

Surgical Options in Ovarian Cancer

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What are the options?

- Immediate Surgical Intervention for all.
- Delayed Surgery
- Secondary Surgery

- *And also:*
- Debulking Surgery
- Supra-radical surgery

Surgical Options in Ovarian Cancer.

Early Stage Disease

- For suspected/Early stage there is a agreement that primary surgery and appropriate staging remains the best approach.
- Complete Pelvic Clearance/Staging OR if *Fertility* an issue – *Fertility Preserving Surgery/Staging*.

Surgical Options in Ovarian Cancer.

Advanced Stage Disease

- This constitutes about 75% of all ovarian cancer patients.
- About 90% are epithelial in origin
- About 5000 cases of advanced disease/year in the UK
- Five year Survival around 40%

Surgical Options in Ovarian Cancer. *Advanced Stage Disease*

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Standard of care in advanced disease

Primary debulking is the agreed standard of care
Followed by normally 6 cycles of platinum based
chemotherapy.

‘Optimum debulking’ is the surgical approach
based on mainly retrospective non-randomised
series.

- WHAT is EVIDENCE??

National Health Service

- *Level A:* Consistent Randomised Controlled Clinical Trial, cohort study, all or none (see note below), clinical decision rule validated in different populations.
- *Level B:* Consistent Retrospective Cohort, Exploratory Cohort, Ecological Study, Outcomes Research, case-control study; or extrapolations from level A studies.
- *Level C:* Case-series study or extrapolations from level B studies.
- *Level D:* Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles

Surgical options

Primary surgery

Primary surgery

Primary surgery

3 cycles of chemotherapy

6 cycles of chemotherapy

3 cycles of chemotherapy

3 cycles of chemotherapy

Delayed Primary surgery

RCT x2

IDS

IDS

3 cycles of chemotherapy

3 cycles of chemotherapy

3 cycles of chemotherapy

RCTx1

SLL

RCTx2

Meta-Analyses [Level C]

Hunter et al. Am J Obstet Gynaecol, Jul 1993 - NO

6962 women, 'Cytoreductive surgery has only a small effect on survival in women With advanced ovarian cancer. The type of chemotherapy used is more important.'

Allen DG et al. Eur J Gynecol Oncol 1995, Lit Search & personal -MAYBE

Communications. 'Optimal cytoreduction appears beneficial – but limited data, and no prospective trials.'

Bristow et al. J Clin Oncol Mar 2002 - YES

Platinum Era only [6885 women] – 'During the platinum era, maximal cytoreduction was one of the most powerful determinants of survival in advanced Ovarian cancer.'

Surgical Options in Ovarian Cancer. *Advanced Stage Disease*

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- *Regarding Primary Surgery and Debulking – we have Level C evidence – in support of this approach.*

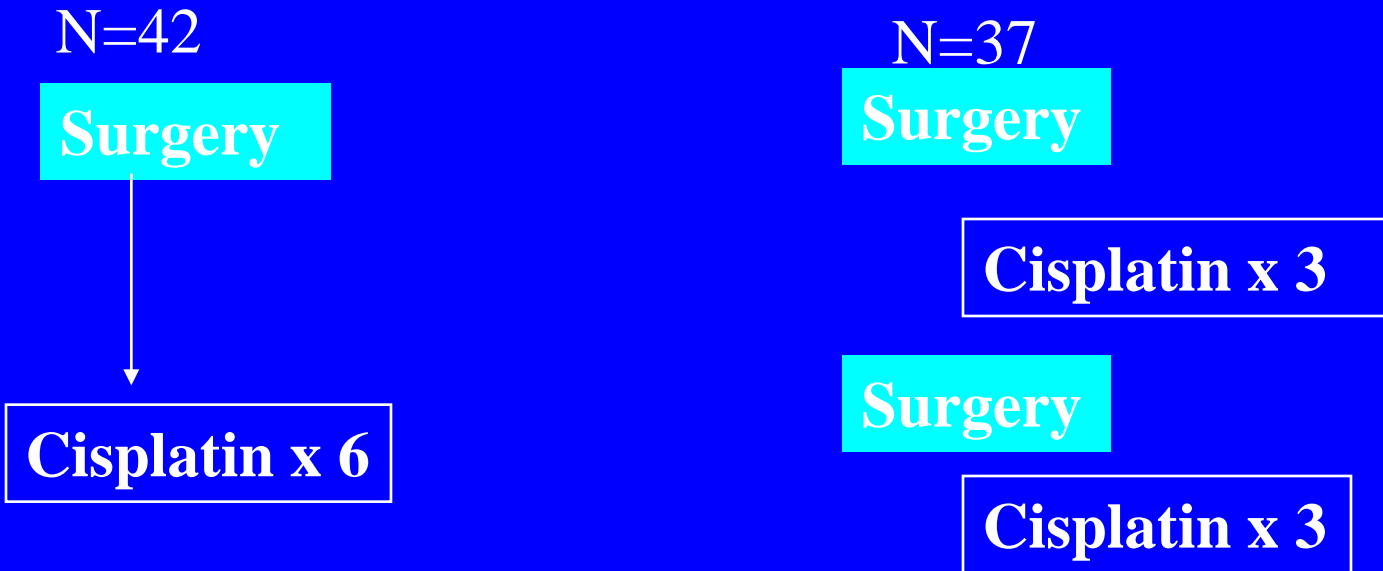
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Interventional Debulking Surgery

Redman et al. BJOG 1994



Median survival – 12 mths.

Median Survival = 15 mths

NOTE – Optimum defined as <2 cms.

Study prematurely ceased – due to interim analysis indicating no survival difference

Interventional Debulking Surgery

Van De Burg et al, N Eng J Med, 1995

429 recruited

319 randomised

Randomisation after 3 cycles of chemotherapy

Overall Median Survival increased by 6 months

Before Debulking	Total	After Debulking		
		No Disease	<1cm	≥ 1cm
No disease	22	22	0	0
<1 cm	22	7*	15	0
≥1cm	83	19*	18*	46
Total	127	48	33	46

Of 127 patients, 44 [34.6%] had a beneficial effect with respect to decreased tumour load. A third had NO disease to resect after 3 cycles of chemotherapy!

A Phase III randomized study of interval secondary cytoreduction in patients with advanced stage ovarian carcinoma with suboptimal residual disease: a GOG study

Rose PG et al.

Inclusion: Responding/Stable after 3 cycles Cisplatin/Taxol

Randomised – surgery vs no surgery – followed by 3 cycles Cisplatin/Taxol

550 registered

216 – IDS

209 - Conventional

Median Survival from Randomisation

IDS	Non IDS
32mths	33 mths

Progression Free Survival

10.5mths	10.8 mths
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GOG – vs - EORTC

- Taxol added – not available at the time of EORTC
- GOG - Surgery performed mainly by trained Gynaecological Oncologist in 96% of all cases.
- Greater amount of debulking achieved in GOG
- Some evaluation time- frames differed.

What are the options?

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- *Supra-radical surgery*

Supra-Radical Surgery

- Who is suitable?
- What is it?
- What is the Evidence Base?

Supra-Radical Surgery

- Definition:
- Peritoneal stripping
- Diaphragmatic stripping
- Liver Resection
- Splenectomy
- Bowel Resection
- Supra-Colic Omentectomy !
- OBJECTIVE – NO RESIDUAL DISEASE

Indications for neoadjuvant chemotherapy

- Thus **NO** primary surgery !

Leuven Policy 2006

1. Tumors larger than 2 cm around the superior mesenteric artery or around the porta hepatis, or
2. Intrahepatic (multiple) metastases or several extraabdominal metastases (excluding resectable inguinal or supraclavicular lymph nodes) larger than 2 cm , or
3. Poor general condition making a “maximal surgical effort” to no residual tumor impossible, or
4. Extensive serosal invasion (e.g. plaques) on the intestines necessitating bowel resections of > 1.5 m [How to determine?]

ESGO – Vergote 2007

? 3. to read – poor physical condition – ie unsuitable for general anaesthesia as deemed by Consultant Anesthetist and Gyn Oncologist.

Supra-Radical Surgery

Morbidity:

- 20-25% Grade 3 and 4
- Inpatient stay – 10-20 days
- Need for ITU

Mortality

- 0-5% - surgical mortality

Supra-radical Surgery

- With such morbidity and mortality there is an ethical obligation to ensure that such procedures are indeed improving survival rates which necessitates a prospective randomised trial.
- And equally – stating ‘you cannot do the surgery and that’s why you disagree’ is not science
- And what if Supra-radical surgery is the best for patients? We may need to change training – but this should be on evidence base rather than assumptions.

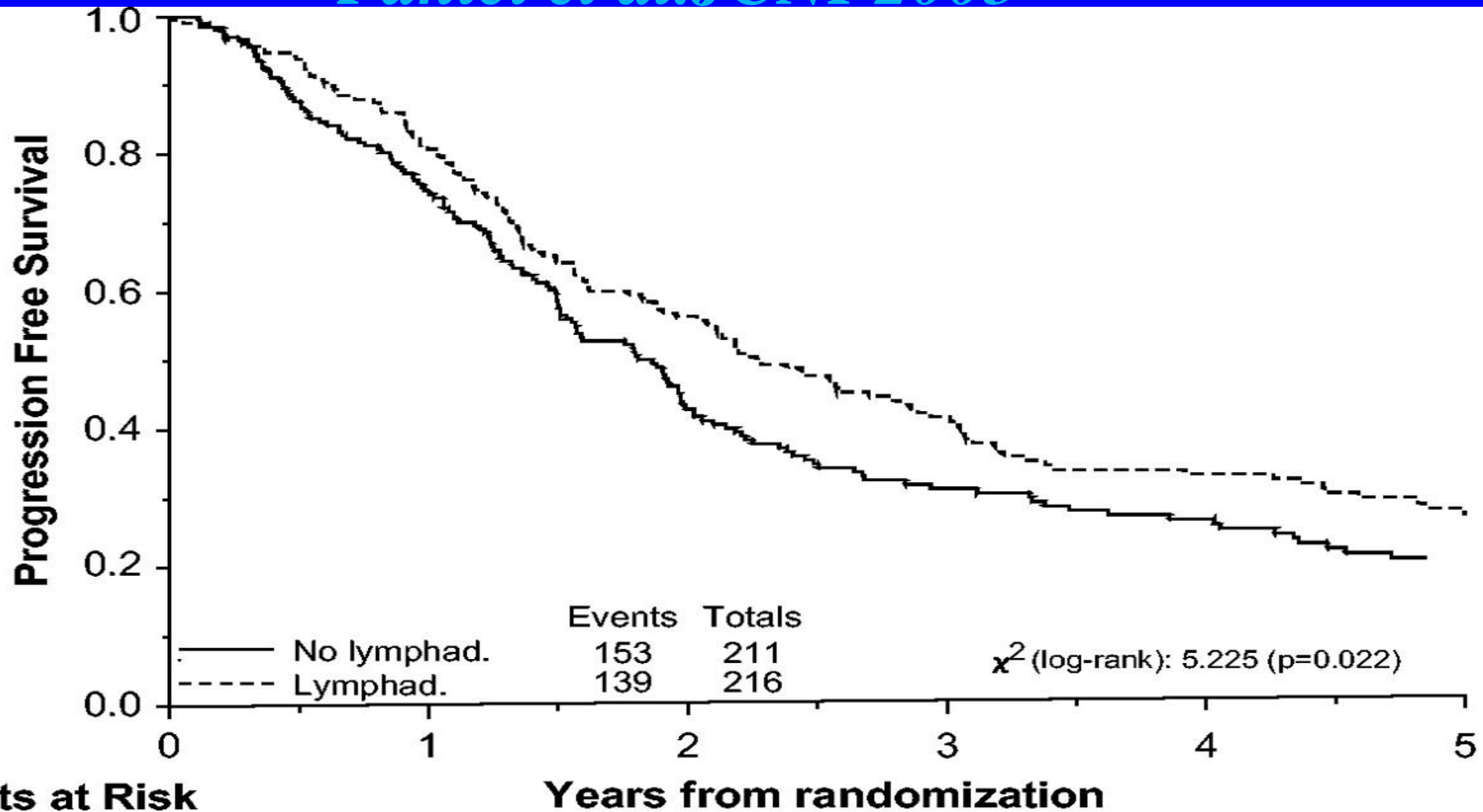
Radical pelvic and para-aortic lymphadenectomy in ovarian cancer

Panici et al, JCO 2005

- **RCT**
- **Optimally debulked patient**
- **427 patients recruited**
- **Randomised to systematic lymphadenectomy vs excision of enlarged nodes only.**
- **Protocol violations excluded from analysis**

Radical lymphadenectomy:

Panici et al. JCO 2005

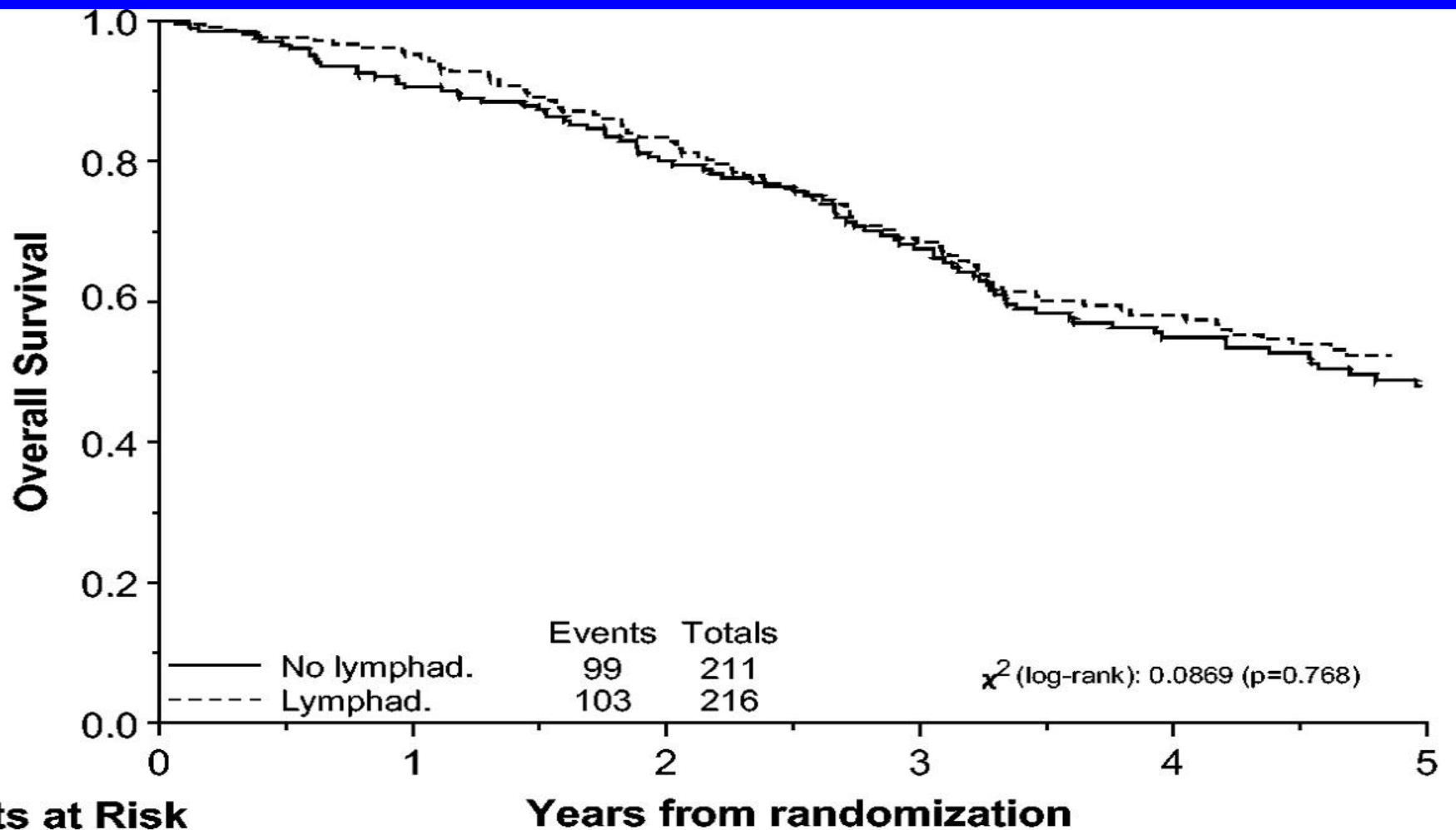


Patients at Risk

Patients at Risk	Years from randomization					
	0	1	2	3	4	5
No lymphad.	211	148	78	51	41	27
Lymphad.	216	166	107	67	51	34

Radical lymphadenectomy:

Panici et al. JCN 2005



Patients at Risk

	0	1	2	3	4	5
No lymphad.	211	177	136	104	78	56
Lymphad.	216	195	153	110	84	64

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Neo-adjuvant chemotherapy

- What is the Evidence?

Neoadjuvant Chemotherapy :Reported Studies

<u>Author</u>	<u>No.</u>	<u>Stage</u>	<u>Treatment</u>	<u>Outcome</u>
Schwartz	59	IIIc/IV	Cx- Debulk	12mths
Surwit	29	IIIc/IV	Chx-Debulk	22.5 mths
Vergote	41	III/IV	IDS	25% at 3 yrs
Vergote	Case Control [>200]		No difference with Primary Chemotx	
Kehoe	31	III/IV	Biopsy/ChemoTx	16 months*

**in those with a Complete Response to Chemotherapy Median survival was 29 mths.*

Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer

Cochrane Database Syst Rev. 2007 Oct 17;(4):CD005343

- One RCT was identified as meeting the inclusion criteria. This trial randomized 85 women and compared standard debulking surgery followed by eight cycles of platinum-based chemotherapy with pre-operative intra-arterial platinum-based chemotherapy and ovarian artery embolization followed by debulking surgery and seven cycles of platinum-based chemotherapy. There was no statistical difference in median overall survival (OS) between the two treatment groups.

[Morrison J](#), [Swanton A](#), [Collins S](#), [Kehoe S](#)

Some Evidence for NAC- Level C

- Ann Surg Oncol. 2009 Aug;16(8):2315-20. Epub 2009 Jun 11.
- **Does neoadjuvant chemotherapy increase optimal cytoreduction rate in advanced ovarian cancer? Meta-analysis of 21 studies.**
- [Kang S, Nam BH.](#)
- *CONCLUSION: The current meta-analysis showed that NAC helped the gynecologic oncologist achieve an increased rate of optimal cytoreduction*

CHORUS

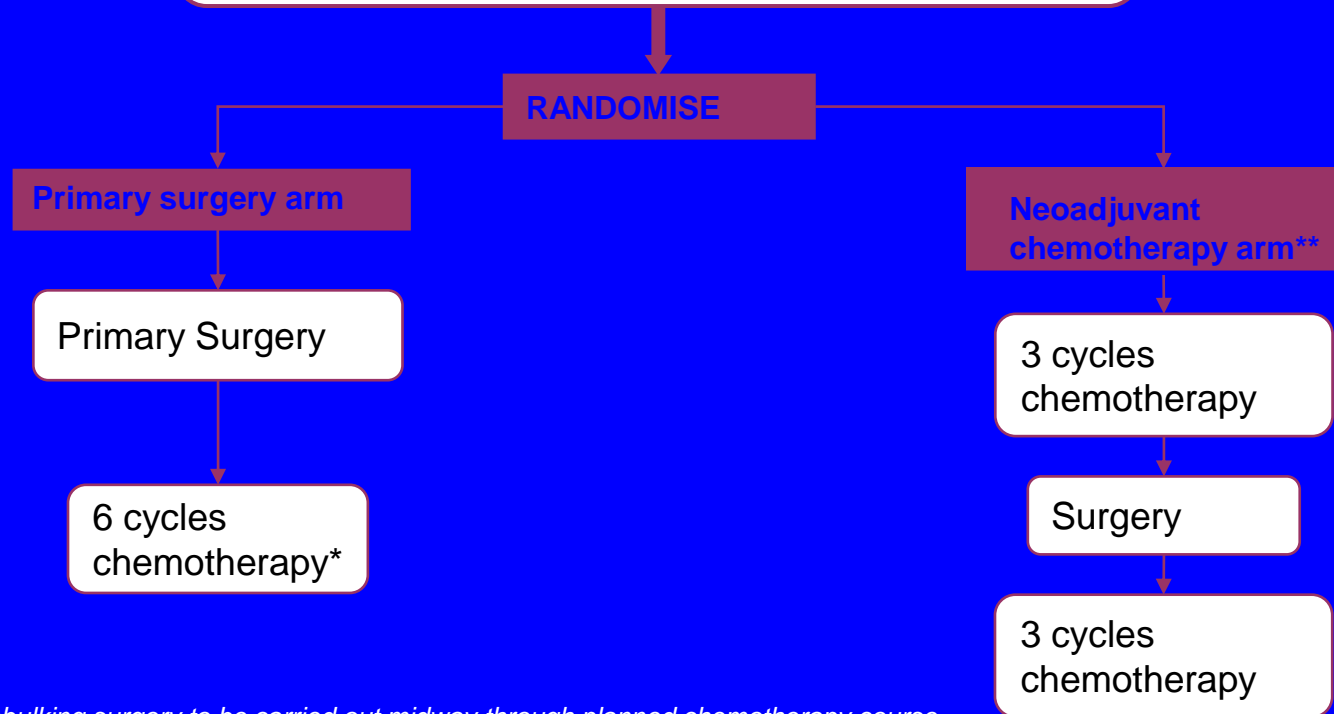
- Chemotherapy or Upfront Surgery
- A randomised trial to determine the impact of timing of surgery and chemotherapy in newly diagnosed patients with advanced epithelial ovarian, primary peritoneal or fallopian tube carcinoma

CHORUS Main Trial Clinical Sites

Aberdeen Royal Infirmary	John Radcliffe Hospital	Scunthorpe
Alexandra Hospital	Leicester General Hospital	Southend Hospital
Arrowe Park	Liverpool Women's Hospital	St Bartholomews Hospital (London)
Beatson West of Scotland Cancer Centre	Luton Hospital	St George's Hospital (London)
Belfast City Hospital	Manor Hospital	St James University Hospital
Bradford Royal Infirmary	Mount Vernon (East and North Herts)	St Mary's Hospital (Manchester)
Broomfield Hospital	Musgrove Park Hospital	St Mary's Hospital (Portsmouth)
Cheltenham General Hospital	Newcastle General Hospital	St Thomas' Hospital
Christie	Norfolk and Norwich University Hospital	Staffordshire General Hospital
City Hospital (Birmingham)	Nottingham City	Stoke Mandeville Hospital/Wycombe
Clatterbridge Centre for Oncology	Poole Hospital	University College Hospital London
Cumberland Infirmary	Princess Royal Hospital (Hull)	University Hospital Coventry and Warwickshire
Derby City General Hospital	Queen Elizabeth Hospital (Gateshead)	University Hospital of North Staffordshire
Derriford Hospital	Raigmore Hospital	Victoria Hospital (Blackpool)
Dumfries and Galloway Royal Infirmary	Royal Blackburn Hospital	Watford General Hospital (West Herts)
Eastbourne Hospital	Royal Cornwall Hospital	Weston Park Hospital
Essex County Hospital	Royal Hallamshire Hospital	Wexham Park Hospital
Frimley Park Hospital	Royal Lancaster Infirmary	Worcestershire Royal Hospital
Gloucestershire Royal Hospital	Royal Marsden Hospital (London)	Worthing Hospital
Hereford County Hospital	Royal Preston Hospital	Wrexham Maelor Hospital
Huddersfield Royal Infirmary	Royal Surrey County Hospital	Wythenshawe Hospital
Ipswich Hospital	Royal Sussex County Hospital	Yeovil District Hospital
James Cook University Hospital	Royal United Bath	Ysbyty Gwynedd

CHORUS Trial design

- Clinical and/or imaging evidence of a pelvic mass with extrapelvic metastatic disease at presentation
- Serum CA125/CEA ratio > 25



Interval debulking surgery to be carried out midway through planned chemotherapy course **ONLY if intention stated at randomisation and if appropriate.*

*** Histologically or cytologically disease confirmation prior to neoadjuvant chemotherapy*

CHORUS eligibility criteria

- Clinical and imaging evidence of a pelvic mass with extrapelvic metastatic disease at presentation. *Randomisation should be carried out **within 4 weeks** of obtaining clinical and imaging evidence of disease.*
- Serum CA 125/CEA ratio > 25
[if the serum CA 125/CEA ≤ 25 and the serum CEA is above the upper limit of normal, the patient should undergo investigations to exclude gastrointestinal cancer]
- Patient planned to receive **carboplatin-based** chemotherapy
- Patient fit to undergo protocol treatment and follow-up
- No concomitant or previous malignancy likely to interfere with protocol treatments or comparisons
- Written informed consent of the patient

CHORUS and EORTC study

- Compatible
- CHORUS recruitment to finish in about 2-3 months.
- The studies will be combined.
- EORTC study – some information available.

EORTC, Vergote

- 704 patients were required in order to show
- Non-inferiority with respect to survival
- between PDS and NACT, with a one-sided
- type I error of 0.05 and a power of 80%.
- The expected median survival in the PDS arm
- was 31 months.
- The expected optimal debulking rate (≤ 1 cm)
- was 50% in the PDS.

Morbidity Data EORTC Vergote

	PDS	Chemo
• Postoperative mortality	2,7%	0,6%
• (< 28 days)		
• Postoperative sepsis	8%	2%
• Fistula (bowel/GU)	1,2% / 0,3%	0,3% / 0,6%
• Operative time (minutes)	180	180
• Red blood cell transfusion	51%	53%
• Hemorrhage Grade $\frac{3}{4}$	7%	1%
• Venous Gr $\frac{3}{4}$	2,4%	0,3%

Survival EORTC Vergote

PDS - 29 months

IDS - 30 months

HR for IDS: 0.98 (0.85, 1.14)

Neoadjuvant Study

- Neoadjuvant therapy does not reduce survival outcome
- May have better QOL aspects
- Needs confirmation with the CHORUS study.
- Sub-Group analysis requires CHORUS and EORTC to combine.

The Evidence now

- One RCT [Level A]
- Second awaited [again Level A]

What are the options?

- Immediate Surgical Intervention for all – *Level C Evidence.*
- Delayed Surgery – **Level A** [awaiting publication]
- Secondary Surgery [**IDS – Level A -2 Trials in disagreement**]
- *And also:*
- Debulking Surgery – **Level C**
- Supra-radical surgery – **Level C/D**

Conclusion

In accordance with agreed levels of evidence – in advanced ovarian cancer the best Surgical Option is neo-adjuvant chemotherapy with surgery after 3 cycles of chemotherapy.

Conclusions

Interval Surgery and delayed chemotherapy

- *J Obstet Gynaecol Can. 2009 Feb;31(2):161-6.*
- **The significance of duration of chemotherapy interruptions due to interval surgery in ovarian cancer patients treated with neoadjuvant chemotherapy.**
- Le T, Fathi KA, Hopkins L, Faught W, Fung-Kee-Fung M. Ottawa
- Ninety-seven patients with complete data were identified. Their median age was 65.4 years. Fifty-four patients (56%) were left with optimal residual disease (< 1 cm), and 43 patients had suboptimal residual disease. The median delay from the last cycle of chemotherapy to the time of surgery was 29 days (range 20-72). The median delay from surgery to resumption of cytotoxic therapy was 23 days (range 8-65). Chemotherapy courses were interrupted for a median of 50 days (range 36-119) around the time of surgery
- **With respect to overall survival, the time to resumption of chemotherapy in days and the time delay in days between the two chemotherapy cycles peri-operatively were identified as statistically significant predictors only in patients with suboptimal residual disease.** In patients with optimal residual disease status, neither the time of interruption between the two chemotherapy cycles peri-operatively nor the time to resumption of chemotherapy after surgical debulking was significantly predictive of overall survival

- We now have studies of the same level of evidence supporting both primary surgery and primary neoadjuvant chemotherapy
- But we could do with more/better evidence!

Neo-adjuvant Chemotherapy

- We seem to have some evidence
- At least one RCT [none done for primary surgery]
- Evidence that chemotherapy an effective way to achieve optimum debulking

What about patients unsuitable for surgery?

If fit enough most are given neo-adjuvant chemotherapy.