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Pattern and impact of metastatic cardiophrenic lymph nodes in advanced epithelial ovarian cancer

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HIGHLIGHTS

- 62% of advanced ovarian cancer have positive cardiophrenic lymphnodes nodes.
- 84% of radiologically positive cardiophrenic nodes (CPLN) sustain metastases.
- Positive CPLN show a significant inverse impact on complete resection rate, PFS and OS.
- Matched pair analysis did not show any therapeutic impact of CPLN resection in FIGO IIIB-IV.

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ABSTRACT

Background. Cardiophrenic lymph nodes (CPLN) define FIGO stage IVB disease. We evaluate the pattern of CPLN metastases, their prognostic impact and the potential role of CPLN resection in patients with epithelial ovarian cancer (EOC).

Methods. Analysis of 595 consecutive patients with EOC treated in the period 01/2011–05/2016. CT scans were re-reviewed by two radiologists. Positive CPLN were defined as ≥5 mm in the short-axis diameter. The role of CPLN resection was evaluated in a case-control matched-pair analysis.

Results. Of 595 patients 458 had FIGO stage IIIB-IV disease. We excluded patients undergoing interval surgery (n = 54), without debulking surgery (n = 32) and without sufficient pre-operative imaging (n = 22), resulting in a study cohort of 350 patients. Of these, 133 (37.9%) had negative CPLN and 217 (62.0%) had radiologically positive CPLN. In patients with postoperative residual tumor, enlarged CPLN had no impact on survival. In patients with complete resection (n = 223), 98 (44.0%) had negative CPLN and a 5-year OS of 69% and a 5-year PFS of 41%; in contrast, in the 125 patients (56.0%) with positive CPLN, 5-year OS was 30% and 5-year PFS was 13%. In 52 patients we resected CPLN. The matched-pair case-control analysis did not demonstrate any significant impact on survival of CPLN resection.

Conclusion. CPLN metastases are associated with impaired PFS and OS in patients with macroscopically completely resected tumor. Intraabdominal residual tumor has a greater prognostic impact than positive CPLN. The impact of the resection of CPLN remains unclear.

1. Introduction

Epithelial ovarian, fallopian tube and peritoneal cancer (EOC) are the second most common gynecologic malignancies in the Western world and the most common cause of death due to gynecologic malignancies [1]. Approximately 75% of patients with EOC are diagnosed with advanced-stage disease, i.e. Fédération Internationale de Gynècologie et d'Obstètrique (FIGO) stages IIIB-IV [2]. FIGO stage and macroscopic complete resection are the most important prognostic factors; only the latter is modifiable by therapeutic intervention. Treatment planning commonly includes a preoperative CT scan to exclude extra-abdominal unresectable tumor masses. Based on the results of clinical and

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radiological imaging diagnostics either upfront debulking surgery aimed at resection of all macroscopic tumor [3–5] or the patient may receive neoadjuvant chemotherapy (NACT) followed by interval debulking surgery. The latter strategy is favored in patients with lesions initially deemed unresectable. A unanimously accepted definition of unresectability is lacking and classification as stage FIGO IV does not reliably identify patients with an unresectable tumor growth pattern [6]. FIGO stage IV disease constitutes a heterogeneous group including both unresectable disease patterns such as diffuse visceral metastases and easily resectable entities, such as cardiophrenic lymph nodes (CPLN) [7]. In the case of resectable lesions complete primary debulking of FIGO stage IV tumors offers clinical benefits comparable with those that can be achieved in stage FIGO III disease [8].

The role of lymph node metastases in the definition of the various FIGO stages has been a matter of debate for decades. In 2014 the FIGO finally published a new classification defining retroperitoneal lymph node metastasis between the inguinal ligament and the diaphragm as regional nodes which are now categorized as FIGO stage IIIA instead of, as in the past, FIGO IIIC [9]. However, the practice of excluding inguinal node metastasis from the regional lymph node system and declaring it a classifier for stage FIGO IVB has also been challenged by new data [10]. CPLN are located above the abdominal cavity and diaphragm. Currently, they define FIGO stage IVB If histologically positive.

The role of CPLN in EOC has been questioned since better diagnostic work-ups and improved techniques have led to higher awareness on the part of radiologists and surgeons on this specific issue. Several papers have reported the feasibility of resecting CPLN [7,11–15]. However, the exact definition of where CPLN are located in EOC is still unclear and neither the prognostic impact of positive CPLN nor the potential therapeutic benefit conferred by their resection has been fully elucidated. Furthermore, the cut-off value used to predict lymph node positivity has never been standardized and ranges from 5 mm [12–17] or 7 mm [18,19] to 10 mm [7,19]. Accordingly, the rate of lymph node metastases has ranged from 45% to over 90%. The aim of our study is to obtain further evidence for this particular metastatic pattern of ovarian cancer and to assess its impact on survival.

2. Methods

We performed an exploratory analysis of the data in our clinical tumor registry, which contains data from all consecutively incoming patients with epithelial, tubal or peritoneal cancer (EOC) treated at our institution. Patients enrolled in the study gave written informed consent and had annual follow-up. Analyses were performed after approval of the local ethics committee. To be eligible for this analysis, the patients had to fulfill the following criteria: histologically proven EOC, upfront surgery in our institution between January 2011 and May 2016 and availability of adequate preoperative imaging. Appropriate diagnostic workups included CT scan (>95%), PET-CT scan and MRI (<5%). CT scans of the abdomen had a slice thickness of ≤5 mm and intravenous contrast was administered. Patients who had received NACT with or without interval debulking and those who had not received any surgical therapy were excluded. Clinical data including surgical and pathologic reports were double-checked and all CT scans were centrally re-reviewed by two experienced radiologists (NV, KUW).

For a description of the pattern of CPLN spread we divided the patients into 3 groups: 1) an anterior right group, including lymph nodes detected on the right side of the heart and lower mediastinum, 2) an anterior left group including lymph nodes detected on the left side of the sternum and anterior to the heart in the lower mediastinum, and 3) a posterior group including lymph nodes detected bilaterally of the spine in the lower mediastinum. CPLN with a diameter of 5 mm or larger along the short axis were regarded as radiologically suspicious. Besides CPLN, we also re-evaluated all regional lymph node regions as well as signs of peritoneal carcinomatosis, pleural effusion, and measured diaphragm thickness. The latter was measured as the largest vertical diameter. Based on our own experience, a 2 mm cut-off was used to separate cases of suspicious and non-suspicious diaphragm thickness. Peritoneal carcinomatosis was defined as any macroscopically visible nodule on the peritoneum.

Since 2014 resection of radiologically proven enlarged CPLN has been introduced stepwise into our routine surgical program for advanced EOC. The technical details of this procedure have already been published [7]. In short, we used the trans-diaphragmatic approach to access radiologically positive lymph nodes on either side of the mediastinum. In our first series we could not detect any procedure-specific complication such as intrathoracic hemorrhage, pleuritis, pneumonia or thoracic fistulas. We started with the excision of CPLN with a short-axis diameter ≥ 10 mm according to the definition of suspicious nodes contained in the Response Evaluation Criteria in Solid Tumors (RECIST) classification [20]. Thereafter, we changed our policy in 2015 and aligned it with the policy of the European Society of Urogenital Radiology (ESUR) guideline [21], which defines suspicious CPLN as lymph nodes with a short-axis diameter of ≥5 mm. For further analysis we formed 3 subgroups, consisting of: radiologically positive CPLN from 5 to 9 mm, positive CPLN ≥ 10 mm and negative CPLN with a short diameter of <5 mm. In addition, we analyzed the cut-off value for CPLN positivity in our own cohort with cut-off finder analyses using R-version 2.15.0 (212-03-30) from 2012 [22]. The latter revealed a cut-off of 4.95 mm.

All surgical debulking procedures were performed by dedicated teams with at least one board-certified gynecologic oncologist, and additional quality measures, as described above, were applied [5,6]. The medical history, clinical examination results and imaging data of all patients were discussed at a pre-operative interdisciplinary tumor board meeting. Here, the strategy of either upfront or interval debulking (IDS) was recommended. No residual disease, is defined as, no macroscopically visible intraabdominal tumor, which is equivalent to only microscopic residual disease. Upfront debulking surgery was followed by systemic therapy with 6 cycles of carboplatin-paclitaxel chemotherapy while patients with IDS received the same chemotherapy divided into 2 times 3 courses [23].

Neither the pre-operative workup nor the postoperative chemotherapy changed over the period of this exploratory analysis.

Progression-free survival (PFS) was defined as the interval from the date of diagnosis to the date of the documented first recurrence. Overall survival (OS) was defined as the time interval from date of diagnosis to date of death or last follow-up. In the absence of such events, survival was censored at the date of the last visit.

To analyze the impact of CPLN resection we created a case-control matched-pair cohort analysis. The following matching criteria were applied: age (+/−5 years), ECOG (0 vs >0), tumor size (pT3b vs pT3c), ascites (</>500 ml) and post-operative tumor residual (no macroscopic vs any residual).

All analyses were performed using IBM SPSS Statistics 23, Chicago 2017. Methods included Kaplan-Meier with log-rank test and Cox's proportional hazard models. p-Values were considered statistically significant if <0.05. However, because of the retrospective nature of our analyses, all significant p-values were interpreted as hypothesis-generating only.

3. Results

Overall, 595 consecutive patients with epithelial ovarian, fallopian and peritoneal cancer (EOC) received their primary therapy at our institution between 01/11 and 05/16. This group included 458 patients with advanced stage disease FIGO IIIB-IV. Of these, 372 (81.2%) underwent upfront debulking surgery. Median follow-up time of these patients was 40 months. During the observation period 109 patients (31.1%) deceased and 184 (52.6%) experienced a recurrence. Median progression-free survival was 25 months and overall survival was 48 months for the whole cohort. The FIGO stage distribution was as follows: Thirty-seven

patients (10.6%) had stage FIGO IIIB, 114 (32.6%) FIGO IIIC and 199 (56.9%) FIGO IV. A total of 163 patients in the latter cohort were classified as FIGO IVB; in this group 22 patients (6.3%) were classified as FIGO IVB exclusively on the basis of histologically confirmed metastatic CPLN (Table 1).

Adequate CT imaging data and a central radiological re-review were available for 350 patients (94.1%), which finally defined the study cohort. Analysis of the data showed that the cut-off threshold for the short-axis diameter for lymph-node metastases was 4.95 mm, confirming our actual strategy of regarding nodes ≥ 5 mm as suspicious. With this definition imaging showed negative CPLN in 133 patients (38.0%). Positive CPLN with a short diameter ≥ 5 mm were diagnosed in 217 patients (62.0%). The latter group included 159 patients with a CPLN diameter ranging from 5 to 9 mm and 58 patients with CPLN ≥ 10 mm (Fig. 1).

The majority of the 217 patients (100%) with radiologically positive nodes showed a pattern of multiple locations. The anterior right location was most frequently affected and contained enlarged nodes in 203 patients (93.5%); these were usually positive at more than one location. Single-site radiologically positive CPLN were observed in only 15.2%, 6.4% and 1.3% of the patients in the anterior right, anterior left, and posterior location, respectively (Supplemental Table S-3).

Additional radiological findings were: 69 patients had (19.7%) pleural effusion; >2 mm thickening of diaphragm was observed in 237 (67.7%); radiologically suspicious lesions were detected on the surface of the liver in 42 patients (12.0%), and signs of peritoneal carcinomatosis were reported in 300 patients (85.7%) (Table 2). Intraoperatively, we detected peritoneal carcinomatosis of the diaphragm in 283 patients (80.9%). Of these, 190 patients (67.1%) had positive CPLN. Diaphragmatic deperitonealization was performed in 232 of 283 patients (81.9%) with carcinomatosis, including full-thickness resection in 52 patients of those 232 patients (22.9%). A similar rate of positive CPLN was found when the 232 patients with peritoneal stripping were analyzed: 67.2% corresponding to 156 of 232 patients. No stripping was performed in 67 patients with a macroscopically positive diaphragm because of larger residual tumor elsewhere. In this subgroup 27 patients (40.2%) had positive CPLN. The analyses of the subgroup of 67 patients (19.1%) without macroscopic diaphragm carcinomatosis showed positive CPLN in 27 patients (40.2%) who presented with CPLN ≥ 5 mm. Enlarged paraaortic lymph nodes were observed in 63 patients (18.0%) and suspicious pelvic lymph nodes were detected by the radiologists in 42 patients (12.0%).

We found a significant correlation between the occurrence of positive CPLN and the above mentioned radiologic criteria presented here in order of the magnitude of effect: extra-diaphragmatic, parietal peritoneal carcinomatosis (odds ratio [OR] 4.31 with 95% confidence interval [CI] 2.27–8.19), diaphragm thickness > 2 mm (OR 3.99, 95% CI 2.49–6.41), liver capsule nodules (OR 2.47, 95% CI 1.14–5.34), and pleural effusion (OR 1.96, 95% CI 1.09–3.53). We did not detect any correlation between pelvic lymph node status or groin lymph nodes and CPLN; moreover, the association of para-aortic lymph node positivity and positive CPLN was weaker (OR 2.48, 95% CI 1.31–4.70) than the association for upper abdominal/diaphragmatic carcinomatosis and OR > 4. A moderately strong but significant relation between positive CPLN and positive para-aortic nodes was also observed if only the pathological lymph node status was analyzed (OR 1.83, 95% CI 1.10–3.01).

A correlation between more advanced carcinomatosis and CPLN was also confirmed by our analysis of surgical resection status. We observed an inverse correlation between the various categories of CPLN and the complete resection rate (Supplemental Table S-1): The larger the CPLN, the higher the amount of peritoneal carcinomatosis in the upper abdomen the lower the complete resection rate and vice versa. Macroscopic complete resection was achieved in 73.7% of patients with negative CPLN and in 60.4% and 50.0% of patients with 5–9 mm and 10+ mm CPLN, respectively ($p = 0.004$).

Consequently, radiologically positive CPLN were associated with a worse outcome in our cohort. The 5-year survival rates were 54% and 21% in patients with negative and positive CPLN, respectively ($p = 0.019$). To assess the potential impact of both CPLN and complete resection, we performed an additional analysis only in the 223 patients in whom complete resection was achieved. Univariate analysis showed a significant impact of CPLN positivity on OS in patients with complete resection. The best prognosis was found in the 98 patients with macroscopically complete resection and negative CPLN (5-year OS 69% and 5-year PFS 41% with a median PFS of 49 months). Positive CPLN decreased the corresponding 5-year OS and PFS rates to 30% and 13%, respectively (OS $p = 0.009$, PFS $p \leq 0.001$; Fig. 2).

A sensitivity analysis revealed a smaller impact if only those 190 patients with complete resection and without resection of the CPLN were considered. In this subgroup, multivariate analysis including established prognostic factors such as age, performance status, histologic subtype, TNM stage and ascites confirmed a moderate impact of CPLN positivity on PFS (HR 1.91, 95% CI 1.26–2.89; $p = 0.002$) but failed to demonstrate a significant impact of CPLN status on OS (HR 1.62; CI 1.19–2.89; $p = 0.079$; Supplemental Table S-2).

To further investigate the impact of CPLN we focused on those 52 patients with excision of radiologically positive CPLN, according to our definition. Thirty-two patients had CPLN with a short-axis diameter of 5–9 mm and 20 patients had CPLN ≥ 10 mm. The radiological diagnosis was confirmed by pathological diagnosis in 84.6% and lymph node metastases in the CPLN were diagnosed in 44 of 52 patients. The mean CPLN short-axis diameter was 8.5 mm (SD 2.9 mm) in those 8 patients with radiologically suspicious but histologically negative CPLN and did not differ from the mean 8.4 mm (SD 2.4 mm) recorded in patients with both histologically and radiologically positive CPLN. To further evaluate the potential role of CPLN resection, we formed a control group of patients with radiologically positive CPLN but without surgical removal. The main reason for not resecting CPLN in these patients was diagnosis before 2014. The control cohort was matched for all the main prognostic factors such as post-operative tumor burden, performance status, TNM stage, age, tumor histology and ascites. Our analysis did not show any significant prognostic impact of CPLN resection when we compared the above-mentioned 52 patients with CPLN resection

Table 1
Patients characteristics and risk factors for radiologically suspect cardiophrenic lymph nodes (short axis diameter ≥ 5 mm); HGS: high grade serous ovarian cancer, CPLN: Cardiophrenic lymph nodes.

Variables	Cardiophrenic lymph nodes		OR (95% CI)	p-Value
	Radiologically negative N = 133 (%)	Radiologically positive (≥5 mm) N = 217 (%)		
Performance status				
ECOG 0	125 (94.9)	206 (94.9)	1	
ECOG > 0	8 (6.o)	11 (5.1)	0.83 (0.33–2.13)	0.705
Histiological type				
High grade	104 (78.1)	198 (91.2)	1	
Others	29 (21.8)	19 (8.7)	0.34 (0.18–0.64)	**0.001**
Ascites				
<500 ml	94 (70.7)	107 (49.3)	1	
≥500 ml	39 (29.3)	110 (50.7)	2.48 (1.57–3.92)	<**0.001**
FIGO stage				
IIIB	23 (17.3)	14 (6.5)	1	
IIIC	52 (39.1)	62 (28.6)	1.96 (0.92–4.19)	0.083
IV	58 (43.6)	141 (65.0)	3.99 (1.92–8.30)	<**0.001**

Bold values indicates significance at $p < 0.05$.

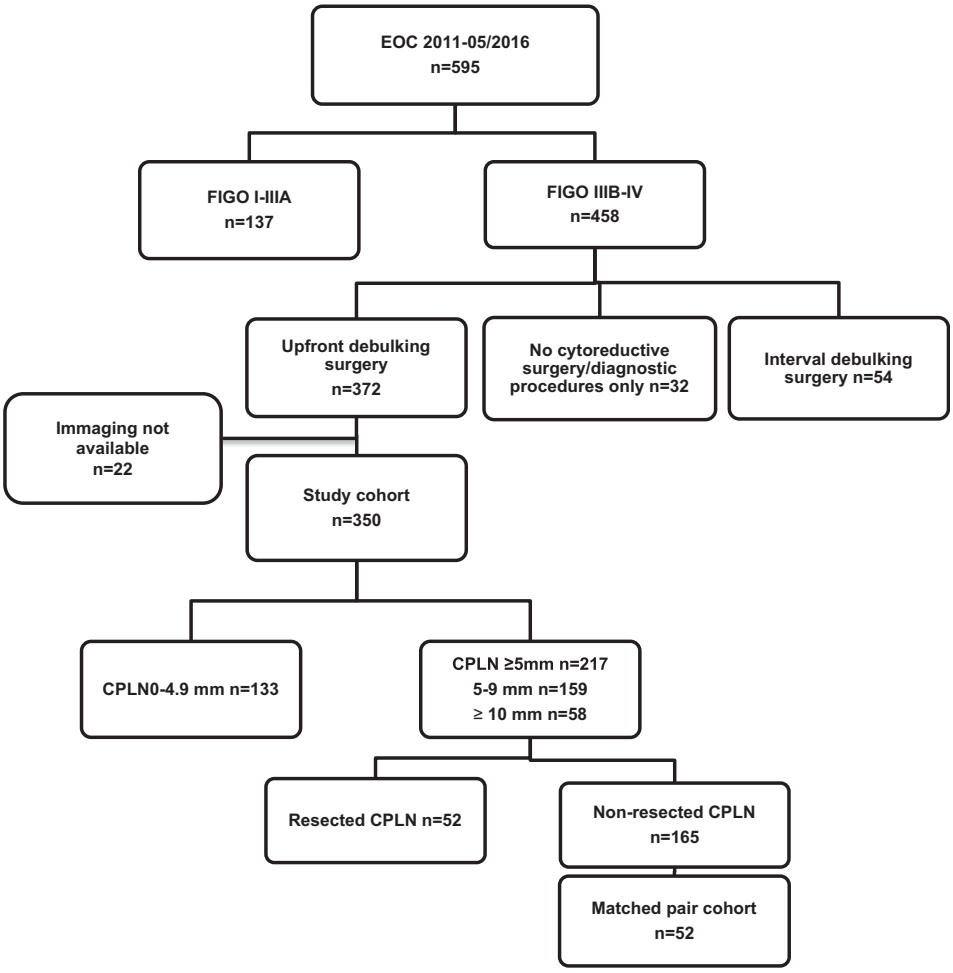

Fig. 1. Patient flowchart. EOC: epithelial ovarian cancer, CPLN: Cardiophrenic lymph nodes.

Table 2
Radiological parameters for neg, 5–9 mm and ≥10 mm cardiophrenic lymph nodes (CPLN).

Radiological parameters of CPLN				
Variables	Negative CPLN	Positive CPLN	OR (CI 95%)	p-Value
n (%)	133 (38.0)	217 (62.0)		
Pleural effusion				
No	115 (86.5)	166 (76.5)	1 (ref.)	
No	18 (13.5)	51 (23.5)	1.96 (1.09–3.53)	**0.024**
Diaphragma thickness				
No	68 (51.1)	45 (20.7)	1 (ref.)	
Yes	65 (48.9)	172 (79.3)	3.99 (2.49–6.41)	<**0.001**
Liver capsule nodules				
No	124 (93.2)	184 (84.8)	1 (ref.)	
Yes	9 (6.8)	33 (15.2)	2.47 (1.14–5.34)	**0.022**
Peritoneal carcinomatosis				
No	34 (25.6)	16 (7.4)	1 (ref.)	
Yes	99 (74.4)	201 (92.6)	4.31 (2.27–8.19)	<**0.001**
Pelvic lymph nodes				
Negative	120 (90.2)	188 (86.8)	1 (ref.)	
Positive	13 (9.8)	29 (13.4)	1.42 (0.71–2.85)	0.318
Paraaortic lymph nodes				
Negative	119 (89.5)	168 (77.4)	1 (ref.)	
Positive	14 (10.5)	49 (22.6)	2.48 (1.31–4.70)	**0.005**
Groin lymph nodes				
No	125 (94)	203 (93.5)	1 (ref.)	
Yes	8 (6)	14 (6.5)	1.08 (0.44–2.64)	0.870

HGS: high grade serous ovarian cancer.

with the matched-pair case-control cohort of patients without removal of the radiologically positive CPLN (Fig. 3).

4. Discussion

The present study is among the largest series focusing on the pattern and potential role of cardiophrenic lymph nodes (CPLN) in advanced ovarian cancer. A systematic central double-reader radiological review revealed positive CPLN in the majority of patients (62%) with advanced epithelial ovarian cancer (EOC). The vast majority of CPLN with a short-axis diameter in excess of 5 mm bear metastases (85%). This rate is in line with other reports of cases with pathologically proven metastases in 67–100% [13,14,24] and confirm a 5 mm cut-off as suggested by the European Society of Urogenital Radiology (ESUR) guideline [21]. Our data indicate that there is a stronger correlation between CPLN positivity and peritoneal carcinomatosis of the upper abdomen and especially of the diaphragm than between CPLN positivity and lymph node status of the typical regional nodes in the pelvic and para-aortic region. The latter finding indicates that the CPLN might not be just a continuum of the para-aortic lymphatic drain. The pattern of CPLN with preference for the right anterior cardiophrenic space may reflect the preference of the right diaphragm surface for peritoneal metastases in EOC. CPLN may just be an indicator of widespread peritoneal carcinomatosis thus explaining the association of CPLN with surgical outcome and complete resection rate. The latter has also been reported by others [16,25]. However, this observation may also be explained by the fact that peritoneal carcinomatosis has been reported to be a negative predictor of resectability on its own [26] rather than by a genuine impact of CPLN on

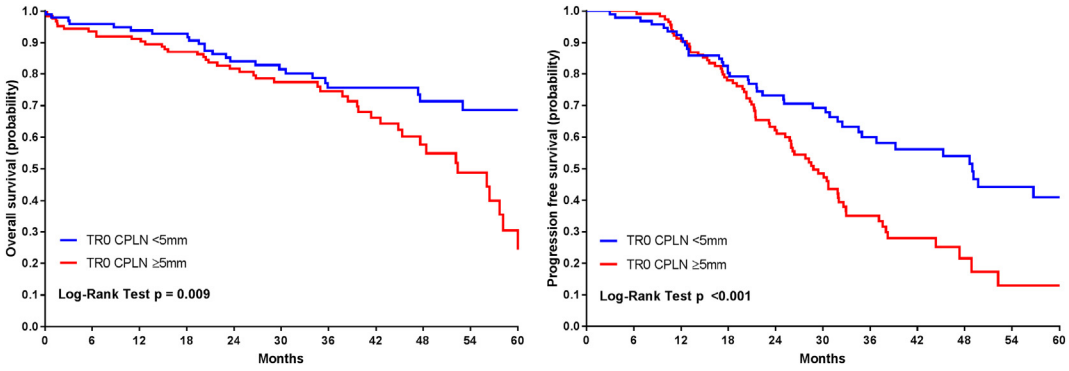

Fig. 2. Overall survival and progression free survival in completely resected patients (TR0) with Cardiophrenic lymph nodes (CPLN) <5 mm versus ≥5 mm.

prognosis. This interpretation is supported by the fact that the impact of CPLN on outcome was minimized if the data are corrected for complete resection. A similar observation has been reported for the impact of peritoneal carcinomatosis that lost its prognostic impact after correction for tumor resection status in recurrent ovarian cancer [27].

We confirmed here the feasibility as already reported in our initial learning curve series on resection of CPLN [7]. Radiologically positive CPLN should not be regarded as a criterion for inoperability as suggested by Kebapci et al. in 2010 [26]. We rather propose that positive CPLN might be an indicator of upper abdominal carcinomatosis and could be used as a criterion for transferring a patient to a specialized center capable of resecting carcinomatosis of the diaphragm – a procedure not established in a significant proportion of gynecological oncology centers worldwide [28–30]. However, the predictive value of positive CPLN for diaphragmatic disease should be further evaluated in a multicentric setting before patient flow can be based on it.

CPLN were mainly neglected in the past or not diagnosed due to lower resolution imaging. As positive CPLN define stage FIGO IVB, recognizing CPLN may lead to a stage shift and FIGO stage IVB (instead of FIGO III) might become the most frequent stage at diagnosis. Treatment algorithms based solely on FIGO stage might be questioned and an association of FIGO IV and ineligibility for upfront surgery should be challenged [31–33]. The lack of specificity of stage IV in the FIGO classification system has been discussed for several specific locations including abdominal wall metastases [34] and inguinal nodes [10]; now CPLN have entered this discussion.

Even more unclear is the therapeutic role of resecting radiologically positive CPLN. Should positive CPLN be regarded as residual tumor or more as an indicator of advanced stage disease not amenable to therapy (as FIGO stage)? Our data support the latter view and do not indicate a positive role for surgical removal of CPLN when compared to a matched control group. This result fits well with recent data from the LION trial [35] indicating that removal of retroperitoneal lymph nodes including clinically occult metastases in >50% of patients did not change outcome. In accordance with Mert et al. [19] we could not demonstrate a significant impact of positive CPLN on survival. Furthermore, even resection of positive CPLN did not confer a significant benefit in our series. One may speculate that the peritoneal sanctuary of occult ovarian cancer cells is much more important than the potential lymph node risk.

The weakness of our data lies in its retrospective nature and the limited case number – even though it is one of the largest series on CPLN so far. The weakness of retrospective radiological diagnosis has been addressed and we performed a central two-reader re-review of all CT scans. A prospectively randomized trial on CPLN will probably not be feasible. Nevertheless, larger multicentric series should confirm the results of this analysis.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2018.11.001.

Potential COI

None of the authors declared any potential COI with respect to the topic of the work presented here, however, some authors (AdB, PH, BA, and FH) had received fees and honoraria for activities outside and without any relation to the presented work.

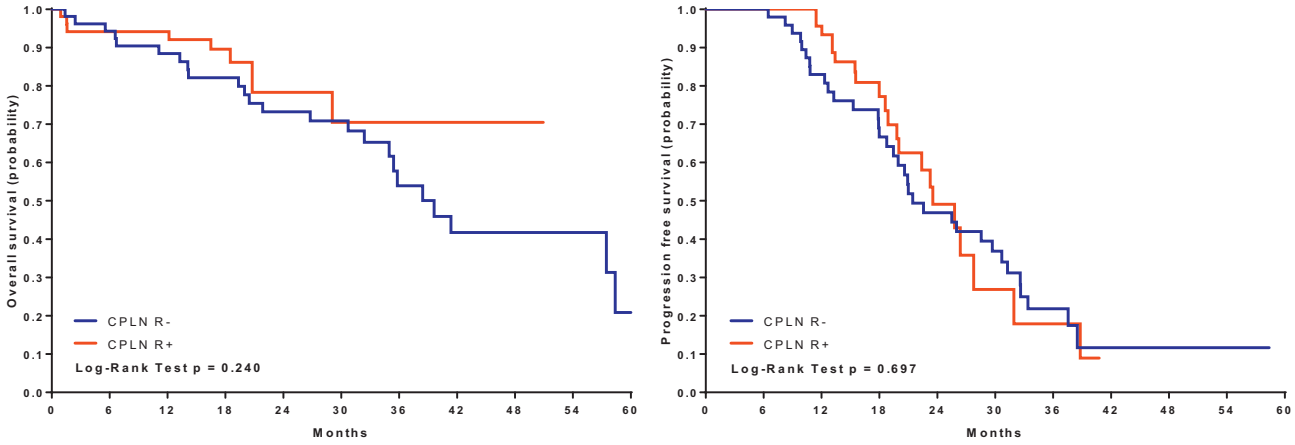

Fig. 3. Overall survival and progression free survival for patients with resected (R+) cardiophrenic lymph nodes (CPLN) versus non resected (R−) CPLN in a matched pair comparison.

CRediT authorship contribution statement

Sonia Prader: Conceptualization, Writing - original draft, Writing - review & editing. **Nils Vollmar:** Investigation, Writing - review & editing. **Andreas du Bois:** Conceptualization, Writing - original draft, Writing - review & editing. **Florian Heitz:** Resources, Writing - review & editing. **Stephanie Schneider:** Resources, Writing - review & editing. **Beyhan Ataseven:** Resources, Writing - review & editing. **Mareike Bommert:** Resources, Writing - review & editing. **Kai-Uwe Waltering:** Investigation, Writing - review & editing. **Sebastian Heikaus:** Investigation, Writing - review & editing. **Jens Albrecht Koch:** Investigation, Writing - review & editing. **Pier Francesco Alesina:** Resources, Writing - review & editing. **Alexander Traut:** Formal analysis, Writing - review & editing. **Philipp Harter:** Resources, Writing - review & editing.

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