ISSN: 2377-9004

Savescu et al. Obstet Gynecol Cases Rev 2019, 6:147
DOI: 10.23937/2377-9004/1410147
Volume 6 | Issue 3
Open Access

Obstetrics and Gynaecology Cases - Reviews

REVIEW ARTICLE

Prognostic Factors for Secondary Cytoreductive Surgery in Recurrent Ovarian Cancer

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Abstract

Ovarian cancer is an aggressive and lethal gynaecologic malignant disease with high capacity of relapse even if complete cytoreductive surgery is performed at the moment of the initial diagnosis. Once the relapses occur large studies focused on the subject of the best therapeutic protocol in order to achieve a good control of the disease. This is a literature review of the studies focused on this topic.

Keywords

Advanced stage ovarian cancer, Cytoreduction, Recurrence

Introduction

Ovarian cancer is one of the most lethal gynaecological cancers. According to Pecorelli S, et al. 37% from ovarian carcinoma are diagnosed in an early stage while the rest, 63% represent FIGO stage III and IV ovarian cancer. Complete surgical procedure, mentioned in NCCN Guidelines Version 3.2014, is essential for correct staging and management of these patients [1]. Chemotherapy following surgery is required with the exception of stage IA in the hope to achieve complete clinical remission after surgical procedure. In advanced ovarian cancer complete clinical response to systemic chemotherapy is achieved only in about 50% and most of them, around 60% of the patients with advanced epithelial ovarian cancer, will ultimately develop recurrent disease or drug resistance [2]. Even if at the time of second look surgery no lesion is identified 30%-50% of patients will develop recurrence [3].

Secondary Cytoreduction in Advanced Stage Ovarian Cancer

Primary cytoreductive surgery in newly diagnosed invasive epithelial ovarian cancer is well accepted while the role of secondary cytoreductive surgery for recurrent cancer remains controversial. In a retrospective study the number of lymph nodes ranging more than 2 cm demonstrated before debulking in patients with advanced peritoneal disease represents a prognostic factor for overall survival. The number of lymph nodes removed with prognostic value was 40 before surgery and 10 when no residual disease was achieved after debulking [4]. Systematic lymphadenectomy improves survival during primary cytoreductive surgery in patients with stage IIIC-IV of epithelial ovarian cancer [5] and it does not influence the survival during secondary cytoreductive surgery [6]. Several studies tried to identify prognostic factors for these groups [7].

The Role of Para-aortic Lymph Node Dissection

Systematic lymphadenectomy is performed with diagnostic purpose in early stage ovarian cancer in order to eliminate the risk of sub-staging the disease and with therapeutic intent although the survival benefit is unknown [8,9]. According to the FIGO classification, FIGO stage IIIc is defined by the presence of pelvic or para-aortic lymph node metastasis and surgical procedure is followed by adjuvant chemotherapy. Different studies have shown that in stage I the incidence of lymph

Citation: Savescu A, Balescu I, Bacalbasa N (2019) Prognostic Factors for Secondary Cytoreductive Surgery in Recurrent Ovarian Cancer. Obstet Gynecol Cases Rev 6:147. doi.org/10.23937/2377-9004/1410147

Accepted: May 25, 2019: **Published:** May 27, 2019

node was 24% while in stage II the reported incidence was 50% [8], but variation of this rate exist (11%-20%) [10]. Significant improvements have been made in the diagnosis of lymph node metastasis however Magnetic Resonance Imaging, Computer Tomography or Positron Emission Tomography are not always able to detect lymph node metastasis properly. The greatest involvement of positive nodes was found in para-aortic group followed closely by both para-aortic and pelvic group and only pelvic lymph nodes on the third place [8]; however in Charité cohort the greatest involvement was seen in pelvic lymph nodes [10]. The size of the largest lymph node was related with the number of positive nodes [8].

Although lymph node dissection is a common procedure used in gynecological cancer surgery most studies do not differentiate between sampling/systematic lymph node dissection [10]. It is mentioned that patients with correct surgical stadialization (pelvic and para-aortic lymph node sampling, partial lymph node dissection, peritoneal biopsies, subdiaphragmatical biopsies) have an overall survival rate higher when compared to the rest of the patients [11]. Other studies seem to consider more reasonable and effective in staging early ovarian cancer by complete lymph node dissection than by simple lymph node sampling [9]. Maggioni, et al. 2006 published the first randomized study on the value of systematic para-aortic and pelvic lymphadenectomy in comparison with lymph node sampling in ovarian cancer macroscopically confined to the pelvis with a five-year progression-free survival higher for those with systemic lymphadenectomy but with no significant differences and in 2007 Chan and co-workers reported a better significant association of lymphadenectomy on overall survival in stage I ovarian cancer patients [12].

Low malignant potential tumors such as borderline epithelial tumors, mucinous histotypes do not present a survival benefit if dissection of para-aortic and pelvic lymph node is made [13].

Visceral Resection as Part of Secondary Cytoreduction

Secondary cytoreductive surgery in recurrent ovarian cancer is a vast entity that includes bowel resection, appendectomy, stripping of the diphragm, splenectomy, partial hepatectomy, partial gastectomy and other surgical procedures. Systematic pelvic and para-aortic lymph node bilateral dissection it is also included [14]. The role of maximum cytoreduction with residual disease < 1 cm in primary surgery of ovarian cancer has positive influence on survival. Because of the benefits (large tumors respond poorly to chemotherapy due to poor blood supply, smaller residual tumors improve the sensitivity of chemotherapy and gives higher chances for tumor eradication before chemoresistance develops) [15] found after initial optimal cytoreductive surgery many practitioner have asked if same benefits can be achieved after secondary surgery and if same criteria's apply.

Many studies have tried to find out the optimal selection criteria for candidates to secondary cytoreductive surgery for recurrent ovarian cancer. Multiple variables were taken into account such as disease-free interval, the size of residual tumour at primary cytoreductive surgery, the response to first-line chemotherapy, the age at recurrence and the size of maximum tumour at recurrence, performance status defined by ECOG (Eastern Cooperative Oncology Group), no apparent multiple diseases, with the remark of no progressive disease during preoperative period, but only four were revealed to be independent prognostic factors: disease-free interval 12 months [16,17], 10 cm tumour at recurrence [16] or 6 cm [15], the number of recurrent tumours [18] and the absence of liver metastases [19]. A meta-analysis published by Bristow, et al. 2009 concluded that only complete cytoreductive surgery described as resection of all macroscopic disease is independently associated with overall post-recurrence survival time [20]. Two authors Morris, et al. 1989 and Munkarah, et al. 2001 found no statistically significant benefit for secondary cytoreduction [21,22] (Table 1).

The results of the study The Descriptive Evaluation of preoperative Selection KriTeria for OPerability in recurrent OVARian cancer (DESKTOP OVAR) I conducted by Harter P, et al. concluded that patients who underwent secondary cytoreduction for epithelial ovarian cancer sensitive to chemotherapy showed that only complete resection was associated with prolonged survival. Based on this conclusion a score for the prediction of complete cytoreduction in recurrent ovarian cancer was established known as The Arbeitsgemeinschaft Gynäkologische Onkologie (AGO)- score. Three variables with independent and significant impact on surgical outcome were identified such as good performance status- ECOG 0, absence of ascites (cut off 500 ml), and absence of residual tumor after primary surgery with the exception of FIGO I/II if they received chemotherapy [23]. DESKTOP II study showed that using this score resecability can be predicted in 76% [24].

Epithelial ovarian cancer has usually three patterns of spreading: by lymphatic spread, by direct extension and by exfoliation of clonogenic cells. The most common place of dissemination is the intraperitoneal surface but rare cases of retroperitoneal metastasis are mentioned [25,26].

It seems that isolated lymph node involvement relapsing disease from epithelial ovarian cancer after primary optimal surgery has a higher progression-free interval than peritoneal disease. It is a more favourable pattern but with higher percentage of recurrence at the same level. However if peritoneal spreading appears after isolated lymph node relapse the disease has usually a rapidly fatal outcome [27]. Secondary cytoreductive

Table 1: Prognostic factors for secondary cytoreductive surgery in recurrent ovarian cancer (univariate analyses for variables at recurrence).

Characteristic	Median survival Onda, et al. [15]	Median survival Eisenkop, et al. [16]	Median survival Zang, et al. [18]
No. of patients	44	87	117
DFI (months)			
3-12			18
13-23			26
≥ 24			40
< 12	23		
≥ 12	47		
6-12		25	
13-36		44.4	
> 36		56.8	
Largest recurrence			
≤ 10 cm		37.3	
> 10 cm		35.6	
< 6 cm	40		NA
≥ 6 cm	14		
No. of recurrent tumours			
Solitary	64	NA	NS
Multiple	27		
Liver metastasis			
Absent	33	NA	NA
Present	20		
Cytoreductive outcome			
Visibly disease free	55	44.4	
Not visibly disease free	22	19.3	
0 cm			_b
≤ 1 cm			26
> 1 cm			14.5
Ascite			
No	NA	35.9	25.5
Yes		35.6	17.5
ECOG performance status			
0	NS	NS	40.5
1			24.5
2			15.0

DFI: Disease free interval; ECOG: Eastern cooperative oncology group; NA: Not analysed, NS: Not significant, _b: The median survival was not reached.

surgery of isolated lymph node plus chemotherapy has a significantly value for survival after recurrence and overall survival when two prognostic factors are taken into count such as age under 58 years and the time to recurrence more than 12 months [28]. Significant improvement of survival after recurrence and overall survival in patients with isolated lymph node relapsed who underwent secondary surgery plus chemotherapy compared to those treated with chemotherapy alone was also mentioned by others [28]. Like others cases the need of criteria selecting patients who can benefit from combined treatment (surgery plus chemotherapy) is required [29]. Although age represents an important factor, case reports of elder patients (78 years) who can benefit from systemic lymphadenectomy as cytoreductive surgery for isolated lymph node relapsing exists [7]. Chemotherapy is the accepted treatment for recurrence but different studies have shown that retroperitoneal nodal disease is less curable by chemotherapy in ovarian cancer compared with disease at other sites, there for the role of systemic lymphadenectomy becomes more important [6,8]. Multiple approaches

Table 2: Prognostic factors in cytoreductive surgery for isolated lymph node relapsing.

Authors	Ferrero, et al. [31]	Fotiu, et al. [29]	Santillan, et al. [33]	Uzan, et al. [32]
Patients	73	21	25	12
Mean age: Years	54	52	55	51
DFI: Months	18	21	16	21
Pre/post-SCS treatment				
Chemotherapy	70	1	1	9
Radiotherapy	0	4	4	15
Chemotherapy + radiotherapy	0	3	1	17
None	3	0	2	1
PFS after relapsing: Months	46	21	10	44
OS after relapsing: Months	60 (64%)	60 (68%)	37	60 (71%)

DFI: Disease free interval; PFS: Progression free survival; OS: Overall survival; SCS: Secondary cytoreductive surgery.

(single or combined) have been described as treatment for isolated lymph node relapse [30]. While the majority of studies are trying to associate chemotherapy, radiotherapy or both chemotherapy plus radiotherapy to surgery and to evaluate the benefits [29,31-33] that seems promising regarding a 5-year survival, few consider local radiation therapy following chemotherapy as an acceptable choice for localized recurrent ovarian cancer, particularly for small masses and lymph nodes recurrences [34] (Table 2).

In cases of advanced ovarian cancers cytoreductive surgery is the recommended treatment [25]. In advanced ovarian cancer pelvic and para-aortic lymph node are not evaluated for staging as in early ovarian cancer, lymph node involvement being known as a prognostic factor [25]. Many have asked if the right approach of lymphadenectomy is only on bulky lymph nodes or on systemic lymphadenectomy. Resection of macroscopically enlarged lymph node is necessary for correct treatment. Different studies have shown that systemic lymphadenectomy improves progression-free but not overall survival in patients with optimally debulked advanced tumors [25].

Conclusions

At this moment clear statistic dates does not exist. Further studies are required for better selection of the patients who can have survival benefit after secondary cytoreductive surgery.

Although all the lymph nodes are removed occasional cases of recurrent ovarian cancer with lymph node metastases spread to multiple sites are mentioned, so radical lymph dissection does not always mean that all cancer cells are removed [7].

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