Surgical management of female genital tract cancers

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Topics covered

- Common terms encountered for hysterectomy
- Surgery for Endometrial cancer
- Surgery for Cervical cancer
- Surgery for vulval cancer
- Surgery for ovarian cancer
- Role of laparoscopy

Some common hysterectomy terms used

- Simple hysterectomy
- Extra facial hysterectomy
- Radical hysterectomy

Subtotal hysterectomy: Hysterectomy without removal of cervix

} None mandates salpingo-ophrectomy

Pan hysterectomy: Simple hysterectomy with removal of BL tubes and ovaries

Endometrial cancer

Staging surgery

- Replaced clinical staging in 1988
- Ideally: Total hysterectomy with BL Salpingo-ophorectomy, BL Pelvic nod, Retroperitoneal LN dissection dissection with or without LN dissection

Role of Lymph-node dissection

Three potential roles for lymphadenectomy:

- To assign a surgical stage, and provide prognostic information
- To treat patients with positive nodes
- To direct adjuvant treatment

We don’t need to be extensive in all women: need to stratify risk

- Surgical time involved
- Surgical risk involved
- Post op morbidity
- In west: Surgical cost

Risk of nodal involvement

- Need to stratify the risk of LN involvement and and extra nodal spread
- Determine the extent of staging as per pre-operative features
  - Endometrial biopsy report: Type and Grade of tumor
  - MRI pelvis: Depth of myometrial invasion, gross cervical disease, significantly enlarged pelvic nodes
  - Incompletely operated post operative specimen

Endometrial cancer patients who need surgical staging

- Grade 3 lesions
- Clear cell or serous carcinomas
- Greater than 50% of myometrial invasion
- Cervical extension
- Grade 2 tumors >2 cm in diameter

Grade, depth of invasion and pelvic nodal metastasis of endometrial carcinoma

	Histologic Grade		
Depth of Myometrial Invasion	G1 ($n = 180$)	G2 ($n = 288$)	G3 ($n = 153$)
Endometrium only ($n = 86$)	0/44 (0%)	1/31 (3%)	0/11 (0%)
Inner third ($n = 281$)	3/96 (3%)	7/131 (5%)	5/54 (9%)
Middle third ($n = 115$)	0/22 (0%)	6/69 (9%)	1/24 (4%)
Outer third ($n = 139$)	2/18 (11%)	11/57 (19%)	22/64 (34%)

Grade, depth of invasion and paraaortic nodal metastasis of endometrial carcinoma

	Histologic Grade		
Depth of Myometrial Invasion	G1 ($n = 180$)	G2 ($n = 288$)	G3 ($n = 153$)
Endometrium only ($n = 86$)	0/44 (0%)	1/31 (3%)	0/11 (0%)
Inner third ($n = 281$)	1/96 (1%)	5/131 (4%)	2/54 (4%)
Middle third ($n = 115$)	1/22 (5%)	0/69 (0%)	0/24 (0%)
Outer third ($n = 139$)	1/18 (6%)	8/57 (14%)	15/64 (23%)

Creasman et al. Cancer 1987

Frequency of nodal metastasis amongst risk factors

Risk Factor	No. of Patients	Pelvic No. (%)	Aortic No. (%)
Histology			
Endometrioid adenocarcinoma	599	56 (9)	30 (5)
Others	22	2 (9)	4 (18)
Grade			
1 Well	180	5 (3)	3 (2)
2 Moderate	288	25 (9)	14 (5)
3 Poor	153	28 (18)	17 (11)
Myometrial invasion			
Endometrial	87	1 (1)	1 (1)
Superficial	279	15 (5)	8 (3)
Middle	116	7 (6)	1 (1)
Deep	139	35 (25)	24 (17)
Site of tumor location			
Fundus	524	42 (8)	20 (4)
Isthmus-cervix	97	16 (16)	14 (14)
CLS involvement			
Negative	528	37 (7)	19 (9)
Positive	93	21 (27)	15 (19)

Creasman et al. Cancer 1987

Incidence of para aortic Ln positivity in the absence of pelvic LN positivity is less than 5%

Results of Systematic Pelvic and Para-aortic Lymphadenectomy from three Large Studies

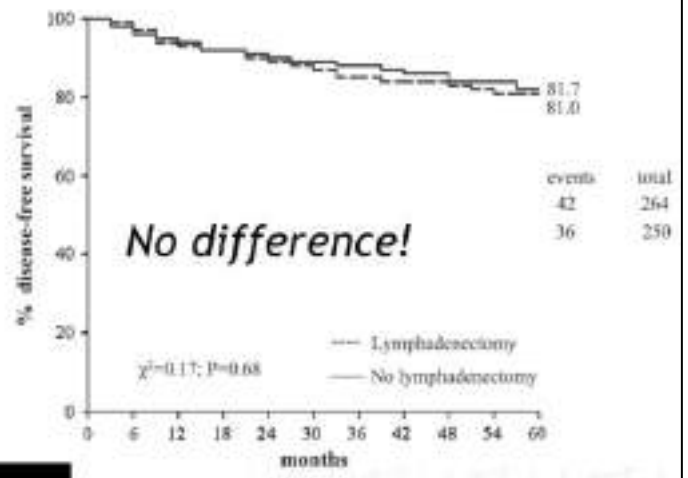
Studies	N	Positive Pelvic Nodes	Positive Pelvic and PA Nodes	Pos PA Nodes if Pos Pelvic Nodes	Isolated PA Metastases	Percent
Nomura et al., 2006 (143)	155	50	24	48%	4	2.6%
Mariani et al., 2008 (144)	281	48	29	60%	9	3.2%
Abu-Rustum et al., 2009 (145)	847	113	61	54%	12	1.4%
Total	1283	211	114	54.3%	25	1.9%

Controversies related to therapeutic role of LN dissection

Italian Study: CONSORT

- **537 stage I pts**
  - 67 recurrence
  - 53 deaths
- **Median f/u : 49 mon**
- **PALND: performed in 26% in the LND arm**

LND improved surgical staging but did not improve survival.



Panici et al., JNCI, 2008

*Largest RCT that has ever been done in early EMca!

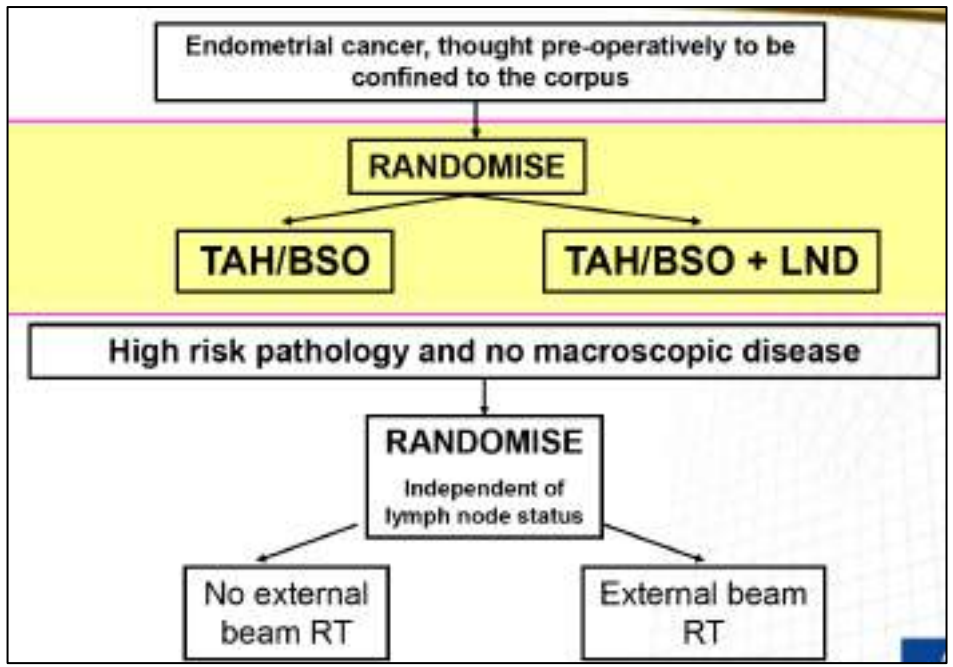
- 4 countries
  - **UK**
  - South Africa
  - Poland
  - New Zealand.

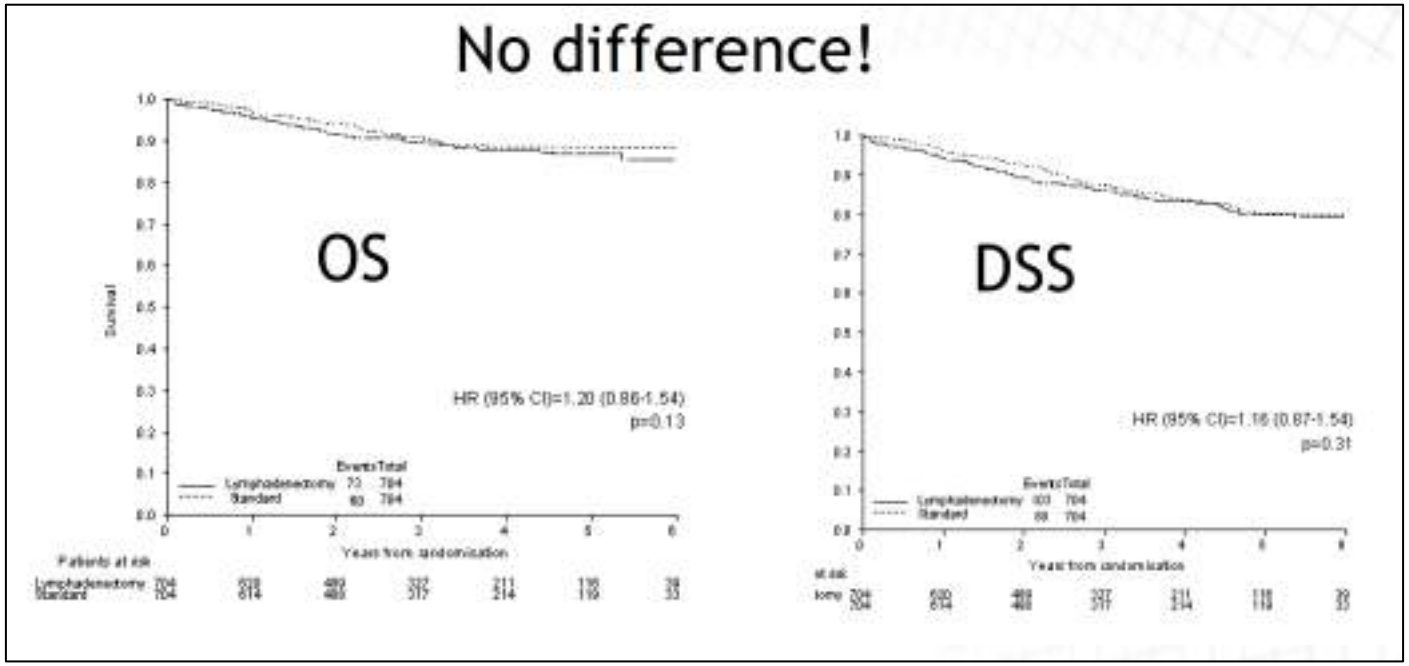
MRC

ASTEC

A Study in the Treatment of Endometrial Cancer

A randomised trial of lymphadenectomy and of adjuvant external beam radiotherapy in the treatment of endometrial cancer (ISRCTN 16571884)





ASTEC study group 2009

Conclusion

No evidence of benefit for PFS/OS for pelvic lymphadenectomy and that it “could not be recommended as a routine procedure for **therapeutic purpose**

Other site metastases

Omental involvement in 18.5% of cases overall, including 22% of serous cancers

In serous carcinoma, carcinosarcoma and undifferentiated carcinoma: Even if the omentum appears normal, a generous biopsy (e.g., 5 × 5 cm) should be taken

Extent of surgery: Mostly its an institutional protocol

Stage and grade		Extent of surgery (In addition to Hysterectomy and adnexetomy)
I	Stage IA, Grade I and Grade 2	No Lymphnode dissection, **In young women ovaries can be preserved**
	Stage IB, Grade I and 2	Pelvic lymph-node disection
	All grade 3 tumors, Non endometroid histologies	Pelvis and Retroperitoneal LNs+/-Omentum
II	Stage 2 (Clinically or in post operative specimen)	Pelvic and paraaortic LNs ***Radical hysterectomy only if cervix grossly involved***
III	Pre operative stage III, Any grade	***Pelvic and RP nodal debulking, Omentectomy***
IV	Pre operative Stage IV, Any grade	• ***Cytoreductive surgery if operable*** • ***Chemotherapy if inoperable/ extra abdominal diease, poor PS***

Sentinel LN dissection: Status

FIRES study

- Resulted in a sensitivity of SLN of 97.2%, a negative predictive value of 99.7% and a false-negative rate of 2.8%
- Majority were IA-B, Grade 1-2 tumors 70-80%)

SHREC Study: In high risk endometrial cancers

- SLN-ICG algorithm had a sensitivity of 98% (95% CI] 89-100)
- Negative predictive value of 99.5%
- Bilateral detection rate 95%

Rossi et al. Lancet Oncol 2017
Persson et al. Eur J Cancer. 2019

Sentinel LN dissection

- An approach to surgical staging in patients with endometrial cancer
- Three routes for dye instillation:
  - injection into the cervix
  - injection around the tumor via a hysteroscope
  - injection into the subserosal myometrium at the fundus.

Carcinoma cervix

Indications for surgery in upfront carcinoma cervix

- 1A1-2
- 1B1-2

- Minority only
- Early disease identified through proper evaluation: clinical and radiological

Stage-wise treatment

Stage	Standard Treatment	Fertility preserving option	Preservation of ovaries
1A1	Extrafacial hysterectomy	LEEP/ Conisation	Option to be given in young women
IA2	Type II radical hysterectomy	Trachelectomy	
IB1-B2	Type III radical hysterectomy	Radical trachelectomy	

Photo correlates

Classification of hysterectomies

Piver–Rutledge–Smith classification (1974)

Type I	Simple hysterectomy
Type II	Modified radical hysterectomy
	Ureters dissected to the point of their entry to the bladder
	Proximal uterosacral ligaments resected
	Medial half of the cardinal ligaments removed
	1–2 cm of upper vagina removed
Type III	Radical hysterectomy
	Removal of as much of the uterosacral ligaments as possible
	Entire width of the parametria is resected
	Upper third of the vagina is removed
Type IV	Extended radical hysterectomy
	As type III but three-quarters of the vagina and paravaginal tissue is removed
Type V	Partial exenteration
	The terminal ureter or a segment of the bladder or rectum is removed along with the uterus and parametria (supralevatorial)

Querleu–Morrow classification of radical hysterectomy

4 types of radical hysterectomy (A–D, below) based on lateral extent of resection. Applies to fertility preserving surgery and laparoscopic/robotic surgery.

Type	Description	Surgical considerations	Indication
A	Minimal resxn of paracervix	Paracervix transected medial to ureter but lateral to cervix. Uterosacral & cardinal ligaments transected close to uterus. Vaginal resxn (<10 mm).	Early invasive cervical cancer (<2 cm), advanced cervical cancer after chemoradiation
B	Transection of paracervix at level of ureter	Partial resxn of uterosacral & cardinal ligaments. Ureter unroofed & mobilized laterally. Vaginal resxn (10 mm).	Early cervical cancer (stage 1A)
C1	Transection of paracervix at junction w/ internal iliac artery (w/ nerve preservation)	Uterosacral ligament transected at rectum, cardinal ligament transected at bladder. Ureter mobilized. 15–20 mm of vagina resected. Hypogastric nerves identified, preserved.	Stages IB–IIA cervical cancer
C2	Transection of paracervix at junction w/ internal iliac artery (w/o nerve preservation)	Paracervix completely transected. Hypogastric nerves not isolated or preserved.	Stages IB–IIA cervical cancer
D1	Laterally extended endopelvic resxn	Resxn of entire paracervix (at pelvic sidewall) & hypogastric vessels	Pelvic exenteration
D2	Laterally extended endopelvic resxn	D1 + resxn of entire paracervix, hypogastric vessels, & adj fascial or musc structures	Pelvic exenteration

From Querleu D, Morrow CP. Classification of radical hysterectomy. *Lancet Oncol.* 2008;9(3):297–303. doi:10.1016/S1470-2045(08)70074-3.

Classification of radical hysterectomy and surgical treatment modalities corresponding

Classification Piver et al 1974	Classification Querler/Morrow (2008)	Surgical treatment modalities for cervical cancer
		Conization
Type 1	Type A	Extra-fascial simple total hysterectomy
Type II-III	Type B	Extended simple total hysterectomy or Semi-Radical hysterectomy
		Radical Trachelectomy
	Type C1	Radical hysterectomy with Nerve-sparing
Type III?	Type C2	Radical hysterectomy (Latzko's or Meigs' surgery) Okabayashi's radical hysterectomy (not equal)
	Type D1	Laterally extended parametrectomy(LEP) (Mibayashi: su per-rasical hysterectomy (TEIIBS))
	D2	D1 + adjacent fascial or muscular structure: laterally extended endopelvic resection(LEEP)
		Pelvic Exenteration

Sentinel LN dissection

SENTICOL study (2011):High sensitivity of 92%, NPV of 98%

Sentinel LN biopsy has been included in the NCCN guidelines for stage IB1 disease (<2 cm tumour)

Still more Validation studies needed: SENTICOL III

Surgery for carcinoma vulva

- Management of primary lesion
- Management of Lymph nodes

Stage	Description
I	**Tumor confined to the vulva**
	IA Tumor size ≤2 cm and stromal invasion ≤1 mm[a]
	IB Tumor size >2 cm or stromal invasion >1 mm[a]
II	**Tumor of any size with extension to lower one-third of the urethra, lower one-third of the vagina, lower one-third of the anus with negative nodes**
III	**Tumor of any size with extension to upper part of adjacent perineal structures, or with any number of nonfixed, nonulcerated lymph node**
	IIIA Tumor of any size with disease extension to upper two-thirds of the urethra, upper two-thirds of the vagina, bladder mucosa, rectal mucosa, or regional lymph node metastases ≤5 mm
	IIIB Regional[b] lymph node metastases >5 mm
	IIIC Regional[b] lymph node metastases with extracapsular spread
IV	**Tumor of any size fixed to bone, or fixed, ulcerated lymph node metastases, or distant metastases**
	IVA Disease fixed to pelvic bone, **or** fixed or ulcerated regional[b] lymph node metastases
	IVB Distant metastases

Surgical management of vulvar cancer

Early vulva cancer:

- Wide radical local excision

  As effective as a radical vulvectomy in preventing local recurrence, but substantially decreases the psychosexual morbidity of the treatment
- Preferred margin in unfixed specimen 2cms, pathological margin 8mm

Groin LN dissection

Indication

Any tumor more than microinvasive disease (>2cms, > 1mm stromal invasion)

Current standard

- Resection of the primary tumor and lymphnodes through separate incisions.
  - Allows better healing compared with en bloc resection of the vulva and groins.
- Both inguinal and femoral nodes should be removed

Groin LN dissection

Tumors <4cms, and > 2cnms from midline: Ipsilateral Groin node dissection only

<u>Indications of BL lymphnode dissection</u>

- Tumors closer to (<2 cm) or crossing the midline, especially those involving the anterior labia minora,
- Very large lateral tumors (>4 cm)
- Positive ipsilateral nodes, should have a bilateral groin node dissection

Role of sentinel LN dissection in early vulvar cancer: GROINSS V study

Indications

- Unifocal tumors confined to the vulva
- Tumors less than 4 cm in diameter
- Stromal invasion more than 1 mm
- Clinically and radiologically negative groin nodes

- If Ipsilateral sentinel lymph node is not detected: a complete ipsilateral inguinofemoral lymphadenectomy must be done.

- If an ipsilateral sentinel lymph node is positive: a complete bilateral inguinofemoral lymphadenectomy is recommended

GROINS VII study

- Investigating the efficacy of groin radiation without inguinofemoral lymphadenectomy for patients with a single positive sentinel lymph node 2 mm or less in diameter

Conclusion: Groin radiotherapy is a safe alternative to inguinofemoral lymphadenectomy in cases of vulvar cancer ≤4 cm with sentinel lymph node metastasis ≤2 mm.

Oonk et al. Int. J Gynecol Cancer 2019

Ovary

- Carcinoma ovary
  - Staging surgery
  - Primary cytoreduction/ Debulking surgery
  - Interval cytoreduction
  - Secondary cytoreduction
  - Intraperitoneal chemotherapy and HIPEC

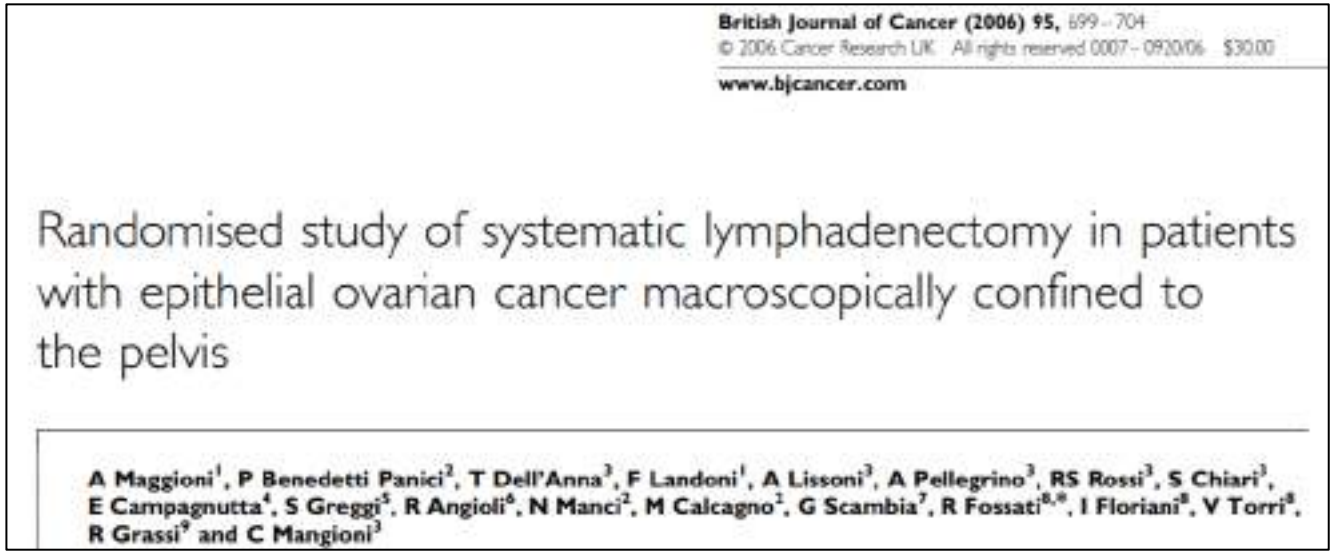
Components of Ovarian cancer staging surgery

Staging surgery Vs debulking/ cytoreductive surgery

- Earlier it was used synonymously
- Advances in imaging techniques helping in pre operative staging
- At times ovarlapping

Lymphadenectomy in Ovarian cancer

Early ovarian cancer



British Journal of Cancer (2006) 95, 699 – 704

www.bjcancer.com

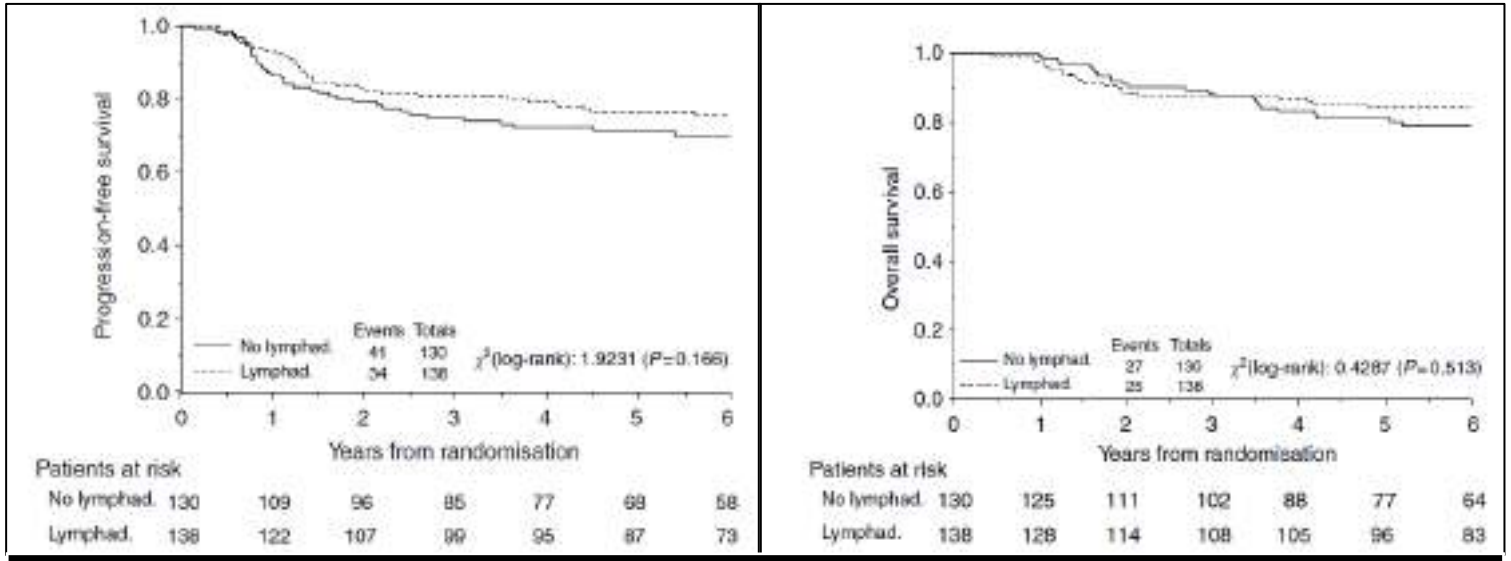
Randomised study of systematic lymphadenectomy in patients with epithelial ovarian cancer macroscopically confined to the pelvis

A Maggioni[1], P Benedetti Panici[2], T Dell'Anna[3], F Landoni[1], A Lissoni[3], A Pellegrino[3], RS Rossi[3], S Chiari[3], E Campagnutta[4], S Greggi[5], R Angioli[6], N Manci[2], M Calcagno[2], G Scambia[7], R Fossati[8,9], I Floriani[8], V Torri[8], R Grassi[9] and C Mangioni[3]

- Macroscopically intrapelvic ovarian carcinoma
- Systemic lymphadenectomy vs pelvic para-aortic nodal sampling
- **Primary objective : Proportion of patient with RP nodal involvement**

Effect on survival

Maggioni et al. BJC 2006



- 9% vs 22% lymph node involvement rates in two arms
- Longer operative time, blood loss, need for blood tranfusions

Multivariable cox propotional hazards analysis for PFS and OS

Rx arm	PFS		OS	
No Lymphadenectomy Vs Lymphadenectomy	HR(95% CI)	P	HR(95% CI)	P
	0.72(0.46 -1.14)	0.16	0.85(0.49-1.47)	0.56

Drawback :

- **<u>Underpowered for survival</u>**
- Increased use of chemo: Patients (90%) with positive nodes and 56% of patients with negative nodes received postoperative chemotherapy

ELSEVIER

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review

Lymph node metastasis in stages I and II ovarian cancer: A review

M. Kleppe [a], T. Wang [a], T. Van Gorp [a,b], B.F.M. Slangen [a,b], A.J. Kruse [a,b], R.F.P.M. Kruitwagen [a,b,*]

[a] Maastricht University Medical Centre, Department of Obstetrics and Gynecology, Maastricht, The Netherlands
[b] GROW, School for Oncology and Developmental Biology, Maastricht, The Netherlands

Incidence of lymph node metastases according to histological subtype.

Reference	Total population	FIGO Stage	Serous			Mucinous			Endometriod			Clear Cell			Undifferentiated/ Others		
			Total	LN+		Total	LN+		Total	LN+		Total	LN+		Total	LN+	
	n		n	n	%[a]	n	n	%[a]	n	n	%[a]	n	n	%[a]	n	n	%[a]
Desteli et al. [23]	33	I	7	1	14.2	8	0	0.0	5	0	0.0	4	0	0.0	9	1	11.1
Harter et al. [15]	48	I	13	2	15.4	8	0	0.0	14	1	7.1	7	0	0.0	6	0	0.0
Morice et al. [11]	85	I	26	8	30.8	20	0	0.0	25	0	0.0	–	–	–	14	9	64.3
Negeishi et al. [12]	150	I–II	35	5	14.3	49	2	4.1	15	3	20.0	46	8	17.4	5	1	20.0
Nomura et al. [16]	79	I–II	12	6	50.0	4	0	0.0	27	2	7.4	36	2	5.6	–	–	–
Onda et al. [7]	59	I–II	21	7	33.3	15	1	6.7	3	0	0.0	16	5	31.3	4	0	0.0
Suzuki et al. [10]	47	I	13	4	30.8	22	0	0.0	3	0	0.0	9	1	11.1	0	0	0.0
Tsumura et al. [8]	73	I–II	23	2	8.7	29	1	3.4	–	–	–	21	4	19.0	–	–	–
Total	574		150	35	23.3	155	4	2.6	92	6	6.5	139	20	14.4	38	11	28.9

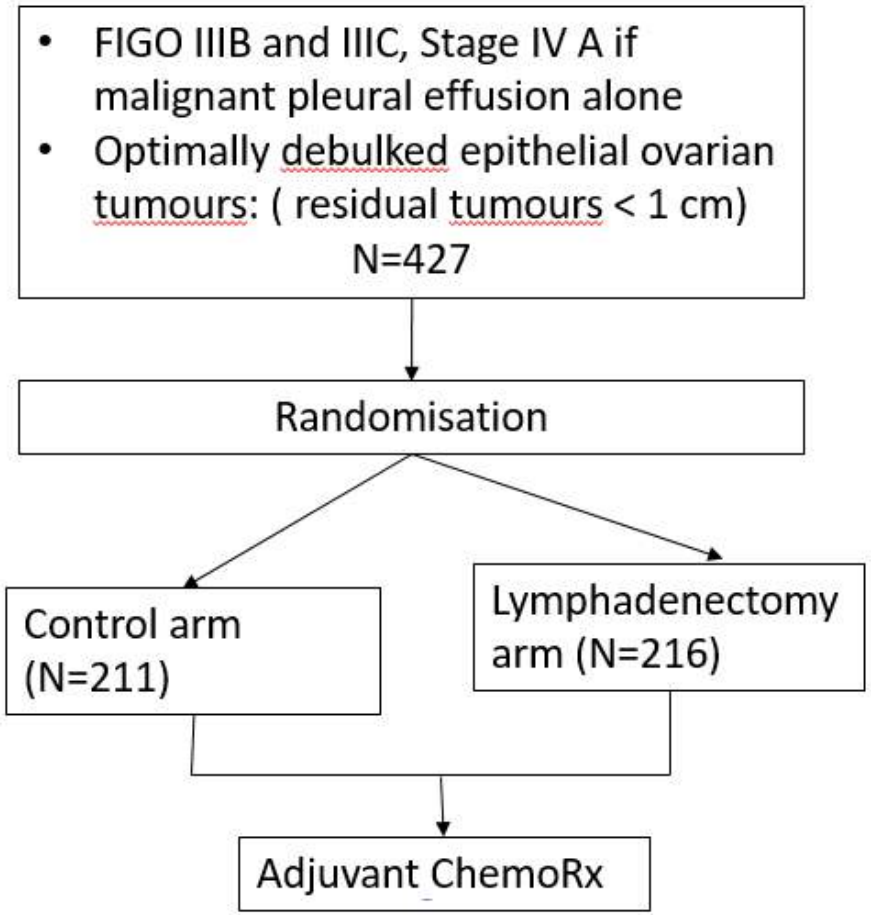
Contralateral lymph node metastases of a unilateral tumour was found in 16% of positive pelvic nodes and 11% of positive para-aortic nodes

ADVANCED OVARIAN CANCER

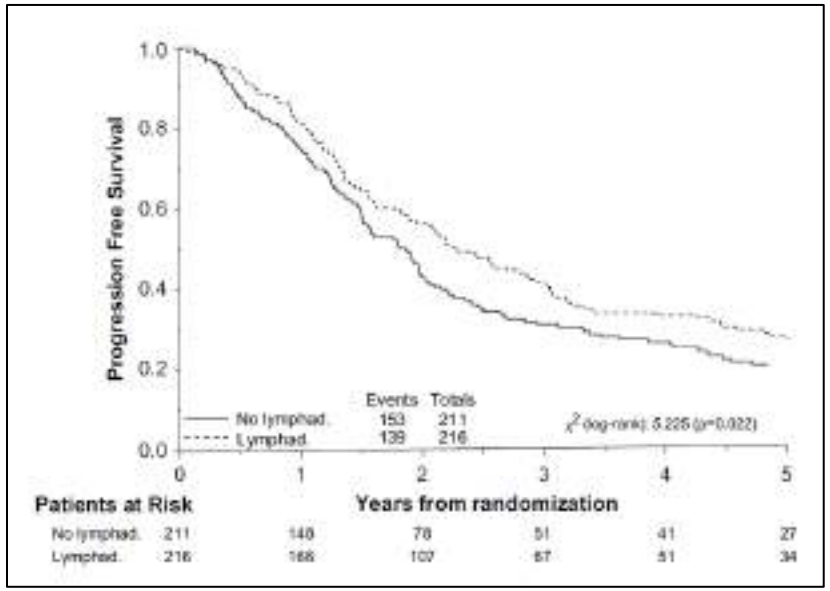
Systematic Aortic and Pelvic Lymphadenectomy Versus Resection of Bulky Nodes Only in Optimally Debulked Advanced Ovarian Cancer: A Randomized Clinical Trial

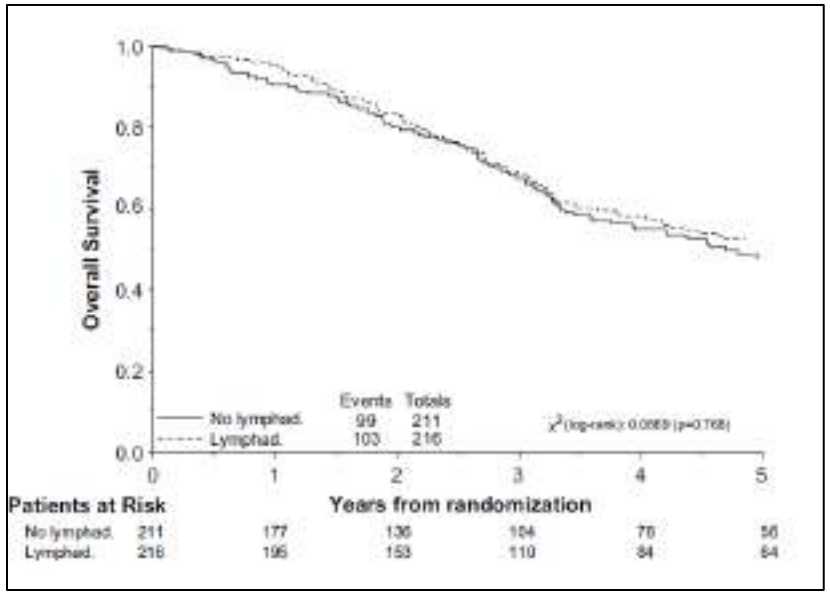
Pierluigi Benedetti Panici, Angelo Maggioni, Neville Hacker, Fabio Landoni, Sven Ackermann, Elio Campagnutta, Karl Tamussino, Raimund Winter, Antonio Pellegrino, Stefano Greggi, Roberto Angioli, Natalina Manci, Giovanni Scambia, Tiziana Dell'Anna, Roldano Fossati, Irene Floriani, Rita S. Rossi, Roberto Grassi, Giuseppe Favalli, Francesco Raspagliesi, Diana Giannarelli, Luca Martella, Costantino Mangioni

DOI: 10.1093/jnci/dji102
Journal of the National Cancer Institute, Vol. 97, No. 8,



Survival Outcomes





Surgical Outcomes

Surgical outcome	No lymphadenectomy (n = 211)	Lymphadenectomy (n = 216)	*P*
Median operating time (min) (25th–75th percentiles)	210 (170–280)	300 (250–360)	<.001
Missing data	5	5	
Median blood loss (mL) (25th–75th percentiles)	650 (400–1200)	1000 (600–1500)	<.001
Missing data	14	10	
Patients transfused (%)	59.2	71.7	.006
Median hospital stay (days) (25th–75th percentiles)	9 (7–12)	9 (7–13)	.21
Missing data	9	10	

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Potential Role of Lymphadenectomy in Advanced Ovarian Cancer: A Combined Exploratory Analysis of Three Prospectively Randomized Phase III Multicenter Trials

Andreas du Bois, Alexander Reuss, Philipp Harter, Eric Pujade-Lauraine, Isabelle Ray-Coquard, and Jacobus Pfisterer

Results

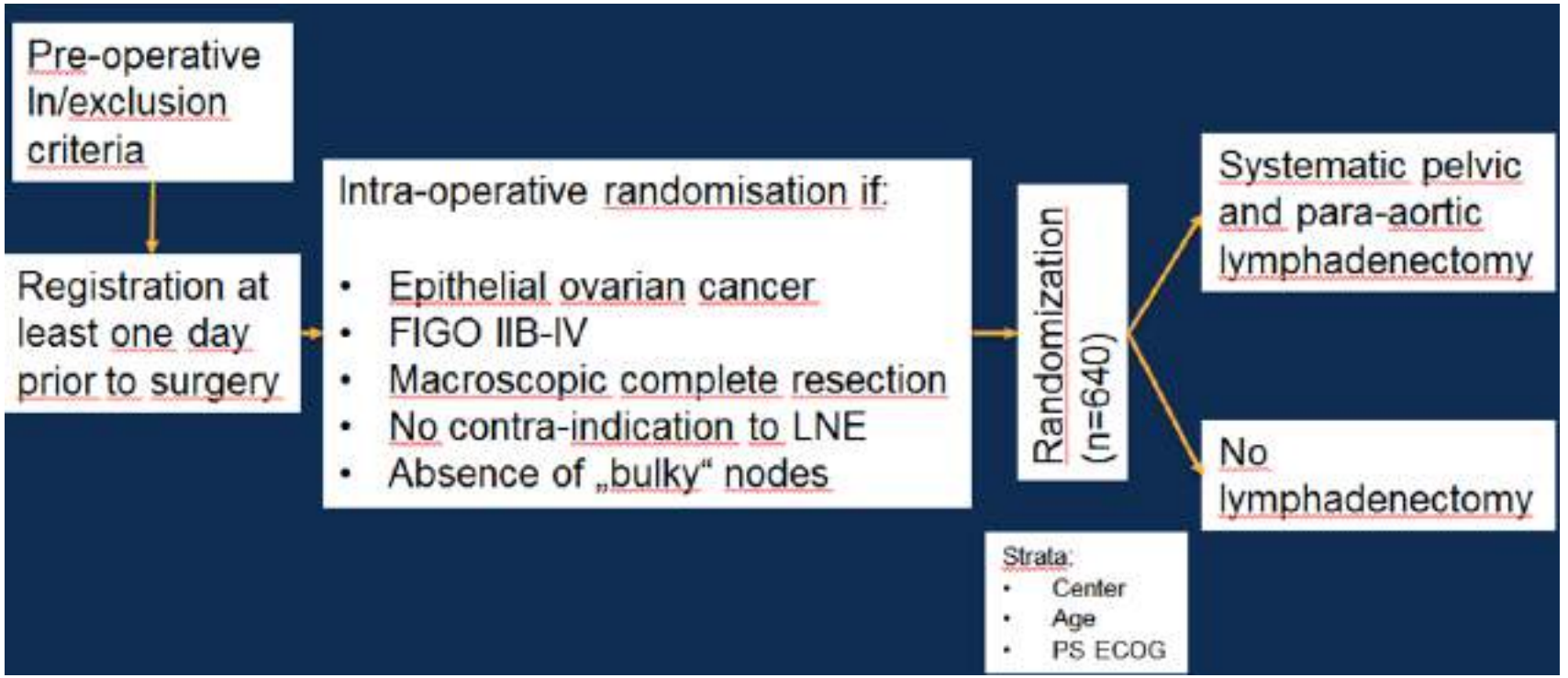
- Multivariate analysis confirmed a significant impact of lymphadenectomy on overall survival
  - (OS; hazard ratio [HR] 0.74; 95% CI, 0.59 to 0.94; *P* .0123).
- Definite benefit in patients with no gross residual disease
- Improved survival irrespective of clinical suspicion

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Lymphadenectomy in Patients with Advanced Ovarian Neoplasms

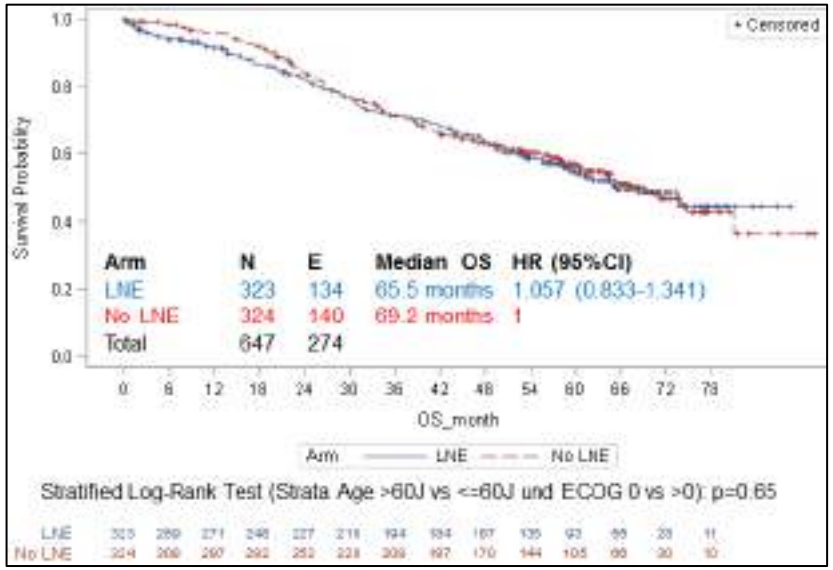
P. Harter, J. Sehouli, D. Lorusso, A. Reuss, I. Vergote, C. Marth, J.-W. Kim, F. Raspagliesi, B. Lampe, G. Aletti, W. Meier, D. Cibula, A. Mustea, S. Mahner, I.B. Runnebaum, B. Schmalfeldt, A. Burges, R. Kimmig, G. Scambia, S. Greggi, F. Hilpert, A. Hasenburg, P. Hillemanns, G. Giorda, I. von Leffern, C. Schade-Brittinger, U. Wagner, and A. du Bois

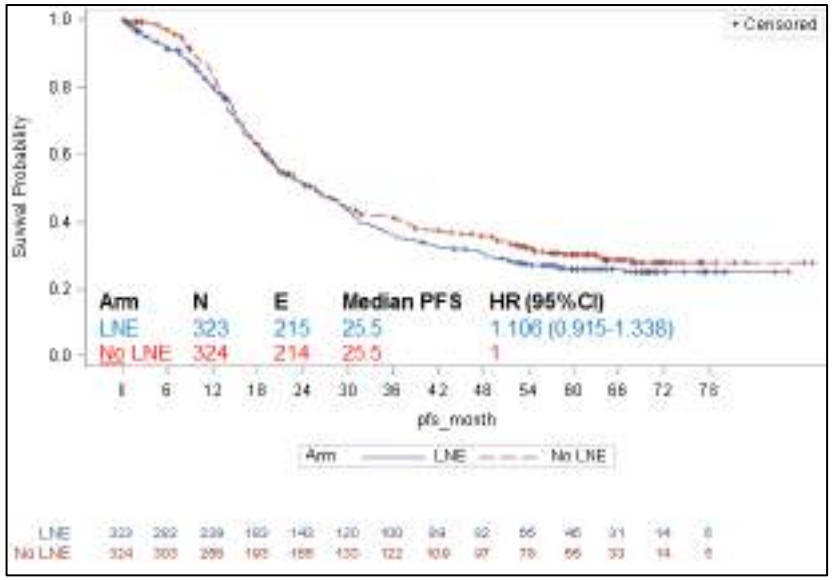


LION: Patient characteristics

	LNE (%), n= 323	No LNE (%), n=324	P-value
Age (median, range) [years]	60 (21-83)	60 (23-78)	0.66
Performance status ECOG 0 ECOG 1	 272 (84.2) 51 (15.8)	 280 (86.4) 44 (13.6)	0.43
Histologic diagnosis before registration	106 (32.8)	106 (32.7)	0.98
CA 125 pre-OP (median, IQR) [U/ml]	416 (138-1276)	347 (122-1025)	0.42
Final histological diagnosis Ovarian / Fallopian Tube / Peritoneal Ca Others	 304 (94.1) 19 (5.9)	 303 (93.5) 21 (6.5)	0.75
Final FIGO stage* I-IIA IIB-IIIA III-IV missing	 15 (4.6) 41 (12.7) 261 (80.8)** 6 (1.9)	 17 (5.2) 52 (16.0) 244 (75.3)*** 11 (3.4)	0.32
Histology: G2/3 serous others	 234 (72.4) 89 (27.6)	 227 (70.1) 97 (29.9)	0.54

Survival Outcomes





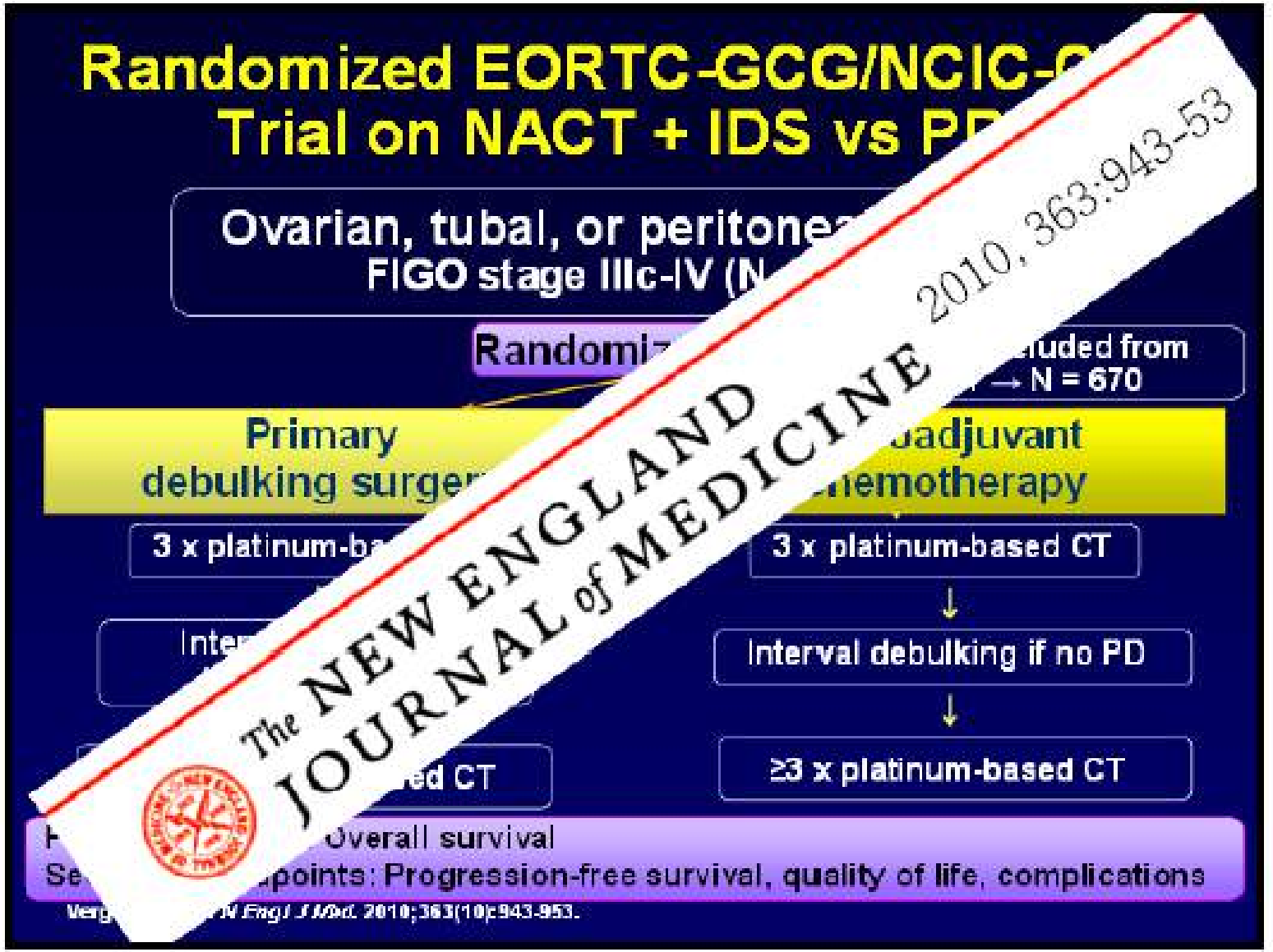
Postoperative complications

	LNE (%)	No LNE (%)	p-value
Infections requiring antibiotics	83 (25.8)	60 (18.6)	0.03
Fever > 38.0° Celsius	41 (12.7)	32 (9.9)	0.21
Sepsis	6 (1.9)	3 (0.9)	0.31
Thrombosis	7 (2.2)	5 (1.6)	0.56
Pulmonary embolism	12 (3.7)	15 (4.6)	0.56
Secondary wound healing	31 (9.6)	19 (5.9)	0.12
Prolonged ileus (conservative management)	15 (4.6)	17 (5.3)	0.72
Peripheral sensoric neurologic event	7 (2.2)	7 (2.2)	0.99
Peripheral motoric neurologic event	10 (3.1)	8 (2.5)	0.63
Asymptomatic lymph cysts	14 (4.4)	1 (0.3)	<0.001
Symptomatic lymph cysts	10 (3.1)	0	0.001
Fistula	5 (1.6)	7 (2.2)	0.56
Readmission rate	40 (12.4)	27 (8.3)	0.09
Rate of re-laparotomy for complications	40 (12.4)	21 (6.5)	0.01
60 day postoperative mortality	10 (3.1)	3 (0.9)	0.049
Platinum + Taxan i.v.	257 (79.6)	274 (84.6)	0.09

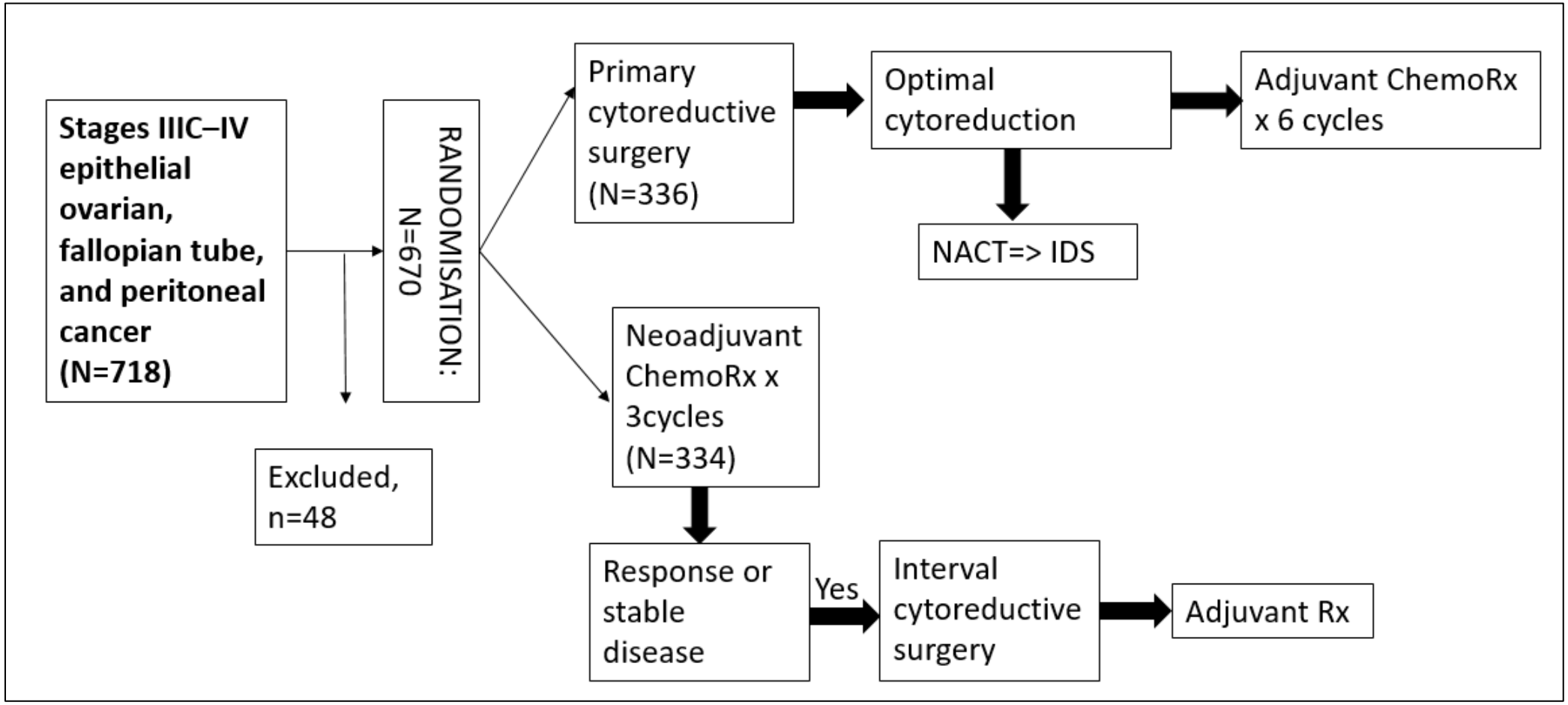
Primary cytoreduction Vs Interval cytoreduction: Controversies

- Meig's: 1934: PDS associated with improved outcomes
- Griffiths reported in 1975 the association between low residual tumour load and improved survival after debulking surgery
  - Efforts at maximum possible cytoreduction
  - Many retrospective series: Supporting the concept (Bristow et al, Chi et al)
- Chi et al (2006) – HR for gross residual ≤ 1cm was 2.09 and for gross residual > 1cm was 3.98

These are talk of era when the role of chemotherapy was emerging!!


Randomized EORTC-GCG/NCIC-
Trial on NACT + IDS vs P
Ovarian, tubal, or peritone
FIGO stage IIIc-IV (N
Randomi
luded from
→ N = 670
Primary
debulking surge
adjuvant
hemotherapy
3 x platinum-ba
3 x platinum-based CT
Inte
Interval debulking if no PD
ed CT
≥3 x platinum-based CT
Overall survival
Se points: Progression-free survival, quality of life, complications
The NEW ENGLAND JOURNAL of MEDICINE 2010, 363:943-53

Trial Design

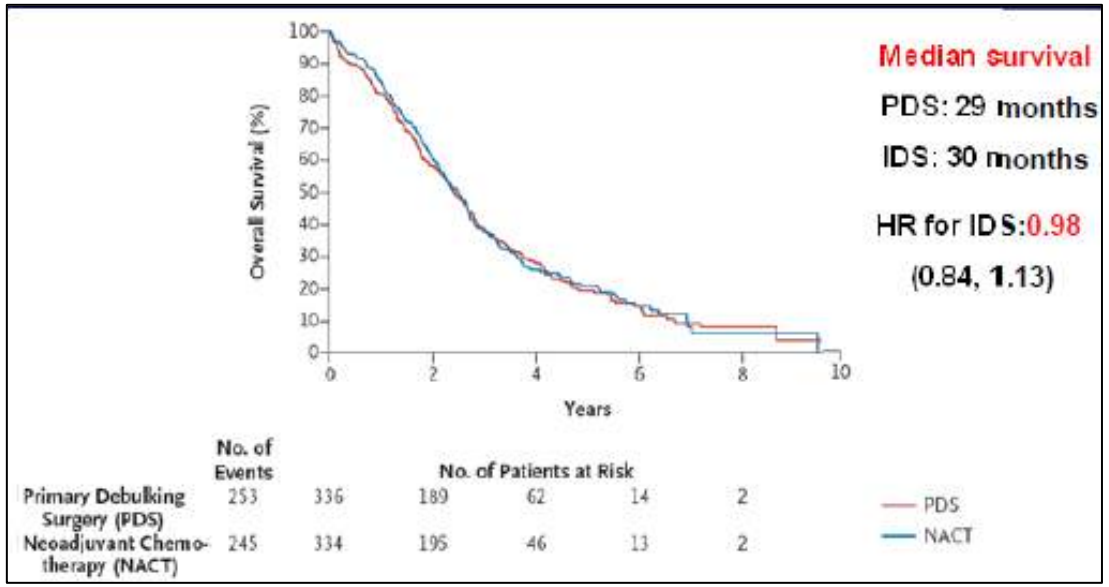


Primary outcome : OS

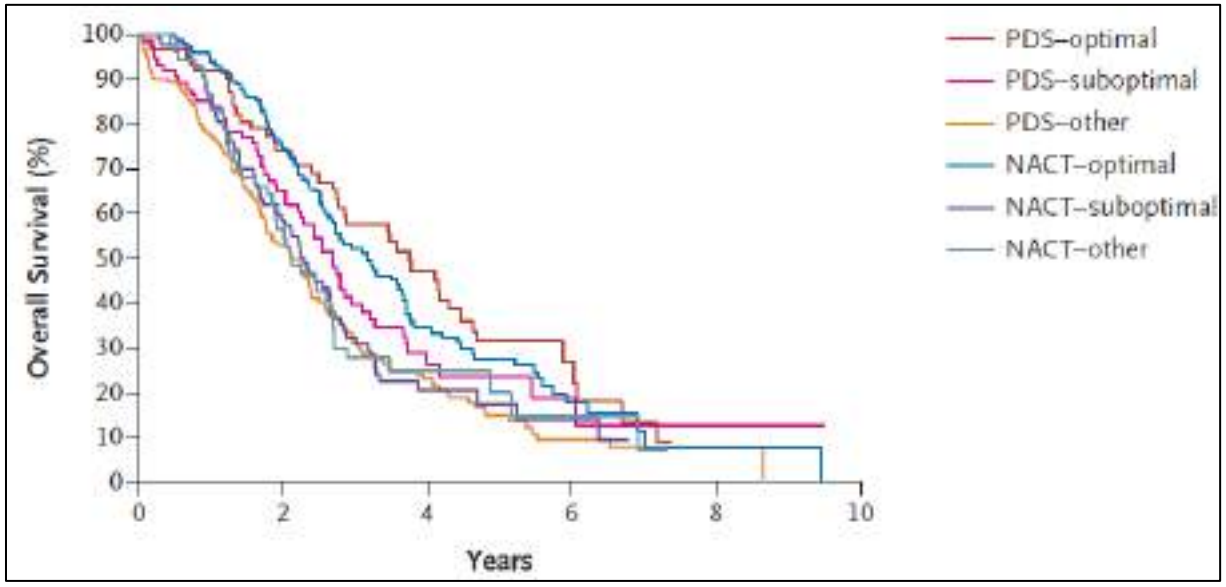
Secondary outcomes :

PFS, surgical morbidity and mortality, QoL and adverse effects

Vergote et al, NEJM 2010



Overall Survival in the Intention-to-Treat Population

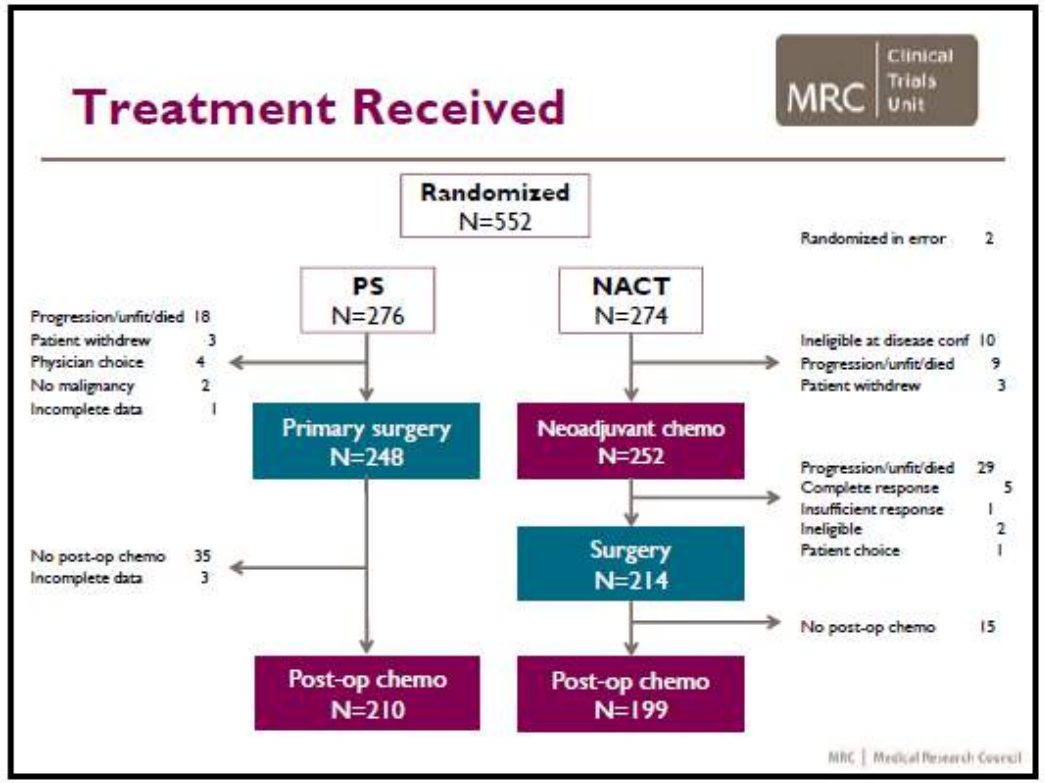


Per protocol analysis: Overall Survival According to Treatment Received & Status with Respect to Residual Tumor

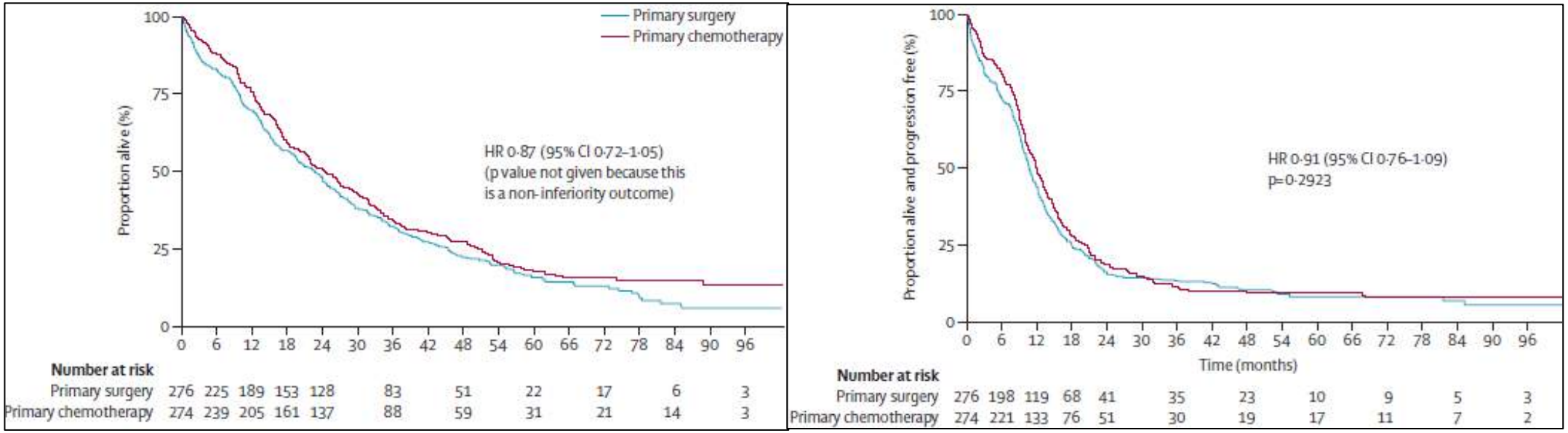
- Optimal debulking (80.6% vs 41.6%) achieved more often in NACT group (RR 2.56)
- In subgroup with pre-op extra-pelvic tumor < 5cm (n=189), PDS significantly improved OS (HR 0.64, 95% CI 0.44-0.93)

Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial

Sean Kehoe, Jane Hook, Matthew Nankivell, Gordon C Jayson, Henry Kitchener, Tito Lopes, David Luesley, Timothy Perren, Selina Bannoo, Monica Mascarenhas, Stephen Dobbs, Sharadah Essapen, Jeremy Twigg, Jonathan Herod, Glenn McCluggage, Mahesh Parmar, Ann-Marie Swart



- Complete debulking rate was only 16% in the PDS group, compared to 40% following neoadjuvant chemotherapy
- Debulking to less than 1 cm residual disease 41% in the primary-surgery group versus 73% in the primary-chemotherapy group, p=0·0001
- Median duration of surgery: 120 minutes in both groups



Kaplan-Meier curves for overall survival (A) and progression-free survival (B)

Kehoe et al. Lancet 2015

Neoadjuvant chemotherapy versus debulking surgery in advanced tubo-ovarian cancers: pooled analysis of individual patient data from the EORTC 55971 and CHORUS trials

Ignace Vergote, Corneel Coens, Matthew Nankivell, Gunnar B Kristensen, Mahesh K B Parmar, Tom Ehlen, Gordon C Jayson, Nick Johnson, Ann Marie Swart, René Verheijen, W Glenn McCluggage, Tim Perren, Pierluigi Benedetti Panici, Gemma Kenter, Antonio Casado, Cesar Mendiola, Gavin Stuart, Nick S Reed, Sean Kehoe, and the EORTC and MRC CHORUS study investigators

- **No difference in median overall survival was noted between patients who underwent neoadjuvant chemotherapy and upfront debulking surgery (27·6 months [IQR 14·1–51·3] and 26·9 months [12·7–50·1], respectively; hazard ratio [HR] 0·97, 95% CI 0·86–1·09; p=0·586).**

Lancet Oncol 2018; 19: 1680–87

Survival analyses from a randomized trial of primary debulking surgery versus neoadjuvant chemotherapy for advanced epithelial ovarian cancer with high tumor load (SCORPION trial) (NCT01461850)

Fagotti A, Ferrandina G, Vizzielli G, Fanfani F, Gallotta V, Chiantera V, Costantini B, Margariti PA, Gueli Alletti S, Cosentino F, Tortorella L, Scambia G.

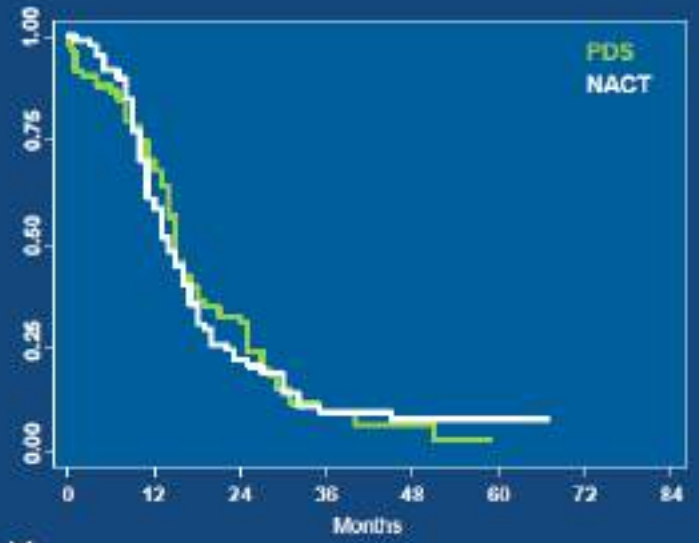
Fondazione Policlinico Universitario A. Gemelli, IRCCS
Università Cattolica del Sacro Cuore, Rome, Italy

	NACT	PCS	
Residual tumor -0 cm	45.5%	57.7%	P=0.206
grade III–IV complications	5.7%	52.7%	P=0.0001

Perioperative moderate/severe morbidity as well as QoL scores were shown to be more favourable in NACT/IDS arm

Fagotti et al. Eu J Cancer 2016

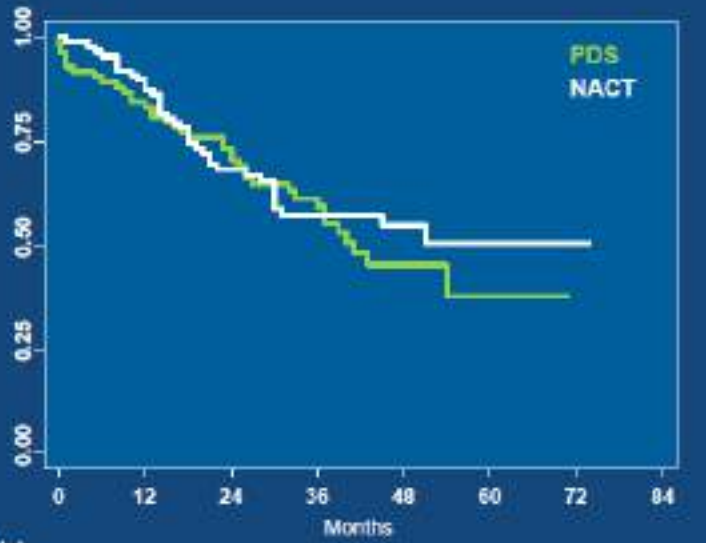
Survival analysis on ITT population



Number at risk

PDS	84	58	24	4	2	0	0	0
NACT	87	53	16	6	4	1	0	0

	PDS	NACT	HR (95% CI) P value
Recurrences	63 (77.4)	72 (82.4)	0.378
Median PFS (mths)	14	15	1.06 (0.77-1.46) 0.729



Number at risk

PDS	84	70	53	31	11	2	0	0
NACT	87	78	49	31	18	5	1	0

	PDS	NACT	HR (95% CI) P value
Deaths	38 (45.2)	36 (41.4)	0.611
Median OS (mths)	41	NR	0.88 (0.56-1.39) 0.593

Fagotti et al. ASCO 2018

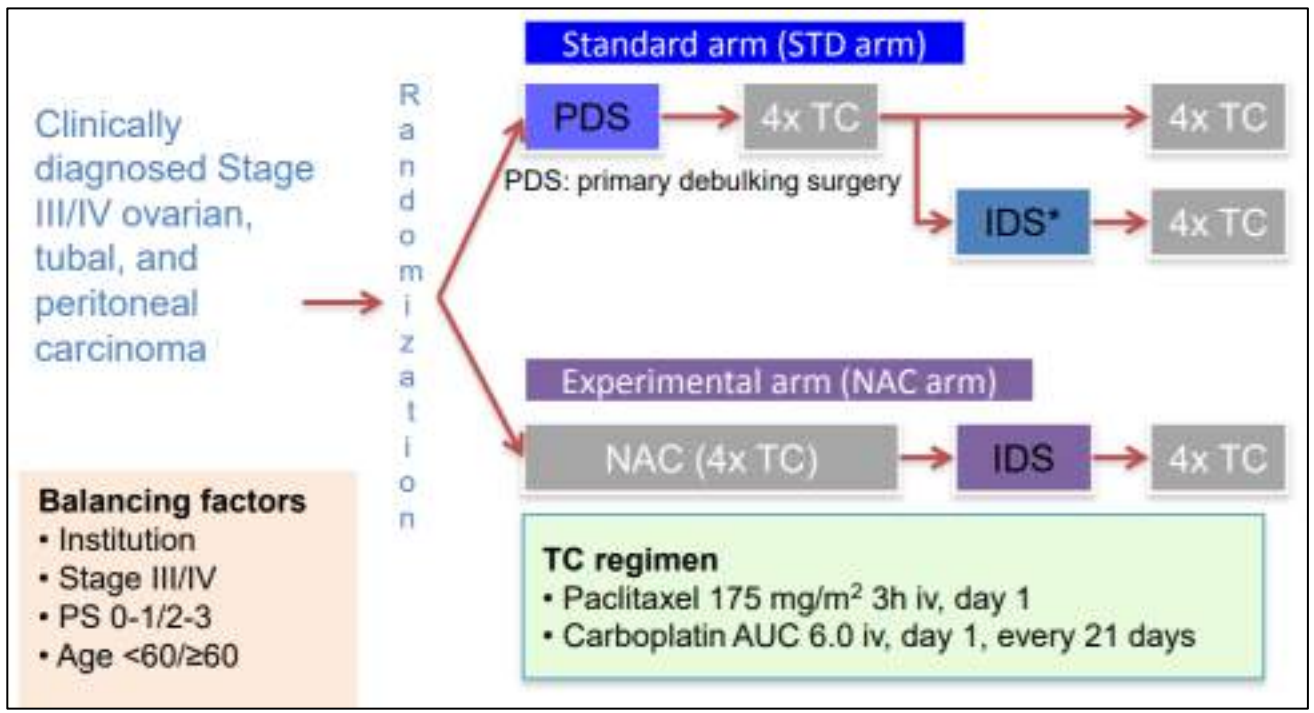
Optimal residual tumor (≤1 cm) was obtained in 92.8% versus 100% (*P* = .02)

Journal of Clinical Oncology > List of Issues > Volume 36, Issue 15_suppl >

GYNECOLOGIC CANCER

Comparison of survival between upfront primary debulking surgery versus neoadjuvant chemotherapy for stage III/IV ovarian, tubal and peritoneal cancers in phase III randomized trial: JCOG0602.

Takashi ONDA, Toyomi Satoh, Toshiaki Saito, Takahiro Kasamatsu, Toru Nakanishi, Kazuhiro Takehara, ...



Outcomes

- Complete resection was achieved in 12% (17/147) of PDS and in 64% (83/130) of IDS in NAC arm.
- Optimal surgery was achieved in 37% of PDS and in 82% (107/130) of IDS in NAC arm.

	PDS	NAC	95% CI
OS (mths)	49	44.3	1.05 (0.84-1.32)
PFS (mths)	15.1	16.4	0.99 (0.77-1.26)

Onda et al, JCO

Cochrane Library

Cochrane Database of Systematic Reviews

Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer (Review)

AUTHOR's CONCLUSION

- Moderate-certainty evidence suggests there is little or no difference in primary survival outcomes between PDS and NACT.
- NACT may reduce the risk of serious adverse events, especially those around the time of surgery, and the need for bowel resection and stoma formation.

Cochrane Database of Systematic Reviews 2019

Secondary cytoreduction

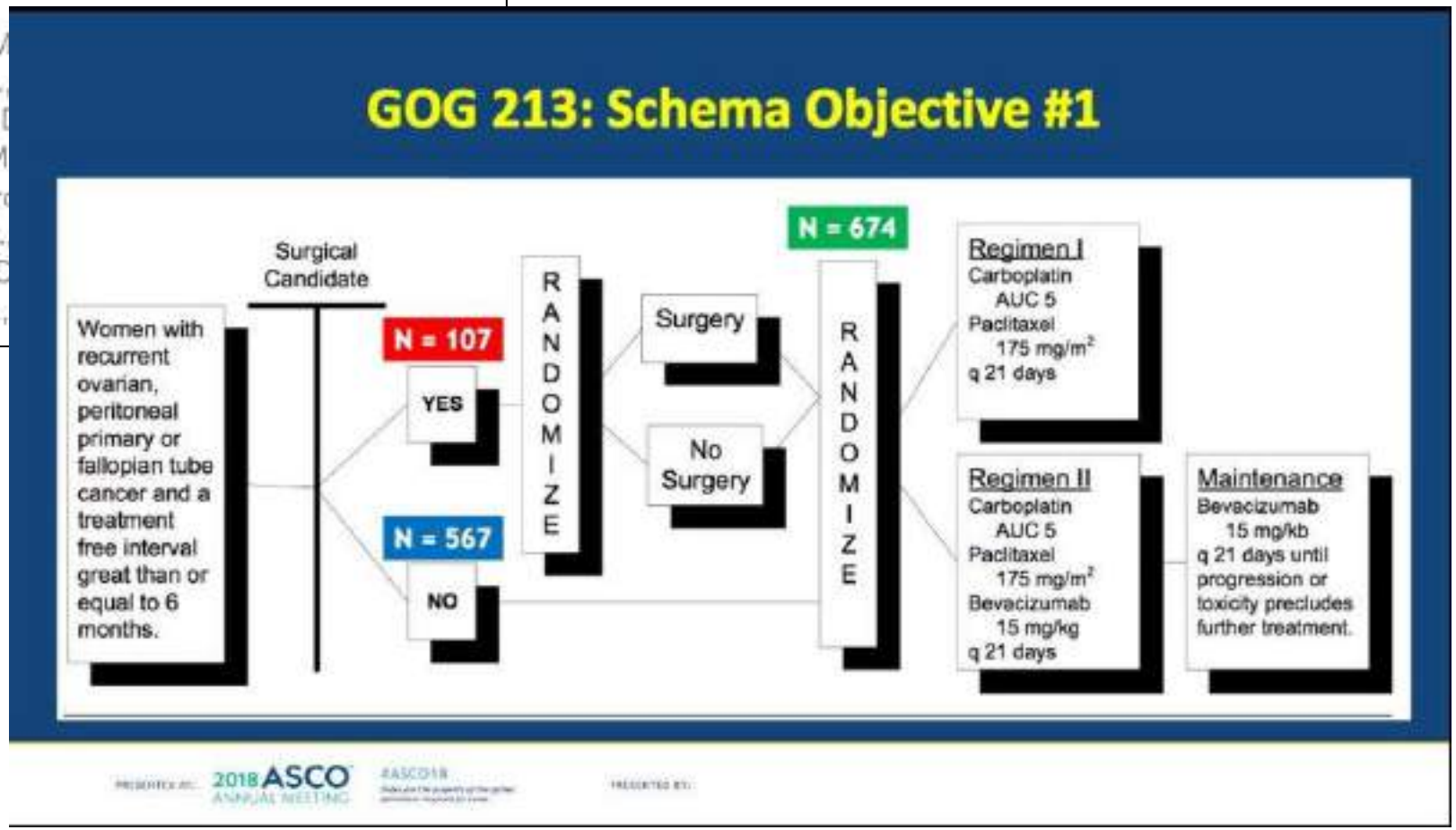
Role of secondary cytoreductive surgery for recurrent ovarian cancer not fully defined till recently

The NEW ENGLAND JOURNAL of MEDICINE

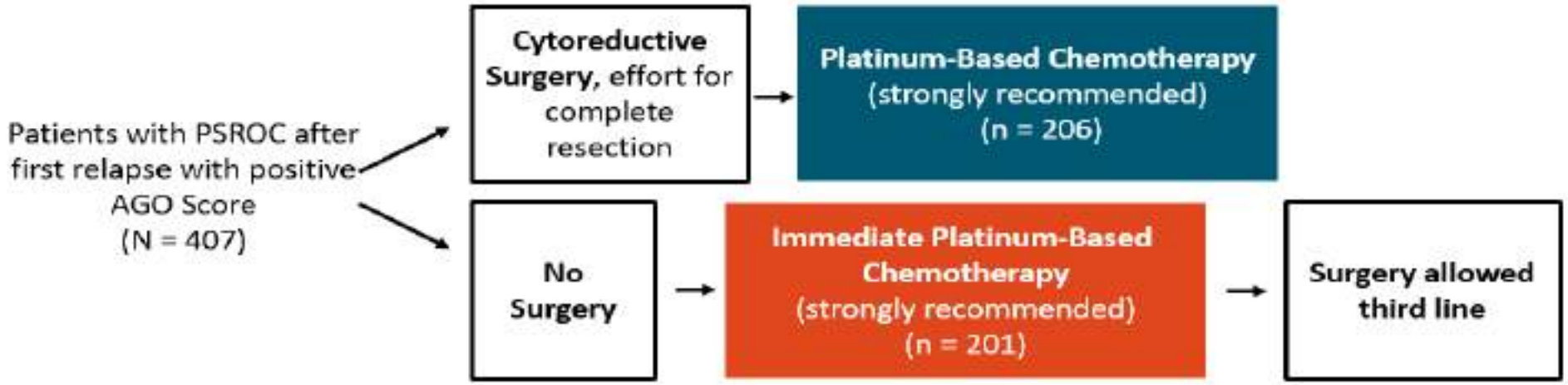
ORIGINAL ARTICLE

Secondary Surgical Cytoreduction for Recurrent Ovarian Cancer

Robert L. Coleman, M.D., Nick M. Spirtos, M
Thomas J. Herzog, M.D., Paul Sabbatini, M.D.,
Jae-Weon Kim, M.D., Sang-Yoon Park, M.D
Joo-Hyun Nam, M.D., Keiichi Fujiwara, M
Ann C. Casey, M.D., Angeles Alvarez Secord
John K. Chan, M.D., Paul DiSilvestro, M.D.,
David E. Cohn, M.D., Krishnansu S. Tewari, M.D
Helen Q. Huang, M.S., Mark F. Brady, Ph.D.,



DESKTOP III: Study Design



- Primary endpoint: OS
- Secondary end points: PFS, Resection rate, treatment burden
- Platinum-free interval exceeded 12 months in 75% of patients
- Almost 90% of patients received platinum-containing second-line chemotherapy in both arms of the trial
- 74.2% of women able to undergo a complete gross resection

Du Bois et al. JCO

SOC1: Trial design

Comparison of three published RCTs

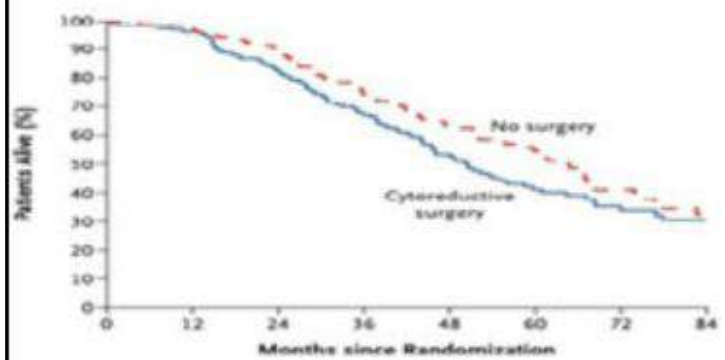
GOG-213, DESKTOP III and SOC-1 Comparison

	GOG-213	AGO Desktop III	SGOG SOC-1
Age	57 years	60.5 years	54 years
Initial Stage III-IV	86%	74.6%	82%
Selection criteria	Individualized for CGR	AGO model	iMODEL + PET-CT
Histology: Serous	86%	85%	81%
Median Platinum-Free Interval	19.7 mos	19.9 mos	16.1 mos
Cross-over to surgery (Control Violation)	2%	4%	6.3%
Complete Gross Resection	67%	74.2	76.7%
Mortality	30-day: 0.4%	90-day: 0.5%	60-day: 0%
Subsequent Surgery in Control Arm after Relapse	NA	11.0%	36.9%
Platinum-based Combination Therapy	100%	89%	? (100%)
The 2nd line bevacizumab	84%	23%	1%
The 2nd line PARPi maintenance	NA	<5%	10%

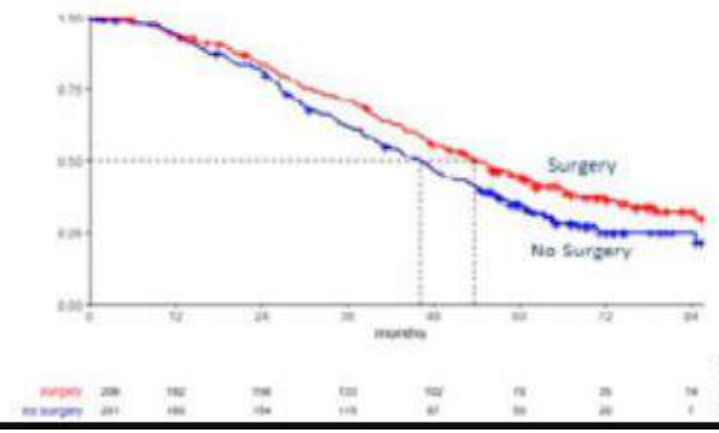
Survival Comparisons in Three Trials of Platinum-Sensitive Recurrent Ovarian Cancer

	GOG-213	AGO Desktop III	SGOG SOC-1
OS – Surgery (median)	53.6 mos	53.7 mos	58.1 mos
OS - No Surgery (median)	**65.7 mos**	46.0 mos	53.9 mos
HR, 95% CI	1.28 (0.92-1.78) **P = NS**	0.75 (0.58-0.96) **P = 0.04**	0.82 (0.57-1.19) **P = NS**

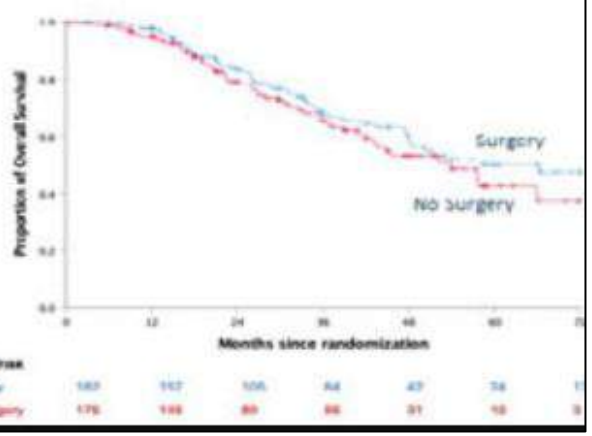
GOG-213



DESKTOP III



SOC-1



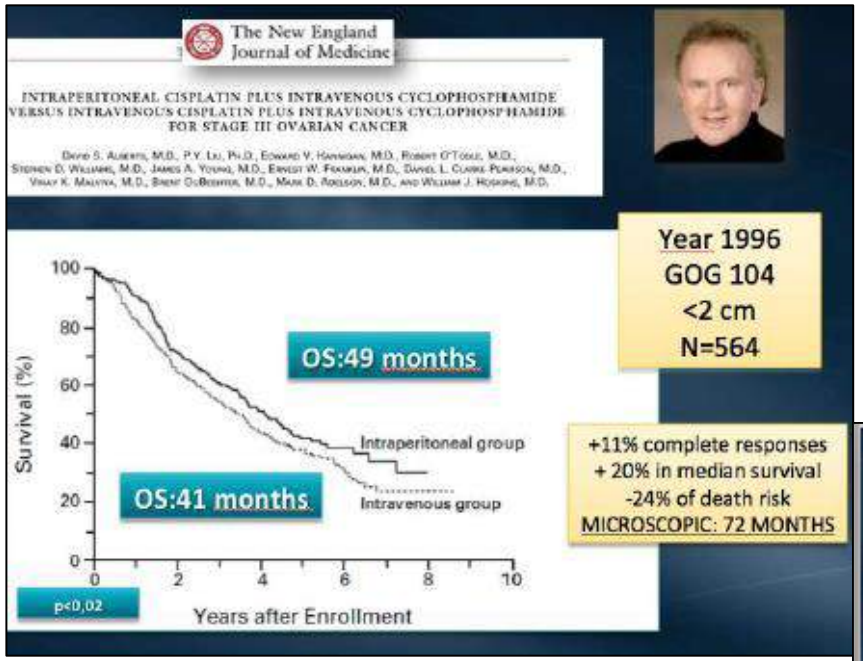
Conclusion

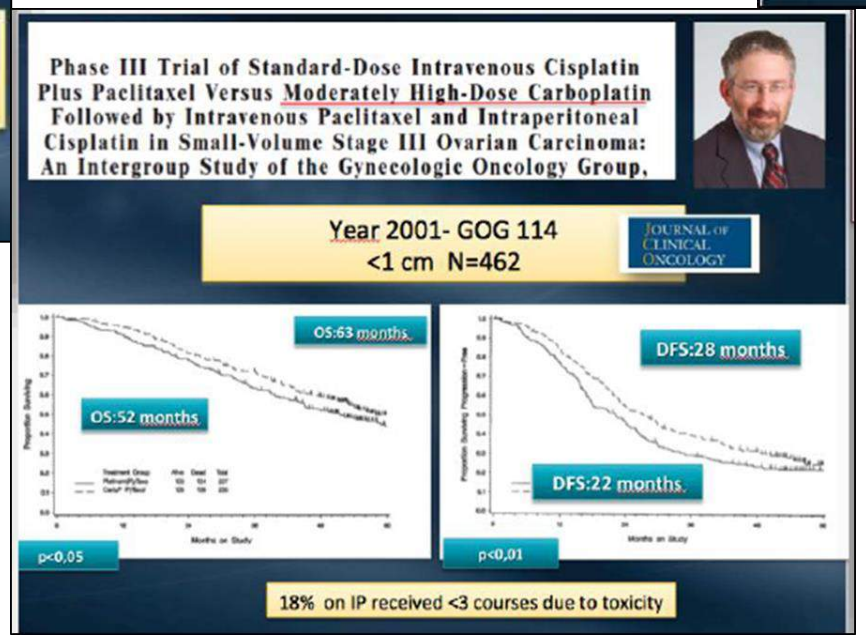
- Choose the patients wisely: Objective predictive scores seems to have an impact on complete resection rates
- Bevacizumab and recently incorporated PARP inhibitors may have significant impact in overall decision making

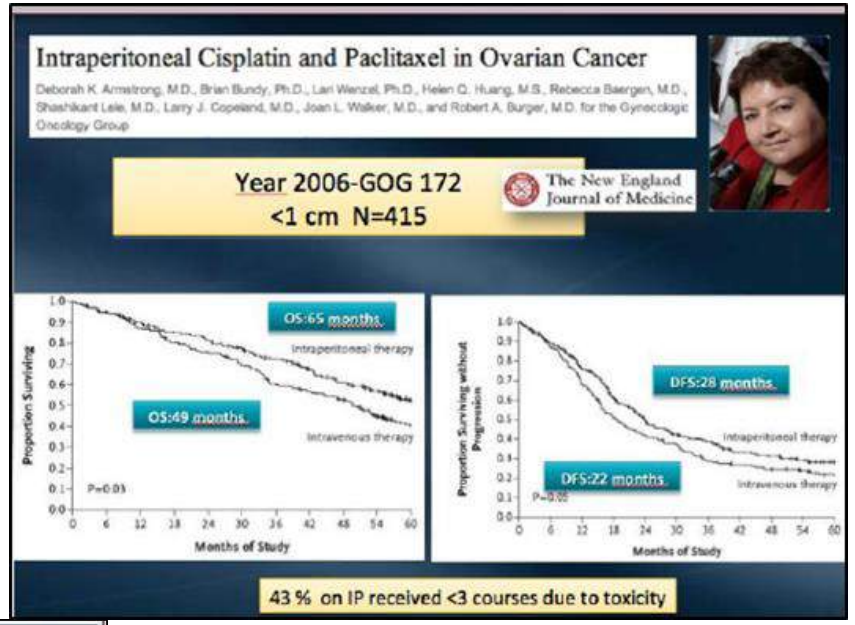
Intraperitoneal chemotherapy

- Ovarian cancer is a peritoneal disease
- Concentration of Cisplatin/ Carboplatin is 15-20 times higher intraperitoneally
- Drug clearance from the peritoneal cavity is significantly slower than from the vascular compartment

RCTs for IP chemoRx







VOLUME 33 · NUMBER 13 · MAY 1 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Long-Term Survival Advantage and Prognostic Factors Associated With Intraperitoneal Chemotherapy Treatment in Advanced Ovarian Cancer: A Gynecologic Oncology Group Study

Devansu Tewari, James J. Java, Ritu Salani, Deborah K. Armstrong, Maurie Markman, Thomas Herzog, Bradley J. Monk, and John K. Chan

Data from GOG protocols 114 and 172 were retrospectively analyzed

The advantage of Intraperitoenal over intravenous chemotherapy extends beyond 10 years.

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.

Cochrane Database of Systematic Reviews

[Intervention Review]

Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer

PLAIN LANGUAGE SUMMARY

Intraperitoneal chemotherapy (administered into the peritoneal cavity) for advanced ovarian cancer improves both overall and disease-free survival

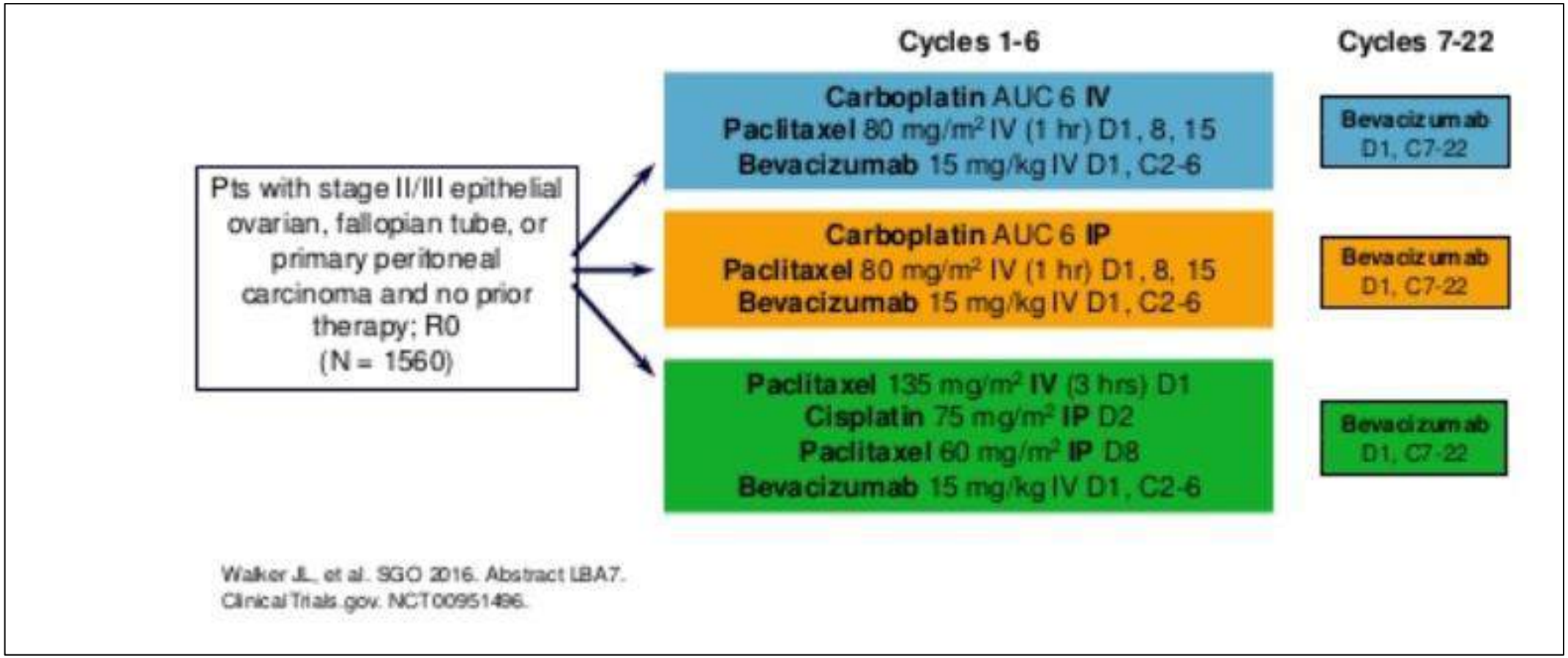
Ovarian cancer commonly spreads through the peritoneal cavity and usually responds to intravenous (IV) chemotherapy. This review compared the effectiveness of IV chemotherapy to chemotherapy administered directly into the peritoneal cavity (intraperitoneal, or IP). The evidence suggests an improvement in survival if some of the chemotherapy is administered via the intraperitoneal route. The disadvantage is an increase in adverse effects principally relating to the presence of a peritoneal catheter, including pain, catheter blockage, gastrointestinal effects and infection.

Intra-peritoneal chemotherapy

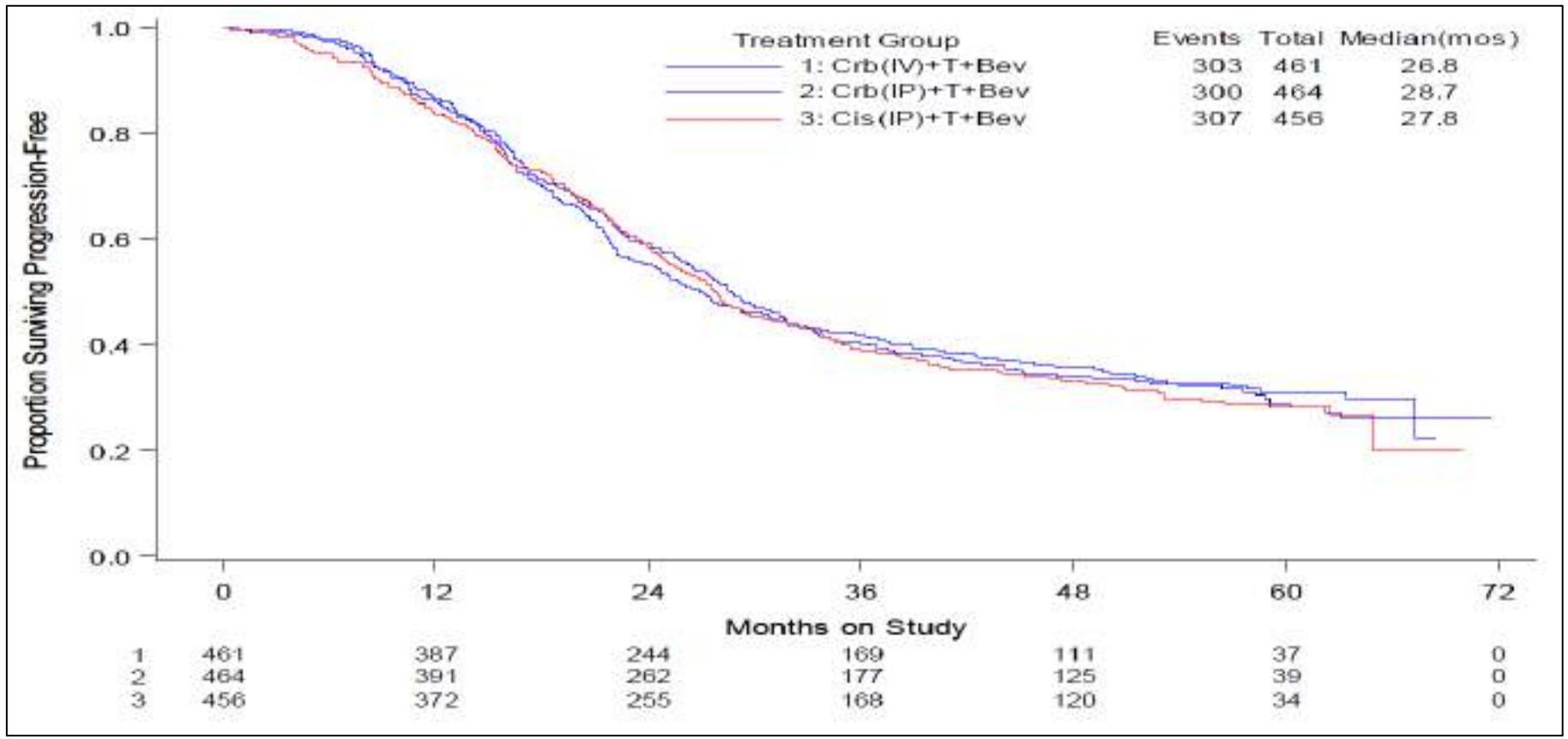
All the RCTs done had some Caveats:

- Either comparison with too old control arm
- Unbalanced control arms
- Too Toxic regimen
- Effect of more intense (dose dense schedule: GOG 172)

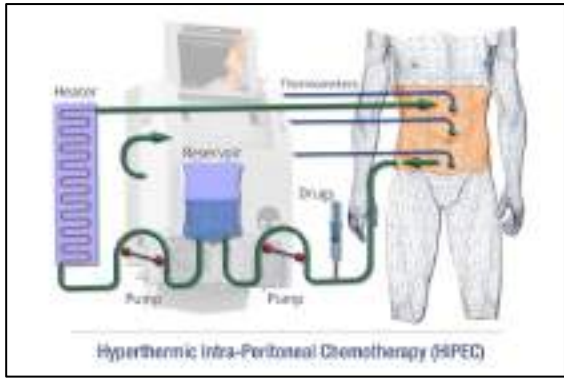
GOG 252: IV vs IP chemotherapy + Bevacizumab in stage II/ III ovarian cancer



GOG 252: Results



Hyperthermic Intraperitoneal chemotherapy: HIPEC



- OS benefit of IP chemotherapy
- Logistic issues and increased toxicities: Catheter-related problems, increased demands on the patient, and gastrointestinal and renal side effects

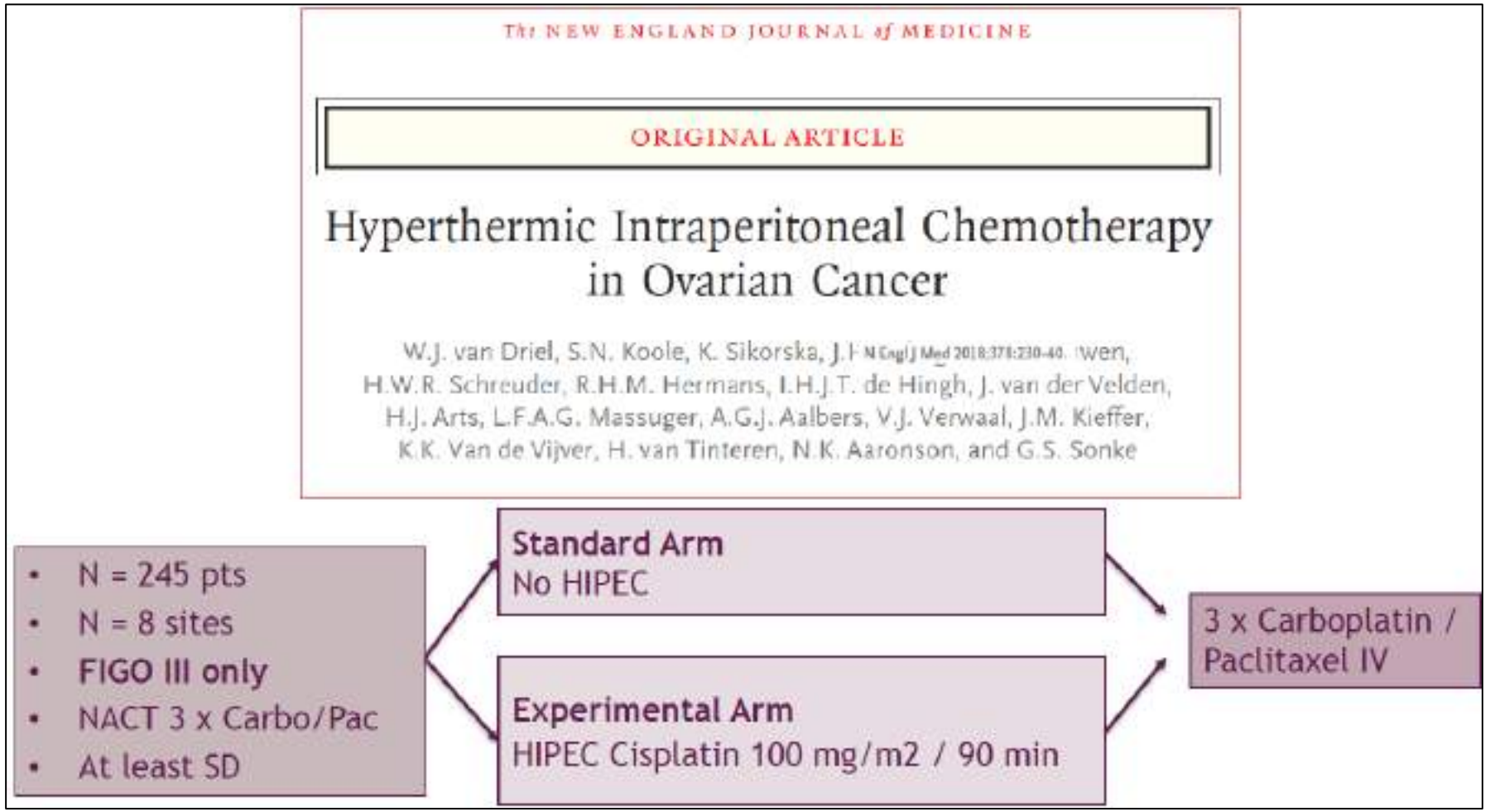
Delivery of the intraperitoneal chemotherapy at the end of surgery can circumvent most of these drawbacks while maintaining its advantages

Benefits of hyperthermia

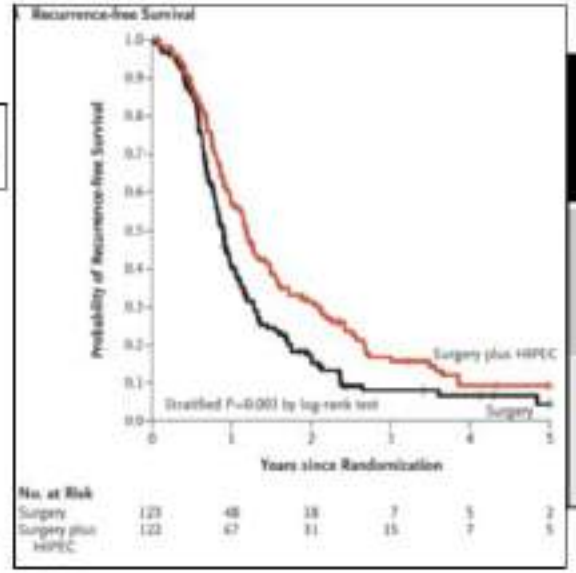
- Increased penetration of chemotherapy at the peritoneal surface
- Increased sensitivity of the cancer to chemotherapy by impairing DNA repair.

- Induction of apoptosis ,activation of heat-shock proteins that serve as receptors for
- natural killer cells,inhibition of angiogenesis, and a direct cytotoxic effect by promoting the denaturation
- of proteins

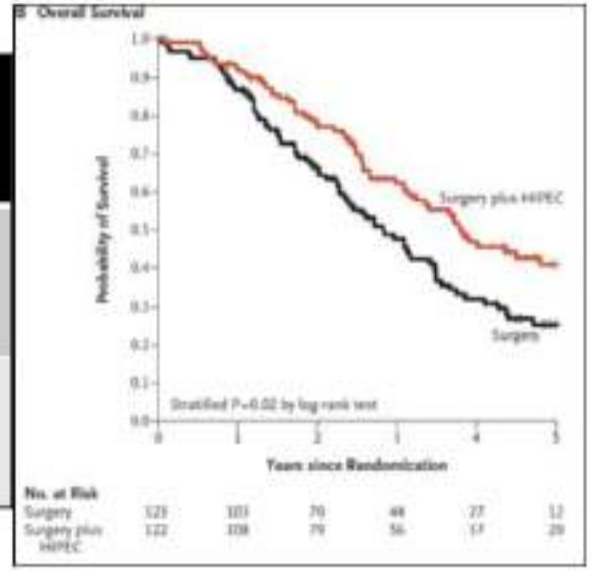
Role of HIPEC in IDS setting



Survival Outcomes



	Sx (mths)	Sx+ HIPEC mths)	HR (95% CI)
RFS	33.9	45.7	0.66; (0.50 to 0.87)
OS	33.9	45.7	0.67 (0.48 to 0.94)



Postop Outcomes

Variable	Surgery (N=123)	Surgery plus HIPEC (N=122)
Median duration of surgery (IQR) — min	192 (153–251)	338 (299–426)
Median duration of hospitalization (IQR) — days¶	8 (7–10)	10 (8–12)
Median time between surgery and start of first cycle of adjuvant chemotherapy (IQR) — days	30 (25–41)	33 (28–41)
Number of completed cycles of adjuvant chemotherapy after surgery — no. (%)		
0	7 (6)	5 (4)
1	2 (2)	0
2	3 (2)	2 (2)
3	111 (90)	115 (94)

Role of Minimally invasive surgery: Carcinoma Endometrium

Role of laparoscopy: (LAP 2 trial, LACE trial)

- Feasible, safe
- Morbidity less
- Equivalent survival outcomes

Role of Minimally invasive surgery: Carcinoma Cervix

LACC trial (2018)

- Phase III randomized control trial: Minimally invasive (laparoscopic or robotic) radical hysterectomy Vs open radical hysterectomy in women with early-stage cervical cancer
- Significantly lower DFS and OS in MIS group

Level I evidence against use of MIS in cervical cncer

Exenteration surgery: Anterior exenteration

- Morbid surgery
- Careful patient selection mandatory

Indications:

- Recurrent cervical or endometrial disease
  - Central disease
  - Not amenable for radiation treatment
  - Upfront IV disease with VVF, Not reaching the lateral walls
- Occasionally in case of residual disease after radiation treatment: Not reaching the lateral walls

Thank you