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

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HIGHLIGHTS

- Lymph node status is a prognostic factor in ovarian cancer.
- Lymph node ratio reflects lymph node spread and surgical extent.
- Lymph node ratio predicts overall survival more concisely.

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ABSTRACT

Objective. Lymph node status is an established prognostic factor in epithelial ovarian cancer (EOC). Lymph node ratio (number of positive LN/number of resected LN) reflects both qualitative and quantitative lymph node spread as well as surgical effort and extent of disease. We evaluated whether LNR is a more precise prognostic factor than conventional lymph node status in patients with EOC.

Methods. The present retrospective study includes 809 patients with EOC, who underwent primary cytoreductive surgery between 2000–2013. Clinico-pathological parameters and survival data were extracted from a prospectively maintained tumor registry database. The optimal cut-off point for LNR was calculated by using Martingale residuals. Survival analyses were calculated using Kaplan–Meier method and Cox regression models.

Results. Lymphadenectomy was performed in 693 (85.7%) out of 809 patients. Median number of removed LN was 64 (IQR 25–75%: 39–84). LNR of 0.25 was identified as the optimal prognostic cut-off value. The estimated 5-year-OS rates were 69.3% for patients with node-negative EOC compared to 33.1% for patients with any lymph node metastasis ($p < 0.001$). The estimated 5-year-OS rates were 42.5% for patients with LNR ≤ 0.25, and 18.0% for patients with LNR > 0.25 ($p < 0.001$). Additionally in multivariate analysis LNR > 0.25 was approved to be an independent prognostic factor for overall survival (adjusted HR 1.44, 95% CI 1.04–2.00; $p = 0.028$).

Conclusion. LNR more precisely predicts overall survival than conventional lymph node status in EOC patients undergoing primary debulking surgery.

Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy [1]. EOC has a very unique tumor biology and pattern of metastasis with predominantly peritoneal and lymphovascular spread and rarely hematological spread. The role of complete tumor resection of mainly intraperitoneal disease has well been described, however, the prognostic value of lymph node metastasis, its impact on residual tumor status and thus, the therapeutic value of comprehensive pelvic and paraaortic lymphadenectomy have not been fully clarified in EOC.

Age, tumor stage, and residual disease are the major prognostic factors in EOC [2,3]. The prognostic value of lymph node metastases is less well defined. However, in clinically apparent stage I disease, the presence of LN metastasis causes an upstaging possibly leading to a subsequent change in treatment.

Studies addressing the therapeutic value of comprehensive pelvic and paraaortic lymphadenectomy in patients with EOC are limited. Retrospective analyses indicate a benefit particularly in optimally debulked ovarian cancer cases and early stage EOC [4,5]. In advanced EOC this benefit has not been consistently shown. Nonetheless,

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complete gross resection of all visible disease after surgery is the surgical goal in treating EOC [6]. The therapeutic role of comprehensive lymphadenectomy in EOC patients is currently being addressed in a prospective randomized controlled trial (lymphadenectomy in ovarian neoplasms (LION) NCT00712218).

Lymph node ratio (LNR) is the number of positive lymph nodes divided by the total number of removed lymph nodes. LNR has been proven to be an important prognostic factor in a variety of malignancies including breast, gastric, esophageal, and non-small cell lung cancer, and melanoma [7–11]. With respect to EOC, one retrospective analysis has reported that high LNR was independently associated with decreased overall survival in patients with advanced EOC [12]. Patients from the Surveillance, Epidemiology, and End Results Program (SEER) were included in this study. A major limitation of this retrospective analysis was the extent of lymphadenectomy. Only 58.0% and 21.1% of patients had ≤10 and 11–20 lymph nodes removed, respectively. Just a small amount of 20.8% of patients had a comprehensive lymphadenectomy with >20 lymph nodes removed.

The aim of our present study was to evaluate the additional prognostic value of LNR compared to conventional lymph node status in patients with EOC that have undergone systematic pelvic and paraaortic lymphadenectomy during primary upfront debulking surgery.

Methods

Patients with first diagnosis of invasive epithelial ovarian, fallopian tube or serous primary peritoneal cancer who attended our tertiary gynecologic oncology center (Horst–Schmidt–Kliniken (HSK), Wiesbaden and Kliniken Essen-Mitte (KEM, Essen)) were prospectively documented in a clinical tumor registry from 2000 until present. All patients' follow-up data are updated annually. In the present study, we included only patients with EOC (n = 906; HSK n = 630; KEM n = 276) who underwent primary upfront cyctoreductive surgery in our institution. Patients receiving neo-adjuvant chemotherapy and subsequently attending our center for interval debulking (n = 97) were excluded. Furthermore, patients with borderline tumors and non-epithelial ovarian cancer were also not included in this analysis. All patients gave informed consent for the surgical procedure and documentation of clinical data in our clinical tumor registry. Surgery was performed by a dedicated surgical team. In all patients with macroscopic residual disease routine intra-operative 2nd opinion was obtained from a senior gynecological oncologist before wound closure. The indication for systematic pelvic and para-aortic lymphadenectomy changed over the study period. Between 2000–2006 systematic lymphadenectomy was performed in patients with age ≤75-years and surgical debulking without residual tumor intraabdominally or tumor residuals up to 10 mm. After 2006 systematic lymphadenectomy was performed only in patients with complete macroscopic tumor resection, whereas in patients with 1–10 mm residual tumor only bulky nodes were resected. For this retrospective analysis we defined systematic lymphadenectomy as a complete procedure when at least 30 lymph nodes were reported in the pathologic specimen. Platinum-based chemotherapy was given stage adapted after surgery to all patients.

To evaluate the optimal cut-off point for LNR (number of positive LN/total resected LN) Martingale residuals [13] was used. Node positive patients were categorized either in low LNR group (≤0.25) or high LNR group (>0.25). For comparison of the total cohort we divided patients into four LN groups: NX (lymphadenectomy not performed), N0 (lymphadenectomy performed, negative for metastasis), LNR ≤ 0.25 (lymphadenectomy performed, positive for metastasis; LNR ≤ 0.25) and LNR > 0.25 (lymphadenectomy performed, positive for metastasis, LNR > 0.25).

To further elucidate the prognostic value of LNR, we additionally performed analysis in a more restrictive patient cohort (complete gross resection — complete LN dissection (CGR-LND group)). Therefore we evaluated the impact of LNR only in patients with tumor stage pT3c, optimal debulking surgery (defined as complete resection) and systematic lymphadenectomy (number of resected LN > 30). This cohort is henceforward referred to as the "CGR-LND group". To eliminate bias caused by a different extent of lymphadenectomy in the low and high LNR groups, we evaluated the number of total lymph nodes removed. Moreover, we compared both groups with respect to length of operation, blood loss, and quantification of surgical effort using the Surgical Complexity Score (SCS) previously described [14].

Statistical analysis was performed using SPSS™ version 20.0 (Chicago, Illinois, USA) and GraphPad Prism® 4 (La Jolla, CA, USA). Cut-off value for LNR was calculated by Martingale residuals. We performed multivariate Cox regression analyses comprising tumor stage, distant metastases, tumor grade, histologic type, patient's age, performance status, and surgical outcome/residual tumor to determine whether the LNR had any significant impact on overall survival (OS). Univariate survival analyses were provided as Kaplan–Meier curves and differences calculated by log-rank tests. Association between LNR and OS was calculated by using a Cox proportional hazard regression model.

Results

809 patients met inclusion criteria for this analysis. Patient and tumor characteristics are shown in Table 1. Two hundred seventy-nine (34.5%) patients were 65 years or older. The majority of patients (n = 686; 84.8%) were in a good performance status (Eastern Cooperative Oncology group; ECOG 0), diagnosed with pT3-stage (n = 581;

Table 1
Patient and tumor characteristics.

Variable	Total cohort		Sensitivity-analysis cohort #	
	Patients (n)	%	Patients (n)	%
Total	809	100	210	100
Age *				
≤64 yr	530	65.5	155	73.8
>64 yr	279	34.5	55	26.2
Performance status				
ECOG 0	686	84.8	200	95.2
ECOG >0	123	15.2	10	4.8
FIGO-stage				
FIGO I	133	16.4	0	
FIGO II	50	6.2	0	
FIGO III	404	49.9	132	62.9
FIGO IV (=M1)	222	27.4	78	37.1
Grade				
Low-grade	57	7.0	4	1.9
High-grade	752	93.0	206	98.1
Histology				
Serous	589	72.8	189	90.0
Others	220	27.2	21	10.0
pN-stage				
NX	116	14.3	0	0
N0	295	36.5	45	21.4
N1	398	49.2	165	78.6
Lymph node resected				
0	116	14.3	0	0
≤30	152	18.8	0	0
>30	541	66.9	210	100
Lymph node ratio (LNR)‡*				
NX	116	14.3	0	0
N0	295	36.5	45	21.4
≤0.25	244	30.2	123	58.6
>0.25	154	19.0	42	20.0
Residual disease after surgery				
0 mm	573	70.8	210	100
1–10 mm	170	21.0	0	0
>10 mm	66	8.2	0	0

* Cut by martingale residue.
‡ LNR is defined as the number of positive nodes divided by the number of resected nodes.
# Sensitivity-analysis cohort (stage pT3c, residual disease 0 mm, systematic lymphadenectomy).