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Clinical and pathological features of isolated pulmonary and liver recurrences in endometrial cancer

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Abstract

Objective: To present the clinic-pathological features of endometrial cancer (EC) patients with isolated liver or lung metastases and to compare the survival differences after diagnosis of recurrent disease.
Material and Methods: The clinical and histopathological data of the patients who were treated with a diagnosis of epithelial EC between January 1993 and May 2013 at Etlik Zubeyde Hanim Teaching and Research Hospital were retrospectively reviewed. Patients with isolated recurrence in liver (ILR) or lung (IPR) were included in the analysis.
Results: The clinical data of 162 patients with recurrent EC were available. Of these, 21 had IPR and 9 had ILR. Patients with ILR presented with more advanced stage, and omental and adnexal involvement was more common compared to patients with IPR. On the other hand, patients with IPR had higher grade disease. Fifty-seven percent of patients with IPR had grade 3 compared to 11% of grade 3 disease in ILR (p=0.02). The median time to recurrence (TTR) was 18 months (range 1-54) in the whole study population. While the median TTR of patients with IPR was 19 months, the median TTR of patients with ILR was 16 months (p=0.204). Both study groups have similar survival. The 1-year post-recurrence survival of IPR and ILR was 66% and 56% (p=0.129), respectively
Conclusion: Although, isolated liver and lung metastases are the result of haematogenous spread in EC, clinic-pathological features of these two recurrence patterns significantly differ. Clinicians should try to categorize these patients separately to better understand the prognostic outcomes.

Key words: Endometrial cancer, Lung metastasis, liver metastasis, haematogenous spread

Introduction

Endometrial cancer (EC) is the sixth most common cancer of women with 320.000 new cases worldwide each year (1). Although patients with EC usually present with early stage disease and have excellent long term survival, 13% of patients recur after initial treatment (2, 3). The failure of primary treatment in patients with poor prognostic factors has been reported as high as 60–70% (4). In high risk EC patients more than 70% of recurrences are complicated with extra-pelvic metastases (5, 6). Recent data suggest that death from EC is mostly due to liver and lung metastases, and this pattern of disease seems similar between low and high-risk histology for patients who died of their disease (7).

Lung is a common host for tumor recurrences and pulmonary metastases result from hematologic spread of EC. Pulmonary involvement is reported in 1.9% to 9% of the first recurrences in EC (8-12). Data on predicting factors for pulmonary recurrences are sparse. Stage IV disease and deep myometrial invasion were found to be associated with pulmonary recurrence(10).

Earlier reports revealed that pulmonary recurrences were related with adverse prognosis which was evident that 75% of patients succumb to disease in the first year of recurrence (9). On the other hand, a recent paper demonstrated that patients with low grade tumors and isolated lung metastases smaller than 2 cm may survive up to 98 months after diagnosis of recurrence (11).

The liver is a common site of metastasis for solid tumors. However the role of liver recurrence from EC is less well defined. Although, most of the previous studies presented liver metastases with other systemic metastatic disease, liver metastasis was also reported to be an independent prognostic factor for diminished survival (13). Both liver and lung metastases were thought to be the result of haematogenous spread; however it is not clear whether the clinical outcomes of these two recurrence sites correspond. In this study, we presented the clinicopathological features of EC patients with isolated liver or lung metastases and compared the survival differences after diagnosis of recurrent disease.

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Material and Methods

The clinical and histopathological data of the patients who were treated with a diagnosis of epithelial EC between January 1993 and May 2013 at Etlik Zubeyde Hanim Teaching and Research Hospital were retrospectively reviewed. Patients with isolated recurrence in liver or lung were included in the analysis. Patients with sarcomatous component in the final pathology were excluded. The revised International Federation of Gynecology and Obstetrics (FIGO) staging system was used to define the surgical stage of the patients (14). The study was approved by the local ethical committee.

Patients with recurrent disease within one month after initial surgery or completion of adjuvant therapy were accepted to have progressive disease. Patients with no evidence of disease at one month follow-up after initial surgery or completion of adjuvant therapy and that recur were included. The period from surgery to recurrence was defined as time to recurrence (TTR) and the period from recurrence to death or last visit was defined as post-recurrence survival (PRS). The period from the surgery to death or last visit defined as follow-up time.

Physical examination and radiological imaging studies were used to diagnose recurrent disease. Recurrent disease limited to liver was defined as isolated liver recurrence (ILR) and the disease limited to lung was defined as isolated pulmonary recurrence (IPR). Response to recurrence treatment was evaluated using WHO criteria (15). According to the assessment made in the first month after treatment, we defined clinical response as following: (a) complete clinical response; disappearance of the macroscopic tumor, (b) partial clinical response; shrinkage over %50 in the macroscopic tumor, (c) stable disease; macroscopic tumor shrinkage less than 50% or not less than 25% growth, (d) progressive disease; more than 25% growth in the macroscopic tumor or macroscopic appearance of new tumor foci.

Patients with complete clinical response were followed every 3 months in the first 2 years, then every 6 months for the following 3 years and then annually. Follow up routine included pelvic examination, abdominopelvic ultrasonography, complete blood count and blood chemistry. Chest X-ray was utilized yearly unless there is a clinical suspicion. Thoracic and/or abdominal computerized tomography was used when needed. Ca-125 level were utilized in the follow-up, even though they weren't used routinely.

Statistical analysis: Statistical analyses were performed using SPSS (SPSS Inc, Chicago IL, USA) version 17.0. The cut-off for statistical significance was set at $p < 0.05$. PRS estimates were determined by using the Kaplan-Meier method. Survival curves were compared using the log-rank test. The factors determining PRS after recurrence couldn't be evaluated in multivariate analysis due to the small population.

Results

The clinical data of 162 patients with recurrent EC were available. Of these, 21 had IPR and 9 had ILR. Median age at diagnosis was 60.5 (range; 40-77) years. The mean preoperative CA-125 level of patients were 80.3 IU/ml and the mean tumor size at first diagnosis was 54.4 (±30.8) mm. The most prominent histology was endometrioid EC in 24 (80%) patients and 17 (56.6%) patients had disease outside the uterus. Clinical and pathological characteristics of the study group were summarized in Table 1.

While 27 patients were left with no residual disease after initial surgery, three patients had suboptimal surgery. Of these, one had residual tumor volume of less than 1 cm and two had residual tumor volume of more than 1 cm. All of the three patients with suboptimal surgery recurred in the liver.

Four patients with IPR and one patient with ILR were treated with salvage surgery. Of these, surgically treated ILR and one of the four patients with IPR were left with no residual disease at the end of the procedures. Other two patients with IPR had suboptimal surgical procedures. Operation note of one the patient with IPR could not be reached. Palliative treatment was offered to five patients with recurrence, and all but one opted for palliation. Rest of the patients was treated with systemic chemotherapy and/or radiotherapy.

Table 2 demonstrates the comparison of surgico-pathological findings between patients with IPR and ILR. Patients with ILR presented with more advanced stage, and omental and adnexal involvement was more common compared to patients with IPR. On the other hand, patients with IPR had higher grade disease. Fifty-seven percent of patients with IPR had grade 3 compared to 11% of grade 3 disease in ILR ($p=0.02$).

Lymph node dissection in the first surgery was more common in patients with IPR than ILR ($p=0.005$). Lymph node metastasis was more prominent in patients with ILR compared to patients with IPR, however this finding was not statistically significant ($p=0.088$).

The mean age of patients with IPR was 62.5 years and the mean age of patients with ILR was 55.7 years (p=0.054) (Table 3). Both patient groups were similar regarding preoperative serum CA-125 levels, mean tumor size, tumor histology, and depth of myometrial invasion, lympho-vascular space invasion, cervical involvement, positive peritoneal cytology, lymph node counts and serum CA-125 levels at recurrence (Table 2 and 3). The median TTR was 18 months (range 1-54) in the whole study population. While the median TTR of patients with IPR was 19 months (range, 1-54), the median TTR of patients with ILR was 16 months (range, 4-36) (p=0.204). Both study groups have similar survival. The 1-year PRS of IPR and ILR was 66% and 56% (p=0.129), respectively (Figure 1).

Table 1. Clinical, surgical and pathological characteristics of patients

Characteristics		n / Mean	% / Median (range)
Age at initial diagnosis		60.4	60.5 (40-77)
Disease free interval (month)		21.3	18 (1-54)
CA 125 level at initial diagnosis (IU/ml)		80.3	29 (1-430)
Tumor size at initial diagnosis (mm)		54.5	50 (15-100)
FIGO 2009 stage	IA	2	6.7
	IB	11	36.7
	II	1	3.3
	IIIA	2	6.7
	IIIC1	3	10
	IIIC2	4	13.3
	IVA	1	3.3
	IVB	6	20
Tumor type	Endometrioid	24	80
	Serous	2	6.7
	Clear Cell	3	10
	Mixed	1	3.3
FIGO grade	1	4	13.3
	2	13	43.3
	3	13	43.3
Depth of myometrial invasion	< ½	4	13.3
	≥ ½ [1]	19	63.3
	Serosal invasion	7	23.3
Lymphovascular space invasion	Negative	11	36.7
	Positive	13	43.3
	Not reported	6	20
Cervical invasion	Negative	21	70
	Stromal	8	26.7
	Not reported	1	3.3
Peritoneal cytology	Negative	24	80
	Positive	4	13.3
	Not reported	2	6.7
Adnexal metastasis	Negative	22	73.3
	Positive	8	26.7
Omental metastasis	Negative	21	70
	Positive	5	16.7
	Not reported	4	13.3
Lymphadenectomy at initial surgery	Not performed	3	10
	Performed	27	90
Number of harvested lymph nodes		45.2	45 (4-93)
Lymph node metastasis	Negative	20	66.7
	Isolated pelvic	5	16.7
	Isolated paraaortic	3	10
	Pelvic & paraaortic	2	6.7
Adjuvant therapy	Not performed	1	3.3
	Performed	29	96.7
Type of adjuvant therapy	Radiotherapy	20	69
	Chemotherapy	7	24.1
	Sandwich therapy [2]	1	3.4
	Concomitant chemoradiotherapy	1	3.4

[1]: Except for uterine serosal invasion,

[2]: Chemotherapy followed by radiotherapy or radiotherapy followed by chemotherapy or sandwich therapy (*3 cycles paclitaxel+carboplatin followed by radiotherapy followed by 3 cycles paclitaxel+carboplatin*)

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Table 2. Comparison of surgical and pathological factors between patients with isolated pulmonary recurrence and isolated liver recurrence.

Surgico-pathological features (%)	Recurrence site		*p value*
	Isolated pulmonary recurrence	Isolated liver recurrence	
FIGO stage III&IV disease	44	89	0.027
Non-endometrioid tumor type	24	11	0.426
Performed lymphadenectomy	100	67	0.005
Metastatic lymph node	29	67	0.088
FIGO grade 3	57	11	0.02
Depth of myometrial invasion ≥ 1/2	81	100	0.16
Positive LVSI	47	71	0.276
Positive cervical invasion	19	50	0.096
Positive peritoneal cytology	10	29	0.212
Adnexal involvement	14	56	0.019
Omental metastasis	10	50	0.029

Table 3. Recurrence site and clinical, surgical and pathological factors

Characteristic	Recurrence site								p
	Isolated pulmonary recurrence				Isolated liver recurrence				
	Mean	Med.	Min.	Max.	Mean	Med.	Min.	Max.	
Age	62.5	61	52	77	55.7	54	40	77	0.054
Removed lymph node number	46.1	48	4	93	41.8	45	8	65	0.759
Tumor size (mm)	53.5	50	15	100	57.5	52.5	25	100	0.832
Preoperative CA125 level (IU/ml)	79.1	28.5	1	430	83.2	29	11	195	0.946
CA125 level at recurrence (IU/ml)	291.4	23	1	3150	220	120	15	650	0.812
Time to recurrence (month)	23.5	19	1	54	16.1	16	4	36	0.204
Follow-up time (month)	39	36	6	108	27.4	23	6	67	0.215

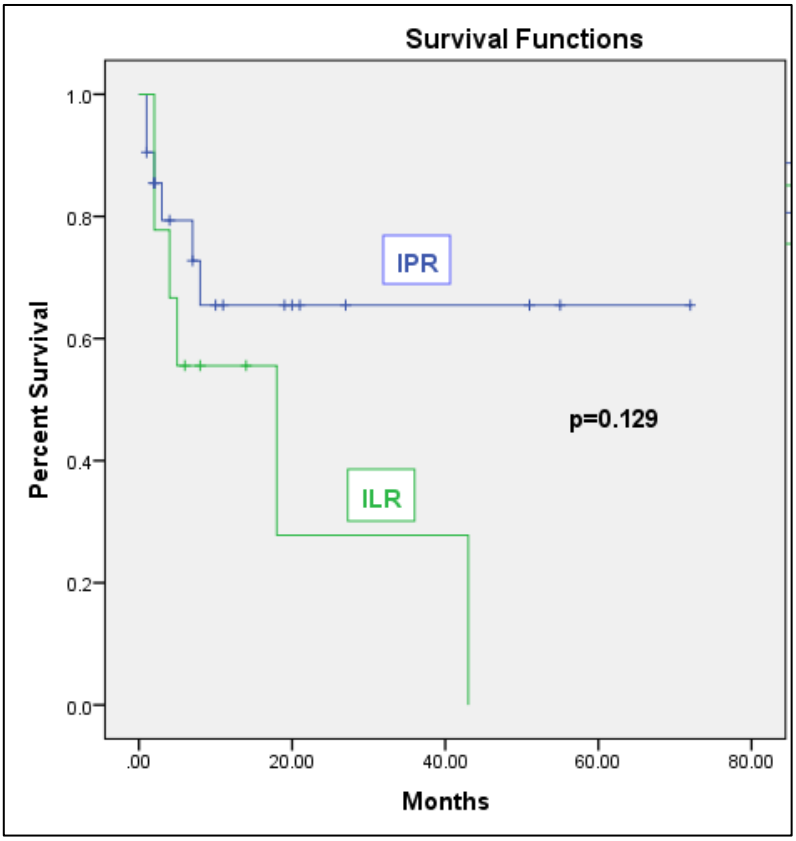

Figure 1. Post-recurrence survival of patients with isolated lung (ILR) and liver (IPR) recurrences.

Discussion

In this retrospective chart review, we presented the outcomes of 30 recurrent EC cases with isolated metastases in liver or lung. Common characteristics of our study group were deep myometrial invasion of the primary tumor (63.3%), advanced disease at first diagnosis (53.3%), and a combination of various high risk features which necessitated an adjuvant treatment modality in 96.7% of the patients. Isolated metastatic disease in lung (IPR) was more common than metastatic liver disease. When we compared the surgicopathological features of IPR and ILR, we found that patients with ILR had statistically significant more advanced disease and omental metastases than patients with IPR. These results show that these two hematogenous spread patterns may be associated with distinct surgicopathological risk factors. Although, survival outcomes of both groups were similarly poor which result into death of more than 40% of the patients at the end of the first year of recurrence, ILR had a statistically non-significant worse prognosis than IPR (p=0.129).

EC usually disseminates with the lymphatic route and hematogenous dissemination is less common. The risk of distant metastases ranges between 4% and 12% and isolated distant failure risk is 4-6% (16). Hematogenous spread in EC include metastases to lungs, liver, bones, brain, spleen, pleura, adrenals and brain (17). Of these, pulmonary metastasis is the most common one which is observed in 2.3% to 8.3% of the cases (18). Previous studies have shown that risk factors for the development of pulmonary metastases in EC were older age, advanced stage disease or higher tumor grade, deep myometrial invasion and involvement of paraaortic lymph nodes or vagina (18). These findings were similar to our results in the current study. Our study group was mainly consisted of patients with stage III or IV and IPR group had higher grade disease than ILR group. The mean time IPR in our study was 23.5 months which represents a figure lying in the lower end of previously reported range 27 to 45.5 months (18). 1-year PRS of IPR group in our study was 66% which was higher than the literature. Although, we could not perform a subgroup analysis to reveal the prognostic factors related with survival, this somewhat favorable survival may be the result of selection of isolated lung recurrences in our study. Most of the studies in the literature which reported poor survival in patients with lung recurrences include patients with multiple distant metastases (9). Optimal management of patients with pulmonary involvement is not clear. While, the fundamental surgical oncology doctrine supports resection of solitary nodules and oligo metastatic disease, patients with multiple, bilateral nodules and/or other systemic disease should be encouraged for participation in clinical trials.

Solid tumors frequently metastasize to the liver. Although, autopsy series have shown that 50% of patients who died of EC will demonstrate hepatic involvement (19), data on the treatment of metastatic disease of EC origin is sparse. In our study group only one patient with ILR were treated with surgery while other patients received systemic chemotherapy. This finding may reflect the effect of historical reports against the surgical treatment of non-colorectal liver metastases which have shown no 5-year survivors after hepatic resection (20). However, recent data revealed favorable outcomes for hepatic resections particularly in the case of isolated liver metastases (21). In the absence of well-structured guidelines, Knowles et al. (21) suggested to use the criteria used for the resection of colorectal metastases and to refer these patients to special hepatobiliary units.

This study has several drawbacks including small sample size and retrospective study design. Long term follow-up in a single tertiary center with major experience is the strong aspect.

Conclusion

In conclusion, both liver and lung metastases were thought to be the result of hematogenous spread, however it is not clear whether the clinical outcomes of these two recurrence sites correspond. Further studies are needed to elucidate the risk factors of IPR and ILR and the prognostic factors related with the treatment. .

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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