RUOLO DELLA CHEMIOTERAPIA ADIUVANTE NEL CARCINOMA DELL'ENDOMETRIO

FAUSTO ROILA

CHIARA SCAFATI

M. FRANCESCA CURRA'

S.C. ONCOLOGIA MEDICA TERNI

Revised FIGO Staging 2009

2009	1988	Definition
Stage I	Stage I	Tumor confined to the corpus uteri
IA	IA-B	No or less than half myometrial invasion
IB	IC	Invasion equal to or more than half of the myometrium
Stage II	Stage	Tumor invades cervical stroma, but does not extend beyond the uterus
–	IIA	Endocervical glandular involvement only
–	IIB	Cervical stromal invasion
Stage III	Stage III	Local and/or regional spread of the tumor
IIIA	IIIA	Tumor invades the serosa of the corpus uteri and/or adnexae[1]
IIIB	IIIB	Vaginal and/or parametrial involvement[1]
IIIC	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes[1]
IIIC1	–	Positive pelvic lymph nodes
IIIC2	–	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV	Stage IV	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA	IVA	Tumor invasion of bladder and/or bowel mucosa
IVB	IVB	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

Stadio FIGO e Sopravvivenza

FIGO stage	Overall survival, percent		
	Two years*	Five years*	Five years¶
IA	97	91	90
IB	97	91	78
IC	94	85	-
II	-	-	74
IIA	93	83	-
IIB	85	74	-
IIIA	80	66	56
IIIB	62	50	36
IIIC	75	57	-
IIIC1	-	-	57
IIIC2	-	-	49
IVA	47	26	22
IVB	37	20	21

* Data from: FIGO for patients treated in 1999 through 2001, using the original 1988 FIGO surgical staging classification (from Int J Gynaecol Obstet 2006; 95:S105).

¶ Data from: SEER database for patients treated in 1988 through 2006, staged according to the 2010 FIGO staging system (from Obstet Gynecol 2010; 116:1141).


STADIO PATOLOGICO
GRADO DI DIFFERENZIAZIONE
ASPETTATIVA DI VITA
FATTORI PROGNOSTICI
ETA’
ISTOTIPO
INFILTRAZIONE SPAZI LINFOVASCOLARI

Classi Di Rischio

Classe di rischio	FIGO 2009	Grado	Istologia
Basso	IA	1-2	E
Intermedio	IB	1-2	E
	IA	3	E
Alto	IB	3	E
	II-II-IV	1-2-3	E
	IA-IB	-	SP/CC

Legenda: **E:** endmoetrioide; **CC** cellule chiare; **SP** sieroso papillifero.

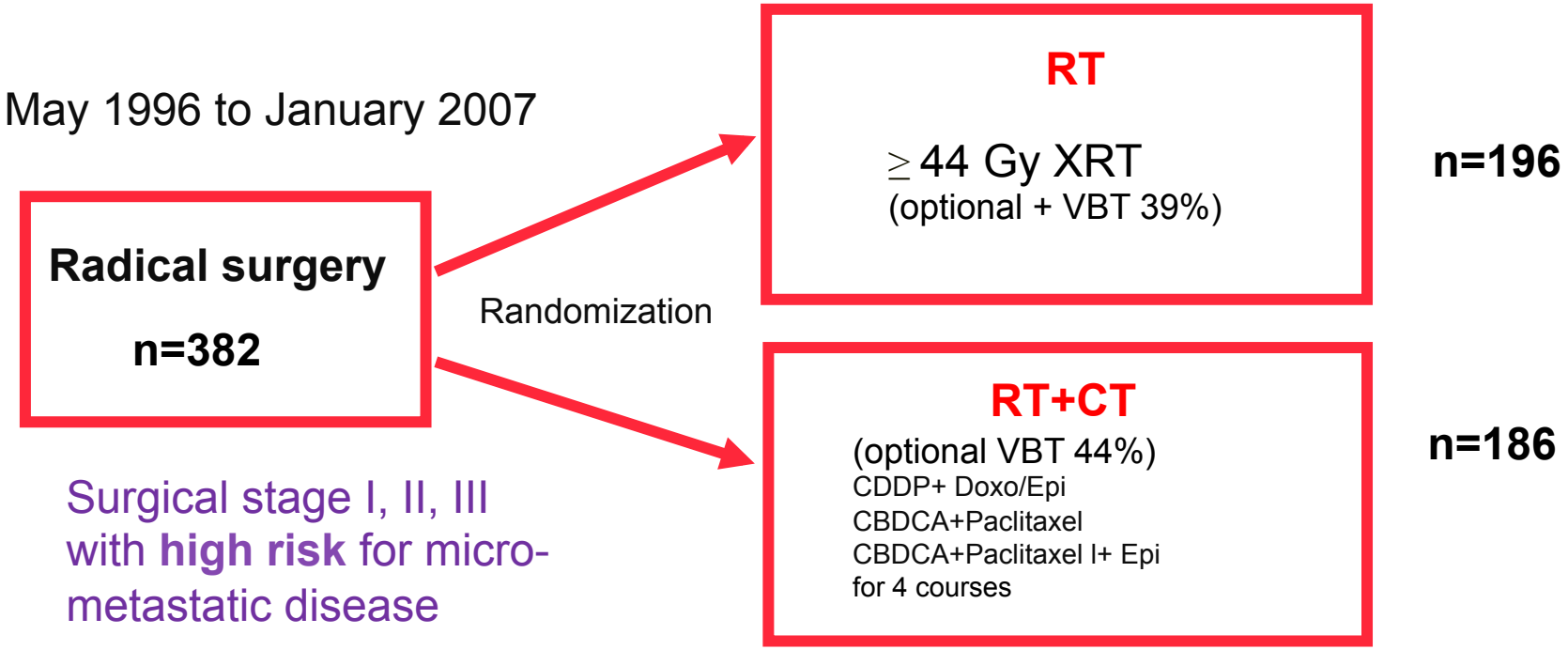
Terapia Adiuvante

Basso Rischio 5-6% di recidive	**Chirurgia**	**OSSERVAZIONE**
Rischio Intermedio 30% di recidive	**Chirurgia**	**RADIOTERAPIA**
Rischio Alto	**Chirurgia**	**?**

Gynecol Oncol. 2004;92(3):744 ;
Lancet. 2000;355(9213):1404.

Chemioterapia Adiuvante dopo Chirurgia e Radioterapia (stadi I-III)

NSGO EC-9501/EORTC-55991



Surgical stage I, II, III with **high risk** for micro-metastatic disease

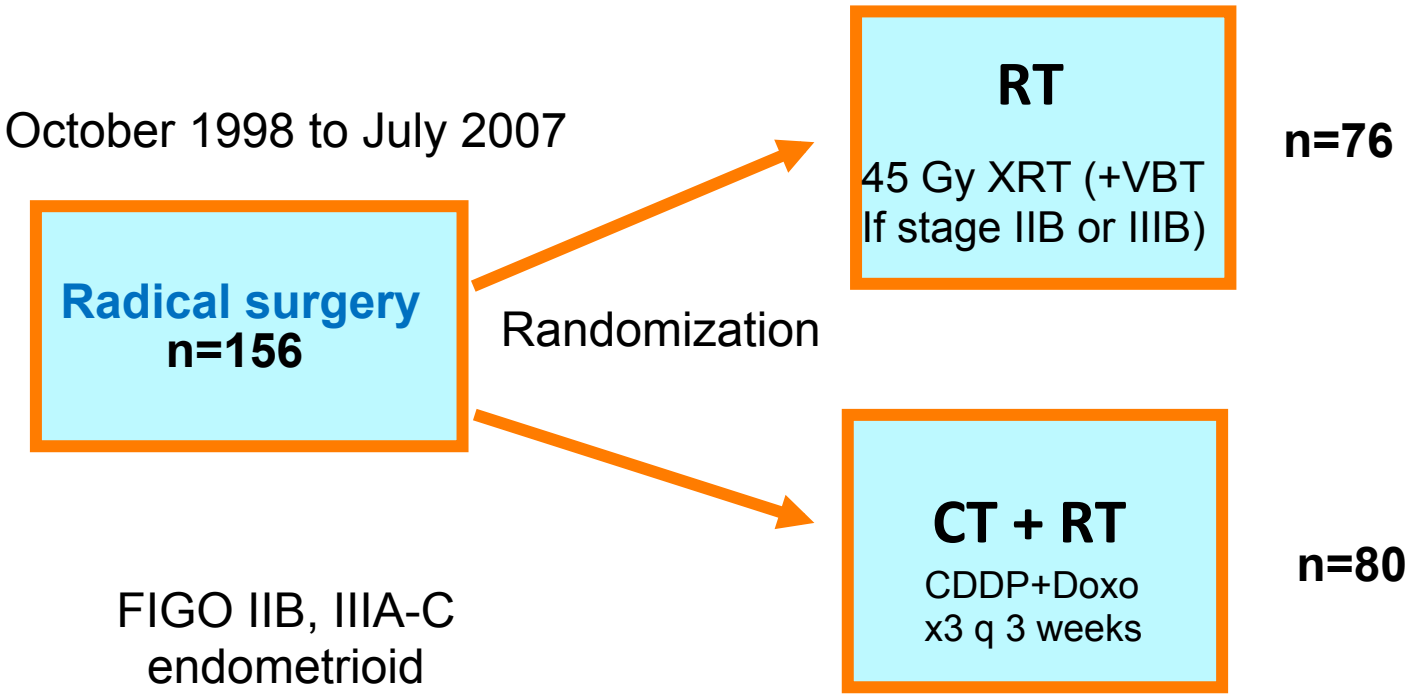
Patients with serous, clear cell, or anaplastic carcinomas were eligible regardless of other risk factors

Primary endpoint

Progression-free survival (PFS)

Hogberg T. Eur J Cancer 2010; 46: 2422-2431

MANGO/ILIADE

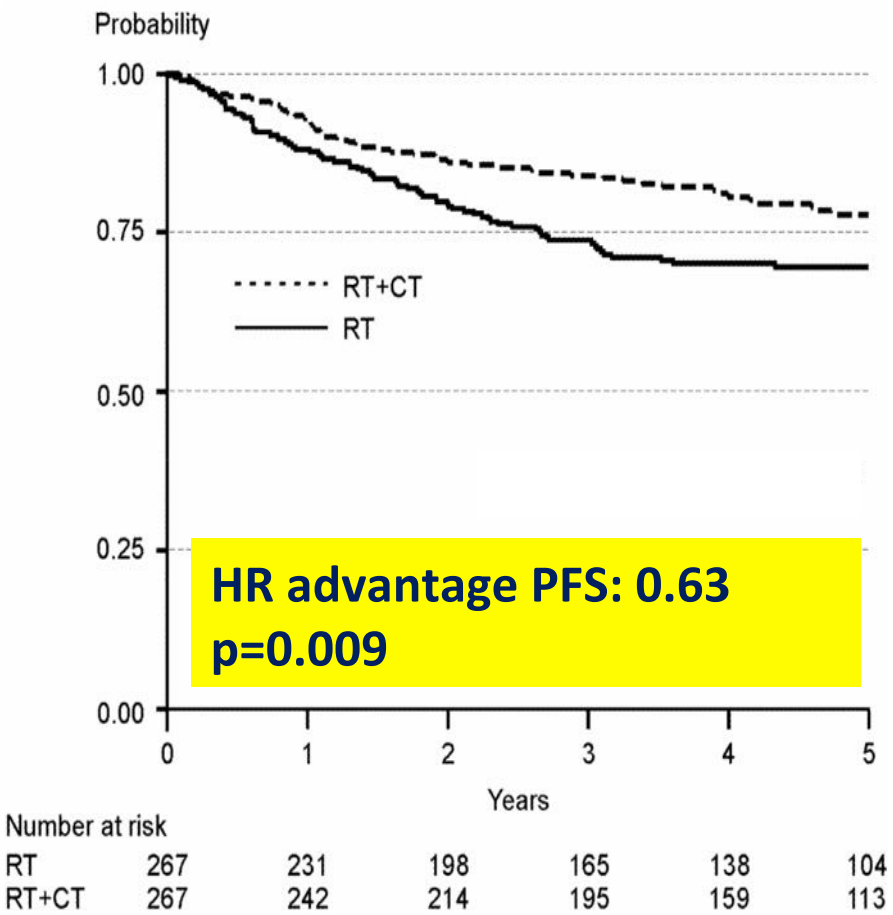


Primary endpoint

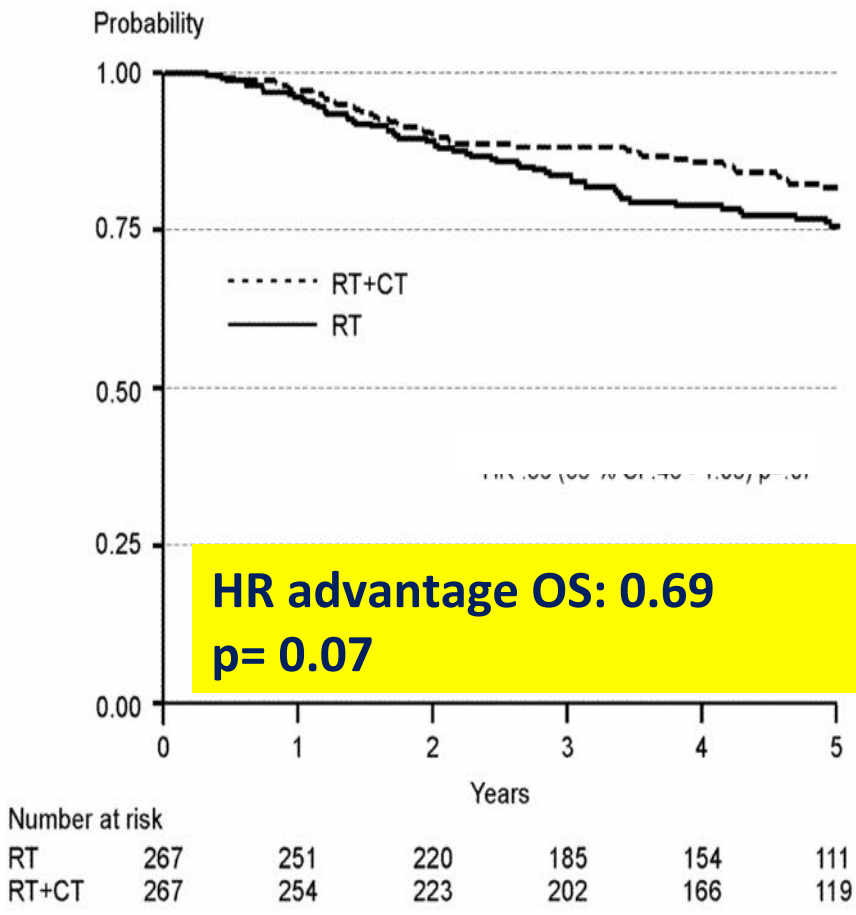
Progression-free survival (PFS)
overall survival (OS)

Hogberg T. et al; *Eur J Cancer* 2010; 46: 2422–31.

NSGO EC-9501/EORTC-55991/MANGO



HR advantage PFS: 0.63
p=0.009



HR advantage OS: 0.69
p= 0.07

Hogberg T. Eur J Cancer 2010; 46: 2422-2431

Gynecol Oncol. 2008 Aug;110(2):190-5. doi: 10.1016/j.ygyno.2008.03.020. Epub 2008 Jun 4.

Surgically staged high-risk endometrial cancer: randomized study of adjuvant radiotherapy alone vs. sequential chemo-radiotherapy.

Kuoppala T[1], Mäenpää J, Tomas E, Puistola U, Salmi T, Grenman S, Lehtovirta P, Fors M, Luukkaala T, Sipilä P.

156 pts: stage IA-B, G3 (n 28)
stage IC-IIIA , G1-3) (n 128)

→ RT 56 Gy (72 pts) (A)

→ RT 56 Gy + 3 cycles of CHT with cisplatin/Epirubicin/ Cyclophosphamide (in a sandwich regimen) (84 pts) (B)

5 year Disease free survival : 84.7% (A) vs 82.1% (B);

Median DFS: 18 months (A) vs 25 months (B);

Median OS: 23 months (A) vs 37 months (B);

- Adjuvant chemotherapy with cisplatin, epirubicin and cyclophosphamide failed to improve OS.
- CT was associated with a low rate of acute toxicity but appeared to increase the risk of bowel complications

Kuoppala T et al; Gynecol Oncol 2008 110:190-5

GOG 34

- Use of adjuvant Doxorubicin after surgery (1) and Radiation therapy (2) for endometrial carcinoma (stage I and II with risk factor for recurrence):

174 pts:

- 92 Doxorubicin (60 mg/m^2 starting dose)
- 89 follow up

→ No significant differences in OS and PFS

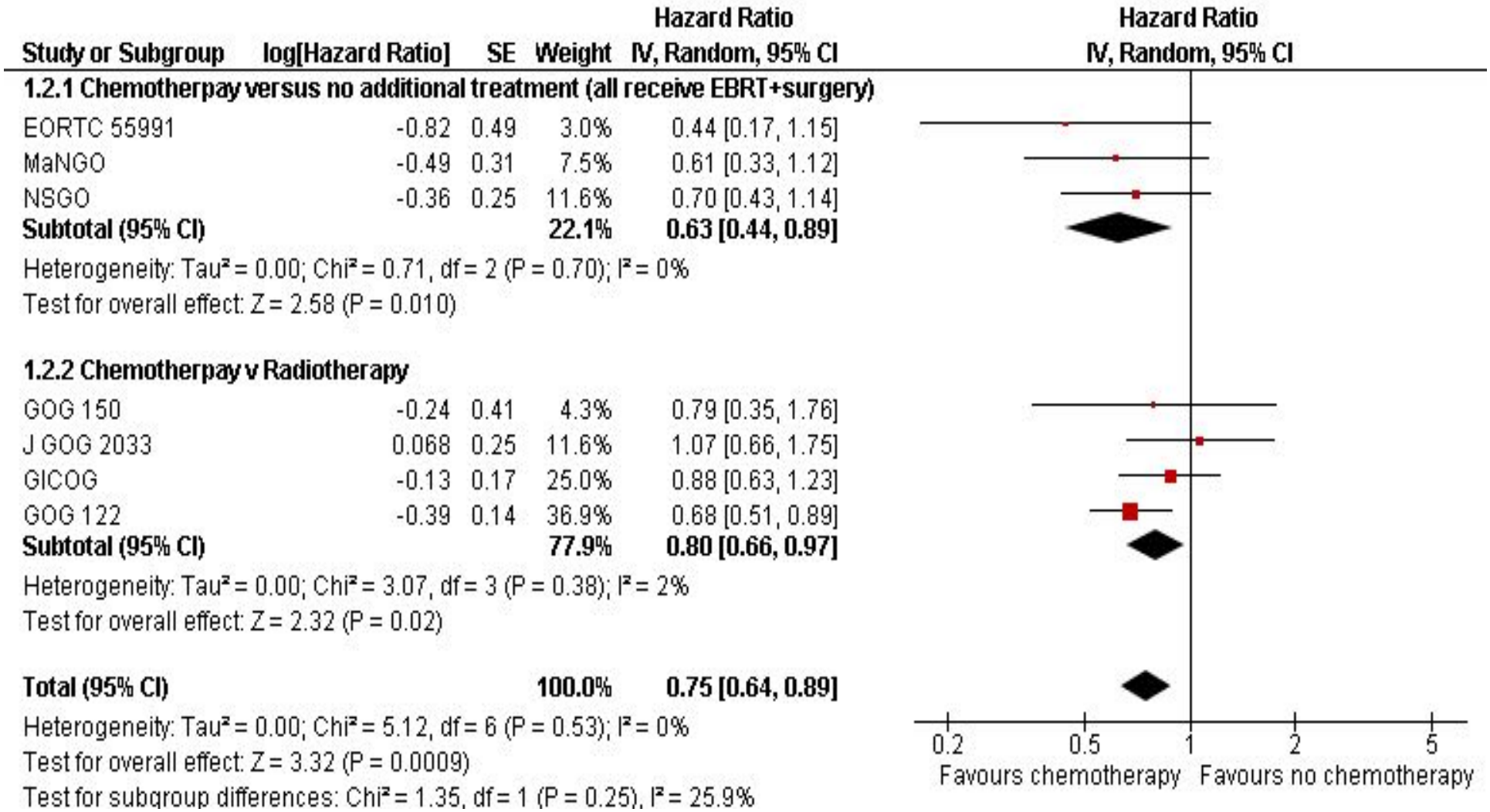
1)TAH-BSO, selective pelvic and para-aortic lymph node dissection, and peritoneal cytology.

2) 50 Gy adjuvant pelvic external radiotherapy (XRT). A para-aortic field was added if para-aortic node metastases were documented.

Limits: small sample size
pts lost to follow up

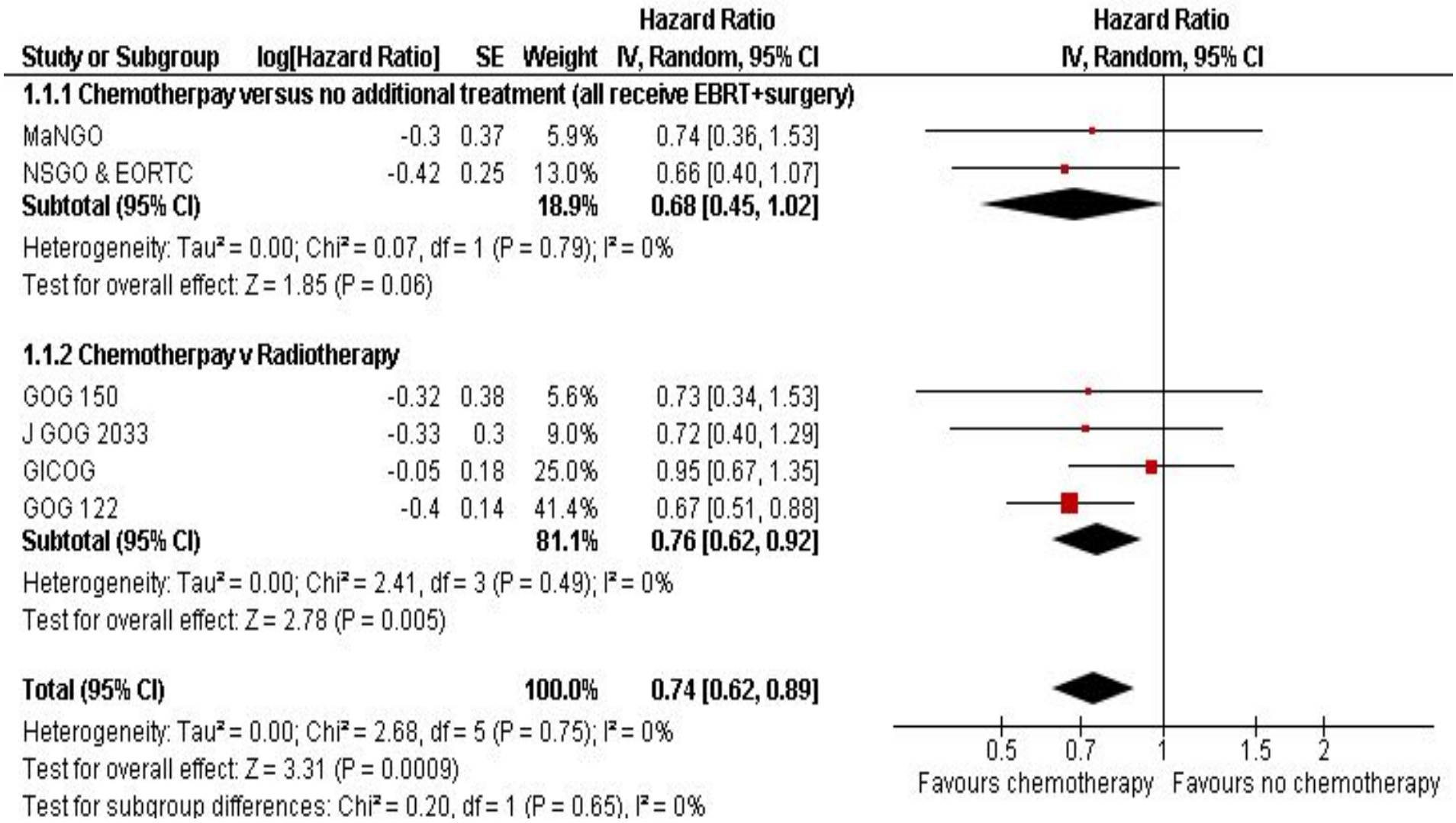
Morrow CP et al. *Gynecol Oncol* 1990; **36**: 166–71.

Forest plot from all the trials of the hazard ratios for death or recurrence (representing progression free survival)



Johnson N. Cochrane Database Syst Rev 2011

Forest plot from all trials of the hazard ratio for death from any cause (representing overall survival)



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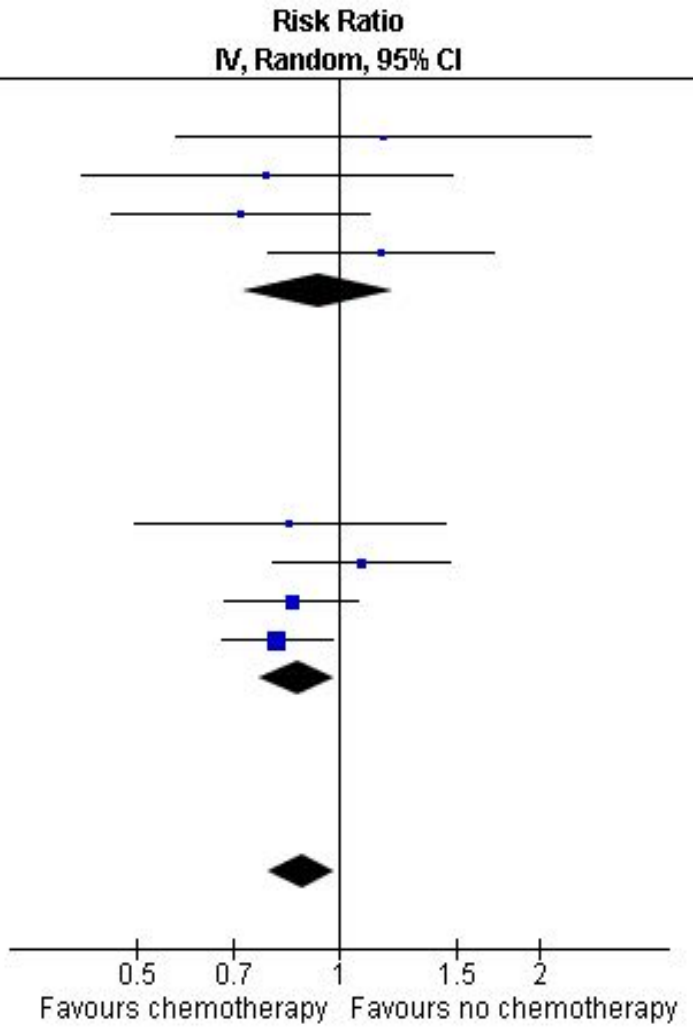
Indiscriminate forest plot for overall survival (risk of death 5 years after randomisation) from all trials of chemotherapy versus any other arm

Study or Subgroup	Favours chemotherapy Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
2.1.1 Chemotherpay versus no additional treatment (all receive EBRT+surgery)						
Kuoppala 2008	15	84	11	72	2.6%	1.17 [0.57, 2.38]
MaNGO	14	80	17	76	3.2%	0.78 [0.42, 1.47]
NSGO & EORTC	28	187	40	191	6.7%	0.71 [0.46, 1.11]
GOG 34	36	92	30	89	8.6%	1.16 [0.79, 1.71]
Subtotal (95% CI)		**443**		**428**	**21.2%**	**0.94 [0.72, 1.22]**
Total events	93		98			
Heterogeneity: Tau² = 0.01; Chi² = 3.32, df = 3 (P = 0.35); I² = 10%						
Test for overall effect: Z = 0.50 (P = 0.62)						
2.1.2 Chemotherapy v radiotherapy						
J GOG 2033	22	192	26	192	4.6%	0.85 [0.50, 1.44]
GICOG	59	174	52	166	13.8%	1.08 [0.80, 1.47]
GOG 122	55	101	67	105	24.7%	0.85 [0.68, 1.07]
GOG 150	91	194	117	202	35.8%	0.81 [0.67, 0.98]
Subtotal (95% CI)		**661**		**665**	**78.8%**	**0.87 [0.76, 0.99]**
Total events	227		262			
Heterogeneity: Tau² = 0.00; Chi² = 2.54, df = 3 (P = 0.47); I² = 0%						
Test for overall effect: Z = 2.16 (P = 0.03)						
Total (95% CI)		**1104**		**1093**	**100.0%**	**0.88 [0.79, 0.99]**
Total events	320		360			
Heterogeneity: Tau² = 0.00; Chi² = 6.15, df = 7 (P = 0.52); I² = 0%						
Test for overall effect: Z = 2.15 (P = 0.03)						
Test for subgroup differences: Chi² = 0.25, df = 1 (P = 0.62), I² = 0%						



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Chemioterapia Adiuvante dopo Chirurgia e Radioterapia (stadi I-III)

- Sono stati condotti cinque studi randomizzati che, considerati singolarmente, non consentono di trarre considerazioni conclusive in quanto non adeguatamente dimensionati

- Una metanalisi ha evidenziato che la chemioterapia riduce il rischio di morte a 5 anni del 6% (di ripresa di malattia del 37% e di morte del 32% se non si considerano gli studi di Kuoppala e Morrow che incrementano significativamente l'eterogeneità della metanalisi)

Chemioterapia vs Radioterapia Adiuvante (Stadi I-III)

GICOG

345 pts with high-risk stage I -III endometrial carcinoma

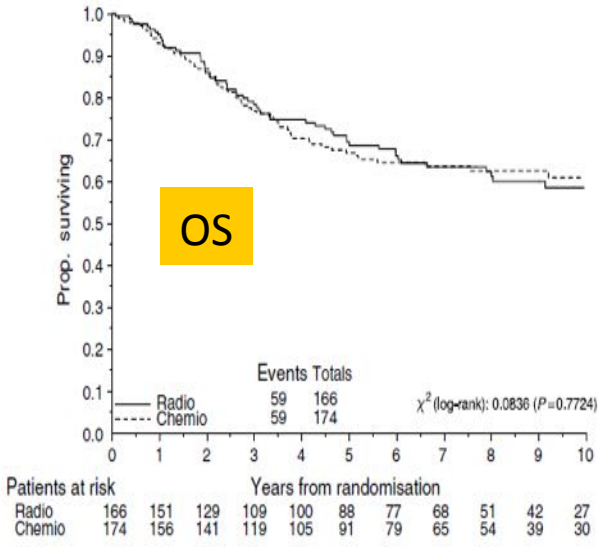
Adjuvant CHT: Cisplatin 50 mg/m^2, Doxorubicin 45 mg/m^2 and Cyclophosphamide 600 mg/m^2 every 28 days for 5 cycles

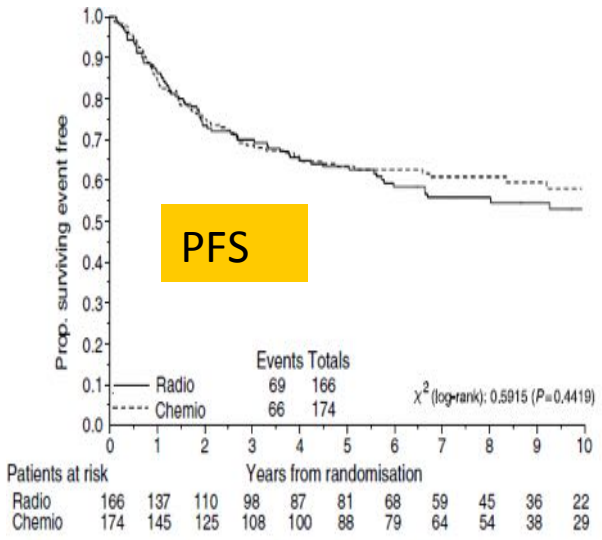
Primary end points: OS and PFS

external RT (45–50Gy on a 5 days week$_1$ schedule).

OS: 3 ys 78% in RT vs 76% in CHT;
5 ys 69% in RT vs 66% in CHT;
7 ys 62% both in RT and CHT

PFS: 3 ys 69% in RT vs 68% in CHT;
5 ys 63% in RT vs 63% in CHT;
7 ys 56% in RT and 60% in CHT





RT delayed local relapses and CHT delayed metastases (no statistical significance)

THIS TRIAL FAILED TO SHOW ANY IMPROVEMENT IN SURVIVAL OF PTS TREATED WITH CHT OR STANDARD RT THERAPY

Maggi R. et al, Br J Cancer 2006; 95: 266 – 271

J GOG 2033

385 pts with intermediate and high-risk (stage Ic-IIIc) endometrial cancer

193 pts received pelvic radiation therapy (PRT)

192 pts received CAP (cyclophosphamide (333 mg/m^2), doxorubicin (40 mg/m^2) and cisplatin (50 mg/m^2) Every 4 weeks for 3 or more courses

No statistically significant differences in progression-free survival and overall survival were observed

5-ys PFS rate: 83.5% in the PRT group vs 81.8% in CAP group

5-ys OS rate: 85.3% in the PRT group vs 86.7% in CAP group

GOG 150

206 pts with carcinosarcoma (all stages FIGO)

105 pts received whole abdominal irradiation (WAI)

101 pts received cisplatin, ifosfamide and mesna (CIM)

No statistically significant advantage in recurrence rate or survival for adjuvant CIM over WAI in patients with uterine CS

Susumu N et al, Gynecol Oncol 2008;108: 226–33.

Wolfson AH et al, Gynecol Oncol 2007;107: 177–85.

VOLUME 24 · NUMBER 1 · JANUARY 1 2006
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Randomized Phase III Trial of Whole-Abdominal Irradiation Versus Doxorubicin and Cisplatin Chemotherapy in Advanced Endometrial Carcinoma: A Gynecologic Oncology Group Study

Marcus E. Randall, Virginia L. Filiaci, Hyman Muss, Nick M. Spirtos, Robert S. Mannel, Jeffrey Fowler, J. Tate Thigpen, and Jo Ann Benda

To compare WAI (1) and doxorubicin-cisplatin (AP) chemotherapy (2) in stage III or IV endometrial carcinoma with postoperative residual disease < 2 cm (GOG 122 trial)

Characteristic	WAI Regimen (n = 202) No.	%	AP Regimen (n = 194) No.	%
FIGO stage†				
IIIA	57	28.2	35	18.0
IIIB	4	2.0	4	2.1
IIIC	90	44.6	100	51.5
IVA/IVB	51	25.2	55	28.4

396 patients with stage III and optimally debulked stage IV disease

Clinical data	WAI	CT
No. of patients	202	194
No. of patients alive	38%	51%
Treatment-related death	4	8
Deaths from cancer	100	78
60-Month PFS (corrected for stage)	38%	60%
60-Month survival (corrected for stage)	42%	55%

1) 30 Gy in 20 fractions, with a 15-Gy boost

2) doxorubicin 60 mg/m^2 and cisplatin 50 mg/m^2 every 3 weeks for seven cycles, followed by 1 cycle of cisplatin

Randall et al, J Clin Oncol 2006; 24:36-44

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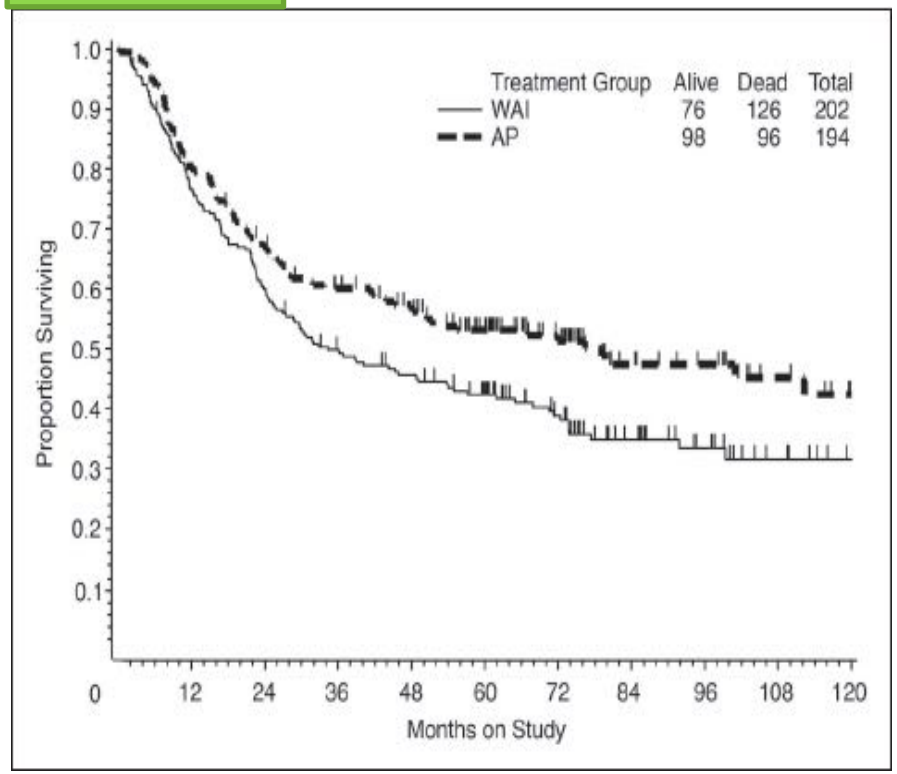
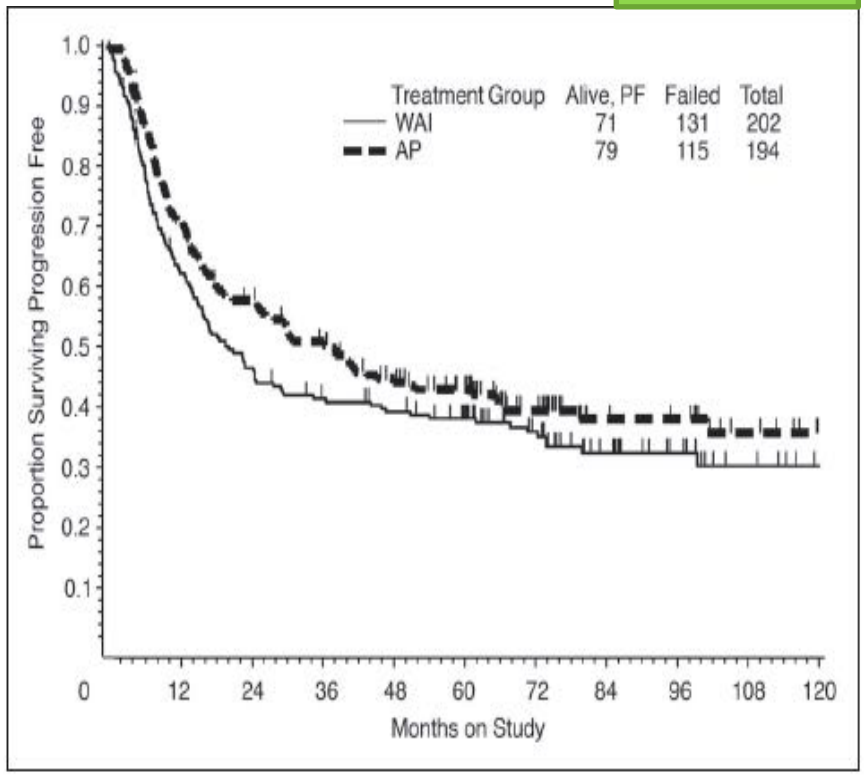
OS



PFS



PFS 50% versus 38% (p = 0.07)
OS 55% versus 42% (p = 0.004)

Randall et al, J Clin Oncol 2006; 24: 36-44

Adverse Event	% of Patients							
	WAI Regimen (n = 190)				AP Regimen (n = 191)			
	Grade				Grade			
	1	2	3	4	1	2	3	4
Leukopenia	4	17	4	< 1	11	23	44	18
Neutropenia	4	4	< 1	0	4	4	18	67
Thrombocytopenia	11	3	2	< 1	34	15	11	10
Other hematologic	18	15	7	< 1	28	31	17	3
Maximum hematologic	17	29	13	2	4	5	20	69
GI	32	36	11	2	20	38	13	7
Hepatic	3	3	2	1	< 1	2	1	0
Genitourinary	13	4	< 1	0	9	9	2	1
Cardiac	0	0	0	0	5	12	11	4
Vascular	1	0	0	0	2	2	< 1	1
Pulmonary	2	2	0	0	4	4	1	< 1
Neurologic	4	1	< 1	0	25	10	6	1
Pain	1	0	< 1	0	8	5	< 1	0
Weakness	2	2	2	0	6	3	3	0
Fatigue	12	5	1	0	14	11	5	< 1
Metabolic	9	6	0	0	6	8	4	< 1
Infection	0	< 1	< 1	0	1	2	4	3
Fever	< 1	2	0	0	6	12	4	2
Allergy	< 1	0	0	0	0	0	0	0
Dermatologic	12	5	< 1	0	10	4	1	< 1
Alopecia†	< 1	0	NA†	NA†	6	69	NA†	NA†

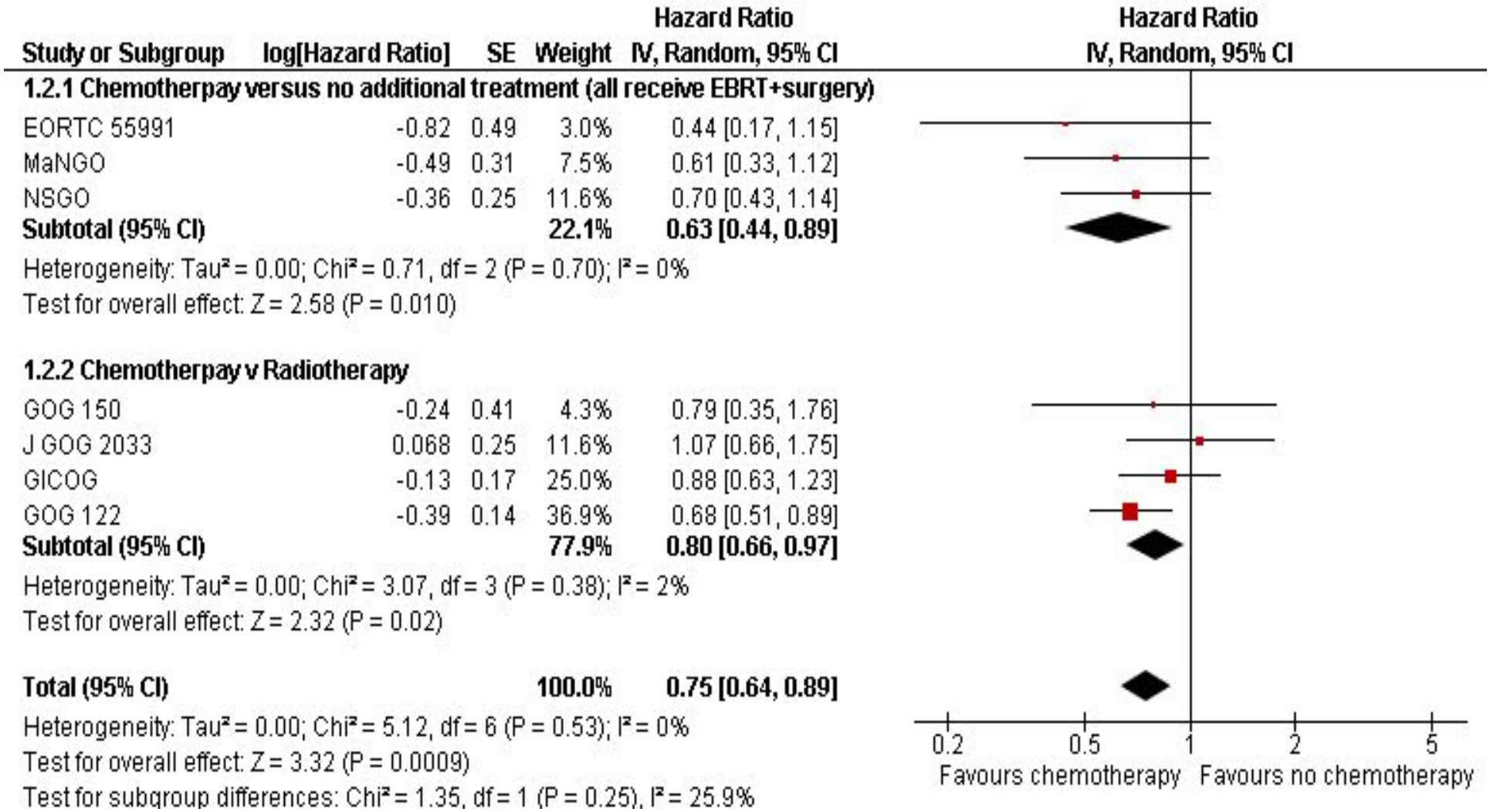
Abbreviations: WAI, whole-abdominal irradiation; AP, doxorubicin and cisplatin; NA, not available.

*Excluded from the analysis are 15 patients (12 on WAI and three on AP) who did not receive protocol therapy.

†Alopecia, grades 3 and 4 not defined.

Grade 3 and 4 adverse effects (hematologic, GI, cardiac, neurologic) were significantly more common in chemotherapy arm

Forest plot from all the trials of the hazard ratios for death or recurrence (representing progression free survival)



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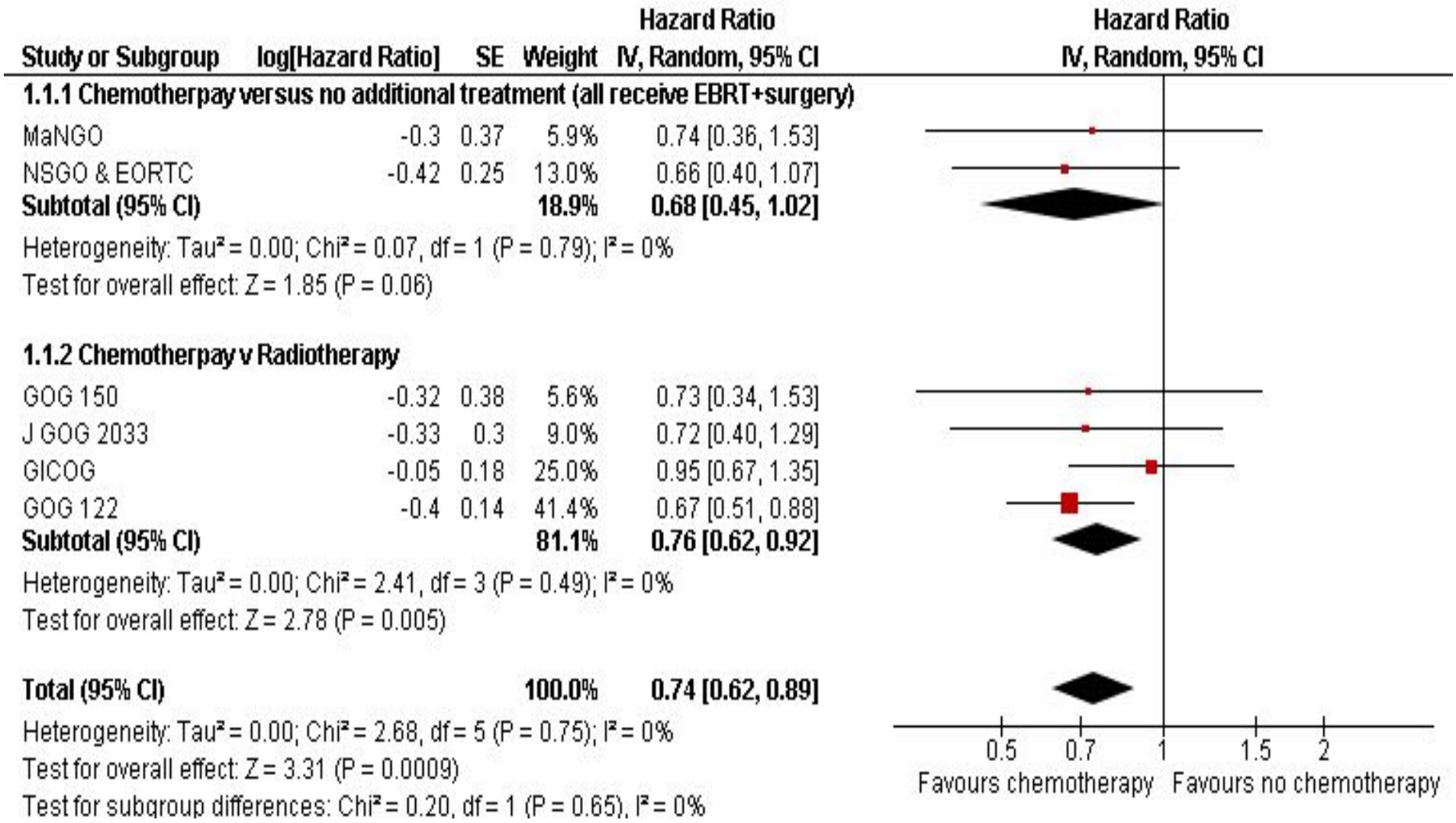
Forest plot from all trials of the hazard ratio for death from any cause (representing overall survival)



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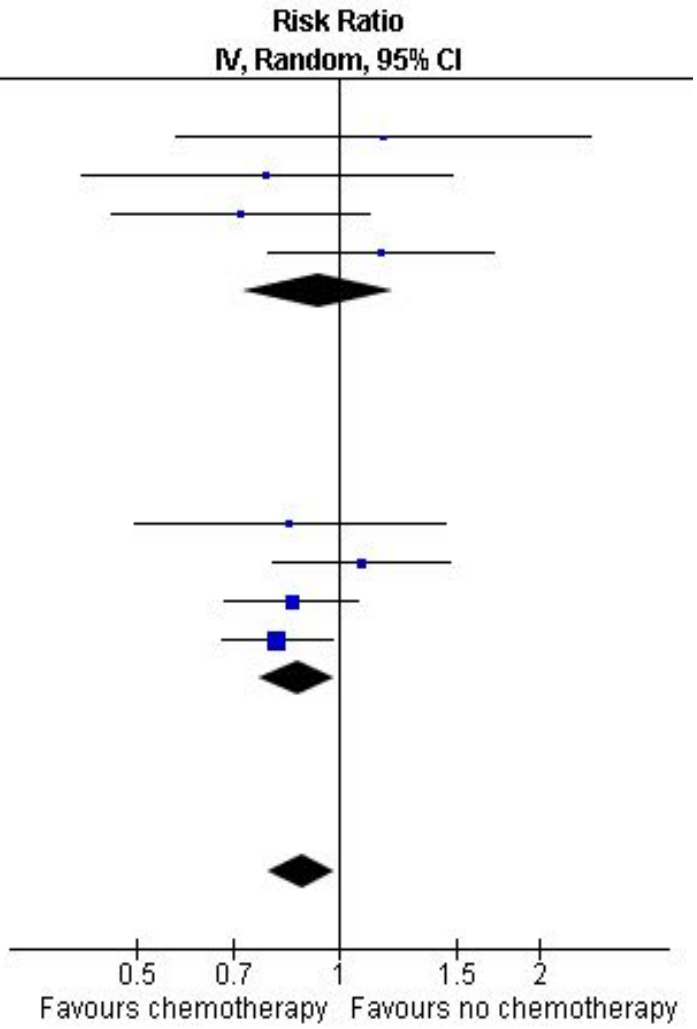

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Chemioterapia vs Radioterapia Adiuvante (Stadi I-III)

- La chemioterapia con regimi convenzionali a base di platino è stata confrontata con la radioterapia dopo la chirurgia, in 4 studi (di cui uno condotto nei carcinosarcomi)

- Una metanalisi in cui sono stati valutati tali studi, ha mostrato una maggiore efficacia della chemioterapia rispetto alla radioterapia, con una riduzione del rischio di recidiva del 20% e del rischio di morte del 24% ed una riduzione del rischio di morte a 5 anni del 13%

Chemioterapia Adiuvante dopo Isterectomia

(Johnson N. Cochrane Database Syst Rev 2011)

- La chemioterapia postoperatoria a base di platino determina un beneficio in progression free survival (+25%), overall survival (+24%) e 5-year survival(+12%) indipendentemente dal trattamento radiante.

- La chemioterapia riduce il rischio di metastasi, potrebbe essere un'alternativa alla radioterapia ed ha un valore aggiunto quando usato con la radioterapia

Terapia Adiuvante negli Stadi Avanzati (III-IV)

Terapia Adiuvante negli Stadi Avanzati (III-IV)

Complete cytoreduction, is the aim of surgery and is associated with a superior OS compared with sub-optimal cytoreduction!

clinical practice guidelines

Annals of Oncology 24 (Supplement 6): vi33–vi38, 2013
doi:10.1093/annonc/mdt353

Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

N. Colombo[1], E. Preti[1], F. Landoni[1], S. Carinelli[2], A. Colombo[3], C. Marini[4] & C. Sessa[5], on behalf of the ESMO Guidelines Working Group*

"…There is no agreement on the standard treatment of women with advanced endometrial cancer. Typically, a combination of surgery, radiotherapy and/or chemotherapy is employed…"

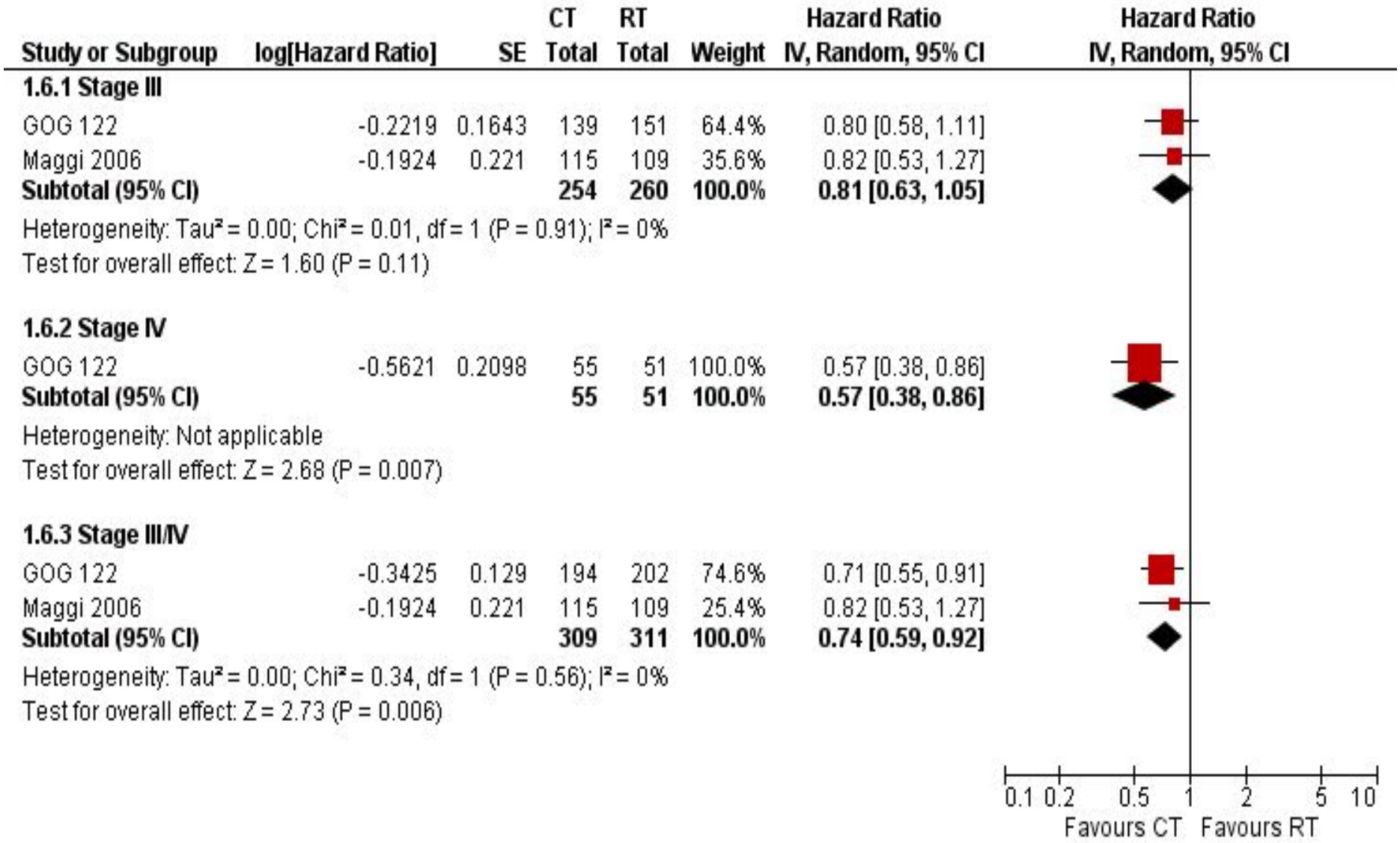
Chemioterapia o Radioterapia per stadi III-IV ?

- Una metanalisi ha riguardato 1269 pazienti (stadio III e IV)

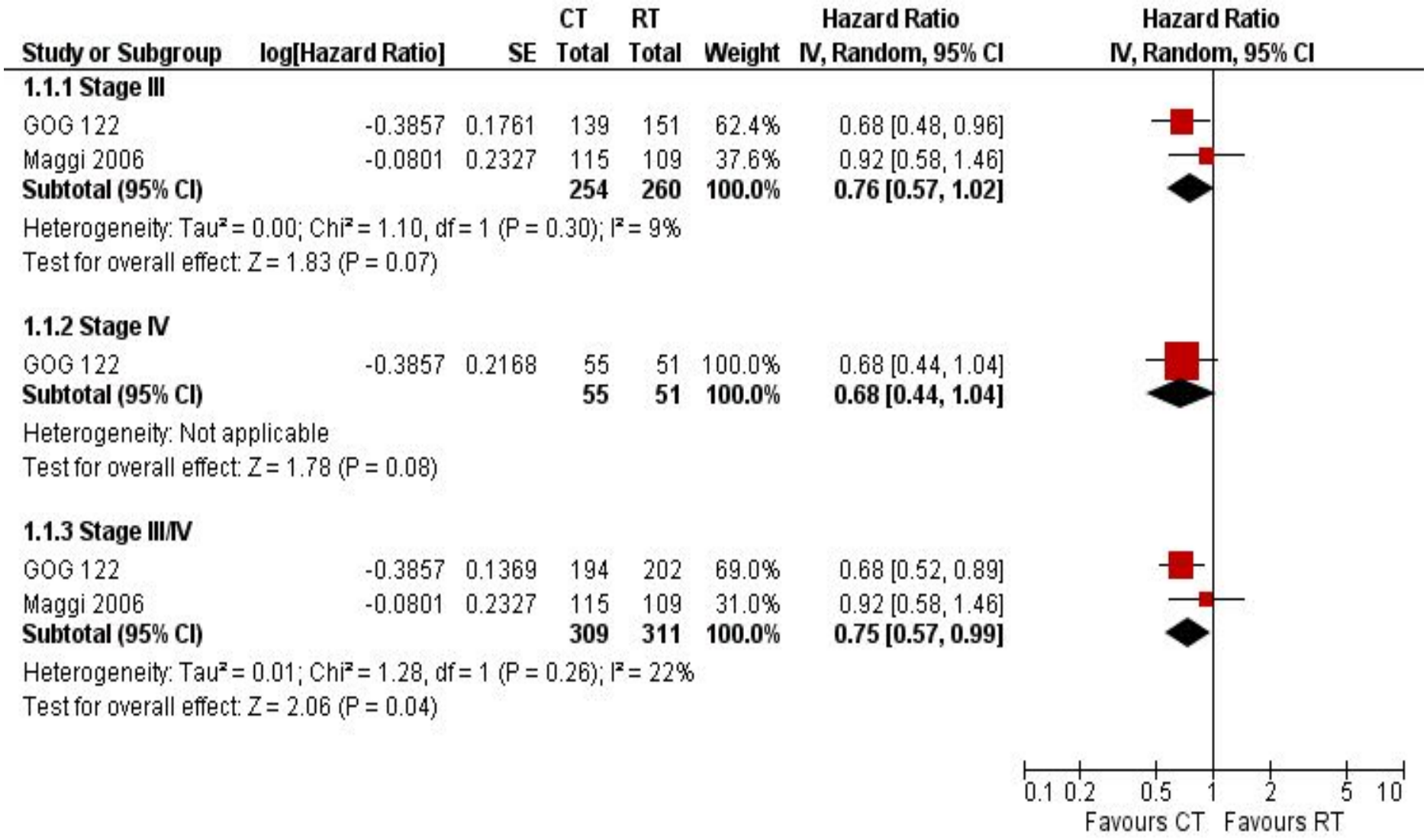
- In 2 studi (620 pazienti) è stata confrontata la chemioterapia con la radioterapia adiuvante dopo chirurgia citoriduttiva

Galaal K, et al. Cochrane Database Syst Rev 2014. May;15

Forest plot of comparison: chemotherapy versus radiotherapy, outcome: PFS (Stage III/IV)

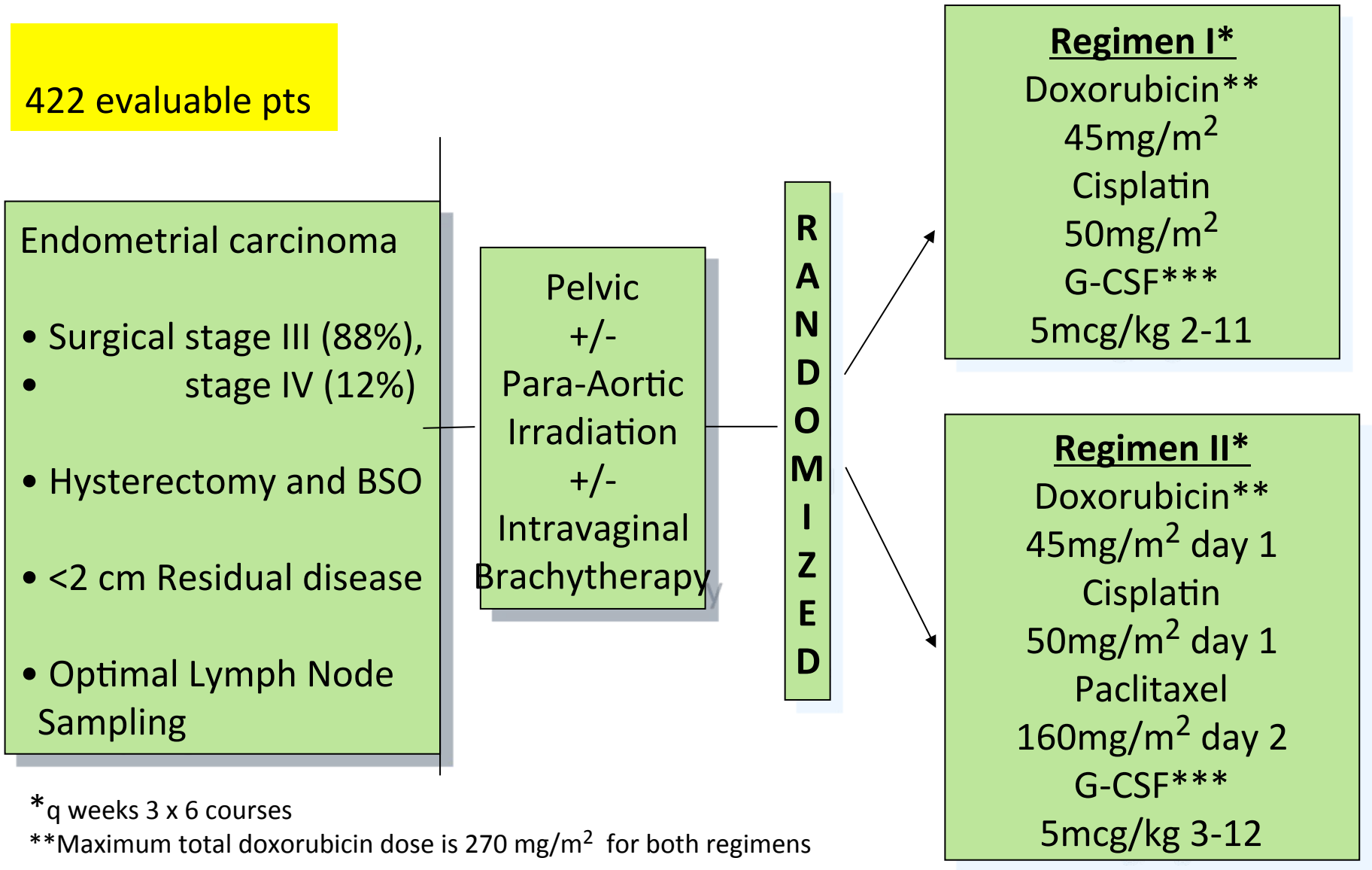


Forest plot of comparison: chemotherapy vs radiotherapy, Outcome: OS (Stage III/IV)



Quale Chemioterapia?

STUDIO GOG 184



*q weeks 3 x 6 courses

**Maximum total doxorubicin dose is 270 mg/m^2 for both regimens

Homesley H.D et al. *Gynecol Oncol*. 2009; 112: 543–552

STUDIO GOG 184

Progression-Free Survival

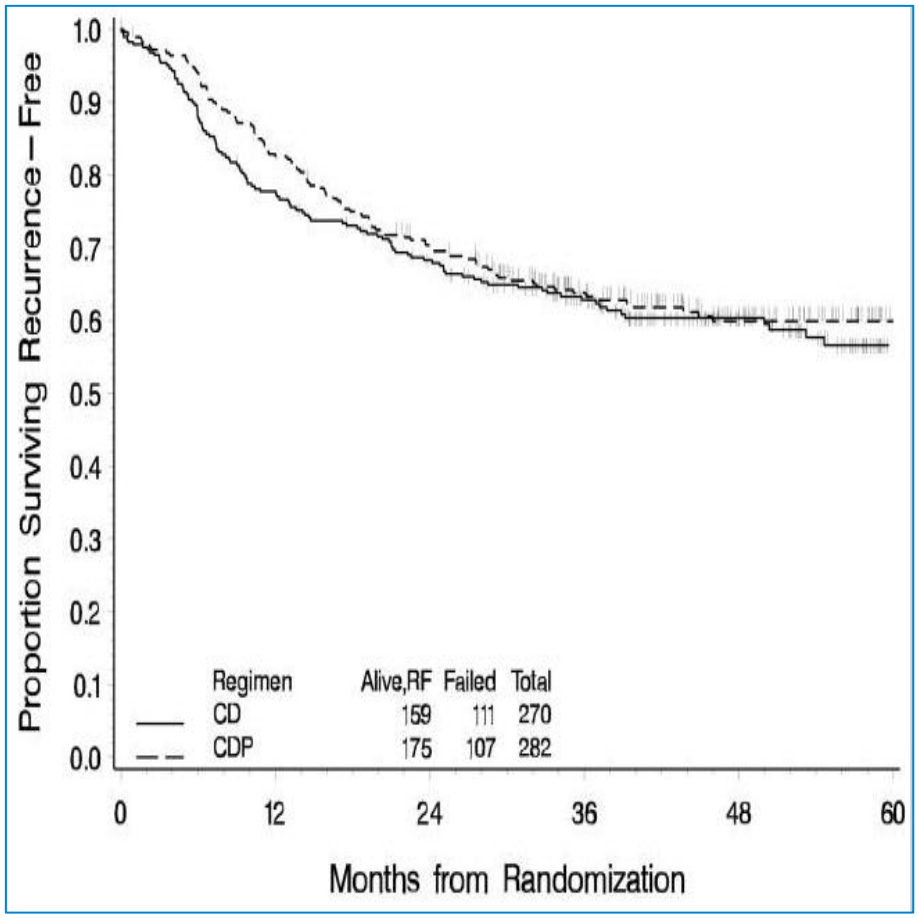


Table 4a. Acute Adverse Events Among Treated Patients

	CD Grade Frequency (N = 261)					CDP Grade Frequency (N = 278)				
Adverse Event term or category	0	1	2	3	4	0	1	2	3	4
Leukopenia*	28	43	58	100	32	7	21	37	95	118
Neutropenia*	71	32	36	63	59	21	21	46	58	132
Thrombocytopenia*	114	92	28	26	1	35	127	49	62	5
Anemia*	36	88	106	30	1	15	58	162	43	0
Gastrointestinal	109	79	57	13	3	108	82	67	18	3
Nausea	67	105	65	24	0	81	102	66	29	0
Vomiting	132	54	52	21	2	141	58	55	23	1
Stomatitis	228	22	10	0	1	237	26	13	2	0
Genitourinary/Renal	195	48	14	4	0	214	37	23	3	1
Infection/Fever*	247	3	7	3	1	239	4	13	19	3
Febrile Neutropenia*	259	1	1	0	0	261	0	3	13	1
Sensory neuropathy*	183	65	8	5	0	94	108	52	23	1
Pain*	126	72	46	16	1	108	69	74	27	0
Myalgia*	243	11	7	0	0	198	28	45	7	0

Homesley HD et al. *Gynecol Oncol*. 2009; 112: 543–552.

Terapia Adiuvante negli Stadi Avanzati (III-IV)

(Galaal K, et al. Cochrane Database Syst Rev 2014. May;15)

- Women with advanced endometrial cancer (FIGO stage III-IV) survived approximately 25% longer if they received chemotherapy after primary surgery

- PFS was 26% longer with adjuvant chemotherapy compared with radiotherapy

- Further research is needed to determine which chemotherapy regimen/s are the most effective and least toxic, and whether the addition of radiotherapy further improves outcomes

STUDIES ONGOING

Study	Target accrual (n)	Stage	Method of staging	Arms of study
GOG 258	180	III; IVA	Surgically, LND required	Cis/volume-directed RT + C/T x 4 cycles vs C/T x 6 cycles
PORTEC-3	500	IBG3 + LVSI; IC/IIAG3; IIB; IIIA (only on cytology if grade 3) or IIC; IB–III serous or clear cell	Surgically, LND optional	Pelvic RT ± VBT(for cervical involvement) vs Cis/RT + C/T x 4 cycles
GOG 249	562 (planned sample size)	I-IIA + HIR; IIB: I–IIB serous/clear cell	Surgically, LND optional	Pelvic RT ± VBT (for cervical involvement) vs VBT +C/T x 3 cycles

Cis: Cisplatin; C/T: Carboplatin and paclitaxel chemotherapy; G: Grade; GOG: Gynecologic Oncology Group; HIR: High-intermediate risk; LND: Lymph node dissection; RT: Radiation therapy; VBT: Vaginal brachytherapy.

Medscape

POSTOPERATIVE RADIATION THERAPY FOR ENDOMETRIAL CANCER: ASCO CLINICAL PRACTICE GUIDELINE ENDORSEMENT OF THE ASTRO EVIDENCE-BASED GUIDELINE

Meyer LA, J Clin Oncol 2015; 33: 2908-13

CONCLUSIONI

- The best available evidence at this time suggests that reasonable options for adjuvant treatment of pts with positive nodes or involved uterine serosa, ovaries/fallopian tubes, vagina, bladder, or rectum include external beam radiation therapy, as well as adjuvant chemotherapy

- **The best evidence for this population supports the use of chemotherapy, but consideration of external beam radiation therapy is reasonable**

CONCLUSIONI

- Radiation therapy without chemotherapy may be considered for some pts with positive nodes or involved uterine serosa, ovaries/fallopian tubes, vagina, bladder, or rectum based on pathologic risk factors for pelvic recurrence

- **Pts receiving chemotherapy seem to have improved survival compared with radiation therapy alone**

CONCLUSIONI

- The best available evidence suggest that concurrent chemoradiation followed by adjuvant chemotherapy is indicated for pts with positive nodes or involved uterine serosa, ovaries/fallopian tubes, vagina, bladder, or rectum

- **Evidence regarding concurrent chemoradiation is limited at this time, and this recommendation is based on expert opinion; we anticipate level-one evidence from upcoming prospective randomized clinical trials (GOG 0258 and PORTEC-3). Chemotherapy may also be considered in certain pts with high-risk early-stage endometrial cancer, and clinical trials addressing this question are under way**

CONCLUSIONI

- Alternative sequencing strategies with external beam radiation and chemotherapy are also acceptable

- **Prospective trials have examined sequential radiation therapy and chemotherapy. Evidence supporting sandwich-type therapy is currently limited**