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Secondary Cytoreductive Surgery for Patients with Isolated Lymph Node Recurrence of Gynecologic Cancer

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Abstract

Objective: Solitary lymph node recurrence means that recurrent tumor is detected only in lymph nodes with no evidence of recurrence at other sites. Secondary Cytoreductive Surgery (SCS) for Isolated Lymph Node Recurrence (ILNR) is an acceptable modality, but the survival benefit of surgery remains controversial. The aim of this study was to evaluate the survival outcome of SCS for ILNR in gynecologic cancer.

Methods: We reviewed the medical records of 18 patients with solitary lymph node recurrence between January 2009 and September 2014 at Seoul St. Mary's Hospital. Demographic, diagnostic, operative, pathologic, and follow-up data were retrospectively reviewed. Survival outcome was calculated using the Kaplan-Meier method.

Results: The mean age at the time of initial diagnosis of gynecologic malignancy was 49.8±6.7 (40-67) years. Two patients (11.1%) were diagnosed with vulvar cancer, 4 patients (22.2%) were diagnosed with cervical cancer, 1 patient (5.6%) was diagnosed with endometrial cancer, and 11 patients (61.1%) were diagnosed with ovarian cancer. The Disease Free Interval (DFI) was 41.3±34.0 (7.0-119.0) months. Eight patients underwent SCS. The mean time of follow up after recurrence was 23.2±17.0 (3.0-61.0) months. The overall survival time of ILNR patients was 49.0 months. The overall survival time of patients who underwent SCS was 34.8 months and that of patients who did not was 53.8 months (P=0.285).

Conclusion: In selected patients with ILNR, SCS can be an effective treatment with low perioperative morbidity. More data are needed to understand the roll of SCS in ILNR patients.

Keywords: Cytoreductive surgery; Lymph node; Recurrence

List of Abbreviation

SCS: Secondary Cytoreductive Surgery; ILNR: Isolated Lymph Node Recurrence; CT: Computed Tomography; PET: Positron Emission Tomography; LN: Lymph Node; CCRT: Concurrent Chemoradiation Therapy; CTx: Chemotherapy; ERT: External Radiation Therapy; RT: Radiation Therapy; BSO: Bilateral Salpingo-Oophorectomy; TO: Total Omentectomy; TAH: Total Abdominal Hysterectomy; RH: Radical Hysterectomy; NED: Negative for Evidence of Disease; EBL: Estimated Blood Loss.

Introduction

Combination chemotherapy, radiation therapy, surgery, hormonal therapy, or immunotherapy can be used as a second-line treatment in recurrent gynecologic cancer; however, the efficacy of the second-line treatment is very limited. The relapse rates of gynecologic cancer differ according to initial stage, tumor grade, and histologic type. In general, recurrence can occur in 6.8%-47% of all cervical cancer patients, 25%-75% of all ovarian cancer patients, and 21%-50% of all endometrial cancer patients [1-4]. Treatment efficacy is associated with initial stage, patient performance, histologic type, extent of the relapse, and duration of disease-free period [5-8].

Secondary Cytoreductive Surgery (SCS) is usually performed in cases that show recurrence after complete remission with primary treatment. The goals of SCS are to prolong survival and to relieve cancer-related symptoms [9]. Numerous studies have reported the efficacy of SCS in prolonging survival in patients with recurrent ovarian cancer, but few have reported the efficacy of SCS in patients with recurrences of other malignancies. Several selection criteria have been suggested for favorable outcome in ovarian cancer: (1) disease-free duration of at least 6 months after completion of initial chemotherapy, (2) small tumor size, and (3) good performance [10,11].

The most common recurrence site is the pelvis, followed by the peritoneum, pleural effusion, liver, lung, lymph nodes, and central nervous system [12]. Lymph node recurrences are common in gynecologic malignancies; but it sometimes develops at other sites within or outside the abdomen. Isolated Lymph Node Recurrence (ILNR) is rare, and studies on ILNR are limited [5]. The incidences of ILNR are reported to be 1.1%-4.2% in ovarian cancer, 2.1% in cervical cancer, and 1.6% in endometrial cancer [1,2,13,14]. There is controversy concerning the treatment of ILNR. Some investigators have reported that radical lymph node dissection is more effective in lengthening progression-free interval than resection of recurrent lymph nodes only, but the overall survival is not significantly different between the 2 dissection methods in ovarian cancer patients [15]. However, Uzan, et al. [8] reported that adjuvant therapy after dissection of recurrent lymph nodes is a favorable prognostic factor for epithelial ovarian cancer. In this study, we reviewed patients with ILNR in gynecologic cancer and evaluated the survival outcome.

Materials and Methods

Between January 2009 and September 2014, a total of 18 patients were diagnosed with ILNR at Seoul St. Mary's Hospital: 2 patients had vulvar cancer, 4 patients had cervical cancer, 1 patient had endometrial cancer and 11 patients had ovarian cancer. ILNR defined as recurrence restricted to lymph nodes with no evidence of recurrence in other organs on Computed Tomography (CT) or Positron Emission Tomography (PET) (Table 1).

Characteristics	n	%
Site		
Vulvar cancer	2	11.1
Cervical cancer	4	22.2
Endometrial cancer	1	5.6
Ovary cancer	11	61.1
Initial Stage		
1	4	22.2
2	5	27.8
3	8	44.4
4	0	0
unknown	1	5.6
Lymph node positivity at initial diagnosis (%)	20.3±31.0	
Adjuvant treatment after operation		
None	3	16.7
Concurrent chemoradiation therapy	3	16.7
Chemotherapy	11	61.1
Radiation only	1	5.6

Table 1: Clinical characteristics at initial diagnosis.

After approval from the Institutional Review Board of our hospital (KC15RISI0320), we reviewed the medical records of patients with ILNR of gynecologic cancer after abstracting data on initial treatment and recurrence. The data included diagnosis, initial stage, age, histologic type, primary treatment, initial lymph node status, distribution of recurrent lymph nodes, size of resected lymph nodes, presence or absence of extra nodal lesions, estimated blood loss at SCS, serum tumor markers at initial diagnosis/recurrent status, and postoperative/intraoperative morbidity. Complete Remission (CR) was defined as disappearance of all signs of cancer in response to treatment by CT, PET CT, serum markers, and physical examination. After CR, patients were seen every 3 months for 2 years, then every 4 to 6 months for 5 years, and annually thereafter. At each visit, the patients were checked by physical examination, serum markers, cytologic examination, and CT or PET CT when needed. Follow-up data included the interval from ILNR to clinical or radiographic disease progression. Survival rate after recurrence and overall survival were calculated by using the Kaplan-Meier method.

Results

Eighteen patients were diagnosed with ILNR, and their mean age was 49.8±6.7 (range 40-67) years. Four patients (22.2%) had stage I, 5 patients (27.8%) had stage II, 8 patients (44.4%) had stage III, and 1 patient had unknown stage at the initial diagnosis. The positivity of lymph nodes at primary operation was 20.3%±31.0%. Three patients were treated with concurrent chemo-radiation, 11 patients were treated with combination chemotherapy, and 1 patient was treated with radiation therapy as an adjuvant treatment after primary operation (Table1).

Clinical characteristics at the time of ILNR are shown in Table 2. The Disease-Free Interval (DFI) was 41.3±33.0 (range 7.0-119.0) months. Four patients (22.2%) were diagnosed with

ILNR within 12 months. The sites of nodal involvement were inguinal: (n=2, 11.1%), pelvic (n=7, 38.9%), para-aortic (n=5, 27.8%), pericardiophrenic (n= 1, 5.6%), and supraclavicular (n= 3, 16.7%). The patients were diagnosed with ILNR based on increased size of lymph nodes on CT (n= 14, 77.8%) and by increased size of lymph nodes on CT and increased FDG uptake on PET (n=4, 22.2%). The maximal size of recurrent lymph nodes ranged from 0.6 to 8.0 cm and median diameter was 2.5 cm. Among them, 8 (44.4%) underwent SCS, whose clinical characteristics are shown in Table 3. The estimated blood loss during SCS ranged from 50 to 1000 ml, and median blood loss was 212.5 ml. No patient experienced significant perioperative morbidity.

Characteristics	n	%
Disease free interval (months)		
Mean (range)	41.3±33.0(7.0-119.0)	
<12	4	22.2
≥12, <24	2	11.1
≥24	12	66.7
ILNR site		
Inguinal	2	11.1
Pelvic LN	7	38.9
Paraaortic	5	27.8
Pericardiophrenic	1	5.6
Supraclavicular	3	16.7
Secondary cytoreductive surgery for recurrent mass		
Y	8	44.4
N	10	55.6
Diagnosis of recurrence		
Increased mass size on CT	14	77.8
Increased mass size on CT + increased FDG uptake on PET CT	4	22.2
ILNR: Isolated Lymph Node Recurrence, LN: Lymph Node, CT: Computed Tomography, PET CT: Positron Emission Tomography-Computed Tomography		

Table 2: Clinical characteristics at the time of ILNR.

Patient No.	1	2	3	4	5	6	7	8
Type of cancer	vulva	vulva	endometrium	Cervix	cervix	ovary	ovary	Ovary
Initial stage	I	I	IIIc1	IIB	IB1	Ia	IIIA1	IIIC
Histologic type	squamous cell carcinoma	sarcoma	endometrioid	squamous	squamous	clear	serous	serous
Age	67	41	52	54	48	47	61	51
Grade	I		I	I	I	III	II	II

Primary treatment	Radical vulvectomy + PLND+ inguinal node dissection	Radical vulvectomy+PLND, RT	TAH+BSO+ PLND+ PALND ERT, CTx	CCRT	RH+ PLND	TAH+BSO+ PLND+ PALND+ TO, CTx	TAH+ BSO+ PLND+ PALND+ TO, CTx	TAH+BSO+ PLND+PALND+ TO + multiple biopsy, CTx
DFI(months)	36	46	104	8	15	77	7	7
Diagnosis of recurrence	CT	CT	CT	CT+PET	CT	CT	CT	CT+PET
Initial tumor marker (IU/ml)	SCC:1.1		CA125:22.4	SCC: 63.6	SCC: 4.7	CA125: 17.6	CA125: 3187	CA125: 4597
Tumor marker at recurrence (IU/ml)				SCC: 43.1	SCC:8.1	CA125: 28.2	CA125: 142.1	Ca125: 17.5
Location of LN	Right inguinal	Right external iliac	Para-aortic	Para-aortic	Right common iliac	Right common	Para-aortic	Left inguinal
Size of LN (cm)	8	7	2.4	1	3.9	3.2	1.3	1.5
Treatment after secondary cytoreductive surgery	ERT		CTx	Para-aortic LN RT	Pelvic RT	CTx	CTx	CTx
Current status	NED	Died from lung metastasis and disease progression	NED	NED	NED	Live with disease	Died from disease progression	Disease progression to the liver and cul-de sac
EBL(CC)	100	1000	100	50	50	200	100	100
Survival time	39	52	111	12	61	87	42	21

PLND: Pelvic Lymph Node Dissection; PALND: Para-Aortic Lymph Node Dissection; CCRT: Concurrent Chemoradiation Therapy; Ctx: Chemotherapy; ERT: External Radiation Therapy; RT: Radiation Therapy; BSO: Bilateral Salpingo-Oophorectomy; TO: Total Omentectomy; TAH: Total Abdominal Hysterectomy; RH: Radical Hysterectomy; LN: Lymph Node; NED: Negative for Evidence of Disease; CT: Computed Tomography; PET: Positron Emission Tomography; EBL: Estimated Blood Loss.

Table 3: Clinical characteristics of the study subjects with SCS.

For the recurrent lymph nodes, 5 patients (27.8%) were treated with radiation therapy on, 11 patients (61.1%) were treated with platinum- based combination chemotherapy, 1 patient was treated with platinum based chemotherapy plus localized radiation therapy, and 1 patient refused further treatment. Despite salvage treatment, 7 patients (38.9%) experienced disease progression. The Overall Survival (OS) after ILNR was 49.0 months, the survival times were 44 months in patients at a DFI of <12months and 50.1months in those at a DFI of ≥12months (P=0.92, Figure1). The survival time was 34.8 months in patients who underwent SCS and 53.8months in those who did not (P=0.28, Figure 2).

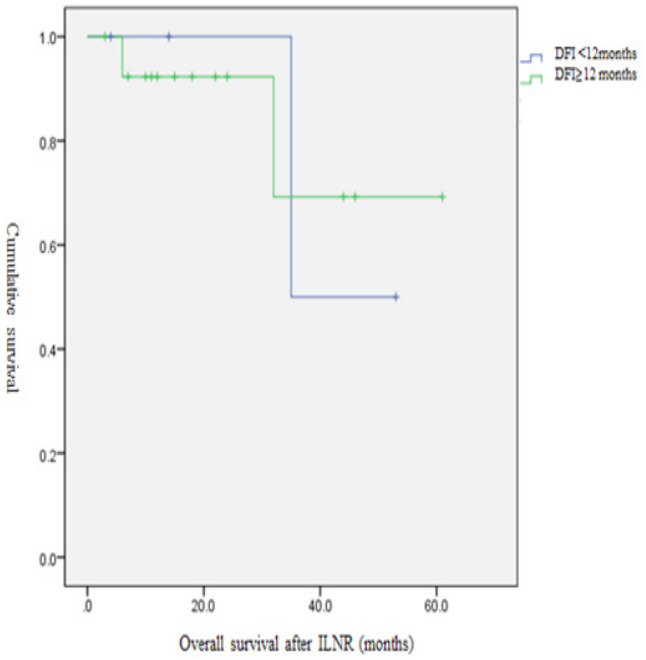

Figure 1: Comparison of overall survival after ILNR according to Disease Free Interval (DFI). There are no significant differences in overall survival according to DFI with the reference interval of 12 months (P = 0.92). ILNR: isolated lymph node recurrence.

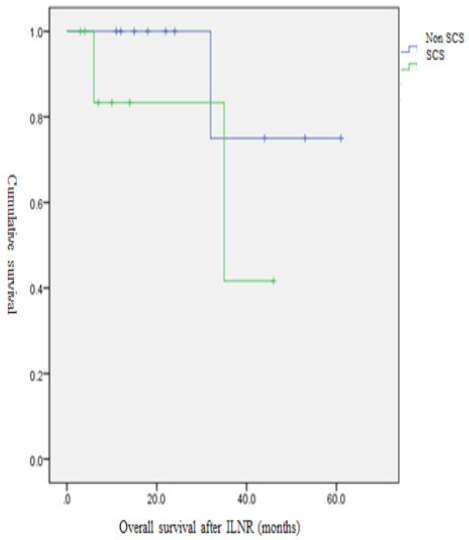

Figure 2: Comparison of overall survival after ILNR according to the performance of Secondary Cytoreductive Surgery (SCS). There are no significant differences in overall survival according to the performance of SCS (P=0.28).

Discussion

Meigs [16] introduced cytoreductive surgery in advanced ovarian cancer and suggested that tumors should be removed as much as possible to enhance the effects of postoperative therapy. Griffiths [17] demonstrated an inverse relationship between residual tumor and survival. SCS reduces the volume of poorly vascularized masses, achieves a more favorable cellular kinetic profile of the remaining malignant cells, decreases the need for chemotherapeutic drugs to achieve further remission, and removes drug-resistant or radiation-resistant masses [2,18]. Legge, et al. [13] reviewed the natural course of ILNR and concluded that ILNR represents a less aggressive pattern, although the occurrence of peritoneal seeding after ILNR results in rapid and fatal outcomes. In their study, 60% of the ILNR patients received chemotherapy alone, the mean progression-free interval was 12 months, and 69% of the ILNR patients survived for 2 years after the diagnosis of recurrence.

Jereczek-Fossa, et al. [19] evaluated the effect of stereotactic body radiotherapy on single lymph node recurrence in patients with gynecologic, gastrointestinal or urologic cancer, 70% of whom showed complete or partial remission with no severe toxicity during therapy. Doses of stereotactic body radiotherapy are limited in previously irradiated areas due to toxicity. The advantages of SCS are that: (1) chemoresistant tumors can be eliminated by SCS, (2) tumor-associated symptoms can be controlled after SCS, and (3) lymph node recurrence can be accurately diagnosed by histologic examination [1]. Bristow, et al. [20] documented that PET CT cannot detect all occult lesions and that only 59% of the positive lesions after radical lymphadenectomy of ovarian cancer are detected in patients with ILNR on PET CT. Glimoreno, et al. [14] reported the advantages of SCS in 8 patients with ILNR of gynecologic cancer. They removed the lymph nodes by the retroperitoneal approach using laparoscopy, and there were no intraoperative or postoperative complications, such as massive bleeding. They also mentioned that SCS is feasible even in the lesion irradiated. There have been many studies on survival after SCS in patients with ILNR of ovarian cancer. Zang, et al. [7] reported that optimal cytoreduction can prolong survival for up to 11 months in patients with platinum-sensitive recurrent ovarian cancer. When the disease recurs 12 months after cessation of primary treatment, it does not show good prognosis even when there is no residual disease after SCS. Uzan, et al. [8] documented that a median survival of 114 months and a 5-year survival rate of 71% were noted in patients with ILNR of ovarian cancer after surgical treatment (Table 2).

Table 4 shows overall survival after ILNR, and good prognostic factors for patients with ILNR of gynecologic cancer. Additionally, patients with ILNR of gynecologic cancer who

underwent SCS, prognosis was better when (1) Gynecologic Oncology Group (GOG) performance is <2, (2) The size of recurrent masses measures 10 cm, (3) the progression-free interval is ≥12 months, and (4) there is no ascites [7,21]. The therapeutic effects of SCS in cervical and endometrial cancers, unlike ovarian cancer, have not yet been fully elucidated. Para-aortic lymph nodes are a common recurrent site after primary treatment in cervical cancer. Many authors have treated isolated paraaortic lymph nodes with radiation therapy because they considered it a regional disease [1]. Niibe, et al. [22] documented that 3-year and 5-year survival rates after radiation therapy were 49.5% and 31.3%, respectively, in patients with isolated paraaortic lymph node recurrence. Singh et al. [23] also reported similar results. In their study, the 5-year survival rate was 100% in patients with isolated para-aortic lymph node recurrence. However, when the recurrent lesion is present in the previously irradiated area, treatment modalities other than concurrent chemoradiation therapy should be considered. Pelvic exenteration is generally believed to be the standard treatment for recurrent cervical cancer [24]. However, systemic chemotherapy is usually performed when recurrence occurs after pelvic exenteration or when the recurrence is not central [25]. However, Mourton et al. [26] reported complete surgical resection in 7 patients with solitary lymph node recurrence after total pelvic exenteration. Approximately 13% of patients with endometrial cancer develop recurrence, and they show poor outcome with a mortality of 25% [27]. Treatment options for recurrent cases are determined according to the distribution of disease or previous treatment methods. Although chemotherapy or radiation therapy is usually performed on patients with lymph node recurrence, exenteration is occasionally performed on patients with central recurrence or resistance to radiation therapy as in our patients [27,28]. Ren, et al. [29] reported that the 5-year survival rate was 42.0% in patients with recurrent endometrial cancer who were treated with salvage cytoreductive surgery. They also mentioned that good prognostic factors are small tumor size and high tumor grade. This study has some limitations: 1) it was retrospective study, 2) a small number of patients were included, and (3) stratification of the study patients according to disease entities was not feasible due to its small sample size.

Author	Uzan, et el. [8]	Santillan, et al. [18]	Foutiou, et al. [30]	Legge, et al. [13]	Niibe, et al. [22]	Ferrero, et al. [2]	Ki, et al
Number of patients	12	25	21	32	84	73	8
Site of cancer	Ovary	Ovary	Ovary	Ovary	Cervix	Ovary	Ovary Cervix Vulva
Overall survival after ILNR (months)	44	37	47	-	-	46	49
Overall survival (months)	5yr survival: 71%	61	66	109	5yr survival : 49.5%	5yr survival: 64%	75.5
Factors associated prolonged survival	Complete resection followed by adjuvant therapy	Optimal surgery(≤ 1cm)	-	Platinum free interval >24 months	Without associated symptoms	-	-

ILNR: Isolated Lymph Node Recurrence

Table 4: Literature review of overall survival, and prognostic factors in patients with isolated lymph node recurrence of gynecologic cancer.

Conclusion

The treatment outcome of recurrent gynecologic cancer after primary treatment is poor, and the clinical course can be fatal. Salvage treatments of recurrent cancer include radiation therapy, chemotherapy, and palliative surgical resection. In selected patients with ILNR, SCS can be the treatment of choice with low perioperative morbidity. Further studies with relatively larger sample size are needed to understand the roll of SCS in ILNR patients.

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