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Role of the Cardiophrenic Lymph Node Status After Neoadjuvant Chemotherapy in Primary Advanced Ovarian Cancer

VERONICA LUENGAS-WUERZINGER[1], FRIEDERIKE RAWERT[1], SABRINA CLAßEN-VON SPEE[1], SAHER BARANSI[1], ESTHER SCHULER[1], KATHARINA CARRIZO[1], PETER MALLMANN[2] and BJOERN LAMPE[1]

[1]*Florence-Nightingale Hospital, Department of Gynaecology and Obstetrics, Düsseldorf, Germany;*
[2]*University Hospital of Cologne, Department of Obstetrics and Gynaecology, Cologne, Germany*

Abstract. *Background/Aim: This study investigated the cardiophrenic lymph node (CPLN) status before and after neoadjuvant chemotherapy (NACT), as its presence seems to have a rather prognostic significance in patients with advanced ovarian cancer. Patients and Methods: The baseline computed tomography scans of 66 patients with advanced ovarian cancer primary treated with NACT between March 2015 and June 2020 were reviewed. A CPLN enlargement was defined as ≥5 mm. Results: 44% (n=29) of the patients had enlarged CPLNs; 10.7% (n=3) showed a complete response, 71.4% (n=20) a partial response, and 17.9% (n=5) a stable disease after NACT. There was no significant difference between the response to NACT measured according to the status of CPLN compared to other biomarkers in the CPLN group. Conclusion: Patients with CPLN enlargement have a tendency to an impaired prognosis. The response of CPLN to NACT was comparable to the response of established biomarkers, adding a monitoring function to the CPLN.*

Ovarian cancer is the second most lethal gynaecologic malignancy in Germany as it is mostly diagnosed at an advanced stage (76% stage III/IV), with a 5-year survival rate of 43% (1). Primary cytoreductive surgery followed by chemotherapy has been the standard treatment for patients with advanced ovarian cancer over the recent decades. An alternative approach of interval debulking surgery following neoadjuvant chemotherapy (NACT) has been investigated in different trials (2-5).

There are well-established prognostic factors for ovarian cancer: the initial International Federation of Gynaecology and Obstetrics (FIGO) stage, a macroscopic complete resection after surgery, histological type and grading, general state of health, and patient's age. The once regularly performed systematic lymphadenectomy at the time of surgery has lost significance since the Lymphadenectomy in Ovarian Neoplasms (LION) trial showed no survival benefits in patients with advanced ovarian cancer and radiologic and clinical unsuspicious retroperitoneal nodes (6). In contrast, the role of the frequently observed enlarged cardiophrenic lymph nodes (CPLNs) has only scarcely been investigated.

The definition of pathologically enlarged CPLN has not been standardized. According to the Response Evaluation Criteria in Solid Tumours (RECIST) guidelines (version 1.1) (7), lymph nodes, regardless of their location, are pathologically enlarged when their short-axis is >10 mm (8). However, diverse studies describe a negative impact in the prognosis of patients with ovarian cancer showing CPLNs with a short-axis of >5 mm (9-12). Hence, we defined a CPLN enlargement according to the ESUR guidelines with a cut-off >5 mm short axis dimension (13).

Anatomically, CPLNs are located above the abdominal cavity between the mediastinum, the heart base, diaphragm and the chest wall, defining a FIGO stage of IVB in ovarian cancer if they are enlarged or histologically positive. Still, previous studies have shown that the survival of ovarian cancer patients relies more on a complete intraabdominal tumour resection, even if the CPLN remain surgically unremoved (9, 14). Therefore, according to existing literature, the presence of enlarged CPLN seems to have a rather prognostic than therapeutic significance.

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Correspondence to: Verónica Luengas-Würzinger, Florence-Nightingale Hospital, Department of Gynaecology and Obstetrics, Kreuzbergstr. 79, 40489 Düsseldorf, Germany. Tel: +49 2114092519, Fax: +49 2114092254, e-mail: luengas-wuerzinger@kaiserswerther-diakonie.de.

Key Words: Ovarian neoplasms, neoadjuvant therapy, lymphatic metastasis, computed tomography.

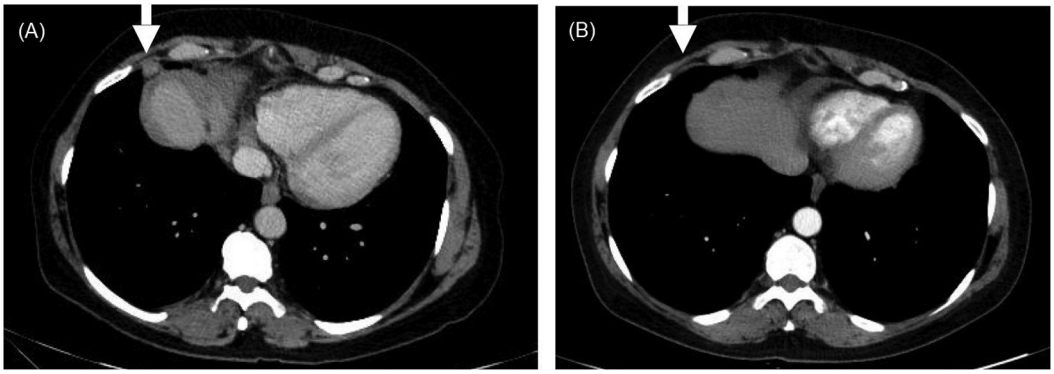

Figure 1. *Example of a cardiophrenic lymph node with a short axis of 7 mm, before (A) and after (B) neoadjuvant chemotherapy.*

The purpose of this retrospective report was to analyse the role of the CPLN status before and after NACT (Figure 1) and to compare its value and response with other clinical and radiological parameters such as the presence of ascites, radiologic enlarged pelvic and para-aortic lymph nodes (PPLNs), CA 125, HE4, the place of recurrence and the Sugarbaker Peritoneal Cancer Index (PCI). The PCI-score was established to objectify the extend of peritoneal carcinomatosis and to predict operability in general surgery (15). It is a useful extension of the existing classification systems for the treatment of OCs and is being used as a parameter for the assessment of resectability in our hospital (16).

Patients and Methods

The study was approved by the appropriate Institutional Review Board (IRB), which waived the requirement for written informed consent.

Between 03/2015 and 06/2020 a total of 66 patients with primary diagnosed FIGO (2014) stage IIIb-IVb ovarian, tubal, and peritoneal carcinoma were treated with NACT as a primary therapy in the Florence Nightingale Hospital in Düsseldorf (*e.g.*, in case of inoperability, patients wish, patients that had already received NACT and were referred to our hospital for surgery *etc.*). All patients underwent staging examinations at the time of diagnosis, including CT scans of the thorax and abdomen, lab works, as well as a diagnostic laparoscopy for histological confirmation of the diagnosis and evaluation of operability. The baseline CT scans of these 66 patients were retrospectively reviewed by our radiologist. To avoid selection bias, the radiologist blindly and randomly analysed the CT scans of all patients without knowing the time of the study or the patient's name. According to the ESUR guidelines, we defined a pathological CPLN enlargement at a cut-off of >5 mm short axis dimension (13). The analysis was performed using patient files, surgical records, radiological records, and intraoperative imaging documentation.

The patients were radiologically classified into a group with (n=29) and without (n=37) enlarged CPLNs at the time of diagnosis. These two groups were compared regarding clinicopathological parameters like the presence of radiologic enlarged PPLNs, presence of ascites, CA 125, HE4 and the Sugarbaker PCI before and after NACT, as well as the time and place of recurrence.

These associations were evaluated using Mann-Whitney *U* or Chi-square tests, defining a statistical significance as $p \leq 0.05$. The differences in survival were determined using the Kaplan–Meier method with log-rank test and Cox's proportional hazard models for uni- and multi-variate analyses.

Among the group with enlarged CPLNs, the response to chemotherapy of the different clinicopathological parameters was evaluated and compared using the linear regression, the binary logistic regression, and the Spearman's rank correlation.

All statistical analyses were performed using the IBM Statistical Product and Service Solutions (SPSS®) Statistics software version 27 for Macintosh (IBM, Armonk, NY, USA).

Results

In a cohort of 66 patients with advanced ovarian cancer undergoing NACT, 44% (n=29) had radiologically enlarged CPLNs and 56% (n=37) had CPLN with a short-axis of <5 mm in the CT scan before starting the therapy. These two groups were analysed at the time of diagnosis for the amount of ascites, CA125 and HE4-levels, preoperative Sugarbaker PCI, and the presence of enlarged PPLNs. Additionally, the residual disease after surgery, the time and site of recurrence, and the progression-free survival (PFS) of these two groups were evaluated.

The median age at diagnosis was 65 years [interquartile range (IQR)=57-75]. We observed a recurrence in 59% (n=39) of the patients and the median PFS was 14 months (IQR=7-20.5). Eighteen (27%) patients died during a median time of follow up of 18 months (IQR=10-29.5).

The levels of CA 125 and HE4, the amount of ascites, the presence of intraabdominal retroperitoneal lymph nodes, and the preoperative Sugarbaker PCI were not significantly different between the two groups at the time of diagnosis (Table I).

Neither did the presence of enlarged CPLNs significantly correlate with a postoperative Sugarbaker PCI, nor did

Table I. *Patient characteristics (n=66).*

	CPLN short-axis ≥5 mm (n=29)		CPLN short-axis <5 mm (n=37)		
	Median	IQR (%)	Median	IQR (%)	*p*-Value
FIGO stage					
IIIA/B	9	31	9	24.3	
IIIC	17	58.6	23	62.2	
IVA/B	3	10.3	5	13.5	
Residual disease after surgery					
Yes	4	13.8	5	13.5	
No	25	86.2	32	86.5	0.974
Recurrence					
Yes	19	65.5	20	54.1	
No	10	34.5	17	45.9	0.347
Place of recurrence					
Abdominal	14	87.5	14	73.7	
Thoracal	1	6.3	1	5.3	
Combined	1	6.3	3	15.8	0.625
Enlarged PPLN					
Yes	8	27.6	6	16.2	0.262
No	21	72.4	31	83.8	
Sugarbaker PCI					
Before NACT	18.1	8-30	18.1	6-27.8	0.872
After NACT	8.07	0.5-13.5	9.05	0-15.5	0.733
CA125 (U/ml)					
Before NACT	868.8	258-1240	1866	98.8-928.8	0.342
After NACT	128.2	12.9-102.8	195.9	23.2-66.8	0.146
Ascites (0-3)*					
Before NACT	1.66	1-3	1.38	0.00-3.00	0.341
After NACT	0.19	0.00-0.00	0.24	0.00-0.00	0.888
HE4					
Before NACT	690.37	152-815	892.23	122-1125	0.707
After NACT	188.45	72.93-296.0	126.13	58.6-128.0	0.245
PFS	HR=1.26		95%CI=0.67-2.38		0.476
OS	HR=1.15		95%CI=0.45-2.93		0.768

CPLN: Cardiophrenic lymph node; NACT: neoadjuvant chemotherapy; IQR: interquartile range; FIGO: International Federation of Gynaecology and Obstetrics; PPLN: pelvic and para-aortic lymph nodes; PCI: peritoneal cancer index; PFS: progression-free survival; OS: overall survival. *The amount of ascites was objectified as follows: 0=no ascites, 1=minimal ascites, 2=moderate ascites, 3=massive ascites.

operability (macroscopic tumour clearance after surgery), achieving a comparable tumour reduction in both groups after NACT.

Patients with enlarged CPLN had a higher probability of getting a recurrence than patients without CPLN (HR=1.26), however the difference was not statistically significant (p=0.476) (Figure 2). The place of recurrence also did not significantly vary between the two groups.

Response to NACT measured by the CPLN in the group with pathologically enlarged CPLNs (n=29) was evaluated. Of these patients, 10.7% (n=3) showed complete response, 71.4% (n=20) showed partial response and 17.9% (n=5) had stable disease according to RECIST guidelines (version 1.1) (7) after NACT. None of the patients had progressive disease in this patient group. One patient was ruled out in regard to the response to NACT, as she did not undertake a control CT scan after chemotherapy.

There was no significant difference between the response to NACT as measured by the CPLN and the response to chemotherapy measured by other factors like PPLN, the CA125-level, the HE4-level, the Sugarbaker PCI, and the amount of ascites.

The response to chemotherapy measured by the CPLN did not significantly influence operability (possibility to reach a macroscopic tumour clearance) (p=0.726). However, the bigger the reduction in the CPLN after chemotherapy, the higher was the probability of getting a recurrence (p=0.013) (Figure 3).

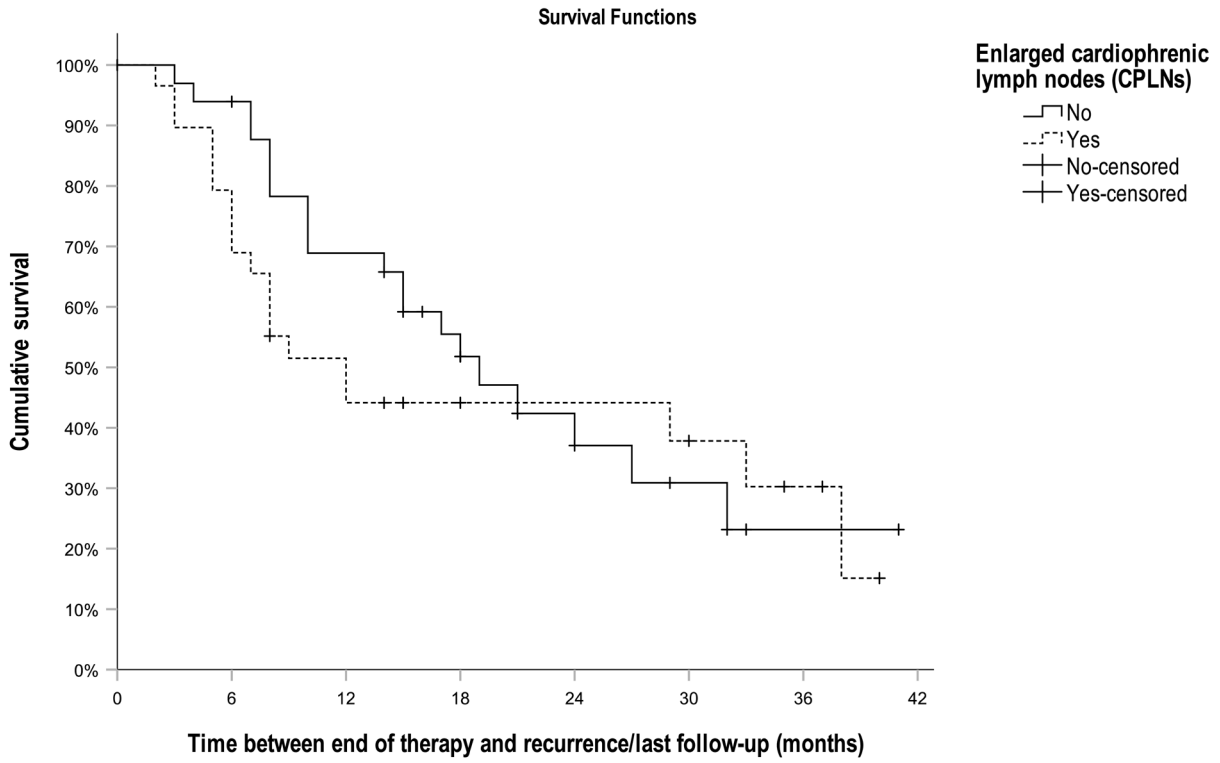

Figure 2. *Progression-free survival in the cardiophrenic lymph node (CPLN) positive and negative group.*

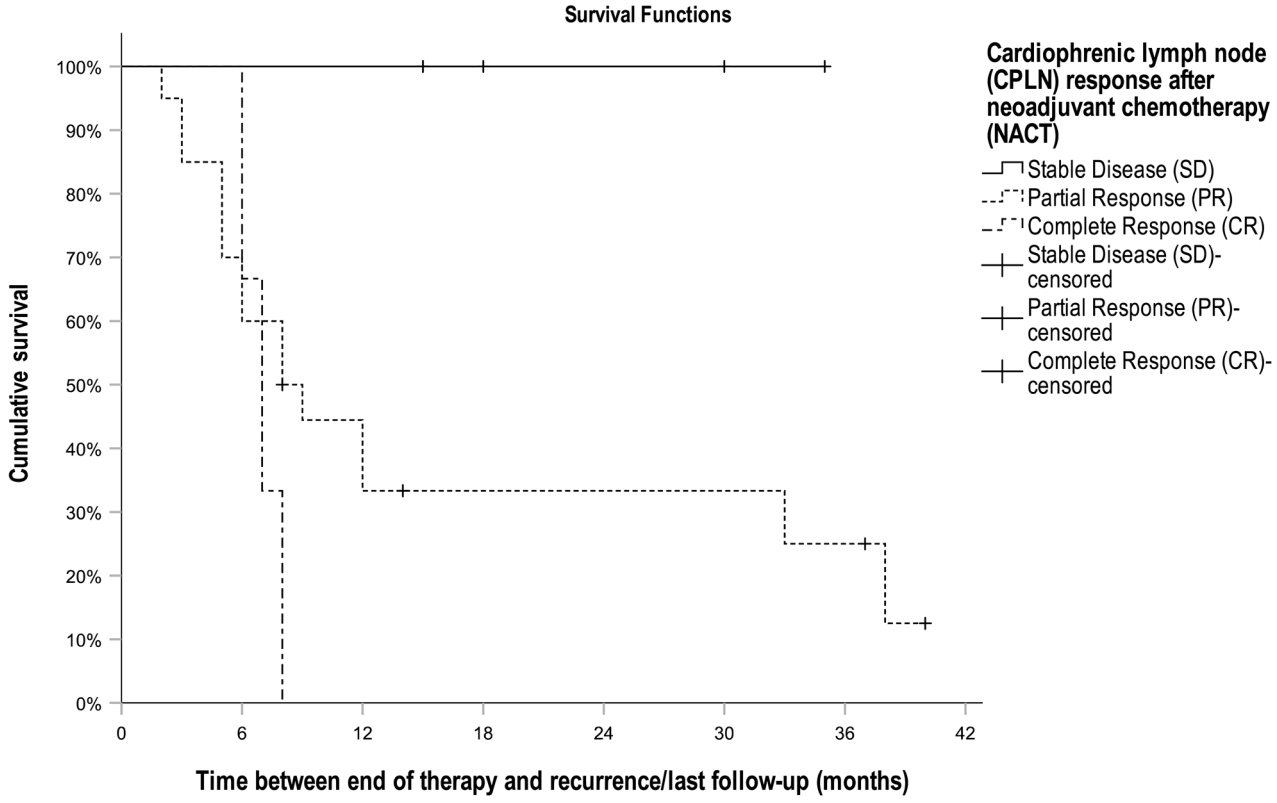

Figure 3. *Cardiophrenic lymph node (CPLN) response after neoadjuvant chemotherapy.*

Discussion

Summary of main results. Our study showed that response to NACT can also be measured by the CPLN in advanced ovarian cancer. This response is comparable to the response measured by established biomarkers (*e.g.*, CA125, HE4, the Sugarbaker PCI, and the amount of ascites).

With a cut-off value of 5 mm short axis to define a CPLN enlargement, 82% of our patients showed at least a partial response to NACT. The bigger the reduction, the higher was the probability of getting a recurrence in these patients, supporting the negative prognostic value of the CPLN. The analysed biomarkers at the time of diagnosis did not significantly vary between the group with enlarged CPLN and the group without.

Results in the context of published literature. In our study cohort, 44% of the patients had radiologic enlarged CPLNs (short axis ≥ 5 mm). In the literature, the described CPLN-detection rates vary between 10.5% and 62% (8, 9, 17-19), depending on the short axis diameter threshold determined for the patient cohort. The higher the short-axis threshold, the lower the detection rate of potentially pathological CPLNs (20). This could be confirmed in our study cohort: if defining a CPLN enlargement at a short-axis of ≥7 mm or ≥10 mm, the percentage of patients with radiologically enlarged CPLNs would have been reduced to 23% (n=15) and 6% (n=4), respectively. Therefore, we chose the ESUR guidelines defined radiologic cut-off of a CPLN short-axis of ≥5 mm (13), as there are also data describing histological detection rates up to 84% with this cut-off (9). This percentage correlates with the response to NACT in 82% of the patients with enlarged CPLNs in our study.

The removal of CPLNs was not routinely performed at the interval debulking surgery in our patient cohort, as its radiological presence was interpreted differently depending on the cut-off value the radiologist used at that time. If the presence of enlarged CPLN would have been considered with a cut-off of ≥5 mm, it would have reflected as extra-abdominal disease involvement causing a stage shift from FIGO III to FIGO IVb in up to 39% (n=26) of our patient cohort. Despite this possible shift, the removal of CPLNs would not have changed the therapy after surgery.

Even if the enlarged CPLNs at the time of diagnosis were not histologically confirmed in the majority of our patients, 82.1% showed at least a partial response to NACT according to RECIST-guidelines (version 1.1). This percentage is comparable to the percentage of histologically confirmed CPLNs described in the literature, lying between 61% and 90% (9, 10, 17, 21, 22). In line with this, the presence of CPLN metastases in around 82.1% of the patients with enlarged CPLN in our patient cohort by means of their response to NACT can be assumed (23), even if they were not histologically confirmed. The significant higher probability of getting a recurrence in patients with a higher reduction in the CPLN after chemotherapy also supports this hypothesis.

Research has shown that patients with radiologically enlarged CPLNs have a worse overall survival (9, 18-20, 24, 25), strengthening its clinical importance. Our data also corroborated a tendency to an impaired prognosis in patients with radiologically enlarged CPLNs, though the time of follow up was too short to be statistically significant. On the other hand, Prader *et al*. revealed that the survival of ovarian cancer patients depends more on a complete intraabdominal tumour resection, even if the CPLN remain surgically unremoved (9). Hence, the intraabdominal tumour spreading in ovarian cancer seems to have a greater impact than the lymphatic spread. This hypothesis is also confirmed by the findings of the LION-trial, were systematic pelvic and paraaortic lymphadenectomy in patients with advanced ovarian cancer was not associated with longer overall survival or PFS, although hidden lymph node metastases were detected in 55.7% of the patients (6). In our study cohort, 90% of the patients could be operated after NACT without residual disease regardless of the presence of CPLNs. During the follow-up time, there was neither a significant difference in the probability of getting a recurrence, nor did the site of recurrence vary between the patients with radiologic enlarged CPLNs and the ones with CPLNs with a short-axis of <5 mm.

Our data demonstrate no significant correlation between enlarged CPLNs and the analysed clinical parameters at the time of diagnosis (Table I). Especially the association between the presence of enlarged CPLN and PPLN could not be proven, which also supports the importance of the intraabdominal over the lymphatic spread in ovarian cancer. Pader *et al*. showed a weaker association between PPLN positivity and CPLN compared to the association of upper abdominal/diaphragmatic carcinomatosis. In addition, we found no significant difference in the response to NACT as measured by the CPLN compared to the response of other biomarkers in the same group of patients. This suggests that the presence of CPLNs itself could have not only a prognostic, but also a monitoring function regarding chemotherapy, which is comparable to the function of other already established biomarkers.

Strengths and weaknesses. So far, there are no previous studies evaluating the CPLN status before and after NACT in advanced ovarian cancer, which gives a new point of view of its implications regarding its monitoring function. By means of the response to chemotherapy, it can be indirectly inferred as a tumour involvement even if the CPLN status is not histologically confirmed.

Our study though has some limitations. Radiologically enlarged CPLNs were not histologically confirmed, as the study relied only on their size. Therefore, we can only make indirect

conclusions regarding their response to chemotherapy. As a pilot study, the study cohort was quite small, and thus our statistical analysis was often not significant. In addition, we selected a patient group treated between 03/2015 and 06/2020, therefore the time used to analyse PFS was too short. The retrospective design of our study may have also caused a selection bias.

Implications for practice and future research. CPLN enlargement in ovarian cancer is not yet a well-established prognostic parameter, despite the fact that it has been shown to correlate with a worse overall survival. Identifying the CPLN status at the time of diagnosis would help to stage patients correctly into a FIGO IVb stage. For this, a general radiological cut-off value to describe the CPLN enlargement should be defined. In addition, the CPLN status seems to also have a monitoring value after chemotherapy.

Larger analysis including data of NACT-treated patients in other centres should be performed to fully evaluate the implication of the CPLN in advanced ovarian cancer.

Conclusion

Consistent with the literature, our data revealed a tendency to an impaired prognosis for patients with radiological CPLN enlargement (9, 18-20, 26). Yet, this correlation was not significant in our patient cohort, probably due to the small number of patients and short follow-up time. Including the CPLNs into the FIGO classification for ovarian cancer would mean an extra abdominal tumour involvement, aggravating the stage of the disease at the time of diagnosis in many patients. For this, a general radiological cut-off threshold for the short axis should be defined. Our data showed that with a radiologic cut-off of >5 mm for the CPLN, it is possible to infer tumour involvement by means of its response to NACT with a tendency to a worse prognosis in these patients.

Nevertheless, the presence of enlarged CPLNs seems to have a rather prognostic value and should therefore not change the current treatment strategy for advanced ovarian cancer. The response to NACT as measured by the CPLN is similar to the response of established parameters like CA125, HE4, ascites, and the Sugarbaker PCI, which gives the CPLN also a monitoring value. Larger studies might be needed to fully evaluate the prognostic role of the CPLN status.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

V. Luengas-Wuerzinger, F. Rawert, B. Lampe and P. Mallmann conceived of the presented work. V. Luengas-Wuerzinger. and F. Rawert developed the theory and performed the computations. S. Baransi and S.Classen von Spee verified the analytical methods. V. Luengas-Wuerzinger wrote the manuscript with support from F. Rawert, K. Carrizo and E. Schuler. P. Mallmann supervised the project. All Authors discussed the results and contributed to the final manuscript.

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