

Prognostic value of radiological recurrence patterns in ovarian cancer

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HIGHLIGHTS

- Radiologically assessed recurrence patterns can help to counsel patients on their prognosis at recurrence.
- A predominantly lymphatic recurrence has a better survival than a predominantly peritoneal or hematogenous recurrence.
- In patients with recurrent disease, the completeness of surgery is associated with the time to recurrence.
- There are no differences in recurrence patterns between patients with complete and incomplete debulking surgery.
- Linking the pattern of recurrence to survival outcomes could lead to differentiated treatment strategies.

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ABSTRACT

Objective. To study the prognostic value of CT assessed recurrence patterns on survival outcomes in women with epithelial ovarian cancer.

Methods. CT scans were systematically re-evaluated on predefined anatomical sites for the presence of tumor in all 89 patients diagnosed with epithelial ovarian cancer between January 2008 and December 2013 who underwent cytoreductive surgery at our institution and developed a recurrence. A Cox proportional hazard analysis was used to test the effect of recurrence patterns on survival.

Results. The median survival time for patients grouped as predominantly intraperitoneal ($n = 62$), hematogenous ($n = 13$) or lymphatic ($n = 14$) recurrence was 25.8 (95% CI 18.4–33.2), 27.6 (95% CI 18.5–36.6) and 52.9 months (95% CI 42.1–63.7), respectively. Univariate Cox regression analysis identified the following prognostic factors: lymphatic recurrence pattern (HR 0.42, 95% CI 0.21–0.85), ascites at diagnosis (HR 2.35, 95% CI 1.46–3.79), residual tumor at initial surgery (HR 2.16, 95% CI 1.36–3.44) and FIGO stage (I–IIIB: HR 0.59, 95% CI 0.33–1.06). The median time to recurrence was 19.5 month for patients after complete debulking surgery, 13.1 months for patients with residual disease ≤ 1 cm and 8.2 months for patients with residual disease > 1 cm after surgery ($P < 0.001$). No differences in recurrence patterns between patients with complete and incomplete surgery were found.

Conclusions. Prolonged survival rates were found in ovarian cancer patients with a predominantly lymphatic recurrence compared to patients with a predominantly peritoneal or hematogenous recurrence. Completeness of surgery was associated with time to recurrence. Classification of recurrence patterns can help counsel patients on their prognosis at the time of recurrence.

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1. Background

Ovarian cancer is the leading cause of death from gynaecologic malignancies in developed countries [1,2]. Because of the late onset of symptoms, 75% of patients are diagnosed with advanced disease [3,4].

In these patients, a combination of cytoreductive surgery and chemotherapy is considered the mainstay of treatment. To improve survival, the goal of cytoreduction in surgery has shifted from optimal, with residual disease ≤ 1 cm, towards a complete debulking with no visible disease left [5]. Despite this aggressive treatment approach, the majority of patients develop recurrent disease leading to five-year survival rates of around 30% [5,6]. Risk factors for recurrence include advanced disease, completeness of debulking surgery, response to chemotherapy, tumor grade and histological tumor type [5,7,8]. Ovarian cancer can spread

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and recur locally in the intraperitoneal cavity by migration of tumor tissue through the peritoneal fluid, via the lymphatic system and/or, more rarely, metastasizes to distant organs by haematogenous spread (e.g. to the liver, spleen and lungs). Recurrent disease is usually multifocal and managed by chemotherapy and in selected cases a secondary debulking surgery is performed [9]. Several studies have previously focused on recurrence patterns in ovarian cancer, that either described a specific subgroup of patients with diffuse intraperitoneal carcinomatosis, or compared discrete with diffuse lesions rather than the location of the recurrence [10–12]. Moreover, the majority of these studies date from >10 years ago before complete debulking with no remaining visible disease became the aim of surgery [10–13]. The aim of the current study was to provide insight in CT assessed recurrence patterns of ovarian cancer and its association with survival. Furthermore, we investigated the time to recurrence and pattern of recurrence after complete, optimal and incomplete debulking surgery.

2. Methods

2.1. Patient selection

A retrospective cohort study was conducted in patients, diagnosed with ovarian cancer and treated at our institution between January 2008 and December 2013. CT scan data at diagnosis and recurrence was analyzed. The study was conducted in accordance with the rules and regulations of the institutional ethical review board, who waived the requirement of prospective informed consent for this retrospective analysis. We identified patients diagnosed consecutively with an ovarian neoplasm through the hospital administration system. Patients who underwent debulking or staging surgery and had a CT scan

available for tumor location assessment at the time of diagnosis as well as at recurrence were included in the study. Patients without recurrent disease or with a non-epithelial or borderline ovarian tumor were excluded.

2.2. Data collection

Clinical and histopathological data were collected retrospectively from medical records. A trained physician, supervised by an experienced specialized radiologist and blinded for the initial report, systematically scored predefined anatomical sites on the presence of tumor tissue on the CT scan at diagnosis and at recurrence (Supplementary Table 1). CT scan at diagnosis was defined as the first scan that detected the ovarian tumor, performed prior to chemotherapy and/or surgery and was used as date of diagnosis. The type of recurrence was grouped into three main categories according to the predominant mode of recurrence: intraperitoneal, hematogenous or lymphatic recurrence. The recurrence type was defined as the location with the largest total number of tumor deposits (i.e. total number of intraperitoneal lesions, enlarged lymph nodes or tumor deposits in distant organs). Lymph nodes measuring ≥ 1 cm in short axis diameter were deemed positive for lymphatic metastases. The results were cross-referenced with the original CT scan report and not adjusted if operative and/or histologic examination was obtained. Overall survival was defined as the interval between the date of treatment initiation to the date of death or last follow up. From patients who were lost to follow up, information from the Municipal Personal Records Database was retrieved on patient status (alive or deceased) and date of death. Time to recurrence was defined as the interval between the date of treatment initiation to the date of first CT scan after treatment with measurable disease. All CT

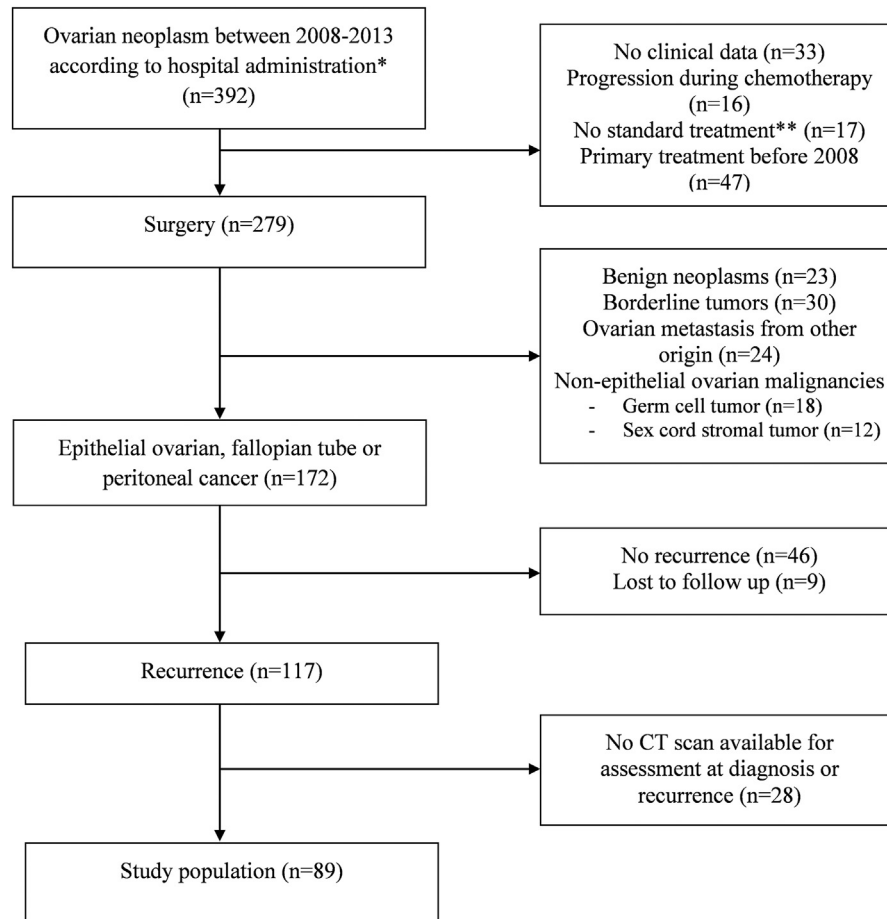


Fig. 1. Patient selection. *Identified through the diagnosis group classification system (DPC). **For example no surgical treatment or palliative resection of obstructive bowel metastases.

Table 1
Characteristics of the study population and stratified by recurrence pattern.

Parameter n (%)	Study population (n = 89)	Intraperitoneal recurrence group (n = 62)	Hematogenous recurrence group (n = 13)	Lymphatic recurrence group (n = 14)
Age at diagnosis (median, range)	66 (18–83)	66 (18–83)	66 (38–83)	63 (49–78)
Histology				
High grade serous	55 (62%)	36 (58%)	10 (77%)	9 (64%)
Mucinous	7 (8%)	7 (11%)	0 (0%)	0 (0%)
Clear-cell	4 (5%)	3 (5%)	0 (0%)	1 (7%)
Endometrioid	2 (2%)	1 (2%)	0 (0%)	1 (7%)
Low grade serous	12 (13%)	7 (11%)	2 (15%)	3 (21%)
Other	9 (10%)	8 (13%)	1 (8%)	0 (0%)
FIGO stage				
I/II	9 (10%)	5 (8%)	2 (15%)	2 (14%)
IIIA/B	9 (10%)	8 (13%)	1 (8%)	0 (0%)
IIIC/IV	71 (80%)	49 (79%)	10 (77%)	12 (86%)
Type of surgery				
Staging surgery	8 (9%)	6 (10%)	1 (8%)	1 (7%)
Primary debulking surgery	38 (43%)	24 (39%)	8 (62%)	6 (43%)
Interval debulking surgery	34 (38%)	24 (39%)	4 (31%)	6 (43%)
Other (multiple surgeries)	9 (10%)	8 (13%)	0 (0%)	1 (7%)
Size of residual disease after surgery*				
0 cm	43 (48%)	27 (44%)	5 (39%)	11 (79%)
0.1–1 cm	34 (38%)	25 (40%)	6 (46%)	3 (21%)
>1 cm	12 (14%)	10 (16%)	2 (15%)	0 (0%)
Type of chemotherapy				
Carboplatin/paclitaxel	71 (80%)	49 (79%)	11 (85%)	11 (79%)
No chemotherapy	8 (9%)	5 (8%)	1 (8%)	2 (14%)
Other	10 (11%)	14 (23%)	1 (8%)	1 (7%)
BRCA status				
Wildtype	26 (29%)	18 (29%)	5 (39%)	3 (21%)
Mutant	6 (7%)	3 (5%)	2 (15%)	1 (7%)
Not assessed	57 (64%)	41 (66%)	6 (46%)	10 (71%)
Follow up in months (median, range)**	31 (2–105)	31 (2–105)	28 (5–85)	54 (16–94)

* Assessed at the end of the surgery by the surgeon.

** From date of CT scan at diagnosis until death of disease or last follow up visit.

examinations of recurrent disease were performed on multidetector CT systems (64–256 detector rows, Philips Medical Systems, Best, the Netherlands) with intravenous contrast only, and acquired in the portal venous phase. Images through the chest and abdomen were reconstructed in the transverse, coronal and sagittal plane with 3–5 mm slice thickness.

2.3. Data analysis

Cox proportional hazard regression analyses were used to evaluate the association of the recurrence pattern, clinical and histopathological features with overall survival. In the multivariate analysis, we investigated the effect of recurrence patterns and adjusted for potential predictors from the univariate model ($P < 0.10$). Schoenfeld residuals were used to test the proportional hazard assumption [14]. Patients lost to follow up after recurrence were censored. In addition, the log-rank test was used to compare the time to recurrence for patients with complete, optimal and incomplete surgery. We used the χ^2 to test for differences in baseline characteristics between patients with an intraperitoneal, hematogenous or lymphatic recurrence pattern. All

statistical tests were two tailed with a significance level set at 0.05. All statistical analyses were performed using SPSS v.25.0 (IBM Corp., Armonk, NY, USA) and R version 3.4.1 (R Foundation for Statistical Computing).

3. Results

3.1. Patient characteristics

We identified 392 consecutive patients with an ovarian neoplasm through the hospital administration system (Fig. 1). Surgery was performed in 279 patients, of whom 172 were diagnosed with epithelial ovarian cancer. Of these 172 cases, 117 patients developed recurrent disease, of whom 28 were excluded because of missing data. Ultimately, 89 patients met all inclusion criteria and formed the study cohort. Characteristics of the study cohort are summarized in Table 1. Median age at diagnosis was 66 years (range 18–83). Most patients had been diagnosed with FIGO stage IIIC/IV disease ($n = 71$, 80%) and a histology of high grade serous ovarian cancer ($n = 55$, 62%). Complete debulking was achieved in 43 patients (48%), 34 patients (38%) had residual

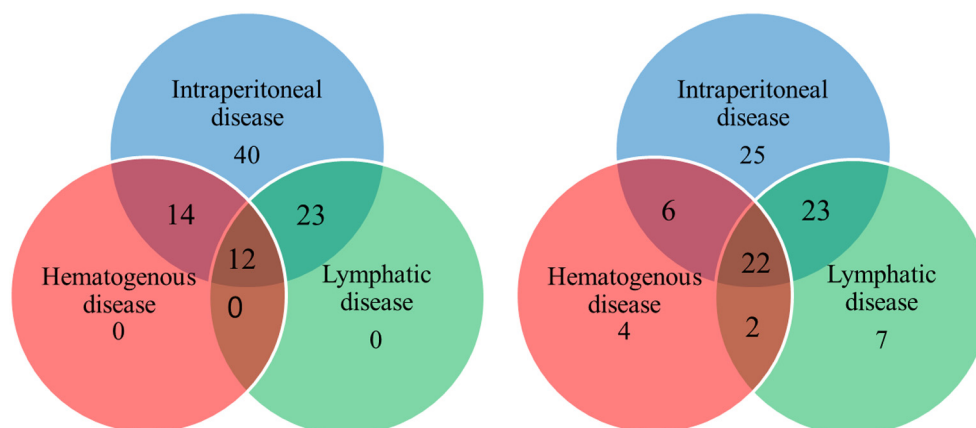


Fig. 2. Overlap in tumor locations at diagnosis (left) and recurrence (right). Numbers represent individual patients.

Table 2
Most frequent recurrence sites.*

Site of recurrence		N (%)
Intraperitoneal recurrence	Overall	76 (85)
	Mesentery	61 (69)
	Supracolic omentum	32 (36)
	Infracolic omentum	30 (34)
	Diaphragm ¹	42 (47)
	Hepatic surface	40 (45)
	Paracolic gutter	52 (58)
	Pouch of Douglas	39 (44)
	Colorectal ¹	36 (40)
	Supradiaphragmatic fat	17 (19)
	Overall	34 (38)
	Liver	27 (30)
Hematogenous spread to distant organs	Lung	8 (9)
	Spleen	8 (9)
	Brain	4 (4)
	Bone	2 (2)
	Overall	54 (61)
Lymphatic recurrence	Iliac ²	30 (34)
	Para-aortic low	23 (26)
	Para-aortic high	20 (22)
	Overall	73 (82)

* all patients had multiple sites of recurrence.

¹ Including outer surface.² Common, external and internal iliac lymph nodes.

disease up to 1 cm diameter and 12 patients (14%) had residual disease >1 cm. The presence of a germline BRCA1/2 mutation, associated with a favourable prognosis in ovarian cancer patients, was evaluated in 36% of the patients and confirmed in 19% of these patients. The median follow up was 31 months (range 2–105). At diagnosis, all patients had intraperitoneal disease and in 55% of the patients concurrent lymphatic and/or hematogenous disease was detected (Fig. 2). At recurrence, in most patients the CT scan revealed a combination of peritoneal, hematogenous and/or lymphatic disease. Intraperitoneal disease was present in 76 patients (85%). The peritoneal surface of the viscera (including mesenteries) was most frequently involved, followed by the paracolic gutters, diaphragm, hepatic surface, pouch of Douglas and the colorectal surface (Table 2). Hematogenous disease spread was detected in 34

patients (38%), most frequently in the liver, lungs and spleen. Lymphatic disease was detected in 54 patients (61%) at recurrence. Tumor locations at diagnosis and recurrence were remarkably similar (Supplementary Table 3).

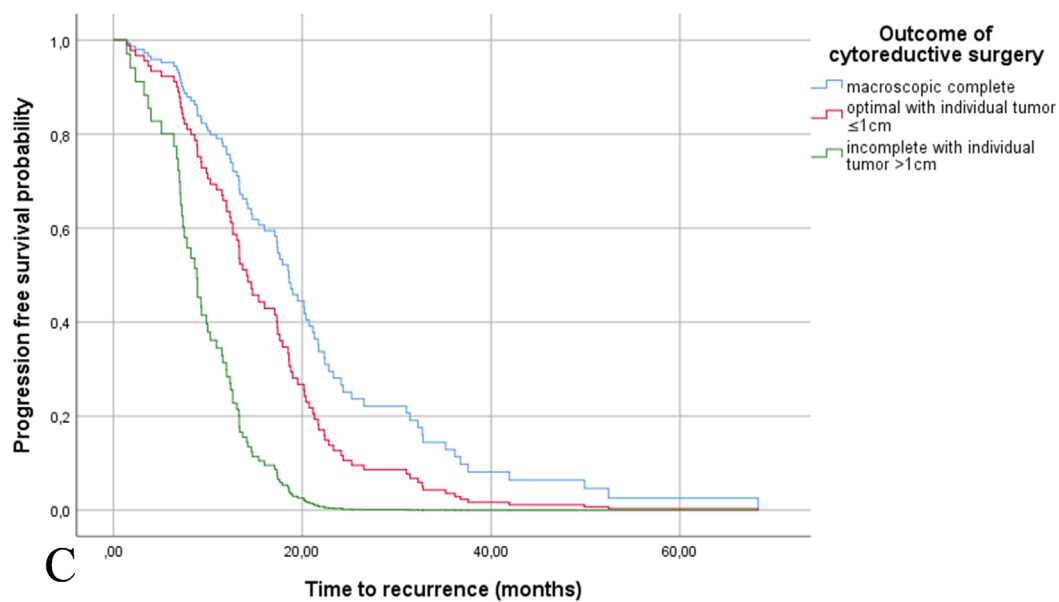
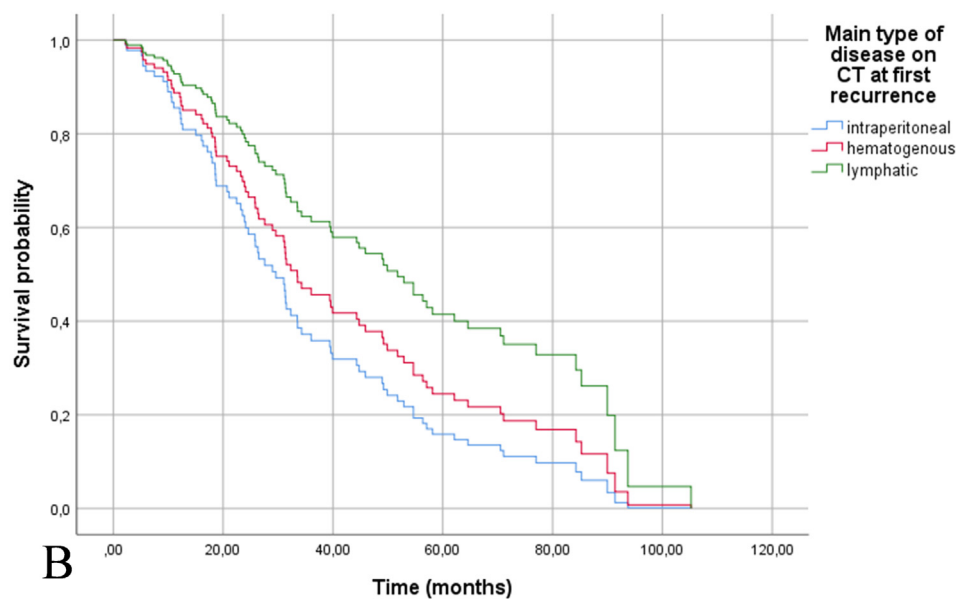
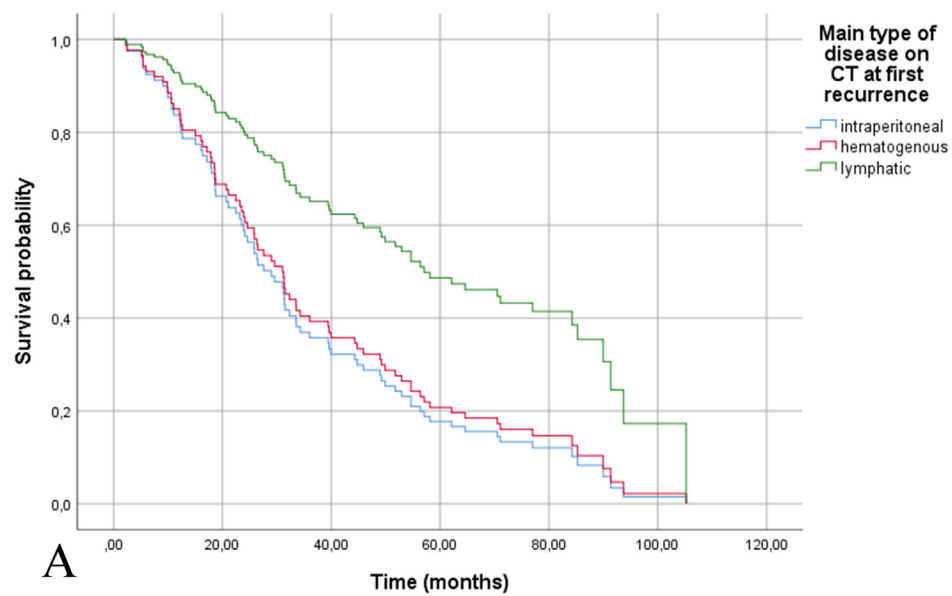
3.2. Grouped recurrence patterns and prognosis

Recurrence patterns were divided into three main categories to investigate their association with prognosis. At recurrence, 62 patients (70%) showed mainly intraperitoneal disease, 13 patients (15%) mainly hematogenous disease spread to distant organs and 14 patients (16%) mainly lymphatic disease on CT scan. There were no significant differences between baseline characteristics of patients with an intraperitoneal, hematogenous or lymphatic recurrence pattern (Table 1). At the end of follow up, 79 of 89 patients with recurrent disease had died (89%), most frequently as a result of bowel obstruction ($n = 35$). Of the deceased patients with a peritoneal recurrence, 53% ($n = 31$) died of bowel obstruction, versus 17% ($n = 2$) and 22% ($n = 2$) in the hematogenous and lymphatic recurrence group, respectively. Patients with a predominant lymphatic recurrence had a significant longer median overall survival (52.9 months, 95% CI 42.1–63.7) as compared to the intraperitoneal (25.8 months, 95% CI 18.4–33.2) and the hematogenous (27.6 months, 95% CI 18.5–36.6) recurrence groups. In addition, the five-year survival rate for patients grouped as lymphatic recurrence was 41.7% (95% CI 22.1–78.6), twice the five-year survival rate of the intraperitoneal recurrence (19.4%, 95% CI 11.6–32.2) and hematogenous (23.1%, 95% CI 8.6–62.3) recurrence groups.

According to univariate Cox regression (Table 3, Fig. 3A), patients with a lymphatic recurrence also had a better overall survival compared to patients with an intraperitoneal recurrence (HR 0.42, 95% CI 0.21–0.85). The presence of residual tumor at initial surgery (HR 2.16, 95% CI 1.36–3.44) and ascites at diagnosis (HR 2.35, 95% CI 1.46–3.79) were associated with a worse prognosis. FIGO stage I–IIIB was associated with a higher survival rate, as compared to FIGO stage IIIC/IV (HR 0.59, 95% CI 0.33–1.06). Age (per year), type of debulking surgery (primary or interval), tumor histology and grade were not significantly associated with overall survival in our cohort conditioned on the

Table 3
Univariate and multivariate Cox regression with overall survival as outcome.

Parameter	Events/no. of patients	Univariate analysis			Multivariate analysis		
		HR	95% CI	P	HR	95% CI	P
Main type of recurrence				0.03			0.15
• Intraperitoneal	58/62	1.0			1.0		
• Hematogenous	12/13	0.91	0.49–1.70	0.76	0.76	0.40–1.45	0.41
• Lymphatic	9/14	0.42	0.21–0.84	0.02	0.49	0.23–1.01	0.05
Age (per year)		1.01	0.99–1.04	0.19	1.01	0.99–1.04	0.22
Residual tumor at initial surgery							
• No visible (0 cm)	35/43	1.0			1.0		
• Residual > 0 cm	44/46	2.16	1.36–3.44	0.001	1.70	1.04–2.80	0.04
Ascites at diagnosis							
• No	29/37	1.0			1.0		
• Yes	50/52	2.35	1.46–3.79	<0.001	1.87	1.12–3.11	0.02
Type of surgery				0.78			
• Primary debulking	33/38	1.0					
• Interval debulking	32/34	1.16	0.71–1.90	0.56			
• Other	14/17	1.21	0.64–2.28	0.56			
FIGO stage							
• I/II/IIIA/B	15/18	0.59	0.33–1.06	0.08	0.80	0.42–1.53	0.51
• IIIC/IV	64/71	1.0			1.0		
Histology				0.12			
• High grade serous	47/55	1.0					
• Low grade serous	11/12	0.90	0.47–1.75	0.76			
• Non-serous	21/22	1.67	0.98–2.85	0.06			
Tumor grade				0.46			
• Not specified	5/5	1.75	0.70–4.40	0.24			
• I–II	18/20	0.95	0.56–1.62	0.85			
• III	56/64	1.0					



presence of a recurrence. Patients with a BRCA 1/2 mutation ($n = 6$) had a favourable prognosis as compared to patients with BRCA wildtype status (HR 0.19, 95% CI 0.05–0.83). At end of follow up, 4 out of the 6 patients with a BRCA mutation were alive versus 3 of 26 patients without a pathogenic BRCA variant. However, since the BRCA status was not assessed in most patients ($n = 57$), this variable was not included in the multivariate analysis. Multivariate analysis including main type of recurrence, age, residual tumor at initial surgery, ascites at diagnosis and FIGO stage retained a prognostic role for residual tumor at initial surgery and ascites (Table 3). The overall survival curves of the adjusted analysis (Fig. 3B) shows a more favourable prognosis for the lymphatic recurrence group as compared to the intraperitoneal and hematogenous recurrence groups, although this effect did just not reach statistical significance in the multivariate analysis (HR 0.49, 95% CI 0.23–1.01, $P = 0.052$).

3.3. Time to recurrence for complete and incomplete debulking

The median time to recurrence was 19.5 months (95% CI 15.9–23.1) for patients after complete debulking surgery, 13.1 months (95% CI 10.6–15.6) for patients with residual disease ≤ 1 cm and 8.2 months (95% CI 0–16.5) for patients with residual disease > 1 cm after surgery (log rank test: $P < 0.001$). Patients with residual disease > 1 cm (HR 4.52, 95% CI 2.25–9.17) as well as patients with residual disease ≤ 1 cm (HR 1.63, 95% CI 1.03–2.58) developed a recurrence within a shorter time period than patients with complete surgery (Fig. 3C). In all groups, the majority of the patients had a predominantly peritoneal recurrence: 27/43 patients (63%) with complete surgery, 25/34 patients (74%) with residual disease ≤ 1 cm and 10/12 patients (83%) with residual disease > 1 cm (Table 1).

4. Discussion

This study found that patients with a predominantly lymphatic recurrence, as diagnosed on CT imaging, had a better prognosis compared with those with a peritoneal or hematogenous recurrence. This suggests that radiological classification of the type of recurrence may help to counsel patients on their prognosis at the time of recurrence.

Previous studies have shown a relatively good prognosis for patients with isolated lymph node recurrences [15,16]. In our study, however, half of the patients in the lymphatic recurrence group had concomitant peritoneal and/or hematogenous disease. It can therefore be assumed that this survival benefit is not limited to patients with isolated lymph node recurrences alone, but may apply to a larger group of patients with predominantly lymphatic disease at recurrence.

Several possible explanations exist for the association between recurrence pattern and survival. First, most patients with ovarian cancer ultimately die of bowel obstruction caused by intraperitoneal disease, which was particularly the case in the predominantly peritoneal recurrence group (53%). Secondly, these tumors may differ in their genomic landscape, leading to differences in behavior [17–20]. Thirdly, patients with intraperitoneal recurrence may have had a higher tumor load at recurrence compared to patients with other recurrence patterns. However, we detected a combination of peritoneal, hematogenous and lymphatic disease at recurrence in most patients, indicating a substantial tumor load in the majority of patients in all subgroups.

In the multivariate analysis, residual tumor at initial surgery and the presence of ascites at diagnosis were significantly associated with worse survival in this cohort of recurrence patients. Patients with a predominantly lymphatic recurrence more frequently had a complete debulking (79%) as compared to the peritoneal (44%) and hematogenous (39%) recurrence groups. However, the survival benefit for the lymphatic

recurrence group remains valid, also when the model is adjusted for residual tumor (Fig. 3B). In addition to the variables with a univariate effect on survival, we included age (per year) in the multivariate model for its known association with survival [21]. Consistent with literature, the type of debulking surgery (primary or interval) was not found to be a prognostic factor [8].

In this study we found that within a group of patients with recurrent disease, the completeness of the initial surgery was related to the time to recurrence. The median time to recurrence was 19.5 months for patients without residual disease after surgery, 13.1 months for patients with residual disease up to 1 cm and 8.2 months for patients with residual disease of > 1 cm. This is a clinically relevant difference for a disease with an overall poor prognosis. Our results confirm the findings of a previous study reporting a median time to recurrence, progression or death of 15.5, 10.1 and 7.8 months after complete surgery, residual disease up to 1 cm, and residual disease > 1 cm, respectively [6]. However, others have reported a median time to recurrence of 13 months for both patients with residual disease up to 1 cm and > 1 cm [3]. In our study of patients in whom ovarian cancer has recurred, the completeness of initial surgery remains a prognostic factor for overall survival. These results underscore the validity of aiming for complete debulking at initial surgery. The relatively low percentage of patients with a complete debulking (48%) in this study can be explained by the study population, which consists solely of patients with recurrent disease. We did not find differences in recurrence patterns between patients having had complete or incomplete surgery. In both groups, the majority of patients developed a peritoneal recurrence.

During the study period, no significant changes in the management of ovarian cancer occurred, except for the aim of surgery in achieving a complete debulking with no visible tumor instead of a debulking with residual tumor of < 1 cm. The follow up time allowed us to determine long term survival outcomes. A limitation of this study is the strict enrolment criteria, such as inclusion of patients with a CT scan available both at diagnosis and recurrence, which resulted in a significant number of exclusions and reducing the sample size.

5. Conclusion

This study shows that radiologically assessed recurrence patterns are associated with prognosis in patients with ovarian cancer. A predominant lymphatic recurrence offers a substantially better survival compared to those patients with a predominant peritoneal or hematogenous recurrence. Our study reaffirms that the completeness of surgery (0 cm, < 1 cm and > 1 cm, respectively) is associated with the time to recurrence. No differences in recurrence patterns between patients with complete and incomplete surgery were found. We are currently working on artificial intelligence methods to automatically assess tumor locations and the pattern of recurrence. Linking the pattern of recurrence to survival outcomes could result in differentiated treatment strategies for recurrences with different prognosis.

CRedit authorship contribution statement

J.F. Roze: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing - original draft. **W.B. Veldhuis:** Conceptualization, Data curation, Investigation, Methodology, Resources, Supervision, Validation, Writing - review & editing. **J.P. Hoogendam:** Conceptualization, Formal analysis, Investigation, Methodology, Software, Visualization, Writing - original draft. **R.H.M. Verheijen:** Conceptualization, Supervision, Writing - review & editing. **R.J.P.M. Scholten:** Conceptualization, Formal analysis, Methodology, Software,

Fig. 3. Cox regression curves. A) Overall survival for type of recurrence. B) Overall survival for type of recurrence adjusted for age, residual tumor at initial surgery, ascites at diagnosis and FIGO stage. C) Time to recurrence per outcome (size of residual disease) after surgery.

Supervision, Validation, Writing - original draft. **R.P. Zweemer:** Conceptualization, Supervision, Validation, Visualization, Writing - review & editing.

Declaration of competing interest

The authors whose names are listed certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ygyno.2020.03.003>.

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