INTERNATIONAL SCHOOL OF SURGICAL ANATOMY
ISSA

Sacro Cuore Don Calabria
Cancer Care Center Negrar - Verona

Cancer Care Center
Numero Verde
800 143 143
Numero per la Cura del Tumore

LA CHIRURGIA PRIMARIA

Manuel Maria Ianieri, MD

Direttore Dipartimento: Marcello Ceccaroni, MD, PhD

Dipartimento per la Tutela della Salute e della Qualità di Vita della Donna
Unità Operativa di Ginecologia Oncologica e Chirurgia Pelvica Mini-Invasiva
Ospedale Sacro Cuore - Don Calabria, Negrar (Verona)
Faculty ISSA -International School of Surgical Anatomy-
Dottorando in Biotecnologie Mediche in Chirurgia Integrata

TAKE HOME MESSAGE

Nowadays, the standard management of EOC is the correct surgical staging in early stages and complete tumour cytoreduction followed by platinum and taxane-based chemotherapy in advanced stages. However, if primary cytoreduction seems not possible due to extensive disease or poor patient condition, patients could be treated with neoadjuvant chemotherapy followed by interval debulking surgery and adjuvant chemotherapy

María Martín-Cameán 2016

IDS

Lymphadenectomy In Ovarian Neoplasm (LION)

optimal/near optimal/suboptimal cytoreduction

Evaluation of optimal cytoreduction

Cytoreduction: what does it means? [1]

- Complete resection at primary debulking surgery is the most important independent prognostic factor in advanced ovarian carcinoma

- Survival is inversely correlated with residual disease after surgery

- Debulking surgery achieves the removal of poorly vascularised tumour where chemotherapeutic agents have poor access. It also removes chemoresistant clones, which are less susceptible to respond to chemotherapy

Cytoreduction: what does it mean? 2

Cochrane Database Syst Rev. 2011 Aug 10;(8):CD007565. doi: 10.1002/14651858.CD007565.pub2.

Optimal primary surgical treatment for advanced epithelial ovarian cancer.

Elattar A[1], Bryant A, Winter-Roach BA, Hatem M, Naik R.

overall survival (64 months vs. 29 months in patients with under 1 cm residual disease) [Nick AM, et al 2015]

- Patients with suboptimal resection will not have an improvement in survival but will suffer an increase in morbility [Gómez-Hidalgo NR 2015, Rutten MJ, et al 2015]

The findings of this review that women with residual disease < 1 cm still do better than women with residual disease > 1 cm should prompt the surgical community to retain this category and consider re-defining it as 'near optimal' cytoreduction, reserving the term 'suboptimal' cytoreduction to cases where the residual disease is > 1 cm (optimal/near-optimal/suboptimal instead of complete/optimal/suboptimal)

When we can reach the goal?

Suidan et al. (2014) identified three clinical and six radiologic criteria associated with suboptimal cytoreduction: age ≥ 60 years (OR 1.32), CA-125 ≥ 500 U/mL (OR 1.47), ASA 3–4 (OR 3.23), retroperitoneal lymph nodes above the renal hilum (including supradiaphragmatic) > 1cm (OR 1.59), diffuse small bowel adhesions/thickening (OR 1.87), perisplenic lesion > 1 cm (OR 2.27),

A Predictive index score ≥ 4 had the highest overall accuracy, identified patients undergoing suboptimal cytoreduction with a sensitivity of 100%,

A significant factor affecting prediction is reliance on surgical expertise to achieve R0 resection [Gómez-Hidalgo NR 2015]

extension to the stomach, spleen, or lesser sac, extension to pelvic sidewall, parametria, or hydroureter, large-volume ascites (seen on all cuts), suprarenal paraaortic lymph nodes ≥ 1 cm (with 2 points), diaphragm or lung disease ≥2 cm or confluent plaque, inguinal canal disease or lymph nodes ≥ 2 cm, liver lesion ≥ 2 cm on surface or parenchymal lesion of any size, porta hepatic or gallbladder fossa disease ≥ 1 cm, Infrarenal paraaortic lymph nodes ≥ 2 cm (with 1 point).[Bristow 2000]

When we can reach the goal?

Eur J Surg Oncol. 2013 Jul;39(7):774-9. doi: 10.1016/j.ejso.2013.03.022. Epub 2013 Apr 16.

Diagnostic accuracy of hand-assisted laparoscopy in predicting resectability of peritoneal

Am J Obstet Gynecol. 2013 Nov;209(5):462.e1-462.e11. doi: 10.1016/j.ajog.2013.07.016. Epub 2013 Jul 24.

A multicentric trial (Olympia-MITO 13) on the accuracy of laparoscopy to assess peritoneal spread in ovarian cancer.

Fagotti A[1], Vizzielli G, De Iaco P, Surico D, Buda A, Mandato VD, Petruzzelli F, Ghezzi F, Garzarelli S, Mereu L, Viganò R, Tateo S, Fanfani F, Scambia G.

⊕ **Author information**

Abstract

OBJECTIVE: The objective of the study was to prospectively evaluate the accuracy of laparoscopy performed in satellite centers (SCs) to describe intraabdominal diffusion of advanced ovarian cancer (AOC).

STUDY DESIGN: Patients with a clinical/radiological suspicion of AOC were included in the protocol. SCs were selected among those surgeons, spending a short intensive training period at the coordinator center (CC) to learn the application of staging laparoscopy (S-LPS) in AOC. All women underwent S-LPS at the SCs, and the surgical procedure was recorded and blindly reviewed at the CC. Calculating specificity, positive and negative predictive values, and the accuracy for each parameter with respect to the CC assessed the diagnostic performance of S-LPS. The Cohen's kappa was used to test the interobserver agreement of each parameter.

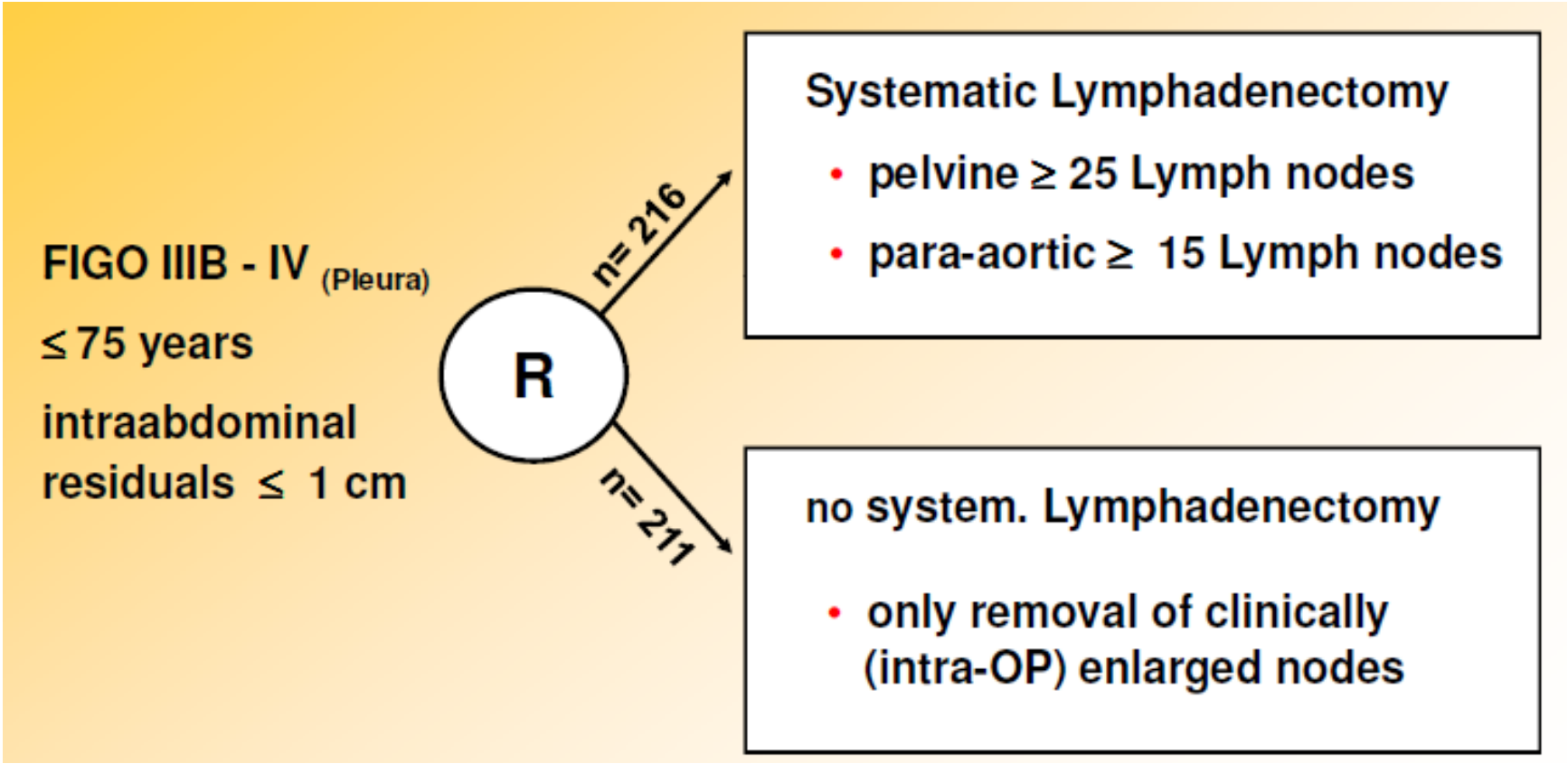
RESULTS: One hundred sixty-eight cases were considered eligible for the study. A per-protocol analysis was performed on 120 cases. The worst laparoscopic assessable feature was mesenteric retraction, whereas the remaining variables ranged from 99.2% (peritoneal carcinomatosis) to 90% (bowel infiltration). All but 1 SC (SC number 4) reached an accuracy rate of 80% or greater for both single parameters and overall score. The Cohen's kappa and the P value for overall predicitive index value were 0.685 and .01, respectively, but improved to 0.773 and .388 after removing the SC number 4 from the analysis.

CONCLUSION: S-LPS allows an accurate and reliable assessment of intraperitoneal diffusion of disease in AOC patients in trained gynecological oncology centers.

Lymphadenectomy in EOC

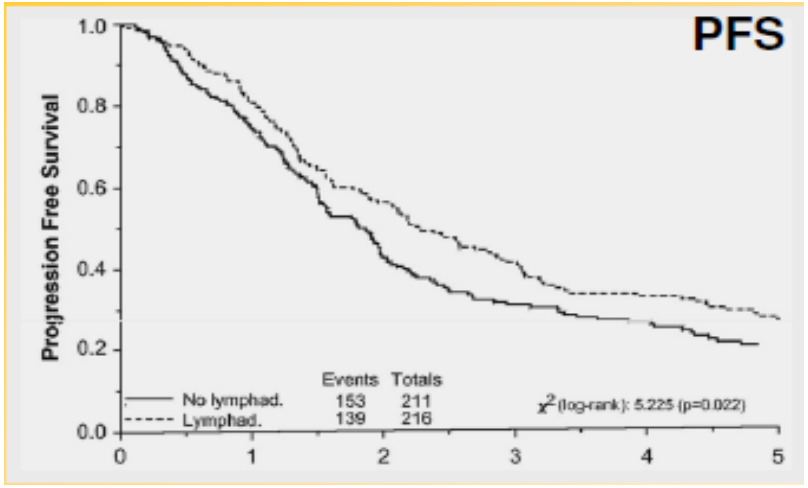
Stage	Intraabdominal residual tumor (Intra-OP)	clinically (intra-OP) / radiologically (pre-OP) negative LN	clinically (intra-OP) / radiologically (pre-OP) positive LN (1cm)
1-2A	0	Yes Staging & complete resection	
2B-3-4	0	YES or NO ?	Yes LNE for debulking
	1-10 mm	YES or NO ?	Yes LNE for debulking
	> 1 cm	NO	NO

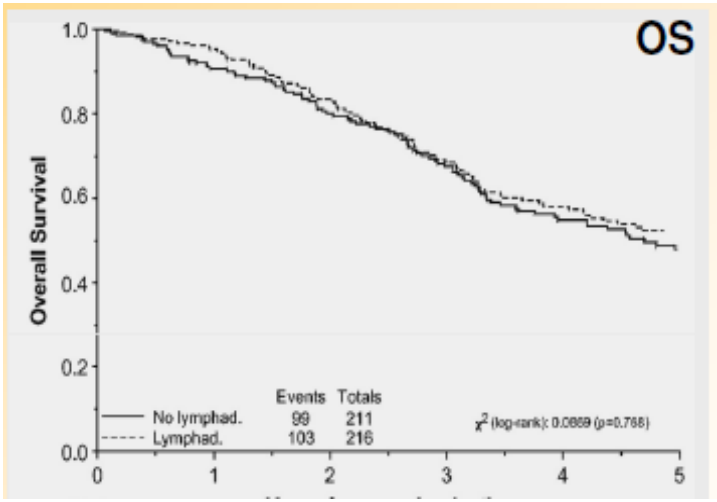
SYSTEMATIC AORTIC AND PELVIC LYMPHADENECTOMY VS. RESECTION OF ANY BULKY NODES ONLY IN OPTIMALLY DEBULKED ADVANCED OVARIAN CANCER: A RANDOMIZED TRIAL



Benedetti Panici P, Maggioni A, Hacker N et al. (2005), J Natl Cancer Inst 97: 560-565

Systematic LNE in Ovarian Cancer FIGO IIIB/C-IV (Pleura) and intra-abdominal residuals ≤ 1 cm showed an advantage in Progression Free-Survival (significant) and Overall Survival (not significant)

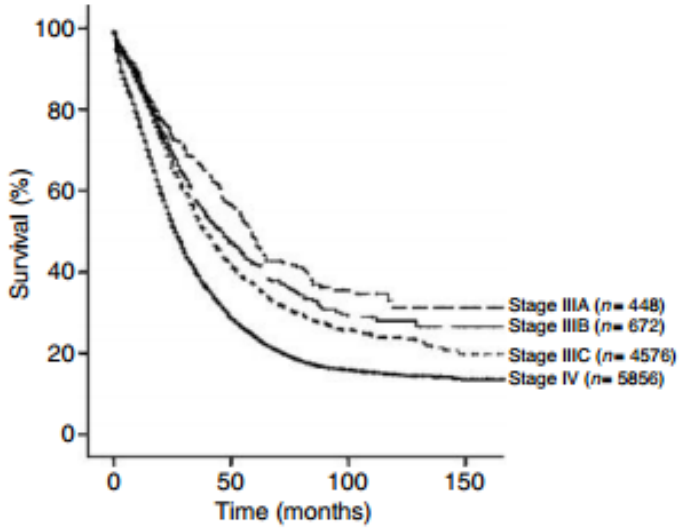




- % 5 Years: 31.2 vs. 21.6 % — 49.5 vs. 48 %
- HR_{all}: 0.75 (p = 0.01) — 0.97 (n.s.)
- $HR_{\text{per protocol}}$: 0.69 — 0.93
- median: + 7 months — + 2.4 months
  (22.4 vs. 29.4) — (56.3 vs. 58.7)

Benedetti Panici P, Maggioni A, Hacker N et al. (2005), J Natl Cancer Inst 97: 560-565

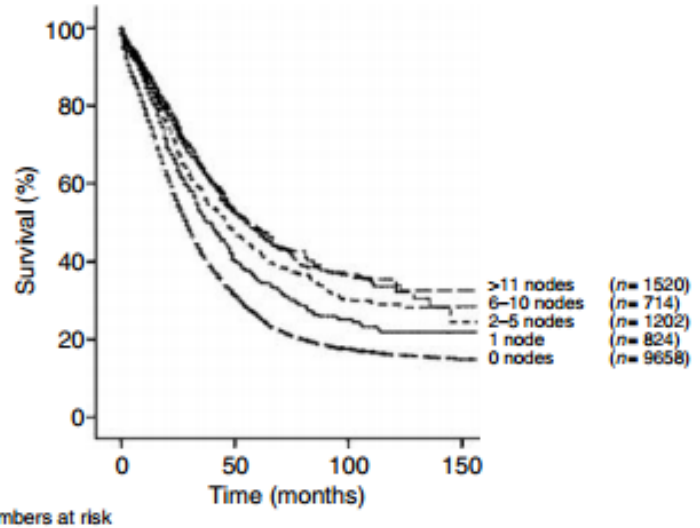
The potential therapeutic role of lymph node resection in epithelial ovarian cancer: a study of 13918 patients



Numbers at risk

Stage IIIA	448	156	40	7
Stage IIIB	672	161	44	6
Stage IIIC	4576	860	149	17
Stage IV	5856	1060	288	53

Figure 1 Kaplan–Meier analysis based on stage of disease ($n = 13918$; $P < 0.001$).



Numbers at risk

0 nodes	9658	1753	426	84
1 node	824	190	46	8
2–5 nodes	1202	298	76	10
6–10 nodes	714	186	47	7
>11 nodes	1520	328	73	6

Figure 2 Kaplan–Meier analysis of patients by extent of lymphadenectomy ($n = 13918$; $P < 0.001$).

In FIGO 3C stage, on multivariate analysis, the extent of lymph node dissection and number of positive nodes were significant independent prognosticators after adjusting for age, year at diagnosis, stage, and grade of disease

Chan JK et al. 2007

Lymphadenectomy in E ovarian cancer

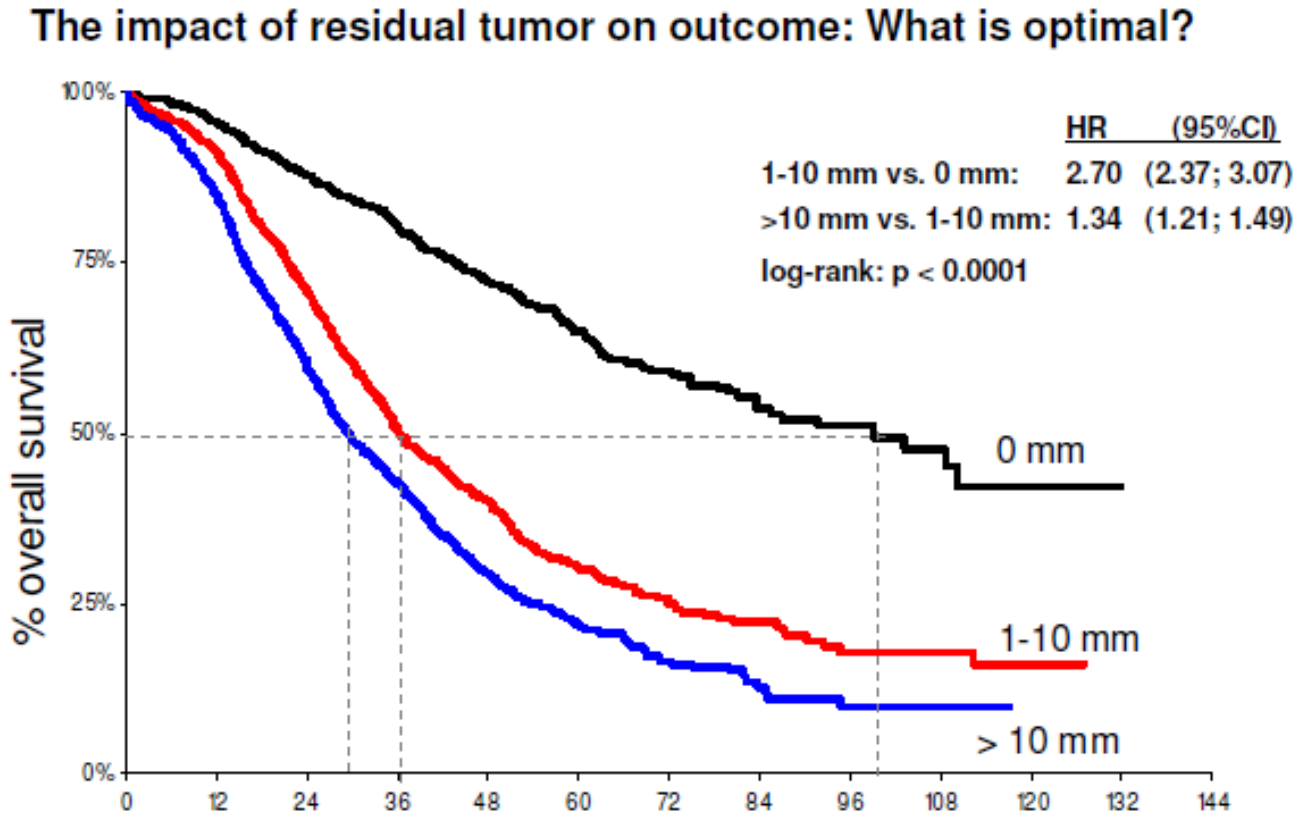
Stage	Intraabdominal residual tumor (Intra-OP)	clinically (intra-OP) / radiologically (pre-OP) negative LN	clinically (intra-OP) / radiologically (pre-OP) positive LN (1cm)
1-2 A	0	Yes Staging & complete resection	
2B-3-4	0	YES or NO ?	Yes LNE for debulking
	1-10 mm	LNE only in very selected pts. after adequate counselling; mostly no LNE	Yes LNE for debulking
	> 1 cm	NO	NO

Lymphadenectomy in E ovarian cancer

Stage	Intraabdominal residual tumor (Intra-OP)	clinically (intra-OP) / radiologically (pre-OP) negative LN	clinically (intra-OP) / radiologically (pre-OP) positive LN (1cm)
1-2 A	0	Yes Staging & complete resection	
2B-3-4	0	YES or NO ?	Yes LNE for debulking
	1-10 mm	LNE only in very selected pts. after adequate counselling; mostly no LNE	Yes LNE for debulking
	> 1 cm	NO	NO

Arguments pro LNE

residual tumor is the strongest prognostic factor in advanced ovarian cancer (and the only factor that can be changed)



- **„optimal" = complete resection,** in addition limited benefit for reduction to ≤ 1cm

A du Bois et al. Cancer 2009; 15: 1234-1244, AGO metaanalysis of 3,126 pts. In 1stline trials with platinum-taxan

Arguments pro LNE

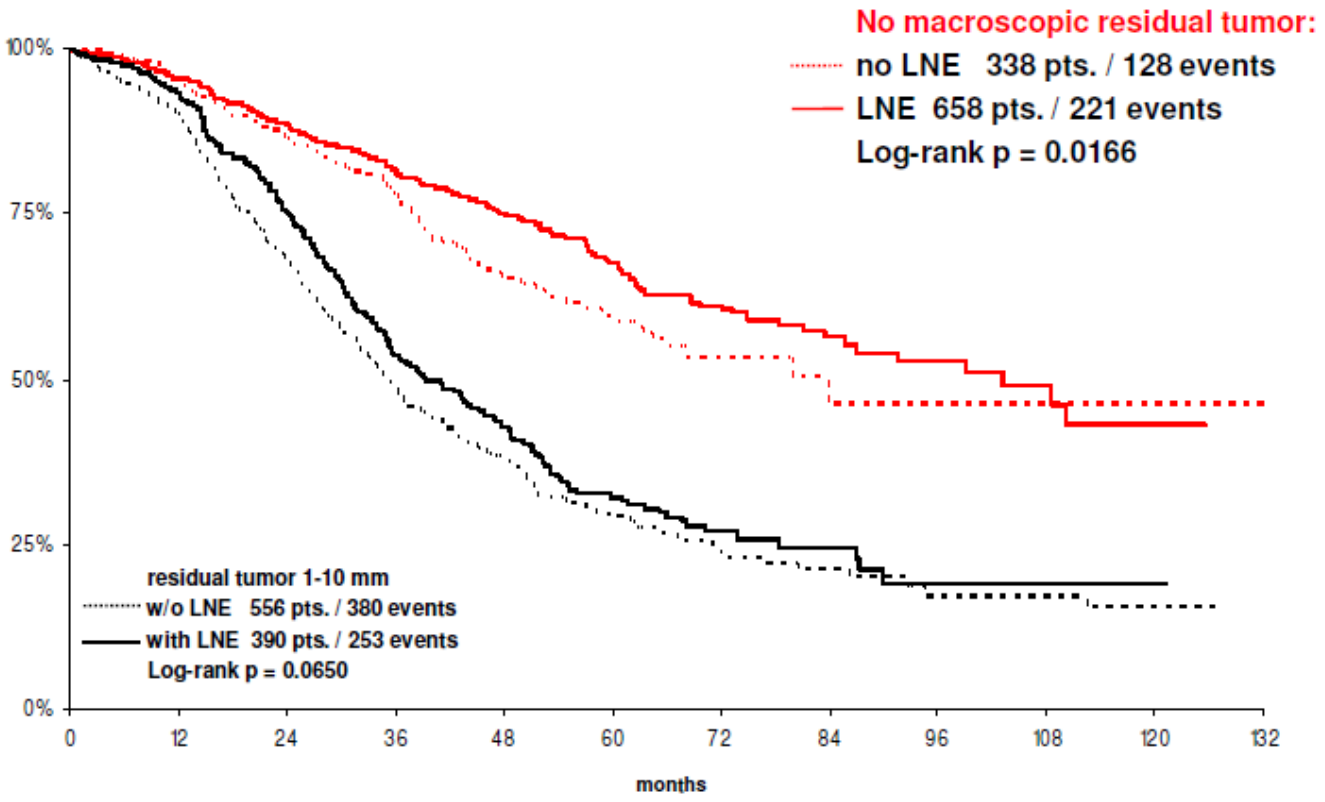
- +/- 30% of pts. with FIGO III OC have radiologically inapparent and non palpable lymph node metastases
  - 28% - Benedetti-Panici P et al., JNCI 2005
  - 36% - Spirtos NM et al., Gynecol Oncol 1995
  - 21% - du Bois A et al., JCO 2010

- when lymphadenectomy is systematically performed, nearly a fourth of patients with 'early-stage' ovarian cancer turns out to have retroperitoneal lymphatic spread (Maggioni 2006)

- without LNE, the group of pts. with intraperitoneally complete resection includes a subgroup of app. 30% who have residuals in non resected lymph nodes

- Is there role for LNE to „complete" so-called complete resection ?
- Is there any evidence for this hypothetic model?

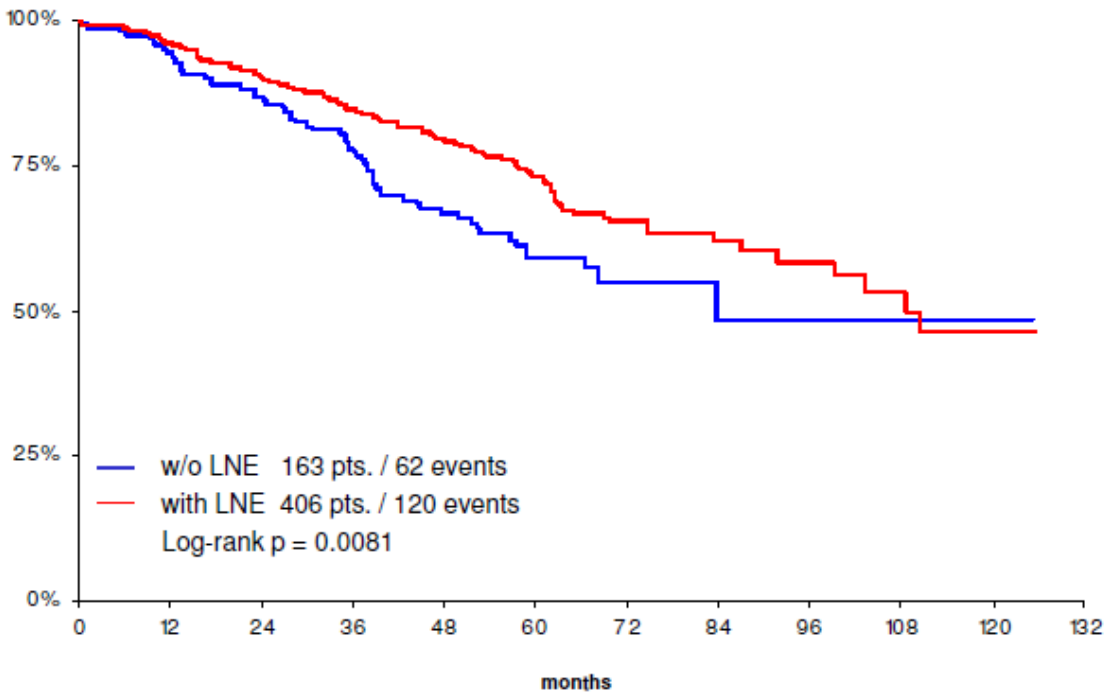
Overall survival in pts. with or without lymphadenectomy (LNE) and no macroscopic (0cm) or small residual tumor up to 1cm diameter



Univariate analysis: significant impact of LNE only in no residuals group

A du Bois et al., J Clin Oncol 28, 2010

Overall survival after lymphadenectomy or no lymphadenectomy in pts. with no gross residual tumor and without pre-/intra-operative suspect lymph nodes clinically (cN0).



Univariate analysis: significant impact of LNE in pts. with non suspect LN and no residual tumor

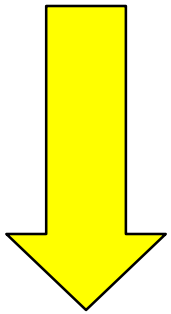
The role of lymphadenectomy

in advanced ovarian cancer and

complete intraabdominal tumor resection (= optimal debulking) and

clinically / radiologically inapparent LN

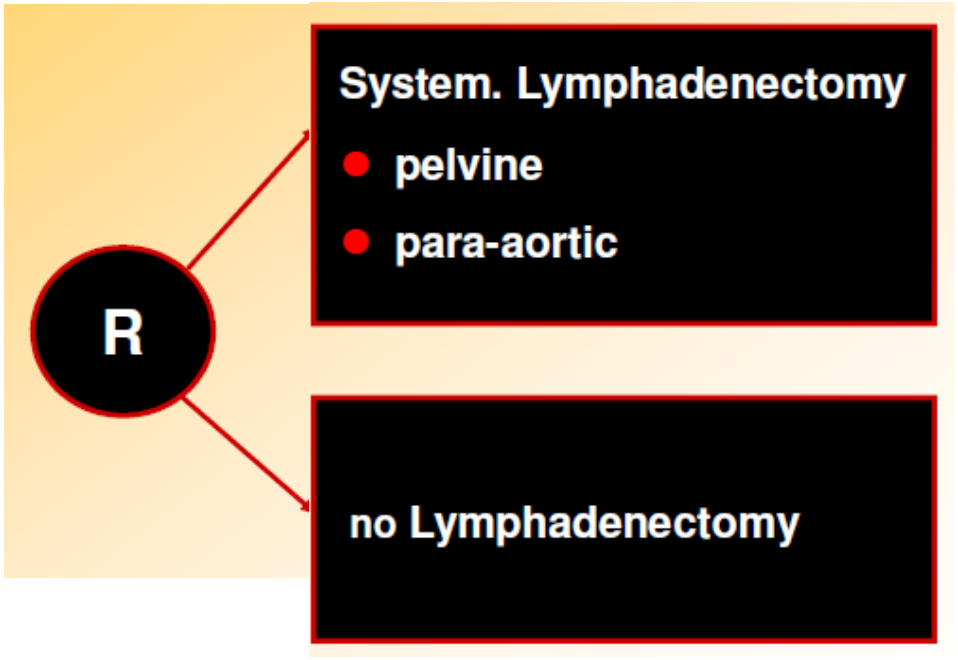
is still not fully understood ! – therefore:



actual study = LION

AGO – OVAR OP.3 (LION)
Lymphadenectomy In Ovarian Neoplasms

- epithelial invasive ovarian cancer
- FIGO IIB - IV
- no macroscopic extra- and intra-abdominal tumor residuals
- no palpable “bulky” lymph nodes



Endpoints: OS, PFS, QoL

Upfront debulking surgery

vs

Interval debulking surgery

…once upon a time ?

Gynecol Oncol. 2006 Dec;103(3):1070-6. Epub 2006 Jul 27.

Platinum-based neoadjuvant chemotherapy and interval surgical cytoreduction for advanced ovarian cancer: a meta-analysis.

Bristow RE[1], Chi DS.

Author information

Abstract

OBJECTIVE: To determine the overall survival and relative effect of multiple prognostic variables in cohorts of patients with advanced-stage ovarian cancer treated with platinum-based neoadjuvant chemotherapy in lieu of primary cytoreductive surgery.

METHODS: Twenty-two cohorts of patients with Stage III and IV ovarian cancer (835 patients) were identified from articles in MEDLINE (1989-2005). Linear regression models, with weighted correlation calculations, were used to assess the effect on median survival time of the proportion of each cohort undergoing maximum interval cytoreduction, proportion of patients with Stage IV disease, median number of pre-operative chemotherapy cycles, median age, and year of publication.

RESULTS: The mean weighted median overall survival time for all cohorts was 24.5 months. The weighted mean proportion of patients in each cohort undergoing maximal interval cytoreduction was 65.0%. Each 10% increase in maximal cytoreduction was associated with a 1.9 month increase in median survival time ($p=0.027$). Median overall survival was positively correlated with platinum-taxane chemotherapy ($p<0.001$) and increasing year of publication ($p=0.004$) and negatively correlated with the proportion of Stage IV disease ($p=0.002$). Each incremental increase in pre-operative chemotherapy cycles was associated with a decrease in median survival time of 4.1 months ($p=0.046$).

CONCLUSIONS: Neoadjuvant chemotherapy in lieu of primary cytoreduction is associated with inferior overall survival compared to initial surgery. Increasing percent maximal cytoreduction is positively associated with median cohort survival; however, the negative survival effect of increasing number of chemotherapy cycles prior to interval surgery suggests that definitive operative intervention should be undertaken as early in the treatment program as possible.

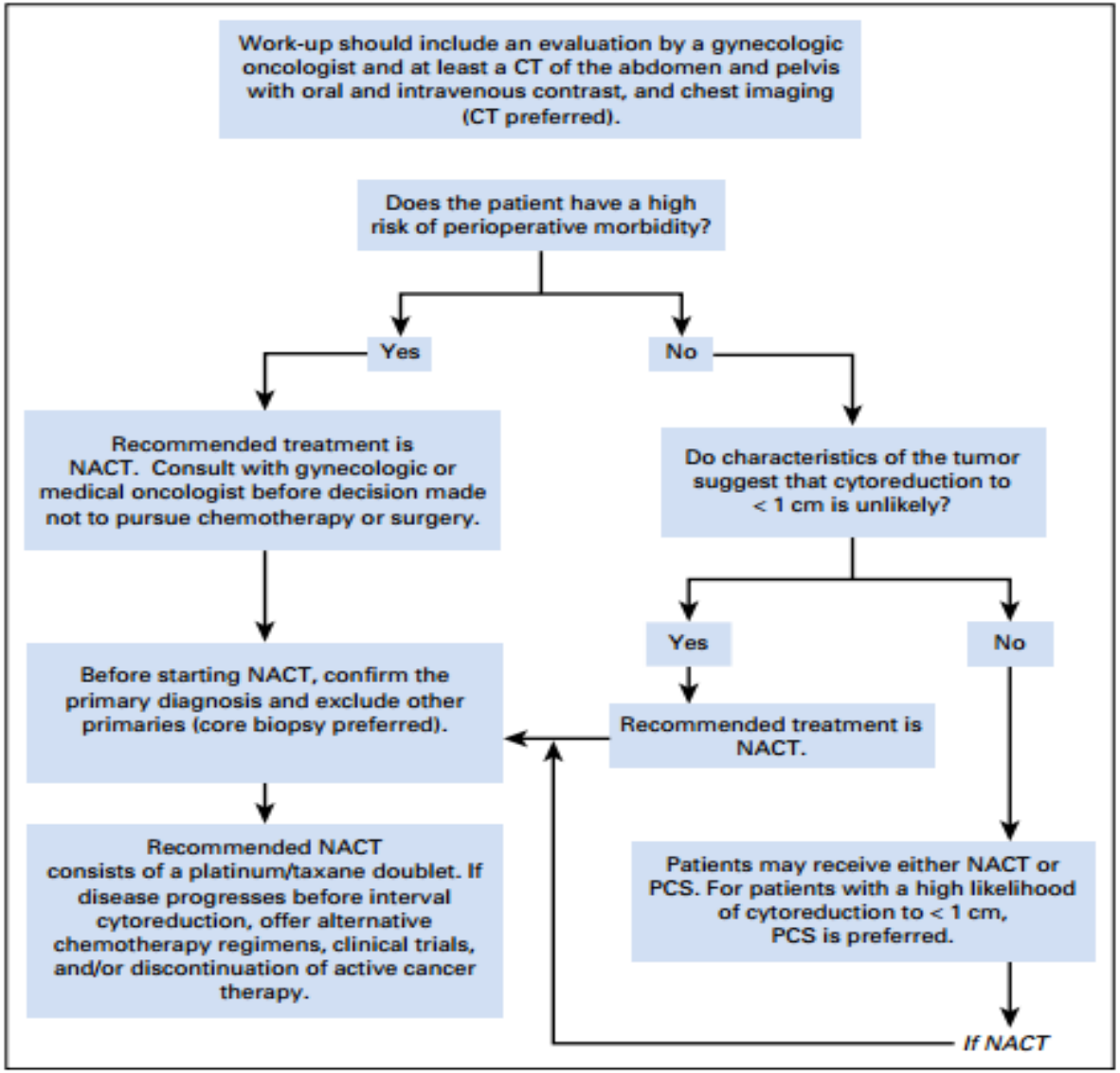


Fig 1. Algorithm for the clinical evaluation and treatment of women with suspected stage IIIC or IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. CT, computed tomography; NACT, neoadjuvant chemotherapy; PCS, primary cytoreductive surgery.

…DON'T FORGET

- Perioperative moderate/severe morbidity as well as QoL scores were shown to be more favourable in NACT/IDS arm than PDS in AEOC patients with very HTL [Scorpion trial phase III: fynal analysis, Fagotti A. 2016]

- In women with stage III or IV ovarian cancer, survival with primary chemotherapy is non-inferior to primary surgery. In this study population, giving primary chemotherapy before surgery is an acceptable standard of care for women with advanced ovarian cancer [CHORUS trial ,Kehoe S 2015]

- Although survival was comparable after primary surgery and neoadjuvant chemotherapy in the overall group of patients with ovarian cancer in the EORTC 55971 trial, we found in this exploratory analysis that patients with stage IIIC and less extensive metastatic tumours had higher survival with primary surgery, while patients with stage IV disease and large metastatic tumours had higher survival with neoadjuvant chemotherapy. For patients who did not meet these criteria, both treatment options led to comparable survival rates [van Meurs HS 2013]

- IDS can represent a suitable approach only when the first complete debulking is not achievable in a tertiary referral hospital. [Vizzielli G. 2015]

…nearest future

Eur J Cancer. 2016 Sep;64:22-31. doi: 10.1016/j.ejca.2016.05.017. Epub 2016 Jun 17.

Comparison of treatment invasiveness between upfront debulking surgery versus interval debulking surgery following neoadjuvant chemotherapy for stage III/IV ovarian, tubal, and peritoneal cancers in a phase III randomised trial: Japan Clinical Oncology Group Study JCOG0602.

Onda T[1], Satoh T[2], Saito T[3], Kasamatsu T[4], Nakanishi T[5], Nakamura K[6], Wakabayashi M[6], Takehara K[7], Saito M[8], Ushijima K[9], Kobayashi H[10], Kawana K[11], Yokota H[12], Takano M[13], Takeshima N[14], Watanabe Y[15], Yaegashi N[16], Konishi I[17], Kamura T[9], Yoshikawa H[2]; Japan Clinical Oncology Group.

Author information

Abstract

BACKGROUND: We conducted a phase III, non-inferiority trial comparing upfront primary debulking surgery (PDS) and interval debulking surgery (IDS) following neoadjuvant chemotherapy (NAC) for stage III/IV ovarian, tubal, and peritoneal cancers (JCOG0602). Two earlier studies, EORTC55971 and CHORUS, demonstrated non-inferior survival of patients treated with NAC. However, they could not evaluate true treatment invasiveness because of adding diagnostic laparotomy or laparoscopy before treatment in over 30% of both arms of EORTC55971 and in 16% of NAC arm of CHORUS.

METHODS: Patients were randomised into the standard arm (PDS followed by eight cycles of paclitaxel and carboplatin [TC]) and NAC arm (four cycles of TC, IDS, and four cycles of TC). In the standard arm, IDS was optional for patients who had undergone suboptimal or incomplete PDS. Treatment invasiveness was compared between arms (UMIN000000523).

RESULTS: Between November 2006 and October 2011, 301 patients were randomised. In the standard arm, 147/149 underwent PDS and 49 underwent IDS. In the NAC arm, 130/152 underwent IDS. The NAC arm required fewer surgeries (mean 0.86 versus 1.32, $p < 0.001$) and shorter total operation time (median 273 min versus 341 min, $p < 0.001$) than the standard arm and required a lower frequency of abdominal organ resection (23.7% versus 37.6%, $p = 0.012$) or distant metastases resection (3.9% versus 10.7%, $p = 0.027$). In the NAC arm IDS, blood/ascites loss was smaller (median 787 ml versus 3235 ml, $p < 0.001$) and albumin transfusion and G3/4 adverse events after surgery in total were less frequent (26.2% versus 58.5%, $p < 0.001$; 4.6% versus 15.0%, $p = 0.005$, respectively).

CONCLUSION: Our findings demonstrated that NAC treatment is less invasive than standard treatment. NAC treatment may become the new standard treatment for advanced ovarian cancer when non-inferior survival is confirmed in the planned primary analysis in 2017.

Upfront debulking surgery

vs

Interval debulking surgery

Cochrane Database Syst Rev. 2016 Jan 9;(1):CD006014. doi: 10.1002/14651858.CD006014.pub7.

Interval debulking surgery for advanced epithelial ovarian cancer.

Tangjitgamol S[1], Manusirivithaya S, Laopaiboon M, Lumbiganon P, Bryant A.

⊕ Author information

Abstract

BACKGROUND: Interval debulking surgery (IDS), following induction or neoadjuvant chemotherapy, may have a role in treating advanced epithelial ovarian cancer (stage III to IV) where primary debulking surgery is not an option.

OBJECTIVES: To assess the effectiveness and complications of IDS for women with advanced stage epithelial ovarian cancer.

SEARCH METHODS: We searched the Cochrane Gynaecological Cancer Group's Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 6, MEDLINE and EMBASE for the original review in to June 2012. We updated the searches in June 2009, 2012 and 2015 for the review updates.

SELECTION CRITERIA: Randomised controlled trials (RCTs) comparing survival of women with advanced epithelial ovarian cancer

AUTHORS' CONCLUSIONS: We found no conclusive evidence to determine whether IDS between cycles of chemotherapy would improve or decrease the survival rates of women with advanced ovarian cancer, compared with conventional treatment of primary surgery followed by adjuvant chemotherapy. IDS appeared to yield benefit only in women whose primary surgery was not performed

using random-effects models.

MAIN RESULTS: Three RCTs randomising 853 women, of whom 781 were evaluated, met the inclusion criteria. Meta-analysis of three trials for overall survival (OS) found no statistically significant difference between IDS and chemotherapy alone (hazard ratio (HR) = 0.80, 95% confidence interval (CI) 0.61 to 1.06, I^2 = 58%). Subgroup analysis for OS in two trials, where the primary surgery was not performed by gynaecologic oncologists or was less extensive, showed a benefit of IDS (HR = 0.68, 95% CI 0.53 to 0.87, I^2 = 0%). Meta-analysis of two trials for PFS found no statistically significant difference between IDS and chemotherapy alone (HR = 0.88, 95% CI 0.57 to 1.33, I^2 = 83%). Rates of toxic reactions to chemotherapy were similar in both arms (risk ratio = 1.19, 95% CI 0.53 to 2.66, I^2 = 0%), but little information was available for other adverse events or quality or life (QoL).

AUTHORS' CONCLUSIONS: We found no conclusive evidence to determine whether IDS between cycles of chemotherapy would improve or decrease the survival rates of women with advanced ovarian cancer, compared with conventional treatment of primary surgery followed by adjuvant chemotherapy. IDS appeared to yield benefit only in women whose primary surgery was not performed

Take home message

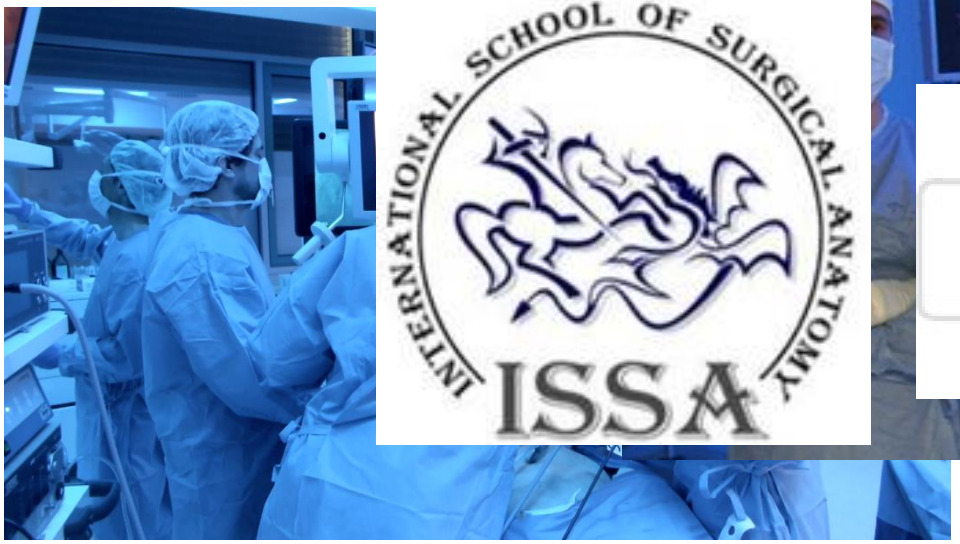
R0= optimal R<1 cm near optimal R>1 cm sub-optimal

Preoperative evaluation: Fagotti score (level 2 grade A)

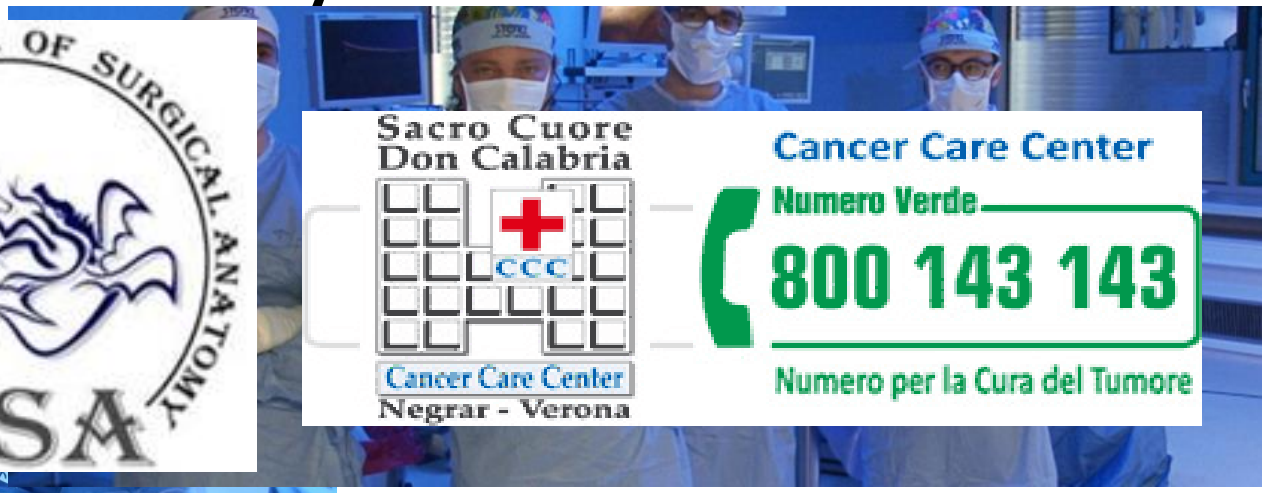
Lymphadenectomy in FIGO IIB-IV, R0, no suspect on node metastasis → LION

IDS ? → no conclusive evidence to determine whether IDS decrease or improve OS in advanced OC

Thank you for your attention

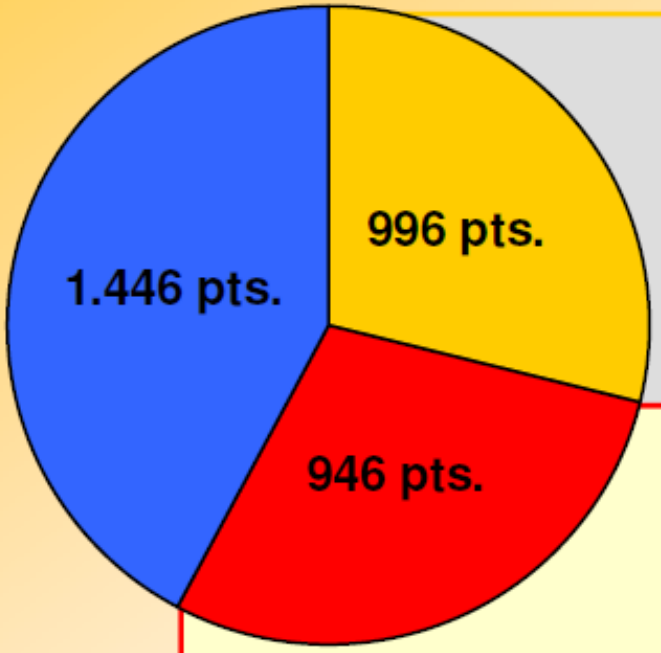


INTERNATIONAL SCHOOL OF SURGICAL ANATOMY
ISSA



Exploratory analysis of 3 randomized AGO-OVAR / GCIG Phase III studies in patients with ovarian cancer FIGO IIB-IV and post-OP platin-paclitaxel therapy (**OVAR 3** *du Bois et al. JNCI 2003;* **OVAR 5** *– du Bois et al JCO 2006;* **OVAR 7**, *Pfisterer et al. JNCI 2006*)

Cave: retrospektive analysis, surgeon's decision pro/con LNE (potential bias !)



Subgroup 1:

- OvCa FIGO IIB-IV
- no macro. residuals

Subgroup of 1+2 (77%):

- clincal/radiological/intra-OP LN status known
- cN0 or cN+

Subgroup 2:

- OvCa FIGO IIB-IV
- residual tumor 0,1 - 1 cm

A du Bois et al., J Clin Oncol 28, 2010