Some insights about LND in advanced Ovarian cancer after LION's roar

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MEMAGO 4
October 11-12, 2019

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

Standards have changed

PRINCIPLES OF PRIMARY SURGERY (1 of 2)[1,2]
(FOR OVARIAN, FALLOPIAN TUBE, AND PRIMARY PERITONEAL CANCER)

In general, a vertical midline abdominal incision should be used in patients with a suspected malignant ovarian neoplasm.[2]

The following procedures should be considered part of the surgical management of patients with ovarian cancer apparently confined to an ovary or to the pelvis:

- On entering the abdomen, aspiration of ascites or peritoneal lavage should be performed for peritoneal cytologic examinations.
- All peritoneal surfaces should be visualized, and any peritoneal surface or adhesion suspicious for harboring metastasis should be selectively excised or biopsied. In the absence of any suspicious areas, random peritoneal biopsies should be taken from the pelvis, paracolic gutters, and undersurfaces of the diaphragm (diaphragm scraping for Papanicolaou stain is an acceptable alternative).
- Total hysterectomy, bilateral salpingectomy, and bilateral oophorectomy should be performed with every effort made to keep an encapsulated mass intact during removal.
- Unilateral salpingo-oophorectomy (USO) for patients desiring to preserve fertility may be considered in select patients. (See OV-A 2 of 2)
- Omentectomy should be performed.
- Aortic lymph node dissection should be performed by stripping the nodal tissue from the vena cava and the aorta bilaterally to at least the level of the inferior mesenteric artery and preferably to the level of the renal vessels.
- Pelvic lymph nodes should be dissected. Removal of lymph nodes overlying and medial to the external iliac and hypogastric vessels, from the obturator fossa anterior to the obturator nerve, and overlying and lateral to the common iliac vessel is preferred.

In general, the following procedures should be part of the surgical management of patients with ovarian cancer involving the upper abdomen in an effort to achieve maximal cytoreduction to < 1 cm residual disease in appropriate circumstances:

- On entering the abdomen, aspiration of ascites or peritoneal lavage should be performed for cytologic examinations.
- Total hysterectomy, bilateral salpingectomy, and bilateral oophorectomy should be performed.
- All involved omentum should be removed.
- Suspicious and/or enlarged nodes should be resected, if possible.
- Those patients with tumor nodules outside the pelvis ≤ 2 cm (presumed stage IIIB) should have bilateral pelvic and periaortic lymph node dissection as previously described.

- Procedures that may be considered for optimal surgical cytoreduction (in all stages) may include:
  - Radical pelvic dissection
  - Bowel resection
  - Diaphragm or other peritoneal surface stripping
  - Splenectomy

Continued on OV-A 2 of 2

PRINCIPLES OF SURGERY (2 of 4)[1]

Newly diagnosed invasive epithelial ovarian cancer apparently confined to an ovary or to the pelvis

In general, every effort should be made during a primary cytoreduction procedure to achieve maximum cytoreduction of all pelvic disease and to evaluate for occult disease in the upper abdomen or retroperitoneum.

- **On entering the abdomen, aspiration of ascites or peritoneal lavage should be performed for peritoneal cytologic examinations.**
- **All peritoneal surfaces should be visualized, and any peritoneal surface or adhesion suspicious for harboring metastasis should be selectively excised or biopsied. In the absence of any suspicious areas, random peritoneal biopsies should be taken from the pelvis, paracolic gutters, and undersurfaces of the diaphragm (diaphragm scraping for Papanicolaou stain is an acceptable alternative).**
- **BSO and hysterectomy should be performed with every effort to keep an encapsulated mass intact during removal.**
- **For selected patients desiring to preserve fertility, USO may be considered.**
- **Omentectomy should be performed.**
- **Para-aortic lymph node dissection should be performed by stripping the nodal tissue from the vena cava and the aorta bilaterally to at least the level of the inferior mesenteric artery and preferably to the level of the renal vessels.**
- **The preferred method of dissecting pelvic lymph nodes is bilateral removal of lymph nodes overlying and anterolateral to the common iliac vessel, overlying and medial to the external iliac vessel, overlying and medial to the hypogastric vessels, and from the obturator fossa at a minimum anterior to the obturator nerve.[2]**

Newly diagnosed invasive epithelial ovarian cancer involving the pelvis and upper abdomen

In general, every effort should be made during a primary cytoreduction procedure to achieve maximum cytoreduction of all abdominal, pelvic, and retroperitoneal disease. Residual disease <1 cm defines optimal cytoreduction; however, maximal effort should be made to remove all gross disease since this offers superior survival outcomes.[3]

- **Aspiration of ascites (if present) should be performed for peritoneal cytologic examinations. All involved omentum should be removed.**
- **Suspicious and/or enlarged nodes should be resected, if possible.**
- **Those patients with tumor nodules outside the pelvis ≤2 cm (presumed stage IIIB) should have bilateral pelvic and para-aortic lymph node dissection as previously described.**
- **Procedures that may be considered for optimal surgical cytoreduction (in all stages) include bowel resection and/or appendectomy, stripping of the diaphragm or other peritoneal surfaces, splenectomy, partial cystectomy and/or ureteroneocystostomy, partial hepatectomy, partial gastrectomy, cholecystectomy, and/or distal pancreatectomy.**
- **Select patients with low-volume residual disease after surgical cytoreduction for invasive epithelial ovarian or peritoneal cancer are potential candidates for IP therapy. In these patients, consideration should be given to placement of IP catheter with initial surgery.**

[1]Fleming GF, Seidman J, Lengyel E, et al: Epithelial ovarian cancer. In Barakat RR, Berchuck A, Markman M, et al. (eds): Principles and Practice of Gynecologic Oncology, 6th ed, Philadelphia, Lippincott Williams & Wilkins, 2013:757-847. Amended by panel.
[2]Whitney CW, Spirtos N. Gynecologic Oncology Group Surgical Procedures Manual. Philadelphia: Gynecologic Oncology Group; 2010.
[3]Chi DS, Eisenhauer EL, Zivanovic O, et al. Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm. Gynecol Oncol 2009;114:26-31.

Continued on OV-A (3 of 4)

NCCN Evidence Blocks™

Most patients have a hysterectomy with BSO, omentectomy, and lymphadenectomy of suspicious/enlarged nodes (see *Principles of Surgery* in the NCCN Guidelines for Epithelial Ovarian Cancer). Some surgeons classify debulking based on the number of procedures. In patients with advanced ovarian cancer who have had complete debulking, data indicate that overall survival is increased in those who receive systematic lymphadenectomy.[187] Patients with low-volume residual disease after surgical cytoreduction for invasive epithelial ovarian or peritoneal cancer are potential candidates for intraperitoneal

PRINCIPLES OF SURGERY[1]

Newly Diagnosed Invasive Epithelial Ovarian Cancer Apparently Confined to an Ovary or to the Pelvis

In general, every effort should be made during a primary cytoreduction procedure to achieve maximum cytoreduction of all pelvic disease and to evaluate for occult disease in the upper abdomen or retroperitoneum.

- On entering the abdomen, aspiration of ascites or peritoneal lavage should be performed for peritoneal cytologic examinations.
- All peritoneal surfaces should be visualized, and any peritoneal surface or adhesion suspicious for harboring metastasis should be selectively excised or biopsied. In the absence of any suspicious areas, random peritoneal biopsies should be taken from the pelvis, paracolic gutters, and undersurfaces of the diaphragm (diaphragm scraping for Papanicolaou stain is an acceptable alternative).
- BSO and hysterectomy should be performed with every effort to keep an encapsulated mass intact during removal.
- For selected patients desiring to preserve fertility, USO or BSO with uterine preservation may be considered. Uterine preservation allows for potential future assisted reproductive approaches.
- Omentectomy should be performed.
- Para-aortic lymph node dissection should be performed by stripping the nodal tissue from the vena cava and the aorta bilaterally to at least the level of the inferior mesenteric artery and preferably to the level of the renal vessels.
- The preferred method of dissecting pelvic lymph nodes is bilateral removal of lymph nodes overlying and anterolateral to the common iliac vessel, overlying and medial to the external iliac vessel, overlying and medial to the hypogastric vessels, and from the obturator fossa at a minimum anterior to the obturator nerve.[2]

Newly Diagnosed Invasive Epithelial Ovarian Cancer Involving the Pelvis and Upper Abdomen

In general, every effort should be made during a primary cytoreduction procedure to achieve maximum cytoreduction of all abdominal, pelvic, and retroperitoneal disease. Residual disease <1 cm defines optimal cytoreduction; however, maximal effort should be made to remove all gross disease since this offers superior survival outcomes.[3]

- Aspiration of ascites (if present) should be performed for peritoneal cytologic examinations. All involved omentum should be removed.
- Suspicious and/or enlarged nodes should be resected, if possible. Resection of clinically negative nodes is not required.
- Those patients with tumor nodules outside the pelvis ≤2 cm (presumed stage IIIB) should have bilateral pelvic and para-aortic lymph node dissection as previously described.
- Procedures that may be considered for optimal surgical cytoreduction (in all stages) include bowel resection and/or appendectomy, stripping of the diaphragm or other peritoneal surfaces, splenectomy, partial cystectomy and/or ureteroneocystostomy, partial hepatectomy, partial gastrectomy, cholecystectomy, and/or distal pancreatectomy.
- Select patients with low-volume residual disease after surgical cytoreduction for invasive epithelial ovarian or peritoneal cancer are potential candidates for IP therapy. In these patients, consideration should be given to placement of IP catheter with initial surgery.

dissection is recommended for those patients with tumor nodules, outside the pelvis, of 2 cm or less (presumed stage IIIB) (see *Principles of Surgery* in the NCCN Guidelines for Epithelial Ovarian Cancer). For young patients who will abruptly enter menopause after surgery, various supportive care measures may be used to help decrease hot flashes and other symptoms.[176-179]

Most patients have a hysterectomy with BSO, omentectomy, and lymphadenectomy of suspicious/enlarged nodes (see *Principles of Surgery* in the NCCN Guidelines for Epithelial Ovarian Cancer). Some surgeons classify debulking based on the number of procedures. In patients with advanced ovarian cancer who have had complete debulking, data indicate that overall survival is increased in those who receive systematic lymphadenectomy.[180] Patients with low-volume residual disease after surgical debulking for stage II or III invasive epithelial ovarian or peritoneal cancer are candidates for intraperitoneal (IP) therapy.[181,182] In these patients, consideration should be given to placement of an IP catheter with initial surgery.[145] Procedures that may be considered for optimal surgical debulking include: radical pelvic dissection, bowel resection and/or appendectomy, lymphadenectomy, diaphragm or other peritoneal stripping, splenectomy, partial hepatectomy, partial gastrectomy, or partial cystectomy and/or ureteroneocystostomy, cholecystectomy, and/or distal pancreatectomy.[162,170,183]

Prise en charge initiale des cancers gynécologiques : Référentiels de la Société Française d'Oncologie Gynécologique*

Coordinateurs: Querleu Denis, Bonnier Pascal, Morice Philippe, Narducci Fabrice

Chirurgie

Intervention standard minimale

- hystérectomie totale, annexectomie bilatérale, omentectomie totale, appendicectomie, curage ganglionnaire pelvien et aortique infrarénal bilatéral, biopsies péritonéales, cytologie péritonéale

*Société Française d'Oncologie Gynécologique, Président: Professeur Denis Querleu;
Secrétaire: Professeur Pascal Bonnier
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❖ *Conclusions de la littérature*

Les 3 méta-analyses publiées sont en faveur des curages systématiques dans les cancers avancés de l'ovaire, de la trompe ou du péritoine primitif (NP1).

Néanmoins, le seul essai randomisé actuellement publié concernant les stades avancés, ne retrouvait pas d'amélioration de la survie globale à 5 ans mais uniquement un allongement de la survie sans récidive, au prix d'une augmentation significative de la morbi-mortalité périopératoire (NP2).

Enfin, il existe un bénéfice en survie aux curages systématiques en présence de ganglions suspects radiologiques ou cliniques (NP2).

Il n'existe pas de donnée concernant la lymphadénectomie pelvienne et lombo-aortique en chirurgie intervallaire.

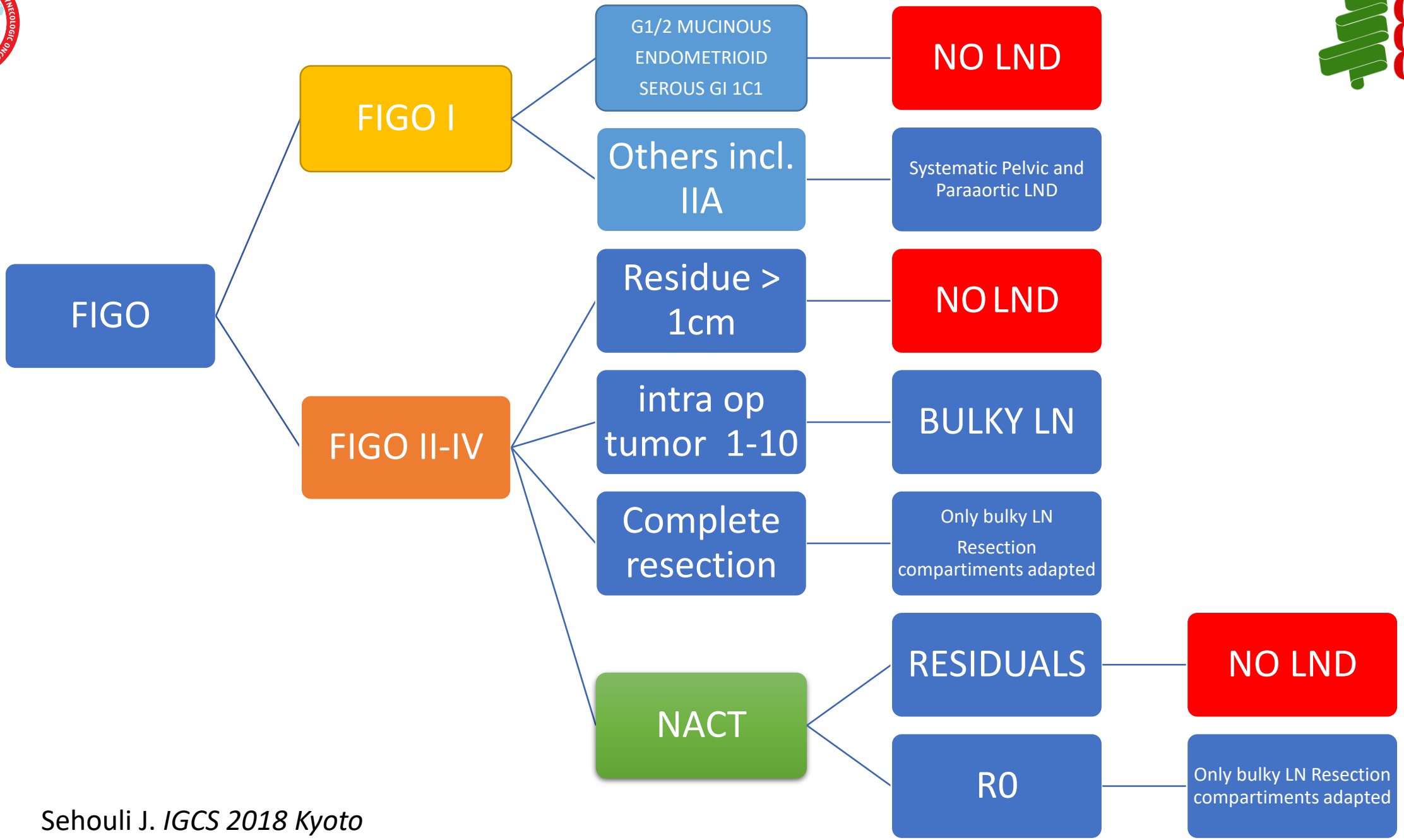
❖ *Recommandations*

La réalisation de lymphadénectomies lomboaortiques et pelviennes est recommandée pour les cancers avancés de l'ovaire, de la trompe ou du péritoine primitif, quel que soit le type histologique,

en cas de suspicion clinique ou radiologique d'adénopathie métastatique pelvienne et/ou lombo-aortique (Grade B).

En l'absence d'adénopathie suspecte clinique ou radiologique et en cas de chirurgie péritonéale complète macroscopique lors d'une chirurgie initiale, la lymphadénectomie peut être omise parce que cela ne modifie pas le traitement médical ni la survie globale, tout en augmentant la morbidité (Grade B).

Les lymphadénectomies supra-rénale, mésentérique, cœlio-hépatique, de l'angle cardio-phrénique ne sont pas recommandées en l'absence d'envahissement (Grade C).



Sehouli J. *IGCS 2018 Kyoto*

The actual Trend

- In case of complete resection of carcinosis:
  - No need for systematic LND if no clinically positive lymph nodes (palpation, imaging…)
  - Remove only bulky nodes, removal of normal lymph nodes will not change the prognosis
- In case of residual tumor, no need for LND
  - The prognosis is already poor due to the residual disease

The actual Trend

- What are the selection criteria ??
- How to assess the patients ??
- Do we have enough convincing data ?

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Was the randomization accurate enough?

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- After complete peritoneal resection, patients underwent randomization if surgical evaluation **showed no macroscopically involved nodes**.

Criterion not definite

Morice P, Pautier P, Gouy S. Lymphadenectomy in advanced ovarian neoplasms. Letter to the editor. N Engl J Med. 2019 June

LION inclusion criteria to be questioned

- **Potential evaluator bias**

- 52 centers were recruiting patients -> **a minimum of 52 surgeons !!!**

- Do these **52 evaluators** have the same clinical skills and experience ?!!

LION inclusion criteria to be questioned

- At 52 centers, at least 1 patient underwent randomization. At the largest center, 78 patients (12% of 647) underwent randomization. We evaluated the effect of lymphadenectomy as compared with no lymphadenectomy within high-recruiting centers (defined as those with ≥21 patients undergoing randomization) and low-recruiting centers (those with ≤20 patients undergoing randomization). Approximately 55% of patients underwent randomization in high-recruiting centers, and 45% underwent randomization in low-recruiting centers. No significant treatment effect was found in either subgroup.

45 % underwent randomization in low-recruiting centers !!!

Concept of “clinically negative lymph nodes”is a limitation !!!

- Pelvic and aortic lymph node metastasis in epithelial ovarian cancer

  Gynecologic Oncology (2007), Pereira et al.

  There was no significant difference between the mean size of positive (1.8 cm) and negative nodes (1.6 cm)

- Can we rely on the size of the lymph node in determining nodal metastasis in ovarian carcinoma?

  International Journal of Gynecological Cancer (2003), Tangjitgamol et al.

  Lymph node size is not a good indicator in determining epithelial ovarian cancer metastasis

Size of lymph node

Table 5
Distribution of positive and negative lymph nodes by size

Size, cm	LN, no. (N=87)	Positive LN (n=35)		Negative LN (n=52)	
		No.	%	No.	%
0.2–0.9	12	4	33	8	67
1–1.9	30	6	20	24	80
2–2.9	30	15	50	15	50
3–3.9	10	6	60	4	40
4–5	5	4	80	1	20

- Pereira et al. have found no significant difference between the mean size of positive (1.8 cm) and negative nodes (1.6 cm), $p = 0.61$

Rationale

Gynecologic Oncology **82,** 143–149 (2001)
doi:10.1006/gyno.2001.6232, available online at http://www.idealibrary.com on IDEAL®

The Clinical Significance of Occult Macroscopically Positive Retroperitoneal Nodes in Patients with Epithelial Ovarian Cancer

Scott M. Eisenkop, M.D.,*[,1] and Nick M. Spirtos, M.D.†

*Womens' Cancer Center: Encino–Tarzana, 5525 Etiwanda Avenue, Suite 311, Tarzana, California 91356; and
†Womens' Cancer Center: Palo Alto, 900 Welch Road, Suite 300, Palo Alto, California 94304-1800

Received January 6, 2001; published online May 31, 2001

- **Incidence of lymph node involvement can reach 66% of the cases**
- with 49% having positive lymph nodes (more than 1 cm in diameter) and 17% having positive lymph nodes not identified by palpation or inspection

- THESE TRIAGING CRITERIAS ARE DANGEROUS
- YOU MAY LEAVE BEHIND YOU LARGE RESIDUALS MISEVALUATED

Massive metastatic lymph nodes can be overlooked

Concept of “clinically negative lymph nodes” !!!

- How many patients underwent preoperative CT or MRI with a reliable measurement to discriminate suspicious nodes according to the Response Evaluation Criteria in Solid Tumors (RECIST)3 (>10 mm)
- What clinical or radiographic node size should be used in making a decision regarding nodal surgery larger than 10, 15, or 20 mm?
- Finally, to exclude bias related to palpation by the surgeon, which node size should oncologists use in routine practice to select patients for lymphadenectomy?

Morice P, Pautier P, Gouy S. Lymphadenectomy in advanced ovarian neoplasms. Letter to the editor. N Engl J Med. 2019 June

Imaging abdomen and pelvis (2)	**X**		**		**	**	**	**	**
Imaging chest (3)	**X**		**		**	**	**	**	**
Informed consent	**X**								
Complete resection		**X**							
Randomization		**X**							
Systematic LNE or no LNE according to randomized allocation		**X**							
QoL	**X**		**X**		**X**		**X**		
Complications				**X**					

chx= chemotherapy, mos = months, LNE = lymphadenectomy, QoL = Quality of life questionnaires

* at discharge of the patient or on 21st day after surgery, whichever occurs first.

** if clincally indicated

*** pre- and intraoperative procedures including randomization

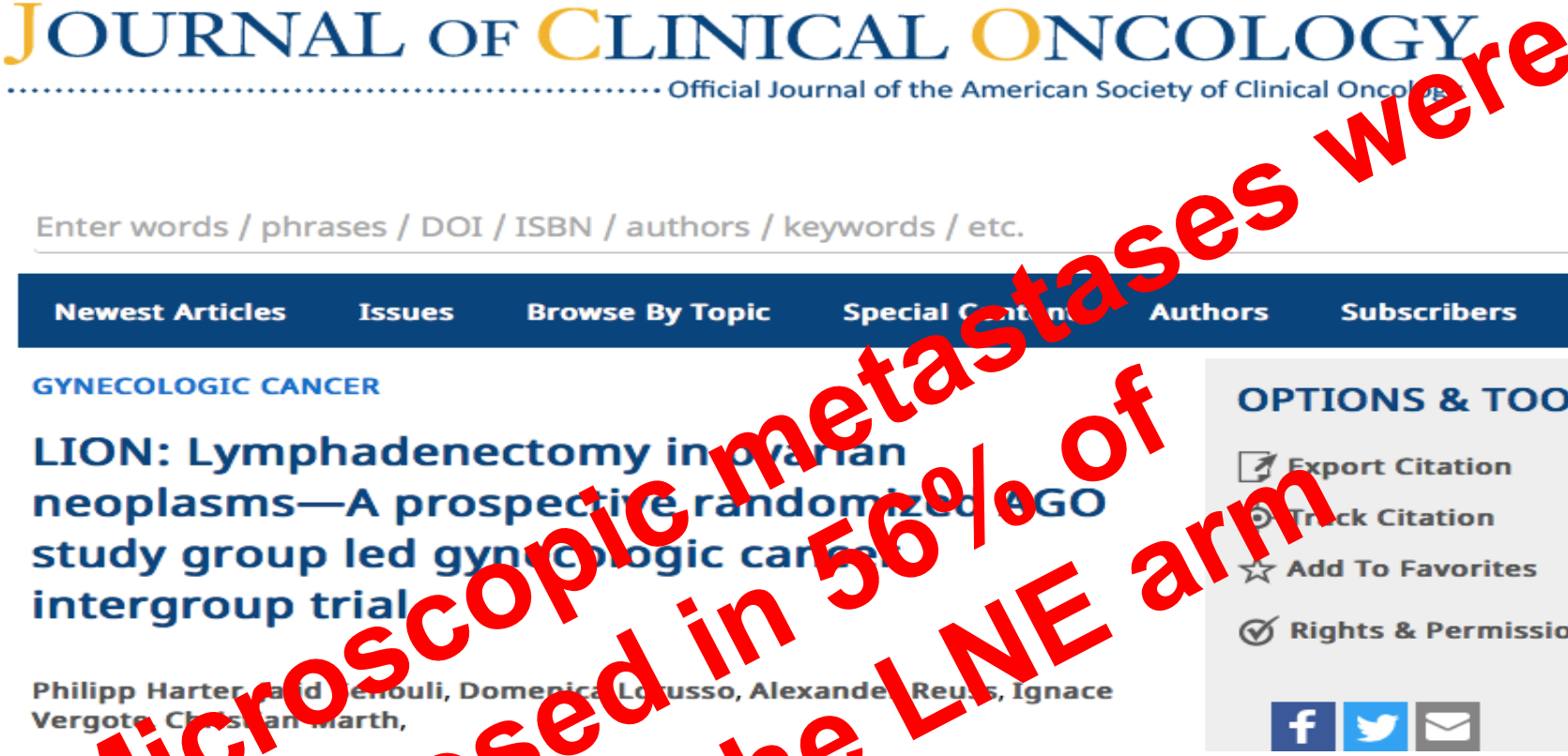
**** visit 2 is within 6 weeks after end of primary chemotherapy or 6 months after surgery, whichever occurs first

***** Structured interview of patient/treating physician with regard to surgical complications within 60 days after surgery

(1) including palpation and ultrasound of pelvis

(2) ultrasound, CT scan, or MRI

(3) x-ray, CT scan, or MRI



Microscopic metastases were diagnosed in 56% of the pts in the LNE arm

- Post-op platinum-taxane based chemotherapy was applied in 85% of the patients in no-LNE arm vs. 80% in LNE arm: **5% more in no-LNE.**
- **EFFECT OF BEV?**
- The LNE arm **neither improved overall survival** (HR: 1.06; 95% CI: 0.83–1.34) **nor progression-free survival** (HR: 1.06; 95% CI: 0.83–1.34) despite adequately removing subclinical retroperitoneal lymph node metastases in 56% of the patients (median number of resected lymph nodes was 57).

International Journal of Gynecological Pathology
34:379–384, Lippincott Williams & Wilkins, Baltimore

Original Article

Lymph Node Micrometastases in Early-Stage Cervical Cancer are Not Predictive of Survival

Michael P. Stany, M.D., Pamela J. B. Stone, M.D., Juan C. Felix, M.D., Charles A. Amezcua, M.D., Susan Groshen, Ph.D., Wei Ye, Ph.D., Kathy L. Kyser, M.D., Robin S. Howard, M.A., Chris M. Zahn, M.D., Laila I. Muderspach, M.D., Scott E. Lentz, M.D., and Mildred R. Chernofsky, M.D.

The presence of LNM was not associated with an unfavorable prognosis nor was it associated with other high-risk clinical or pathologic variables predicting recurrence.

VOLUME 33 · NUMBER 10 · APRIL 1 2015

JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Breast Cancer Axillary Staging: Much Ado About Micrometastatic Disease

Erica L. Mayer, *Dana-Farber Cancer Institute, Boston, MA*
Laura S. Dominici, *Dana-Farber/Brigham and Women's Cancer Center, Boston, MA*

See accompanying article on page 1119

Same story.....

- sentinel lymph nodes in breast cancer : micrometastatic did not change the survival

Micrometastasis?

- having microscopic metastasis is as if metastasis did not existed
- so we are probably comparing the same population having a parameter (micrometastasis) that is not important on survival without the effect of lymphadenectomy
- who said that ovarian cancer needs removal of normal lymph nodes in order to improve survival
- it would be the only cancer that will benefit from removal of normal lymph nodes

LION Trial – Characteristics of patients

	Lymphadenectomy Group (N = 323)	No-Lymphadenectomy Group (N = 324)
Final FIGO stage – no. (%)		
I to IIA	15 (4.6)	17 (5.2)
IIB to IIIA	41 (12.7)	52 (16.0)
IIIB to IV	261 (80.8)	244 (75.3)
Missing data	6 (1.9)	11 (3.4)

Lymph node count

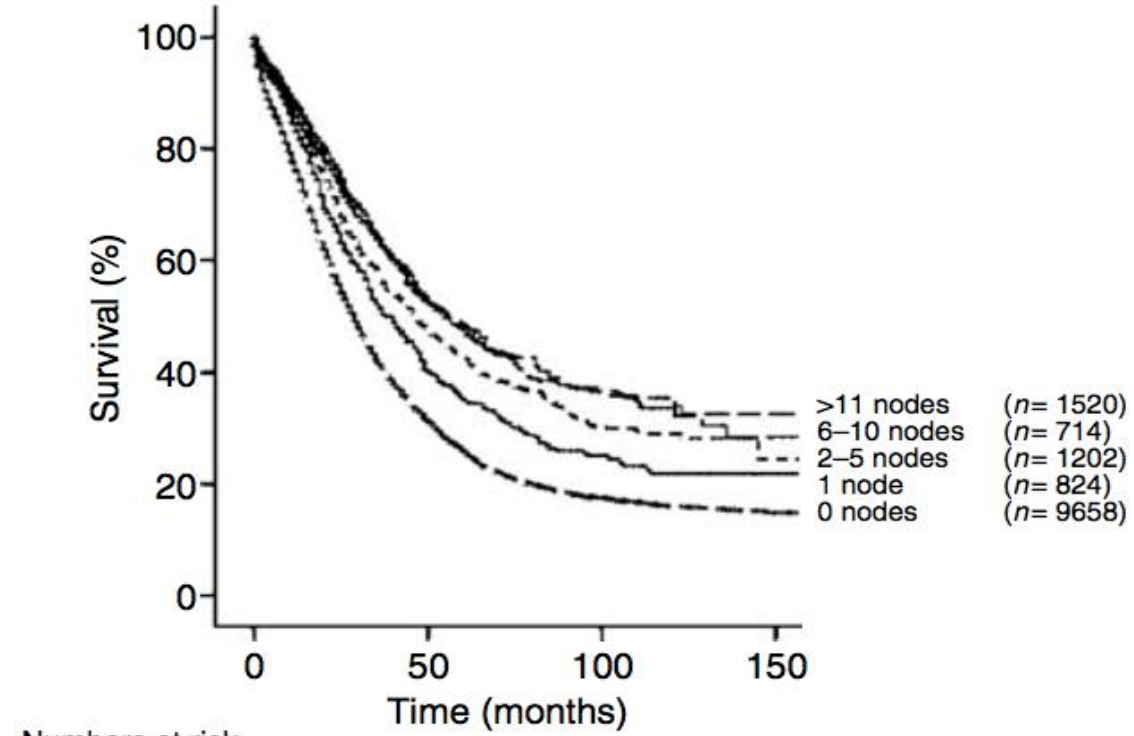
The potential therapeutic role of lymph node resection in epithelial ovarian cancer: a study of 13 918 patients

British Journal of Cancer (2007) 96, 1817 – 1822 Chan JK et al.

Table 5 Multivariate analysis

Prognostic factor	Hazard ratio	95% confidence interval	P-value
Age at diagnosis[a]	1.018	1.016–1.019	$P<0.005$
Year of diagnosis[b]	0.977	0.970–0.984	$P<0.005$
Stage[c]	1.266	1.220–1.315	$P<0.005$
Grade[d]	1.933	1.684–2.219	$P<0.005$
Histology[e]	1.994	1.716–2.316	$P<0.005$
Extent of lymphadenectomy[f]	0.911	0.861–0.964	$P=0.001$
Positive nodes[g]	1.338	1.215–1.473	$P<0.005$

[a]Continous. [b]Continous. [c]Stage IIIA/B *vs* IIIC *vs* IV. [d]Grade 1 *vs* 2–3. [e]Others *vs* clear cell. [f]0 *vs* 1 *vs* 2–5 *vs* 6–10 *vs* ⩾11. [g]No *vs* yes.



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 ($n = 13918$; $P < 0.001$).

- **A more extensive lymph node dissection** (0, 1, 2–5, 6 – 10, 11 – 20, and >20 nodes) was associated with an improved 5-year disease-specific survival of 26.1, 35.2, 42.6, 48.4, 47.5, and 47.8%, respectively (P < 0.001)

Chan et al. 2007

Contents lists available at ScienceDirect

Surgical Oncology

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

"The impact of debulking surgery in patients with node-positive epithelial ovarian cancer: Analysis of prognostic factors related to overall survival and progression-free survival after an extended long-term follow-up period"

Augusto Pereira [a, *], Tirso Pérez-Medina [b], Javier F. Magrina [c], Paul M. Magtibay [c], Ana Rodríguez-Tapia [d], Tatiana Cuesta-Guardiola [a], Irene Peregrin [e], Elsa Mendizabal [a], Santiago Lizarraga [a], Luís Ortiz-Quintana [a]

Table 2
Univariate analysis of overall survival (N = 116) in node-positive EOC patients.

Age (years)	N	OS (%)	RR	95%C I	P
Overall number of nodes removed					
>40	42	26.2	1.00	–	NS
31–40	18	5.56	1.28	1.03–1.58	
21–30	19	5.26	1.28	1.04–1.58	
11–20	20	20.0	1.08	0.82–1.44	
1–10	17	23.5	1.04	0.75–1.43	

LION: Characteristics of surgery

	LNE (%)	No LNE (%)	Difference	p-value
Study procedure according to randomisation	320 (99.1)	313 (96.6)		
Resected LN total (median, IQR) Para-aortic LN Pelvic LN	57 (45-73) 22 (16-33) 35 (26-43)			
Lymph node metastases	180 (55.7)			
Duration (median, IQR) [min]	340 (270-420)	280 (210-360)	+ 1 hour	<0.001
Blood loss (median, IQR) [ml]	650 (400-1000)	500 (300-900)	+ 150 ml	<0.001
Transfusions Massive transfusions (> 10 RBC/24h)	205 (63.7) 7 (2.2)	181 (56.0) 2 (0.6)	+ 8%	0.005 0.09
Fresh-frozen plasma	117 (36.3)	96 (29.7)	+ 7%	0.07
Intermediate/Intensive Care Unit	250 (77.6)	223 (69.4)	+ 8%	0.01

What about the lymph node ratio????

What about the number of involved lymph nodes

Prognostic value of lymph node ratio in patients with advanced epithelial ovarian cancer

Gynecologic Oncology (2014), Ataseven 2014

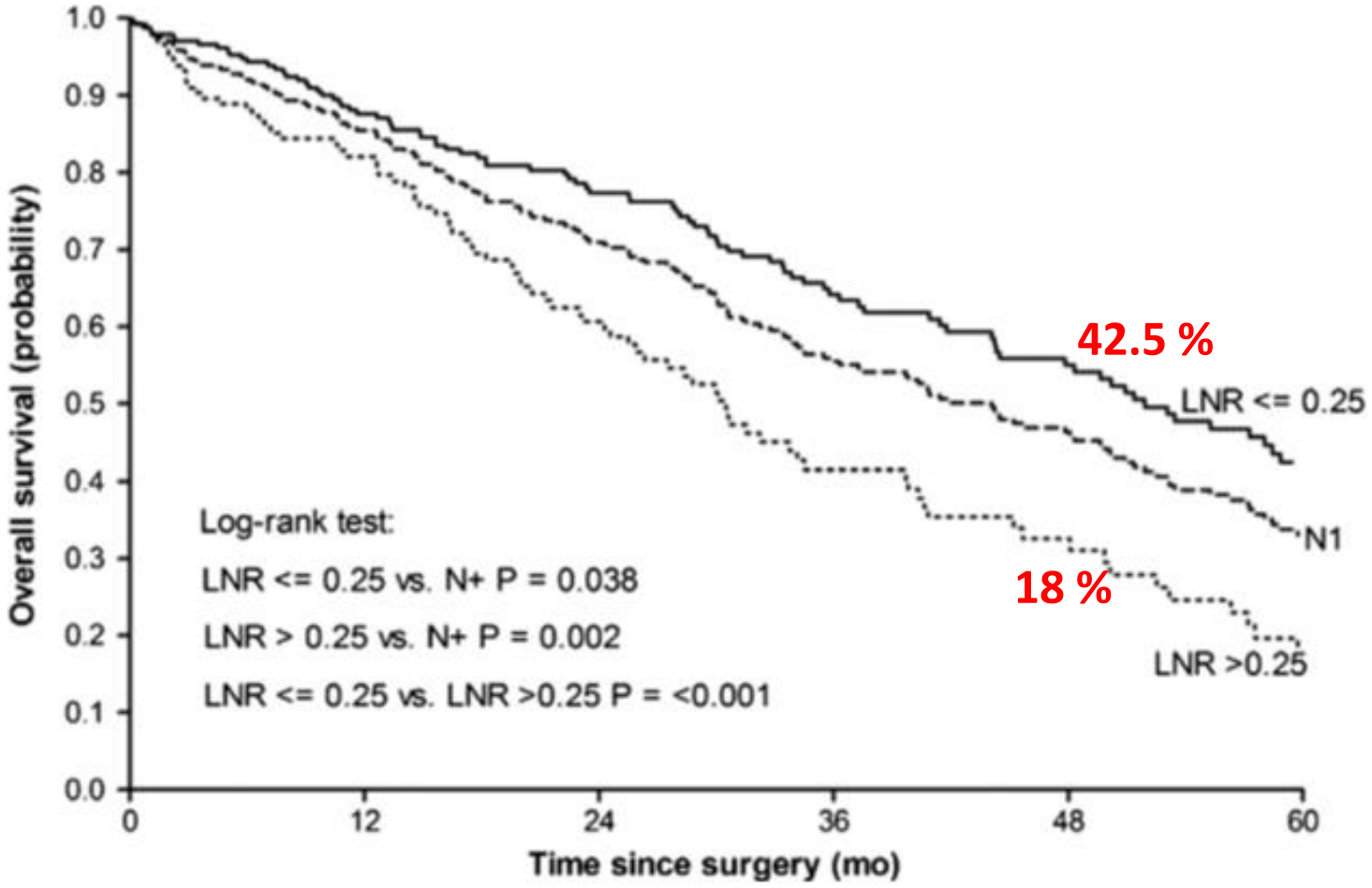
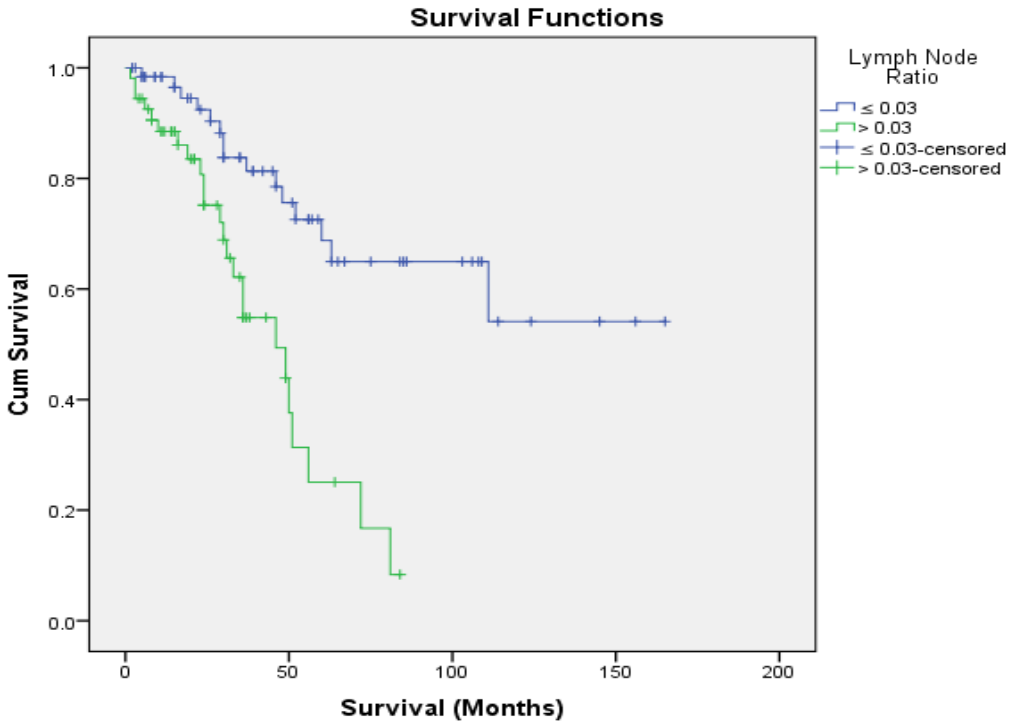


Fig. 2. Overall survival by lymph node ratio (LNR). Kaplan–Meier.

Lebanese experience with cytoreductive surgery in ovarian cancer: a single institution series

ATALLAH D, MOUBARAK M, DAGHER B, EL KASSIS N, EL HAJJ H, CHAHINE G
Saint Joseph University, Hôtel- Dieu de France University Hospital
Beirut, LEBANON



In our series of 161 patients with ovarian cancer, we have noted that patients with a lymph node ratio < 0.03 had a mean survival of **50 months vs. 27 months** in patients with a lymph node ratio > 0.03 (P = 0.000)

Methods I: Selection of centers

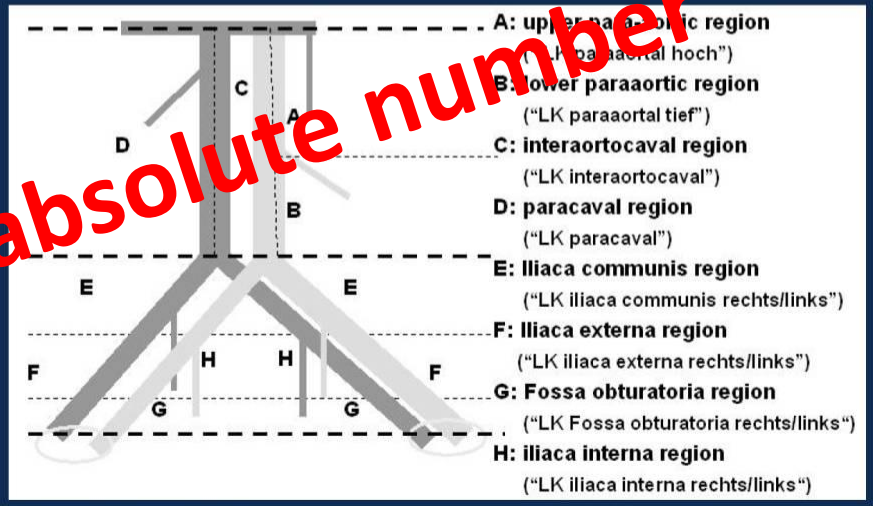
All centers had to qualify before participation in the LION trial

- 12 anonymous surgical and pathologic reports of patients with systematic pelvic and para-aortic lymphadenectomy of the preceeding 12 months

Surgery was defined adequate, if

- *at least 20 pelvic and 10 para-aortic lymph nodes were removed*
- *The surgical report describes systematic lymphadenectomy covering all pre-defined anatomical regions*[1]

Accepting an absolute number



[1]Harter P, et al. Int J Gynecol Cancer 2007

Presented by: Philipp Harter
AGO & KEM
Essen, Germany

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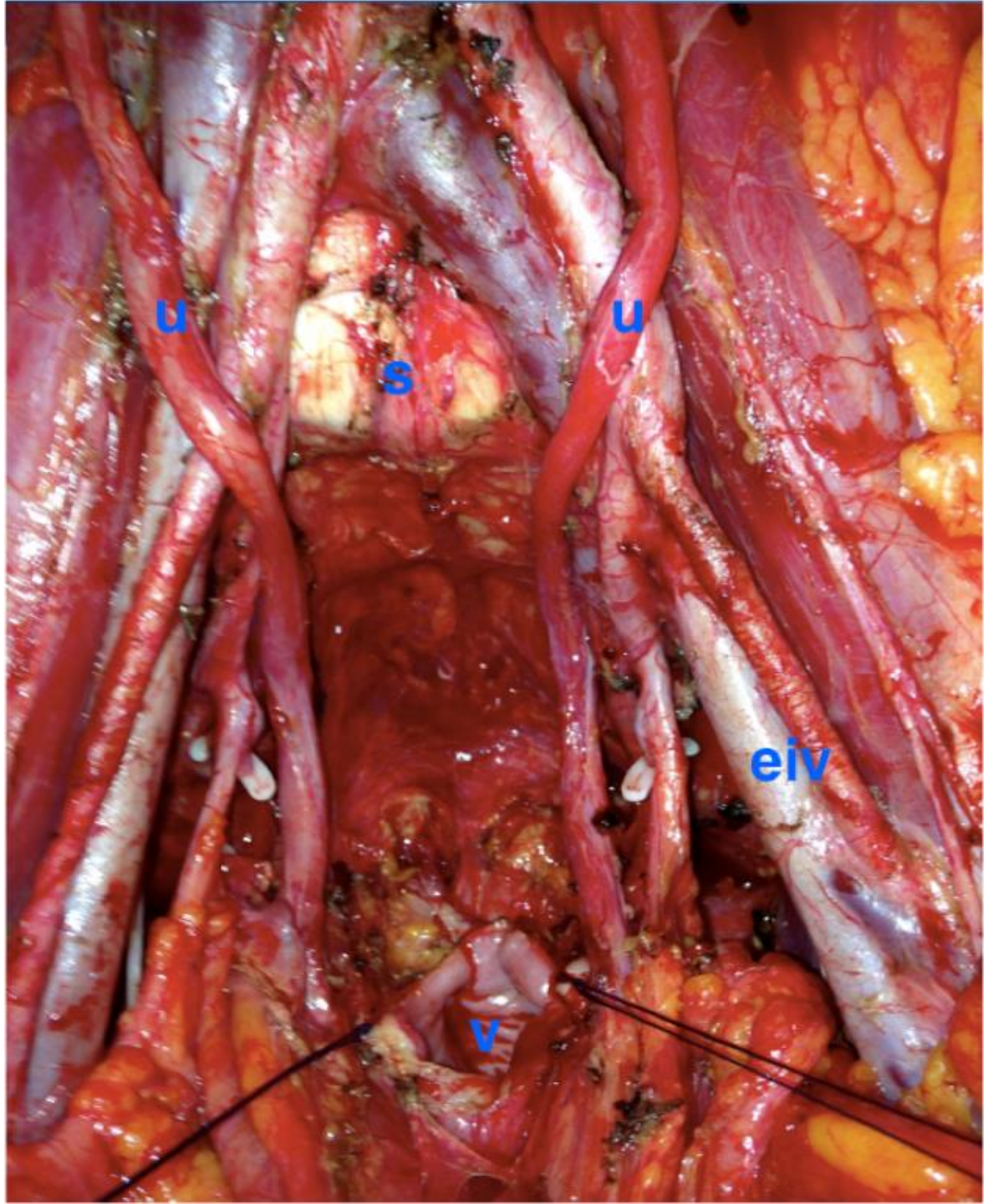

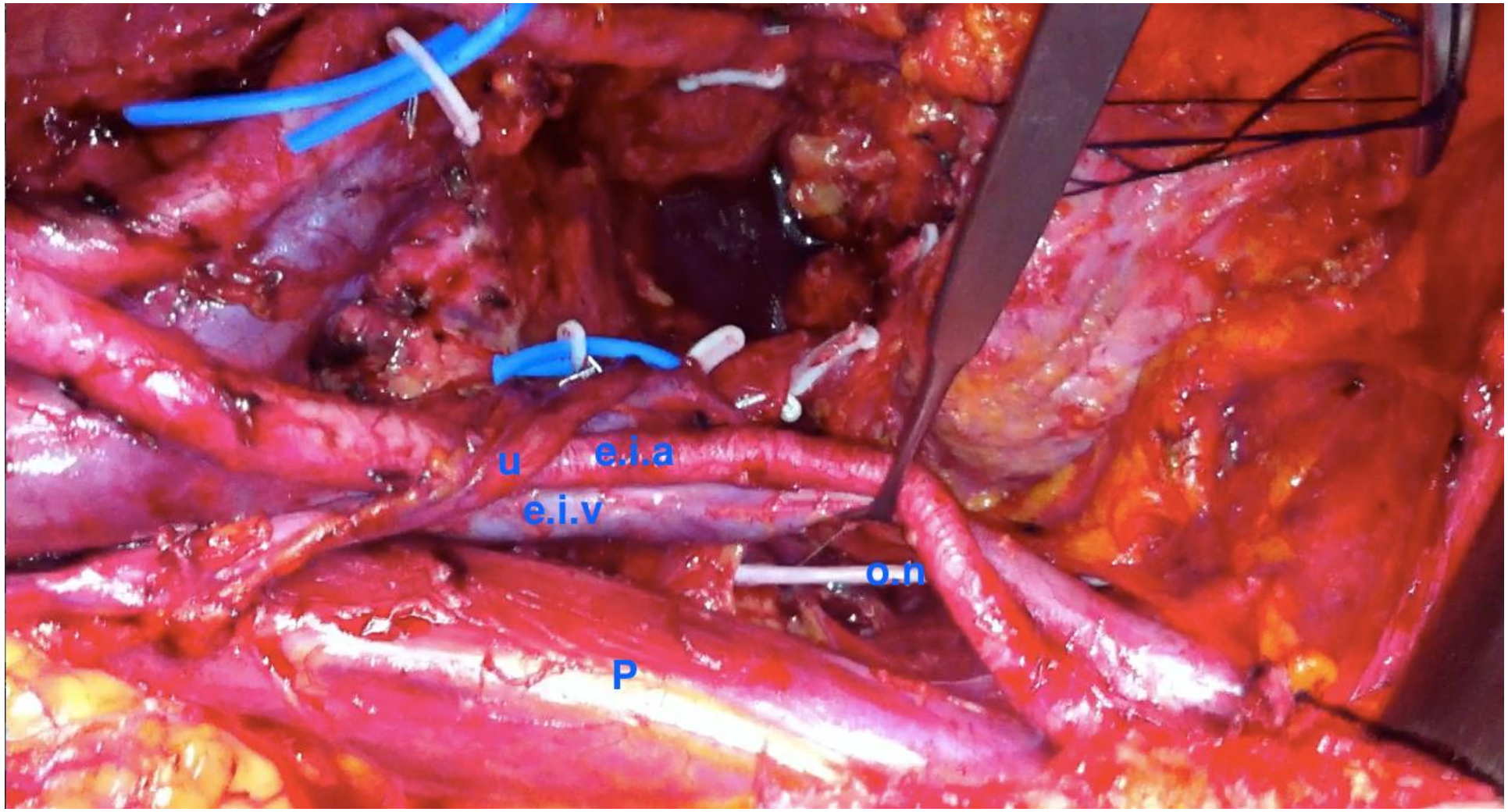
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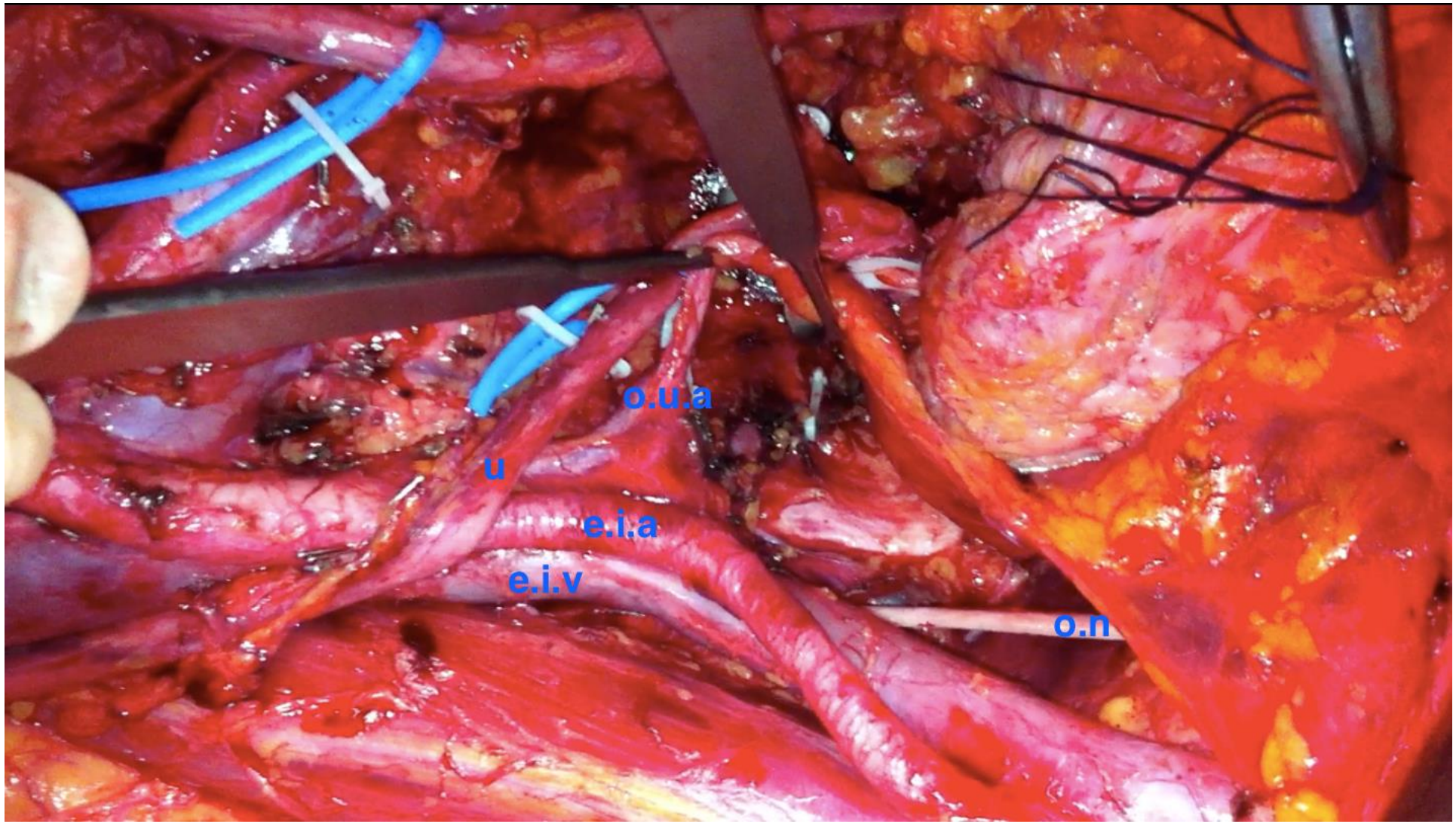
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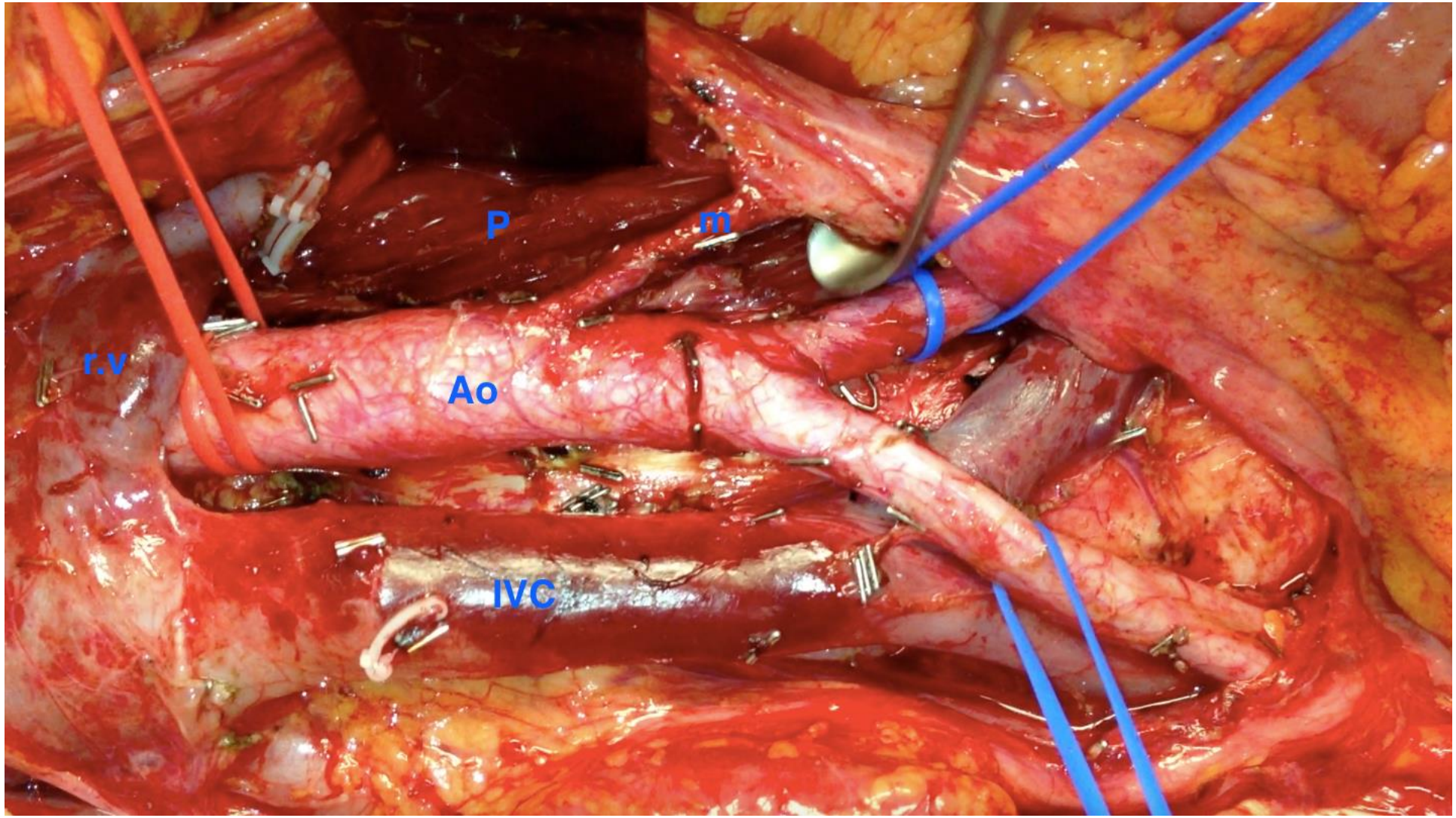
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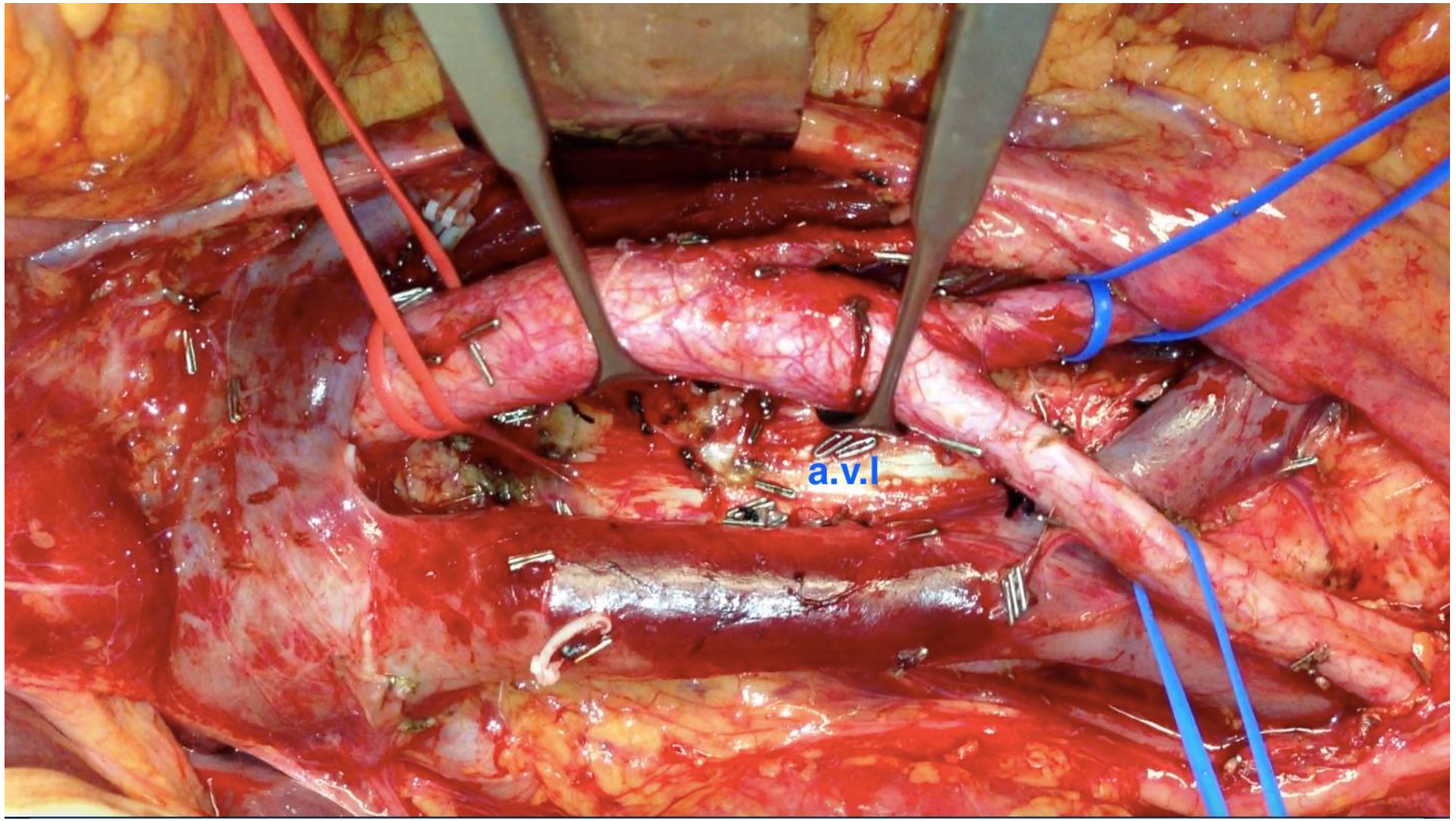
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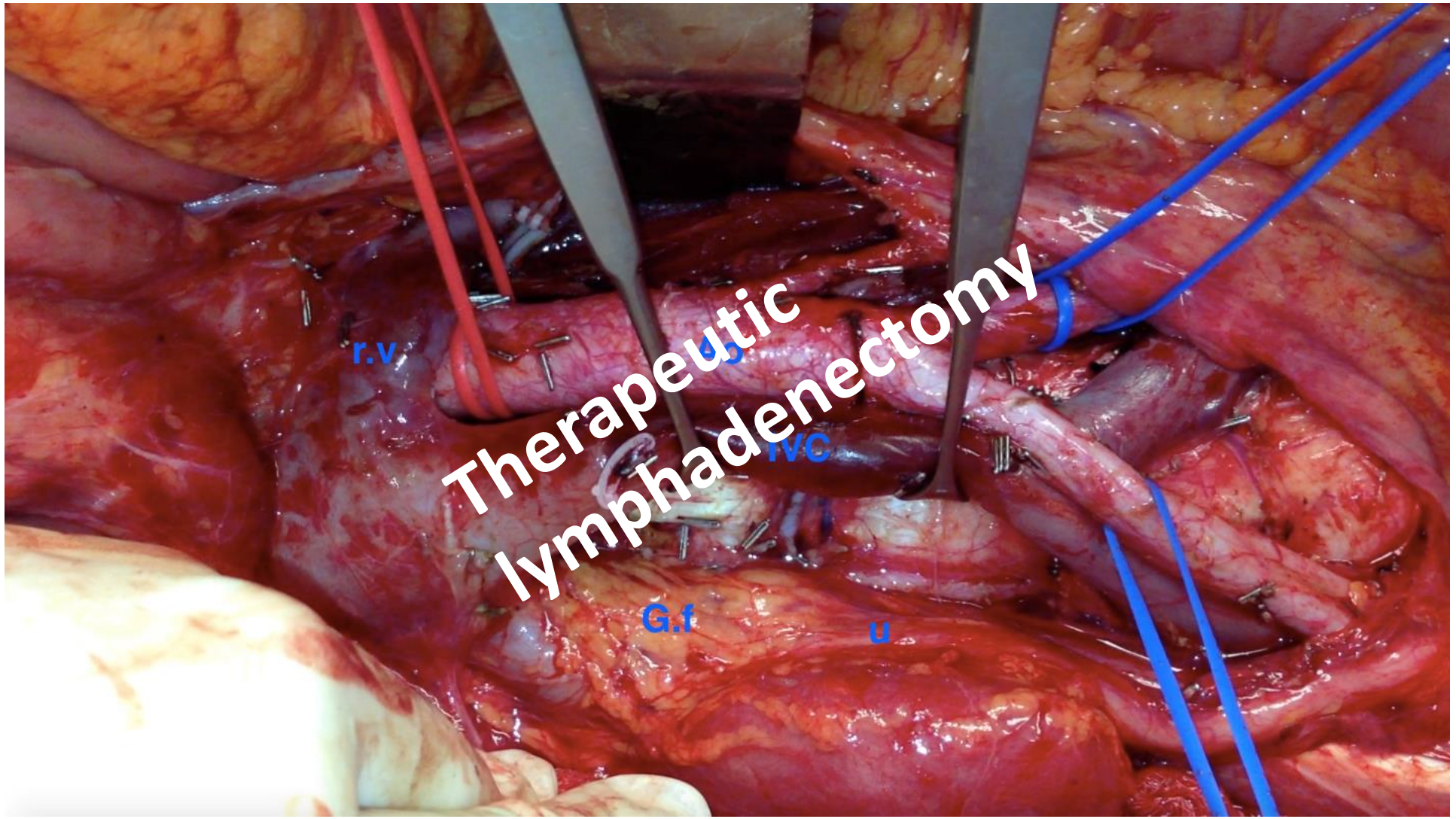
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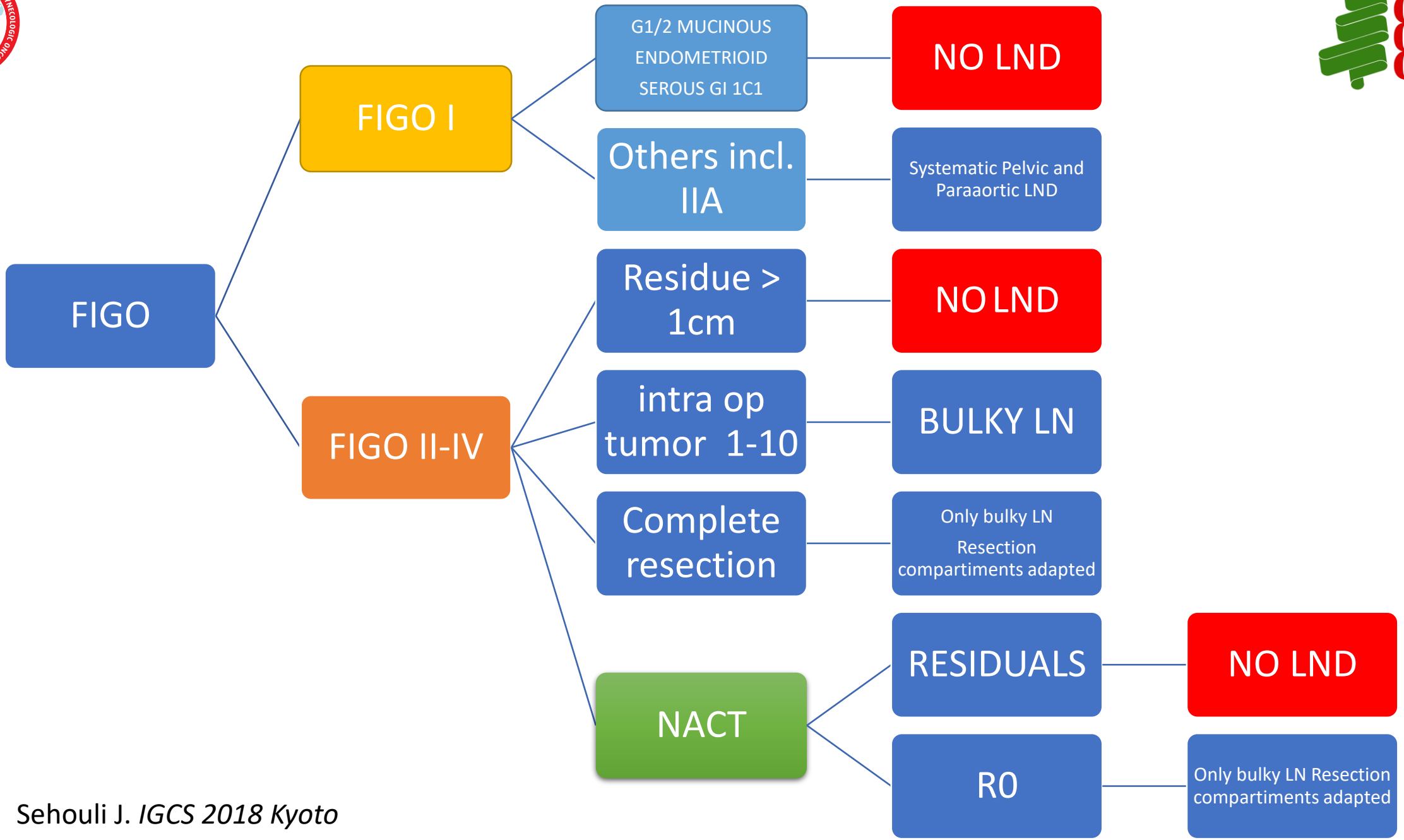
Therapeutic lymphadenectomy

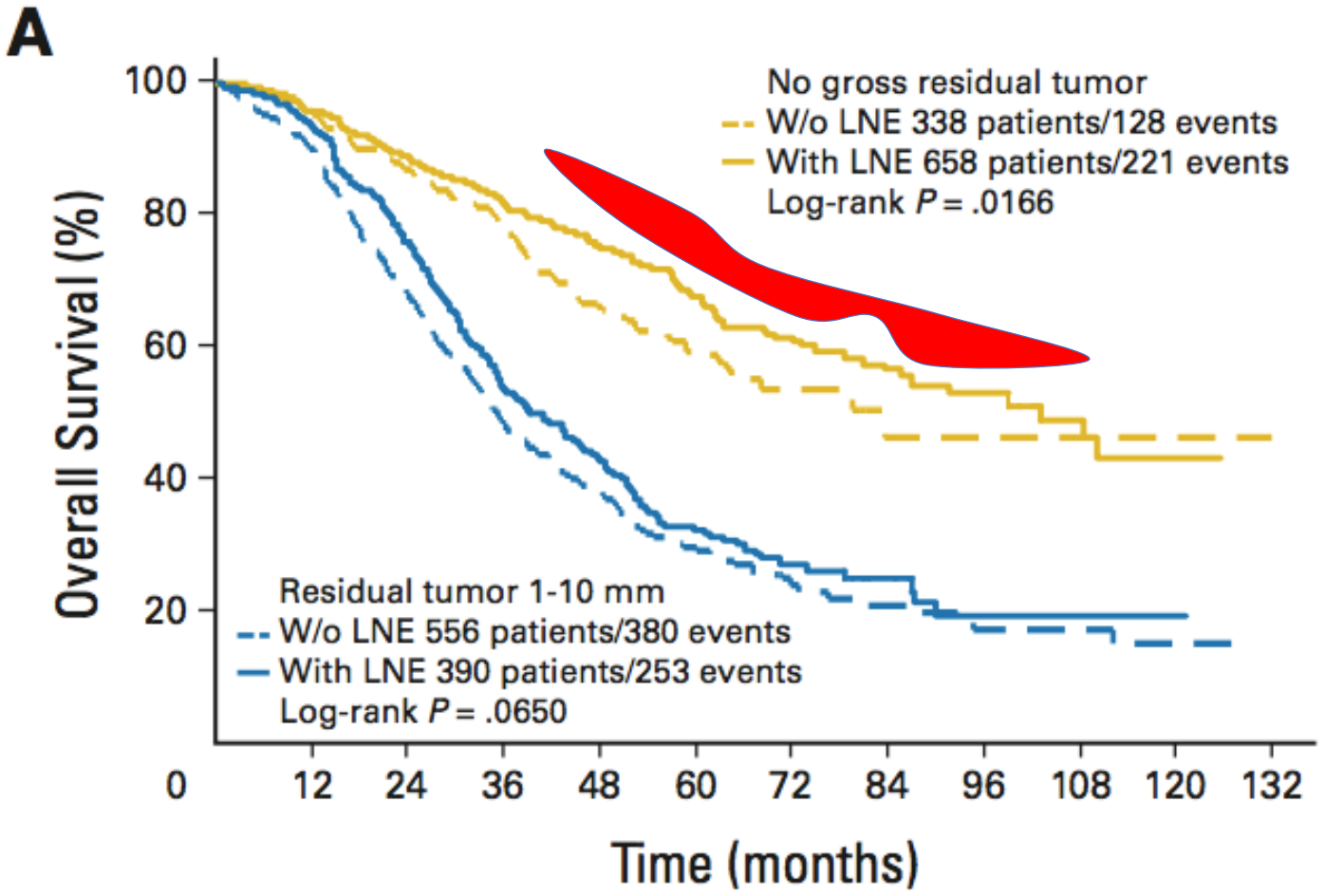
WHAT IS HAPPENING ON THE WAKE OF LION'S ROAR



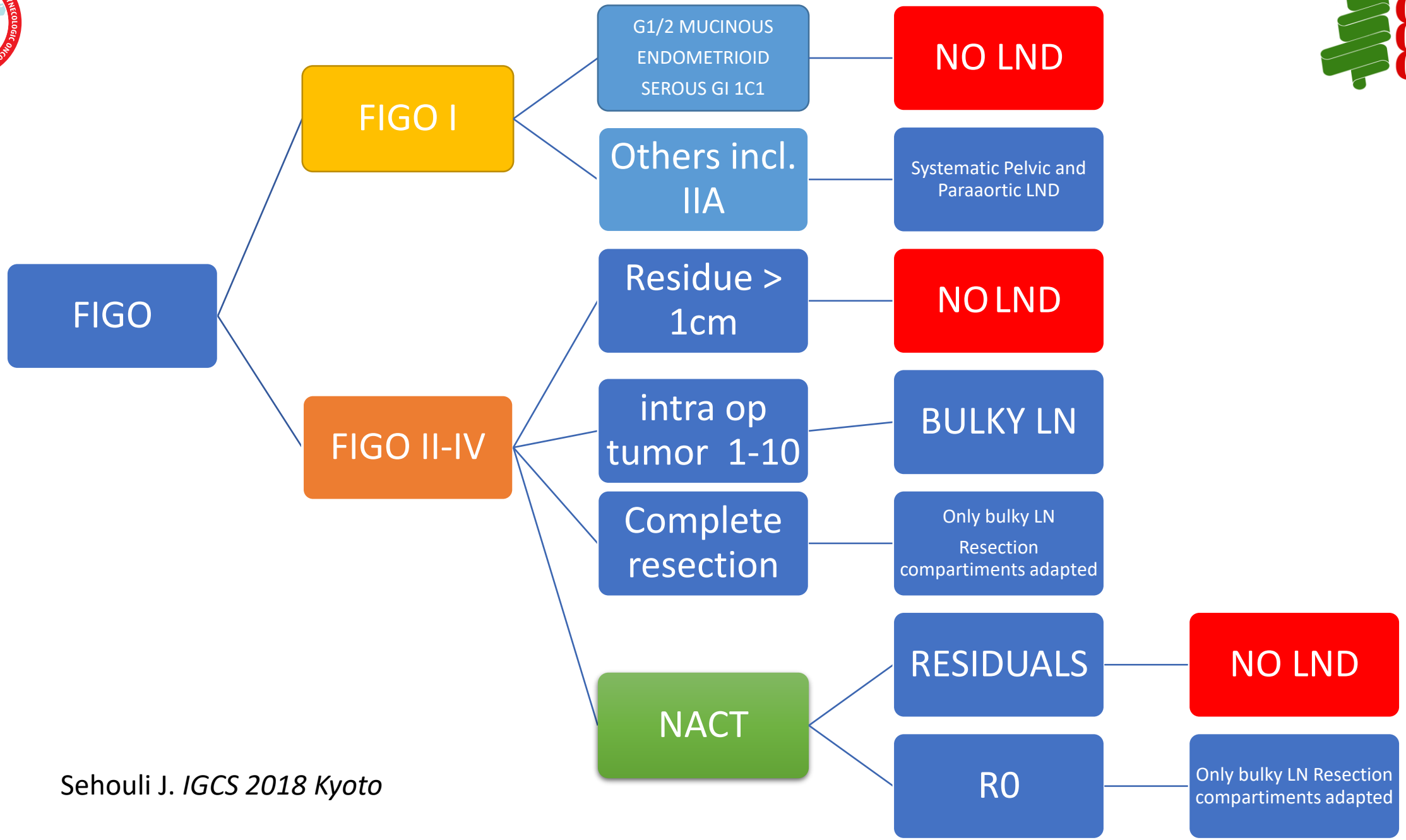
Sehouli J. *IGCS 2018 Kyoto*

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

Journal of Clinical Oncology (2010) 28, *du Bois et al.*



Lymphadenectomy was associated with **superior survival** in patients who underwent **complete intraperitoneal debulking and without gross residual disease** at the end of the surgery

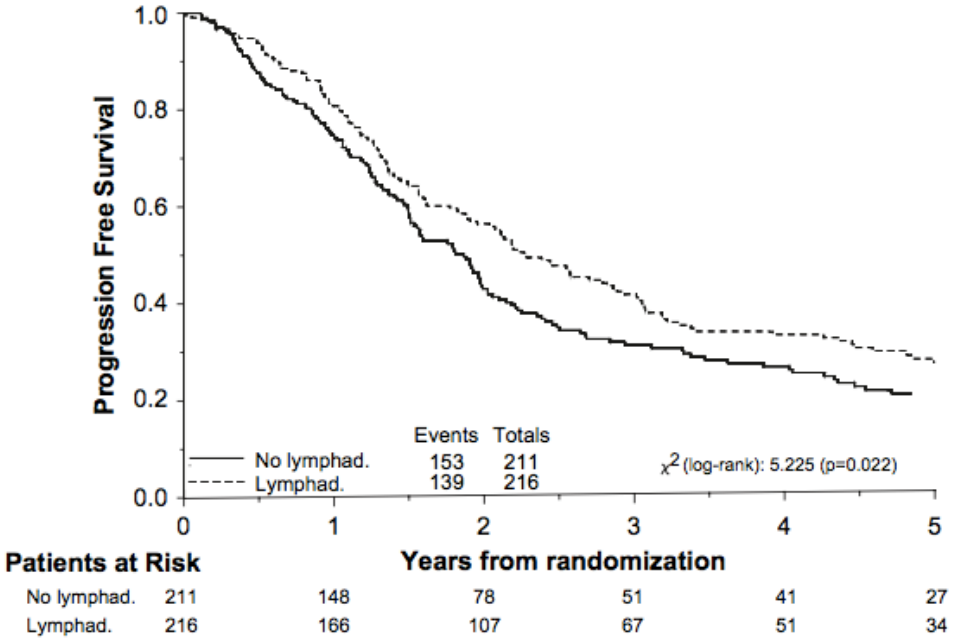


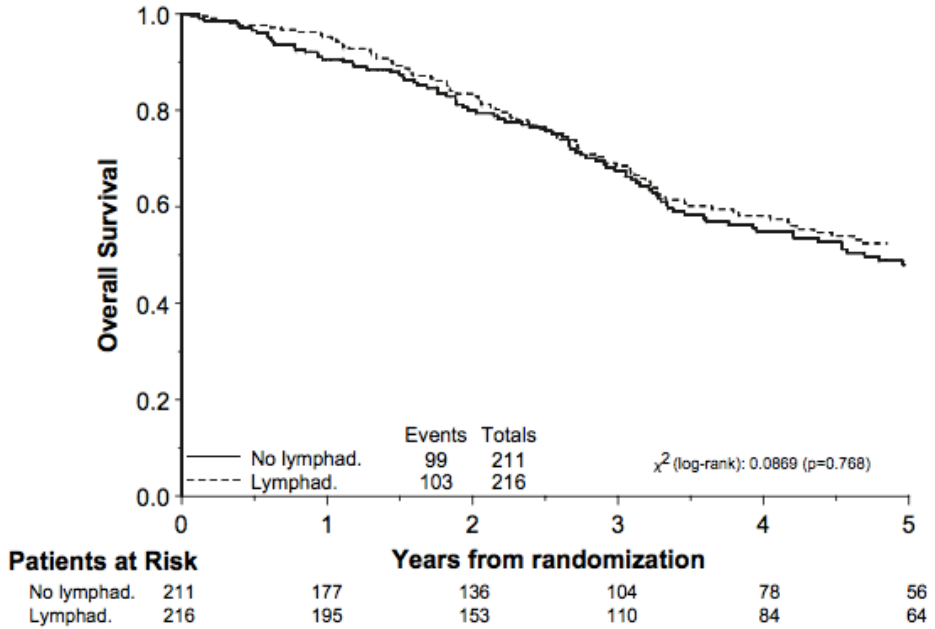
Sehouli J. *IGCS 2018 Kyoto*

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

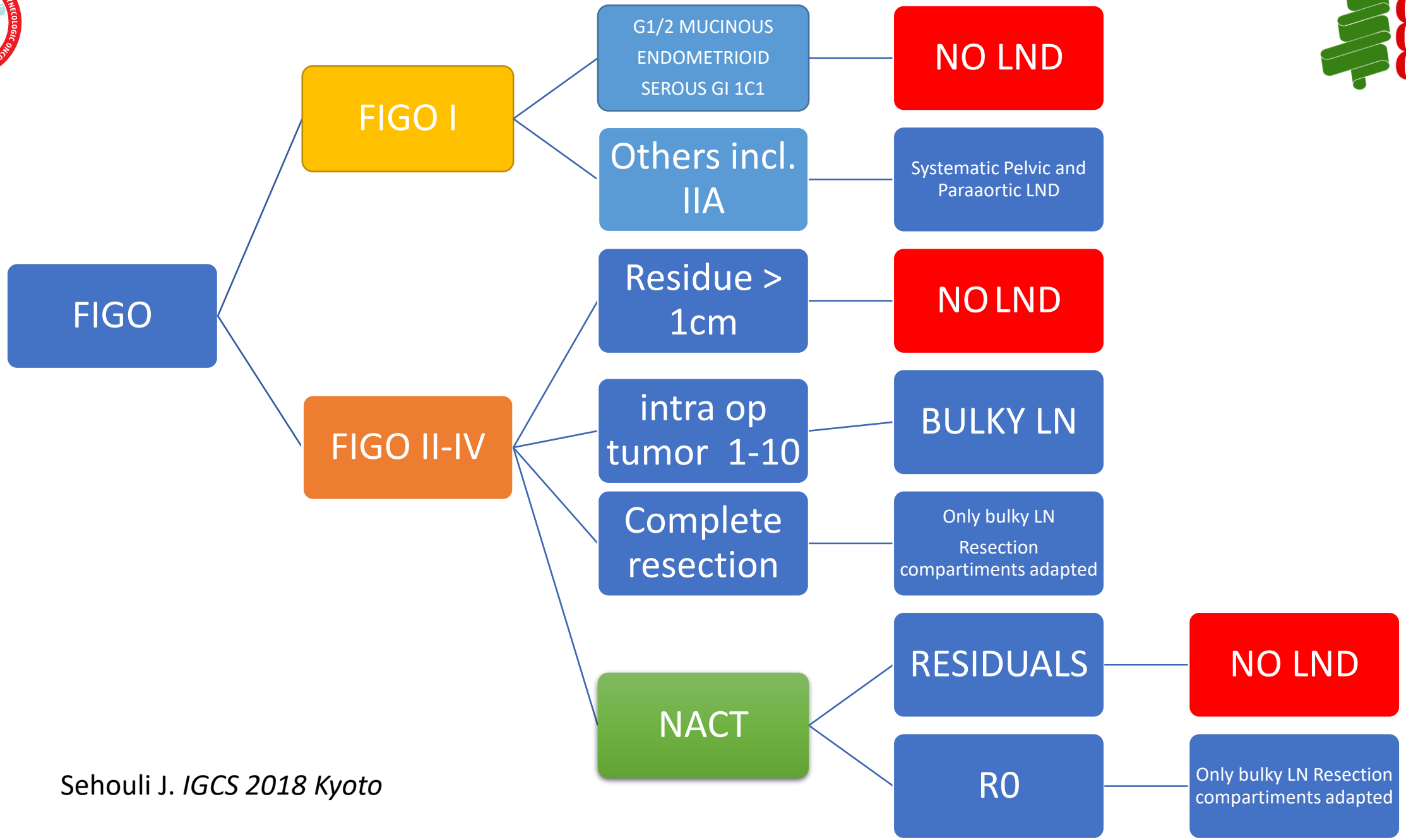
- First randomized controlled trial addressing the value of lymphadenectomy in advanced ovarian cancer
- 427 patients with stage IIIB and IIIC
- with residual tumor of less than 1 cm
- were randomly assigned to undergo systematic pelvic and para-aortic lymphadenectomy (n = 216) or resection of bulky nodes only (n = 211)





- Significant improvement of progression free survival (with 7-month benefit)
- Overall survival was similar in the systematic lymphadenectomy arm and the bulky nodes resection arm

Panici et al. 2005



Sehouli J. *IGCS 2018 Kyoto*

TO REMOVE or NOT TO REMOVE?!!!

- There is no data in the neoadjuvant setting
- And the problem is :
  - We are extrapolating these findings into the neoadjuvant setting
  - ALERT !!!

TO REMOVE or NOT TO REMOVE?!!!

- Removing a normal lymph node will not impair the survival

- But leaving lymph nodes with residual DISEASE will definitely change the prognosis of the disease

TO REMOVE or NOT TO REMOVE?!!!

- In clinically node negative, LND should not be done because it increases morbidity
- How can we be sure that the nodes are clinically negative ?!!
- What was showed in the LION trial is not applicable → it contradicts all what was said in the literature

Idea of Sentinel lymph node in ovarian cancer

Original Research ajog.org

GYNECOLOGY

Sentinel-node biopsy in early-stage ovarian cancer: preliminary results of a prospective multicentre study (SELLY)

Stefano Uccella, MD; Camilla Nero, MD; Enrico Vizza, MD; Virginia Vargiu, MD; Giacomo Corrado, MD; Nicolò Bizzarri, MD; Fabio Ghezzi, MD; Francesco Cosentino, MD; Luigi Carlo Turco, MD; Anna Fagotti, MD; Giovanni Scambia, MD

To dissect or not dissect ?!!

- **If the surgeon is not going to remove all the lymph nodes, it's better to do not dissect**

- **The fact of dissecting all the spaces make a reoperation after a recurrence catastrophic and very dangerous !!!**

- When there is slight indication to perform a lymph node dissection ➔

Remove everything

The question is : **ERA after LION ??**

- Are we going to still have surgeons who will have the expertise to operate on after lymph node recurrence ?!!!!
- This should be highly considered

LND after recurrence

International Journal of Surgery 69 (2019) 61–66

Contents lists available at ScienceDirect

International Journal of Surgery

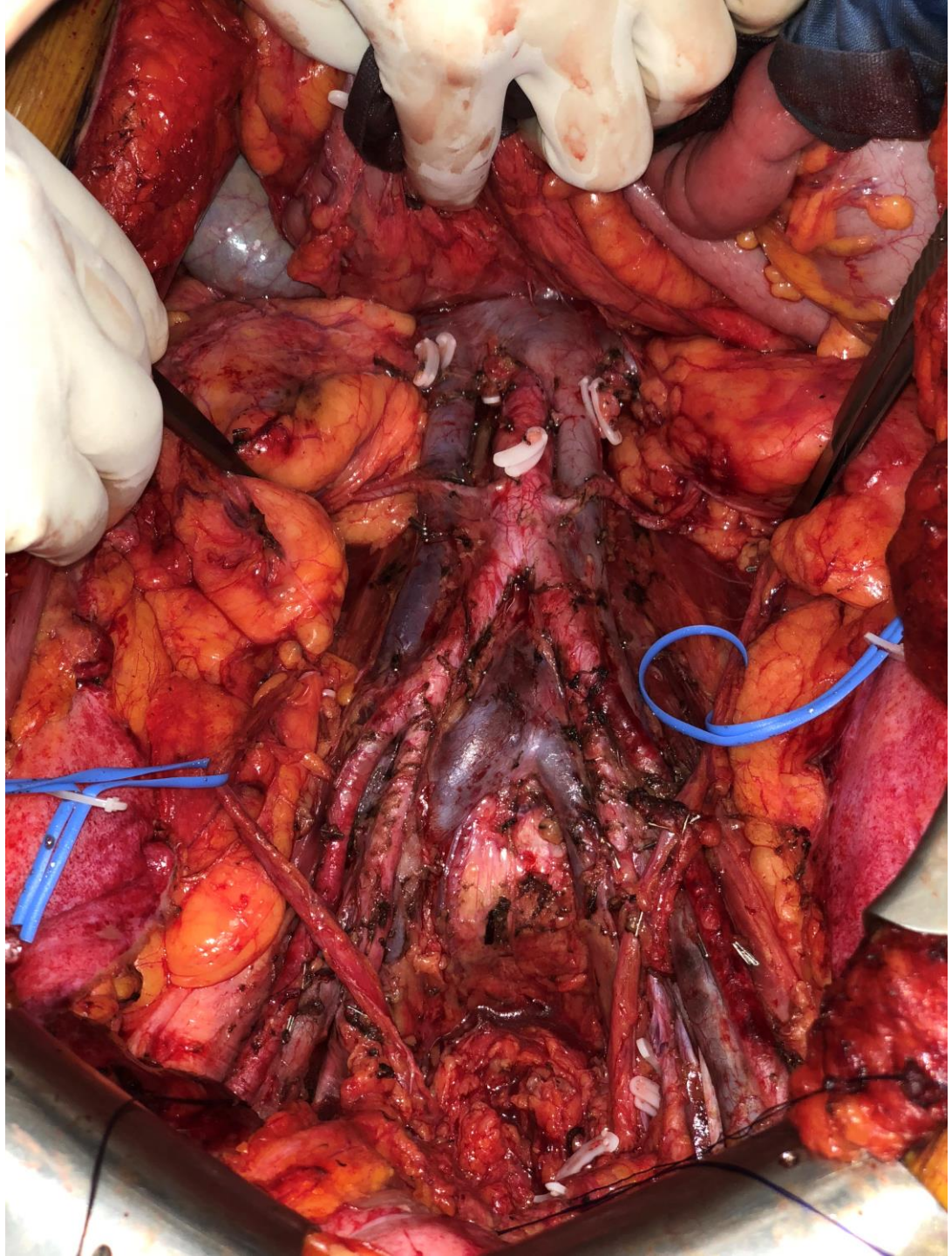
journal homepage: www.elsevier.com/locate/ijsu

Review

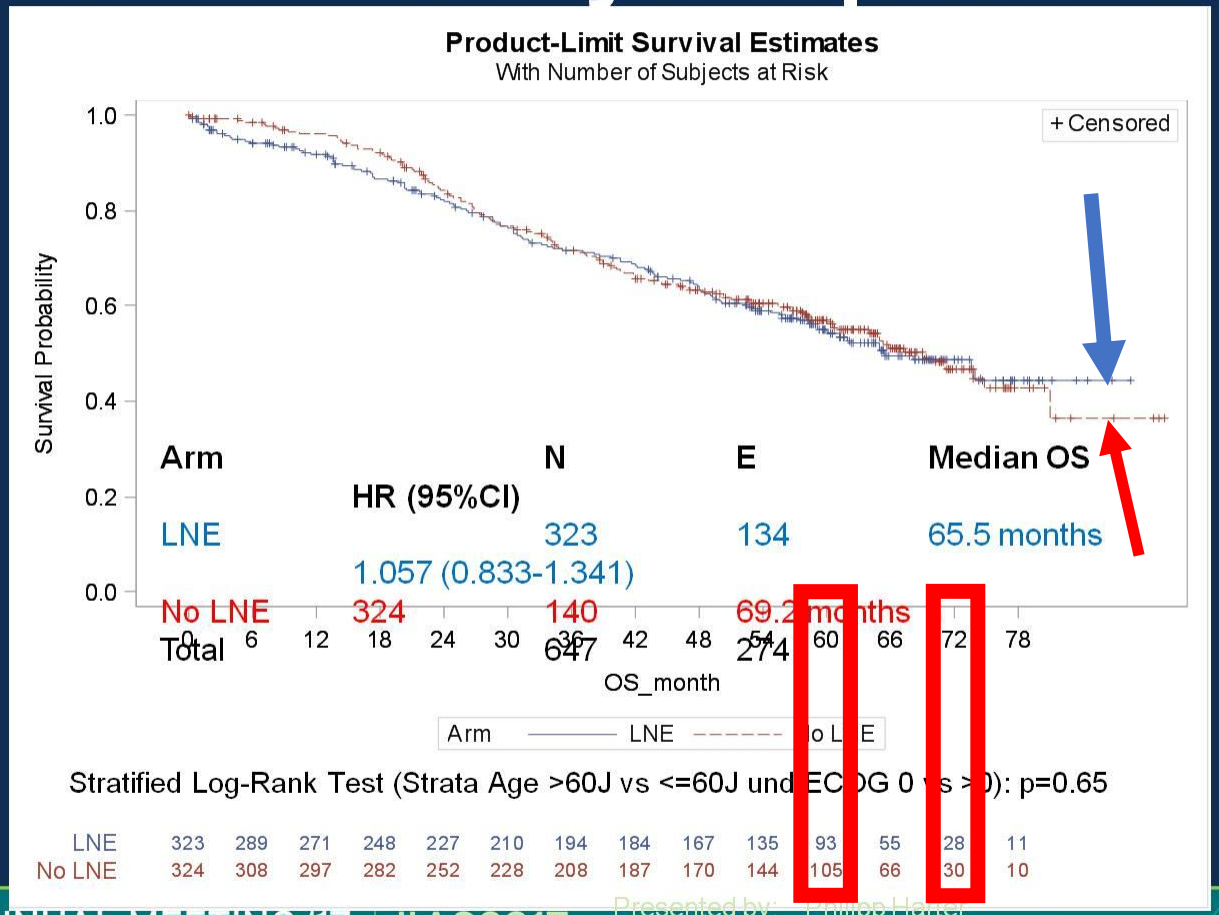
Survival outcomes of ovarian cancer patients treated with secondary cytoreductive surgery for isolated lymph node recurrence: A systematic review of the literature

Vasilios Pergialiotis[a,*], Anastasia Androutsou[a], Eleni Papoutsi[a], Ioannis Bellos[a], Nikolaos Thomakos[b], Dimitrios Haidopoulos[b], Alexandros Rodolakis[b]

Prolonged survival (> 110 months) may be seen as a realistic target for a significant number of these patients when systematic lymphadenectomy is performed.



LION: Primary endpoint OS



With a longer follow up, survival may be better for the LNE arm v/s no LNE

Current Problems in Cancer 43 (2019) 151–159

Contents lists available at ScienceDirect

Current Problems in Cancer

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

Association of lymphadenectomy and survival in epithelial ovarian cancer

Ozlem Ercelep [a,*], Melike Ozcelik [a], Mahmut Gumus [b]

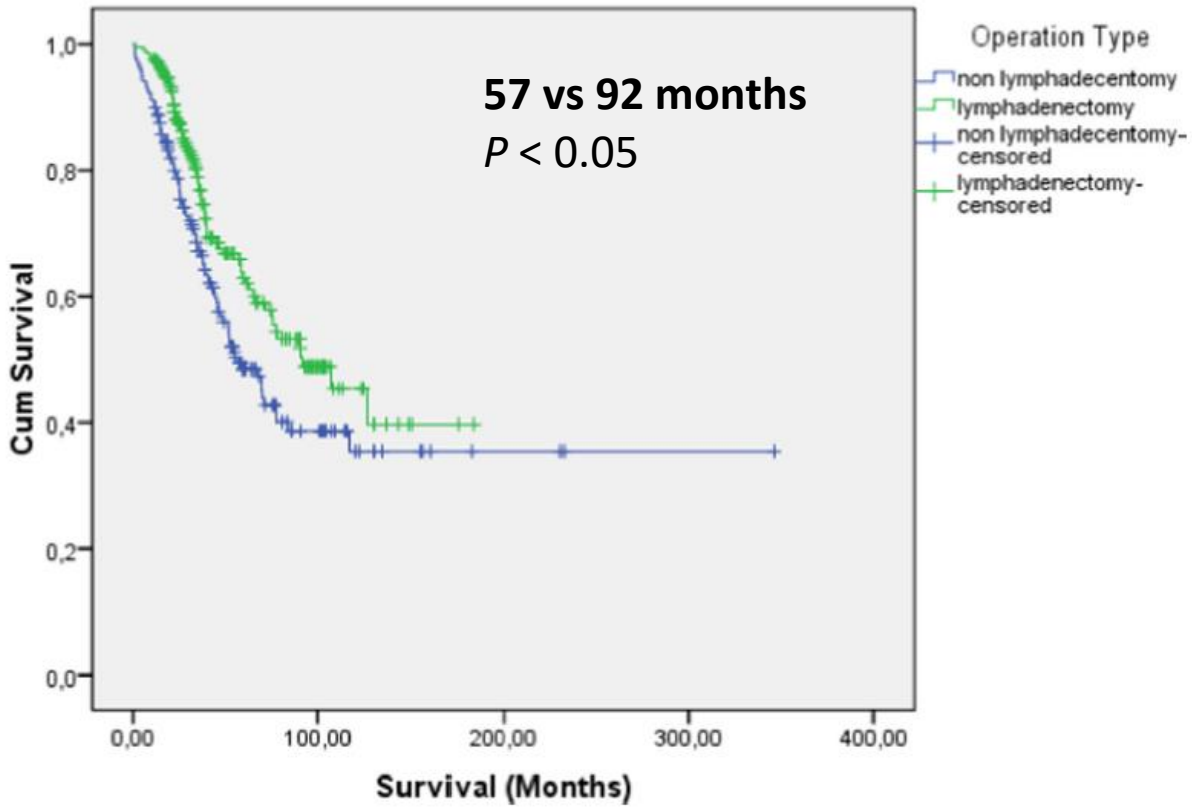


Fig. 1. Overall survival (OS) in patients with or without lymphadenectomy.

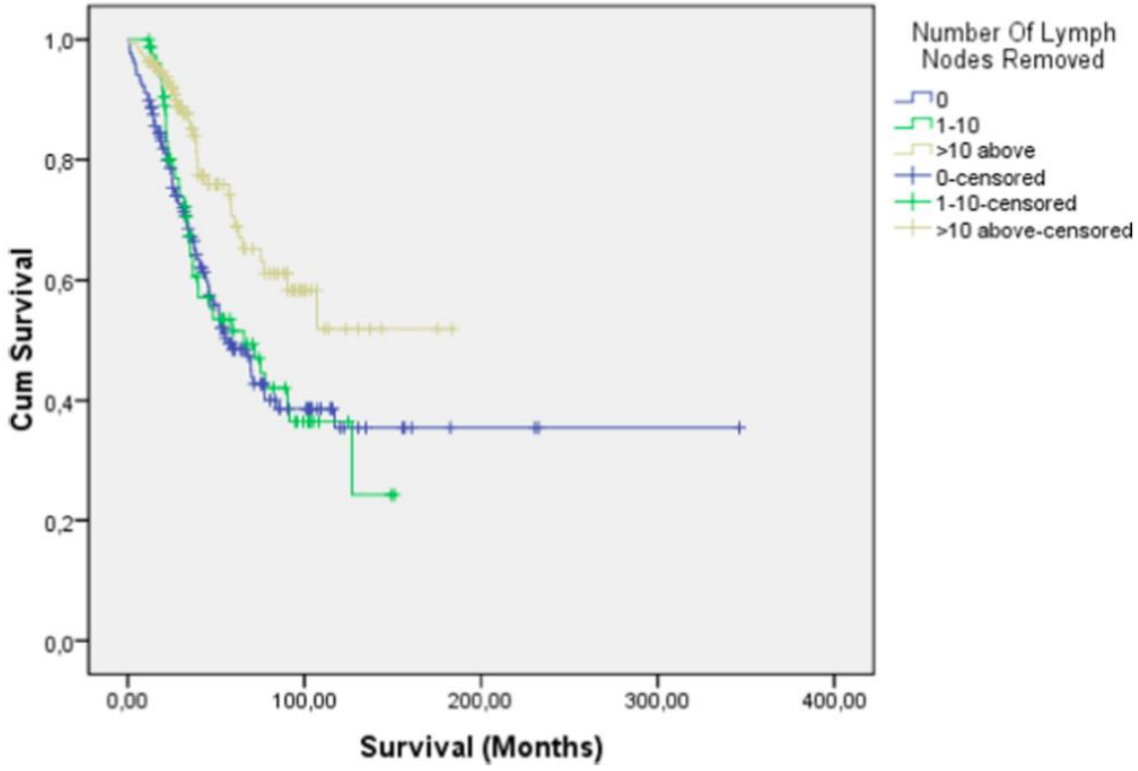


Fig. 2. Overall survival (OS) in patients w.r.t. number of lymph nodes removed.

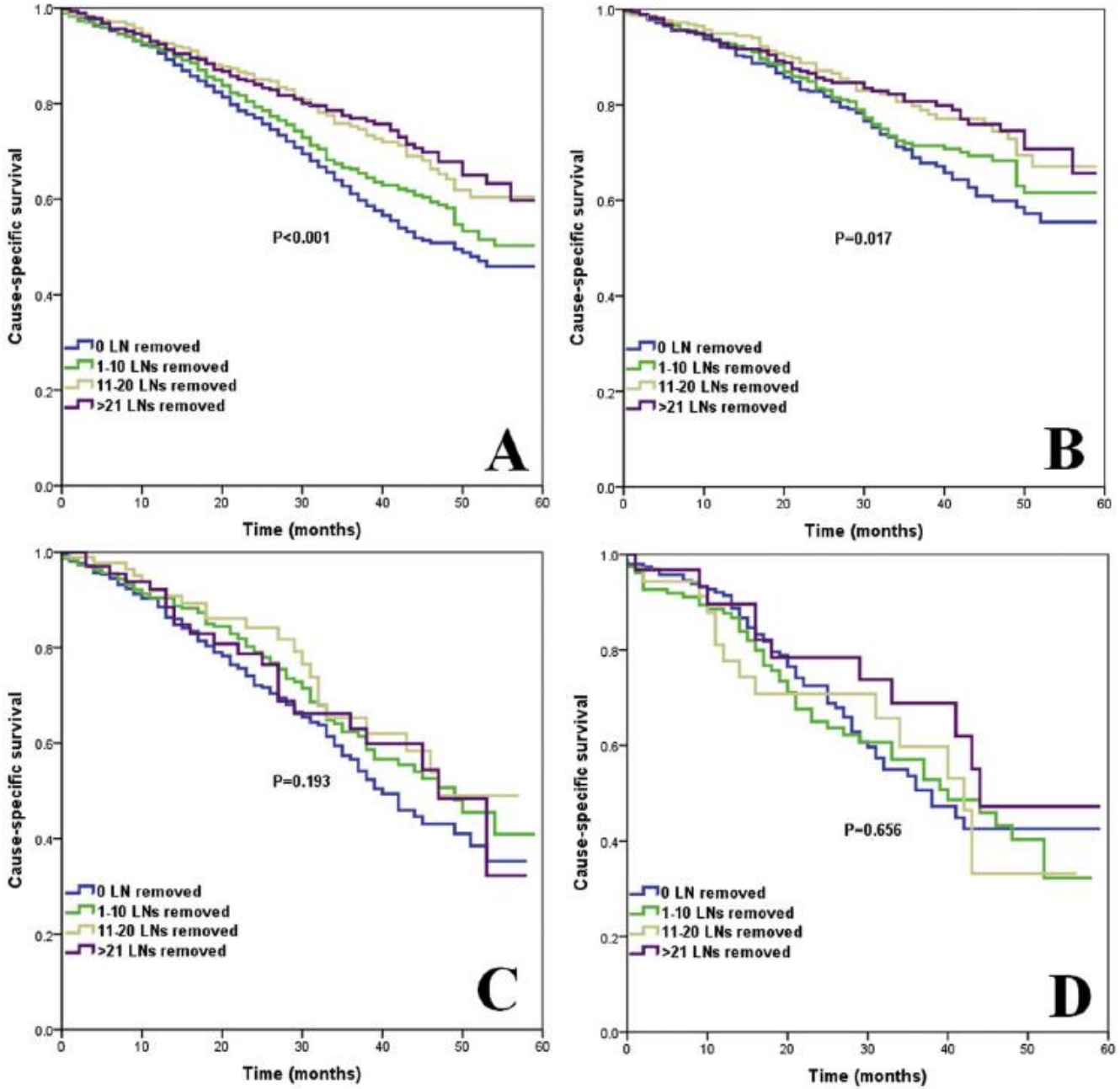


Fig. 1. Impact of lymphadenectomy on cause-specific survival in the entire cohort (A), in those with no residual tumor (B), in those with residual tumor ≤1 cm (C), and in those with residual tumor > 1 cm (D).

Last word

- Omitting a systematic lymphadenectomy from a cytoreductive surgery where a huge effort was made to leave no residual disease needs to be revised and readapted
- Prospective studies **with long-term follow-up** need to be conducted
- It may prove the survival benefits of a systematic lymphadenectomy in the standard of care of ovarian cancers
- The surrogate would be sentinel lymph node in ovarian cancer