4Th MEMAGO CONGRESS
Middle East & Mediterranean Association of Gynecological Oncology
October 11-12, 2019 | Rosewood Hotel, Abu Dhabi

Any role for the lymph node ratio (LNR) in endometrioid endometrial cancer (EC)?

Mehmet Mutlu MEYDANLI, M.D.
Department of Gynecologic Oncology
Ankara City Hospital
University of Health Sciences, Ankara, TURKEY

European Journal of Obstetrics & Gynecology and Reproductive Biology 240 (2019) 310–315

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

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

Full length article

A novel multivariable prediction model for lymphatic dissemination in endometrioid endometrial cancer: The lymph node Metastasis Risk Index

Mehmet M. Meydanli, Koray Aslan, Murat Oz*, Kamil H. Muftuoglu, Ibrahim Yalcin, Yaprak Engin-Ustun

Zekai Tahir Burak Women's Health Hospital, Talatpasa Blv, Ankara, Turkey

Meydanli MM. Eur J Obstet Gynecol Reprod Biol **2019 Sep;**240: 310-315

State clearly why we shouldn't perform a sentinel lymph node mapping as a standard procedure?

- Several retrospective studies revealed **“increased lymph node ratio” (LNR)** as an independent prognosticator associated with decreased survival outcomes in women with stage IIIC EC.
- The therapeutic effect of lymphadenectomy (if any) seems to be limited solely to the group of patients with positive nodal status.
- Based on those data associated with **LNR**, patients with macrometastatic SLN deserve at least a postoperative imaging in order to exclude gross bulky residual nodal metastases.

Original Article

INTERNATIONAL JOURNAL OF GYNECOLOGICAL CANCER

SATEN III—Splitting Adjuvant Treatment of stage III ENdometrial cancers: an international, multicenter study

Ilker Kahramanoglu,[1] Mehmet Mutlu Meydanli,[2] Siarhei Taranenka,[3] Ali Ayhan,[4] Coskun Salman,[5] Muzaffer Sanci,[6] Fuat Demirkiran,[1] Firat Ortac,[7] Dimitrios Haidopoulos,[8] Vladyslav Sukhin,[9] Dilyara Kaidarova,[10] Artem Stepanyan,[11] Farah Farazaneh,[12] Shamistan Aliyev,[13] Elena Ulrikh,[14] Dina Kurdiani,[15] İbrahim Yalcin,[2] Siarhei Mavrichev,[3] Huseyin Akilli,[4] Mustafa Erkan Sarı,[2] Andrei Pletnev,[3] Koray Aslan,[2] Tugan Bese,[1] Murat Kairbayev,[16] Dimitrios Vlachos,[8] Murat Gultekin[5]

Kahramanoglu I. Int J Gynecol Cancer **2019 Oct, 29(8)** : 1271-1279

Why were the survival outcomes of pts undergoing adjuvant radiotherapy better than pts undergoing adjuvant chemoradiation in stage IIIC endometrioid endometrial cancer?

- **LNR** was significantly increased in the chemoradiation group when compared to the radiotherapy and chemotherapy groups.
- **LNR** is a parameter based on two variables; the number of metastatic lymph nodes (LNs), and the number of LNs removed.
- If the number of involved LNs is high when the number of removed LNs remains relatively limited, then the **LNR** would appear artificially increased.
- Therefore, it has been suggested that **LNR** is most meaningful when comprehensive lymphadenectomy is utilized routinely in surgical practice
- **LNR** in endometrial cancer has been proposed as an important prognostic factor. Increased LNR has been shown to be independently associated with poorer survival outcomes

LNR works in the publishing process

Lymph Node Ratio (LNR) - Definition

$$LNR = \frac{\#\text{ of metastatic LNs}}{\text{total }\#\text{ of LNs removed}}$$

- LNR has been recently used as a prognostic tool in node-positive endometrial cancer (EC)

- Previous retrospective studies have shown LNR to be associated with worse survival outcomes in EC.

Chan JK, Br J Cancer 2007;97:605-11.

Polterauer S, Obstet Gynecol 2012;119:1210-8.

Fleming ND, Int J Gynecol Cancer 2015;25:1437-44.

Ayhan A, J Gynecol Oncol 2018; 29(4):e48.

LNR in EC - 1

- LNR is most meaningful when comprehensive lymphadenectomy is utilized routinely in surgical practice.

Polterauer S, Obstet Gynecol 2012;119:1210-8.

- LNR must be tied to adjuvant therapy in this patient population.

Fleming ND, Int J Gynecol Cancer 2015;25:1437-44.

LNR in EC - 2

- Some of the previous studies which have investigated the prognostic significance of LNR in EC were hampered by
  - the limited number of median LNs removed

Chan JK, Br J Cancer 2007;97:605-11.

Polterauer S, Obstet Gynecol 2012;119:1210-8.

Fleming ND, Int J Gynecol Cancer 2015;25:1437-44

  - lack of adjusted adjuvant therapies

Chan JK, Br J Cancer 2007;97:605-11.

Polterauer S, Obstet Gynecol 2012;119:1210-8.

  - inclusion of non-endometrioid and mixed histologies

Polterauer S, Obstet Gynecol 2012;119:1210-8.

Fleming ND, Int J Gynecol Cancer 2015;25:1437-44

British Journal of Cancer (2007) 97, 605 – 611

www.bjcancer.com

The impact of the absolute number and ratio of positive lymph nodes on survival of endometrioid uterine cancer patients

JK Chan*,[1], DS Kapp[2], MK Cheung[3], K Osann[4], JY Shin[3], D Cohn[5] and PL Seid[2]

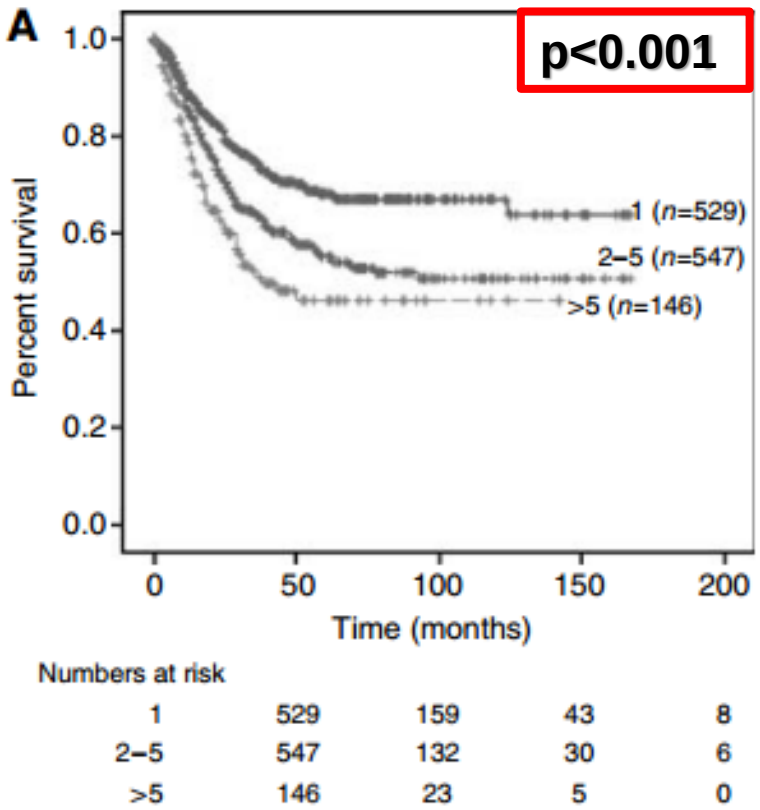
- 1222 node positive endometrioid ECs (stage IIIC and IV) from National Cancer Institute Registry
- **The 5-y OS rate for LNR≤0.1: 77.3%**
- **The 5-y OS rate for LNR 0.1-0.5: 60.7%**
- **The 5-y OS rate for LNR>0.5: 40.9%**

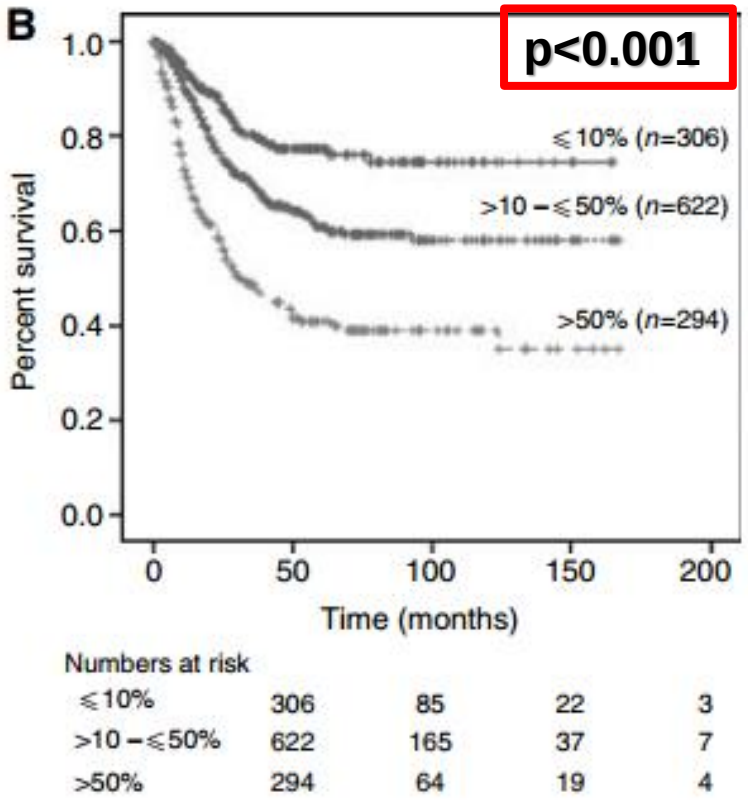
- However, the authors did not provide details on adjuvant therapy modalities and recurrences.
- They only reported that 63% of their patients received adjuvant radiotherapy.

DSS

Absolute number and ratio of positive nodes in corpus cancer

JK Chan *et al*



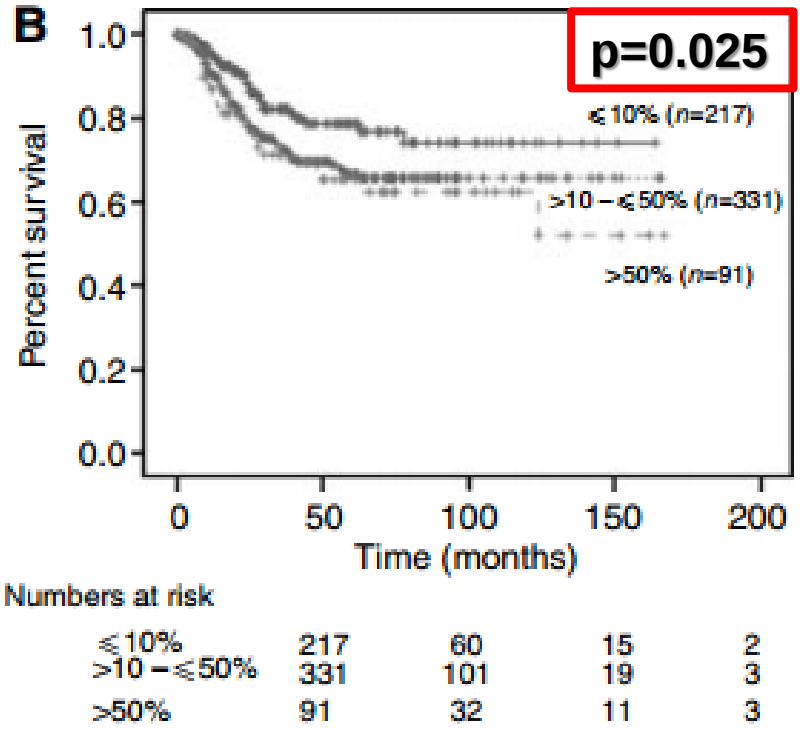


DSS

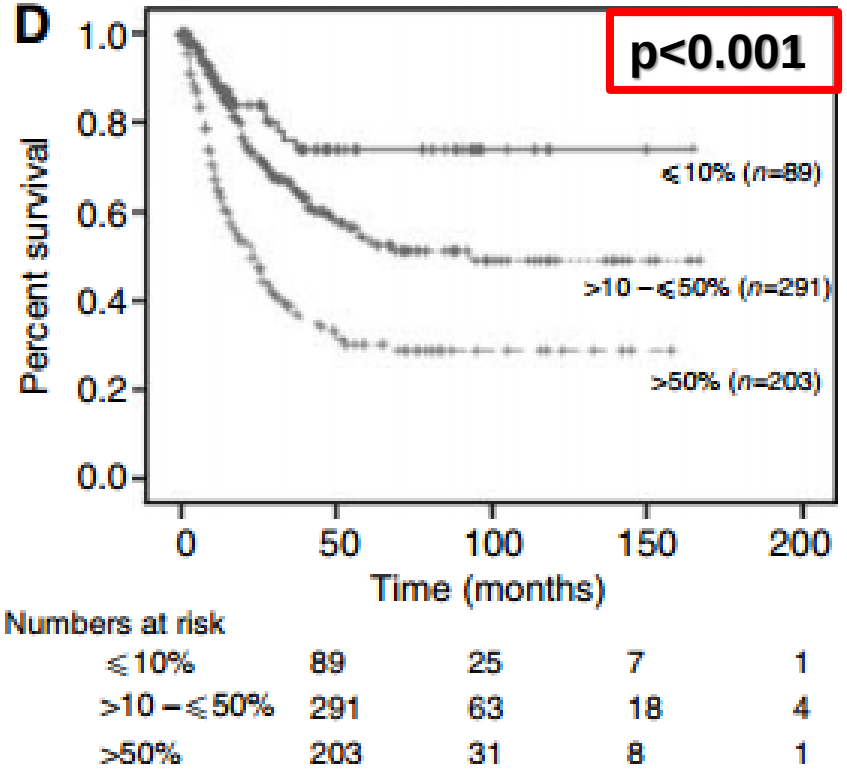
Absolute number and ratio of positive nodes in corpus cancer

JK Chan *et al*

Stage IIIC



Stage IV



Prognostic Value of Lymph Node Ratio and Clinicopathologic Parameters in Patients Diagnosed With Stage IIIC Endometrial Cancer

Stephan Polterauer, MD, Susan Khalil, MD, Oliver Zivanovic, MD, Nadeem R. Abu-Rustum, MD, Gerda Hofstetter, MD, Nicole Concin, MD, Christoph Grimm, MD, Alexander Reinthaller, MD, Richard R. Barakat, MD, and Mario M. Leitao Jr, MD

- 216 pts with FIGO stage IIIC EC
  - **The 5-y OS rate for LNR≤0.1 : 79%**
  - **The 5-y OS rate for LNR 0.1-0.5 : 60.6%**
  - **The 5-y OS rate for LNR>0.5 : 35.8%**

- In multivariate analysis, **only LNR** was associated with both PFS and OS.

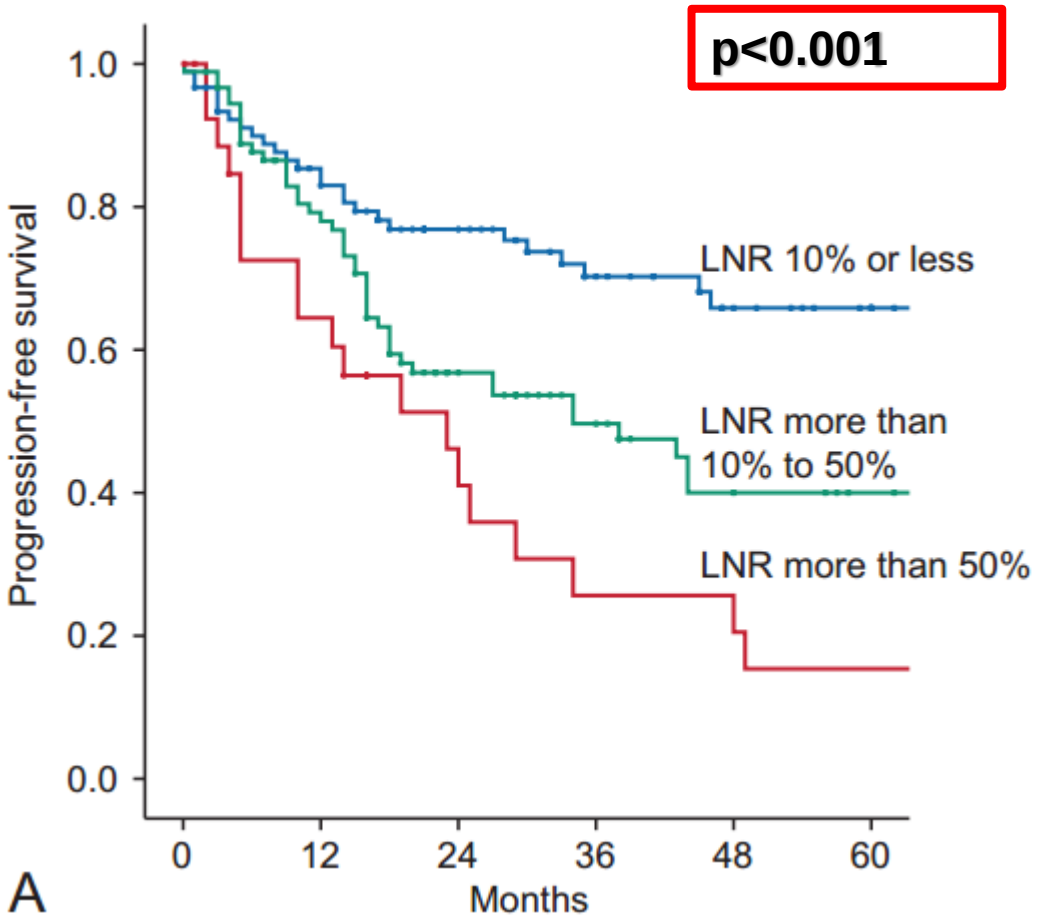
Polterauer S, Obstet Gynecol 2012;119:1210-8.

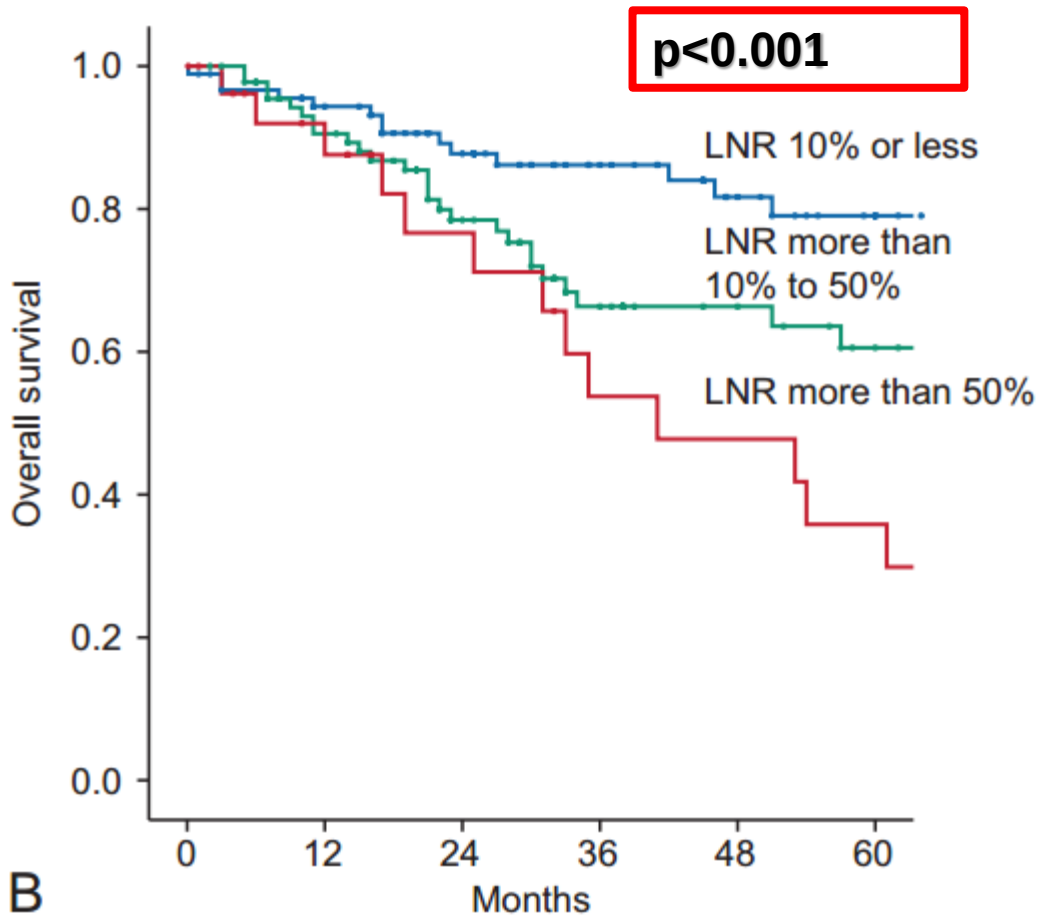
Prognostic Value of Lymph Node Ratio and Clinicopathologic Parameters in Patients Diagnosed With Stage IIIC Endometrial Cancer

Stephan Polterauer, MD, Susan Khalil, MD, Oliver Zivanovic, MD, Nadeem R. Abu-Rustum, MD, Gerda Hofstetter, MD, Nicole Concin, MD, Christoph Grimm, MD, Alexander Reinthaller, MD, Richard R. Barakat, MD, and Mario M. Leitao Jr, MD

- In the subgroup of patients with stage IIIC EC who had **at least 10 LNs** examined by pathology (n=123), LNR was shown to be a significant prognosticator for PFS and OS, whereas the number of removed LNs was not.
- The authors included all histologies, of which 30% were non-endometrioid.
- Only 13% (n=28) of the patients had a LNR >0.5.

Polterauer S, Obstet Gynecol 2012;119:1210-8.


p<0.001
Progression-free survival
1.0
0.8
0.6
0.4
0.2
0.0
LNR 10% or less
LNR more than
10% to 50%
LNR more than 50%
0
12
24
36
48
60
Months
A


p<0.001
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
LNR 10% or less
LNR more than
10% to 50%
LNR more than 50%
0
12
24
36
48
60
Months
B

Impact of Lymph Node Ratio and Adjuvant Therapy in Node-Positive Endometrioid Endometrial Cancer

Nicole D. Fleming, MD, Pamela T. Soliman, MD,* Shannon N. Westin, MD,* Ricardo dos Reis, MD,† Mark Munsell, PhD,‡ Ann H. Klopp, MD, PhD,§ Michael Frumovitz, MD,* Alpa M. Nick, MD,* Kathleen Schmeler, MD,* and Pedro T. Ramirez, MD**

- A total of 124 EC pts;
  - IIIC1 (n=64)
  - IIIC2 (n=60)
- For women with stage IIIC endometrioid EC who underwent surgical staging with ≥10 nodes removed (n=81)
  - **The median PFS for LNR >0.5: 25.2 mo**
  - **The median PFS for LNR ≤0.5: 135.6 mo**
- The authors have suggested that LNR may define a subgroup of stage IIIC ECs at increased risk of recurrence.
- Adjuvant radiotherapy was associated with decreased recurrence risk.

Fleming ND, Int J Gynecol Cancer 2015;25:1437-44.

J Gynecol Oncol. 2018 Jul;29(4):e48
https://doi.org/10.3802/jgo.2018.29.e48
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

Impact of lymph node ratio on survival in stage IIIC endometrioid endometrial cancer: a Turkish Gynecologic Oncology Group study

Ali Ayhan [1], Nazlı Topfedaisi Ozkan [2], Murat Öz [2], Günsu Kimyon Comert [3], Zeliha Firat Cuylan [2], Gonca Çoban [1], Osman Turkmen [3], Baki Erdem [4], Hanifi Şahin [2], Özgür Akbayır [4], Murat Dede [5], Ahmet Taner Turan [3], Husnu Celik [1], Tayfun Güngör [2], Ali Haberal [1], Macit Arvas [6], Mehmet Mutlu Meydanli [2]

Materials and Methods - 1

- Pts with pure endometrioid EC having positive nodal status at the end of final pathology report from six gynecologic oncology centers in Turkey.
- Exclusion criteria
  - women with non-endometrioid type EC,
  - pts with mixed histologies,
  - those with a total number of LNs removed < 10 at the end of final pathology report,
  - women with stage IV disease

Ayhan A, J Gynecol Oncol 2018; 29(4):e48.

Materials and Methods - 2

- Surgical staging consisted of total hysterectomy, bilateral salpingo-oopherectomy, pelvic and para-aortic lymphadenectomy, and peritoneal washings.

- A systematic lymph node dissection (LND) was defined as removal of more than 20 nodes

Thomas MB, Gynecol Oncol 2007;107:186-9.

- An adequate lymphadenectomy was defined as the removal of at least 10 pelvic, and 5 para-aortic LNs

Nomura H, Int J Gynecol Cancer 2006;16:799-804.

Materials and Methods - 3

- LNR was stratified into two groups:
  - **LNR1 (≤0.15)**, and
  - **LNR2 (>0.15)**
- The LNR was arbitrarily set to 0.01 units and the log-rank test was performed with overall survival (OS) to determine the appropriate cut-off value
- **Based on the results of these analyses, we used a cutoff value of 0.15, which yielded the most significant result.**

Ayhan A, J Gynecol Oncol 2018; 29(4):e48.

Results - 1

Charecteristics of 207 women with node-positive endometrioid EC	
FIGO stage **IIIC1** **IIIC2**	 101(48.8%) 106 (51.2%)
The median duration of follow-up	40 months (range 1-228 mo)
The median number of total LNs harvested	45 (range, 10-134)
The median number of pelvic LNs removed	32 (range, 4-76)
The median number of para-aortic LNs removed	14 (range, 1-57)
Systematic lymphadenectomy	196 women (94.7%)
Adequate lymphadenectomy	141 women (68.1%)
The median LNR	0.054 (range, 0.006-1.0)
Women with LNR≤0.15	167 (80.7%)
Women with LNR>0.15	40 (19.3%)

Ayhan A, J Gynecol Oncol 2018; 29(4):e48.

Results - 2

	Survival rate (%)	p
The 5-year PFS rate for LNR ≤0.15 **The 5-year PFS rate for LNR >0.15**	76.1% 58.5%	P=0.04
The 5-year OS rate for LNR ≤0.15 **The 5-year OS rate for LNR >0.15**	87.0% 62.3%	P=0.005

Ayhan A, J Gynecol Oncol 2018; 29(4):e48.

PFS

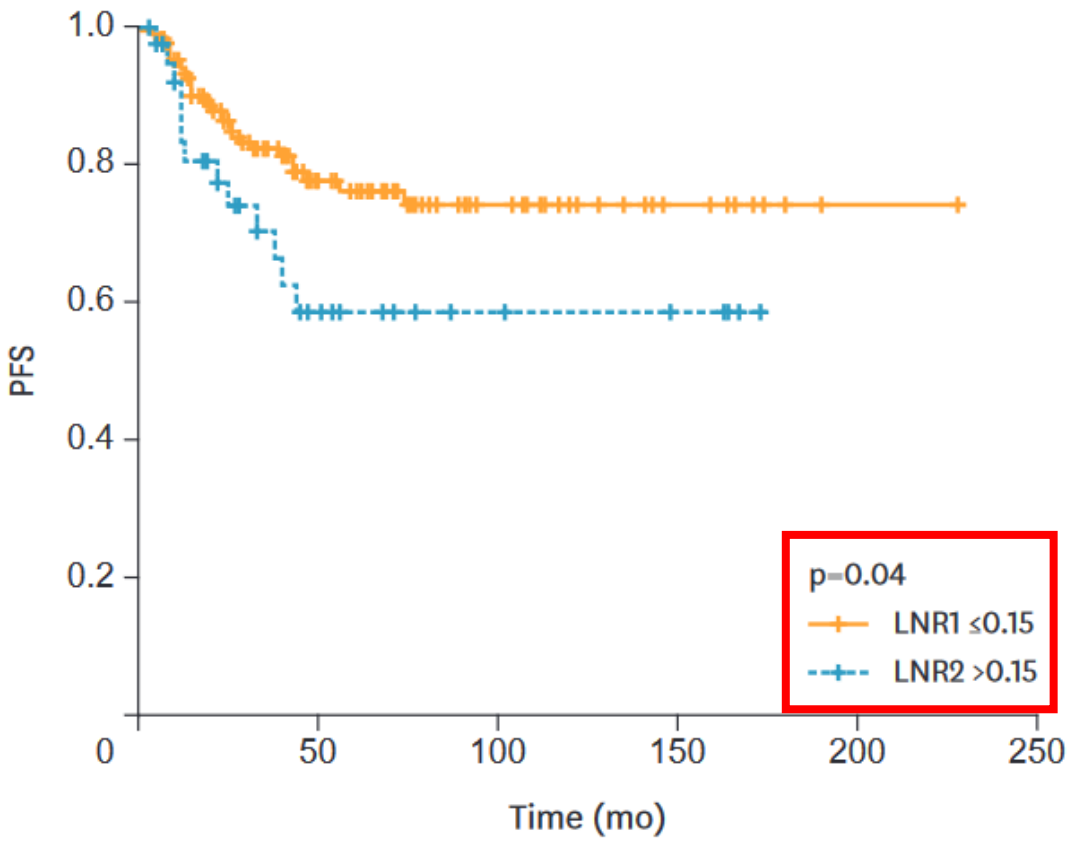


Fig. 1. PFS analyses with regard to LNR (LNR1 ≤0.15 [n=167], LNR2 >0.15 [n=40]). LNR, lymph node ratio; PFS, progression-free survival.

OS

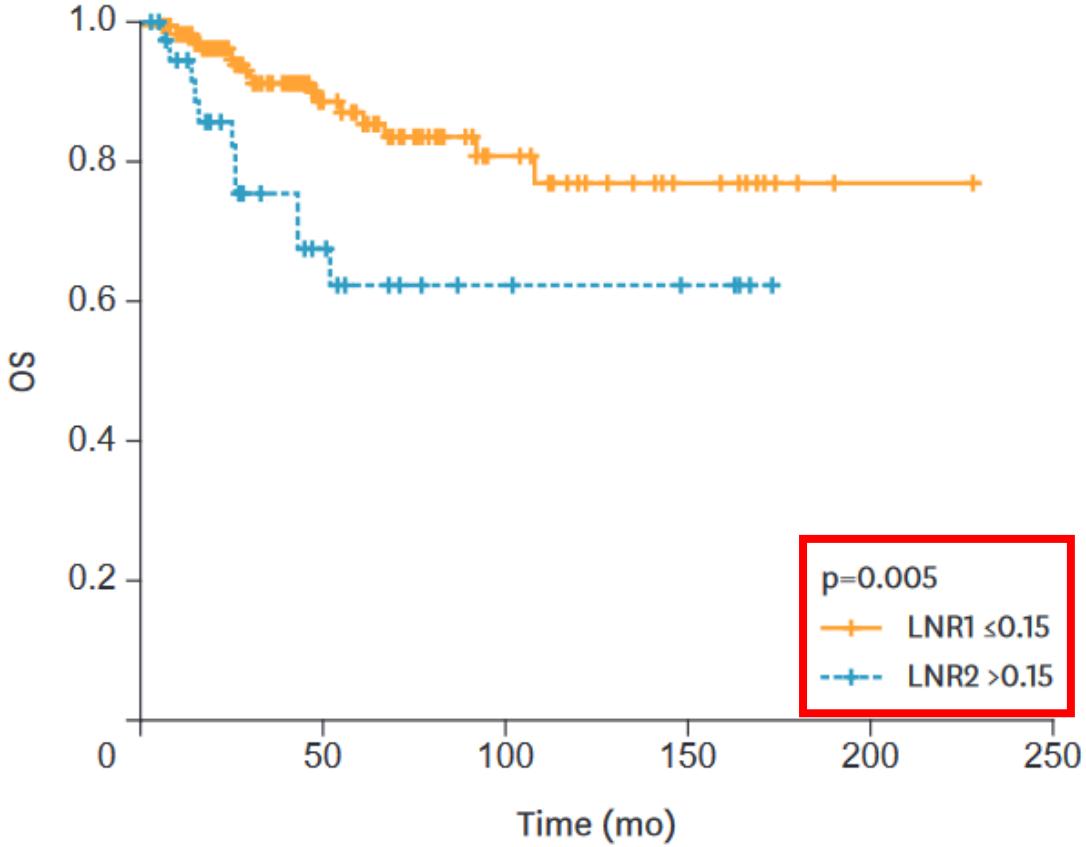


Fig. 2. OS analyses with regard to LNR (LNR1 ≤0.15 [n=167], LNR2 >0.15 [n=40]). LNR, lymph node ratio; OS, overall survival.

Ayhan A, J Gynecol Oncol 2018; 29(4):e48

Table 2. Univariate and multivariate analyses of all patients for PFS

Characteristic	No. of events (PFS*)	Univariate analyses p	HR	Multivariate analyses	
				95% CI	p
Age (yr)		0.002	2.96	1.58–5.50	0.001
<60	16/114 (81.8)				
≥60	18/93 (61.0)				
Grade		0.850			
1	7/40 (74.6)				
2	22/97 (70.5)				
3	14/70 (73.0)				
Stage		0.250			
IIIC1	19/101 (76.5)				
IIIC2	25/106 (69.0)				
Lymphovascular space involvement		0.480			
Negative	7/38 (73.3)				
Positive	36/169 (72.9)				
Cervical stromal involvement		0.020	2.45	1.33–4.52	0.004
Yes	19/65 (55.2)				
No	25/142 (79.6)				
Adnexal metastasis		0.860			
Yes	8/37 (72.0)				
No	36/170 (73.0)				
Depth of MMI (%)		0.070			
50 or less	6/53 (83.5)				
More than 50	38/154 (68.8)				
Peritoneal washings		0.840			
Negative	38/175 (72.3)				
Positive	6/32 (75.3)				
Adjuvant therapy		0.930			
Chemotherapy alone	15/58 (66.9)				
Radiotherapy alone	13/53 (69.2)				
CRT	16/96 (74.6)				
LNR		0.020	2.05	1.07–3.93	0.030
≤0.15	31/167 (76.1)				
>0.15	13/40 (58.5)				

Table 3. Univariate and multivariate analyses of all patients for OS

Characteristic	No. of events (OS*)	Univariate analyses p	HR	Multivariate analyses	
				95% CI	p
Age (yr)		0.002	3.87	1.74–8.62	0.001
<60	7/114 (90.3)				
≥60	15/93 (70.9)				
Grade		0.055			
1	3/40 (87.7)				
2	10/97 (83.9)				
3	13/70 (75.1)				
Stage		0.580			
IIIC1	11/101 (84.5)				
IIIC2	12/106 (75.6)				
Lymphovascular space involvement		0.160			
Negative	1/38 (87.0)				
Positive	25/169 (79.1)				
Cervical stromal involvement		0.006	3.57	1.7–7.46	0.001
Yes	14/65 (66.1)				
No	12/142 (88.7)				
Adnexal metastasis		0.16			
Yes	5/37 (81.6)				
No	21/170 (82)				
Depth of MMI (%)		0.070			
50 or less	2/53 (95.8)				
More than 50	24/154 (76.8)				
Peritoneal washings		0.630			
Negative	22/175 (82.2)				
Positive	4/32 (79.6)				
Adjuvant therapy		0.620			
Chemotherapy alone	7/58 (78.4)				
Radiotherapy alone	6/53 (85.1)				
CRT	13/96 (80.0)				
LNR		0.002	3.35	1.57–7.19	0.002
≤0.15	15/167 (87.0)				
>0.15	11/40 (62.3)				

Conclusion of the Study

- Women with LNR > 0.15 were 2.05 times more likely to have recurrent disease and 3.3 times more likely to die of their tumors when compared to women with a LNR ≤ 0.15.

Ayhan A, J Gynecol Oncol 2018; 29(4):e48

LNR as a prognostic factor in EC - 1

- LNR has been suggested as a newly emerging prognostic factor in EC during the last decade.
- Ratio-based nodal disease seems to be a relatively more objective measure of nodal tumor burden compared to number-based nodal category.

LNR as a prognostic factor in EC - 2

- LNR may obviate possible confounding effect related to the number of regional LNs that varies in each individual.

- However, nodal count stands as the most important parameter that needs to be satisfied in order to yield LNR as a reliable product .

LNR as a prognostic factor in EC - 3

- The total number of LNs removed is dependent on
  - the thoroughness of LN dissection
  - the comprehensiveness of the pathological examination
  - the nodal yield of the specific patient.

- LNR has been recognized as a parameter which has the advantage of reflecting the number of metastatic LNs as well as the extent of LN dissection

“SLN only concept” in EC - 1

- A large part of the gynecological oncology community is currently moving towards a “sentinel lymph node (SLN) biopsy only” concept.

- May SLN mapping be safely substituted for complete pelvic and para-aortic lymphadenectomy in patients that would otherwise be considered appropriate for a more comprehensive lymphatic assessment ?

Tanner EJ, Gynecol Oncol 2015; 138: 41-5

“SLN only concept” in EC - 2

- The likelihood of finding other positive LNs in the setting of positive SLN is **34.8%**
- This risk increases up to **60.8%** when the involved SLN is macrometastatic
- It is unknown that whether there is a therapeutic value of further LN dissection if the SLN is macrometastatic, or whether those patients should simply be treated with chemotherapy

Touhami O, Gynecol Oncol 2015; 138: 41-5

“SLN only concept” in EC - 3

- Retrospective studies revealed “**increased**” LNR as an independent prognosticator associated with decreased survival outcomes in women with stage IIIC EC.

Chan JK, Br J Cancer 2007; 97: 605-11.

Ayhan A, J Gynecol Oncol 2018; 29 (4): e48

- Therefore, the therapeutic effect of lymphadenectomy **(if any)** seems to be limited solely to the group of patients with positive nodal status.
- Based on those data associated with LNR, patients with macrometastatic SLN deserve at least a postoperative imaging in order to exclude gross bulky residual nodal metastases.

“SLN only concept” in EC - 4

- It seems more logical to execute systematic lymphadenectomy for women with macrometastatic SLN depending on the data coming from retrospective studies associated with the prognostic value of LNR in EC.
- On the contrary, “SLN only concept” recommends adjuvant chemotherapy for all SLN positive patients as chemotherapy would be expected to sterilize **all probable residual disease** in the LNs left in situ.
- However, the therapeutic effect of adjuvant chemotherapy on gross bulky residual nodal disease seems to be limited.

Conclusion

- The results of retrospective studies suggest LNR as a meaningful prognostic factor in stage IIIC endometrioid EC.

The 4th
MEMAGO CONGRESS
Middle East & Mediterranean Association
of Gynecological Oncology

Thank you for your attention