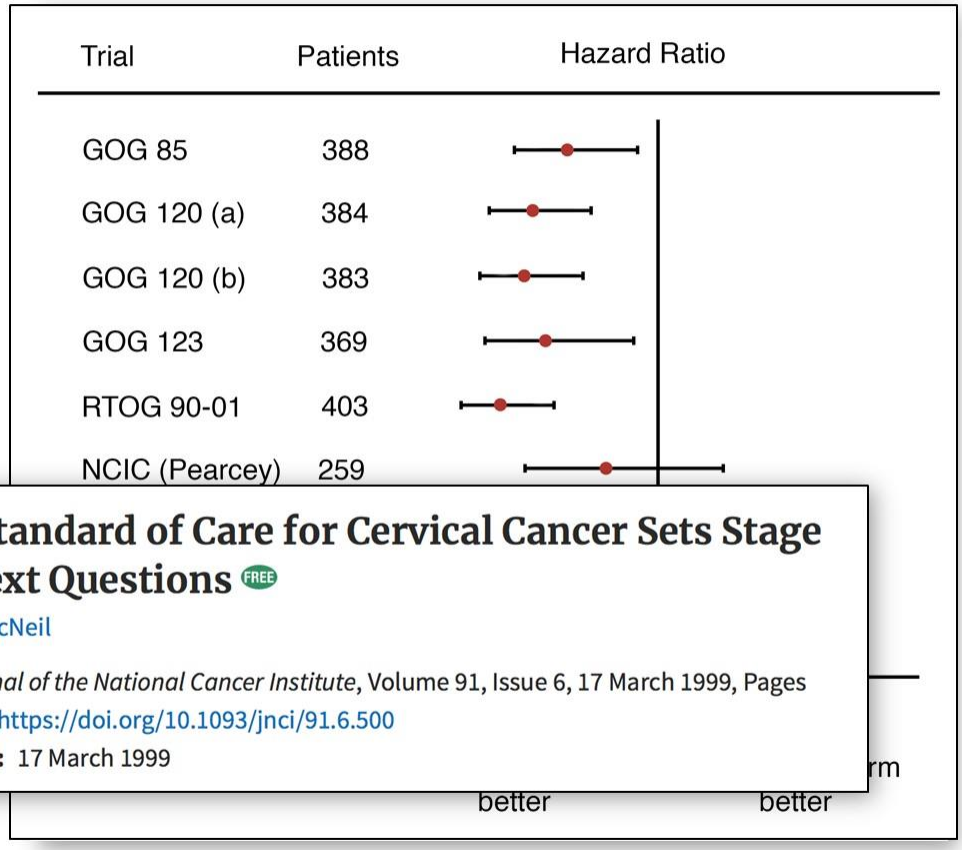
Then came the chemoradiation trials

- 1999-2000: 5/6 trials of cisplatin CT-RT are positive



Then came the chemoradiation trials

- 1999-2000: 5/6 trials of cisplatin CT-RT are positive
  - ➢ New standard of care



New Standard of Care for Cervical Cancer Sets Stage For Next Questions FREE

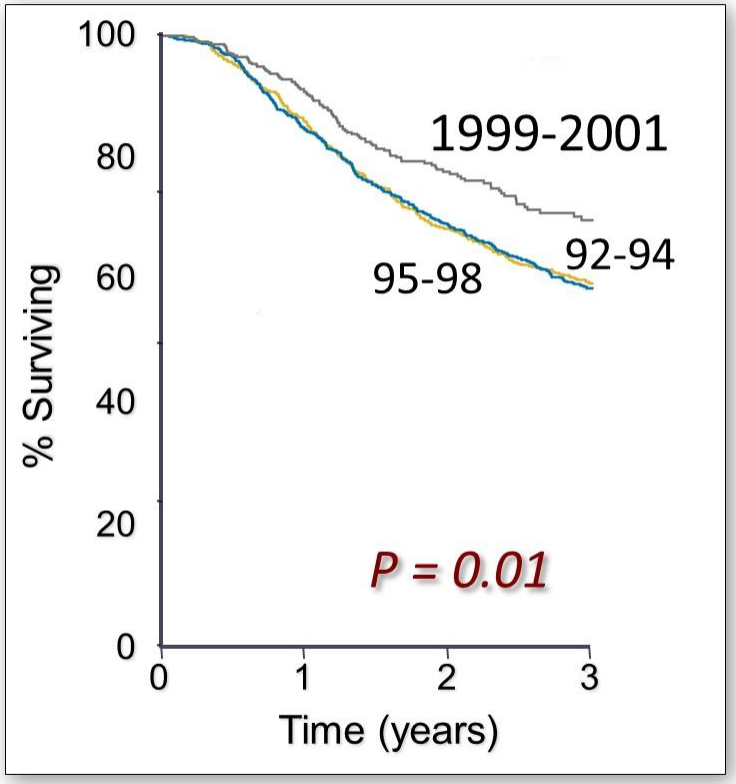
Caroline McNeil

JNCI: Journal of the National Cancer Institute, Volume 91, Issue 6, 17 March 1999, Pages 500a–501, https://doi.org/10.1093/jnci/91.6.500

Published: 17 March 1999

Chemo-radiation for cervical cancer

- 1999-2000: 5/6 trials of cisplatin CT-RT are positive
  - ➢ New standard of care
- 2007: Canadian epidemiologic study shows survival improved

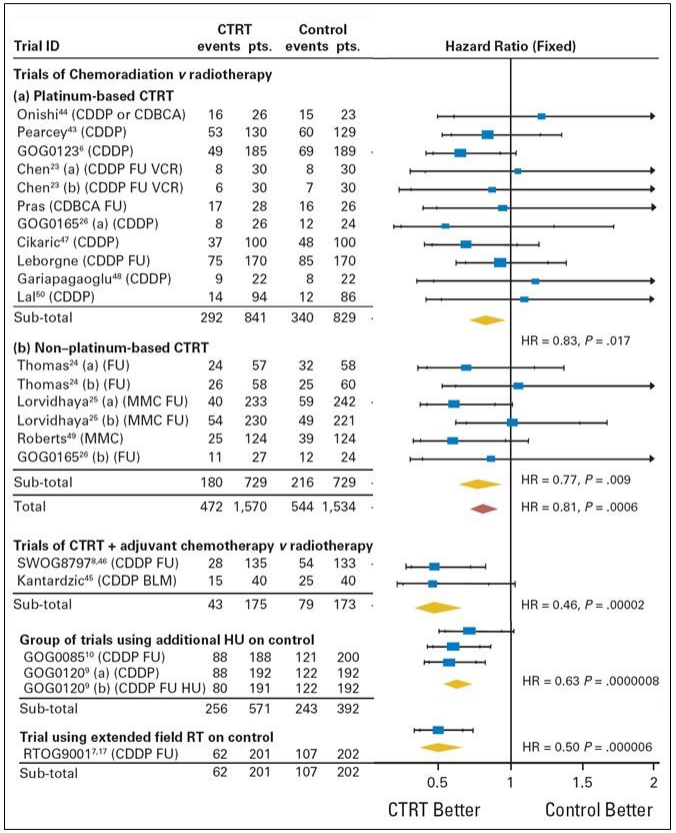


Pearcey et al. J Clin Oncol 25:2383, 2007

Meta-analysis using individual patient data from randomized trials

Chemoradiotherapy for Cervical cancer Meta-analysis Collaboration (CCCMAC); J Clin Oncol 26:5802, 2009

- 1999-2000: 5/6 trials of cisplatin CT-RT are positive
  - ➢ New standard of care
- 2007: Canadian epidemiologic study shows survival improved
- 2009: Confirmatory meta-analysis



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Trial Design

Cervical carcinoma of squamous or adeno(squamous) cell type

FIGO stage Ib2, IIa >4cm, or IIb

R

Arm 1:
NACT + Sy

Neoadjuvant cisplatin-based chemotherapy (≥225 mg/m²) followed by radical hysterectomy

N=314

Arm 2:
CTRTx

Concomitant radiation and chemotherapy 45-50 Gy plus boost + weekly ≥40mg/m² cisplatin

N=312

\+

N=626

Endpoints:

- Primary: overall survival (OS) at 5 years
- Secondary: PFS, toxicity & QoL

Stratification:

- Age (<50 vs >50), Cell type, FIGO stage (1994), and Institution

Statistics:
OS at 5 years in the CTRTx arm assumed 67%. To detect a 10% difference with a 2-sided α of 5% and power of 80% a total sample size of 625 patients with 5 years of follow-up is needed.

Quality Assurance Program:
A quality assurance project was implemented to check the accuracy of data collection and investigate protocol adherence in the different treatment modalities.

Protocol Treatment

NACT+Sy: Neoadjuvant cisplatin-based chemotherapy + radical hysterectomy.

- Chemo: Planned total cisplatin dose is **at least 225 mg/m²** (equivalent of ≥25 mg/m² per week).
- Surgery: Radical hysterectomy within **6 weeks** after last chemotherapy administration.

Adjuvant (chemo)radiotherapy is recommended in case of positive lymph nodes or tumor invasion into the parametria or < 5mm from the resection borders.

CTRTx: **Concomitant radiation and chemotherapy**.

- RTx: External radiotherapy at **45-50 Gy** is given to the pelvis combined with external **boost** or **brachytherapy**. Minimal total dose is 75 Gy EQD2 to point A or 80 Gy to high risk PTV) within 50 days. Radiotherapy should start within 8 hours after chemo administration.
- Chemo: Concomitant chemotherapy with an initial **dose ≥ 40 mg/m² cisplatin** will be administered weekly during radiotherapy. Planned total cisplatin dose is **200-240 mg/m²**.

Adjuvant hysterectomy is allowed in case of histologically proven residual tumor.

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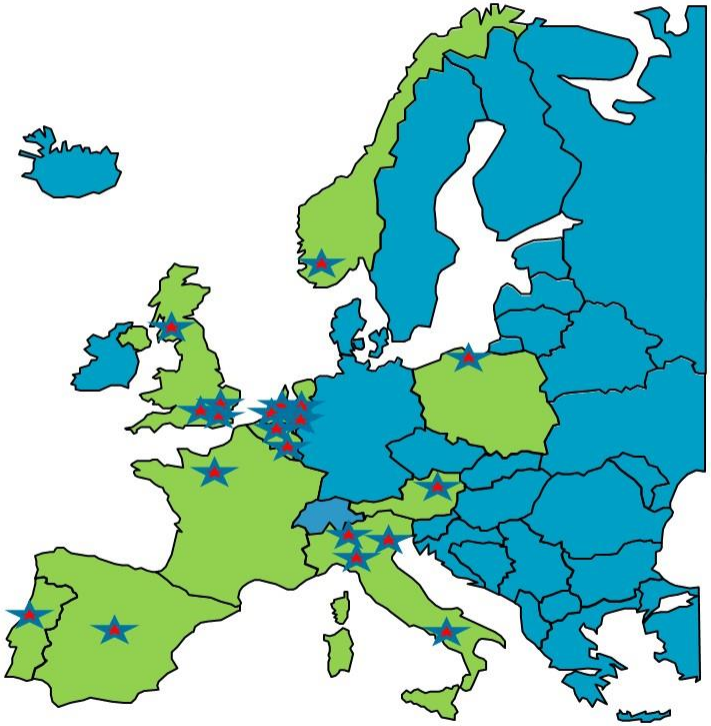
EORTC 55994 countries activated



25 EORTC Gynecological Cancer Group institutions from 10 countries:

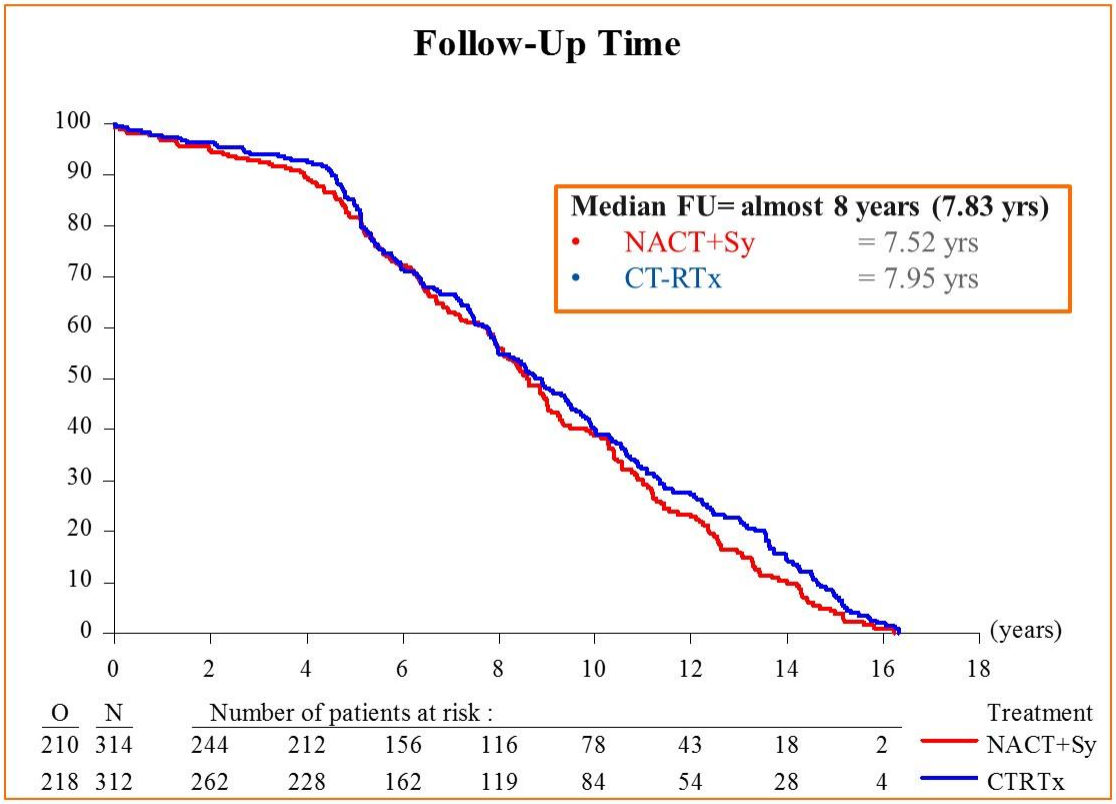
- Belgium
- Netherlands
- Italy
- Poland
- Spain
- Portugal
- France
- UK
- Austria
- Norway

<u>Enrolment Period:</u>

626 patients between May 2002 and Jan 2014

Accrual & follow-Up

Accrual / year	
N (%)	All patients (N=626)
Year of entry	
2002	21 (3.4)
2003	76 (12.1)
2004	56 (8.9)
2005	60 (9.6)
2006	65 (10.4)
2007	55 (8.8)
2008	72 (11.5)
2009	40 (6.4)
2010	56 (8.9)
2011	41 (6.5)
2012	31 (5.0)
2013	27 (4.3)
2014	26 (4.2)



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Baseline characteristics

	NACT + Sy (N=314)	CTRTx (N=312)
Median age, years	46	47
ECOG PS 0/1	88% / 12%	88% / 12%
FIGO Stage:		
Ib2	26%	28%
IIa > 4 cm	15%	15%
IIb	57%	57%
Type of cervical carcinoma		
squamous cell	85%	85%
adenocarcinoma	10%	11%
adenosquamous cell	5%	4%
BMI		
≤ 25 / 25-30 / > 30	38% / 27% / 23%	40% / 31% / 15%

3 FIGO III; 1 FIGO IV;
2 FIGO stage unknown

1 clear cell; 2 unknown

BMI / BSA not available if no chemo started

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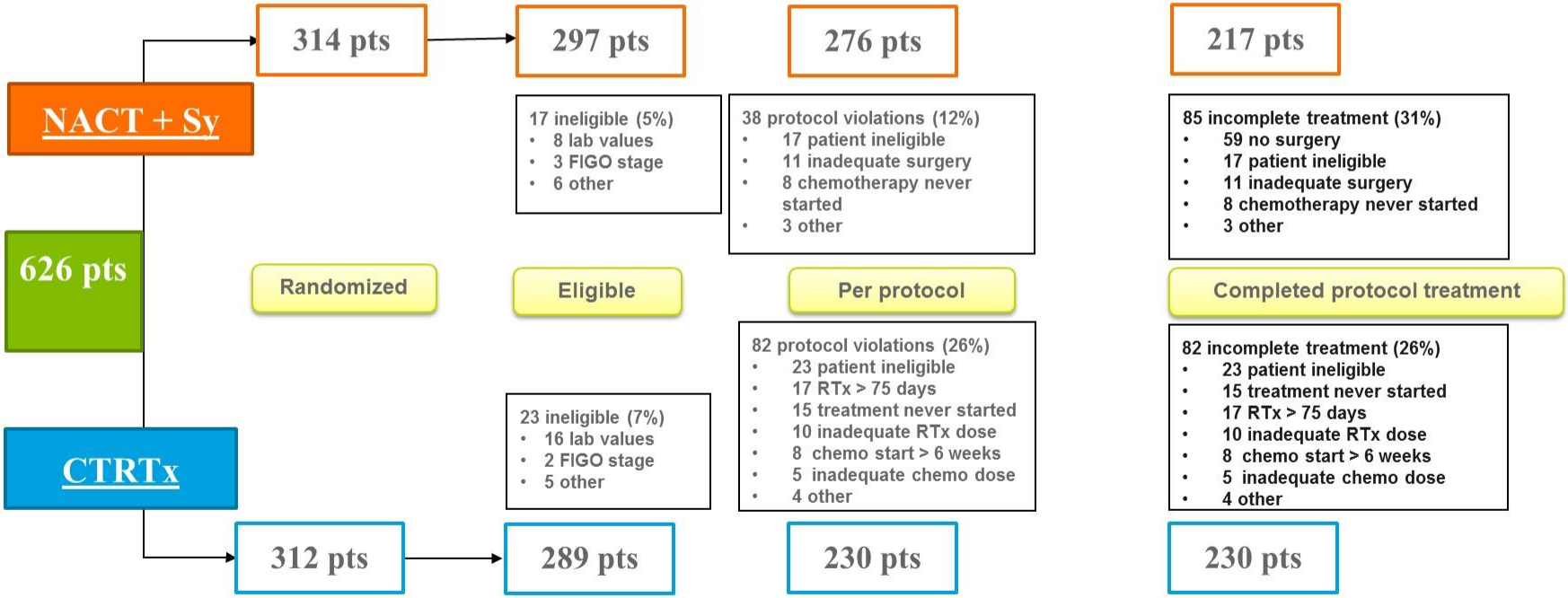
Study Flowchart



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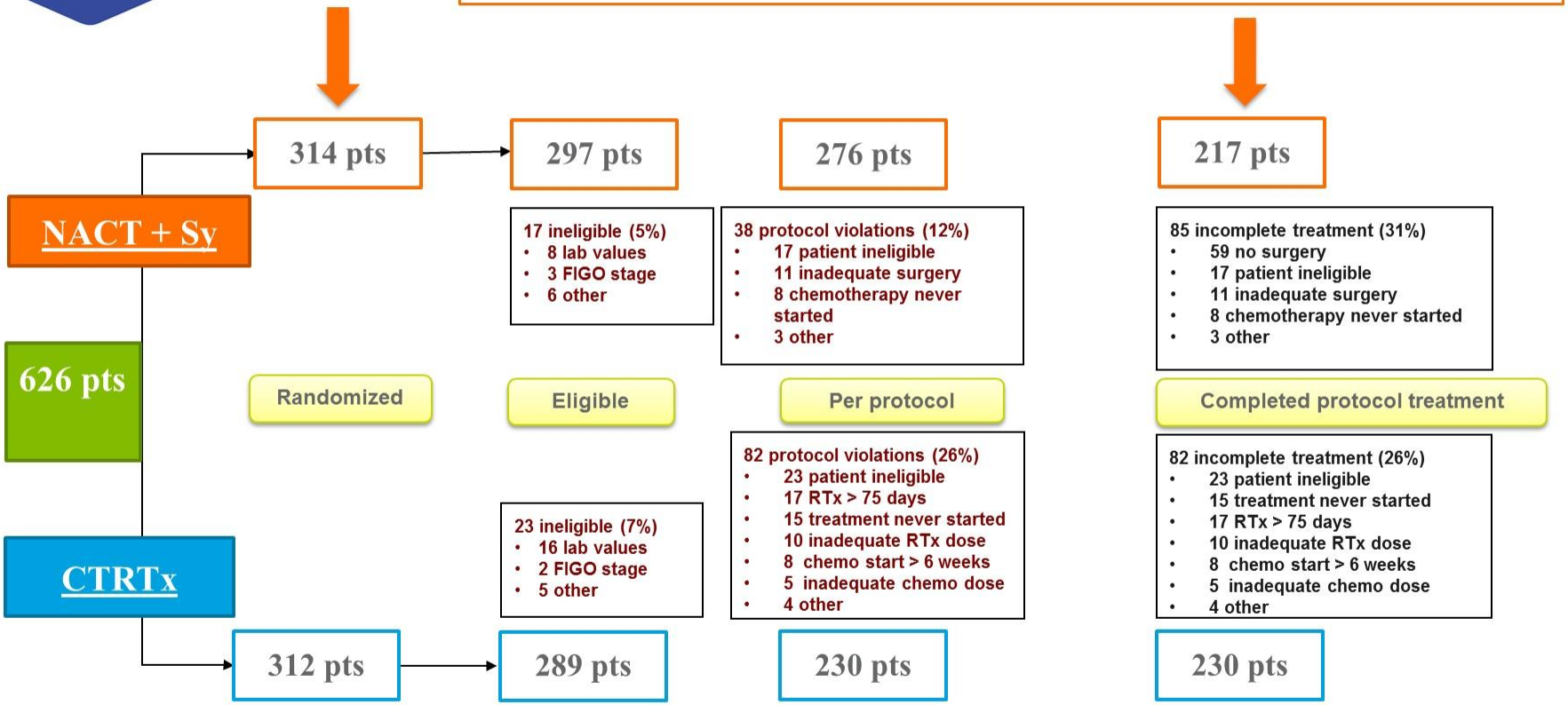

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Treatment compliance: NACT+Sy

- Of the 314 patients, 74 (24%) received no surgery.
- Main reasons:
  - Chemotherapy toxicity: 25 (34%)
  - Progression: 18 (24%)
  - Insufficient response: 12 (16%)
  - Patient refusal: 10 (14%)
  - Protocol violation 6 (8%)
  - Other 3 (4%)

- Of the 314 patients, 240 (76%) received surgery.
- Type of surgery was:
  - Piver-Rutledge III: 86%
  - Piver-Rutledge IV: 4%
  - Piver-Rutledge V: 6%
  - Other: 5%
- Chemotherapy:
  - Cisplatin mono: 46%
  - Cisplatin + PT: 20%
  - Cisplatin + PT + Ifos: 19%
  - Cisplatin + Other: 15%

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Treatment compliance: CTRTx

- Of the 312 patients, 20 (6%) received no CTRT
- Main reasons:
  - Patient refusal: 11 (55%)
  - Protocol violation: 5 (25%)
  - Withdrawal of consent: 2(10%)
  - Physician decision: 2 (10%)

- Of the 312 patients, 292 (96%) received CTRT
- Median dose: 46 Gy (pelvic)
- External boost: 123 (42%)
- Brachy: 280 (97 %)
- Chemotherapy:
  - Cisplatin mono: 87%
  - Cisplatin + Taxol: 13%

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Pathological evaluation
NACT+Sy arm*

Response	N	%
Complete Response	54	23 %
Optimal Response	35	15 %
Suboptimal	124	52 %
Other	27	11 %

Complete *= no microscopic residual disease*
Optimal *= carcinoma in situ or stromal invasion < 3 mm*
Suboptimal *= neither complete nor optimal*
Other *= not assessable, missing, unknown*

*Pathological evaluation available for 240 patients who underwent protocol surgery

	N	%
Parametrial invasion		
No	180	75 %
Yes	49	20 %
Unknown	11	5 %
Vascular invasion		
No	135	56 %
Yes	57	24 %
Unknown	48	20 %
Surgical margins		
Negative	201	84 %
Positive	32	13 %
Unknown	7	3 %
Pelvic Nodes		
Negative	170	71%
Positive	66	27%
Unknown	4	2%

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Pathological response to NACT+Sy

	Complete	Optimal	Sub-opt	Other	
Cisplatin alone	19%	13%	52%	16%	N=119
Cisplatin + Paclitaxel (+/- Other)	28%	17%	52%	3%	N=94
Cisplatin + Other	22%	15%	48%	15%	N=27
	N=55	N=35	N=124	N=26	N=240

32%

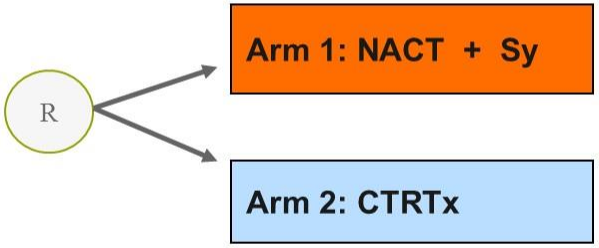
45%

37%

Cisplatin alone has the lowest response rate with 32% (38/119) reporting either complete or optimal response, however this difference is not statistically significant

Adverse event collection

Treatment period:	**Follow-up period (> 8 weeks after EOT):**
- Each cycle: CTC v2 - After surgery: Surgical complications (CTC v2) - 8 wks after EOT: CTC v2 + Chassagne	(until PD or new anti-cancer treatment): - Year 1: 3-monthly Chassagne - Year 2-5: 6-monthly Chassagne



Follow-up (min. 5 years)

Treatment period:	**Follow-up period (> 8 weeks after EOT):**
- Each cycle: CTC v2 - 8 wks after EOT: CTC v2 + Chassagne	(until PD or new anti-cancer treatment): - Year 1: 3-monthly Chassagne - Year 2-5: 6-monthly Chassagne

Treatment period: CTC grade 3/4

N (%)	Treatment		Total (N=591)
	NACT+Sy (N=299)	CTRTx (N=292)	
	122 (40.8%)	**66 (22.6%)**	**188 (31.8%)**
Gastrointestinal	**34 (11.4)**	**20 (6.8)**	**54 (9.1)**
Blood/Bone Marrow	**36 (12.0)**	**15 (5.1)**	**51 (8.6)**
Infection	25 (8.4)	8 (2.7)	33 (5.6)
Cardiovasular	10 (3.3)	11 (3.8)	21 (3.6)
Renal/genitourinary	16 (5.4)	4 (1.4)	20 (3.4)
Hemorrhage	15 (5.0)	2 (0.7)	17 (2.9)
Constitutional	7 (2.3)	8 (2.7)	15 (2.5)
Dermatology	14 (4.7)	1 (0.3)	15 (2.5)
Metabolic	8 (2.7)	5 (1.7)	13 (2.2)
Neurology	9 (3.0)	2 (0.7)	11 (1.9)
Pain	3 (1.0)	7 (2.4)	10 (1.7)

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Follow-up period: Chassagne score gr 3/4

N (%)	Treatment		Total (N=583)
	NACT+Sy (N=293)	CTRTx (N=290)	
	44 (15.0%)	**60 (20.7%)**	**104 (17.8%)**
Small bowel	**5 (1.7)**	**21 (7.2)**	**26 (4.5)**
Bladder and urethra	**13 (4.4)**	**11 (3.8)**	**24 (4.1)**
Ureter	**12 (4.1)**	**11 (3.8)**	**23 (3.9)**
Uterus-vagina-vulva	**6 (2.0)**	**14 (4.8)**	**20 (3.4)**
Colon (non sigmoid)	5 (1.7)	8 (2.8)	13 (2.2)
Pelvic soft tissues	6 (2.0)	5 (1.7)	11 (1.9)
Rectum	4 (1.4)	5 (1.7)	9 (1.5)
Sigmoid colon	1 (0.3)	5 (1.7)	6 (1.0)
Bone	4 (1.4)	2 (0.7)	6 (1.0)
Peripheral nerves	3 (1.0)	3 (1.0)	6 (1.0)
Hemopoietic tissue	2 (0.7)	2 (0.7)	4 (0.7)
Non specific abdominal	1 (0.3)	1 (0.3)	2 (0.3)
Vesicular	1 (0.3)	1 (0.3)	2 (0.3)
Stomach and duodenum	0 (0.0)	1 (0.3)	1 (0.2)
Cutaneous	0 (0.0)	1 (0.3)	1 (0.2)

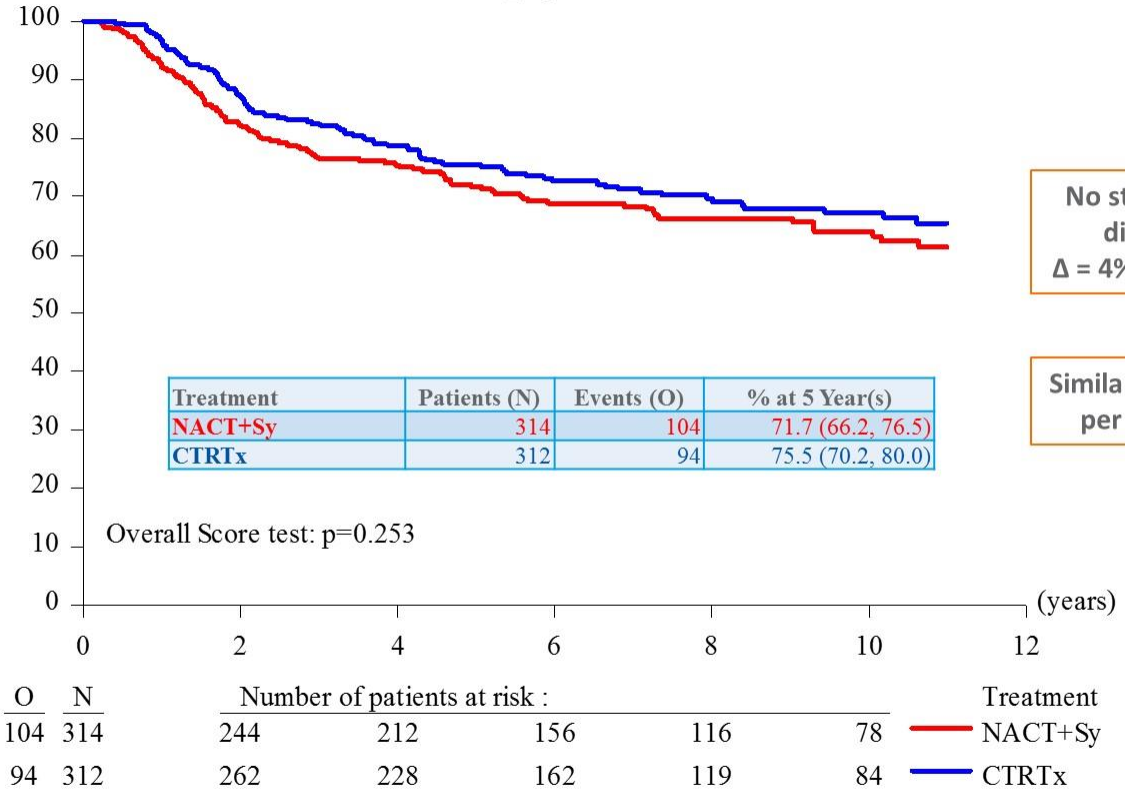
Two patients in CTRTx arm died due to complications:
- Chronic small bowel obstruction + malabsorption eventually death
- Infection following surgery for rectal stricture.

Adjuvant treatment after normal protocol completion: 27% and 8%

	NACT+Sy –arm (222)		CTRTx-arm (257)	
	N	%	N	%
No adjuvant treatment	160	73	237	92
Radiotherapy	32	14		
Surgery			10	4
Combination	28	13	10	4

Overall survival

ITT population



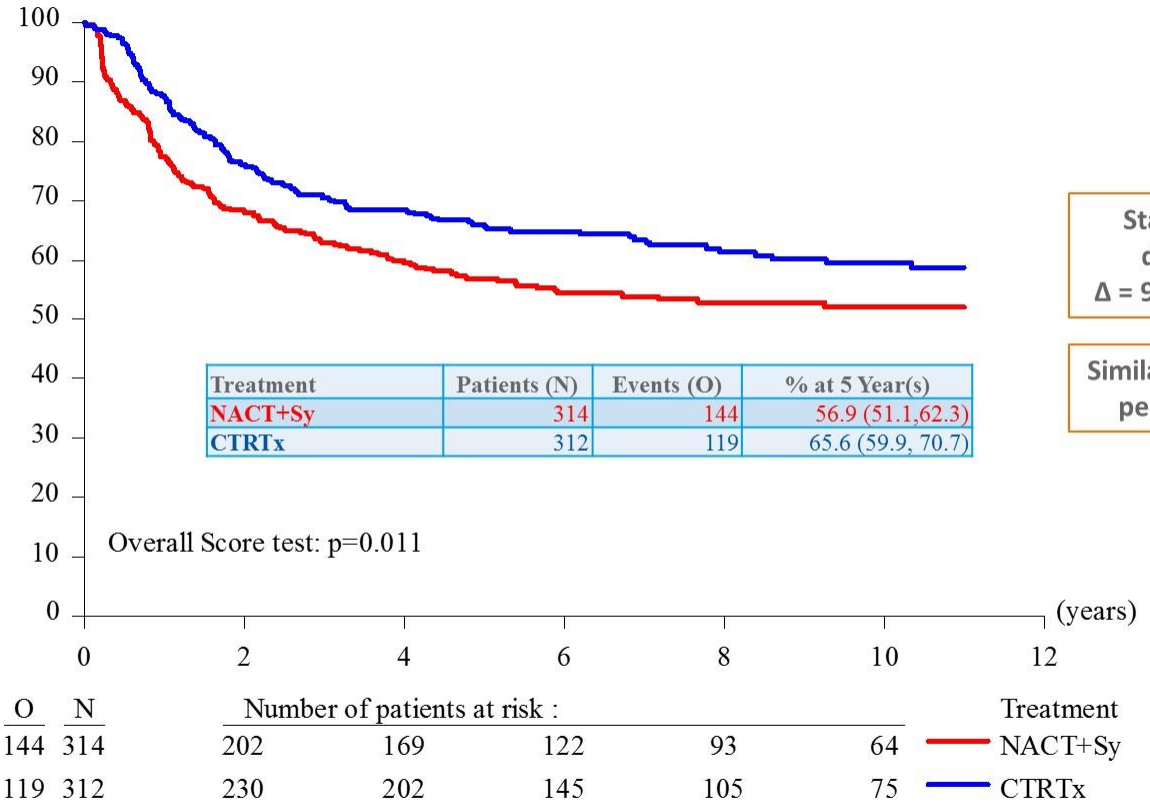
Treatment	Patients (N)	Events (O)	% at 5 Year(s)
NACT+Sy	314	104	71.7 (66.2, 76.5)
CTRTx	312	94	75.5 (70.2, 80.0)

No statistically significant difference at year 5
Δ = 4% (-3% - 12%); p=0.297

Similar results in eligible and per protocol population

PFS

ITT population



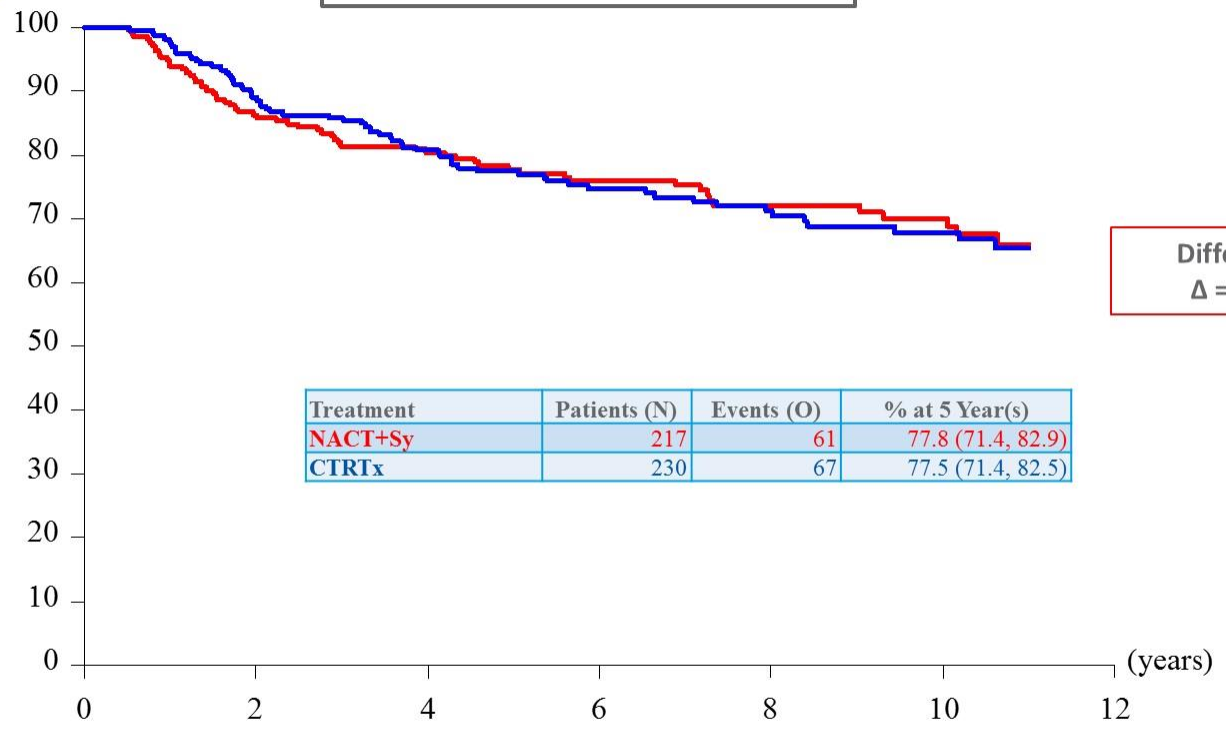
Treatment	Patients (N)	Events (O)	% at 5 Year(s)
NACT+Sy	314	144	56.9 (51.1,62.3)
CTRTx	312	119	65.6 (59.9, 70.7)

Statistically significant difference at year 5
Δ = 9% (2% - 18%); p=0.021

Similar results in eligible and per protocol population

Overall survival

On patients who completed treatment



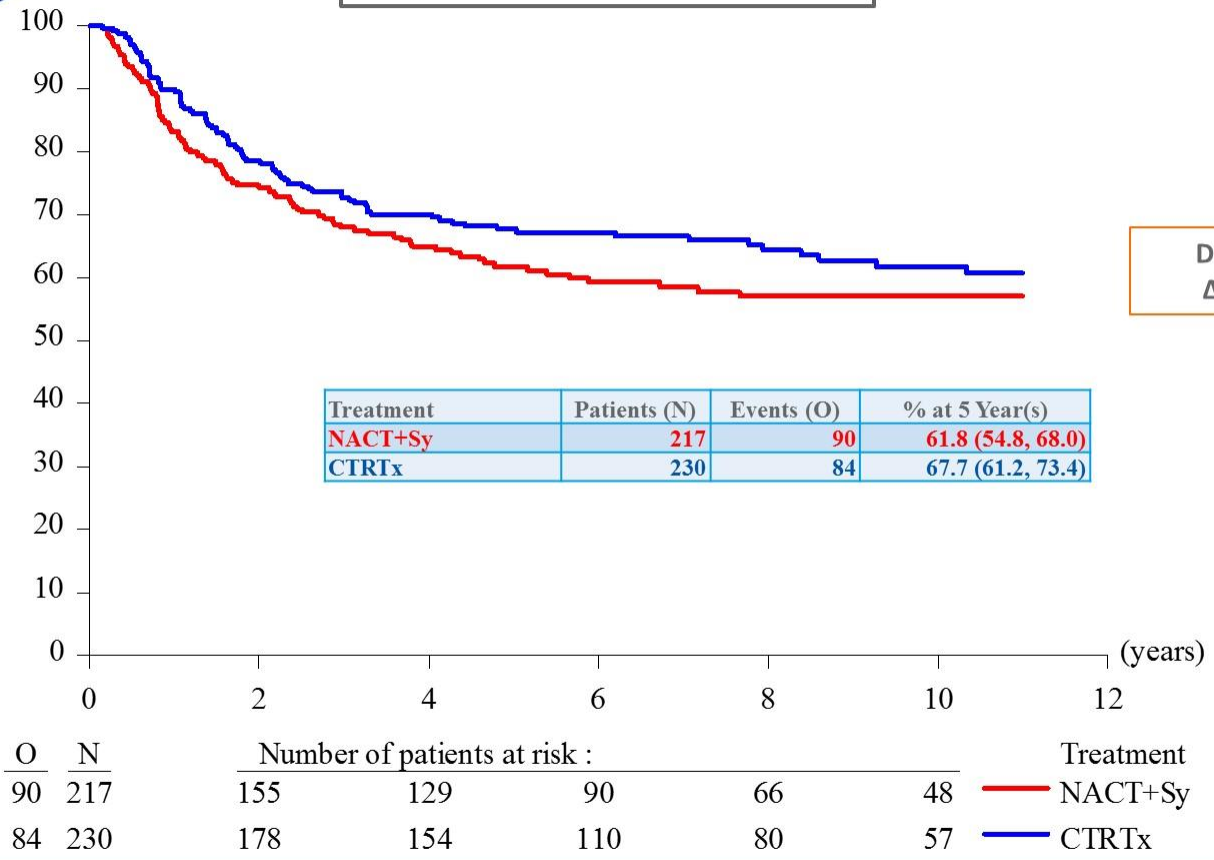
Treatment	Patients (N)	Events (O)	% at 5 Year(s)
NACT+Sy	217	61	77.8 (71.4, 82.9)
CTRTx	230	67	77.5 (71.4, 82.5)

Difference at year 5
Δ = 0% (-9% - 9%)

O	N	Number of patients at risk :					Treatment
61	217	179	158	117	84	58	NACT+Sy
67	230	201	174	121	89	63	CTRTx

PFS

On patients who completed treatment



Treatment	Patients (N)	Events (O)	% at 5 Year(s)
NACT+Sy	217	90	61.8 (54.8, 68.0)
CTRTx	230	84	67.7 (61.2, 73.4)

Difference at year 5
Δ = 7% (-17% - 3%)

p=0.154

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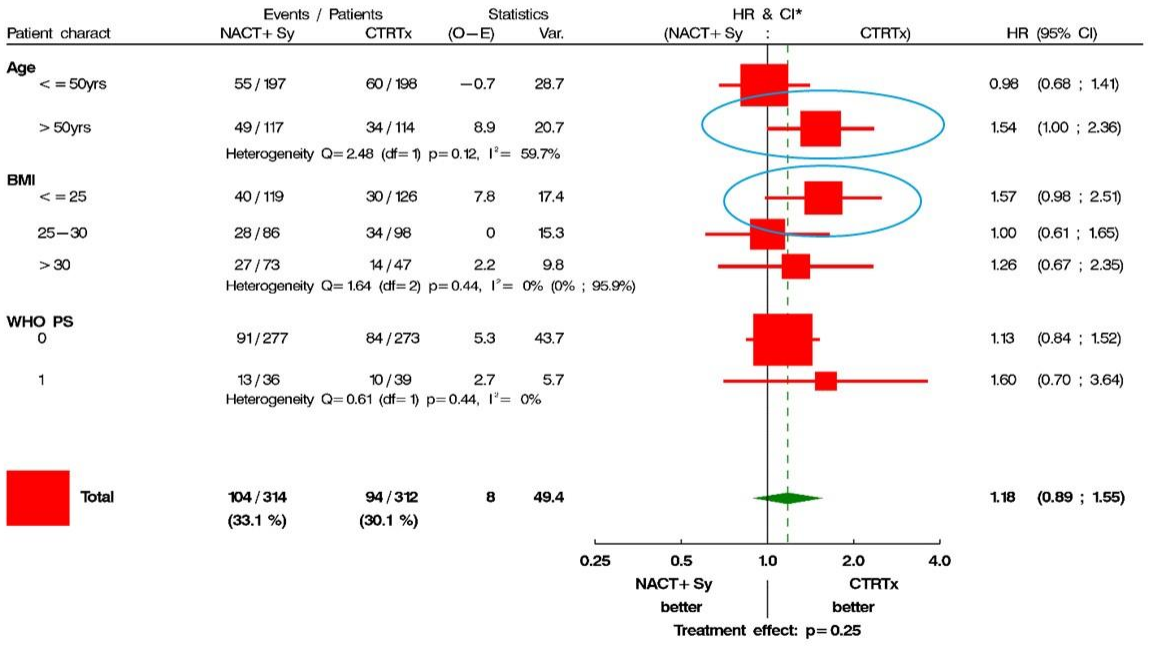
Overall Survival

Subgroups with more CTRTx benefit:

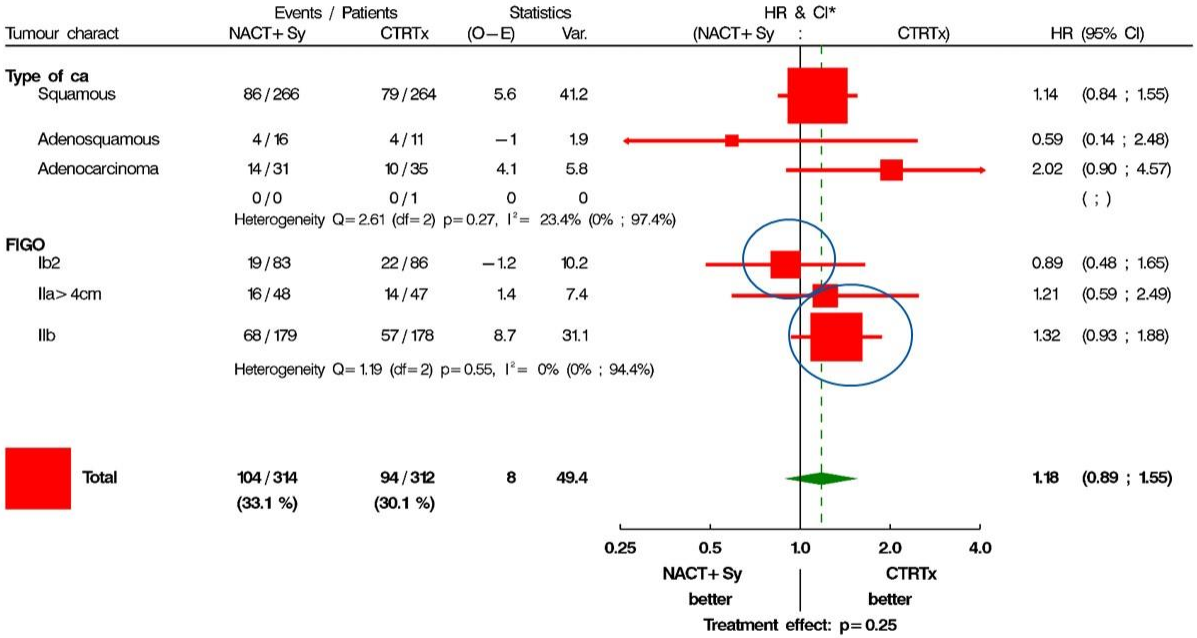
- age > 50
- low BMI



*95% CI everywhere

Overall Survival

	Pts (N)	Events (O)	OS at 5yr (%)	Δ OS at 5yr (%)
FIGO Ib2				
NACT+Sy	83	19	82%	-6%
CTRTx	86	16	76%	
FIGO IIa>4cm				
NACT+Sy	48	16	69%	+6%
CTRTx	47	14	75%	
FIGO IIb				
NACT+Sy	179	68	68%	+8%
CTRTx	178	57	76%	



*95% CI everywhere

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EORTC-55994 vs Gupta trial
results

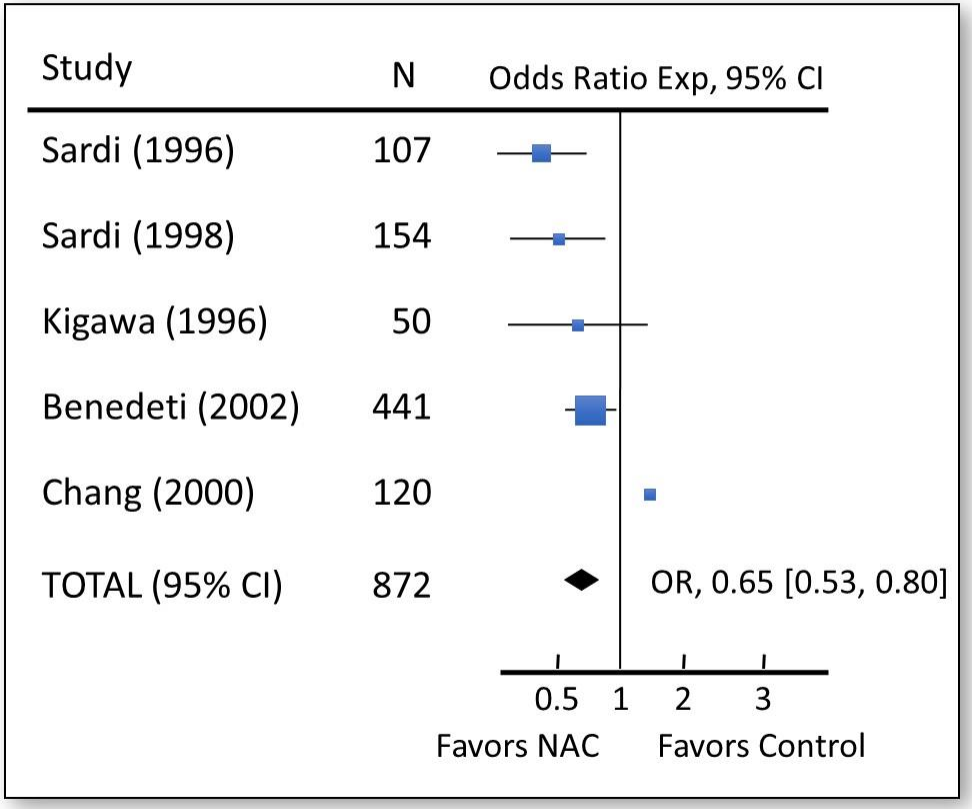
	EORTC 55994	GUPTA
5 year DFS	HR=0.74	HR=0.72
NACT+Sy	58.8%	69.3%
CTRTx	67.1%	76.7%
5 year OS	HR=0.88	HR=0.98
NACT+Sy	72.5%	+/- 75%
CTRTx	75.5%	+/- 75%

Similar results in OS and PFS

Neoadjuvant chemotherapy before surgery vs definitive RT for locally advanced disease (Cochran meta-analysis, 2004)

- OS improved with NAC
- Critiques:
  - GOG-188 not included (negative trial)
  - Most gave postop RT in NAC/hyst arm
  - Definitive RT often suboptimal
    - Low dose, protracted (often >10 wks)
  - Control was RT only (not chemoRT)

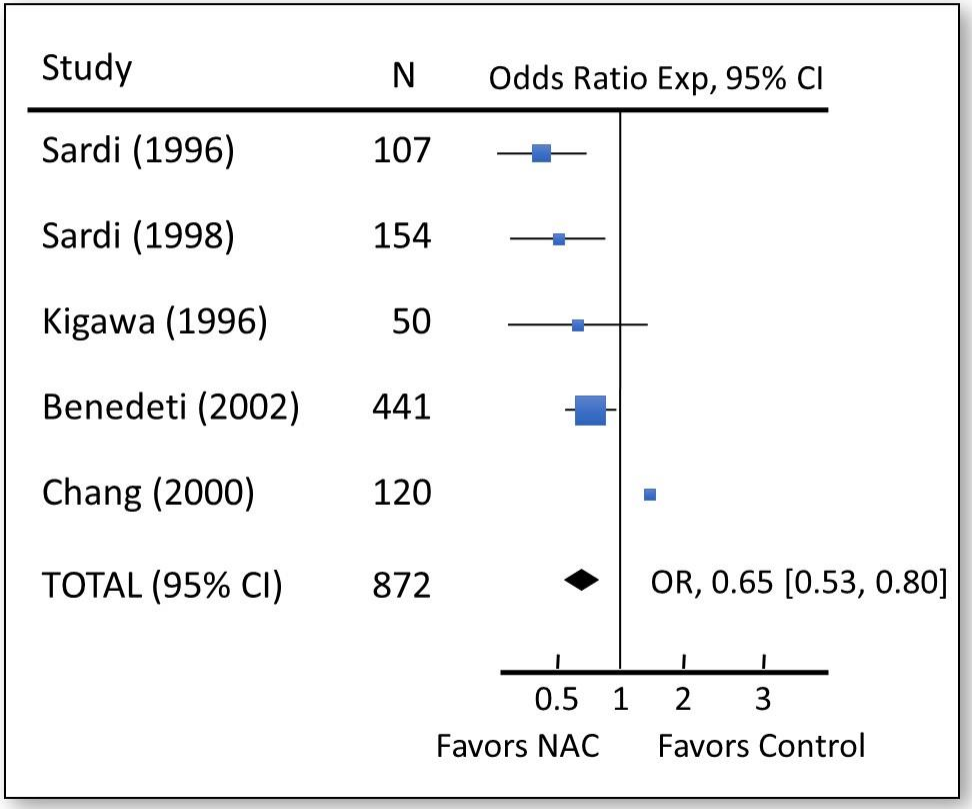
Results could not be generalized to settings where optimized ChemoRT was available.



Neoadjuvant chemotherapy before surgery vs definitive RT for locally advanced disease (Cochran meta-analysis, 2004)

- OS improved with NAC
- Critiques:
  - GOG-188 not included (negative trial)
  - Most gave postop RT in NAC/hyst arm
  - Definitive RT often suboptimal
    - Low dose, protracted (often >10 wks)
  - Control was RT only (not chemoRT)

How would NACT before surgery compare with chemoradiation?



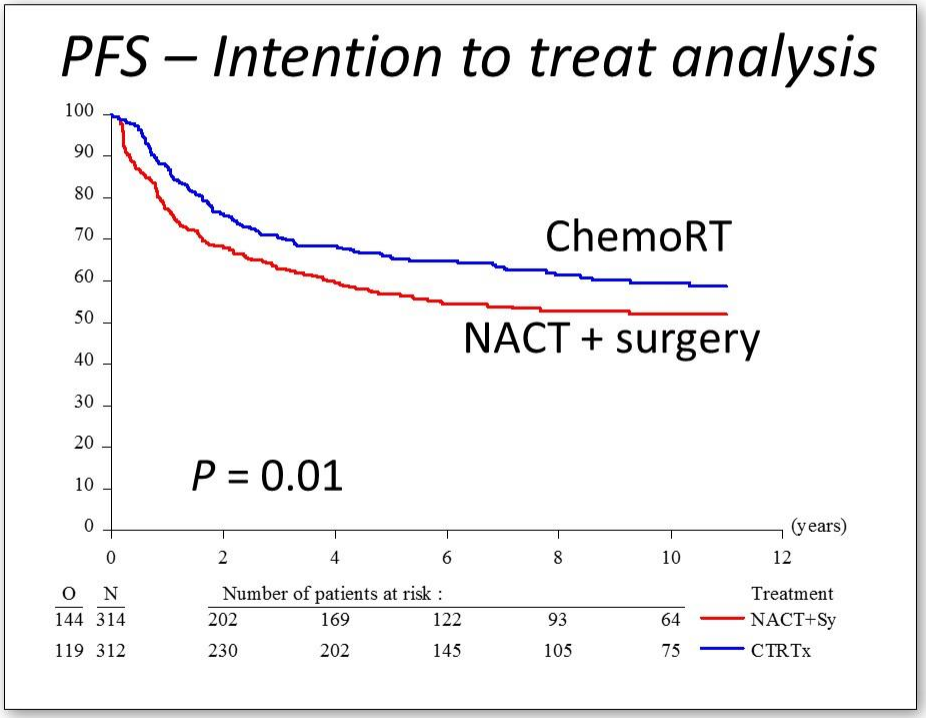
Neoadjuvant chemotherapy before surgery vs chemo-RT for locally advanced disease—a treatment still searching for a role

Kenter et al. ASCO 2019

Why was NAC not more successful?

A good response rate is not enough-

- 24% were unable to undergo surgery
- 10% had P-R type IV or V hyst
- Many still required RT
  - 13% margin +; 27% positive nodes; ?salvage



Neoadjuvant chemotherapy before surgery vs chemo-RT for locally advanced disease—a treatment still searching for a role

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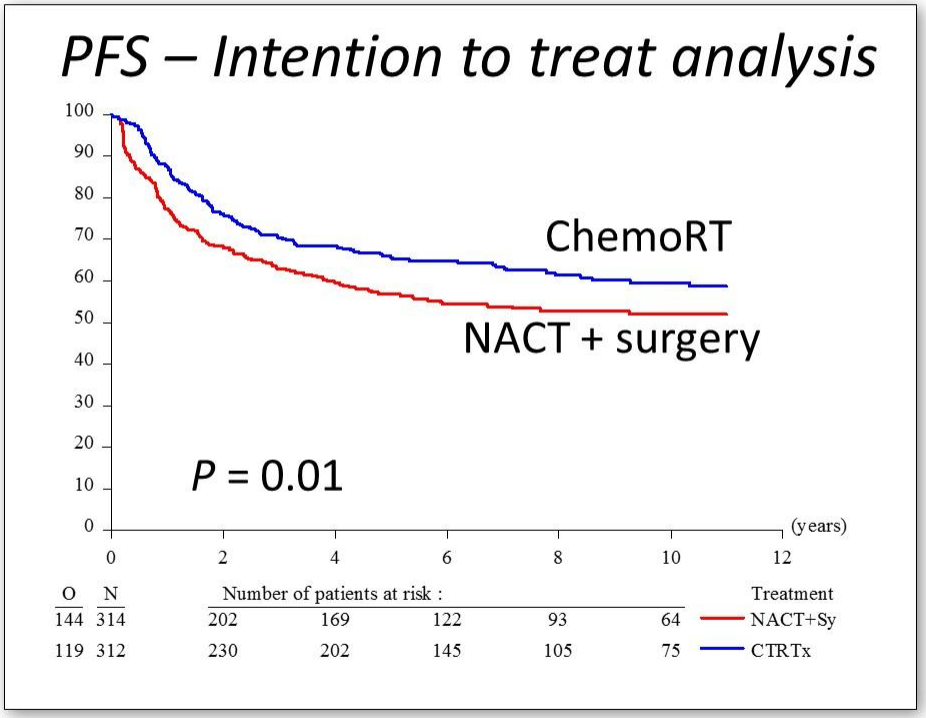
Other possible concerns—

- Chemo may obscure sites of residual disease that require RT
- NAC may compromise subsequent chemo-RT if required



Neoadjuvant chemotherapy before surgery vs chemo-RT for locally advanced disease—a treatment still searching for a role

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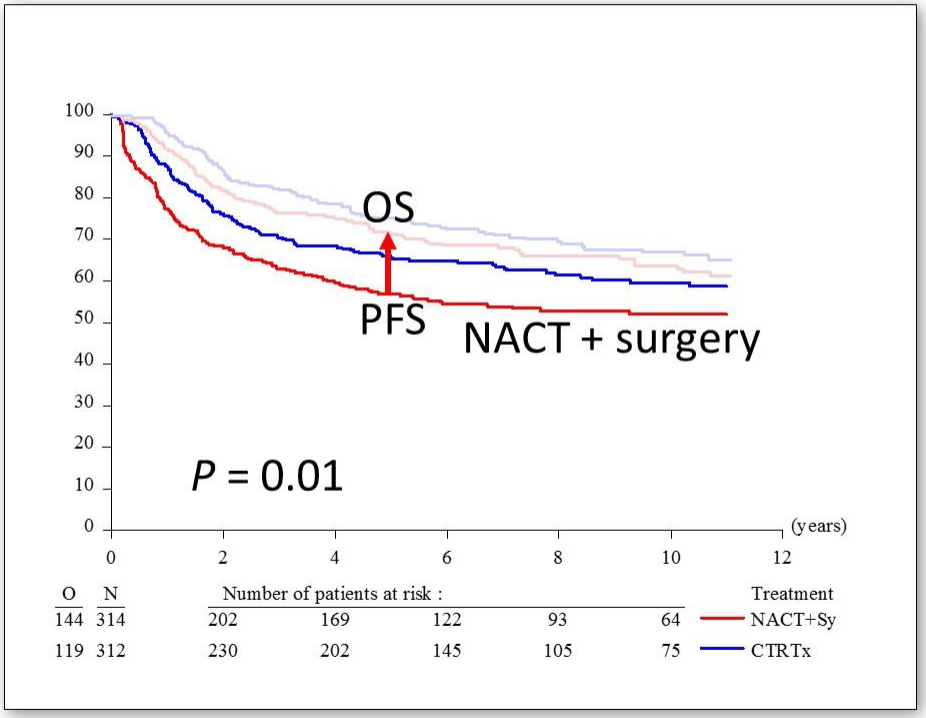
Question:

Why is the 5-year OS for NAC ~ 17 percentage points higher than PFS?

- Salvage?
- Missing survival events?




NACT+S
RT/CT

Summary and conclusion

RCT in 626 patients with cervical cancer stage Ib2-IIb

Median FU 8 years 198/626=32% death and 263= 42% events

OS 72% in NACT+Sy arm and 76% in CTRTx arm (*not ss*)

PFS 57% in NACT+Sy arm and 66% in CTRTx arm (*ss*)

Difference in PFS disappears for patients completing total treatment

Trend for better results in NACT+Sy arm for stage Ib2

Trend for better results in CTRTx arm 2 for stage IIb, BMI<25 and age> 50 yr

Trend for better results in NACT+Sy arm for combination chemo (CIS + T ?)

Short term gr 3 and 4 toxicity higher in NACT+Sy arm (41 vs 22%)

Long term toxicity higher in CTRTx arm (15 vs 21%)

55994 EORTC Study ASCO 2019 Presentation

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Investigators EORTC Gyneacological Cancer Group:

Austria: Schratter-Sehn A. **Belgium:** Altintas S, De Greve J, Goffin F, Kridelka F, Vergote I, Vermorken JB. **France:** Joly F. **Italy:** Colombo A, Colombo N, Donadello N, Ferrero A, Franchi M, Greggi S, Katsaros D, Landoni F, Zola P. **Netherlands:** Ansink A, Gaarenstroom K, Kenter G, Massuger L, Ottevanger N, van Baal WM, Van Der Velden J, Van Doorn H, Van Dorst E, Verheijen R. vd Steen E. **Norway:** Kristensen GB. **Poland:** Kobierska A, Kobierski J. **Portugal:** de Oliveira CF, Frutuoso C. **Spain:** Casado-Harraez A. **United Kingdom:** Jyothirmayi R, Nordin A, Reed N, Rustin G.

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Back-up slides for discussion

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EORTC-55994 vs Gupta trial (JCO 2018): overview

	EORTC 55994	GUPTA
Sample size - NACT+Sx - CT-RTx	626 - 314 - 312	633 - 316 - 317
Accrual	12 yrs (2002-2014)	13 yrs (2003-2015)
Median follow-up	8 years	5 years
1ry endpoints	OS at 5 years	DFS at 5 years OS at 5 years
Center	Multicenter	Monocenter
Chemotherapy	Several regimens	1 regimen
Radical surgery received in the NACT+Sx arm	77% (240 / 313)	72% (227 / 316)

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EORTC-55994 vs Gupta trial

baseline characteristics

	EORTC 55994	GUPTA
Median age	47 years	49 years
WHO PS		
0	88%	92%
1	12%	8%
Type of cervical ca		
squamous	85%	100% (elig. criteria)
adenosquamous	4%	0%
adenocarcinoma	11%	0%
FIGO stage		
Ib2	27%	18%
IIa	15%	25%
IIb	57%	57%

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EORTC-55994 vs Gupta trial
results

	EORTC 55994	GUPTA
5 year DFS	HR=0.74	HR=0.72
NACT+Sy	58.8%	69.3%
CTRTx	67.1%	76.7%
5 year OS	HR=0.88	HR=0.98
NACT+Sy	72.5%	+/- 75%
CTRTx	75.5%	+/- 75%

Similar results in OS and PFS