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ORIGINAL ARTICLE

Correlation Between Pelvic Peritoneal Disease and Nodal Metastasis in Advanced Ovarian Cancer: Can Intraoperative Findings Define the Need for Systematic Nodal Dissection?

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Abstract

To explore the relationship of peritoneal, and rectal involvement with lymph nodal metastases to identify clinical parameters to guide systematic nodal dissection in advanced ovarian cancer (stage 3c). It is a retrospective study of stage III C epithelial ovarian cancers undergoing cytoreductive surgery with systematic nodal dissection, from January 2011 to December 2016. LS3 score is a cumulative score given for the presence of size 3 lesion (peritoneal disease measuring more than 5 cm) in regions 5, 6, and 7. The depth of rectal involvement was assigned progressive numerical values from 1 (for serosa) to maximum 4 (for mucosa) to generate rectal involvement score. There were 91 patients. 48.35% patients had LS3 lesions in regions 5, 6, 7. Of these, 36% (27/44) had positive nodes. Of the 41 node-positive cases, 43.9% had single and 34.14% had two station involvements. Rectum was involved in 47 patients (51.64%), serosal involvement being the most common type (50.57%). Twenty patients had positive mesorectal nodes (42.55%). The presence of rectal involvement was influenced by the Peritoneal Carcinomatosis Index (PCI) score, the presence of LS3 in lower quadrants ($p = 0.008$), and LSE score of lower quadrants ($p = 0.003$). With the increasing depth of rectal infiltration, mesorectal positivity increased significantly ($p = 0.000$). In multivariate analysis, lower quadrant (regions 5, 6, 7) PCI, LS3 in lower quadrants, LS3 score, rectal involvement score, and the total number of lines of chemotherapy significantly affected different nodal disease parameters. In advanced ovarian cancer, LS3 disease in regions 5, 6, and 7 and rectal involvement directly impact the nodal metastasis and hence mandates a systematic nodal dissection. Mesorectal nodal involvement significantly increases with the increasing depth of rectal involvement necessitating systematic mesorectal nodal clearance for all rectal resections.

Keywords Nodal dissection in ovarian cancer · Correlation between peritoneal disease and nodal metastasis · Clinical parameters for nodal dissection

Introduction

Nodal involvement in epithelial ovarian cancer (EOC) increases with stage [1, 2]. Nodal involvement is a bad prognostic factor for survival [3–7]. The role of systematic lymphadenectomy in advanced ovarian cancer (stage 3 and stage 4) remains uncertain with questionable therapeutic benefit. A randomized controlled trial comparing systematic nodal dissection (SND) to the removal of only bulky nodes in advanced ovarian cancer (stages 3 and 4) showed that the progression-free survival (PFS) is better in the systematic arm, but there was no effect on overall survival (OS) [8]. Another RCT showed nonsignificantly higher PFS and OS in systematic lymphadenectomy arm compared to nodal sampling. But by authors' own admission, this trial may have lacked the power to estimate the effect of nodal dissection. And the study included disease confined to pelvis only [9]. A large cohort retrospective study showed that lymphadenectomy and its extent positively affected disease-specific survival in stage 3 and 4 ovarian cancer [4]. This highlights that there is some undefined benefit of SND in advanced ovarian cancer. However,

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systematic nodal dissection increases the total operative time, leads to more blood loss and increased post-operative morbidity [8]. The concerns with SND in early-stage ovarian cancer is overtreatment and complications while in advanced stage, it is about whether it gives benefit in terms of survival. Finding a subset of patients, based on available clinical parameters, who may benefit the most from SND, is essential to balance the claimed benefits of SND with the morbidity.

Aims and Objectives

The aim of this retrospective study was to explore the possibility of a correlation between the extent and pattern of peritoneal involvement, based on intra-operative findings, with lymph nodal metastases to define a group of patients that would benefit the most with SND. We also aimed to evaluate the influence of rectal involvement on nodal metastasis.

Materials and Methods

Data was collected retrospectively from prospectively maintained databases at two institutions. All stage III C EOC patients undergoing cytoreductive surgery (CRS) and SND, with or without hyperthermic intraperitoneal chemotherapy (HIPEC), from January 2011 to December 2016 are included in the study. Patients' demographics, treatment details (past and present), pathological details, and follow-up details were obtained from a prospectively maintained database.

Exclusion

Patients in whom nodal dissection was not performed or in whom data was not available were excluded. Patients in whom the Peritoneal Carcinomatosis Index (PCI) details and nodal pathological details and patterns of nodal distribution were missing were excluded. All patients were evaluated with complete history and physical examination, ca 125 levels, CECT of thorax, abdomen and pelvis.

Selection of Cases for Primary Upfront CRS + Nodal Dissection

Patients' performance status (PS), the possibility of optimal CRS and presence of ascites were taken into account to select patients for upfront CRS with systematic nodal dissection. Patients who were not deemed fit for upfront surgery received induction chemotherapy. The choice of chemotherapeutic regimen was at treating medical oncologist's discretion. Patients presenting with suboptimal surgery were also evaluated in a similar manner and selected for either upfront surgery or chemotherapy based on the same criteria mentioned earlier.

Surgical Treatment Protocol

All surgeries were done with an attempt to achieve optimal cytoreduction. Upon exploration, the disease extent was mapped using Sugarbaker's Peritoneal Carcinomatosis Index (PCI). All the involved peritoneum was removed. The prophylactic peritonectomy procedure was not carried out in any of the patients. Systematic nodal dissection was done including retroperitoneal, common iliac, and pelvic nodes. The extent of nodal dissection was based on the imaging and intraoperative findings. Patients, who had visceral resections as a part of CRS underwent systematic nodal dissection of the respective organs. Patients who got optimal cytoreduction received cisplatin-based HIPEC by open method.

Pathologic Assessment

All the resected peritoneal quadrants, visceral resections and nodal dissections underwent careful evaluation for the presence of the disease.

Statistical Analysis

For generating "LS3 scores", each lower segment (quadrants 5, 6, 7) was assessed for lesion size (LS) score of the peritoneal disease. The presence of LS3 i.e peritoneal disease measuring more than 5 cm, was given 1 point while anything less than LS3 was given a score of 0. Then, scores of all three quadrants were added to generate a score which we called "LS3 score." This was done to test the hypothesis that the increased burden in the pelvis increases the risk of nodal metastasis.

Progressive involvement of rectum from serosa to mucosa (based on patholgical analysis) was assigned numerical values: serosa = 1, muscular = 2, submucosa = 3, mucosa = 4. These values were collectively termed "rectal involvement score." This score was used to analyze the impact of the depth of rectal infiltration on nodal metastasis.

Treatment was divided into two categories: upfront surgery and post-chemotherapy surgery (including recurrent, interval, and salvage CRS) based on whether patients had received prior chemotherapy.

SPSS version 20.0 was used for the statistical analysis.

Categorical variables were compared with the chi-square test. Means are compared with *T* test and ANOVA test. Independent factors which are found to affect the nodal disease were compared using multivariate analysis. In homogeneous data, correlation was tested with Pearson's correlation test. For non-homogenous data and datasets with outliers, Spearman's rank coefficient test was used. The linear correlation between the factors being assessed was tested to satisfy the hypothesis for correlation tests.

Table 1 Characteristics of patients and treatment patterns

Parameters	Numbers	
Median age	50.46 years (range: 19–70)	
Type of surgery	Upfront: 34	
	Post-chemotherapy: 57	
Prior chemotherapy ($n = 59$)		
Number of cycles	Mean = 5.54 (range 2–14)	
	Median = 6	
Number of lines	Mean 1.52 (range 1–4)	
	Median 1.0	
Prior surgical score	0	$n = 17$
	1	$n = 12$
	2	$n = 17$
	3	$n = 15$
	4	$n = 1$
	6	$n = 1$
	Not available	$n = 28$
ca 125 (U/mL)	Mean	696
	Median	190
PCI	Mean 14.57 range (1–36)	
	Median 12.5	
Mean PCI	Upfront surgery	15.3
	Post chemotherapy surery	14.5
PCI in lower quadrants	Mean 5.8 (range 0–9)	
	Median 6	
LS3 lesion in lower quadrants	Yes 44	
	No 47	
LS3 score in lower quadrants (mean)	1.1	
Visceral resections	Yes 53	
	No 38	
Colorectal resections	52	
HIPEC	Yes 38	
	No 47	
	Data not available 6	
Pathology	Serous 72	
	Mucinous 6	
	Endometrioid 3	
	Clear cell 2	
	Not available 8	
Grade	Low 2	
	Intermediate 5	
	High 67	
	Data not available 17	
Overall nodal positivity	Positive 41	
	Negative 50	
Nodal distribution in node-positive cases	Only pelvic nodes	3
	Only RP nodes	2
	RP + pelvic nodes	5
	RP + pelvic + visceral	3
	Only visceral + other sites	5
	RP + pelvic + non-visceral	2
	RP + visceral	01
	Pelvic + non-visceral	2
	RP + pelvic + visceral + non-visceral	3
	RP + non-visceral	1
	Only visceral	13
	Data missing	1
No of stations involved	1 station 18	
	2 stations 14	
	3 stations 5	
	4 stations 3	
	Data missing 1	

RP=retroperitoneal

Results

There were 117 patients who underwent CRS+ SND+ /− HIPEC for EOC in the two centers involved in the study. All the cases were performed by two surgeons who are experienced in CRS for EOC. Nineteen patients were excluded from the study for lack of data on nodal disease. Six patients were removed from study due to lack of details on PCI distributions and one patient was excluded since the pathology was nonepithelial ovarian cancer. In the end, 91 patients were available with full data, for analysis.

Table 1 shows patient and tumor characteristics. Majority of the patients (62.63%) underwent surgery post-chemotherapy. PCI scores in upfront surgery and post-chemotherapy surgery (15.3 vs 14.2) were comparable ($p = 0.132$). 48.35% (44 out of 91) patients had LS3 lesions in the regions 5, 6, and 7. And 61.36% (27 out of 44) of those patients had the node-positive disease. 73.62% patients (67 patients out of 91) had

Table 2 Correlation between rectal involvement and other parameters

Independent variable	p value for rectal involvement score	p value for overall rectal involvement
LS3 score in lower quadrant	0.091	0.003
LS3 I lower quadrants	0.088	0.008
Total PCI in lower quadrants	0.246	0.088
Grade of tumor	0.222	0.728
Histology	0.995	0.053
Primary vs non-primary	0.475	0.513
No of cycles	0.470	0.692
No of lines	0.058	0.320
PCI less than 20 or more	0.620	0.004
PCI less than 15 or more	0.423	0.001

Table 3 Impact of depth of rectal infiltration on mesenteric nodal positivity

Rectal involvement score	Mesorectal nodal involvement			*p* value
	Yes	No	Not applicable	
0			44	0.000
1	4	24		
2	5	1		
3	4	1		
4	7	1		

high-grade tumors; 79.12% (72 out of 91) had serous histology. In node-positive cases (41 cases), 43.9% had single station involvement, and 34.14% had two station involvements. Rectum was involved in 47 patients (51.64%). While the involvement of the serosa alone was the most common occurrence (50.57%), it reached mucosa in 8 patients (17%). Twenty patients had positive mesorectal nodes (42.55%).

On analyzing the correlations (Supplementary Table 1), we found a positive correlation between prior chemotherapy and the presence of nodal disease ($p = 0.007$). Serous histology showed a significantly positive correlation with perinodal extension (PNE) ($p = 0.022$). The depth of rectal invasion showed a positive correlation with the overall nodal positivity, the number of stations involved, and PNE ($p = 0.01$, 0.07, and 0.016 respectively). Overall, PCI and PCI of lower 3 quadrants also showed a direct correlation with the number of involved nodal stations. LS3 presence and LS3 score of lower quadrant showed a significant direct correlation with all nodal parameters. HIPEC correlated positively with PNE.

Table 2 shows the correlation between rectal involvement and disease burden along with other parameters. On contingency tables, we did not find any influence of disease burden and primary tumor characters on the depth of rectal involvement but the presence of rectal involvement was significantly influenced by PCI score, the presence of LS3 in lower quadrants, and LS3 score of lower quadrants (Table 3).

Table 3 shows that with the increasing depth of rectal infiltration, mesorectal nodal positivity increases significantly.

Table 4 shows the impact of various patient and treatment parameters on nodal disease variables. The presence of LS3, LS3 score, and rectal involvement score significantly affected all nodal parameters. With the increasing number of lines of chemotherapy, the nodal disease came down significantly. PCI of more than 15 significantly increased the overall nodal positivity and the number of stations involved.

Table 5 shows a multiple regression analysis of all the factors shown to be affecting the nodal parameters in univariate analysis. Presence of LS3 in lower quadrants and LS3 score independently affected the number of nodal stations involved ($p = 0.046$ and 0.005 respectively). The overall nodal positivity was affected by rectal involvement score ($p = 0.033$) and a total number of lines of chemotherapy (0.027). Perinodal extension was significantly affected by total PCI in region 5, 6, and 7 and the LS3 score in lower quadrants ($p = 0.028$ and 0.009 respectively).

ROC curves for overall nodal positivity were analyzed to determine the LS3 score which covers the maximum area under the curve. The LS3 score of 3 covered the maximum area (66%) for overall nodal positivity compared to that of LS3 score more than 1 (62.4%) (Supplementary Fig. 1).

Discussion

Several studies have addressed the factors determining nodal metastasis in ovarian cancer. A retrospective study of stage 1–3 ovarian cancer determined that histology, grade, and ca 125 at the onset can be used to determine the need to do SND [10]. Grade and histology [11, 12], bilateral disease [12, 13], menopause [13], and ca 125 [12, 14, 15] have been found to affect nodal metastasis in early ovarian cancer [11–13] and in all stages as well [14, 15]. Very few reports have studied the peritoneal disease for its impact on nodal disease [1, 2, 16]. In one such report, the peritoneal disease was divided into three categories—pelvic only (ED1), beyond pelvis but abdomen confined (ED2), and metastatic (ED3). The study showed that the number of positive pelvic nodes increased with increasing extent of the involvement. Correspondence analysis revealed associations between ED1 and negative nodes, ED2 and positive aortic/pelvic nodes, and ED3 and positive external and common iliac nodes [16]. This can be correlated very well with the pattern of spread of ovarian disease. However, this study did not analyse the other potential factors that may have affected the nodal metastasis.

Sakai et al. [17] and Tsuruchi et al. [1] found the omental disease to be the most important factor affecting pelvic nodal metastasis based on multivariate analysis. Both the studies analyzed various disease sites in univariate analysis and included all stages of ovarian cancer.

In comparison to this study, we used the PCI score, the presence of LS3, and LS3 score to analyze the association. We focused on the pelvic peritoneal disease specifically because this is the most common peritoneum involved and hence most commonly encountered clinical scenario both in primary as well as non-primary settings [18]. We also evaluated the impact of rectal involvement and its extent on nodal disease as rectum is commonly involved with locally advanced ovarian cancer. Our aim was to identify intraoperative parameters based on which a decision to go ahead with systematic nodal dissection can be taken on the table until the time more definitive and refined evidence for the same comes along.

We did not find any significant correlation between grade, histology, and nodal disease. We did not have complete data

Table 4 Impact of different variables on nodal parameters (univariate analysis)

Factors	Number of stations involved					*p* value	Overall nodal positivity		*p* value	Perinodal extension			*p* value
	0	1	2	3	4		Positive	Negative					
Primary	22	6	4	1	1	0.664	12	22	0.148	5	8	19	0.148
Non-primary	27	12	10	4	2		29	28		14	19	20	
Prior chemotherapy						0.378			0.132				0.130
Yes	28	12	10	5	2		30	29		15	19	21	
No	21	6	4	0	1		11	21		4	8	18	
No of lines						*0.020*							*0.018*
0	19	5	4	0	0		9	19	0.448	4	6	18	
1	16	7	6	1	0		15	16		5	10	13	
2	8	4	0	2	2		8	9		4	8	4	
3	2	0	1	2	0		3	2		4	0	1	
4	0	1	0	0	0		1	0		0	0	1	
No of cycles						*0.022*			0.057				0.060
Histology													
Serous	37	15	12	4	3	0.932	35	37	0.456	16	21	31	0.882
Mucinous	3	2	0	1	0		3	3		2	1	3	
Endometrioid	3	0	0	0	0		0	3		0	1	2	
Clear cell	1	0	1	0	0		1	1		0	1	1	
Others	1	0	0	0	0		0	1		–	–	–	
Grade						0.545			0.307				
Low	2	0	0	0	0		0	2		0	1	1	0.919
Inter	2	3	0	0	0		3	2		1	2	2	
High	31	14	13	5	3		36	31		17	20	27	
Rectal involvement									0.130				0.419
Yes	23	13	5	3	1	0.121	23	24		11	16	19	
No	25	4	7	2	1		14	25		7	8	19	
Info missing	1	1	2	0	1		4	1		1	3	1	
Rectal involvement score									*0.000*				*0.000*
0	26	5	9	2	2	*0.001*	18	26		8	11	20	
1	22	4	0	1	0		0	23		3	6	19	
2	1	2	2	1	0		5	1		3	3	0	
3	0	4	1	0	0		5	0		0	5	0	
4	0	3	2	1	1		8	0		5	2	0	
Visceral resections						0.658							
Yes	26	13	7	3	2		26	27	0.365	12	18	22	0.688
No	23	5	7	2	1		15	23		7	9	17	
PCI													0.102
Less than 15	31	11	5	0	1	*0.018*	18	31	*0.038*	9	11	24	
15 or more	15	7	9	5	2		23	16		10	16	12	
Less than 20	36	14	9	2	1	0.172	27	36	0.265	12	18	28	0.448
20 or more	10	4	5	3	2		14	11		7	9	8	
Total PCI of lower 3 quadrants						0.103		0.068					0.051
LS3 in lower quadrant													
Yes	16	12	8	4	2	*0.039*	27	17	*0.002*	13	15	13	*0.028*
No	33	6	6	1	1		14	33		6	12	26	
LS3 score of lower quadrant													
0	33	6	5	1	1	*0.018*	13	33	*0.001*	5	12	26	*0.006*
1	5	5	2	0	0		8	5		3	4	3	
2	6	0	1	1	0		2	6		2	0	6	
3	5	7	6	3	2		18	6		9	11	4	
CC score													
CC0	34	12	9	3	2	0.659	27	34	0.496	14	18	25	0.700
CC1	12	6	4	2	1		13			5	8	11	
CC2	0	0	1	0	0		13			0	1	0	
CC3	–	–	–	–	–		1	0		–	–	–	
HIPEC													
Yes	16	11	5	2	2	0.258	21	17	0.148	12	13	10	0.037
No	29	6	9	3	1		19	29		7	13	25	

Data in italics are *p* values of less than 0.05

on ca 125 and hence, we could not analyze it. But our findings also suggest that peritoneal disease is more important determinants of nodal disease than primary tumor characteristics (Tables 4 and 5). This may indicate that once the

Table 5 Multiple regression analysis results

Variables	Significant factors affecting the variables	*p* value	Confidence interval	Adjusted R^2 value (%)
Number of nodal stations	Number of lines	0.064	− 5.3 to − 0.23	26.5
	LS3 in lower quadrants	0.046	0.03–2.44	
	LS3 score in lower quadrants	0.005	0.21–1.12	
Overall nodal positivity	No of cycles	0.027	− 0.07 to − 0.004	18.7
	Rectal involvement score	0.033	− 0.208 to − 0.009	
	LS3 score in lower quadrants	0.081	− 0.4 to 0.024	
Perinodal extension	LS3 score in lower quadrant	0.009	− 0.930 to − 0.136	29.1
	No. of lines	0.068	− 0.69 to 0.025	
	Total PCI in lower quadrants	0.028	0.016 to 0.266	

peritoneal disease is established, the other factors play a less important role in nodal metastasis. But it is difficult to draw concrete conclusions based on this database where majority of the tumors were serous and high grade.

We have also analyzed the impact of overall PCI on the nodal disease. PCI of less than 15 showed significance in univariate analysis but not in the multivariate analysis thus confirming our hypothesis that the site of higher disease burden affects the nodal disease independently of the overall PCI. Hence, an overall PCI score may not be a guide to the need for systematic nodal dissection. But the presence of LS3 in any of the lower quadrant lesions and the overall LS3 score directly affect the nodal metastasis (Table 5). On ROC curves, the areas covered by various LS3 scores were only marginally different (Supplementary Fig. 1) where the LS3 score of 3 covered the maximum area (66%). Based on these findings, we can recommend systematic nodal dissection for all patients who show the presence of any LS3 lesions in the lower quadrants, the possibility of nodal positivity being highest in cases where all three lower regions have LS3 lesions.

In the present cohort, more than 50% of patients underwent rectal resections for complete cytoreduction. In Di Giorgio et al.'s report, the depth of rectal involvement progressively increased with increasing peritoneal disease burden [19]. But there was no impact of depth of infiltration and the overall PCI on the mesenteric nodal disease. On the contrary, in our findings, the rectal involvement was influenced by PCI score and the presence of LS3 in lower quadrants but the depth of infiltration of the rectum was independent of any of the disease variables (Table 2). These findings suggest the presence of a higher disease burden in the pelvis indicates a possible need for the rectal resection. We also noted a significant correlation between rectal depth of infiltration and mesorectal nodal positivity (Table 3) contrary to Di Giorgio et al.'s report [19]. These findings suggest that a total mesorectal excision along with mesorectal nodal clearance similar to primary rectal cancer has to be carried out whenever rectal resection is done for optimal cytoreduction.

We are unable to deduce the reason behind the chemotherapy being a significant factor for the nodal disease. Selection bias could be one explanation as node-positive patients may have received more number of chemotherapies and more lines of chemotherapy.

Limitations

The study is done in a retrospective manner. It included advanced ovarian tumors treated surgically in both primary and non-primary settings which also included patients who were initially treated with suboptimal surgery. Hence, the patient pool is heterogeneous. The chemotherapy cycles and drugs were also heterogeneous and may have affected the results. Prospective studies will be able to throw more light on this subject.

Conclusions

In advanced ovarian cancer, the peritoneal disease burden directly impacts the nodal metastasis, wherein the disease burden in the lower quadrants plays the most important role. The presence of LS3 in lower quadrant mandates a systematic nodal dissection in all cases. Mesorectal nodal involvement significantly increases with increasing depth of rectal involvement. Hence, in all rectal resections carried out for optimal clearance, total mesorectal excision is necessary to acheive complete mesorectal nodal clearance.

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