Radiology

Patterns and Prognostic Importance of Hepatic Involvement in Patients with Serous Ovarian Cancer: A Single-Institution Experience with 244 Patients[1]

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Purpose: To evaluate the frequency, patterns, and prognostic importance of metastatic hepatic involvement in serous ovarian cancer.

Materials and Methods: This institutional review board-approved retrospective study, with waived informed consent, included 244 patients with pathologically proven serous ovarian cancer (mean age ± standard deviation, 59 years ± 10.7; range 19–93 years). Electronic medical records and all available imaging studies over a median follow-up of 44 months (interquartile range [IQR], 27–70) were reviewed to identify the frequency of liver parenchymal invasion (LPI) from perihepatic peritoneal metastasis and hematogenous liver metastases. The associations and prognostic importance of LPI and hematogenous metastases were studied by using univariate and multivariate Cox proportional analysis.

Results: Eighty-four of 244 patients (34%) developed perihepatic metastases, of whom 55 (23%) developed LPI after median of 43 months (IQR, 25–63). Hematogenous hepatic metastases developed in 38 of 244 patients (16%) after median of 42 months (IQR, 26–64). At multivariate analysis, age (P = .008; hazard ratio [HR]: 1.03; 95% confidence interval [CI]: 1.009, 1.07) and suboptimal cytoreduction (P = .03; HR, 2.13; 95% CI: 1.12, 4.07) were associated with LPI. Increasing age (P = .01; HR, 1.04; 95% CI: 1.008, 1.08), high-grade tumor (P = .01; HR, 6.75; 95% CI: 1.44, 120.5), and advanced stage (P = .03; HR, 3.16; 95% CI: 1.94, 4.56) were associated with hematogenous metastases. Overall survival with and without LPI was similar (median, 80 months; IQR, 50–not reached vs 123 months; IQR, 49–279; P = .6). Hematogenous metastases were associated with significantly shorter survival at univariate (median 63 months, IQR 43–139 vs 145 months, IQR 50–not reached; P = .006) and multivariate analyses (P = .03; HR, 1.88; 95% CI: 1.14, 3.28).

Conclusion: Differentiating hematogenous metastases and LPI is important for radiologists; hematogenous metastases are associated with shorter survival, while LPI does not adversely affect survival and prognostically behaves like peritoneal disease.

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Epithelial ovarian cancer is the most common cause of gynecologic cancer death in the United States; there will be an estimated 21 290 new cases and 14 180 deaths in the United States in 2015 (1). The majority of patients present with advanced disease, with approximately of 84% of high-grade serous carcinomas manifesting as stage IIIc (2,3). The most common sites of metastatic disease in serous ovarian cancer include the liver, peritoneum, and lymph nodes (4,5). Liver involvement in patients with ovarian cancer may result from hematogenous spread or secondary to liver parenchymal invasion (LPI) from perihepatic peritoneal metastases (4,6). Distinction between perihepatic disease and hematogenous hepatic metastases is important as the International Federation of Gynecology and Obstetrics (FIGO) staging classify perihepatic capsular metastases as stage III and hematogenous hepatic metastases as stage IV (2); however, there is no clear guidance regarding LPI in the FIGO staging or in the National Comprehensive Cancer Network guidelines (2,7). This distinction is important because patients with stage IV ovarian cancer are more likely to have unresectable disease, often require neoadjuvant therapy, may have suboptimal cytoreductive surgery, and have worse survival (8–10).

The presence of LPI from a perihepatic peritoneal metastasis has been previously described; however, the exact frequency of LPI over the patient's disease course remains unknown (11,12). While there are reports suggesting that LPI may necessitate hepatic wedge resections, the precise effect of LPI on the surgical technique remains unknown (11,12). The prognostic importance, including any effect on survival, of LPI is also unknown (12,13). Therefore, we aimed to evaluate the frequency, timing, and prognostic importance of hematogenous hepatic metastases and LPI in patients with serous ovarian cancer.

Advances in Knowledge

- One-third (84 of 244, 34%) of patients with serous ovarian cancer developed hepatic involvement over the course of the disease; liver parenchymal invasion (LPI) from perihepatic peritoneal metastases developed in 55 (23%) and hematogenous hepatic metastases developed in 38 (16%).
- At multivariate analysis, increasing age (P = .008; hazard ratio [HR], 1.03; 95% confidence interval [CI]: 1.009, 1.07) and suboptimal cytoreduction (P = .03; HR, 2.13; 95% CI: 1.12, 4.07) were associated with LPI.
- Hematogenous metastases were associated with increasing age (P = .01; HR, 1.04; 95% CI: 1.008, 1.08), high-grade tumor (P = .01; HR, 6.75; 95% CI: 1.44, 120.5), and advanced stage (P = .03; HR, 3.16; 95% CI: 1.94, 4.56).
- Hematogenous metastases were associated with significantly shorter survival at multivariate analysis (P = .03; HR, 1.88; 95% CI: 1.14, 3.28); however, LPI did not adversely affect the overall survival (median, 80 months vs 123 months; P = .6).

Materials and Methods

Study Population

In this institutional review board–approved, Health Insurance Portability and Accountability Act–compliant, retrospective study performed at a tertiary cancer center, informed consent was waived. The electronic radiology database was searched from January 2012 to December 2012. A total of 308 patients with ovarian cancer were identified. Of these, 256 had pathologically proven serous ovarian cancer (both low and high grade) and 12 were excluded due to metastatic nonovarian cancer or inadequate medical records, leaving 244 in our final patient population (median age ± standard deviation, 59 years ± 10.7; median follow-up, 44 months; interquartile range [IQR], 27–70) (Fig 1). Of these, we have previously reported the metastatic spread, with a focus on thoracic metastases, in 186 patients with high-grade serous to optimize the use of cross-sectional chest imaging; however, we did not evaluate the presence or absence of LPI or the prognostic importance of the different patterns of hepatic involvement (14).

CT Technique

At our institution, abdominal computed tomographic (CT) examinations are performed by using a 64-detector CT scanner (Somatom Sensation 64; Siemens Medical Solutions, Forcheim, Germany or Toshiba Aquilion 64; Toshiba Medical Systems, Tustin, Calif). For routine abdominal CT, patients are scanned in

Implications for Patient Care

- It is important to clarify in the radiology report the type of liver involvement in patients with ovarian cancer because hematogenous liver metastases are associated with a shorter overall survival, while LPI does not adversely impact the survival.
- Liver parenchymal involvement has prognosis similar to that of peritoneal metastases; however, identifying LPI is important especially when cytoreductive surgery is contemplated.

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Abbreviations:
CI = confidence interval
IQR = interquartile range
LPI = liver parenchymal invasion

Author contributions:
Guarantors of integrity of entire study, A.C.O., N.H.R., A.B.S.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, A.C.O., S.H.T., M.B.A.; clinical studies, A.C.O., B.S., S.H.T., A.D.V.d.A., N.H.R.; experimental studies, M.B.A., A.D.V.d.A., N.H.R.; statistical analysis, A.C.O., A.B.S.; and manuscript editing, all authors

Conflicts of interest are listed at the end of this article.

Figure 1

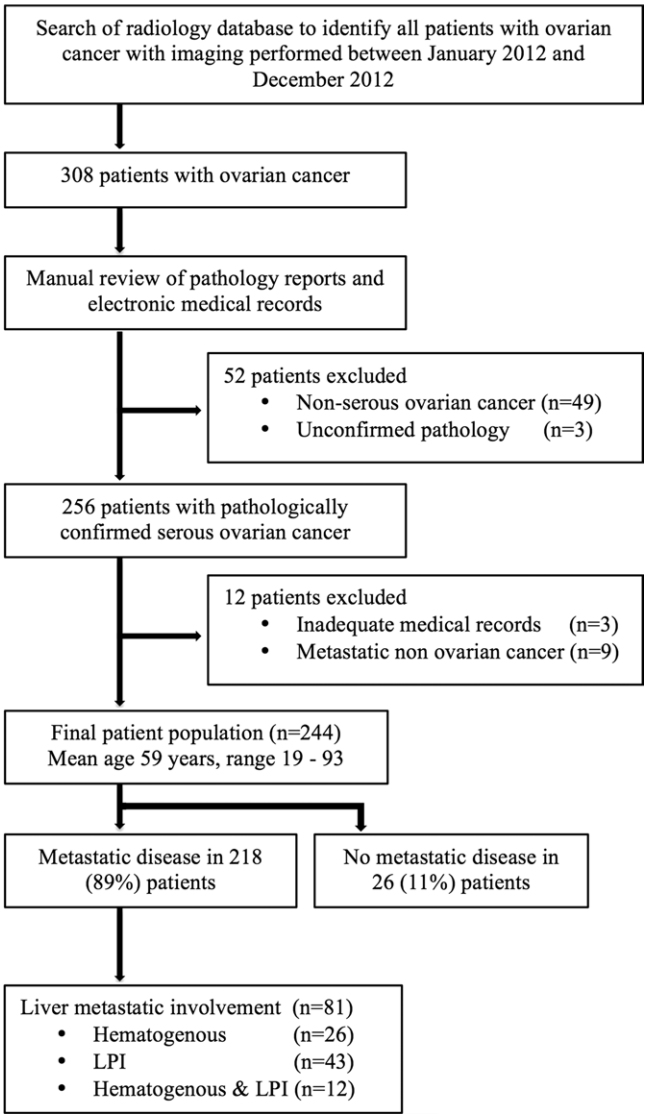


Figure 1: Flowchart detailing patient selection.

the supine position, from diaphragmatic domes to pubic symphysis (0.6–1.0-mm collimation, pitch of 0.65–1.00, 120 kVp, and 160–280 mA), and images are reconstructed in 5-mm axial plane and 3-mm coronal plane. The examinations are supplemented with oral and intravenous contrast material, unless there is a contraindication to intravenous contrast material such as a history of severe contrast agent allergy or renal dysfunction (estimated glomerular filtration rate ≤ 30). Iohexol (Omnipaque 300, 300 mg of iodine per milliliter; GE Healthcare, Barrington, Ill) is administered as intravenous contrast agent by using an automated injector (Stellant; Medrad, Warrendale, Pa) at a rate of 2–3 mL/sec; 100 mL is administered if estimated glomerular filtration rate is greater than 60 and 75 mL is administered if it is 30–60 or weight is below 55 kg.

Image Interpretation and Data Collection

We chose the year 2012 for the selection of an unbiased patient sample. Once the patients with ovarian cancer were identified, we looked at all available abdominal images from initial diagnosis onwards of the 244 patients to identify the patients with perihepatic metastases, LPI (secondary to peritoneal spread), and those with hematogenous hepatic metastases. When the initial diagnosis of ovarian cancer was prior to 2012, the follow-up and image review started at the time of original diagnosis. If the patients had their original diagnosis at an outside institution, their images were uploaded onto our picture archiving and communication system (PACS). The abdominal CT scans of these patients were reviewed in consensus by two fellowship-trained radiologists (A.O.N. with 6 years of experience and A.S. with 10 years of experience) to confirm the presence and type of hepatic involvement, including presence or absence of hematogenous metastases and LPI, as well as the dates of initial detection of liver involvement. The CT scans were reviewed on a commercially available PACS workstation (GE Centricity; GE Healthcare). Images in the axial and coronal planes were used for confirmation of hepatic involvement. Any prior studies were used to detect and follow perihepatic peritoneal metastases that developed LPI over time. The total number of CT scans that were reviewed in consensus was 3135, with a mean of 12.8 scans (range, 2–59 CT scans). Any follow-up studies were used to confirm the presence of LPI and hematogenous metastases. In addition to the original reading, to study the interobserver agreement, two additional blinded readers (S.H.T. with 9 years of experience and M.B. with 7 years of experience) independently reviewed the studies in random order to note presence or absence of LPI or hematogenous liver metastases. One of the reviewers (A.O.N.) performed the same assessment the second time to assess intraobserver agreement. This second assessment was performed in random order in a separate session, at least 3 months apart to avoid any recall bias.

LPI has been previously defined as replacement of the liver parenchyma by a perihepatic metastasis or

protrusion of a perihepatic metastasis into the liver with an ill-defined, irregular, or obliterated lesion-liver interface (11). We used the previously described criteria but we added in the following criteria to be more stringent due to lack of pathologic correlation. In addition, to distinguish between LPI and simple liver scalloping from perihepatic metastases, we further defined LPI as having depth of invasion longer than the length of contact between the perihepatic lesion and the liver surface (Figs 2–5). Any equivocal cases were reassessed on follow-up studies for confirmation. No equivocal lesions between LPI and hematogenous metastases were noted. There were three cases that were equivocal between perihepatic metastasis and LPI; these were assessed on a single follow-up study. In all three cases, LPI was definitively present on the follow-up study so the interval to LPI was calculated by using the date of the CT where the finding of LPI was first questioned. The date of diagnosis of ovarian cancer, date of development of perihepatic metastases, and the date of hematogenous hepatic metastases were documented. In addition, we also recorded presence or absence of any abdominal metastatic disease, peritoneal disease anywhere, and abdominopelvic lymphadenopathy (Fig 6). The number of perihepatic metastases with LPI and hematogenous metastases (four categories: solitary, 2–4, 5–10, > 10 metastases), as well as the size of the largest metastasis in each category, were recorded on the first CT that showed new LPI and/or new hematogenous metastases.

Finally, medical records were reviewed to collect the following information: age, size of the primary tumor, tumor grade (high grade and low grade), stage at presentation (limited vs advanced), breast cancer susceptibility gene 1 and 2 (*BRCA*) mutational status (*BRCA* mutation present or absent), and degree of cytoreduction (optimal vs suboptimal). Pathologic grade 3 tumors were considered high grade and grade 1 and 2 tumors were considered low grade. The stage of the tumor was assessed by using the International Federation of Gynecology and Obstetrics staging, where stage I is tumor confined to the ovaries, stage II the tumor involves one or both ovaries with pelvic extension below the pelvic brim, stage III involves spread outside the pelvis to the peritoneum and/or metastases to

Figure 2

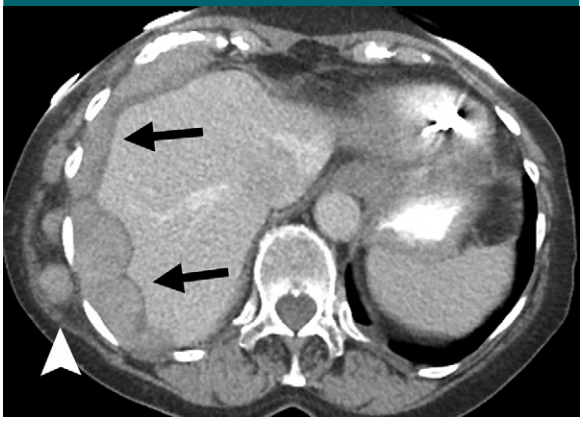
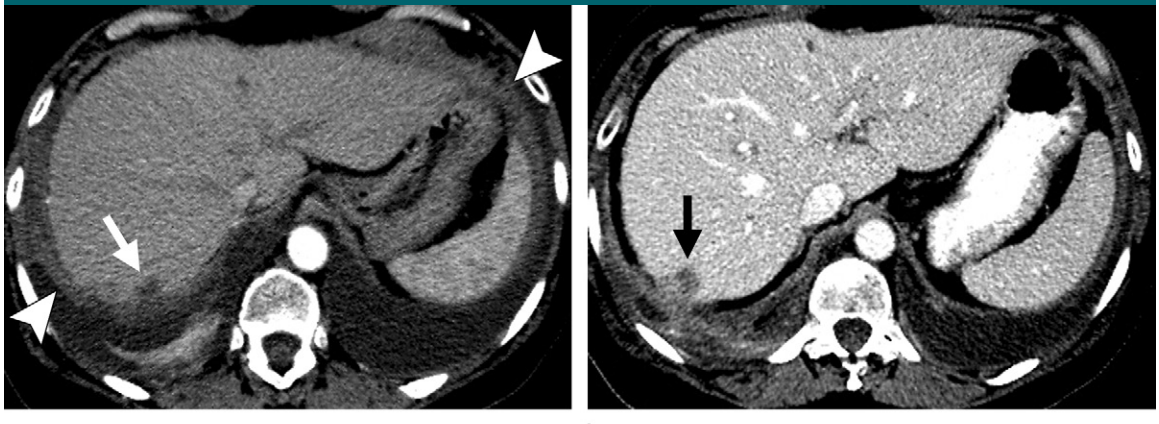


Figure 2: Axial contrast material–enhanced CT scan in a 75-year-old patient with papillary serous adenocarcinoma and extensive perihepatic scalloping without invasion (arrows). The patient also had right-sided chest wall disease (arrowhead).

Figure 3



a. **b.**

Figure 3: Axial contrast-enhanced CT scans in a 68-year-old patient with low-grade serous adenocarcinoma. **(a)** Image shows small-volume upper abdominal ascites (arrowheads) and **(b)** image obtained 2 months later. There was a perihepatic metastasis (arrow) in segment 7 that increased in size and developed an invasive component between the two axial CT scans, with agreement between all reviewers.

the retroperitoneum, and stage IV has distant metastatic disease (2).

Stage I and II tumors were considered limited stage as they are limited to the pelvis, and stage III and IV tumors were considered advanced stage as there is spread outside the pelvis. Suboptimal cytoreduction was based on the surgical reports and was defined as 1 cm or greater residual tumor after surgery as per the National Comprehensive Cancer Network guidelines where optimal cytoreduction means any residual disease is less than 1 cm (15).

Statistical Analysis

The initial consensus review was used for data analysis. The proportion of patients in perihepatic metastases with LPI and hematogenous metastases groups who have four or fewer or five or more metastases was compared by using the Fisher exact test. The size of the largest lesion in each category was compared by using the Student *t* test.

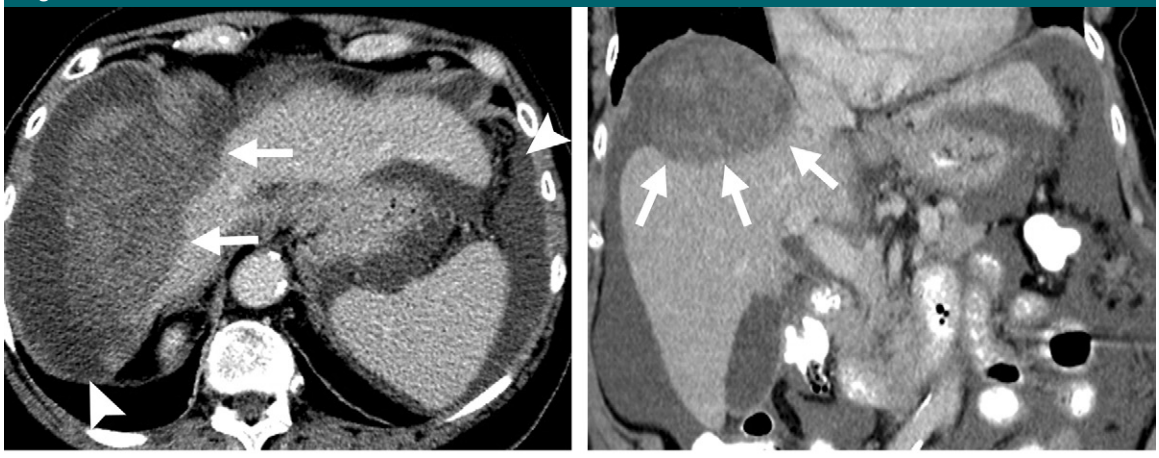
The interobserver agreement for assessment of LPI or hematogenous metastases was assessed by using Krippendorff α; Krippendorff α value of less than .667 indicates low interobserver

Figure 4

a. b.

Figure 4: **(a)** Axial and **(b)** coronal contrast-enhanced CT scans in a 57-year-old patient with serous adenocarcinoma. It may be difficult to distinguish between LPI (arrow) and hematogenous on axial image (**a**) but coronal image (**b**) helps demonstrate LPI with extension into the liver parenchyma, with agreement between all reviewers.

Figure 5



a. b.

Figure 5: **(a)** Axial and **(b)** coronal contrast-enhanced CT scans in a 74-year-old patient with papillary serous adenocarcinoma and moderate abdominal ascites (arrowheads). There is an apparent ill-defined soft tissue in the dome of the liver on axial image (**a**) suspicious for LPI (arrows). On coronal image (**b**) there is smooth, well-defined liver metastasis interface (arrows) with no visible invasive component, with agreement between all reviewers.

Figure 6

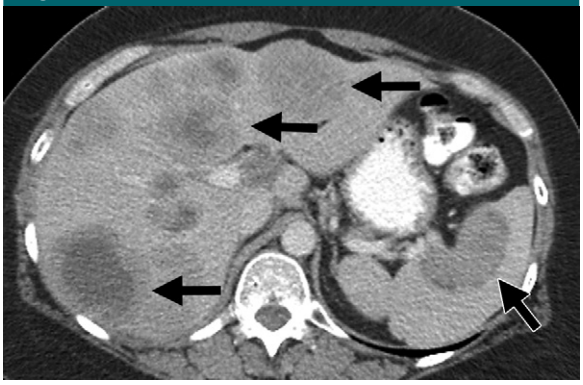


Figure 6: Axial contrast-enhanced CT scan in a 53-year-old patient with poorly differentiated serous adenocarcinoma demonstrates hematogenous hepatic and splenic metastases (arrows), with agreement between all reviewers.

agreement and that of .800 or more indicates good interobserver agreement (16,17). The intraobserver agreement was assessed by using kappa statistic; κ value < 0.2 indicates poor agreement; 0.2–0.4, fair agreement; 0.4–0.6, moderate; 0.6–0.8, good; and 0.8–1, very good agreement (18). Krippendorff alpha test was used because it can handle any number of readers in contrast to kappa, which can only be used with two readers.

The association of the following patient and primary tumor characteristics on LPI and hematogenous metastases was studied by using univariate and multivariate analyses: age, size of the primary tumor, grade (high vs low), stage at presentation (limited vs advanced), degree of cytoreduction (optimal vs suboptimal), and *BRCA* mutational status (*BRCA* mutation present or absent). Univariate analysis was performed by using Student *t* test for continuous variables (age, size) and Fisher exact test for categorical variables (grade, stage, *BRCA* status, degree of cytoreduction). Multivariate analysis was performed by using Cox proportional hazards model. For both LPI and hematogenous metastases, features that had *P* value of .2 or less were included in the multivariate analysis. *BRCA* status was not included in the multivariate analysis due to a large number of patients who did not undergo *BRCA* testing.

The impact of LPI and hematogenous metastases on survival in relation to patient age, size of the primary tumor, grade (high vs low), stage at presentation (limited vs advanced), degree of cytoreduction (optimal vs suboptimal), and *BRCA* mutational status (*BRCA* mutation present or absent) was assessed with univariate and multivariate analyses. Univariate analysis was performed by using the Log-rank test and by construction of Kaplan-Meier curves for binary variables (grade, stage, cytoreduction, *BRCA* status, LPI, and hematogenous metastases) and by using Cox regression for the continuous variables (age and size). Multivariate analysis was performed by using Cox-proportional hazards model. A two-sided *P* value less than .05 was considered to indicate a statistically significant difference. Krippendorff α value was calculated by using an online software (ReCal: *http://dfreelon.org/utils/recalfront/*); all other statistical analyses were performed by using JMP Pro 12.0.1 (SAS Institute, Cary, NC) (19).

LPI (a result of peritoneal disease spread) and hematogenous metastases did occur in some patients concurrently. These were dealt with in two separate analyses. Therefore, if they both developed in the same patient, both processes were included separately in both the statistical analyses. Time to development of both the processes was used in the respective analyses.

Results

Frequency of Liver Involvement

The final patient population characteristics are detailed in Table 1. Of the 244 patients included, 218 (89%) developed abdominal metastatic disease though only eight (3%) patients had liver as the initial metastatic site. Peritoneal carcinomatosis developed in 204 of 244 (83%) patients and abdominal lymphadenopathy developed in 121 (50%). Perihepatic peritoneal metastases were seen in 84 (34%). LPI developed in 55 (23%) patients at a median of 43 months from diagnosis (IQR, 25–63); three patients had LPI at diagnosis and three additional patients had presence of LPI on the first postoperative scan at a median of 3 months (range, 2–4 months). Hematogenous hepatic metastases developed in 38 of 244 (16%) patients at a median interval of 42 months from diagnosis (IQR, 26–64); only one had a liver metastasis at presentation. A total of 81 of 244 patients had LPI and/or hematogenous metastases (43 had LPI, 26 had hematogenous metastases, and 12 had both LPI and hematogenous metastases). Of the 12 patients with both LPI and hematogenous metastases, four developed LPI first, two developed hematogenous metastases first, and in six patients both were detected concurrently.

Of 55 patients with LPI, 24 (44%) had a solitary liver invasion, 28 (51%) had two to four lesions, two (4%) had five to 10 lesions, and one (2%) patient had more than 10 lesions. Of 38 patients with hematogenous metastases, 13 (34%) had a solitary hepatic lesion, 11 (29%) had two to four lesions, four (11%) had five to 10 lesions, and 10 (26%) patients had more than 10 lesions. Patients with LPI more frequently had fewer than five lesions (52 of 55 [95%] vs 24 of 38 [63%], P = .0001). There was no difference in the size of the largest lesion between LPI and hematogenous metastases (mean, 2.5 cm ± 1.4 vs 2.1 cm ± 1.4; P = .16).

Table 1

Clinical Characteristic of 244 Patients with Serous Ovarian Cancer

Characteristic	No.
At presentation	
Mean age (y)	59
Standard deviation	10.7
Range	19–93
Grade of serous ovarian cancer	
Low (grades 1 and 2)	35 (14)
High (grade 3)	207 (85)
Unknown	2 (1)
Mean size of primary tumor (cm)	6.5
Standard deviation	4.9
Range	2.2–40
Size unknown	32
Stage	
I	8 (3)
II	15 (6)
III	205 (84)
IV	16 (7)
BRCA mutational status	
BRCA 1	32 (13)
BRCA 2	14 (6)
BRCA negative	94 (38)
Unknown/not tested	104 (43)
At follow-up	
Abdominal metastatic disease	
Present	218 (89)
Absent	26 (11)
Peritoneal disease	
Present	204 (84)
Absent	40 (16)
Perihepatic peritoneal disease	84 (34)
Abdominal lymphadenopathy	
Present	121 (50)
Absent	123 (50)
Hepatic involvement metastases	81 (33)
LPI	43 (17)
Hematogenous	26 (11)
Hematogenous and LPI	12 (5)
Survival	
Alive	170 (70)
Dead	74 (30)

Note.—Unless otherwise indicated, data are the number of patients and data in parentheses are percentages.

Table 2

Associations of LPI with Univariate and Multivariate Logistic Regression Analyses

			P Value		
Characteristic	LPI Present	LPI Absent	Univariate Analysis	Multivariate Analysis Cox Model	Hazard Ratio*
Mean age ± SD (y)	61 ± 8.3	58 ± 11.2	.08	.008	1.03 (1.009, 1.07)†
Age range (y)	37–83	19–93	…	…	…
Cancer grade	…	…	.28	NA	…
Low (*n* = 35)	5 (5)	30 (86)	…	…	…
High (grade 3) (*n* = 207)	50 (24)	157 (76)	…	…	…
Mean size ± SD (cm)	6.5 ± 6.7	6.5 ± 4.2	.98	NA	…
Stage			.11	.29	…
Advanced (*n* = 221)	53 (24)	168 (76)	…	…	2.06 (0.58, 13.07)
Limited (*n* = 23)	2 (9)	21 (91)	…	…	Reference
Cytoreduction			.03‡	.02‡	…
Optimal (*n* = 119)	21 (18)	98 (82)	…	…	Reference
Suboptimal (*n* = 59)	19 (32)	40 (68)	…	…	2.13 (1.12, 4.07)
BRCA mutation			.19	NP	…
Present (*n* = 46)	7 (15)	39 (85)	…	…	…
Absent (*n* = 94)	24 (26)	70 (74)	…	…	…

Note.—Grade information is missing in two patients; *BRCA* status not tested in 104 patients. Unless otherwise indicated, data in parentheses are percentages. NA = not applicable, NP = not performed, SD = standard deviation.

* Data in parentheses are 95 CIs.

† Hazard ratio is per unit change (unit = 1 year).

‡ Statistically significant result.

LPI occurred more frequently in the right lobe of the liver (31 of 55, 56%), followed by both lobes simultaneously (17 of 55, 31%), and least frequently in the left lobe (seven of 55, 13%). In contrast, hematogenous metastases occurred most frequently in both lobes simultaneously (23 of 38, 60%), followed by the right lobe (14 of 38, 37%), and least often in the left lobe alone (one of 38, 3%). There was very good intraobserver agreement (κ = 0.91). The three readers had high interobserver agreement (α = .81) for assessment of LPI or hematogenous metastases. There was reader disagreement regarding nine cases (six cases with two readers reporting LPI and one reader reporting hematogenous metastases, and three cases with two readers reporting hematogenous metastases and one reader reporting LPI). Among the six patients who developed concurrent LPI and hematogenous liver metastases, the findings were concordant between the readers for five patients and in the remaining patient one reviewer recorded that LPI developed before hematogenous metastases.

Associations of Liver Involvement

Suboptimal cytoreduction was the only feature significantly associated with LPI from perihepatic metastases (*P* = .03) at univariate analysis (Table 2). At multivariate analysis with Cox regression model, LPI was associated with increasing age (*P* = .008; hazard ratio, 1.03 per year; 95% confidence interval [CI]: 1.009, 1.07) and suboptimal cytoreduction (*P* = .03; hazard ratio, 2.13; 95% CI: 1.12, 4.07).

Hematogenous metastases were associated with increasing age (*P* = .03), high-grade tumor (*P* = .02), and advanced stage (*P* = .03) at univariate analysis (Table 3). At multivariate analysis with Cox regression model, hematogenous metastases were associated with increasing age (*P* = .01; hazard ratio, 1.04 per year; 95% CI: 1.008, 1.08), high-grade tumor (*P* = .01; hazard ratio, 6.75; 95% CI: 1.44, 120.5), and advanced stage (*P* = .03; hazard ratio, 3.16; 95% CI: 1.94, 4.56).

Prognostic Impact of Hepatic Involvement

The perihepatic-free survival occurred at a median of 37 months from diagnosis (IQR, 21–60; range, 0–261). The LPI-free survival occurred at a median of 43 months from diagnosis (IQR,

Table 3

Associations of Hematogenous Hepatic Metastases with Univariate and Multivariate Logistic Regression Analyses

Characteristic	HM Present	HM Absent	*P* Value: Univariate Analysis	*P* Value: Multivariate Analysis Cox Model	Hazard Ratio*
Mean age ± SD (y)	62 ± 8.0	58 ± 11.1	.03†	.01†	1.04 (1.008, 1.08)‡
Age range (y)	49–84	19–93	…	…	…
Metastases grade			.02†	.01†	…
Low (grade 1,2) (*n* = 35)	1 (3)	34 (97)	…	…	Reference
High (grade 3) (*n* = 207)	37 (18)	170 (82)	…	…	6.75 (1.44, 120.5)
Mean size ± SD (cm)	6.7 ± 4.4	6.5 ± 5.1	.83	…	…
Stage			.03†	.007†	…
Advanced (*n* = 221)	38 (17)	183 (83)	…	…	3.16 (1.94, 4.56)
Limited (*n* = 23)	0 (0)	23 (100)	…	…	Reference
Cytoreduction			.99	…	…
Optimal (*n* = 119)	18 (15)	101 (85)	…	…	…
Suboptimal (*n* = 59)	9 (15)	50 (85)	…	…	…
BRCA mutation			.4	…	…
Present (*n* = 46)	8 (17)	38 (83)	…	…	…
Absent (*n* = 94)	12 (13)	82 (87)	…	…	…

Note.—Grade information is missing in two patients; *BRCA* status not tested in 104 patients. Unless otherwise indicated, data in parentheses are percentages. HM = hematogenous metastases, SD = standard deviation.

* Data in parentheses are 95 CIs.

† Statistically significant result.

‡ Hazard ratio is per unit change (unit = 1 year).

25–63; range, 0–185) and hematogenous metastases-free survival occurred at a median of 42 months from diagnosis (IQR, 26–64; range, 0–94). The time to LPI versus the time to hematogenous metastases was not statistically significant at univariate analysis (P = .37). The time from development of perihepatic metastases to LPI occurred at a median of 0 months (IQR, 0–9; range, 0–152). The time interval between development of perihepatic metastases and LPI was significantly shorter than the time to development of hematogenous metastases ($P < .0001$).

The overall survival of patients with LPI from perihepatic metastases was similar to those without LPI (median, 80 months; IQR, 50–75th percentile not reached vs median, 123 months; IQR, 42–279; P = .6). This remained true even when patients with perihepatic metastases without LPI, those with LPI alone, and those with both LPI and hematogenous metastases were separately analyzed (P = .69; Fig 7). Even among the patients who developed peritoneal disease (n = 204), presence or absence of LPI had no effect on survival (median, 80 months; IQR, 50–75th percentile not reached vs median, 123 months; IQR, 49–279; P = .89). On the other hand, patients with hematogenous liver metastases had significantly shorter survival compared with those without hematogenous metastases (median, 63 months; IQR, 43–139 vs median, 145 months; IQR, 50-not reached; P = .006) (Fig 8). At univariate analysis, age (P = .001), tumor size (P = .02), high-grade tumor (P = .04), advanced stage (P = .004), and presence of hematogenous liver metastases (P = .006) were associated with worse survival (Table 4). At multivariate analysis, hematogenous metastases remained independently associated with shorter survival (P = .03; hazard ratio, 1.88; 95% CI: 1.14, 3.28); however, LPI was not associated with shorter survival at univariate or multivariate analysis (Table 4).

Discussion

While it is known that LPI can develop from perihepatic peritoneal metastases in patients with ovarian cancer, the exact frequency and clinical importance of LPI is unknown. In our study, LPI occurred in 23% (55 of 244) of patients and hematogenous metastases developed in 16% (38 of 244) after a similar interval of 43 and 42 months, respectively. Increasing age and suboptimal cytoreduction were associated with LPI at multivariate analysis, while increasing age, high-grade tumor (grade 3), and advanced stage disease (stages III and IV) were associated with hematogenous metastases. Hematogenous liver metastases were associated with significantly shorter survival at multivariate analysis (P = .006). On the contrary, the overall survival of patients with or without LPI was similar (P = .6), indicating that prognostically LPI still behaves like peritoneal disease.

The development of LPI from perihepatic metastases has been described in only one previous study (11). In the study by Akin et al, 36% of patients had perihepatic metastases and 9% had LPI confirmed at histologic examination, though 94% of their patient population was newly diagnosed ovarian cancer patients imaged prior to initial surgical intervention (11). Our study shows that LPI commonly develops over the course of disease at a median of 43 months. In our patient population, perihepatic metastases developed in 34% and LPI developed in 23% (55 of 244 and 38 of 244, respectively).

Correct identification and reporting of LPI is important for two reasons. First, distinction between perihepatic peritoneal metastases with simple scalloping of the liver surface and LPI is particularly important, as focal hepatic wedge resections may be needed for the latter at surgery to achieve optimal cytoreduction. Surgical removal of all visible metastatic disease has been shown to favorably improve the prognosis, with an inverse correlation

Figure 7

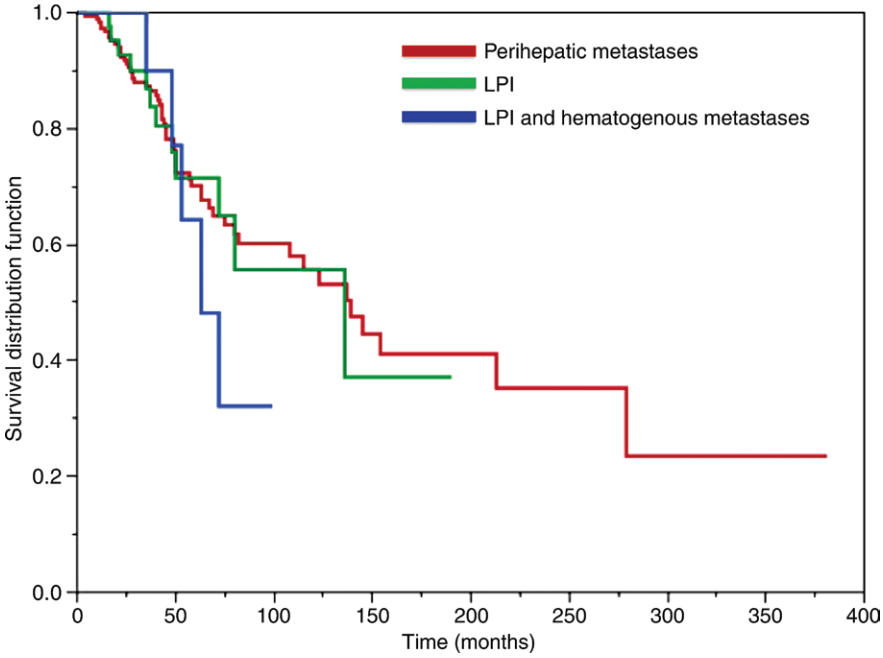


Figure 7: Kaplan Meier curve compares survival of patients with perihepatic metastases and no LPI (red), with LPI only (green), and with both LPI and hematogenous metastases (blue). Presence of LPI was associated with a similar survival to perihepatic metastases alone ($P = .69$).

Figure 8

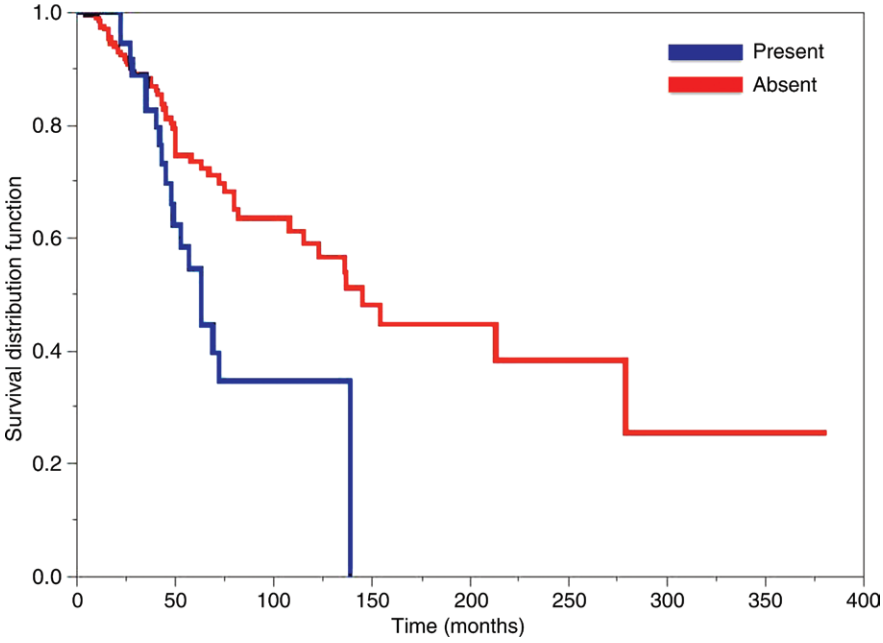


Figure 8: Kaplan Meier curve compares survival of patients with (blue line) hematogenous hepatic metastases and patients without (red line). Presence of hematogenous hepatic metastases was associated with a shorter overall survival ($P = .006$).

between the volume of disease remaining after cytoreductive surgery and survival (9,13,20,21). Akin et al describe LPI in six patients, and 11 patients at time of surgery had either wedge resection or partial hepatectomy (11). Another study also evaluated the need for hepatobiliary consultation in dealing with LPI at the time of debulking surgery and postulated that liver invasion of perihepatic metastases in multiple locations may preclude resection (12). At our institution, patients with LPI undergo hepatic wedge resection (based on informal communication with our gynecologic oncology surgeons). In our study, we focused on the follow up of ovarian cancer patients over time, and we found that the perihepatic metastases and LPI had no difference in overall survival; therefore, LPI could be treated as stage III disease. The accuracy of CT in the detection of peritoneal disease has been confirmed in prior studies (22,23). It may be challenging to distinguish between LPI and hematogenous metastases on axial images alone but reviewing prior studies and multiplanar imaging is helpful, in particular coronal imaging. Akin et al assessed the sensitivity in detecting LPI at CT, which was 100% for an experienced oncology radiologist and 50% for a radiologist with less oncology imaging experience (11). Second, accurate identification of LPI and distinction between LPI and hematogenous metastases is also important because these two are associated with a very different prognosis. While hematogenous metastases can also be treated with wedge resection or partial hepatectomy as part of cytoreductive surgery (24–28), these are associated with a worse prognosis and may need either primary or neoadjuvant chemotherapy prior to surgery to downstage the disease (3). The same is true when hematogenous metastases occur later in the course of disease. Detection of hematogenous metastases indicates a shorter overall survival even after primary treatment, while LPI does not adversely affect the survival and prognostically behaves like peritoneal disease. Given this difference in the prognosis of hematogenous metastases and LPI, it is

Table 4

Effect of Various Factors on the Survival Using Cox-Proportional Hazard Model

Characteristic	*P* Value Univariate	Cox Model for LPI		Cox Model for Hematogenous Metastases	
		P Value	Hazard Ratio*	*P* Value	Hazard Ratio*
Age†	.0001‡	.001‡	1.04 (1.02, 1.07)	.002‡	1.04 (1.02, 1.07)
Tumor size†	.02‡	.10	0.95 (0.09, 1.44)	.07	0.95 (0.89, 1.01)
High grade	.04‡	.79	1.13 (0.51, 2.99)	.93	0.96 (0.43, 2.59)
Advanced stage	.004‡	.01‡	6.08 (1.32, 107.8)	.03‡	5.16 (1.11, 91.8)
Suboptimal cytoreduction	.11	…	…	…	…
BRCA mutation present	.25	…	…	…	…
LPI	.61	.56	1.19 (0.67, 2.24)	…	…
Hematogenous liver metastases	.006‡	…	…	.03‡	1.88 (1.14, 3.28)

* Data in parentheses are 95% CIs.

† Odds ratios are per unit change (unit for age = 1 year; unit for size = 1 cm).

‡ Statistically significant result.

important for the radiologist to distinguish between these two patterns of hepatic involvement; in this study, there was good interobserver agreement and very good intraobserver agreement in differentiating LPI from hematogenous metastasis. It is important that LPI should be clearly stated in the radiology report and should not simply be labeled as "hepatic metastases," a term that is often perceived by the referring clinicians as hematogenous spread.

To our knowledge, the clinical factors associated with LPI in ovarian cancer have also not been previously studied. Both LPI and hematogenous metastases were associated with increasing age at multivariate analysis, consistent with prior studies where more advanced disease was seen in older patients (3,29). Suboptimal cytoreduction was also associated with LPI, which is intuitive because an incomplete surgical resection would make the patient more prone to peritoneal recurrence, a precursor for LPI (4,30). This is further substantiated by the fact that there was no relationship between suboptimal cytoreduction and hematogenous metastatic disease, which was associated with higher tumor grades and advance stage disease.

One of the limitations of this study includes its retrospective design. We did not use pathologic confirmation as the reference standard for LPI. A limitation of our study is that the four reviewers report clinical studies with the potential for recall bias. However, the scans reviewed were obtained over several years, and many were obtained before the readers worked in this institution. Furthermore, there are many radiologists in our group reading clinical studies, so not all cases were initially interpreted clinically by our reviewers. Although the second set of readers assessed the cases independently, they all work in the same department on a daily basis, which could potentially contribute to the high interobserver agreement. Another limitation is that data from the initial consensus review were used for analysis. In our study, the overall survival was not statistically significant between patients with and those without LPI, although the median overall survival was 80 months compared with 139 months, respectively. A larger study may have demonstrated a statistical difference. Finally, survival comparisons are difficult given the many different treatment algorithms utilized, some of which may have been influenced by imaging findings.

In conclusion, liver involvement in the form of LPI and hematogenous metastases is seen in a substantial proportion of patients with metastatic ovarian cancer. LPI is associated with increasing age and suboptimal cytoreduction, while hematogenous metastases are associated with increasing age, high-grade tumor, and advanced stage disease (stages III and IV). Hematogenous liver metastases and LPI are prognostically different; hematogenous metastases indicate shorter overall survival, while LPI behaves similar to peritoneal metastases without adversely affecting the survival. However, LPI should be carefully documented, especially prior to cytoreductive surgery, because it can potentially impact the surgical technique.

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